

Light-Promoted Organocatalysis with N-Heterocyclic Carbenes

Andreas Mavroskoufis,^[a] Michael Jakob,^[a] and Matthew N. Hopkinson^{*[a]}

The combination of N-heterocyclic carbene (NHC)-organocatalysis with photochemical activation can lead to unprecedented reaction pathways not observed without light. A selection of dual catalytic systems merging NHCs with photoredox catalysis, for example, have leveraged the ability of NHCs to stabilize intermediate radical species and facilitate single electron transfer events. Furthermore, NHCs can transiently modulate the

photochemical properties of a substrate and enable direct absorption of otherwise photoinactive organic compounds. In this Concept article, the recent advances in this rapidly developing field are summarized. For each transformation, a particular focus is placed on the mechanistic aspects of the process while key features that highlight the synthetic potential of the light mediated NHC organocatalysis are presented.

1. Introduction

The discovery of N-heterocyclic carbenes (NHCs) ranks among the most significant advances of recent years. Nowadays, NHCs rival phosphines as ligands in organometallic chemistry, and continue to find widespread use in many other areas of inorganic chemistry and materials science.^[1] Many NHC classes including triazolylidenes, thiazolylidenes and imidazolylidenes have also emerged as powerful organocatalysts capable of mediating synthetically important and, in many cases, enantioselective organic transformations. While most of the initial breakthroughs focused on umpolung reactions of aldehydes, other reactivity modes have since been developed and the scope of products accessible through NHC organocatalysis continues to rise year on year.^[2] Despite these great advances, however, most reactions remain closely related to classical aldol-like processes. The key Breslow intermediate formed in NHC-catalyzed reactions of aldehydes is essentially an enamine derivative and exhibits reactivity consistent with a conventional nucleophile. Similarly, acyl azolium species and the corresponding enolates generated with substrates at the carboxylic acid oxidation level typically react in the same fashion as their classical analogs.


The recent studies exploring radical reactivity in NHC organocatalysis are therefore especially intriguing. As also demonstrated in the inorganic and biochemical literature,^[3] NHCs are excellent stabilizers of radical species and in the last few years, an increasing number of NHC-catalyzed organic transformations involving open-shell intermediates

have been developed.^[4,5] These processes have revealed new mechanistic possibilities for NHC organocatalysis that have the potential to dramatically expand the scope of available transformations.

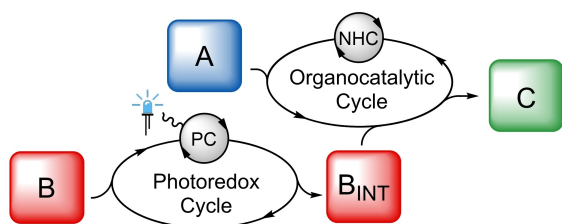
While most of the radical reactions have been conducted under thermal conditions, some reports have combined NHC organocatalysis with photochemical activation (Scheme 1).^[6] For example, dual catalytic processes with additional ruthenium or iridium-based photocatalysts have been developed that benefit from the mild and controlled generation of radical species inherent to visible light photoredox catalysis.^[7,8] Some cases involve the NHC and photoredox catalysis cycles separately activating two different substrates, which are then coupled together *in situ* ("Decoupled NHC/photoredox catalysis", Scheme 1, Path a). In a selection of recent examples, however, the two cycles are more intimately combined with the NHC-containing intermediates engaging in single electron transfer (SET) steps with the photocatalyst. These "cooperative NHC/photoredox" processes leverage the ability of NHCs to stabilize radical intermediates and modulate the reduction potentials of the organic substrates (Scheme 1, Path b). Furthermore, very recent reports have demonstrated that NHC-catalyzed photochemical transformations can be conducted without an additional photocatalyst. In these "photo-NHC"-catalyzed processes, the interaction between the NHC organocatalyst and the substrate leads to an intermediate species or complex that is itself capable of absorbing light (Scheme 1, Path c). This possibility opens up another new reactivity mode for NHC organocatalysts as transient modulators of the absorption and excited state characteristics of otherwise photoinactive substrates.^[9]

