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PPh₃/NaI driven photocatalytic decarboxylative radical cascade alkylarylation reaction of 2-isocyanobiaryls†

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The first triphenylphosphine/sodium iodide driven photocatalytic decarboxylative cascade cyclization of 2-isocyanobiaryls with alkyl *N*-hydroxyphthalimide (NHP) esters was developed. This operationally simple protocol results in multiple carbon–carbon bond formation under transition metal free conditions, affording a novel and environmentally benign entry to producing 6-alkyl phenanthridines with moderate to good yields.

Introduction

Visible-light photocatalysis has been widely recognized as a powerful tool in organic synthesis to construct carbon–carbon or carbon–heteroatom bonds.¹ Through reactive intermediates such as radicals and radical ions, unique reactions that are previously inaccessible under thermal conditions can be accessed. Significant advances have been realized in this field by employing metal based catalysts² or organic dyes^{3a–d} as photoredox catalysts. However, employing these metal based photoredox catalysts has certain disadvantages: such as; they are expensive, potentially toxic and limited availability.^{3e} Recently, visible light driven photoredox catalysis employing inexpensive chemicals such as combination of triphenylphosphine/sodium iodide and CeCl₃ emerged as a robust alternative to generate radical entities under mild reaction conditions.⁴ This approach replaces metal based photocatalysts by inexpensive catalysts, thus overcoming some of the aforementioned problems.

Phenanthridine, a privileged structural core motif found in natural products.⁵ Many synthetic phenanthridine derivatives show bioactive and pharmaceutical properties, including anti-tumoral, antibacterial, antiviral, cytotoxic, and DNA inhibitory properties.^{6,7} In addition, phenanthridine derivatives reveal significant optoelectronic properties.⁸ Therefore, the development of new and efficient methods for the preparation of

phenanthridine derivatives has gained significant importance in academic research. Recently, a cascade radical pathway involving radical addition to 2-isocyanobiaryls and subsequently intramolecular homolytic aromatic substitution has been developed,⁹ which allows the rapid assembly of a phenanthridine framework with high efficiency. In 2012, Chatani's group disclosed Mn(III)-mediated radical cascade reaction of 2-isocyanobiaryls with boronic acid under thermal conditions.¹⁰ Subsequently, several groups put their efforts for the construction of 6-substituted phenanthridines through the reaction of 2-isocyanobiaryls with corresponding carbon radical precursors, such as simple alkanes,¹¹ alcohols,^{11a} ethers,¹² aldehydes,¹³ 2-bromide ethyl esters,¹⁴ aryl sulfonyl chlorides¹⁵ and 1,3-dicarbonyl compounds.¹⁶ Although these reported methods have their own specific applications, but remains associated with certain disadvantages such as employing metal catalysts, harsh reaction condition and use of stoichiometric amounts of oxidants. Very recently, few groups reported a metal-free approach that utilizes aryl amines,¹⁷ carboxylic acids,¹⁸ hydrazines¹⁹ acyl peroxides,²⁰ as a carbon radical precursor, which appears to be an environmentally benign method for accessing 6-substituted phenanthridines. However, most of acyl peroxides, alkyl amines and hydrazines are commercially unavailable. Thus, further new methodologies are quite desired for the synthesis of 6-substituted phenanthridines.

Recently decarboxylative functionalization of alkyl *N*-hydroxyphthalimide (NHP) esters in carbon–carbon bond formation reactions have gained a significant importance, as they convert widely available and inexpensive chemicals into valuable chemicals and reactive intermediates for synthesis.²¹ Photo decarboxylation of alkyl *N*-hydroxyphthalimide (NHP) esters has been widely used for organic synthesis,²² as the liberation of phthalimide and volatile CO₂ as a by-products indicates a strong driving force for the reaction, forming versatile radical intermediates to build more valuable products. Herein, we report the first PPh₃/NaI driven photocatalyzed

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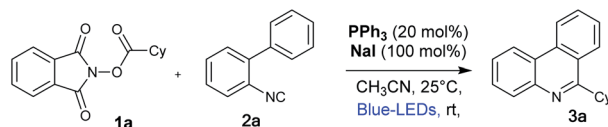


decarboxylative cascade alkylarylation reaction of 2-isocyanobiaryls in the presence of visible light irradiation at room temperature.

