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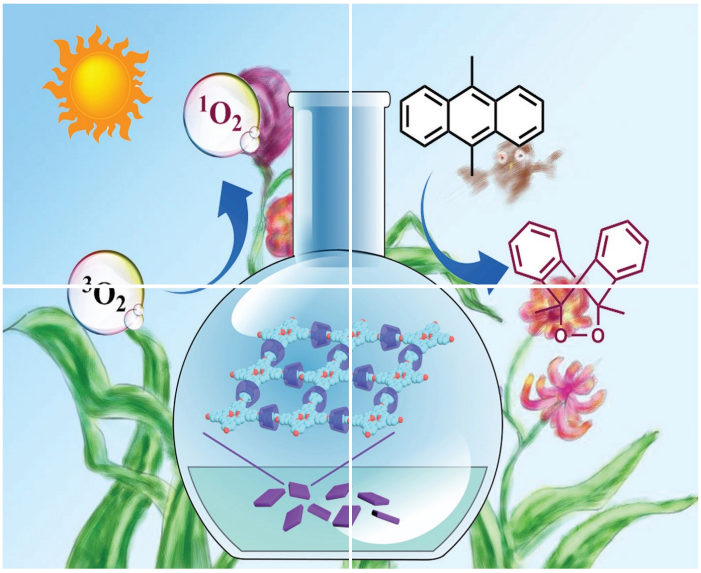

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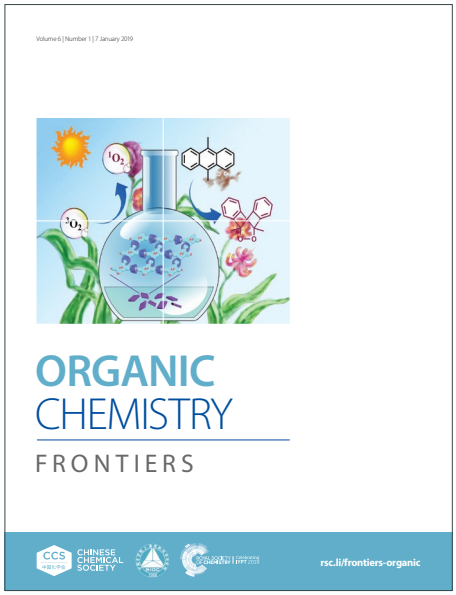

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DOI: 10.1039/D5QO01032B

ARTICLE

Cooperative N-Heterocyclic Carbene/Photocatalysis: Visible-light promoted tandem α-sp³ C–H activation and reductive *N*-alkylation of Tetrahydroisoquinolines

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

DOI: 10.1039/x0xx00000x

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While N-heterocyclic carbenes (NHCs) have played a vital role as organocatalysts due to their Umpolung reactivity toward carbonyl or imine carbons, activation of sp³-carbons via single-electron transfer (SET) processes remains challenging and under-developed. Recently, coupling of NHC catalysis with photocatalysis for SET process have gained attention. Herein, we report visible-light and NHC-catalyzed tandem α-sp³ C–H activation and reductive *N*-alkylation of tetrahydroisoquinoline (THIQ) with *o*-hydroxybenzaldehdes. The key step in this process is the formation of a photoactive species between *o*-hydroxybenzaldehydes and a base, which functions as a self-photocatalyst, eliminating the need for an external photocatalyst or photoactivator. Subsequent reaction of photoactive species with NHC leads to Breslow intermediate followed by intramolecular hydrogen atom transfer (HAT) and benzylic activation to form of *N*-benzylated 3,4-dihydroisoquinolin-1(2*H*)-ones. The salient features of this work include the use of sunlight as the visible-light source and molecular oxygen as the oxidant under mild reaction conditions, highlighting the green chemistry aspects of this approach.

Introduction

N-heterocyclic carbenes, frequently employed as ligands for transition metals, are superior to their phosphine and imine counterparts due to their unique electronic properties, steric requirements and their susceptibility to oxidation, making them front-runners in transition-metal catalysis.[1,2] In 1943, Ukai et.al demonstrated that coenzyme thiamine (Vitamin B1) can be employed as the catalyst for benzoin reaction.[3] Later, Breslow elucidated the mechanism, which pave the way for the origin of NHC as organocatalyst.[4] The applicability of NHC as an organocatalyst can be attributed to their Umpolung reactivity towards the electrophilic carbonyl or imine carbons to generate several reactive intermediates like Breslow intermediate, aza-Breslow intermediate, acylazolium, enolate, homoenolate etc. via two-electron reaction pathway.[5-9] However, electrophiles containing sp³-carbons are difficult to be activated via NHC catalysis. The first report on an NHC-catalyzed single-electron transfer (SET) pathway was reported in 2001, featuring the crystal structure of the free radical intermediate.[10] Since then, only a few reports have explored NHC-catalyzed SET pathways using various single-electron oxidants[11-17] or reductants,[18,19] making this approach rather limited. To enhance the effectiveness of NHC catalysis beyond single-catalyst systems, many research groups have successfully combined NHCs with other catalytic systems with ease, thus adding another dimension to its applicability via cooperative catalysis.[20-27]

