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Isocyanide-Based Multicomponent Reactions Promoted by Visible Light Photoredox Catalysis

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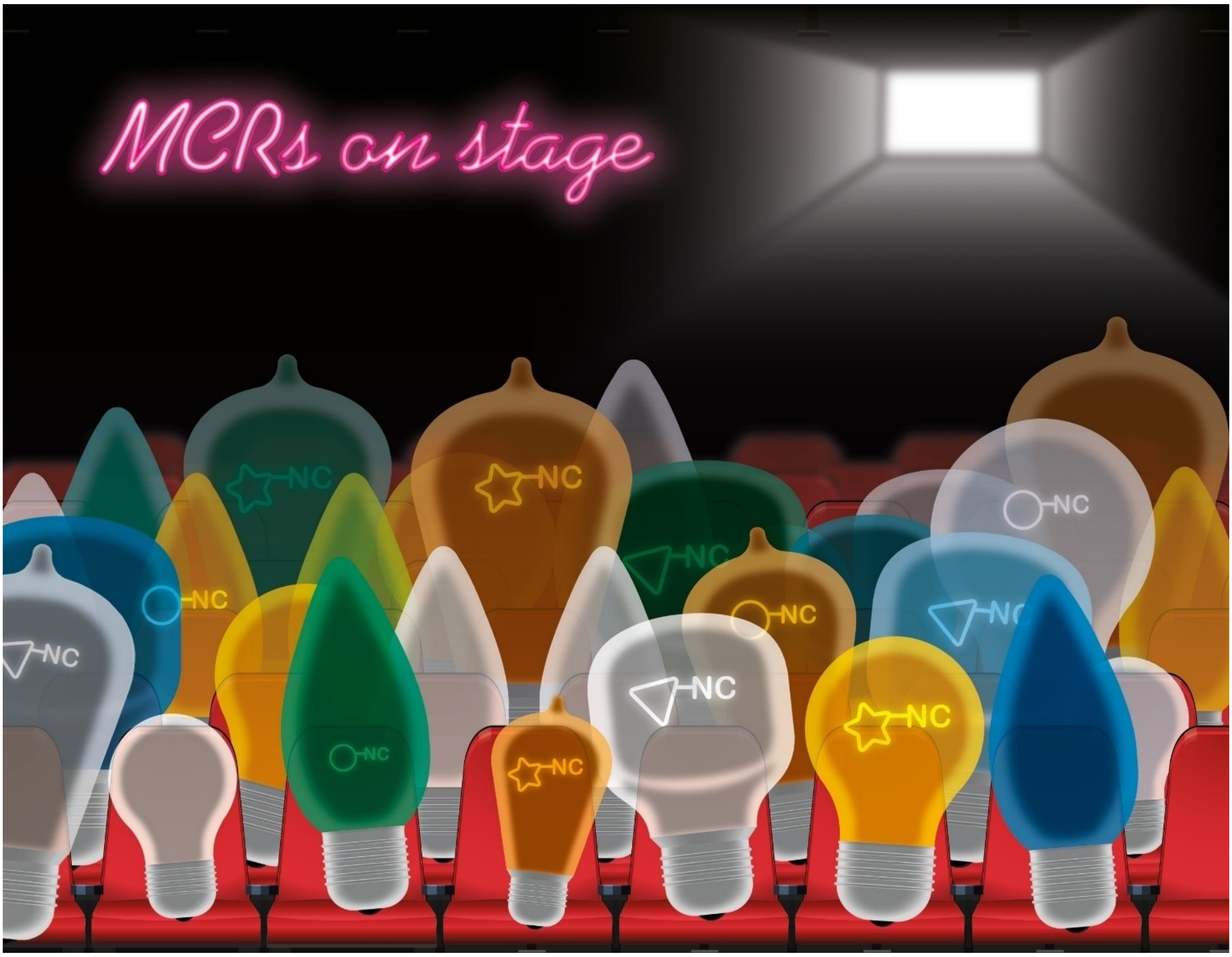

Abstract: Isocyanide-based multicomponent reactions claim a one century-old history of flourishing developments. On the other hand, the enormous impact of recent progresses in visible light photocatalysis has boosted the identification of new straightforward and green approaches to both new and known chemical entities. In this context, the application of visible light photocatalytic conditions to multicomponent processes has been promoting key stimulating advancements. Spanning from radical-polar crossover pathways, to photoinduced and self-catalyzed transformations, to reactions involving the generation of imidoyl radical species, the present literature analysis would provide a general and critical overview about the potentialities and challenges of exploiting isocyanides in visible light photocatalytic multicomponent reactions.

1. Introduction

While most of organic compounds can be described as nucleophiles/ electrophiles, dipoles/ dipolarophiles, electron donors/acceptors, radical acceptors or precursors of a radical species, isocyanides encompass such dichotomies being recognized as a special class of functional groups.[1,2] Beside standing for key nucleophilic players in multicomponent reactions (MCRs), the most venerable being the Passerini and the Ugi reactions,[3,4] they can also react as dipolarophiles in cycloaddition reactions,[5] as electron-donors to form organometallic complexes, and as geminal radical acceptors in photochemical processes. The organometallic chemistry of isocyanides spans from the possibility to be exploited as electrophiles by coordination with a Lewis acid (σ-complexes), to palladium/ copper promoted insertions (π-complexes),[6] as innocent ligands to generate metal-based photoredox catalysts,[7] to pharmaceutical agents such as technetium (^{99m}Tc) sestamibi (Cardiolite®) used in nuclear medicine imaging. Furthermore, the possibility to behave as somophiles in reactions with open-shell species, contributes to the charming aura enfolding their manifold reactivity. While most of literature contributions hinge on two-component three-center reactions involving 2-isocyanobiphenyls and/or vinylisocyanides,[8] three- or more-component transformations involving isocyanides and radical species have been poorly reported. The potential of imidoyl radicals as key intermediates in multicomponent transformations has been pioneered by Nanni et al. back in the 1995 to form cyclopenta-fused quinoxalines, with the radical species generated by heating at reflux temperature a benzene solution of a radical initiator (i.e., AIBN).[9] Recently, the tremendous impact of visible light photoredox catalytic approaches to build on unachievable molecular frameworks and to access (bio)relevant scaffolds with unprecedented efficiencies has completely changed the way to design new chemical reactions in terms of both synthons (i.e., suitable radical precursors) and retrosynthetic disconnections.[10] The generation of open-shell species under exceptionally mild reaction conditions enabled by visible light photocatalytic methodologies can be considered as ideal to study new light triggered multicomponent processes thus merging the advantages of a convergent, atom-economical, and easy-to-perform chemistry (MCRs) with the green innate properties of photocatalysis such as renewable energy source, low amounts of catalyst, no high temperatures and pressure, chemoselectivity, and functional group orthogonality.[11] Accordingly, we herein highlighted the opportunities and the challenges of bringing into play isocyanide electronic properties in visible light photochemical multicomponent processes. Literature has been divided into four main sections based on the generation in situ, by means of photocatalysis, of a species reacting with isocyanides via 2-electron pathways, i.e., 1) reactions involving radical-polar crossover pathways and 2) photoinduced MCRs. Recent reports by us showed how isocyanides could directly interact with visible light either being photoactive, in case of aromatic ones, or by forming electron-donor/acceptor (EDA) complexes: such finding has been highlighted in a third section. A fourth section has been focused on the isocyanides' reactivity as geminal radical acceptors thus involving the generation of an imidoyl radical intermediate. The analysis of the current literature as well as the implications and the trends of the recent fascinating developments will certainly stimulate further progress in the field.

2. Radical-Polar Crossover Pathways

Since Ivar Ugi discovered the eponymous 4-component reaction (Ugi 4-CR) in 1952, it has been a source of inspiration for generations of chemists working at the development of new multicomponent processes.[12] The latter, indeed, have often been discovered by replacing one of the components of the Ugi 4-CR traditionally being an aldehyde or a ketone, an amine, an isocyanide, and a carboxylic acid (Scheme 1).

Alternatively, the scope of the Ugi 4-CR was expanded either by generating in situ the oxo-component starting from reduced analogues such as alcohols or via oxidation of the amine to iminium ion.[13] As shown by Rueping et al., the ease of visible light oxidation of aromatic tertiary amines under mild reaction conditions led to the first report about an Ugi-like 3-component reaction involving *N*,*N*-dimethylanilines **1**, isocya-

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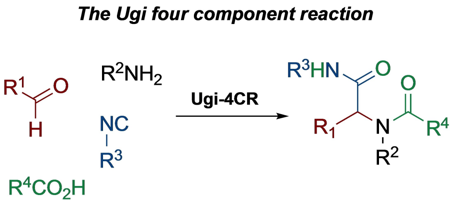

Scheme 1. The Ugi-4CR.

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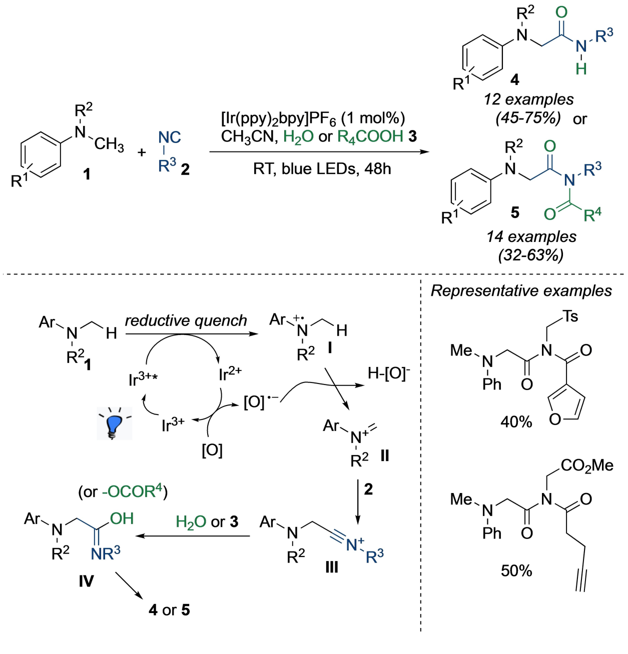
nides **2**, and either water or carboxylic acids **3** as the nucleophilic partner (Scheme 2).[14]

The reaction led, respectively, to α-amino amides **4** and α-amino imide products **5** and took place in acetonitrile (dried by adding 3 Å molecular sieves when a carboxylic acid was used as the nucleophile), at room temperature, in the presence of a 1 mol % loading of $[Ir(ppy)_2bpy]PF_6$ as the optimum photocatalyst, under irradiation with 1 W blue LEDs 30 cm strip. The substrate scope was wide, with *N*,*N*-dimethylanilines bearing both electron-donating or electron-withdrawing groups at the *para* or *meta* position being suitable starting materials, as well as aliphatic and differently substituted aromatic carboxylic acids (i.e., 4-bromo, 3-methoxy, 2-fluorobenzoic acid, 1-naphthoic acid, or 3-furancarboxylic acid), and both primary and secondary aliphatic isocyanides. Interestingly, when *N*-ethyl-*N*-methylaniline was employed as the amine component, the methyl group was chemoselectively oxidized. In general, the reaction worked well, and the desired α-amino amides **4** or imides **5** were obtained with yields spanning from moderate to good. It is worth noting that the same products would require toxic formaldehyde if synthesized via a classic Ugi 4-CR. The proposed reaction mechanism implied the reductive quenching of the excited Ir^{3+*} photocatalyst and the formation of an Ir^{2+} complex and a radical cation **I** as the consequence of a SET oxidation of the aromatic tertiary amine **1**; molecular oxygen then regenerated the ground state Ir^{3+} photocatalyst while furnishing a superoxide radical anion, which abstracted a hydrogen atom from the radical cation **I**, thus leading to the formation of the corresponding iminium ion **II**. The latter was then intercepted by the isocyanide to afford a nitrilium ion intermediate **III**, whose trapping by water or carboxylic acid and

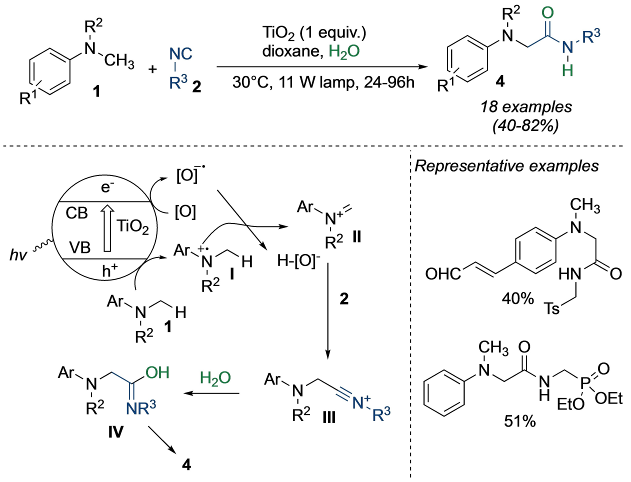


Scheme 2. Iridium catalyzed Ugi-like 3CR involving tertiary aromatic amines, isocyanides and either water or carboxylic acids.

further rearrangement finally provided the amide **4** or imide product **5**, respectively.