Results and discussions

Inspired by the recent work of Shang and Fu (Fig. 1) who developed photocatalytic decarboxylative alkylations mediated by triphenylphosphine/sodium iodide,^{4d} we wondered how these activated carboxylic acids (**1**) would behave under similar reaction conditions (Fig. 1) in presence of 2-isocyanobiaryls (**2**). At first, we chose **1a** and **2a** as model reactants to optimize the reaction conditions for the desired decarboxylative radical cascade alkylarylation using inexpensive PPh₃/NaI as a photocatalyst. To our delight, when a solution of 1.5 equiv. of **1a** with 1.0 equiv. of **2a** in the presence of PPh₃ (20 mol%) and NaI (100 mol%) in acetonitrile was illuminated with a blue LED (455 nm) at 25 °C for 24 h, product **3a** was formed in 84% yield (Fig. 2, entry 1). Replacement of NaI by KI also proceeded smoothly to give product **3a** in 80% yield (Fig. 2, entry 2). The product formation **3a** was slightly decreased upon employing other iodide salts (Fig. 2, entries 3 and 4). Solvents such as dimethylsulfoxide (DMSO) and dimethylformamide (DMF) in place of MeCN afforded **3a** in 65% and 60% yield respectively (Fig. 2, entries 5 and 6). While solvents such as acetone, chloroform (CHCl₃) and EtOAc had a deleterious effect on the reaction outcome (Fig. 2, entries 7–9). When triphenyl phosphine was replaced by other phosphines such as PCy₃ and P(*o*-tol)₃, caused a drastic reduction in the yield of the reaction (Fig. 2, entries 10 and 11). Substitution of PPh₃ by other nitrogen donors such as DMAP, Et₃N observed trace amount of product (Fig. 2, entries 12 and 13). Additionally, control experiments confirmed that a catalytic amount of PPh₃ and continuous blue light irradiation were necessary for the reaction to occur. Not even traces amount of **3a** were observed in the absence of light or the PPh₃ (Fig. 2, entries 15 and 17).

With the optimized reaction conditions in our hand, we survey the scope of the reaction. As shown in Fig. 3, a broad range of alkyl NHP esters (**1**), reacted with 2-isocyanobiphenyl (**2a**) providing the corresponding 6-alkyl phenanthridines in good to moderate yields. Different types of secondary cyclic (**1a–1b**) and acyclic (**1c–1f**) alkyl NHP esters participate in this reaction to provide good yields (**3a–3f**, 67–78%). We were pleased to find that different functional groups such as amide



Entry	Deviations from standard reaction conditions	3a (%) ^[a]
1	none	84(78) ^[b]
2	KI instead of NaI	80
3	TBAI instead of NaI	66
4	LiI instead of NaI	38
5	DMSO instead of CH ₃ CN	65
6	DMF instead of CH ₃ CN	60
7	Acetone instead of CH ₃ CN	44
8	CHCl ₃ instead of CH ₃ CN	33
9	EtOAc instead of CH ₃ CN	28
10	P(Cy) ₃ instead of PPh ₃	5
11	P(<i>o</i> -tol) ₃ instead of PPh ₃	2
12	Et ₃ N instead of PPh ₃	4
13	DMAP instead of PPh ₃	3
14	without NaI	18
15	without PPh ₃	0
16	without light NaI and PPh ₃	0
17	without blue light	0

Fig. 2 Optimization of the reaction conditions. **1a** (0.3 mmol), **2a** (0.2 mmol), PPh₃ (20 mol%), NaI (100 mol%), CH₃CN (3 mL) at 25 °C, 455 nm LED for 24 h. ^[a]NMR yields using benzyl alcohol as internal standard. ^[b]Isolated yield.

(**1g**) and ketone (**1h**) can be tolerated in our reaction conditions to produce the corresponding 6-substituted phenanthridines (**3g** and **3h**) in 65% and 68% yield. Tertiary alkyl NHP esters were smoothly converted to 6-alkyl phenanthridines in good yields (**3i–3k**, 70–77%). Primary alkyl NHP-esters containing variety of functional groups readily participated in this reaction and gave corresponding 6-alkyl phenanthridines in good to moderate yields. Primary alkyl NHP-esters derived from isovaleric acid, 4-phenyl butyric acid and 3-bromo-phenyl propionic acid gave the corresponding 6-substituted phenanthridines (**3l–3n**) in moderate yields (60–63%). Terminal alkynes (**1o**) and alkenes (**1p**) are tolerated under these reaction conditions gave the corresponding products **3o** and **3p** in 58% and 56% yield. Also, primary alkyl NHP-esters (**1q** and **1r**) derived from 2-methoxy acetic acid and 4-oxopentanoic acid were successfully converted to 6-alkyl phenanthridines **3q** and **3r** in moderate yields (57% and 56%).

