

## REVIEW

### Recent Free-Radical Reactions

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Received: 6 August 2018;

Accepted: 5 September 2018;

Published online: 30 November 2018;

AJC-19155

This review highlights the most recent syntheses of free radical reactions, which included numerous processes (photoredox catalysis free-radical reactions, free-radical cascade processes reactions, Minisci-type free radical alkylation reactions and metal-catalysis free radical reactions). A photoredox-catalyzed C–H functioning of aromatic heterocyclic utilizing an assortment of various, alkyltrifluoroborates has been mentioned. Utilizing organo-photocatalyst and a moderate oxidant, conditions malleable for functionalizing complex aromatic heterocyclics are outlined to prepare a oriental agent for late-stage derivatization. Radical alkylations of aromatic heterocyclic (Minisci reactions) appear a more direct functionalization of particular, C–H bonds. For the ground mentioned above, alkylation designing using radical have recently risen to significance for the late-stage functionalization of aromatic heterocyclic framework. Therefore, this issue is the primary point of the present survey, which thinks about work from the most recent five years. The work is ordered by the key procedures associated with the synthesis of free-radical reactions, planning to give researchers a simple comprehension of this free radical–reactions-based science and to give bits of knowledge to provide insights for further investigations.

**Keywords:** Multicomponent reaction, Free-radical, Cascade processes, Photoredox, Chemoselective, Alkynylation, Minisci reaction.

## INTRODUCTION

Free radical reactions are one of the most coveted simulated objectives has been increasingly popular, very versatile and very important method in organic synthesis and due to their considerable and precious applications in different fields are widely used in the past few years. Free radical reactions can be efficient in the preparation of a large number of organic compounds which has been found large applications in many areas of life due to the ease of use of this method, accuracy, selectivity and required mild condition. Free radical reactions have many types of reaction *e.g.*, cyclization, decarboxylation, additions reactions, hydrogen atom abstractions and alkylation *etc.* [1a]. Free radicals are very supportive for the synthesis of cycles, atomic relocating permit effective groups to combine and facilely used to generate a number of ligations in one step [1b]. Likewise, the improvement of radical-mediated, C–C bond-forming transmutation has also attracted increasing attention. Usually, these protocols tolerate good selectivity, are highly convenient with collective functional

groups and often required mild effective conditions [2,3]. Recently much attention has been paid on preparation of free-radical reaction cascade processes is characteristic step-provision and clarity of, procedure which perform the most dynamic and effective synthetic organic transmutation. The addition of radicals to unsaturated bonds generated new radicals, which then undergo addition to other unsaturated bonds and create free radicals. This reaction sequence, when takes place repeatedly, finally leads to the formation of polymers [4]. Yet the typical radical polymerization sequence also characteristic the core of free radical induced multi-component assembling reactions, supposing, that the individual steps take place in a controlled manner regarding to the gradation and the number of constituents [5].

By tedious preparation of the carefully prepared previous case, uni-molecular radical cascade access to complex natural products were effectively accomplished in the previous century [6]. Multicomponent free-radical-mediated cyclization-based strategies are powerful material toward molecular complexity and, hence, they have been used to successfully creating poly-

heterocyclic compounds. However, most of the reports characterize the use of these strategies include the preparation of monoheterocyclic compounds. On this basis, it is remarkable that the combination of MCRs with free-radical-based cyclization is also a suitable area to qualify the chemical space. Progresses in organometallic have been made in the recent years [7]. In dissimilarity, free radical mediated effective reactions prevail to be recognized [8]. To enable modification of molecules with increasing complexity essentially biomolecules with different sensitive effective groups, new chemoselective synthesis with ameliorate effective groups similarity and temperate reaction conditions are desired [9,10]. Landais and Godineau [8] pronounced that the chemoselectivity in the reaction of each reactant is major for good planned radical synthesis.

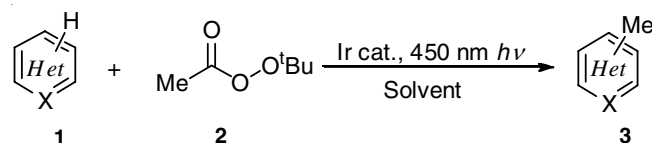
Formation of one carbon-carbon bond *via* splitting of dual C-H bonds, likewise called cross-dehydrogenative coupling (CDC), act for the ultimate atom-economic, spotless and effective organizing in synthetic organic chemistry. In the last few years, remarkable realization in the field of transition-metal-catalyzed ( $sp^2$ ) C-H functionalization have been accomplished [11,12]. Yet, it stayed inspiring to recognize an inert C-H bond [13]. Hence, reorganization of highly effective procedures for dehydrogenative C-C bond establishment *via* immediate C-H functionalization is highly eligible [14]. Radical alkylations of aromatic heterocyclic (Minisci reactions) [15] show a more direct functionalization of specific C-H bonds. For this cause, radical alkylation organizing has latterly stand up to importance for the late-stage functionalization of aromatic heterocyclic process. Even though Minisci and co workers at first used silver oxidants at high temperatures to create radicals from the relating carboxylic acids. Newly McCallum and Barriault [16] illustrated an effective cascade Minisci synthesis *via* a photocatalysis process in radical reactions. All these rules and idea supply proposition for styling inventive radical reactions [17].

Due to the rapid growth of free radical reactions of organic compounds in the last five years in quantity and quality, it was interesting to survey of all the recently published articles in the period from 2014 up to 2018 and if necessary, some of previous work in the field of free radical reactions. The paper includes the latest findings of the researchers and usefully provides reaction details for the most important reaction mechanism as well as numerous references to the original literature.

**Photo-redox free radical reactions:** Over the time, the critical and advantageous highlights of the photo-radical chemistry-selectivity, all inclusive statement, reactivity and consistency- have added to make it a broadly perceived and fundamental synthetic tool, designed to be utilized increasingly for the advancement of complex engineered methodologies.

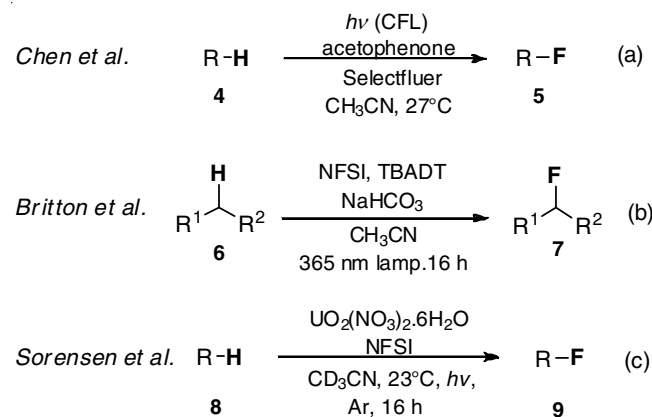
Dirocco and co-workers [18] have developed a flexible synthetic toward biologically active polyheterocycles through direct C-H functionalization of polysubstituted 5-membered ring (imidazole) and 6-membered (pyridines, pyrimidines and pyrazines) with alkyl (methyl and ethyl) agents using visible-light photoredox catalysis process (Scheme-I). This reaction mechanism started with initiating step through excitation of Ir(III) catalyst to give its excited state Ir(III)\*. Subsequently,

the direct reduction of *tert*-butyl peracetate **2** by Ir(III)\* produces  $\alpha$ -peroxy radical. The latter can decompose to *tert*-butoxy radical and acetic acid through homolytic cleavage of the weak O-O bond. The efficient  $\beta$ -scission of the *tert*-butoxy radical moiety, allows a good generation of methyl radical, which, is trapped by the protonated heterocycle **1**. Finally, oxidation of the resultant amino-radical cation by Ir(IV), affords the desired product **3** and regenerate the active catalyst substrate. Using mild conditions (ACN/AcOH/TFA at room temperature) for the generation of methyl radical or other radical species, allow active remarkable scope in the complex framework of Minisci-type C-H functionalization.



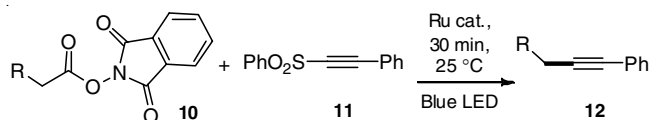
Scheme-I: Methylation of heterocycles through photoredox catalyst

Chen *et al.* [19] illustrated the synthesis of a visible-light encouraged metal-free C-H fluorination as photocatalyst, Photoexcited acetophenone was used through irradiation by a household compact fluorescent lamp (CFL) (Scheme-IIa). The similar method was illustrated by Britton employing the tetrabutylammonium salt of decatungstate (TBADT)/N-fluorobenzenesulfonimide (NFSI) with the adding of NaHCO<sub>3</sub> to support the operation of fluorination [20] (Scheme-IIb). Later, Sorensen *et al.* [21] in the same way utilized a visible-light photocatalyst for C-H bond fluorination using UO<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O as catalyst with the combination of fluorine atom source NFSI (Scheme-IIc).



Scheme-II: Synthesis of a visible-light encouraged metal-free C( $sp^3$ )-H fluorination

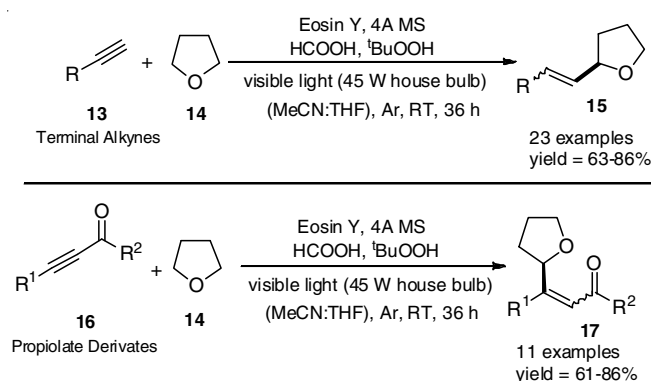
Later, a visible light induced reductive decarboxylative alkynylation C( $sp^3$ )-C( $sp$ ) bond coupling process has similarly been developed by Chen *et al.* [22], starting from alkynyl phenylsulfone and readily available carboxylic acids within 30 min at room temperature in organic or aqueous solvents (Scheme-III). In addition to the alkyl, alkyl halide, silyl and aryl substituted, various functional groups were tested in this reaction such as aldehydes, alcohols, carboxylic acids and  $\alpha$ -heteroatom such as indoles. Furthermore, the chemoselective alkynylation was compatible with biomolecules and did not



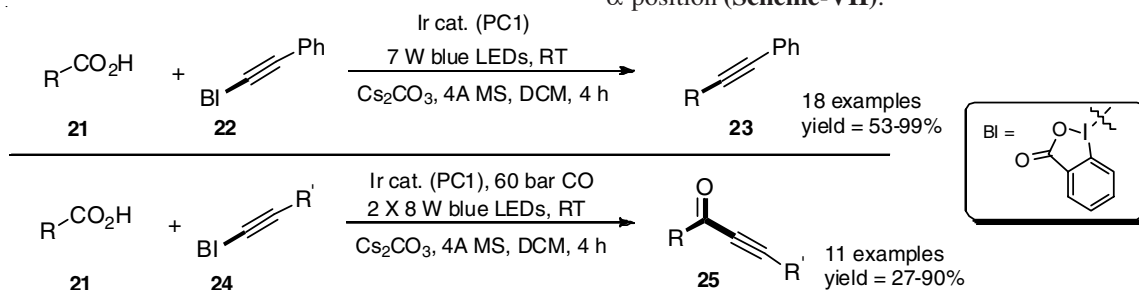
**Scheme-III:** Visible-light induced decarboxylative alkylation of N-acyloxypthalimide

affect on the activity of protein enzyme. The reaction sequence is achieved by generation of  $\text{Ru}^{\text{I}}$  from reaction  $\text{Ru}^{\text{II}}$  with DIPEA/HE [23]. The reduction of the N-acyloxypthalimide **10** by  $\text{Ru}^{\text{I}}$  via single-electron transfer gives phthalimide intermediate. The latter can undergo elimination reaction under reductive cleavage step and the carboxyl radical released  $\text{CO}_2$  to yield the alkyl radical. Further  $\alpha$ -addition reaction to the alkynyl sulfone **11**, gives the phenylsulfonyl radical and the expected alkyne product **12** from good to excellent yields.