The same authors later described an analogous transformation leading to α-amino amides by using titanium dioxide TiO_2 as a cheap, readily available, and non-toxic heterogeneous photocatalyst (Scheme 3).[15] Variously substituted *N*,*N*-dimethylaniline derivatives **1** were reacted with isocyanides **2** and water in 1,4-dioxane, at 30 °C, in the presence of a stoichiometric amount of TiO_2, under irradiation with an 11 W fluorescent lamp. The desired α-amino amides **4** were obtained in moderate to good yields, with a good functional group tolerance, including methyl-, chloro-, bromo-, ketone, and unsaturated aldehyde functionalities on the anilines' aromatic moiety and isocyanides bearing different functional groups such as esters or phosphonates.

The heterogenous photocatalyst proved to be easy to recover by simple centrifugation and was efficiently recycled in up to five consecutive cycles. According to the mechanism proposed by the authors (Scheme 3), the visible-light induced promotion of an electron from the valence to the conduction band of TiO_2 left a hole in the valence band which could promote the oxidation of *N*,*N*-dimethylaniline **1**; the latter afforded the dimethylaniline radical cation **I**, while a superoxide radical anion was generated via SET from TiO_2 conduction band to molecular oxygen. The $O_2^{\bullet-}$ mediated H-abstraction from **I** subsequently gave the corresponding iminium ion **II**, which reacted with isocyanide and water, as shown before, eventually resulting in the final amide product **4**.

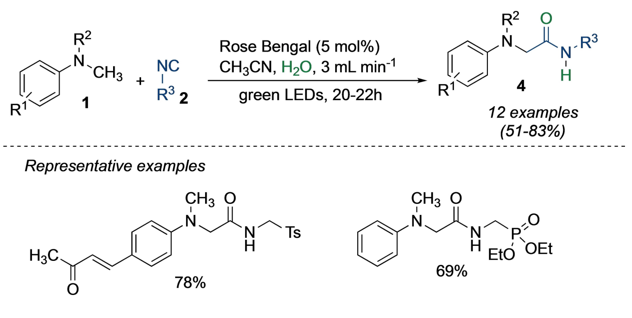


Scheme 3. Titanium dioxide promoted Ugi-like 3CR involving tertiary aromatic amines, isocyanides and water.

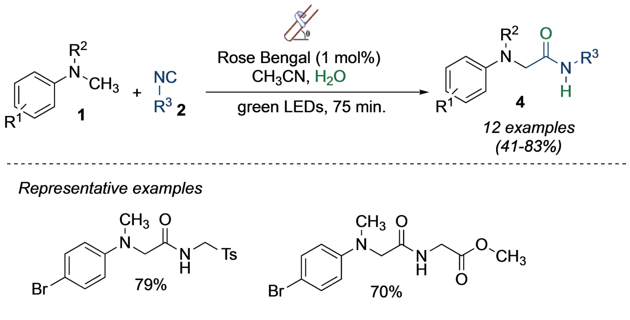
A further development was reported by Bootwicha et al., and consisted of a continuous flow procedure for the efficient metal-free, visible light photoredox-catalyzed α-functionalization of aromatic tertiary amines **1** (Scheme 4).[16] In addition to *aza*-Henry, Mannich, Strecker, and phosphonylation reactions, the authors described the oxidative Ugi-like 3-CR of *N*,*N*-dimethylanilines **1**, aliphatic isocyanides **2**, and water carried out in an $MeCN/H_2O$ mixture, at a flow rate of 3 $mL\,min^{-1}$, under green LEDs irradiation, by using rose bengal as the organophotocatalyst (Scheme 4). Importantly, the flow procedure provided the desired α-amino amides **4** in shorter times and higher yields, compared to the batch conditions.

Stubbs and co-workers additionally improved this approach by performing the reaction with a thin film microfluidic vortex device (Scheme 5): it enabled the distribution of the reaction mixture in a dynamic thin film on the wall of an angled rapidly rotating reaction tube, with the thickness of the film simply controlled by varying the speed of rotation and the tilt angle.[17] This allowed intense micro-mixing and homogenous irradiation of the reaction mixture, with significantly shorter times than those previously reported for batch and channel flow chemistry processes and either improved or comparable yields.

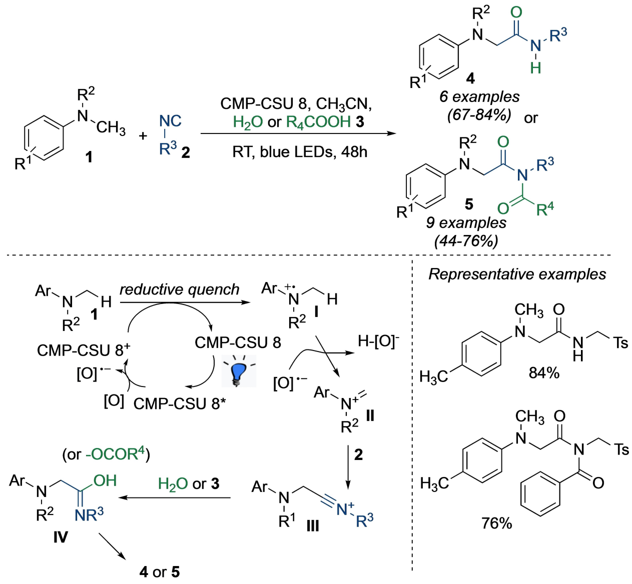
In the last few years, conjugated micro-/mesoporous polymers (CMPs) have been emerging as a versatile platform for designing efficient, metal-free, and non-toxic recyclable heterogeneous photocatalysts. In this regard, Yu and co-workers developed a new phenothiazine-core CMP-CSU8 able to promote an Ugi-3 CR (Scheme 6).[18] More in detail, CMP-CSU8, derived from 10-(4-(9*H*-carbazol-9-yl)phenyl)-3,7-di(9*H*-carbazol-9-yl)-10*H*-phenothiazine (TCTB), proved to be superior either to metal-based catalysts such as CuCl and $Ru(bpy)_3Cl_2$ or other heterogeneous photocatalysts such as *g*-C_3N_4 and $BiVO_4$ in promoting the cross-dehydrogenative coupling of aromatic tertiary amines **1** with aliphatic isocyanides **2** and either water or carboxylic acids **3**. The reaction proceeded smoothly in acetonitrile, at room temperature, under O_2 atmosphere and 14 W blue LEDs irradiation, giving the corresponding products **4** and **5** in moderate to good yields. The heterogeneous photocatalyst could be easily recovered through precipitation



Scheme 4. Metal-free photoredox catalyzed Ugi-like 3CR under continuous flow conditions.



Scheme 5. Metal-free photoredox catalyzed Ugi-like 3CR using thin film vortex microfluidics.



Scheme 6. CMPs photoredox catalyzed Ugi-like 3-CR.

or centrifugation and it almost completely retained its photocatalytic activity after five cycles.

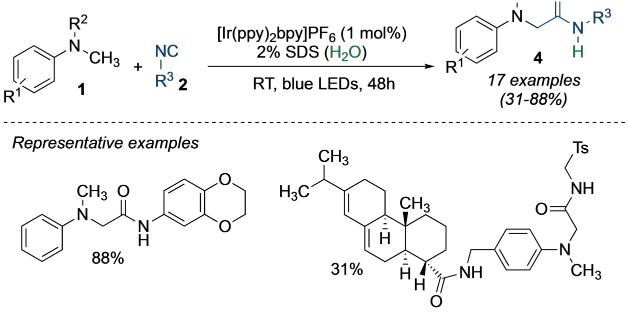
The authors proposed a reaction mechanism based on the oxidative quenching of the excited CMP-CSU8* photocatalyst upon its irradiation with visible-light (Scheme 6): a SET involving molecular oxygen led to CMP-CSU8$^+$, superoxide radical $O_2^{\bullet -}$ and $^1O_2$; CMP-CSU8$^+$ then oxidized *N,N*-dimethylaniline substrates **1**, regenerating the ground state photocatalyst. The subsequent abstraction of a hydrogen atom from the radical cation **I** yielded the iminium ion intermediate **II**, which was then intercepted by the isocyanide **2** affording the corresponding nitrilium ion **III**. The latter underwent nucleophilic attack by water or a carboxylate anion **3** leading to the intermediate **IV**, whose final rearrangement resulted, respectively, in the amide **4** or imide product **5**.

We recently contributed to the field of oxidative Ugi-type 3-CRs by reporting an *in water* protocol enabled by the merging of micellar and photoredox catalysis (Scheme 7).[19]

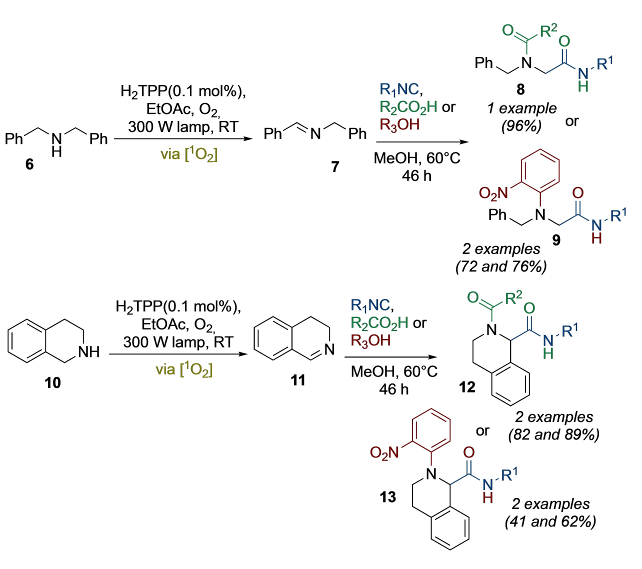
N-methyl-*N*-alkyl aromatic amines **1** were reacted with isocyanides **2** in a 2 wt % SDS water solution, at room temperature, in the presence of [Ir(ppy)$_2$bpy]PF$_6$ as the best performing photocatalyst, under 30 W blue LEDs irradiation for 48 h. Both electron-rich and electron-poor dimethylaniline derivatives gave the desired amide products **4** in good yields, as well as variously substituted aromatic and aliphatic isocyanides. Interestingly, less satisfactory results were obtained when different micellar systems (i.e., TPGS-750-M, Triton-X, CTAC) were employed as the reaction media. In order to investigate the reaction environment at the atomic level, solution 1D- and 2D NMR experiments were performed, for the first time, in the presence of paramagnetic probes and revealed a *reverse polarity* principle, according to which the use of photocatalyst/surfactant pairs with opposite charges could provide the localization of the photocatalyst on the micelles' surface thus leading to an improved catalytic efficiency with respect to water alone.

In addition to aromatic tertiary amines, benzyl amine derivatives were also reported as suitable substrates to be in situ photo-oxidized to the corresponding imines, which are able to undergo an Ugi-like 3-CR. The first account about such a transformation was reported in 2009 by Che, who developed a two-step one-pot protocol for oxidative Ugi-type reactions starting from secondary benzylic amines (Scheme 8).[20]

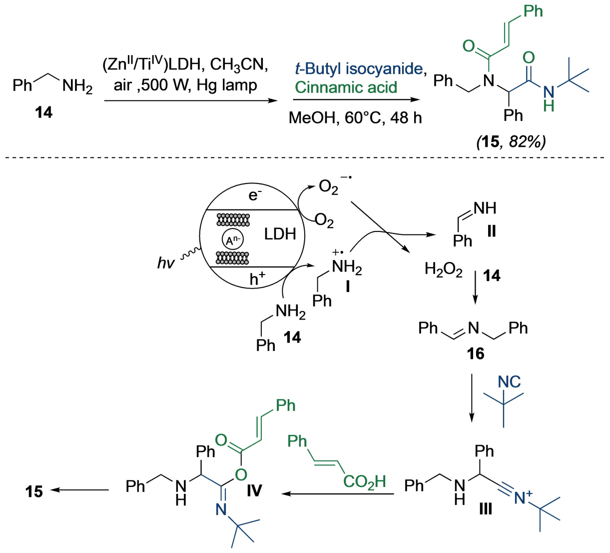
Dibenzylamine **6** and 1,2,3,4-tetrahydroisoquinoline **10** were quantitatively oxidized by singlet oxygen generated in the presence of a tetraphenylporphyrin photosensitizer, under O_2 atmosphere and irradiation with a 300 W tungsten lamp. When the oxidation was complete, replacement of ethyl acetate with methanol followed by in situ addition of *t*-butyl or benzyl isocyanide and a carboxylic acid afforded the Ugi products **8** and **12** in good or excellent yields, after stirring the reaction mixture at 60 °C for 46 h. 2-Nitrophenol was also employed instead of carboxylic acids, leading to the desired Ugi-Smile products **9** and **13** in moderate to good yields. Just one example involving benzylamine, *t*-butyl isocyanide, and cinnamic acid was later described by Tung et al. (Scheme 9).[21] The



Scheme 7. Photoredox catalyzed Ugi-like 3-CR under micellar conditions.



