

Recent Advances in Organic Synthesis Using Light-Mediated N-Heterocyclic Carbene Catalysis

Leyre Marzo^{*,[a]}

The combination of photocatalysis with other ground state catalytic systems have attracted much attention recently due to the enormous synthetic potential offered by a dual activation mode. The use of *N*-heterocyclic carbene (NHC) as organocatalysts emerged as an important synthetic tool. Its ability to harness umpolung reactivity by the formation of the Breslow intermediate has been employed in the synthesis of thousands of biologically important compounds. However, the available coupling partners are relatively restricted, and its combination

with other catalytic systems might improve its synthetic versatility. Thus, merging photoredox and *N*-heterocyclic carbene (NHC) catalysis has emerged recently as a powerful strategy to develop new transformations and give access to a whole new branch of synthetic possibilities. This review compiles the NHC catalyzed methods mediated by light, either in the presence or absence of an external photocatalyst, that have been described so far, and aims to give an accurate overview of the potential of this activation mode.

1. Introduction

Catalysis has become an indispensable tool in organic synthesis. Indeed, an important amount of synthesized organic compounds has undergone at least one catalytic transformation to be obtained. Among the different types of catalysis, in the past decade, photocatalysis emerged as a powerful and ecofriendly alternative.^[1] It has allowed the development of highly applicable synthetic routes using visible light as the energy source to promote these transformations. In it, the photocatalyst converts the absorbed light into chemical energy by promoting chemical transformations into the organic compounds present in the media. The mild reaction conditions employed in the photocatalytic approaches have made possible its combination with other ground state catalytic systems achieving new dual activation modes that expanded enormously the synthetic opportunities.^[2] In particular, the combination of photocatalysis with *N*-heterocyclic carbenes (NHCs) has appeared recently as an interesting alternative. NHCs have become very popular structures as they are commonly employed as ligands in organometallic chemistry affording similar or better results than phosphines,^[3] in the synthesis of new materials,^[4] and also as organocatalysts.^[5] Notably, their use as organocatalysts has been extensively exploited for the synthesis of bioactive molecules among others. Its activation mode harnesses the

umpolung reactivity of aldehydes and some acid derivatives via the formation of the Breslow intermediate with a nucleophilic character, giving access in many cases to stereoselective processes. Fusing this unusual reactivity with visible light photocatalytic activation modes has provided a larger variety of coupling partners and therefore has expanded the scope of transformations that can be achieved.^[6] However, although the first example combining both catalytic systems was described more than eight years ago, its expansion to the date has not been as broad as one might have expected. In this review we aim to collect all the examples, stereoselective or not, that have been described so far to give a complete and updated overview of the field. The review will be divided in two main sections, the first one dedicated to NHC-photocatalyzed approaches, and the second one collecting light-mediated reactions that do not require the use of an external photocatalyst.

2. Dual Photoredox and NHC catalysis

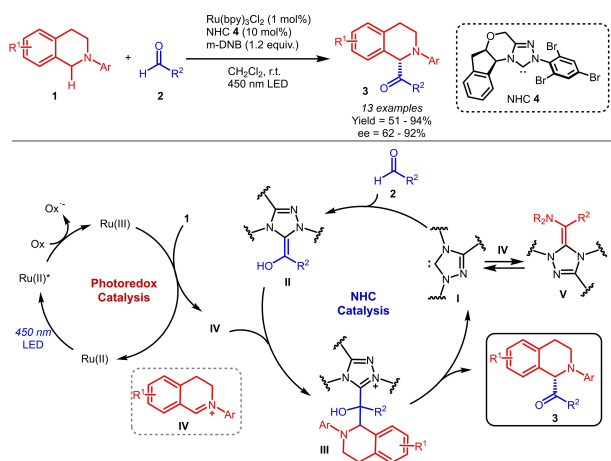
In 2012, Di Rocco and Rovis demonstrated for the first time the compatibility between photocatalysis and *N*-heterocyclic carbene catalysis. In this impressive pioneering strategy, they described an enantioselective direct α -acylation of amines by chiral NHC-activation of aldehydes and visible light-mediated photooxidation of tertiary amines (Scheme 1).^[7] With this transformation, a branch of biologically important scaffolds became accessible with H₂ as the only byproduct of the reaction. The proposed reaction mechanism consists of two non-cooperative catalytic cycles that activate each of the components. On one hand, photoexcited Ru(bpy)₃^{2+*} is oxidized by *meta*-dinitrobenzene (*m*-DNB)^[8] to Ru(bpy)₃³⁺, that presents higher oxidation power and consecutively oxidizes the tertiary amine **1** to form the corresponding iminium ion **IV**. On the other hand, the pre-generated NHC **I** condensate with the aldehyde **2** to form **II**, that reacts with the iminium ion **IV**, affording **III**, that evolves to the α -amino ketone **3** and regenerates **I**. A possible secondary

