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Strategies for the Photocatalytic Generation of Carbanion Equivalents for Reductant-Free C–C Bond Formations

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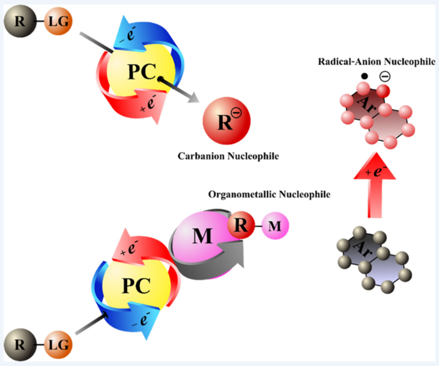

CONSPECTUS: The use of photocatalysis in organic chemistry has encountered a surge of novel transformations since the start of the 21st century. The majority of these transformations are driven by the generation and subsequent reaction of radicals, owing to the intrinsic property of common photocatalysts to transfer single electrons from their excited state. While this is a powerful and elegant method to develop novel transformations, several research groups recently sought to further extend the toolbox of photocatalysis into the realm of polar ionic reactivity by the formation of cationic as well as anionic key reaction intermediates to furnish a desired product.

Our group became especially interested in the photocatalytic formation of anionic carbon nucleophiles, as the overall transformation resembles classical organometallic reactions like Grignard, Barbier, and Reformatsky reactions, which are ubiquitous in organic synthesis with broad applications especially in the formation of valuable C–C bonds. Although these classical reactions are frequently applied, their use still bears certain disadvantages; one is the necessity of an (over)stoichiometric amount of a reducing metal. The reducing, low-valent, metal is solely applied to activate the starting material to form the organometallic carbanion synthon, while the final reaction product does generally not contain a metal species. Hence, a stoichiometric amount of metal salt is bound to be generated at the end of each reaction, diminishing the atom economy. The use of visible light as mild and traceless activation agent to drive chemical reactions can be a means to arrive at a more atom economic transformation, as a reducing metal source is avoided. Beyond this, the vast pool of photocatalytic activation methods offers the potential to employ easily available starting materials, as simple as unfunctionalized alkanes, to open novel and more facile retrosynthetic pathways. However, as mentioned above, photocatalysis is dominated by open-shell radical reactivity. With neutral radicals showing an intrinsically different reactivity than ionic species, novel strategies to form intermediates expressing a polar behavior need to be developed in order to achieve this goal.

In the last couple of years, several methods toward this aim have been reported by our group and others. This Account aims to give an overview of the different existing strategies to photocatalytically form carbon centered anions or equivalents of those in order to form C–C bonds. As the main concept is to omit a stoichiometric reductant source (like a low-valent metal in classical organometallic reactions), only redox-neutral and reductant-free transformations were taken into closer consideration. We present selected examples of important strategies and try to illustrate the intentions and concepts behind the methods developed by our group and others.

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highly reducing photocatalyst can activate suitable aromatic compounds to generate the corresponding radical-anion. This way, nucleophilic C(sp^2)- instead of C(sp^3)-centers can be generated in absence of a stoichiometric reductant.

1. INTRODUCTION

The formation of carbon—carbon bonds is at the core of organic synthesis, as these transformations provide the foundation to generate more complex organic compounds from simpler ones. Thus, the design and development of new methodologies for this reaction class is of prime importance in order to arrive at a desired product in an ever simpler, more efficient and more benign manner.[4]

A common strategy to furnish C—C bonds is the simple attack of a carbanionic nucleophile to a carbon electrophile. One of the oldest and most well-known reaction utilizing this approach is the Grignard reaction. In the classical protocol, zerovalent magnesium is added to an organohalide to generate a highly nucleophilic organometallic reagent (R-MgX), which acts as carbanion synthon.[5] The so-called Grignard reagent is capable of reacting with various electrophiles such as aldehydes, ketones, carbon dioxide, amides, and several more (Figure 1A),[6] opening facile access to valuable compounds, used in the synthesis of fine chemicals, pharmaceuticals and natural products.[6,7]

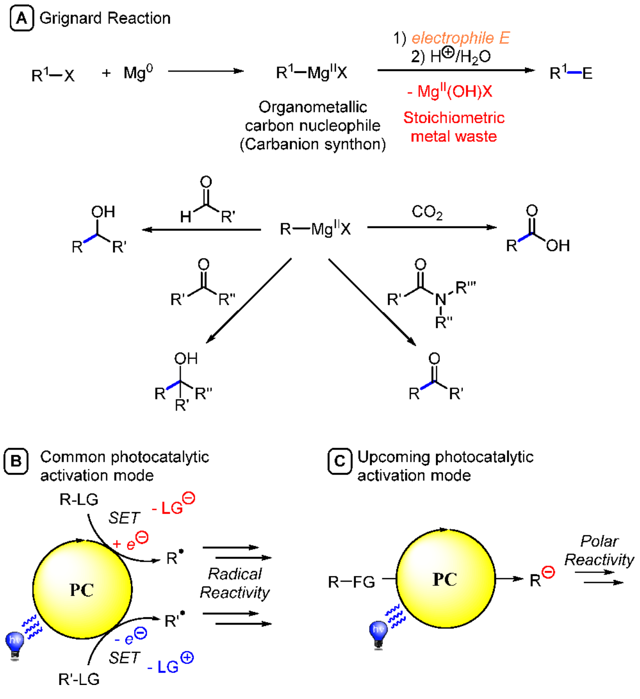

Figure 1. Molecule activation via the classical formation of an organometallic reagent vs photocatalysis.

While the applications of organomagnesium and other nucleophilic organometallic reagents like organozinc (e.g., in Reformatsky reactions),[8] organochromium (e.g., in Nozaki—Hiyama—Takai—Kishi reactions),[9] and several more[10] are manifold, their use still bears certain disadvantages. Besides the potentially harsh conditions and scarce availability of the required nucleophile precursor (in most cases an organohalide),[11] the main drawback is the necessity of an (over)-stoichiometric reducing metal source. The low-valent metal is however only needed as a reductant for the activation of the starting material and is not incorporated in the final product itself, thus leading to an (over)stoichiometric amount of metal salt waste at the end of the reaction.

Instead of utilizing reducing low-valent metals for the activation of organic molecules, visible light as a traceless energy source can be harnessed to drive chemical reactions as well.[12] Over the last decades, photocatalysis has emerged as a powerful methodology for various transformations and bond formations previously unattainable under thermal conditions and its advance in the synthetic field is summarized in several comprehensive reviews.[13] Yet, the main activation mode of photocatalytic reactions in organic chemistry is single-electron oxidation or reduction (termed photoredox catalysis), mostly leading to the formation of neutral radicals that drive the desired transformation (Figure 1B). Due to these single electron processes, photocatalytic reactions are dominated by open-shell radical reactivity, while the formation of polar ionic species as reactive key intermediates is more elusive (Figure 1C).