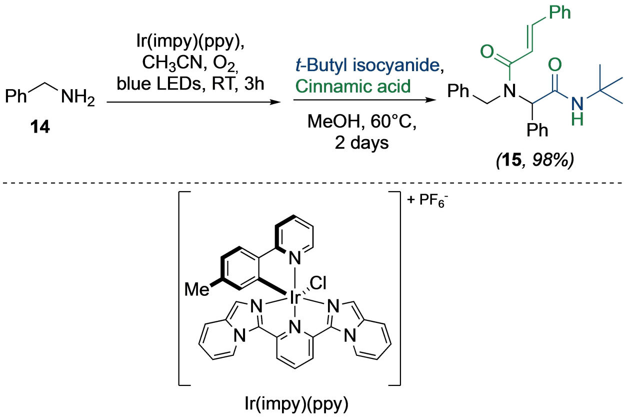
Scheme 8. Oxidative photoredox catalyzed Ugi-like 3CR starting from dibenzyl amine and 1,2,3,4-tetrahydroisoquinoline.



Scheme 9. Oxidative Ugi 3-CR using (Zn^{II}/Ti^{IV})LDH as a photocatalyst.

authors used a (Zn^{II}/Ti^{IV})LDH (LDH=Layered Double Hydroxide) with a Zn^{II}/Ti^{IV} ratio of 6:1 as a stable, economical, and reusable photocatalyst for the selective oxidative coupling of benzylic amines to imines, under aerobic condition and irradiation with a 500 W high-pressure mercury lamp. After the photocatalytic oxidation of benzylamine **14**, (Zn^{II}/Ti^{IV})LDH was removed by centrifugation and the imine was refluxed with cinnamic acid and *t*-butylisocyanide in methanol, to obtain the Ugi product **15** in a good 82% yield. Since the addition of SOD (superoxide dismutase, $O_2^{\bullet-}$ scavenger), caused a severe drop in the imine yield, $O_2^{\bullet-}$ was supposed to play a critical role in the oxidation process. The authors suggested that light irradiation of (Zn^{II}/Ti^{IV})LDH resulted in the promotion of electrons to the conductive band (CB), thereby leaving holes in the valence band; this enabled the reduction of molecular oxygen to $O_2^{\bullet-}$, while benzylamine **14** was simultaneously oxidized by the photogenerated holes. The superoxide radical anion then abstracted a proton and a hydrogen atom from the benzylamine radical cation **I**, leading to H_2O_2 and benzenemethanimine **II**. Addition of the latter to a new molecule of benzylamine **14** gave rise to the imine intermediate **16** after ammonia elimination. Alternatively, the hydrolysis of benzenemethanimine **II** could result in the generation of benzaldehyde, whose condensation with the starting benzylamine **14** afforded the corresponding imine **16** (not shown). The Ugi reaction then proceeded as usual with the sequential additions of the isocyanide and the carboxylic acid to form the intermediate **IV**, which after the Mumm rearrangement finally gave the imide product **15**.

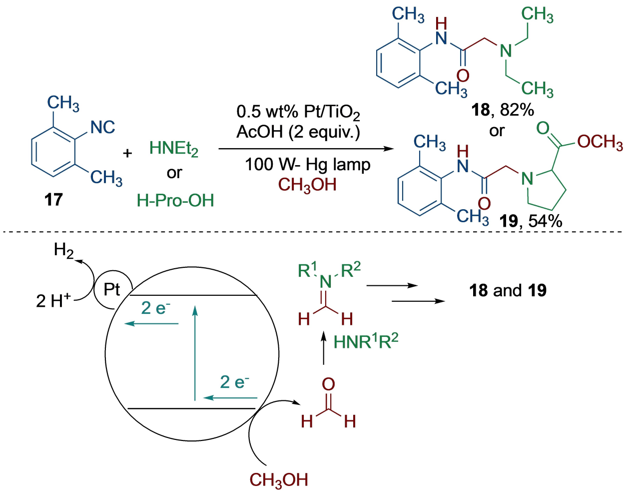
The same transformation was then carried out by Kawamura and co-workers in order to evaluate the photocatalytic performance of the newly developed iridium(III) complex Ir(impy)(ppy), based on the pincer type imidazo[1,5-*a*]pyridine ligand (Scheme 10).[22]



Scheme 10. Oxidative Ugi 3-CR using Ir(impy)(ppy).

The oxidative coupling of benzylamine **14**, performed in the presence of a 15 mol % loading of Ir(impy)(ppy), under O_2 atmosphere and 1 W blue LEDs irradiation, was complete after only three hours, and, following the addition of *t*-butyl isocyanide and cinnamic acid, led to the Ugi product **15** in a near quantitative yield. Singlet oxygen was recognized as the key oxidant species, as indicated by the significant decrease in the absorption spectra of 1,3-diphenylisobenzofuran (DPBF) - which is known to react with singlet oxygen - observed in the presence of Ir(imp)(ppy) upon irradiation.

As an alternative to the use of amines, photochemically oxidized in situ to imines or iminium ions, C. Uyeda et al. showed that it was possible to exploit methanol as a more stable precursor of formaldehyde, which then could react with an amine and an isocyanide in an Ugi-type 3-component reaction (Scheme 11).[23] The alcohol oxidation was promoted by Pt/TiO$_2$ particles as heterogeneous photocatalyst: while the highly oxophilic nature of the TiO$_2$ surface enabled the selective binding and dehydrogenation of the alcohol in the presence of

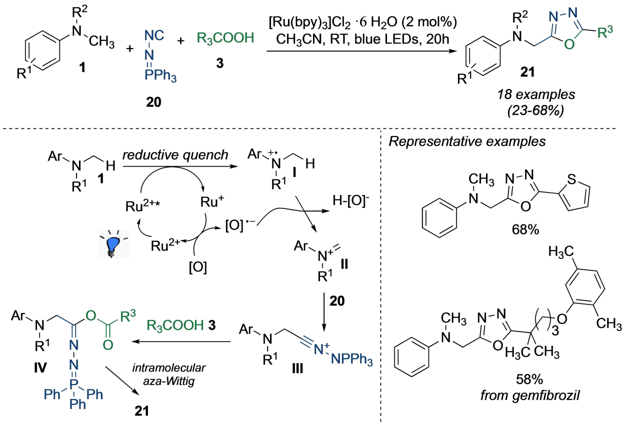


Scheme 11. Oxidative Ugi 3-CR promoted by Pt/TiO$_2$ particles.

other oxidizable groups (i.e., the secondary amine), the efficient proton reduction provided by Pt metal allowed the reaction to be carried out under strictly anaerobic conditions, generating H_2 as the sole stoichiometric byproduct. Albeit this transformation requires irradiation with a 100 W mercury lamp as the light source, it represents an interesting application leading to lidocaine **18** and analogue **19** in 82% and 54% yield, respectively.

The chemical space accessible via photo-oxidative Ugi-type 3-CRs could be further expanded by using multifunctionalized starting materials.[24] In this context, we recently gained access to 1,5-disubstituted 1,3,4-oxadiazole derivatives via a one-pot visible-light photocatalytic Ugi/*aza*-Wittig cascade involving *N*-alkyl-*N*-methylanilines **1**, carboxylic acids **3**, and *N*-isocyanoiminotriphenyl phosphorane **20** (Scheme 12). The photo-induced Ugi-like 3-CR took place as usual, but the peculiar structural features of the isocyanide enabled a domino intramolecular cyclization leading to the oxadiazole core as in products **21**. Interestingly, while previously reported routes to 1,5-disubstituted 1,3,4-oxadiazoles were all limited to strongly nucleophilic secondary aliphatic amines, our photocatalytic protocol enabled the incorporation of aromatic tertiary amines. Both electron-rich and electron poor dimethylaniline derivatives **1**, as well as aromatic, heteroaromatic, and aliphatic carboxylic acids **3** reacted smoothly in dry acetonitrile, at room temperature, with $[Ru(bpy)_3]Cl_2 \cdot 6\ H_2O$ being used as the optimum photocatalyst under 30 W blue LEDs irradiation. The reductive quenching of the exited Ru(II)* photocatalyst by *N,N*-dimethylaniline afforded Ru^+ and a radical cation **I**; regeneration of the photocatalyst in the presence of oxygen as the oxidant provided a superoxide radical anion, which triggered the formation of an iminium ion **II** upon hydrogen atom abstraction from the radical cation **I**. Hence, the iminium ion **II** underwent nucleophilic attack by *N*-isocyanoiminotriphenylphosphorane **20** to generate the nitrilium ion **III**, followed by addition of the carboxylate **3** to give the α-adduct **IV**. The latter eventually provided the desired 1,3,4-oxadiazole **21** after a domino intramolecular *aza*-Wittig reaction, with loss of triphenylphosphine oxide.

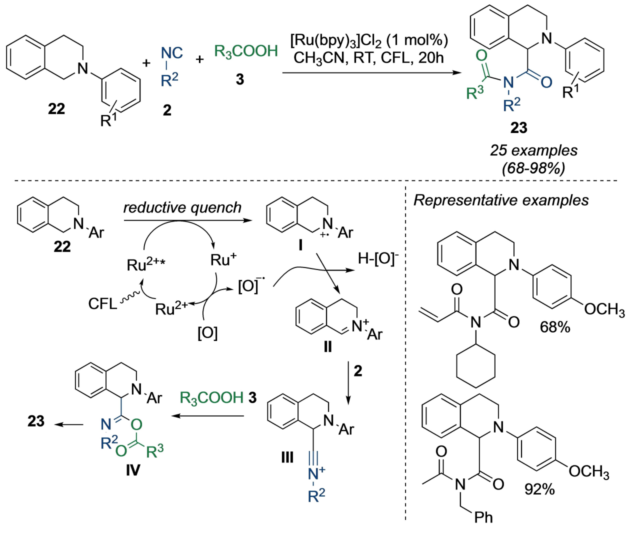
Related to the Ugi 4-CR, the Joullié-Ugi 3-component reaction involves a cyclic imine, an isocyanide, and a carboxylic acid. The possibility to exploit in situ the visible light photoredox catalytic oxidation of a tertiary cyclic aromatic amine to an iminium ion derivative, then intercepted via a multicomponent process, was first described by Feng et al. back in 2015.[25] The reaction was carried out in CH_3CN, at room temperature, employing $Ru(bpy)_3Cl_2$ as the photocatalyst, under aerobic condition and irradiation with a 12 W household lamp (Scheme 13).



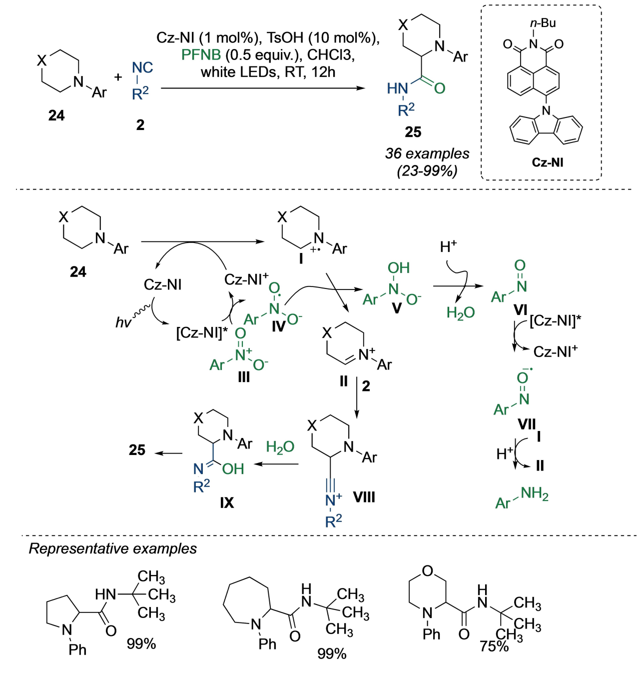
Scheme 12. Photoredox catalytic Ugi-like/ *aza*-Wittig 3-CR.

A range of different *N*-aryl-1,2,3,4-tetrahydroisoquinolines **22** bearing both electron-donating and electron-withdrawing groups at the *meta* or *para* position proved to be suitable substrates for the photocatalytic oxidation, and good to excellent yields were obtained when cyclohexyl- and benzyl isocyanide, both electron-rich and electron-poor aromatic isocyanides **2** as well as aliphatic, aromatic, and heteroaromatic carboxylic acids **3** were employed as the starting materials. A plausible reaction pathway was depicted in Scheme 13: under visible-light irradiation, the excited Ru(II)* photocatalyst was able to promote a SET oxidation of *N*-aryl-1,2,3,4-tetrahydroisoquinoline substrates **22**, leading to the amine radical cation **I** and the reduced Ru^+ complex. The latter was oxidized back to the ground-state Ru^{2+} complex by molecular oxygen, thus producing a superoxide radical anion, which was responsible for the abstraction of a hydrogen atom from the amine radical cation **I**. The so-formed cyclic iminium ion **II** was then intercepted by the isocyanide **2** giving the nitrilium ion **III**, whose trapping by a carboxylate anion **3** to form **IV** and subsequent rearrangement finally provided the imide product **23**.

The collection of tertiary cyclic aromatic amines suitable for the transformation was later extended by Xu and co-workers to saturated *aza*-heterocycles other than *N*-aryltetrahydroisoquinolines, namely *N*-phenylpyrrolidine, *N*-phenylpiperidine, *N*-phenylmorpholine, *N*-phenylazepane, and some others (Scheme 14).[26] These transformations required the design and the development of a novel naphthalimide-based organic



Scheme 13. Photoredox catalytic Joullié-Ugi 3-CR.