[a] Dr. L. Marzo
Organic Chemistry Department, Módulo 1
Universidad Autónoma de Madrid,
C/Francisco Tomás y Valiente, 7, Cantoblanco 28049 Madrid, Spain
E-mail: Leyre.marzo@uam.es
<https://leyremarzo.wordpress.com>

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Scheme 1. Enantioselective α -acylation of tertiary amines.

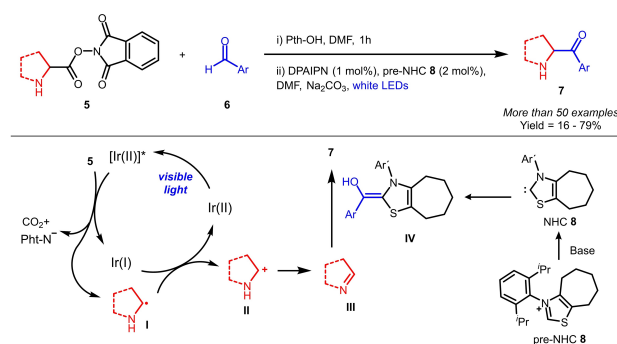
unproductive pathway might be the formation of the azabreslow intermediate **V**, but this process is reversible in the presence of a weak acid, re-entering the catalyst in the cycle. The reaction performs well with aliphatic aldehydes, although α -branched ones present a loss in the reactivity. On the tertiary amine side, while electron withdrawing substituents are well tolerated and provide excellent results, electron donating ones do not react, affording primarily the competing dimerization products that demonstrate the radical character of the reaction.

After this pioneering enantioselective example from Rovis, Miyabe described the oxidative functionalization of cinnamaldehyde derivatives through the photocatalytic oxidation of the Breslow intermediate.^[9]

Afterwards, and focusing on designing a mild and highly tolerant method that could be applied in biomolecular chemistry and engineering, Shi and Feng developed a racemic version for the α -amino acylation of amino acids.^[10] Ideally, medicinally compatible reactions should present a good functional group tolerance, be free of metal reagents and toxic additives and also have neutral pH at room temperature. The strategy developed by Shi and Feng meets those criteria while providing biologically valuable compounds. They have designed a new α -amino acylation reaction between the redox-active NIPH derived α -amino esters prepared *in situ*, and aldehydes improving the compatibility of the method with biologically or medicinally directed syntheses (Scheme 2).^[11]



L. Marzo received her PhD in Organic Chemistry in 2015 from the Universidad Autónoma de Madrid. Then, she became a postdoctoral Alexander von Humboldt fellow with Prof. B. König at the University of Regensburg. In 2018 she returned to the Universidad Autónoma de Madrid. Her research interest include the development of new photocatalytic reactions and the elucidation of the reaction mechanisms behind those transformations.

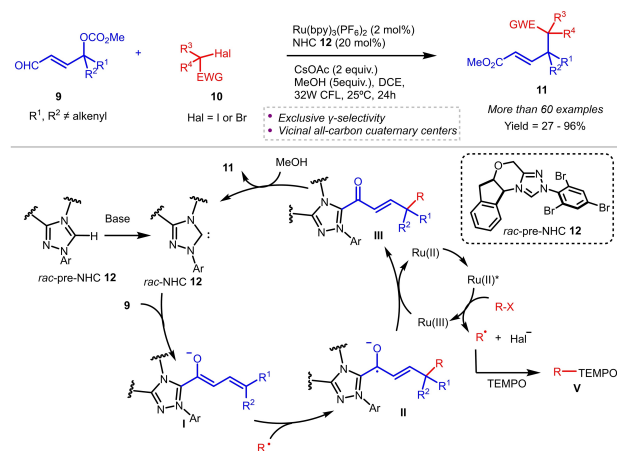


Scheme 2. α -Amino-acid modification merging photoredox and NHC catalysis.

Combination of visible light mediated photoredox and *N*-heterocyclic carbene catalysis permitted the derivatization of a large variety of α -amino acids, including natural products, and diverse keto-peptides could be prepared with this method.

