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Selective C(sp³)-H activation of simple alkanes: visible light-induced metal-free synthesis of phenanthridines with H₂O₂ as a sustainable oxidant†

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The visible light-induced metal-free C(sp³)-H phenanthridinylation of simple alkanes with isonitrile is developed with H₂O₂ as a terminal green oxidant. This reaction features good yields and selectivities, mild conditions, and a broad substrate scope with gaseous alkanes involved, allowing practical access to valuable alkyl-substituted phenanthridine derivatives.

Introduction

N-Heterocycles are ubiquitous in natural products and biologically active molecules.¹ They have been playing a privileged role in drug discovery thanks to their significant ability to improve solubility and facilitate the salt formation property, both of which are important for oral absorption and bio-availability.² Phenanthridines, a typical kind of valuable *N*-heterocycle applied as drugs or drug candidates in medicinal chemistry, have been proved to show different biological activities, such as antibacterial, antitumoral, cytotoxic, and antileukemic activities.³ In the past decade, a cascade reaction of radical addition to 2-isocyanobiaryls has become a practical method for the synthesis of 6-substituted phenanthridine derivatives.⁴ On the other hand, simple alkanes, which are major constituents of petroleum and natural gas, are widely distributed and abundant in nature. However, only a small amount of them are used as economical chemical feedstocks⁵ due to their intrinsic inertness and uncontrollable chemoselectivity which result in great difficulty in the direct activation of C(sp³)-H bonds in simple alkanes.⁶ Thus merging the transformation of natural alkanes with the construction of ponderable *N*-heterocycles brings economic and ecological

benefits, as well as great scientific challenges to synthetic chemistry.⁷ In 2014, Cheng,^{7a} Huang^{7b} and Liu^{7c} groups respectively realised the peroxide-promoted phenanthridinylation of simple alkanes with isonitrile through a radical pathway at over 100 °C (Scheme 1a).

Recently, visible light-induced photoredox hydrogen atom transfer (HAT) catalysis has been developed as a mild and efficient strategy for diverse functionalisation of simple alkanes.⁸ With this strategy, many research groups have successfully realised the arylation of simple alkanes with *N*-heterocycles.⁹ In these outstanding reaction systems, excess oxidants, including persulfates,^{9a-c} DTBP,^{9d} Selectfluor,^{9e-f} and hypervalent iodines,^{9g-h} have been applied, producing quantitative wasteful reduction byproducts (Scheme 1b). Aqueous H₂O₂ has emerged as a green oxidant with high oxygen atom economy and H₂O as the only reduction byproduct.¹⁰ To the best of our knowledge, dehydrogenative cross-coupling of

Previous Approaches

(a) Traditional methods for synthesis of substituted phenanthridines with simple alkanes

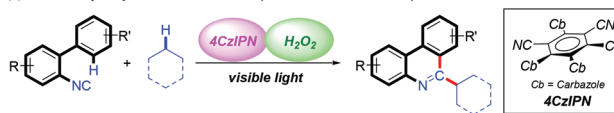


(b) Photocatalytic arylation of simple alkanes with HAT catalysis



This work

(c) Photocatalytic synthesis of substituted phenanthridines with simple alkanes



• metal-free synthesis • green oxidants • mild conditions • applied to gaseous alkanes

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Scheme 1 Merging C(sp³)-H activation of natural alkanes with the construction of ponderable *N*-heterocycles. BPO = benzoyl peroxide, DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide, and PC = photocatalyst.

N-heteroarenes with aliphatic C–H bonds has rarely been explored with aqueous H₂O₂ as the terminal oxidant. With the extension of our longstanding interest in visible light-mediated synthetic reactions,^{4g,11} we report here a photocatalytic HAT strategy to realise the metal-free synthesis of substituted phenanthridines with 2-isocyanobiaryls and simple alkanes (Scheme 1c). We used an important organic light-emitting diode material, 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4-CzIPN), as a photocatalyst and the green oxidant H₂O₂ as a HAT catalyst precursor. The protocol exhibited good yields and selectivities under mild conditions and was successfully applied to gaseous alkanes.

