Review

Recent Advances for the Synthesis of Dihydroquinolin-2(1*H*)-ones *via* Catalytic Annulation of *α,β*-unsaturated *N*-arylamides

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Abstract: 3,4-Dihydroquinolin-2(1*H*)-ones represent a class of valuable bioactive compounds with six-membered nitrogen-containing heterocyclic structures. The development of simple, mild and efficient synthetic methods has been widely concerned by synthetic chemists. In this review, we have summarized a series of different synthetic strategies for the synthesis of dihydroquinoline-2(1*H*)-ones *via* catalytic annulation of *α,β*-unsaturated *N*-arylamides in the past decade, including covering electrophilic cyclization, radical initiated cyclization and photochemical cyclization reactions. Besides, the substrate scope and mechanistic details are also discussed. This paper will provide a useful reference for the development of diverse synthesis methodologies of 3,4-dihydroquinolin-2(1*H*)-ones.

Keywords: 3,4-dihydroquinolin-2(1*H*)-one; *α,β*-unsaturated *N*-arylamides; radical; photochemical; annulation

1. Introduction

3,4-Dihydroquinolin-2(1*H*)-one skeleton is an important nitrogen-containing heterocyclic structural unit, which widely exists in natural products, drugs and other bioactive compounds [1-6]. In the past few years, functionalized 3,4-dihydroquinolin-2(1*H*)-ones have been synthesized and applied to antibiotics, anticancer, antiviral and other important drugs. As shown in Figure 1, selected bioactive compounds containing 3,4-dihydroquinoline-2(1*H*)-ones have been listed. For example, (+)-Scandine is an alkaloid compound isolated from the twigs and leaves of Melodinus suaveolens, and has been used in the treatment of atherosclerosis [1]. Research also showed that HIV-1 reverse transcriptase inhibitors **B** could improve antiviral activities against single (K103N) and double (K103N/L100I) mutant viruses [2]. Additionally, (-)-Pinolinone, separated from the roots of boronia pinnata, could strengthen inhibitory effects on Epstein-Barr virus in early antigen (EBV-EA) activation [3]. CYP11B2 (aldosterone synthase) offered possible treatment for breast cancer and the coinstantaneous cardiovascular diseases [4]. Furthermore, Yaequinolones J1, which was extracted from Penicillium sp. FKI-2140, showed toxicity against artemia salina (brine shrimp) [5]. 1-Aryl-3,4-dihydroquinolin-2(1*H*)-one **F** was discovered as a potent norepinephrine reuptake inhibitor [6], and so on. Therefore, the synthesis of 3,4-dihydroquinolin-2(1*H*)-one skeleton compounds will provide more opportunities for the discovery of new bioactive molecules.

The importance of this skeleton compound has stimulated activities of the synthesis community to develop new transformation strategies, which can obtain 3,4-dihydroquinoline-2(1*H*)-one compounds. In the past decades, some new synthetic methods have been continuously developed, such as Pd-catalyzed Heck reduction-cyclization reaction [7], Pd-catalyzed cyclopropane ring expansion [8], Mn-mediated intramolecular cyclization [9], and Rh-mediated Michael-addition (1,4-additions) of the boronic acid to enone [10], and so on [11-14]. Among these, using *α,β*-unsaturated *N*-arylamides as the key substrates *via* different cyclization reactions has been shown as a fast, simple

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and atom economic strategy. Those methodologies include electrophilic cyclization reaction, radical initiated cyclization reaction and photochemical cyclization reaction. This review will focus on the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones by using *α*,*β*-unsaturated *N*-arylamides as the key substrates in the last decade, and we hope this review will serve as a useful reference for organic chemists to discover more novel strategies for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

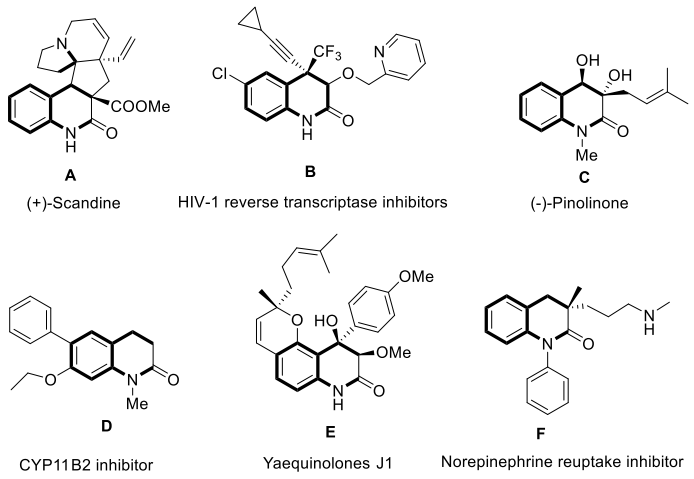

Figure 1. Examples of medicinally active compounds containing 3,4-dihydro-2(1*H*)-quinolinones.

2. Synthesis of 3,4-dihydroquinolin-2(1H)-ones *via* electrophilic cyclization reactions

Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones *via* intramolecular Friedel-Crafts alkylation using *α*,*β*-unsaturated *N*-arylamides as the key substrate has been achieved. Some Brønsted acids, such as H_2SO_4 [15], TsOH [16], CF_3COOH [17], polyphosphoric acid (PPA) [18] and Lewis acid $AlCl_3$ [19], were used for the construction of 3,4-dihydroquinolin-2(1*H*)-ones, in which trifluoroacetic acid (TFA) was the most suitable acid for this reaction (Figure 2).

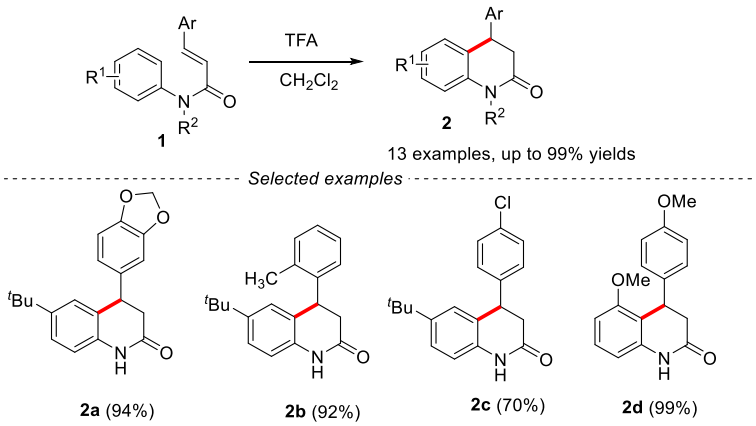

Figure 2. Trifluoroacetic acid-mediated hydroarylation for synthesis of 3,4-dihydroquinolin-2 (1*H*)-ones.

However, the disadvantages of these reactions are the use of excessively strong acids or high temperature, and the limited range of substrates, especially for the synthesis of 3-substituted dihydroquinolin-2(1*H*)-ones. Therefore, it is still necessary to develop new synthesis methods under mild conditions.

In 2017, a mild and effective methodology was developed by Zhang's group for the synthesis of *cis*-4-aryl-3-arylthio-3,4-dihydroquinolin-2(1*H*)-ones *via* electrophilic sulfenylation and cyclization of *N*-arylcinnamamides with *N*-arylthiosuccinimides in the presence of $BF_3{\cdot}OEt_2$ [20]. Except for the $BF_3{\cdot}OEt_2$, BBr_3 was also effective for the reaction. The reaction showed a broad substrate scope. A series of *N*-methyl-*N*-arylcinnamamides were found to be effective in this reaction, and the *cis*-4-aryl-

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3-arylthio-3,4-dihydroquinolin-2(1*H*)-ones **4** were obtained in moderate to excellent yields with high stereoselectivity. *N*-arylcinnamamides **1** having F, Cl, Br, Me, and MeO groups on the phenyl ring were well tolerated in this reaction. An electrophilic cyclization mechanism was proposed as shown in Figure 3. Firstly, the reaction of *N*-thiosuccinimides **3** reacted with $BF_3{\cdot}OEt_2$ to generate the electrophilic thio intermediate **5**. Then, the thio cation **5** was added to the C=C bond of *N*-arylcinnamamides **1** *via* an electrophilic addition process to produce intermediate **6**, which further went through intramolecular cyclization to form intermediate **7**. Finally, product **4** was formed through the release of a proton.

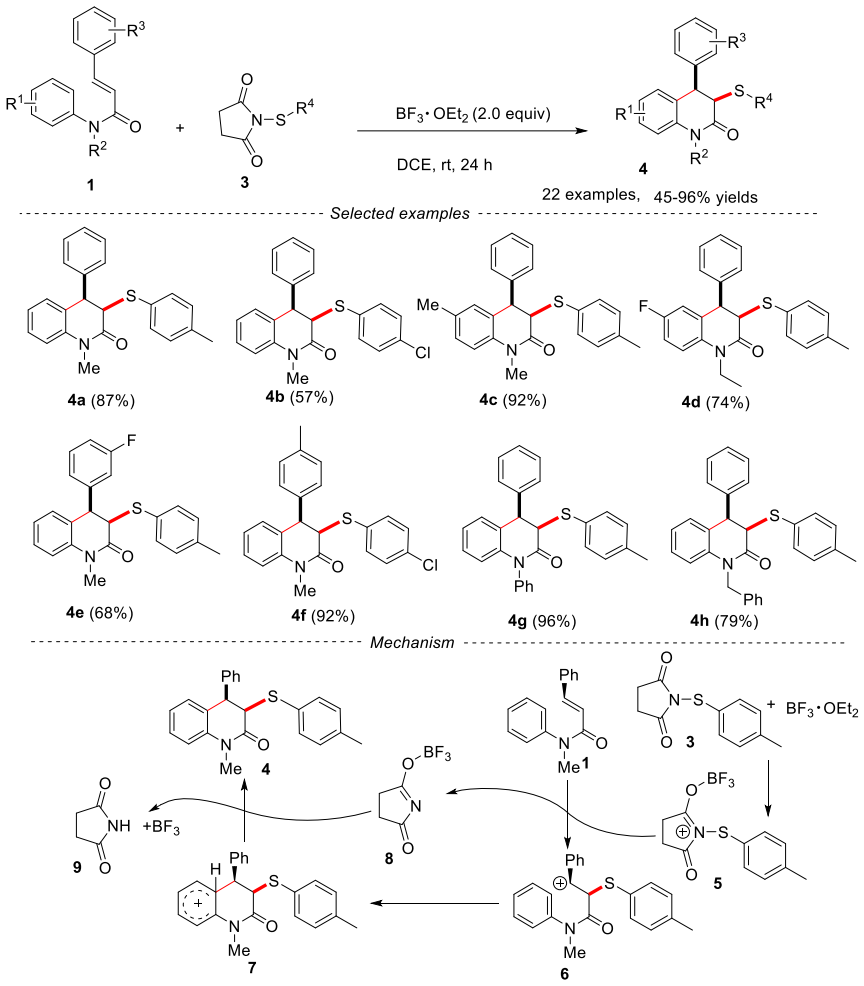

Figure 3. Synthesis of *cis*-4-aryl-3-arylthio-3,4-dihydroquinolin-2(1*H*)-ones *via* electrophilic sulfenylation and cyclization of *N*-arylcinnamamides with *N*-arylthiosuccinimides.

Reducing the emission of waste to the environment and developing green and atomic economy synthesis technologies are the long-term development goals of synthetic chemists. In 2022, the oxone-mediated direct arylhydroxylation of *N*-arylcinnamamides was developed by He's group for the synthesis of hydroxyl-containing 3,4-dihydroquinolin-2-ones [21]. Oxone is a cheap, stable and nontoxic inorganic reagent, which acted as an oxidant for the epoxidation of alkenes and the proton source for the subsequent ring-opening Friedel-Crafts alkylation. This reaction provided an atom-economy strategy for the synthesis of 3-hydroxy-3,4-dihydroquinolin-2-one. The reaction showed a wide functional groups tolerance. The substrates with methyl or *n*-butyl group on the nitrogen atom worked smoothly, providing the desired products in good to excellent yields. *N*-arylcinnamamides bearing an electron-donating substituent gave higher yields under the given conditions. Acrylamide substrates with alkyl substituents on the *β*-position of vinyl group gave the desired products in good yields. However, acrylamide substrates having methyl group on both the *α*- and *β*-position of vinyl

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group afforded a mixture of unidentified products. An epoxidation and subsequent Friedel-Crafts alkylation mechanism was proposed as shown in Figure 4.

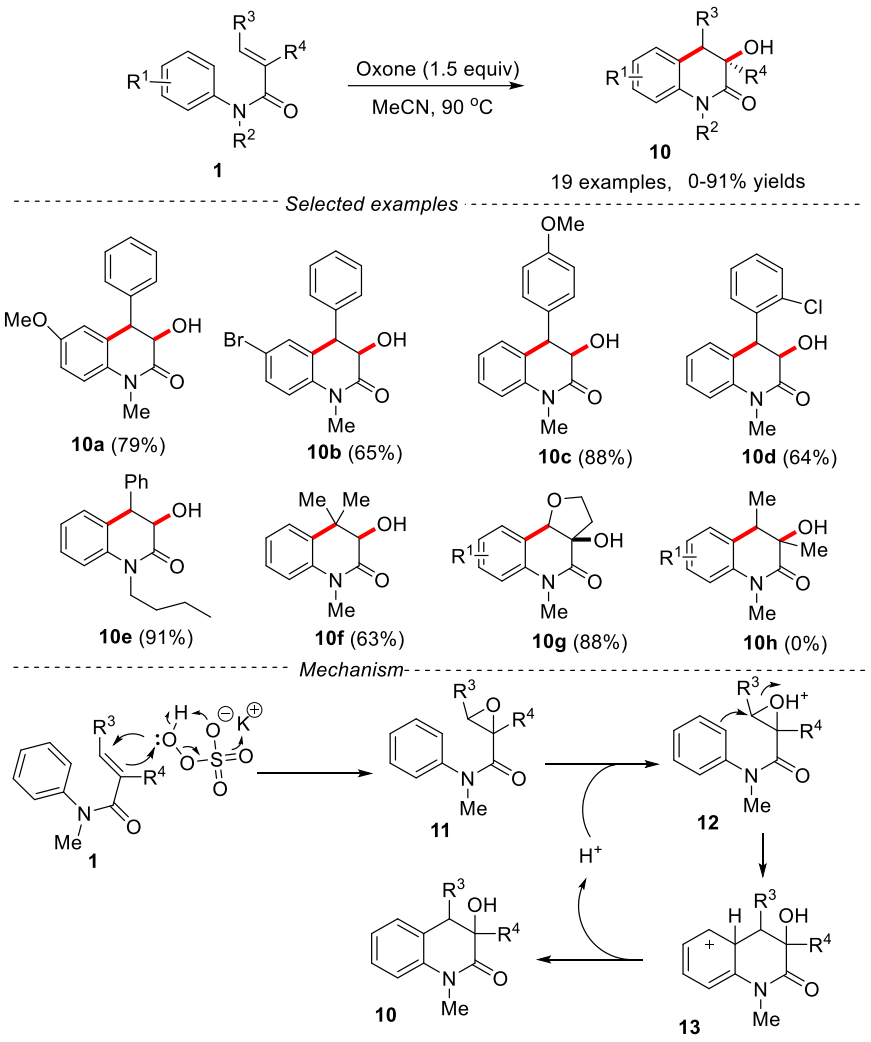

Figure 4. The oxone-mediated direct arylhydroxylation of *N*-arylcinnamamides for the synthesis of hydroxyl-containing 3,4-dihydroquinolin-2-ones.

3. Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones *via* different free radicals initiated cyclization reactions

3.1. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using alkyl radicals.

3.1.1. Carboxylic acids as alkyl radical precursors

Carboxylic acid is an easily obtained chemical raw material, which is widely used in organic synthesis because of its stable nature and easy treatment. More importantly, in the presence of oxidants, carboxylic acids are easy to decarboxylate and produce alkyl radicals [22]. In 2014, Mai and co-workers reported the synthesis of 3,4-disubstituted dihydroquinolin-2(1*H*)-ones by decarboxylation of *N*-arylcinnamamides and aliphatic carboxylic acid using $AgNO_3$ as catalyst, $K_2S_2O_8$ as oxidant and MeCN/H_2O (1:1) as solvents [23]. Various primary, secondary and tertiary aliphatic carboxylic acids were tolerated in the reaction, delivering the desired product in moderate to good yields. The mechanism showed that the reaction might undergo a free radical process. Firstly, Ag^+ was oxidized by the $S_2O_8^{2-}$ to produce Ag^{2+}, sulfate radical anion and sulfate anion. Then, Ag^{2+} obtained a single electron from carboxylic acid **14** to produce carboxylic radicals **16**, which further underwent a decarboxylation process to provide the alkyl radical **17**. Then, the alkyl radical **17** was

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added to the substrate **1** and further went through intramolecular cyclization to form intermediate **19**. Finally, the sulfate radical anion abstracted a hydrogen from **19** to give the final product **15** (Figure 5).

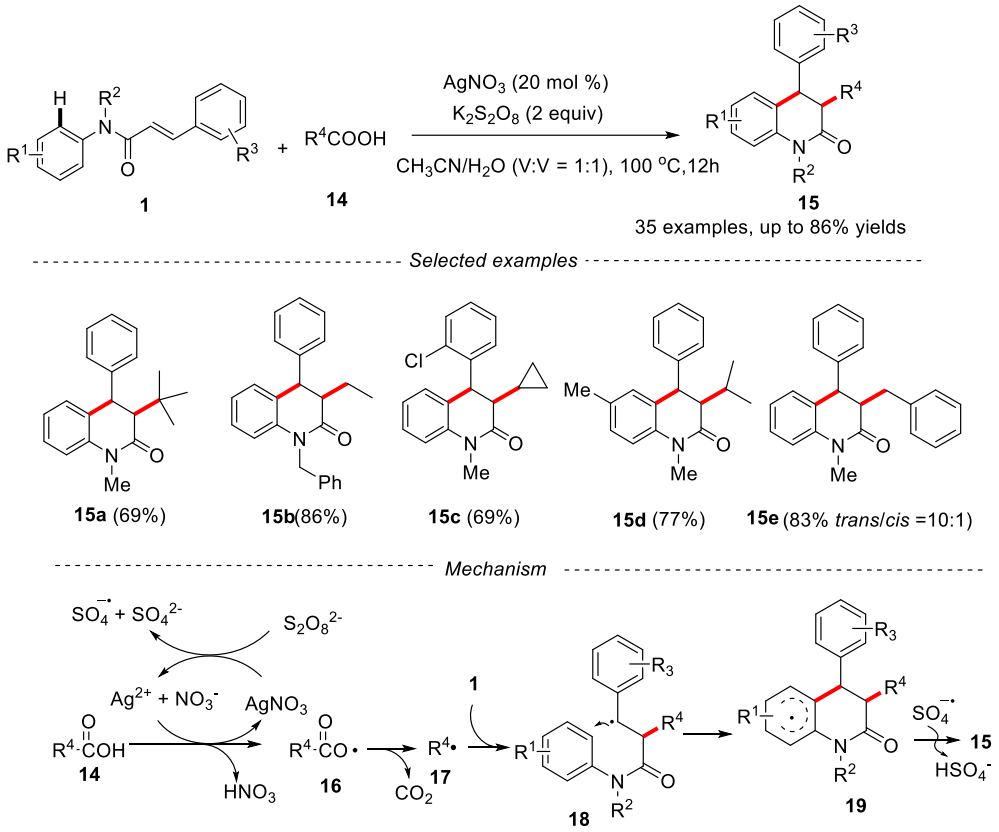

Figure 5. Synthesis of 3,4-substituted dihydroquinolin-2(1*H*)-ones by decarboxylation of *N*-arycinamamides with aliphatic carboxylic acids.