Similarly, to the mechanism described by Rovis, on one hand, the aldehyde reacts with the NHC catalyst **8**, formed upon reaction of the pre-NHC **8** with the base (CsCO₃ or Na₂CO₃), forming the Breslow intermediate **IV**. On the other hand, Ir(III)* reduces **5**, affording the α -amino radical intermediate **I**, after releasing CO₂. Consecutive oxidation of the alkyl radical **I** by Ir(II), regenerates the photocatalytic cycle and affords **II**, that evolves to the iminium ion **III**. Final reaction between **III** and **IV** yields the final product **7**.

The tandem NHC/photocatalysis has given access to the synthesis of γ -alkylated esters employing alkyl radicals as demonstrated by Ye and Gao (Scheme 3),^[12] starting from γ -carbamate enals and alkyl halides. One of the main goals of this reaction is allowing the synthesis of all-carbon quaternary centers that are so challenging to construct. Additional insaturations (double or triple bond) in the enal do not modify the γ -regioselectivity, except when the oxidized enals bore vinyl substituents in the γ -position, in which case, ϵ -alkylated



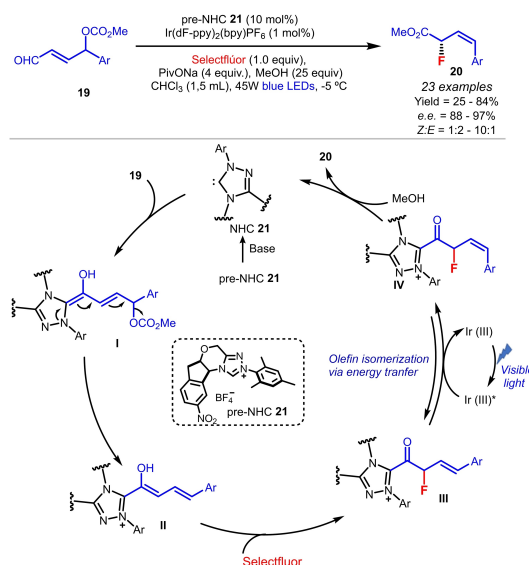
Scheme 3. γ -Alkylation of aldehydes mediated by photoredox and NHC catalysis.

products are delivered via a trienolate intermediate. Regarding the mechanism of the reaction, the formation of the transient alkyl radical was confirmed by observation of the radical coupling product of its reaction with TEMPO **V**. Thus, upon visible light irradiation, the photocatalyst reaches the excited state Ru(II)^* , from where it reduces the alkyl halide **10**, yielding the alkyl radical ($\text{R}\cdot$). This alkyl radical reacts with the dienolate intermediate **II**, generated from **I** and the enal **9**, to generate the radical intermediate **III**. **III** is finally oxidized by Ru(III) , closing the photocatalytic cycle, and affording intermediate **IV**, that upon reaction with MeOH, yields the final product **11**.

Following this line of research, Ye has demonstrated that this alkylation method can be expanded to other interesting systems. On one hand, the incorporation of difluoromethyl moiety into bioactive molecules is a robust strategy in drug discovery due to the importance of fluorinated compounds in pharmaceutical.^[13] Here, Ye has expanded the previous method for the introduction of γ -difluoroalkyl substituents (Scheme 4a).^[14] This approach has provided the first method to obtain γ -difluoroalkyl- α,β -unsaturated esters with the creation of an all-carbon quaternary center.

On the other hand, ring opening of cyclopropanes has been largely explored, but in many cases is limited to heteroatom nucleophiles or enolates.^[15] Taking advantage of the activation afforded by the NHC- α,β -unsaturated enal, Ye described the γ -alkylation after cyclopropane ring opening, with the photocatalytically generated Csp^3 alkyl radicals (Scheme 4b).^[16] The reaction performed well with different alkyl radicals **17**, and the presence of boronic esters, olefins or α,β -unsaturated esters were also well tolerated. Different attempts to expand the scope of the cyclic enal completely failed, but a large variety of alcohols could be employed to close the NHC-catalytic cycle.