Results and discussion

The first glimpse of success was obtained by performing the reaction of 2-isocyanobiphenyl (**1a**) and cyclohexane (**2a**) with the combination of an Ir catalyst (**A**) and TBHP as the model reaction under the irradiation of 30 W 395 nm LEDs, which provided 6-cyclohexanyl phenanthridine (**3a**) in 52% yield as shown in Table 1, entry 1. Investigation on different photocatalysts showed 4-CzIPN (**D**) to be the best choice (entries 1–6). Then diverse additives were tried to promote the reaction efficiency, and DIPEA exhibited the best result (entries 4, 7–12). Next, the effect of solvents was explored. Here, CH₃CN provided the highest yield (entries 11, 13–16). Other oxidants, such as H₂O₂, DTBP, and (NH₄)₂S₂O₈, were chosen to replace TBHP (entries 17–19). To our delight, the yield increased to 89% by using aqueous H₂O₂ (entry 17). Reducing the equivalent of cyclohexane resulted in a decreasing yield of **3a** even with extended reaction time (entry 20). Control experiments proved that the reaction could not be performed without light irradiation (entry 21) or under air atmosphere (entry 22).

With the optimized conditions in hand, the scope of 2-isocyanobiphenyls with substituents on the phenyl rings was surveyed first (Table 2, left column). A variety of 2-isocyanobiphenyls (**1**) reacted with cyclohexane (**2a**) smoothly under the standard reaction conditions, affording the desired phenanthridines in good yields (**3a–3p**). Many functional groups, such as methyl (**3b**, **3i**, and **3k**), *tert*-butyl (**3g**), naphthyl (**3h**), methoxyl (**3c**, **3l**, and **3o–3p**), fluoro (**3e** and **3m**), chloro (**3f** and **3j**), and trifluoromethyl (**3d** and **3n**) groups, were introduced into the final products at different substituted positions, proving the excellent functional group tolerance of the reaction. Significantly, an alkyl-substituted *trisphaeridine* (**3p**), an important alkaloid isolated from *Narcissus asturiensis*,¹² was successfully synthesised in 58% yield with this strategy. To further demonstrate the practicability of this method, a gram-scale synthesis with **1a** (5.6 mmol, 1.00 g) and **2a** was performed, producing 1.24 g of **3a** in 84.8% yield without the obvious loss of efficiency (for more details, see Fig. S1†).

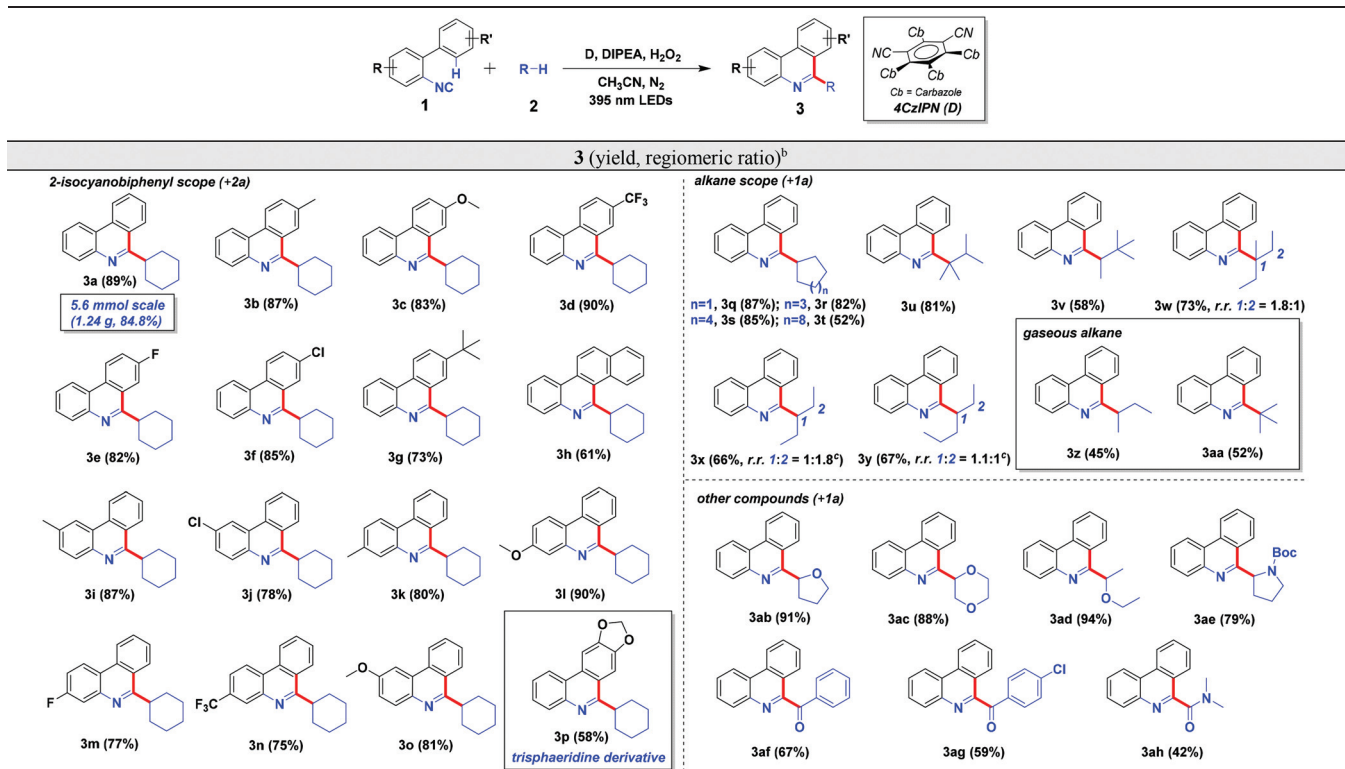
Subsequently, other alkanes were examined to extend the application scope (Table 2, right column). It was gratifying to find that a variety of alkanes including cyclic (**3a** and **3q–3t**)

