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# Recent trends in the deformylative C-H arylation/alkylation of (hetero)arenes with aldehydes

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ABSTRACT

Direct C-H functionalization of unactivated (hetero)arenes with organohalides or sulfonates has proven to be an effective strategy for the formation of new $C_{(aryl)}$-$C_{(aryl/alkyl)}$ bonds. However, organo(pseudo)halides are mainly highly toxic, which is unfavourable for large-scale and sustainable use. As an alternative to this method, deformylative C-H functionalization of (hetero)arenes with aldehydes has been suggested to be effective because it could further enrich the synthetic methodology due to low-cost, nontoxicity, and easy accessibility of aldehydes. In this review, we focus on the recent advances in this promising and hot research topic which may inspire further research in this domain.

## 1.Introduction

The functionalization of aromatic compounds is an important unit reaction in the production of various organic chemicals, drugs, active pharmaceutical ingredients, and other pharmaceutically and agriculturally important compounds [1]. In this context, direct C–H functionalization of (hetero)arenes has emerged as a powerful and cost-effective strategy for the synthesis of functionalized complex molecules from simple, readily available feedstocks [2-5]. This strategy avoids the requirement of pre-functionalized starting materials and offers several advantages over traditional methods, including reducing the number of steps required and minimizing the amount of waste produced [6]. Among various $C_{(aryl)}$–H functionalization reaction, C-C bond forming reactions are particularly important because carbon skeletons exist in numerous pharmaceuticals and biologically active molecules (Scheme 1) [7].

Conventional cross-coupling reactions require organo(pseudo)halides as electrophilic coupling partners, which are not environmentally friendly and not naturally abundant [8]. To bypass these limitations, in recent years unactivated C–O, C–N and carbonyl electrophiles have emerged as promising alternatives to (pseudo)halides [9-12]. In this regard, the utilization of aldehydes as inexpensive, nontoxic, and readily available coupling partners has attracted growing interest in both academic and pharmaceutical laboratories [13-16]. Since a number of significant advances in this appealing research arena have occurred over the past few years, a comprehensive review on this fast-growing field seems to be timely. Herein, we will provide a comprehensive overview of the recent advances and developments on the construction of $C_{(arvl)}$-$C_{(arvl)}$ and $C_{(arvl)}$-$C_{(alkyl)}$ bonds through the deformylative arylation/alkylation of $C_{(aryl)}$-H bonds with aldehydes, with an aim to inspire and encourage

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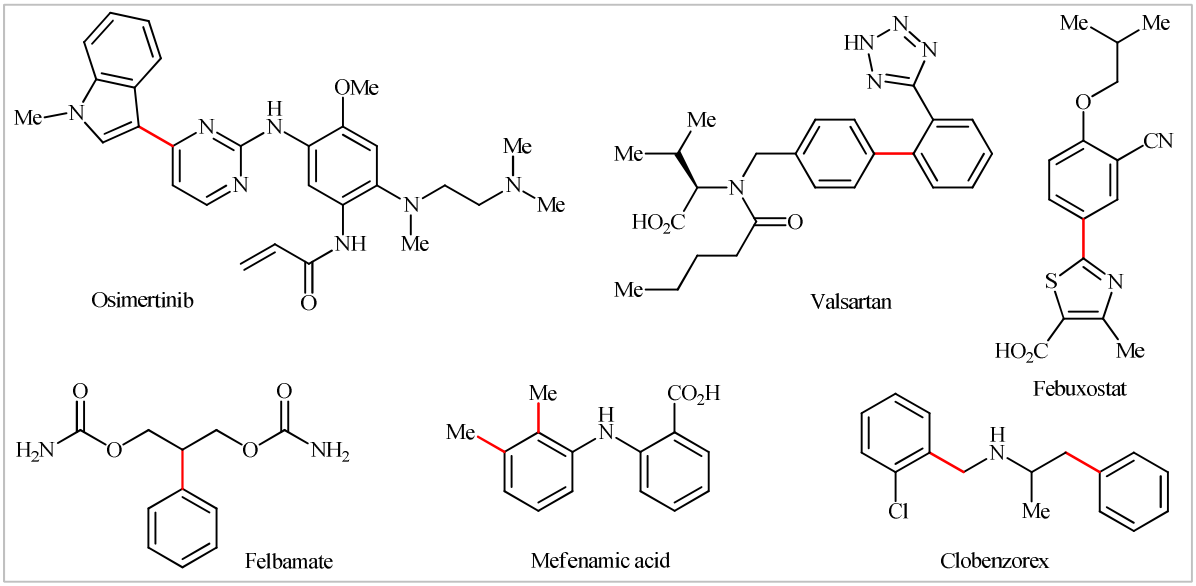
scientists to conduct more research in this domain so that synthesis of biologically important compounds through this reaction can become a reality.




**Scheme 1.** Selected examples of $C_{(aryl)}$-$C_{(aryl)}$ and $C_{(aryl)}$-$C_{(alkyl)}$ bond containing FDA-approved drugs.