While, Wang *et al.* [24] reported straightforward application of visible-light photocatalysis in the vinylation process of tetrahydrofuran with alkynes via direct C-H bond functionalization using organic dye sensitization, *tert*-butyl hydroperoxide (*t*-BuOOH) and 45 W household light bulb (**Scheme-IV**). The protocol, depends on the preparation of a range of vinyl tetrahydrofurans that found in biological, medicinal and natural products [25], followed by reaction with various terminal alkynes and propiolate derivatives. Firstly, the reaction started with excited eosin Y eosin  $\text{Y}^*$  upon visible light sensitization, followed by transfers energy to *t*-BuOOH. The latter undergoes homolytic cleavage of the weak O-O bond and produce simultaneously *t*-butoxy radical and hydroxyl radical. The hydrogen abstraction from tetrahydrofuran **14** producing  $\alpha$ -oxy radical intermediate to give the desired products **15** and **17** in 61 to 86 % yields via addition reaction to both terminal alkyne **13** and propiolate derivatives **16**.

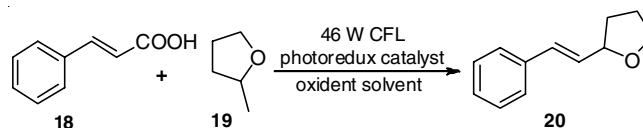


**Scheme-IV:** Visible-light induced C-H functionalization protocol to vinyl-tetrahydrofurans



**Scheme-VI:** Decarboxylative alkylation and carbonylative alkylation of carboxylic acid under photoredox catalysis process

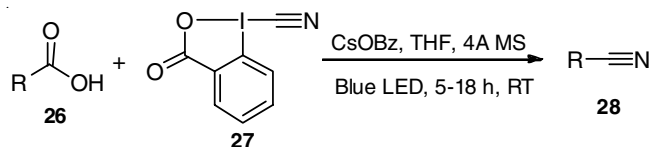
Liu *et al.* [26] have been worked in synthesis of a visible-light mediated alkenylation via oxidative decarboxylative combining tetrahydrofuran **19** with cinnamic acid derivatives **18** (**Scheme-V**). The result study of the condition of the reaction allowed to say that the amalgamation of  $\text{Ru}(\text{bpy})_3\text{Cl}_2$  in 2 mol % and benzoyl peroxide (BPO), was detected to be the preferable condition for photo-catalyzing at room temperature. The (*E*)-(2-arylvinyl)tetrahydrofuran **20** was formed with elevated electivity.



**Scheme-V:** A decarboxylative coupling strategy to vinyl furans

Furthermore, Xiao and co-workers [27] have reported new synthetic method for direct decarboxylative and carbonylative alkylation of carboxylic acid under photoredox catalysis conditions. These two reactions allow preparation of new alkynes and ynones in high yields. Generally, the reaction proceeds smoothly and compatible with different cyclic carboxylic acids and the expected products were isolated in high yields (50-90 %) under optimal conditions (**Scheme-VI**). To get more insights into the mechanism of this reaction, plausible reaction pathways were suggested with carboxylic acid and phenyl-substituted EBX as the model compounds. Initially, a cyclohexyl radical is formed via single-electron transfer process between the photo excited of  $\text{Ir}^{\text{III}}$  to carboxylic acid **21**, followed by radical addition reaction to the alkynylating reagents **22** and **24**, followed by elimination reaction and produce the expected alkyne products **23** with generation of benziodoxolonyl radical  $\text{BI}^{\cdot}$ , which sustain the radical chain. In presence CO in the decarboxylative carbonylation reaction, the intermediate can be trapped by carbon monoxide and provide the expected ynone products **25** with generation of  $\text{BI}^{\cdot}$ .

Waser and co-workers [28] reported the effective usage of the one-step transformation of aliphatic carboxylic acids **26** to the relating nitriles utilizing an iridium photoredox catalyst. They observed that immediate response of the radical framed by iridium-intervened decarboxylation was bring down in vitality for the alkylation, while single electron exchange (SET) to shape an iminium moderate followed by cyanide expansion was preferable for cyanation reaction. The reaction forward in significant yields **28** with naturalistic and non-naturalistic  $\alpha$ -amino and  $\alpha$ -oxy acids **27**, bearing a wide extent of nitriles with stellar acceptance of the substituents in the  $\alpha$ -position (**Scheme-VII**).



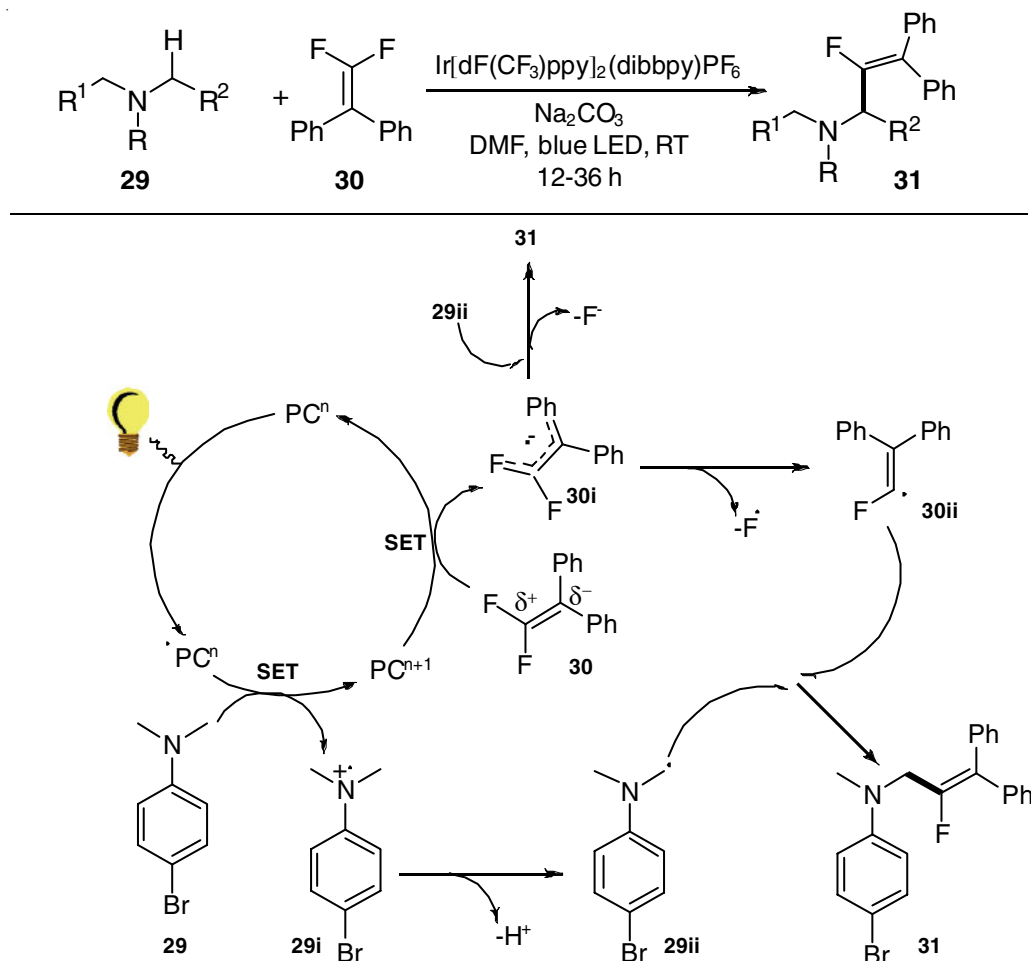
**Scheme-VII:** Decarboxylative cyanation of carboxylic acids using photoredox catalyst process

Hashimi group [29] in 2016 has built up a visible-light advanced radical-radical cross-coupling interaction of *gem*-difluoroalkenes **30** with monofluoroalkenylation of dimethylamino subsidiaries **29**. As photocatalyst in these work, Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> was utilized under blue LED light. In this transformation non-cyclic, cyclic N-Ar and aliphatic tertiary amines were all around managed. In (**Scheme-VIII**) a radical-radical coupling between an aminoalkyl radical and a monofluoroalkenyl radical is suggested. Initially, the energized state photocatalyst delivered under obvious light illumination experienced single-electron exchange (SET) by pulling in one electron from the tertiary amine to create radical cation **29i**, which upon deprotonation created an aminoalkyl radical **29ii**. Consequent SET decrease of *gem*-difluoroalkene **30** gave radical anion **30i**, creating fluoride and fluoroalkenyl radical **30ii** by means of C-F bond discontinuity. Particular cross coupling of the less responsive radical with the more receptive monofluoroalkenyl radical at that point would endure the required item **31** as indicated by the chemoselective radical C-C hetero-

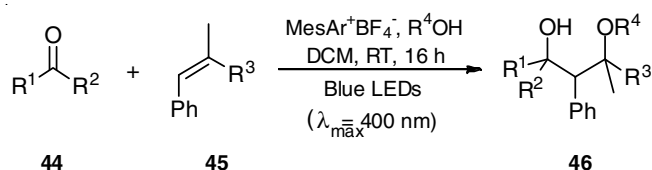
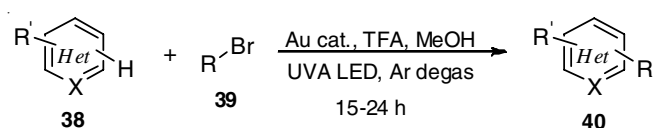
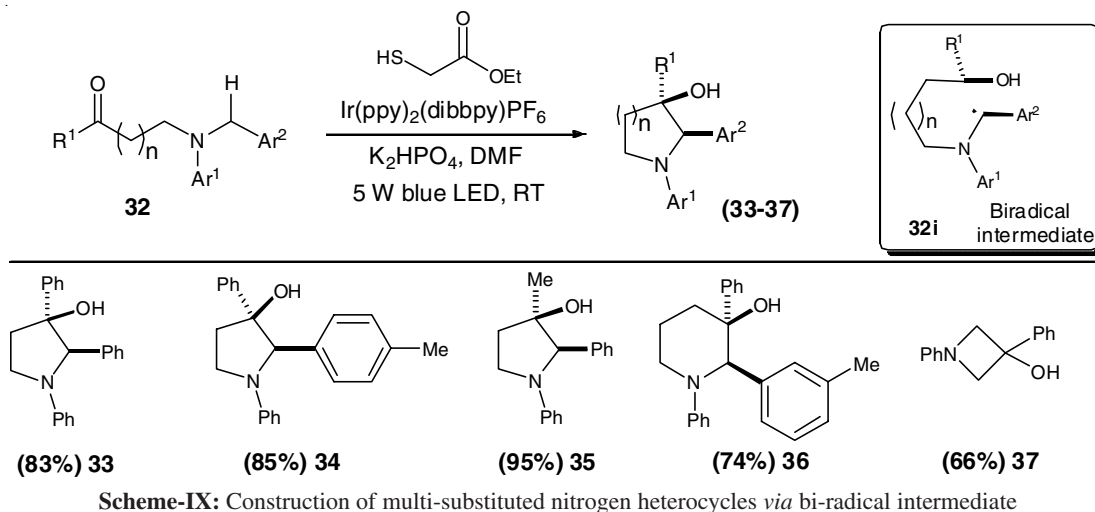
coupling of aminoalkyl radical with radical anion and consequent disposal of fluoride could likewise affectively abstracted the product **31**.

