OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Merging Visible Light with Cross-Coupling: The Photochemical Direct C−H Difluoroalkylation of Imidazopyridines

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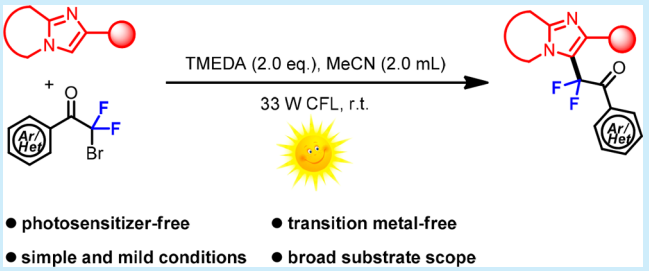
Supporting Information

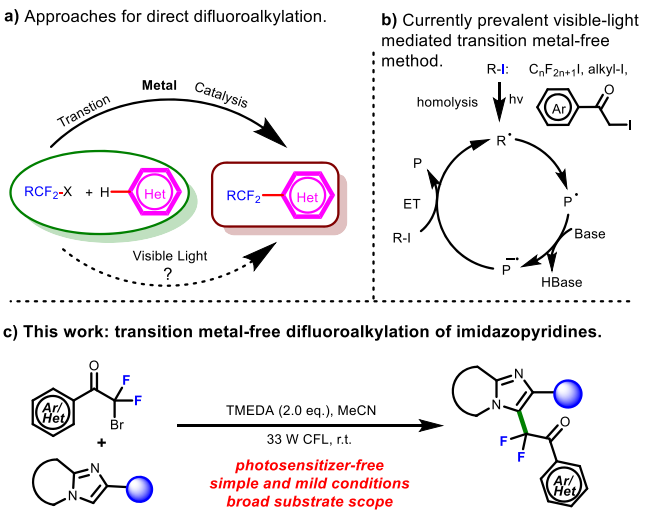
ABSTRACT: A transition-metal-free protocol for the difluoroalkylation of imidazopyridines with bromodifluoroaryl ketones promoted by visible light irradiation is presented. This protocol is distinguished by simple, mild, and catalyst-free reaction conditions with a wide reaction scope, which is complementary to existing difluoroalkylation strategies by photoredox scenarios. Additionally, this protocol potentially offers a new way for streamlining the synthesis of compounds containing the difluoro moiety.



The difluoromethylene group (CF_2), which represents an isosteric analogue of the oxygen atom,[1] is an architecturally important motif in numerous bioactive molecules and pharmaceuticals.[2] The introduction of C−F bonds into small molecules has been widely accepted in drug design to solve drug metabolism problems.[3] Direct C−H difluoroalkylation of arenes is an efficient tool to construct pivotal C−CF_2 bonds, for which tremendous efforts have been committed; however, these mainstream developments are limited to the transition-metal-mediated methods (Scheme 1a).[4] Although Ir,[5] Ru,[6] Cu,[7] Pd,[8] Ni,[9] and Fe[10]-catalyzed difluoroalkylation reactions were reported extensively, there still remains an urgent need for the synthesis of such a pivotal structural moiety with environmentally friendly conditions. The transition-metal-free strategy, undoubtedly, emerged as a novel promising area for chemical synthesis.[11] In the past two years, visible light-promoted transition-metal-free protocol involving a distinct photocatalyst-free, visible light-mediated, radical generation event is particularly appealing in organic synthesis but was only minimally explored.[12] To the best of our knowledge, no example using visible light-promoted transition-metal-free method in the direct difluoroalkylation of arenes has been reported.

The seminal work on visible light-induced transition-metal-free protocol from Studer et al.[12b−g] and Aggarwal et al.[12a] demonstrated the peculiar photochemical behavior of alkyl iodides in radical chemistry (Scheme 1b). In such cases, alkyl radicals generated upon the light-induced C−I bond homolysis can be converted into products over one or several steps. This strategy allows for the direct and economical transformations of architecturally complex bond constructions that are usually impossible via classical photoredox pathways in the absence of photosensitizer. Despite the impressive progress, the radical precursors are only limited to alkyl iodides, while a rare precedent has been realized with alkyl bromides. This lack of development stems from the difficulty in the homolysis of the C−Br bond compared to the C−I bond when using visible

