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Photochemical Decarboxylative C(sp^3)−X Coupling Facilitated by Weak Interaction of N-Heterocyclic Carbene

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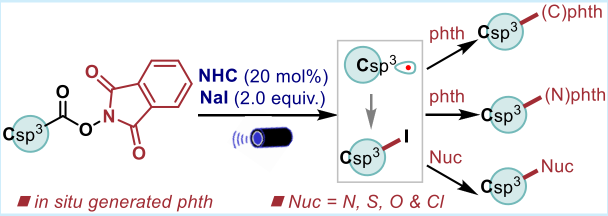
ABSTRACT: While *N*-hydroxyphthalimide (NHPI) ester has emerged as a powerful reagent as an alkyl radical source for a variety of C−C bond formations, the corresponding C(sp^3)−N bond formation is still in its infancy. We demonstrate herein transition-metal-free decarboxylative C(sp^3)−X bond formation enabled by the photochemical activity of the NHPI ester−NaI−NHC complex, giving primary C(sp^3)−(N)phth, secondary C(sp^3)−I, or tertiary C(sp^3)−(meta C)phth coupling products. The primary C(sp^3)−(N)phth coupling offers convenient access to primary amines.



Primary amines make up an important class of compounds in biological and synthetic chemistry that are featured in various pharmaceuticals.[1] They can be prepared by traditional approaches such as Gabriel reaction, Curtius rearrangement, Schmidt reaction, and Delépine reaction (Scheme 1A).[2] However, considering the issues of safety, material sourcing, and reagent cost associated with these methods, and green trends in modern synthetic chemistry, there is a great demand to address these problems as much as possible. In the recent decade, functional group transfer radical reactions have proven to be a powerful tool for the construction of synthetically important bonds. With the development of first-row transition-metal catalysis, photoredox catalysis, and electrochemistry, *N*-hydroxyphthalimide (NHPI) ester that can be readily prepared from ideal feedstock chemicals (i.e., carboxylic acids) has emerged as a powerful functional group transfer reagent for the generation of the alkyl radical in a variety of cross-couplings (Scheme 1B).[3] However, compared with the great progress in the construction of carbon−carbon bonds, carbon−heteroatom bond formations with the reagent are still in their infancy.[4] In this context, the *N*-alkyl bond forming reaction is particularly significant and continues to be a challenge at the forefront of synthetic chemistry.[4g,5] In 2017, Fu, Peters, and co-workers reported a photoinduced, copper-catalyzed decarboxylative C(sp^3)−N coupling of NHPI esters, which offers a valuable alternative to the traditional Curtius rearrangement for preparing protected amines.[6] Further efforts by the Hu group resulted in a dual copper/photoredox catalysis for the cross-couplings of NHPI esters and benzophenone imines or anilines for the synthesis of alkyl amines and anilines (Scheme 1C).[7]

Recent interest in the photoactive electron donor−acceptor (EDA) complex has led to numerous advances for the generation of a wide range of synthetically important radicals, providing new possibilities of utilizing NHPI esters.[8] For example, Aggarwal and co-workers found that NHPI esters could form the key heteroleptic ternary complex with a DMA solvent molecule and bis(catecholato)diboron for the generation of alkyl radicals.[4l] Recently, Fu, Shang, and co-workers developed the photocatalytic decarboxylative alkylations, wherein the formation of a tricomponent EDA complex of NHPI, NaI, and PPh_3 was the key to their success.[9] Drawing inspiration from these elegant studies, we wondered whether the EDA strategy could be used for decarboxylative carbon−heteroatom bond formations, thus unleashing wider applications of NHPI esters through a new reactivity pattern.

The electrostatic interaction of an alkali-metal cation enables the creation of new types of activation modes for a variety of transformations.[10] Specifically, N-heterocyclic carbenes (NHCs),[11] which have recently emerged as powerful catalysts for photochemical transformations,[12,13] could construct new architectures with the alkali metal via weak electrostatic interaction,[14] which differs in comparison to those in traditional NHC-catalyzed protocols that are reliant on the formation of covalent bonds.[15] Very recently, we found that the weak electrostatic interaction of NHC and NaI could facilitate the photochemical iodination of N-alkenoxypyridinium salts.[16] On the basis of the information presented above, we envisioned that an alternative approach could be devised for the formation of the photon-absorbing EDA complex among NHPI esters, NHC, and NaI. Specifically, we expected that, after cross-coupling of the alkyl radical and iodine radical