In order to avoid the use of silver salts, a milder method for the synthesis of alkylated dihydroquinolinones was developed by Du's group [24]. The inexpensive $FeCl_2{\cdot}4H_2O$ was used as catalyst and DMF was used as solvent in the reaction, and the peresters (or peroxides) easily prepared from aliphatic acids were used as alkylating reagents and single electron oxidants. A series of alkylated dihydroquinolinone derivatives were obtained in moderate to excellent yields (up to 91%) with excellent diastereoselectivity (dr > 20:1). Peresters prepared from primary acids or secondary acids were effective for this reaction. However, the use of tertiary perester led to only a trace amount of isolated product due to steric hindrance. Peroxides also worked well under the given conditions, delivering the desired alkylated products with good diastereoselectivity. The mechanism showed that the reaction underwent a free radical process. The single-electron transfer (SET) from Fe(II) to perester resulted in the breaking of the O–O bond of perester to produce alkyl radical **22**, CO_2 and $^tBuO^-$. Then alkyl radical **22** reacted with *α,β*-unsaturated amide **1** *via* a radical addition/cyclization and re-aromatization process to give the final product (Figure 6).

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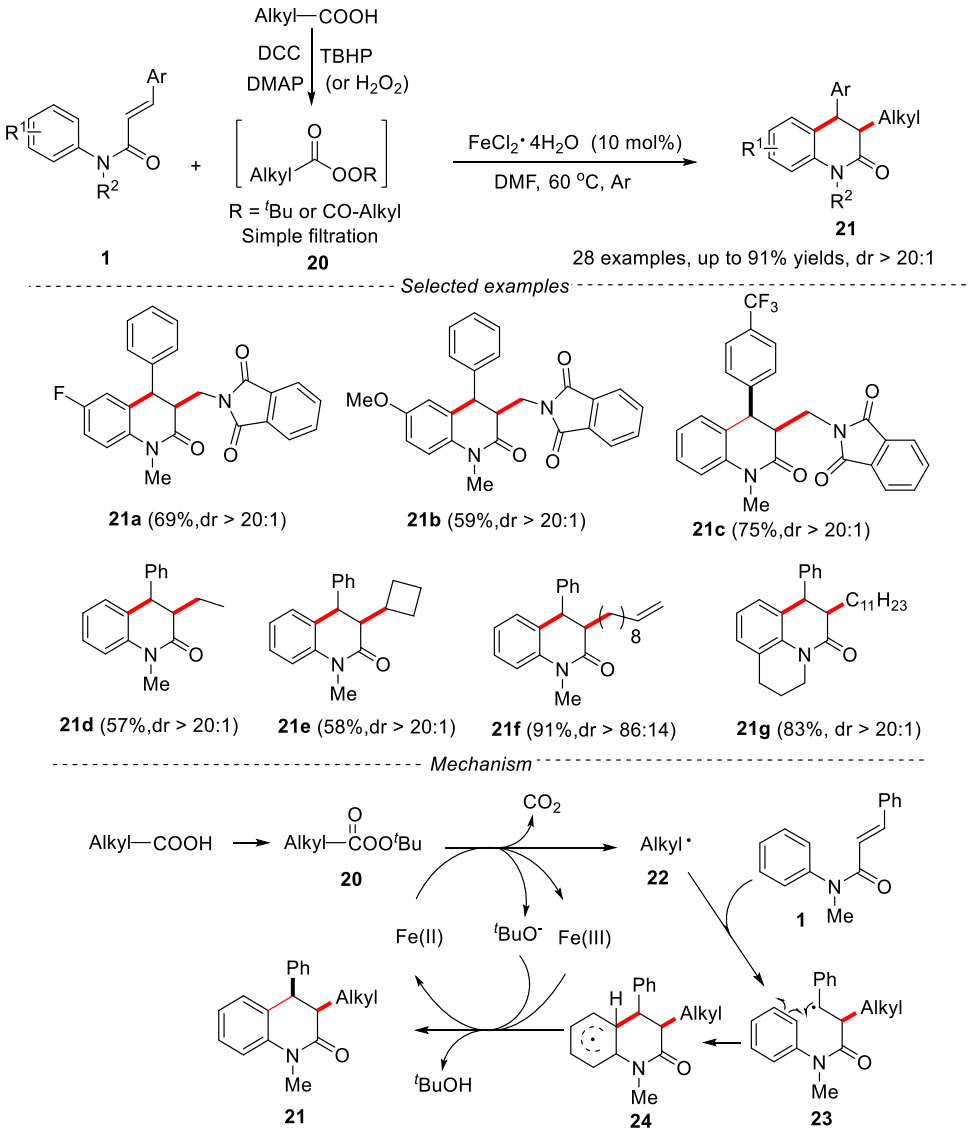

Figure 6. $FeCl_2$-catalyzed decarboxylative radical alkylation/cyclization of *N*-phenylcinnamamide for the preparation of dihydroquinolin-2(1*H*)-ones.

3.1.2. Alkyl halides as alkyl radical precursors

Alkyl halides are commercially available, accessible substrates and have been widely used in various organic reactions. The alkyl halides containing a,*β*-hydrogen might be suitable as alkyl radical precursors in the palladium-catalyzed difunctionalization of activated alkenes [25-27].

In 2016, Duan's group developed a palladium-catalyzed alkylarylation of acrylamides with unactivated alkyl halides for the synthesis of dihydroquinolinone and a variety of functionalized oxindoles [28]. $PdCl_2$ was used as catalyst, 1,1'-bis(diphenylphosphino)ferrocene (dppf) was used as ligand, and diglyme was used as solvent. The cinnamamide **1** reacted with cyclohexyl bromide to provide the desired dihydroquinolinone in 39% yield. Mechanistic investigation revealed that this reaction underwent a cascade radical pathway (Figure 7).

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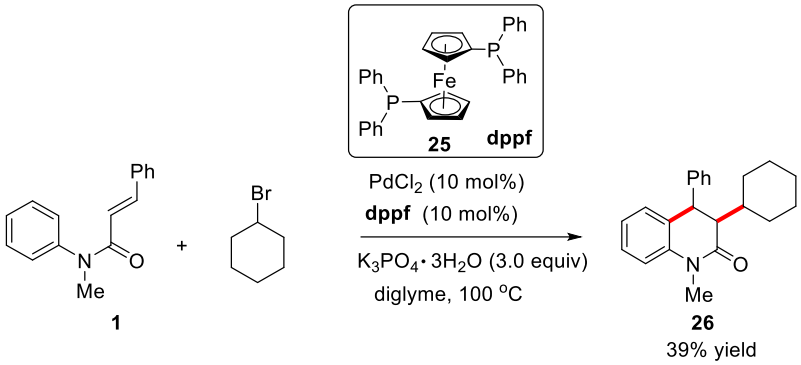

Figure 7. Pd-catalyzed alkylarylation of acrylamides with unactivated alkyl halides for synthesis dihydroquinolinone 3,4-dihydroquinolin-2(1*H*)-ones.

Recently, excited-state palladium photocatalysis has become a powerful reagent for inducing single-electron transfer (SET) reactions involving unactivated alkyl C–X bonds (*X* = Br, I). Photoexcitation of Pd(0) is conducive to forming alkyl radical Pd(I) intermediate by the single-electron oxidative addition of alkyl C–X bonds [29, 30]. In this regard, in 2021, Zhang's group reported visible-light-induced Pd-catalyzed intermolecular radical cascade reaction of *N*-phenylcinnamamide with cyclohexyl bromide for the preparation of 3,4-dihydroquinolin-2(1*H*)-ones [31]. The optimization results of test conditions showed that Xantphos was proved to be the most suitable ligand and that Cs_2CO_3 was the best base for the reaction. *N*-arylcinnamamides bearing -Cl or -Me group was found to be effective under the given conditions, and the corresponding products were smoothly afforded in moderate yields with good dr values (Figure 8).

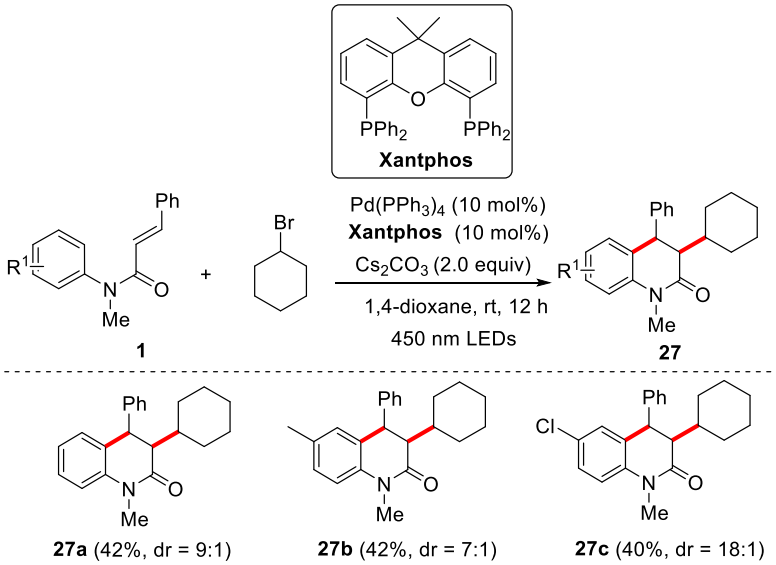

Figure 8. Visible-light-induced Pd-catalyzed intermolecular radical cascade reaction of *N*-phenylcinnamamide with cyclohexyl bromide for the preparation of 3,4-dihydroquinolin-2(1*H*)-ones.

A free radical mechanism was proposed in Figure 9. Firstly, Pd (0) complex underwent a single electron transfer process with cyclohexyl bromide under the condition of LEDS irradiation to produce the cyclohexane Pd(I) radical species. Then, cyclohexane radical **28** was added to the double bond of substrate **1** to generate intermediate **29**, which underwent an intramolecular cyclization and deprotonation process to obtain the final product **27** and regenerate Pd(0) catalyst.

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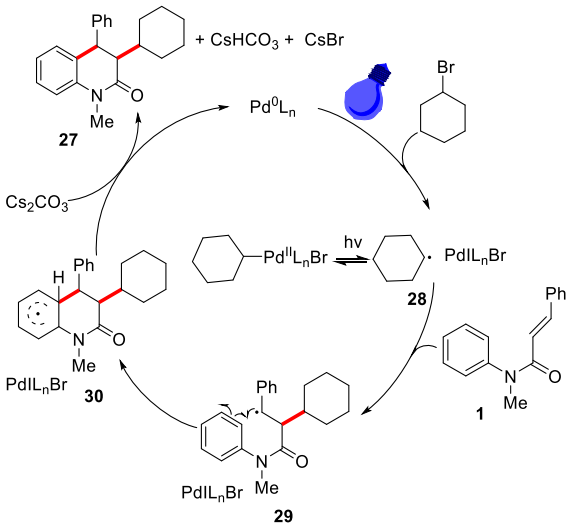

Figure 9. The mechanism of the Pd-catalyzed intermolecular radical cascade reaction of *N*-phenylcinnamamide with cyclohexyl bromide.

3.1.3. Hypervalent iodine (III) reagent (HIR) as alkyl radical precursors

In the past decades, the strategic combination of transition-metal catalysts with hypervalent iodine(III) reagent (HIR) has been widely used in the bifunctionalization of olefins [32]. In 2020, Wang and co-workers have described rhenium-catalyzed alkylarylation of cinnamamides with $PhI(O_2CR)_2$ *via* decarboxylation reaction for the synthesis of 3,3-disubstitued dihydroquinolin-2(1*H*)-ones using $Re_2(CO)_5$ as catalyst (Figure 10) [33].

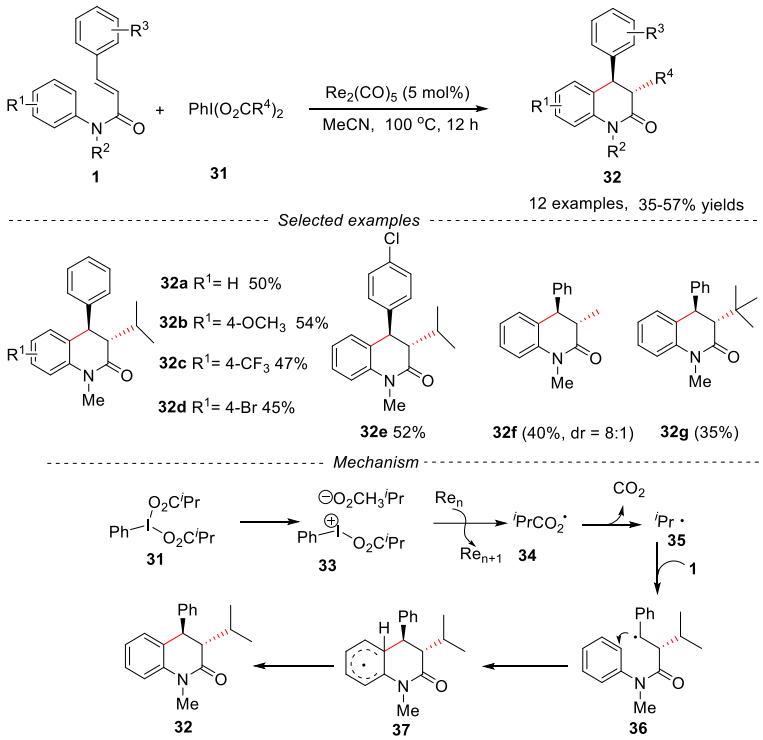

Figure 10. Rhenium-catalyzed alkylarylation of cinnamamides with $PhI(O_2CR)_2$ *via* decarboxylation for the synthesis of 3,3-disubstitued dihydroquinolin-2(1*H*)-ones.

Cinnamamides bearing electron-donating and electron-withdrawing substituents reacted smoothly with $PhI(O_2C^iPr)_2$ to provide dihydroquinolinones in moderate yields. Different hypervalent iodine(III) reagents were also investigated. When $PhI(OAc)_2$ was used under the given

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conditions, two different isomers **32f** (8:1) were obtained in 40% yield. The decrease of diastereoselectivity might be due to the lower steric hindrance of the methyl group in product. However, when $PhI(O_2C^tBu)_2$ was used as reaction reagent, only *trans*-3,4 dihydroquinolin-2(1*H*)-one **32g** was obtained in lower yield due to the larger steric hindrance of ^{t}Bu group. The mechanism showed that the reaction underwent a free radical process. Firstly, the I–O bond in HIR broke to afford ionic species **33**, then the rhenium catalyst transferred an electron to species **33** to produce acyloxy intermediate **34**, which further released CO_2 to form isopropyl radical **35**. Subsequently, the isopropyl radical **35** reacted with the substrate **1** *via* a radical addition, 6-*endo* cyclization and re-aromatization processes to produce the product **32.**

3.1.4. Aliphatic aldehydes as alkyl radical precursors

Aldehydes are cheap and easily available chemicals. It has great advantages to synthesize various organic compounds through the decarbonylation of aldehydes in the presence of oxidants [34,35]. In this regard, Yang and Pei's groups developed Fe-catalyzed decarbonylative cascade reaction of *N*-arylcinnamamides with aliphatic aldehydes for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones (Figure 11) [36].

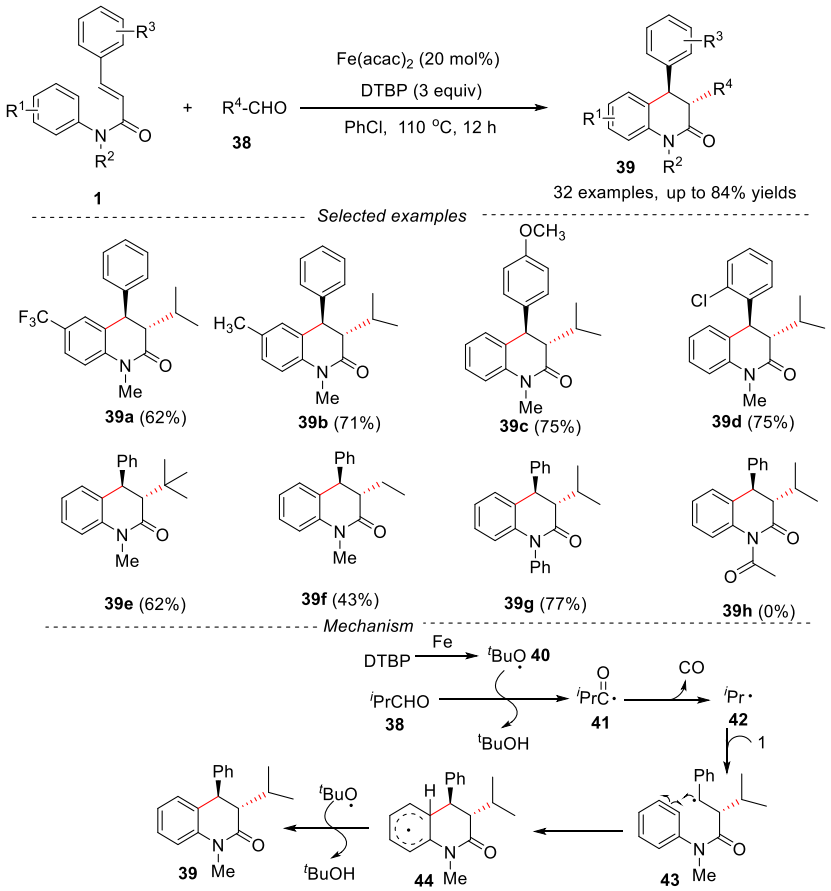

Figure 11. Fe-catalyzed decarbonylative cascade reaction of *N*-arylcinnamamides with aliphatic aldehydes for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

In this reaction, a series of iron salts such as $FeCl_2$, $FeCl_3$, $FeSO_4$, $Fe_2(SO_4)_3$, $Fe(acac)_2$, $Fe(acac)_3$, $FeBr_2$, and $Fe(OAc)_2{\cdot}4H_2O$ were scanned, and $Fe(acac)_2$ was the best choice. DTBP (di-*tert*-butyl peroxide) was used as oxidant and PhCl was used as solvent. The reaction showed a wide range of substrates. *N*-arylcinnamamides bearing both electron-withdrawing or electron-donating were well tolerated, and the corresponding 3,4-disubstituted dihydroquinolinones could be obtained in good yields. The steric hindrance and electron effect of substituents were not obvious for this cascade reaction. Interestingly, pyridine units could also be introduced into *N*-arylcinnamamide substrates,

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providing the desired product in moderate yields. Different aliphatic aldehydes were also tested, secondary and tertiary alkyl aldehydes worked well in this reaction. However, when a primary alkyl aldehyde was used as reactant, a lower yield was observed due to the self-aldol condensation and the poor stability of primary radicals. Electron-donating groups on the N atom, such as Me, Et, Ph, *n*-Bu, Bn were effective. However, when the substrate had Ac group on the N atom, the reaction failed to give the desired product. The mechanism study showed that the reaction involved a free radical process. Firstly, the iron catalyst accelerated the homolytic cleavage of DTBP to generate a *tert*-butoxy radical **40**, which abstracted a hydrogen atom from aldehyde **38** to produce the radical intermediate **41**. Then, radical **41** released CO to form isopropyl radical **42**. Subsequently, the isopropyl radical **42** reacted with the substrate **1** *via* a radical addition, 6-*endo-trig* cyclization and re-aromatization process to give the final product **39.**

At the same time, Luo and Liu's groups described a metal-free method for the synthesis of alkylsubstituted 3,4-dihydroquinolin-2(1*H*)-one derivatives through cascade oxidative decarbonylative radical addition/cyclization of *N*-arylcinnamamides with aliphatic aldehydes in PhF [37]. The reaction also showed a wide range of substrates. The cinnamamides having electron-donating or electron-withdrawing groups were well tolerated, and the corresponding products were obtained in moderate to good yields. *N*-Me and *N*-^{n}Bu substituted *N*-cinnamamides reacted well in this transformation, affording the target products in moderate yields. However, *N*-H substrate failed to give the expected product. Interestingly, when *N*-methyl-*N*-phenyl-3-(pyridin-2-yl) acrylamide was used as substrate, the corresponding product **46f** was obtained in 62% yield. However, when oxygen heterocyclic acrylic amide was used, only trace product could be detected. A variety of aliphatic aldehydes were compatible in this reaction (Figure 12).