Likewise, there has been a remarkable interest in visible-light-promoted photochemical transformations as they offer an environmentally benign alternative energy source and align with the green chemistry principles.[28-33] A noteworthy aspect of visible-light-mediated processes is their ability to generate highly reactive radical intermediates under mild and environmentally benign reaction conditions. Sunlight offers a sustainable alternative to thermal activation, being an abundant, non-hazardous energy source with zero carbon emissions, thus aligning well with the principles of green chemistry. Additionally, employing atmospheric oxygen as the oxidant minimizes the need for toxic peroxide-based oxidants and reduces by-product formation, thereby improving reaction rates and selectivity.[34] In recent years, there are few reports on synthetic strategies under neutral and oxidative conditions using cooperative NHC/light catalysis. The first report on NHC/light cooperative catalysis appeared in 2012 when DiRocco and Rovis reported a chiral NHC/Ru (III) dual catalytic system for the asymmetric acylation of *N*-aryl tetrahydroisoquinolines (THIQs) using *m*-dinitrobenzene as the oxidant.[35] Subsequently, numerous organic transformations utilizing NHC-visible-light cooperative catalysis have been reported, employing either metal-based[36-44] or metal-free[45-51] photocatalysts. Recent developments have shown that NHC-catalyzed photochemical reactions can be performed without the need for an external photocatalyst or photoactivator. In these cases, intermediates/complexes obtained from the interaction

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Supplementary Information available: The data supporting this article have been included as part of the Supplementary Information.Crystallographic data for **3h** has been deposited at the CCDC under 2430429 and can be obtained from [URL of data record, format https://www.ccdc.cam.ac.uk/data_request/cif]

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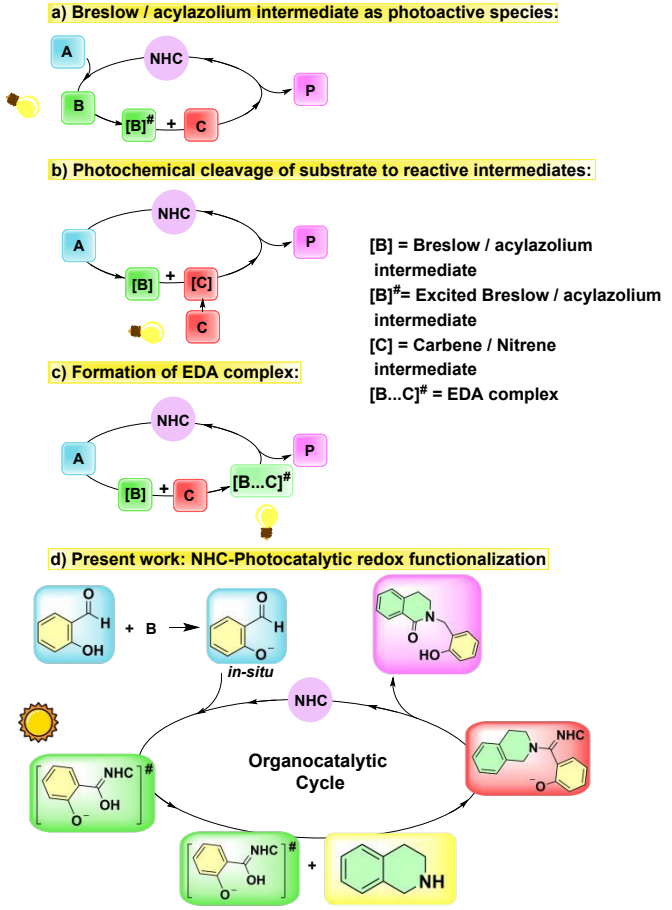
between the NHC and a suitable substrate can absorb light, generating photo-excited species that undergo subsequent reactions with other substrates to produce the desired product. This strategy introduces a novel activation mode for NHC organocatalysis, allowing them to generate short-lived intermediates from intrinsically photo-inactive substrates.[52,53]

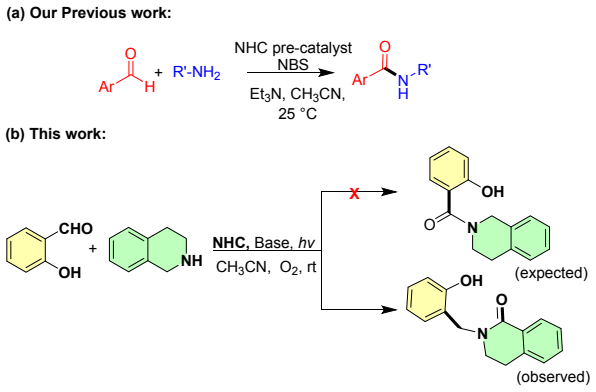
The possible pathways for photo-NHC catalysis performed in the absence of photocatalysts are shown in Scheme 1. In first case, Breslow/acylazolium intermediates formed between the NHC and the reactant absorbs light and was converted to their excited state and reacts subsequently with another reagent via SET pathway to form the desired products (Scheme 1a).[54-57] Light was employed to generate nitrene/carbene intermediates from the corresponding diazo compounds which on reaction with NHC to form enolate/Breslow intermediate followed by reaction with suitable substrates to generate the desired products (Scheme 1b).[58-60] Photo-NHC-catalysis can also proceed via the formation of Electron donor-Acceptor (EDA) complex which absorbs light facilitating the reaction (Scheme 1c).[61,62]



Scheme 1 Possible pathways of photo-NHC catalysis.