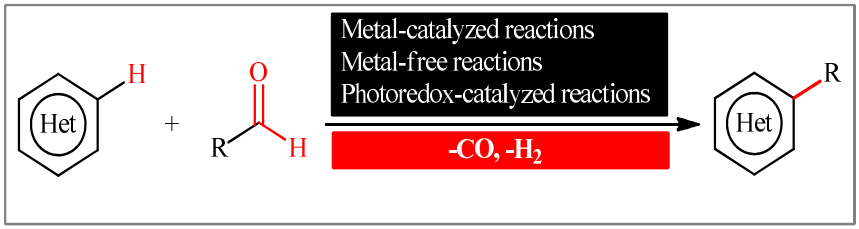


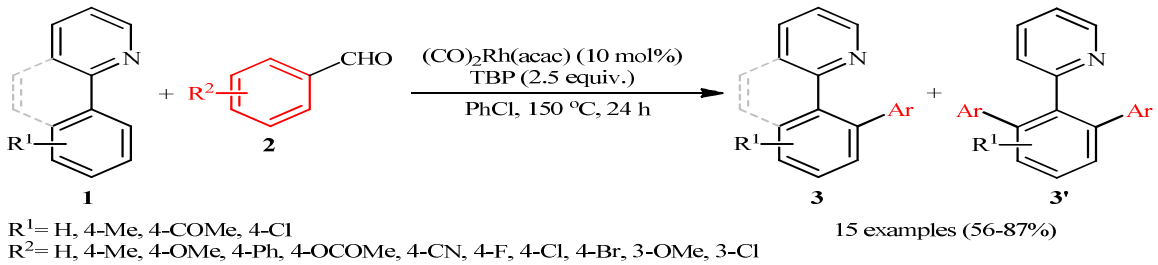

**Figure 1.** Deformylative C-H arylation/alkylation of (hetero)arenes with aldehydes.

## 2. $C_{(aryl)}$-H arylation reactions

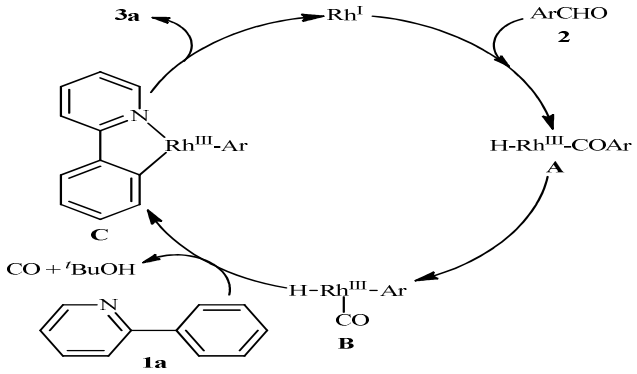
### *2.1. Metal-catalyzed reactions*

One of the earliest reports on the synthesis of biaryls through metal-catalyzed oxidative decarbonylative coupling of aryl C-H bonds appeared in 2010 [17], when arenes bearing a pyridine ring as the directing group 1 underwent a smooth site-selective arylation with various aromatic aldehydes 2 in the presence of $(CO)_2Rh(acac)$/*tert*-butyl peroxide (TBP) combination as a catalytic system using chlorobenzene as the reaction medium to give the corresponding decarbonylative coupling products 3 in good to high yields (Scheme 2). Although complete regioselectivity was observed for the C–H *ortho*-arylation, a mixture of mono- and bis-arylated products was formed under these conditions, which may require tedious purification steps. Moreover, requirement for a high reaction temperature (150 °C) might limit the application profile of this method. It should be mentioned that replacing $(CO)_2Rh(acac)$ with some other ruthenium catalysis (*e.g.*, $[Ru(COD)Cl_2]_n$, $Rh(COD)_2BF_4$, $[Rh(COD)Cl]_2$, $[(CO)_2RhCl]_2$, $RhCl_3$) led to much lower yields or even no desired product at all. The suggested mechanistic pathway for this transformation is displayed in Scheme 3. The reaction starts with the formation of Rh(III)-complex A, H-$Rh^{III}$-COAr, through oxidative addition of aldehyde 2 to the Rh(I)-catalyst. Next, extrusion of CO from this intermediate at elevated temperature generates intermediate B, which after reaction with 2-arylpyridine 1a through C-H bond activation followed by dehydrogenation promoted by TBP affords theruthenacyclic intermediate C. Finally, reductive elimination of intermediate C affords the expected biaryl product 3a and regenerates the Rh(I) catalyst.

Seven years later, Jana and co-workers applied the merge of $Pd(OAc)_2$ with $K_2S_2O_8$ as the catalytic system for the same reaction at room temperature [18]. Interestingly, in this case, the corresponding diaryl ketones were selectively obtained through a dehydrogenative C–H acylation pathway without any of biaryl product formation.



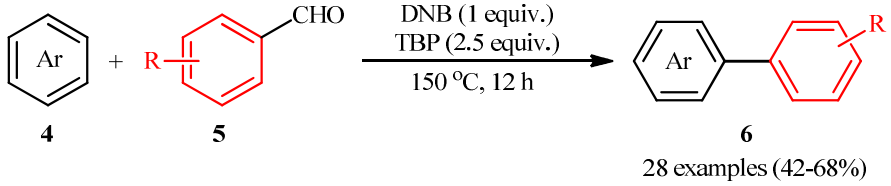

**Scheme 2.** Rh-catalyzed deformylative C-H arylation of 2-arylpyridines **1** with benzaldehydes **2**.




**Scheme 3.** Mechanistic proposal for the reaction in Scheme 2.

*2.2. Metal-free reactions*

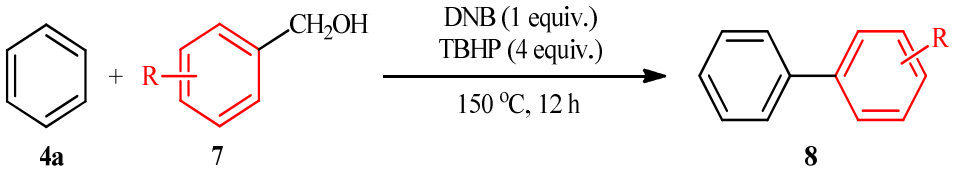
In 2015, Yang's research team reported the first example of the synthesis of biaryl compounds through oxidative decarbonylative coupling of aromatic aldehydes with arenes under metal-free conditions [19]. They discovered that the treatment of simple arenes 4 with different aromatic aldehydes 5 in the presence of TBP as an oxidant and *o*-dinitrobenzene (DNB) as an additive under solvent-free conditions for 12 h produced corresponding biaryls 6 in moderate yields, complete mono-selectivity, and moderate to high *ortho*-regioselectivity (Scheme 4). In this transformation, arenes played a dual role as the substrates and the solvent. Interestingly, the outcome of reaction almost was not dependent on the electronic nature of the aldehyde substituent; therefore, different functional groups such as fluoride, chloride, bromide, cyanide, methoxy, and ester can be used as substituents in the phenyl ring periphery of aldehydes. Regarding the influence of the substituents on arenes, both electron-deficient and slightly electron-rich arenes were tolerated by this protocol, but more electron-rich arenes (*e.g.*, anisole) were not suitable substrates for this transformation. Based on substrates scope, *ortho*-regioselectivity, radical trapping experiments and DFT calculation studies, the authors suggested that this C-C bond forming reaction proceed *via* a non-chain radical homolytic aromatic substitution (HAS) type mechanism.