Furthermore, in 2016, new coupling for the construction of multi-substituted nitrogen heterocycles *via* biradical intermediate was build up by Zhu *et al.* [30]. Remarkably, yield increasing was observed when utilized substrates carrying a strong electron-poor group on the aromatic ring. In the suggested mechanism, photoinduced single-electron oxidation obtained a thiyl radical, which released H from 3-(benzyl(phenyl)amino)-1-phenylpropan-1-one **32**, affording the  $\alpha$ -amino radical. Meantime, electron transfer to the carbonyl group of the reactant by the reduced photocatalyst provide biradical intermediate **32i**, which like to tolerate intramolecular coupling in its less restrained conformation, producing a *cis*-isomer in the main diastereomer (**33-37**) (**Scheme-IX**).

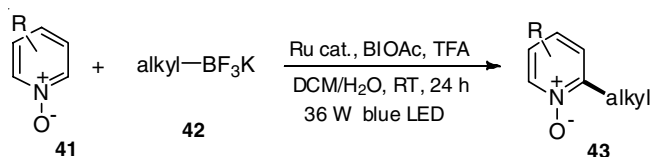
Furthermore, McCallum and Barriault [16] developed visible light photo-redox protocol toward direct C-H alkylation of heteroarenes with bromoalkanes using gold catalyst. Thus, generation of nucleophilic alkyl radical from readily available bromoalkane **39** *via* an oxidation step with [Au<sub>2</sub>(dppm)<sub>2</sub>]Cl<sub>2</sub> dimeric catalyst in MeOH at room temperature, followed by subsequently addition reaction at electron deficient locations of heteroarene **38** to produce aminyl radical. The latter is then oxidized by [Au<sub>2</sub>(dppm)<sub>2</sub>]<sup>3+</sup> to give new C-C bond formation alkylated heteroarene products **40** in 25 to 98 % yields (**Scheme-X**).



**Scheme-VIII:** Visible-light promoted radical-radical cross-coupling reaction of difluoroalkenes with dimethylamino derivatives



In parallel with successful photoredox reactions to construct a variety of significant heterocyclic system, Xu and co-workers [31] developed first example of C2 alkylation of pyridine N-oxides. Various functional groups, for example, halo-arene ring, ether, amide, trifluoromethyl and unprotected alcohol were compatible with the reaction conditions and providing the corresponding products up to 85 % yields (**Scheme-XI**). The proposed mechanism for the described transformation of alkyl-TEMPO involves generation of an alkyl radical from alkyltrifluoroborate **42**, followed by reaction with both electron-deficient (4-methylpyridine N-oxide) and electron-rich (4-trifluoromethylpyridine N-oxide) **41** under mild conditions (dichloromethane as the solvent at room temperature) for 24 h to give the final product **43**.

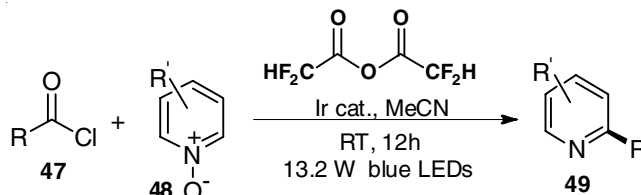


**Scheme-XI:** C2-Alkylation of pyridine N-oxide using photoredox catalyst

Furthermore, The Glorius group [32] also reported a novel strategy for the intermolecular radical addition to the carbonyls under visible light photoredox process. This method represents *via* photoexcitation the hole catalyst to accelerate the key *in situ* Bronsted acid activation of carbonyl compounds such as aldehyde and ketone **44**, followed by intermolecular trapping by alkyl radical **45** under mild conditions to give the desired product **46**. In fact, the scope and limitation in this work, set that aldehydes provided higher yields products than ketones (**Scheme-XII**).

**Scheme-XII:** Visible-light photoredox induced the intermolecular radical addition to carbonyls

In 2018, Stephenson and co-workers [33] described simple photoredox catalyst process mediated redox-neutral protocol for the decarboxylative alkylation of heteroarenes **49**. Here, the reaction depended on using Minisci reagent, which involved the direct C-H alkylation of heterocyclic N-oxides **48** by alkyl centred radical. Wide variety of useful carboxylic acids derivatives **47** are used as alkylating agents under the mild conditions, qualify a flexible alkylation method (**Scheme-XIII**).

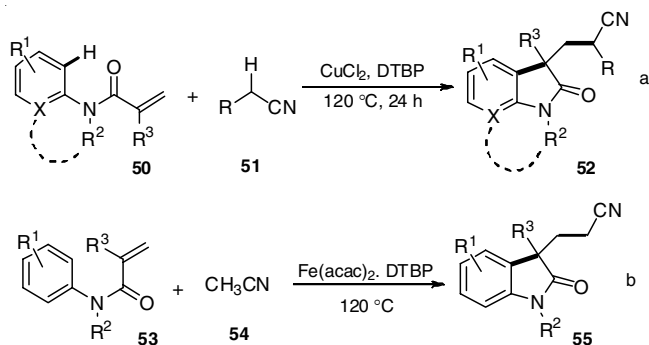


**Scheme-XIII:** Visible light mediated decarboxylative alkylation of heterocycles

**Free-radical cascade processes reactions:** Free radical reactions have been a powerful protocol leading to carbon-carbon or carbon-heteroatom bond formation *via* cascade radical, particularly in the field of natural product synthesis. In parallel, multicomponent reactions allow the installation of several bonds in a single operation, without purifications of the intermediates, modification of the reaction conditions and/or further addition of reagents. These advantages are obvious when the multistep synthesis complexity increases in proportion to the number of steps.

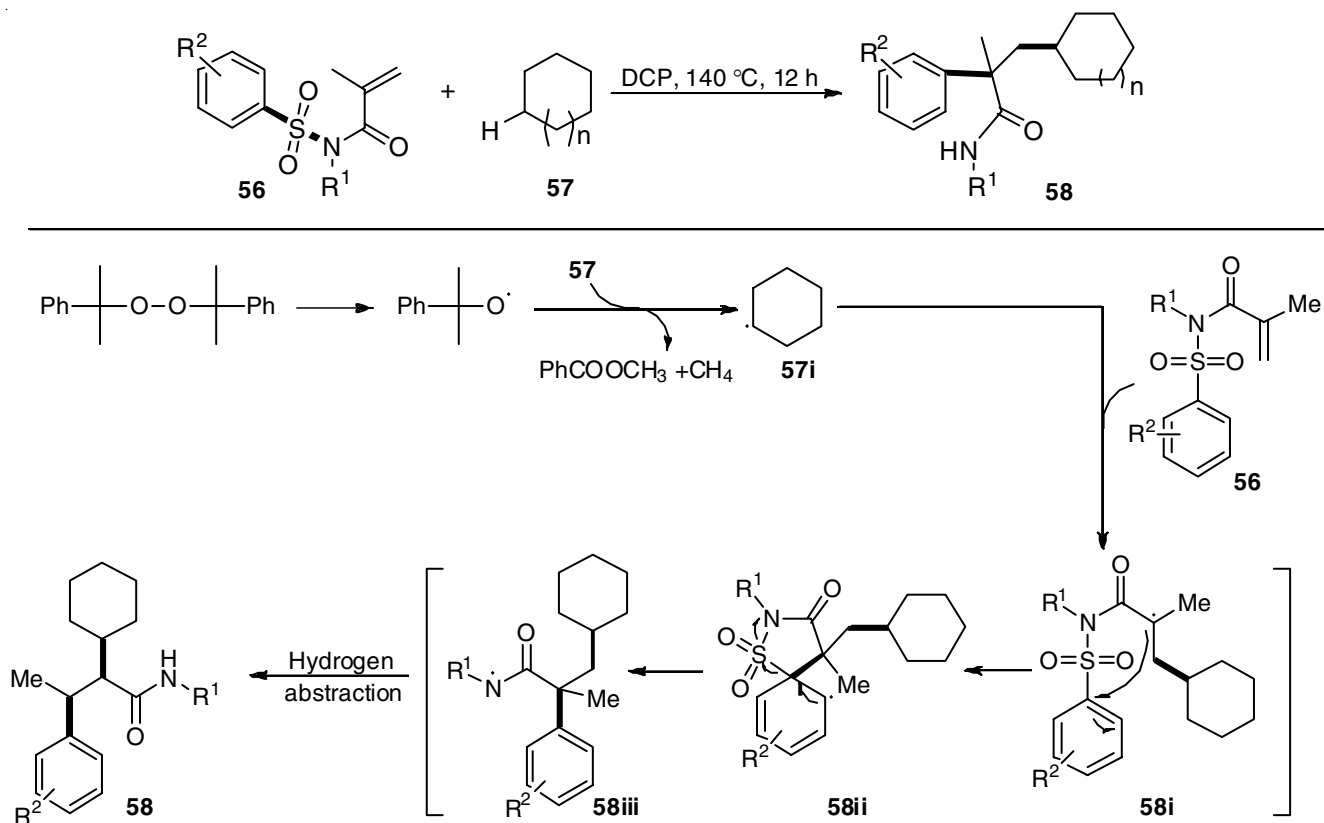
Copper(II) chloride as the catalyst and DTBP as the radical initiator were used to completing a radical cascade cyanomethylation of N-arylacrylamides (**50** and **53**) with acetonitriles (**51** and **54**). The conversion could be dramatically suppressed

by radical scavengers such as TEMPO and BHT. Proceeding reactions was not identically, easily undergo with N-methyl and N-benzyl N-phenylacrylamides (**50** and **53**), while with the NH and N-acetyl N-phenylacrylamides was not [34] (**Scheme-XIV**).



