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N-Heterocyclic Carbene Catalyzed Photooxidation: Intramolecular Cross Dehydrogenative Coupling of Tetrahydroisoquinoline-Tethered Aldehydes

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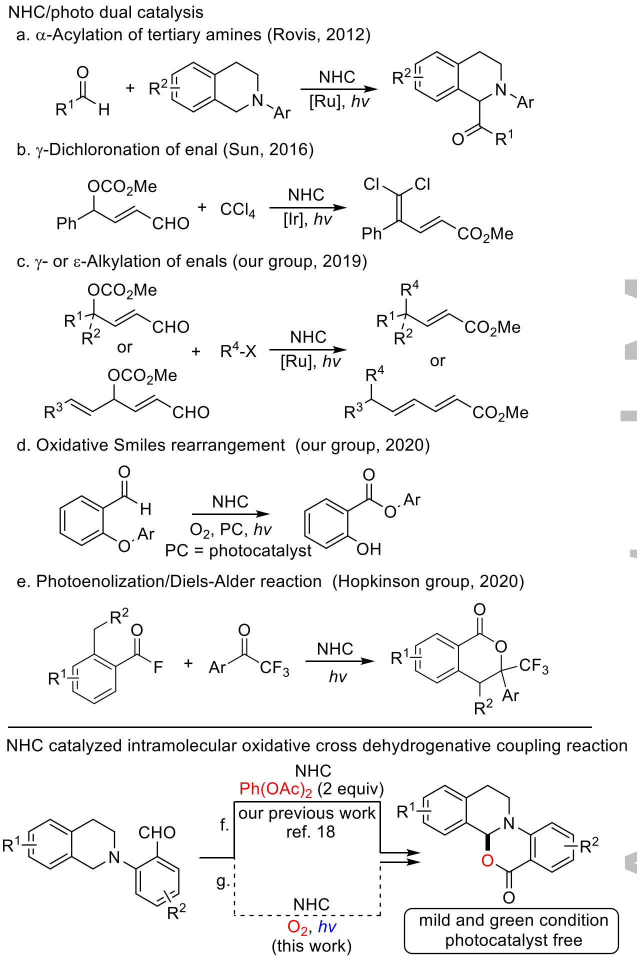
Abstract. An N-heterocyclic carbene catalyzed photooxidation reaction via intramolecular cross dehydrogenative coupling of tetrahydroisoquinoline-tethered aldehydes was developed, giving the corresponding oxidative cyclization products in moderate to good yields. This reaction features mild conditions with oxygen as the terminal oxidant in the absence of photocatalyst.

Keywords: N-heterocyclic carbene; photocatalysis; organocatalysis; oxidation; dehydrogenative coupling

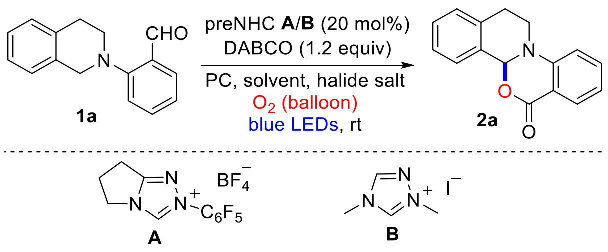
In the past decades, N-heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts, especially for the construction of heterocycles.[1] The cooperative catalysis of NHC with other catalysts, such as transition-metals,[2] Brønsted acids,[3] Lewis acids[4] and other organocatalysts,[5] provides new possibility beyond single catalysis.[6] Photoredox catalysis, which activates substrates by excited photosensitizers, exhibits great potential for inert-bond activation.[7] In recent years, several photo/NHC cooperative catalysis has been developed. In 2012, Rovis and co-workers disclosed a pioneering photo/NHC dual catalysis for α-acylation of tertiary amines (Scheme 1a).[8] Lately, Sun group reported one example of photo/NHC cocatalyzed γ-dichloromethylenation of enal (Scheme 1b).[9] Recently, we reported the photo/NHC cocatalyzed γ-and ε-alkylation of γ-preoxidized enals (Scheme 1c),[10] and an NHC/photo-cocatalyzed oxidative Smiles rearrangement of *O*-aryl salicylaldehydes in the presence of 9-mesityl-10-methylacridin-10-ium perchlorate as the photocatalyst (Scheme 1d).[11] Very recently, the Hopkinson group reported an interesting photoenolization/Diels–Alder reaction of acyl fluorides via photo-NHC catalysis (Scheme 1e).[12]



Scheme 1. NHC/photo dual catalysis and NHC catalyzed intramolecular cross oxidative dehydrogenative coupling reactions.

