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# Difunctionalization of Dienes, Enynes and Related Compounds via Sequential Radical Addition and Cyclization Reactions

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**Abstract:** Radical reactions are powerful in creating carbon–carbon and carbon–heteroatom bonds. Designing one-pot radical reactions with cascade transformations to assemble the cyclic skeletons with two new functional groups is both synthetically and operationally efficient. Summarized in this paper is the recent development of reactions involving radical addition and cyclization of dienes, diynes, enynes, as well as arene-bridged and arene-terminated compounds for the preparation of difunctionalization cyclic compounds. Reactions carried out with radical initiators, transition metal-catalysis, photoredox, and electrochemical conditions are included.

**Keywords:** radical; difunctionalization; addition; cyclization; diene; enyne



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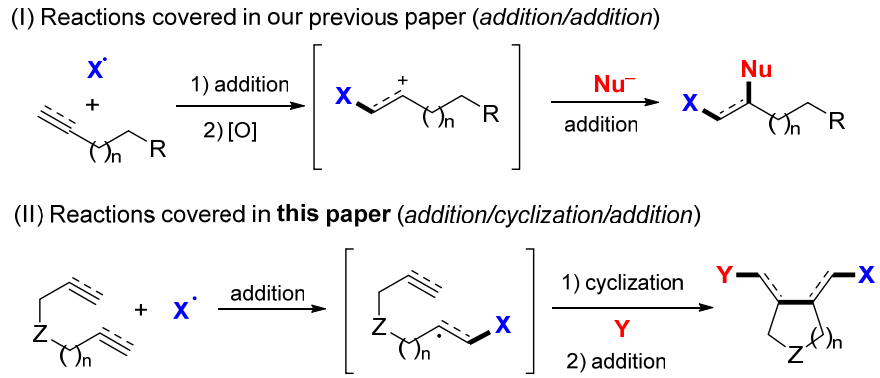
## 1. Introduction

Synthetic radicals are a topic of current interest due to their feasible radical transformations, such as addition, cyclization, coupling, atom/group transfer, rearrangement and fragmentation, which are powerful in the construction of carbon–carbon bonds, carbon–heteroatom bonds and the formation of diverse ring skeletons [1,2]. The recent developments on photoredox catalysis [3] and electrochemical reactions [4] have sped up the research in this field. Among the board scope of free radical reactions, the radical difunctionalization of alkenes and alkynes has attracted special attention since the substrates are readily available, the reaction process is operationally simple, and two functional groups are introduced to the products in regio- and diastereoselective fashions.

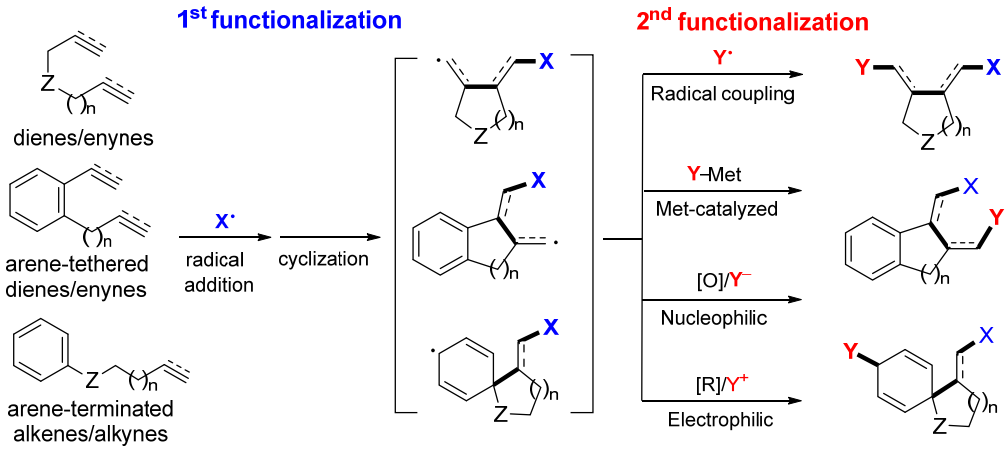
There is a large number of reviews on the radical difunctionalizations [5–16]. In a recent paper from our group, we summarized radical addition followed by nucleophilic addition for 1,2- and remote difunctionalizations to introduce X and Y groups to the products (Scheme 1, I) [17]. Presented in this paper is another kind of radical difunctionalization that is initiated with the addition of radical $X^{\cdot}$ followed by radical cyclization and then a second functionalization with Y through coupling or addition to obtain the product (Scheme 1, II).

More information on the radical addition and cyclization-based difunctionalization reactions is shown in Scheme 2. There are three different kinds of substrates: (I) dienes, diynes, and enynes; (II) arene-tethered dienes or enynes; and (III) arene-terminated alkenes and alkynes. The cyclized radical intermediates could have four ways for the second functionalization with Y: (I) coupling with radical Y; (II) metal-catalyzed reaction with Met-Y; (III) oxidation to a cation and then undergoing nucleophilic reaction with $Y^{-}$; and IV) reduction to an anion and then undergoing electrophilic reaction with $Y^{+}$. The difunctionalization reactions could be carried out as a one-pot reaction with the following cascade reaction sequence: (1) addition of the initial radical $X^{\cdot}$ to introduce the first functional group; (2) radical

cyclization to form the ring; and (3) second functionalization with Y to obtain the product. Compared to the two kinds of reactions shown in Scheme 1, the first one is relatively simple and has been well established. The second one can generate structurally more attractive fused-, bridged-, or spiro-ring systems, but they are more synthetically challenging and under active development. The reactions presented in this paper are organized based on three kinds of starting materials shown in Scheme 2. Reaction-related substrates are also discussed in the last section of the paper.




**Scheme 1.** Two kinds of radical difunctionalization reactions.



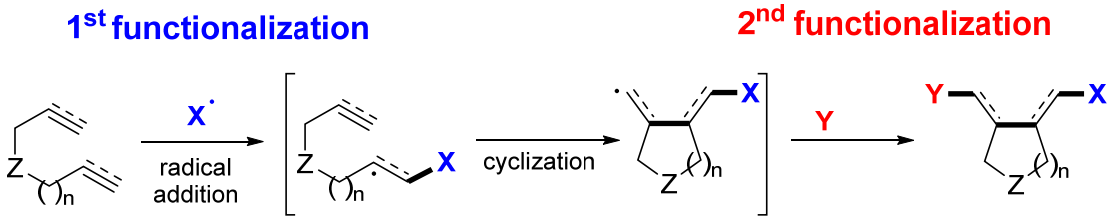

**Scheme 2.** Radical addition and cyclization-based difunctionalizations.

The radical reactions presented in this paper could be conducted using one of the following methods: (1) using radical initiators such as azodiisobutyronitrile (AIBN), *t*-butyl nitrite (*t*-BuONO), aryldiazonium tetrafluoroborates; peroxides such as dicumyl peroxide (DCP), di-*t*-butyl peroxide (DTBP), and *t*-butyl hydroperoxide (TBHP) and *t*-butyl peroxybenzoate (TBPB); (2) using single electron transfer (SET) agents such as hypervalent iodine reagents (HIRs), hypervalent bromine reagents (HBrRs), ceric ammonium nitrate (CAN), $Mn(OAc)_2$, and $Na_2S_2O_5$; (3) under photoredox catalysis such as $Ru(bpy)_3Cl_2$ and $Ir(ppy)_3$), $[Ir(dtbbpy)(ppy)_2]PF_6$, *N*-methyl-9-mesityl acridinium ($Mes\text{-}Acr^+$), *fac*-$Ir(ppy)_3$, $Na_2$-Eosin Y; and (3) through electrochemical reactions.

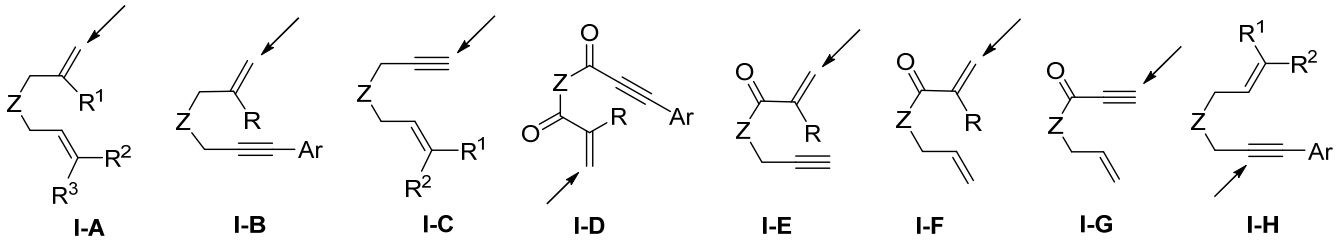
A wide range of functional groups could be incorporated to the products through the difunctionalization reactions, which include halogens (Cl, Br and I), aryl (Ar), alkyl (R), cyano (CN), trifluoromethyl ($CF_3$) or perfluoroalkyl ($R_F$), 2-ethoxy-1,1-difluoro-2-oxoethyl ($CF_2CO_2Et$) or 2-ethoxy-1-fluoro-2-oxoethyl ($CHFCO_2Et$), 2-cyanopropan-2-yl ($C(CH_3)_2CN$), carbamoyl ($CONH_2$), aryl carbonyl (ArCO), alkyl carbonyl (RCO), hydroxy (OH), carbamoyl oxy ($O_2CNR_2$), azido ($N_3$), amino ($NR_2$), aryldiazenyl (Ar-N=N), nitro ($NO_2$), nitroso (NO), sulfonyl (Ts), trifluoromethylthio ($CF_3S$), methylthio ($CH_3S$), arylthio (ArS), phosphorus ($PO(OR)_2$), alkyl silyl ($R_3Si$), aryl silyl ($Ar_3Si$), phenylselanyl (PhSe) and heteroatom-containing groups.

## 2. Reaction of Dienes and Enynes

Presented in this section are the radical addition and cyclization-initiated difunctionalization reactions of 1,n-dienes and -enynes with a reaction sequence shown in Scheme 3. The common substrates include dienes (**I-A**), enynes (**I-B**, **I-C**, **I-H**), dienyl amides (**I-F**), enynyl amides (**I-D**, **I-E**, **I-G**) with the Z as a carbon or heteroatom (Scheme 4). Since there are two unsaturated carbon–carbon bonds in the substrates which are available for the radical addition, the regioselectivity for the initial radical addition is critical. As indicated in Scheme 4, the steric hindrance (**I-A** to **I-D**) and conjugation effect of the groups, such as C=O and Ar (**I-E** to **I-H**), are the major factors to direct the position for the initial radical addition.

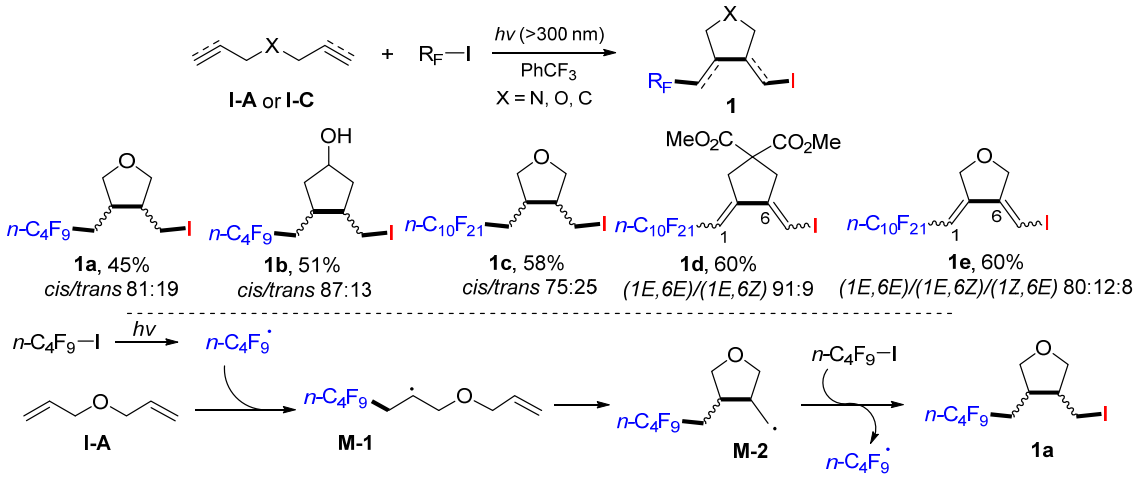



**Scheme 3.** General reaction scheme for difunctionalization of dienes and enynes.



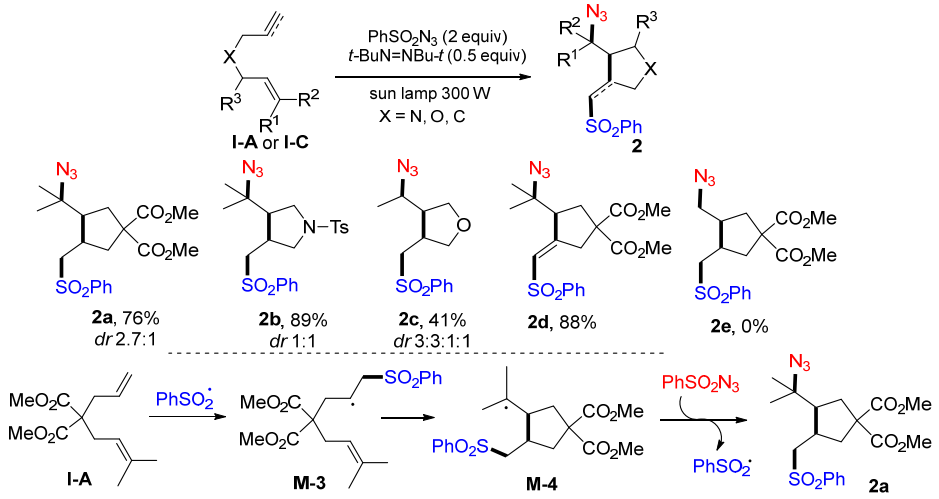

**Scheme 4.** Diene and enyne compounds with pointed position for the initial radical addition.

In 2005, Ogawa and coworker reported a near-UV light-mediated radical reaction of dienes, diynes, and enynes for the synthesis of iodoperfluoroalkylated cyclic products. The reactions of dienes, diynes, or enynes and perfluoroalkyl iodides in $PhCF_3$ under the irradiation of xenon lamp afforded products **1** as a mixture of *cis/trans* isomers in moderate-to-good yields (Scheme 5) [18]. A proposed mechanism indicated that the *n*-$C_4F_9$ radical generated from *n*-$C_4F_9I$ under the light adds to diene. The intermediate **M-1** undergoes 5-*exo* cyclization to give alkenyl **M-2,** which then reacts with *n*-$C_4F_9I$ through the iodine atom transfer to give product **1a**.



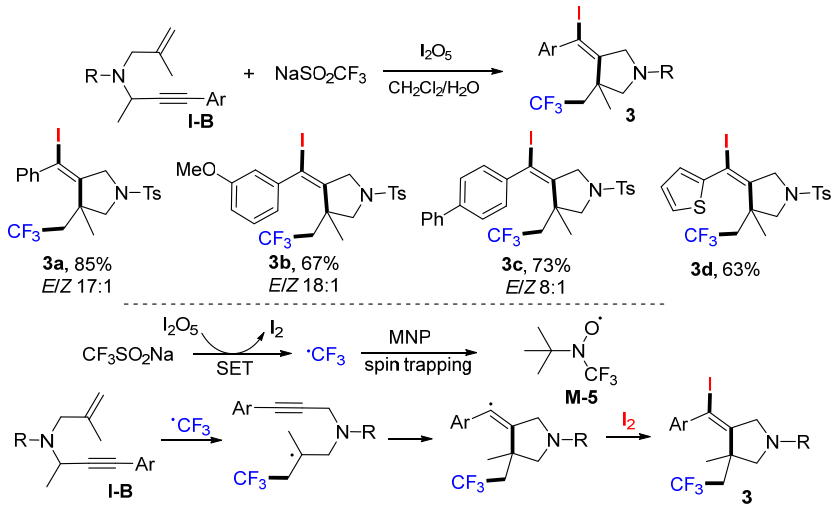

**Scheme 5.** Synthesis of iodoperfluoroalkylated products.

A sun lamp-mediated radical reaction for making azidosulfonylated cyclic products was reported by the Renaud group in 2008. Dienes, diynes, or enynes in dry benzene reacted with benzenesulfonyl azide with radical initiator di-*t*-butyldiazene to give azidosulfone products **2** in moderate-to-excellent yields (Scheme 6) [19]. This method is good for the formation of tertiary and secondary azides **2a–d**, but not for primary azide **2e**. The reaction process involves the addition of $PhSO_2$ radical to the less hindered alkene to form intermediate radical **M-3**, 5-*exo* cyclization for radical **M-4**, and $N_3$ radical transfer from $PhSO_2N_3$ to give product **2a**.




**Scheme 6.** Synthesis of azidosulfonylated cyclic products.

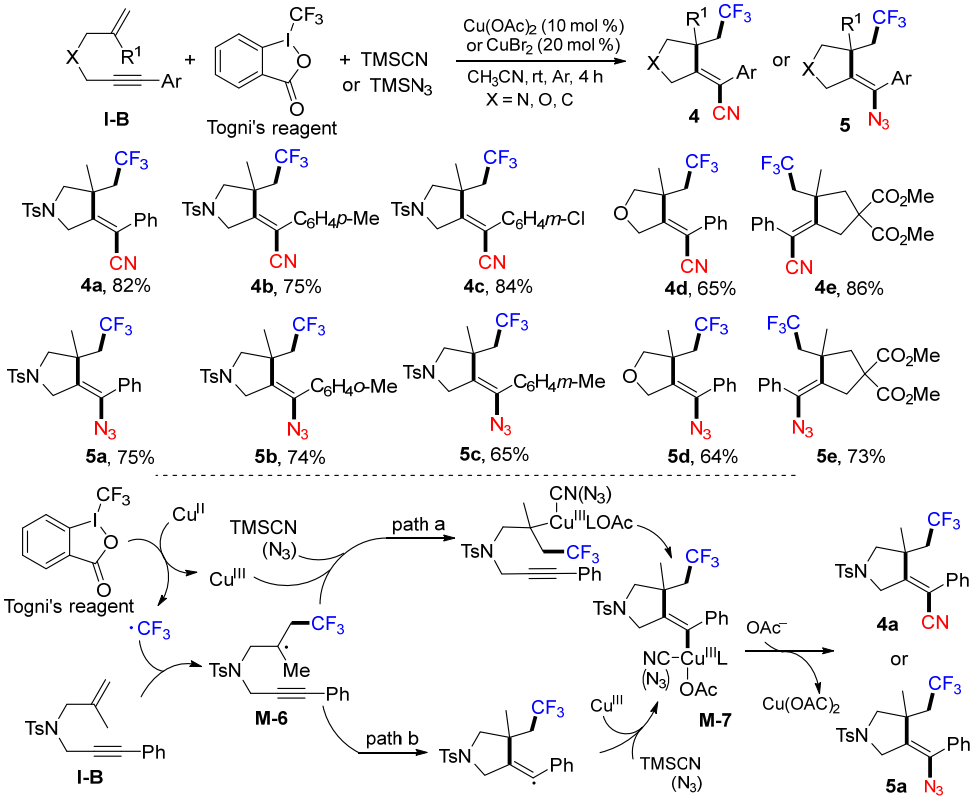
1,6-Enynes are the most popular substrates for radical reactions to make difunctionalized five-membered rings. A method for making iodotriflouromethylated *N*-heterocycles was reported by the Liu group in 2014. The reaction of 1,6-enynes, $NaSO_2CF_3$ and $I_2O_5$ in $CH_2Cl_2/H_2O$ afforded pyrrolidines products **3** in moderate-to-high yields (Scheme 7) [20]. The $CF_3$ radical generated from $NaSO_2CF_3$ through SET of $I_2O_5$ adds to the alkenyl group of 1,6-enynes followed by cyclization and the capture of iodine to give products **3**. The $CF_3$ radical could be trapped by 2-methyl-2-nitrosopropane (MNP) to form **M-5** for ESR detection.




**Scheme 7.** Synthesis of iodotriflouromethylated pyrrolidines.

A method for cyclative trifluoromethylation of 1,6-enynes was reported by the Liang group in 2014. The reaction of 1,6-enynes, Togni's reagent, and TMSCN (or $TMSN_3$) in $CH_3CN$ under the catalysis of $Cu^{II}$ gave $CF_3$-containing heterocycles **4** and **5** (Scheme 8) [21]. The $CF_3$ radical produced from the Togni's reagent under the catalysis of $Cu^{II}$ adds to

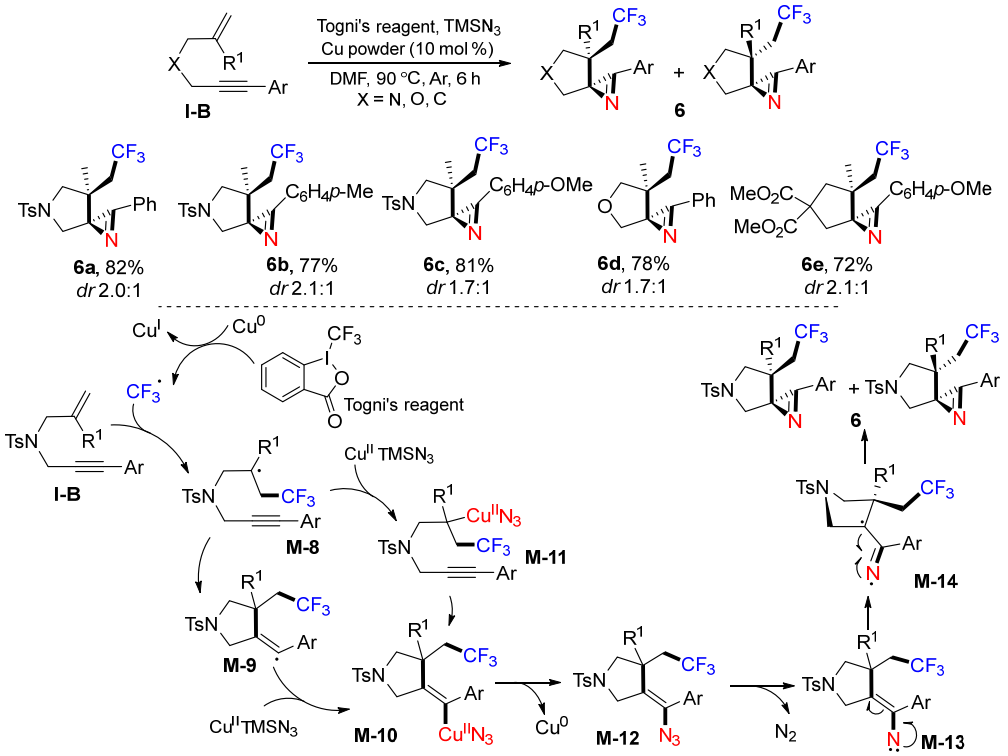
the C=C double bond of 1,6-enyne to form the radical intermediate **M-6,** which is converted to cyclized metal complex **M-7** through path a or path b. At the last step, the reaction of **M-7** with TMSCN or $TMSN_3$ gives corresponding cyanotrifluoromethylated or azidotrifluoromethylated five-membered ring products **4a** or **5a**.



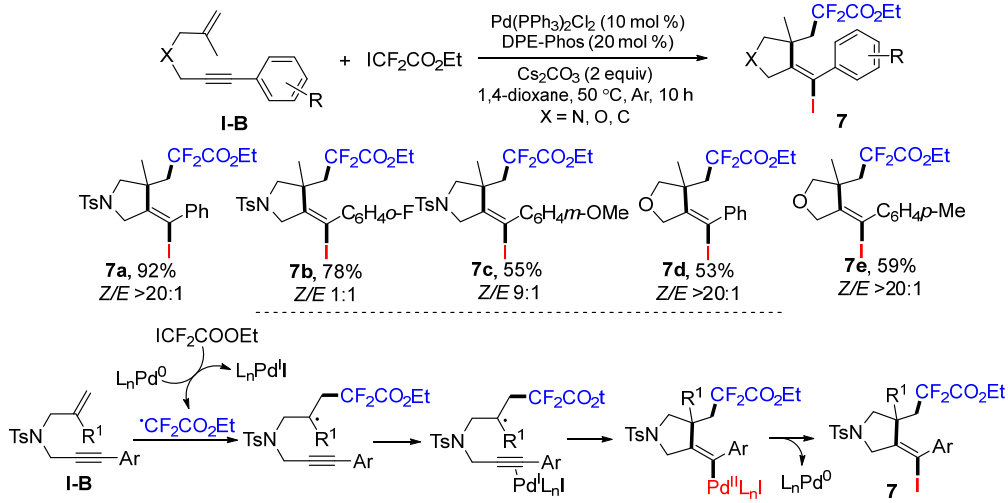

**Scheme 8.** Synthesis of cyanotrifluoromethylated or azidotrifluoromethylated heterocycles.

A Togni's reagent-based synthesis of $CF_3$-substituted spiro 2*H*-azirines was reported by the Liang group in 2015. The reaction of 1,6-enynes with Togni's reagent and $TMSN_3$ in the presence of $Cu^0$ powder as a catalyst afforded diastereomeric products **6** in good-to-excellent yields (Scheme 9) [22]. A proposed mechanism suggests that the $CF_3$ radical generated from Togni's reagent through SET of $Cu^0$ is added to the C=C bond of 1,6-enyne to produce the radical intermediate **M-8.** Sequential 5-*exo* cyclization and trapping of the radical **M-9** with $Cu^{II}$ and $TMSN_3$ give $Cu^{II}$ azide complex **M-10**. Complex **M-10** may also be obtained from the formation of complex **M-11** and subsequent cyclization. Reductive elimination of **M-10** followed by the elimination of $N_2$ from azide **M-12** gives alkenyl nitrene **M-13**. The cyclization of **M-14,** a resonance structure of alkenyl nitrene **M-13**, gives the spiroketal products **6** as a pair of diastereomers.

Liang's lab introduced a method for Pd-catalyzed radical cyclative iododifluoromethylation of 1,6-enynes in 2015. The reaction of 1,6-enynes and ethyl difluoroiodoacetate in dioxane under the catalysis of $Pd(PPh_3)_2Cl_2$ and bis-[2-(diphenyl-phosphino)phenyl]ether (DPE-Phos) gave iododifluoromethylated heterocycles **7** in good-to-excellent yields (Scheme 10) [23]. The $CF_2CO_2Et$ radical is generated from $ICF_2CO_2Et$ through the reduction of $Pd^0L_n$. Radical addition to the C=C double bond of 1,6-enynes followed by the cyclization to $Pd^IL_nI$-activated alkyne group and reductive elimination of the $Pd^0L_n$ gives iododifluoromethylated products **7**.




**Scheme 9.** Synthesis of $CF_3$-substituted spirocyclic 2*H*-azirines.



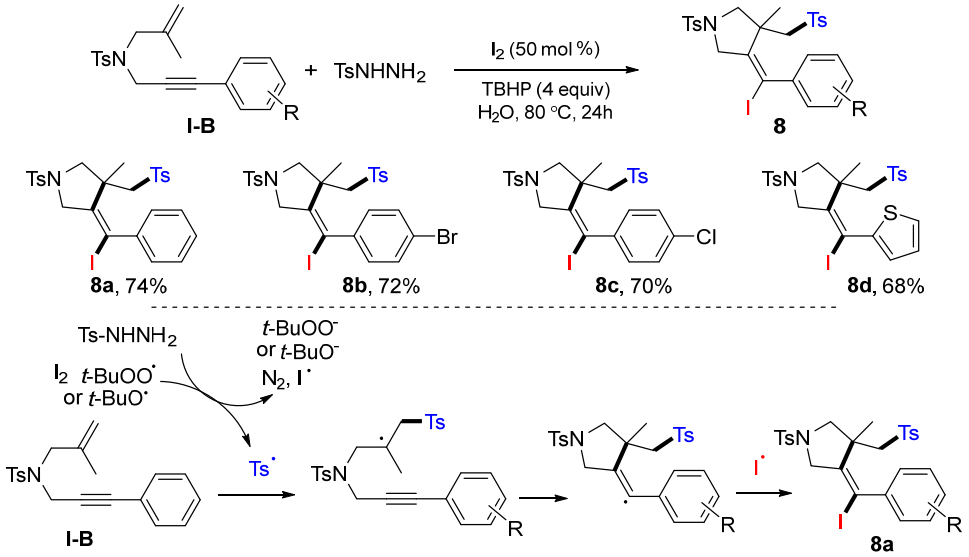

**Scheme 10.** Synthesis of iododifluoromethylated heterocycles.

A sulfonyl radical-initiated iodosulfonylation reaction of 1,6-enynes was reported by the Liang group in 2016. The reaction of 1,6-enynes and sulfonyl hydrazide in the presence of $I_2$/TBHP gave five-membered heterocycles **8** in good-to-excellent yields (Scheme 11) [24].

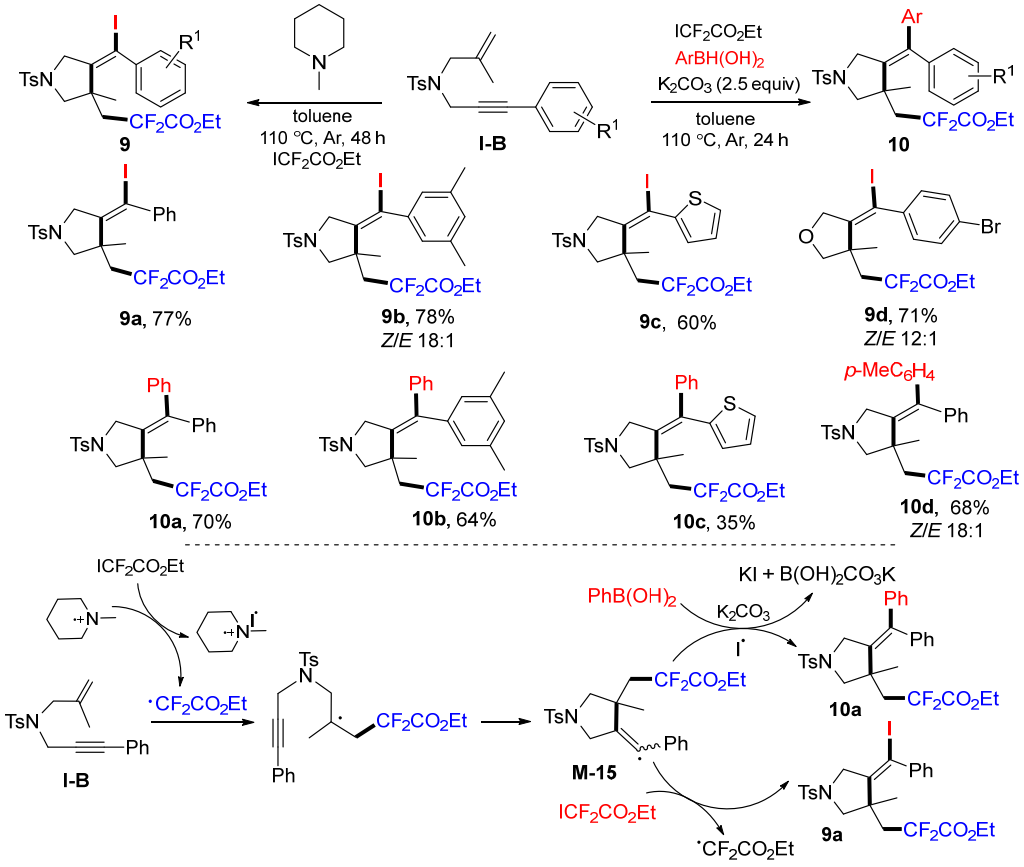
A proposed mechanism indicated that the sulfonyl radical generated from the reaction of sulfonyl hydrazide and TBHP adds to the C=C double bond of 1,6-enyne, followed by the radical cyclization and coupling with iodine radical, to give product **8a**.

In 2018, the Liang group introduced radical cyclization of 1,6-enynes for the synthesis of substituted pyrrolidine derivatives. The reaction of 1,6-enynes, $ICF_2CO_2Et$ in the presence of *N*-methylpiperidine or borophenylic acids/$K_2CO_3$ afforded substituted pyrroles **9** or **10** in moderate-to-good yields (Scheme 12) [25]. The initial $CF_2CO_2Et$ radical generated from the reaction of $ICF_2CO_2Et$ adds to the C=C double bond of the 1,6-enyne followed by 5-*exo* cyclization to give radical intermediate **M-15**. Radical **M-15** abstracts

iodo atom from iododifluoromethylation to give product **9a**; otherwise, coupling of **M-15** with borophenylic acid gives product **10a**.