Recently, interest in the photocatalytic generation of anionic carbon nucleophiles has increased and several groups have described the formation of carbanions as key intermediates for the construction of carbon—carbon bonds.[14] Utilizing a photocatalytically generated carbanion intermediate for a subsequent C—C bond formation has the potential to overcome the above-mentioned downsides involving the use of nucleophilic organometallic reagents, as a stoichiometric metal amount can be avoided. Further, the photocatalytic activation of functional groups beyond (pseudo)halides, together with the potential sequence of radical followed by anionic reactivity can open novel transformations and reaction pathways. This way, readily available starting materials as simple as unfunctionalized alkanes can be used in order to furnish the desired product in high or even full atom economy under mild conditions. This Account discusses the most important strategies for the photocatalytic reductant-free generation of carbon nucleophiles for subsequent C—C bond formations, developed by our group and others.

2. CARBANION GENERATION VIA RADICAL REDUCTION

2.1. Radical Reduction after Trapping with a Double Bond

So far, carbon nucleophiles in photocatalysis have mainly been generated by the reduction of a neutral radical species rendering a carbanion intermediate. In order to arrive at a net redox-neutral and thus reductant-free transformation, the required radical needs to be generated by an oxidation process to harness the reducing equivalent necessary for the following radical reduction. The transformation of a radical species into a species showing ionic reactivity can be termed as radical-polar crossover. As numerous radicals are rather short-lived, the most common strategy is to use alkenes bearing stabilizing substituents as traps for the in situ formed radical. Thus, a more persistent radical may be generated, which can then be reduced in a subsequent step (Figure 2). The resulting carbanion is afterward able to react with a suitable electrophile giving the desired product.

In 2017, the Martin group used this strategy for the generation of carbanions in a synthetic manner.[15] In their report on the intermolecular dicarbofunctionalization of styrenes with CO_2 (Figure 3), trifluoromethyl sulfinates (2)

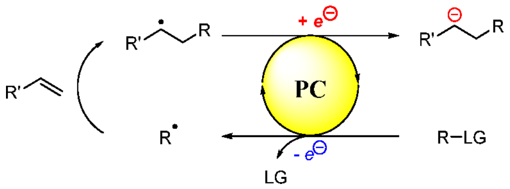

Figure 2. General strategy for the generation of carbanions after radical trapping.

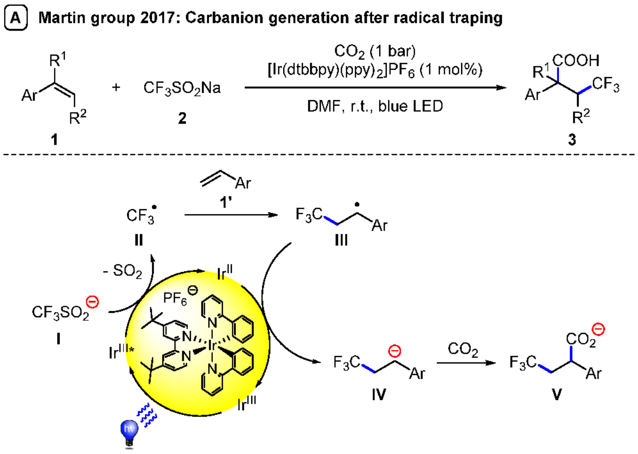

Figure 3. Carbanion generation after radical trapping with CO_2 as electrophile.

were used as radical precursors. After their photocatalytic oxidation, the generated $CF_3^{\bullet}$ radical (**II**) was trapped by styrene. The resulting benzylic radical (**III**) was reduced to the corresponding carbanion (**IV**) by the reduced photocatalyst species, the intermediacy of which was supported by D_2O labeling. The anionic intermediate is further able to add to CO_2, generating the carboxylate (**V**) and after protonation the targeted carboxylic acid as product.

The same concept was independently developed by the group of Song, using highly active benzenesulfonothioates instead of CO_2 as electrophile for the formation of C–S bonds. Further, also simple alkenes could be used as radical traps involving aliphatic carbon nucleophiles.[16] Several impressive variants of this strategy have since then been developed, mostly using CO_2 as the electrophile.[17] Examples comprise the use of $H-P(O)R_2$ phosphonyl compounds[17a] and simple silanes[17b] as radical precursor to achieve the corresponding alkene difunctionlization.

Besides the intermolecular addition to carbonyl compounds, the strategy of radical reduction after trapping has been widely used for intramolecular reactions. In these types of reactions, the carbanion intermediate is reported to follow various reaction pathways typical for an anionic intermediate, such as S_N2 and S_NAr substitutions, as well as E1cb eliminations (Figure 4).

Intramolecular cyclizations via an S_N2 mechanism were pioneered by Molander and co-workers (Figure 4A).[18] In their seminal report, α-iodo alkylbis(catecholato)silicates (**4**) were used as radical precursors. Oxidation of these compounds leads to iodomethyl radicals (**VI**) that can add to styrenes (**1**). After reduction of the thus formed radical (**VII**), the generated carbon nucleophile (**VIII**) substitutes iodine, forming a cyclopropane. The transformation shows that a photocatalytically formed carbon nucleophile is capable of engaging in S_N2 reactions, the mechanism of which is supported by density functional theory calculations. Following this report, the concept has been used for the synthesis of several classes of cyclic compounds utilizing various radical precursors such as silicates,[19] carboxylic acids,[20] as well as alcohols[21] and leaving groups like tosylate[22] besides halides. Various ring sizes ranging from three- to seven-membered rings, including strained four-membered cycles[23] have been constructed as well.

As mentioned above, the strategy was recently exploited for a photocatalytic S_NAr reaction as well, showcasing the broad applicability of photocatalitically generated carbanion intermediates (Figure 4B).[24] Mostly sulfinates (**2**) were again used as radical precursor for the addition to vinyl ureas (**6**). After radical reduction, the corresponding carbanion (**IX**) is arylated via a Truce–Smiles rearrangement.