Chiral allylic fluorides are useful synthons for radioactive probes for PET imaging, in pharmaceuticals or agrochemicals and also in material chemistry.^[17] In the literature, many examples allow the preparation of *E*-allylic fluorides,^[18] but the corresponding *Z*-isomer remained a challenge. Based on the ability of some photocatalyst to isomerize double bonds upon energy transfer from the excited state,^[19] Huang and Chen overviewed that employing a combination of *N*-heterocyclic carbene catalysis to carry out the fluorination step and a photocatalyst, *Z*-allylic fluorinated compounds could be obtained (Scheme 5).^[20] For this purpose, two issues needed to be

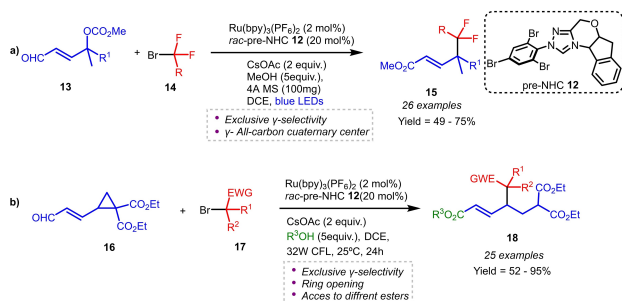


Scheme 5. Asymmetric α -fluorination/isomerization cascade.

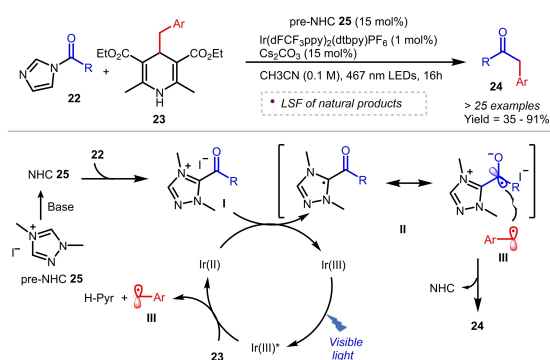
addressed: i) the photocatalyst could react not only as the photosensitizer, but also as a photoredox catalyst, promoting single electron transfer steps; ii) racemization of the final product due to the high acidity of the α -allyl- α -fluoro ester moiety and the basic conditions of the reaction. They could achieve the goal starting from the oxidized enals **19** and carrying out the reaction with a combination of $[\text{Ir(dFppy)}_2(\text{bpy})]\text{PF}_6$ and the NHC **21** in the presence of selectfluor. Under these conditions a variety of γ -aryl α -fluorinated enals could be successfully obtained, achieving better results with electron-deficient arenes than with electron-rich ones. However, in the presence of alkyl substituents in the γ -position, the reaction is completely suppressed.

Mechanistically, the enal **19** reacts with NHC **21** to form the dienolate **II** upon releasing of CO_2 and MeOH. **II** reacts with selectfluor leading to the γ -fluorinated intermediate **III**. This intermediate is now photosensitized by the $[\text{Ir(III)}]$ photocatalyst, and in the excited state isomerizes to the intermediate **IV**. To prove that the isomerization only takes place in intermediate **III**, the authors carried out the reaction in the absence of light and photocatalyst obtaining the *E*-**20**. In addition, they submitted this product to the initial photocatalytic conditions (light and $[\text{Ir(III)}]$ catalyst) and observed mainly decomposition products, discarding the possible isomerization of *E*-**20**. Therefore, both experiments were indicating that the isomerization step is taking place in the intermediate **III**. Finally, reaction between **IV** and MeOH affords *Z*-**20**, and regenerates the NHC-catalyst.

The combination of photoredox and NHC catalysis has allowed the oxidation of the Breslow intermediate that circumvents some of the previous limitations such as the use of stoichiometric toxic oxidants.^[21] Scheidt and coworkers reported the synthesis of ketones instead of esters,^[22] via the coupling of alkyl radicals with acyl radicals (Scheme 6).^[23] To find the ideal matching of reagents, the authors employ semi-high-through-



Scheme 4. Visible light mediated γ -Fluoroalkylation of oxidized enals and ring opening and γ -alkylation of cyclopropane enals.

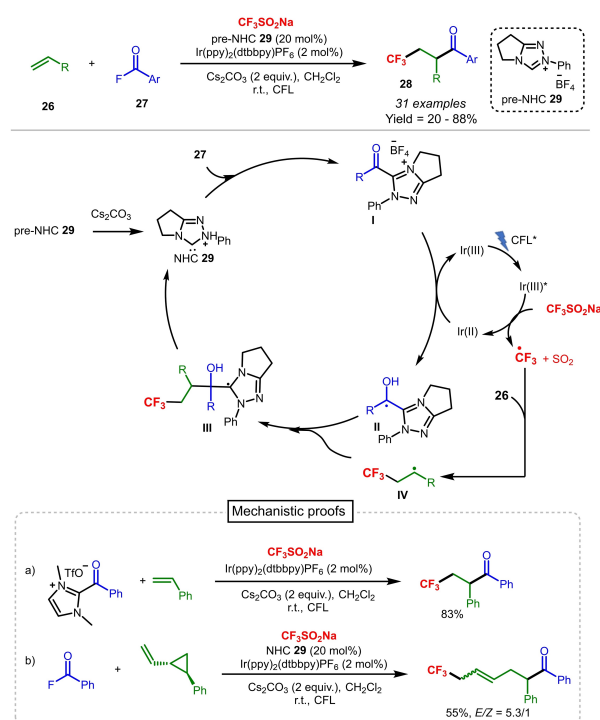


Scheme 6. Cooperative photoredox/NHC catalyzed synthesis of ketones from acyl imidazoles.