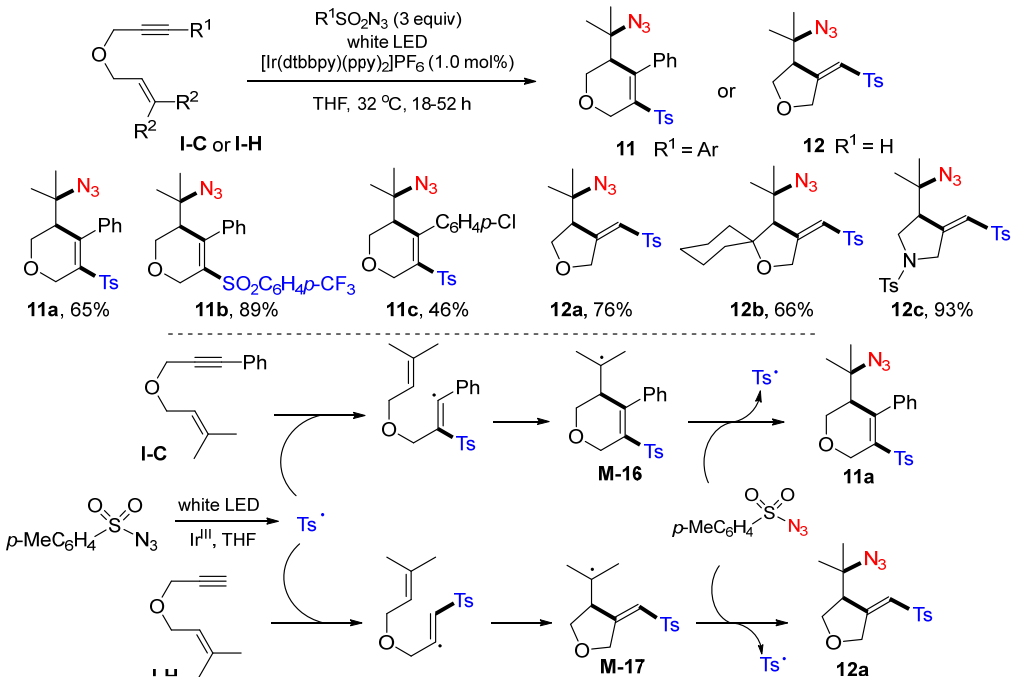

**Scheme 11.** Synthesis of iodosulfonylated five-membered heterocycles.




**Scheme 12.** Synthesis of functionalized pyrrolidines.

A visible light-mediated radical sulfonylative and azidosulfonylative cyclization of 1,6-enynes for the synthesis of highly functionalized heterocycles was introduced by the Lam group in 2017. The reaction of 1,6-enynes and sulfonyl azides in THF in the presence of a photoactive iridium complex afforded difunctionalized heterocycles **11** or **12** in moderate-to-excellent yields (Scheme 13) [26]. The use of THF as the solvent was critical for the success

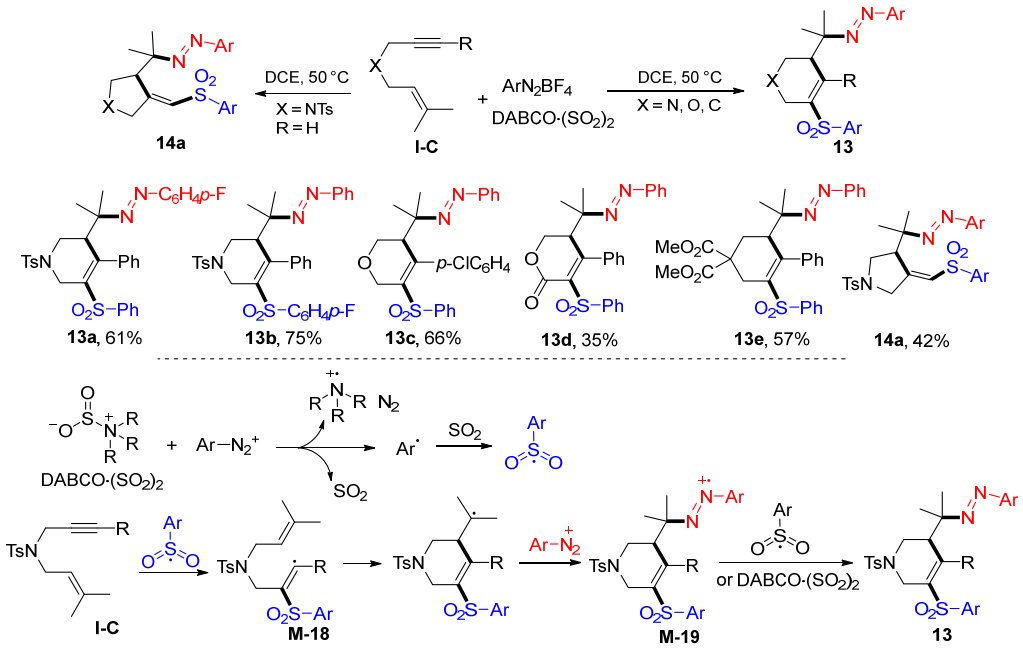
of the reactions. The reaction mechanism suggests that the sulfonyl radical generated from $TsN_3$ under the visible light catalysis of $[Ir(dtbbpy)(ppy)_2]PF_6$ adds to the triple bond of 1,6-enyne, followed by cyclization of the vinyl radical, giving six-membered tertiary radical **M-16**. Product **11a** is then obtained via azidation of **M-16** with the arylsulfonyl azide and the sulfonyl radical is regenerated. When $R^1$ is H, addition of the sulfonyl radical happens at the terminal carbon of the triple, followed by cyclization of the vinyl radical to give five-membered ring product **12a.**



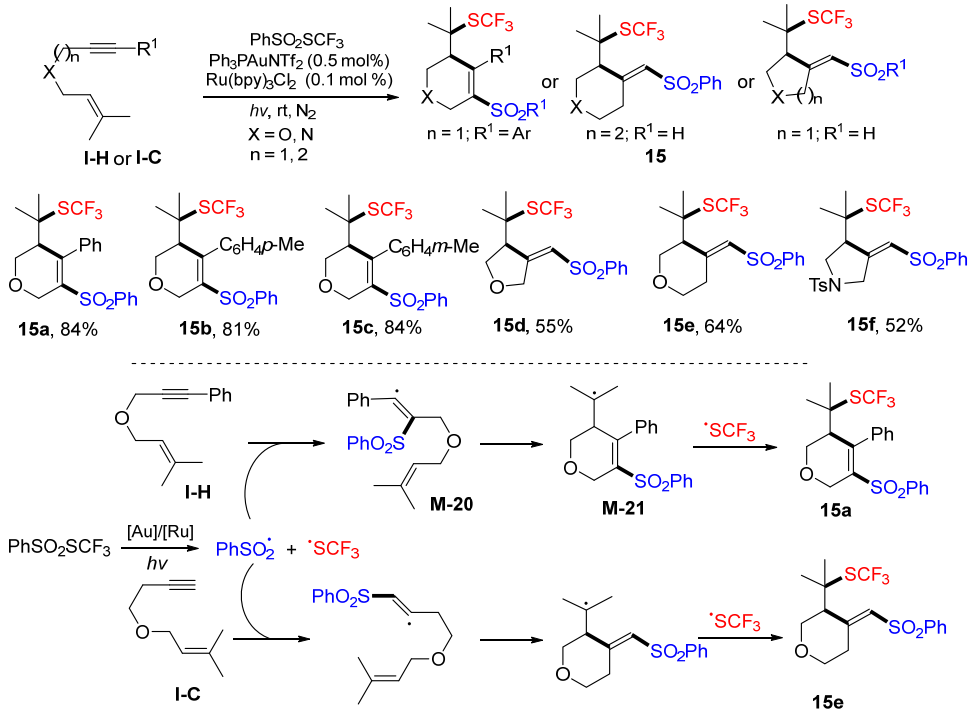

**Scheme 13.** Synthesis of azidosulfonated heterocycles.

The Wu group, in 2017, introduced a reaction of 1,6-enynes with $DABCO{\cdot}(SO_2)_2$ and two equivalents of $ArN_2BF_4$ in DCE to give diazosulfonated six-membered heterocycles **13** in moderate-to-good yields (Scheme 14) [27]. Five-membered heterocycles **14a** could be obtained using unsubstituted terminal alkynes as the substrates. The reaction mechanism suggests that the initially sulfonyl radicals, generated from the reaction of $ArN_2BF_4$ with $DABCO{\cdot}(SO_2)_2$, adds to the C≡C bond of 1,6-enynes to form vinyl radical **M-18,** followed by 6-*exo* cyclization and trapping with aryldiazonium cation to give intermediates **M-19**. The last step SET of arylsulfonyl radical or $DABCO{\cdot}(SO_2)_2$ to radical **M-19** gave products **13**.

The Xu group, in 2018, introduced a visible light-mediated radical atom transfer radical cyclization (ATRC) of 1,6- and 1,7-enynes for the synthesis of sulfonyl and trifluoromethylthio functionalized vinylsulfones. In the ATRC reactions, two functional groups are from the same reagent. The reaction of enynes and $PhSO_2SCF_3$ in the presence of $PPh_3AuNTf_2$ and $Ru(bpy)_3Cl_2$ under the irradiation of blue LED afforded five- or six-membered vinylsulfones **15** in good yields (Scheme 15) [28]. A proposed mechanism for the reaction of 1,6-enyne indicated that the sulfonyl radical generated from $PhSO_2SCF_3$ under photocatalysis of $PPh_3AuNTf_2$ and $Ru(bpy)_3Cl_2$ adds to the triple bond to form benzyl radical **M-20,** followed by 6-*exo* cyclization to give tertiary radical **M-21**. It then couples $CF_3S$ radical to give product **15a**. For the reaction of a 1,6-enyne without substitution on the terminal carbon ($R^1$ = H), sulfonyl radical adds to the terminal carbon of alkyne followed by 5-*exo* cyclization, leading to product **15d**. A similar process for the reaction of 1,7-enyne, which has no terminal carbon substitution on alkyne, affords product **15e**.

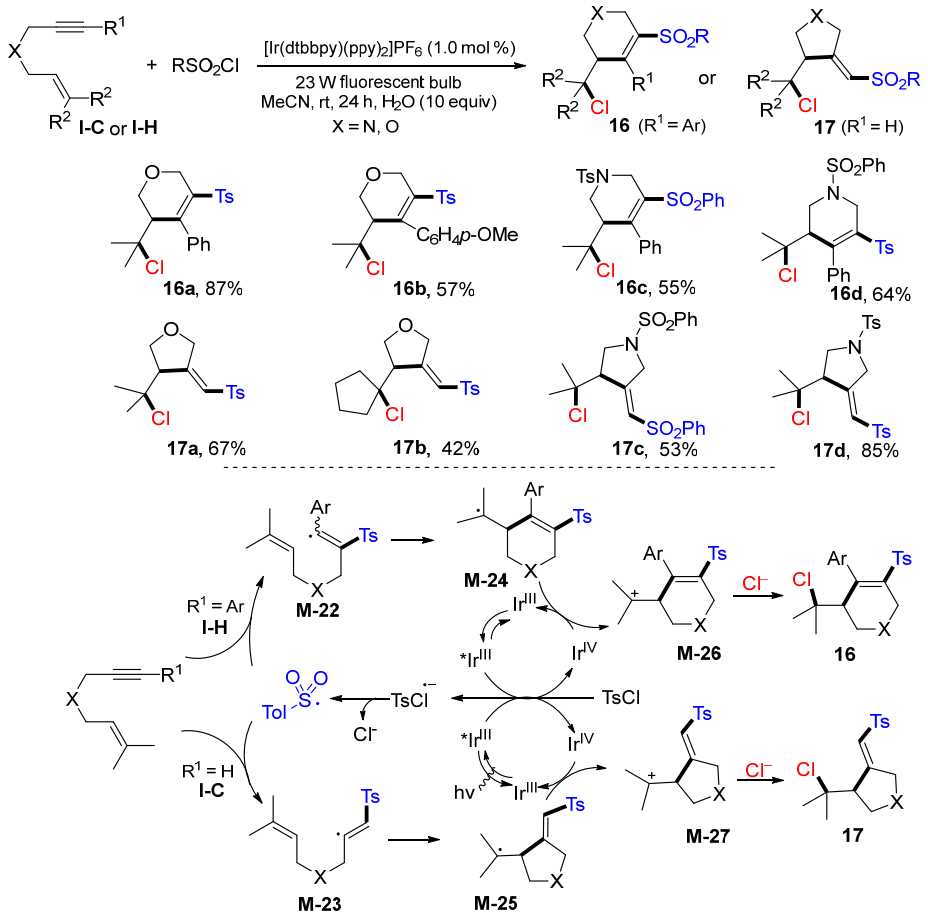


**Scheme 14.** Synthesis diazosulfonated heterocycles.



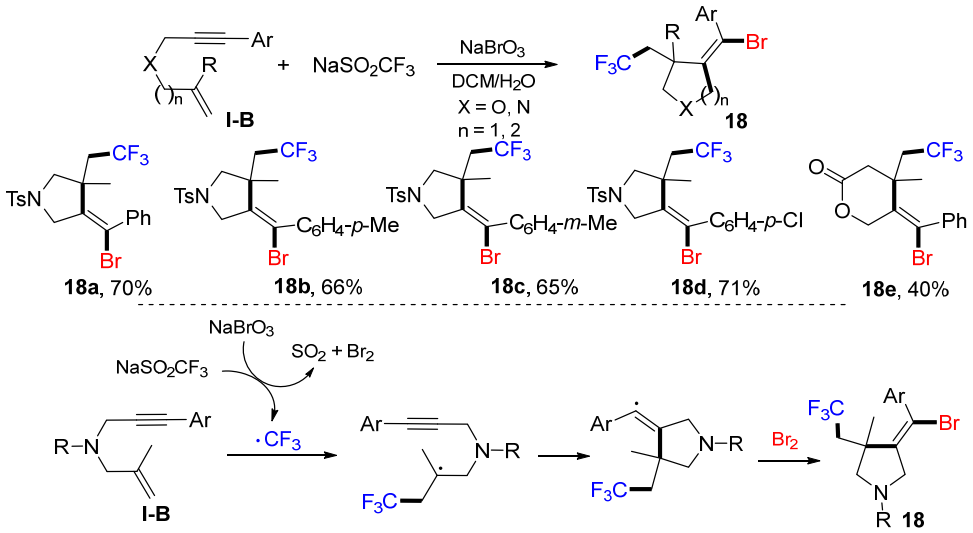
**Scheme 15.** Synthesis of sulfonyl and trifluoromethylthio functionalized vinylsulfones.

A visible light-mediated ATRC of 1,6-enyne for the preparation of chloroalkyl-substituted cyclic alkenyl sulfones using sulfonyl chlorides as the key reactants was reported by the Zhu group in 2018. The reactions of 1,6-enynes and sulfonyl chlorides in the presence of $[Ir(dtbbpy)(ppy)_2]PF_6$ under the irradiation of blue LED gave five- or six-membered chloroalkyl-substituted cyclic alkenyl sulfones **16** or **17** (Scheme 16) [29]. As the reaction mechanism indicated, the sulfonyl radical generated from TsCl under the photoredox of $[Ir(dtbbpy)(ppy)_2]PF_6$ adds to the C≡C bond of the 1,6-enyne followed by 5-*exo* or 6-*exo* cyclization to form the carbon radicals **M-24** or **M-25**. They are oxidized to carbocations **M-26** and **M-27** and then react with chlorine anion to form products **16** and **17**, respectively.



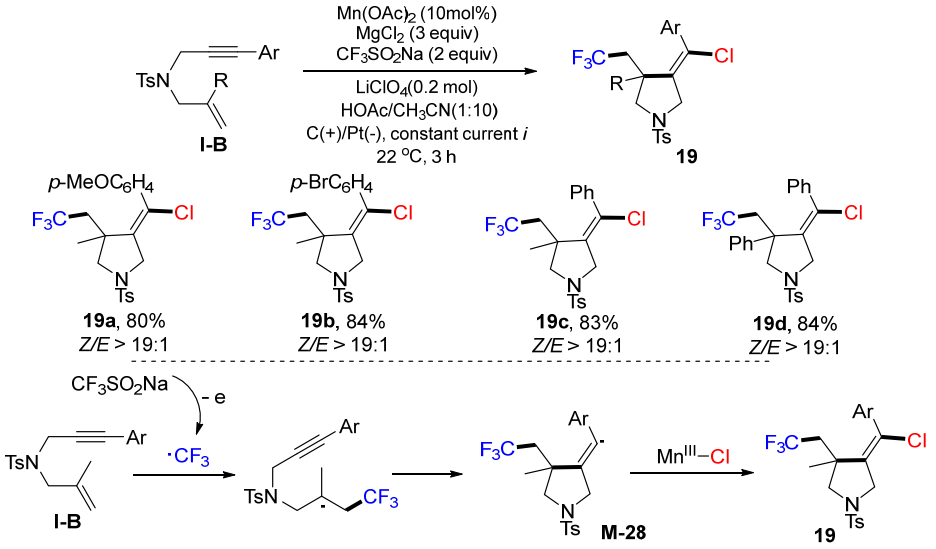

**Scheme 16.** Synthesis of five- and six-membered alkenyl sulfones.

In 2018, the Liu group reported the synthesis of bromotrifluoromethylated five- and six-membered heterocycles. The reaction of 1,6- or 1,7-enynes, $NaSO_2CF_3$ and $NaBrO_3$ in DCM/$H_2O$ produced products **18** in good yields (Scheme 17) [30]. The $CF_3$ radical, generated from the reaction of $NaSO_2CF_3$ and $NaBrO_3$, adds to the terminal carbon of alkene followed by 5-*exo* or 6-*exo* cyclization (n = 2) and then Br-atom abstraction to give product **18**.



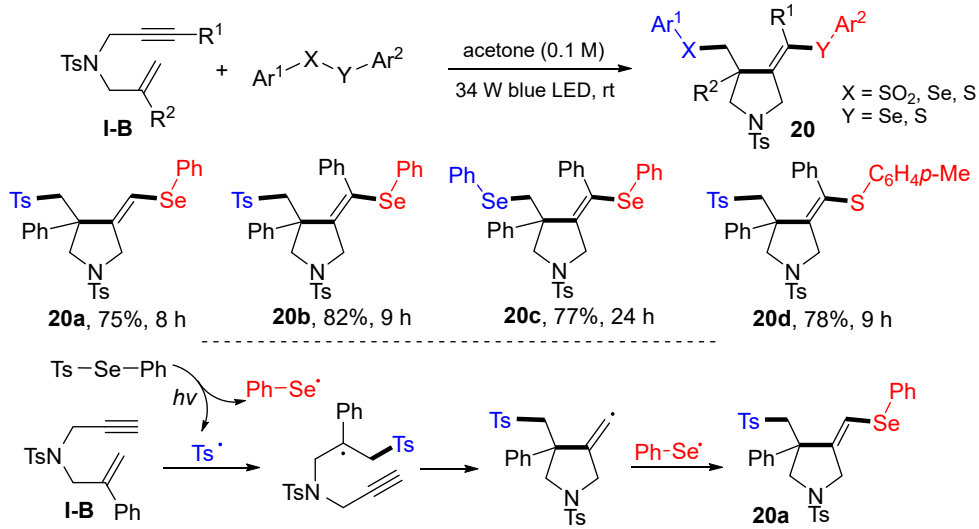

**Scheme 17.** Synthesis of bromotrifluoromethylated five- and six-membered heterocycles.

Lin and coworkers reported an electrochemical reaction for the preparation of chlorotrifluoromethylated pyrrolidines in 2018. The reaction was carried out using HOAc-MeCN as solvent at room temperature under electrochemical conditions. The reaction of 1,6-enynes, $CF_3SO_2Na$ and $MgCl_2$ in the presence of $LiClO_4$ and $Mn(OAc)_2$ gave chlorotrifluoromethylated pyrrolidines **19** in excellent yields (Scheme 18) [31]. The initial $CF_3$ radical generated from the anodically coupled electrolysis adds to the C=C double bond of 1,6-enynes followed by 5-*exo* cyclization to afford the vinyl radical **M-28,** which couples with the Cl radical to give product **19**.



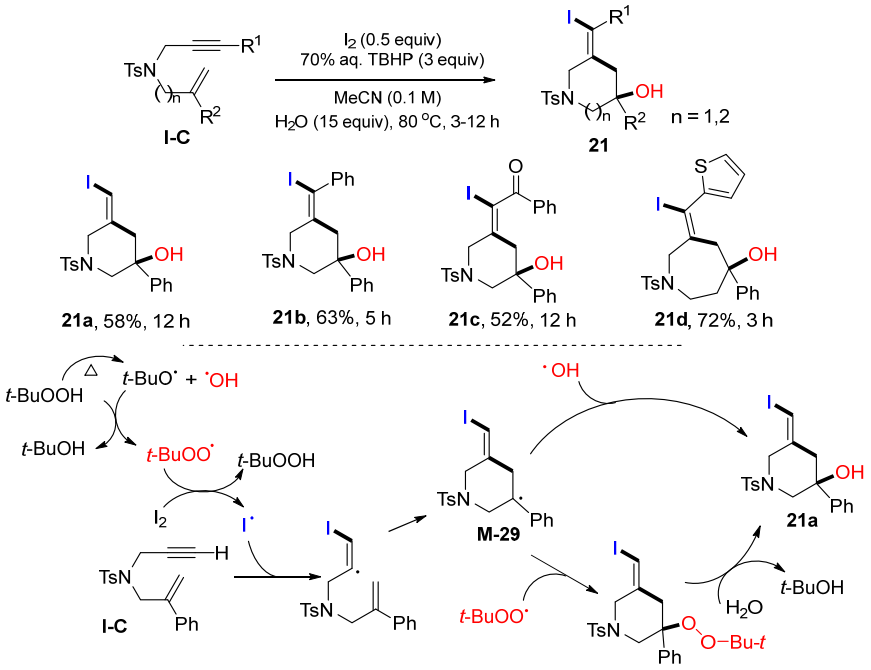

**Scheme 18.** Synthesis of chlorotrifluoromethylated pyrrolidines.

A visible light-promoted reaction of 1,6-enynes for the synthesis of difunctionalized pyrrolidines was introduced by the Wang group in 2020. The reaction of 1,6-enynes, and chalcogens (such as benzenesulfono–selenoate) in acetone at room temperature under the radiation of blue LED afforded products **20** in moderate-to-good yields (Scheme 19) [32]. The reaction mechanism suggests that tosyl and phenylselenyl radicals are generated from Se-phenyl 4-methylbenzenesulfonoselenoate under photo irradiation. The tosyl radical adds to the C=C bond of 1,6-enyne followed by 5-*exo* cyclization and capture of phenylselenyl radical to give product **20a**.



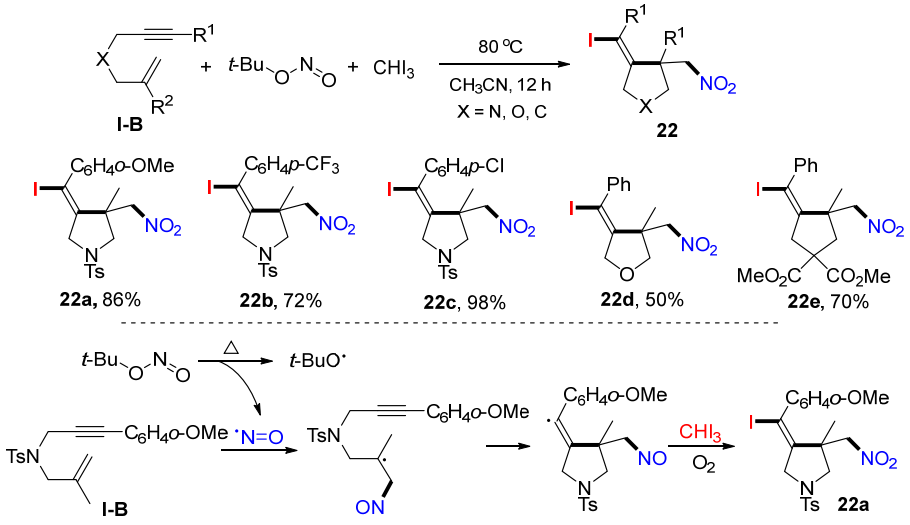

**Scheme 19.** Synthesis of functionalized pyrrolidines.

An iodine radical-initiated reaction for the synthesis of difunctionalized *N*-heterocyclic compounds was reported by the Wang group in 2020. The reactions of 1,6- or 1,7-enynes, TBHP and $I_2$ in $CH_3CN$ gave compound **21** in moderate-to-good yields (Scheme 20) [33]. The reaction mechanism suggests that iodide radical, generated from the reaction of $I_2$ with TBHP, adds to the C≡C triple bond of enyne followed by 6-*exo* cyclization to yield tertiary radical **M-29**. Addition of hydroxyl radical or *t*-butylperox radical to **M-29** could lead to the formation of product **21a.**



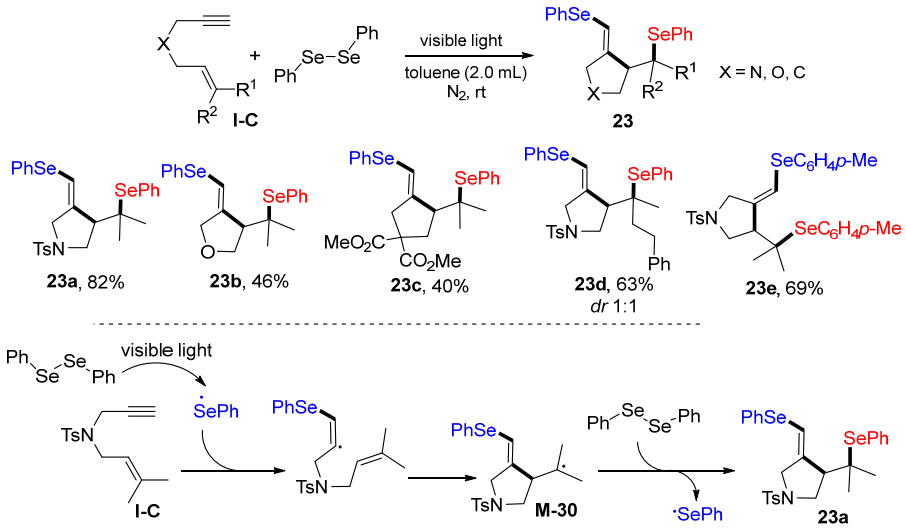

**Scheme 20.** Synthesis of iodo and hydroxy-functionalized *N*-heterocyclics.

In 2021, Zhu and co-workers reported the synthesis of iodo- and nitro-functionalized cyclic compounds such aspyrrolidines, tetrahydrofurans, and cyclopentanes. The reaction of 1,6-enynes, *t*-BuONO, and iodoform in $CH_3CN$ under heating gave five-membered heterocycles **22** in moderate-to-excellent yields (Scheme 21) [34]. The reaction mechanism suggests that nitroso radical formed from the homolysis of *t*-BuONO adds to the C=C bond of the 1,6-enyne followed by 5-*exo* cyclization, oxidation to cation, and then iodination with $CHI_3$ to give product **22a**.



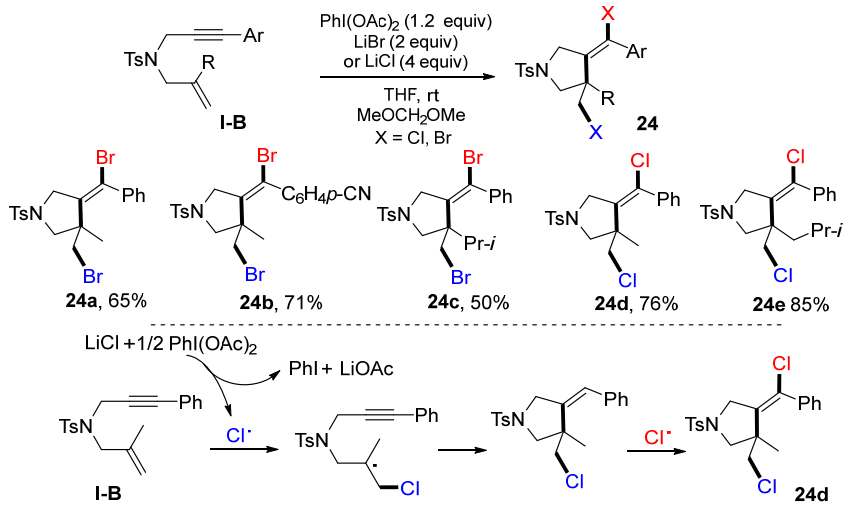

**Scheme 21.** Synthesis of iodo- and nitro-functionalized cyclic compounds.

In 2021, Zhu and co-workers reported diarylselenylative cyclization reaction of 1,6-enynes for the synthesis of five-membered heterocycles. The reaction of 1,6-enyne and diaryldiselane in toluene under the radiation of light at room temperature afforded products **23** in moderate to good yields (Scheme 22) [35]. The reaction mechanism shows that the PhSe radical generated via photo homolytic cleavage of PhSeSePh adds to the triple bond of 1,6-enyne followed by 5-*exo* cyclization to form tertiary carbon radical **M-30**, which then couples with PhSe radical to give product **23a**.




**Scheme 22.** Synthesis of diarylselenylated five-membered rings.

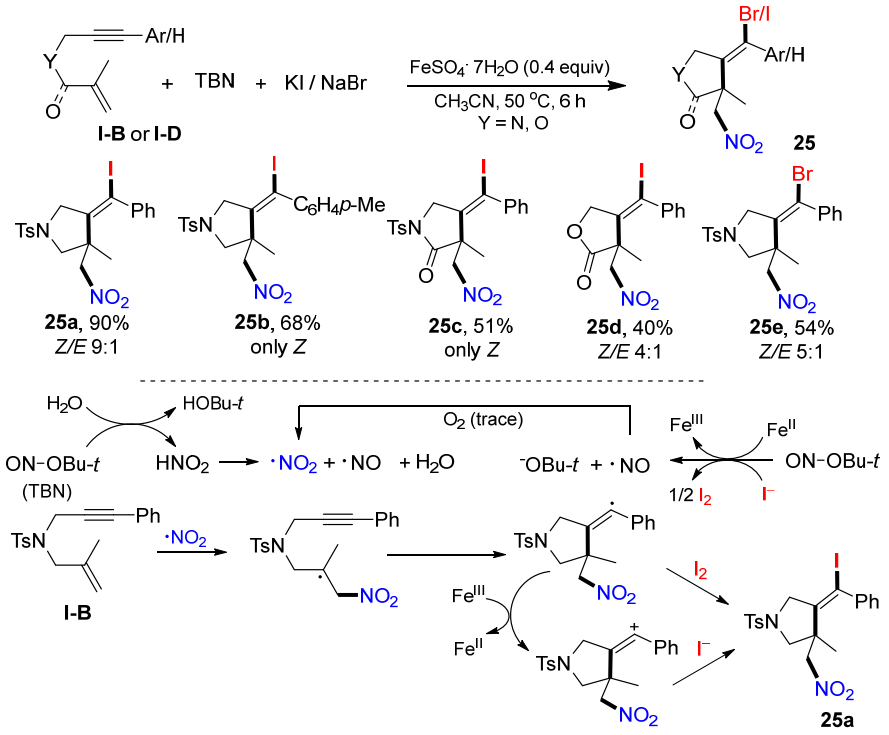
The reaction of 1,6-enynes for the synthesis of dihalogenated pyrrolidines was reported by the Tong group in 2021. The reaction of 1,6-enynes, $PhI(OAc)_2$ and lithium halide at room temperature gave product **24** in moderate-to-good yields (Scheme 23) [36]. A suggested mechanism for the reaction with LiCl indicated that the Cl radical generated via a single electron oxidation of LiCl with $PhI(OAc)_2$ adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization and Cl atom abstraction to give dichloro pyrrolidine **24d**.




**Scheme 23.** Synthesis of dihalogenated pyrrolidines.

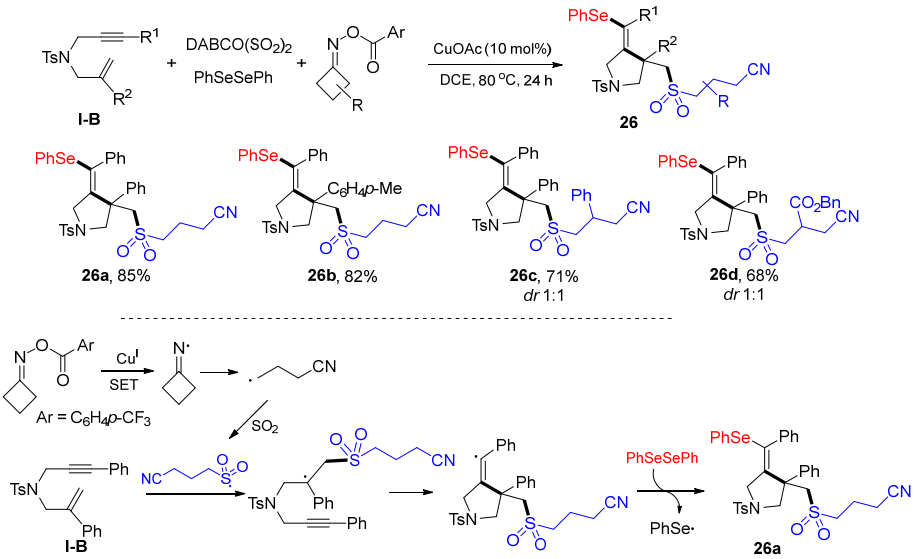
In 2021, Li and Tian's lab reported Fe-catalyzed radical reaction of 1,6-enynes for the synthesis of difunctionalized heterocycles. The reaction of 1,6-enynes, *t*-butyl nitrite (TBN) and KI or NaBr as materials in $CH_3CN$ under the catalysis of $FeSO_4 \cdot 7H_2O$ gave products **25** in good-to-excellent yields (Scheme 24) [37]. As shown in the proposed mechanism,

$NO_2$ radical produced from TBN adds to the C=C bond of 1,6-enyne followed by 5-*exo* cyclization to give vinyl radical. This radical intermediate is iodinated through two possible pathways to give target product **25a**.



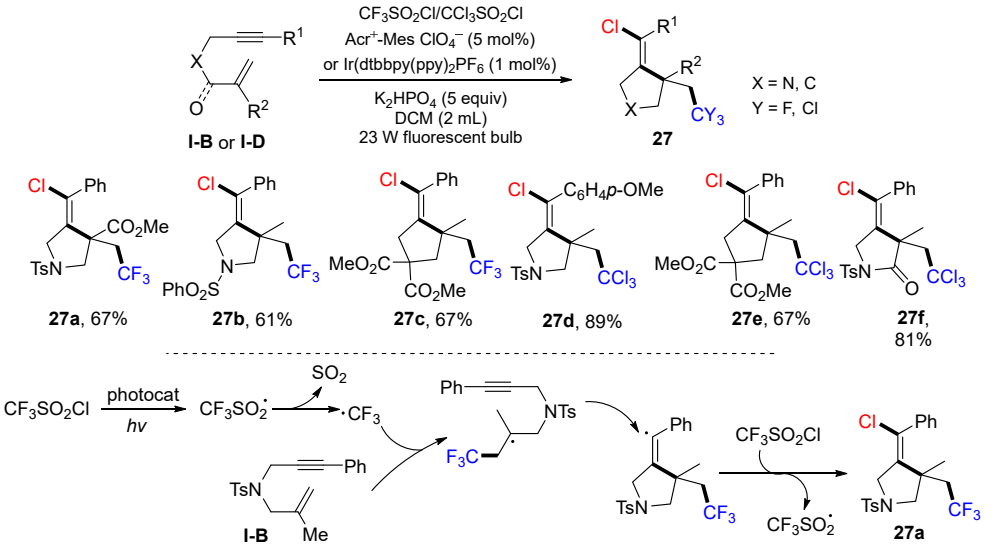

**Scheme 24.** Synthesis of nitrohalogenated heterocyclic compounds.

A Cu-catalyzed radical reaction of 1,6-enynes for the synthesis of cyanoalkylsulfonylated pyrrolidines was introduced by He and coworkers in 2021. The reaction of 1,6-enynes, diselenides, $DABCO(SO_2)_2$ and cyclic ketone oxime esters in DCE with CuOAc as a catalyst afforded functionalized pyrrolidines **26** in moderate-to-good yields (Scheme 25) [38]. As indicated in the proposed mechanism, cyanoalkylsulfonyl radical generated from the reaction of cyclic ketone oxime esters and $DABCO(SO_2)_2$ adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization and then couples with PhSe radical to give product **26a**.