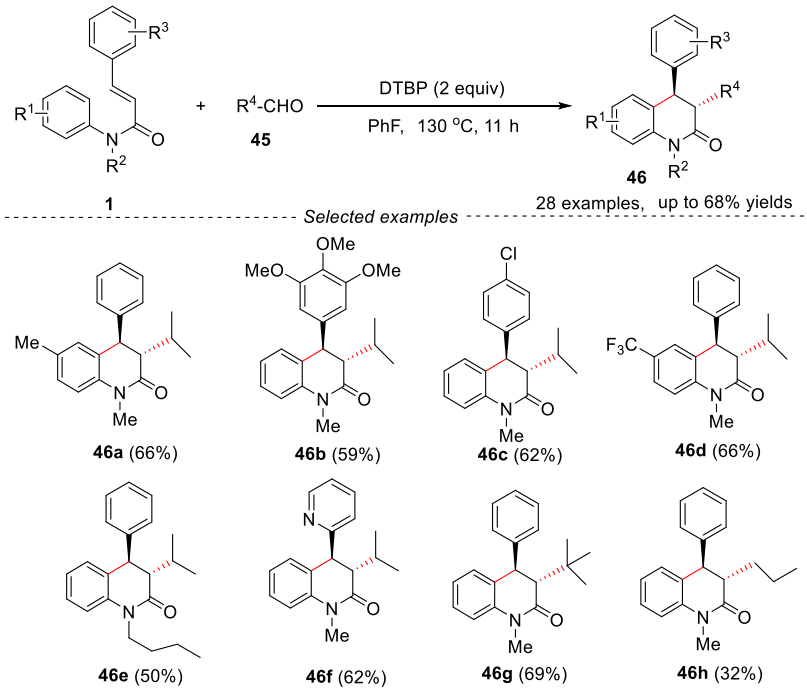

Figure 12. A metal-free catalyzed method for the synthesis alkylsubstituted 3,4-dihydroquinolin-2(1*H*)-one derivatives by reactionof *N*-arylcinnamamides with aliphatic aldehydes in PhF.

3.1.5. Cyclohexanone oxime ester as alkyl radical precursors

Recently cyclohexanone oxime ester has been used in organic synthesis as a precursor of cyanoalkyl radicalsand considerable attention has been paid to the selective γ-cyanoalkyl radical functionalization generated from cyclobutanone oxime ester [38]. In 2018, the copper-catalyzed cyclization of *N*-methyl-*N*-arylcinnamamides with cyclobutanone *O*-acyl oximes has been delveloped by Guo's group for the synthesis of cyanoalkylated dihydroquinolin-2(1*H*)-ones [39]. *N*-methyl-*N*-arylcinnamamides having electron-withdrawing or electron-donating groups on the

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phenyl rings of the cinnamic acid gave the desired products in moderate to good yields. Cinnamamide bearing a methoxyl group at the *para* position of the anilide moiety was also compatible in this reaction, delivering the desired product in 51% yield. A reasonable reaction mechanism was proposed in Figure 13. Firstly, Cu(I) catalyst transferred an electron to cyclohexanone oxime ester **47** to give the iminyl radical **49**, which underwent *β*-scission to produce the cyanoalkyl radical **50.** Then, the cyanoalkyl radical **50** reacted with substrate **1**, producing intermediate **51**, which was followed by intramolecular cyclization and deprotonated to give the desired product **48**.

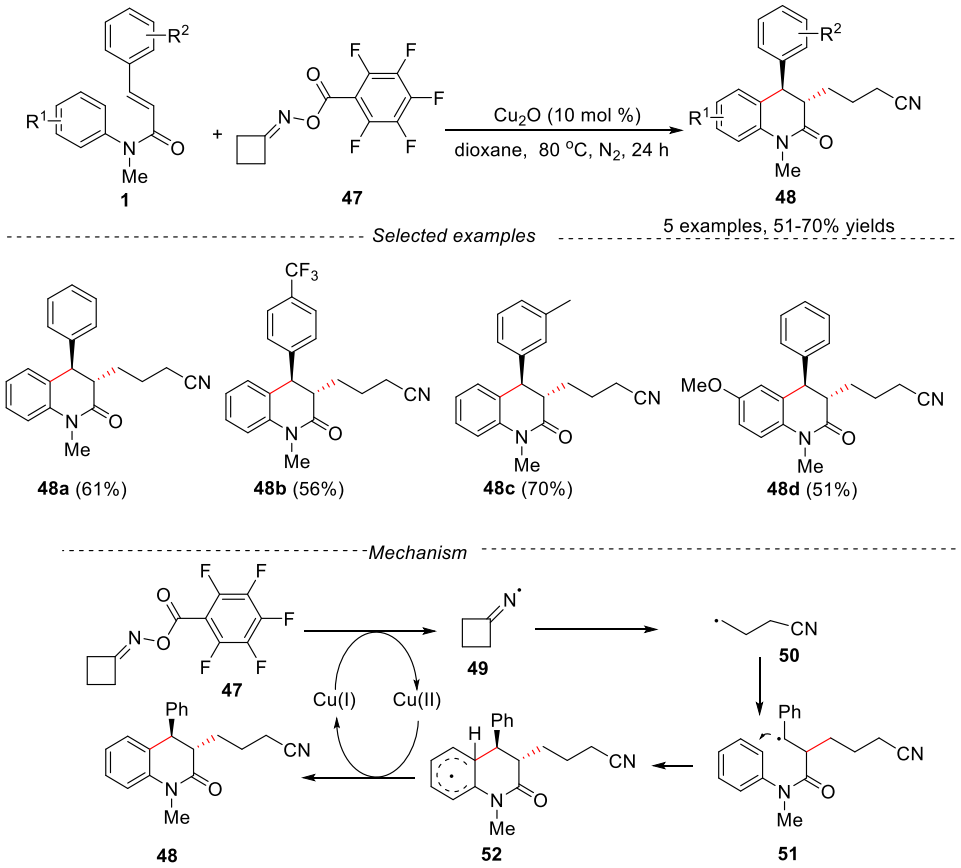

Figure 13. Cu-catalyzed cyanoalkylarylation of *N*-arylcinnamamides with cyclobutanone oxime esters for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

3.1.6. Organoboronic acid as alkyl radical precursors

Although trialkylboranes [40] and organotrifluoroborates [41] have been used as the source of alkyl radicals in organic chemistry, the development of directly commercially available alkyl boronic acids was relatively limited. Only a few studies use boronic acid as alkyl radical the precursors mainly because boronic acid has a high oxidation potential [42]. In 2018, Liu's group described an alkylating method for the synthesis of alkylsubstituted 3,4-dihydroquinolin-2(1*H*)-one derivatives using cyclohexyl boronic acid as cyclohexyl radical precursor and oxygen as oxidant [43]. The advantage of this reaction was that no transition metal catalyst was used. A series of *N*-methyl-*N*-arylcinnamamides were found to be effective substrates, the corresponding alkylated 3,4-dihydroquinolin-2(1*H*)-ones were obtained in moderate to good yields with excellent chemoselectivity. Only *anti*-isomers of 3-cyclohexyl-1-methyl-4-aryl-3,4-dihydroquinolin-2(1*H*)-ones were observed under the given conditions. The mechanism showed that the reaction might undergo a free radical process. The reaction of cyclohexyl boronic acid and molecular oxygen would produce the key cyclohexyl radical **56**, which was added to olefin to further form radical intermediate **58** after cyclization. Subsequently, a hydrogen atom transferred (HAT) from **58** to **55** would give product **54** and peroxyboronic acid, which would lead to the formation of boronic acid finally (Figure 14).

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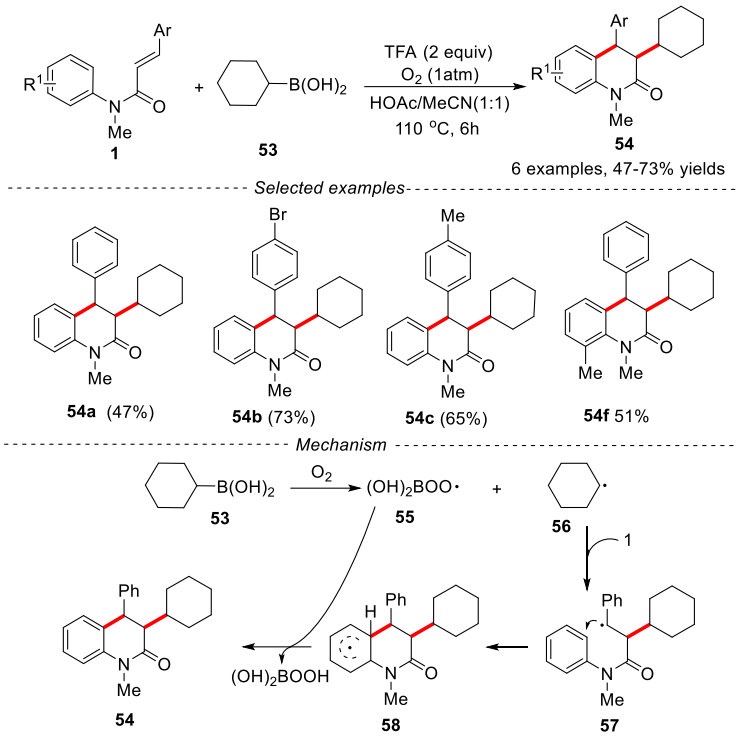

Figure 14. Synthesis of alkylsubstituted 3,4-dihydroquinolin-2(1*H*)-one derivatives using cyclohexyl boronic acid as cyclohexyl radical precursor and dioxygen as oxidant.

3.1.7 Breaking C (sp^3)-H bonds as alkyl radical precursors

Breaking various sp^3 C-H bonds, such as C-H bonds of alkanes, C-H bonds adjacent to heteroatoms, benzyl and allyl C-H bonds and carbonyl compounds are easy to generate relatively stable free radicals.

In 2014, Mai's group developed a metal-free protocol for the synthesis of 3,4-disubstituted dihydroquinolin-2(1*H*)-ones through tandem cyclization of reaction of *N*-arylcinnamamides with pentane-2,4-dione using $K_2S_2O_8$ as oxidant and MeCN/H_2O (3:3) as solvents [44]. Both electron-withdrawing and electron-donating at the phenyl ring of cinnamic acid were well tolerated, and the corresponding dihydroquinolin-2(1*H*)-ones could be obtained in moderate yields. Except for methyl group, other groups such as -Bz and -CH_2CH_2CN at the N atom (R^2) were also investigated under the given conditions, and the reaction still proceeded well. Pyridine substituents in substrates **1** were also compatible in this reaction, delivering the desired product in 46% yield. When ethyl 3-oxobutanoate or 1-phenylbutane-1,3-dione were used as substrates, the expected products were not obtained (Figure 15).

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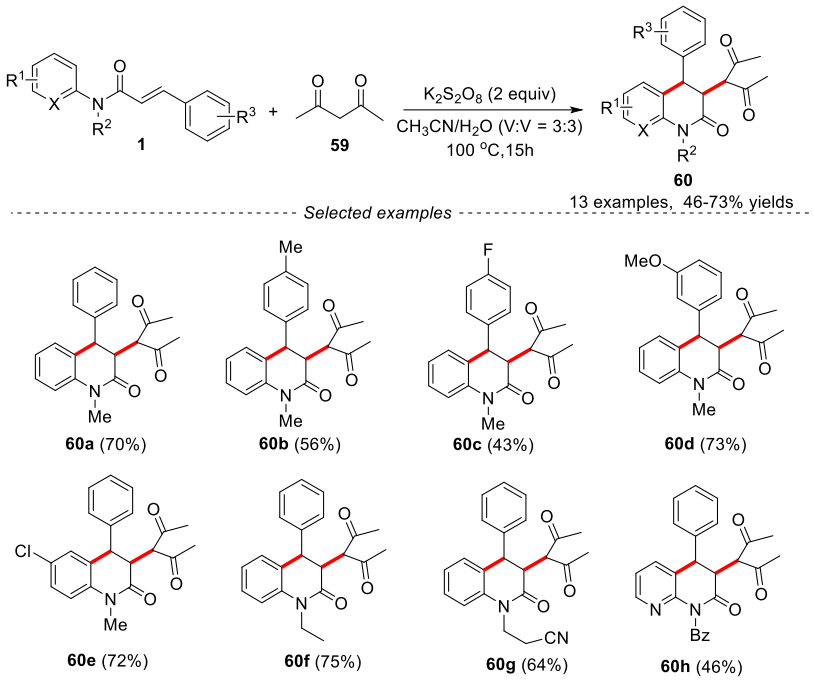

Figure 15. Tandem cyclization of *N*-arylcinnamamide with pentane-2,4-diones for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

In 2016, Duan's group developed a copper-catalyzed tandem method for the synthesis of dihydroquinolin-2(1*H*)-ones through cascade radical addition/cyclization of *N*-arylcinnamamides with benzyl hydrocarbons. (Figure 16).

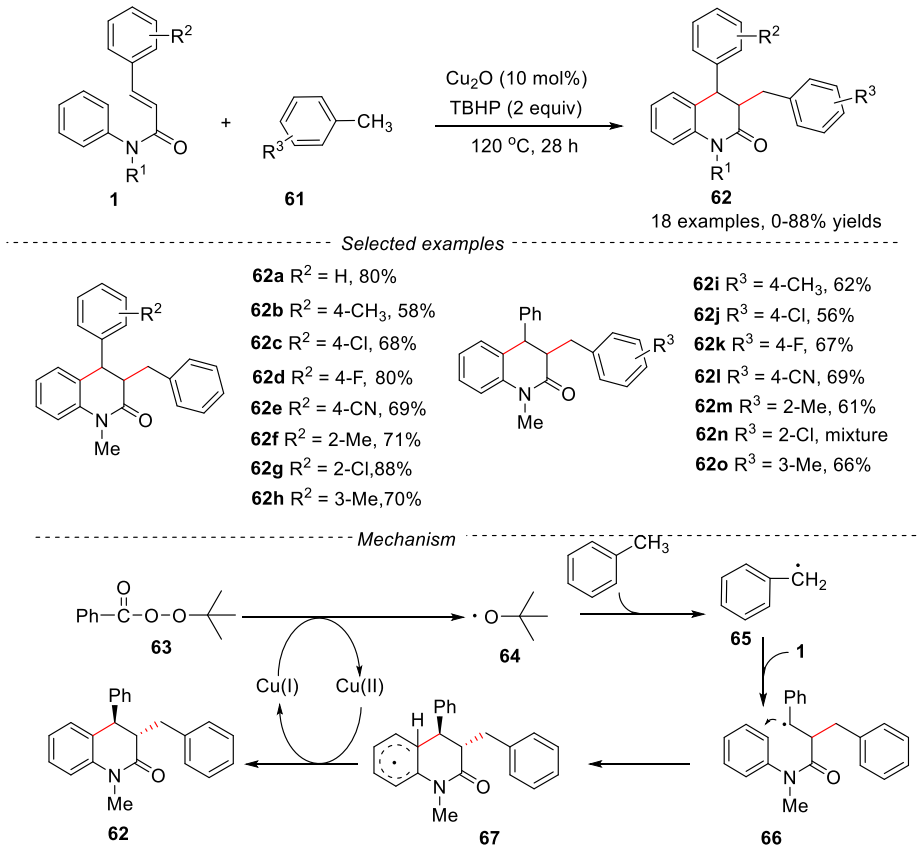

Figure 16. Copper-catalyzed tandem method for the synthesis dihydroquinolin-2(1*H*)-ones by cascade radical addition/cyclization of *N*-arylcinnamamides with benzyl hydrocarbons.

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Cu_2O was used as catalyst and *tert*-butylperoxy benzoate (TBPB) as oxidant [45]. The reaction tolerated a series of substituted *N*-phenylcinnamamides and toluene derivatives, leading to the desired dihydroquinolinones in moderate to good yields. The mechanism study showed that the reaction underwent a free radical process. The homolytic cleavage of the TBPB in the presence of Cu_2O catalyst produced a *tert*-butoxyl radical **64**, which was abstracted a hydrogen from the toluene to generate the key benzyl radical **65**.

Further, other types of substrates, such as cyclohexane, cyclopentane, 1,4-dioxane, tetrahydrofuran and isopropanol were all effective under the given conditions, and the corresponding products were obtained in moderate to good yields. However, when a cyclohexene was used as substrate, only a trace amount of the desired product was observed (Figure 17).

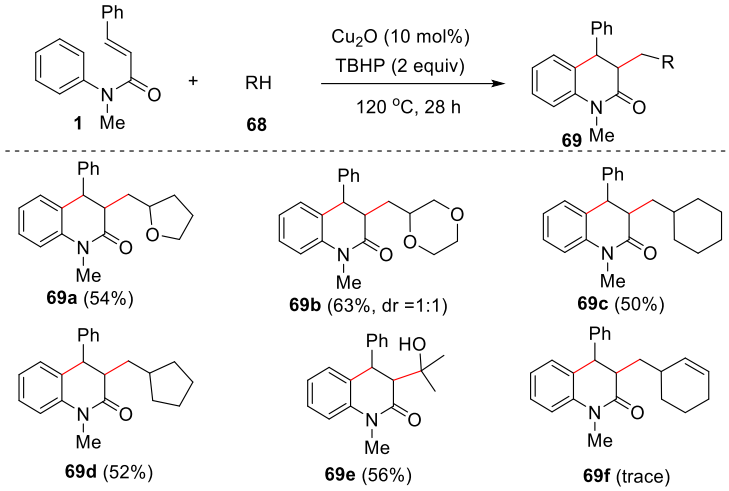

Figure 17. Copper-catalyzed tandem method for the synthesis of dihydroquinolin-2(1*H*)-ones by cascade radical addition/cyclization of *N*-arylcinnamamides with ether, alcohols and alkanes.

Recently, Zhang's group developed a photo-induced oxidative radical cascade cyclization of *N*-methyl-*N*-arylcinnamamides with methanol at room temperature [46]. The reaction avoided the use of expensive photocatalysts and was carried out under very mild conditions. The corresponding hydroxyalkylated dihydroquinolin-2(1*H*)-one was obtained in 45% yield. A reasonable reaction mechanism was proposed in Figure 18. Under the irradiation of LEDs, $(NH_4)_2S_2O_8$ underwent homolytic cleavage to form sulfate radical anions, which abstracted the α-H from the methanol to give the hydroxyalkyl radical **72**. Then, the hydroxyalkyl radical **72** reacted with substrate **1** *via* an addition/cyclization process to give intermediate **74,** which was further oxidized by sulfate radical and deprotonated anion in the presence of Na_2CO_3 to give the desired product **71**.

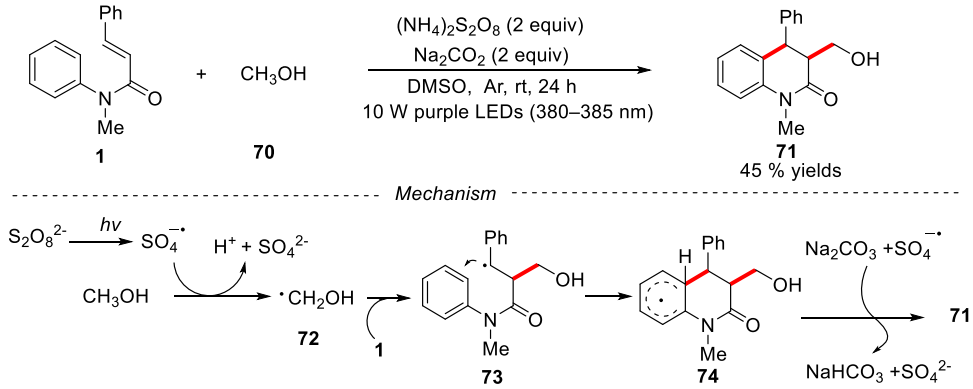

Figure 18. Photo-induced C(sp^3)-H functionalization for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

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Liu's group reported a novel palladium-catalyzed oxidative arylalkylation of alkenes to construct cyano substituted oxindoles and 3,4-dihydroquinolin-2(1*H*)-one using 2,2'-bipyrimidine **75** as ligand, $PhI(OPiv)_2$ as oxidant and AgF as additive [47]. It was found that the AgF was indispensable to the reaction and AgF played a role to promote the C(sp^3)-H bond cleavage in acetonitrile. Only one example was reported for cyano-containing dihydroquinolinone. The desired product **76** was obtained in 77% yield (Figure 19).