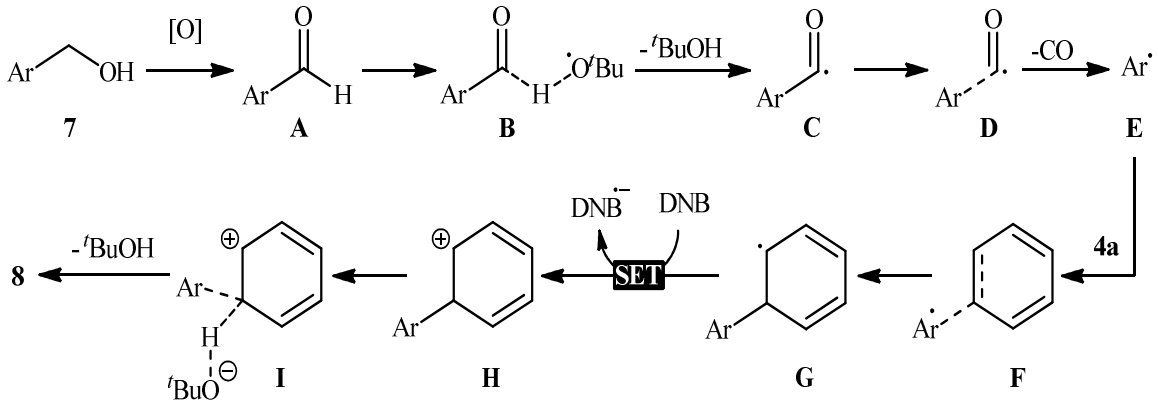

Ar= benzene, toluene,fluorobenzene, chlorobenzene, (trifluoromethyl)benzene, *p*-xylene, *m*-xylene, *o*-xylene,1,4-$(CF_3)_2$-benzene, 1,4-$(Cl)_2$-benzene, 1,3-$(CF_3)_2$-benzene, 1,2-$(Cl)_2$-benzene, 1,2-$(F)_2$-benzene, 1-Cl-4-$CF_3$-benzene
R= H, 4-Me, 4-$^t$Bu, 4-OMe, 4-$CO_2$Me, 4-CN, 4-F, 4-Cl, 4-Br, 4-$CF_3$, 3-Cl, 3-CN, 2-Cl, 2,3-$(CH=CH)_2$, 3,4-$(CH=CH)_2$

**Scheme 4.** Yang's synthesis of biaryls 6.

Shortly afterwards, Kumar and Shah reported *tert*-butyl hydroperoxide (TBHP)-mediated version of the same reaction where the requisite aldehydes were prepared *in situ* from benzyl alcohols [20]. Thus, by employing the combination of DNB with TBHP, mono-selective C-H arylation of benzene 4a with various benzyl alcohols 7 afforded the corresponding biaryls 8 in moderate to good yields within 12 h (Scheme 5). A tolerance for 2-pyridinemethanol was also demonstrated. However, thiazol- and oxazole-methanol did not furnish the desired products. These authors demonstrated relatively significant scope of the benzyl alcohol component, but very limited scope of the arene substrate as the benzene was the only arene examined in this scenario. Based on preliminary mechanistic investigations, the authors proposed that this C-C bond forming reaction proceeds through the following key steps (Scheme 6): (i) initial formation of benzaldehyde A *via* oxidation of benzyl alcohol 7 by TBHP; (ii) abstraction of a hydrogen atom from aldehyde by *tert*-butoxy radical to give the acyl radical B; (iii) decarbonylation of acyl radical B to provide aryl radical E; (iv) addition of the newly formed radical E to benzene 4a leads to the formation of phenylcyclohexadienyl radical G; (v) transfer of an electron (SET) from phenylcyclohexadienyl radical G to DNB to afford phenyl cyclohexadienyl cation H and $DNB^{\bullet-}$; and (vi) deprotonation of the phenyl cyclohexadienyl cation H by *tert*-butoxide anion to form the final biaryls 8.




**Scheme 5.** Metal-free oxidative coupling of benzyl alcohols 7 with benzene 4a.



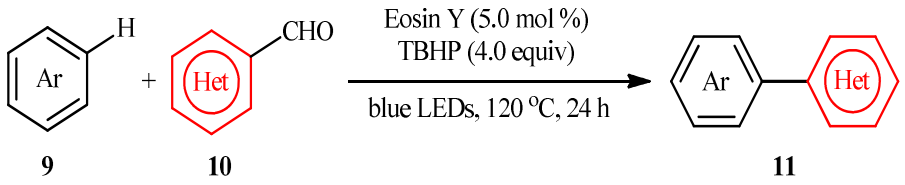

**Scheme 6.** Mechanistic proposal for the formation of biaryls 8.

*2.3. Photo-catalyzed reactions*

Very recently, Zhang and colleagues disclosed the first photocatalytic decarbonylative C-H arylation of arenes 9 with benzaldehydes 10 by using eosin Y an organo-photocatalyst and TBHP as the oxidant [21].

The reactions were done at 120 °C upon irradiation with a 455 nm light-emitting diode (LED) and solvent-free conditions, tolerated various important functional groups on both reaction components and gave corresponding biaryls 11 in rather poor to quantitative yields (Scheme 7). Although the decarbonylation products were obtained in satisfactory yields, the regioselectivities of *ortho*-, *meta*-, and *para*-positioned products were difficult to control under these reaction conditions. The results indicated that except aromatic aldehydes, aliphatic, allylic, vinylic, and acetylenic aldehydes could also be tolerated in this reaction. Noteworthy, other photocatalysts such as eosin B, fluorescein sodium salt, acid red 52, $Acr^{+}$-Mes $ClO_4^{-}$, $Ru(bpy)_3Cl_2$, and *fac*-$Ir(ppy)_3$ were also found to promote this reaction, albeit at lower efficiencies.