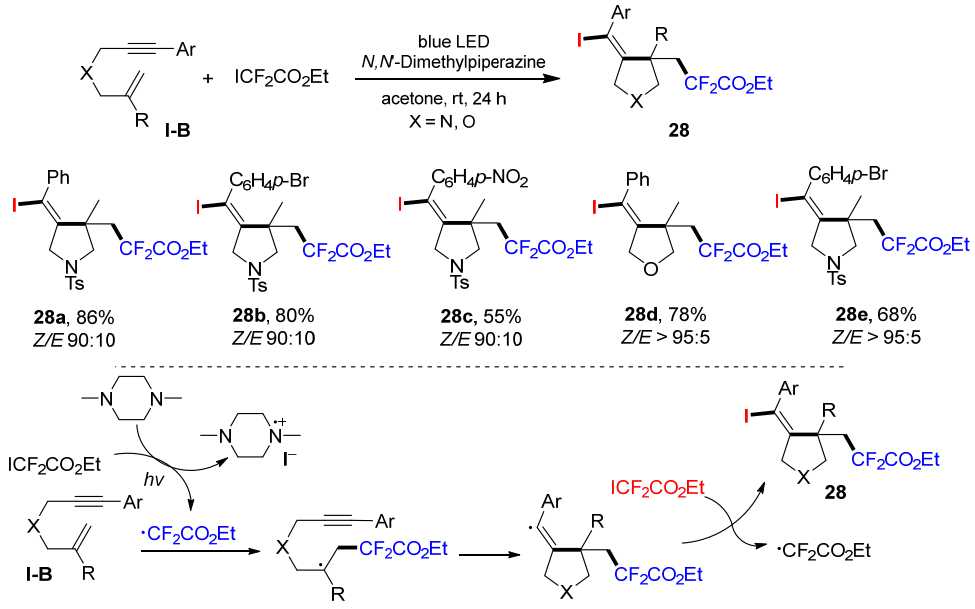

**Scheme 25.** Synthesis of cyanoalkylsulfonylated pyrrolidines.

In 2019, Zhu and Hou's group reported a visible light-mediated radical reaction for the synthesis of chlorotrifluoromethylated and chlorotrichloromethylated pyrrolidines, cyclopentanes and related compounds. The reaction of 1,6-enynes and $CF_3SO_2Cl$ (or $CCl_3SO_2Cl$) in $CH_2Cl_2$ using $Acr^+$-Mes or Ir(dtbbpy(ppy)$_2$PF$_6$ as a photocatalyst gave products **27** in good-to-excellent yields (Scheme 26) [39]. A proposed mechanism indicated that $CF_3$ radical generated from $CF_3SO_2Cl$ via SET adds to the C=C bond of 1,6-enynes, followed by 5-*exo* cyclization and coupling with Cl radical, to give product **27a**.



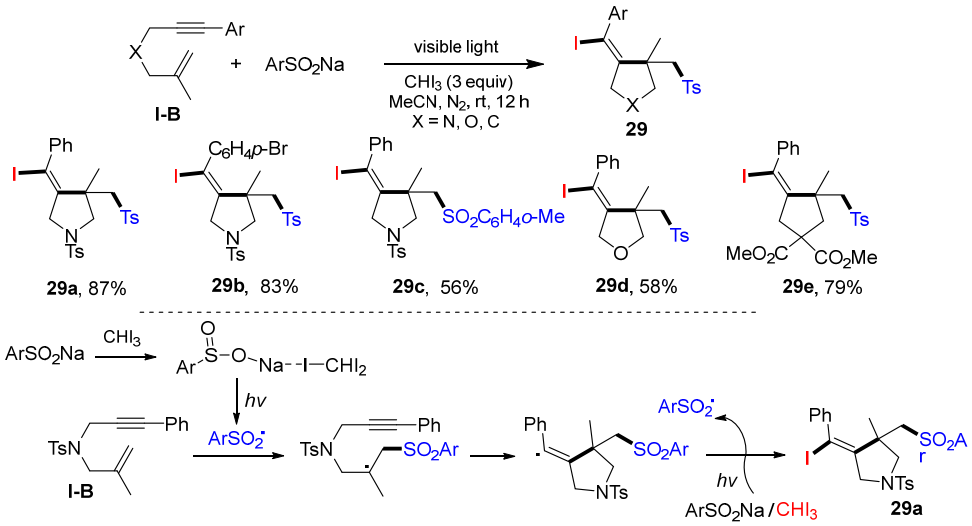

**Scheme 26.** Synthesis of functionalized five-membered rings.

In 2022, Li and Yang reported a visible light-promoted reaction of 1,6-enynes for the synthesis of the iodovinyl- and $CF_2$-functionalized heterocycles. The reaction of 1,6-enynes, $ICF_2CO_2Et$ under the radiation of blue LED afforded products **28** in good-to-excellent yields (Scheme 27) [40]. The reaction mechanism suggests that $CF_2CO_2Et$ radical derived from $ICF_2CO_2Et$ adds to the C=C double bond of 1,6-enyne, followed by 5-*exo* cyclization and capture of iodine atom from $ICF_2CO_2Et$, to give product **28**.



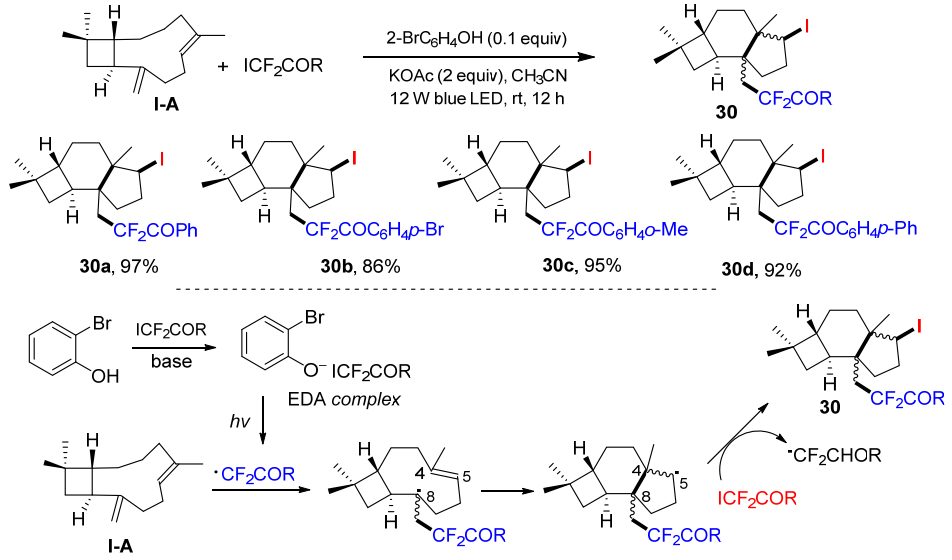

**Scheme 27.** Synthesis of iodovinyl- and $CF_2$-functionalized heterocycles.

Zhu and co-workers, in 2022, reported a photo synthetic method for making iodo- and sulfonyl-containing cyclic compounds. The reaction of 1,6-enynes, $ArSO_2Na$, and iodoform in $CH_3CN$ under visible light irradiation gave products **29** in good-to-excellent yields (Scheme 28) [41]. The reaction mechanism suggests that $ArSO_2$ radical derived from $ArSO_2Na$ adds to the C=C double bond of 1,6-enyne, followed by 5-*exo* cyclization and iodine atom transfer from the complex of $ArSO_2Na$ and $CHI_3$, to give product **29a**.




**Scheme 28.** Synthesis of iodo- and sulfonyl-containing cyclic compounds.

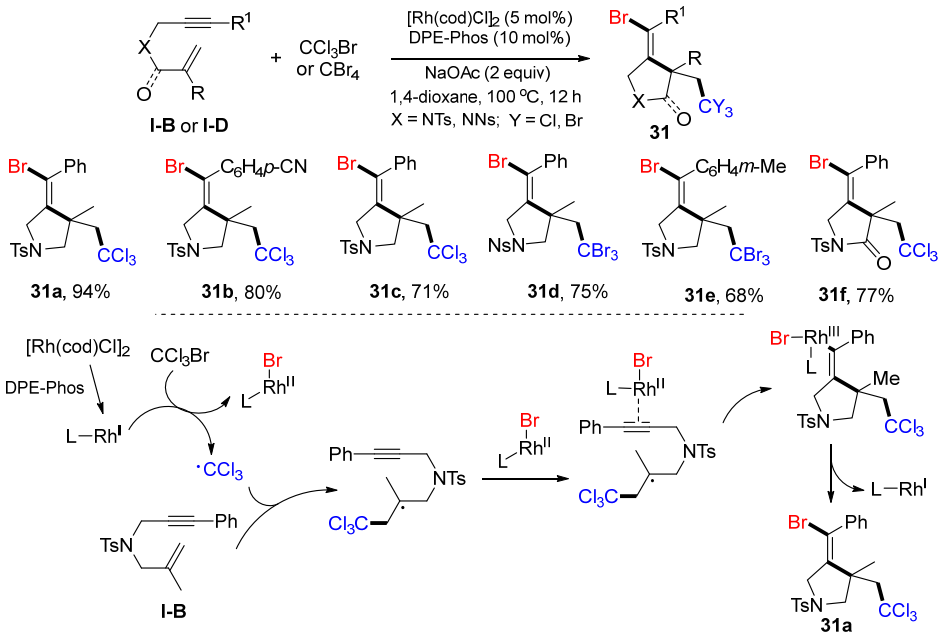
In 2022, a photo reaction of *β*-caryophyllene, a 1,5-diene with one alkene in the ring and another one out of the ring, for the synthesis of iodo- and $CF_2$-containing protoilludanes was reported by the Huang group. The reaction of *β*-caryophyllene and $ICF_2COR$ in the presence of 2-bromophenol and base under the irradiation of blue LED afforded functionalized protoilludanes **30** in excellent yields (Scheme 29) [42]. A reaction mechanism suggests that the EDA complex generated from 2-bromophenol and $ICF_2COR$ leads to the formation of $CF_2COR$ radical. It then selectively adds to C8 of *β*-caryophyllen, followed by the cyclization and abstraction of iodine atom from $ICF_2COR$ to give the product **30**.




**Scheme 29.** Synthesis of iodo- and $CF_2$-containing protoilludanes.

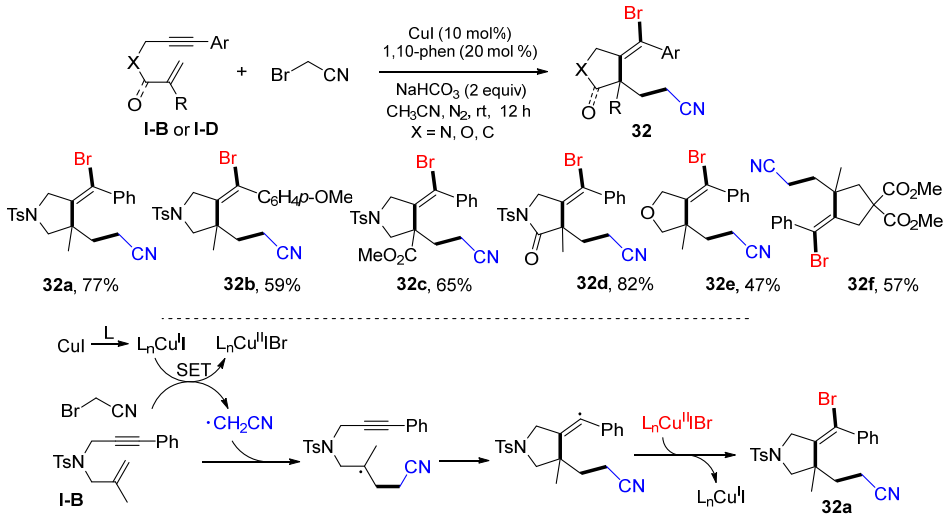
In 2019, the Liu group reported a met-catalyzed reaction of 1,6-enynes or 1,6-enynyl amides for the synthesis of bromotrihalomethylated pyrrolidines. The reaction of 1,6-enynes,

and $CCl_3Br$ or $CBr_4$ in 1,4-dioxane under the catalysis of $[Rh(cod)Cl]_2$ and DPE-Phos at 100 °C for 12 h gave products **31** in moderate-to-good yields (Scheme 30) [43]. The reaction mechanism suggests that $CCl_3$ radical, generated from $CCl_3Br$ under the catalysis of $[Rh(cod)Cl]_2$ and DPE-Phos, adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization to $Rh^{II}$-LBr activated alkyne and then L-$Rh^{I}$ elimination to give product **31a**.




**Scheme 30.** Synthesis of bromotrihalomethylated pyrrolidines.

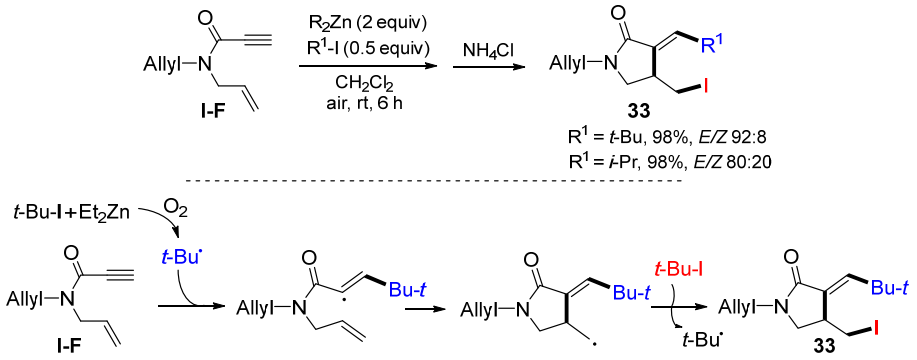
Hou and coworkers, in 2022, reported a Cu-induced radical reaction of 1,6-enynes for the synthesis of functionalized five-membered rings. The reaction of 1,6-enynes, $BrCH_2CN$ in the presence of CuI, 1,10-phenanthroline and $NaHCO_3$ in $CH_3CN$ afforded products **32** in good yields (Scheme 31) [44]. The reaction mechanism suggests that the $CH_2CN$ radical derived from $BrCH_2CN$ adds to C=C double bond of 1,6-enyne followed by 5-*exo* cyclization and bromine atom-transfer to give product **32a**.




**Scheme 31.** Synthesis of functionalized five-membered rings.

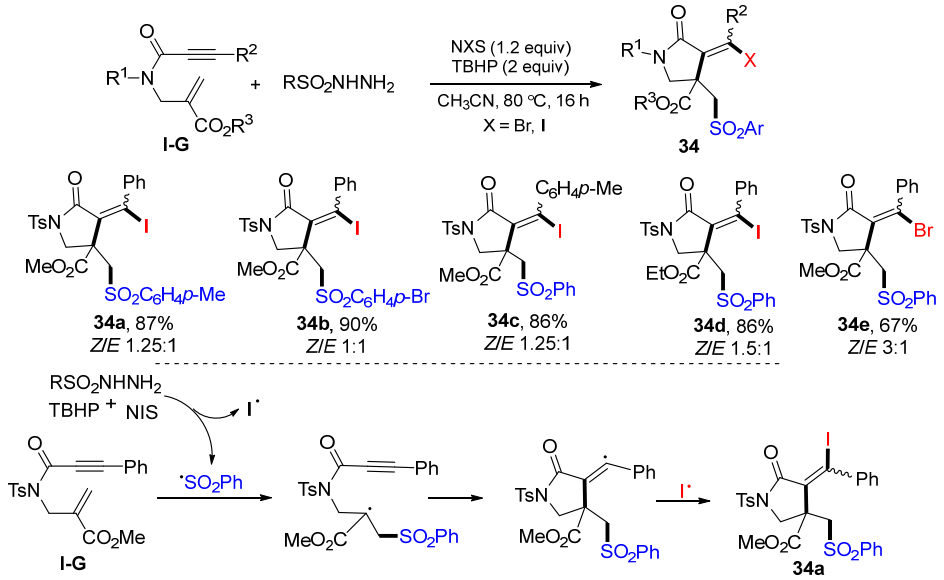
1,6-Eneynyl amides are another kind of popular substrates for radical reactions in the synthesis of functionalized 2-pyrrolidones [45]. In 2008, Feray and Bertrand reported an $R_2Zn$-mediated radical reaction of 1,6-eneynyl amides for the synthesis of functionalized

pyrrolidin-2-ones. The reaction of 1,6-eneynyl amides and alkyliodides in the presence dialkylzinc at room temperature gave product **33** in high yields as a mixture of *E*/*Z* isomers (Scheme 32) [46]. The reaction mechanism suggests that the *t*-butyl radical, generated from the reaction of *t*-BuI and $R_2Zn$ in the presence of oxygen, selectively adds to the triple bond of amide to form a stabilized vinyl radical, which then undergoes 5-*exo* cyclization followed by iodine atom transfer from *t*-BuI to give product **33**.



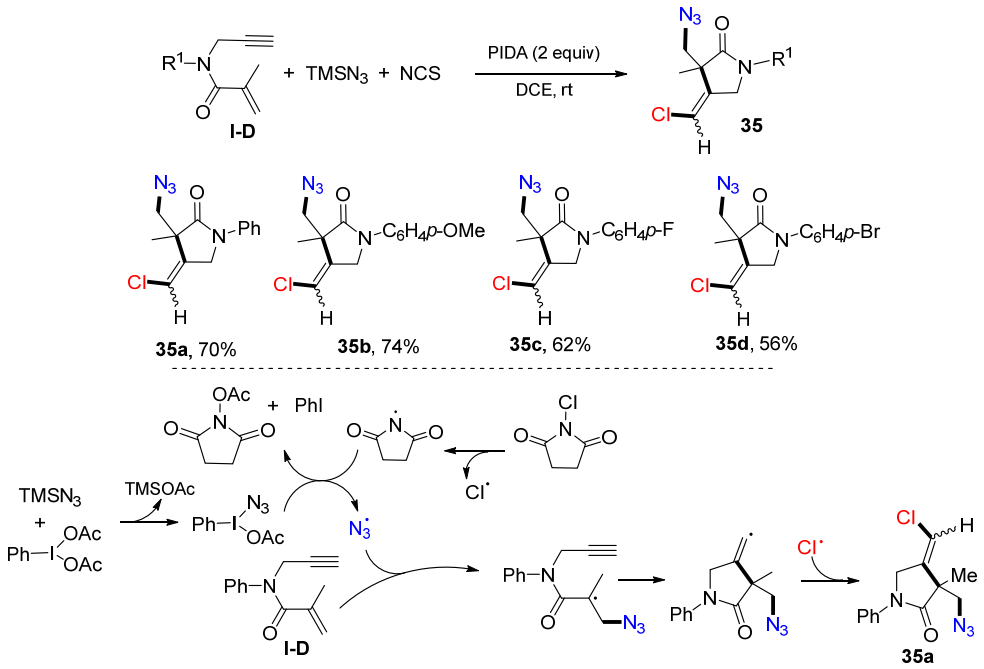

**Scheme 32.** Synthesis of functionalized pyrrolidin-2-ones.

Xuan and co-workers introduced a reaction of 6-enynyl amides for the synthesis of substituted 2-pyrrolidinones in 2018. The reaction of 6-enynyl amides, NIS (or NBS), and sulfonyl hydrazide in $CH_3CN$ and in the presence TBHP afforded $\gamma$-lactams **34** in good to excellent yields (Scheme 33) [47]. The reaction mechanism suggests that sulfonyl radical generated from arylsulfonyl hydrazide adds to the C=C double bond of amide followed by 5-*exo* cyclization and then coupling with iodine radical to give product **34a**.



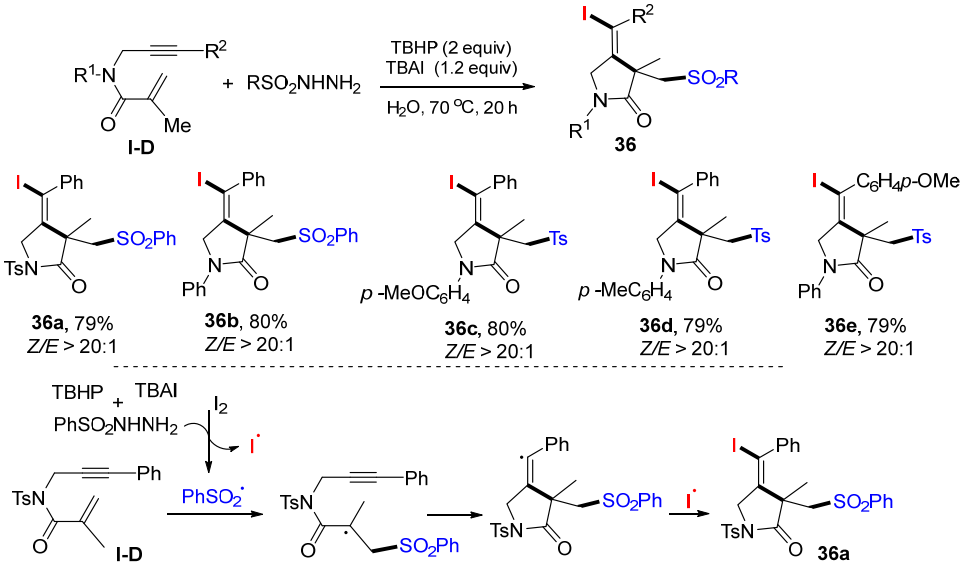

**Scheme 33.** Synthesis difunctionalized $\gamma$-lactams.

Wei and co-workers reported a protocol of cyclative chloroazidation of 1,6-enynyl amides for the synthesis of substituted 2-pyrrolidinones in 2018. The reaction of 1,6-enynyl amides, $TMSN_3$ and NCS in DCE in the presence of PIDA gave product **35** in moderate yields (Scheme 34) [48]. The reaction mechanism suggests that $N_3$ and Cl radicals were generated from $TMSN_3$ and NCS. The addition of $N_3$ radical to the C=C double bond of amide followed by 5-*exo* cyclization and coupling with the Cl radical affords product **35a**.




**Scheme 34.** Synthesis of difunctionalized pyrrolidin-2-ones.

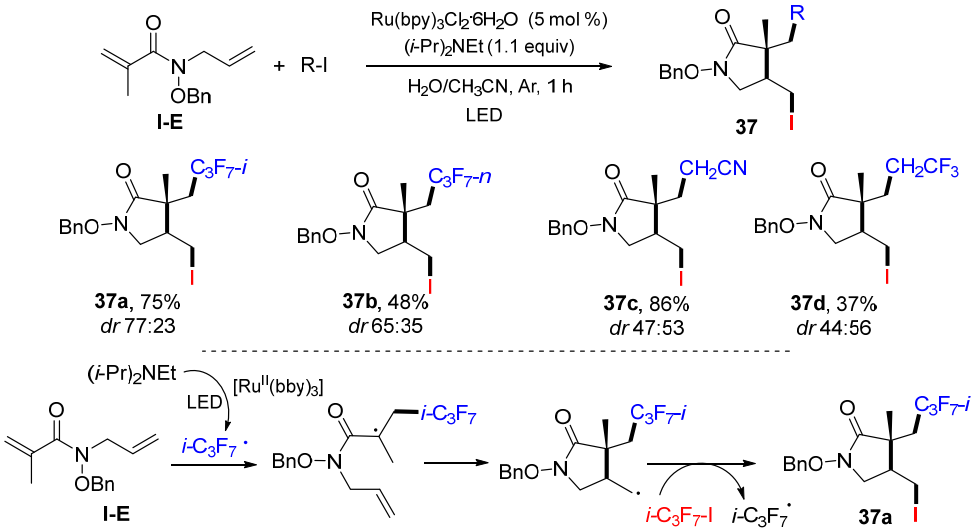
In 2022, Li and coworkers reported a reaction of 1,6-enynyl amides for the synthesis of $\gamma$-lactams. The reaction of 1,6-enynyl amides and sulfonyl hydrazides in $H_2O$ at 70 °C for 20 h in the presence of TBHP gave product **36** in moderate-to-good yields (Scheme 35) [49]. The reaction mechanism suggests that $PhSO_2$ radical, generated from the reaction of $PhSO_2NHNH_2$ with TBHP and TBAI, adds to the C=C double bond of amide followed by 5-*exo* cyclization and coupling with iodine radical to give product **36a**.




**Scheme 35.** Synthesis difunctionalized $\gamma$-lactams.

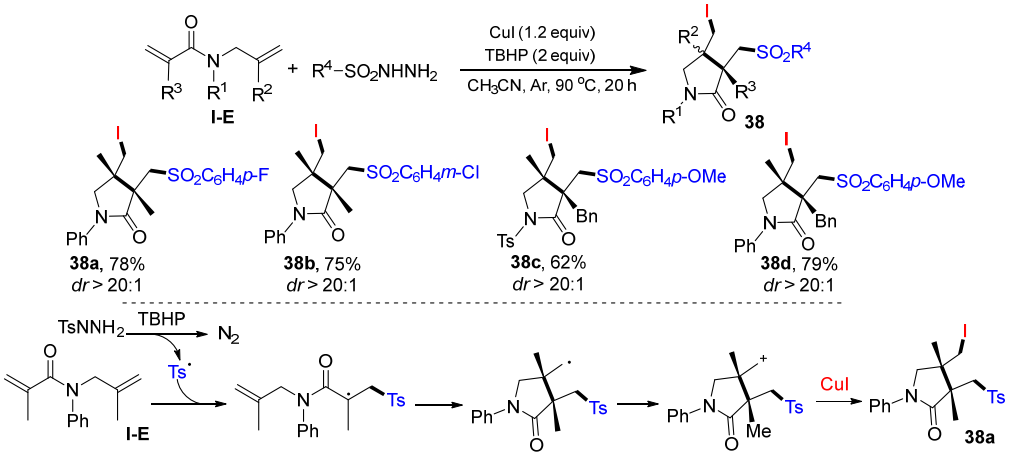
A photoredox ATRC reaction of 1,6-dienyl amides for the synthesis of functionalized pyrrolidin-2-ones was developed by the Miyabe group in 2015. The reaction of 1,6-dienyl amides and iodoalkanes in aqueous media and catalyzed by $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and $(i\text{-}Pr)_2NEt$ gave product **37** in fair-to-good yields (Scheme 36) [50]. Other than $i\text{-}C_3F_7I$, other iodo compounds such $ICH_2CN$ and $ICH_2CF_3$ are also good radical precursors. The reaction mechanism suggests that the $i\text{-}C_3F_7$ radical generated from *i*-PrI via the photoredox process

adds to the C=C double bond of amide, followed by 5-*exo* cyclization and then iodine atom transfer from *i*-PrI to give product **37a**.




**Scheme 36.** Synthesis of difunctionalized pyrrolidin-2-ones.

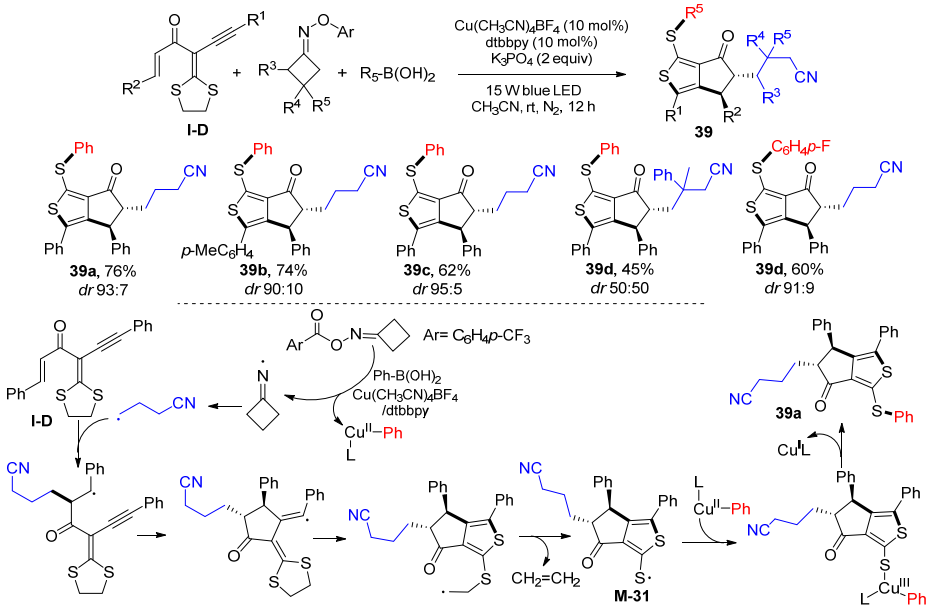
Li and Wei, in 2021, reported a Cu-catalyzed radical reaction of 1,6-dienyl amides for the synthesis of substituted $\gamma$-lactams. The reaction of 1,6-dienyl amides and $RSO_2NHNH_2$ in $CH_3CN$ in the presence of CuI and TBHP gave product **38** in moderate-to-good yields (Scheme 37) [51]. The reaction mechanism suggests that the sulfonyl radical, generated from the reaction of $RSO_2NHNH_2$ with TBHP, adds to the C=C double bond of amide followed by 5-*exo* cyclization, oxidation to carbocation, and trapping $I^-$ anion of CuI to provide iodosulfonylation of product **38a**.




**Scheme 37.** Synthesis difunctionalized $\gamma$-lactams.

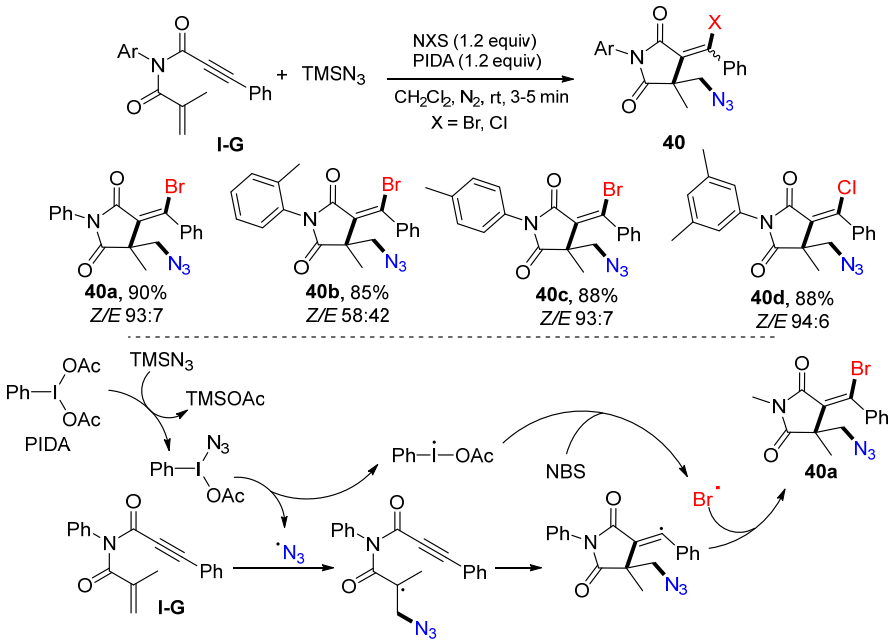
A photoredox reaction of carbonyl-containing 1,6-enynes for the synthesis of cyclopentanone derivatives was reported by Zhou, Yu and their coworkers in 2020. The reaction of *gem*-dialkylthio enynes, cyclobutanone oxime esters, and boronic acids in the presence of $Cu(CH_3CN)_4BF_4$, dtbbpy and $K_3PO_4$ in $CH_3CN$ under irradiation of blue LED gave functionalized aryl thienyl sulfide **39** in moderate-to-good yields and with good chemo- and diastereoselectivities (Scheme 38) [52]. The reaction mechanism suggests that $\gamma$-cyanoalkyl radical, generated from homolytic $\alpha,\beta$-C−C cleavage of *N*-centered iminyl, which is derived from cyclobutanone oxime esters, adds to the C=C bond of *gem*-dialkylthio 1,3-enyne followed by 5-*exo* cyclization, radical rearrangement and fragment of ethylene to give

sulfur-centered radical **M-31**. Radical **M-31** reacts with the $LCu^{II}Ph$ complex followed by reductive elimination to give product **39a**.




**Scheme 38.** Synthesis of aryl thienyl sulfides.

A reaction of 1,6-enynyl with two carbonyl groups for the synthesis of functionalized succinimides was introduced by the Rong group in 2020. The reaction of 1,6-enynyl amides, NBS or NCS, $TMSN_3$, and PIDA in DCM at room temperature for 3–5 min afforded products **40** as *E*/*Z* isomers in excellent yields (Scheme 39) [53]. The reaction mechanism suggests that the azide radical, resulting from the reaction of PIDA and $TMSN_3$, adds to alkene moiety of 1,6-enyne, followed by 5-*exo* cyclization and coupling with the bromine radical from NBS, to give product **40a**.

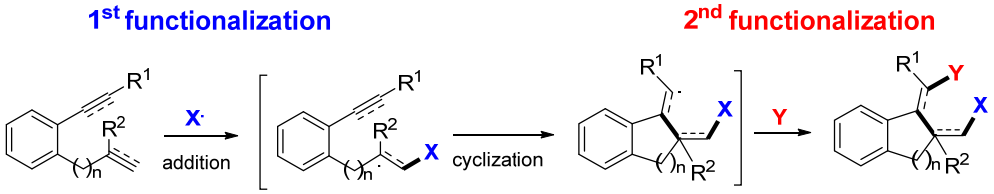



**Scheme 39.** Synthesis of functionalized succinimides.

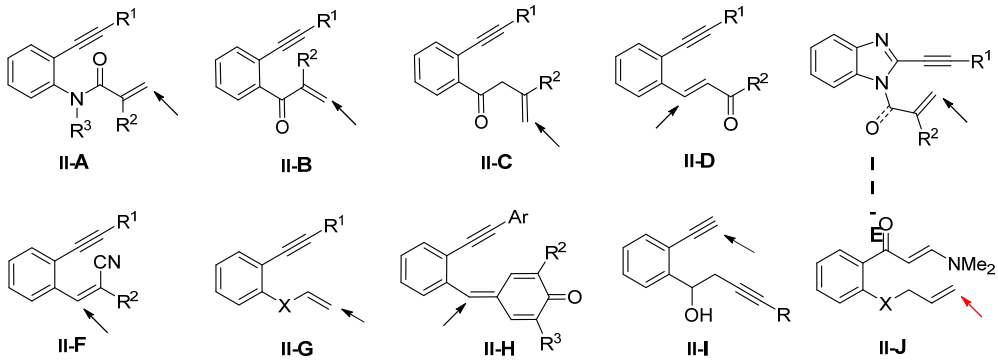
## 3. Reaction of Arene-Tethered Dienes and Enynes

Presented in this section are the radical addition and cyclization-initiated difunctionalization reactions of arene-bridged 1,n-dienes -diynes, and -enynes with a reaction sequence

shown in Scheme 40. It is noteworthy that most substrates found in the literature are enynes but not dienes (like **II-J**) or diynes (like **II-I**) (Scheme 41). The enynyl substrates include the most popular 1,7-enynyl amides **II-A** and other ones containing the carbonyl group (**II-B** to **II-E**). Other substrates may contain heteroatom or conjugate groups (such as CN and Ar) at the terminal carbon of the unsaturated bonds (**II-F** to **II-H**). Between the two unsaturated carbon–carbon bonds in the substrates, the regioselectivity for the initial radical addition is directed by the steric and the conjugation effects of the substituents. The $R^1$ group on the terminal carbon of alkyne is commonly employed to block the initial radical addition to the alkyne. Substrate **II-J** is an exception in which the initial radical addition does not go to the conjugated alkene.



