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.

In the past decades, N-heterocyclic carbenes (NHCs) have witnessed remarkable achievements, and they are complementary to other organocatalysts and enable the creation of new activation modes that were previously unobtainable. A driving force is the great variety of reactive intermediates that can be generated with NHCs (Scheme 1A). Despite this progress, most of these transformations proceed via electron-pair-transfer pathways; the corresponding reactions via single-electron-transfer (SET) processes remain challenging.

In recent years, cooperative catalysis with NHCs has remarkably improved the reaction efficiency and selectivity that are unobtainable by using single-catalyst systems (Scheme 1B). Interestingly, cooperative NHC/Lewis acid catalysis has strongly dominated this field, with comparatively less synergistic combination of NHC catalysis with other types of catalysis reported in the literature. Recently, there has been growing interest in harnessing the synergistic interplay of NHCs and photochemistry to develop new activation modes that provide more efficient and selective alternatives to classical approaches. An early example of dual NHC/photocatalysis was reported by Rovis and co-workers. In their system, the photocatalyst Ru(bpy)_3Cl_2 and NHC were employed for the α-acylation of tertiary amines. In 2016, an NHC/photo co-catalyzed γ-dichloromethylation of enal was reported by Sun and co-workers. Although these examples have shown the synthetic utility of dual NHC/photocatalysis, further development of this strategy to create new activation modes is still highly desirable. This manuscript aims to provide a brief summary of light-driven NHC-catalyzed reactions and highlight recent publications in this area.

School of Chemical Sciences, University of the Chinese Academy of Sciences, Beijing 100049, China. E-mail: chen.xiangyu@rwth-aachen.de
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 tetrahydroisoquinolinel-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 Cs\(_2\)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 \textit{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 \((4 + 2)\) 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. 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 (\(Ir^{III*}\)); then cleavage of the radical cation \(25\) provides the benzyl radical. The following reduction of the acyl triazolium intermediate \(26\) via \(Ir^{II}\) gives the crucial azolium radical \(27\). The final coupling of the benzyl radical and the radical inter-
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 homoeonolate 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