**Scheme-XIV:** A radical cascade cyanomethylation of N-arylacrylamides with acetonitriles

Later a metal-free cascade alkylation of alkanes with N-phenyl-N-(phenylsulfonyl)methacrylamides by a cyclization intermediate process has been developed by Zhu *et al.* [35]. In the suggested mechanism, an alkyl radical could be framed from hydrogen atom, deliberation by peroxide. The addition of an alkyl radical **57i** to the alkene **56** afforded radical intermediate of the route **58i**. The 5-ipsocyclization on the fragrant ring created intermediate of the compound **58ii** and a rapid desulfonation yielded the key amidyl radical **58iii**. After hydrogen deliberation, amidyl radical **58iii** can changed over to the coveted item **58** (**Scheme-XV**).

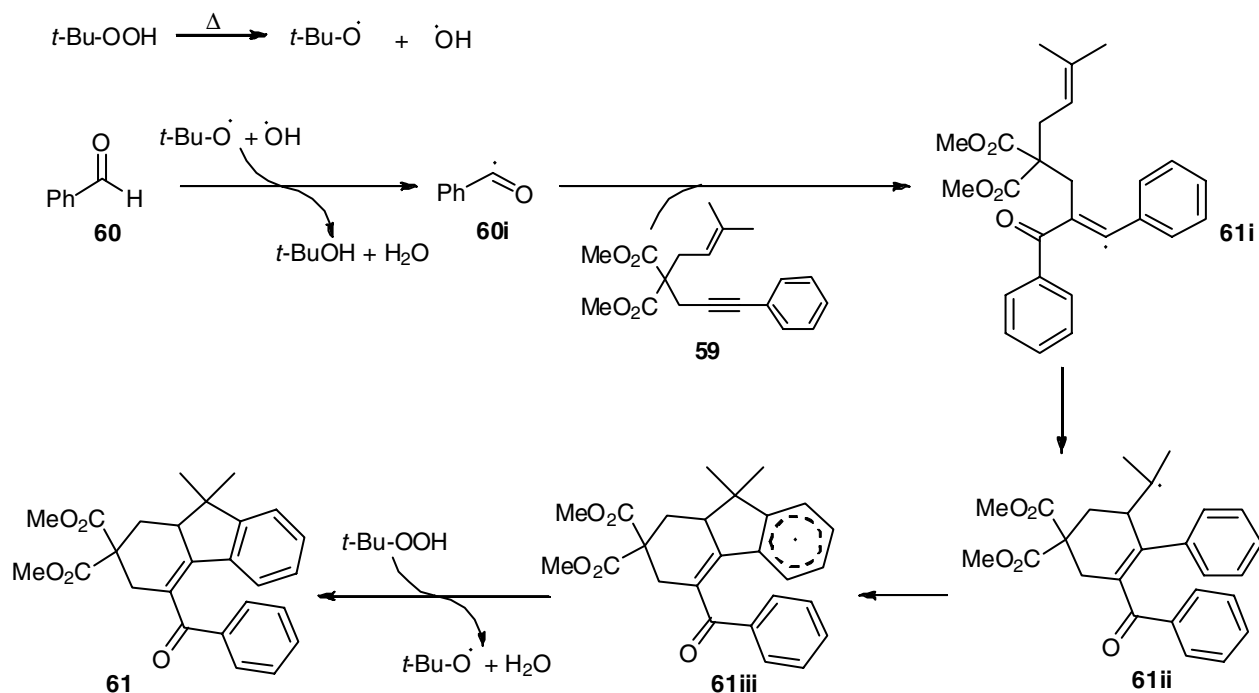
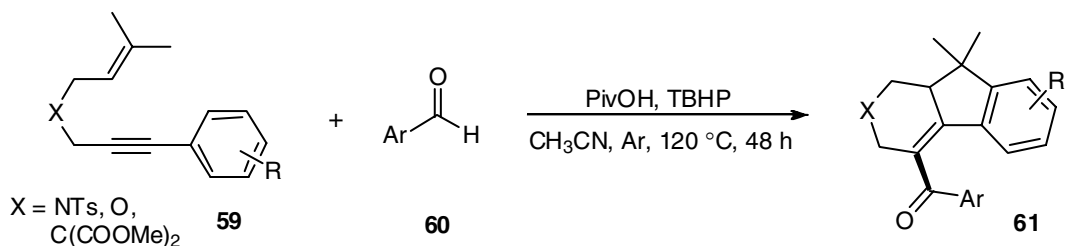


**Scheme-XV:** A metal-free cascade alkylation of alkanes with N-phenyl-N-(phenylsulfonyl)-methacrylamides by a cyclization intermediate

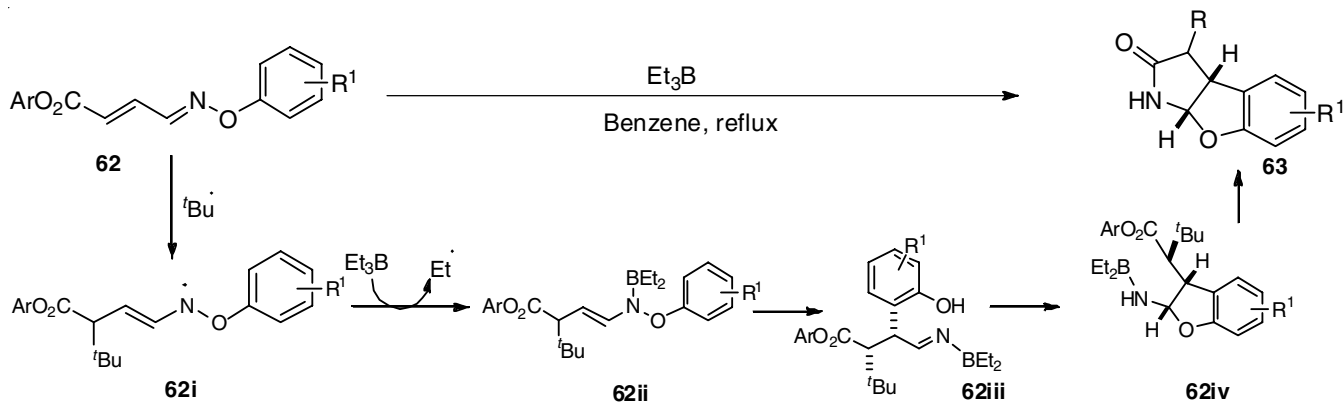
Ethers can also assist for this cascade radical oxidative difunctionalization of alkynoates for the preparation of tri-substituted olefins under metal catalysis [36] or metal-free conditions [37].

The cascade cyclization of 1,6-enynes **59** with aldehydes **60** for the preparation of fluorene derivatives **61** under metal-free conditions was carried out by Liang and co-workers [38]. The reaction proceeded easily with different aromatic and heteroaromatic aldehydes but yet was restricted to aliphatic aldehydes. A radical substitution mechanism was confirmed by intramolecular and intermolecular kinetic isotope effect (KIE) experiments and radical suppression tests. Amid the suggested mechanism, the acyl radical **60i** was produced from the aldehydes **60** *via* a hydrogen releasing process. The addition of the acyl radical **60i** to the C-C triple bond formed the radical **61i**. The aromatization procedure, trailed by the intramolecular addition of radical **61ii** to the arene, produced the intermediate radical **61iii**. The radical **61iii** was further oxidized to generate the desired product **61** (**Scheme-XVI**).

Miyata *et al.* [39] reported a flexible access to the construction of benzofuro[2,3-b]pyrrol-2-ones component biologically active natural products by domino reaction *via* radical addition, [3,3] sigmatropic rearrangement, cyclization and lactamization cascade process. The proposed mechanism (**Scheme-XVII**) started firstly with addition of  $t\text{Bu}^\bullet$  radical to the C-C double bond producing aminyl radical **62i**, which can have trapped by  $\text{Et}_3\text{B}$  to form N-borylenamine **62ii**. The latter undergoes [3,3] sigmatropic rearrangement forming six-membered transition state lead to the formation of syn- $\alpha$ -arylimine **62iii**. Further cyclization of **62iv** and lactamization would also lead to expected product **63**.



**Scheme-XVI:** The cascade cyclization of 1,6-enynes with aldehydes for the preparation of fluorene derivatives under metal-free conditions

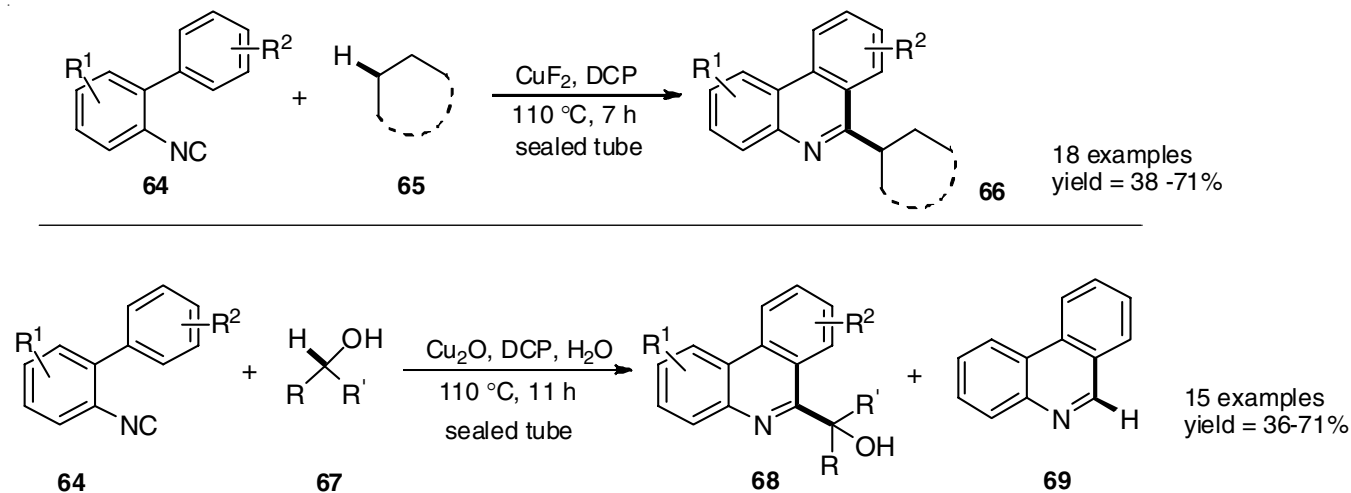


**Scheme-XVII:** Direct synthesis of benzofuro[2,3-b]pyrrol-2-ones *via* cascade reaction

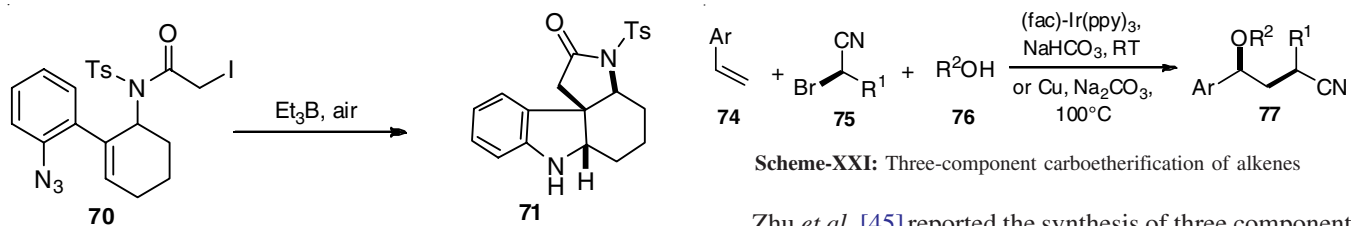
Recently, free radical reaction has been used for preparation of series of 6-alkylated phenanthridine derivatives *via* novel functionalization of (*sp*<sup>3</sup>) C-H and (*sp*<sup>2</sup>) C-H bonds. In this context, Liu group [40] reported straightforward copper catalyst mediate free cascade addition/cyclization of isocyanides with various of simple alkane and alcohol substituted (**Scheme-XVIII**). The mechanism strategy of this reaction proposed formation of the alkyl radical through hydrogen abstraction of an alkane **65** or  $\alpha$ -hydroxy C-H of the alcohol **67**. Alternatively, addition of the alkyl radical to the biphenyl

isocyanide **64** gives the imidoyl radical species, followed by further intramolecular cyclization producing the products **66**, **68** and **69** in moderate to good yields under the optimal reaction conditions.