In this context, we envision that NHC-catalysis can be coupled with visible-light for activation of benzylic sp^3 C–H bond under environmentally benign conditions in the absence of photocatalysts or photosensitizers based on our expertise in oxidative NHC catalysis[63-67] and visible-light-mediated synthesis of biologically significant compounds.[68] We envisage that a simultaneous α-sp^3 C–H activation and reductive *N*-alkylation of THIQ with aldehydes can be achieved via Photo/NHC catalysis under visible-light and molecular oxygen as the oxidant.

Our research was driven by the hypothesis that simultaneous α-sp^3 C–H activation and reductive *N*-alkylation of tetrahydroisoquinoline (THIQ) could be achieved under aerobic photo/NHC catalytic conditions.



Scheme 2 Origin of the proposed hypothesis.

This idea stemmed from our previous work on the amidation of primary amines using NHC catalysis with NBS as oxidant (Scheme 2a).[63] Encouraged by these findings, we aimed to extend the methodology into the photochemical domain, focusing on the amidation of THIQ under visible light and aerobic conditions, thereby contributing to the advancement of NHC-catalyzed transformations (Scheme 2b).

Results and discussion

To validate our proposed hypothesis for the tandem α-sp^3 C–H activation and reductive *N*-alkylation of THIQ with aldehyde under photo/NHC-catalysis, *o*-hydroxybenzaldehyde (**1a**) and THIQ **2a** were taken as the model substrates and the results were tabulated as Table 1. After extensive optimisation of the reaction parameters (See Supporting Information), we identified the use of NHC-**A** (20 mol%) as the catalyst and Et_3N (1.1 equiv.) as the base in CH_3CN under sunlight and open atmosphere as the optimal conditions, yielding the desired *N*-benzylated 3,4-dihydroisoquinolin-1(2*H*)-one **3a** in 76% isolated yield (entry 1). The expected product can be obtained with other NHC catalysts, albeit with diminished yields (entries 2–6 and Supporting Information). Other organic bases also proved effective for this reaction, but the yields were comparatively lower than those achieved with Et_3N and a similar trend was observed with inorganic bases as well (entries 7–11 and Supporting Information). When *tert*-butyl hydroperoxide (TBHP) was used as the oxidant instead of oxygen, only 30% of the desired product **3a** was formed, with 3,4-dihydroisoquinolin-1(2*H*)-one **8** emerging as the major product (entry 12). When the reaction was conducted in the absence of light as well as under N_2 atmosphere, it failed completely (entries 13, 14 and Supporting Information). A similar

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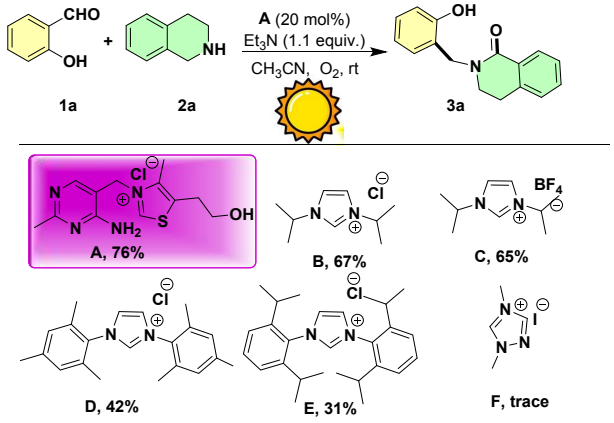
observation was made in the absence of either NHC or base as the catalyst (entries 15, 16). These control experiments revealed that light, O_2, and NHC are essential for the desired α-sp³ C–H activation and reductive *N*-benzylation of THIQ. Finally, instead of light as the source of energy, when the reaction was performed under thermal heating, only 59% of the desired product was observed (entry 17). In thermal dark condition, the product formation was not observed which indicates that the light is essential for the formation of product (entry 18).

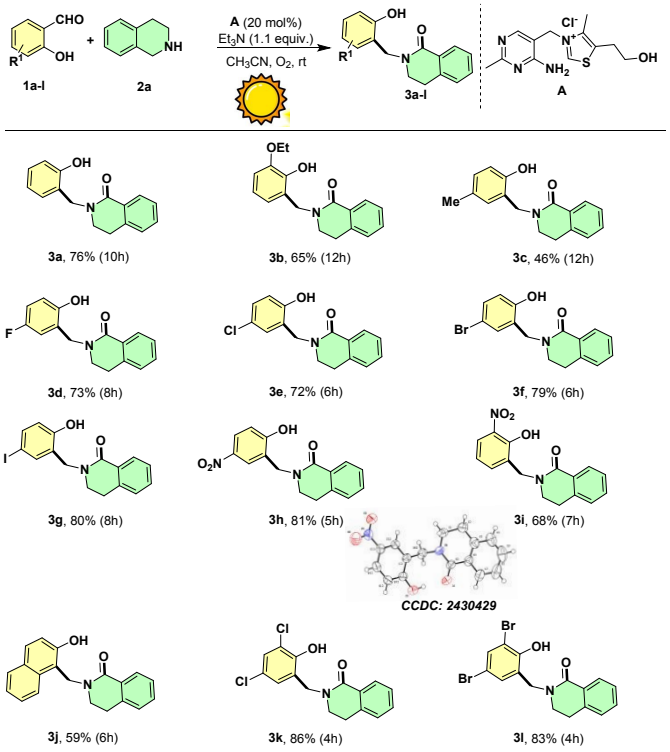
Table 1 Optimization of the Reaction Conditions[a]