Although it is not a C–C bond formation between two previously unconnected carbon centers, it is worth noting at this point that the radical reduction approach is, as far as number of publications, most commonly applied for the

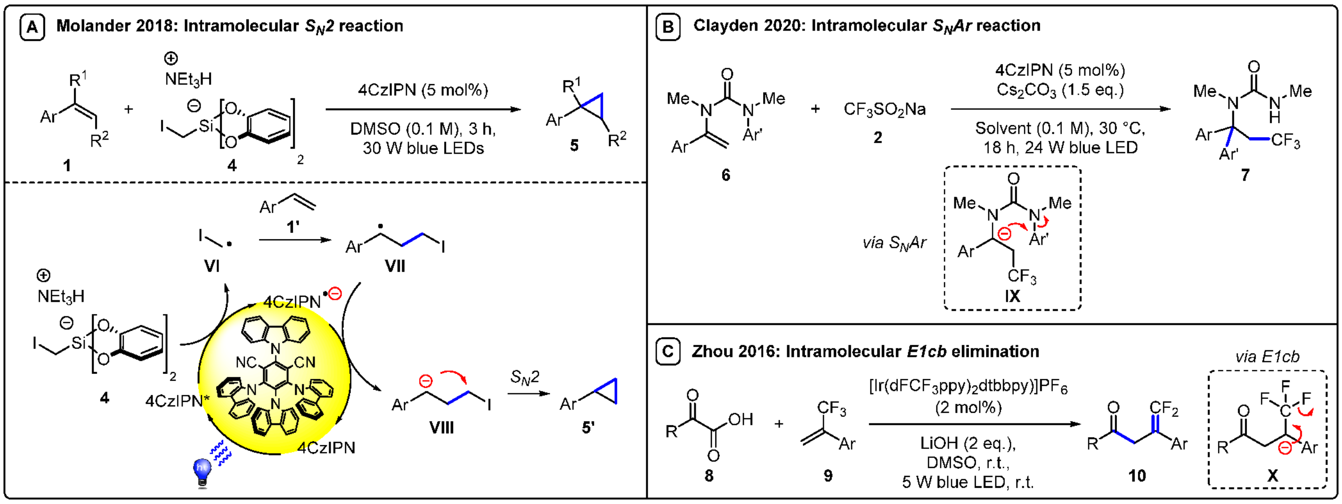

Figure 4. Carbanion generation after radical trapping for an intramolecular C–C bond formation following S_N2 (A), S_NAr, (B) and E1cb (C) mechanisms.

generation of alkenes via an E1cb elimination (Figure 4C). Various examples with different radical precursors and leaving groups have been developed. Mostly, fluoride[25] is used as leaving group yielding valuable *gem*-difluoroalkene products if it originates from a CF_3 moiety. Bromide,[26] acetate,[27] and *tert*-butyl carbonate[28] can be used as leaving groups as well. A selected example of an early report is shown in Figure 4C.

2.2. Radical Reduction from a Single Precursor Molecule

The concept of radical reduction after trapping is already quite well established and has been used for many desirable reactions. However, it has the disadvantage that two separate molecules have to be combined first in order to enable the generation of a carbanion. While this is beneficial for the (di)functionalization of alkenes, it lacks the versatility of classic organometallic reactions such as the Grignard reaction, where almost any molecule with a suitable prefunctionalization can be transformed into an anionic intermediate.

Thus, our group aimed to generate a carbanion intermediate from a single precursor molecule, using the radical reduction approach (Figure 5). In terms of reaction design, we reasoned that the carbanion precursor is required to have three main attributes. It needs to be activated by single-electron oxidation in order to arrive at a net redox-neutral transformation. The thus generated radical intermediate should be reasonably stable in order to avoid a rapid hydrogen atom abstraction or homocoupling and last, the radical should exhibit a reduction potential high enough to allow for its transformation into the carbanion.

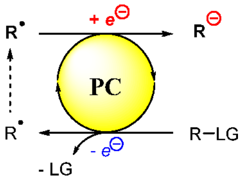

Figure 5. General strategy for the carbanion generation from a single precursor molecule.

The conditions are met for broadly available phenylacetic acids (**11**) (Figure 6A).[1] Carboxylates (**XI**) are easily oxidized ($E_{1/2}^{\mathrm{Ox}}$ range of 1.5−1.0 V vs. SCE depended on substituents)[29] to render carbon centered radicals after the extrusion of CO_2. The benzylic position stabilizes both, the radical and anion intermediate, allowing a subsequent radical reduction ($E_{1/2}^{\mathrm{Red}}$ = −1.45 V vs. SCE for the unsubstituted benzyl radical, **XIII**).[30] The thus generated carbon nucleophile (**XIV**) was capable of adding to an aliphatic aldehyde (**12**) as electrophile to give the desired alcohol product (**13**) after protonation of the alcoholate (**XV**). The prominent side reaction under these conditions is the simple decarboxylation of the starting material rendering the corresponding toluene derivative. The side product is originating from the reaction of the carbanion intermediate with a proton source or from a hydrogen atom abstraction of the benzyl radical. Less active carbonyl compounds like ketones are rather inefficient electrophiles, giving the product only in traces (**14**), presumably due to a faster protonation.

In terms of intermolecular reactions, the concept of photocatalytic radical reduction was up to this point only reported for CO_2 (vide supra), aromatic aldehydes,[31] benzenesulfonothioates,[16] and highly electron-deficient Michael acceptors[32] as electrophiles.

The individual steps of the proposed mechanism were supported experimentally. The photocatalyst was quenched by the addition of the tetrabutylammonium carboxylate of

