Dual N-heterocyclic carbene/photocatalysis: a new strategy for radical processes

Qiang Liu and Xiang-Yu Chen

While N-heterocyclic carbenes (NHCs) have played an important role as Lewis-base organocatalysts and developed recently into a full chapter of this exciting area of organocatalysis, NHC-catalyzed single-electron-transfer (SET) processes are still challenging and underdeveloped. Recently, NHC catalysis has been successfully combined with photoredox catalysis for SET reactions and this turned out to be a promising strategy. This article focuses on the recent advances of the combination of photoredox catalysis with NHC catalysis.

At present, there are two types of reaction modes associated with dual NHC/photocatalysis. One is the combination of classical NHC-intermediates and the generated radicals via photocatalysis. The other is the use of a new kind of NHC-derived radical intermediate via photocatalysis (Scheme 1C).

Recently, Ye and co-workers have made important contributions to dual NHC/photocatalysis by using reaction mode a. They successfully realized the \( \gamma \)- and \( \epsilon \)-alkylation of enals via dual NHC/photocatalysis, offering direct access to \( \gamma \) - and \( \epsilon \)-alkylated esters \( 3 \) in very good yields.\(^7\) Notably, the challenging vicinal all-carbon quaternary centers could be efficiently constructed by using this strategy (Scheme 2A). The key step of this transformation was the formation of an alkyl radical via photocatalysis and a dienolate/trienolate intermediate via NHC catalysis.

To investigate the mechanism of this alkylation reaction, several control experiments, such as radical trapping and radical clock experiments, were carried out. The plausible mechanism is proposed in Scheme 2B. The alkyl radical \( 7 \) is generated via photocatalysis from alkyl halide while the dienolate intermediate \( 4 \) is generated from enal \( 1 \) via NHC catalysis. The alkyl radical \( 7 \) reacts with the dienolate intermediate \( 4 \) to afford the homoenoate radical \( 5 \), which undergoes single-electron transfer (SET) oxidation with the radical cation of the photocatalyst to give \( \alpha,\beta \)-unsaturated acyl azolium intermediate \( 6 \). Lastly, the acyl azolium intermediate \( 6 \) is trapped by methanol to afford the corresponding product \( 3 \) and liberate the NHC catalyst.

Subsequently, the same group further expanded this strategy to the ring-opening and \( \gamma \)-alkylation of cyclopropane enal (Scheme 2C).\(^8\) This method provided an efficient access to \( \gamma \)-alkylated \( \alpha,\beta \)-unsaturated esters \( 9 \). A series of alcohols and brominated compounds \( 2 \) reacted smoothly to deliver the target products \( 9 \) in 52–95% yields. Unfortunately, other enals, such as epoxy enals and several other cyclopropane enals, failed to couple with brominated compounds.
proposed that the dienolate intermediate could be generated from \( \gamma \)-cyclopropane enal through NHC-catalyzed C–C bond cleavage, which was in agreement with Zhao’s pathway.\(^9\) The following similar steps to those in Scheme 2B afforded the product 9 and closed the catalytic cycle.

Apart from the above-mentioned contributions, Ye and co-workers also developed the oxidative Smiles rearrangement reaction via dual NHC/photocatalysis (Scheme 2D).\(^{10}\) Here, O-aryl salicylaldehydes were transformed into aryl salicylates in the presence of oxygen as the oxidant. This study revealed that the oxidation of the Breslow intermediate was achieved by oxygen with acridinium and NaI as the (co)catalysts and offered a new methodology for oxidative NHC catalysis. Later, this strategy was successfully extended to the intramolecular cross-dehydrogenative coupling of tetrahydroisoquinoline-tethered aldehydes (Scheme 2E).\(^{11}\) Notably, this photoinduced oxidative reaction worked well without an external photocatalyst and an excited Breslow intermediate facilitated the photooxidation course.