Scheme 14. Photoredox catalytic Joullié-Ugi 3-CR using Cz-NI as a photocatalyst.

photocatalyst (Cz-NI) that completely outperformed commonly used transition-metal or organic photocatalysts in promoting the cross-dehydrogenative coupling of *N*-aryl-*aza*-heterocycles with both aromatic and aliphatic isocyanides and water. When performed in CHCl$_3$, at room temperature, under nitrogen atmosphere and white LEDs irradiation, in the presence of TsOH as acid cocatalyst, PFNB (*p*-fluoronitrobenzene) as external oxidant, and Cz-NI as the photocatalyst, the reaction provided the expected amide products **25** with good to almost quantitative yields (Scheme 14).

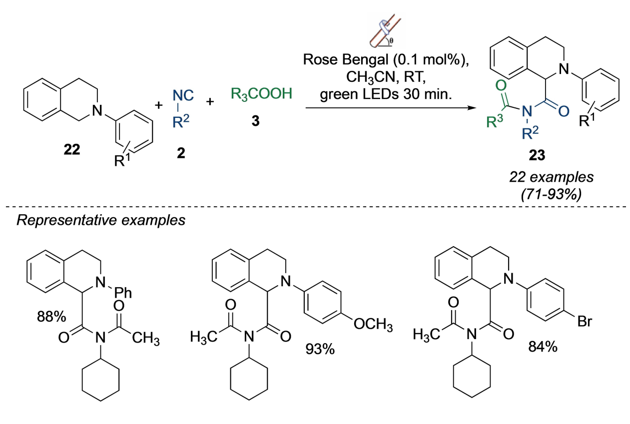
A wide range of functional groups including halogens, ether, thioether, cyano, ester, trifluoromethyl, amido, and aldehyde functionalities proved to be well tolerated under these reaction conditions. Based on a series of mechanistic experiments, the authors proposed a catalytic cycle entailing the excitation of the ground-state photocatalyst upon visible-light absorption and the oxidation of the excited [Cz-NI]* mediated by PFNB; this resulted in the oxidized [Cz-NI]$^+$ and in the PFNB radical anion. [Cz-NI]$^+$ then accepted an electron from the amine **24**, leading to the corresponding radical cation **I** while regenerating the ground state photocatalyst. A subsequent HAT from the amine radical cation **I** to the PFNB radical anion resulted, respectively, in the cyclic iminium ion **II** and the intermediate **V**, the latter dehydrating into pentafluoro-nitrosobenzene **VI** in acidic environment. The isocyanide attack to the iminium ion **II** gave the nitrilium ion intermediate **VIII**, which, after the addition of water, finally provided the desired amide product **25**. The authors also suggested that pentafluoro-nitrosobenzene **VI** itself could further accept an electron from the amine and furnish a pentafluoro-nitrosobenzene radical anion **VII**, able to abstract a hydrogen atom from the amine radical cation **I** and give the key iminium ion intermediate **II** and pentafluoroaniline, as detected by GC-MS analysis. This could contribute to the high quantum yield ($\Phi = 2.3$) observed for the transformation.

As for the Ugi 3-CR, Stubbs et al. reported an interesting application of a thin film microfluidic vortex (FMV) device to the Joullié-Ugi 3-CR, with notable advantages in terms of both times and catalytic efficiency (Scheme 15).[27]

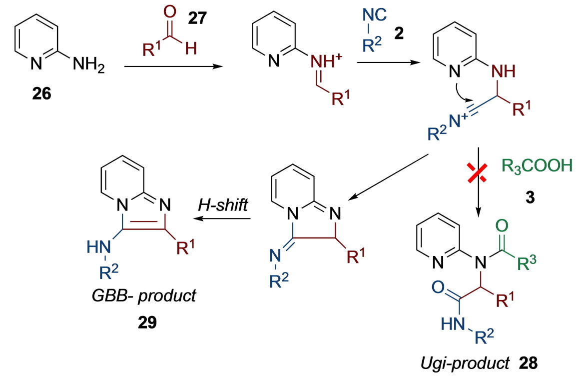
They described the cross-dehydrogenative coupling of *N*-aryltetrahydroisoquinolines **22** and both aromatic and aliphatic isocyanides **2**, and carboxylic acids **3**. The reaction performed in acetonitrile, at room temperature, in the presence of rose bengal, under green LEDs irradiation, at 5000 rpm rotational speed and 45° tilt angle was completed after only 30 min. Furthermore, the amplification of the reaction surface area, which allowed its more effective and homogenous irradiation, led to a significant reduction in the amount of the photocatalyst needed (from 1 to 0.1 mol % loading). Nevertheless, the yields were comparable or even higher than those reported in literature.

The Groebke-Blackburn-Bienaymé 3-component reaction (GBB 3-CR) has been serendipitously and concurrently discovered by three different research teams working at the synthesis of large libraries of Ugi 4-CR products for HTS campaigns.[28] Actually, the story tells that when the starting amine component was 2-aminopyridine **26**, no Ugi adduct **28** was observed but an unexpected cyclic compound **29**, not incorporating the carboxylic acid moiety **3** was isolated (Scheme 16). In the last decades the GBB 4-CR has been extensively exploited in medicinal chemistry thanks to the drug-like properties of aminoazoles and to the ease of create large libraries of diverse compounds in short times, which is key for synthetic medicinal chemists.[29]

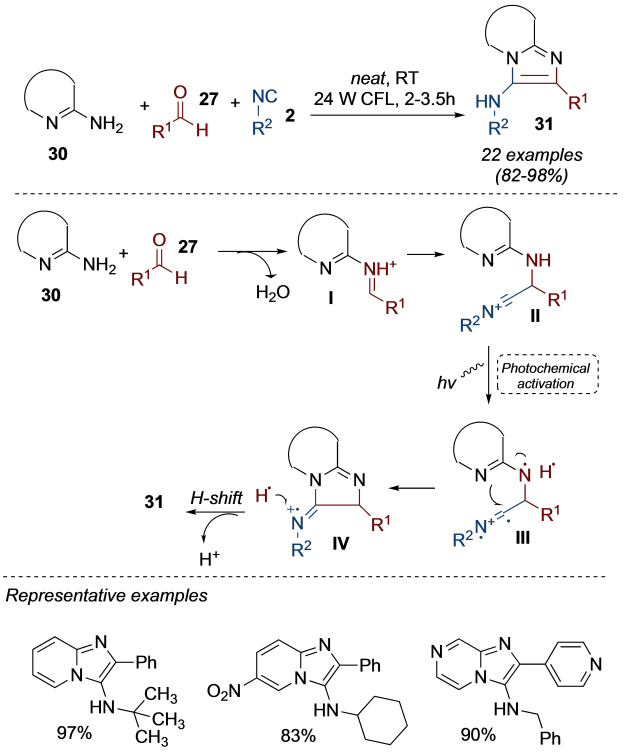
A GBB 3-CR promoted by visible light was reported by Siddiqui et al. in 2018 as a green strategy to access pharmaceutically relevant imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*]thiazoles **31** under catalyst- and solvent-free conditions (Scheme 17).[30] As highlighted by the authors, while previously reported methods often required catalysts such as either Lewis or Brønsted acids, volatile solvents, high temperatures, and long reaction times, the new-developed protocol simply made



Scheme 15. Photoredox catalytic Joullié-Ugi 3-CR under FMV conditions.



Scheme 16. The Groebke-Blackburn-Bienaymé 3-component reaction (GBB 3-CR).



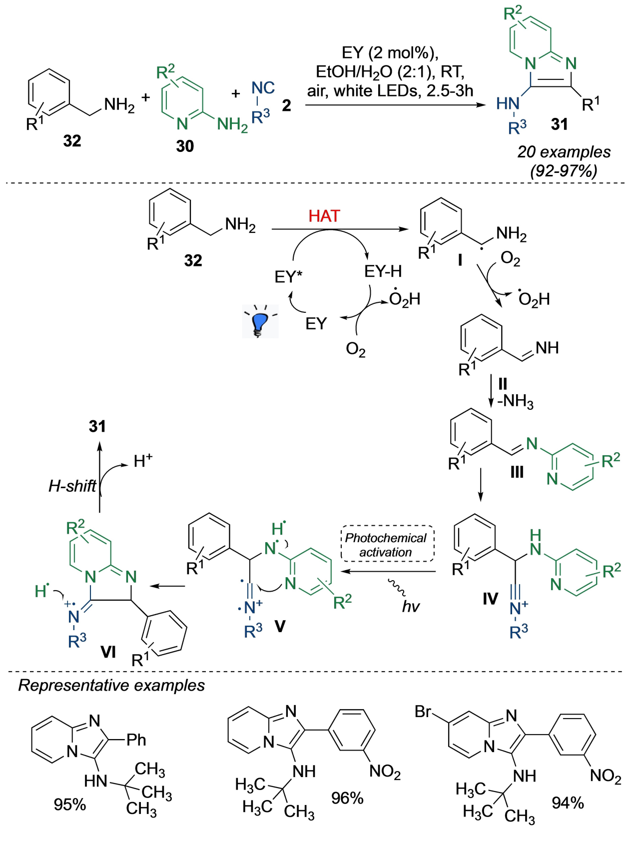
Scheme 17. The photocatalyzed GBB 3-CR.

aldehydes **27**, isocyanides **2**, and 2-aminoheterocycles **30** to react one-pot, at room temperature, under irradiation with a 24 W CFL.

The reaction was completed in approximately 3 h and provided the expected imidazopyridine and imidazothiazole derivatives **31** in excellent yields when a wide range of aromatic and heteroaromatic aldehydes **27**, primary, secondary, and tertiary aliphatic isocyanides **2** and both electron-rich and electron-poor aminoazines **30** were employed as the starting building blocks. From a mechanistic point of view the reaction proceeded via the formation of the Schiff base **I** deriving from the aldehyde **27** and the 2-aminoheterocycle **30**, and its subsequent nucleophilic attack by the isocyanide **2**. At this point, a photochemical activation of the so obtained nitrilium ion **II** was supposed to induce the generation of the radical intermediate **III**, whose intramolecular cyclization, followed by 1,3-*H* shift, finally resulted into the desired product **31**. However, the proposed mechanism raises doubts for the generation of a free hydroxyl radical and would request further investigation.

More recently, the possibility to start from benzylamines, in situ oxidized to imines by means of eosin Y as a readily available and metal-free HAT photocatalyst, was reported by Singh and co-workers (Scheme 18).[31] More in detail, they synthesized a library of 3-aminoimidazo[1,2-*a*]pyridines **31** by reacting differently substituted benzylamines **32**, 2-aminopyridines **30**, and isocyanides **2** in a 2:1 EtOH/H_2O mixture, at room temperature, in the presence of a 2 mol % loading of eosin Y, under irradiation with 22 W white LEDs.

This operationally simple and environmentally friendly procedure gave the desired products **31** in short times and with excellent yields. While both electron-poor and electron-rich benzylamines successfully reacted under the optimized conditions, the scope of 2-aminopyridines **30** and isocyanides **2** was poorly described with *tert*-butyl isocyanide as the sole investigated isocyanide. Since a direct SET between benzylamine **32** and excited eosin Y was excluded due to the values of their redox potentials, a HAT from the benzylic C–H of benzylamine to the excited photocatalyst was supposed to



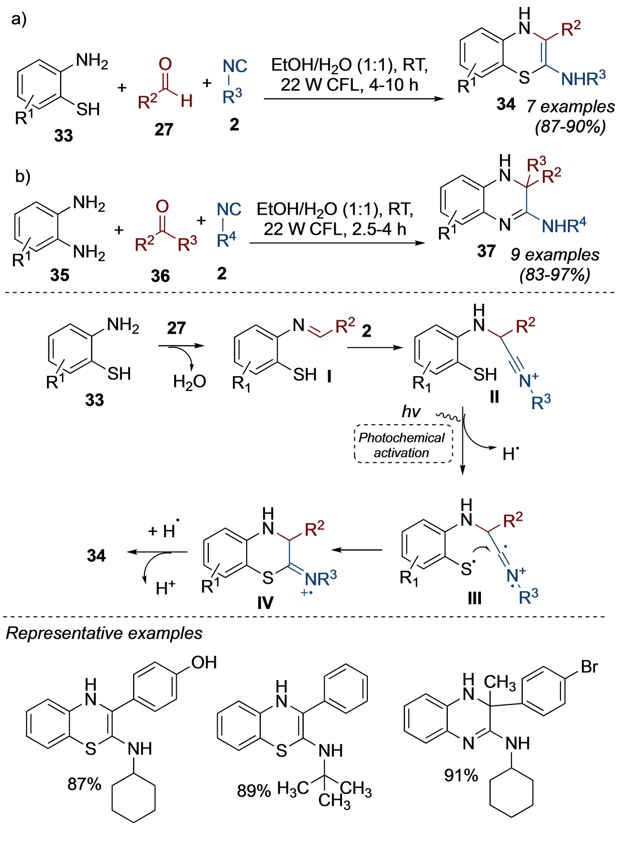
Scheme 18. The photocatalyzed GBB 3-CR starting from benzylamines **32**, 2-aminopyridines **30**, and isocyanides **2**.

generate the benzylic radical intermediate **I**. The latter further underwent the transfer of a hydrogen atom to molecular oxygen, resulting in benzylimine **II**. O_2 from the air was also responsible for a reverse HAT from the reduced eosin EY–H, thus having a key role in regenerating the ground-state photocatalyst. Benzylimine **II** could then react with a 2-aminopyridine **30** to give, after ammonia elimination, the imine intermediate **III**, whose interception by the isocyanide **2** provided the corresponding nitrilium ion **IV**. Finally, photoactivation of the nitrilium ion **IV** to give **V** followed by its radical cyclization led, as described previously, to the desired product.