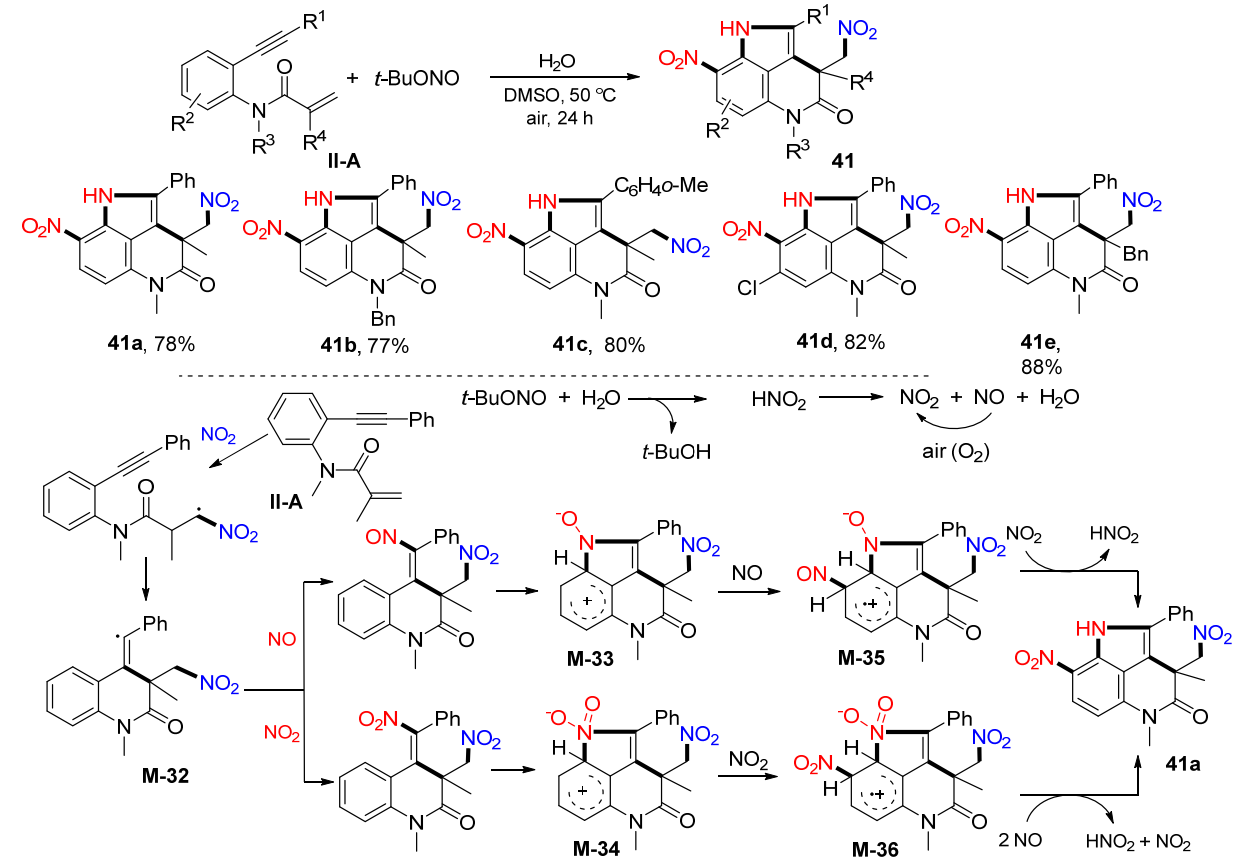

**Scheme 40.** General reaction for the difunctionalization of arene-bridged dienes and enynes.



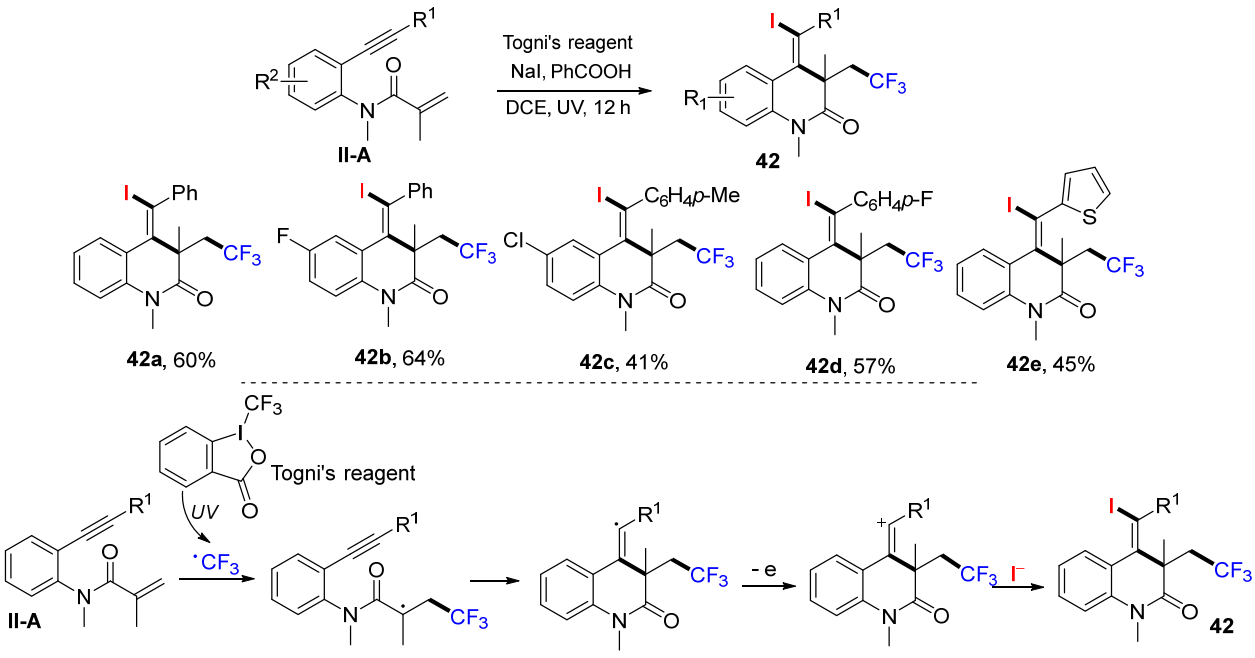

**Scheme 41.** Arene-bridged enynes, dienes, and diynes with pointed position for the initial radical addition.

Benzene-tethered 1,7-enynyl amides are popular substrates for radical difunctionalization reactions. In 2014, the Li group introduced a reaction of such substrates for the synthesis of dinitropyrrolo[4,3,2-*de*]-quinolinones. The reaction of 1,7-enynyl amides and *t*-BuONO in DMSO afforded product **41** in good-to-excellent yields (Scheme 42) [54]. It was found that the amount of $H_2O$ had a significant influence on the reaction. The reaction mechanism suggests that $NO_2$ radical generated in situ from *t*-BuONO adds to the C=C double bond of amide followed by 6-*exo* cyclization to form intermediate **M-32**. The reaction of **M-32** with NO or $NO_2$ radical followed by electrophilic addition of NO or $NO_2$ radical to the phenyl ring gave cationic intermediates **M-33** and **M-34**. Cationic radical intermediates **M-35** and **M-36** were produced through the treatment of the cationic intermediates **M-33** and **M-34** with NO or $NO_2$ radical and then lead to the formation of product **41a** after the redox reaction.

The Wu group, in 2016, introduced a photoredox reaction of benzene-tethered 1,7-enynyl amides for the synthesis of trifluoroethyl-substituted 3,4-dihydroquinolin-2(*1H*)-ones. The reaction of 1,7-enynyl amides and Togni's reagent in the presence of NaI and $PhCO_2H$ under UV irradiation gave **42** in moderate-to-good yields (Scheme 43) [55]. The proposed mechanism indicated that trifluoromethyl radical derived from the Togni's reagent adds to the C=C double bond of amide, followed by 6-*exo* cyclization and oxidation to cation for the reaction with iodide anion, to give product **42**.



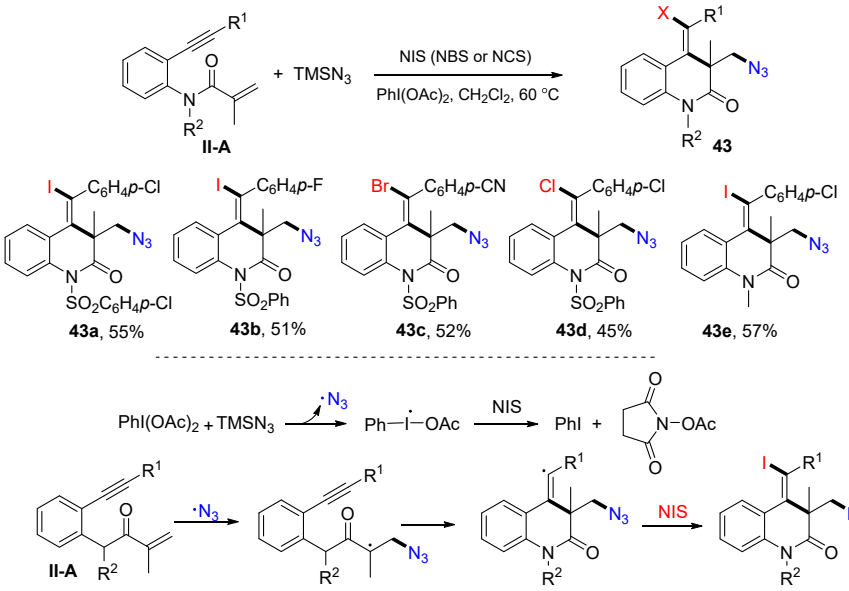

**Scheme 42.** Synthesis of dinitropyrrolo[4,3,2-*de*]-quinolinones.




**Scheme 43.** Synthesis of iodotrifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones.

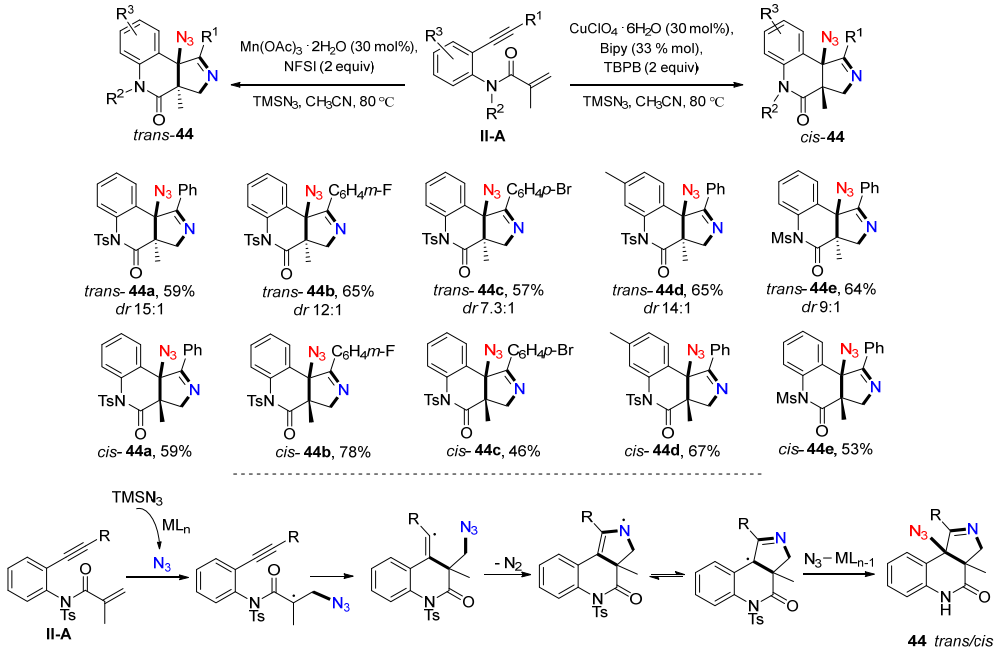
In 2016, the Jiang group reported a reaction of benzene-bridged 1,7-enynyl amides for the synthesis of substituted 3,4-dihydroquinolin-2(1*H*)-ones. The reaction of 1,7-enynyl amides, $TMSN_3$ and NIS (or NBS and NCS) in the presence of $PhI(OAc)_2$ in $CH_2Cl_2$ gave products **43** in good-to-excellent yields (Scheme 44) [56]. A reaction mechanism suggests

that $N_3$ radical generated from the reaction of $PhI(OAc)_2$ and $TMSN_3$ adds to the C=C double bond of amide followed by 6-*exo* cyclization and coupling with iodine radical from NIS to give product **43**.



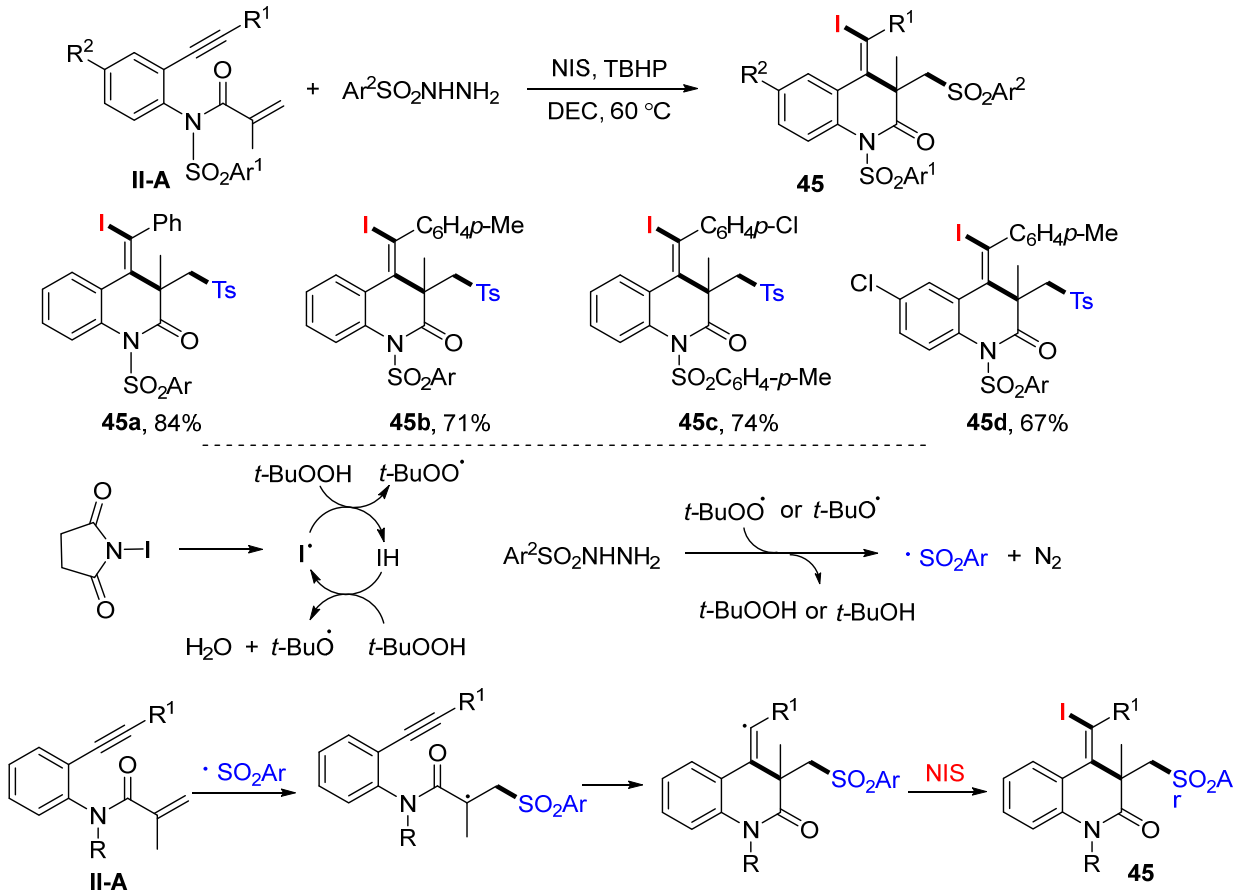

**Scheme 44.** Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

A transition metal-mediated radical reaction of benzene-bridged 1,7-enynyl amides for the synthesis of substituted pyrrolo[3,4-*c*]quinolinones was reported by the Wan group in 2016. The *trans*-fused products were obtained when using $Mn^{III}$ as a catalyst, whereas *cis*-products were obtained using $Cu^{II}$ as a catalyst. The reactions of amides and $TMSN_3$ in the presence of $Mn(OAc)_3$/NFSI or $Cu(ClO_4)_2$/TBPB in $CH_3CN$ afforded *trans*- or *cis*-fused products **44,** respectively, in good-to-excellent yields (Scheme 45) [57]. A reaction mechanism suggests that $N_3$ radical generated from $TMSN_3$ adds to the C=C double bond of amides followed by 6-*exo* cyclization, releasing of $N_2$, then azido group transfer to afford the desired *trans*- or *cis*-fused product **44**.




**Scheme 45.** Synthesis of azido-substituted pyrrolo[3,4-*c*]quinolinones.

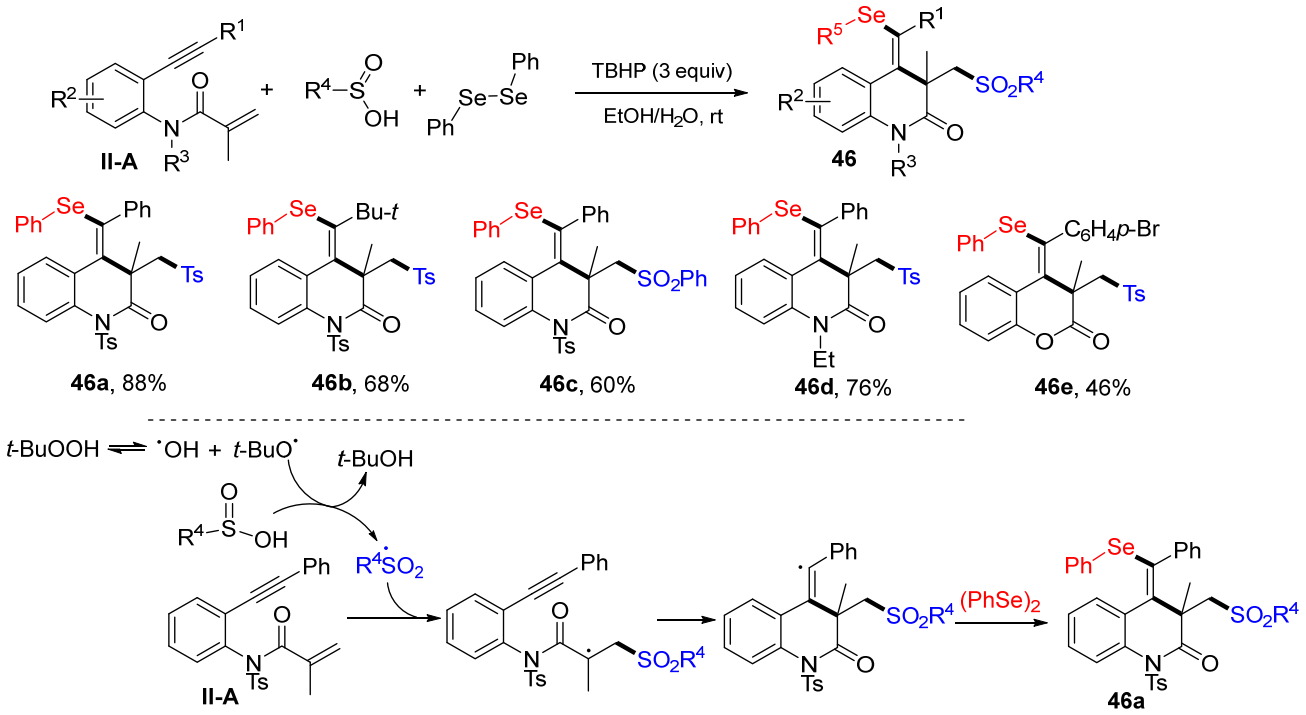
The Tu group reported a method for the synthesis of densely functionalized 3,4-dihydroquinolin-2(1*H*)-ones in 2016. The reaction of benzene-tethered 1,7-enynyl amides, arylsulfonyl hydrazides and NIS (or NBS) in DEC in the presence of TBHP afforded product **45** in good-to-excellent yields (Scheme 46) [58]. The reaction mechanism suggests that the sulfonyl radical derived from sulfonyl hydrazides adds to the C=C double bond of amides, followed by 6-*exo* cyclization and coupling with iodine radical from NIS, to give product **45**.



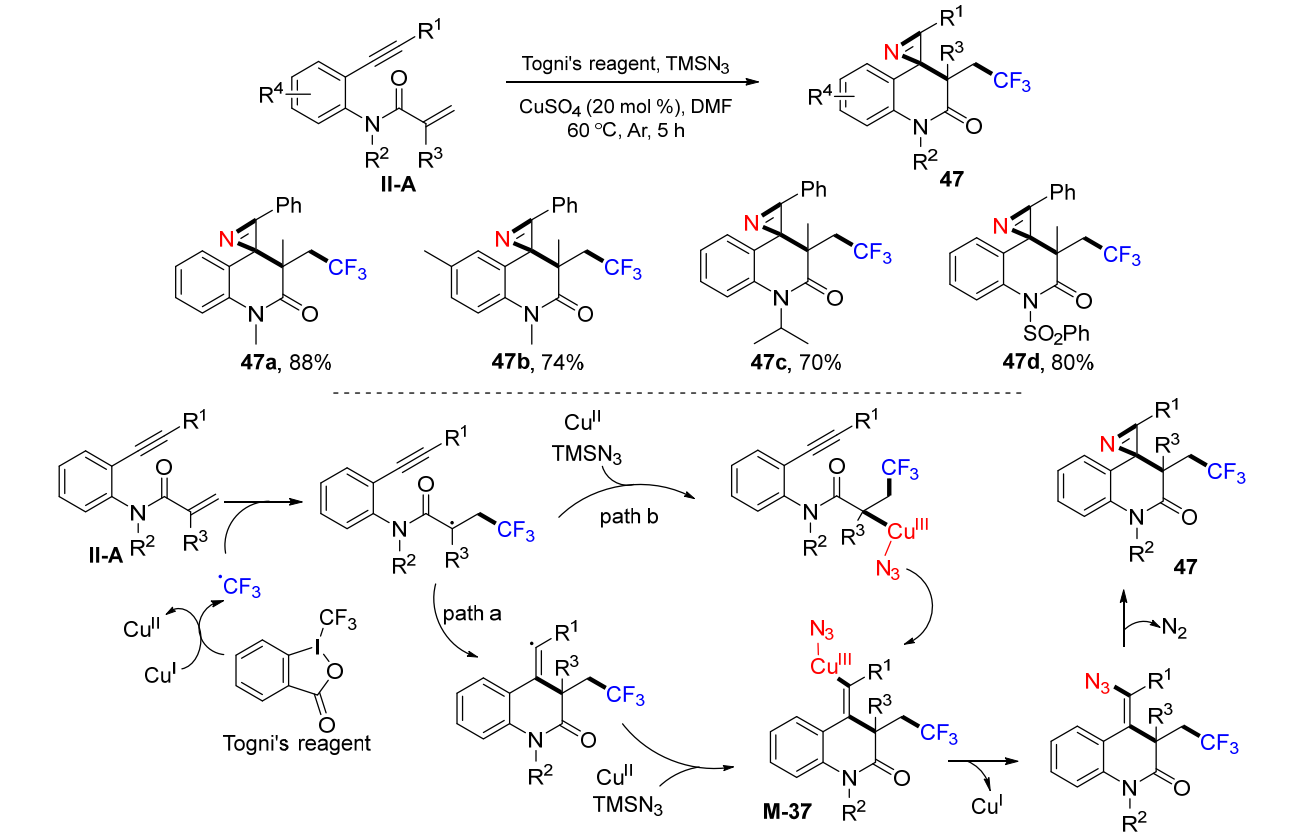

**Scheme 46.** Synthesis of functionalized 3,4-dihydroquinolin-2(1*H*)-ones.

A new method for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones was reported by the Guo group in 2017. The reaction of benzene-tethered 1,7-enynyl amides, sulfinic acids and diphenyl diselenides in EtOH-$H_2O$ and in the presence of TBHB to give product **46** in moderate-to-excellent yields (Scheme 47) [59]. Carrying out the reaction under micro flow conditions could reduce the reaction time to less than 1 min. The reaction mechanism suggests that the sulfonyl radical, produced from the arylsulfinic acid with the oxidation of TBHP, adds to the C=C double bond of amide followed by 6-*exo* cyclization and coupling with phenylselenyl radical to give product **46a**.

A Cu-catalyzed radical trifluoromethylative spirocyclization reaction of benzene-tethered 1,7-enynyl amides for the synthesis of trifluoromethyl-substituted 1′*H*-spiro-[azirine-2,4′-quinolin]-2′(3′*H*)-ones was introduced by the Han group in 2017. The reaction of amides, Togni's reagent and $TMSN_3$ in DMF and in the presence of $Cu^{II}$ catalyst gave product **47** in good-to-excellent yields (Scheme 48) [60]. The reaction mechanism suggests that the $CF_3$ radical from Togni's reagent adds to the C=C double bond of amides; then, it goes through path a or b to give cyclized $Cu^{III}$-azido complex **M-37,** followed by reductive catalyst elimination and denitrogenative cyclization to give product **47**.



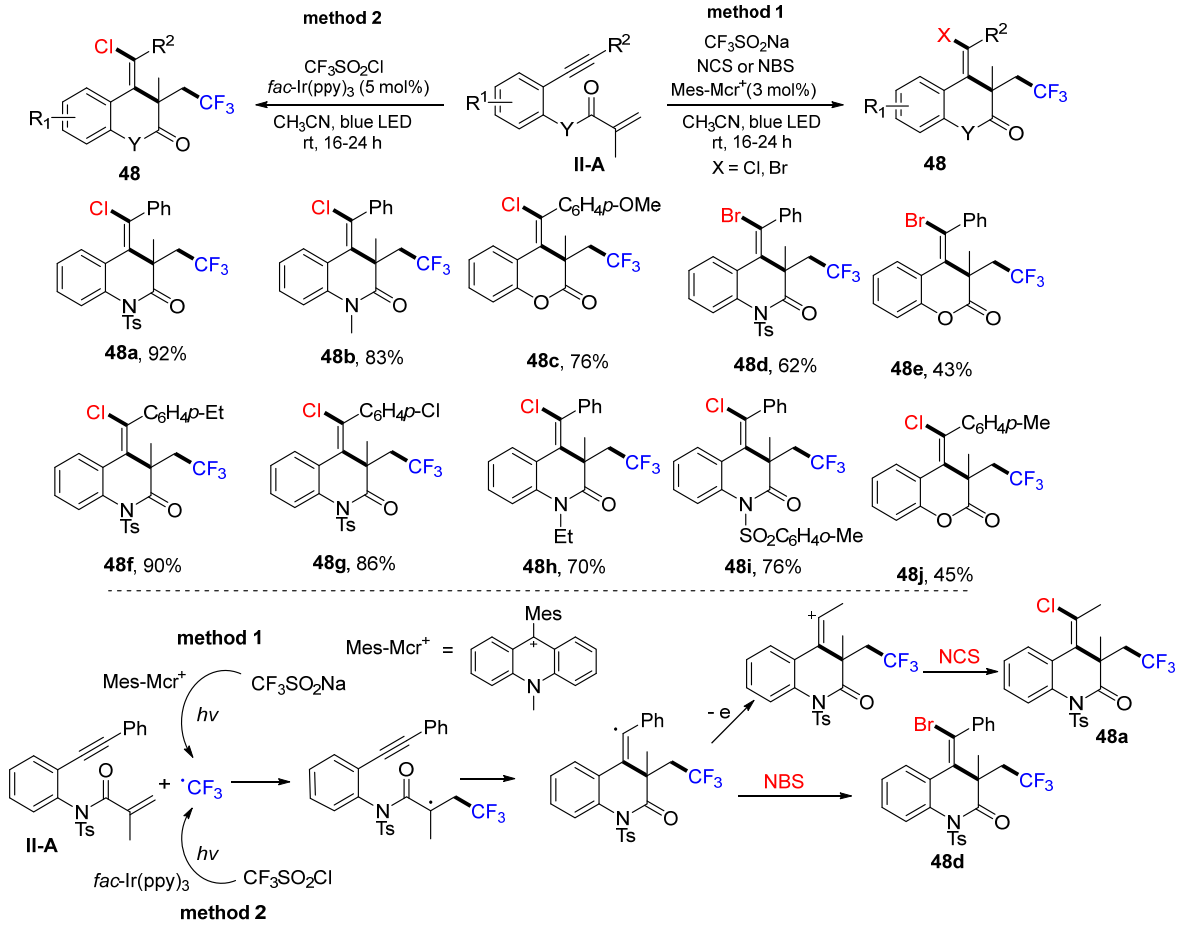

**Scheme 47.** Synthesis of functionalized 3,4-dihydroquinolin-2(1*H*)-ones.




**Scheme 48.** Preparation of spiro[2,5]azirinequinolinones.

The Guo group, in 2019, reported two photoredox methods for the synthesis of trifluoroethyl-substituted 3,4-dihydroquinolin-2(*1H*)-ones. Method 1 is the reaction of 1,7-enynyl amides, $CF_3SO_2Na$, NCS (or NBS) using photocatalyst *N*-methyl-9-mesityl acri-

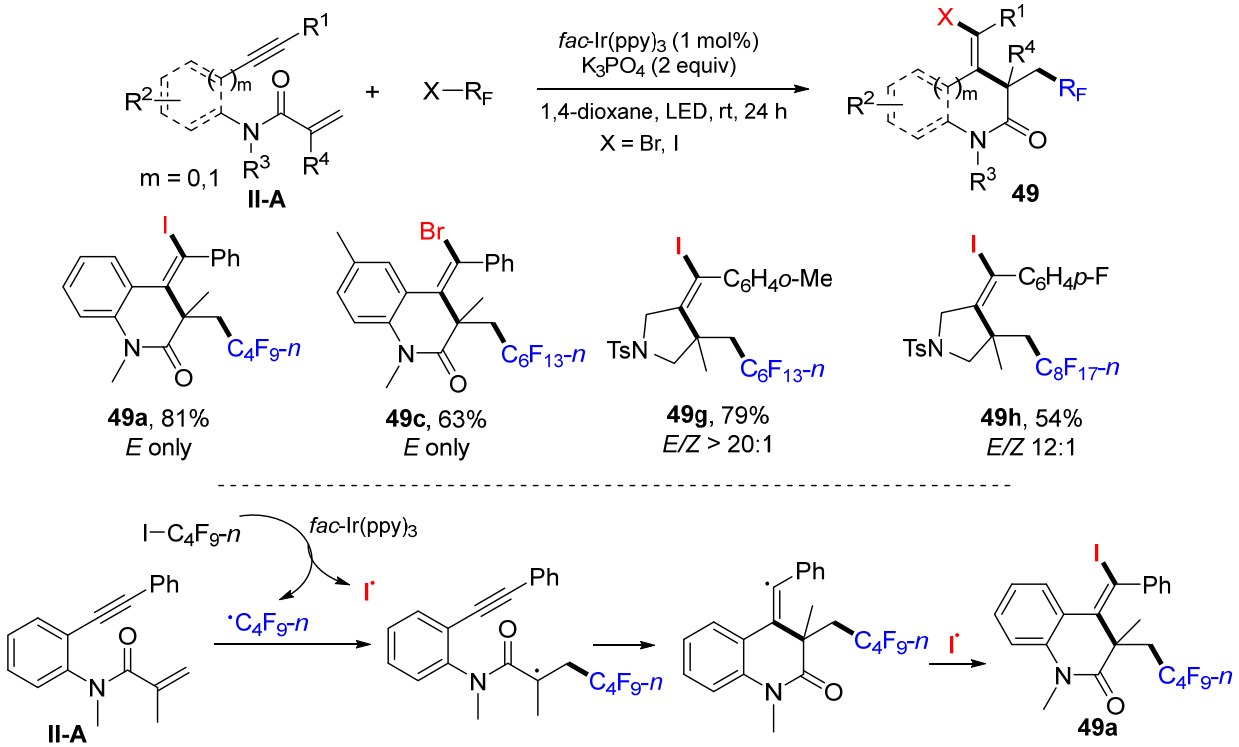
dinium (Mes-Acr$^+$). Method 2 is the reaction of 1,7-enynyl amides and $CF_3SO_2Cl$ using photocatalyst *fac*-Ir(ppy)$_3$. These two methods gave product **48** in moderate-to-excellent yields (Scheme 49) [61]. The proposed reaction mechanism indicated that for method 1, the $CF_3$ radical generated from the $CF_3SO_2Na$ under the photocatalysis of Mes-Acr$^+$ adds to the C=C bond of amide followed by 6-*exo* cyclization and coupling with bromo radical from NBS to give product **48d**. In method 2, the $CF_3$ radical generated from the $CF_3SO_2Cl$ under the photocatalysis of *fac*-Ir(ppy)$_3$ goes through similar addition, cyclization and halogen atom abstraction processes to afford product **48a**.