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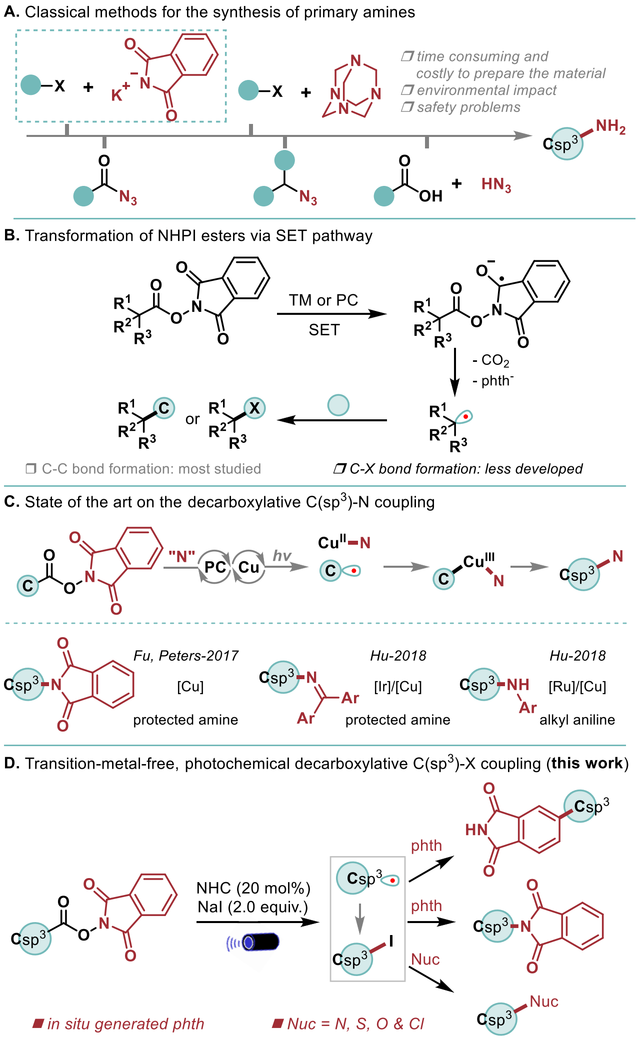
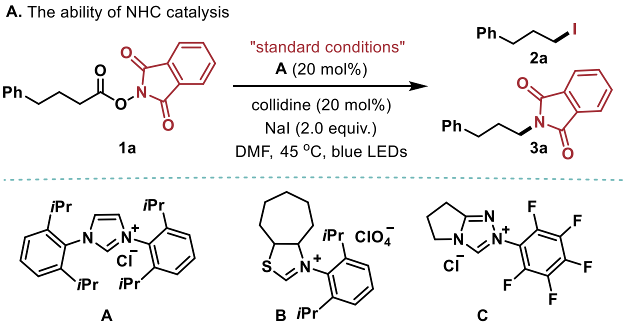
Scheme 1. Motivation and Synthetic Strategy



generated from photoactivation of an EDA complex, the resultant iodoalkane may undergo an S_N2 process with the *in situ*-generated phthalimide anion to form a C−N bond. Notably, our finding reveals the intriguing effects of NHC to improve the efficiency of this process. Herein, we report decarboxylative N-alkyl bond formation enabled by the photochemical activity of the NHPI ester−NaI−NHC complex. Moreover, the strategy offers a convenient way to construct C(sp^3)−C(sp^2), C(sp^3)−S, C(sp^3)−O, and C(sp^3)−Cl bonds (Scheme 1D).

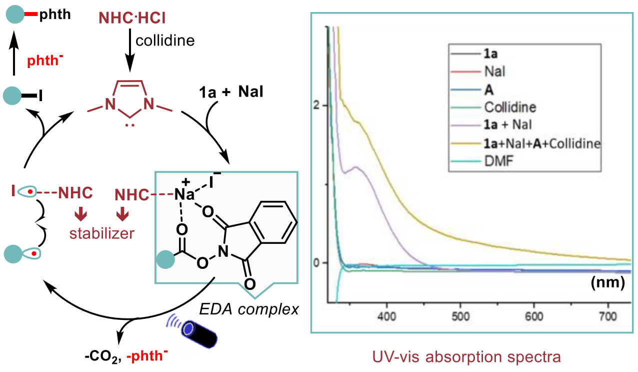
Initially, a mixture of NHPI ester **1a** and NaI in DMF was irradiated with blue light-emitting diodes (460 nm, 50 W). The desired protected amine **3a** was obtained in 36% yield, suggesting the formation of an EDA complex between **1a** and NaI (Scheme 2A, entries 1 and 2). Considering the electrostatic interaction of NHC, we then evaluated the potential of NHC catalysis. To our delight, the use of **A** as the precatalyst and collidine as the base delivered the desired product **3a** in 63% yield (entries 3 and 4). Control experiments demonstrated the requirement of precatalyst **A** and the base for improving reaction efficiency (entries 5 and 6). The employment of thiazolium or triazolium precatalysts **B** and **C** failed to give the desired product **3a** (entries 7 and 8, respectively). Solvent screening showed that the reaction was fastidious to the solvents. The less polar solvent acetone delivered the