Scheme 1. Difluoroalkylation Technology



Received: July 17, 2019

DOI: 10.1021/acs.orglett.9b02487
Org. Lett. XXXX, XXX, XXX−XXX

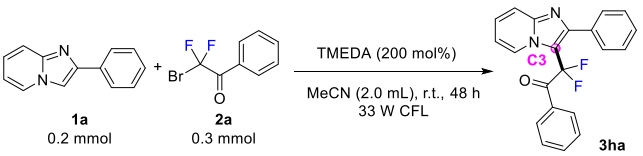
light as the energy source; however, the C−Br bond homolysis is necessarily required as a radical initiation step to drive the desired transition-metal-free mediated cycle.

Recently, we found that alkyl bromides, such as α-bromo difluoroacylarenes, exhibit specific photochemical properties, which can deliver difluoroalkyl radicals upon irradiation to achieve difluorocarbonylation and radical cyclization of oxazoline olefins via transition-metal-free protocol.[13] Alkyl bromides have several advantages for photoinduced transition-metal-free protocol compared with alkyl iodides as radical source: (1) most alkyl bromides are readily commercially available and more affordable; (2) alkyl bromides are easier to handle than the severe lachrymatory alkyl iodides; (3) most alkyl bromides are abundant and structurally diverse synthons. However, the mechanistic understanding of photochemical transition-metal-free strategy induced by alkyl bromides is currently far less clear than the alkyl iodides. The experimental influencing factors and the structural effect for alkyl bromide-mediated transition-metal-free strategy are still insufficiently investigated. For example, when phenacyl iodides and phenacyl bromides were, respectively, applied to the photochemical alkylation of the vinyl boronate complexes, alkyl iodides worked well, but alkyl bromides performed poorly.[12a]

Fused bicyclic five- to six-membered heterocycles (e.g., imidazo[1,2-α]pyridine) are prominent scaffolds due to their prevalence in many biologically active drugs,[14] such as zolpidem, alpidem, saripidem, and necopidem.[15] Indeed, tremendous progress has been reported in the C-3 functionalization of imidazoheterocycles over the past decade;[16] however, the majority of current methods in this area require the use of transition metals, stoichiometric oxidants, and harsh reaction conditions. Developing an efficient and green synthetic method to functionalize the imidazoheterocycle skeletons such as the C-3 difluoroalkylated imidazo[1,2-α]pyridines is therefore highly desirable. In this paper, we describe a simple and efficient difluoroalkylation protocol of various imidazopyridines with α-bromo difluoroacylarenes through transition-metal-free photoelectron catalysis (Scheme 1c), which distinguishes from the traditional methods for the modification of imidazo[1,2-α] pyridines. This transformation should be of fundamental interest, especially for the area of medicinal chemistry, because the metabolically important difluoroalkyl moiety and a structurally prominent heteroarene are fused together in this protocol.

Guided by our exploration in difluoroalkylation,[13,17] we decided to utilize bromodifluoroaryl ketones as radical precursors, since they have been proven to be readily single-electron transfer (SET)-reduced. Reactions conducted with 2-phenylimidazo[1,2-α]pyridine (**1a**) as the C-radical acceptor and 2-bromo-2, 2-difluoro-1-phenylethan-1-one (**2a**) as the C-radical precursor are shown in Table 1. Under the optimal reaction conditions with a mild organic base (tetramethylethylenediamine, TMEDA), a solvent (acetonitrile, MeCN), and irradiation by 33 W compact fluorescent light (CFL) bulb at room temperature, we obtained an exclusively C3-selective cross-coupled product **3ha** in 77% yield (entry 1). Performing the reaction using TMEDA as an organic base in MeCN for a series of different reaction time revealed that the longer reaction time had a more positive influence on the reactivity (entries 1−3). It was found that TMEDA played a pivotal role in this reaction. It not only captured the bromine anion but also unplugged the proton of intermediate **II** to give a radical anion **III** (vide infra). The reaction did not occur at all in the absence of base (entry 4). Using 2,6-lutidine gave a lower yield of 40% (entry 5). More basic tertiary amines, such as triethylamine (Et_3N) and *N*,*N*-di-isopropylethylamine (DIPEA), still exhibited inferior reactivity to that of TMEDA (entries 6 and 7). Interestingly, the difluoroalkylation of imidazopyridines could also proceed by using an inorganic base such as Cs_2CO_3 in the replacement of TMEDA (entry 8), since Cs_2CO_3 has been proven to be an excellent base and electron transfer agent.[18] However, K_2CO_3 significantly reduced the efficiency of the reaction (entry 9). Further screening demonstrated that solvents, such as dimethylacetamide (DMA), dichloromethane (DCM), and methyl *tert*-butyl ether (MTBE), are less effective (entries 10−12). Intriguingly, the use of 5 W blue light-emitting diodes (LEDs) with a wavelength of only ∼460 nm instead of 33 W CFL bulb, led to a significant drop in yield (entry 13). We speculate that the residual near-ultraviolet light from fluorescent light source influences the degree of homolysis of **2a** and its subsequent reactivity on the photoinduced transition-metal-free method. Notably, the essential role of visible light irradiation was confirmed in the next control experiments (entries 14 and 15): no detectable product was observed when the reaction was conducted in dark or even heated conventionally at 80 °C, excluding the possibility of thermal induction. Moreover, the exposure of the reaction to air completely prevented the reaction to occur for the desired product (entry 16).