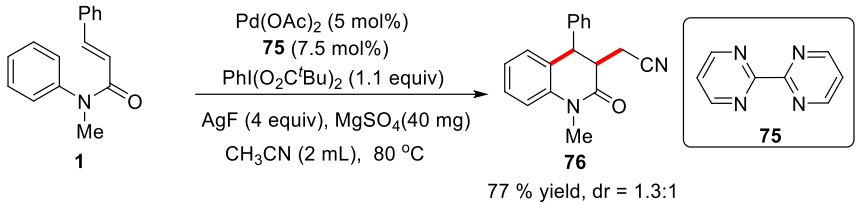

Figure 19. Palladium-catalyzed oxidative arylalkylation of alkenes to construct cyano substituted oxindoles and 3,4-dihydroquinolin-2(1*H*)-one.

In 2018, Luo and Zhang's groups described a silver-induced tandem radical addition/cyclization of *N*-arylcinnamamides in CH_3CN for the synthesis of cyano-containing 3,4-dihydroquinolin-2(1*H*)-ones (Figure 20) [48].

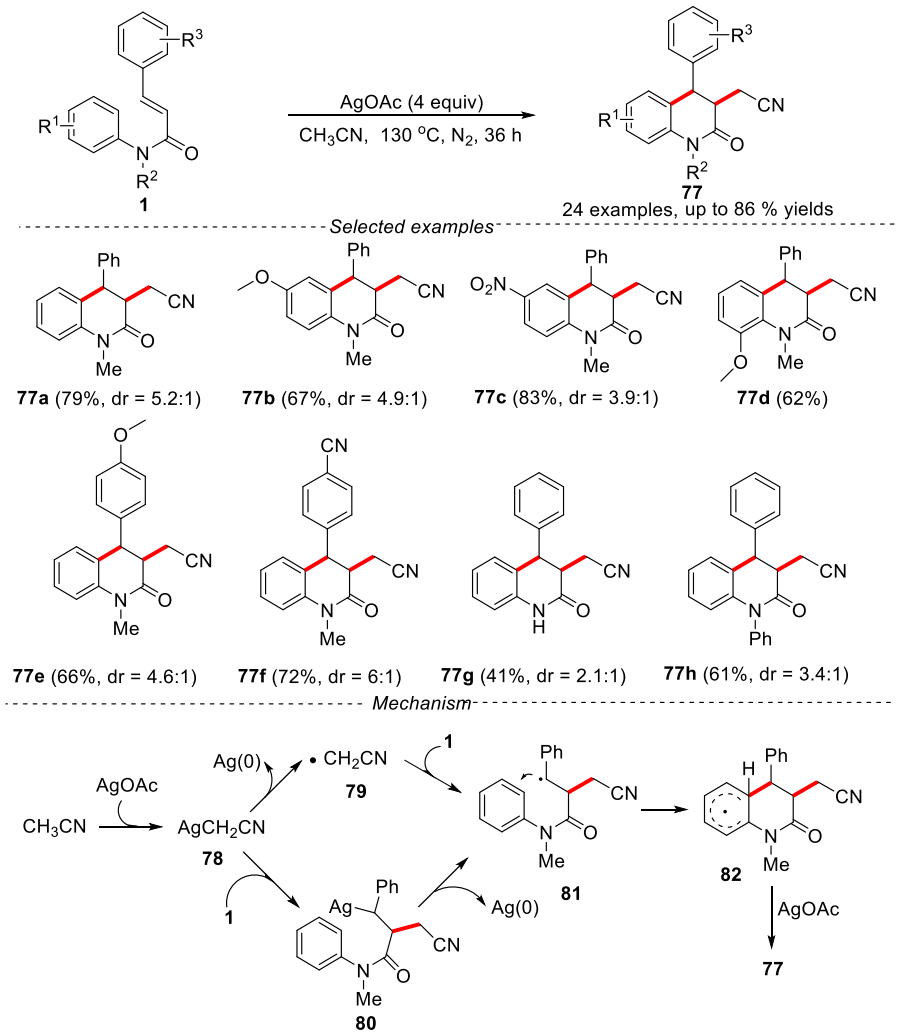

Figure 20. Silver-induced tandem radical addition/cyclization for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

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The reaction exhibited good functional groups compatibility. The electron-withdrawing groups at the *para* position of the substrates gave better results compared to that with the electrondonating groups. Different groups at the *N* atom (R^2) were also investigated under the given conditionsand the *N*-phenyl-substituted substrate gave a yield of 61%. Interestingly, the unprotected or -Ts protected substrate on the *N* atom was also suitable for this reaction. Although lower yields of products were obtained, it was noteworthy that these products were not easy to obtain through the usual free radical addition/cyclization process. The mechanism indicated that the reaction underwent a free radical process. Firstly, CH_3CN reacted with AgOAc to generate $AgCH_2CN$ species. There might be two pathways to produce radical **81**. One was that $AgCH_2CN$ cleaved Ag(0) to form $\cdot CH_2CN$, which was added to the substrate **1** to produce radical **81.** The other was that $AgCH_2CN$ was added to the double bond of **1** to provide intermediate **80,** followed by a silver-induced formation of radical intermediate **81**. Then, the intermediate **81** further went through an intramolecular radical cyclization process to form the intermediate **82**. Finally, the intermediate **82** was oxidized by AgOAc to give the product **77**.

In 2018, Huang and Hu's groups developed a Nickel-catalyzed reaction of *N*-arylcinnamamides with tertiary benzylamines *via* C-N bond activation for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones (Figure 21) [49].

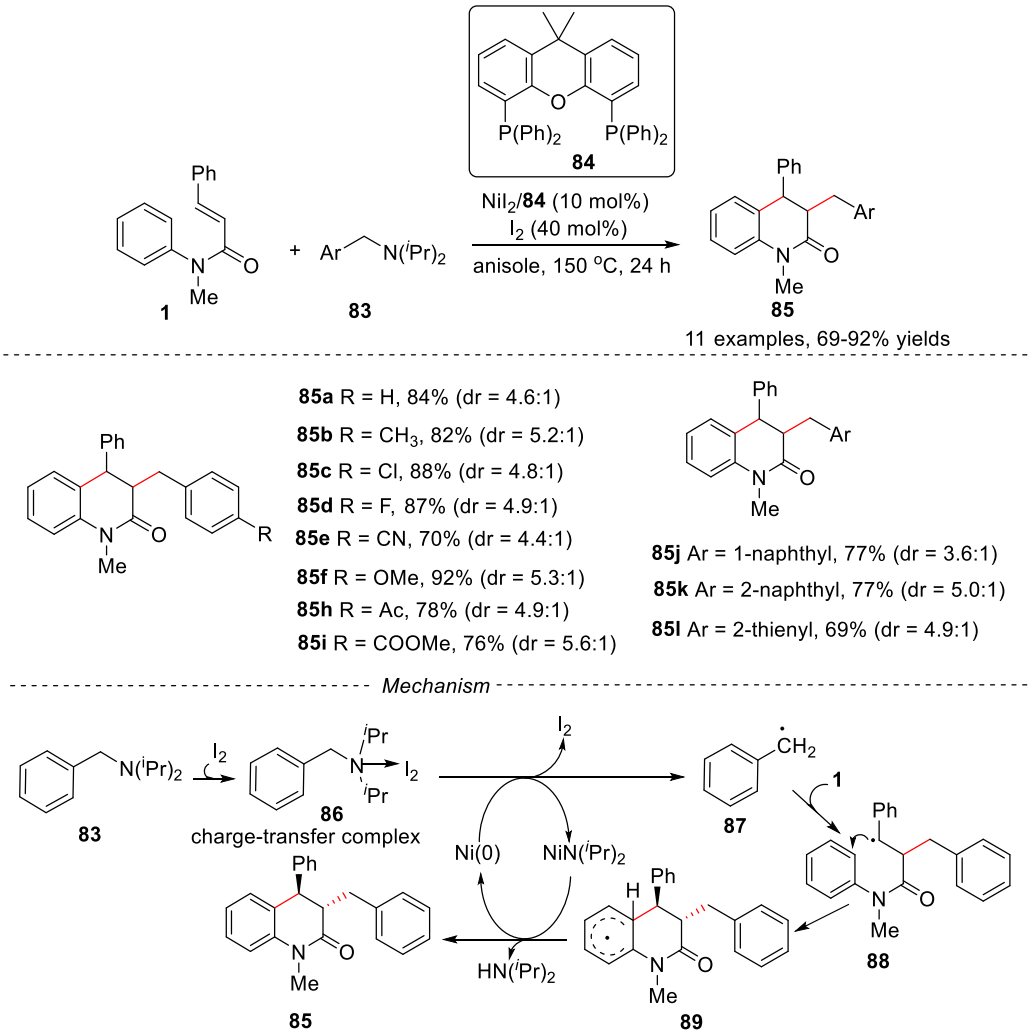

Figure 21. Nickel-Catalyzed tandem radical addition/cyclization for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

NiI_2 and I_2 were used as catalysts, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene **84** was used as ligand and anisole was used as solvent. Tertiary benzylamines **1** having different substituents on the phenyl ring worked well, leading to the six-membered ring dihydroquinolinones **85** in good

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to excellent yields. Apart from phenylsubstituted amines, naphthyl-substituted amines and thienyl-substituted were also compatible in this reaction, providing the corresponding products in good yields. The reaction went through a free radical reaction process. Firstly, tertiary benzylamines reacted with I_2 to form the amine-I_2 charge-transfer complex **86**, which was extracted a single electron from Ni(0) to generate a benzyl radical **87**. Then benzyl radical **87** reacted with substrate **1** underwent an addition/ cyclization process to produce intermediate **89.** Finally, intermediate **89** was oxidized by Ni(I) *via* single-electron transfer (SET) to give product **85** and regenerate Ni(0)-catalyst.

3.2. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using fluoroalkyl radicals

3.2.1. Using CF_3SO_2Na or HCF_2SO_2Na as fluorine sources

Trifluoromethyl substituted organic compounds have been widely used in medicine, pesticides, materials. Therefore, it is of great research value to develop efficient and practical synthetic methods to prepare trifluoromethyl substituted organic compounds. Langlois' reagent (CF_3SO_2Na) is a stable and cheap free radical trifluoromethylation reagent. It has been widely used in the trifluoromethylation reaction of olefins and aromatics in recent years [50,51]. Under oxidation conditions, the reagent usually undergoes single electron transfer, resulting in C-S bond breaking to generate trifluoromethyl radical and SO_2. Therefore, in organic synthesis, it can be used as a donor of trifluoromethyl radical to realize diversified trifluoromethylation conversion. In 2014, Mai and co-workers described the silver-catalyzed method for the synthesis of CF_3-containing 3,4-dihydroquinolin-2(1*H*)-ones using the CF_3SO_2Na as a donor of trifluoromethyl radical sources [23]. $AgNO_3$ was used as catalyst, $K_2S_2O_8$ was used as oxidant and CH_3CN/H_2O (1:1) was used as solvents. Various cinnamamides reacted smoothly with CF_3SO_2Na, affording the desired trifluoromethylated products in moderate yields with excellent diastereoselectivity. However, when (*E*)-1-(3,4-dihydroquinolin-1(2*H*)-yl)-3- phenylprop-2-en-1-one was used as substrate, the mixture products **91f** and **91f'** were obtained as two stereoisomers under the same reaction conditions (Figure 21).

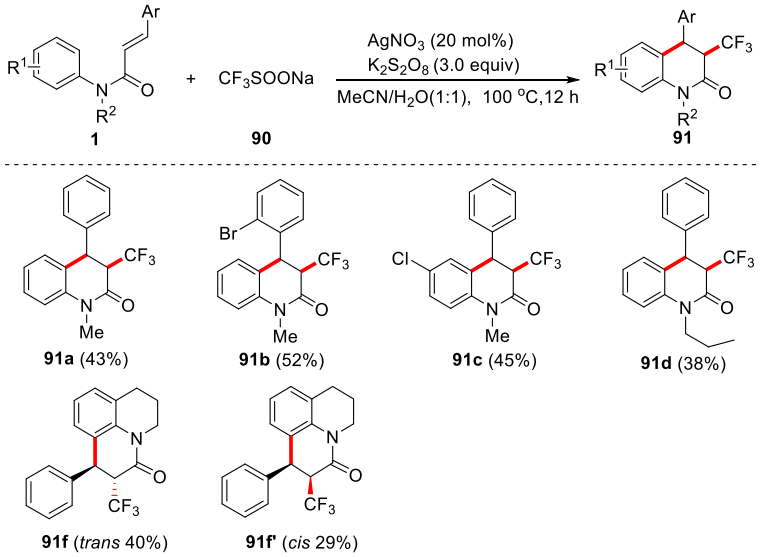

Figure 22. Silver-catalyzed method for synthesizing CF_3-containing 3,4-dihydroquinolin-2(1*H*)-ones using CF_3SO_2Na as CF_3 radical source.

In 2019, Deng and co-workers reported a metal-free, air oxidation difluoromethylation of *N*-arylacrylamides using Eosin B as photocatalyst and HCF_2SO_2Na as difluoromethyl sources [52]. Only one example of synthesizing 3,4-dihydroquinolin-2(1*H*)-ones was reported. The HCF_2-containing 3,4-dihydroquinolin-2(1*H*)-ones **93** were obtained in 33% yield. A plausible photo-induced reaction mechanism was proposed in Figure 23. Firstly, the excited Eosin B* species was formed under the irradiation of white LED light, then an electron transferred from HCF_2SO_2Na to [Eosin B]* to produce [Eosin B]$^{\bullet-}$ and difluoromethyl radical **95**. After that, the difluoromethyl radical **95** reacted with

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substrate **1** by an addition/ cyclization process to afford intermediate **97**. One electron was transferred from [Eosin B]$^{\bullet-}$ to O_2 to give peroxide radical anion ($O_2^{\bullet-}$) and regenerate the Eosin B catalyst. The intermediate **97** was oxidized by peroxide radical anion ($O_2^{\bullet-}$) and deprotonated to give product **93** (Figure 23). In ESR experiment, the species of peroxide radical anion was observed, which further proved the rationality of this mechanism.

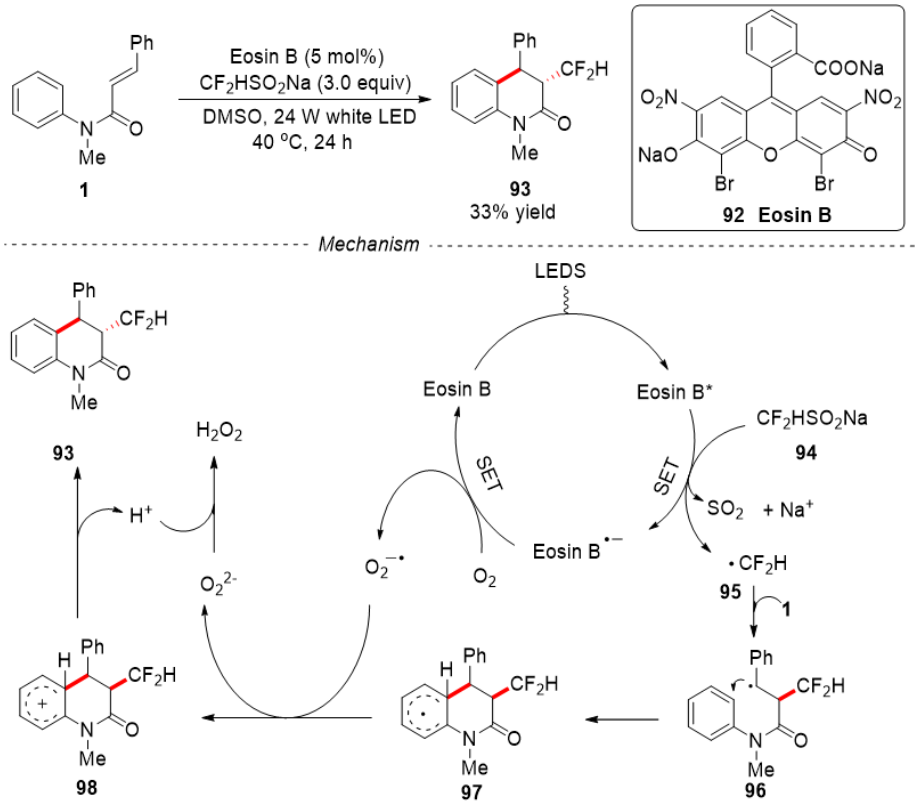

Figure 23. A white LED light induced reaction of *N*-arylacrylamides with HCF_2SO_2Na using the Eosin B as photocatalyst.

In 2019, Ruan and coworkers developed an electrochemical di- and trifluoromethylation/cyclization of *N*-substituted acrylamides for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones [53]. The reaction was performed in an undivided cell equipped with a graphite anode and a Ni plate cathode by using $^{n}Bu_4NPF_6$ as the electrolyte under a constant current of 4 mA, and MeCN as reaction solvent. Control experiments showed the reaction might undergo a free radical process. Firstly, CF_3SO_2Na lost one electron on the anodic to generate intermediate **101**, which further released SO_2 to produce the trifluoromethyl radical **102.** Then, the trifluoromethyl radical **102** reacted with *α, β*-unsaturated *N*-arylamides **1** to generate intermediate **104** through an addition/cyclization process. Then intermediate **104** underwent anodic oxidation to generate intermediate **105**, which was deprotonated to give the desired product **106** (Figure 24).

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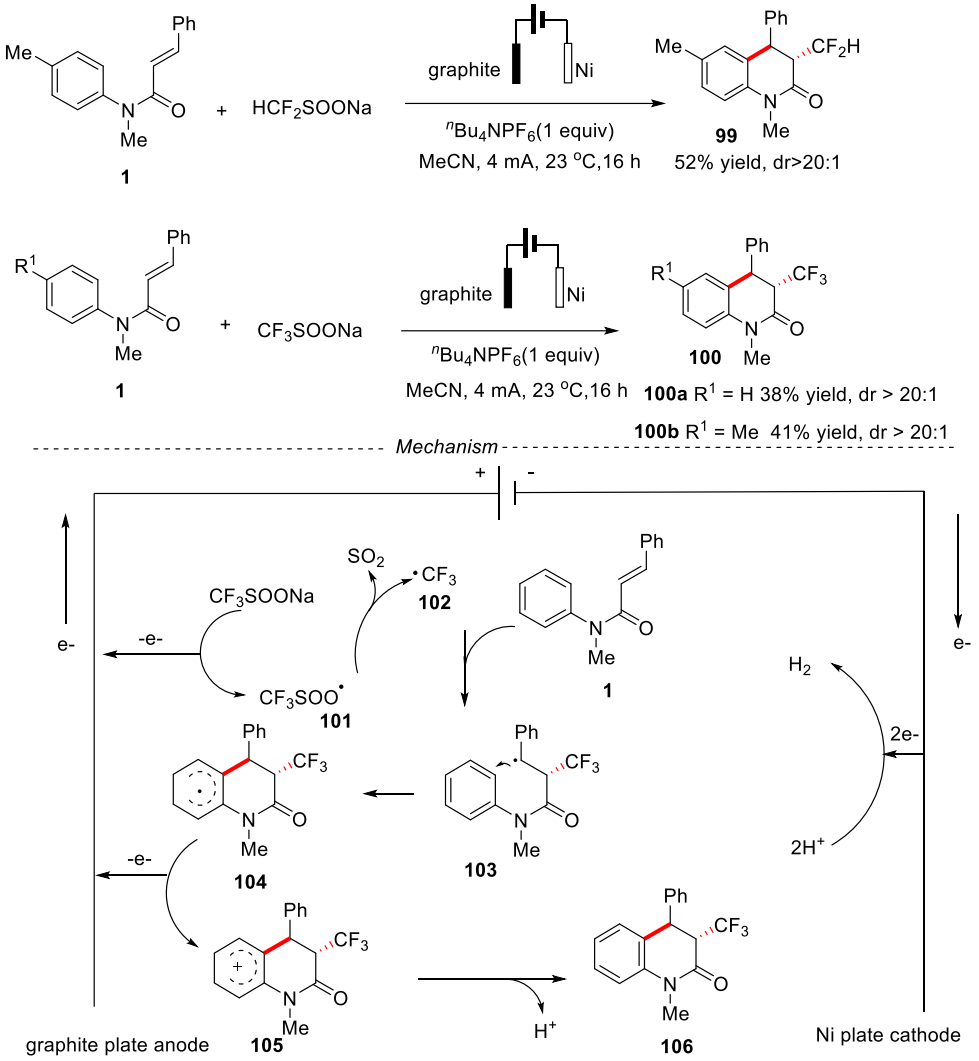

Figure 24. Di- and trifluoromethylation/cyclization of *N*-substituted acrylamides for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones by an electrochemical method.