Scheme 2. Optimization of the Reaction Conditions[a]



Entry	modifications	Yield of **2a**, **3a** (%)	
1	no precatalyst **A**, no collidine, no light irradiation	ND	0
2	no precatalyst **A**, no collidine	--^{b}	36
3	standard conditions	--	63
4	room temperature	--	23
5	no collidine	--	35
6	no precatalyst **A**	--	38
7	precatalyst **B** as the catalyst	--	trace
8	precatalyst **C** as the catalyst	--	trace
9	acetone as the solvent	40	trace
10	THF, DCM or toluene as the solvent	trace	trace
11	TEMPO (3.0 equiv.) was added	ND	ND

B. Plausible mechanism

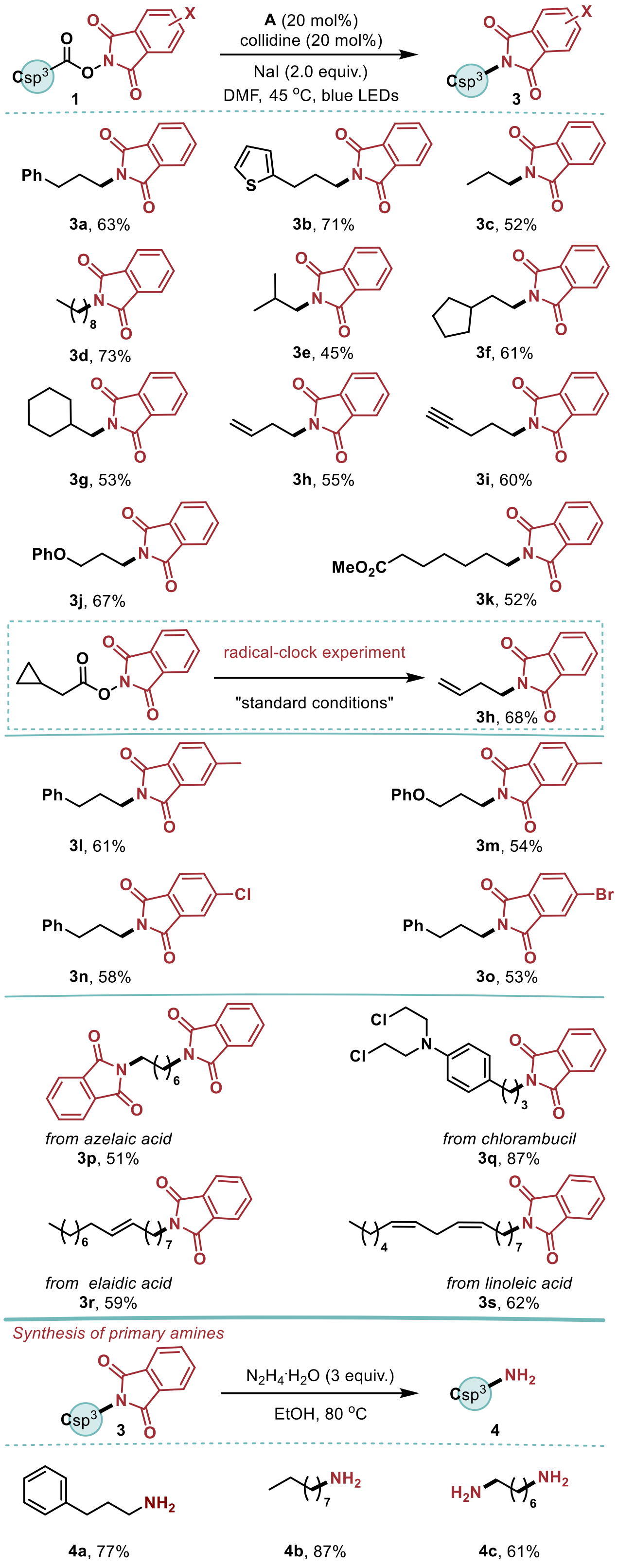


[a]Yield of isolated products **2a** and **3a** after chromatography. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl. [b]For entries 2−8, a minute amount of **2a** was observed via GCMS, but unisolated.