In this article, we provide a concise overview of NHC organocatalysis involving photochemical activation highlighting the key conceptual advances and their synthetic potential. The material is categorised according to the proposed reaction mechanism focussing on how light activation and the NHC-catalytic cycle are combined. In each section, pioneering studies illustrating the distinct

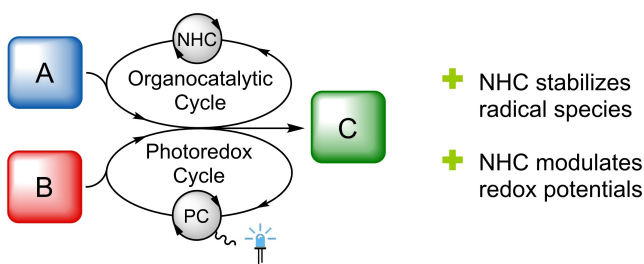
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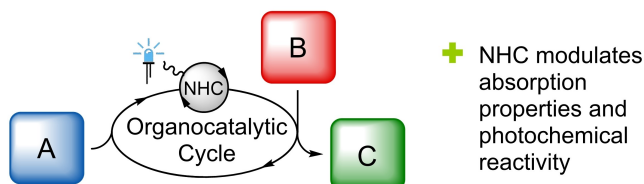
a) Decoupled NHC/Photoredox Catalysis



b) Cooperative NHC/Photoredox Catalysis



c) Photo-NHC Catalysis



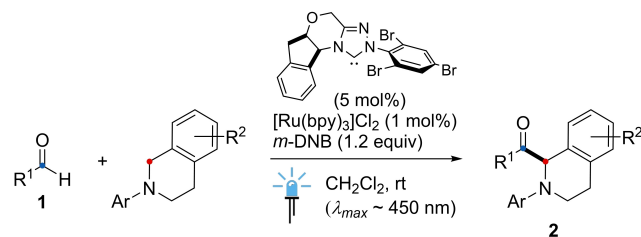
Scheme 1. General mechanistic pathways combining NHC organocatalysis and light activation. Path a) Decoupled NHC/photoredox catalysis. Path b) Cooperative NHC/photoredox catalysis. Path c) Photo-NHC catalysis.

catalytic pathway is discussed while key features highlighting the synthetic potential of light mediated NHC organocatalysis are discussed.

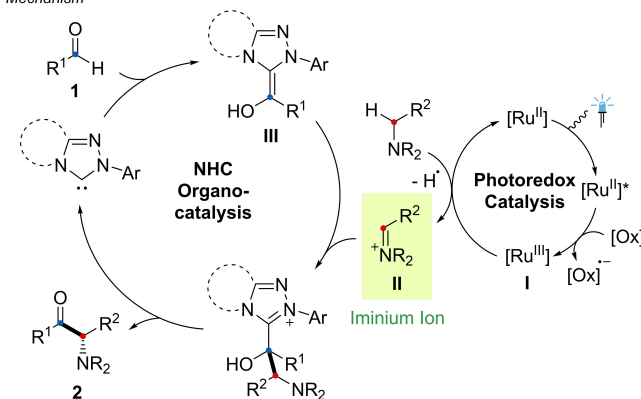
2. Decoupled NHC/Photoredox Catalysis

The first publication combining NHC organocatalysis and photocatalysis was presented by DiRocco and Rovis in 2012.^[10] Interested in the photogeneration and trapping of iminium species, they envisioned a method for the catalytic oxidative asymmetric α -acylation of tertiary amines using the Breslow intermediate as a catalytically generated nucleophile (Scheme 2).