Table 1 Optimization of the reaction conditions with 2-isocyanobiphenyl (**1a**) and cyclohexane (**2a**)^a

Entry	Catalyst	Peroxide	Additive	Solvent	Yield ^b %
1	A	TBHP	—	CH ₃ CN	52
2	B	TBHP	—	CH ₃ CN	61
3	C	TBHP	—	CH ₃ CN	45
4	D	TBHP	—	CH ₃ CN	63
5	E	TBHP	—	CH ₃ CN	trace
6	—	TBHP	—	CH ₃ CN	9
7	D	TBHP	Na ₂ HPO ₄	CH ₃ CN	26
8	D	TBHP	NaHCO ₃	CH ₃ CN	33
9	D	TBHP	NET ₃	CH ₃ CN	82
10	D	TBHP	pyridine	CH ₃ CN	76
11	D	TBHP	DIPEA	CH ₃ CN	85
12	D	TBHP	HCl	CH ₃ CN	54
13	D	TBHP	DIPEA	Cyclohexane	29
14	D	TBHP	DIPEA	CH ₂ Cl ₂	trace
15	D	TBHP	DIPEA	THF	trace
16	D	TBHP	DIPEA	DMSO	12
17	D	H ₂ O ₂	DIPEA	CH ₃ CN	89
18	D	DTBP	DIPEA	CH ₃ CN	70
19	D	(NH ₄) ₂ S ₂ O ₈	DIPEA	CH ₃ CN	16
20 ^c	D	H ₂ O ₂	DIPEA	CH ₃ CN	42
21 ^d	D	H ₂ O ₂	DIPEA	CH ₃ CN	0
22 ^e	D	H ₂ O ₂	DIPEA	CH ₃ CN	0

^a Reaction conditions: **1** (0.15 mmol), cyclohexane (10 equiv.), catalyst (0.01 equiv.), oxidant (3 equiv.), additive (0.1 equiv.), and CH₃CN (1.5 mL) under N₂ and 30 W 395 nm LEDs for 48 h. ^b Isolated yield. ^c Cyclohexane (6 equiv.) for 72 h. ^d No light. ^e Under air. TBHP = *tert*-butyl hydroperoxide and DIPEA = *N,N*-diisopropylethylamine.

