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Visible-Light-Triggered Directly Reductive Arylation of Carbonyl/Iminyl Derivatives through Photocatalytic PCET

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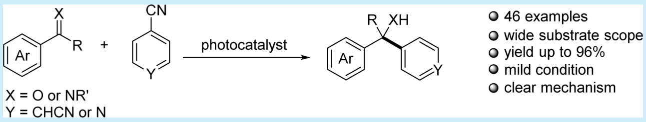
Supporting Information



ABSTRACT: The first visible-light-mediated radical−radical cross-coupling strategy that enables the direct arylation of carbonyl/iminyl derivatives in the presence of Et_3N has been realized. Such an atom-economical protocol furnishes a broad scope of arylation products such as secondary/tertiary alcohols and amines via a PCET process that facilitates the challenging reduction of C═X (X = O, N). Mechanistic investigation indicates two photocatalytic redox cycles were involved in the process, and Et_3N was proved to serve as a dual reductant and proton donor. Moreover, the isolated byproducts and controlled experiments could be considered as powerful supporting evidence for our hypothesis.

Compounds with carbon−heteroatom double bonds (ketones, aldehydes, and imines) are valuable synthetic precursors in organic chemistry for the new C−C bond construction.[1] Among which one of their extraordinary application is the preparation of alcohols or amines, which are synthetically reactive intermediates and necessary building blocks for many bioactive and pharmaceutical structures, by means of reductive nucleophilic additions.[2−4] Traditional technologies on such transformations (especially for carbonyl compounds) rely on air- and moisture-unstable organolithium, organomagnesium, or organozinc reagents.[5] In addition, the demands of functional group compatibility also limit their wider application. To address such drawbacks, some alternative strategies, such as the organometallic reagents (Zn, Mg, In, Sn, Sm, Ti, etc.) engaged Barbier−Grignard-type reactions[6] which even performed in water, the transition-metal complex (Rh, Pd, Ni) catalyzed addition of nonmetallic reagents (such as boron, silicon compounds) onto carbon−heteroatom double bonds,[7] and the phosphonium salt mediated reductive alkylation[8] or arylation[9] have been developed as more efficient tools. However, substrate limitations and cost issues have inspired chemists to focus continuous efforts on searching for less conventional and ecocompatible techniques.

Proton-coupled electron transfer (PCET) has been recognized as an elementary redox process in which both a proton and an electron traveled in a concerted manner, and it plays a critical role across biochemistry and material domains.[10] Recently, the applications of PCET in organic synthesis, especially in the photochemical reactions, have become one of the most advanced hotspots. Numerous excellent achievements have been made,[11] e.g., the homolytic activation of O−H bonds of alcohols or N−H bonds of amines[12,13] and the direct reduction of π-bonds of unsaturated carbon−heteroatom compounds,[14] all of which were inaccessible by using the classical HAT method.

In particular, the synthetic applications of ketyl and iminyl radicals derived from the reductive umpolung of carbonyls/iminyls, in most cases with the aid of Lewis acids, on the PECT-mediated photocatalytic platform have been highlighted but limited to coupling with alkyl radicals or the intra-/intermolecular addition to unsaturated bonds.[11,14] For example, In 2015, Rueping's group reported the reductive homocoupling of aldehydes, ketones, and imines to the corresponding dimerization products;[15] in addition, their further research revealed a photocatalytic approach to the access of 1,2-diamines and alkamines via α-amino radicals and ketyl radicals[16] (Scheme 1, i). In respect to the reaction of double bonds, in 2003, Knowles detailed an intramolecular ketyl−olefin cyclization via PECT.[17] Recently, Ngai developed the first β-selective coupling of alkenylpyridines with aldehydes and imines catalyzed by visible light (Scheme 1, ii).[18] These protocols not only demonstrate the capacity of PECT to access the required radical synthons but also provide alternatives for the reductive C−C coupling on unsaturated carbon−heteroatom bonds. Nonetheless, to the best of our knowledge, general photochemical strategies that directly achieve the cross-coupling of ketyl and iminyl radicals with aryl radicals or radical ion intermediates have never been explored, which might be mainly due to the large steric hindrance and high reduction potential of the substrates. Herein, we report the first photocatalytic reductive arylation reaction of carbonyl/iminyl derivatives. Such a concept was primarily based on the PCET that enabled access to ketyl/iminyl radical and the feasible generation of an aryl radical via a well-established photoredox mode by using dicyanobenzene as a precursor.[19]