3.2.2. Using Ph_3PCH_2FI as fluorine sources

Although precious metal catalysts and photocatalysts have been widely used in organic synthesis, it is still necessary to develop protocols using non-photocatalysts and transition metal catalysts due to the fact that those catalysts inevitably produce pollutants. In 2021, Chen and Wang's groups developed a simple photolysis procedure to realize monofluoromethylation, difluoromethylation and trifluoromethylation of various alkenes [54].

Monofluoromethylated quinolin-one was obtained in 52% yield with 88:12 dr ratio. This strategy avoided the use of oxidants and photocatalysts, promoting SET to generate the corresponding CH_2F radicals by using the σ-hole effect of phosphonium salts **107**, because of its lower reduction potential and much lower stability than its similar CHF_2 and CF_3 groups. Hence, this reaction provided a new strategy to produce CH_2F radical by a simple method (Figure 25).

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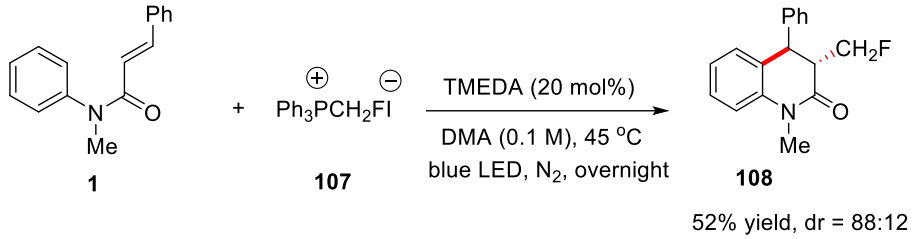

Figure 25. Blue LED light induced mono-fluoromethylation of phenylcinnamamide using phosphonium salts 107 as fluorine sources.

3.2.3. Using Togni's Reagents as fluorine sources

Togni's Reagents is a kind of trifluoromethylation reagent with high reactivity. It can not only react with a series of nucleophilic reagents to efficiently realize electrophilic trifluoromethylation, but also be compatible with a variety of sensitive functional groups. It has been widely used to synthesize trifluoromethyl-containing organic compounds [55-57]. In 2015, a copper-catalyzed method was developed by Wang and co-workers for the synthesis of trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones by cascade radical addition/cyclization of *N*-phenylcinnamamides with Togni's Reagents using CuI as catalyst and $CHCl_3$ as solvent (Figure 26) [58].

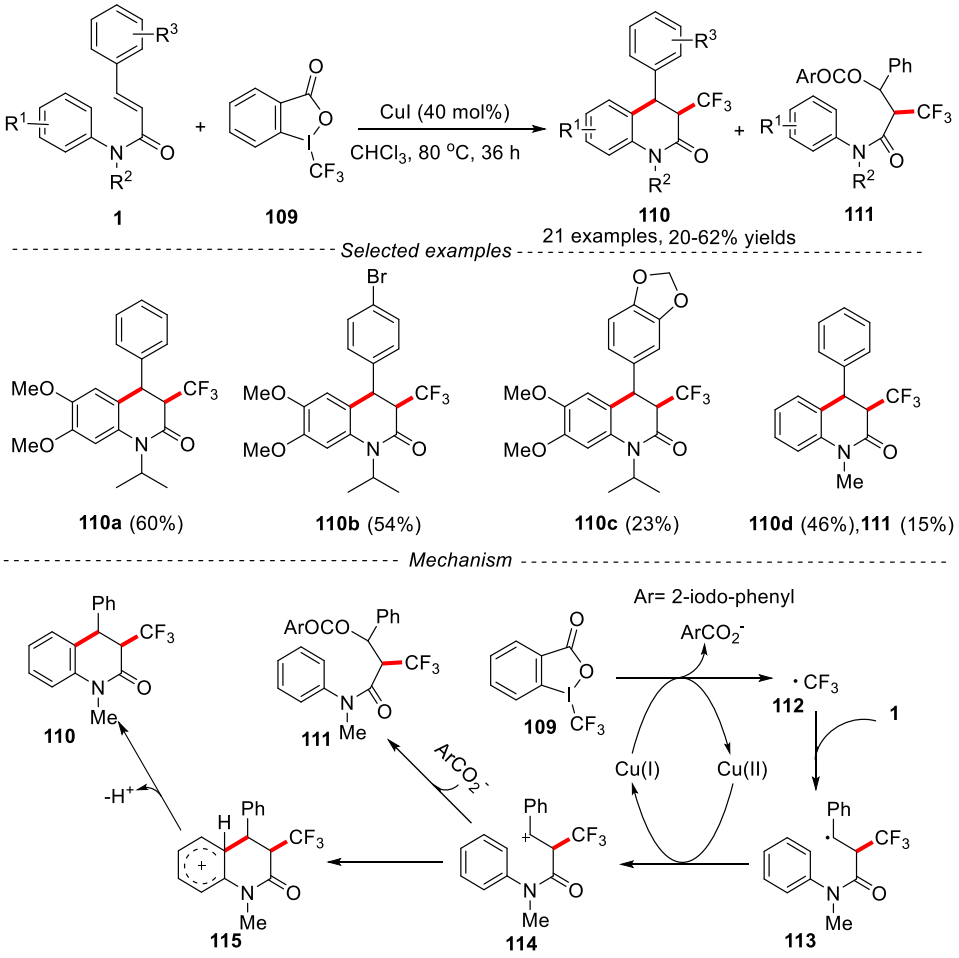

Figure 26. A CuI-catalyzed protocol for the synthesis of trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones.

The reaction showed a wide functional groups tolerance. Different *N*-protected groups, such as Me, Et, *i*-Pr, Bn, *t*-butyloxycarbonyl (Boc) and CH_2COOEt were compatible with this reaction, and the desired products were obtained in moderate to good yields. However, when *N*-Ts(*N*-*para*-

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toluenesulfonyl) protected substrate was tested, almost no target product was obtained. Cinnamamides bearing an electron-withdrawing substituents, such as -F, -CF_3, -CN or Br groups in the *ortho*, *meta*, or *para* position worked well under the given conditions, affording the expected products in good yields. However, cinnamamide with electron-donating substituents mainly provided by-products of oxytrifluoromethylation along with low yields of cyclization products. The substrates with two electron-donating substituents in the aniline ring afforded the higher yields compared with those substrates with no substituent or only one methoxy substituent. A reasonable reaction mechanism was proposed in Figure 26. Initially, CuI reacted with Togni's Reagents to generate a trifluoromethyl radical, and then the trifluoromethyl radical was added to the double bond of substrate **1** to produce free radical intermediate **113.** Further, **113** was oxidized to carbocation **114** by Cu(II) *via* a single electron transfer process. Finally, carbocation **114** underwent an intramolecular electrophilic cyclization and deprotonation process to obtain the final product **110.** However, the carbocation **114** was attacked by 2-iodobenzoate, giving the oxytrifluoromethylation byproducts **111** *via* a nucleophilic addition process.

In 2015, Xia and his colleagues developed visible-light induced cascade reaction of *N*-arylcinnamamides with Togni's reagent for the synthesis of CF_3-containing 3,4-disubstituted dihydroquinolinones and 1-azaspiro [4.5] decanes using *fac*-Ir(ppy)$_3$ as photocatalyst (Figure 27) [59].

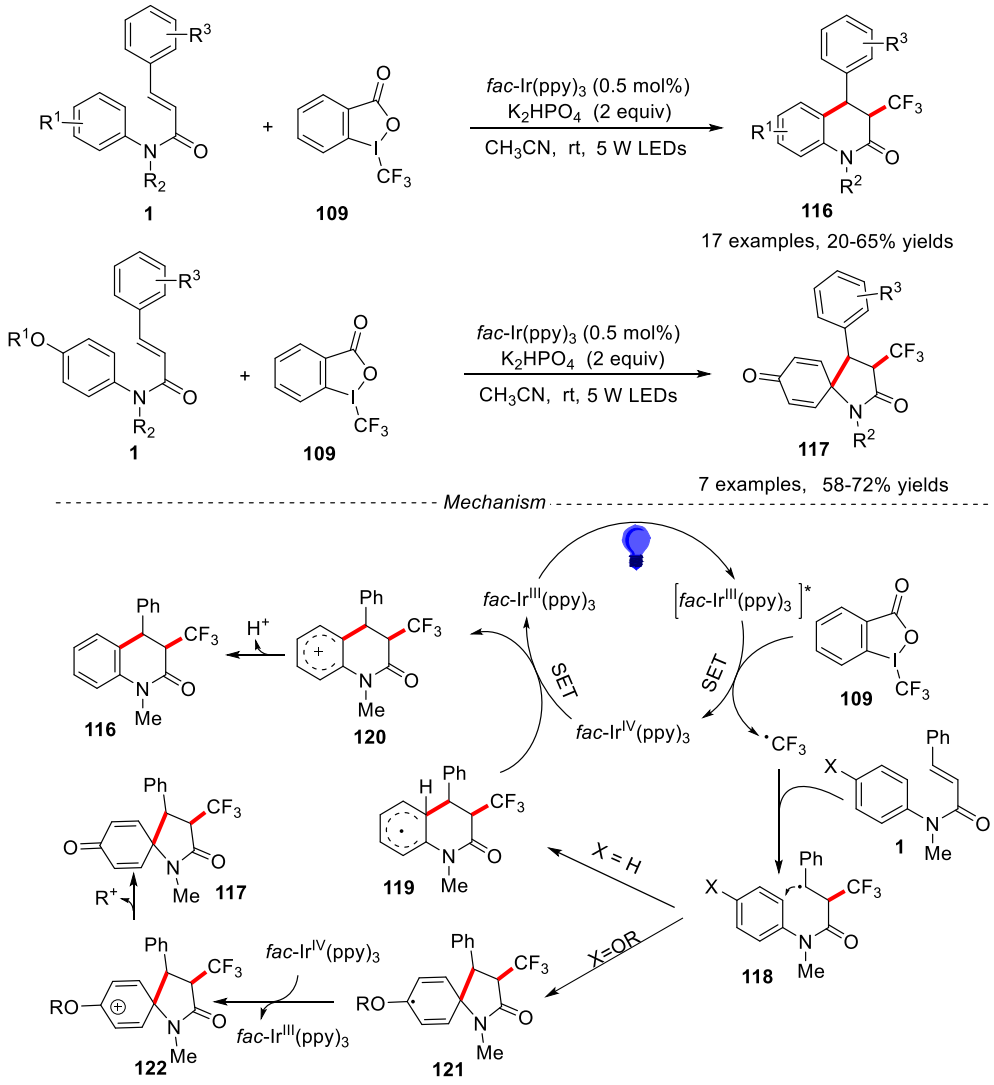

Figure 27. Visible-light induced reaction of *N*-arylcinnamamides with Togni's reagent for the synthesis of CF_3-containing 3,4-disubstituted dihydroquinolinones and 1-azaspiro[4.5] decanes.

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The substituent of *N*-arylcinnamamides would affect the final product. The *N*-arylcinnamamides with different groups such as Me, Cl, Br and F on the *para*-position of anilines were tolerated under the reaction conditions, providing the dihydroquinolinones in moderate yields. However, when the *para*-position of anilines was substituted by -OH, or -OTBS group, 3,4-disubstituted 1-azaspiro [4.5] decanes were obtained in moderate to good yields. *Ortho*-Me substituent on the aniline ring gave the relatively lower yield due to steric hindrance. Substrates with different *N*-protecting groups such as Me, Et, Ph and Bn were effective under the given conditions and provided the desired products in moderate to good yields. A plausible mechanism was described in Figure 27**.** Firstly, the excited state [*fac*-Ir^{III} $(ppy)_3$]* was generated under the irradiation of blue LEDs. Then, [*fac*-$Ir^{III}(ppy)_3$]* transferred an electron to Togni's reagent led to trifluoromethyl radical and generated the *fac*-$Ir^{IV}(ppy)_3$ species. Subsequently, the trifluoromethyl radical was added to the double bond of the substrate **1** to generate the radical intermediate **118**, which was further cyclization by the different processes to produce the intermediate **119** and **121**. Finally, **119** or **121** was oxidized by *fac*-$Ir^{IV}(ppy)_3$ and lost H^+ or R^+ to give the desired product **116** or **117**.

3.2.4. Using $BrCF_2COOEt$ as a CF_2 sources

Except for Togni's reagent, $BrCF_2COOEt$ have been widely used as a CF_2 sources in organic synthesis [60,61]. A visible-light induced method was also developed by Zhu's group for the synthesis of HCF_2COOEt-containing 3,4-disubstituted dihydroquinolinones and 1-azaspiro[4.5]decanes [62]. It has been found that the position of the substituent on the cinnamic ring had a great influence on diastereoselectivity. When the cinnamic ring had a *meta* or *ortho* substituent, and two pairs of enantiomers could be observed due to steric hindrance. When there was no or only one *para* substituent on the cinnamic ring, only *trans* diastereoisomers were obtained. For the *para*-position substituted anilines with F or CF_3 group, the reaction also worked well, providing the desired products in good yields. However, for the *para*-position of anilines was substituted by OH or OCH_3 group, 3,4-disubstituted 1-azaspiro[4.5]decanes **124** were obtained in moderate yields (Figure 28).

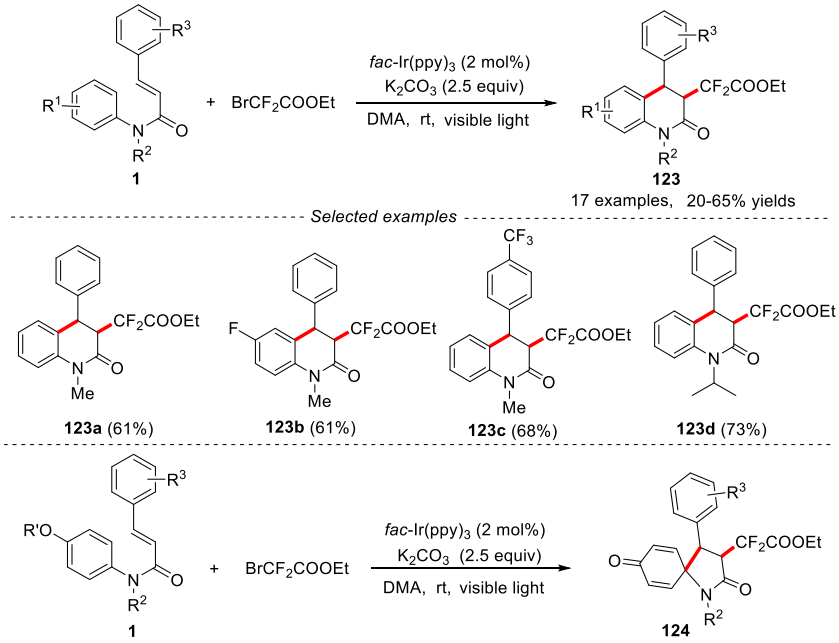

Figure 28. Visible-light induced cascade reaction of *N*-arylcinnamamides for the synthesis of HCF_2COOEt-containing 3,4-disubstituted dihydroquinolinones and 1-azaspiro[4.5]decanes.

3.3. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using chloroalkyl radicals

Chloromethyl groups are found in many bioactive natural products. The introduction of chloromethyl into organic molecules is of great significance for the synthesis of diverse organic

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molecules. A Cu-catalyzed cross-dehydrogenative coupling of *N*-arylcinnamamides with chloroform has been developed by Yu and co-workers using *tert*-butyl peroxybenzoate as oxidant [63]. Trichloromethyl substituted dihydroquinolin-2(1*H*)-ones were obtained in 78% yield. This mechanism indicated that the trichloromethyl radical might be involved in this cyclization process (Figure 29).

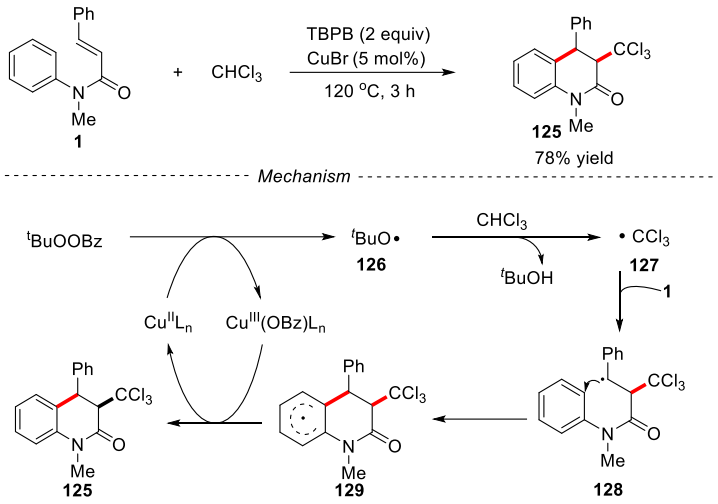

Figure 29. Copper-catalyzed cross-dehydrogenative coupling of *N*-arylcinnamamides with chloroform for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

Tang and co-workers developed $Mn(OAc)_3$-mediated radical dichloromethylation of arylacrylamides or *N*-phenylcinnamamide for the preparation of chloro-containing oxindoles or 3,4-dihydroquinolin-2(1*H*)-ones [64]. When *N*-methyl-*N*-phenylcinnamamide was used, the desired 3,4-dihydroquinolin-2(1*H*)-one was obtained in 39% yield. The cheap and easily prepared $Mn(OAc)_3{\cdot}2H_2O$ was used in this reaction. The reaction mechanism was manganese (III)–*o*-tolylboronic acid mediated radical oxidative dichloromethylation and cyclization of *N*-phenylcinnamamide with dichloromethane (Figure 30).

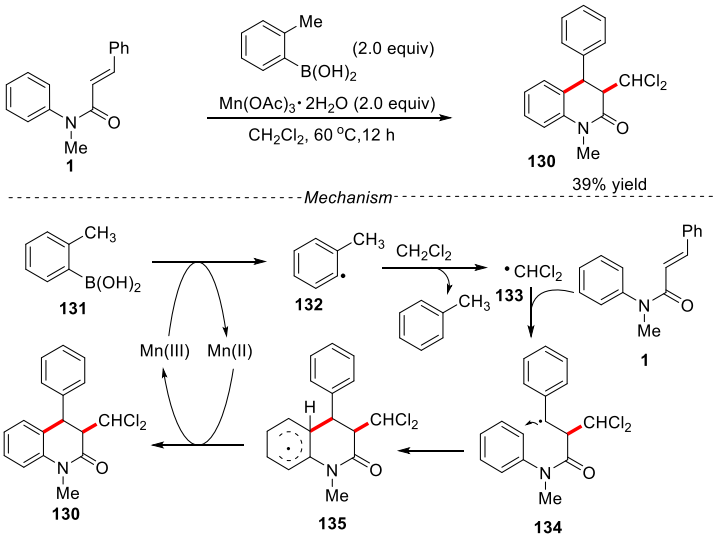

Figure 30. $Mn(OAc)_3$-mediated radical dichloromethylation of *N*-phenylcinnamamide for the preparation of chloro-containing 3,4 dihydroquinolin-2(1*H*)-one.

3.4. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using acyl radicals

Carboxylic acids are rich and cheap organic compounds with diverse structures. Synthetic chemists have been trying to apply these compounds to participate in new organic transformation.

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In 2015, Wallentin and co-workers reported a visible-light photocatalytic tandem acylarylation of olefins by using carboxylic acids as acyl radical precursors for the synthesis of different heterocyclic compounds [65]. When *N*-phenylcinnamamide reacted with benzoic acid in the presence of the *fac*-Ir(ppy)$_3$ photocatalyst, 2,6-lutidine and DMDC (dimethyl dicarbonate) under visible-light irradiation, the corresponding dihydroquinolinone was obtained in 32% yield. The mechanism showed that the reaction underwent a free radical process. Benzoic acid reacted with dimethyl dicarbonate (DMDC) to form a mixed anhydride intermediate **138**, which could be transferred to key acyl radicals **140** through a single-electron reduction pathway, along with CO_2 and methanoate as by products (Figure 31).