Tetrahydroisoquinoline (THIQ) motif is widely present in natural and non-natural compounds possessing versatile bioactivities,[13] which attracts chemists to develop synthetic methodologies for its construction and transformations.[14] The cross dehydrogenative-coupling (CDC) has become an efficient tool for C-C or C-X bond formation via activation of C(sp^3)-H bond.[15] Nowadays, CDC reactions for the transformation of THIQs with different oxidative agents, such as DDQ, nitro-(hetero)arenes and carbocations, and/or in combination with transition-metal catalysts have been well established.[16] Among them, visible-light-induced CDC reactions of THIQs have received considerable attention for their mild and environmentally benign redox conditions.[17] Recently, our group disclosed an NHC catalyzed intramolecular α-oxygenation of amines using hypervalent iodine (III) agent as the terminal oxidant (Scheme 1f).[18] To further improve the practicality and atom economy of this methodology, herein, we report an NHC catalyzed photooxidation reaction utilizing oxygen as the oxidant (Scheme 1g). Notably, this photo-promoted oxidative CDC reaction proceeds well without external photocatalyst.

Table 1. Reaction optimization.[a]



Entry	PC (mol%)	Halide (mol%)	Solvent	Yield (%)[b]
1	Ir(ppy)$_3$ (2)	/	CH_3CN	14
2	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	CH_3CN	66
3	Ir(ppy)$_3$ (2)	nBu$_4$NI (20)	CH_3CN	68
4	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	DMF	56
5	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	DMSO	29
6	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	toluene	trace
7	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	1,4-dioxane	trace
8[c]	Ir(ppy)$_3$ (2)	nBu$_4$NI (10)	CH_3CN	trace
9	/	nBu$_4$NI (10)	CH_3CN	75
10[d]	/	nBu$_4$NI (10)	CH_3CN	7
11	/	KI (10)	CH_3CN	76
12	/	NaI (10)	CH_3CN	77
13	/	nBu$_4$NBr (10)	CH_3CN	trace
14	/	nBu$_4$NCl (10)	CH_3CN	trace
15[e]	/	/	CH_3CN	trace
16[f]	/	NaI (10)	CH_3CN	32
17[g]	/	NaI (10)	CH_3CN	27

[a] General conditions: **1a** (0.2 mmol), preNHC **A** (0.04 mmol, 20 mol%), DABCO (1.2 equiv), halide salt (0.02 mmol, 10 mol%), PC (0.004 mmol, 2 mol%), solvent (2 mL), irradiated under 18 × 1W blue LEDs at room temperature for 48 h under O_2 atmosphere (balloon).

[b] Isolated yields.

[c] No preNHC was added.

[d] Without irradiation.

[e] PreNHC **B** was used instead of **A**.

[f] Air was directly used instead of O_2.

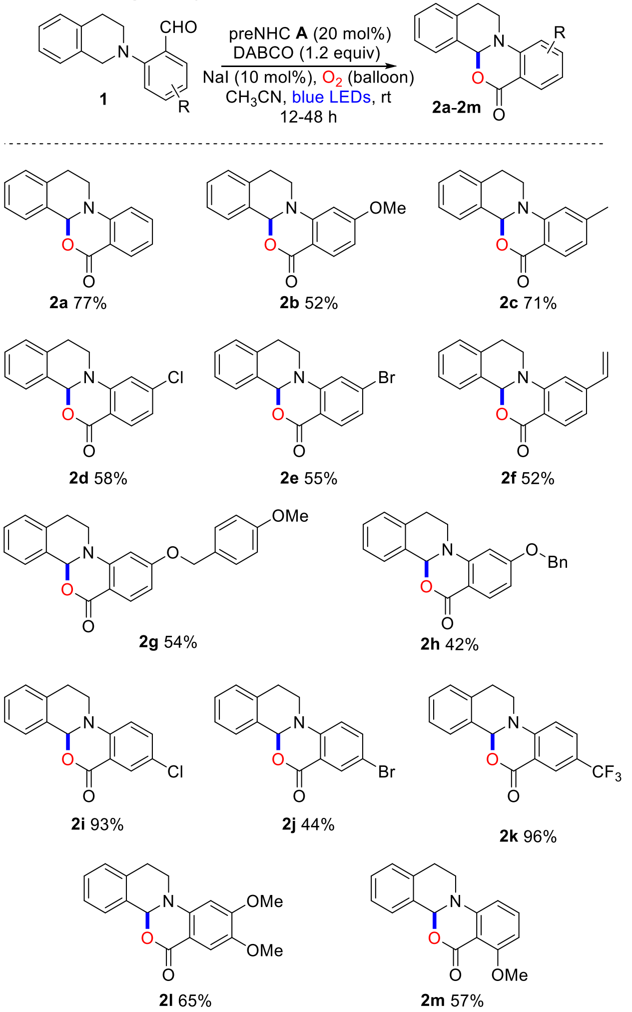
[g] H_2O_2 (30% aq., 4.5 equiv) was used instead of O_2.