Entry	Variation from standard conditions	Yield of 3a (%)
1	None	76
2	**B** instead of **A**	67
3	**C** instead of **A**	65
4	**D** instead of **A**	42
5	**E** instead of **A**	31
6	**F** instead of **A**	trace
7	Cs_2CO_3 as base	34
8	K_2CO_3 as base	-
9	*t*-BuOK as base	62
10	DBU as base	31
11	DIPEA as base	70
12	TBHP instead of air	30[b]
13	No light	ND[c]
14	N_2 instead of O_2	ND[d]
15	No NHC	ND
16	No Et_3N	ND
17	80 °C instead of light	59
18	80 °C instead of light (In dark)	-

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (2.0 equiv.), NHC-precatalyst (20 mol %), base (1.1 equiv.) at rt in CH_3CN (2.0 mL) under irradiation with sunlight in open air for 4 h. [b]3,4-Dihydroisoquinolin-1(2*H*)-one **8** was formed along with the product. [c]In the dark. [d]Under N_2 atmosphere by degassing air.

With optimized conditions in hand, we then set out to investigate the scope of the visible-light and NHC-catalysed redox reaction by varying structurally different *o*-hydroxybenzaldehydes (Scheme 3). The key step in this reaction is the *in situ* formation of a photoactive species, generated through the interaction between *o*-hydroxybenzaldehyde and the base, which is crucial for light absorption and subsequent transformations. Thus, the reaction failed with simple aldehydes without *o*-hydroxy substituent or with other *o*-substituted benzaldehydes (See Supporting Information) and works well with substituted *o*-hydroxybenzaldehdes as the substrates.

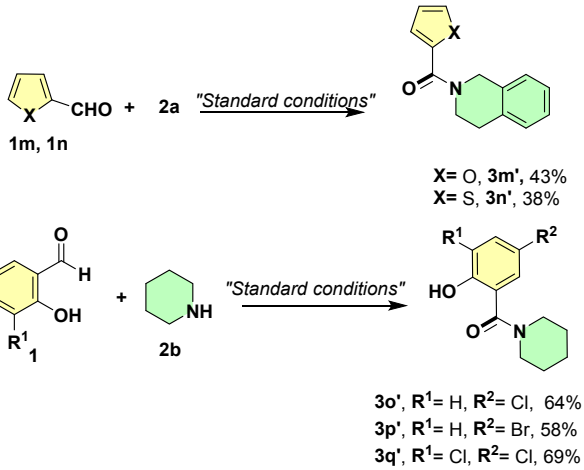


Scheme 3 Substrate scope for the tandem α-sp³ C–H activation and reductive *N*-alkylation of THIQ. Reaction conditions: **1a-l** (1.0 equiv.), **2** (2.0 equiv.), NHC-precatalyst **A** (20 mol%), and Et_3N (1.1 equiv.) at rt in 2.0 mL of CH_3CN under sunlight, open air.

Irrespective of the electronic nature and position of the substituent, the desired products were obtained in moderate to good yields. When 3-ethoxy-2-hydroxybenzaldehyde was used as the substrate, the desired product **3b** was obtained in a moderate yield of 65%, whereas with 5-methyl-2-hydroxybenzaldehyde only 46% of the corresponding product **3c** was obtained. Notably, 5-fluoro, chloro-, bromo-, and iodo-substituted *o*-hydroxybenzaldehydes were successfully converted into the desired products **3d**–**3g** with yields ranging from 72% to 80%. Additionally, 5-nitro-2-hydroxybenzaldehyde was converted into the expected product **3h** with an excellent yield of 81%. In similar lines, with 3-nitro-2-hydroxybenzaldehyde, the yield of the corresponding product **3i** is slightly lowered. 1-Hydroxy-2-naphthaldehyde could be coupled with THIQ to give the expected product **3j** in 59% yield. Moreover, the reaction was compatible with highly functionalized 3,5-dichloro- and 3,5-dibromo-2-hydroxybenzaldehydes affording the products in 86% and 83% respectively (**3k**, **3l**).