iodination product **2a** in 42% yield instead of the amination product, possibly due to the low solubility of phth salts in acetone (entry 9). Other solvents, including THF, DCM, and toluene, were ineffective under the conditions described herein (entry 10). Additionally, complete inhibition of the reaction was observed by the addition of the radical scavenger TEMPO to the standard reaction conditions (entry 11).

A possible mechanism for this C(sp^3)−N bond formation process is outlined in Scheme 2B. The electrostatic interaction of the NHPI ester and NaI allows the formation of an EDA complex. The addition of NHC further facilitates EDA complex formation. Upon visible light excitation, the photoactive EDA complex can undergo single-electron transfer to generate the phthalimide anion, alkyl radical, and iodine radical. The stabilization of NHC ensures productive C(sp^3)−I bond formation, which could be attacked by the *in situ*-generated phthalimide anion to afford the final protected amines. The UV−vis spectra reveal the formation of the EDA complex between NHPI ester and NaI. While the UV−vis spectra of NHPI ester and NaI are silent in the visible region, a

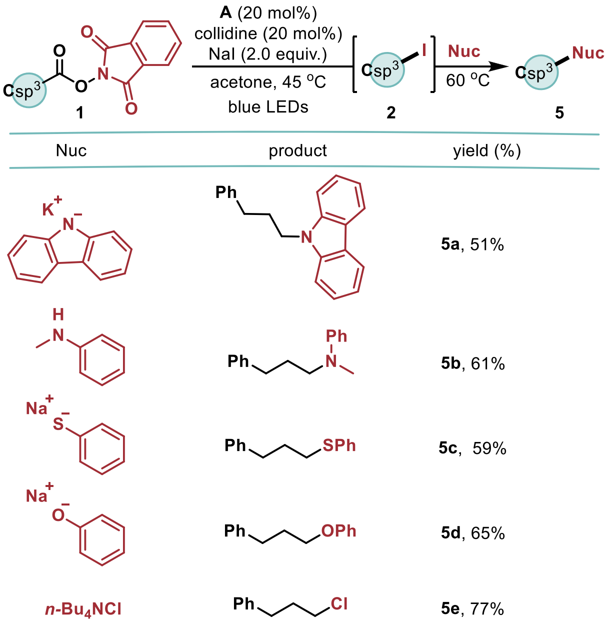
Scheme 3. Reaction Scope[a]



[a]Yield of isolated products **3** and **4** after chromatography.

significant red-shift appears with their mixture. The addition of NHC causes a further red-shift, suggesting its stabilization role in EDA complex formation.

Scheme 4. Construction of C(sp^3)−N, −S, −O, and −Cl Bonds[a]



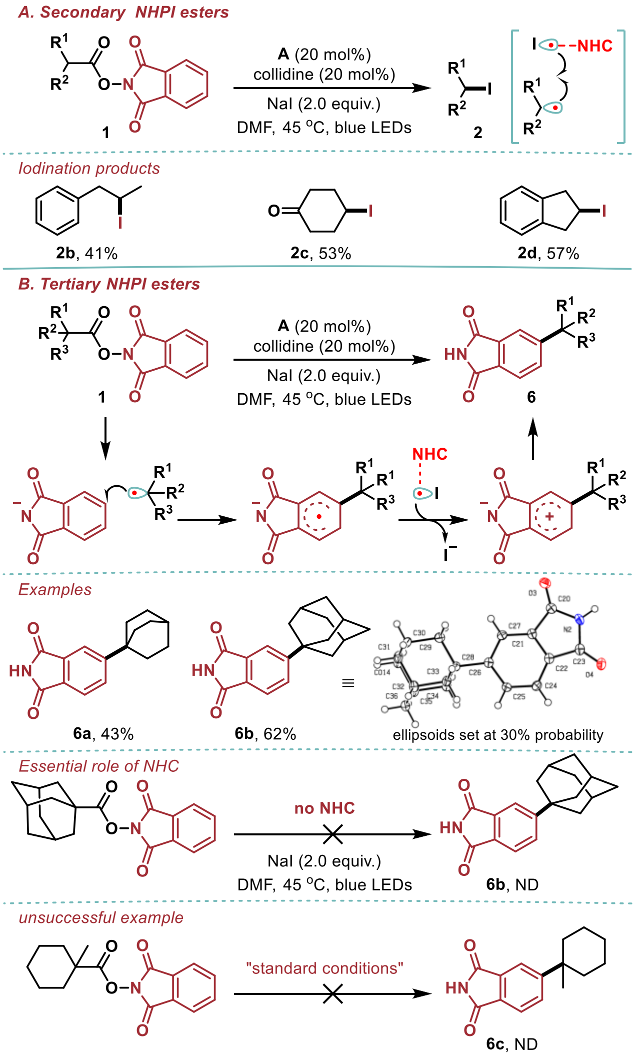
[a]Yield of isolated products **5** after chromatography.