and linear (**3u–3aa**) ones could couple with 2-isocyanobiphenyl to give the desired alkylated phenanthridines in moderate to good yields. The regiomer ratios (*r.r.*) towards different positions of alkanes were also investigated. The results (such as 1.8 : 1 for **3w**, 1 : 1.8 for **3x**) showed that the regioselectivities were decided by the stabilities of the corresponding generated carbon radicals (3°/2°/1°) and quantities of hydrogens with the same chemical environment.^{11a,13} Products obtained from trapping 1° carbon radicals were not observed in this system. Furthermore, fixing natural gaseous alkanes and assembling them onto valuable *N*-heteroarenes is a fundamentally intriguing challenge in organic synthesis.¹⁴ Here, two components of liquid petroleum gas (LPG), *n*-butane and *iso*-butane, were respectively applied as alkane substrates in this protocol. Fortunately, the reactions provided the target cross-coupling products in moderate yields at ambient temperature and pressure (**3z**, and **3aa**). Various organic compounds, such as ethers, amines, and aldehydes, have been successfully acylated *via* photo-induced C–H activation by other research groups.¹⁵

Table 2 Substrate scope for the photo-induced phenanthridinylation of simple alkanes and other compounds with isonitrile^a

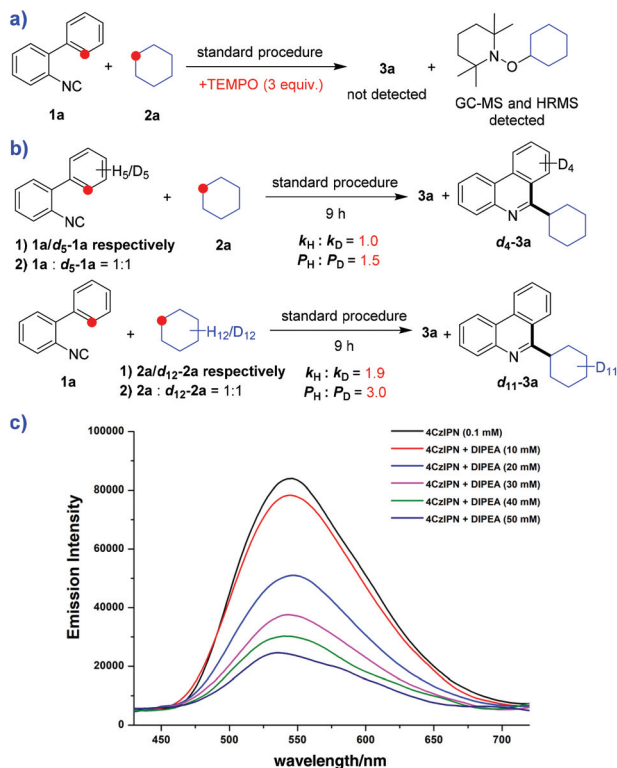
^a Reaction conditions: **1** (0.15 mmol), **2** (10 equiv.), **D** (0.01 equiv.), DIPEA (0.1 equiv.), H₂O₂ (3 equiv.), and CH₃CN (1.5 mL) under N₂ and 30 W 395 nm LEDs for 48 h. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy.

Even so, trying some typical compounds with this green method remains an approach to expand the substrate scope and further investigate the regioselective properties. Depending on the results of **3ab–3ac**, the phenanthridinylation of ethers and amines efficiently and regioselectively proceeded at the alpha position of oxygen and nitrogen atoms due to the enhanced radical stabilities.¹⁶ C(sp²)-H activation of aldehyde and formamide groups was also realised with moderate yields under the standard reaction conditions (**3af–3ah**).