Renaud group [41] reported a mild and novel approach toward the synthesis of aspidosperma and strychnos alkaloids *via* cascade radical cyclization reaction (**Scheme-XIX**). This sequence is based on the formation of quaternary carbon center of **70** through cyclization cascade process, followed by reaction with aryl azide radical intermediate, furnishing the 5-membered



**Scheme-XVIII:** Copper-catalyzed radical cascade reaction of isocyanides with simple alkanes and alcohols



**Scheme-XIX:** Approach toward synthesis of aspidosperma and strychnos alkaloids *via* cascade radical cyclization reaction

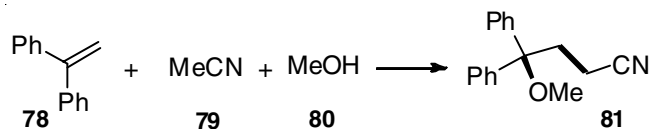
**Scheme-XXI:** Three-component carboetherification of alkenes

ring of the pyrrolocarbazole framework. Generally, the reaction proceeded smoothly with triethylborane in presence of air ( $O_2$ ) without need for any hydrogen source, affording the desired product **71** as a single diastereomer.

In 2018, Wu and co-workers [42] described a cascade  $C(sp^3)$ -S bond cleavage and C-S formation radical cyclization for the construction of 2-isocyanoaryl thioethers derivatives. Various functional groups isocyanide **72** are tolerated with H-phosphorus oxides organoboronic acids or alkyl radical precursors and 2-isocyanoaryl thioethers **73** were obtained with yield up to 89 % (**Scheme-XX**). Mechanistic studies revealed that the cycloaddition proceed through formation of imidoyl radicals intermediate **72i**, which attack the unsaturated carbon atom.

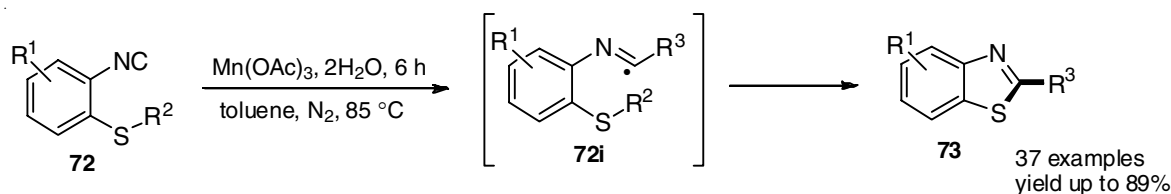
**Free-radical multicomponent reactions:** Many tandem free-radical three multicomponent processes have been described over the last 20 years. There are little work of multi-component carbo etherification synthesis to describe the way and allow the preface of more artificially many-sided functional handles [43,44]. Recently Lei *et al.* [43] depict the carbo etherification of styrene **74** as multicomponent with alcohols **76** and  $\alpha$ -bromo alkyl nitriles **75** (**Scheme-XXI**). The compound **77** was very benefit because of the cyano group, which can easily converted to further functional group.

Zhu *et al.* [45] reported the synthesis of three component reaction from 1,1-diphenylethylene **78** with acetonitrile and methanol. They examined the condition of the reaction and observed that no difunctionalized product was detected when copper acetate was used as catalyst. By replacing  $Cu(OTf)_2$  as catalyst, the compound **81** was produced. The result of searching best condition for this reaction was detected in combination of 1,1-diphenylethylene with  $Cu(OTf)_2$  is (2:1 mol ratio), ideal ratio of MeCN **79**/MeOH **80** is 1:1 (**Scheme-XXII**).



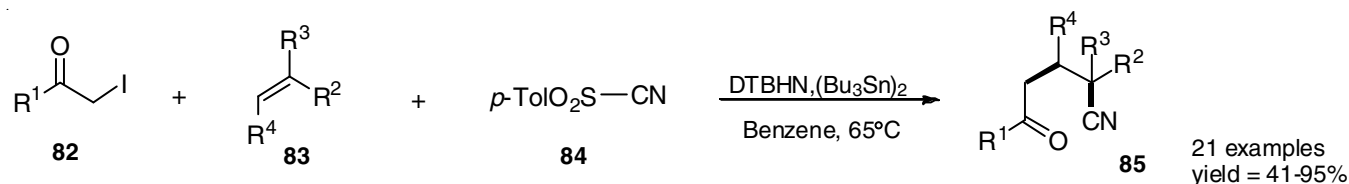
**Scheme-XXII:** Carboetherification reaction

Recently, the free-radical three carbo-cyanation using *p*-tosyl cyanide as cyanide source have been described by Landais group [46]. Addition of alkyl carbon radical **82** across the  $\pi$ -system of electron-rich olefins **83** through free-radical pathways, followed by trapping with commercially available electrophilic *p*-tosylcyanide acceptor **84**, could give carbo-cyanation product **85** (**Scheme-XXIII**). Various electron-rich olefins were more compatible with many functional groups like, ketones, esters, nitriles and amides.



**Scheme-XX:** Intramolecular radical cascade reactions of isocyanides





Simultaneously, the same group [47] applied the carbo-alkenylation process on the various substitution pattern in the olefins, in the development of several useful multicomponent processes that encompass the successive formation of C-C bond (**Scheme-XXIV**). The new different *Z*- and *E*-vinyl aryl sulfonyl acceptors bearing a substituent that can undergo  $\beta$ -fragmentation to sustain the radical chain, including  $\text{SO}_2\text{Ph}$  were good candidates for this purpose. The mechanism reaction proceeds through the generation of a radical species by abstraction of a xanthates or halides group **86**, **90** and **94** by tin. The alkyl radical thus generated then adds onto the less hindered end of an olefins **87**, **91**, **95**, producing a nucleophilic radical which is trapped by the electrophilic vinylsulfonyl acceptors **88**, **92** and **96**, yielding products **89**, **93** and **97** in moderate yields along with the phenylsulfonyl radical, which propagates the radical chain.

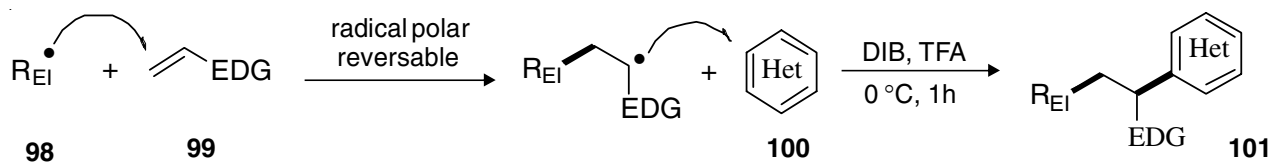
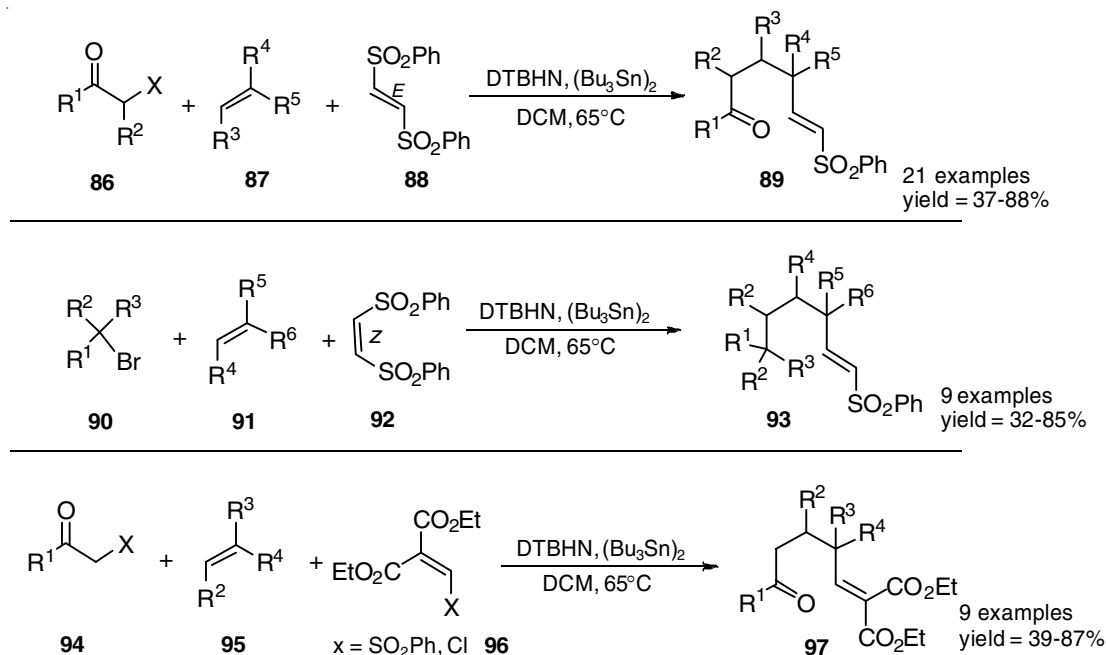
In 2017, based on the radical polar effect, Liu group [48] developed a mild and efficient route to an intermolecular azido-heteroarylation of simple alkanes through radical multicomponent cascade reaction. A possible mechanism proposed started with multicomponent Minisci reaction, including addi-

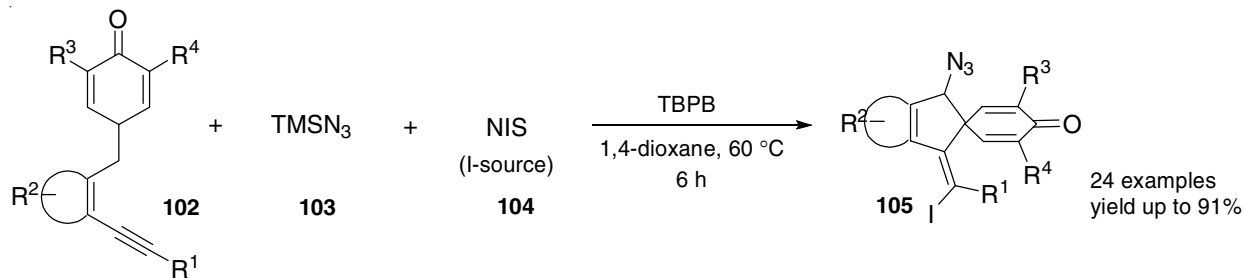
tion reaction of the electrophile radical **98** to an electron-rich olefin **99**. The nucleophilic alkyl radical thus generated then trapped by heterocycle **100**, yielding product **101** in (**Scheme-XXV**). Polarity of radical species strongly influencing the overall kinetic of the reaction.