Table 1. Optimization of Reaction Conditions[a]



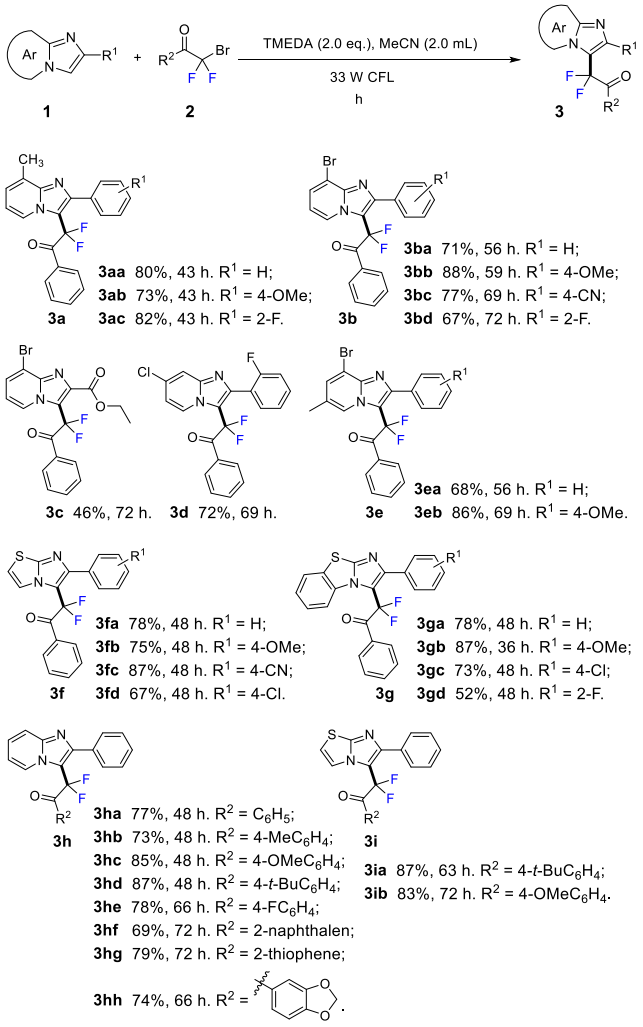
entry	variation from standard conditions	yield[b]
1	none	77
2	8 h	31
3	21 h	63
4	without base	/
5	2,6-lutidine instead of TMEDA	40
6	Et_3N instead of TMEDA	63
7	DIPEA instead of TMEDA	65
8	Cs_2CO_3 instead of TMEDA	45
9	K_2CO_3 instead of TMEDA	<10
10	DMA instead of MeCN	44
11	DCM instead of MeCN	37
12	MTBE instead of MeCN	65
13	5 W blue LEDs instead of 33 W CFL	12
14	reaction in the dark	/
15	80 °C without irradiation	/
16	under air	Mess

[a]Reactions were performed on a 0.2 mmol scale using 1.5 equiv of **2a** and 2.0 equiv of base, [**1a**] = 0.1 M, and a 33 W CFL bulb to illuminate the reaction vessel. [b]Yields are those of products isolated by column chormatography. DMA = *N*,*N*-dimethylacetamide, MTBE = methyl *tert*-butyl ether, Et_3N = triethylamine, DIPEA = *N*,*N*-di-isopropylethylamine, TMEDA = tetramethylethylenediamine.