At the very beginning, our design of the coupling reaction was based on the combination of photocatalyst (transition metal complexes) with NHC catalyst. Thus, we initiated our investigation by employing tetrahydroisoquinoline-derived benzaldehyde **1a** as the substrate, molecular oxygen as the oxidant and Ir(ppy)$_3$ as the photocatalyst (Table 1). As a result, the desired CDC product could be afforded in 14% yield when the reaction was carried out under 18 W blue LED irradiation at room temperature with 1.2 equiv of DABCO as the base and acetonitrile as the solvent (Table 1, entry 1).

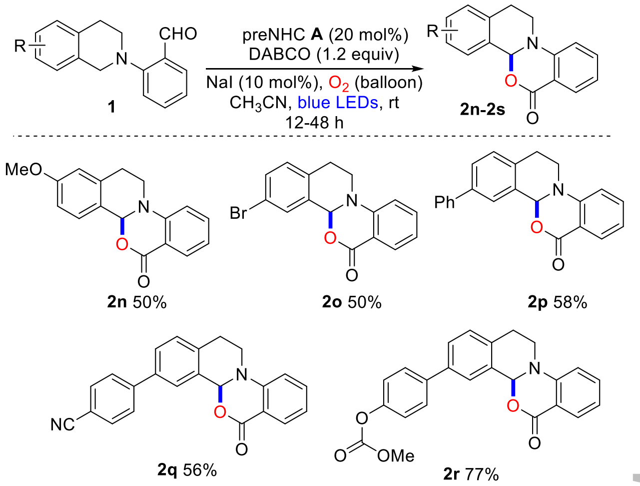
To further improve the efficiency, a catalytic amount of tetrabutylammonium iodide (TBAI), which often served as (co)catalyst in oxidation reactions,[19] was added to the reaction system. To our delight, the yield improved dramatically (66%, entry 2), while further increasing the loading of TBAI did not give a significant improvement (68%, entry 3). Solvent screening revealed that DMF, DMSO, toluene or dioxane gave no better results than acetonitrile (entries 4-7). The reaction could not proceed in the absence of preNHC (entry 8). To our surprise, the corresponding coupling product could be isolated in 75% yield in the absence of iridium photocatalyst (entry 9). However, the reaction could not proceed well without blue LED irradiation, giving **2a** in only 7% yield (entry 10), which confirmed the involvement of photoactivation without photocatalyst. Then, further screening of halide salts revealed that KI or NaI gave similar results (entries 11 and 12), while only trace amount of **2a** was afforded using tetrabutylammonium bromide (TBAB) or tetrabutylammonium chloride (TBAC) instead (entries 13 and 14), which demonstrated the significance of iodide. Thus, NaI was selected as the iodide source for further optimization test for its very low cost. However, when triazolium iodide **B** was used as the NHC precursor without the addtion of NaI, only trace amount of **2a** was detected for the reaction (entry 15). It should be noted that decreased yield was resulted when air or H_2O_2 (aq.) was used as the oxidant instead of molecular oxygen (entries 16 & 17).

With the optimized reaction conditions in hand, the substrate scope was then explored. Substrates with various substituents on tetrahydroisoquinoline-derived benzaldehyde were evaluated (Scheme 2). It was found that benzaldehydes with electron-donating (5’-OMe and 5’-Me) or electron-withdrawing groups (5’-Cl and 5’-Br) at C-5’ position gave the corresponding CDC products in moderate to good yields (**2b-2e**). It is worth noting that substrates with 5’-vinyl, 5’-*p*-methoxybenzyloxy and 5’-benzyloxy, which were sensitive to strong oxidative conditions, could be well tolerated in this reaction system (**2f-2h**). Substrates with electron-withdrawing groups (4’-Cl, 4’-Br and 4’-CF_3) at the C-4’ position could also afford the desired coupling products in moderate to good yields (**2i**-**2k**). 4',5'-Dimethoxy substituted and 3'-methoxy substituted aldehydes worked as well (**2l** and **2m**). Notably, the corresponding carboxylic acid from the aldehyde was detected as the side product for those reactions in low yields.