Next, the scope of 2-isocyanobiaryls was examined. As shown in Fig. 3, first, the electronic variation at the *para* position of the Ar² ring was studied with NHP-esters (**1a** and **1i**). Electron withdrawing groups such as cyano, fluoro, chloro, bromo, trifluoro methyl, trifluoromethoxy groups were all well tolerated, giving 6-substituted phenanthridines (**3s–3x**) in 50–65% yields. Electron donating groups such as *t*butyl, ethyl, methoxy gave the corresponding 6-alkyl substituted phenanthridines (**3y–3aa**) in 72–75% yields. Next *ortho*- and *meta*-substituted 2-isocyanobiphenyls were tested in our reaction conditions. In case of *ortho*-phenyl substituted 2-isocyanobiphenyl gave the corresponding substituted phenanthridines (**3ab**) in 58% yield. In case of *meta*-methyl substituted 2-isocyanobiphenyl gave the corresponding 6-alkyl phenanthridine (**3ac**) as a single regioisomer in 66% yield. In case of *meta-para* substituted 2-

Shang and Fu (Science, 2019)

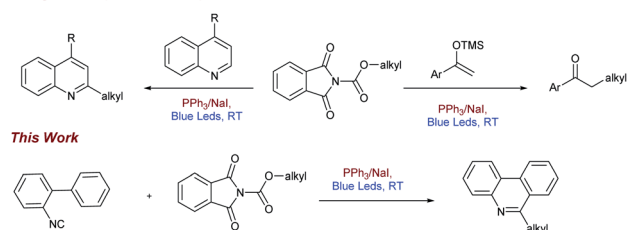


Fig. 1 Decarboxylative alkylations driven by PPh₃/NaI photoredox catalysis.

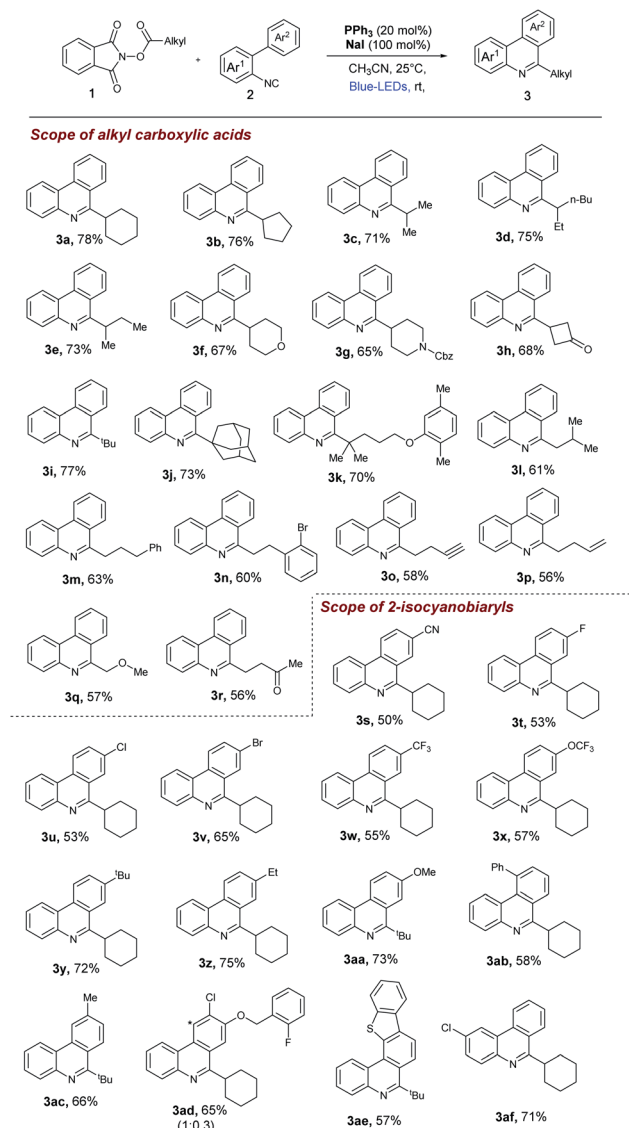
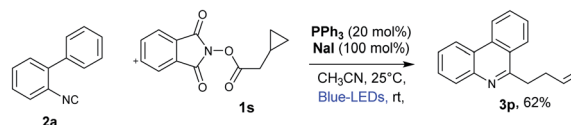


Fig. 3 Decarboxylative cascade alkylarylation reaction of 2-isocyanobiaryls with alkyl NHP-esters. Reaction conditions as given in Fig. 2 (entry 1). Isolated yields, average of at least two independent runs. *regioisomer.