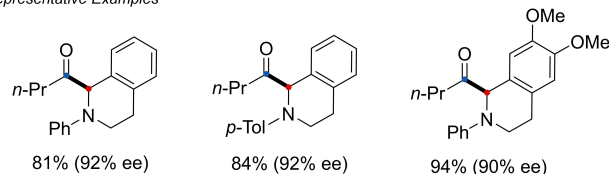
Inspired by the well-documented ability of ruthenium(II) pyridyl complexes to act as catalysts for photooxidation reactions,^[7] a dual catalytic system was developed employing $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ ($\text{bpy} = 2,2'$ -bipyridine) and a triazolium salt as a chiral NHC pre-catalyst. Irradiation of $[\text{Ru}(\text{bpy})_3]^{2+}$ with blue light ($\lambda_{\text{max}} \sim 450 \text{ nm}$) in the presence of a suitable oxidative quencher affords the Ru(III) species ($[\text{Ru}(\text{bpy})_3]^{3+}$, I, $E_{1/2}^{\text{III/II}} = +1.29 \text{ V vs. SCE}$), which is known to initiate single electron oxidation of tertiary amines. Hydrogen atom abstraction leads to an iminium ion II, which is a potent electrophile that reacts with the Breslow intermediate III



Mechanism



Representative Examples



Scheme 2. Dual-catalyzed NHC/photoredox asymmetric α -acylation of tetrahydroisoquinolines by DiRocco and Rovis.^[10]

generated upon activation of an aliphatic aldehyde substrate 1 by the triazolylidene NHC. Finally, elimination releases the desired α -aminoketone product 2 and regenerates the organocatalyst.

This study represented a significant advance for NHC organocatalysis and confirmed its compatibility with photoredox catalysis for the first time. The successful combination of the two catalysis modes was not a foregone conclusion as NHCs and several catalytic intermediates containing them are sensitive to oxidative conditions. The choice of 1,3-dinitrobenzene (m -DNB) as a mild oxidant proved critical in this regard with the more oxidising species BrCCl_3 leading instead to catalyst poisoning. Optimization studies revealed, however, that sub-stoichiometric amounts of m -DNB could be employed with adventitious O_2 in the reaction mixture serving as the terminal oxidant. Several features of this first report highlight the potential of light mediated NHC organocatalysis in organic synthesis. Using just 10 mol% of the NHC pre-catalyst and 1 mol% of the photocatalyst, an array of important α -aminoketone products 2 could be obtained in high yields directly from readily available aliphatic aldehydes and tetrahydroisoquinolines. The dual catalysis strategy thus builds on the synthetically appealing umpolung reactivity of NHC organocatalysts and benefits from the mild and sustainable reaction conditions

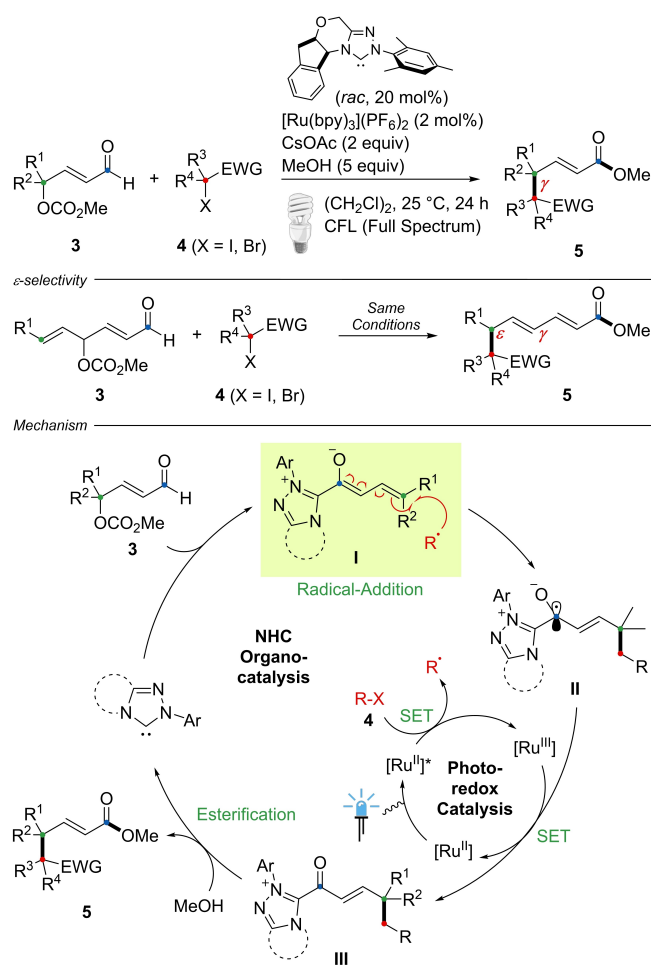
available with photoredox catalysis. Moreover, the presence of the chiral NHC during the key stereodetermining step in the mechanism allows for high levels of enantioinduction with products **2** being delivered in ee's up to 92%. Asymmetric induction is notoriously challenging in photochemical transformations due to the high reactivity of excited state or radical species. New strategies that allow for efficient enantioinduction in photochemistry are therefore highly sought.