With respect to the lower reduction potential of aldehydes compared to ketones (benzaldehyde, $E_{red} = -1.93$ V vs SCE),[20] our investigation was initially launched on the reaction between the readily available benzaldehyde **1a** and 1,4-dicyanobenzene (1,4-DCB). After a series of screenings on photocalyst, solvent, and other impact factors, we defined the reaction of **1a** in the presence of catalyst **3b** (1.0 mmol %), 1,4-DCB (2.0 equiv), and

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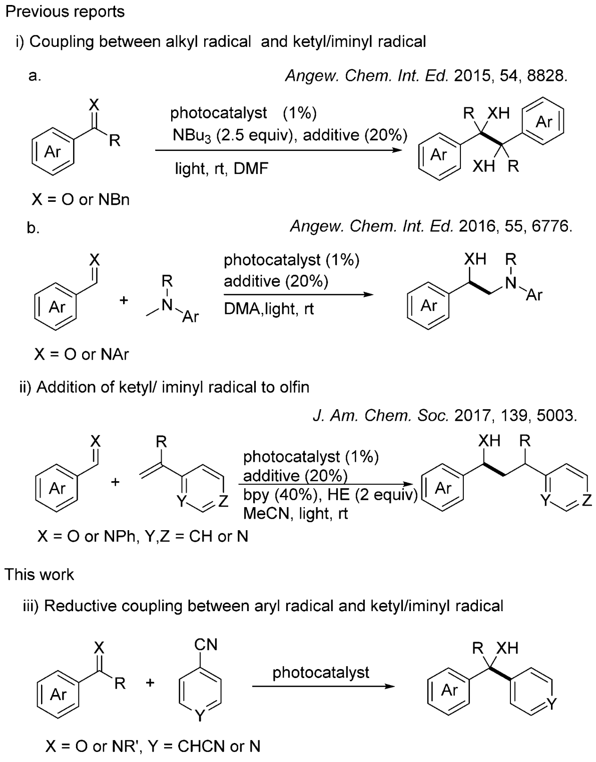
Scheme 1. Previous Work and This Work

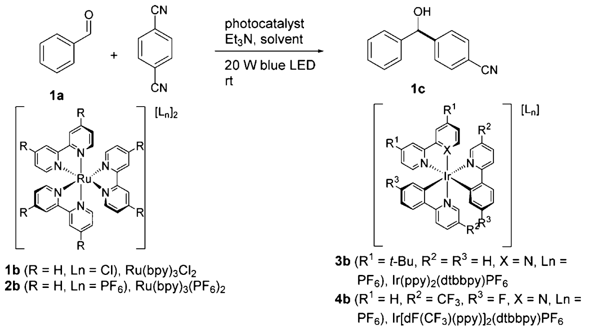


triethylamine (3.0 equiv) in MeOH with the protection of nitrogen under the irradiation of a 20 W blue LED at room temperature as the optimized conditions (Table 1).

With the optimal conditions in hand, we then turned our attention to evaluate the reactivity of aldehydes. As outlined in Scheme 2, all the tested aromatic aldehydes were found to be competent substrates to yield the corresponding alcohols within 7 h under mild conditions (**1c**–**13c**). Functional groups regardless of electron-donating (methyl, methoxyl, phenyl, etc.) or electron-withdrawing nature were well tolerated with the reaction conditions. Delightfully, product **5c** with *p*-methoxyl on the benzene ring was obtained in a highest yield 96%. In addition, substrates with large groups, such as phenyl and *tert*-butyl, could furnish the corresponding products in 43% and 56% yield, respectively (**8c**, **9c**). Polysubstituted substrates **10a**–**12a** were also suitable for the reaction conditions to afford the products in good yields (**10c**–**12c**, 62–76%). Notably, this protocol was also applicable with other aromatic aldehydes such as naphthaldehyde (**13c**).