put experimentation (HTE), that consists of the evaluation of numerous reaction components in parallel. HTE revealed that Hantzsch esters **23**^[24] afforded better results than alkyl silanes,^[25] silicates^[26] or potassium trifluoroborates^[27] as the alkyl radical source. Moreover, as precursors of the azolium radical, acyl imidazoles **22** performed better than perfluorophenyl esters or acyl chlorides. Thus, employing [Ir(dF(CF₃)₂ppy)₂(dtbbpy)]PF₆ in combination with the NHC precursor and Cs₂CO₃ as the base, a variety of alkyl or (hetero)-aryl acyl imidazoles could be converted in the corresponding ketones, bearing also functional groups such as esters that are not compatible with the traditional methods. To demonstrate the functionality of the method, they could apply it for the late-stage functionalization of pharmaceutical compounds such as a Micardis or a Pradin derivative. The reaction mechanism starts with the oxidation of the Hantzsch ester **23** by the excited photocatalyst, to afford the transient alkyl radical **III** and Ir(II). Consecutive reduction of the acyl triazolium **I** closes the catalytic cycle and affords intermediate **II** that couples with **III** to afford the final products **24**. The authors also perform the reaction in the presence of a chiral NHC catalyst, but the ketone is obtained with low enantioselectivity, although it provides an overview of the potential of the method.

In addition to acyl imidazoles, acyl fluorides are species susceptible of being activated by *N*-heterocyclic carbene catalysis as demonstrated by Studer and coworkers (Scheme 7).^[28] In this recent work, the authors performed an impressive cascade reaction between alkenes **26**, acyl fluorides **27** and the Langlois reagent to prepare β -trifluoro methylated alkyl aryl ketones **28** (Scheme 7). The reaction performs well with aryl or heteroaryl acyl fluorides, and presents a large group tolerance, although is sensitive to steric effects (lower yields are obtained in the presence of *ortho* substituents in **27**). On the alkene side, while styrenes bearing either electron-donating or -withdrawing substituents or heteroaryl alkenes perform well, aliphatic olefines afford lower yields.

The reaction mechanism starts with the oxidation of the Langlois reagents by the excited photocatalyst, to afford a CF₃ radical upon elimination of SO₂. Further reaction of the CF₃ radical with the alkene **26** generates intermediate **IV**. Acyl fluoride **27** reacts with NHC to form the acylazolium **I**, that is

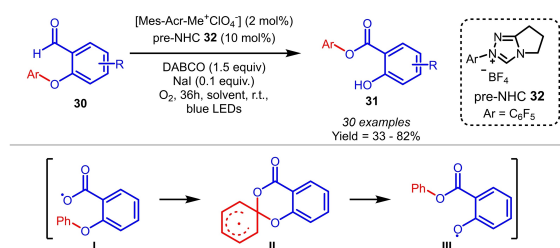


Scheme 7. NHC/photoredox catalyzed synthesis of β -alkyl trifluoro methylated alkyl aryl ketones.

reduced by Ir(II), closing the photocatalytic cycle and affording intermediate **II**. Consecutive reaction between **II** and **IV** affords intermediate **III**, that evolves to products **28** by releasing the NHC, closing this catalytic cycle. Interesting additional mechanistic proofs corroborate this proposal. Acyl azolium **I** was corroborated as key intermediate of the reaction because after its isolation and submission to the reaction conditions, the expected product was obtained in 83% yield (Scheme 7a). Moreover, the radical nature of the reaction is further documented by the acyltrifluoromethylation of a cyclopropyl alkene, obtaining exclusively the ring opening product (Scheme 7b).