3. Cooperative NHC/Photoredox Catalysis

While the first report by DiRocco and Rovis elegantly demonstrates the compatibility of NHC organocatalysis and photocatalysis, each cycle operates essentially in isolation. Photoredox oxidation of an amine affords an active electrophile, which subsequently participates in a conventional NHC-catalyzed reaction. By contrast, in a selection of recent studies, photoredox and NHC catalysis operate in a more cooperative fashion with NHC-containing catalytic intermediates themselves undergoing single electron oxidation or reduction.

For example, the groups of Sun^[11] and Ye^[12] reported dual catalytic reactions where the activation of a conjugated enal substrate by the NHC catalyst provides an excellent acceptor for photogenerated radicals. In Ye's report, an oxidative quenching cycle with a selection of electron-deficient alkyl halides **4** delivers organic radicals (Scheme 3).^[12] Concurrently, addition of the NHC to the aldehyde function of the enal **3** followed by elimination of the γ -carbonate leaving group affords an extended acyl azolium enolate intermediate **I**. The terminal double bond in this species is both more sterically accessible than the internal alkene in enal **3** and electronically better matched to the photogenerated electrophilic alkyl radical. Moreover, radical addition leads to an NHC-containing radical species **II** that is highly stabilized by a range of mesomeric and captodative effects. The ability of azolium moieties to stabilize open-shell species has been extensively documented and a range of "bottleable" NHC-containing inorganic and organic radicals have been synthesized and isolated.^[3,4d-f] Delocalisation into the azolium itself is thought to play a major part in this stabilization and, in recent years, open shell species have been considered as reaction intermediates for a range of non-photochemical NHC-catalyzed transformations.^[4,5] The photo- and organocatalytic cycles intertwine directly in the next step of the reaction with single electron oxidation regenerating the ground state $[\text{Ru}(\text{bpy})_3]^{2+}$ photocatalyst and affording an acyl azolium species **III**. Addition/elimination with methanol then releases the product **5** and regenerates the NHC organocatalyst.

Using this strategy, Ye and co-workers were able to prepare a wide range of γ - and ϵ -alkylated esters **5** in mostly moderate to high yields between 27% and 98%. The method benefits from the mild conditions, operational



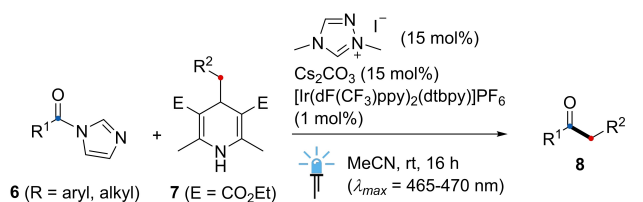
Scheme 3. Dual-catalyzed NHC/photoredox γ - and ϵ -alkylation of enals by Ye and co-workers.^[12]