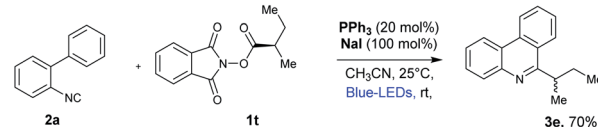
isocyano biphenyl gave the 6-alkyl phenanthridines (3ad) as mixture of regio-isomers 65% yield. Dibenzothiofuran and benzyloxy groups can be tolerated in our reaction conditions. In case of 2-isocyano biphenyl containing dibenzothiofuran with alkyl NHP-ester (1i) gave the 6-alkyl phenanthridine (3ae) in 57% yield. Finally, we tested one example of 2-isocyanobiphenyl (2a) by introducing substitution on Ar^1 ring was studied with NHP-esters (1a) in our reaction conditions provided 6-alkyl phenanthridine (3af) in 71% yield. Further, we have found that Katritzky's *N*-cyclohexylpyridinium salt (4) and Togni's reagent (5) can be activated by PPh_3/NaI system to deliver 3a (75% yield) and 6-trifluoromethyl substituted phenanthridine (3ag) in good yield (78% yield, see ESI†).

The efficiency of our photocatalytic decarboxylative radical cascade cyclization leads us to conduct some preliminary

Radical-clock experiment



Racemization of chiral carboxylic acids



Plausible reaction mechanism

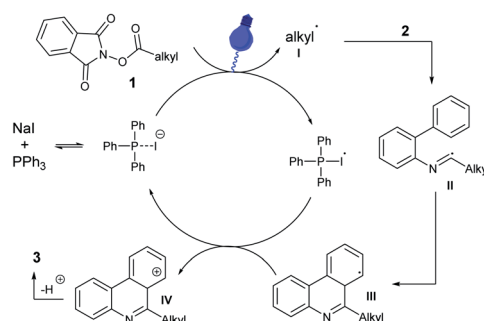


Fig. 4 Preliminary mechanistic investigations; (Upper) radical clock experiment; (Center) racemization of chiral alkyl NHP-ester; (Bottom) plausible reaction mechanism.

mechanistic studies (Fig. 4). As anticipated ON/OFF experiment indicated that our reaction required continuous blue light irradiation to proceed (see ESI†). We currently believe that this decarboxylative cascade cyclization reaction could proceed *via* the generation of alkyl radicals. In a radical clock experiment using alkyl NHP-ester (1s) derived from 2-cyclopropylacetic acid under our reaction conditions, the ring-opened product 3p was isolated (Fig. 4, upper). Moreover, secondary chiral alkyl NHP-ester (1t) derived from enantiopure (*S*)-2-methylbutanoic acid provided the racemic 6-alkyl substituted phenanthridines product 3e (Fig. 4, center).

Based on these experimental observations and the report of Rui Shang and Yao Fu *et al.*^{4d} we propose that the decarboxylative cascade cyclization reaction proceeds *via* formation of charge transfer complex (CTC)²³ (see ESI† for UV-visible absorption spectra) between PPh_3 , NaI and NHP-ester (1a) (Fig. 4).^{4d} After photo fragmentation of this CTC complex generates key alkyl radical I and $\text{PPh}_3\text{-I}^\cdot$. Subsequently, the generated alkyl radical is added to 2-isocyanobiaryl 2, which produce imine radical II that can form intermediate III through an intramolecular radical cyclization. Further oxidation of III by $\text{PPh}_3\text{-I}^\cdot$ ($E_{\text{red}} = 0.69$ vs. SCE)^{4d} produces the corresponding carbocation IV and NaI, PPh_3 . The carbocation IV loses a proton under reaction conditions to provide the desired product 3.

Conclusions

In summary, we have developed a general strategy for the catalytic, radical decarboxylative cascade alkyl arylation of alkyl



NHP-esters using an inexpensive PPh_3/NaI system as a photocatalyst. This operationally simple protocol allows an efficient synthesis of 6-substituted phenanthridines in moderate to good yields under metal free conditions. Furthermore we showed that in our photocatalytic conditions, different carbon radical precursors can be activated to deliver 6-substituted phenanthridines.

Conflicts of interest

There are no conflicts to declare.

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