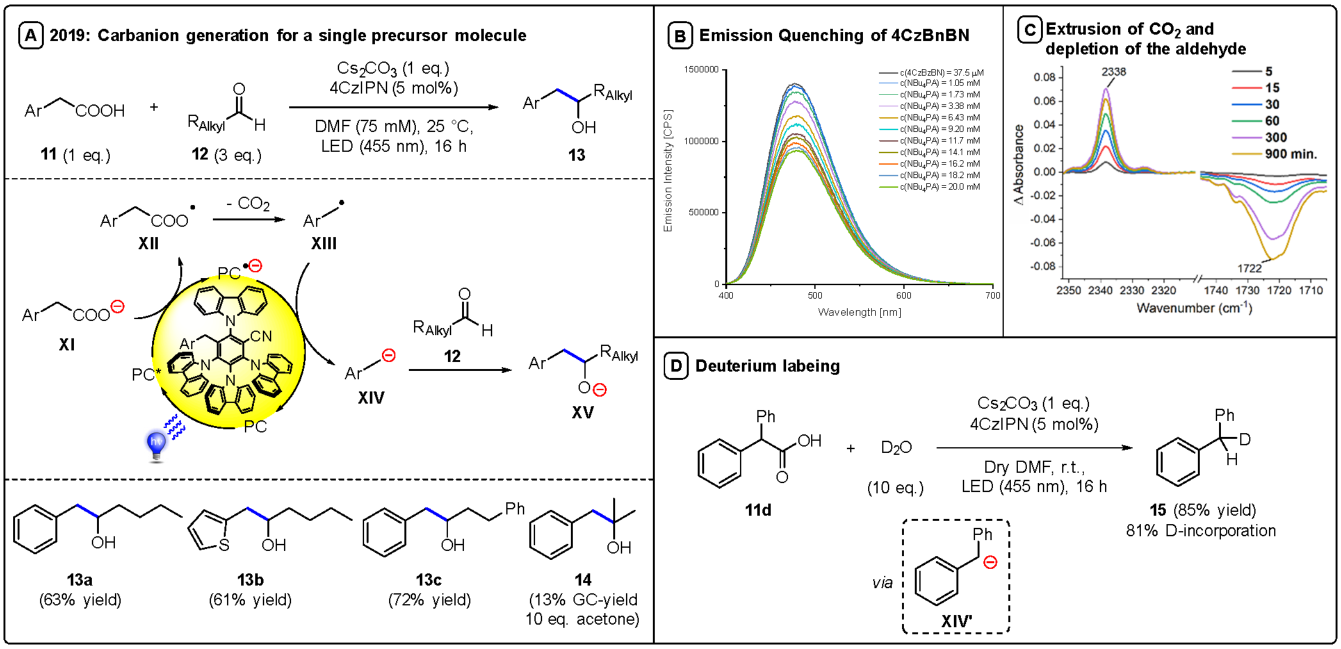

Figure 6. (A) Photocatalytic generation of a carbon nucleophile from a single precursor molecule and its addition to aliphatic aldehydes. (B) Emission quenching of the in situ generated photocatalyst 4CzBnBN (from 4CzIPN and phenylacetic acid) by addition of the tetrabutylammonium salt of phenylacetic acid. Reproduced with permission from ref 1. Copyright 2019 Royal Society of Chemistry. (C) In situ IR measurement of the standard reaction mixture while irradiation with a 455 nm LED. The formation of CO_2 is detected at 2338 cm^{-1} while the depletion of the aldehyde starting material is monitored at 1722 cm^{-1}. Reproduced with permission from ref 1. Copyright 2019 Royal Society of Chemistry. (D) Deuterium labeling of a selected carbanion precursor.

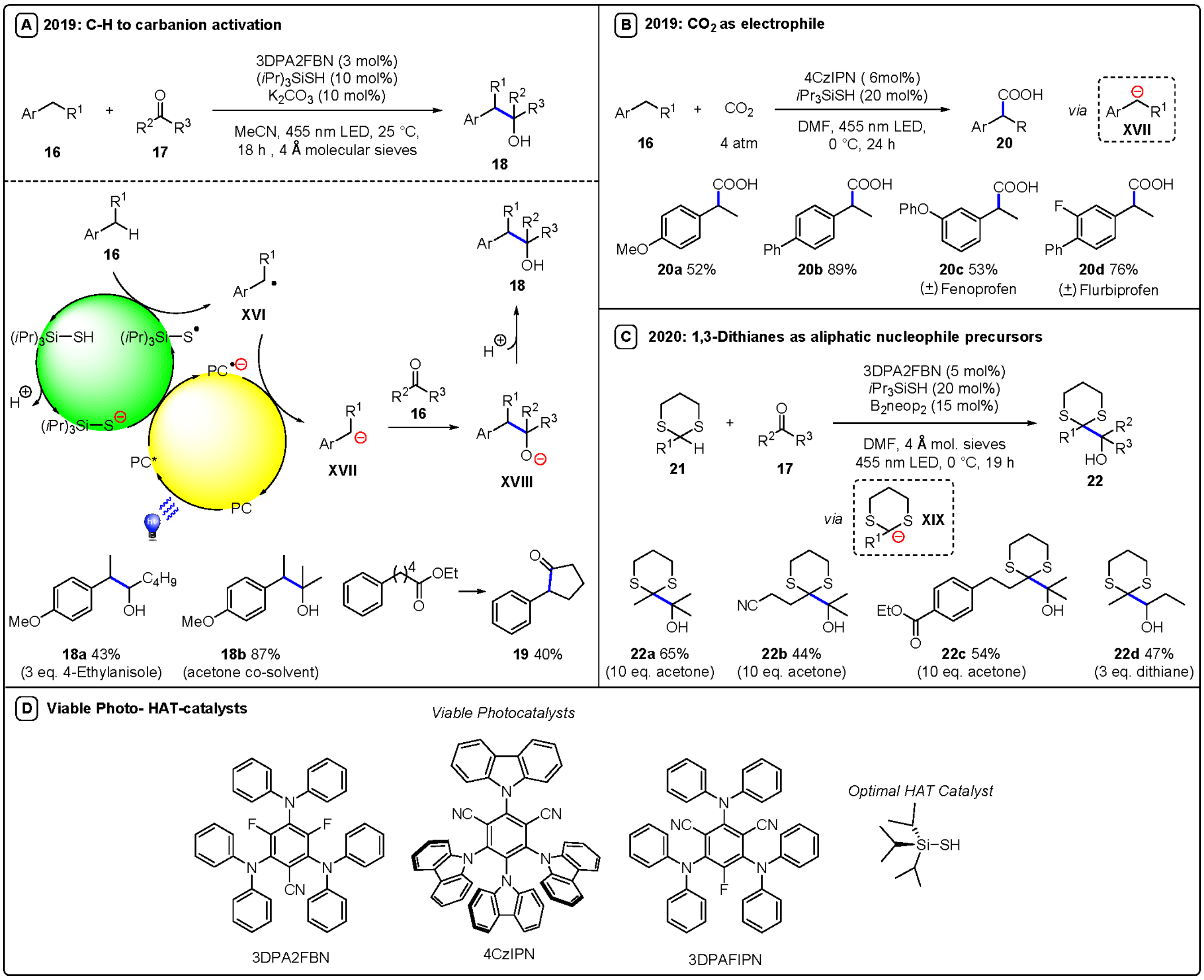

Figure 7. (A) C−H to carbanion activation for the benzylation of aldehydes, ketones and esters (only intramolecularly). (B) C−H to carbanion activation with CO_2 as electrophile. (C) 1,3-Dithianes as purely aliphatic carbanion precursors for a base-free Corey-Seebach reaction. (D) Viable photocatalysts and HAT catalysts.

phenylacetic acid, indicating their interaction under the influence of light, likely by an SET from the carboxylate to the photocatalyst (Figure 6B). The following CO_2 extrusion could be observed by recording in situ IR-spectra of the standard reaction mixture during irradiation, simultaneously showing the depletion of the aldehyde starting material (Figure 6C). Lastly, the generation of an anionic intermediate was supported by deuterium labeling studies. Diphenylacetic acid (**11d**) as a selected example could be deuterated when using D_2O as electrophile under the standard reaction conditions (Figure 6D). With diphenylmethane exhibiting a C−H bond dissociation energy (BDE) of 84.5 kcal/mol,[33] the diphenylmethane radical intermediate is not expected to abstract a deuterium atom from D_2O (H_2O BDE = 118.1 kcal/mol).[33] On the other hand, a diphenylmethane anion is expected to abstract D^+ from D_2O when comparing the respective pKa values (pKa = 32.3 for diphenylmethane[34] and pKa = 31.4 for H_2O,[35] both in DMSO), thus indicating the formation of an ionic intermediate.