simplicity and high functional group tolerance typical of visible light photoredox catalysis and employs the widely available racemic Rovis triazolylidene NHC. Challenging vicinal all-carbon quaternary centers could be efficiently constructed while exclusive ϵ -regioselectivity was obtained with extended enal substrates featuring a δ,ϵ -double bond. This remarkable regioselectivity is likely influenced by the steric bulk of the Rovis NHC with alkyl radical attack being directed to the least hindered end of the extended π -system. The large distance between the azolium fragment and the newly generated C–C bonds at the γ - or ϵ -position, however, means that only low levels of enantioinduction (ee < 29%) were obtained using an enantiopure NHC.

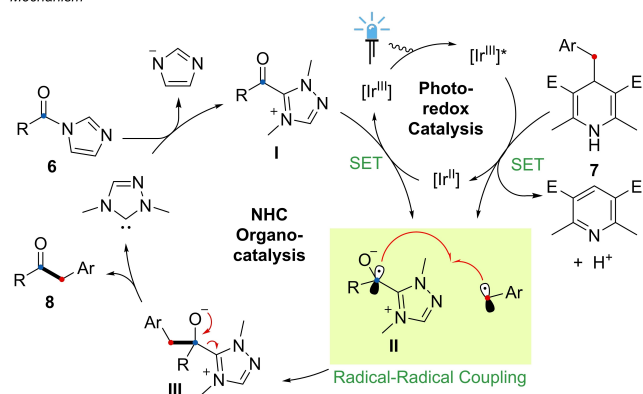
Recently, the Scheidt group presented a novel carboacylation method employing a cooperative NHC/photoredox catalysis approach.^[13] In this process, activation of the benzoyl imidazole substrate **6** by the NHC does not provide a more active alkene species for a radical addition step but instead enables direct single electron reduction of the carbonyl group by the photocatalyst. Benzyl radicals are first generated upon reductive quenching of a blue light-

excited Ir(III) photocatalyst by a Hantzsch ester derivative (7, Scheme 4). Addition of the NHC to the carbonyl group of substrate 6 followed by elimination of imidazole meanwhile affords an acyl azolium salt I. The cationic triazolium fragment in this species serves as a strongly electron withdrawing group that considerably reduces the reduction potential and allows for single electron reduction by the reduced photocatalyst. Furthermore, the resulting radical II is likely stabilized through delocalization of the spin density into the azolium fragment. The new C–C bond is then formed in a subsequent radical-radical coupling step that exploits the persistent radical effect^[14] with elimination of the NHC from species III providing the final ketone product 8.

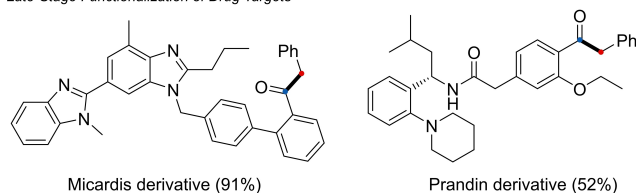
The above mechanism was supported by radical trapping experiments with TEMPO while cyclic voltammetry of acyl triazolium species I and substrate 7a confirmed the expected role of the NHC in lowering the reduction potential of the carbonyl group. A scope investigation employing a variety of substituted aromatic and aliphatic acyl imidazoles, and mostly benzyl Hantzsch esters, allowed for the preparation of a wide range of ketones 8 in generally moderate to good yields up to 80%. As for the other methods employing photoredox catalysis, this reaction benefits from mild reaction conditions and thus



Mechanism



Late-Stage Functionalization of Drug Targets



Scheme 4. Dual-catalyzed NHC/photoredox radical alkylation of acyl imidazoles by Scheidt and co-workers.^[13] (dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine).

