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COMMUNICATION

Benzylic C-H Heteroarylation of *N*-(Benzyloxy)phthalimides with Cyanopyridines Enabled by Photoredox 1,2-Hydrogen Atom Transfer

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A visible light initiated α -C(sp³)-H arylation of *N*-(benzyloxy)phthalimides with cyanopyridines for the construction of highly valuable pyridinyl-containing diarylmethanols, including bioactive motif-based analogues, is reported. This method enables arylation of the C(sp³)-H bonds adjacent to an oxygen atom through alkoxy radical formation by O-N bond cleavage, 1,2-hydrogen atom transfer (HAT), arylation and C-CN bond cleavage cascades, and offers a means to exploitation of 1,2-HAT modes to incorporate functional groups for constructing functionalized alcohols.

Diarylmethanols, especially variants possessing heteroaryls, are important core structural motifs in bioactive natural products, pharmaceuticals and materials.¹ Accordingly, substantial efforts have been paid to the discovery of efficient strategies to prepare diarylmethanols.²⁻⁴ General methods for their synthesis include addition of aryl nucleophiles (e.g., aryl organometallic reagents) to aryl carbonyl compounds² and reduction of diaryl ketone derivatives.³ Despite impressive progress in the field, the known transformations have some disadvantages, such as limited substrate scope, unsatisfactory selectivity, and the generation of a stoichiometric amount of chemical waste. Furthermore, the construction of heteroaryl-containing diarylmethanol scaffolds, especially nonsymmetric ones, has been sporadically documented in a few papers and is an even great challenge, with most concerning addition of heteroaryl-metallic reagents to the carbonyl compounds. Thus, the development of general and sustainable routes toward diarylmethanols, especially nonsymmetric heteroaryl-containing diarylmethanols, is highly desirable and urgent.

Recent advances have showed the C(sp³)-H radical functionalization reaction enabled by a hydrogen atom transfer (HAT) process represents a new synthetic alternative to ionic reactions for increasing molecular complexity.⁵ Typical strategies involve radical functionalization of the C(sp³)-H bonds in alcohols and their derivatives,⁶⁻⁷ which is achieved by the formation of alkoxy radical intermediate followed by HAT, featuring high efficiency and excellent site-selectivity (Scheme 1a upper). However, only a few papers that employ the HAT strategy to site-selectively introduce a functional group to the C(sp³)-H bonds in alcohols and their derivatives have been reported, and the most commonly explored transformations relied on 1,5-HAT.⁶ At present, approaches via 1,2-HAT have been significantly less investigated,⁷ which mainly focus on direct conversion of the hydroxy group to the carbonyl group (e.g., aldehydes, ketones).^{7a-i} Very recently, Lan, Chen and co-workers⁷ⁿ have reported a new 1,2-HAT strategy for α -allylation of *N*-(alkyloxy)phthalimides for the synthesis of allyl alcohols beyond the formation of carbonyl compounds wherein visible light induced transformation of the C(sp³)-H bonds adjacent to an oxygen atom to the alkoxy radical followed by 1,2-HAT and allylation (Scheme 1a lower). Although only a special ethyl 2-((phenylsulfonyl)methyl)acrylate as the external functional reagent was used to accomplish this α -C(sp³)-H allylation, we envisioned that employing visible light sensitive functional reagents, such as heteroaryl-based reagents, would allow the functionalization of α -C(sp³)-H bonds of *N*-(alkyloxy)phthalimides via 1,2-HAT to access functionalized methanol derivatives.

Herein, we report a new strategy for producing pyridinyl-containing diarylmethanols via α -C(sp³)-H arylation of *N*-(benzyloxy)phthalimides with cyanopyridines⁸ enabled by the visible light photoredox catalysis (Scheme 1b). Visible light-induced cleavage of the O-N bond results in the formation of benzyloxy radical is crucial, allowing 1,2-HAT and arylation cascades to access highly valuable nonsymmetric diarylmethanols, including bioactive motif-based analogues.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

For 24 h.

thus offering potential in the late stage modification (**3da**, **3ga**). Terminal and internal alkynes **1h–i** were well tolerated (**3ha–la**), making the protocol more attractive in synthesis. Notably, this protocol was applicable to the incorporation of the important pharmacophore cores,⁹ including ethisterone, adamantane and proline motifs, into the diarylmethanol frameworks (**3ja–la**), thereby providing a vistas for the translational potential of this protocol in pharmaceutically relevant field. Heteroaryl (e.g., furan-2-yl, 3-methylthiophen-2-yl) possessing substrates **1n–o** were viable for furnishing nonsymmetrical diheteroarylmethanols **3na–oa**. Delightedly, tertiary alcohols **3pa** could be constructed in moderate yield.