The concept of generating a carbanion equivalent from a single precursor could be successfully shown using benzylic carboxylic acids. However, considering the total transformation, CO_2 is generated as stoichiometric byproduct and one equivalent of base is used for the formation of the carboxylate, diminishing the atom economy. Additionally, ketones are ineffective electrophiles, overall leaving room for improvement.

We envisioned that an approach to resolve these shortcomings may be the formation of the required carbon centered radical directly from the C−H bond. Executing this in an oxidative manner paves the way to a catalytic redox-neutral C−H to carbanion activation. This way, the desired transformation can be executed in full atom economy, as a prefunctionalization is avoided. Further, the efficiency can be elevated, as the starting material is reformed if the carbon nucleophile engages with a proton as electrophile.

The envisioned reaction design for this transformation was based on the merger between hydrogen atom transfer (HAT) and photocatalysis (Figure 7A). Common indirect HAT-catalysts can be activated by photocatalytic single-electron oxidation, yielding a radical species capable of abstracting C−H bonds from simple organic compounds.[36] Similar to the previous system, the generated carbon centered radical should then be convertible to the carbanion via reduction by the reduced photocatalyst. The merger of benzonitrile-based donor–acceptor photocatalysts[37] and $i\mathrm{Pr_3SiSH}$ as the HAT-catalyst (Figure 7D) was found as a competent system to orchestrate such a C–H to carbanion activation in the benzylic position (Figure 7).[2,38] The proposed reaction mechanism thus operates as follows: the $i\mathrm{Pr_3SiSH}$ HAT-catalyst is deprotonated in the presence of a base opening its facile oxidation by the excited photocatalyst. This SET step renders the reduced photocatalyst ($\mathrm{PC}^{\bullet-}$) and simultaneously the activated HAT-catalyst species ($(i\mathrm{Pr})_3\mathrm{Si{-}S}^{\bullet}$). The sulfur centered radical is expected to abstract a hydrogen atom from the benzylic position rendering a stabilized radical species (**XVI**). The reduction equivalent stored on the photocatalyst from the previous oxidation is then utilized to convert the radical into the desired carbanion intermediate (**XVII**). The hence formed nucleophilic species is then capable to form C–C bonds with suitable electrophiles. In terms of electrophiles, carbonyl compounds including aldehydes, ketones, esters (only intramolecularly) (Figure 7A), as well as $\mathrm{CO_2}$ (Figure 7B) proved to be viable. Notably, ketones were in this case even higher yielding coupling partners than the more reactive aldehydes. This is due to the HAT catalyst being prone to abstract the carbonyl hydrogen atom from aldehydes arising from a polarity match,[39] leading to undesired side reactions. Accordingly, $\mathrm{CO_2}$ was found to be a more suitable electrophile as well.

In theory, this strategy illustrates the most atom economic, simple and straightforward method to synthesize the illustrated coupling products. Yet, the current conditions still bear two main limitations. First, high yields are only obtained if the electrophile is present in large excess (not the case for aldehydes). This is easily applicable for $\mathrm{CO_2}$ or simple ketones like acetone, but less desirable for more complex electrophiles. Second, only sufficiently activated C–H bonds, such as the benzylic ones, can be converted into to the carbanion equivalent.

Based on the proposed mechanism, the realm of potential carbanion precursors is governed by the limits of both catalysts. The activated HAT species ($i\mathrm{Pr_3SiS}^{\bullet}$) (S–H BDE approximately 88.9 kcal/mol)[40] needs to be capable of abstracting the corresponding hydrogen atom. Further, the reduced photocatalyst species ($E_{1/2}$(3DPA2FBN/3DPA2FBN$^{\bullet-}$) = −1.92 V vs. SCE)[37] is required to be reductive enough to convert the carbon-centered radical into the active carbanion species. These conditions are, e.g., met for ethylbenzene, as it shows a C–H BDE of 85.4 kcal/mol[33] and the ethylbenzyl radical is reported to exhibit a reduction potential of $E_{1/2}^{\mathrm{Red}} = -1.60$ V vs. SCE.[30]

However, these values are rather to be taken as guideline, as they represent thermodynamic boundaries and kinetic barriers need to be considered as well. This is especially crucial for the hydrogen atom abstraction step. Here, the activation barrier is predicted to decrease with an increasing electronegativity difference between the involved radical species, rendering a sufficient polarity match indispensable.[39b] With regard to the here presented system, this means that only C–H bonds rendering sufficiently nucleophilic (i.e., electron rich) radicals can be employed, as $i\mathrm{Pr_3SiS}^{\bullet}$ is an electrophilic radical. Positions that would give rise to electron poor and thus easily reducible electrophilic radicals (e.g., in α-carbonyl positions), are likely to fail in the HAT step.

With these factors in mind, the aim was to expand the scope beyond benzylic C–H bonds. Radicals in the α-position to a heteroatom are generally regarded as nucleophilic.[39b] In the case of sulfur, the C–H acidity is increased as well, indicating the stabilization of the carbanion species.[41] Both aspects are desirable for the developed PC/HAT catalyst system, and indeed, the carbanion nucleophile can also be generated in purely aliphatic systems, where the radical and anion intermediate are stabilized by two sulfur atoms, e.g., with 2-methyl-1,3-dithiane (C–H BDE = 88.2 kcal/mol; $E_{1/2}^{\mathrm{Red}} = -1.87$ V vs. SCE for the dithiane radical) (Figure 7C).[40] Using 1,3-dithianes (**21**) as carbanion precursors, a photocatalytic base-free Corey–Seebach reaction was developed. Opposite to the classical method, the product was obtained without the addition of a strong organometallic base (e.g., nBuLi) thus furnishing the desired product in full atom economy. Further, the absence of base allowed the presence of base- and nucleophile-sensitive functional groups.

Looking ahead, a more potent and efficient catalytic system needs to be developed in order to substantially broaden the substrate scope as far as nonactivated C–H bonds. Efforts toward this goal are currently ongoing in our research group.