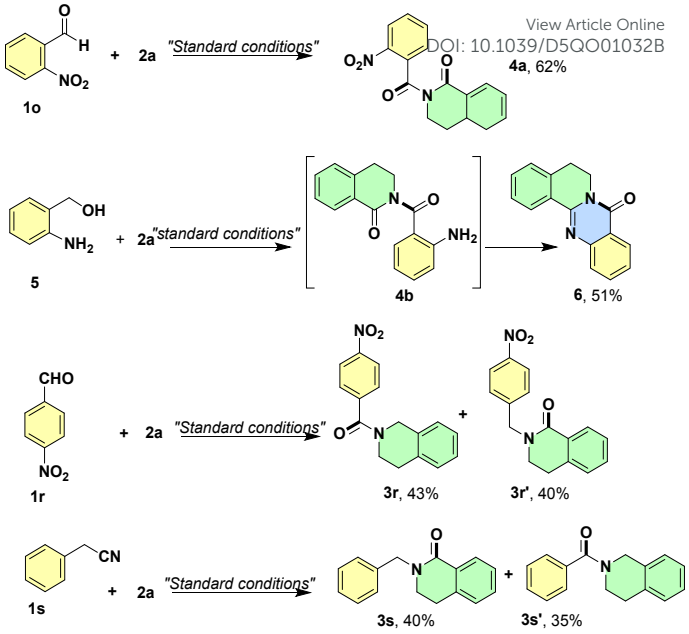
Apart from 2-hydroxybenzaldehydes, when the reaction was performed with other visible light-absorbing aldehydes, the reaction proceeded to give different products (Scheme 4). For instance, when the reaction was carried out with furan-2-carboaldehyde (**1m**) and thiophene-2-carbaldehyde (**1n**), instead of the expected redox product, the corresponding *N*-

aroylated product **3m'** and **3n'** were obtained in 43% and 38% respectively. Instead of THIQ, when piperidine was taken as secondary amine, we observed the amidation product **3o'**-**3q'**in moderate to good yield. In case of 2-nitrobenzaldehyde (**1o**), instead of the expected redox product, the corresponding dual oxidised, α-sp^3 C–H activated, *N*-benzoylated product of THIQ **4a** was obtained in good yield. When THIQ (**2a**) was reacted with 2-aminobenzylalcohol **5**, 5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one **6** was obtained as the product. This suggested that the reaction proceeds via the *α*-sp^3 C–H activation of THIQ and subsequent intramolecular cyclization to afford the observed product. When 4-nitrobenzaldehyde (**1p**) was used as the coupling partner, the expected redox product (**3r**) was observed along with the *N*-benzoylated product of THIQ (**3r**').

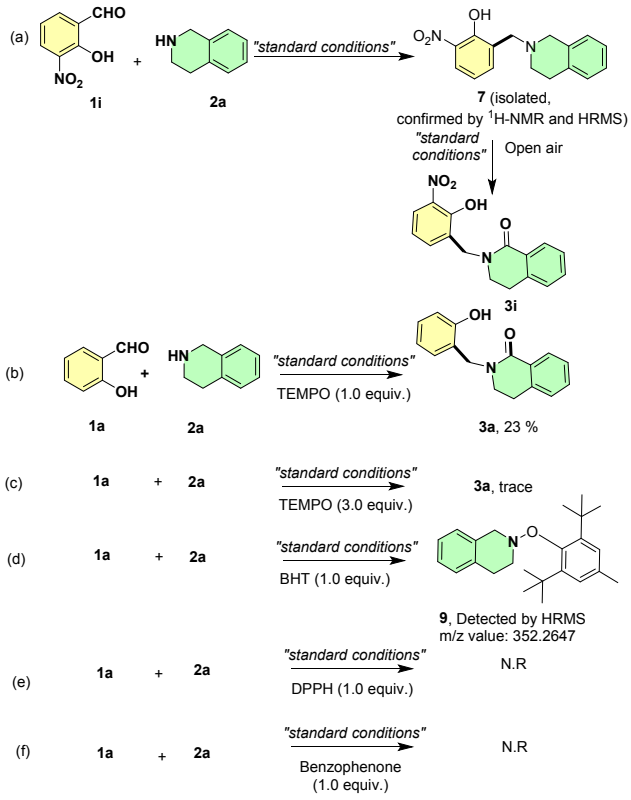


Scheme 4 Substrate scope of amidation Standard conditions: **1**, (1.0 equiv.), **2** (2.0 equiv.), NHC-precatalyst **A** (20 mol %), and Et_3N (1.1 equiv.) at rt in 2.0 mL of CH_3CN under sunlight, open air.

Likewise, when 2-phenylacetonitrile (**1q**) was used as the alkyl source, a similar outcome was observed, yielding both the redox product (**3s**) and the *N*-benzoylated product of THIQ (**3s'**) in nearly equal ratios (Scheme 5). In order to gain insight into the mechanism of this reaction, we have carried out several experiments as shown in Scheme 6. When THIQ **2a** was reacted with 2-hydroxy-3-nitrobenzaldehyde **1i** under standard reaction conditions, the intermediate 2-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-6-nitrophenol **7** was obtained which was isolated and confirmed by ^{1}H-NMR and HRMS along with the expected product **3i** (Scheme 6a). The isolated intermediate **7** when prolonged under the standard reaction conditions in the presence of atmospheric O_2, was converted to the expected product **3i**. The radical mechanism can be ascertained by performing the reaction employing radical quenching reagents under the standard reaction conditions. When 1.0 equiv. of TEMPO was added to the reaction, a significant drop in the product yield was observed (Scheme 6b) and with 3.0 equiv. of TEMPO, the reaction failed completely, indicating that the reaction proceeds via a radical pathway (Scheme 6c). This observation was further substantiated by the reaction with 1.0 equiv. of BHT, where the reaction failed to deliver the product



Scheme 5 Substrate scope of other alkylating agents Standard conditions: **1o-q**, 5 (1.0 equiv.), **2a** (2.0 equiv.), NHC-precatalyst **A** (20 mol %), and Et_3N (1.1 equiv.) at rt in 2.0 mL of CH_3CN under sunlight, open air.