The Smiles rearrangement has been enormously employed for the preparation of arenes and heteroarenes in natural products and consists in the migration of an aryl ring via intramolecular nucleophilic aromatic ipso-substitution.^[29] In this communication, Ye reports an oxidative Smiles rearrangement for the synthesis of aryl silicates mediated by a cooperative *N*-heterocyclic carbene/photo-catalysis (Scheme 8).^[30] The reaction involves the creation of two new C–O bonds, and the key reaction step is the radical Smiles rearrangement from intermediate **I** to **III**, via the formation of the spirocyclic intermediate **II**. The reaction affords good results either with electron donating or withdrawing substituents as the aryl migrating groups. It is worth noting that even arenes bearing electron-donating groups, that failed to migrate under the classical Smiles conditions, performed good in this reaction.

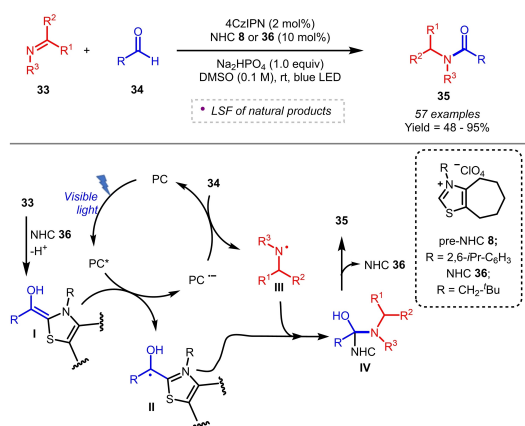
Amides are an important structural motif present in thousands of natural products, agrochemicals or drug mole-



Scheme 8. NHC/photocatalyzed oxidative Smiles rearrangement.

cules, and are key intermediates to access other functional groups.^[31] Thus, the development of new catalytic strategies to prepare them in an atom economical manner still result of great interest. Taking into account the relevance of these structures, Shu has recently developed an impressive and exquisite method to prepare them, starting from aldehydes and imines enabled by the umpolung of the imine and carried out under redox-neutral conditions (Scheme 9).^[32]

Upon visible light excitation, the photocatalyst reaches the excited state, and then is able to oxidize the Breslow intermediate I, affording intermediate II and the corresponding radical anion. This radical anion now reduces the imine, generating the *N*-centered radical III, that couples with II, affording IV that evolves to 35 delivering the NHC catalyst. The authors perform a number of experiments that support the mechanistic proposal depicted before: i) EPR studies reveal the formation of a *N*-centered radical intermediate assigned to intermediate III; ii) TEMPO addition into the reaction shuts it down, and the adduct formed by 34 with TEMPO is detected, highlighting the radical nature of the reaction; iii) on-off experiments discard the radical chain pathway; iv) luminescence experiments evidence that only the Breslow intermediate I interacts with the excited photocatalyst. Moreover, they explore a broad range of substrates. On one hand, a large variety of aryl imines are tolerated, but they are limited to imino ester derivatives. On the other hand, a broad scope of aldehydes is accessible, and the reaction presents a highly functional group tolerance. In addition, the method could be applied to the late-



Scheme 9. Catalytic redox neutral synthesis of amides.

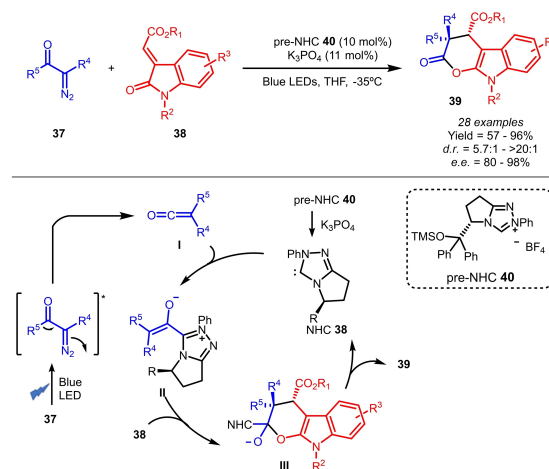
stage functionalization of several natural products, demonstrating the synthetic utility of this brilliant methodology.

3. Light mediated NHC catalyzed transformations

In addition to the number of transformations that combine NHC and photocatalysis, there are also some examples of photochemical transformations mediated by NHC catalysis. One type of transformation is the one that involves a photochemically generated species in a NHC catalytic cycle, as in the case of Hui, that has described one of the few stereoselective methods in this line of research. They have developed a synthesis of tetrahydropyrano[2,3-*b*]indoles bearing all-carbon quaternary stereocenters, through a [4 + 2] cycloaddition reaction with 3-alkylenoxindoles,^[33] taking advantage of the photolytic Wolff rearrangement that allows the *in situ* preparation of ketenes from α -diazoketones (Scheme 10).^[34] The reaction starts with the formation of the ketene intermediate I upon excitation of the α -diazoketone and further rearrangement. Next, intermediate II is formed by reaction between I and the NHC catalyst, and this intermediate undergoes the [4 + 2] cycloaddition reaction to afford intermediate III in a stereoselective manner. Final releasing of the NHC catalyst closes the catalytic cycle and yields product 39.