Mechanistic investigations reveal that this reaction most likely proceeds through a radical pathway *via* photothermal excitation to generate an aryl radical by decarbonylation of aldehydes.




**9** **10** **11**

49 examples (22-98%)

Ar= 2,5-$(Me)_2$-$C_6H_4$, 2,5-$(F)_2$-$C_6H_4$, 2,5-$(Cl)_2$-$C_6H_4$, 2,5-$(Br)_2$-$C_6H_4$, 2,5-$(CF_3)_2$-$C_6H_4$, 2-Cl-5-$CF_3$-$C_6H_4$, 2-Cl-5-Me-$C_6H_4$, 2-Cl-5-$^t$Bu-$C_6H_4$, 2-Cl-5-OMe-$C_6H_4$, *o*/*m*/*p*-OMe-$C_6H_5$, *o*/*m*/*p*-Cl-$C_6H_5$, *o*/*m*/*p*-I-$C_6H_5$

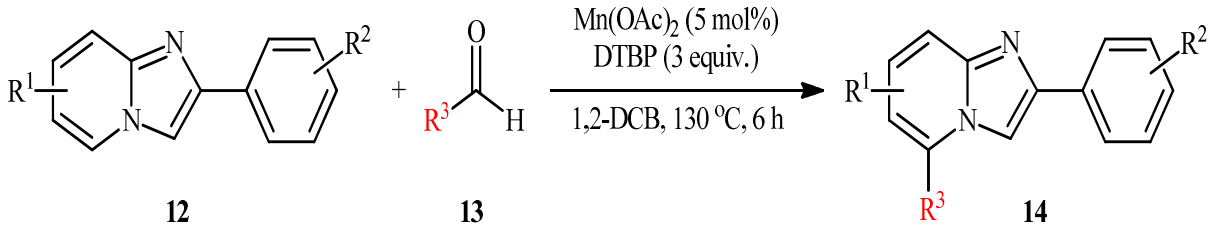
(Het)Ar= 4-Me-$C_6H_4$, 4-$^t$Bu-$C_6H_4$, 4-OMe-$C_6H_4$, 4-COMe-$C_6H_4$, 4-$CO_2$Me-$C_6H_4$, 4-F-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-$CF_3$-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 4-CN-$C_6H_4$, 4-$SO_2$Me-$C_6H_4$, 3-Me-$C_6H_4$, 3-Cl-$C_6H_4$, 3-$NO_2$-$C_6H_4$, 2-naphthyl, 2-pyridyl, 4-pyridyl, 3-furyl, 3-thienyl

**Scheme 7.** Photo-catalyzed decarbonylative C-H arylation of arenes 9 with benzaldehydes 10 developed by Zhang.

## 3. $C_{(aryl)}$-H alkylation reactions

### *3.1. Metal-catalyzed reactions*

Despite the fact that transition metal catalysts lie at the heart of cross-coupling reactions, the reported examples of the deformylative alkylation of $C_{(aryl)}$–H bonds with aliphatic aldehydes using metal catalysts are scarce. In fact, only one example of such a reaction was reported in the literature till date. In this study, Samanta and Hajra described the regioselective C5-alkylation of imidazopyridines with various aliphatic aldehydes using $Mn(OAc)_2$ as a low-cost commercially available catalyst [22]. A screening of reaction variables indicated that DTBP (di-*tert*-butyl peroxide) and 1,2-DCB were the most effective oxidant and solvent, respectively. With these optimized reaction conditions, a variety of C5-alkylated imidazo[1,2-*a*]pyridines **14** were obtained in moderate to excellent yields from the corresponding imidazo[1,2-*a*]pyridines **12** and aliphatic aldehydes **13** (Scheme 8). However, aromatic aldehydes and formamides failed to produce any product under the optimized conditions. It should be noticed that this interesting regioselective alkylation reaction was also worked well with other heteroarenes such as benzothiazole, benzoxazole, pyridine, pyrazine, pyrimidine, quinoxaline, and phthalazine. However, applicability of simple arenes as starting materials was not investigated in this study. The system was also amenable to the regioselective cross-dehydrogenative coupling of imidazo[1,2-*a*]pyridines with a variety of simple alkanes, cyclic and acylic ethers providing C5-alkylated imidazo[1,2-*a*]pyridine products in satisfactory yields. The authors proposed mechanism for the formation of C5-alkylated imidazo[1,2-*a*]pyridines **14** involves the initial hemolytic cleavage of the oxidant DTBP with the aid of Mn(II) to produce the *tert*-butoxyl radical with the *tert*-butoxy Mn(III) species. Subsequently, *tert*-butoxyl radical abstracts a hydrogen atom from aldehyde 13 to provide the acyl radical A. The formation of alkyl radical B occurs next, followed by its attacks at the C5-position of imidazo[1,2-*a*]pyridine 12 to give intermediate C that, after one-electron oxidation affords cationic intermediate D. Then, the intermediate D transforms to the final product 3 by a deprotonation process (Scheme 9).




**12** **13** **14**

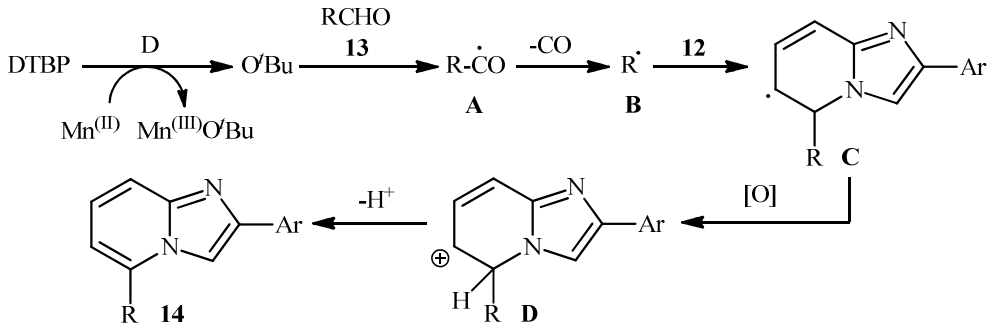
21 examples (49-89%)