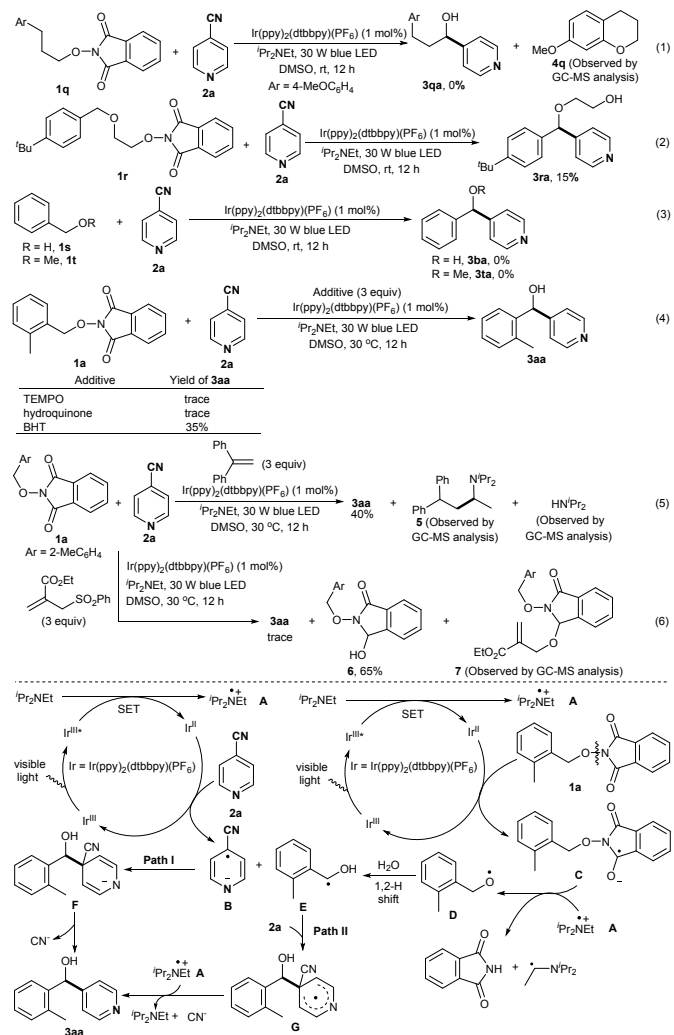
The optimized conditions were general for benzylic C-H heteroarylation with various cyanopyridines (**3bb–bj**). A number of substituents, such as Ph, 4-MeOC₆H₄, 4-vinylC₆H₄, 4-MeOC₆H₄, 4-CF₃C₆H₄, 4-PhC₆H₄, Cl and (trimethylsilyl)ethynyl, at 2 position of the pyridine ring were accommodated, affording **3bb–bh** in moderate to good yields. Using 3-F-4-cyanopyridine **2i** delivered **3bi** smoothly in 67% yield. Gratifyingly, 2-cyanopyridine **2j** also underwent the benzylic C-H heteroarylation successfully (**3bj**). However, both quinoline-4-carbonitrile **2k** and isoquinoline-1-carbonitrile **2l** were unsuitable substrates (**3bk–bl**).

As shown in Scheme 2, using 2-(3-(4-methoxyphenyl)propoxy)isoindoline-1,3-dione **1q** gave the intramolecular cyclization product **4q**, not the desired product **3qa** (Eq 1). For 2-(2-((4-*tert*-butyl)benzyl)-oxy)ethoxy)isoindoline-1,3-dione **1r** the 1,5-HAT reaction occurred to afford **3ra** (Eq 2). The results suggest that this current protocol includes a HAT process, and the alkyl chain of the *N*-(alkyloxy) moiety affects the chemoselectivity. However, both benzyl alcohol **1s** and benzyl methyl ether **1t** were not suitable substrates (Eq 3), implying that generation of the alkoxy radical requires the phthalimide group to assist it. The reaction of substrate **1a** with **2a** was inhibited by a radical scavenger, TEMPO, hydroquinone, 2,6-di-*tert*-butyl-4-methyl-phenol (BHT) (Eq 4), 1,1-diphenylalkene (Eq 5) or ethyl 2-((phenylsulfonyl)methyl)acrylate⁷ⁿ (Eq 6). Notably, the reaction was inhibited by 1,1-diphenylalkene attributing to reaction with ⁱPr₂NEt to form **5** and ⁱPr₂NH, and was suppressed by 2-((phenylsulfonyl)methyl)acrylate due to its direct reaction with both ⁱPr₂NEt and **1a** leading to **6** and **7**, suggesting a different mechanism from the results of Lan/Chen group⁷ⁿ and verifying ⁱPr₂NEt as the single-electron transfer reagent. The light turn/off experiments support this current protocol *via* visible light photoredox catalysis (Figure S2; Supplementary Information).