Scheme 6 Control Experiments. Standard conditions: **1** (1.0 equiv.), **2** (2.0 equiv.), NHC-precatalyst **A** (20 mol %), and Et_3N (1.1 equiv.) at rt in 2.0 mL of CH_3CN under sunlight, open air.

miserably, BHT-adduct **9** (See Supporting Information) was detected by ESI-HRMS (Scheme 6d). The radical quenching behavior for this photo-NHC redox process was studied by

carrying out the reaction in presence of **2a** with 2-diphenyl-1-picrylhydrazyl (DPPH) as the radical scavenger. When Breslow intermediate was added to this, the absorption wavelength (λ_{max} = 518 nm) corresponding to the DPPH showed a hypochromic shift, which indicates **I** is responsible for radical initiation due to photoexcitation (Scheme 6e and Fig. 1). Further, when the reaction was monitored in the presence of triplet state quencher, benzophenone, the reaction doesn't proceed as expected under this condition (Scheme 6f).[36,47]

To identify the origin of fluorescence in our reaction, we combined different reactants and observed their fluorescence behaviour (See Supporting Information). Among various combinations, we found that treating *o*-hydroxybenzaldehyde with Et_3N resulted in fluorescent solution and we combined various substituted *o*-hydroxybenzaldehydes with Et_3N and recorded their emission spectra (See Supporting Information). Of these, 3,5-dichloro-2-hydroxybenzaldehyse (**1k**) shows greater intensity, making it the suitable compound for further photochemical studies. If the reaction carried out in the absence of Breslow intermediate, the significant excitation followed by quenching was not observed which indicates the formed Breslow intermediate is the photoactive species and get excited (Fig. 2).

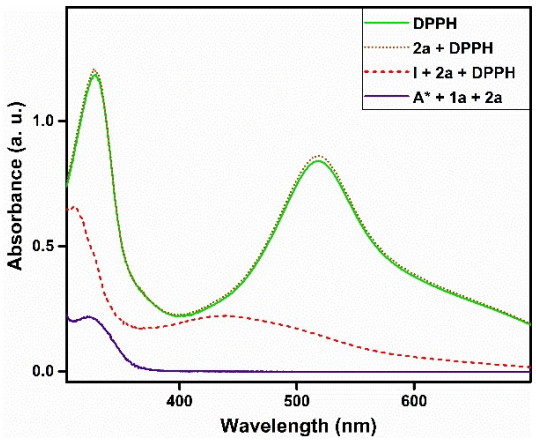


Fig. 1 Radical quenching experiment: absorbance spectra were recorded in CH_3CN as the solvent at 1 x 10^{-6} M solutions: DPPH (green lined), **2a** with DPPH (orange dotted), Breslow intermediate **I**, **2a** with DPPH (red dashed), **A*** (NHC), **1a**, **2a** (purple lined).

Then luminescence quenching experiments were examined in different time intervals (Fig. 3). Initially, on adding **1k** with Et_3N, the emission intensity increases followed by the addition of NHC (0-15 min). From this we have concluded that a photoactive species was formed when **1k** reacts with Et_3N and further addition of NHC resulted in Breslow intermediate that can absorb light and gets converted into excited Breslow intermediate. Upon adding THIQ to the reaction mixture, we observed significant quenching which was further supported by the excitation studies (see supporting information). When **2a** was added to the Breslow intermediate, significant change in the absorption and excitation spectra was observed. This may be attributed to the excited state complex formation which could be either radical cation/anion or electron donor-acceptor pairs.

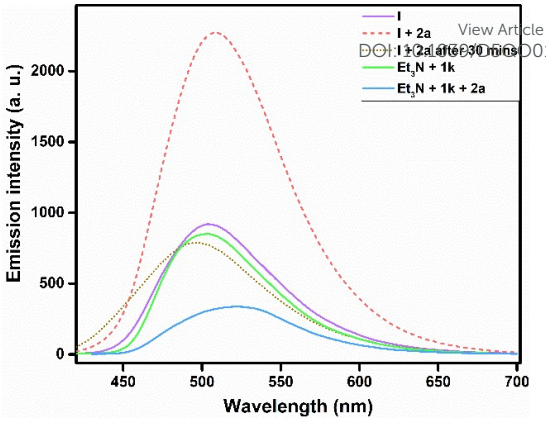


Fig. 2 Emission spectra of reactant **1k** under standard condition in 1 x 10^{-3} M: Determination of photoactive species.