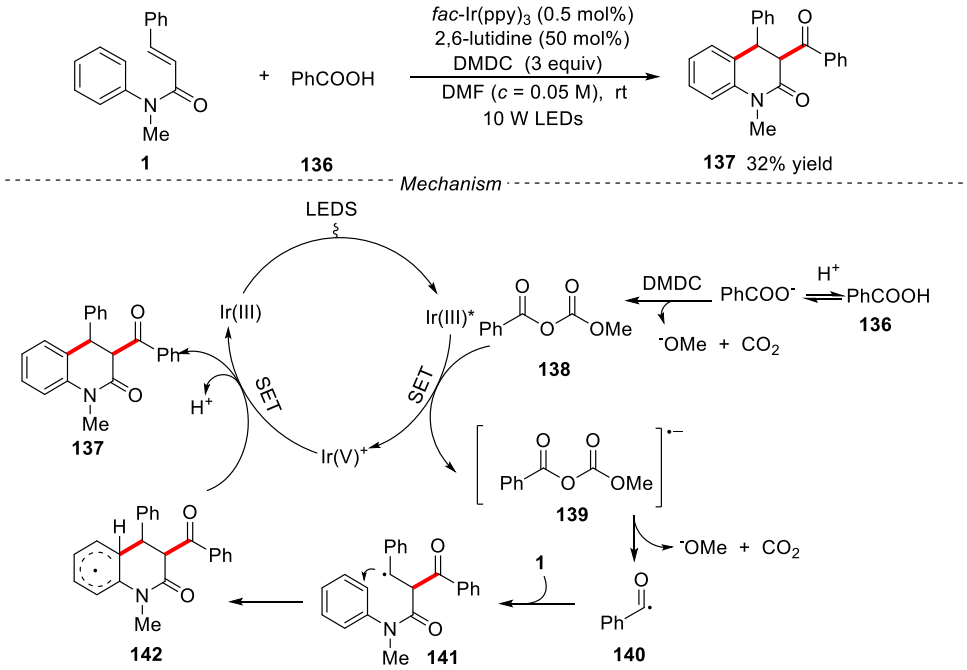

Figure 31. Photo-induced C(sp^3)-H functionalization for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

α-Keto acids are cheap, easily available and relatively stable organic compounds. Its have been widely used as acylating agents in transition metal catalyzed decarboxylation coupling reactions and photo-induced acyl radical conversion reactions. In 2014, Mai and co-workers developed a silver-catalyzed protocol for the synthesis of 3-acyl-4-aryldihydroquinolin-2(1*H*)-ones or 3-acyl-4-arylquinolin-2(1*H*)-ones *via* intermolecular radical addition/cyclization of *N*-phenylcinnamamide with *α*-keto acids in CH_3CN/H_2O media [66]. It has been found that 3-acyl-4-aryldihydroquinolin-2(1*H*)-ones **144** or 3-acyl-4-arylquinolin-2(1*H*)-ones **145** could be selectively obtained by adjusting the amount of $K_2S_2O_8$. The reaction showed a wide range of substrates. Electron-withdrawing and -donating substituted groups on the phenyl ring of cinnamic acid worked well, affording the corresponding products in moderate yields. Different protective groups on the nitrogen atom, such as -Me, -Bn and -CH_2CH_2CN were effective in this reaction, providing the final products in moderate yields. Both aliphatic and aromatic keto acids were compatible in this reaction (Figure 32).

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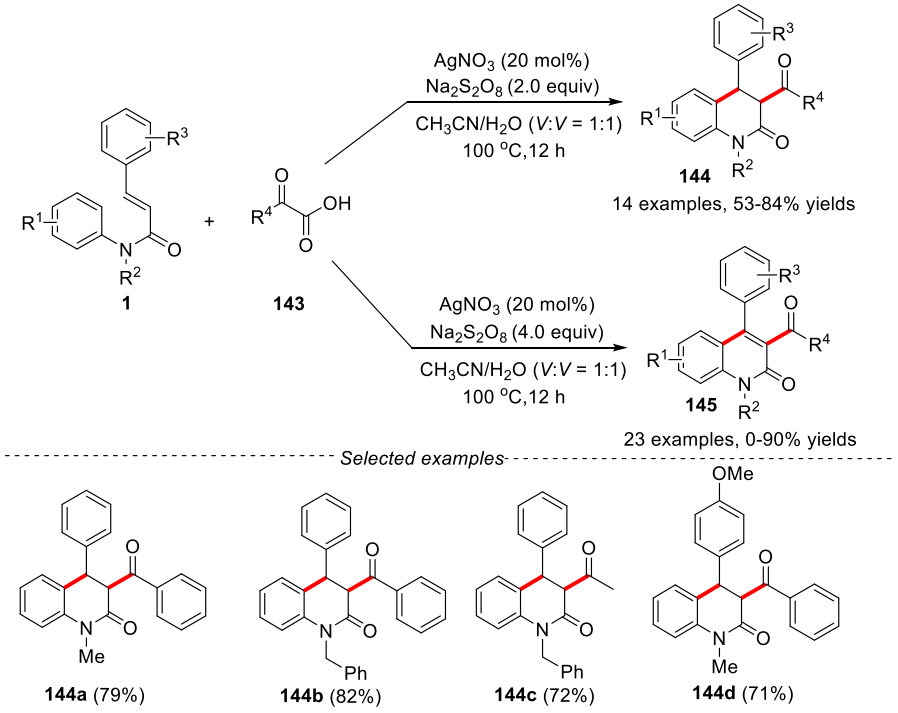

Figure 32. A silver-catalyzed protocol for the synthesis of dihydroquinolin-2(1*H*)-ones or quinolin-2(1*H*)-ones *via* intermolecular radical addition/cyclization of *N*-phenylcinnamamide with keto acids.

At the same time, a similar result was reported by Duan's group [67]. In this transformation, the decarboxylation coupling/cyclization reaction occurred using acetone/H_2O as solvents under much milder condition (Figure 33).

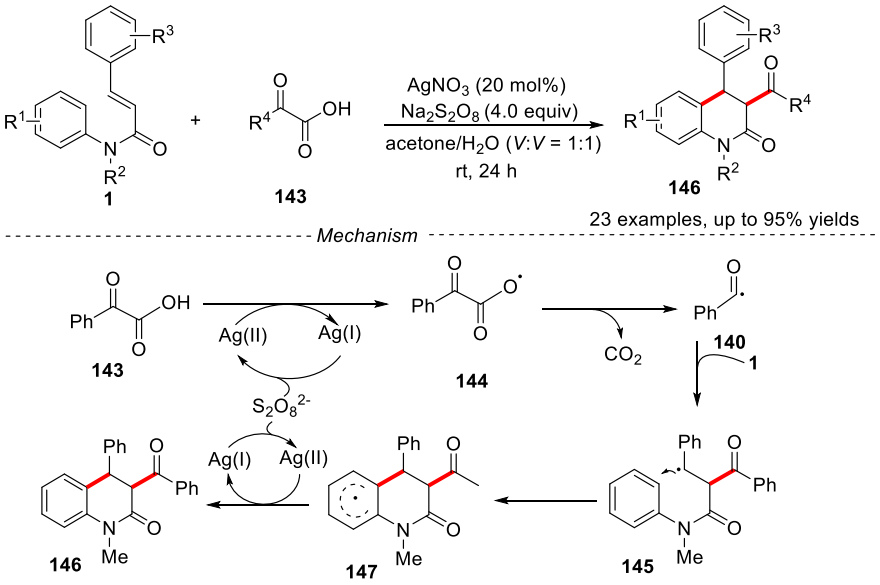

Figure 33. A silver-catalyzed protocol for the synthesis of dihydroquinolin-2(1*H*)-ones *via* radical addition/cyclization of *N*-phenylcinnamamide with keto acids.

The reaction showed a broad substrate scope and excellent functional groups tolerance. A variety of valuable substituted dihydroquinolinones could be easily obtained in moderate to excellent yields with high stereoselectivity. When free radical scavengers such as 2,2,6,6-tetramethylpiperidine oxide (TEMPO) and butylated hydroxytoluene (BHT) were added to the reaction under the standard conditions, the reaction was significantly inhibited, which indicated that the reaction might undergo a free radical reaction process. Ag (I) transferred one electron to keto acid to obtain free radical

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intermediate **144,** which was further decarboxylated to obtain the key acyl radical **140**. The key acyl radical was reacted with substrate **1** *via* a radical addition/cyclization and re-aromatization process to give the final product **146.** This high stereoselectivity could be explained by the intermediate **147**, which led to the *trans*-isomer due to minimizing the strain of benzoyl and phenyl groups on six-membered ring.

In 2015, a metal-free catalyzed method was reported by Mai and co-workers for the synthesis of 3-acyl-4-aryldihydroquinolin-2(1*H*)-ones by cascade radical addition/cyclization of *N*-arylcinnamamides with aldehyde [68].

In this reaction, TBAB (tetrabutylammonium bromide) was used as catalyst, $K_2S_2O_8$ was used as oxidant. Different solvents such as DCE, DMF, CH_3CN, EtOAc, dioxane and EtOH were tested for this transformation, and DCE gave the best results. The reaction also showed a wide range of substrates. The substrate scope revealed that the aromatic aldehyde bearing electron-donating groups gave higher yield than those having electron-withdrawing groups on the phenyl ring. When the aromatic aldehydes with strong electron-withdrawing groups, such as $-CF_3$ and $-NO_2$ were used as substrates, no desired products were detected. Except for aromatic aldehydes, aliphatic aldehydes such as acetaldehyde and propyl aldehyde were also compatible in this reaction, affording the target products in moderate yields. The *N*-arylcinnamamides with electron-donating and electron-withdrawing groups on the various positions were tolerated in this reaction, delivering the corresponding dihydroquinolinones in moderate yields. A possible mechanism was proposed in Figure 34. Firstly, using the catalyst of TBAB, the homolytic cleavage of the $S_2O_8^{2-}$ produced the sulfate radical anions. Then the sulfate radical anion was abstracted a hydrogen atom from aldehyde to generate acyl radical **140**. Subsequently, the acyl radical **140** reacted with the substrate **1** *via* a radical addition, *6-endo-trig* cyclization and re-aromatization process to give the final product **149**.

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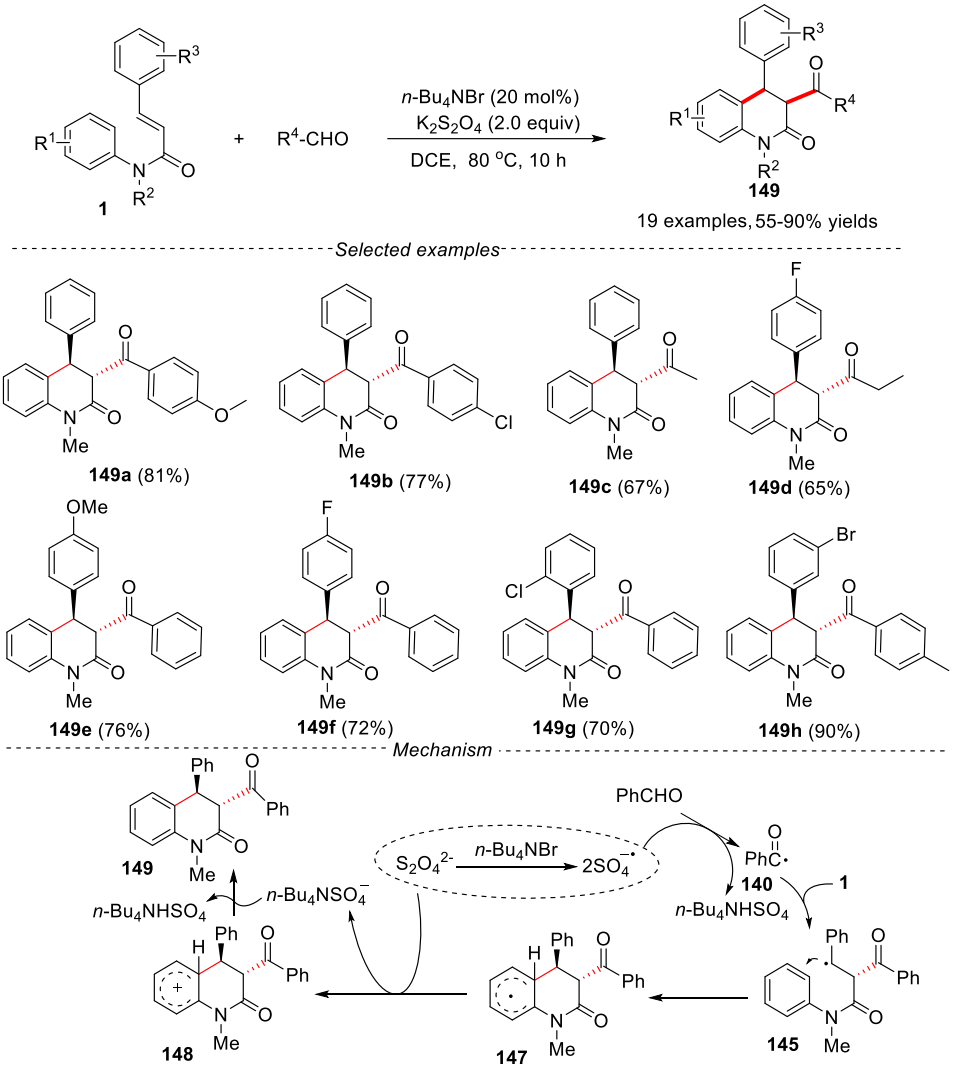

Figure 34. *n*-Bu4NBr catalyzed method for the synthesis of 3-acyl-4-aryldihydroquinolin-2(1*H*)-ones by cascade radical addition/cyclization of *N*-arylcinnamamides with aldehyde.

Oxime esters have been widely used as a kind of important builing blocks in the synthesis of nitrogen-containing compounds by thermal decomposition, transition metal catalysis or light-induced interruption. [69]. The *N*-O bond or C-C could be activated to form highly active iminyl radicals or acyl radicals. In 2019, Fan and co-workers developed a photocatalytic method for C-C bond activation of oxime ester to generate acyl radical using *fac*-Ir(ppy)3 as catalyst under mild conditions [70]. Only one example was reported, in which 3,4-dihydroquinolin-2(1*H*)-one **153** was obtained in 34% yield. A free radical mechanism was involved in the reaction process. Under the irradiation of blue-LED light, the photocatalyst *fac*-Ir(ppy)3 was converted to the excited state [*fac*-Ir(ppy)3] *, which further transferred an electron to oxime ester **151**, leading to the *N*-O bond of oxime ester was dissociated to form iminyl radicals, which underwent fast C-C bond homolysis and elimination of 1 molecule of CH3CN to produce the key acyl radical **154**. Next, the addition of the acyl radical **154** to substrate **1** gave the raidical intermediate **155,** which was further underwent an intramolecularcyclization process to form intermediate **156**. Finally, intermediate **156** was oxidized by the Ir(V)+ species to ggive the product **153** and regenerate the Ir(III) catalyst. (Figure 35).

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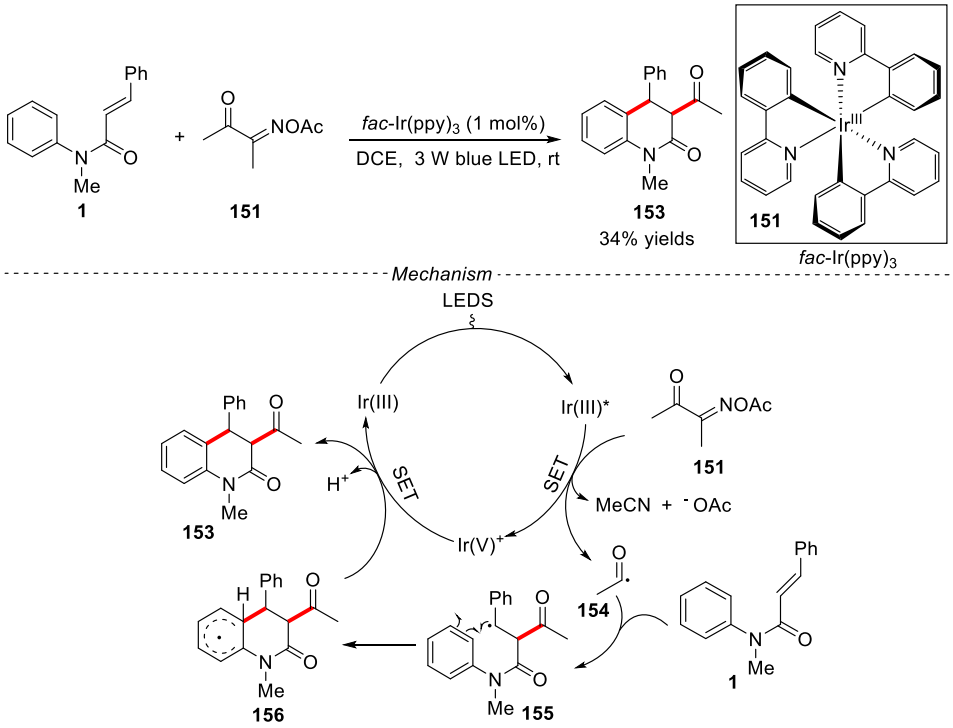

Figure 35. A photocatalytic strategy for the synthesis of dihydroquinolin-2(1*H*)-one from *N*-methyl-*N*-arylcinnamamides with oxime ester.

3.5. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using phosphorus-containing free radicals.

Phosphorus-containing compounds widely exist in organic compounds, such as drugs, natural products and materials [71, 72]. In recent years, the development of simple and effective methods has attracted significant attention of organic synthesis chemists for the synthesis of containing phosphorus organic heterocyclic compounds. In 2016, a silver-catalyzed cascade cyclization of cinnamamides with diphenylphosphine oxide was developed by Zhu's group for the synthesis of dihydroquinolin-2(1*H*)-ones [73]. The different silver salts, such as $AgNO_3$, Ag_2CO_3 and AgOAc were screened, and $AgNO_3$ gave the best results. $Mg(NO_3)_2{\cdot}6H_2O$ was more effective additive, and 0.3 equiv was found to be the ideal amount for the use of additive. MeCN was the most suitable solvent and the optimized reaction temperature was 100 °C. A broad range of cinnamamides bearing electron-donating and electron-withdrawing groups were well tolerated under the given conditions, providing the corresponding dihydroquinolin-2(1*H*)-ones **158** in moderate to good yields. Different *N*-protected groups, such as Me, Et, ^{i}Pr, ^{n}Bu, and Bn were compatible in this reaction, and the desired products were obtained in moderate to good yields. When radical inhibitor 2,2,6,6-tetramethylpiperidine oxide (TEMPO) was added to the reaction system, the reaction was significantly inhibited, indicating that the reaction experienced a free radical process. The key phosphonyl radical **159** was formed through the reaction of P(O)H compounds **157** with Ag(I) salt (Figure 36). The products could be transferred through the demethylation process, providing free *N*-protected dihydroquinolin-2(1*H*)-ones.