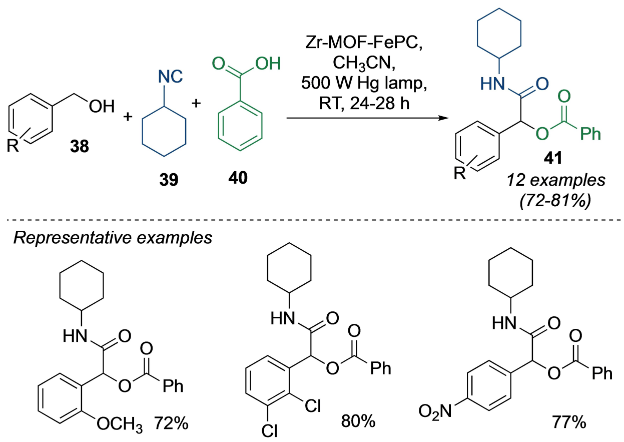
The GBB 3-CR could be considered, among others, as an "interrupted Ugi reaction".[32] This subclass of Ugi-type reactions often involves 3-component 4-center reactions where a tethered nucleophile intercepts intramolecularly the nitrilium ion to give cyclic derivatives. In this context, Yadav N. et al. reported the synthesis of benzothiazine adducts **34** by exploiting a visible light triggered intramolecular cyclization of a sulphur radical onto the nitrilium ion intermediate (Scheme 19a).[33]

The reaction involved *o*-aminothiophenols **33**, aromatic aldehydes **27**, and aliphatic isocyanides **2** straightforwardly reacting in a 1:1 EtOH/H_2O mixture, at room temperature, under 22 W CFL irradiation, and represented a green and facile route to access 1,4-benzothiazine derivatives **34** with a high atom economy. Interestingly, when ketones **36** and *o*-phenylenediamines **35** were employed in place of aromatic aldehydes **27** and *o*-aminothiophenols **33**, respectively, a variety of 3,4-dihydroquinoxaline derivatives **37** were obtained in good to excellent yields (Scheme 19b). A plausible reaction mechanism was depicted in Scheme 19: it entailed the formation of the imine **I** and its interception by the isocyanide **2** leading to the nitrilium ion intermediate **II**. The latter underwent photochemical activation generating the sulfur radical **III**, whose intramolecular cyclization on the isocyanide carbon atom, followed by 1,3-*H* shift, finally resulted in the benzothiazine product **34**.

Older than the Ugi 4-CR, the Passerini 3-component reaction (P-3CR) was serendipitously discovered by the Italian chemist Mario Passerini in 1922. He was attempting the characterization of *p*-isocyano azobenzene by reacting the isocyanide functional group with peracetic acid, formed in situ from acetic acid and hydrogen peroxide, and using acetone as a solvent. After stirring the reaction mixture for seven days Passerini observed the formation of an unexpected product that resulted be the three-component adduct incorporating acetone, acetic acid, and the *p*-isocyano azobenzene.[24] The P-3CR is nowadays considered a milestone in the field of MCRs, claiming a myriad of further studies including medicinal chemistry applications and enantioselective versions, which led to the discovery of new multicomponent related transformations.[34] Among them, the possibility to expand the scope of the starting components to alcohols, as precursors of aldehydes and ketones, has been pioneered by Zhu et al. who reported the in situ IBX mediated oxidation.[35] In 2017, Azarifar et al. developed the one-pot tandem UV-light photooxidative P3-CR of alcohols mediated by zirconium-based MOFs (Scheme 20).[36] These high porous coordination polymers - consisting of twelve-coordinated Zr_6 nodes, bridged by dicarboxylate linkers - were postsynthetically modified to incorporate Fe(III) complexes, and the resulting Zr-MOF-FePC proved to efficiently catalyze the photooxidation of a variety of benzyl alcohols **38** to the corresponding aldehydes, reacting in situ with cyclohexyl isocyanide **39** and benzoic acid **40** to afford α-acyloxy amides **41**. Although Zr-MOF-FePC required UV-light irradiation to exhibit optimum catalytic activity, it could be easily recovered by centrifugation at the



Scheme 19. Photocatalyzed interrupted Ugi reactions leading to 1,4-benzothiazines **34** and 3,4-dihydroquinoxalines **37**.

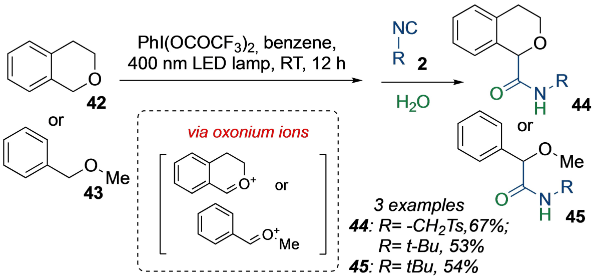


Scheme 20. Photocatalyzed oxidative Passerini 3-CR.

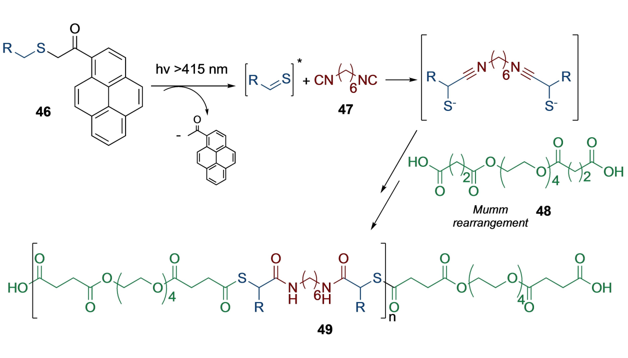
end of the reaction and was efficiently reused for at least two more cycles without significant loss of activity.

Interestingly, the visible light photooxidation of benzyl ether derivatives **42** and **43** to oxonium ions, followed by the addition of an isocyanide and water, was reported by Maruoka et al. while developing a strategy for the direct benzylic esterification of alkylbenzenes via the photolysis of [bis(trifluoroacetoxy)iodo]-benzene (PIFA) (Scheme 21).[37] While the reaction with alkylbenzenes led to the desired benzyl ester derivatives, when isochroman **42** was employed as a substrate a hydroxylated product was recovered, probably due to the generation of a cyclic oxonium ion after the elimination of the trifluoroacetoxy group, and its subsequent hydrolysis during the work-up procedures. This hypothesis was confirmed by carrying out the photoreaction of isochroman **42** or benzyl methyl ether **43** with PIFA under standard condition, followed by the addition of different nucleophiles, including TosMIC and *t*-butylisocyanide, in the attempt of intercepting the oxonium ion intermediate; this resulted in the expected amide derivatives **44** and **45**, respectively, with moderate yields.

More recently, D'hooge and Barner-Kowollik described how highly reactive thioaldehydes, generated in situ from a suitable photoactive precursor **46**, could be involved in a Passerini multicomponent polymerization to generate soft matter materials **49** (Scheme 22).[38] More in detail, irradiation of pyreneacyl sulfide derivatives **46** with visible-light triggered a Norrish II elimination reaction yielding thioaldehydes, which in presence of diisocyanide monomers (1,6-diisocyanohexane **47**) and diacid monomers (tetraethylenedisuccinic acid **48**) underwent a step-growth polymerization enabling the incorporation of thioester moieties directly into the polymer backbone. Such a procedure allowed to bypass the need to first synthesize a thioester-containing monomer and provide a straightforward route to soft matter materials that could be easily degraded by aminolysis or chain expanded by the selective insertion of thiirane into the thioester moiety.



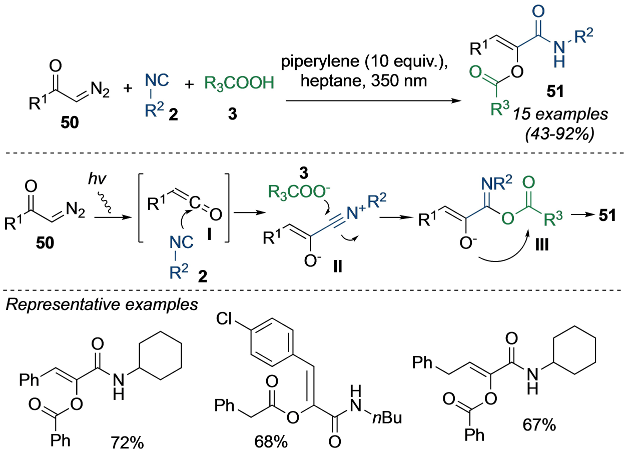
Scheme 21. Photocatalyzed oxidative Passerini 3-CR starting from benzyl ether derivatives.



Scheme 22. Visible light photoinduced Passerini multicomponent polymerization.

3. Photoinduced MCRs

The photoinduced generation of unstable species under visible light irradiation has demonstrated to be crucial for promoting three-component reactions involving isocyanides. To this end, meaningful examples have been reported by Basso A. et al., who exploited the formation in situ of ketenes **I** upon irradiation of α-diazoketones **50** in order to further react them with an isocyanide **2** and a carboxylic acid **3** to give stereo-defined captodative olefins **51** (Scheme 23).[39] The reaction scope involved aromatic, heteroaromatic, and aliphatic α-diazoketones **50**, a wide range of both aromatic and aliphatic carboxylic acids **3** and isocyanides **2** with yields ranging from 43 to 92%. According to Scheme 23, the proposed mechanism relied on the nucleophilic attack of the isocyanide **2** to the electrophilic ketene **I** with formation of a nitrilium ion **II**, followed by further attack of the carboxylate anion **3** to form the α-adduct **III**. An intramolecular transacylation gave the desired olefin **51**. Worthy of note, when the ketene intermediate **I** was generated upon base-mediated dehydrochlorination of an acyl chloride, it reacted with the carboxylic acid **3** to give a mixed anhydride. The latter could then regenerate a molecule of ketene **I** or react with an additional molecule of the carboxylic acid, thus releasing the carboxylic acid derivative of the starting acyl chloride. As a consequence, the presence of such different species affected the chemoselectivity and the reaction yield. In this case, the photochemical generation of ketenes **I** from α-diazoketones **50** was crucial to afford smoothly the desired captodative olefins **51**.

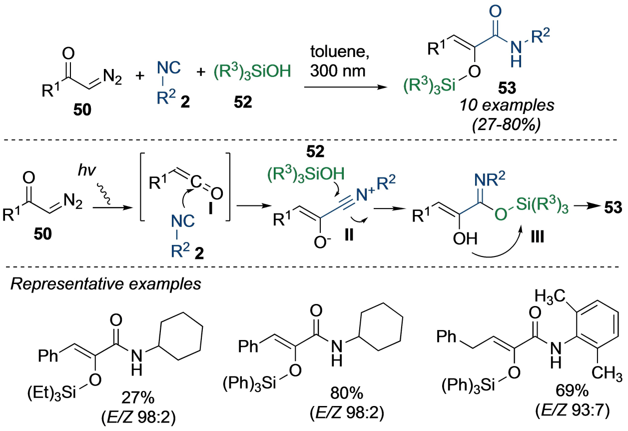


Scheme 23. Photoinduced multicomponent synthesis of captodative olefins **51**.

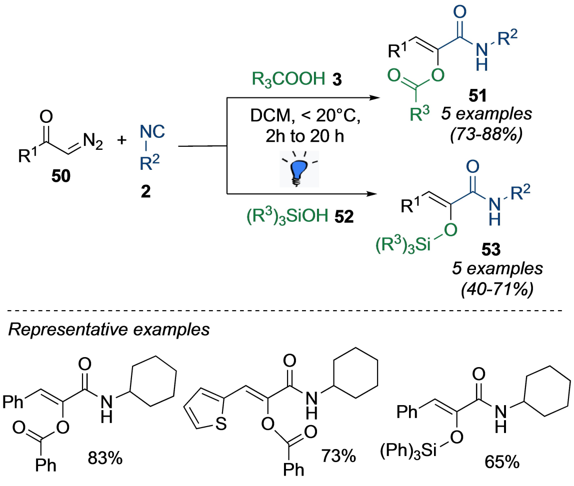
Later on, the same group developed a photoinduced multicomponent synthesis of α-silyloxy acrylamides **53** by replacing the carboxylic acid component with a silanol **52** (Scheme 24).[40]

A collection of 10 different derivatives was obtained in moderate to good yields, in some cases with complete *E*/*Z* selectivities. The mechanistic hypothesis, similar to the reaction with carboxylic acids, involved the attack of the silanol **52** to the nitrilium ion **III**, followed by 1,3-migration of the silyl functional group.