Furthermore, Yao and co-workers [49] developed a novel construction of biologically interesting spiro[4,5]deca-6,9-dien-8-ones *via* cascade three-multicomponent iodoazidation of *para*-quinone methides **102**. The proposed mechanism of the synthetic method proceeds through cascade radical 1,6-addition, followed by 5-*exo*-dig and finally radical coupling operation, furnishing the expected product **105** included new C-N, C-C and C-I bonds formation (**Scheme-XXVI**).

**Free radical Minisci reactions:** The Minisci reaction outputs regioselectively and becomes strong the introduction of a wide range of alkyl [50], aryl and acyl groups. Due to the simple candid materials and straightforward reaction conditions, the reaction has many implementations in heterocyclic chemistry.

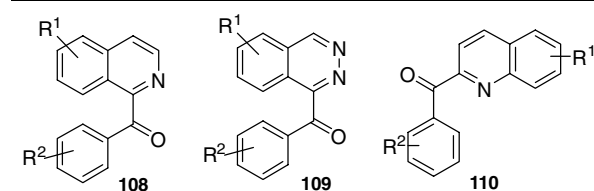
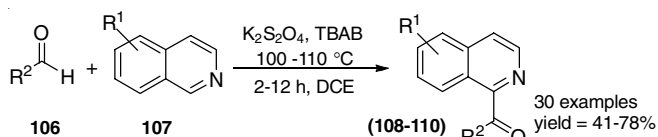
Prabhu group [51] focused their effort on the acylation of quinoline, isoquinoline and quinoxaline derivatives moieties mediated metal-free Minisci intermediate. This sequence is





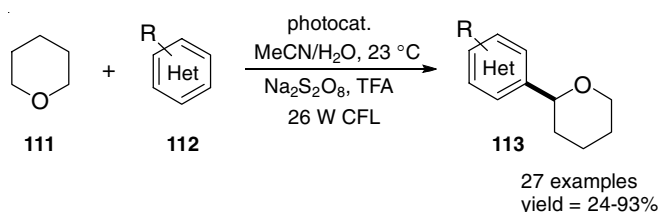
**Scheme-XXVI:** Synthesis of spirocyclohexadienone through cascade radical/cyclization of *p*-quinone methides

based on abstracted of H from the aldehyde **106** to produce the acyl radical. Addition of the latter to the variety of isoquinoline derivatives **107** in presence of TBAB (30 mol %) and  $K_2S_2O_8$  as an oxidant, should produce the corresponding products (**108-110**) (**Scheme-XXVII**).



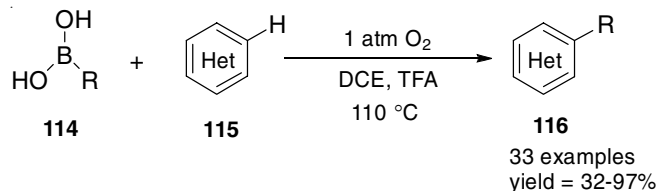
**Scheme-XXVII:** Acylation of isoquinoline derivatives through metal-free Minisci reaction

While MacMillan and Jin [52] described a direct and an efficient protocol for the direct  $\alpha$ -arylation of cyclic and acyclic ethers with heteroarenes (pyridine and isoquinoline) *via* visible light and mediated C-H functionalization and Minisci intermediate (**Scheme-XXVIII**). The mechanistic details demonstrated by generation of  $\alpha$ -oxyalkyl radical from dialkyl ether **111** under visible light photoredox catalyst cycle, followed by selective C-H bond functionalization through Minisci-intermediate coupling with electron-poor heteroarenes **112**, producing the  $\alpha$ -oxy heteroarene product **113**.



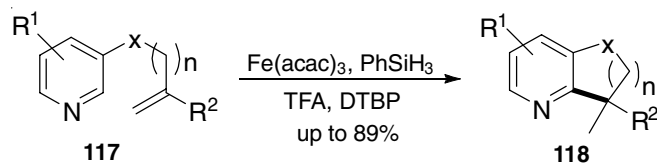
**Scheme-XXVIII:**  $\alpha$ -Heteroarylation with ethers via Minisci-type reaction

Liu and Zhang [53] described a convenient and green approach toward radical alkylation of heteroarenes with boronic acids through oxygen-mediated Minisci-type reaction. The reaction proceeds *via* autoxidation of organoboronic acid **114**, followed by generation of alkyl radical. Subsequently, a convenient C-H alkylation functionalization *via* Minisci-intermediate coupling with heteroarenes **115**, yielding the desired products **116** (**Scheme-XXIX**).



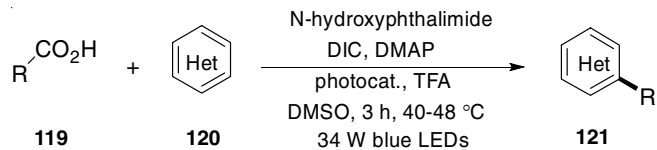
**Scheme-XXIX:** Heteroalkylation with alkylboronic acid *via* Minisci-type reaction

Starr and Bordini [54] described a fluent, reasonable and low-cost approach for the construction of dihydropyrano-pyridine and 1,2,3,4-tetrahydronaphthiridine compounds through intramolecular Minisci-type reaction. The proposed mechanism based on the generation of carbon radical cation of the alkene chain **117** on protonated pyridine promoted by Fe complex. Finally, the intermolecular cyclization gives the expected product **118** (**Scheme-XXX**).



**Scheme-XXX:** Hydropyridylation of lefins *via* intramolecular Minisci-type reaction

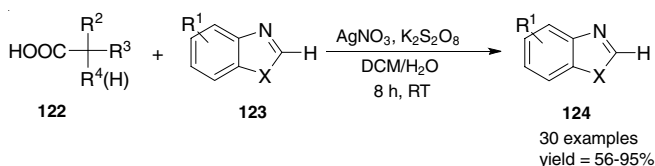
In 2018, Sherwood group [55] developed in one pot a flexible Minisci-type protocol included an organic photocatalyst and carboxylic acids under visible light process and mild conditions (**Scheme-XXXI**). Under optimal conditions, the possible mechanism proceeds through generating the alkyl radical by reductive fragmentation step in presence of *N*-(acyloxy)phthalimide, followed by addition the alkyl radical intermediate **119** onto protonated pyridine **120** and producing the protonated product **121** along the catalytic cycle.



**Scheme-XXXI:** Organocatalyzed photoredox-mediated Minisci reaction

**Metal-catalyst free-radical reactions:** Moreover, Zhao group [15] designed a mild, an efficient and first method for the decarboxylative alkylation of benzothiazoles, thiazoles and benzoxazoles with carboxylic acids under silver catalytic cycle route (**Scheme-XXXII**). A reasonable mechanism of the decarboxylative cross-coupling reaction is proposed *via* reaction

the carboxylic acid **122** with Ag(II) cation, generating the alkyl radical and lose of CO<sub>2</sub> molecule. The obtained free radical undergoes hydrogen atom abstraction from C2-benzothiazole **123** producing benzothiazole radical. Finally, the two radical combined and led to produce the final desired product **124** with moderate to excellent yields.



**Scheme-XXXII:** Decarboxylative of benzothiazoles with carboxylic acids using Ag catalyst

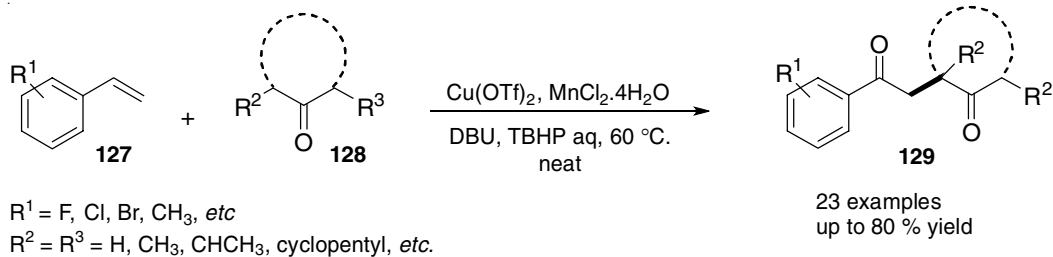
Later on, the design an efficient route toward synthesis of  $\beta$ -azido alcohol derivatives **126** via manganese-catalyzed oxidative hydroxyazidation of olefins **125** has been developed by Jiao's group [56]. The azido radical **103** generation via initiating Mn-catalyst by ambient air as oxidant is the successful key for this conversion. The reaction is value by its wide substrate range, high adequacy and inexpensive Mn-catalyst, simple protocol under air and mild conditions at room temperature (**Scheme-XXXIII**).



**Scheme-XXXIII:** Direct approach to  $\beta$ -azido alcohols using Mn catalyst

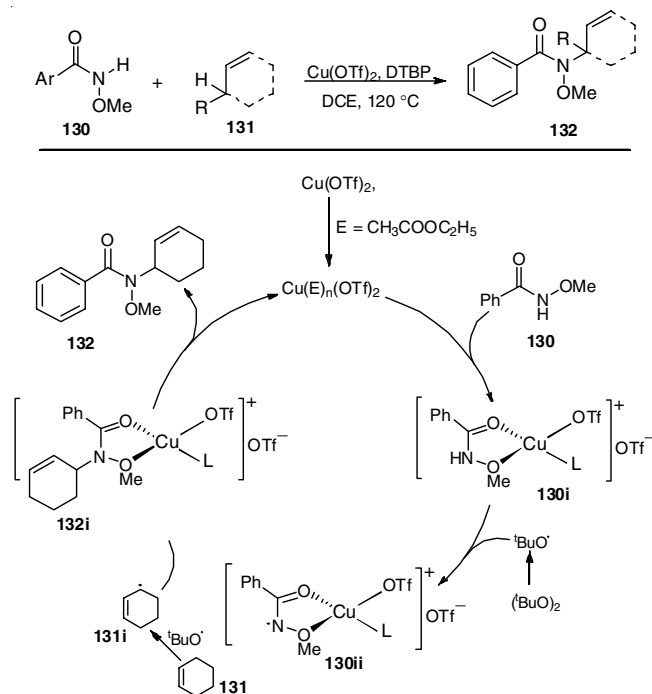
Li and co-workers [57] reported a facile route of C-C bond formation via dual copper/manganese co-catalyzed direct oxidative-coupling reaction of terminal vinylarenes **127** with ketones **128** (**Scheme-XXXIV**). The mechanism proposed generation of butoxy radical initiated by Mn-catalyst, followed by reaction with ketone to give  $\alpha$ -carbon ketone radical intermediate. Finally, the reaction between the ketone radical and vinylarene, transform to the expected product **129** with yield up to 80 %.