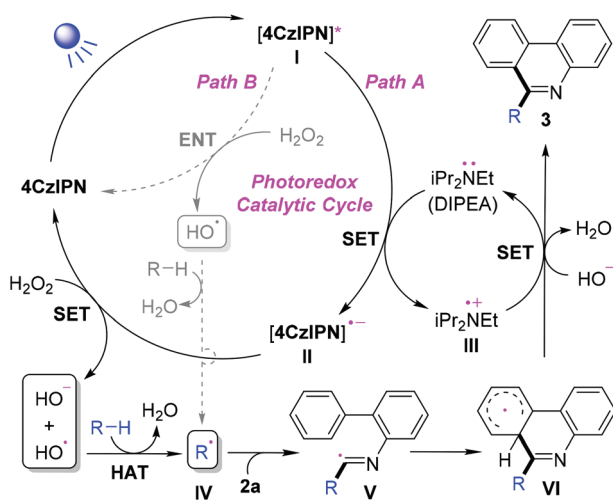
As shown in Scheme 2, some mechanistic experiments were performed to clarify the reaction mechanism. A radical trapping experiment with the addition of the radical-trapping reagent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was first performed (Scheme 2a). The reaction was completely inhibited, and a radical adduct from TEMPO and a cyclohexyl radical formed *in situ* was successfully detected using GC-MS and HRMS, reflecting that the reaction involves a radical pathway (for more details, see Fig. S2–S4[†]). The kinetic isotope effect (KIE) of C(sp²)-H cleavage was evaluated by using (a) **1a**/*d*₅-**1a**, respectively, as substrates or (b) a 1:1 mixture of **1a** and *d*₅-**1a** as the substrate to produce **3a**. The magnitude of the KIE values given by $k_{\text{H}}/k_{\text{D}}$ ¹⁷ and $P_{\text{H}}/P_{\text{D}}$ ¹⁷ was 1.0 and 1.5, respectively, for the dissociation of C(sp²)-H bonds. The KIE values of C(sp³)-H cleavage were also measured as 1.9 and 3.0 with the same strategy using cyclohexane and *d*₁₂-cyclohexane as sub-

strates (Scheme 2b, for more details, see Fig. S5–S7[†]). These values indicated that the radical-intermediated HAT process is a “rate-determining step”, while the C(sp²)-H cleavage process is just a “product-determining step” in this catalytic system.¹⁷ Then Stern–Volmer fluorescence quenching experiments were carried out to investigate the single electron transfer (SET) processes. As presented in Scheme 2c, 548 nm fluorescence caused by 4-CzIPN was observed when it was excited at 405 nm, and the addition of DIPEA made the fluorescence intensity decrease dramatically. Meanwhile, the subsequent experiments showed that other reagents including H₂O₂ and cyclohexane in the system did not quench the fluorescence (for more details, see Fig. S12–S13[†]), which indicated an SET between 4-CzIPN and DIPEA. The quantum yield of the reaction generating **3a** was calculated as 0.033 (for more details see, the ESI), suggesting that radical chain processes made a small contribution to generate the target phenanthridine products.¹⁸

According to the results above, a possible mechanism for the visible light-mediated phenanthridinylation is proposed in Scheme 3. First, the photocatalyst 4-CzIPN transforms to its excited state **I** under light irradiation. Next, a SET from DIPEA to **I** provides the two radicals **II** and **III**. Sequentially, another SET between **II** and H₂O₂ generates a hydroxyl anion and a HAT-active hydroxyl radical regenerating the photocatalyst. A subsequent HAT from alkane to hydroxyl radical results in the



Scheme 2 (a) Radical trapping experiment with TEMPO. (b) Kinetic isotope effect experiments with **1a/d₅-1a** and **2a/d₁₂-2a**. (c) Stern-Volmer fluorescence quenching experiments with 4-CzIPN (0.1 mM) and different concentrations of DIPEA excited at 405 nm.



Scheme 3 Proposed reaction pathway.

alkyl radical **IV**. Addition of **IV** to **2a** affords the imidoyl radical **V**, intramolecular aromatic addition of **V** gives the radical intermediate **VI**, and oxidative dehydrogenation of **VI** with **III** and hydroxyl anions provides the final product **3a** regenerating DIPEA. When no DIPEA exists in the reaction system, an energy transfer (ENT) process between **I** and H_2O_2 is supposed

to produce the HAT-active hydroxyl radical instead of the SET process (path B).^{9c-d} The reported low efficiency of ENT between **I** and peroxides^{9c} is a possible explanation for the obviously increased yield with the addition of DIPEA.

Conclusions

We have developed a mild and green system for the visible light-induced metal-free synthesis of substituted phenanthridines *via* C(sp³)-H activation of simple alkanes with aqueous H_2O_2 as the terminal oxidant. The reaction showed many advantages including mild and environmentally friendly conditions, broad substrate scope with the capable use of gaseous alkanes, good functional group tolerance, and low cost. An alkyl-substituted *trisphaeridine*, an important alkaloid isolated from *Narcissus asturiensis*, was successfully prepared with this strategy. We believe that this strategy will find wide application in the synthesis of phenanthridine derivatives.

Conflicts of interest

There are no conflicts to declare.

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