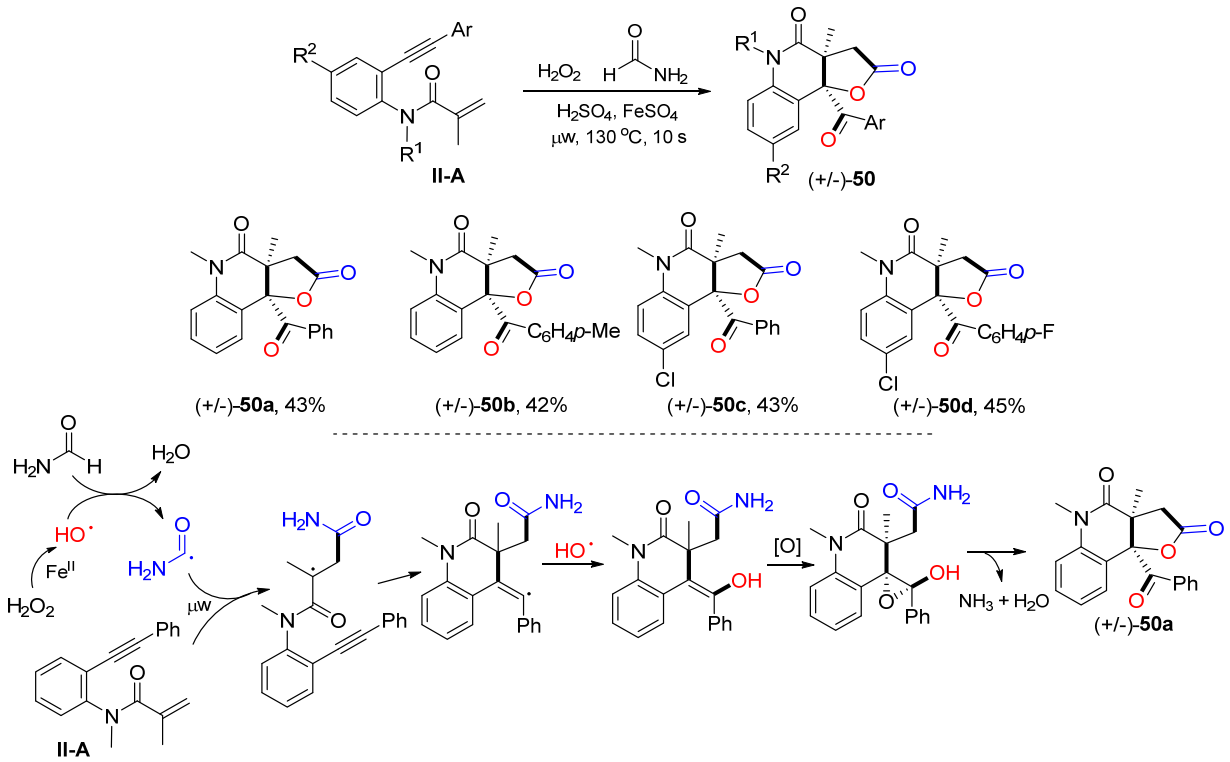

**Scheme 49.** Synthesis of trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones.

A visible light-induced radical reaction for the synthesis of haloperfluorinated *N*-heterocycles was reported by the Tang group in 2019. The reaction of 1,6- or 1,7-enynyl amides, perfluoroalkyl iodides/bromides in 1,4-dioxane and in the presence of *fac*-Ir(ppy)$_3$ and $K_3PO_4$ under blue LED irradiation afforded product **49** in good yields and stereoselectivity (Scheme 50) [62]. The reaction mechanism suggests that *n*-$C_4F_9$ radical generated under the photocatalysis with of *fac*-Ir(ppy)$_3$ adds to the C=C bond of amide, followed by 6-*exo* cyclization and coupling with iodine radical, to selectively give product **49a** as the *Z*-isomer.

The Andrade group reported an ultrafast Fe-promoted reaction for the synthesis of 2-quinolinone-fused $\gamma$-lactones in 2021. The reaction of benzene-tethered 1,7-enynyl amides and formamide and Fenton's reagent under microwave irradiation for 10 s gave product **50** in a good overall yield (Scheme 51) [63]. The reaction mechanism suggests that the hydroxyl radical generated from Fenton's reaction adds to the C=C double bond of amide followed by 6-*exo* cyclization, coupling with hydroxyl radical, epoxidation, and lactonization to give product **50a**.



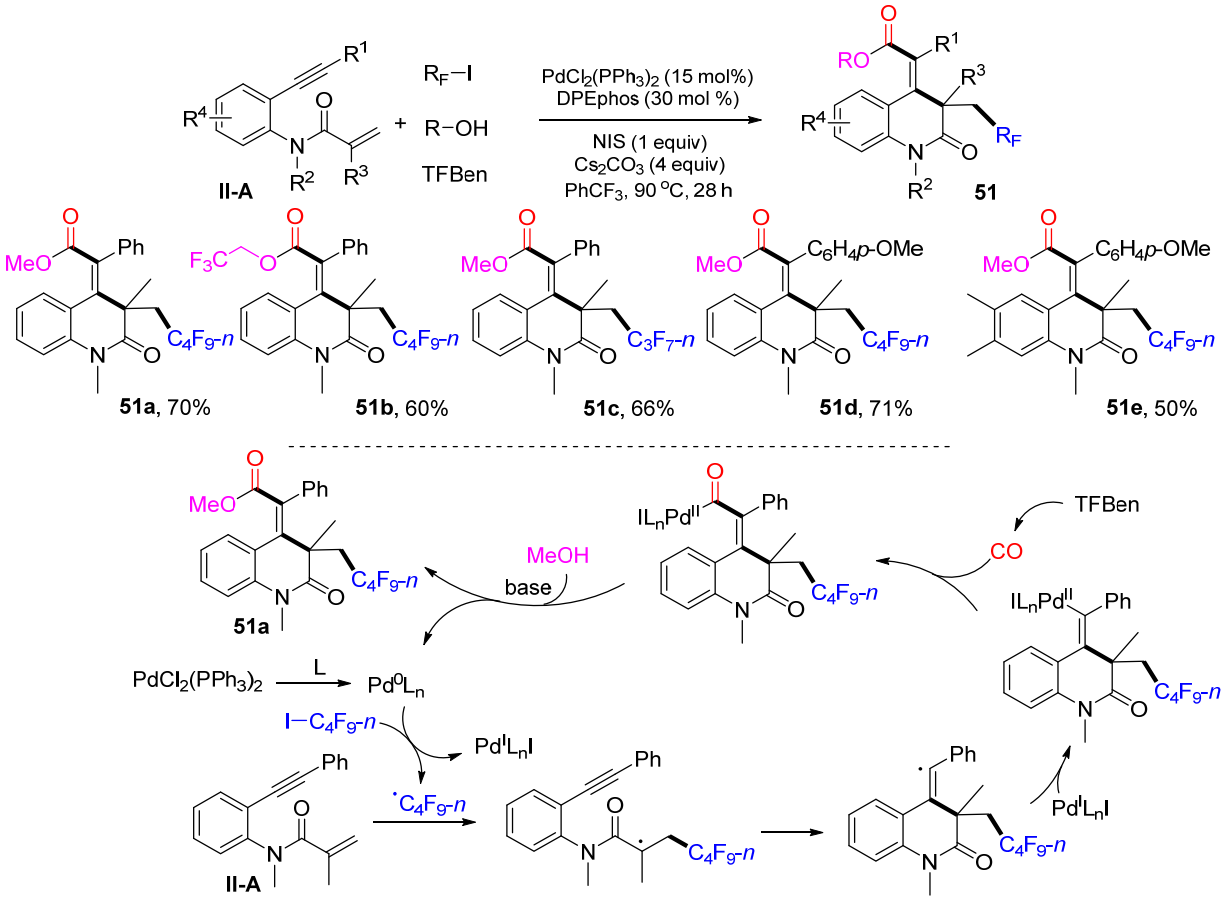

**Scheme 50.** Synthesis of haloperfluorinated *N*-heterocycles.




**Scheme 51.** Synthesis of 2-quinolinone-fused $\gamma$-lactones.

In 2022, Wu, Ying and their coworkers introduced a Pd-catalyzed reaction for the synthesis of perfluoroalkyl and carbonylated 3,4-dihydroquinolin-2(1*H*)-ones. The reaction of 1,7-enynyl amides, perfluoroalkyl iodides, alcohols and benzene-1,3,5-triyl triformate (TFBen) in $PhCF_3$ and in the presence of $PdCl_2(Ph_3P)_2$, DPEphos, NIS, and $Cs_2CO_3$ gave

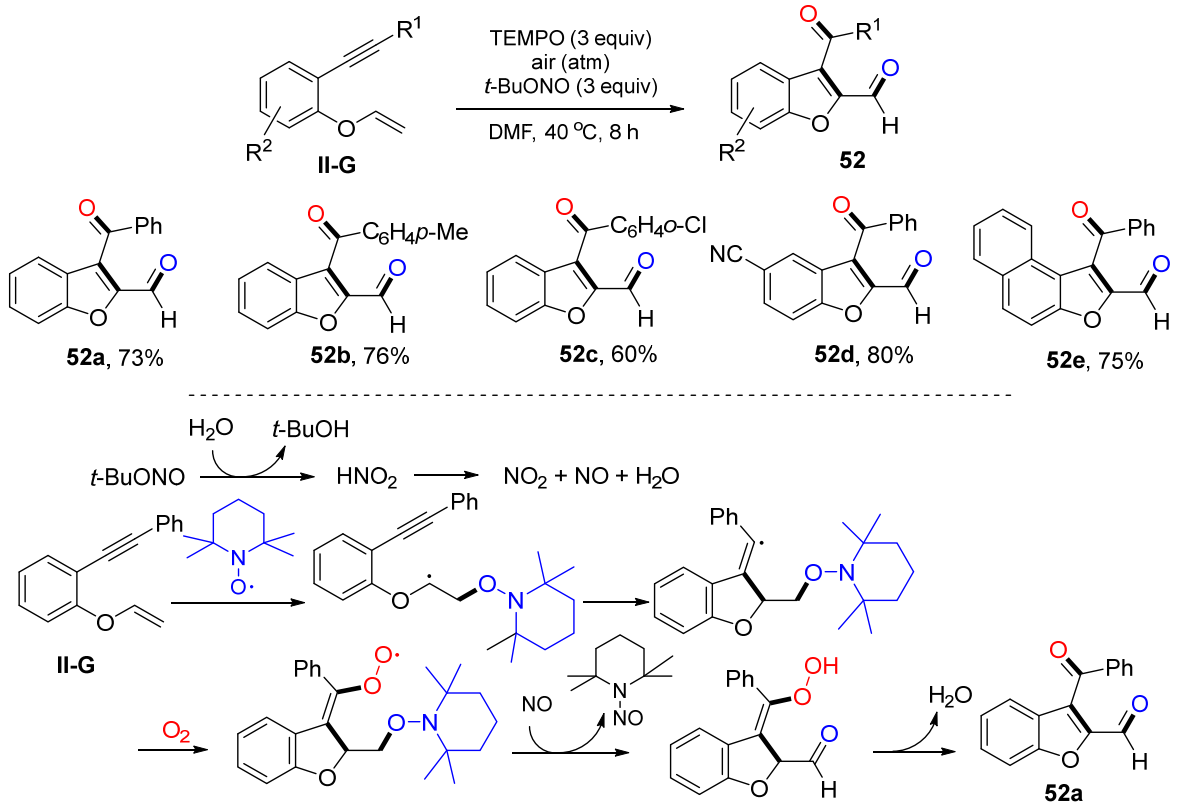
product **51** in high yields with excellent *E*/*Z* selectivity (Scheme 52) [64]. In this reaction, TFBen was used as the CO source and alcohols when making the ester products. A reaction mechanism suggests that the *n*-$C_4F_9$ radical derived from *n*-$C_4F_9I$ adds to the C=C double bond of amide followed by 6-*exo* cyclization, incorporation with the Pd-catalyst, CO insertion, and esterification with MeOH to afford product **51a**.



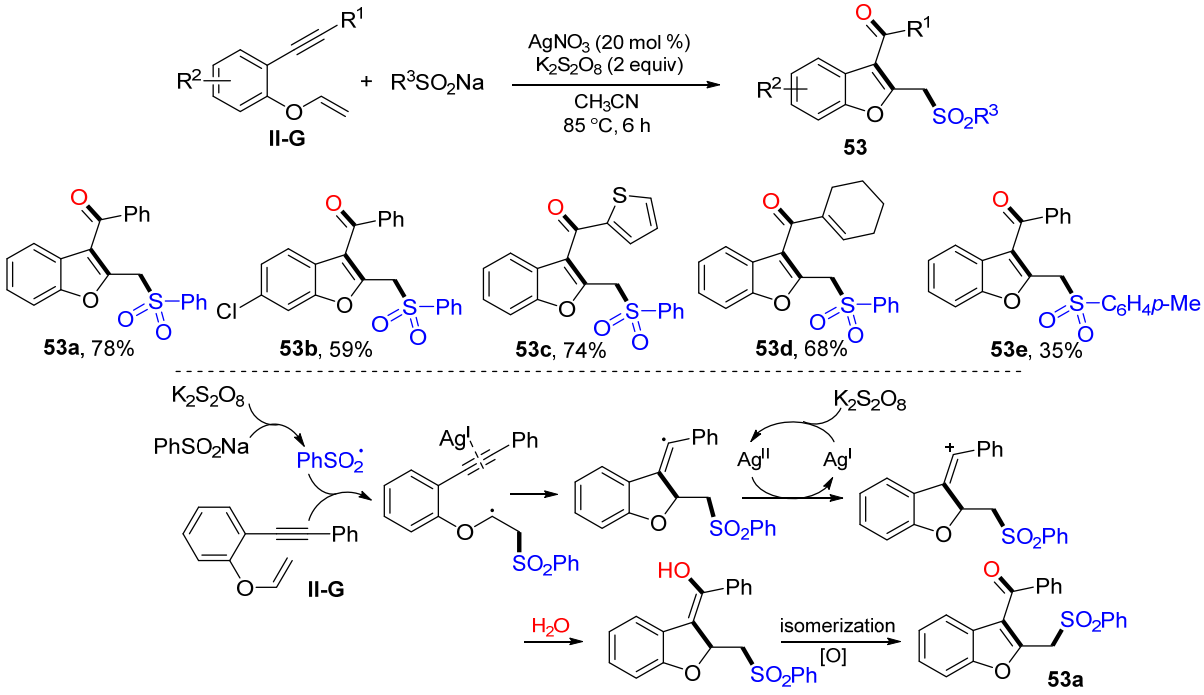

**Scheme 52.** Synthesis of perfluoroalkyl and carbonylated 3,4-dihydroquinolin-2(1*H*)-ones.

Benzene-linked 1,6-eneynyl ethers are a class of good substrates for radical difunctionalization. Li and coworkers reported a reaction of such substrates for the synthesis of dicarbonylated benzofurans in 2015. The reaction of benzene-linked 1,6-eneynyl ethers, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), *t*-BuONO and $O_2$ in DMF at 40 °C for 8 h gave product **52** in moderate-to-good yields (Scheme 53) [65]. Two oxygen atoms were introduced to the product from $O_2$ and TEMPO, respectively. *t*-BuONO is a key reagent which provides $NO_2$ and NO after decomposition of $HNO_2$. The reaction mechanism suggests that the addition of TEMPO to the C=C double bond of ethers followed by 5-*exo* cyclization, trapping of $O_2$, oxidative cleavage of the N-O bond to release 2,6,6-tetramethyl-1-nitroso-piperidine, and O-O bond cleavage/isomerization to afford product **52a**.

An Ag-catalyzed reaction of 1,6-eneynyl ethers for the synthesis of sulfonyl-methylated benzofurans was reported by Wu, Jiang and their coworkers in 2017. The reaction of benzene-linked 1,6-eneynyl ethers and sodium sulfinates in $CH_3CN$ and in the presence of $K_2S_2O_8$ and $AgNO_3$ afforded product **53** in moderate-to-good yields (Scheme 54) [66]. The reaction mechanism suggests that the sulfonyl radical generated from the oxidation of $PhSO_2Na$ adds to the C=C double bond of ethers followed by 5-*exo* cyclization, oxidation to cation, nucleophilic addition of $H_2O$, and enol/ketone isomerization to give product **53a**.



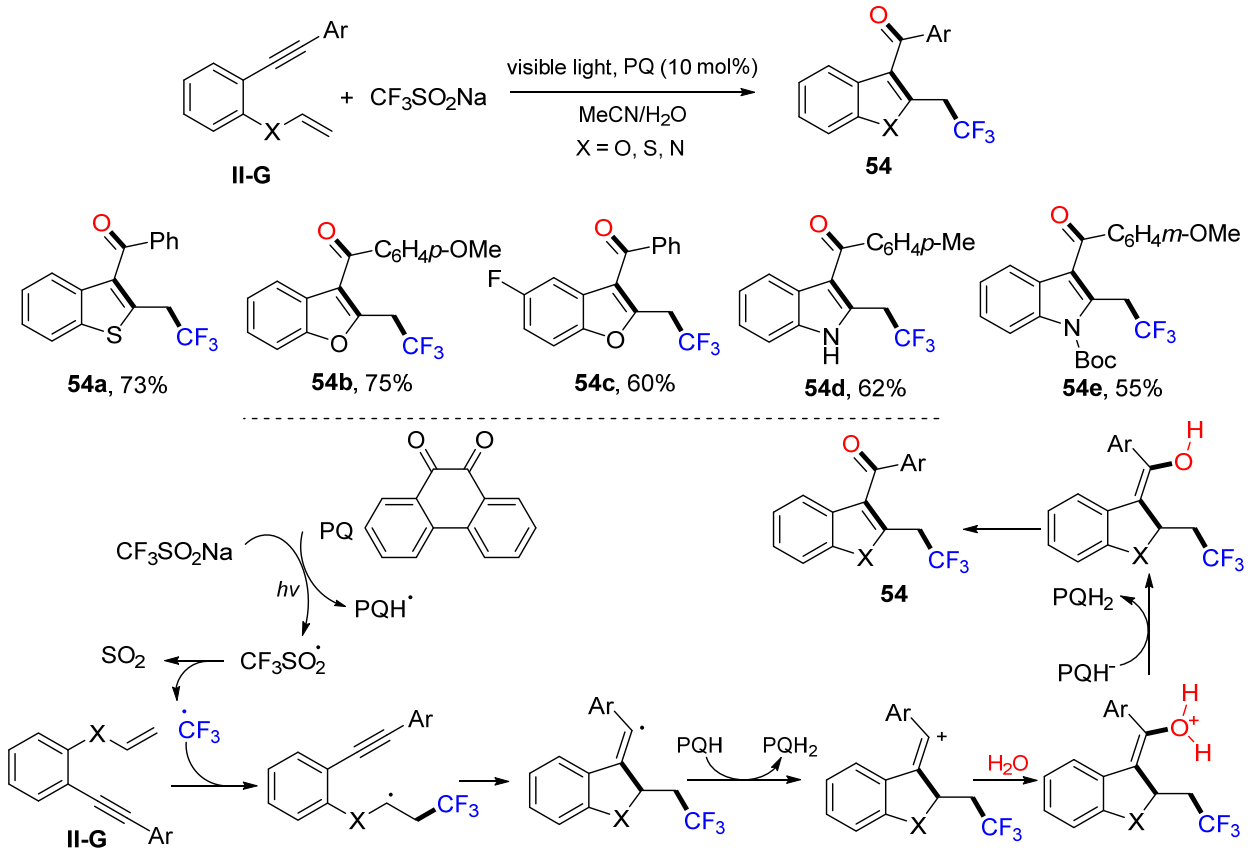

**Scheme 53.** Synthesis of dicarbonylated benzofurans.




**Scheme 54.** Synthesis of carbonyl and sulfonylmethylated benzofurans.

In 2017, Kumar and coworkers reported a visible light-induced reaction for the synthesis of trifluoromethylacylated benzofurans, benzothiophenes, and indoles. The reaction of 1-ethynyl-2-(vinyloxy)-benzenes and $CF_3SO_2Na$ in $CH_3CN/H_2O$ using phenanthrene-9,10-dione (PQ) as a photoredox catalyst gave heterocycles **54** in good yields (Scheme 55) [67].

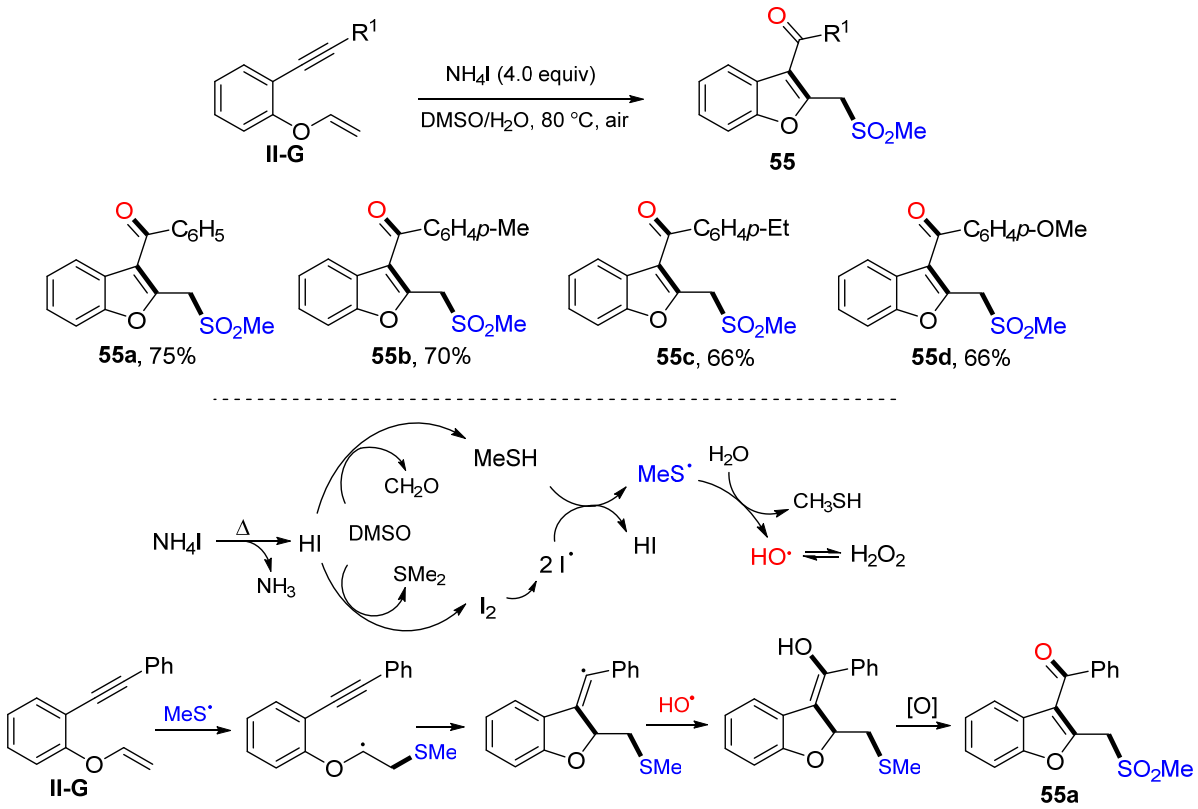
The proposed reaction mechanism suggests that the $CF_3$ radical, generated from $CF_3SO_2Na$ with photo-activated PQ, adds to the C=C double bond of 1-ethynyl-2-(vinyloxy)-benzenes followed by 5-*exo* cyclization, electron transfer from PQH radical, $H_2O$ addition and deprotonation, resulting in product **54**.



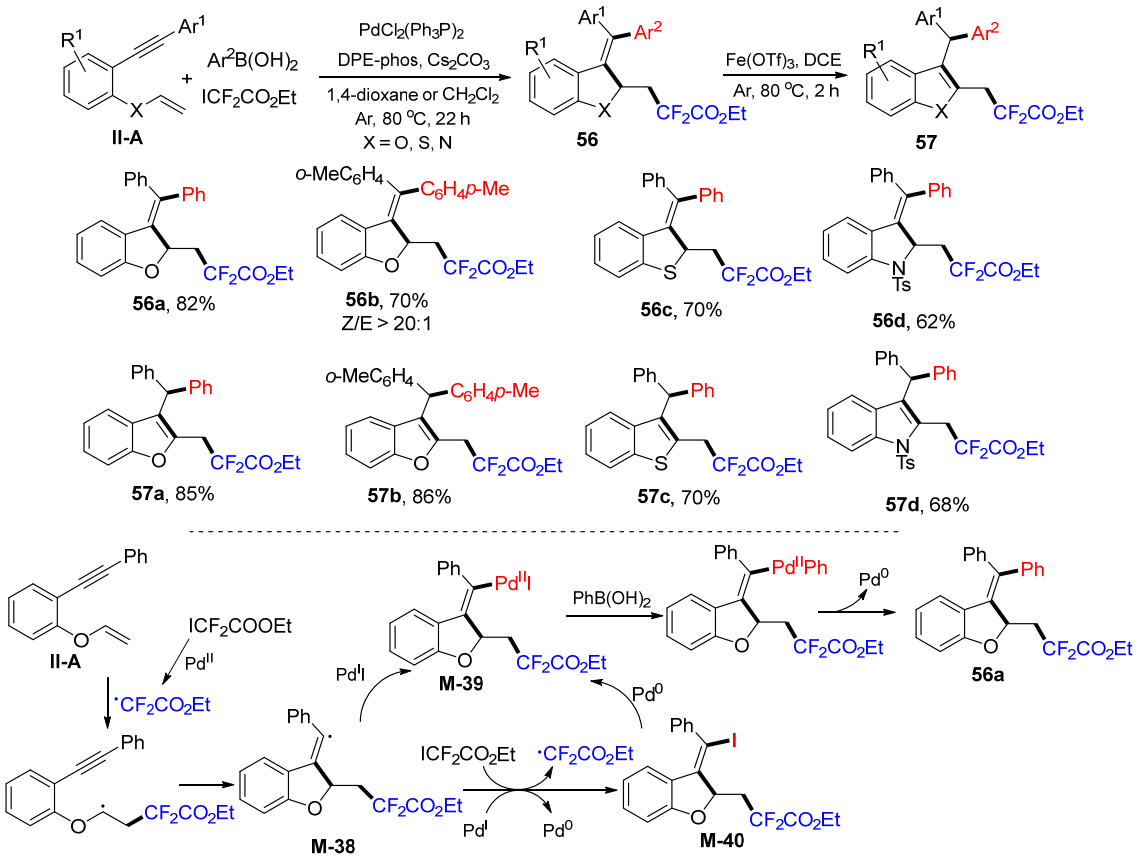

**Scheme 55.** Synthesis of trifluoromethylated and acylated heterocycles.

A reaction of 1,6-eneynyl ethers for the synthesis of sulfonylacylated benzofurans was introduced by the Sun group in 2018. The reaction of oxygen-linked 1,6-enynes, DMSO and $H_2O$ in the presence of $NH_4I$ afforded product **55** in moderate-to-high yields (Scheme 56) [68]. A reaction mechanism suggests that the reaction between DMSO and $NH_4I$ produced MeS and OH radicals. Addition of MeS radical to the C=C double bond of ethers followed by 5-*exo* cyclization, OH radical coupling, axidation of sulfide, and keto-enol tautomerism resulted in product **55a**.

In 2020, the Zhang group introduced a Pd-catalyzed radical oxidative aryldifluoroalkylation of benzene-tethered 1,6-enynes for the synthesis of difluoroalkylated benzofuran, benzothiophene, and indole derivatives. The reaction of 1,6-enynes, ethyl difluoroiodoacetate and arylboronic acids 1,4-dioxane or DCE under the catalysis of $PdCl_2(PhP_3)_2$ and DPE-phos gave product **56** in moderate-to-good yields (Scheme 57) [69]. The resultant products can be converted into aromatic five-membered rings **57** via $Fe(OTf)_3$-catalyzed isomerization. A reaction mechanism suggests that the $CF_2CO_2Et$ radical generated from $ICF_2CO_2Et$ adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization to form **M-38** and then reacts with $Pd^{I}I$ to form intermediate **M-39**. Intermediate **M-39** could also be generated from **M-38** through iodine transfer with $ICF_2CO_2Et$ and then with $Pd^0$. Coupling **M-39** with phenylboronic acid finishes the reaction and gives product **56a**.

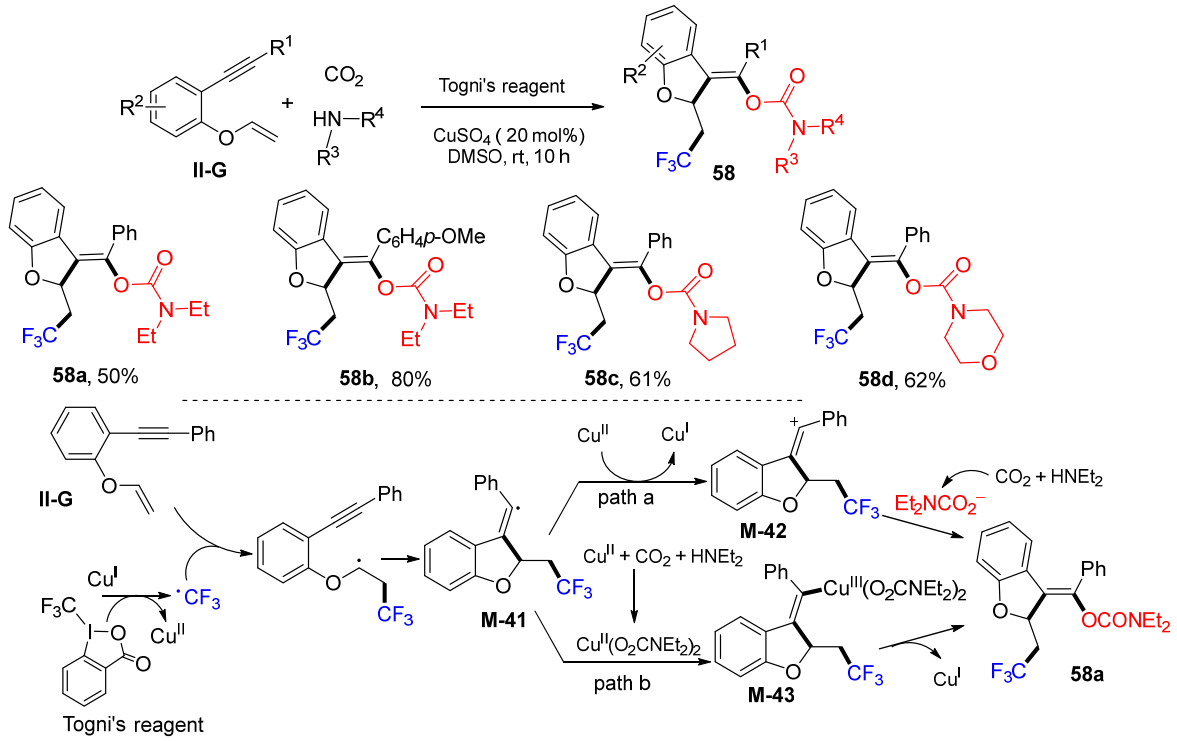



**Scheme 56.** Synthesis of difunctionalized benzofurans.




**Scheme 57.** Synthesis of aryldifluoroalkylated heterocycles.

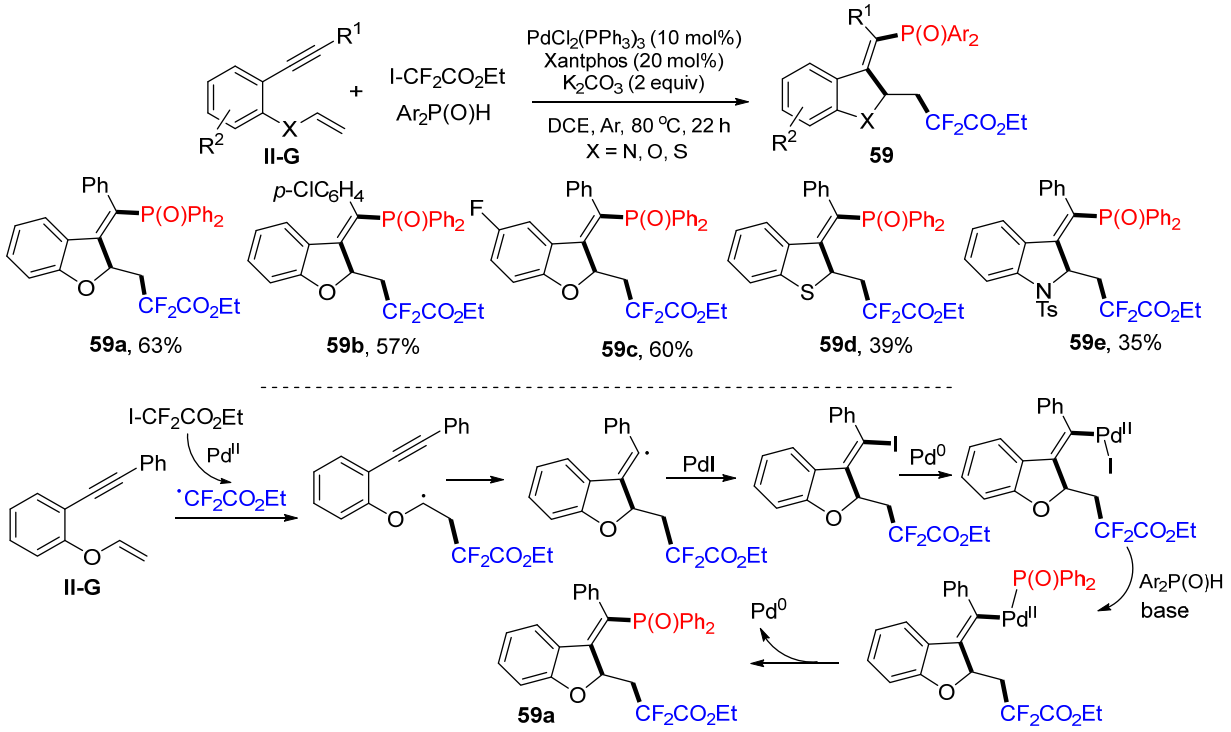
A Cu-catalyzed radical reaction of benzene-tethered 1,6-enynes for the synthesis of trifluoroethylated dihydrobenzofurans was reported by the Jiang group in 2019. The reaction of 1,6-enynes, Togni's reagent, $CO_2$ and amines in DMSO under the catalysis of $CuSO_4$ gave products **58** in good yields (Scheme 58) [70]. The proposed reaction mechanism suggests that the $CF_3$ radical derived from the Togni's reagent adds to 1,6-enynes followed by *5-exo* cyclization to form radical **M-41**. Then, it might have two pathways to form product **58a.** In path a, vinyl radical **M-41** is oxidized by $Cu^{II}$ to a cation **M-42**, followed by trapping with carbamate anion to form **58a**. Alternatively, in path b, vinyl radical **M-41** reacts with $CuSO_4$, $CO_2$, and amine to form carbamato complex **M-43**, which leads to the formation of product **58a** after reductive elimination of the catalyst.