While the first reports employed UV light irradiation to promote the Wolff rearrangement of α-diazoketones **50** to ketenes **I**, more recently it has been shown that, despite a limited absorbance in the visible light region, it was possible to obtain both captodative olefins **51** and α-silyloxy acrylamides **53** under blue LEDs light irradiation (Scheme 25).[41] Interestingly, while UV light led to side processes, the visible light reaction showed a quantum yield close to 100% and enabled improved selectivity and broader scope both in batch and under continuous flow conditions.



Scheme 24. Photoinduced multicomponent synthesis of α-silyloxy acrylamides **53**.

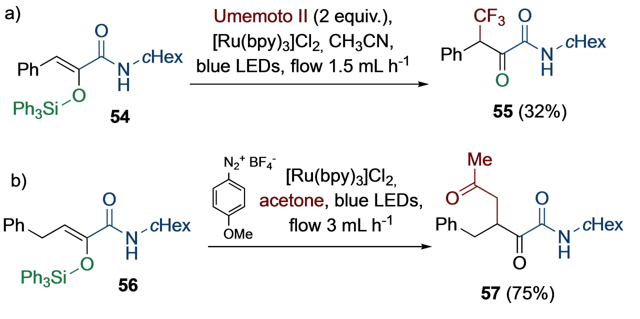


Scheme 25. Visible light photoinduced synthesis of captodative olefins **51** and α-silyloxy acrylamides **53**.

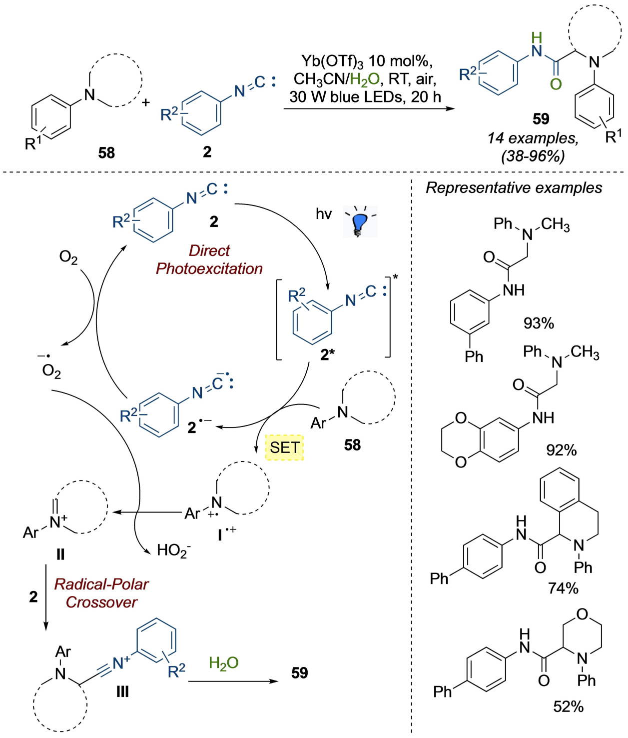
Furthermore, the mildness of visible light reaction conditions empowered the combination in tandem with other visible light mediated transformations, thus increasing the affordable chemical space (Scheme 26). More in detail, derivative **54** underwent a trifluoromethylation to α-ketoamide **55** in 32% yield by reacting with the Umemoto II reagent, in the presence of a ruthenium-based photocatalyst, in MeCN under blue LEDs irradiation (Scheme 26a), while derivative **56** afforded 1,4-diketone **57** in an overall 40% (based on two steps) upon reaction with 4-methoxyphenyl diazonium tetrafluoroborate, and $[Ru(bpy)_3]Cl_2$ in acetone under blue LEDs irradiation (Scheme 26b). Interestingly, the first transformation was performed both in batch and under continuous flow conditions, while for the second one the crude mixture was directly reacted in a flow system.

4. Self-Catalyzed Photoinduced MCRs

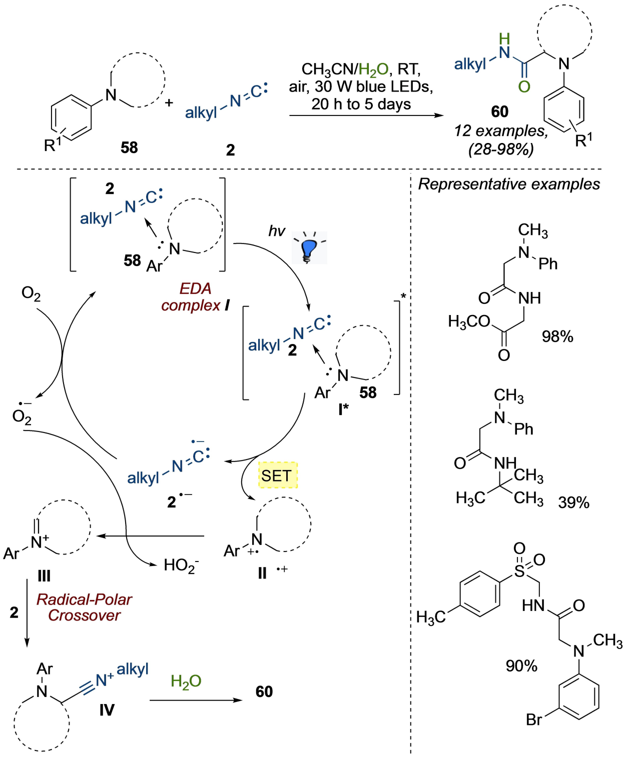
Following our interest in visible light photocatalytic reactions involving isocyanides, we recently experienced once more as they could be a never-ending source of surprises. While investigating the possibility to perform some Ugi-like MCRs starting from aromatic tertiary amines **58**, isocyanides **2**, and a third component we discovered that aromatic isocyanides could be harnessed as photocatalysts in the α-amino C(sp^3)–H functionalization (Scheme 27).[42] Accordingly, by mixing an aromatic isocyanide **2** and an *N*,*N*-dimethylaniline **58** in a MeCN/water mixture, at room temperature, under air and 30 W blue LEDs irradiation, in the presence of a 10 mol% loading of $Yb(OTf)_3$, it was possible to obtain a wide range of amide derivatives **59** in good to excellent yields (up to 96%). Both fluorescence and absorption experiments supported the ability of aromatic isocyanides **2** to reach an excited state upon visible light irradiation and to be quenched by an aromatic tertiary amine **58**, therefore indicating a possible SET event, which would trigger the formation of an amine radical cation **I**. Further abstraction of a hydrogen atom from **I** mediated by superoxide radical anion, formed in situ from molecular oxygen to regenerate the ground state isocyanide, led to the iminium ion **II** (Scheme 27). The latter was then intercepted by the isocyanide



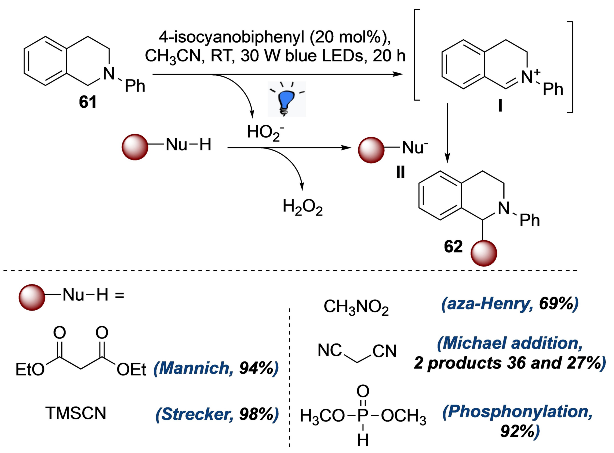
Scheme 26. Coupling of ketene 3-CRs with other visible light photoredox processes.



Scheme 27. Visible light photocatalytic Ugi 3-CR with aromatic isocyanides.



Scheme 28. Visible light photocatalytic Ugi-3CR with aliphatic isocyanides.



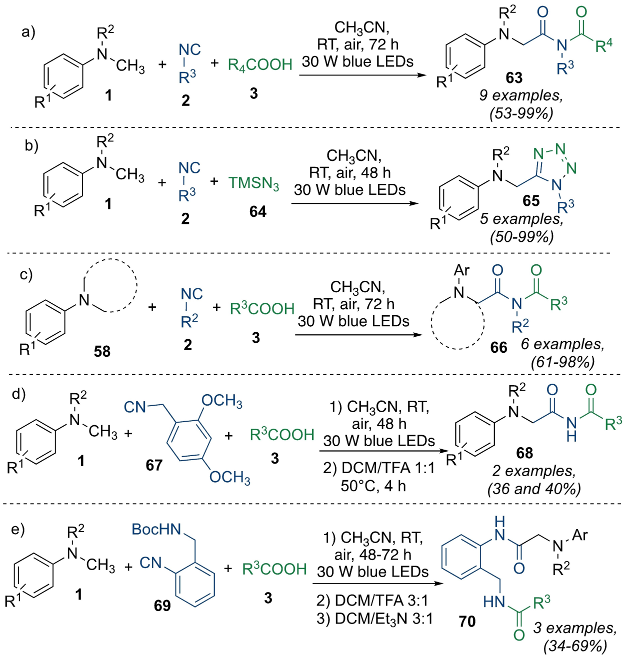
Scheme 29. Michael-type addition reactions promoted by 4-isocyanobiphenyl as a photoredox catalyst.

2 to give a nitrilium ion **III**, which was then hydrolyzed to amide **59**.

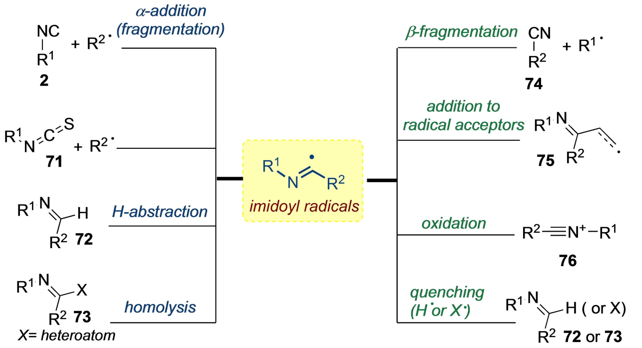
Surprisingly, the reaction proceeded even with aliphatic isocyanides for which absorption experiments indicated the formation of an Electron Donor/Acceptor (EDA) complex with the aromatic tertiary amine (Scheme 28). A small library of 12 examples with yields up to 98% proved a good substrate scope for both the amine and the isocyanide starting materials. Besides investigating the scope of this self-catalyzed Ugi-type three-component reaction, the photocatalytic activity of 4-isocyanobiphenyl was tested in a small collection of visible light promoted transformations such as Mannich, Strecker, *aza*-Henry, Michael addition, and phosphonylation reactions (Scheme 29).

Here, the isocyanide mediated generation of the iminum ion **I** from *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **61** was followed by the addition of either carbon and heteroatom (pro)nucleophiles such as diethyl malonate, cyanotrimethylsilane, nitromethane, malononitrile, and dimethyl phosphite. Interestingly, the resonance-stabilized carbanions **II** (Michael donors) were formed thanks to the hydroperoxide anion HO_2^-, formed in situ from molecular oxygen in the regeneration of the ground state isocyanide, without requiring the addition of any further base.

Shortly after, the scope of the Ugi-like self-catalyzed visible light photochemical transformation was further expanded to a range of multicomponent reactions including the Ugi 3-CR, the Ugi-tetrazole 3-CR, the Ugi-Joullié 3-CR, the synthesis of secondary imides via cleavable isocyanide, and an Ugi-Deprotection-Mumm transacylation (UDeM) sequence (Scheme 30).[43] After short rounds of reaction conditions optimization, a selection of both aliphatic and aromatic isocyanides **2** was reacted with diverse carboxylic acids **3** including complex structures such as ibuprofen, biotin, indomethacin, and cholic acid in acetonitrile under 30 W blue LEDs irradiation to give the desired α-amino amides **63** in up to quantitative yields (Scheme 30a). These photocatalytic conditions were also successfully applied with cyclic tertiary amines **58** such as *N*-phenyltetrahydroisoquinoline, *N*-phenylpyrrolidine, and *N*-phe-



Scheme 30. Visible light self-catalyzed Ugi-like multicomponent reactions.



Scheme 31. Origins and fates of imidoyl radicals.

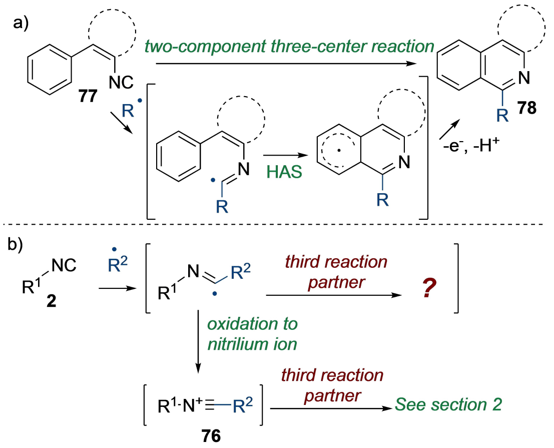
nylpiperidine (Scheme 30b) while the replacement of carboxylic acids **3** in the Ugi reaction with azidotrimethylsilane **64** enabled a [3+2] cyclization leading to 1,5-disubstituted tetrazole derivatives **65** in good to excellent yields thus further proving the mildness and the robustness of isocyanides as visible light photocatalysts (Scheme 30c). The functional group orthogonality and the potential to enable a fast and easy diversification of the Ugi-like scaffolds were proven in the synthesis of secondary imides **68** using 2,4-dimethoxybenzyl isocyanide **67** as a cleavable one (Scheme 30d) and in an UDeM sequence leading to peptidomimetics **70** (Scheme 30e).