Cu(OTf)<sub>2</sub> was used as the impetus and DTBP was utilized as oxidant specialist in DCE as dissolvable in the work which conveyed by Lei and associates [58] represented a copper-catalyzed C-H/N-H radical/radical cross coupling for the blend of allylic amine. N-Methoxybenzamide subsidiaries bearing electron-donor on the aryl rings **130**, managed the relating items in preferred yields over those with electron-deficients. The EPR identified that with N-methoxybenzamide, the coor-



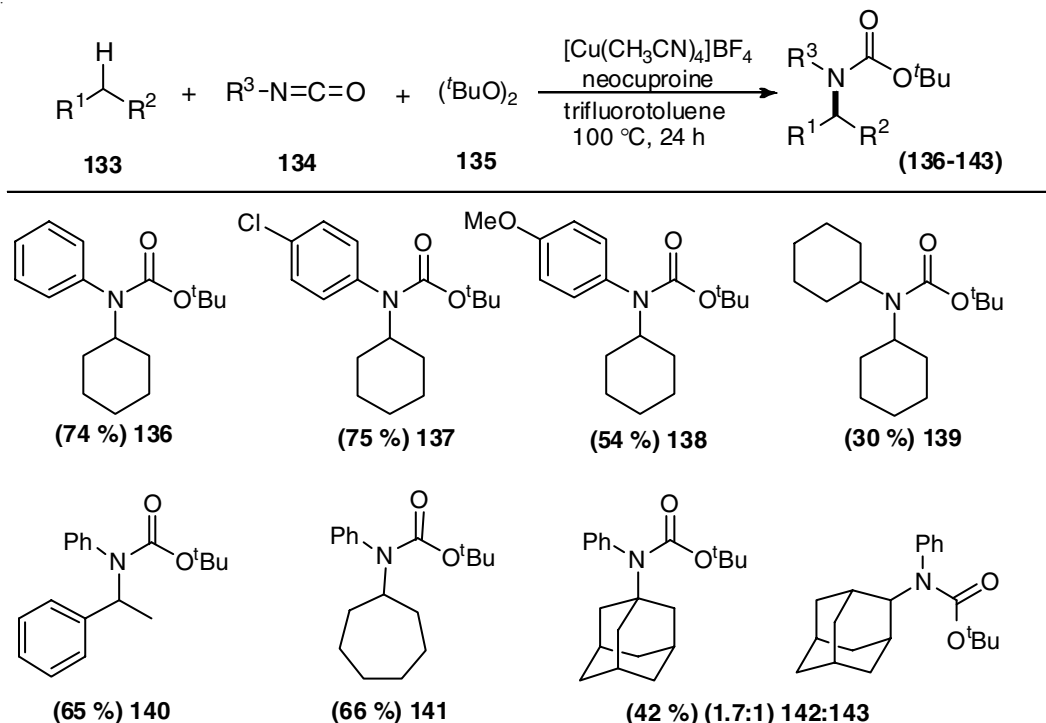
**Scheme-XXXIV:** Oxidative-coupling reaction of vinylarenes with ketones using Cu/Mn catalyst

dination structure of copper changed amid the oxidation procedure. The cation [Cu(OTf)<sub>2</sub>(PhCONHOMe)<sub>2</sub>]<sup>2+</sup> **130i** was demonstrated by ESI-MS investigation, which experienced hydrogen discharging to acquire the nitrogen-focused radical Cu(II) species **130ii**. The specific cross-coupling of **130ii** and the carbon-focused radical **131i** give complex **132i**. Eventually, **132i** released Cu(OTf)<sub>2</sub> and acquired the relating result **132** to finish the catalytic cycle (**Scheme-XXXV**).



**Scheme-XXXV:** A copper-catalyzed C-H/N-H radical/radical cross coupling for the synthesis of allylic amine

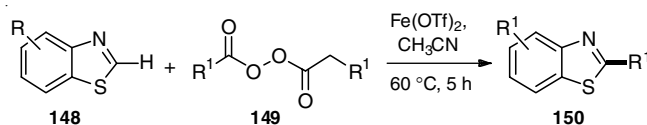
A copper mediated intermolecular C-H bond functionalization between un-activated alkanes **133** and isocyanates **134** was outlined by Kanai and co-workers [59], which could supplied the tertiary carbamates (**136-143**) specifically, catalyzed by abundantly accessible first-period of transition metal complexes with (tBuO)<sub>2</sub> as the oxidant **135**. A suggested mechanism including a Cu(I)-Cu(II)-Cu(III) redox catalytic cycle is outlined by the authors (**Scheme-XXXVI**). The Cu(II)-amide species could be delivered from the reaction of a *tert*-butoxy radical with an isocyanate and consecutively oxidation of the Cu(I) species. The combine of this Cu(II)-amide complex with the *in situ* produced alkyl radical containing Cu(III) species, which can award the tertiary carbamate compound after reductive process.



**Scheme-XXXVI:** A copper mediated intermolecular C(*sp*)-H bond functionalization between unactivated alkanes and isocyanates

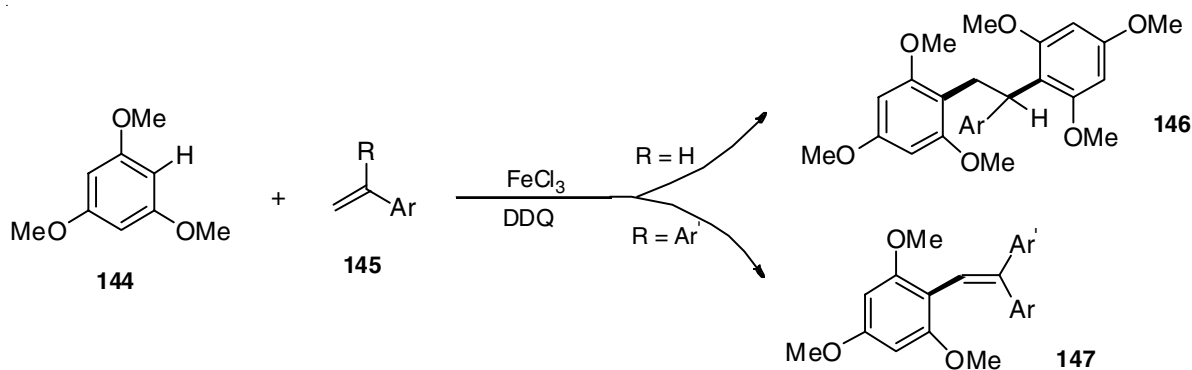
Another iron-catalyzed oxidative C-H/C-H cross-coupling between electron-donor aromatic rings **144** and alkenes **145** in which FeCl<sub>3</sub> was utilized as catalyst joined with the oxidant DDQ carried out by Lei and colleagues [60]. As indicated by radical catching and electron paramagnetic reverberation (EPR) analysis, the proposed system predicts that the DDQ was critical in this transformation, which first oxidizes to frame the aryl radical cation species. At the point, when R is a H atom, the tertiary ethane compound **146** was obtained through cross-coupling between the aromatic rings and the alkene. In addition, when R is an aryl, the triaryl-ethylene compound **147** was formed (**Scheme-XXXVII**).

Alternatively, C-H alkylation of heterocycles route *via* iron catalyst have been developed recently by Bao *et al.* [61] and co-workers. The C-H alkylation of benzothiazole **148** process proceeds through a single-electron transfer iron catalytic cycle. This transformation produce alkyl radical **149** and benzothiazole radical intermediates, that can recombine together to obtain the expected C2-alkylated benzothiazole product **150** with yield up to 93 % (**Scheme-XXXVIII**).

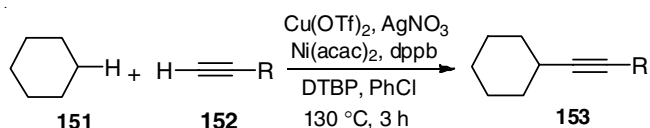


**Scheme-XXXVIII:** Direct C-H alkylation of heterocycles using Ir catalysts

Lei and co-workers [62] have developed the strategy for C-C bond formation through multi-metallic catalyzed radical oxidative process. The unusual radical oxidative cross coupling of unactivated alkenes C(*sp*<sup>2</sup>)-H **151** with terminal alkynes C(*sp*)-H **152** using Cu/Ni/Ag catalytic system, offers a facile approach toward synthesis of various internal alkynes derivatives (**Scheme-XXXIX**). Mechanism proposed proceeds through the combine work of copper and silver in C-H activation of terminal alkyne, followed by transmetalated with Ni catalyst to produce alkynyl Ni (II) complex. On the other hand, generation of the alkyl radical *via* hydrogen abstraction from <sup>t</sup>BuO<sup>•</sup>. Finally, the coupling reaction of two radicals, furnished the desired product **153** with yield up to 91 %.