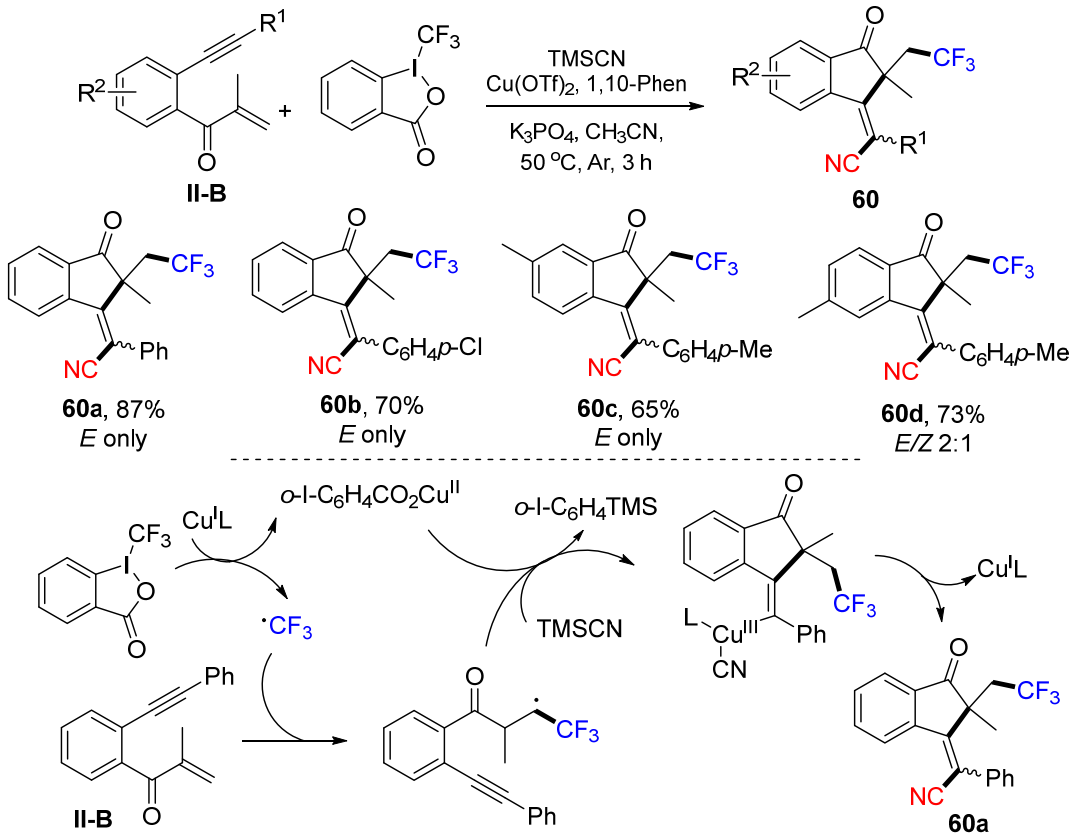

**Scheme 58.** Synthesis of trifluoromethyl dihydrobenzofurans.

Gao, Ying and their coworkers reported a Pd-induced radical reaction for the synthesis of difluoroalkyl- and alkenylphosphinyl-functionalized heterocycles in 2021. The reaction of 2-vinyloxy arylalkynes, $ICF_2CO_2Et$ and diphenylphosphine oxides in DCE under the catalysis of $PdCl_2(PPh_3)_2$ and Xantphos gave product **59** in good yields and stereoselectivity (Scheme 59) [71]. A reaction mechanism suggests that the $CF_2CO_2Et$ radical derived from $ICF_2CO_2Et$ under the catalysis of $Pd^{II}$ adds to the C=C double bond of 2-vinyloxy arylalkynes followed by 5-*exo* cyclization and iodine atom transfer from PdI, through the oxidative addition of $Pd^0$ to vinyl iodide, formation of diphenylphosphine oxide complex, reductive elimination of Pd catalyst to give product **59a**.

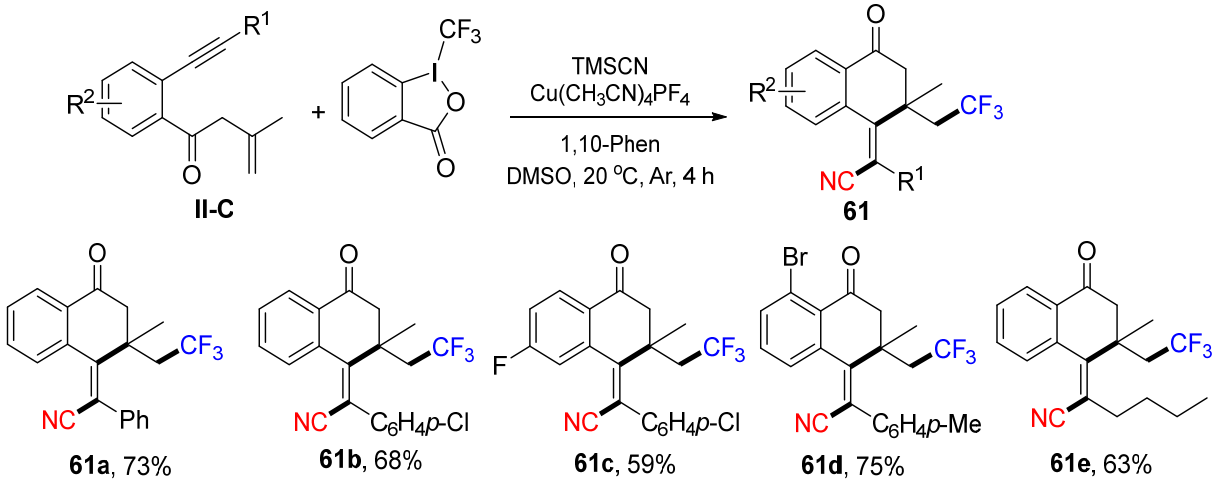
Using benzene-tethered and carbonyl-containing 1,6-enynes as a substrate for Cu-catalyzed radical reaction for the construction of cyanotrifluoromethylated 1-indanones was introduced by the Jiang group in 2020. The reaction of benzene-tethered 1,6-enynes, Togni's reagent and trimethylsilyl cyanide (TMSCN) under the catalysis of $Cu(OTf)_2$ gave product **60** in good yields (Scheme 60) [72]. A reaction mechanism suggests that the trifluoromethyl radical generated from Togni's reagent under the catalysis of $Cu^{II}$ adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization, formation of $Cu^{III}$-complex containing CN, and reductive elimination of the Cu-catalyst to give product **60a**. By using benzene-tethered 1,7-enynes, the Jiang group extended the reaction scope for the synthesis of cyanotrifluoromethylated (*Z*)-3,4-dihydronaphthalen-1(2*H*)-ones **61** (Scheme 61) [73].




**Scheme 59.** Synthesis of aifluoroalkyl and alkenylphosphinylated heterocycles.

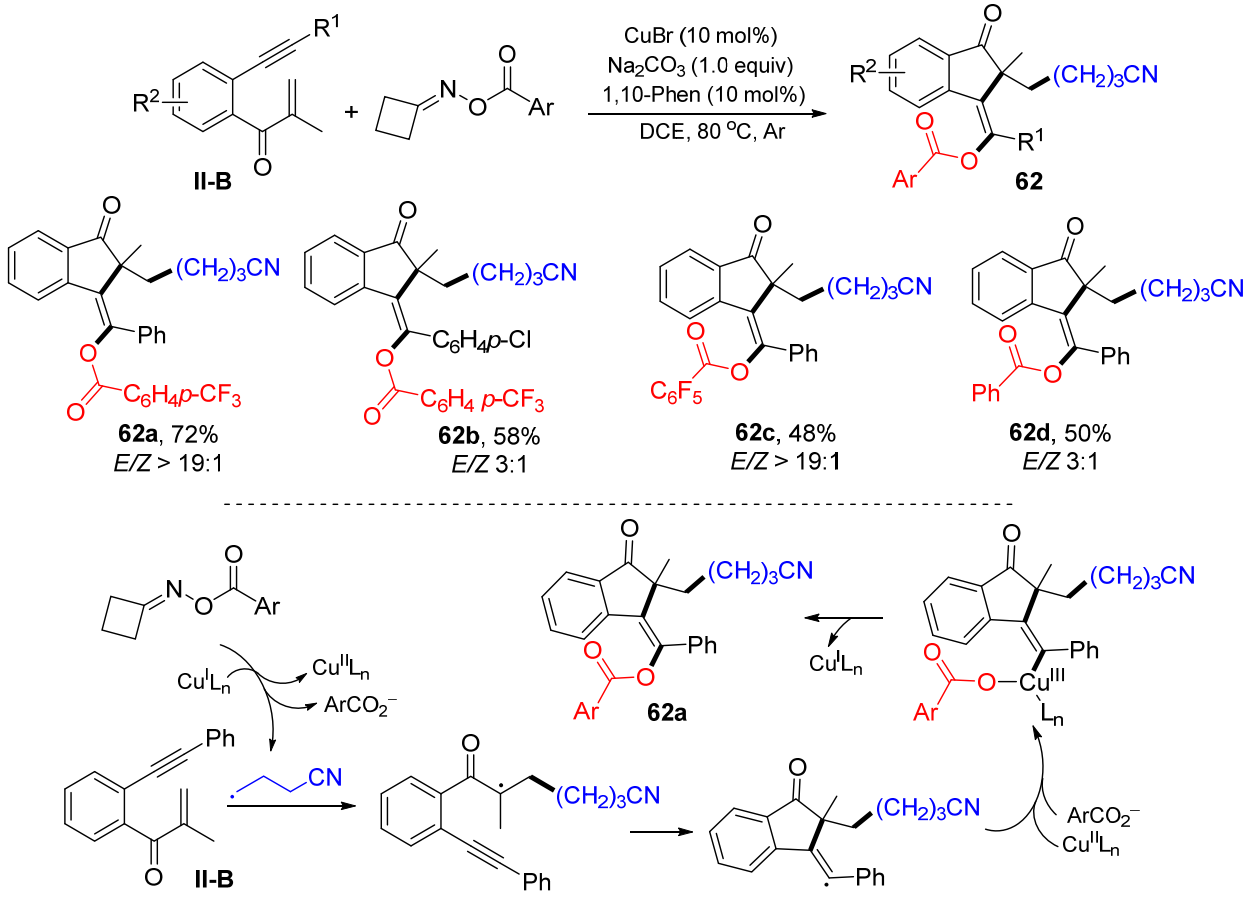



**Scheme 60.** Synthesis of cyanotrifluoromethylated 1-indanones.



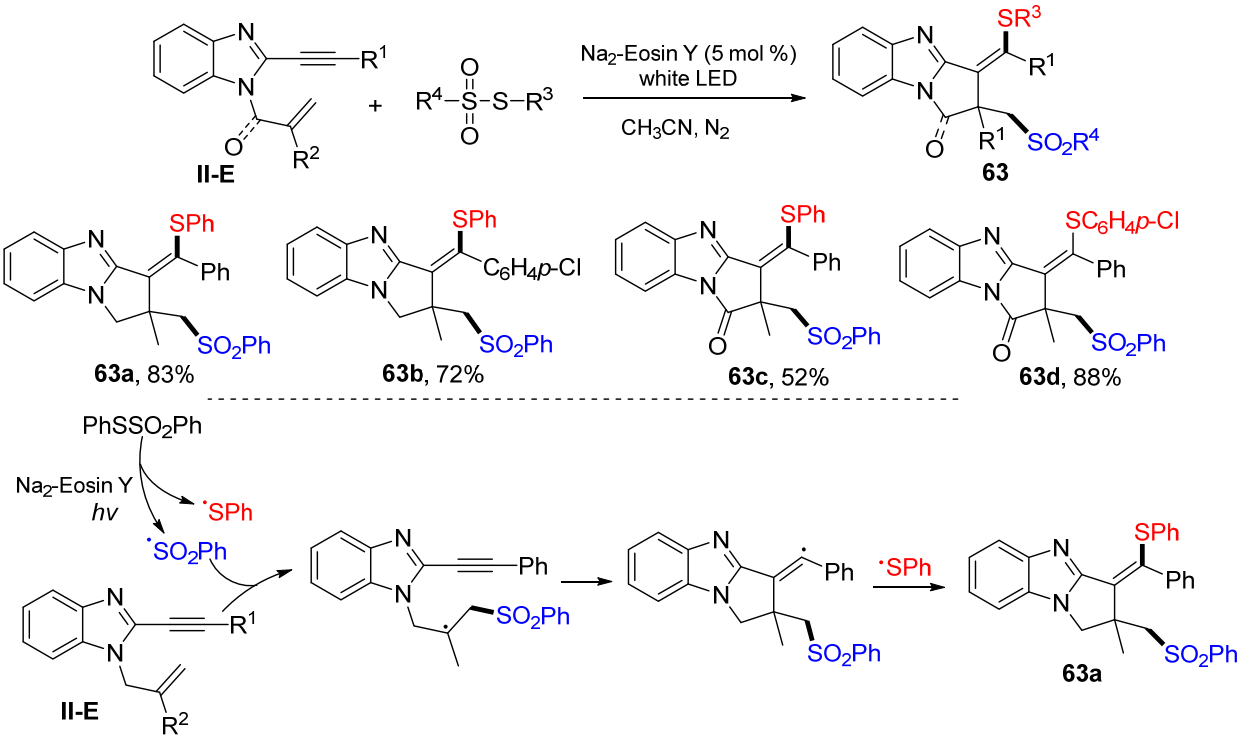

**Scheme 61.** Synthesis of cyanotrifluoromethylated (*Z*)-3,4-dihydronaphthalen-1(2*H*)-ones.

A Cu-catalyzed radical for the synthesis of cyanoalkyl and ester-functionalized 1-indanones was introduced by the Jiang group in 2021. The reaction of 1,6-enynes, cyclobutanone oxime esters in DCE at 80 °C under the catalysis of CuBr and1,10-Phen gave product **62** in good yields (Scheme 62) [74]. Both functional groups come from cyclic oxime esters. A reaction mechanism suggests that the γ-cyanoalkyl radical, generated from cyclic oxime ester via a SET process with $Cu^{I}L_n$, adds to the C=C double bond of 1,6-enyne followed by 5-*exo* cyclization, formation of a $Cu^{III}$ complex containing the ester group, and reductive elimination $Cu^{I}L_n$ to give product **62a**.




**Scheme 62.** Synthesis of cyanoalkyl and ester-functionalized 1-indanones.

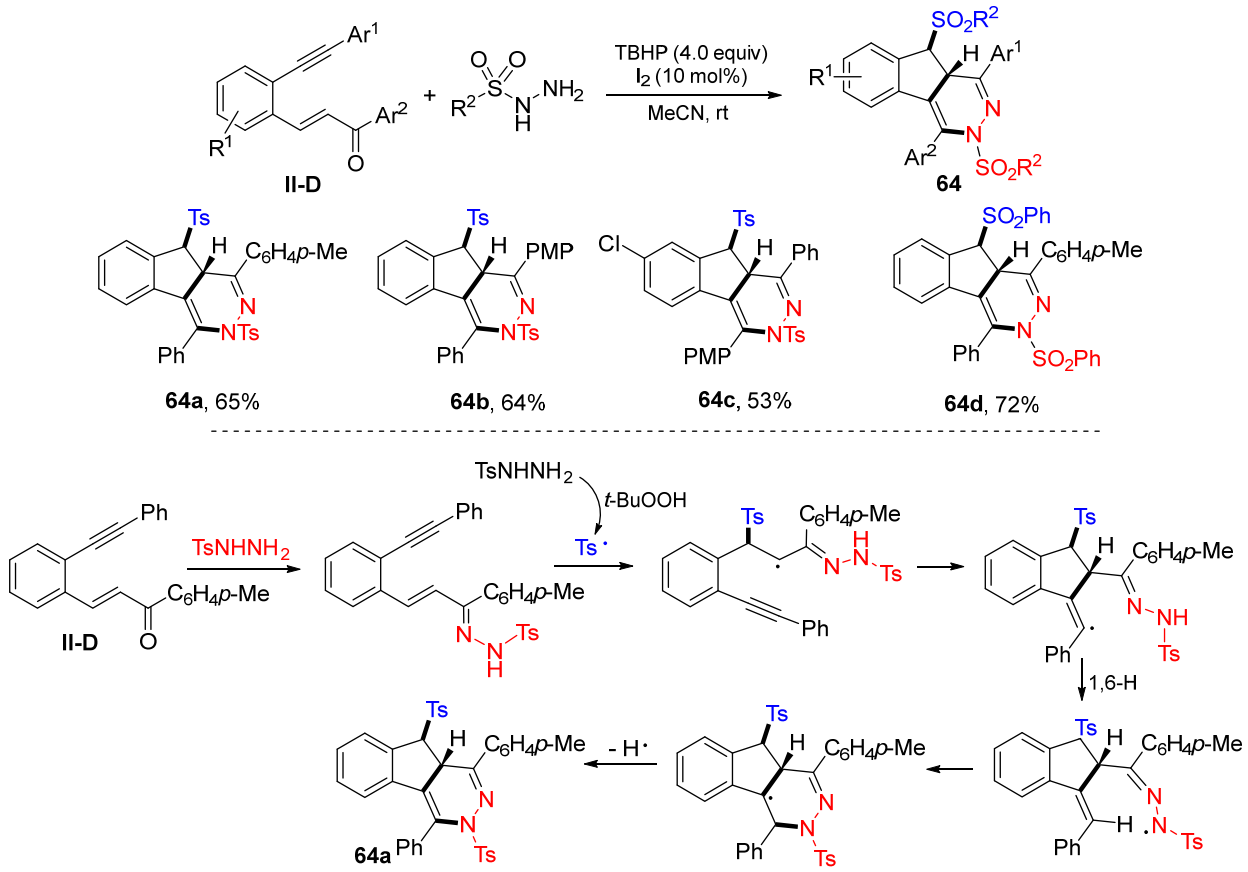
A visible light-induced radical reaction of benzene-tethered 1,6-enynes for the synthesis of the thiosulfonylated pyrrolo[1,2-*a*]benzimidazoles was reported by the Chen group in 2021. The reaction of 1,6-enynes and $PhSO_2SPh$ in $CH_3CN$ under the photo catalysis of $Na_2$-Eosin Y gave **63** in moderate-to-good yields (Scheme 63) [75]. The reaction mechanism suggests that the sulfonyl radical derived from $PhSO_2SPh$ adds to the C=C double bond of 1,6-enynes followed by 5-*exo* cyclization and coupling with the SPh radical to afford product **63a**.




**Scheme 63.** Synthesis of the thiosulfonylated pyrrolo-[1,2-*a*]benzimidazoles.

The Tu and Jiang groups, in 2016, reported a radical reaction of 1,5-enynes for the synthesis of sulfonylated indeno[1,2-*d*]pyridazines. The reaction of 1,5-enynes, arylsulfonyl hydrazides in $CH_3CN$ and in the presence of $I_2$ and TBHP gave products **64** in good yields (Scheme 64) [76]. A reaction mechanism suggests that sulfonylhydrazone, generated from the condensation of 1,5-enynes with the arylsulfonyl hydrazide, reacts with the tosyl radical, which is also derived from arylsulfonyl hydrazide followed by 5-*exo* cyclization, 1,6-H atom transfer, 6-*endo* cyclization of the N-radical, and aromatization to give product **64a**.

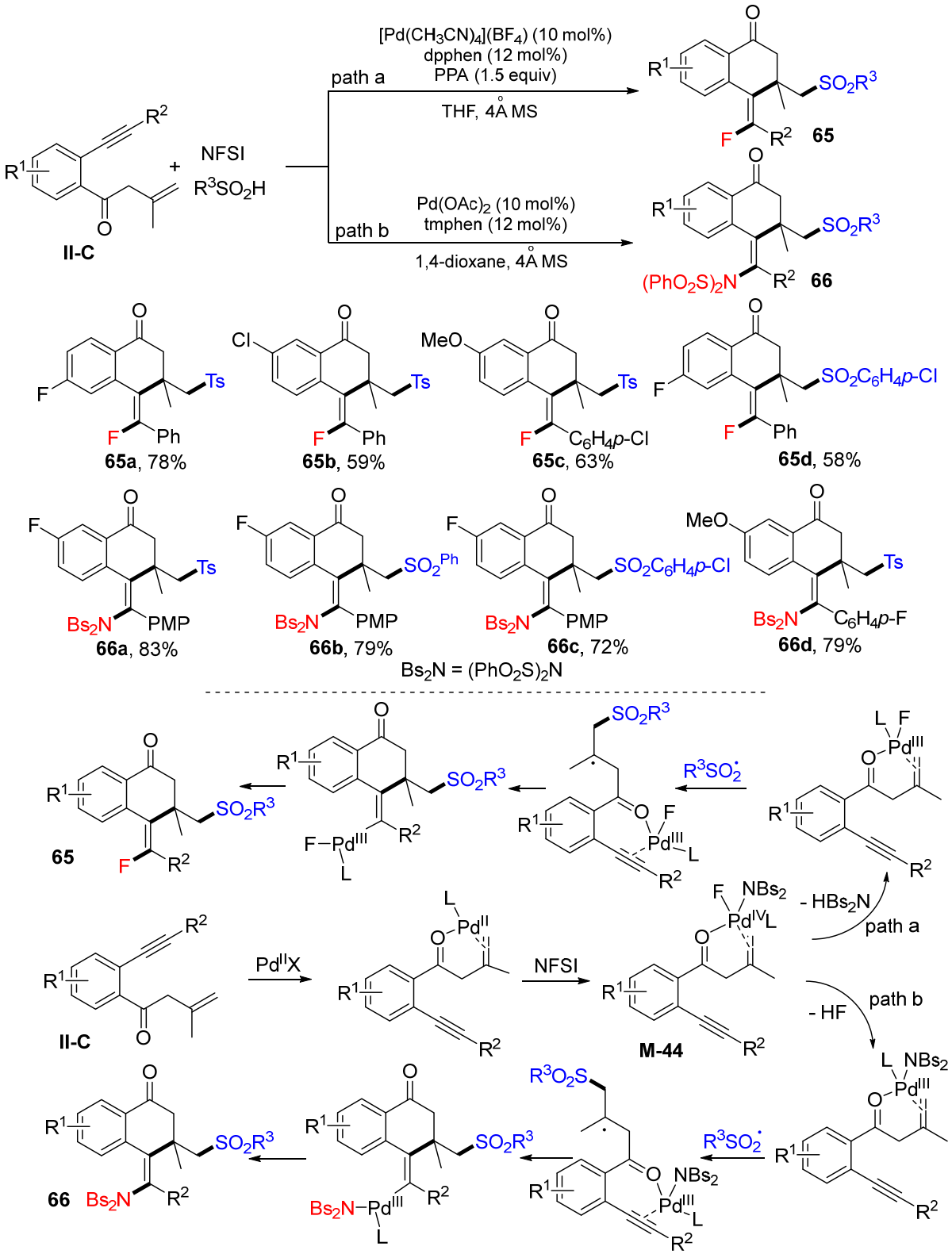
A Pd-catalyzed radical cyclization of 1,7-enynes for the synthesis of functionalized (*E*)-3,4-dihydro-naphthalen-1(2*H*)-ones was reported by Jiang, Tu and their coworkers in 2018. The reaction of 1,7-enynes, sulfinic acids and *N*-fluorobenzenesulfonimide (NFSI) in THF under the catalysis of $[Pd(CH_3CN)_4](BF_4)_2$ gave **65** in good yields and high stereoselectivity (Scheme 65) [77]. A possible reaction mechanism suggests that 1,7-enynes generate a $Pd^{II}$ complex which then reacts with NFSI to form $Pd^{IV}$ complex **M-44** for following two pathways. Under the reaction conditions for path a, complex **M-44** eliminates $HBs_2N$, followed by the addition of $R^3SO_2$ radical, 6-*exo* cyclization, and reductive elimination of Pd catalyst to give fluorosulfonated product **65**. Under the reaction conditions for path b, HF is released from complex **M-44** followed by the similar reaction process of $R^3SO_2$ radical addition, 6-*exo* cyclization, and reductive elimination of Pd catalyst to give benzenesulfonylated products **66**.



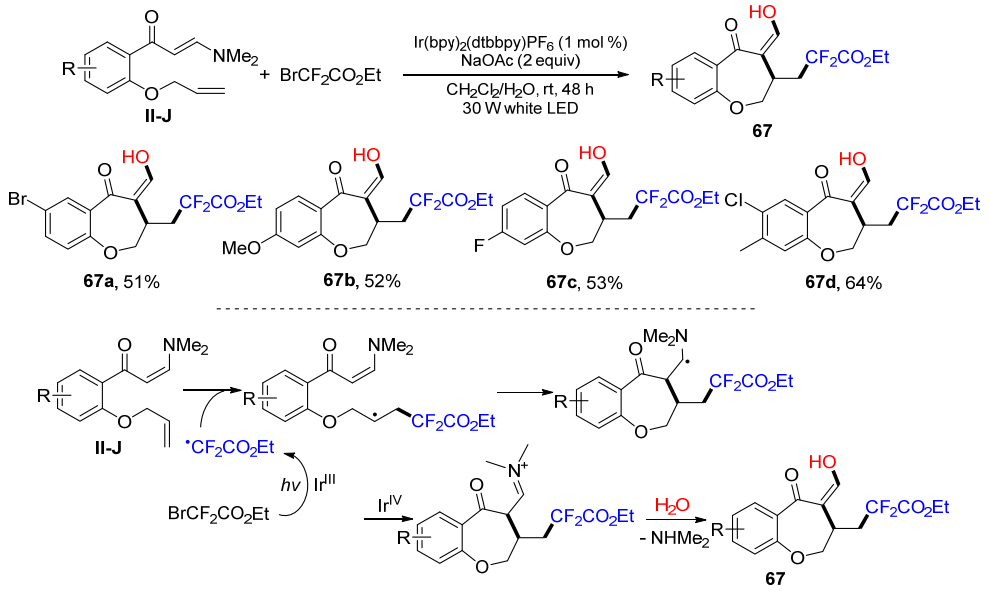

**Scheme 64.** Synthesis of disulfonylated indeno[1,2-*d*]pyridazines.

Using of benzene-tethered 1,8-dienes for Ir-catalyzed oxidative difluorinative radical cyclization for the preparation of enol and $CF_2$-containing benzoxepines was reported by the Yang group in 2018. The reaction of 1,8-dienes and $BrCF_2CO_2Et$ in $CH_2Cl_2/H_2O$ under the photoredox catalysis with $Ir(dtbbpy)(bpy)_2PF_6$ afforded benzoxepine product **67** in good yields (Scheme 66) [78]. A reaction mechanism suggests that the $CF_2CO_2Et$ radical, generated from $BrCF_2CO_2Et$ under the photocatalysis of $Ir(dtbbpy)(bpy)_2PF_6$, adds to the C=C double bond of 1,8-dienes followed by 7-*exo* cyclization, the formation of an iminium ion through the oxidization of $[Ir^{IV}(dtbbpy)(bpy)_2PF_6]^+$, and iminium hydrolysis to give product **67**.

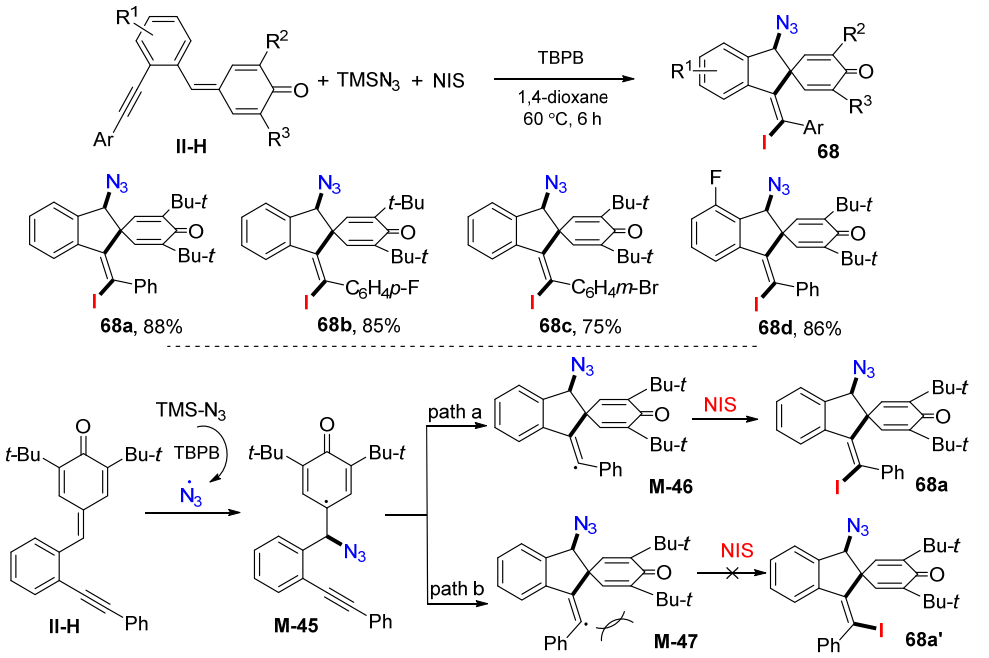
Using unique benzene-tethered 1,5-enynes, the use of 4-(2-ethynylbenzylidene)cyclohexa-2,5-dien-1-ones for the synthesis of substituted spiroindene compounds was introduced by Yao in 2018. The reaction of 1,5-enynes, $TMSN_3$ and NIS in dioxane in the presence of TBPB gave product **68** in good-to-excellent yields (Scheme 67) [79]. The suggested reaction mechanism indicated that $N_3$ radical derived from $TMSN_3$ adds to the double bond of 1,5-enynes to give cyclohexadienone radical **M-45** (path a), which then undergoes 5-*exo* cyclization to form spirocyclic vinyl intermediates **M-46**, followed by iodine atom transfer from NIS to selectively give iodo- and azido-functionalized spiroindene products **68a** as an *E*-isomer. Due to the steric hindrance of **M-47**, cyclization through path b leading to the formation of *Z*-product **68a'** is unfavorable.




**Scheme 65.** Synthesis of functionalized 3,4-dihydroquinolin-2(1*H*)-ones.



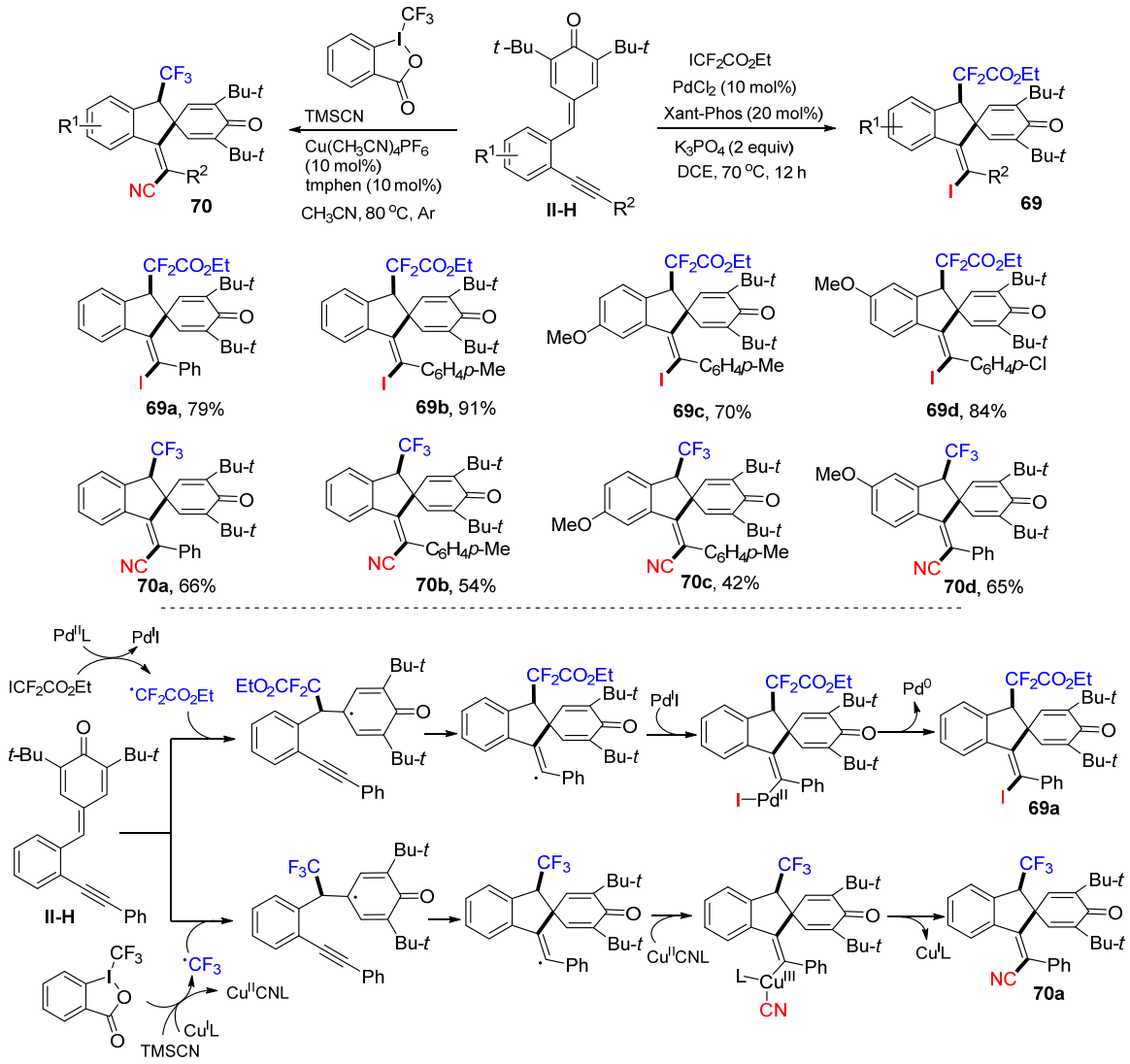

**Scheme 66.** Synthesis of enol and $CF_2$-containing benzoxepines.




**Scheme 67.** Synthesis of iodo- and azido-functionalized spiroindenes.

A metal-catalyzed radical spiroannulation of 1,5-enynes for the synthesis of fluorine-containing (Z)-spiroindenes was reported by Jiang's group in 2020. The reaction of 1,5-enynes and $ICF_2CO_2Et$ in DCE at 70 °C under the catalysis of $PdCl_2$ and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthenes (Xant-Phos) gave iododifluoro-acetylated product **69** in good yields (Scheme 68) [80]. However, the use of $BrCF_2CO_2Et$ or $C_4F_9I$ as the fluoroalkylation reagents failed to give the corresponding (Z)-spiroindenes. Another reaction of 1,5-enynes, Togni's reagent and TMSCN in $CH_3CN$ at 50 °C under the catalysis of $Cu(OAc)_2$ and 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) gave trifluoromethylated products **70**. For the synthesis of **69a**, the reaction mechanism suggests that the $CF_2CO_2Et$ radical derived from $ICF_2CO_2Et$ adds to the C=C double bond of 1,5-enynes followed by 5-*exo* spirocyclization, formation of the $Pd^{II}$-I complex, and reductive elimination of Pd catalyst to afford iododifluoroacetylated product **69a**. In the synthesis of $CF_3$-functionalized

products **70,** the $CF_3$ radical derived from Togni's reagent has a similar spirocyclization mechanism to form cyanotrifluoromethylated spiroindene product **70a**. The Tu and Jiang groups extended this reaction in the synthesis of iodosulfonylated spiroindenes, which involves an ionic instead of a radical cyclization [81].