To explore the reaction scope, various imidazo[1,2-α] pyridines were investigated. As shown in Scheme 2, a broad range of imidazopyridines **1** with diverse substituents on the arene moiety (Ar) and/or the pyridine ring underwent efficient cross-coupling. These included methyl- and methoxyl-substituted substrates, which afforded cross-coupled products in

DOI: 10.1021/acs.orglett.9b02487
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of the C−H Difluoroalkylation in the Transition-Metal-Free Protocol[a,b]



[a]Reaction conditions unless otherwise specified: **1** (0.2 mmol), **2** (0.3 mmol), TMEDA (0.4 mmol), MeCN (2.0 mL), room temperature, under Ar_2 atmosphere, for 36−72 h. [b]Yields are reported for the isolated products.

good yield (**3aa** and **3ab**, 80% and 73% yield, respectively). Imidazopyridines possessing various halogens, such as fluorine, chlorine, and bromine, which were useful modules for further functionalization, were well-compatible, and the desired products could be obtained in moderate to good yields (**3ac**, **3ba**−**3bd**, **3c**, **3d**, and **3ea**−**3eb**). Remarkably, the CN substituent, which was a strong electron-withdrawing group, proceeded well to produce the target molecule **3bc** in good yield. Notably, the 2-ester-substituted imidazopyridine could also be reacted smoothly to obtain the target product **3c**, albeit with 46% yield. To expand the potential utility of this protocol for medicinal chemistry, we then turned our attention to examine the tolerance of other imidazoheterocycles, such as imidazo[2,1-*b*]thiazole and benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives, which were pivotal building skeletons in medicinal chemistry.[19] Neutral imidazo[2,1-*b*]thiazoles furnished the desired products **3fa** and **3fd** with fair yields. Reaction with either electron-donating (methoxy) or electron-withdrawing (cyano) substrates proceeded successfully to give **3fb** and **3fc** in 75% and 87% yields, respectively. The cross-coupling reaction also worked with benzo[*d*]-imidazo[2,1-*b*]thiazoles bearing various functional groups such as methoxy, chloro, and fluoro moieties via transition-medal-free strategy (**3ga**−**3gd**). More substituted α-bromodifluoroacylarene-coupling partners were explored next. α-Bromodifluoroacylarenes **2** bearing diverse electronic and steric substituents at the *para*-position of the aryl ring gave the cross-coupled imidazo[1,2-α]pyridines **3ha**−**3he** in moderate to excellent yields (73−87%). It was worth noting that difluoroacylarenes derived from polycyclic arenes **3hf** and **3hh** were also well-tolerated. Besides arene substrates, heteroaromatic ring, such as thiophene ring, was also compatible with the reaction, leading to coupling product in 79% yield (**3hg**). The mild reaction conditions enable the imidazo[2,1-*b*]thiazoles to react well with *t*-Bu- and OMe-substituted difluoroacylarenes, producing desired products in 87% and 83% yields, respectively (**3ia** and **3ib**).