Encouraged by the satisfactory results using aldehydes, we attempted to extend the substrate scope to ketones, which were regarded as a big challenge due to their high reduction potentials (acetophenone, $E_{\text{red}} = -2.11$ V vs SCE).[20] Gratifyingly, the reactions were carried out successfully when a broad range of aromatic ketones were submitted to the standard conditions. However, minor defects were found that showed most substrates could not be fully consumed even with prolonged reaction times. As shown in Scheme 2, a series of acetophenone derivatives with diverse substituents on the benzene ring could effectively couple with 1,4-DCB to provide functionalized products in moderate to high yields (**14c**–**22c**). Replacing R_s (R_s = methyl) with other chain or cyclic aliphatic groups, the transformations were also amenable with the corresponding ketones (**23c**–**28c**). Moreover, benzocycloketones with different ring sizes as well as benzoheterocyclones successfully demonstrated the compatibility of this protocol (**29c**–**32c**). Similar to the photochemical behavior of polysubstituted benzaldehydes, the coupling reaction of analogous ketone substrate was proven to be viable to form the corresponding product in moderate yield (**33c**). In addition, other tertiary aromatic alcohols such as heterocyclic and polycyclic aromatic adducts could be easily implemented via this method (**34c**, **35c**).

Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst (mmol %)	solvent	yield[b] (%)
1	**1b** (5)	MeCN	none
2	**2b** (5)	MeCN	none
3	**3b** (5)	MeCN	40
4	**4b** (5)	MeCN	35
5	**3b** (5)	MeOH	45
6	**3b** (5)	DMF	40
7	**3b** (5)	DMSO	none
8	**3b** (5)	THF	none
9	**3b** (1)	MeOH	55 (31)[c]
10	**3b** (0.5)	MeOH	35
11[d]		MeOH	none
12[e]	**3b** (1)	MeOH	none

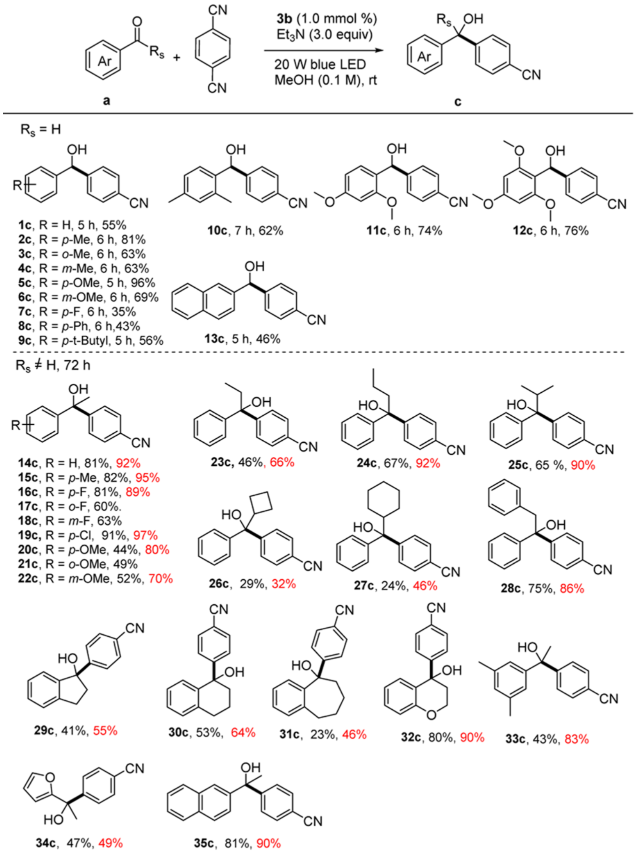
[a] Reaction conducted with 0.2 mmol of **1a**, 0.4 mmol of 1,4-DCB, 0.6 mmol of Et_3N in 2.0 mL of solvent, 20 W blue LED, under N_2 atmosphere unless otherwise noted. [b] Isolated yield. [c] Reaction system under air atmosphere. [d] Reaction conducted without photocatalyst. [e] Reaction conducted in dark.