Substrates with different substituents on the THIQ skeleton were then evaluated (Scheme 3). The THIQ with 6-OMe gave the corresponding product in moderate yield (**2n**). Aldehydes bearing 7-Br or 7-Ph were effective in generating the targeted products with moderate efficiency (**2o** and **2p**). In addition, cyano and methoxycarbonyl groups on the aromatic ring were also tolerable to give the desired coupling product in good yields (**2q** and **2r**).

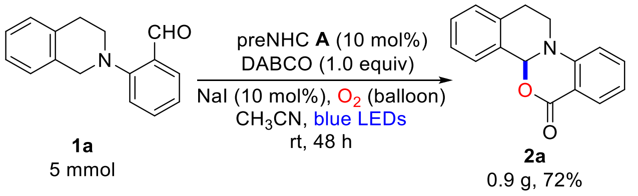


Scheme 2. Substrate scope: Variation of the substituents in benzaldehyde.



Scheme 3. Substrate scope: Substituents on the aryl ring of THIQ skeleton.

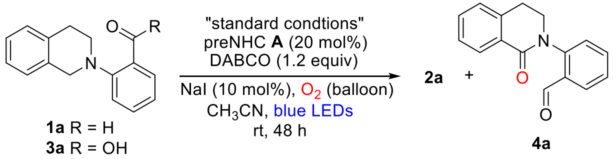
The model reaction could be scaled up even with a decreased preNHC loading (10 mol%) and product **2a** was obtained without apparent loss of yield (72%, Scheme 4).



Scheme 4. Gram-scale reaction.

To obtain further insight into the mechanism of this photo-promoted NHC-catalyzed CDC reaction, a series of control experiments were conducted (Table 2). In the absence of NHC catalyst, only 17% of the desired product could be detected by NMR analysis of the crude reaction mixture along with 25% of amide byproduct **4a** (Table 2, entry 1). The reaction did not occur without visible light irradiation even at higher temperature (40 °C) (entry 2). Radical quenching experiment revealed that the reaction was inhibited when 1.5 equiv of TEMPO was added (entry 3), which indicates the possible involvement of a radical intermediate. The reaction of THIQ-tethered benzoic acid **3a** instead of aldehyde **1a** gave the corresponding product **2a** in 32% NMR yield in the absence of NHC catalyst (entry 4). The significant loss of the yield indicated that the acid could participate in the reaction but possible not an active intermediate for the reaction of aldehyde. In addition, the CDC reaction of **3a** could not proceed in the absence of either visible light or molecular oxygen (entries 5 and 6). These experiments suggest the intermediate generated from aldehyde and NHC is possibly involved in the photoredox process.

Table 2. Control experiments.[a]



Entry	Variation from standard conditions	Yield (%)[b]	
		2a	**4a**
1	No preNHC	17	25
2	No irradiation, 40 °C	trace	/
3	TEMPO (1.5 equiv)	trace	/
4	**3a** instead of **1a**, no preNHC	32	/
5	**3a** instead of **1a**, no irradiation	0	/
6	**3a** instead of **1a**, no O_2	0	/

[a] Standard conditions: **1a** (0.2 mmol), preNHC **A** (0.04 mmol, 20 mol%), DABCO (1.2 equiv) and NaI (0.02 mmol, 10 mol%) in CH_3CN (2 mL), and irradiated under 18 × 1W blue LEDs at room temperature for 48 h under O_2 atmosphere (balloon).

[b] NMR yield with 1,3,5-trimethoxybenzene as internal standard.

The fluorescence spectra of aldehyde and the reaction mixture with aldehyde and NHC under irradiation at 446 nm were then investigated (Figure 1). It was found that both of them showed fluorescence but with a slight redshift for the reaction mixture (red line), probably due to the formation of an intermediate from aldehyde and NHC catalyst.