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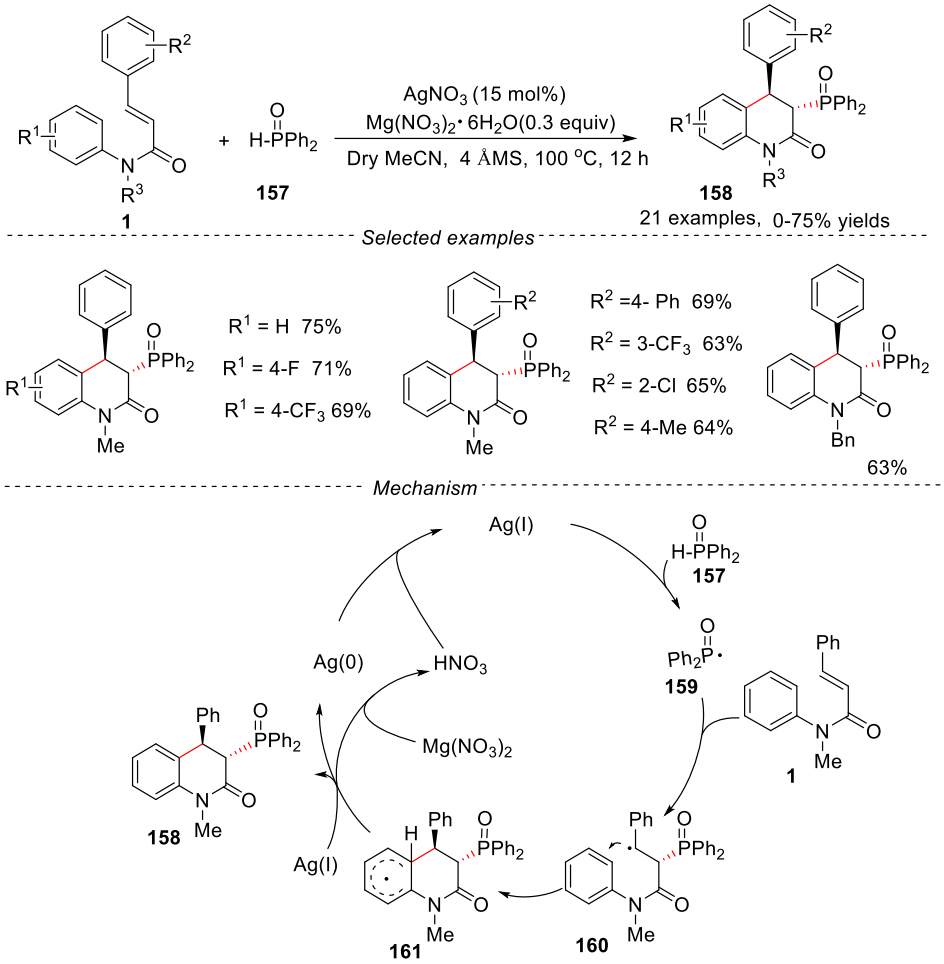

Figure 36. Silver-catalyzed cascade cyclization of cinnamamides with diphenylphosphine oxide for the synthesis of dihydroquinolin-2(1*H*)-ones.

3.6. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using sulphur-containing free radicals

In 2015, Wang and Tian reported a tandem sulfenylation/cyclization of *N*-arylacrylamides with sulfonyl hydrazides in the presence of iodine for the selective synthesis of 3-(sulfenylmethyl)oxindoles and 3- sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones [74]. In this reaction, iodine played multiple roles as an oxidant, a reductant, and a radical initiator. *β*-Substituted *N*-arylacrylamides reacted with sulfonyl hydrazides, followed by *6-endo-trig* cyclization to afford 3-sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones in good yields (Figure 37).

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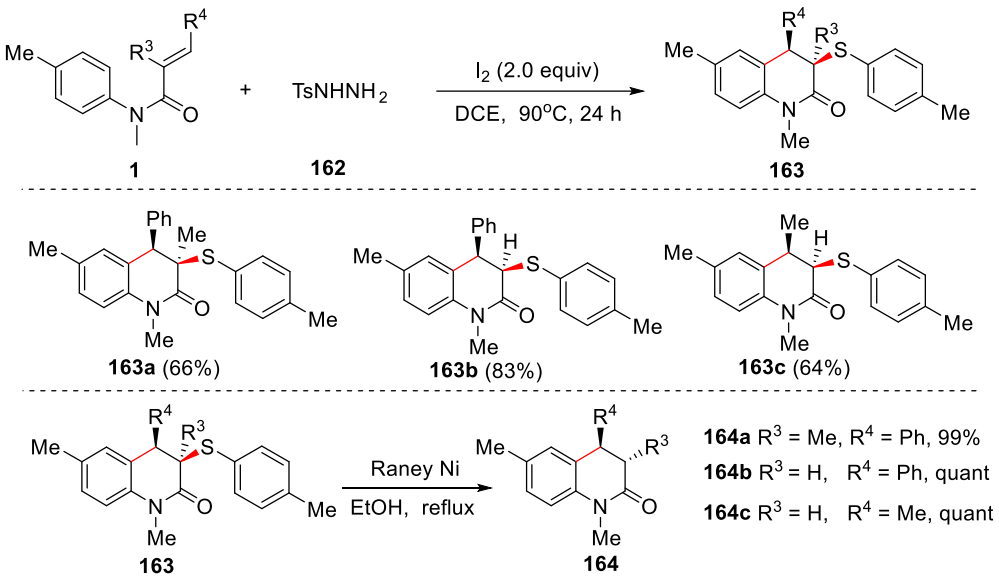

Figure 37. A tandem sulfenylation/cyclization of *N*-arylacrylamides with sulfonyl hydrazides for the synthesis of 3-sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones.

A reasonable reaction mechanism was proposed in Figure 38. At the beginning, sulfonyl hydrazide **162** reacted with I2 to give sulfinic acid **166** and sulfenyl iodide **167.** There might be two pathways to produce thiosulfonate **168**. One was that sulfinic acid **166 was** reduced by I2 to form thiosulfonate **168**. The other was that sulfinic acid **166** nucleophilicly attacked sulfenyl iodide **167** to give thiosulfonate **168**. Further thiosulfonate **168** was reduced by I2 to give disulfide **169**. After that, both thiosulfonate **168** and disulfide **169** were attacked by iodine radical generated from iodine upon heating to give sulfenyl radical **172**, which was reacted with *α,β*-unsaturated amide **1** *via* a radical addition/cyclization and re-aromatization process to give the final product **163.**

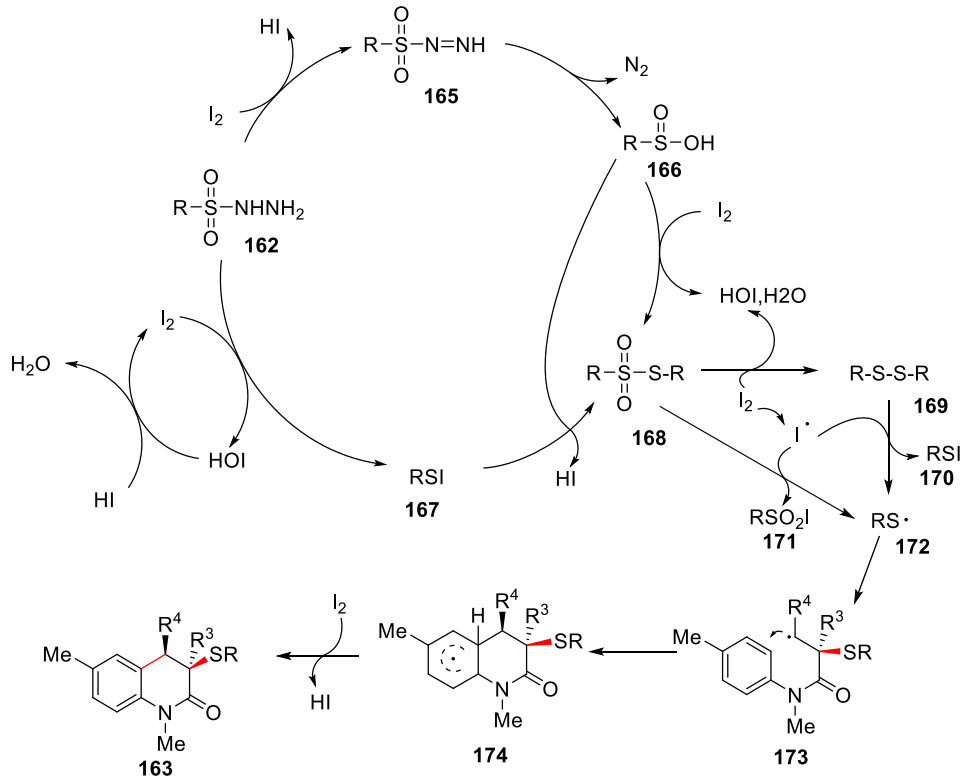

Figure 38. The mechanism for the synthesis of 3-sulfenyl-3,4-dihydroquinolin-2(1*H*)-ones.

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Sulfonates and sulfonic acids have been widely used in organic synthesis, material science, natural products and pharmaceutical chemistry. The introduction of sulfonic acid functional groups into the molecule can significantly adjust the water solubility and polarity of the compounds [75]. In this context, in 2022, $Mn(OAc)_3{\cdot}2H_2O$-promoted radical sulfonation from *N*-phenylcinnamamides and potassium metabisulfite ($K_2S_2O_5$) was developed by Liang's group for the synthesis of sulfonyl-containing 3,4-dihydroquinolin-2(1*H*)-one [76]. The substrate scope revealed that withdrawing groups at *para* position of the anilines gave excellent yields. The electron-donating or -withdrawing groups on the aromatic ring that was located at the *beta*-position of double bonds were well tolerated, affording the corresponding products in excellent yields. The sulfonyl-containing 3,4-dihydroquinolin-2(1*H*)-one could be further converted to aldehyde **177** in DMF. This reaction probably proceeded *via* the elimination of sulfonyl moiety followed by the in-situ Vilsmeier–Hack formylation (Figure 39).

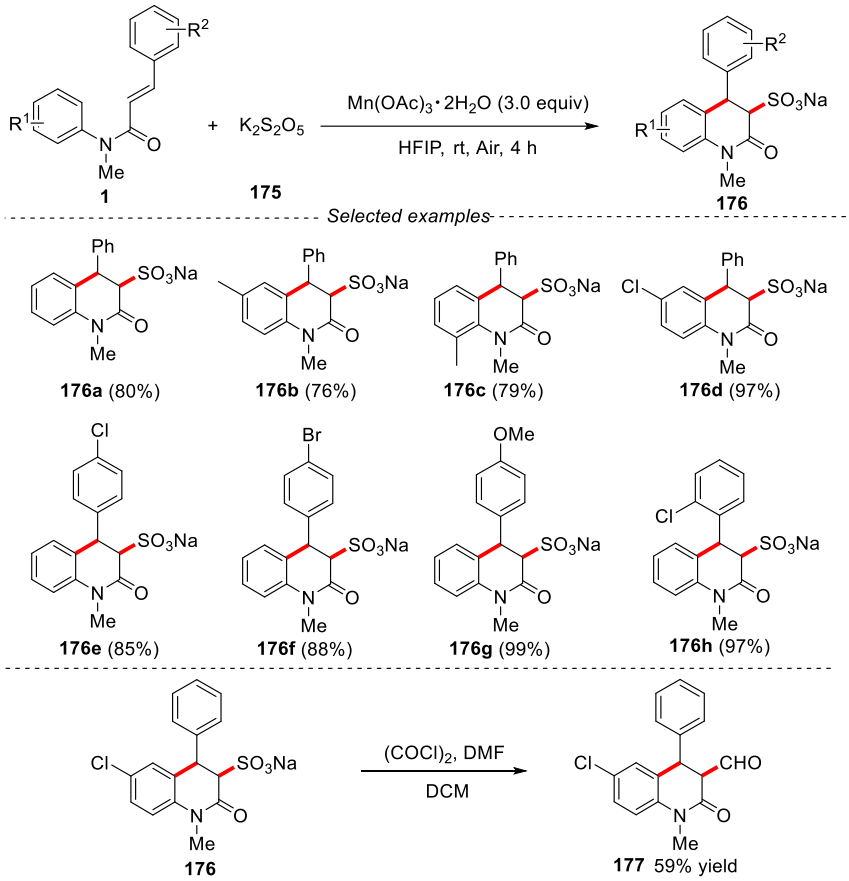

Figure 39. $Mn(OAc)_3$-promoted radical sulfonation of *N*-phenylcinnamamide for the preparation of 3,4 dihydroquinolin-2(1*H*)-ones.

3.7. Synthesis of 3,4-dihydroquinolin-2(1H)-ones using selenyl free radicals

In the past few years, electrochemistry has become an attractive method in the field of organic synthesis due to its environmental friendliness and practicality. Because of the use of electrons as oxidation or reduction reagents, synthetic electrochemistry can achieve oxidation and reduction reactions without the need for transition metal catalysts or toxic reagents.

In this regard, in 2020, Chen and co-workers successfully developed an electrochemical approach for the synthesis of functionalized 3,4-dihydroquinolin-2(1*H*)-ones **179** through cascade selenylation/cyclization of *N*-arylcinnamamides with diphenyl diselenide **178** [77]. The reaction was performed in an undivided cell equipped with a platinum anode and a Fe plate cathode by using $^{n}Bu_4NPF_6$ as the electrolyte under a constant current of 8 mA, and MeCN as solvent. An evaluation of substrate scope revealed that a series of substituted *N*-arylcinnamamides were smoothly converted

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to the selenylated 3,4-dihydroquinolin-2(1*H*)-ones in moderate to good yields with high diastereoselectivity (Figure 40).

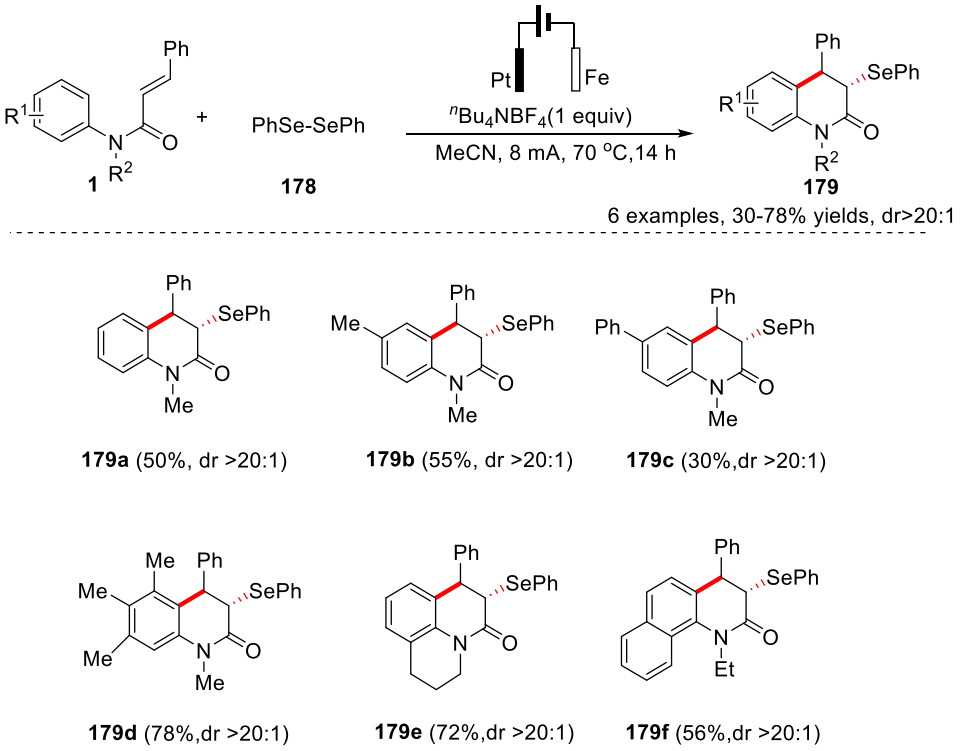

Figure 40. Cascade selenylation/cyclization of *N*-arylcinnamamides with diphenyl diselenide for the the synthesis of functionalized 3,4-dihydroquinolin-2(1*H*)-ones.

In 2021, Pan's group also reported an electrochemical protocol for the construction of C-Se bond *via* tandem cyclization of *N*-arylacrylamides or *N*-arylcinnamamide with diselenides [78]. In this transformation, platinum plates was used as anode and graphite rods was used as cathode, $^{n}Bu_4NPF_6$ was used as the electrolyte under a constant current of 15 mA, and CH_3CN/1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the co-solvents. Only one example was reported, the 1-methyl-4-phenyl-3-(phenylselanyl)- 3,4-dihydroquinolin-2(1*H*)-one **180** was obtained in 35% yield along with the formation of 1-methyl-4-phenylquinolin-2(1*H*)-one **181** with a yield of 50%. A possible mechanism was proposed in Figure 41. PhSeSePh lost one electron on the anodic to form selenium free radical **183** and selenium cation **184.** The selenium free radical **183** was added to the double bond of substrate **1** to generate radical intermediate **186,** which underwent an intramolecular cyclization to lead to radical intermediate **187**. Finally, **187** underwent anodic oxidation and deprotonation to produce the final product **180** (path a). In another way selenium cation **184** was added to the double bond of the substrate **1** to generate the cation intermediate **189**, which underwent an intramolecular cyclization and deprotonation leading to the formation of product **180** (path b) (Figure 41).

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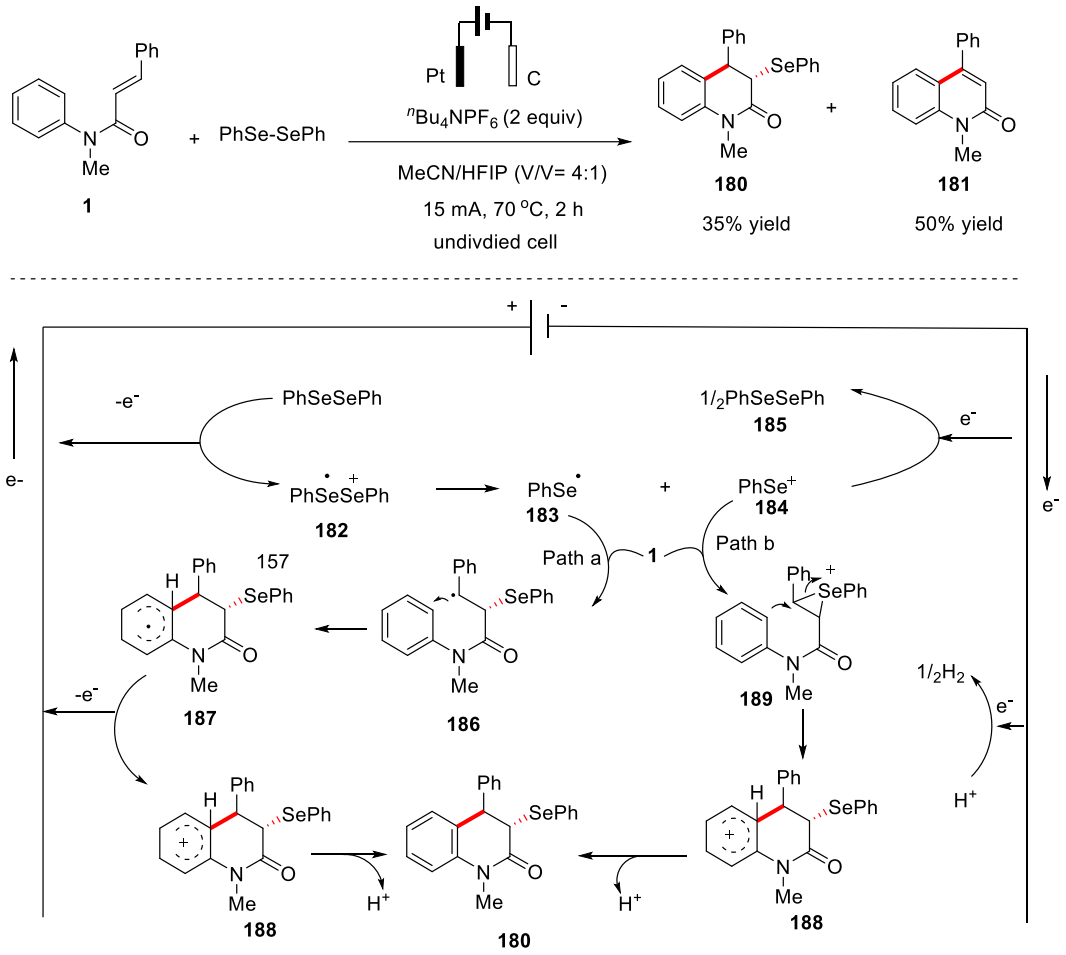

Figure 41. An electrochemical protocol for the synthesis of 3,4-dihydroquinolin-2(1*H*)-one *via* tandem cyclization of *N*-arylcinnamamide with diselenides.