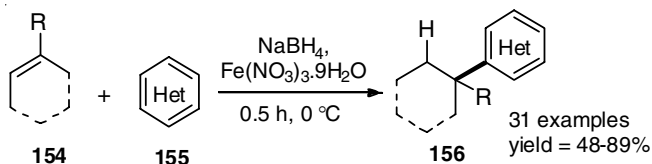


**Scheme-XXXVII:** Iron-catalyzed oxidative C-H/C-H cross-coupling between electron-donor arenes and alkenes

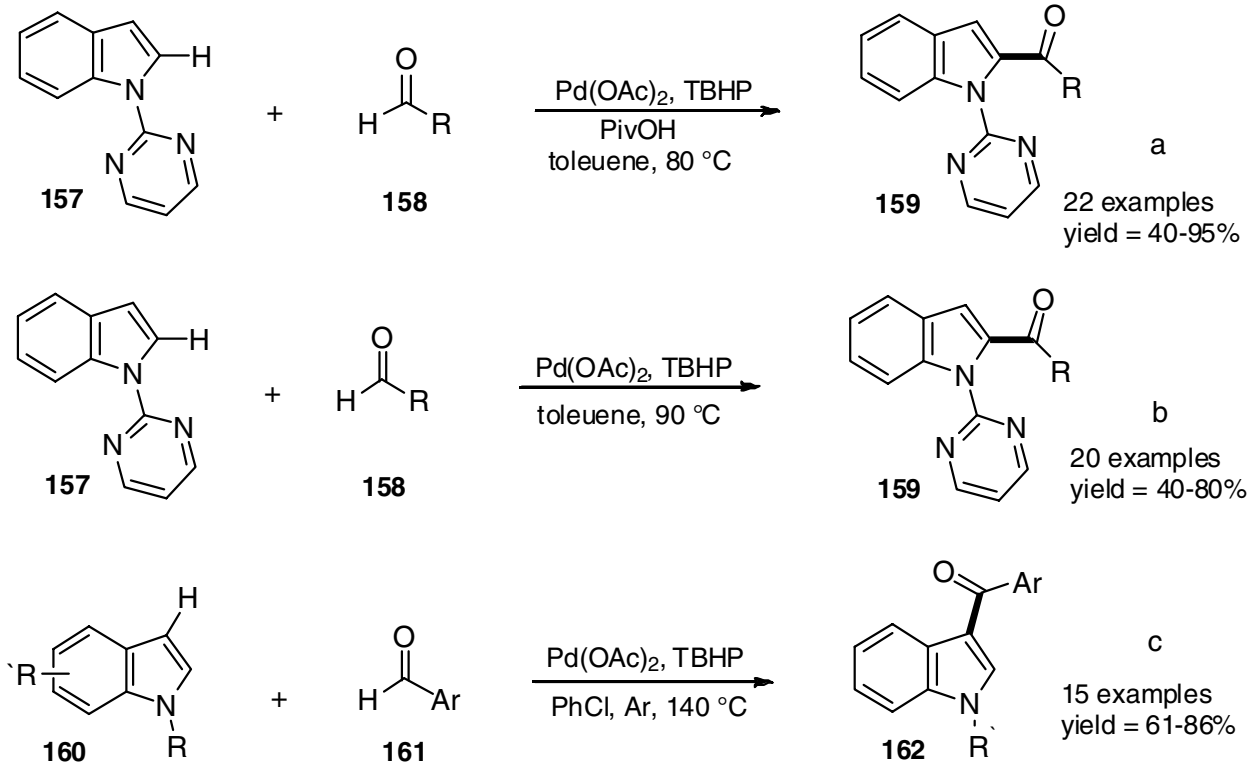


Scheme-XXXIX: Oxidative radical coupling process using Cu/Ag/Ni catalyst

Furthermore, Liu group [63] reported a suitable process for the construction of C-C bond formation protocol employing a free radical-interceded intermolecular hydroheteroarylation of alkenes **154**. It is noteworthy that using Fe(III) catalyst and  $\text{NaBH}_4$  in 1 h at  $0^\circ\text{C}$  proved to be the optimal conditions to get a wide range of alkylated heterocycle products **156** in higher yield (Scheme-XL).

Scheme-XL: Fe(III)/ $\text{NaBH}_4$  promoted free-radical hydroheteroarylation of alkenes

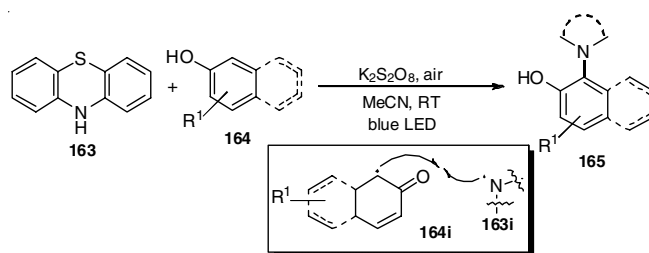
An efficient convention for the Pd-catalyzed C2-acylation of pyridine-ensured indoles, which awards for the utilizing of various conjugated aldehydes as acyl sources, using TBHP as oxidant and PivOH as an added substance, was reported by Liu *et al.* [64] as illustrated in (Scheme-XLIa). Here, combination of N-pyrimidine-protected indoles **157** as substrates and aldehydes **158** as the coupling specialist, aryl indoles **159** were formed in a good income as provided by Sekar and Kumar [65] group and illustrated in (Scheme-XLIb). Kianmehr *et al.* [66] reported that the Pd-catalyzed oxidative acylation of



Scheme-XLI: Synthesis of an efficient protocol for the Pd-catalyzed C2-acylation of pyridine-protected indoles

indoles **160** with aldehydes **161** happens at the 3-directions of indoles **162** as shown in (Scheme-XLIc).

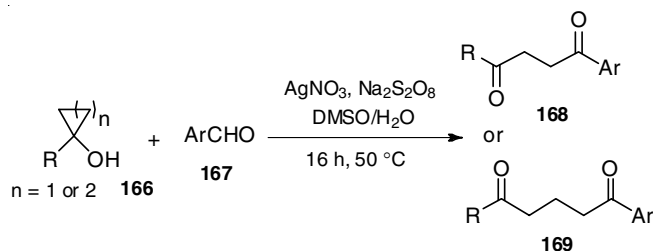
Effectively, Xia and collaborators [67] have been utilized a visible-light mediated amination of phenols without photograph impetus. Cyclic anilines **163** was utilized with single regioselectivity through a radical cross-dehydrogenative coupling process  $\text{K}_2\text{S}_2\text{O}_8$  was provide as oxidizing agent at room temperature. A gram-scale attraction was truly led with TMS secured sesamol, while at the same time Ac-and Bz-protected sesamols don't yield any product. The C-N compound **165** was formed through the specific coupling of the phenoxonium radical **164i** and the transient N-radical **163i**. In same time Patureau and Jin [68] revealed another way to deal with a radical cross dehydrogenative coupling for the amination of phenols, using sodium periodate as an oxidant at  $40^\circ\text{C}$  as illustrated in Scheme-XLII.



Scheme-XLII: A visible-light mediated amination of phenols in the absence of photo catalyst

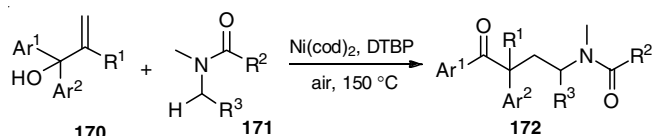
Furthermore, Zhu and co-workers [69] disclosed an efficient silver-catalyzed ring-opening acylation of cyclopropanols and cyclobutanols through intermolecular oxidative

radical addition to aromatic aldehydes (**Scheme-XLIII**). The reaction proceeds through generation of cycloalkanoxy radical from ring-opening operation of cycloalkyl **166**, followed by an intermolecular addition to the aldehyde **167** and give alkoxy radical. Subsequently, the latter can be converted to carbon radical, which can undergo a single-electron transfer under oxidation reaction step, results the desired 1,4 and 1,5-diketone products **168** and **169** with yield up to 92 %.



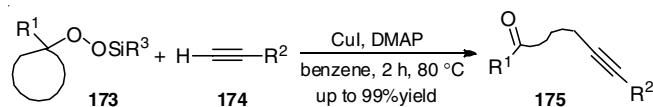
**Scheme-XLIII:** Synthesis of 1,4 and 1,5-diketones using silver catalyst

Furthermore, a nickel-catalyzed oxidative C-H functionalization of  $\alpha,\alpha$ -diaryl allylic alcohols with amides comprising 1,2-aryl immigration was outlined by Tu *et al.* [70]. This method is used to synthesize  $\alpha$ -amino ketones **172** including an all-carbon quaternary compounds. The observing of acetamido methyl radical in the reaction, was proved by a restrict test with TEMPO (**Scheme-XLIV**).

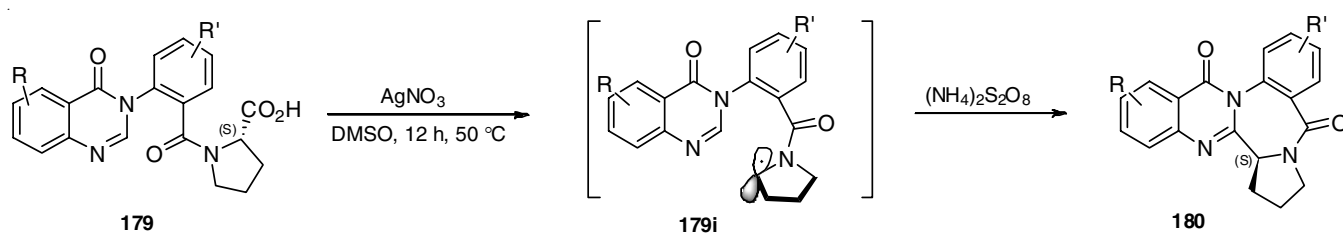


**Scheme-XLIV:** A nickel-catalyzed oxidative C(*sp*)-H functionalization of  $\alpha,\alpha$ -diaryl allylic alcohols with amides

Maruoka and co-workers [71] described a suitable method for the synthesis of internal alkynes from the coupling reaction between terminal alkynes C(*sp*) and alkylsilyl peroxide C(*sp*<sup>3</sup>) *via* copper-catalyzed mediated the radical reaction (**Scheme-XLV**). Generally, this reaction forwards *via* generation of alkoxy radical from alkylsilyl peroxide **173**, followed by  $\beta$ -fragmentation and produce the alkyl radical intermediate. Thus, the coupling between the latter and copper-alkynyl complex would afford the final product **175** with yield up to 99 %.

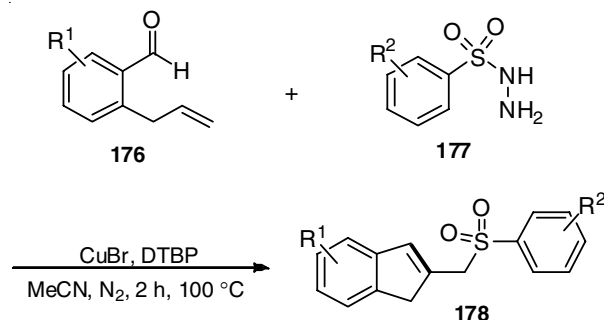


**Scheme-XLV:** Synthesis of internal alkynes using copper catalyst



**Scheme-XLVII:** Synthesis of circumadatin alkaloids *via* radical reactions and Ag catalyst

Furthermore, a flexible strategy for the synthesis of biological cyclic sulfonylmethyl-1*H*-indene derivatives [72] have been described by Zhang group [73] for the first time. The new reaction method based on the 5-*exo*-trig cyclization of alkenyl aldehydes **176** through Cu(I)-mediated sulfonyl radical intermediate. The conversion retains comparatively various substrate range with good functional group compatibility, led to the vinylsulfonylation of unactivated alkenes and produce the final indene product **178** (**Scheme-XLVI**).



**Scheme-XLVI:** Synthesis of sulfonylmethyl 1*H*-Indene derivatives

Later on, Mhaske and Mahajan [74] reported the approach toward synthesis of circumadatin alkaloids. Herein, the new C(*sp*<sup>3</sup>)-C(*sp*<sup>2</sup>) bond formation in the product was obtained through oxidative decarboxylative asymmetric intramolecular radical cyclization using silver nitrate and ammonium persulfate in DMSO solvent at 50 °C for 12 h (**Scheme-XLVII**). The suggested mechanism proceeds through generation of a chiral radical intermediate **179i** from the oxidative decarboxylation step of proline derivatives **179**, followed by cyclization with internal electrophilic position of quinazolinone to obtain the best product yield **180**.

## Conclusion

Due to the rapid growth in the synthesis of organic compounds, which find way in various fields (pharmaceutical, industry, environmental chemistry, natural chemistry *etc.*). Herein, the description of one-pot synthetic strategy, based on free radical reactions, allowed the swift construction of different new compounds by free-radical which included numerous processes (photoredox catalysis free-radical reactions, free-radical cascade processes reactions, Minisci-type alkylation reactions, synthesis of free radical multicomponent reactions and metal-catalysis free radical alkylation).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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