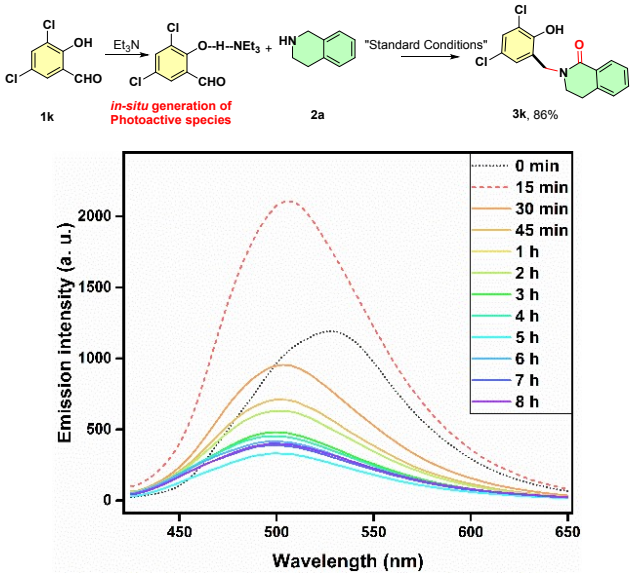
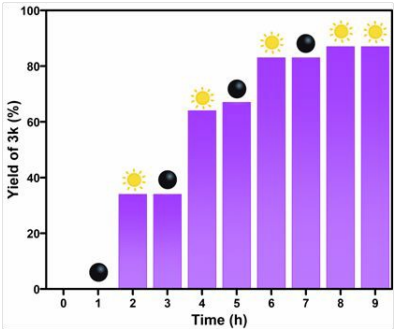


Fig. 3 Emission spectra of reactant **1k** under standard condition in 1 x 10^{-3} M over a time interval of 0 min-8h. For first 1 h the time interval the spectra were recorder for every 15 mins followed by the time interval of 1 h.

The light on-off experiments indicated that the reaction proceeded via a catalytic radical mechanism rather than a radical chain pathway (Fig. 4).[54]



On-Off	
Time	Yield of 3k (%)
1	0
2	34
3	34
4	64
5	66
6	83
7	83
8	87
9	87

Fig. 4 Light on-off experiment under standard conditions: dark circle represents reaction carried out in dark, sun represents the reaction carried out in sunlight in the time interval of 1 h.

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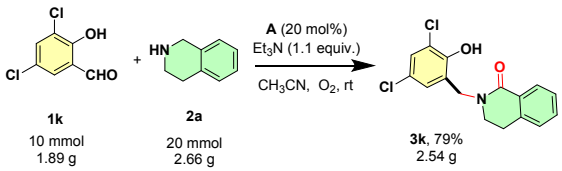


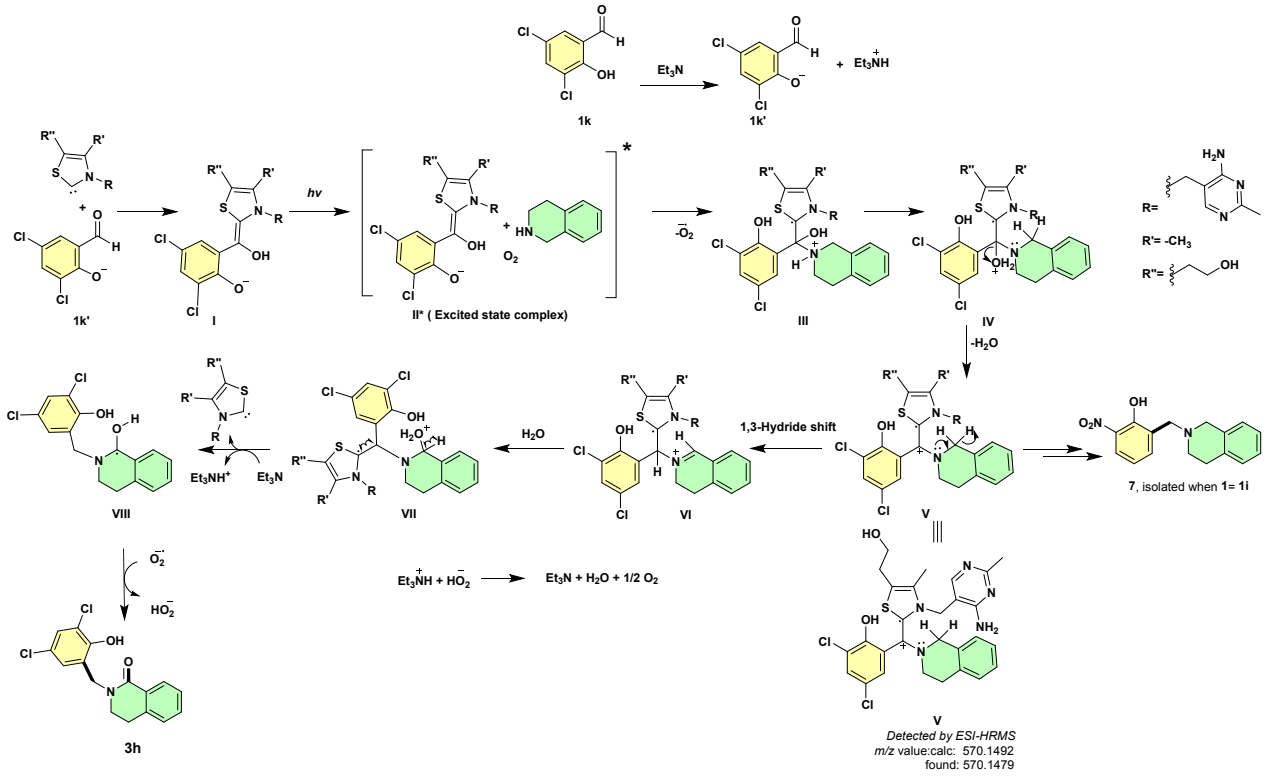
Scheme 7. Gram scale synthesis.