$R^1$= H, 7-Me, 7-OMe, 8-Me

$R^2$= H, 4-Me, 4-OMe, 4-$SO_2$Me, 4-F, 4-Cl, 4-CN, 4-$CF_3$, 3-Br, 3,4-$(CH{=}CH)_2$

$R^3$= $^i$Pr, $^n$Bu, $^t$Bu, $^{sec}$Bu, $^{sec}$Pent, $^{iso}$Pent, $^c$Hex, 3-Hept

**Scheme 8.** Mn-cayalyzed deformylative alkylation of imidazo[1,2-*a*]pyridines 12 and aliphatic aldehydes 13.

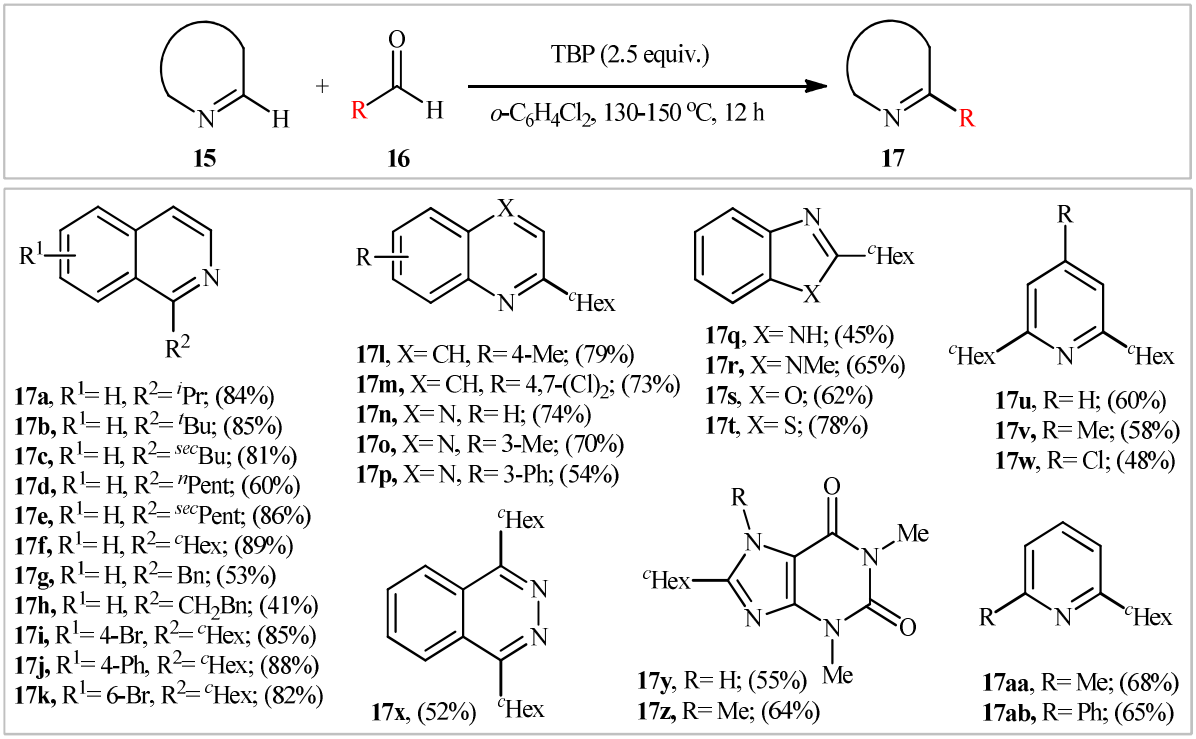



**Scheme 9.** Proposed mechanism for the formation of C5-alkylated imidazo[1,2-*a*]pyridines 14**.**

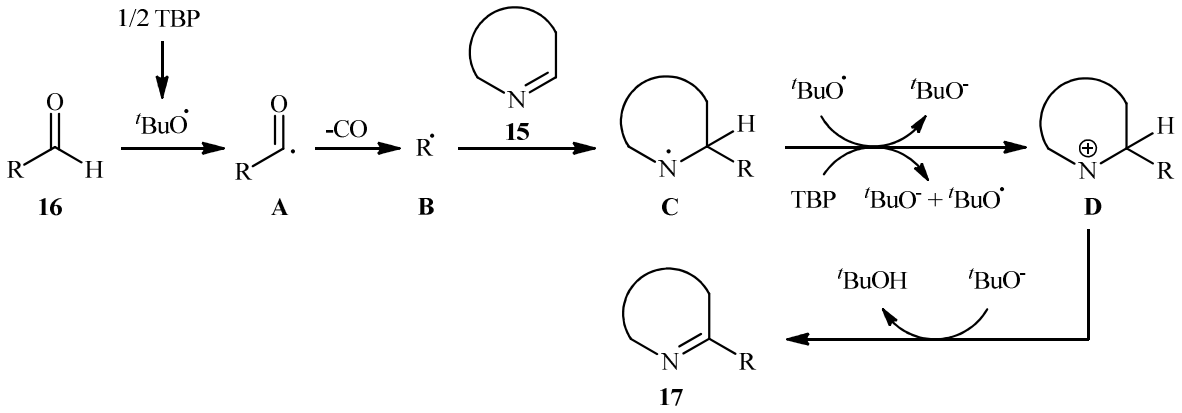
*3.2. Metal-free reactions*

In 2015, Tang, Kang, and Yang described an efficient transition-metal-free direct alkylation of $C_{(aryl)}$-H bonds with aliphatic aldehydes *via* radical-promoted decarbonylation under open air [23]. They carefully tested several oxidants and solvents, and the system TBP/*o*-$C_6H_4Cl_2$ was found to be superior. Under the optimized conditions, various *N*-heteroarenes 15 and aliphatic aldehydes 16 reacted to give good yields of the corresponding alkylated products 17 within 12 h (Scheme 10). This metal-free decarbonylative coupling reaction tolerated all three kinds of primary, secondary, and tertiary aliphatic aldehydes and various kinds of electron-deficient heterocycles (*e.g.*, quinoline, quinoxaline, isoquinoline, pyridine, pyrazine, pyrimidine, phthalazine, purine, imidazole, thiazole, and oxazole).