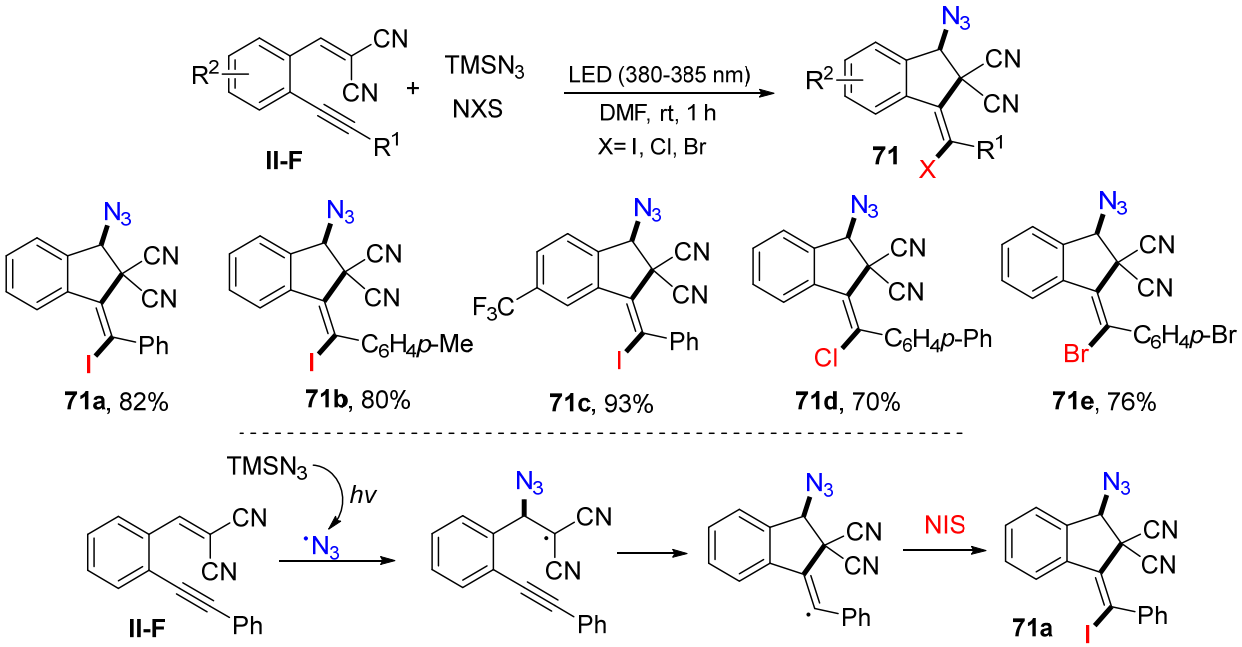



**Scheme 68.** Synthesis of functionalized spiroindene compounds.

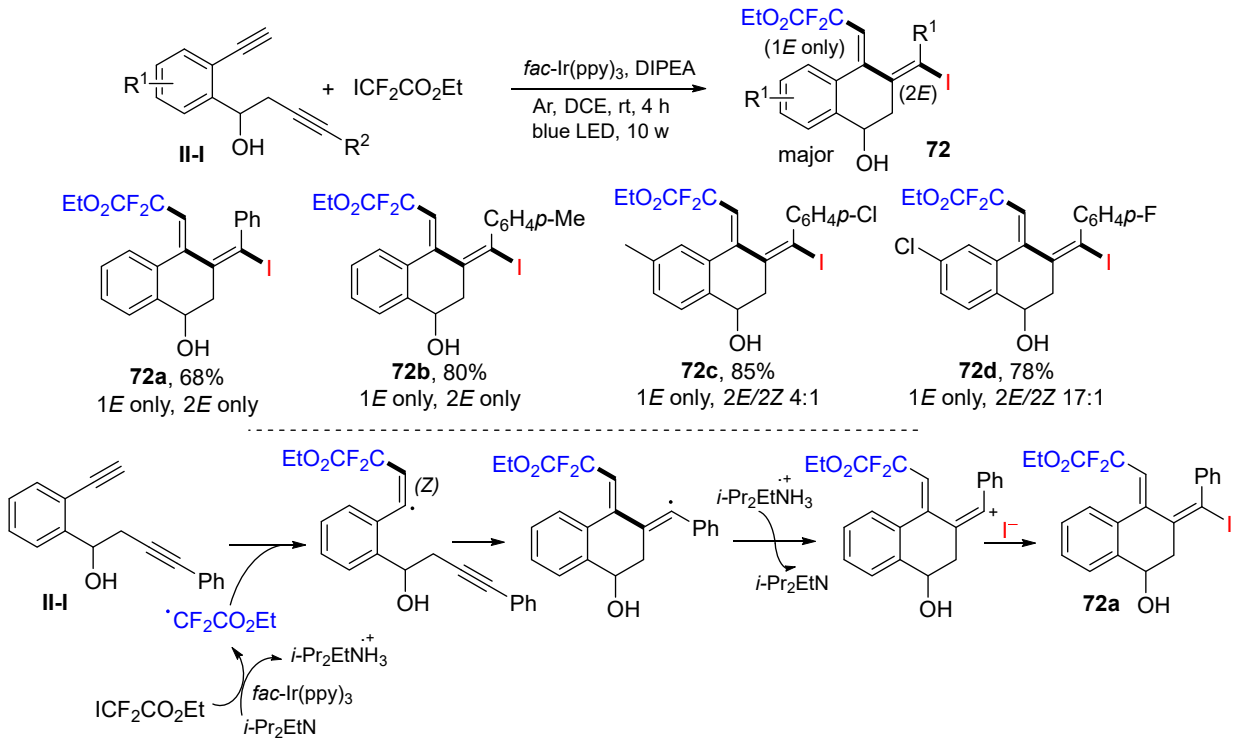
Using dicyano-substituted benzene-tethered 1,5-enynes for a visible light-driven radical haloazidative cyclization for the synthesis of holoazido-functionalized indenes was accomplished by the Li group in 2020. The reaction of 1,5-enynes, $TMSN_3$, and *N*-iodo (bromo or chloro) succinimide in DMF under the radiation of LED (380–385 nm) afforded product **71** in moderate-to-good yields (Scheme 69) [82]. The suggested reaction mechanism indicated that the azide radical generated from $TMSN_3$ under the photo conditions adds to the double bond of 1,5-enyne followed by 5-*exo* cyclization and I-atom transfer from NIS to give product **71a**.

Using benzene-tethered 1,7-diynes for the synthesis of iododifluoroacetal tetrahydronaphthalen-1-ols was introduced by the Jiang group in 2021. The reaction of 1,7-diynes and $ICF_2CO_2Et$ under photoredox catalysis with *fac*-Ir(ppy)$_3$ gave difluoromethyl-containing (1*E*,2*E*)-tetrahydronaphthalen-1-ols **72** bearing two exocyclic C=C double bonds as major stereoisomers in good yields (Scheme 70) [83]. A reaction mechanism suggests that the $CF_2CO_2E$ radical derived from $ICF_2CO_2Et$ under the photocatalysis adds to the

terminal alkyne of 1,7-diyne followed by 6-*exo* cyclization, SET of DIPEA to form cation, and nucleophilic addition with iodide anion to give (1*E*,2*E*)-product **72a** as a major isomer.




**Scheme 69.** Synthesis of holoazido-functionalized indenes.

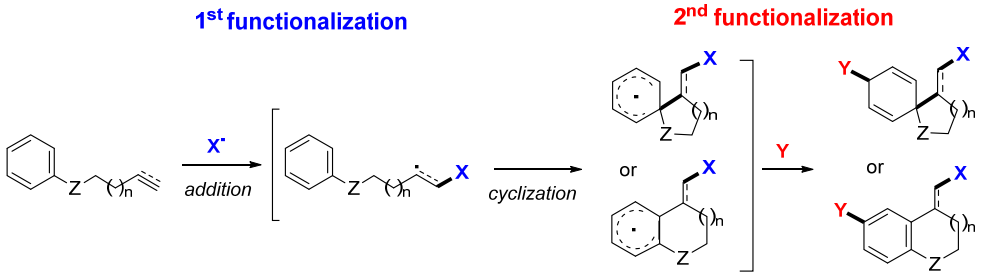



**Scheme 70.** Synthesis of iododifluoroacetal tetrahydronaphthalen-1-ols.

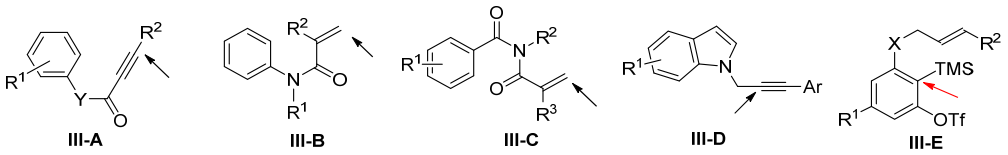
## 4. Reaction of Arene-Terminated Alkenes and Alkynes

Presented in this section are the radical addition and cyclization-initiated difunctionalization reactions of arene-terminated alkenes and alkynes with a reaction sequence shown in Scheme 71. For the class of substrates shown in Scheme 72, the initial radical addition happens at the alkene or alkyne groups instead of the arene. Sequential radical cyclization

leads to the formation of spiro- or fused-ring compounds. The only exception is the reaction of substrate **III-E**. The radical is added to the benzyne ring (via the benzyne intermediate). Among the general substrates, the reactions of alkynes **III-A** (arylpropiolamides if Y is NR) for making spiro compounds are much more popular than those of substrates **III-B** to **III-E** for making fused cyclic products.

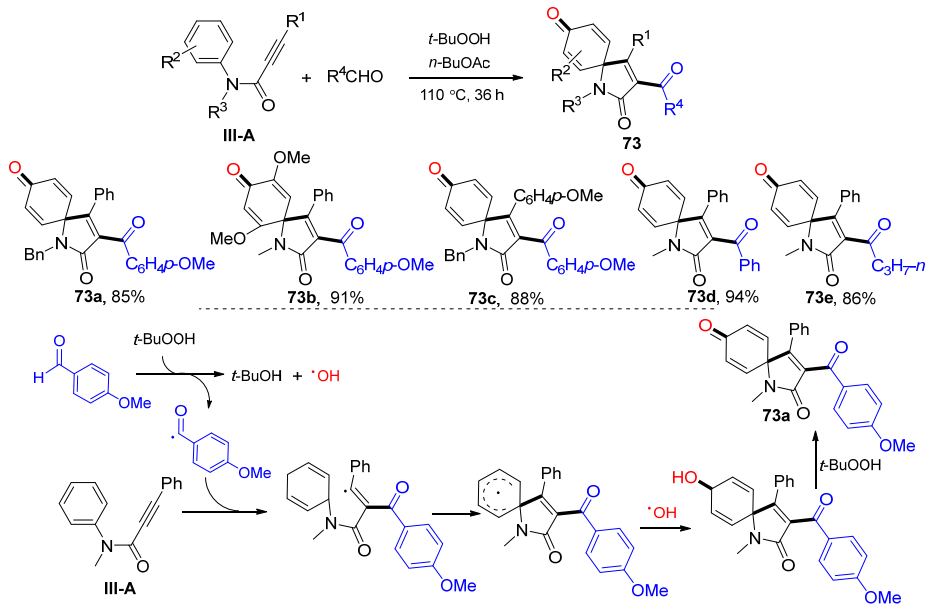



**Scheme 71.** General reaction scheme for the difunctionalization of arene-terminated alkenes and alkynes.

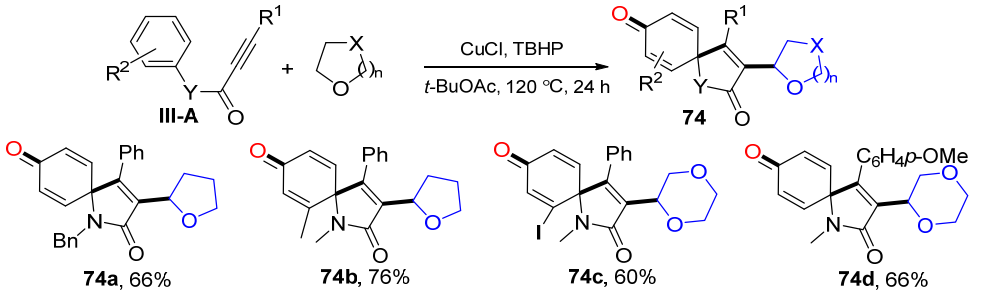



**Scheme 72.** Aryl-terminated alkenes and alkynes with the pointed position for the initial radical addition.

There are several reports on the reaction of arylpropiolamides for the synthesis of 3-functionalized azaspiro[4,5]trienones. In 2014, Li and co-workers reported a radical spirocyclization reaction of arylpropiolamides for the synthesis of 3-acylated azaspiro[4,5]trienones. The reaction of alkynyl amides and aldehydes in the presence of TBHP gave product **73** in good-to-excellent yields (Scheme 73) [84]. The reaction mechanism suggests that the carbonyl radical generated from aldehyde adds to alkyne followed by *ipso*-carbocyclization, coupling with OH radical and oxidation of OH group to give 3-acylspiro[4,5]trienone **73a**. In 2014, Li's group also reported a Cu-catalyzed radical spirocyclization of aryl alkynyl amides for the synthesis of azaspiro[4,5]trienones. The reaction of arylpropiolamides and cyclic ethers in *t*-BuOAc under the catalysis of $Cu^{II}$ and TBHP gave product **74** in good yields (Scheme 74) [85].

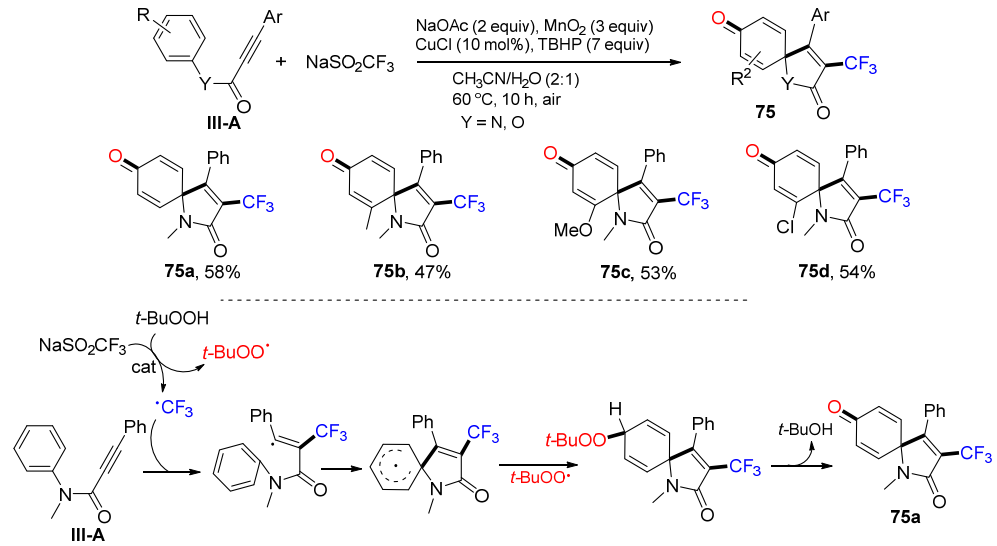



**Scheme 73.** Synthesis of 3-acyl azaspiro[4,5]trienones.




**Scheme 74.** Synthesis of substituted azaspiro[4,5]trienones.

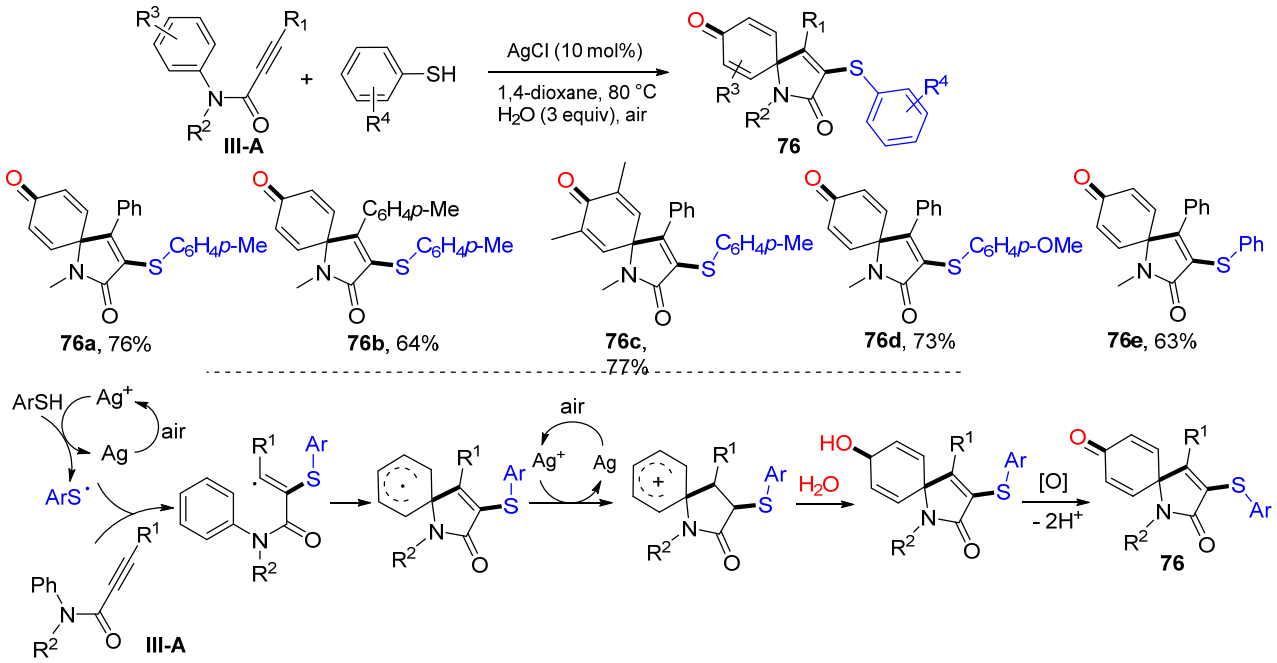
A Cu-catalyzed radical spirocyclization of arylpropiolamides for the synthesis of 3-triflouromrthylated azaspiro[4,5]trienones was reported by the Liang group in 2015. The reaction of alkynyl amides and $NaSO_2CF_3$ (Langlois' reagent) in $CH_3CN$ in the presence of TBHP, $MnO_2$ and CuCl gave product **75** in good-to-excellent yields (Scheme 75) [86]. The reaction mechanism suggests that the $CF_3$ radical derived from the Langlois' reagent adds to the C≡C triple bond followed by *ipso*-carbocyclization, coupling with the *t*-BuOO radical, and elimination of *t*-BuOH to give product **75a**.



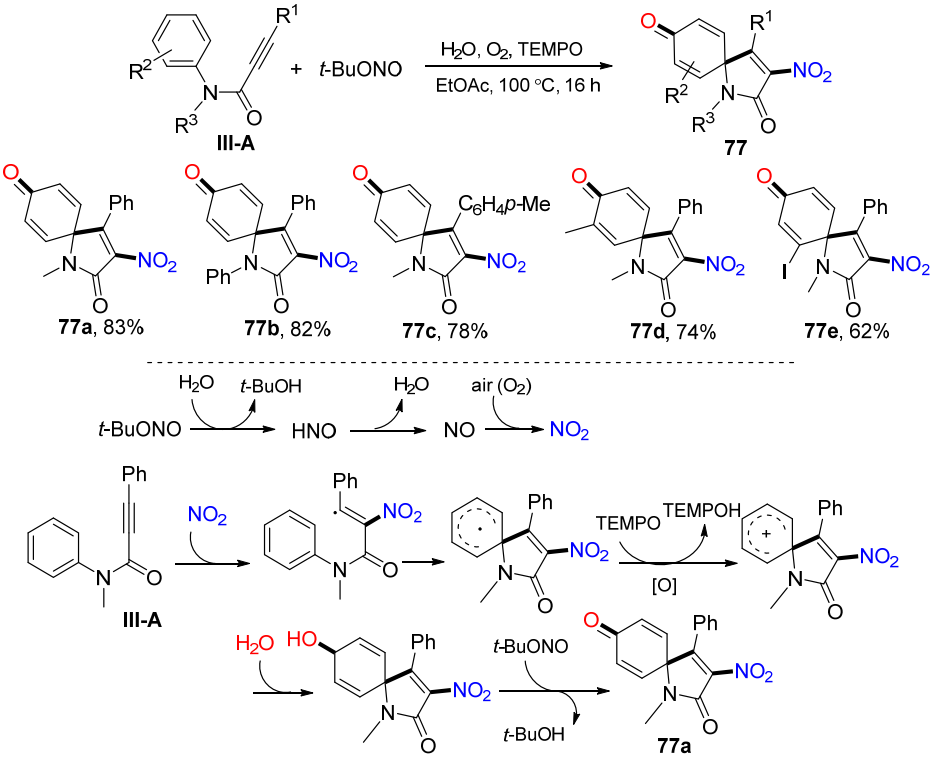

**Scheme 75.** Synthesis of 3-trifluoromethyl azaspiro[4,5]trienones.

In 2015, the Wang group introduced an Ag-catalyzed radical spirocyclization of arylpropiolamides for the construction of 3-arylthiolated azaspiro[4,5]trienones. The reaction of alkynyl amides, thiophenols and $H_2O$ in 1,4-dioxane under the catalysis $Ag^I$ gave product **76** in moderate-to-good yields (Scheme 76) [87]. A proposed reaction mechanism suggests that the thiyl radical produced from thiophenol adds to the carbon triple bond of arylpropiolamides followed by the *ipso*-carboncyclization, SET to form carbocation, nucleophilic addition of $H_2O$, and oxidization of OH to give product **76**.

A TEMPO-mediated radical nitrative spirocyclization of arylpropiolamides for the preparation of 2-nitrated azaspiro[4,5]trienones was introduced by Li's group in 2015. The reaction was carried out using arene-terminaled 1,5-enynes and *t*-BuONO in EtOAc in the presence of $O_2$ and TEMPO to give nitrated spiro compound **77** in moderate-to-good yields (Scheme 77) [88]. A reaction mechanism suggests that $NO_2$ generated from the oxidization of NO adds to the carbon triple bond of arylpropiolamide followed by *ipso*-carbocyclization, TEMPO oxidation to form cation, nucleophilic addition of $H_2O$, and oxidization to give product **77a**.

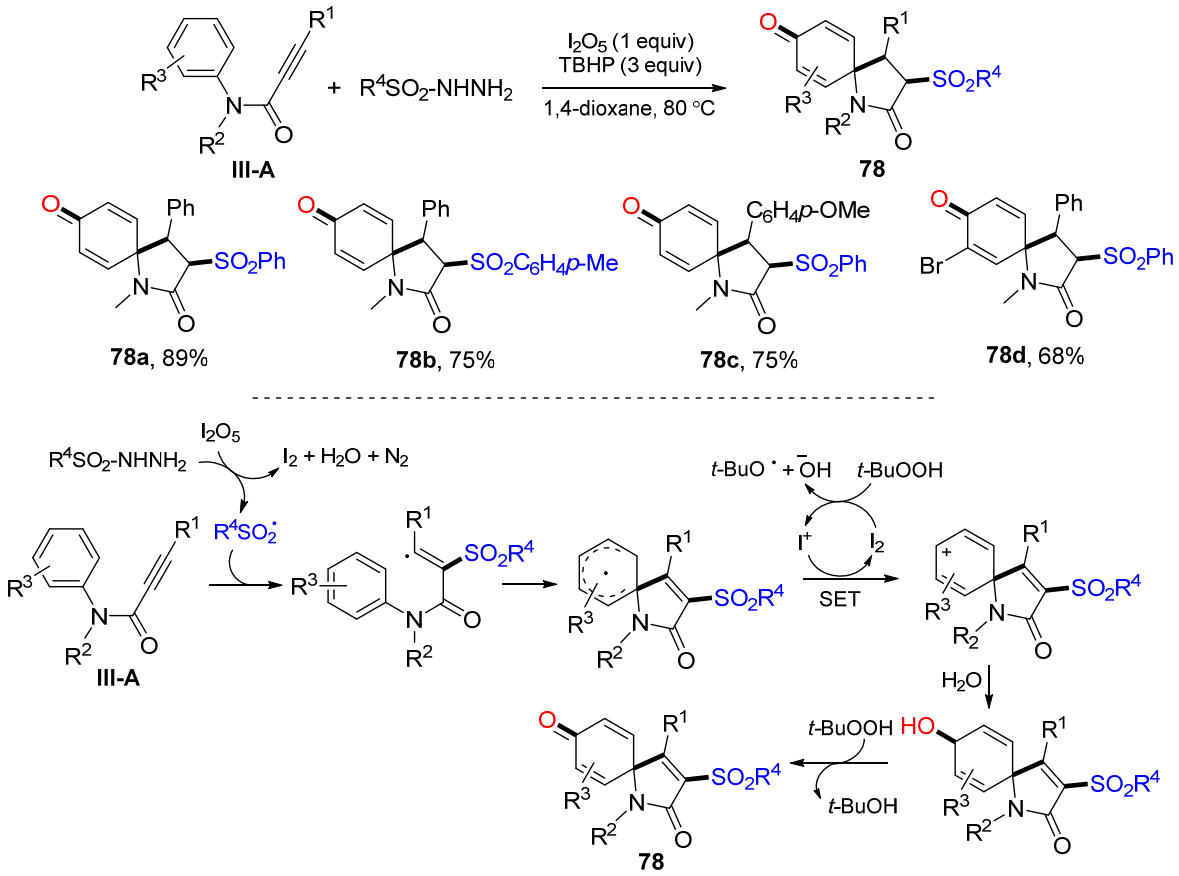



**Scheme 76.** Synthesis of 3-arylthiolated azaspiro[4,5]trienones.



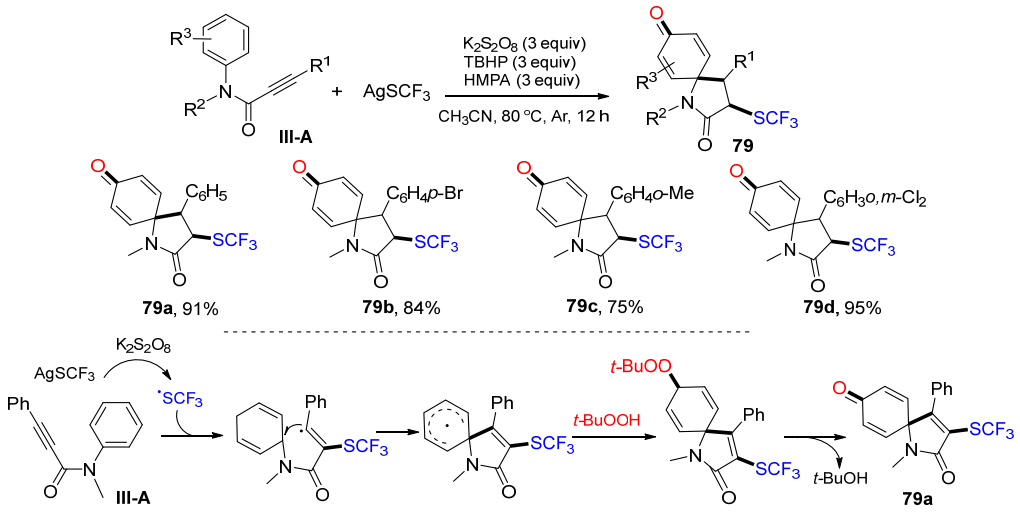

**Scheme 77.** Synthesis of 3-nitralated azaspiro[4,5]trienones.

In 2015, Wang and co-workers developed an oxidative radical spirocyclization reaction of arylpropiolamides for the preparation of 3-sulfonated azaspiro[4,5]trienones. The reaction of arylpropiolamides and sulfonylhydrazide in the presence of TBHP and $I_2O_5$ afforded product **78** in moderate-to-good yields (Scheme 78) [89]. The reaction mechanism suggests that the sulfonyl radical derived from sulfonylhydrazide adds to the carbon triple bond of amides followed by *ipso*-cyclization, SET to form cyclohexadienyl cation, nucleophilic addition of $H_2O$, and finally oxidation with TBHP to give product **78**.



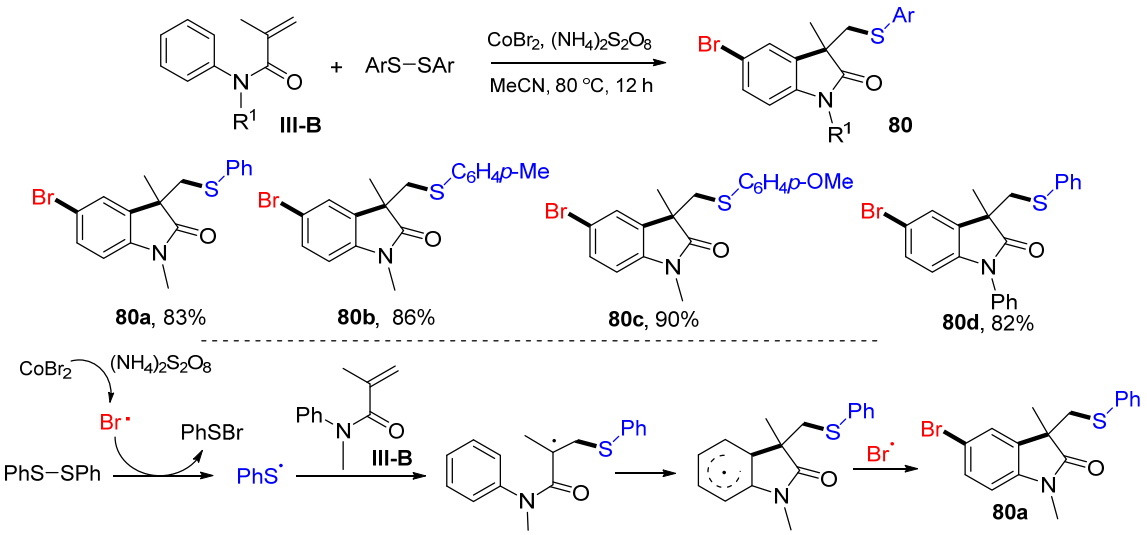

**Scheme 78.** Synthesis of 3-sulfonated azaspiro[4,5]trienones.

A new method for radical spirocyclization of arylpropiolamides to synthesize 3-sulfonated azaspiro[4,5]trienones was reported by Liu's group in 2016. The reaction of amides and $AgSCF_3$ in $CH_3CN$ in the presence of $K_2S_2O_8$ and TBHP gave product **79** in excellent yields (Scheme 79) [90]. A proposed reaction mechanism suggests that the $CF_3S$ radical derived from $AgSCF_3$ adds to the carbon double bond of amides, followed by *ipso*-carbocyclization, coupling with *t*-butylperoxy radical, and elimination of *t*-BuOH to give product **79a**.




**Scheme 79.** Synthesis of $SCF_3$-substituted azaspiro[4,5]trienones.

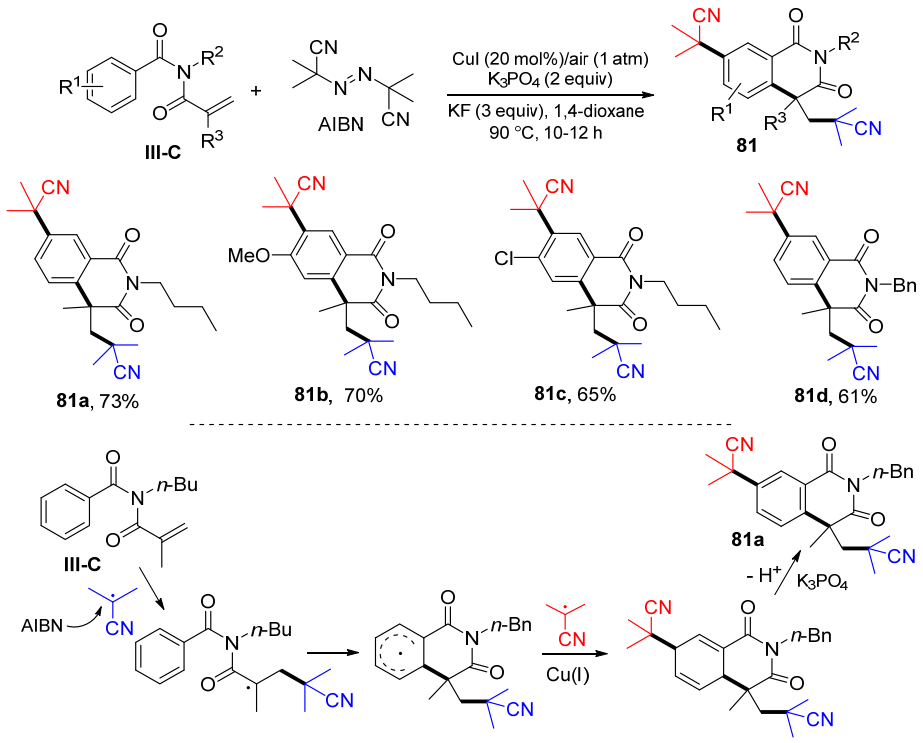
Other than the reactions of arylpropiolamides for making the spiro compounds described above, the reactions of *N*-phenylacrylamides have also been developed for making fused-cyclic products. In 2022, Zhang and co-workers reported a Co-promoted reaction for the synthesis of bromoarylthiolated heterocyclic compounds. The reaction of *N*-arylacrylamides and disulfides in $CH_3CN$ in the presence of $CoBr_2$ and $(NH_4)_2S_2O_8$ gave functionalized product **80** in good-to-excellent yields (Scheme 80) [91]. The reaction mechanism suggests that bromine and PhS radicals for the difunctionalization are generated from the reaction of $CoBr_2$ and PhSSPh. The PhS radical adds to the terminal carbon of the double bond of amides, followed by cyclization and bromo radical coupling to give product **80a**.



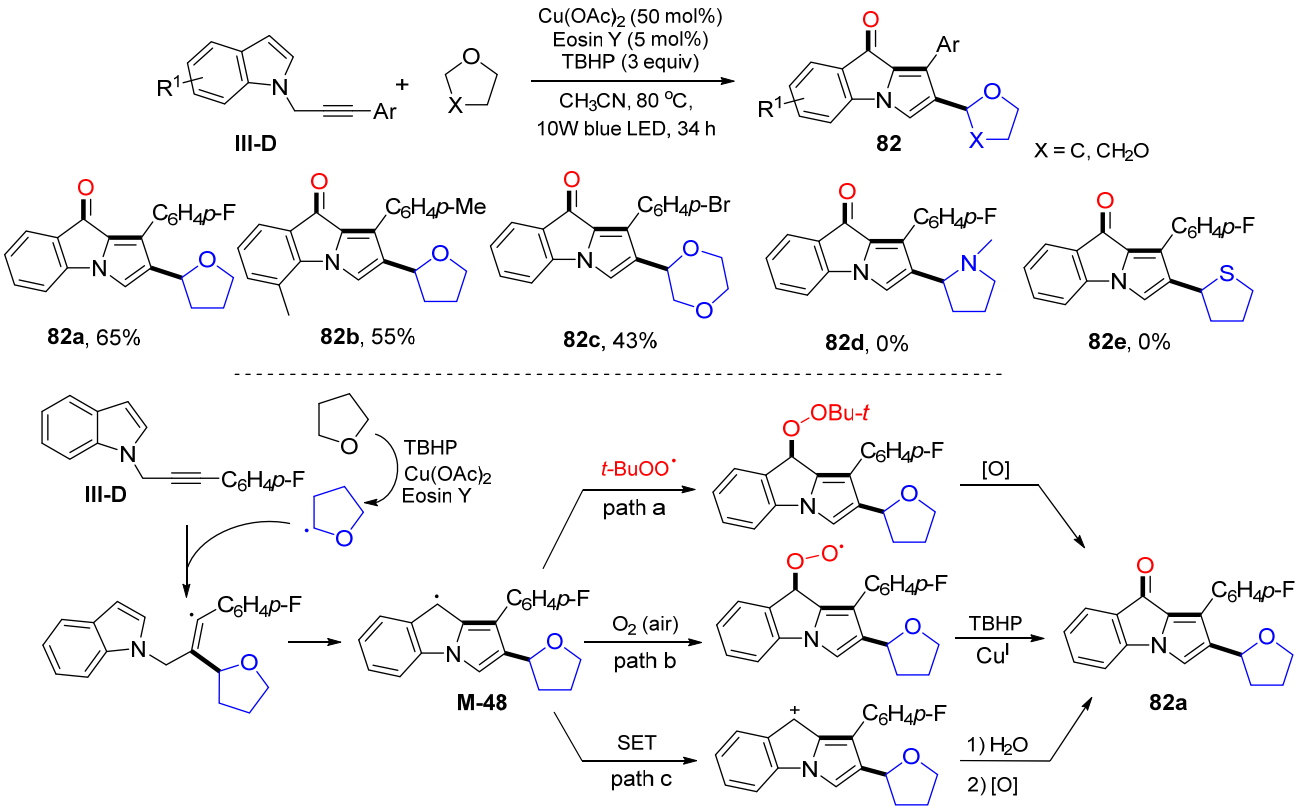

**Scheme 80.** Preparation of cyclopentanes.

The reaction of methacryloyl benzamides could result in six-membered ring-fused products. This work was reported by Tang, Chen and their co-workers in 2016 in the development of a Cu-catalyzed radical reaction for the synthesis of dicyanoisoproylated isoquinolinediones. The reaction of methacryloyl benzamides and AIBN in dioxane in the presence of CuI, KF, and $K_3PO_4$ gave product **81** in good-to-excellent yields (Scheme 81) [92]. The reaction mechanism suggests that homolytic cleavage of AIBN gives two $CNMe_2C$ radicals. One of them adds to the carbon double bond of amides, followed by 6-*exo* cyclization to the benzene ring, selectively trapping the second $CNMe_2C$ radical under the assistance of CuI, and final step aromatization to give isoquinoline-1,3(2*H*,4*H*)-dione **81a**.