The reaction is highly dependent on the *N*-protecting group, obtaining the best result with a benzyl group. Other esters, and electron-donating or withdrawing substituents in the aromatic ring are well tolerated. On the contrary, the reaction is highly dependent on the method to generate the ketene, affording no conversion when the ketene is prepared from the 2-phenylbutanoyl chloride with triethyl amine. Despite this limitation, the scope of ketenes that undergoes this reactivity is relatively general.

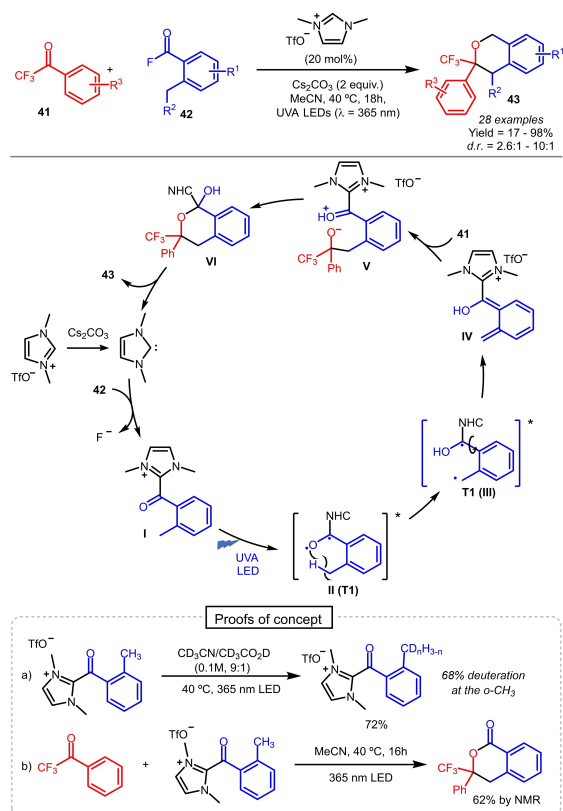
A second kind of photochemical transformations mediated by NHC catalysis are those in which the photoactive species is



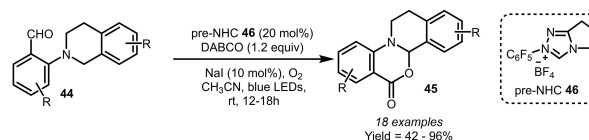
Scheme 10. Visible light mediated synthesis of tetrahydropyrano[2,3-*b*]indoles.

one of the intermediates of the catalytic cycle. As it has been shown in previous examples in this review, aryl carboxylic acid derivatives can react with NHCs to afford the corresponding azolium intermediates. These intermediates are indeed ketones that could be excited in a comparable manner to benzophenones. Furthermore, this second heteroarene (the NHC) can affect the absorption properties of the intermediate. Taking advantage of these characteristics, Hopkinson and coworkers have exploited the capability of NHC to act as a “transient aryl group” to enable the engagement of unsuitable substrates in photochemical reactions. Thus, they have described a photoenolization/Diels-Alder (PEDA) reaction of acyl fluorides **42** with trifluoromethyl phenones **41** (Scheme 11).^[35] To corroborate NHC-photoactivation concept they isolated compound **I** (see proofs of concept Scheme 11a) and submitted it to UVA irradiation for 16 h with a deuterated solvent. Obtention of the deuterated compound **D-I** confirmed that upon UVA irradiation, the hydroxy-*o*-quinodimethane (*o*-QDM) intermediate **IV** is formed. Thus, the next step was to submit it to the PEDA reaction with **41** successfully obtaining the desired isochroman-1-one **43** (see proofs of concept Scheme 11b). With this successful result, they have developed the NHC-catalyzed PEDA reaction, that presents a good functional group tolerance either in the acyl fluoride or in the ketone.

The mechanistic proposal starts with the formation of intermediate **I**, that upon light irradiation gets excited and undergoes intersystem crossing (ISC) to afford a triplet excited state **T1** (II). Fast 1,5-HAT gives rise to the dienol biradical **T1**



Scheme 11. NHC mediated photoenolization/Diels-Alder reaction.