3. METAL-ASSISTED GENERATION OF CARBANION EQUIVALENTS

A conceptually different approach toward the photocatalytic generation of a carbanion equivalent is the capture of a radical with a metal leading to a nucleophilic organometallic species. The required reduction equivalent thus originates from the metal, donating an electron to the radical to furnish a carbanionic species, similar to the Grignard reaction. After reaction with the desired electrophile, the oxidized metal is reduced by the photocatalyst to regenerate its active form (Figure 8). If the required carbon radical is directly or indirectly formed by an oxidation process, the reaction is net redox-neutral and can be executed without the addition of a stoichiometric reductant.

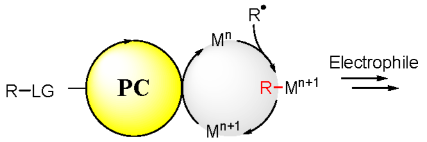

Figure 8. General strategy for the metal-assisted generation of a carbanion equivalent.

In 2018, the Glorius group utilized this concept to arrive at a photocatalytic Nozaki–Hiyama–Takai–Kishi (NHTK) reaction requiring only a catalytic amount of chromium, instead of an (over)stoichiometric quantity used in the classical method (Figure 9A).[42] Allyl arenes (**23**) were used as nucleophile precursors giving a neutral radical (**XX**) after photocatalytic oxidation and deprotonation. After trapping with a Cr(II) source, the corresponding nucleophilic organometallic Cr(III) species (**XXI**) is capable of adding to an aldehyde as electrophile furnishing the reaction product after protonation. Afterward, the Cr(III) species is reduced to Cr(II) closing both the metal and photocatalyst cycle.

Simultaneously, the Kanai group developed the same concept using a highly oxidative acridinium based catalyst in order to enable the use of simple alkenes as starting material and chiral ligands to induce chirality.[43] Further, they expanded

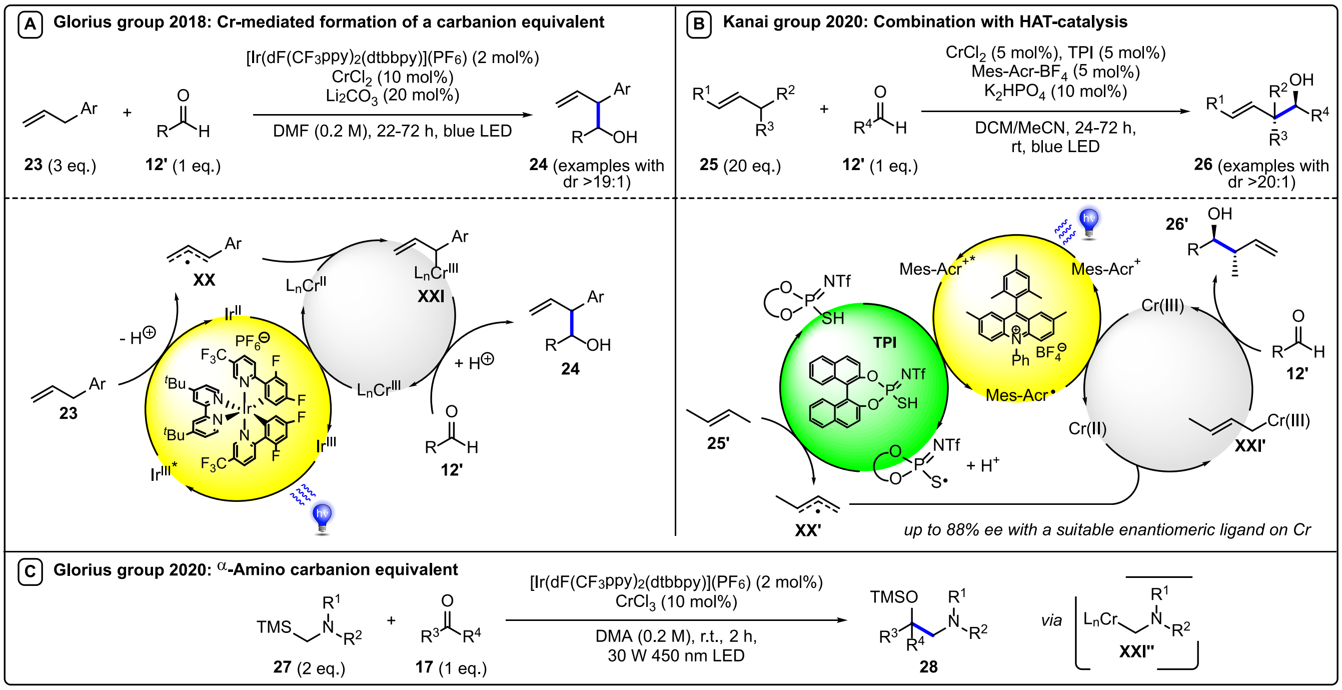

Figure 9. Examples for the photocatalytic generation of nucleophilic organometallic species. (A) NHTK reaction is catalytic in chromium. (B) C–H activation to organochromium of simple alkenes. (C) Generation of a carbanion equivalent in the α-amino position.

this strategy by the combination with HAT-catalysis (Figure 9B), in a similar manner as described in section 2.2.[44]

So far, the vast majority of the carbanion equivalents generated in a photocatalytic manner are, naturally, in the α-position to an anion stabilizing group, e.g., benzylic or allylic anions. A likely reason is that the carbanion needs to be sufficiently stabilized in order to facilitate its reduction by the photocatalyst. The use of a metal catalyst can resolve this issue, as the photocatalyst is then only required to reduce the oxidized metal species instead of the carbon-centered radical. Dependent on the metal, this can be significantly more facile considering solely the redox-values (e.g., $E(Cr^{3+}/Cr^{2+}) = -0.65$ V vs. SCE).[45] A trade-off might be that the formed organometallic species is less reactive due to its C–metal bond. In the case of chromium, the nucleophilic organochromium species is generally only capable to attack aldehydes as electrophiles, while less active ketones are mostly unsuitable substrates.[9,46]

The group of Glorius exploited this strategy for the generation of carbanion equivalents in α-position to amines.[47] In this transformation, α-TMS amines (**27**) were used as radical precursors (Figure 9C). Surprisingly, even ketones were viable electrophiles and the TMS-protected α-amino alcohol (**28**) was obtained in full atom economy. However, the transformation shows a quantum yield of 12.5, revealing that a non-photocatalytic mechanism seems to be the main pathway of this transformation.