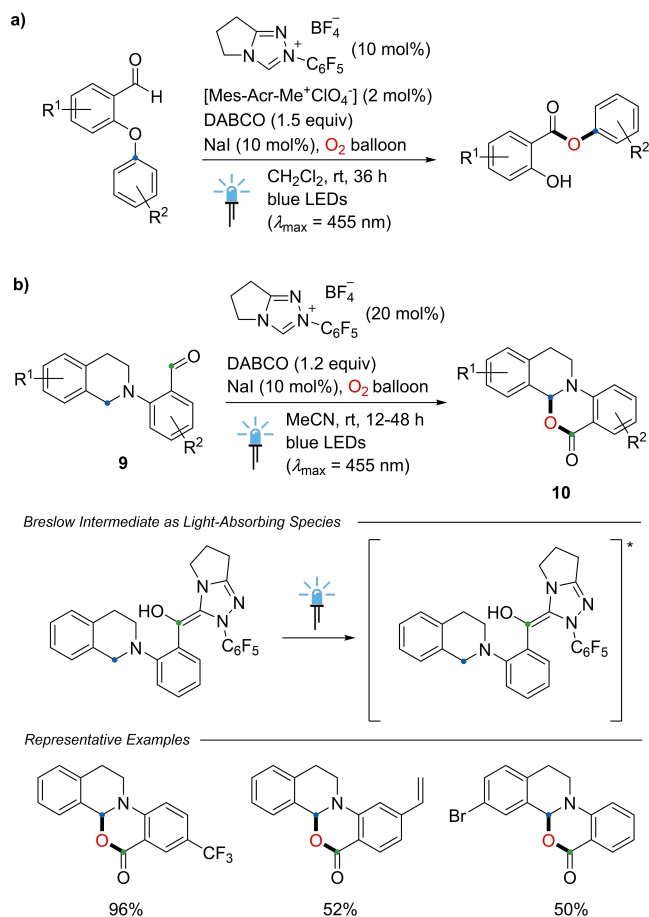
exhibits a wide functional group tolerance. This attractive feature was nicely demonstrated by the late stage functionalization of three pharmaceutically relevant compounds. Furthermore, a first attempt was made towards the development of an enantioselective process using a chiral Rovis-type NHC although only a low enantiomeric ratio of 66:34 was obtained.

4. Photo-NHC Catalysis

The Miyabe^[15] and Ye^[16,17] groups have combined NHC organocatalysis with photooxidation of aldehydes. These reactions exploit the typical umpolung reactivity of NHCs, where addition of the catalyst to the electron-deficient substrate and proton transfer provides an electron-rich enamine-like Breslow intermediate. Rather than engaging as a nucleophile, under appropriate oxidative conditions, this species can undergo two single electron oxidation steps affording, after addition/elimination, the corresponding carboxylic acid or ester. In an initial report by Ye and co-workers incorporating a subsequent Smiles rearrangement of a salicylic acid derivative, a dual NHC/photoredox catalysis system was employed using the organic dye 9-mesityl-10-methylacridinium perchlorate (Mes–Acr–Me⁺, Scheme 5a).^[16] While this reaction employs a cooperative NHC/photoredox strategy similar to those discussed in the previous section, in a very recent study, photooxidation of an aldehyde substrate was achieved without an additional photocatalyst.^[17] Instead, the authors proposed a mechanism in which the Breslow intermediate derived from the tetrahydroisoquinoline-tethered aldehyde substrate 9 itself acts as the key photoactive species, absorbing light and undergoing oxidative quenching with O₂ (Scheme 5b). Further single electron oxidations facilitated by an iodide co-catalyst, hydrolysis of the resulting acyl azolium species and cyclisation afford the final tetracyclic products 10. Although further studies are required to fully elucidate the nature of the light-absorbing species in this process, the potential enabling of single electron transfer events with NHC-containing intermediates upon direct light irradiation is an intriguing avenue for future research.^[18]