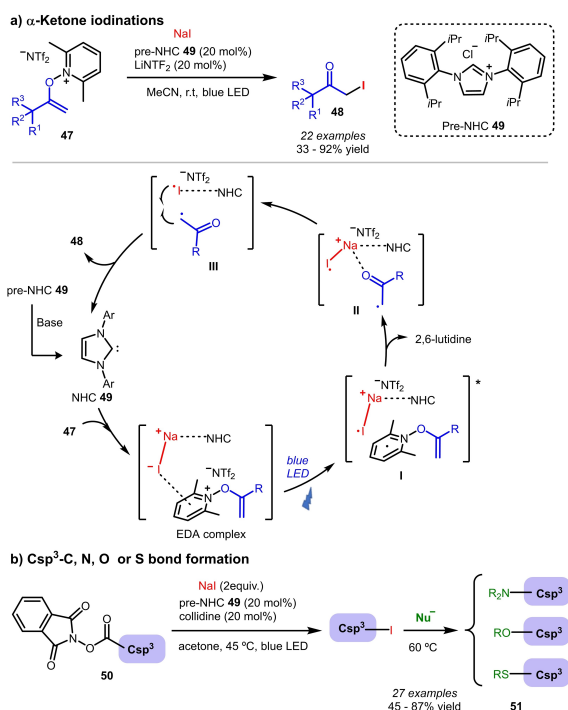
Scheme 12. Intramolecular cross dehydrogenative coupling of tetrahydroisoquinolines-tethered aldehydes.

(III). Further rotation and relaxation lead to the ground state *o*-QDM **IV** that undergoes the cycloaddition reaction with **41**. This cycloaddition can take place in a concerted Diels-Alder manner, or stepwise as shown in Scheme 11, via the formation of intermediate **V**. Finally, releasing the NHC catalyst form **VI**, yields **43** and closes the catalytic cycle.

Taking also advantage of the formation of a photoactive intermediate, Ye has reported an intramolecular cross dehydrogenative coupling of tetrahydroisoquinolines-tethered aldehydes (Scheme 12).^[36] The activation of the aldehyde moiety with the NHC catalyst affords the Breslow intermediate, that is photoactive, initiating upon blue light irradiation an oxidative radical reaction that affords the cyclized products in moderate to excellent yields.

Finally, Wang and Chen have described an additional activation mode that involves the formation of a photoactive EDA complex. This activation mode is very interesting in terms of sustainability and economics, since it avoids the use of expensive transition metal or organic dyes as photocatalyst. It is based on the use of an electron donor and an electron acceptor that do not absorb light by themselves, but together they form a colored complex in the ground state able to absorb light and undergo photochemical transformations.^[37]

Based on the previous work from Krick and Westerhausen that demonstrated the formation of an orange biscarbene adduct with sodium iodide,^[38] they overviewed that this aggregate might be employed in combination with an electron acceptor molecule to form EDA complexes and perform new photochemical transformations. Using this approach, the authors have described an α -ketone iodination reaction starting from *N*-alkenoxypyridinium salts and the NHC-NaI aggregate (Scheme 13a).^[39] The mechanistic proposal, supported by theoretical calculations, would start with the formation of a ground state ternary complex between **47**, NHC **49** and NaI. Upon blue light irradiation the complex reaches the excited state **I** in which single electron transfer (SET) from the iodine to the lutidine moiety takes place affording intermediate **II** after releasing of 2,6-lutidine upon N–O bond cleavage. The authors claim that this lutidine is responsible for the deprotonation step that affords the NHC **49**. Then, the two radicals dissociate affording the RCOCH_2 radical and the NHC-stabilized iodine radical. Final combination of the two radicals yields the final product **48** and regenerates the catalyst. After this first example, they took advantage of the reactivity of these iodinated intermediates to introduce different nucleophiles as amines, alcohols or thiols (Scheme 13b).^[40]



Scheme 13. Activation through photoactive EDA complex formation.

4. Conclusion

Recently, the combination of *N*-heterocyclic carbenes (NHC) and photocatalysis has emerged as an interesting and useful tool in organic synthesis. This review summarizes the examples described so far and brings to light the synthetic potential of merging the reactivity of photocatalytically generated transient radicals with the well established NHC organocatalysis. As shown in this review, most of the new methods described are non-asymmetric or racemic, although the first example demonstrated the ability of NHC to induce chirality in photocatalytic reactions. Thus, the main conclusion of this review is that while this research area presents a great opportunity to develop new transformations, there is still a particularly big window for improvement in the development of asymmetric transformations.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Light • NHC • Photocatalysis • Radicals • Synthesis

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