5. MCRs Involving the Generation of an Imidoyl Radical Intermediate

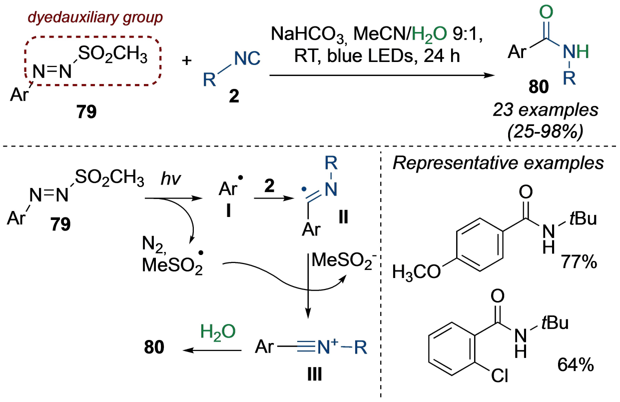
Imidoyl radicals could be generated via hydrogen atom abstraction from aldimines **72**, via homolytic fragmentation of a suitable precursor **73**, and via addition of a radical species to either an isothiocyanate **71** or to isocyanides **2**, the last being the most exploited and general route thanks to the somophilic behavior and the wide availability of isocyanides and to their orthogonality in a plethora of reaction conditions (Scheme 31).[44] Once they have been generated, imidoyl radicals could meet different fates: 1) α- fragmentation to give an isocyanide and a radical species; 2) β-fragmentation to a nitrile **74** and a radical species; 3) further addition to a radical acceptor, for example, an alkene, an alkyne, or a tethered aromatic sp^2-bond as in intramolecular cyclizations; 4) oxidation to nitrilium ion **76**; 5) quenching with a further radical species as in atom transfer radical addition (ATRA) or hydrogen atom transfer (HAT) reactions (Scheme 31).

Far back as 2007, Nanni D. et al. highlighted the attractiveness of generating imidoyl radicals as intermediates for the synthesis of heterocyclic compounds, for example, indoles, phenanthridines, pyrrolidines, quinolines, quinoxalines, and fused polycyclic derivatives such as camptothecin and related analogues via cyclizations, annulation, and cascade reactions involving the addition to unsaturated bonds as for alkenes, alkynes, and (hetero)aromatic rings. Imidoyl radicals have also been efficiently employed in intermolecular reactions leading to the synthesis of carbonyl compounds, amides, and nitriles.[45] Nevertheless, the procedures reported so far often required harsh reaction conditions such as UV light irradiation, high temperatures, and/or the use of excess quantities of an initiator (e.g., peroxides, AIBN, and peroxydicarbonates). Since then, the study and the exploitation of imidoyl radicals as key intermediates have found plenty of applications and more recently, the availability of mild conditions thanks to visible light photoredox catalytic generation of open shell species has further boosted the interest in such a class of reactive (not isolable) compounds.[46] While two-component three-center photochemical MCRs involving 2-isocyanoaryls and vinylisocyanides **77** and proceeding via intramolecular homolytic aromatic substitution (HAS) have been extensively studied with a wide range of open shell species (isocyanides radical insertion reactions) (Scheme 32a), literature reports about three- or more component reactions involving suitable radical precursors, isocyanides, and a third partner are poorly available (Scheme 32b). This could be probably due to thermodynamically favored oxidation of imidoyl radicals to nitrilium ions,[47] which are then smoothly converted to amides thus preventing further inter-molecular addition of a third species other than water. In this realm, an interesting three-component visible light driven reaction leading to aromatic amides via radical arylation of isocyanides was reported by Malacarne M. et al. (Scheme 33).[48]

The transformation did not require any photocatalyst as it involved photolabile and bench-stable arylazo sulfones **79** bearing a dyedauxiliary group, which upon irradiation at 450 or 410 nm reached a singlet nπ* excited state, undergoing homolysis of the N–S bond and releasing N_2 and an aryl radical species **I**. The latter was then trapped by the somophilic



Scheme 32. a) Radical isocyanide insertion reactions; b) intermolecular interception of imidoyl radicals.

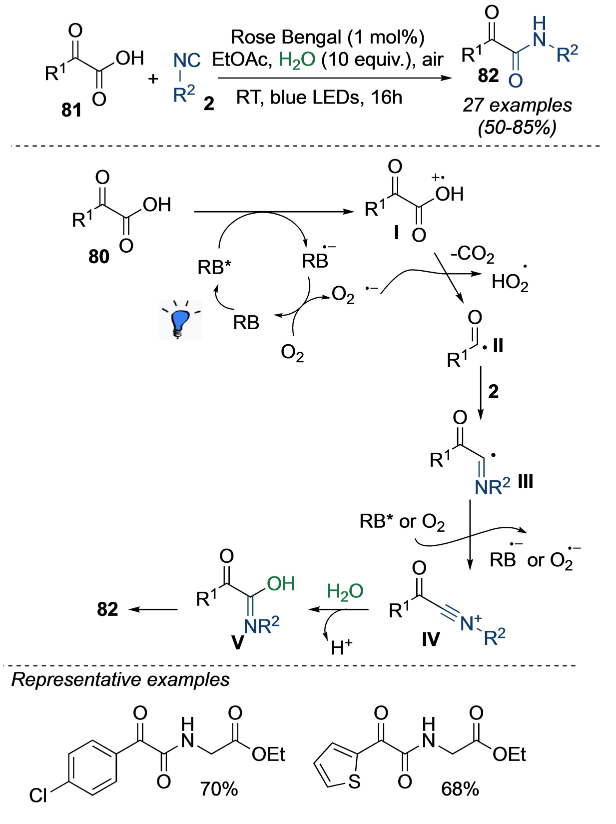


Scheme 33. Visible light triggered 3-CR leading to amides **80**.

isocyanide, to give an imidoyl radical **II**, which was oxidized via SET by methane-sulfonyl radical to nitrilium ion **III**. Further addition of water led to benzamides **80**. Interestingly, the trapping of the aryl radical **I** by the isocyanide was faster than hydrogen atom transfer with minimum formation of reduced aryl compounds.

Arylation of *tert*-butyl and cyclohexyl isocyanide was achieved in good to moderate yields with both electron-rich and electron-poor aryldiazosulfones, while the use of 2-morpholinoethyl isocyanide led to the synthesis of the anti-depressive moclobemide and a small library of related analogues in discrete yields (34–45 %).

Later on, Y. Lv et al. reported the synthesis of α-ketoamides **82** from α-oxocarboxylic acids **81**, isocyanides **2**, and water via rose bengal mediated generation of an acyl radical intermediate **II** (Scheme 34).[49] The latter was then intercepted by the isocyanide to give an imidoyl radical **III**, which was promptly oxidized to nitrilium ion **IV** and finally hydrolyzed to give an α-ketoamide **82**. The substrate scope was wide, involving both electron-rich and electron-poor α-oxocarboxylic acids as well as heterocyclic ones with good yields. The scope of the isocyanide as reaction partner was comparable encompassing primary, secondary, and tertiary aliphatic isocyanides as well as aromatic ones.



Scheme 34. Visible light photoredox catalytic decarboxylative acylation of isocyanides to α-ketoamides **81**.

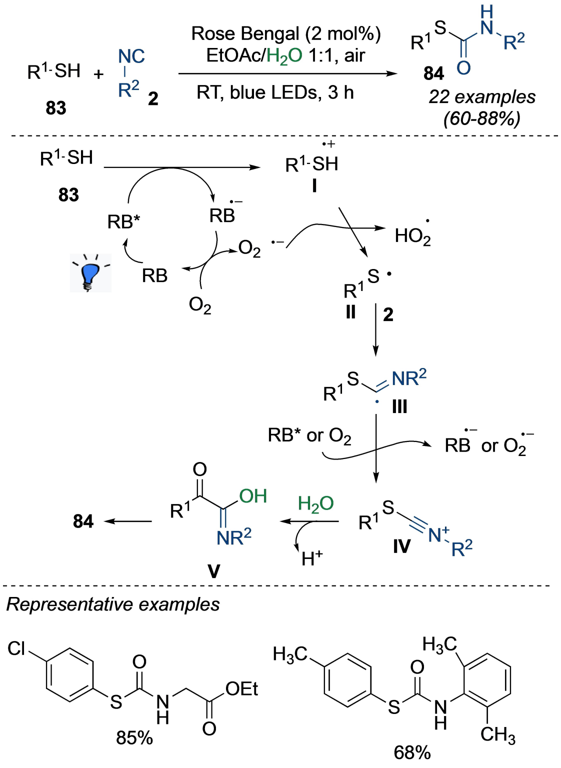
Besides aryl and acyl radicals, isocyanides have also been showed to efficiently add thyil radicals **II** leading to thiocarbamates **84** after rose bengal mediated oxidation to nitrilium ion **IV** and further addition of water (Scheme 35).[50]

The reaction scope was excellent as well with both electron-rich and electron-poor aromatic thiols and aliphatic ones **83**, while only aliphatic isocyanides were investigated, except for a single example.

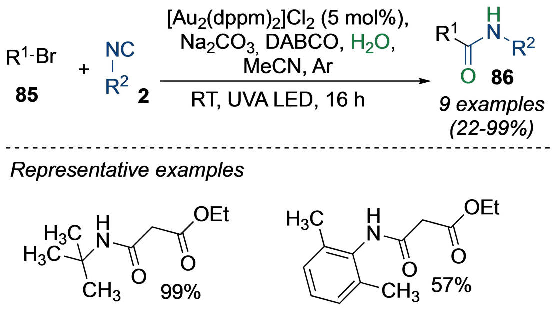
The possibility to get amide derivatives **86** starting from alkyl bromides **85**, isocyanides **2**, and water was at first investigated in 2018 by S. Rohe et al. under photoredox gold catalysis (Scheme 36).[51] By using a dimeric gold (I) photoredox catalyst $[Au_2(dppm)_2]Cl_2$ under UVA LED irradiation, the authors were able to generate an alkyl radical from an unactivated bromoalkane **85**, which then added onto an isocyanide to give an imidoyl radical. The latter underwent, as ever, a SET event to nitrilium ion, which was hydrolyzed to amide **86**.

More recently, we developed a visible light photocatalytic functionalization of isocyanides **2** to secondary amides **89** and **90** (Scheme 37).[52]

The reaction was performed in acetonitrile under 30 W blue LEDs irradiation and was efficiently promoted by *fac*-Ir(ppy)$_3$ as the photocatalyst, Na_2CO_3 as a base, and DABCO as a sacrificial electron donor. The bromoalkanes substrate scope was limited

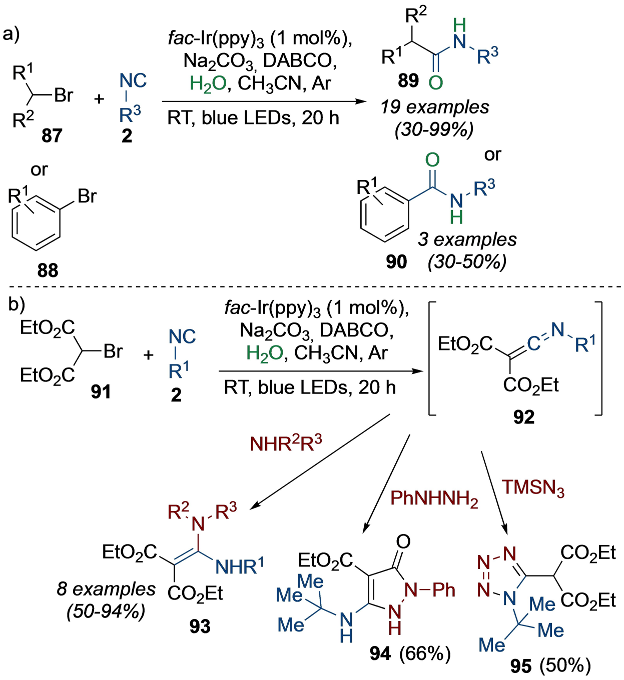


Scheme 35. Visible light photoredox catalytic synthesis of thiocarbamates from thiols, isocyanides, and water.