To extend the scope of this reaction, we further employed aromatic imines to demonstrate the compatibility of this methodology. As summarized in Scheme 3, series of imine derivatives were effectively transformed into the desired amine products (**1e**–**6e**) in acceptable yields. Remarkably, substrate **6d**, which was derived from an aromatic ketone, was also suitable for the reaction conditions to furnish its corresponding product with a quaternary center.

Furthermore, we evaluated the generality of this protocol by using other nitriles (2-methylterephthalonitrile and isonicotinonitrile) as potential coupling partners. It was found that the methyl on 1,4-DCB did not hinder the reaction progress to couple with both aldehydes and ketones, leading to the photoinduced products in a similar fashion (Scheme 4, **1f**–**3f**). Notably, the arylation of aldehyde led to an inseparable alcohol mixture (**1f**/**1f′**), while the ketone system afforded tertiary alcohol as the only product (**2f**–**3f**), which might be due to the steric effect of R. Additionally, we were delighted to find that isonicotinonitrile could serve as a brilliant coupling partner and deliver the corresponding products in good to high yields (**4f**–**5f**).

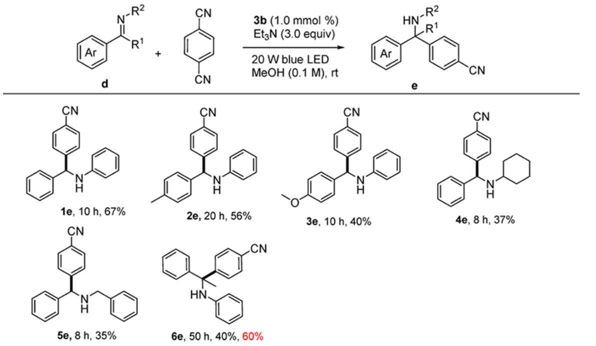
To gain more insight into the mechanistic details, a series of control experiments were conducted by using **1a** as the

Scheme 2. Photocatalytic Arylation between Carbonyl Derivatives and 1,4-DCB[a]



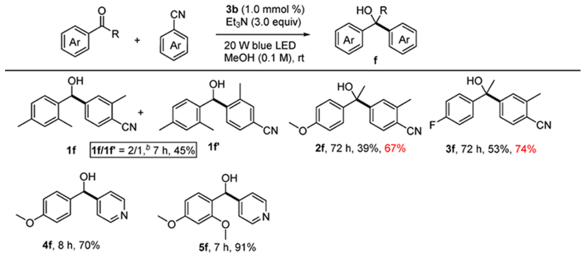
[a]Reaction conditions: 0.2 mmol of **a**, 0.4 mmol of 1,4-DCB, 0.6 mmol of Et$_3$N, 1.0 mmol % of **3b** in 2.0 mL of MeOH, under N$_2$ atmosphere, 20 W blue LED; isolated yields are shown; isolated yields marked in red were based on recovered starting material.

Scheme 3. Photocatalytic Arylation between Imines and 1,4-DCB[a]



[a]Reaction conditions: 0.2 mmol of **d**, 0.4 mmol of 1,4-DCB, 0.6 mmol of Et$_3$N, 1.0 mmol % of **3b** in 2.0 mL of MeOH, N$_2$ atmosphere, 20 W blue LED; isolated yields are shown; isolated yields marked in red were based on recovered starting material.