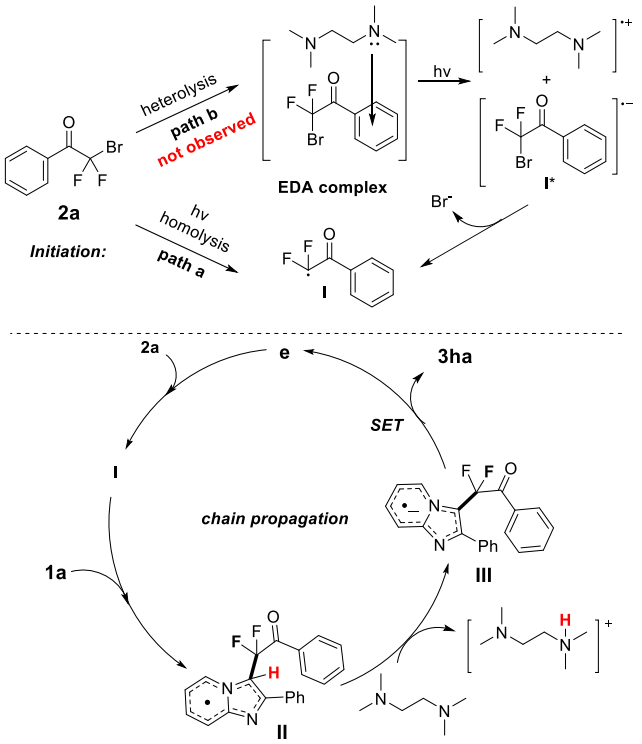
After the substrates scope was evaluated, several control and comparative experiments were performed to shed light on the reaction mechanism (see Supporting Information). In initial experiments, the photoinduced transition-metal-free cross-coupling reaction of **1a** with 2-bromoacetophenone **4** or α-monofluoroacetophenone **6** could not occur under standard conditions (Scheme S1). These results suggested that the CF_2 group of α-bromo, α-difluoroaryl ketones plays a crucial role in this transformation. Subsequently, two radical trapping experiments were conducted. When a radical inhibitor, 1,1-diphenylethylene **8**, was introduced into the reaction solution of **1a**, α-bromodifluoroacylarene **2c**, and TMEDA in MeCN, the reaction was partly suppressed; that is, only 25% yield of the desired product was obtained, accompanied by 68% of starting material recovery. Meanwhile, the CF_2COAr-trapped compound **9** was isolated in 70% yield (Scheme S2). Comparatively, this reaction was completely suppressed in the presence of 2.0 equiv of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical scavenger, and the CF_2COAr-trapped product **10** was detected by high-resolution mass spectrometry (HRMS; Scheme S3). Thus, these results suggest that a free-radical process is involved in the reaction.

On the basis of the experiment results described above and in our previous reports,[13] a postulated mechanism is depicted in Scheme 3. We assume that the visible light irradiation of the photosensitive **2a** may induce an energy transfer, affording the excited intermediate **2a**, which undergoes a rapid C−Br bond homolysis to generate the difluoroacyl radical species **I** (path a). Alternatively, the report of tertiary amines to form electron donor−acceptor complexes (EDACs) with electron-accepting molecules of high electron affinity[20] suggests that the lone-pair electrons of TMEDA could engage in such a molecular aggregation with **2a** (path b); however, the optical absorption spectrum did not demonstrate a bathochromic displacement in the visible spectral region (see Supporting Information), affirming that path a is the only possible mechanic path. The difluoroacyl radical **I** then regioselectively attaches to the C3 position of **1a** to afford radical intermediate **II**. **II** will be deprotonated by TMEDA to give the key heteroaryl radical anion **III**,[21] which then reduces **2a** by SET to eventually afford the target product **3ha** and difluoroacyl radical **I**.

In summary, we have developed a direct C−H difluoroalkylation of heteroarenes. The photosensitizer-free, visible-light-mediated C−CF_2 cross coupling comprises two highly important partners, namely, structurally privileged imidazopyridines and the metabolically pivotal difluoroalkyl moiety, by transition-metal-free strategy. Notably, transition-metal-free

DOI: 10.1021/acs.orglett.9b02487
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Proposed Mechanism



C−H difluoroalkylation is not currently well-explored, and the photochemical potential of α-bromodifluoroacylarenes to actively participate in the transition-metal-free reaction promoted by visible light is still not well-established. The available data suggest that the introduction of the cheap, handily accessible, and modular α-bromodifluoroacylarenes into visible light reactions might exhibit a powerful alternative to existing photochemical C−I homolysis techniques or classical metallaphotoredox scenarios.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02487.

General experimental procedures; mechanistic consideration; compound characterization data; ^{1}H, ^{19}F, and ^{13}C spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Science and Technology Research Program of Chongqing Municipal Education Commission (KJZH17129, KJQN201801321, KJZD-M201801301), the Natural Science Foundation Project of CQ CSTSC (CSTC2015ZDCY-ZTZX120003, cstc2018jszx-cyzd0110, and cstc2018jszx-cyzdX0023), and the Scientific Research Foundation of the Chongqing Univ. of Arts and Sciences (Z2016BX02). We also thank Ms. H. Z. Liu of Chongqing Univ. of Arts and Sciences for obtaining the LC/MS, HRMS, and NMR data.

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