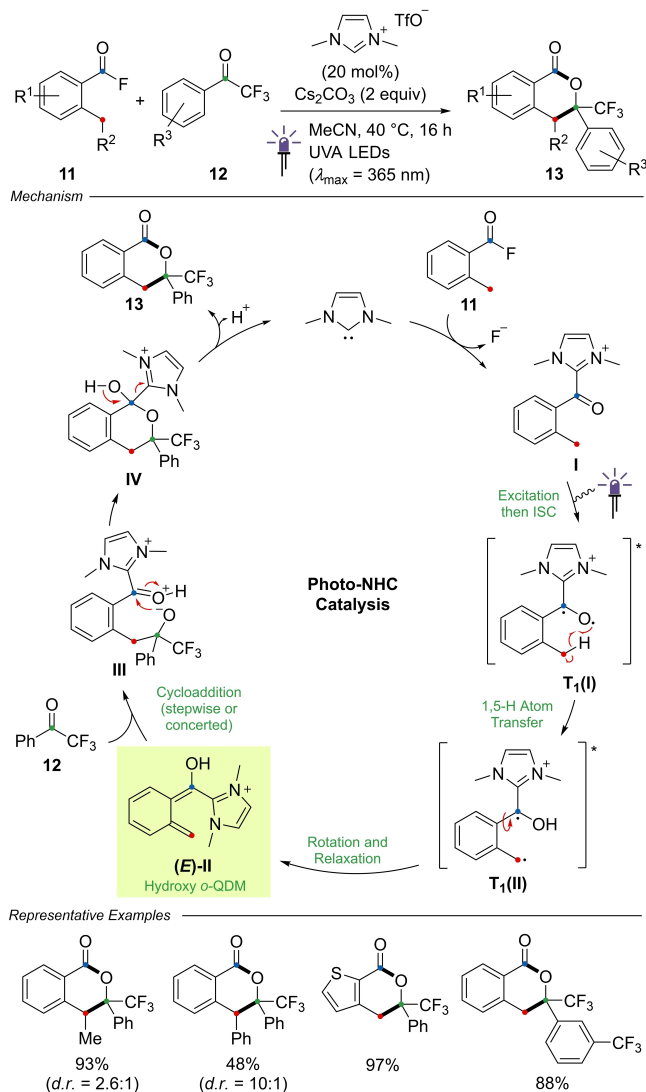
Our group has recently reported a conceptually different kind of NHC-catalyzed photochemical transformation involving the direct excitation of NHC-containing catalytic intermediates.^[19] Whereas the previously discussed approaches have exploited NHCs' ability to stabilize radical species and facilitate electron transfer steps, we instead considered whether NHCs could directly influence the photochemical properties of organic chromophores. Using this "photo-NHC" catalysis approach, otherwise inaccessible photochemical pathways could be accessed from new classes of substrate, expanding the scope of some classical photochemical transformations.

In a proof of concept study, we investigated an imidazolylidene-catalyzed photoenolization Diels-Alder (PEDA) reaction of acid fluorides 11 with trifluoroacetophe-



Scheme 5. a) Dual-catalyzed NHC/photooxidation/Smiles rearrangement.^[16]
 b) NHC-Catalyzed photooxidation/cyclization in the absence of a photocatalyst.^[17] DABCO = 1,4-diazabicyclo[2.2.2]octane.

ones **12** leading to isochromanone derivatives **13**. The proposed mechanism of this process is shown in Scheme 6. Upon deprotonation of the NHC pre-catalyst with Cs_2CO_3 , the imidazolylidene IMe (1,3-dimethylimidazolylidene) reacts with the acid fluoride **11**, releasing F^- and generating the *ortho*-toluoyl azolium intermediate **I**. This species is structurally similar to benzophenone derivatives and would be therefore expected to absorb light at longer wavelengths than the corresponding acid fluoride. Indeed, a comparison of their respective absorption spectra revealed a significant red shift upon addition of the NHC with absorption occurring in the near-UV region up to ca. 400 nm. Similarly, species **I** is expected, after inter-system-crossing, to populate a lowest energy triplet excited state $\text{T}_1(\text{I})$ comparable to that populated by benzophenone. Fast 1,5-hydrogen atom transfer (1,5-HAT) from the *ortho*-benzylic position to the radical-like carbonyl oxygen atom in $\text{T}_1(\text{I})$ gives rise to the triplet dienol biradical $\text{T}_1(\text{II})$. Such photoenolization steps are well established for aromatic ketones but are seldom observed with substrates at the carboxylic acid oxidation level.^[20,21] Rotation of $\text{T}_1(\text{II})$ before relaxation leads to the ground-state hydroxy *ortho*-quinodimethane (*o*-QDM) (**E-II**), which can react with the dienophile