In a similarly intriguing reaction, the Yahata group generated a carbanion equivalent from simple alkanes, such as cyclohexane, using tetrabutylammonium decatungstate as highly active HAT- and photocatalysts. However, a stoichiometric amount of $CrCl_3$ (3 equiv) is required.[48] The concept of a metal assisted carbon nucleophile formation was further extended in a few other reports. An example is the previous radical trapping with alkenes similar to section 2.1.[49] It is worth noting, at this point, that a conceptually similar transformations has been reported with a titanium complex[50] instead of chromium. However, this transformation operates in a net-reductive manner.

4. RADICAL ANIONS AS NUCLEOPHILES

So far, only the generation of sp^3 carbanion equivalents was discussed. However, there are numerous examples for the use of organometallic sp^2 carbon nucleophiles in the construction of several valuable compounds,[51] rendering the development of more atom economic and mild methods desirable. At the same time, the photocatalytic formation of sp^2 nucleophiles is challenging when applying the so far described strategies. Options for the oxidative generation of sp^2-centered radicals, e.g., aryl radicals, by the use of a cleavable leaving group are limited.[17c,52] Similarly, a C–H activation by HAT for a full atom economic transformation is due to the high C–H BDE (112.9 kcal/mol for benzene)[33] challenging as well, with, to the best of our knowledge, no photocatalytic method being reported so far. Even if possible, selectivity issues in the presence of sp^3 C–H bonds would be impending.

Our group attempted to tackle this problem by pursuing a different strategy (Figure 10). Although radical anions are regarded as poor nucleophiles,[53] aromatic systems reduced with alkali metals are still reported to be capable of adding to CO_2 as electrophile.[54] This should still be valid for photo-

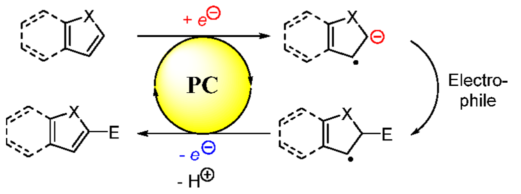

Figure 10. General strategy for the use of radical-anions as nucleophiles.

catalytically formed radical anions. Yet, aromatic systems exhibit a fairly negative reduction potential ($E_{1/2}^{\text{Red}} = -2.63$ V vs SCE in MeCN for naphthalene),[53] thus requiring highly reductive photocatalysts for their activation.[55]

Last year, we established the use of deprotonated 2,3,6,7-tetramethoxyantracen-9(10*H*)-one (TMA^-) (see Figure 11 for its structure) as a highly reductive photocatalyst for the activation of aryl halides.[56] Judging from its estimated redox potential ($E_{1/2}(\text{TMA}^{\bullet}/\text{TMA}^{-*}) = -2.92$ V vs SCE), the exited anion should be able to form the radical anion of naphthalene derivatives. Indeed, an interaction between naphthalene derivatives and the photocatalyst could be observed by emission quenching, supporting the generation of a radical anion. Gratifyingly, the presence of CO_2 as electrophile led to the formation of the desired carboxylic acid (Figure 11).[3]

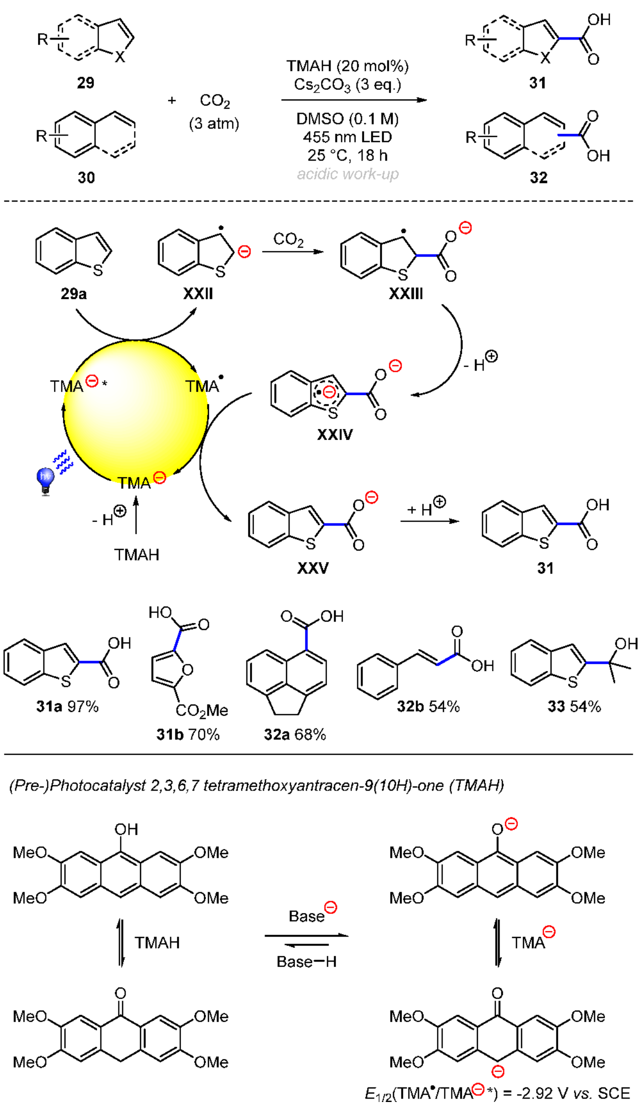

Figure 11. Redox-neutral photocatalytic C−H carboxylation of arenes and styrenes with CO_2.

In the proposed mechanism, the precatalyst TMAH is activated by deprotonation in the presence of a base to give the visible light absorbing TMA^- anion. After photoexcitation (455 nm LED), the strongly reducing TMA^{-*} species is proposed to transfer an electron to a suitable arene, rendering the radical species of the photocatalyst ($\text{TMA}^{\bullet}$) and the nucleophilic radical anion (**XXII**). This carbon centered nucleophile is capable of forming the desired C−C bond by adding to CO_2 as an electrophile, leading to the formation of a radical carboxylate (**XXIII**). This intermediate is proposed to undergo rapid deprotonation in the presence of a base to regain resonance. The resulting radical dianion **XXIV** is expected to be a sufficiently strong reductant to regenerate the active photocatalyst TMA^- ($E_{1/2}(\text{TMA}^{\bullet}/\text{TMA}^-) = -0.51$ V vs SCE) and to yield the corresponding carboxylate (**XXV**).

As the final product is furnished after protonation, the transformation is executed in full atom economy under net redox-neutral conditions. However, 3 equiv of base (Cs_2CO_3) is required to reach the optimal yield. Ketones are viable electrophiles as well (**33**), whereas aldehydes were not compatible with the reaction conditions, likely due to the reaction of the aldehyde with the anionic catalyst itself. Various aromatic systems including styrene (**32b**) could be used as carbon nucleophile precursors furnishing the desired product. The extension of this carbon nucleophile formation strategy toward nonaromatic systems and aldehydes as electrophiles is currently under investigation.