Atom economy (%)	AEf (%)	*E*-factor	PMI	RME (%)
83.03	71.38	4.09	5.09	60.6

Table 2 Green Chemistry metrics calculation, Atom Economy (%), Atom Efficiency (AEf) (%), *E*-factor, Process Mass Intensity (PMI), Reaction Mass Efficiency (RME) (%) for **3k.**

The adaptability of the present strategy for the synthesis of *N*-benzylated 3,4-dihydroisoquinolin-1(2*H*)-ones has been investigated using the optimized product on a gram scale. The reaction of 3,5-dichloro-2-hydroxybenzaldehydes **1k** and THIQ **2** under optimized condition gave the desired product **3k** in a good yield of 79% (Scheme 7). In order to establish the environment-friendliness of the present redox-process, various green chemistry metrics were calculated as Table 2 and they show notably high values, with AE, AEf, *E*-factor, RME and PMI for **3k**.[69]

Based on the control experiments and fluorescence studies, we have confirmed the *in situ* formation of photoactive species and have proposed a plausible mechanism for this dual NHC/photocatalysis activation of THIQ (Scheme 8). Initially, *o*-hydroxybenzaldehyde (**1a**) reacts with the base, generating **1a'** which exhibit fluorescence.[70] Base generate free carbene from the NHC precatalyst and aiding in the formation of the Breslow photoactive species **I**. THIQ (**2a**) reacts with Breslow intermediate (**I**) in the presence of molecular oxygen to form a excited state complex **II***,[71] which subsequently generates the intermediate **III**.[72,73] Proton transfers from the nitrogen of the THIQ moiety to the benzylic oxygen leads to intermediate **IV** which on dehydration generates intermediate **V** (confirmed by ESI-HRMS and isolation of compound **7**). An intramolecular 1,3 hydride shift gives **VI** and further nucleophilic addition of water molecule forms intermediate **VII**.[74] Intramolecular hydrogen atom transfer (HAT) and the removal of proton in the presence of base leads to form intermediate **VIII** with the regeneration of NHC.[75] Finally removal of hydrogen radical by the superoxide radical anion[73] leads to the final product **3**.



Scheme 8 Plausible mechanistic pathway for the tandem α-sp^3 C–H activation and reductive *N*-alkylation of THIQ.

Conclusions

In summary, a visible-light and NHC-catalyzed tandem *α*-sp^3 C–H activation and reductive *N*-alkylation of THIQ with *o*-hydroxybenzaldehydes has been demonstrated at room temperature for the first time. The reaction follows a dual intramolecular hydrogen atom transfer mechanism coupled with benzylic oxidation, with molecular oxygen acting as the oxidant. Mechanistic and fluorescence quenching experiments suggest that an *in situ* formation of photoactive species between *o*-hydroxybenzaldehyde and Et$_3$N, which serves as the self-photocatalyst, thus eliminating the need for external photo-catalyst or photo-activator. The emission intensity of the photoactive species **1'** correlates directly with the efficiency of the NHC/visible-light photocatalyzed process. We expect this

DOI: 10.1039/D5QO01032B

tandem NHC/visible-light photocatalysis strategy to pave the way for a plethora of NHC- and visible-light-catalyzed carbon–heteroatom bond formation processes. Further mechanistic aspects for this tandem α-sp^3 C–H activation and reductive *N*-alkylation will be explored in due course.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

"There are no conflicts to declare".

Data availability

The data supporting this article have been included as part of the ESI.

Acknowledgements

C. U. M. acknowledges financial support from Anusandhan National Research Foundation (ANRF), New Delhi, India, for the award of a core research grant: CRG/2021/006424 and DST-FIST (SR/FST/CS-I/2018/62) for NMR analysis. This work was also supported by Council of Scientific and Industrial Research (CSIR-ASPIRE): 01WS(032)/2023-24/EMR-II/ASPIRE and SASTRA in house research funding: SASTRA-TRR-SCBT.

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View Article Online
DOI: 10.1039/D5QO01032B

The data supporting this article have been included as part of the Supplementary Information.

Crystallographic data for **3h** has been deposited at the CCDC under 2430429 and can be obtained from [URL of data record, format https://www.ccdc.cam.ac.uk/data_request/cif]

Expert in the field of NHC Catalysis