Scheme 6. NHC-Catalyzed photoenolization/Diels-Alder (PEDA) reaction of acid fluorides with trifluoroacetophenones.^[19]

12 in a formal cycloaddition process, potentially in a two-step sequence involving intermediate **III**. Elimination of the NHC from cycloadduct **IV** in the presence of the base then releases the product **13** and completes the catalytic cycle.

Under the optimized reaction conditions using the simple imidazolylidene IMe, a wide range of substituted acid fluorides **11** and trifluoroacetophenone derivatives **12** could be successfully employed. While 3 equivalents of the acid fluoride were required to overcome undesired hydrolysis, in most cases good to excellent yields ranging up to 99% of the isochromanone products **13** were obtained. Control reactions without UVA light or the NHC all led to no product formation while stoichiometric studies on an independently synthesised *ortho*-toluoyl imidazolium intermediate **I** supported the intermediacy of this NHC-containing species in the catalytic reaction. Several interesting observations were also made while testing different NHC organocatalysts during the reaction optimization. An effi-

cient process was observed only for a selection of sterically unencumbered imidazolylidenes with commonly employed thiazolylidene and triazolylidene organocatalysts proving ineffective. These results suggest that different NHC structures could have different influences on photoreactivity and are worthy of further study. Finally, the key role of the NHC as a transient modulator of the absorption properties and photochemical reactivity of the carbonyl group was supported by TD-DFT calculations (CAM-B3LYP/6-311G**). Simulations on *ortho*-toluoyl azolium intermediate **1** mirrored the experimental results in showing that the key 1,5-HAT step is highly favoured from excited azolium T₁(I). By contrast, direct excitation of acid fluoride **12** was shown to proceed only at much shorter wavelengths with 1,5-HAT from the corresponding excited state being highly unfavoured.

5. Conclusion

While NHC organocatalysis has found widespread use over the last few decades, its combination with photochemical activation has only recently started to attract significant attention. In most cases, a dual catalysis approach employing photoredox catalysis has enabled unprecedented radical reaction pathways. These reactions are also practically attractive as they benefit from the mild and sustainable reaction conditions typical with visible light activation. Moreover, the presence of the NHC during a key stereo-inducing step can allow for enantioselective reactions, which are notoriously challenging under photochemical conditions. While the ability of NHC-fragments to stabilize intermediate radical species and modulate reduction potentials are key features in photoredox processes, NHC organocatalysts can also directly influence the photochemical properties of organic substrates. Such photocatalyst-free systems can allow hitherto unsuitable substrates to absorb light at synthetically practical wavelengths and engage in classical photochemical transformations. Given the youth of this field, the diversity of available NHCs and the ever-increasing understanding of their organocatalytic and photochemical reactivity, many more exciting developments should be expected in the coming years.

Acknowledgements

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 420535461 (gefördert durch die Deutsche Forschungsgemeinschaft (DFG) – Projektnummer 420535461) and the State of Berlin (Elsa Neumann Scholarship to M.J.).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: N-Heterocyclic carbenes · organocatalysis · photochemistry · photoredox catalysis · single electron transfer

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Manuscript received: May 27, 2020
Revised manuscript received: June 29, 2020
Accepted manuscript online: July 1, 2020
Version of record online: July 28, 2020