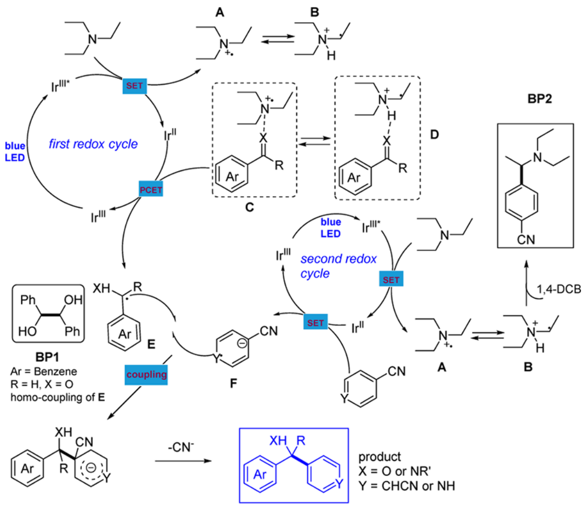
Scheme 4. Photocatalytic Arylation Using Other Nitriles as Coupling Partners[a,b]



[a]Reaction conditions: 0.2 mmol of aldehydes or ketones, 0.4 mmol of nitriles, 0.6 mmol of Et$_3$N, 1.0 mmol % of **3b** in 2.0 mL of MeOH, N$_2$ atmosphere, 20 W blue LED; isolated yields are shown; isolated yields marked in red color based on recovered starting material. [b]The ratio determined by ^{1}H NMR.

representative substrate. (See SI, Scheme S1 for details). We have respectively investigated the effect of TEMPO, inorganic base and the amount of triethylamine on the reaction outcome. Moreover, two key byproducts, **BP1** and **BP2**, were obtained in the controlled experiments. These discoveries indicated this coupling protocol proceeded via a free radical pathway, and two redox cycles might be involved in the catalytic process.

Scheme 5. Proposed Reaction Mechanism



Therefore, a tentative visible-light catalytic mechanism was proposed as shown in Scheme 5. Upon absorption of visible light, the photocatalyst Ir^{III} was initially excited into Ir^{III}*, which subsequently underwent a SET oxidation of the sacrificial reductant Et$_3$N to afford Ir^{II} and the radical cation **A**. On the basis of previous reports,[15] a three-electron bond (**C**) formed between the generated Lewis acidic species **A** and the nucleophilic C═X system or a hydrogen bond (**D**) between the tautomer **B** and C═X bond favored the reduction of carbonyl/iminyl catalyzed by Ir^{II} via a PCET process, thus leading to the radical intermediate **E**, and returned the photocatalyst to its ground state Ir^{III}. On the other hand, a second redox cycle also proceeded through the competitive formation of the cyanoaryl radical anion **F**. In such a process, Et$_3$N was as well identified as a reductive quencher to reduce the excited Ir^{III}* to Ir^{II}. However, under the irradiation of light, 1,4-DCB or isonicotinonitrile might perform a single-electron oxidation of the Ir^{II} to regenerate the Ir^{III} species to deliver the intermediate **F**. Finally, an intermolecular radical−radical cross-coupling took place between **E** and **F**, thus affording the desired reduction product by elimination of a cyanide anion. Additionally, the generation way of compounds **BP1** and **BP2** could be clearly distinguished in this mechanistic scheme.

In conclusion, we have developed an atom-economical radical−radical cross-coupling method that opened an alternative door for carbonyl/iminyl derivatives to unexplored reactivities. This versatile protocol provided a convenient appoach to achieve the reductive arylation of the C═X bond enabled by visible light, leading to a broad range of secondary/tertiary alcohols and amine products. Such a finding could be regarded as a very complementary work to the addition of C═X by an unsaturated double bond or alkyl radical. Furthermore, the mechanistic investigation showed that two redox cycles were involved in this photoreaction, and the challenging reduction of the C═X bond was successfully realized by PECT. Notably, the speculation was strongly supported by the isolated byproducts and controlled experiments. With a view to the operational simplicity and mild conditions, we believe this green, economic protocol will find more extensive application in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01677.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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