4. Synthesis of 3,4- dihydroquinolin-2(1*H*)-ones using photoredox cyclization

Photocyclization of acrylanilides **1** to the corresponding 3,4-dihydroquinolin-2-ones was first described by Chapman and co-workers [79]. Later, the research mainly focused on the mechanism of photocyclization using high-energy UV light stimulation with high pressure Hg lamps. These reactions showed a narrow range of substrates [80, 81]. To resolve this problem, developing a general and simple system was still desired for the preparation of 3,4-dihydroquinolin-2-ones. In this regard, in 2021, Chi and co-workers developed a photo-induced 6π cyclization of *N*-arylacrylamides for the synthesis of 3,4- dihydroquinolin-2(1*H*)-one using luminescent platinum (II) complex **Pt-2** as photocatalyst [82]. It was found that additives played a very important role in this reaction. Inorganic bases such as Cs_2CO_3, Na_2CO_3, K_2CO_3, and K_3PO_4 as additives could dramatically improve the product yield. The reaction showed a broad substrate scope and good functional groups compatibility. Substrates with both electron-withdrawing and electron-donating on the *para*-position of anilines were well tolerated, providing the corresponding dihydroquinolin-2(1*H*)-ones in 30-99% yields. Although *N*-arylamides bearing *meta* substituents exhibited good reactivity as well, the mixture of products were obtained albeit with poor regioselectivity**.** Substrates with other alkyl and aromatic substituents on nitrogen atoms were also effective in this transformation. Substrates with a phenyl group at the *α* and *β* position of *N*-arylamides also afforded products in good yields. Heteroaromatic substrates such as quinoline, benzothiazole, 1,2,3,4-tetrahydroquinoline and indoline worked well under the given conditions, providing the desired products in good to excellent yields. Further applying this method to the total synthesis of natural products (±)-**SIPI6360** was realized [83] (Figure 42).

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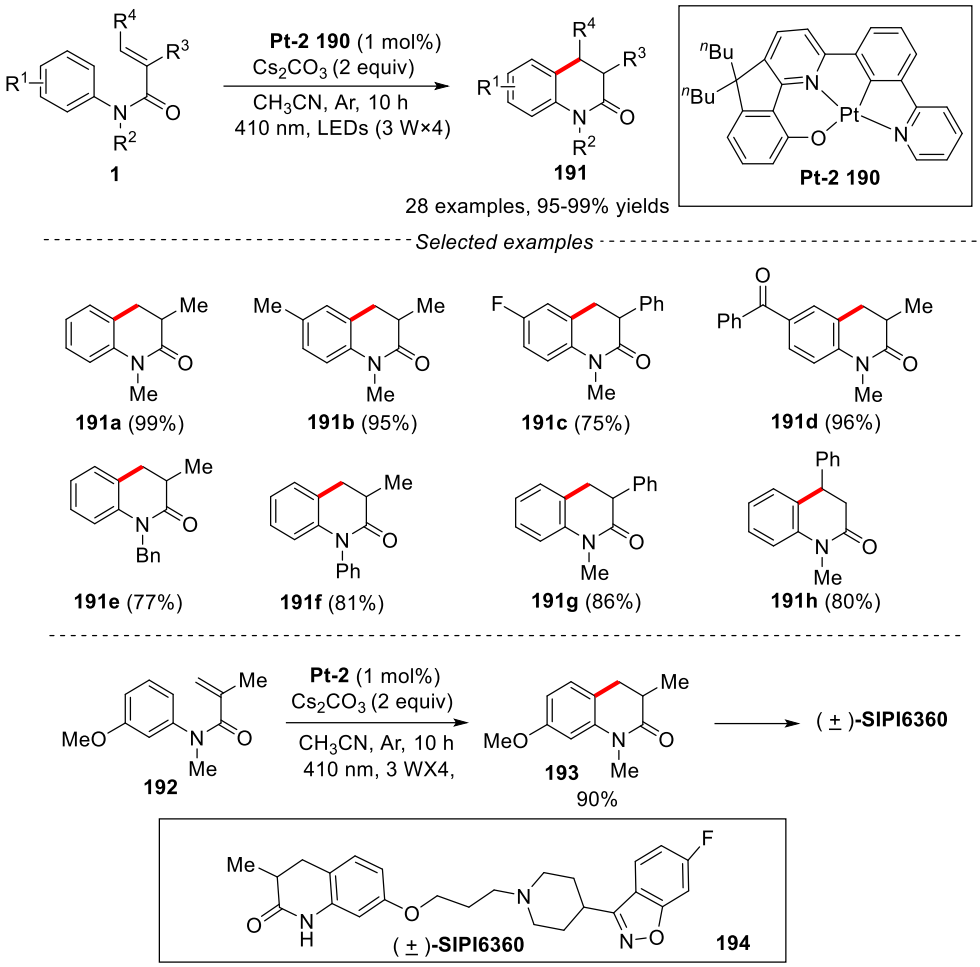

Figure 42. A photo-induced 6π cyclization of *N*-arylacrylamides for the synthesis of 3,4-dihydroquinolin-2(1*H*)-one.

Although the use of expensive metal catalysts has achieved great success, there are still strong desire for chemists to develop metal-free method for these important transformations due to people's attention to environmental issues and saving synthetic costs. In 2021, Petersen's group described a thioxanthone-catalyzed method for the synthesis of 3,4-dihydroquinolin-2-ones *via* a 6π-photocyclization process [84]. *N*-methyl-*N*,2-diphenylacrylamide bearing electron-withdrawing or electron-donating groups on the aniline such as -F, -Cl, -Br, -I, -OMe were well tolerated using **2-CTX** as catalyst, providing the target products in good yields. However, substrates with strong electron-withdrawing groups gave poor yields. *N*-methyl-2-phenyl-*N*-(pyridin-2-yl) acrylamide also reacted smoothly with a good yield. Variation of the aromatic groups at the 3-position were also well tolerated, affording the desired products in good to excellent yields. Switching the aromatic substitution to the 4- position, only 32% isolated yield was obtained with a 1:2 E/Z ratio. A proposed mechanism was proposed in Figure 43. Under the light irradiation, the ground state **2-TX** was transferred to the excited state ^{1}**2-TX*,** which further underwent internal conversion and rapid intersystem crossing (ISC) to produce its triplet state ^{3}2-TX*. Then, triplet state ^{3}**2-TX*** transferred the energy to substrate **1** *via* triplet energy transfer (TET) process to produce the triplet state of substrate **197** and return the catalyst to its ground state **2-TX.** The triplet state of substrate **197** went through a 6π-electrocyclization to give intermediate **198**, which transferred product **200** either by a direct *[1,5]-H* shift process or *via* a two-step re-aromatization−tautomerization process. The mechanism of free radicals might also be involved in the photochemical process [85,86] (Figure 43).

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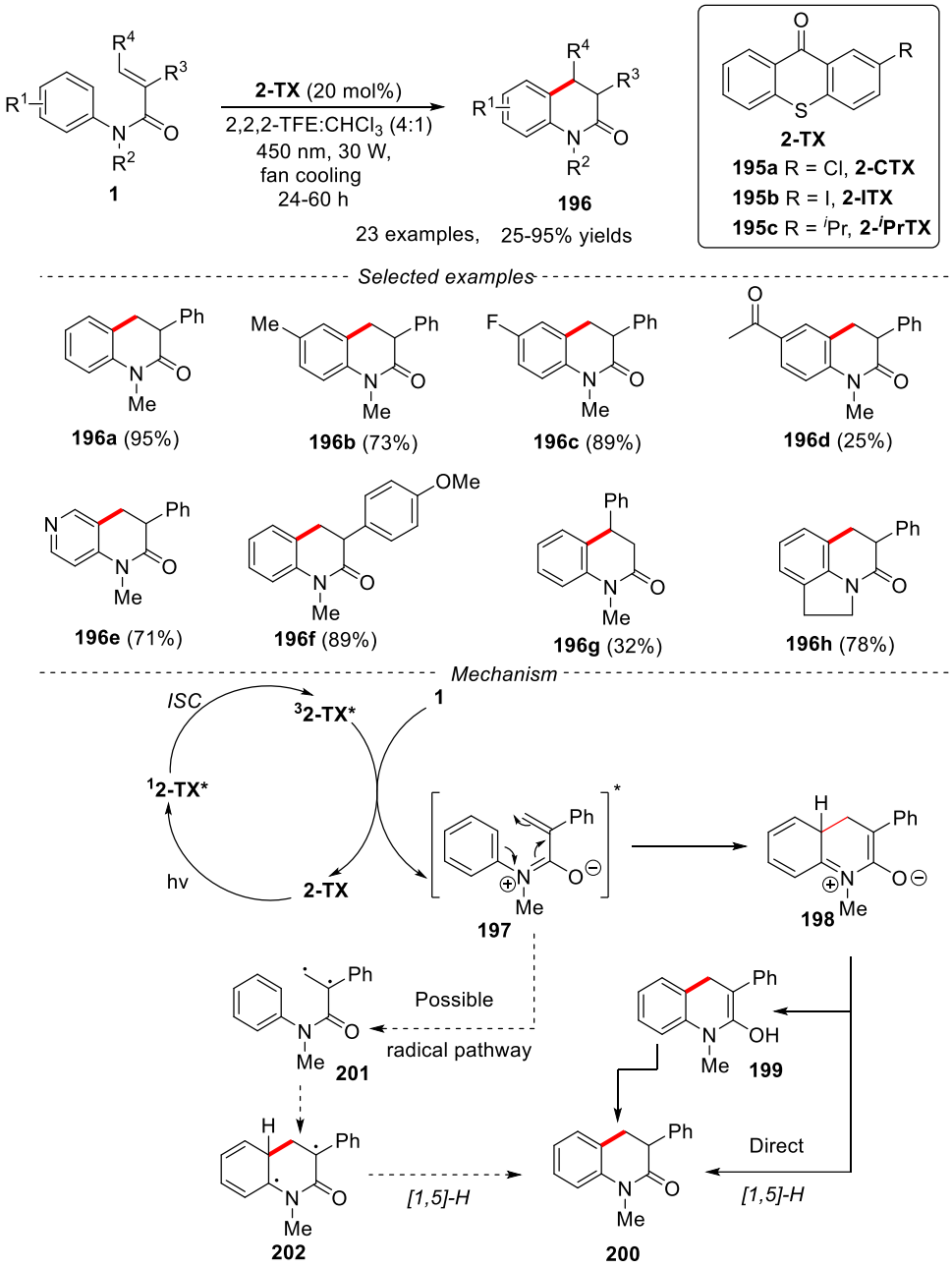

Figure 43. A thioxanthone-catalyzed method for the synthesis of 3,4-dihydroquinolin-2-ones *via* a 6π-photocyclization process.

In 2022, Huang and Ji's groups developed a visible-light induced photoredox cyclization of *N*-Arylacrylamides for the synthesis of dihydroquinolinones [87]. 4CzIPN was used as a photosensitizer and acetonitrile was used as reaction solvent. Cinnamamides bearing different groups in the *para* position were tolerated under the given conditions, affording the expected products in good to excellent yields. 2-phenylacrylamides reacted smoothly to give 3-arylquinolinone derivatives in moderate to excellent yields. 2-Methylacrylamides with electron-donating groups gave better results. Substrates derived from 1-naphthylamine and 2-naphthylamine showed high reactivity. Firstly, under the visible-light irradiation, the triplet state of substrate **205** generated *via* triplet energy transfer (TET) from the photosensitizer. Then the addition to the aniline moiety generated the 1,4-diradical intermediate **206,** which underwent an internal conversion and rapid intersystem crossing (ISC) to generate intermediate **207,** followed by the process of deprotonation to give the desired product (path a). Alternatively, the [*1,3]-H* shift of 1,4-diradical **206** proceeds to form the triplet state

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of intermediate **208**, which further underwent an internal conversion and rapid intersystem crossing (ISC) process to give the final product **204** (path b) (Figure 44).

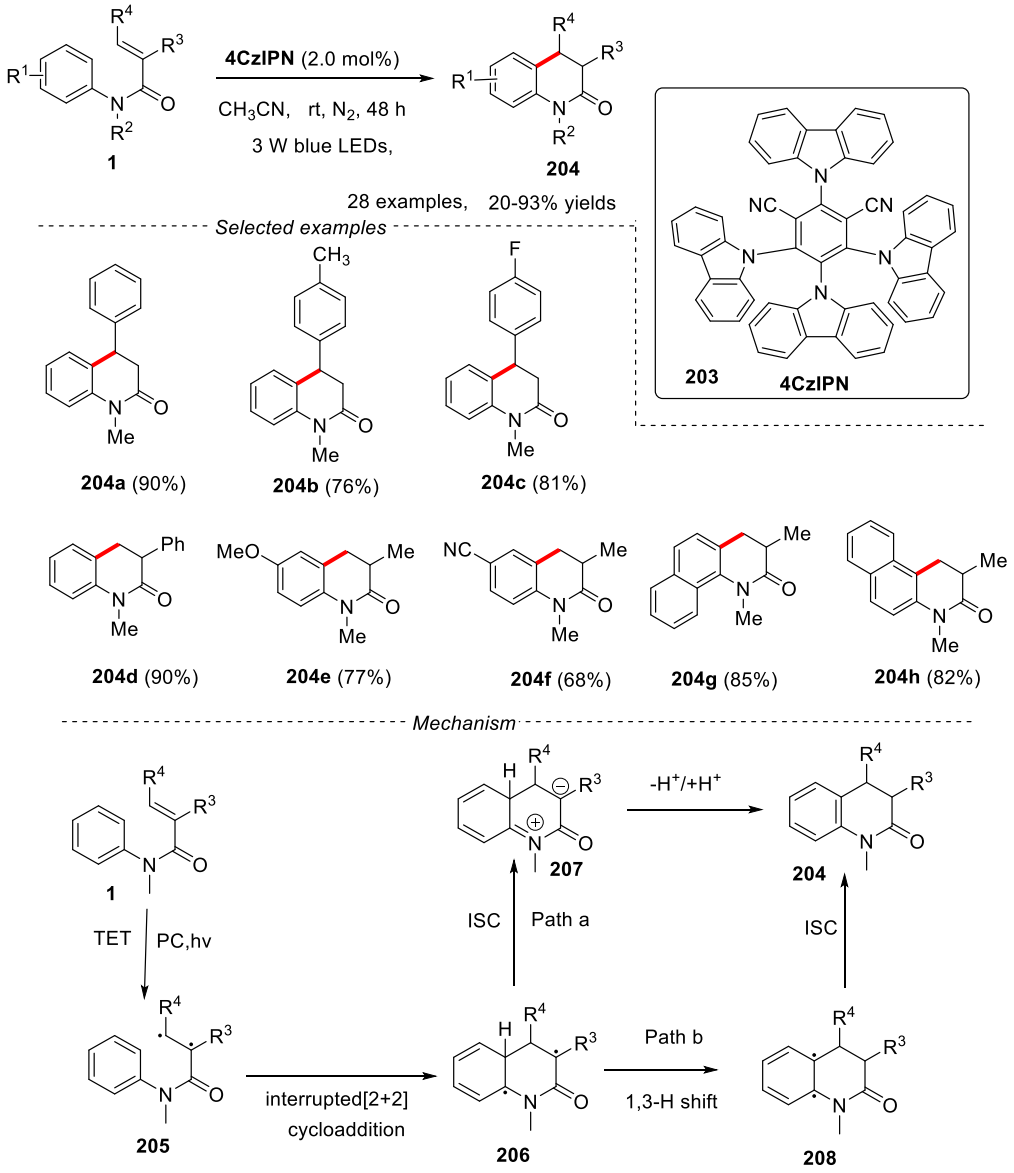

Figure 44. A visible-light induced photoredox cyclization of *N*-Arylacrylamides for the synthesis of dihydroquinolinones using 4CzIPN as catalyst.

The application of 6π-photocyclization methods were also applied for the synthesis of 3,4-dihydroquinolin-2-ones in the field of asymmetric synthesis. A thiourea/urea catalytic method for the 6π-photocyclization of acrylanilides has been reported for the synthesis of 3,4-dihydroquinolin-2-one [88]. However, poor enantioselectivity was observed in this reaction. Recently, the application of "axial to point chirality transfer" strategy has been shown effectively for the synthesis of 3,4-dihydroquinolin-2-ones with high enantioselectivity [89-91]. However, the substrate scope was limited. In 2023, catalytic enantioselective 6π-photocyclization of acrylanilides was developed by Paton and Smith's groups using $Ir((5\text{-}CF_3)(4'\text{-}t\text{-}Bu)ppy)_3$ as photocatalyst in the presence of $Sc(OTf)_3$ and chiral ligand [92]. In this reaction, chiral Lewis acid complexes that was generated through the reaction with $Sc(OTf)_3$ and chiral ligand, played a very important role and could enable selective energy transfer from a photosensitizer to facilitate enantioselective triplet state reactions. A series of substituted dihydroquinolones were obtained in moderate to excellent yields with high diastereo and enantioselectivity. The acrylanilides with various alkyl groups on the N atom, such as Me, Bn, *n*-Pr, isobutyl, allyl and PMB were well compatible with the reaction. By introducing a 3-substitued group

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on aniline ring, cyclization onto either *ortho* position was viable, resulting in the formation of two regioisomers. For the *para*-position substituted anilines with a variety of functional groups, the substrates bearing electron-donating substituents gave higher yields under the given conditions (Figure 45).

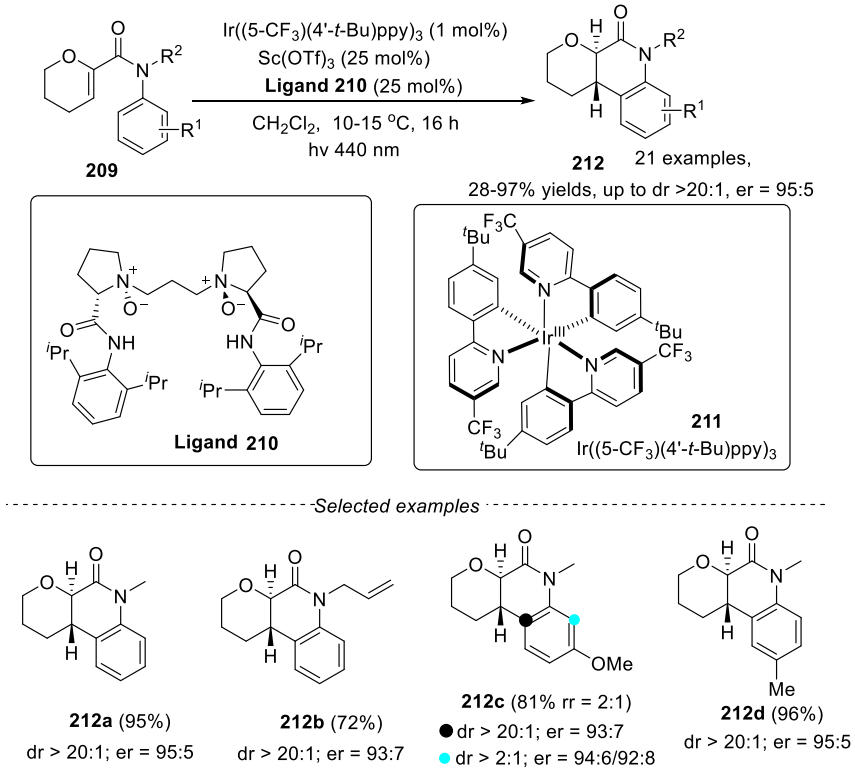

Figure 45. Catalytic enantioselective 6π-photocyclization of acrylanilides using Ir((5-CF_3)(4′-*t*-Bu)ppy)$_3$ as photocatalyst in the presence of chiral Lewis acid complexes.

5. Conclusions

The synthetic methods of 3,4-dihydroquinolin-2(1*H*)-one derivatives have been reviewed in this paper. Using *α,β*-unsaturated *N*-arylamides as the key substrate by applying simple and mild reaction conditions to synthesize 3,4-dihydroquinoline-2 (1*H*)-one is an effective strategy. In these synthesis methods, the application of electrophilic cyclization reaction, free radical initiated cyclization and 6π photochemical cyclization provides a sustainable choice for the synthesis of 3,4-dihydroquinoline-2 (1*H*)-one.

Despite significant progress has been made in this field and shown its potential application, there are still some key problems to be solved in this field: (1) Developing efficient photochemical catalysts and high regioselective synthesis methods are still in demand. (2) Developing green synthesis protocols by using non-toxic organic reagents is still a challenging area for the synthesis of organic molecules with biological activity. (3) Expanding to the field of asymmetric synthesis to synthesize chiral molecules and natural products with pharmaceutical activity has a broad space. Therefore, it is a long-term development goal in this field to design new and cheap catalytic systems and apply them to the synthesis of natural products, functional materials and drug molecules under mild conditions.

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