Considering the complete transformation, a slightly related strategy was developed by the groups of Yu[57] and Walsh.[58] Here, aromatic imines were reduced to the corresponding radical anion by a photocatalyst. Subsequently, a hydrogen abstraction from a sacrificial hydrogen atom donor yielding a carbanion intermediate is proposed before the addition of CO_2 or aldehydes as electrophiles. Although, this reaction is an overall net reduction requiring a stoichiometric reductant (the hydrogen atom donor), it illustrates an interesting strategy for the formation of a carbanion equivalent.

5. IN SITU GENERATION OF A LABILE LEAVING GROUP

A more indirect approach toward a net redox-neutral carbanion formation is the photocatalytic transformation of a functional group into a leaving group which is prone to furnish a carbanion after its extrusion (Figure 12). Our group recently employed this strategy for a photocatalytic Wolff−Kishner-type reaction, opening the possibility for a facile difunctionalization using radical and anionic reactivity (Figure 13).[59]

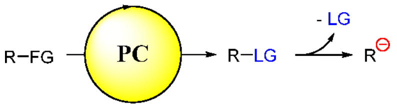

Figure 12. General strategy for the in situ generation of a labile leaving group.

N-Tosylhydrazones (**34**) were used as latent carbanion precursors. After oxidation of a thiolate (**XXVI**) by the excited Ir-based photocatalyst, the in situ formed thiol radical (**XXVII**) is proposed to add to the *N*-tosylhydrazone which leads to the cleavage of a tosyl radical yielding the crucial diazine intermediate (**XXIV**). Deprotonation and extrusion of N_2 renders the desired carbanion equivalent (**XXV**), capable of adding to CO_2 or aldehydes as electrophiles. The photocatalytic cycle is closed by reduction of the tosyl radical to its anion, rendering the overall transformation redox-neutral. The reaction is also possible with CF_3SO_2Na instead of the thiol as radical precursor, yielding the corresponding *gem*-difluoroalkene after E1cB elimination of one fluorine via the carbanion

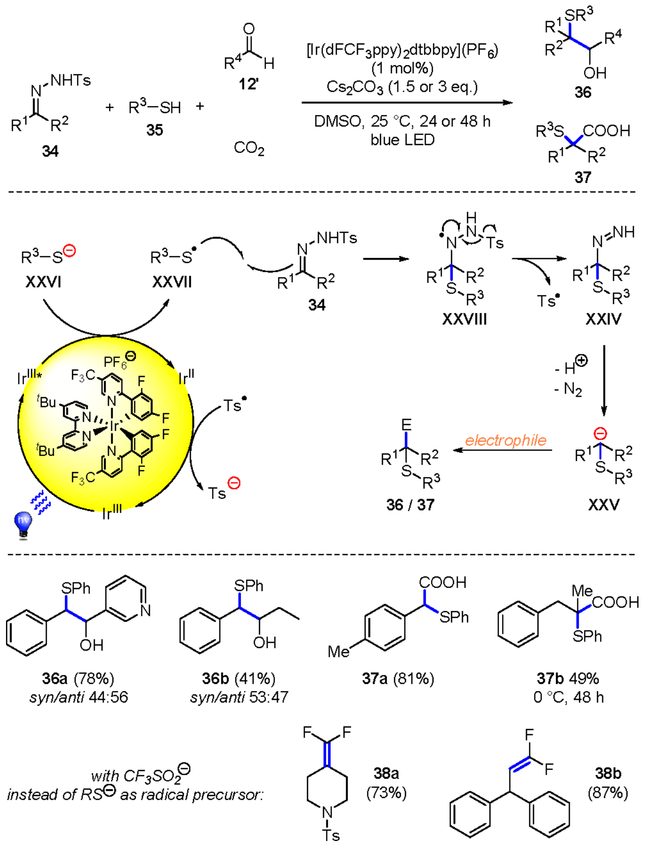

Figure 13. Difunctionalization of carbonyls via a visible-light photoredox catalytic radical-carbanion relay.

intermediate (**38**). While the strength of this transformation is the difunctionalization and installation of a geminal CF_2 alkene, opening easy access to valuable reaction products, 1.5 or 3 equiv of base is required and tosylate and N_2 are stoichiometric byproducts. The formation of a stoichiometric byproduct is, however, inevitable using this strategy.

A related, yet net reductive approach was presented last year, where an α-boryl carbanion was generated as a key intermediate starting from the reduction of aromatic aldehydes.[60] It is further worth noting, at this point, that a related, non-photocatalytic, ruthenium catalyzed carboxylation using aromatic hydrazones and CO_2 was recently reported as well.[61]

6. CONCLUSION

The photocatalytic generation of polar carbon nucleophiles instead of neutral carbon centered radicals to drive a desired chemical reaction is an emerging field in photocatalysis. With its potential mild and metal-free conditions alongside the option of radical, followed by anionic bond formations, it gained the attention of several research groups. It offers an alternative to classical organometallic reactions operating under milder and more atom economic conditions by excluding the use of a stoichiometric (organo)metallic reductant. Beyond that, novel reaction pathways starting from simpler, more available, and easier to handle starting materials can be developed using this approach, enabling intriguing retrosynthetic pathways. Additionally, the merger with enantioselective catalysis can bring new grounds for forging C−C bonds in an asymmetric manner. As this research area is not older than approximately 5 years, it is still in its infancy and we expect new strategies to be disclosed in the near future, together with the boundaries of the above-described strategies to be extended and pushed further by our group and others.

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Notes

The authors declare no competing financial interest.

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Karsten Donabauer received his B.Sc (2015) and M.Sc (2017) in Chemistry from the University of Regensburg, Germany, under the supervision of Prof. Ivana Fleischer and Prof. Burkhard König, respectively. Thereafter, he joined the group of Prof. Burkhard König as Ph.D. student. His current research interest focuses on the photocatalytic generation of carbanion equivalents.

Burkhard König received his Ph.D. in 1991 from the University of Hamburg. He continued his scientific education as a postdoctoral fellow with Prof. M. A. Bennett, Research School of Chemistry, Australian National University, Canberra, and Prof. B. M. Trost, Stanford University. Since 1999 he is a full professor of organic chemistry at the University of Regensburg. His current research interests are the development of synthetic methodologies in photoredox catalysis and photoswitchable bioactive ligands.

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■ DEDICATION

Dedicated to Prof. Henning Hopf on the occasion of his 80th birthday.

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