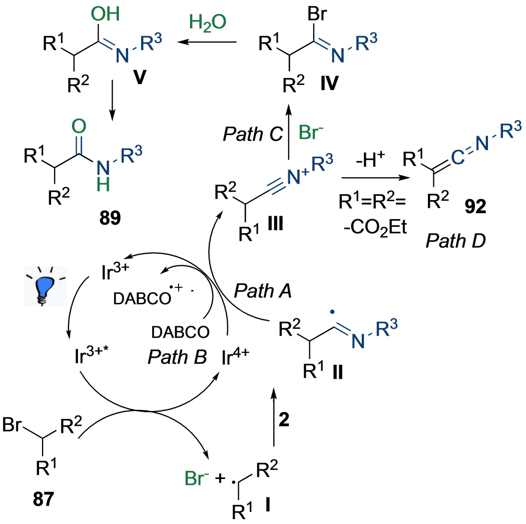


Scheme 36. Gold photoredox catalytic synthesis of amides **86**.

to electron-poor ones, while a wide range of aliphatic and aromatic isocyanides proved to be competent reaction partners. The optimized reaction conditions afforded the desired amide also when performed under sunlight irradiation and on a gram scale. Interestingly, when diethyl bromomalonate **91** was used, a ketenimine **92** was obtained, which could be used as a chemical platform, so that the addition in situ of a third component such as an amine, an arylhydrazine, or azidotrimethylsilane enabled a two-step one-pot multicomponent synthesis of ketene aminals **93**, and cyclic derivatives such as pyrazolones **94** and tetrazoles **95** (Scheme 37b). According to Scheme 38, indeed, an alkyl radical intermediate **I** was formed from bromoalkanes **87** upon a SET mediated by Ir^{3+*}; isocyanide addition led to the imidoyl radical **II**, which could be then oxidized to nitrilium ion **III** by either Ir^{4+} (Path A) or DABCO



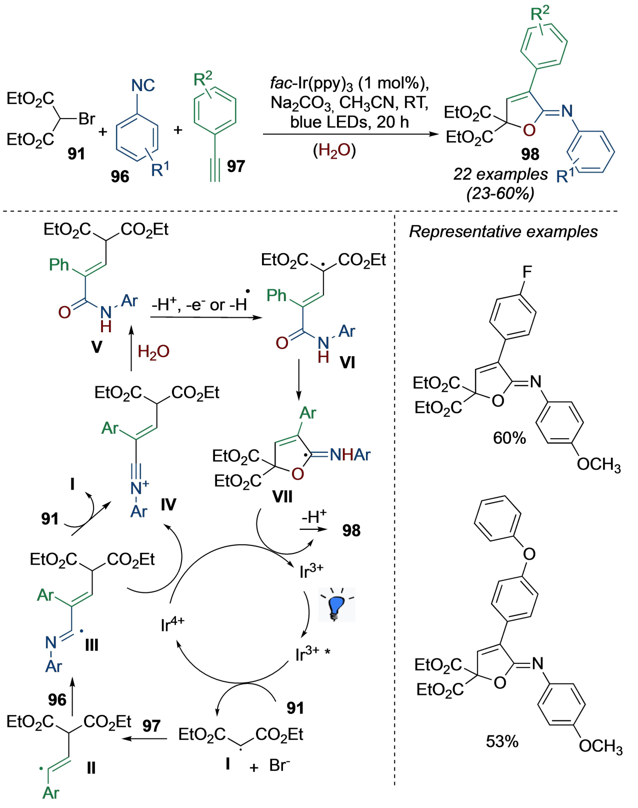
Scheme 37. Visible light photoredox catalytic MCRs for the synthesis of amides and ketene aminals.



Scheme 38. Mechanistic hypothesis for the visible light photoredox catalytic MCRs for the synthesis of amides **89** and ketene imines **92**.

(Path B). Depending on the bromoalkane, the nitrilium ion **III** could be hydrolyzed to amide **89** (Path C) or converted to ketenimine **92** upon base-mediated proton abstraction (Path D).

Concomitantly, our laboratory also developed a three-component photoredox catalytic domino cascade to iminofurans **98** starting from diethyl bromomalonate **91**, aryl acetylenes **97**, and aryl isocyanides **96** (Scheme 39).[53] To our knowledge this stands for the first example of a visible light photocatalytic reaction involving the insertion of a vinyl radical **II** into the

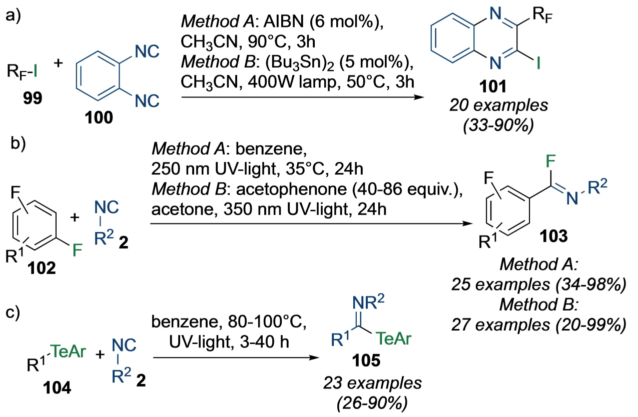


Scheme 39. Photocatalytic multicomponent domino cascade to iminofurans **98**.

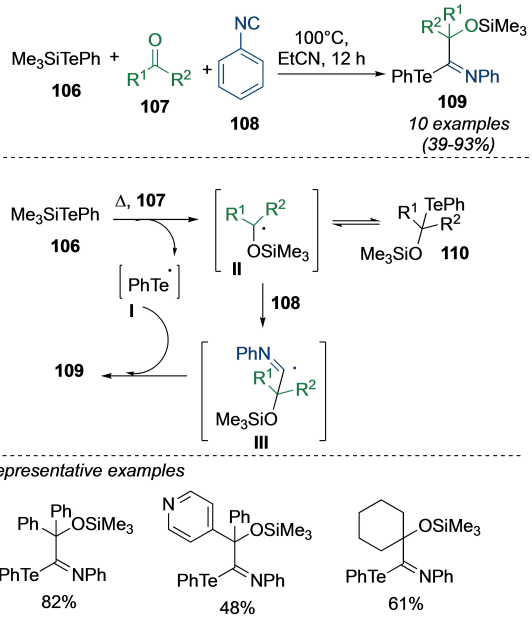
somophilic isocyanide. As in Scheme 39, the alkyl radical **I**, generated upon Ir^{3+*} mediated SET reacted with the triple bond of the aryl acetylenes **97** to afford the radical intermediate **II**, which in turn added to the isocyanide **96** to generate the imidoyl radical intermediate **III**. The latter was then oxidized by Ir^{4+} to nitrilium ion **IV**, thus regenerating the ground state photocatalyst Ir^{3+}. Addition of water to give the amide **V** and further oxidation/deprotonation step, probably occurring thanks to bromomalonate **91** reduction to alkyl radical **I** in a chain-reaction, led to intermediate **VI**, which underwent cyclization to **VII** and to the final iminofuran **98** upon loss of a proton. Nevertheless, it is not possible to exclude that the formation of such derivatives could proceed via hydrogen atom transfer from the amide **V** to the photogenerated alkyl radical **I**, which was hence converted to diethyl malonate. The reaction scope involved both electron-poor and electron-rich aromatic isocyanides and aryl acetylenes, with yields ranging from 39 to 60%, quite good for a multicomponent triple domino process. This transformation highlighted the huge potentialities of isocyanide-based photocatalytic multicomponent reactions involving the generation of imidoyl radicals, worthy of note if considering that the rules and the requirements for their development are still poorly investigated.

Although beyond the scope of this review, pioneering examples of such potentialities requiring either UV irradiation or heating are available in literature.[54] In these reactions the imidoyl radical, once formed upon addition of a radical species to the isocyanide, further reacted with a second radical to formally give an *isocyanide insertion*. In this context, two-component transformations involving an Atom-Transfer-Radical-Addition (ATRA) mechanism starting from either (perfluoro)alkyl iodides **99** (Scheme 40a) or perfluoro arenes **102** (Scheme 40b) were reported by Studer et al.,[55] while Yamago S. et al. back in 2001 described both synthetic and theoretical studies about group-transfer imidoylation of organotellurium compounds **104** (Scheme 40c).[56]

Similar group transfer reactions have been exploited in multicomponent processes. For instance, Miyazoe et al. in 2000 exploited silyl tellurides **106** as excellent precursors for silyl-centered radicals, which were engaged in a three-component reaction with carbonyl compounds **107** and phenyl isocyanide **108** under thermal conditions (Scheme 41).[54a] The substrate



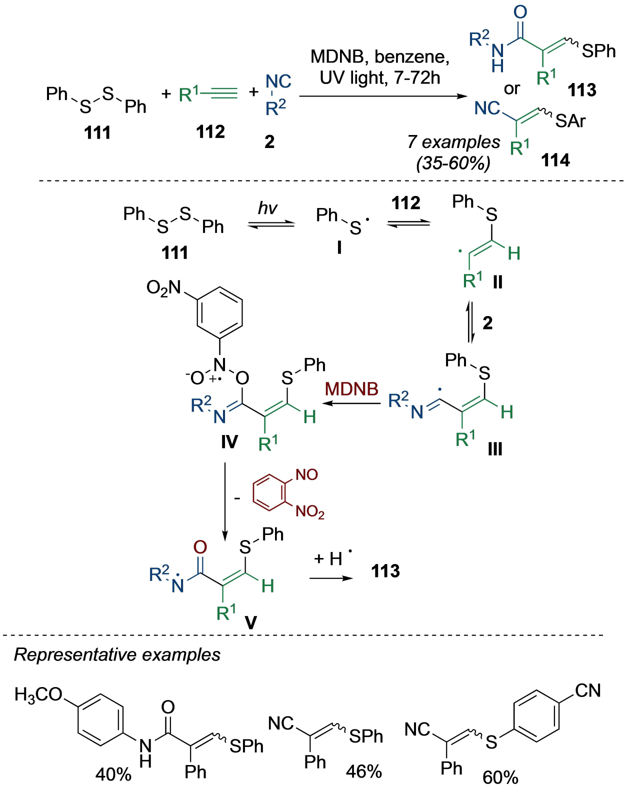
Scheme 40. Atom- and group- transfer radical addition reactions of isocyanides.



Scheme 41. Three-component reaction of silyl tellurides **106**, carbonyl compounds **107** and phenyl isocyanide **108**.

scope was investigated with a selection of both aromatic and aliphatic carbonyl compounds, with yields ranging from 39 to 93%. Based on mechanistic experiments, the authors proposed a reaction pathway involving the generation of a silyl radical followed by its addition to the carbonyl compound to generate a Te-centered radical **I** along with the carbon-centered radical **II**. Subsequent reaction of the latter with the isocyanide **108** gave the imidoyl radical **III**, which underwent a group-transfer reaction to form **109**. At the same time, **II** could also give the organotellurium compound **110** able to regenerate **II**. Worthy of note, the authors also showed how the C–Te bond of **109** could be further harnessed to obtain for example α-hydroxy carbonyl compounds.

In the same year, Leardini R. et al. reported the three-component radical cascade reaction of aromatic disulfides **111**, alkynes **112**, and aromatic isocyanides **2** to give either β-arylthio-substituted acrylamides **113** or acrylonitriles **114** (when *t*-butyl isocyanide was used as the starting material) under photolytic conditions (Scheme 42).[54b] The reaction proceeded via addition of a sulfanyl radical **I** to the alkyne with formation of a vinyl radical **II**, which readily added to the isocyanide to form the imidoyl radical **III**. The latter was then trapped with *m*-dinitrobenzene (MDNB) to form acrylamide derivatives **113**. In the absence of a suitable trapping agent the imidoyl radical could either undergo a β-fragmentation to acrylonitriles **114** or give back the vinyl radical and the isocyanide in a reversible process. A mixture of *E* and *Z* isomers were obtained in moderate to good yields, and optimum conditions required UV irradiation and a nitrogen atmosphere with reaction times of 7–72 h at room temperature.



Scheme 42. Three-component reaction of aromatic disulfides **111**, alkynes **112**, and aromatic isocyanides **2**.

6. Conclusion and Outlook

In conclusion, the present literature revision would provide a critical analysis of both potentialities and challenges entailed in the development of new visible light photo-triggered IMCRs. Spanning from radical-polar crossover pathways exploited, for example, in the Ugi-like and the Passerini-like processes to the photoinduced transformations as for the generation in situ of ketenes from diazoketones, it is clear how the application of visible light photocatalytic conditions could be key to expand both the substrate and the reaction scope of cornerstone MCRs. Accordingly, these photocatalytic approaches enabled the exploitation of widely available nucleophiles such as amines and alcohols as precursors of electrophiles such as imine/iminium ions and carbonyls -aldehydes and ketones- under mild oxidative conditions. Depending on the reaction partners these new oxidative photocatalytic MCRs would provide either new chemical approaches to well-known scaffolds or completely new ones, difficult or impossible to synthesize via conventional procedures. Even more stimulating, it has also been shown how the photoactivity of isocyanides could boost the green nature of MCRs by avoiding the use of an additional external catalyst. On the other hand, the possibility of engaging isocyanides as somophiles, i.e., as radical acceptors, to generate imidoyl radicals followed by further trapping with either a radical acceptor or a radical species (such as in ATRA reactions) still poses major challenges. Nevertheless, the different possible fates that imidoyl radicals could undergo makes them fascinating species worthy of further investigations and we are confident that visible light photocatalysis could unveil new exciting developments in the field.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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