The reaction of *N*-propargylindoles could result in the formation of products with a core of 9*H*-pyrrolo[1,2-*a*]indol-9-one. In 2022, Du and coworkers developed photoredox radical cyclization of *N*-propargylindoles for the synthesis of 2-substituted 9*H*-pyrrolo-[1,2-*a*]indol-9-ones. The photo reaction of *N*-propargylindoles and cyclic ethers in MeCN at 80 °C in the presence TBHP and dual catalysts $Cu(OAc)_2$ and Eosin Y give product **82** in moderate yields (Scheme 82) [93]. The proposed mechanism suggests that a THF radical, generated from the reaction of THF with TBHP and the catalysts, adds to the carbon triple bonds of *N*-propargylindoles followed by 5-*exo* cyclization to give intermediate **M-48**. Intermediate **M-48** could have three paths to give product **82a**, (1) **M-48** couples with *t*-BuOO radical and then oxidation; (2) **M-48** traps $O_2$ then reacts with TBHP and CuI catalyst; (3) **M-48** oxidized to cation through SET process and then oxidized OH to C=O.



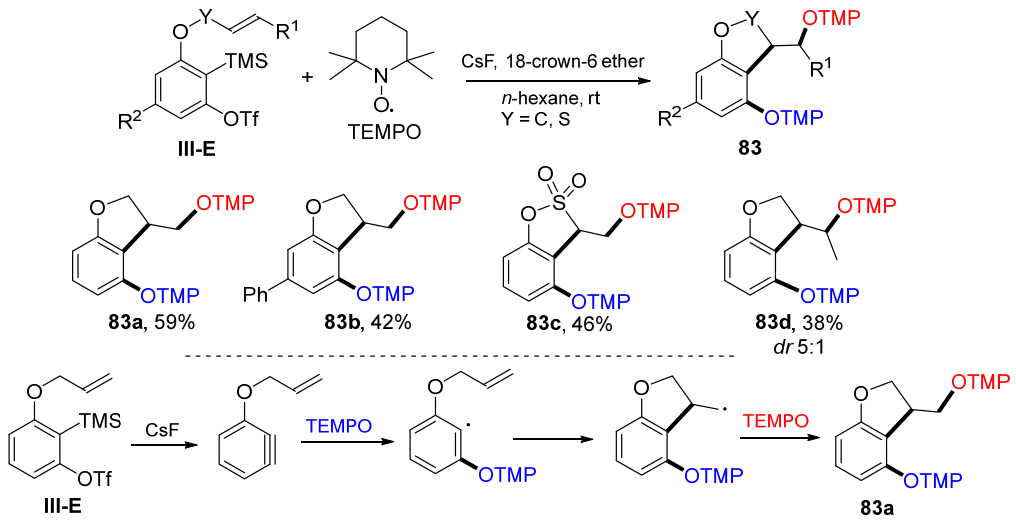

**Scheme 81.** Synthesis of dicyanoisoproylated isoquinolinediones.




**Scheme 82.** Synthesis of 2-substituted 9*H*-pyrrolo[1,2-*a*]indol-9-ones.

Other than the addition of an initial radical to the alkene or alkyne group on the side chain presented in previous cases, a radical could add to benzene if the ring is converted to a benzyne. In 2021, the Studer group reported such a reaction in the synthesis of substituted

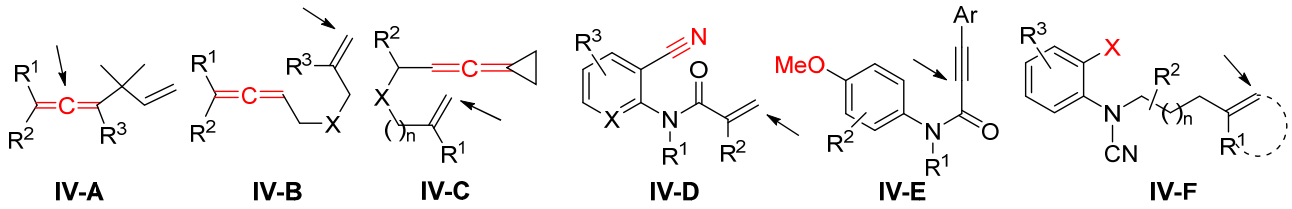
five-membered heterocycles. The reaction of arenes bearing 1,2-TMS and OTs groups with TEMPO in the presence of CsF and 18-crown-6 ether gave product **83** in moderate yields (Scheme 83) [94]. A proposed reaction mechanism suggests that arene is first converted to benzyne with the treatment of CsF and then reacts with TMPO radical followed by *5-exo* cyclization and coupling with the second TEMPO to give product **83a**.




**Scheme 83.** Synthesis of diTEMPO-substituted benzofuran and analogs heterocycles.

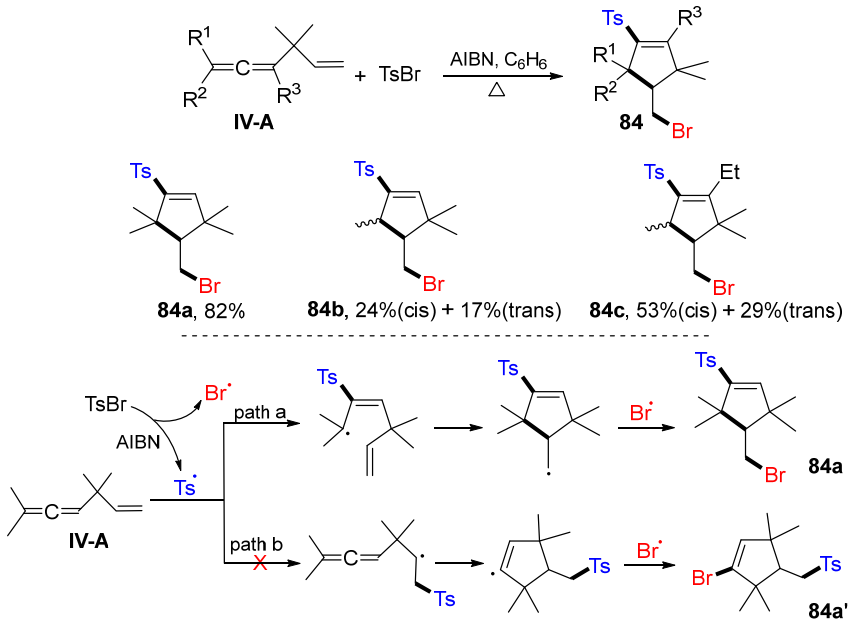
## 5. Reaction of Other Alkene and Alkyne Compounds

Presented in this section are the radical addition-initiated difunctionalizations of alkene- and alkyne-related compounds that cannot be fit in the previous sessions in terms of substrates or reaction mechanism. As shown in Scheme 84, substrates **IV-A** to **IV-C** are 1,n-eneallenes; the cyano group in enenitrile **IV-D** is responsible for the second functionalization; arene-terminated enyne **IV-E** has a preexisting MeO group on the benzene ring which will be converted to a new functional group during the reaction; arene-terminated **IV-F** has a leaving group X which will be displaced by a new group at the step of second functionalization. Since the reactions of these substrates are not the major focus of this paper, only selected examples are highlighted.



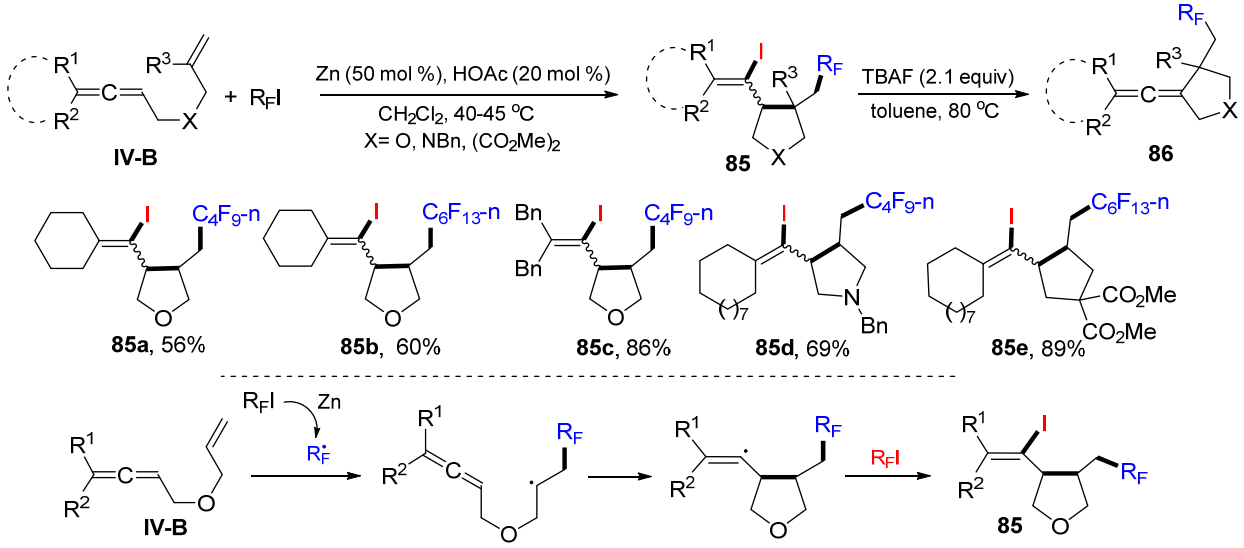

**Scheme 84.** Other alkene and alkyne compounds with the pointed position for the initial radical addition.

An early example of radical difunctionalization of eneallenes was reported by the Hatem group in 1995 for the synthesis of bromo- and tosyl-functionalized cyclopantenes. The reaction of eneallenes and tosyl bromide in benzene using AIBN as a radical initiator gave product **84** (Scheme 85) [95]. A proposed reaction mechanism suggests that the tosyl radical generated from TsBr adds the central carbon of allene, followed by 5-*exo* cyclization and coupling with bromine radical, to give product **84a**. Addition of tosyl radical to alkene instead of allene could be possible. However, since no expected product **84a′** was isolated, path b is less favorable than path a.




**Scheme 85.** Preparation of tosyl-substituted cyclopentanes.

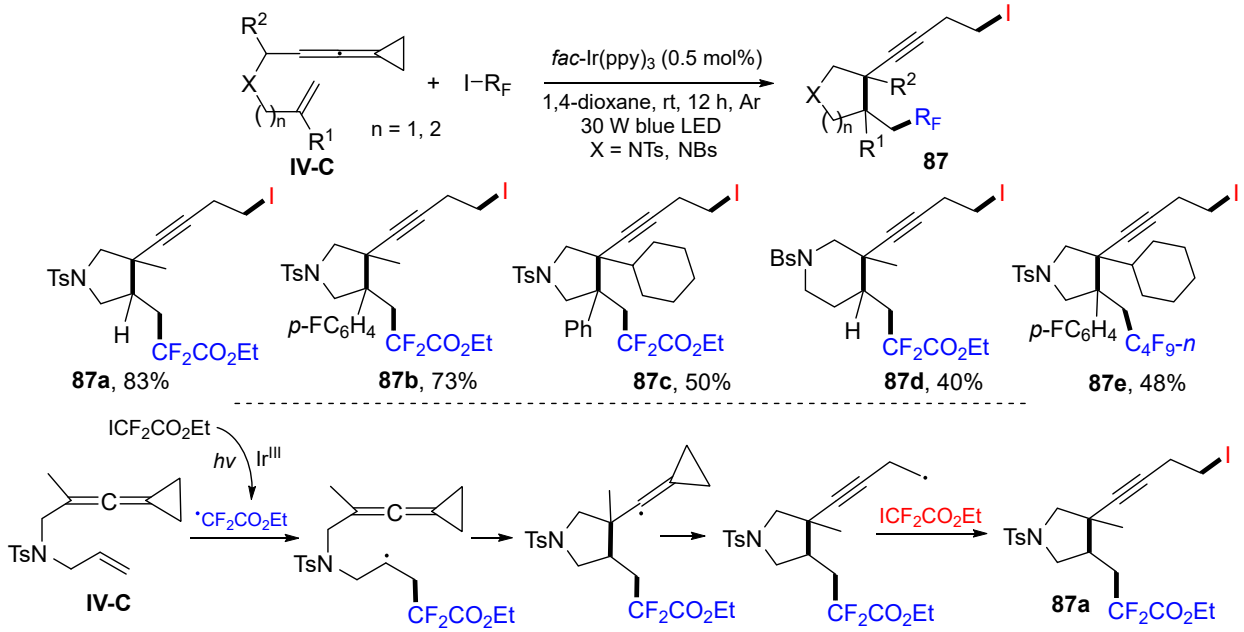
A later example for the reaction of eneallenes was reported by the Ma group in 2012. It is a Zn-catalyzed radical cyclization for the synthesis of iodoperfluoroalkylated five-membered rings. The reaction of eneallenes and $R_FI$ in $CH_2Cl_2$ in the presence of Zn powder and HOAc gave product **85** in moderate-to-good yields (Scheme 86) [96]. It is worth mentioning that the two diastereomers of the product **85** could be converted into 3-(1-enylidene)heterocyclopentanes **86** through the TBAF-promoted dehydroiodination reaction. A mechanism for the racial reaction suggests that the perfluoroalkyl radical generated from $R_FI$ adds to the alkene carbon of eneallenes followed by 5-*exo* cyclization and coupling with the iodine radical from $R_FI$ to give product **85**.




**Scheme 86.** Synthesis of iodoperfluoroalkyl substituted five-membered rings.

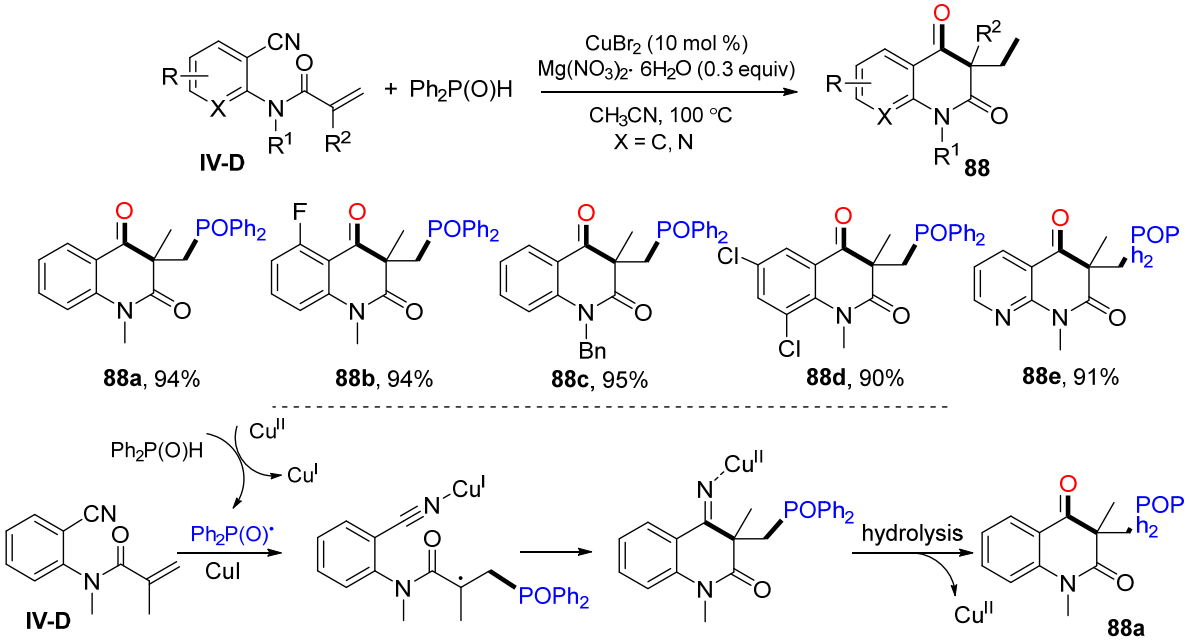
A more recent example of eneallene reaction was reported by the Shi group in 2021. It is a visible light-induced radical reaction of ene-vinylidenecyclopropanes (ene-VDCP) for the synthesis of iodoperfluoro-alkylated *N*-heterocycles. The reaction of ene-VDCP, $ICF_2CO_2Et$ or $ICF_2CF_2CF_2CF_3$ in 1,4-dioxane under the blue LED photocatalysis with *fac*-Ir(ppy)$_3$ gave **87** in good yields and stereoselectivity (Scheme 87) [97]. The reaction mechanism suggests that the $CF_2CO_2Et$ radical, generated from $ICF_2CO_2Et$ under the photolysis, adds to the

terminal carbon of alkene followed by 5-*exo* cyclization, cyclopropane ring-opening, and extraction of iodine atom from $ICF_2CO_2Et$ to give the final product **87a**.



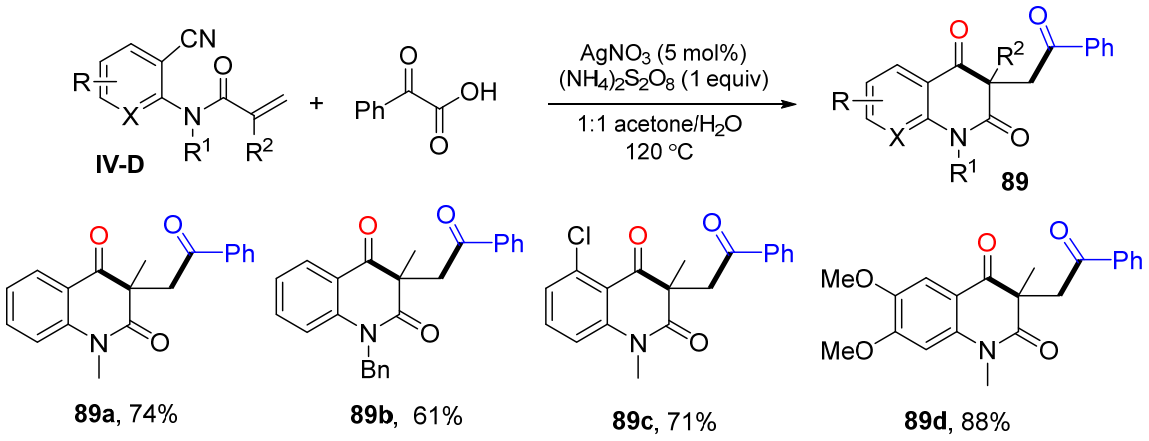

**Scheme 87.** Synthesis of iodoperfluoroalkylated *N*-heterocycles.

An interesting example of using the cyano group as a radical acceptor for the difunctionalization reaction was reported by the Li group in 2015. It is a Cu-catalyzed radical cyclization of arene-tethered enenitrile for the synthesis of substituted quinoline-2,4(1*H*,3*H*)-diones. The reaction of *o*-cyanoarylacrylamide and diphenyl-phosphine oxide in $CH_3CN$ in the presence of $CuBr_2$ and $Mg(NO_3)_2{\cdot}6H_2O$ gave phosphinylated quinoline-2,4(1*H*,3*H*)-diones **88** in good-to-excellent yields (Scheme 88) [98]. The reaction mechanism suggests that the $Ph_2P(O)$ radical derived from $Ph_2P(O)H$ under $Cu^{II}$ catalysis adds to the C=C double bond of amide followed by 6-*exo* cyclization to the CN group and hydrolysis with $H_2O$ to give final product **88a**.



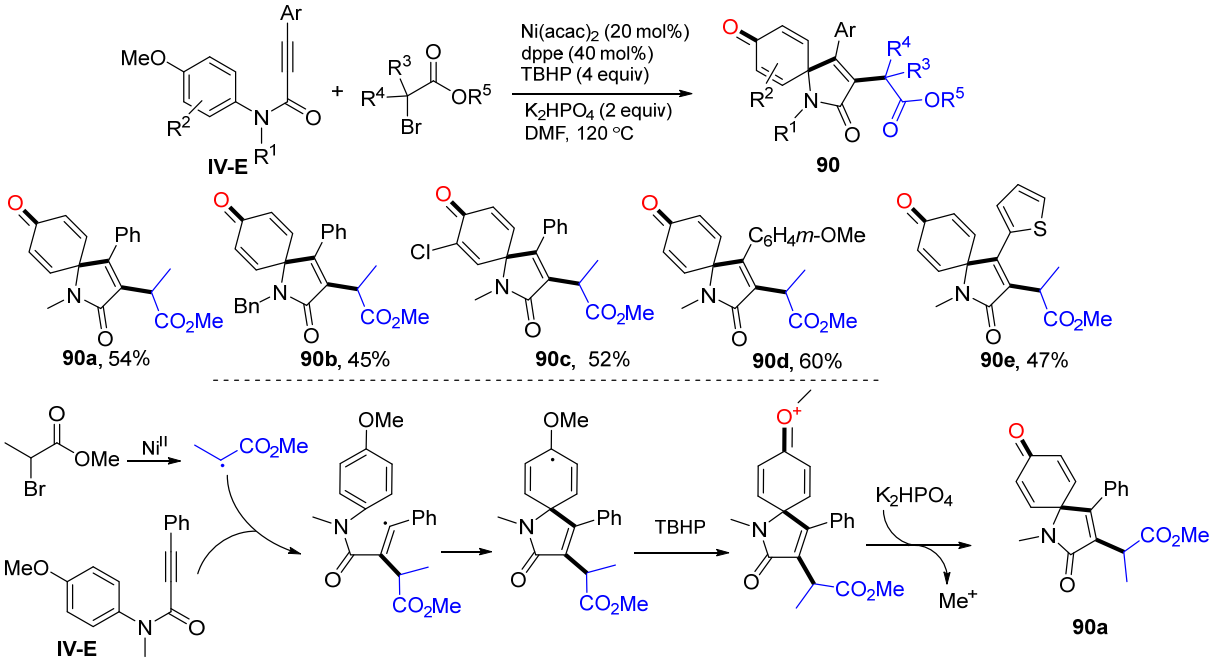

**Scheme 88.** Synthesis of phosphinylated quinoline-2,4(1*H*,3*H*)-diones.

In 2016, the Li group also reported a decarboxylative radical reaction of *o*-cyanoarylacrylamides for the preparation of carbonylated quinoline-2,4(1*H*,3*H*)-diones. The reaction of *o*-cyanoarylacrylamide and α-keto acids in acetone-$H_2O$ at 120 °C under the catalysis of $AgNO_3$ and $(NH_4)_2S_2O_8$ gave product **89** in good yields (Scheme 89) [99].



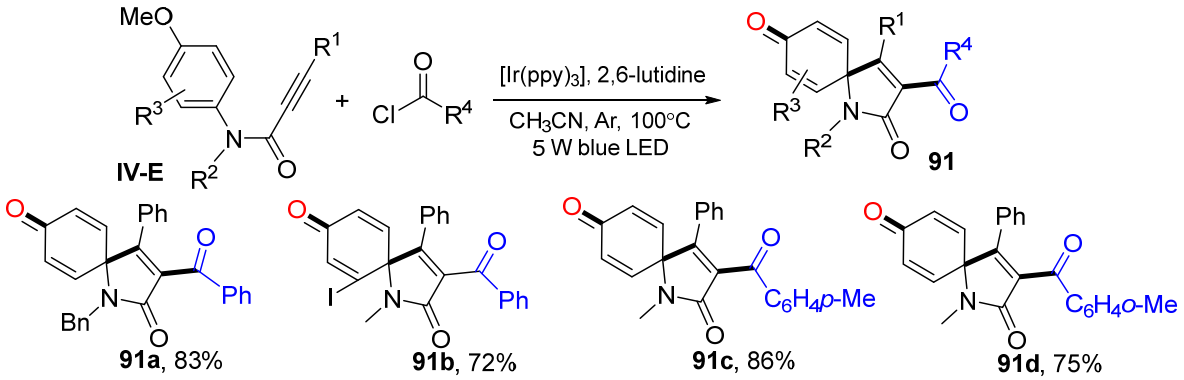

**Scheme 89.** Synthesis of phosphinylated quinoline-2,4(1*H*,3*H*)-diones.

Having a MeO group on the benzene ring is a useful synthetic approach to assist radical cyclization and for dearomatization. In 2017, Li and co-workers developed a Ni-promoted radical spirocyclization of *N*-(*p*-methoxyaryl)propiolamides for the synthesis of 3-substituted azaspiro[4,5]trienones. The reaction of amides and α-bromo esters in DMF in the presence of $Ni(acac)_2$, 1,2-bis(diphenylphosphino)ethane (dppe), TBHP and $K_2HPO_4$ gave product **90** in moderate yields (Scheme 90) [100]. A proposed mechanism suggests that alkyl radical derived from α-bromo esters adds to the triple bond of amide followed by *ipso*-carbocyclization, oxidation with TBHP to form oxonium cation, and a final step of demethylation to give product **90a**. The MeO group on the aromatic ring is critical for the radical cyclization and formation of the carbonyl group through diaromatization. The product generated from this method is similar to that presented in Scheme 73, in which there is no preexisting MeO group on the benzene ring.



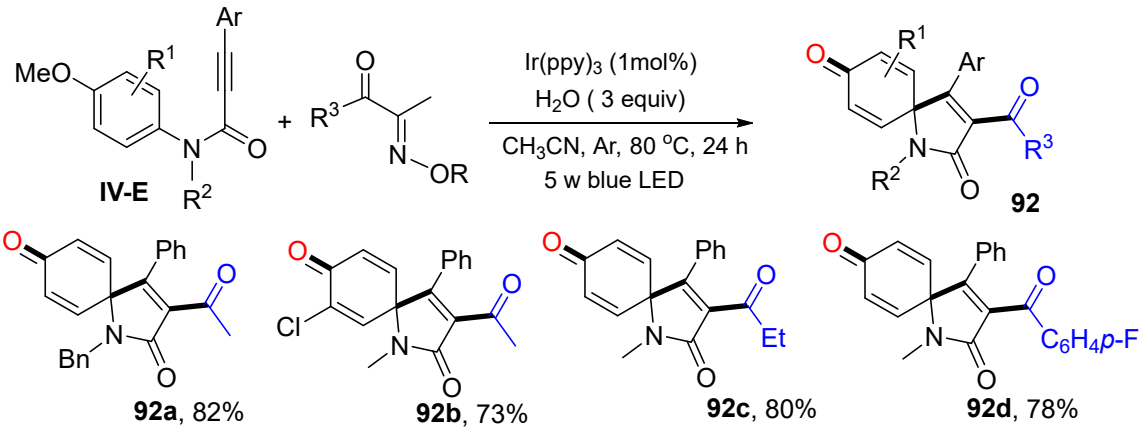

**Scheme 90.** Synthesis of 3-alkyl azaspiro[4,5]trienones.

Using a similar synthetic strategy and the alkyne substrate, in 2018, Liu and co-workers reported a visible light-mediated radical spirocyclization of *N*-(*p*-methoxyaryl)-propiolamides for the synthesis of 3-acylspiroc (Scheme 91) [101]. The photo reaction of alkynes and benzoyl chloride in $CH_3CN$ in the presence of $Ir^{III}(ppy)_3$ and 2,6-lutidine gave product **91** in good-to-excellent yields.



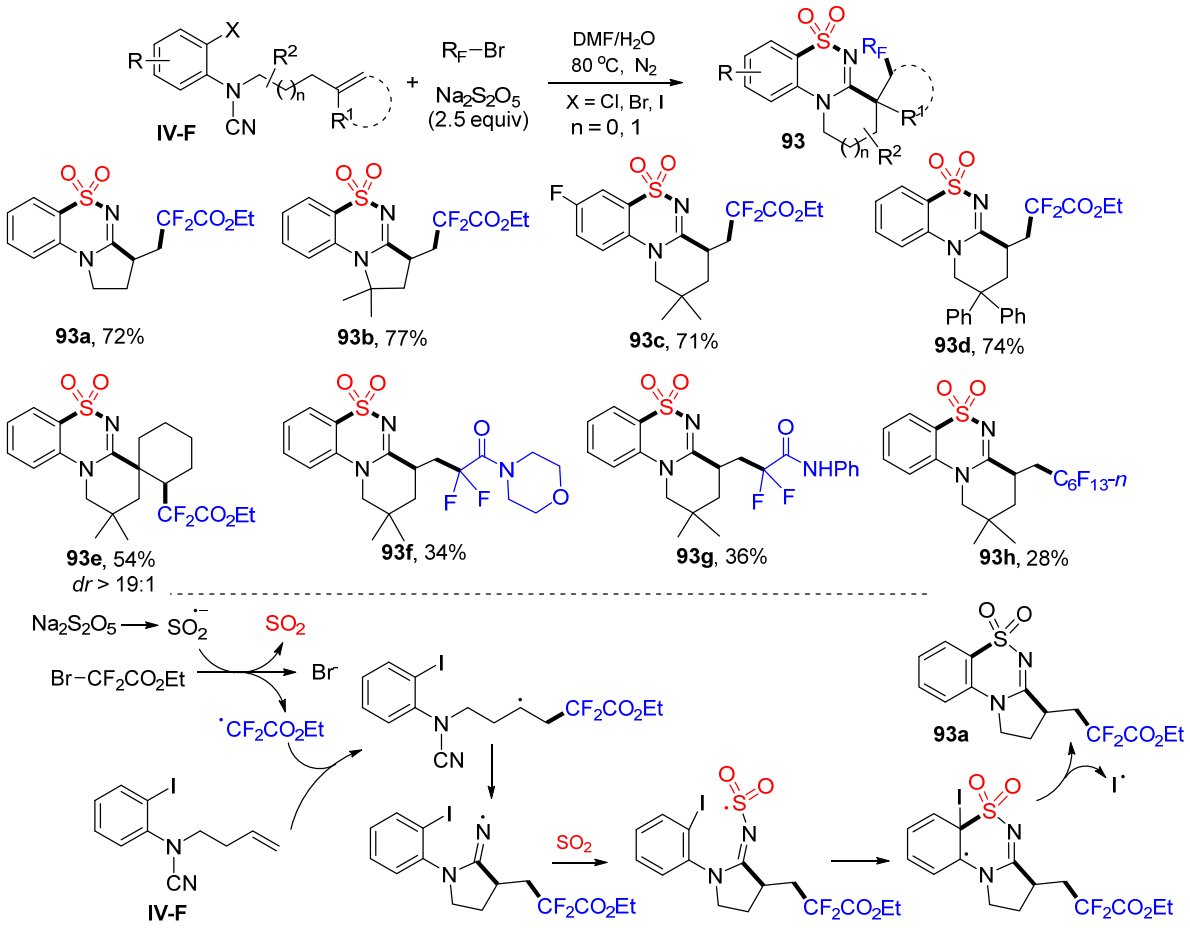

**Scheme 91.** Synthesis of 3-acyl azaspiro[4,5]trienones.

Scheme 92 shows another example of the reaction of *N*-(*p*-methoxyaryl)-propiolamides developed by Liu's group also for the synthesis of 3-acylspiro[4,5]trienones [102].The photoredox reaction of alkynes, acyl oxime esters, $H_2O$ under the catalysis of $Ir(ppy)_3$ gave product **92** in good yields.




**Scheme 92.** Synthesis of 3-acyl azaspiro[4,5]trienones.

The last example in this section is the reaction of arene-terminated alkene, which has a leaving group X on the aromatic ring. Liao and coworkers employed this substrate in the synthesis of functionalized benzosultams. The reaction of *N*-(2-haloaryl)cyanamide, bromodifluoroalkyl reagents and $Na_2S_2O_5$ in DMF and $H_2O$ at 80 °C afforded product **93** in good yields (Scheme 93) [103]. A proposed reaction mechanism suggests that the $CF_2CO_2Et$ radical derived from $BrCF_2CO_2Et$ $SO_2$ adds to the carbon double bond of amide followed through 5-*exo* cyclization to the CN group, capture of $SO_2$ (generated from $Na_2S_2O_5$) to form sulfonyl radicals, cyclization to the benzene ring at the carbon with iodine, and a last step of deiodo aromatization to give product **93a**.




**Scheme 93.** Synthesis of functionalized benzosultams.

## 6. Conclusions

Radical reactions are powerful and versatile synthetic methods for making carbon–carbon and carbon–heteroatom bonds. Designing one-pot and cascade radical transformations to make cyclic ring skeletons are highly efficient and operationally straightforward methods. Summarized in this article are the radical addition followed by cyclization reactions to make difunctionalized cyclic molecules. The second functionalization could be achieved through radical coupling, transition metal-assisted reaction, and nucleophilic or electrophilic substitution reactions, which significantly broaden the scope of difunctionalization reactions. Reactions of substrates such as dienes, diynes, and enynes, as well as of their arene-bridged and terminated analogs, are presented. In addition to conventional radical reactions using radical initiators or under transition metal-catalysis, the recent development of photoredox and electrochemical reactions have enhanced the scope of the radical difunctionalizations. In addition to the difunctionalization of unsaturated carbons such as alkenes and alkynes, we expect to see more development on difunctionalization reactions involving other functional groups, such as CN and $N_3$. We also expect to see more applications in the synthesis of biologically significant molecules and natural products.

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