However, applicability of simple arenes as starting materials was not investigated in this study. A drawback of the protocol is the requirement for drastic conditions of temperature (130-150 °C), which may limit its range of applications. The mechanistic pathway of this oxidative decarbonylative coupling reaction is shown in Scheme 11, and involves the initial formation of *tert*-butoxy radical through the homolytic cleavage of TBP, which then abstracts the aldehyde 16 hydrogen atom to provide the acyl radical A. Next, decarbonylation of the newly formed radical affords alkyl radical B. Subsequently, reaction of this radical with heteroarene 15 gives the radical C which delivers the cation D after a single electron transfer to the *tert*-butoxy radical and/or TBP. Finally, deprotonation of this cation by a *tert*-butoxide anion furnishes the observed alkylated product 17.

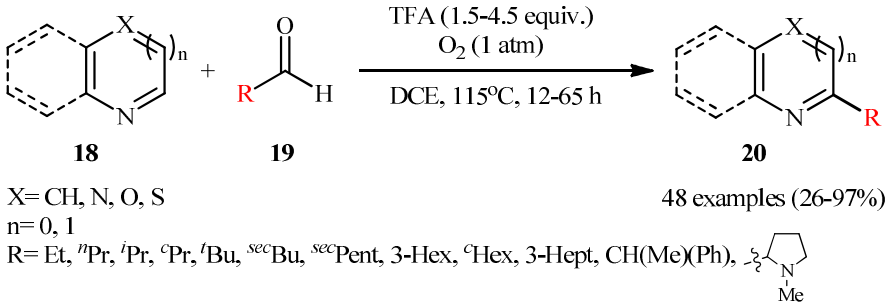



**Scheme 10.** TBP-promoted decarbonylative coupling of aliphatic aldehydes 16 with azaarenes 15.



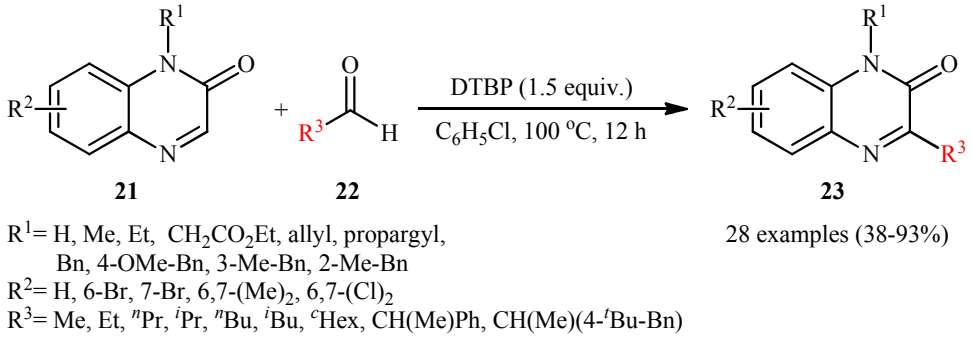

**Scheme 11.** Mechanistic proposal for the reaction in Scheme 10.

The synthesis of alkylated azaarenes 20 in moderate to excellent yields (up to 97 %) was also reported by Paul and Guin through the metal-free oxidative decarbonylative coupling reaction of the corresponding azaarenes 18 with aliphatic aldehydes 19 employing trifluoroacetic acid (TFA) as an additive and oxygen as an environmentally benign oxidant (Scheme 12) [24]. The authors proposed a SET pathway based mechanism for their reaction similar to the report described by Yang group. Later, this innovative research group disclosed that when DCE was replaced by EtOAc, the corresponding heteroaryl–alkyl ketones were selectively obtained through a dehydrogenative C–H acylation pathway without any of alkylated heteroarene product formation [25].




**Scheme 12.** Paul-Guin's synthesis of alkylated azaarenes **20**.

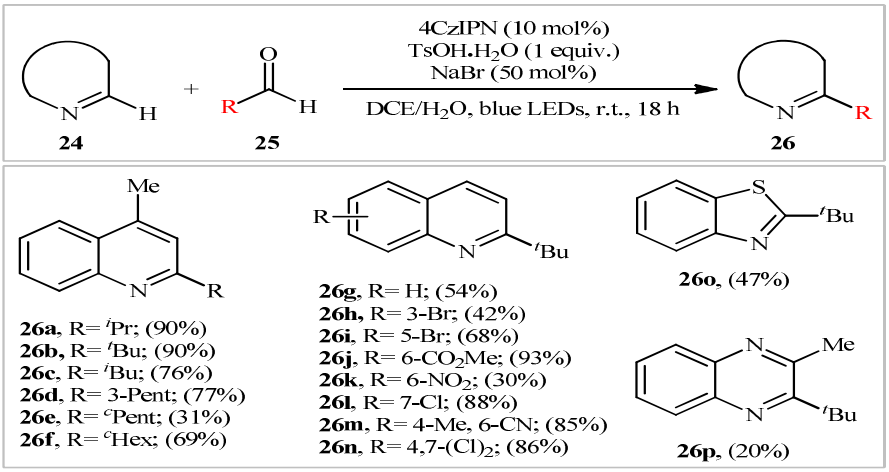
Along this line, recently, Yao, Lin, and co-workers synthesized a series of biologically important 3-alkylquinoxaline-2(1*H*)-one derivatives 23 *via* regioselective alkylation of quinoxaline-2(1*H*)-ones 21 with aliphatic aldehydes 22 employing DTBP as an oxidant under catalyst-free conditions [26]. The corresponding 3-alkylquinoxaline-2(1*H*)-ones 23 were obtained in moderate to high yields, ranging from 38% to 93% (Scheme 13). Notably, both NH-free and *N*-subtitled quinoxaline-2(1*H*)-ones and a variety of cyclic and acyclic aldehydes worked well under optimized conditions. However, phenylacetaldehyde was not compatible with this scenario. The results demonstrated that the electronic character of the substituents in the quinoxaline-2(1*H*)-ones have no obvious effects on this reaction.