The possible mechanisms for this α-C(sp³)-H arylation protocol were proposed (Scheme 2).^{5–8} The Ir^{III}* excited state is formed from the Ir^{III} species under blue LED light, followed by reduction with ⁱPr₂NEt to afford the active Ir^{II} species and the ⁱPr₂NEt radical cation **A**. The single electron reduction (SER) of 4-cyanopyridine **2a** by the active Ir^{II} species delivers the 4-cyanopyridine radical anion **B**^{8m} and regenerates the Ir^{III} species.⁸ Meanwhile, the SER of *N*-((2-methylbenzyloxy)phthalimide **1a** by the active Ir^{II} species yields the radical intermediate **C** and then reaction with the radical cation **A** forms the benzyloxy radical **D**.⁷ⁿ The radical **D** undergoes 1,2-HAT assisted by H₂O to form the benzyl carbon-centered radical **E** (also supported the results of entry 12; Table 1).^{7d,7k} The cross coupling between the radical **B** and the radical **E** offers the intermediate **F**

(Path I),⁸ which sequentially undergoes cleavage of C-CN bonds to afford the desired product **3aa**.
DOI: 10.1039/D0CC03619F

we cannot rule out Path II wherein the direct addition of the radical **E** to **2a** to form the intermediate **G**, followed by single electron reduction by the radical cation **A** and C-CN bond cleavage to afford product **3aa**.



Scheme 2. Other *N*-(Alkyloxy)phthalimides **1**, Control Experiments and Possible Mechanisms.

In summary, we have developed a novel, general and robust method for the α-C(sp³)-H arylation of *N*-(alkyloxy)-phthalimides with readily accessible cyanopyridines as the pyridinyl group resources through a visible light photoredox-enabled 1,2-HAT of the alkoxy radical process. The use of both a blue-light-sensitized Ir(ppy)₂(dtbbpy)(PF₆) photocatalyst and an organic base was crucial for accomplishment of the α-C(sp³)-H arylation reaction with high efficiency and excellent selectivity. This method allows transformation of various *N*-(alkyloxy)phthalimides and cyanopyridines to highly valuable pyridinyl-containing diarylmethanols, including bioactive motif-based analogues, by a sequence of the O-N bond cleavage, 1,2-HAT, arylation and C-CN bond cleavage, and can be expected as a versatile strategic design to other type of two radical cross coupling via 1,2-HAT.

We thank the National Natural Science Foundation of China (Nos. 21625203, 21871126 and 21901100) for financial support.

Conflict of interest

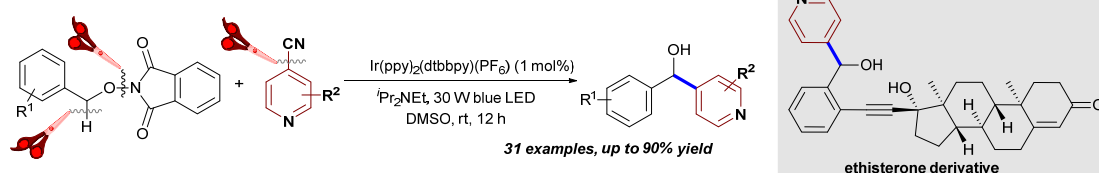
There are no conflicts to declare.

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Benzylic C-H Heteroarylation of *N*-(benzyloxy)phthalimides with Cyanopyridines Enabled by Photoredox 1,2-Hydrogen Atom Transfer

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Visible light initiated α -C(sp³)-H heteroarylation of *N*-(benzyloxy)phthalimides with cyanopyridines via 1,2-hydrogen atom transfer is depicted.