With the optimized conditions in hand, we subsequently examined the generality of the method (Scheme 3). A series of NHPI esters with acyclic, cyclic alkyl, alkenyl, alkynyl, ether, and ester groups worked well to give the corresponding products **3a**−**3k** in moderate to good yields. A radical clock experiment gave the desired protected amine **3h** in 68% yield. This was also true for the substituted phthaloyl derivatives, giving rise to the protected amines **3l**−**3o** in 53−61% yields. The utility of this mild amination protocol has been further demonstrated by the late-stage structural modification of natural product carboxylic acids and drugs. The reactions of substrates with diverse scaffolds all worked well, providing the desired products **3p**−**3s** in reasonable yields under the reaction conditions. Protected amines derived from chlorambucil, elaidic acid, and linoleic acid were obtained in 51−87% yields. The substrate bearing bis(*N*-hydroxyphthalimide) ester gave the corresponding bis(protected amine) product **3p** in 51% yield. In addition, the final primary amines **4a**−**4c** could be easily prepared by a subsequent deprotection process.

The synthetic utility of this method was further demonstrated by constructing other types of carbon−heteroatom bonds from the *in situ*-generated iodoalkanes (Scheme 4). Several amine, alcohol, and thiol nucleophiles were tolerable, affording the corresponding products **5a**−**5d** in 51−65% yields. In addition, alkyl chloride **5e** could be obtained in 77% yield by using *n*-Bu_4NCl.

To test whether secondary and tertiary substrates are tolerable, several secondary NHPI esters were first subjected to the conditions described herein (Scheme 5A). Complete consumption of the NHPI esters was observed, but the amination products were not detected. Instead, the iodination products **2b**−**2d** were obtained, probably due to the limitation of the S_N2 reaction toward sterical substrates. These results provided support for our proposed mechanism for the intermediacy of the iodoalkanes. Unexpectedly, the C-alkylation of phthalimide was achieved when cyclic tertiary NHPI esters were employed as the substrates, as demonstrated

Scheme 5. Reactions of Secondary and Tertiary NHPI Esters



by the X-ray structure of **6b** (Scheme 5B). Substituted phthalimides **6a** and **6b** likely arose from tertiary NHPI esters by addition of a radical to phthalimide, followed by single-electron oxidation and a proton transfer process. This application demonstrates the usefulness of the NHC−NaI−NHPI ester system and opens a convenient entry for the synthesis of phthalimides, which make up an important class of biologically active compounds.[17] Notably, no alkylation product was observed in the absence of NHC, suggesting the importance of the weak interaction of NHC. The acyclic tertiary NHPI esters were also tested. Puzzlingly, no desired products **6c** were observed under current conditions, which we currently do not understand. To the best of our knowledge, the reaction mode of **6a** and **6b** has not been reported. The further development and application of this mode, as well as the study of the mechanism, are ongoing.

In conclusion, we have developed a transition-metal-free, NHC-aided carbon−heteroatom bond-forming reaction of NHPI esters under blue light irradiation, which serves as a simple alternative to traditional methods for synthesizing primary amines. A two-stage mechanism was proposed for this process, including photochemical alkyl iodide formation reaction, and the following S_N2 reaction of the *in situ*-generated phthalimide anion. This transformation is characterized by mild and simple conditions and avoids expensive photocatalysts, transition metals, and ligands. Notably, the C-alkylation transformations highlight for the reactions of NHPI esters that the weak interaction of NHC can enable new reactivity patterns compared to the known methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03006.

Experimental details, characterization data, and spectra (PDF)

Accession Codes

CCDC 2026142 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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