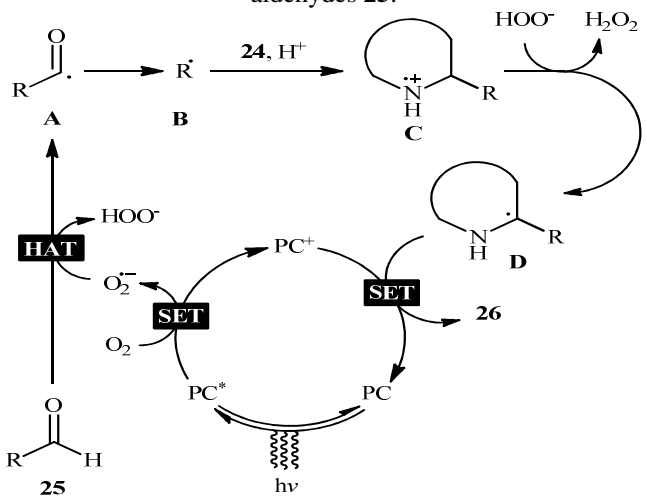

**Scheme 13.** DTBP-promoted direct alkylation of quinoxaline-2(1*H*)-ones **21** with aliphatic aldehydes **22**.

*3.3. Photo-catalyzed reactions*

In 2019, Ji and Huang along with their co-workers informed for the first time the usefulness of photocatalysts for the decarbonylative alkylation of $C_{(aryl)}$–H bonds with aliphatic aldehydes [27]. To evaluate the catalytic activity of different photocatalysts, 4-methylquinoline and 2-ethylhexanal were chosen as the model substrates for the aerobic decarbonylative alkylation under visible light irradiation. Among the various commercially available photocatalysts [*e.g.*, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $Ru(bpy)_3PF_6$, rose bengal, 4CzIPN, eosin Y], 4CzIPN was found to be more effective, which gave a better yield of the desired decarbonylative alkylation product. In a pursuit to further improve the yield, NaBr was added as an additive to the reaction mixture. Various acids such as $(PhO)_2PO_2H$, $TsOH{\cdot}H_2O$, $CH_3SO_3H$ and $CF_3SO_3H$ were examined and a good yield of product was obtained when using $TsOH{\cdot}H_2O$ as an acid additive. Under the optimized conditions, various *N*-heteroarenes 24 reacted efficiently with simple aliphatic aldehydes **25** to give the corresponding C2-alkylated *N*-heteroarenes 26 in modest to high yields and excellent selectivity (Scheme 14). The plausible mechanism for this transformation is outlined based on a series of control experiments such as radical trapping and Stern–Volmer quenching experiments (Scheme 15). At the beginning of the reaction, photoexcitation of the ground state photocatalyst 4CzIPN (PC) by visible light forms the excited state photocatalyst (PC*), which after single electron transfer (SET) to $O_2$ produces a superoxide radical anion ($O_2^{\bullet-}$) and highly oxidized ($PC^+$). Next, abstraction of a hydrogen atom from aldehyde 25 by the superoxide radical anion generates an acyl radical B, which subsequently decomposes into an alkylradical B by decarbonylation. Then, radical addition of B to the charged *N*-heteroarene 24 yields the radical cation C. Finally, the sequential deprotonation of C and single-electron oxidation by ($PC^+$) affords the final alkylated heteroarene 26.

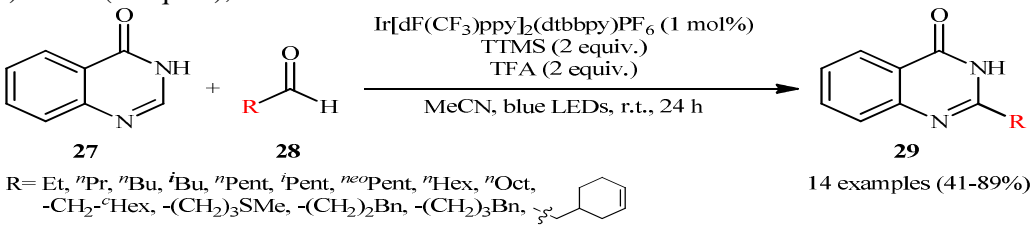



**Scheme 14.** Selected examples of visible-light-mediated photoredox decarbonylative alkylation of *N*-heteroarens **24** with aliphatic aldehydes **25**.



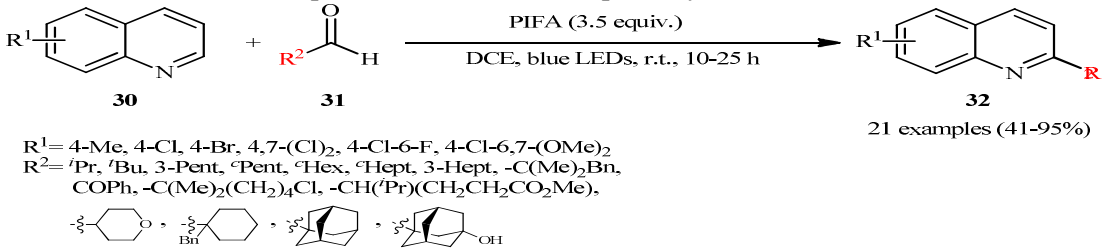

**Scheme 15.** Mechanistic proposal from the formation of C2-alkylated N-heteroarenes **26**.

Concurrently, Wang's research team presented an efficient photoredox-mediated C-H alkylation of quinazolin-4(3*H*)-one 27 with aliphatic aldehydes 28 under ambient conditions [28]. The results of this investigation indicated that the optimum condition for this transformation was the combination of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.0 mol%), tris(trimethylsilyl)silane (2 equiv.), and trifluoroacetic acid (2 equiv.) as a catalytic system using MeCN as the solvent. Under optimized conditions, the reaction tolerated a diverse set of cyclic and acyclic aliphatic aldehydes and gave the desired C2-alkylated quinazolin-4(3*H*)-ones 29 in moderate to good yields (Scheme 16). Interestingly, the catalytic system was also effective for the decarbonylative C-H alkylation of various *N*-heteroarenes with aliphatic ketones.