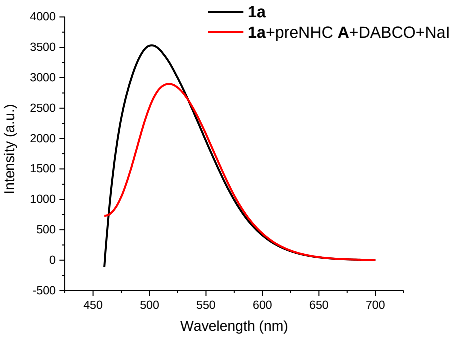


Figure 1. Fluorescence spectra of **1a** and the reaction mixture, recorded in CH_3CN in 1 cm path quartz cuvettes (excited at 446 nm). [**1a**] = 0.05 M, [preNHC **A**] = 0.01 M, [DABCO] = 0.06 M, [NaI] = 0.005 M.

Based on the control experiments and fluorescence spectra, we speculate that the activation of aldehyde by NHC promotes the whole photooxidation process. A plausible mechanism is presented as follows (Figure 2). The addition of carbene (**I**), generated in situ under basic conditions, to aldehyde provides the corresponding Breslow intermediate (**II**). The excited Breslow intermediate **(II*)** under photoexcitation is oxidized by O_2 via a SET process to give a radical pair **III** of amino radical cation and superoxide radical anion. The 1,2-H shift of amino radical cation followed by proton abstraction by superoxide radical affords α-amino radical **IV**,[17a, 20] which is further oxidized to iminium **VI**[21] via α-iodoamine **V** under iodide catalysis.[22] The oxidation of Breslow intermediate by oxygen generates a radical cation **VII**, followed by deprotonation gives zwitterionic radical species **VIII**. The intermediate **VIII** is further oxidized by the in situ generated hydroperoxide radical to afford acyl azolium intermediate **IX**,[11] which is hydrolysed to regenerate NHC catalyst and provide the iminium/carboxylate intermediate **X** after deprotonation under basic condition. Intramolecular nucleophilic addition to the iminium affords the final product.

In summary, we have developed a photo-promoted N-heterocyclic carbene catalyzed intramolecular cross dehydrogenative coupling of tetrahydroisoquinoline-tethered aldehydes. The corresponding oxidative cyclization products were obtained in moderate to good yields. This reaction features mild conditions using molecular oxygen as the terminal oxidant without photocatalyst. Based on the control experiments, an excited Breslow intermediate is proposed for the photooxidation process. Detailed mechanism investigation and further application of this NHC-catalyzed photooxidation are underway in our laboratory.

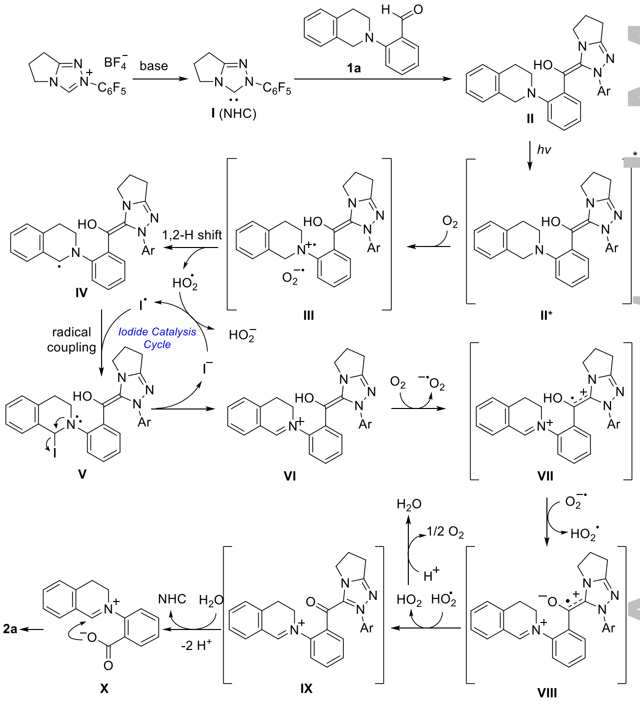


Figure 2. Plausible mechanism.

Experimental Section

To a 25 mL Schlenk tube equipped with a rubber septum and a magnetic stir bar was charged with tetrahydroisoquinoline derivative **1a** (47.4 mg, 0.2 mmol), preNHC **A** (14.5 mg, 0.04 mmol), DABCO (26.9 mg, 0.24

mmol), and NaI (3.0 mg, 0.02 mmol). The tube was evacuated and backfilled with O_2 (balloon) and was added CH_3CN (2.0 mL) with a syringe. The mixture was then irradiated by 18 W blue LEDs. After 12-48 h, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (200−300 mesh) to afford the desired product **2a**.

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