Simultaneously, Hopkinson and co-workers developed a novel protocol for the Diels–Alder reaction of acid fluorides with trifluoromethyl ketones via reaction mode b (Scheme 3A).\(^{12}\) In their system, 1,3-dimethylimidazolium triflate C as the precatalyst and \( \text{Cs}_2\text{CO}_3 \) as the base were
employed under the irradiation of UVA LEDs. A range of acid fluorides 14 and trifluoromethyl ketones 15 were investigated to verify the wide substrate scope tolerance. Unfortunately, other classes of nonenolizable ketones, such as 2-ketoesters and isatins, didn’t work under the current conditions. To gain insight into the reaction mechanism, stoichiometric studies and time-dependent DFT calculations were conducted to support the mechanistic scenario where the combination of the NHC and the acid fluoride led to an interim change in the absorption properties and photochemical reactivity of the carbonyl function. The proposed mechanism is shown in Scheme 3B; the in situ generated NHC reacts with acid fluoride 14a to deliver the o-toluoyl azolium intermediate 17 and releases $F^-$. This azolium intermediate 17 can be excited under UVA irradiation and provides the triplet excited state intermediate 18 after intersystem crossing. Rapid 1,5-H abstraction from the o-benzylic position to the radical-like carbonyl oxygen produces the triplet dienol biradical 19. Rotation of this biradical before relaxation results in the ground state 20, which reacts with the trifluoromethyl ketone 15a in a $\text{[4 + 2]}$ cycloaddition process to afford the cycloadduct 21. Finally, elimination of the NHC in the presence of the base gives the desired product 16a and completes the catalytic cycle.

Most recently, another elegant example of combining photocatalysis with NHC catalysis has been demonstrated by Scheidt and co-workers.13 They developed a novel NHC/photo co-catalyzed alkylation reaction between acyl imidazoles 22 and Hantzsch esters 23 for the efficient synthesis of ketones 24 (Scheme 4A). This method enabled the coupling of an acyl radical with an alkyl radical by using the triazolium salt D as the precatalyst and iridium photocatalyst. To further demonstrate the utility of this method, various pharmaceutical carboxylic acid drugs, such as telmisartan, repaglinide and dehydrocholic acid, were applied for the one-step direct alkylation reaction to afford the corresponding ketone products in moderate to good yields. A series of control reactions and radical-trapping experiments were performed, which indicated that the oxidation of the Hantzsch ester occurred prior to the reduction of the acyl azolium. The proposed reaction pathway is shown in Scheme 4B. The Hantzsch ester 23a is oxidized to generate the radical cation 25 using the photoexcited catalyst (Ir$^{\text{III}^*}$); then cleavage of the radical cation 25 provides the benzyl radical. The following reduction of the acyl triazolium intermediate 26 via Ir$^{\text{II}}$ gives the crucial azolium radical 27. The final coupling of the benzyl radical and the radical inter-

![Scheme 3](image_url)  
**Scheme 3** NHC/photo co-catalyzed Diels–Alder reaction of acid fluorides with trifluoromethyl ketones via reaction mode b.

![Scheme 4](image_url)  
**Scheme 4** NHC/photo co-catalyzed alkylation of acyl imidazoles with Hantzsch esters via reaction mode b.
mediate 28 affords the desired ketone 24c and liberates the NHC catalyst.

In summary, as demonstrated by the examples discussed, dual NHC/photocatalysis will lead to the development of a wide range of novel transformations with broad synthetic applications. This methodology has shown its potential advantage of introducing radicals into NHC catalysis. Although the NHC/photo co-catalyzed reaction is now at the stage of infancy, these studies have impressively illustrated that combining photocatalysis and NHC catalysis is a prospective strategy. In future research, several challenges need to be addressed; a wide range of NHC derived intermediates—especially homoenolate equivalents and α,β-unsaturated acyl azolium intermediates—should be investigated, and compared with well-developed NHC-catalyzed asymmetric reactions, the development of enantioselective approaches is still needed.

Conflicts of interest
There are no conflicts to declare.

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Notes and references


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