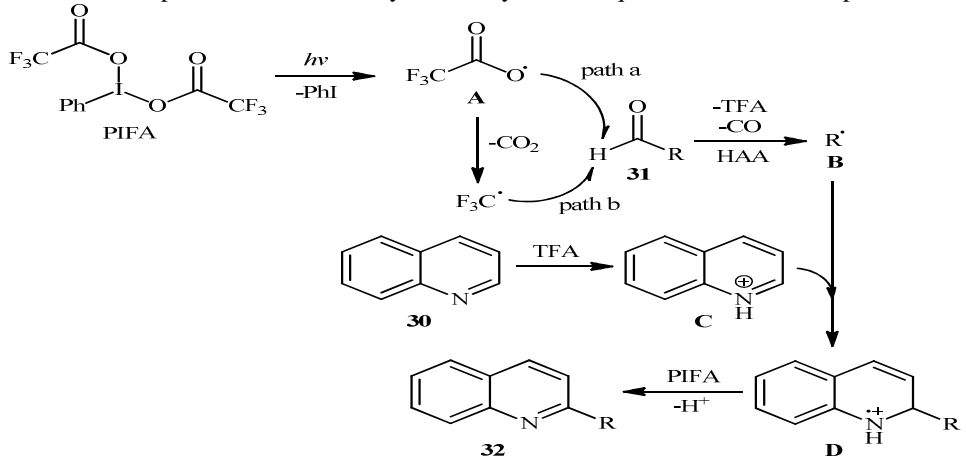



**Scheme 16.** Wang's synthesis of C2-alkylated quinazolin-4(3*H*)-ones **29**.

Drawing inspiration from these works, Zhu and colleagues described an interesting regioselective metal-free photoinduced direct C2-alkylation of quinolines 30 by using aliphatic aldehydes 31 as the alkyl source in the presence of over-stoichiometric amounts of phenyliodine bis(trifluoroacetate) (PIFA) under irradiation with blue LEDs (Scheme 17) [29]. Noteworthy, when the C2-position of quinoline was blocked, the alkylation preferred the C4-position. Apart from quinolines, isoquinolines, pyridines, pyrimidines, pyrazines, and thiazoles were also compatible with this scenario. Notably, in the case of isoquinolines, the alkylation took place selectively at the 1-position. The reaction could also be easily scaled up to the gram-scale as exemplified by the formation of 4-chloro-2-cyclohexylquinoline on a 2.18-g scale (89%). It was noteworthy that the authors nicely applied their methodology to the late-stage functionalization of complex drug molecules, *e.g.*, quinoxyfen (a fungicide) and voriconazole (an antifungal). Mechanistic investigation revealed that the reaction follows a SET pathway (Scheme 18).

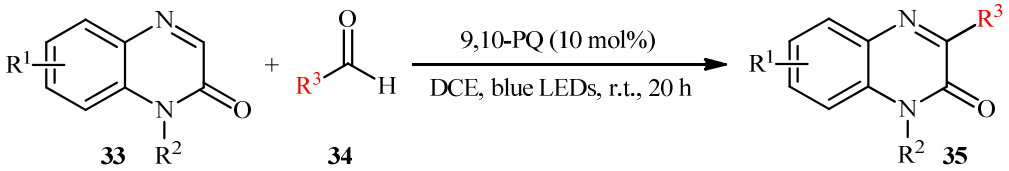



**Scheme 17.** Metal-free photoinduced deformylative alkylation of quinolines **30** with aliphatic aldehydes **31**.




**Scheme 18.** Proposed mechanism for the reaction in Scheme 17.

Along this line, Wang, Sun, and co-workers showed that phenanthrene-9,10-dione (9,10-PQ) was able to promote the selective C3-alkylation of quinoxalin-2(1*H*)-one derivatives 33 with aliphatic aldehydes 34 under the irradiation of blue LEDs and in the absence of any ligand or additive at room temperature (Scheme 19) [30]. Various secondary and tertiary aliphatic aldehydes were compatible with this protocol. However, primary aliphatic aldehydes and benzaldehydes were inert under standard conditions.




**33** **34** **35**

$R^1$= H, 6-Me, 6-OMe, 6-F, 6-Cl, 6-Br, 6-$CO_2$Me, 6-$CF_3$, 6-CN, 7-F, 7-Cl, 7-$CO_2$Me, 7-$CF_3$, 6,7-$(Me)_2$, 6,7-$(Cl)_2$, 6,7-$(CH{=}CH)_2$-
$R^2$= H, Me, Et, Bn, Ph, $CH_2CO_2$Me, allkyl, propargyl
$R^3$= $^i$Pr, $^t$Bu, $^{sec}$Bu, 3-Pent, $^c$Pent, $^c$Hex

21 examples (62-87%)

**Scheme 19.** Wang, Sun's synthesis of C3-alkylated quinoxalin-2(1*H*)-ones **35**.

## 4. Conclusion

Direct C–H functionalization represents a powerful strategy for direct conversion of the ubiquitous C–H bonds into various C–C bonds without functional group manipulations, thus makes synthetic schemes shorter, cleaner, and more efficient. Traditionally, these reactions have heavily relied on organohalides and pseudo-halides as electrophilic-coupling partners, which are not environmentally friendly and not naturally abundant. Consequently, many efforts have been made in seeking alternatives to organo(pseudo)halides and various unactivated C–O, C–N and carbonyl electrophiles developed as viable electrophilic partners. Aldehydes, as some of the most important building blocks in organic chemistry, have been widely used to synthesize many other value-added chemicals due to their fascinating reactivities and versatile transformations. These inexpensive, easily available, and environmentally friendly compounds have recently been utilized as coupling partners in various carbon-carbon and carbon-heteroatom cross-coupling reactions. As illustrated, they have been successfully applied as arylation and alkylation agents for the direct $C_{(aryl)}$–$C_{(aryl)}$ and $C_{(aryl)}$-$C_{(alkyl)}$ bond forming reactions. However, majority of the reactions covered here suffer from the requirement for elevated temperatures. Therefore, development of novel catalytic systems that allow deformylative C-H functionalization of (hetero)arenes with aldehydes under ambient condition are highly desirable. We conclude this review by hoping that it will stimulate researchers to further exploration and research in this interesting and novel arena of cross-coupling reactions.

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