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7 Photoredox catalyzed α -functionalization of amines – visible light mediated carbon-carbon and carbon-hetero bond forming reactions

7.1 Introduction

The direct functionalization of unreactive C–H bonds is one of the major challenges for synthetic organic chemists. It allows the sustainable formation of new carbon-carbon or carbon-heteroatom bonds without prefunctionalization of substrates and, thus, without the generation of undesirable amounts of waste.

In particular, cross-dehydrogenative coupling (CDC) allows an operationally simple and environmentally benign approach to the direct functionalization of C–H bonds in the presence of an oxidant, ideally molecular oxygen, with water being the sole by-product [1].

Typically, various transition metal salts are applied to CDC reactions, in which a C–H bond, adjacent to a tertiary nitrogen atom, can be functionalized through oxidation by the transition metal catalyst to an intermediate iminium ion, which is then intercepted by various C–H nucleophiles under the formation of a new C–C bond (Figure 7.1).

Cross-dehydrogenative coupling [1], pioneered by C. J. Li using copper catalysis in the early 2000s [2], is an ideal blueprint for photoredox catalysis [3], as photoredox catalysts allow the oxidation of tertiary amines to the corresponding iminium ions [4, 5], which are the crucial intermediates in CDC reactions. Stephenson and co-workers demonstrated the applicability of CDC in photoredox catalysis in 2010 in their publication on the visible light mediated aza-Henry reaction [6].

So far, different homogeneous and heterogeneous photoredox catalysts have been identified to be applicable to visible light mediated CDC reactions. The most commonly used are Ru(II) poly-bipyridyl and Ir(III) poly-pyridyl complexes [7] (Figure 7.2) which were shown to be highly efficient catalysts for the oxidative functionalization of C–H bonds adjacent to nitrogen atoms. The substitution pattern of the bipyridyl and aryl-pyridyl ligands has shown to be of critical importance for this transformation and the formation of the intermediate iminium ion can be adapted to the subsequent trapping reaction resulting in less side product formation.

In addition to homogeneous transition metal complexes, organic dyes, such as Eosin Y and Rose Bengal (Figure 7.3), proved to be efficient catalysts for various visible light mediated cross-dehydrogenative transformations [8]. Organic dyes are of particular importance, as they are inexpensive (Eosin Y is about 50 times less expensive per gram than Ru(bpy)₃Cl₂; bpy = 2,2'-bipyridine) and commercially

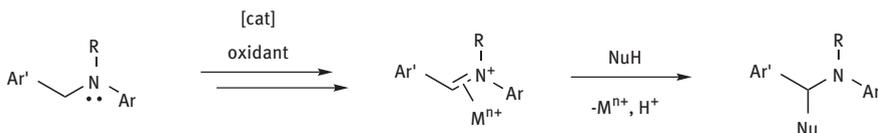


Figure 7.1: CDC reaction of tertiary amines with nucleophiles.

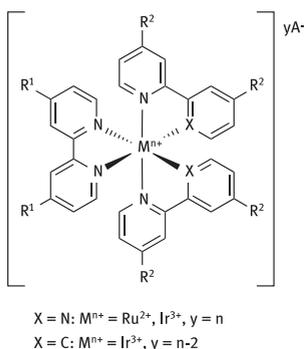


Figure 7.2: Ru and Ir complexes applied in photoredox catalysis.

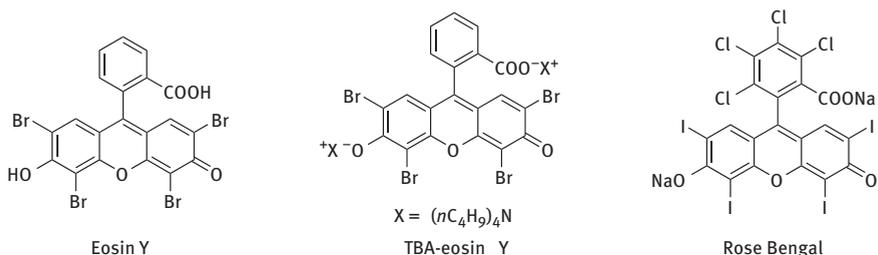


Figure 7.3: Organic dyes applied as photoredox catalysts.

available in decent quantities. This is of particular importance for the synthetic applicability of photoredox catalysts, as they typically also possess relatively high molecular weights. For instance, the typically applied $[Ru(dtb-bpy)_2bpy](PF_6)_2$ (dtb-bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) has a molecular weight of 1202 g/mol. Even though catalyst loadings of typically 1 mol% can be realized, this results in a significant amount of expensive catalyst, while the Eosin Y (648 g/mol) is only about a half of the molecular weight of a typical Ru(II) based catalyst. Thus, the development of organic dye catalyzed cross-dehydrogenative transformations is of considerable interest.

Apart from homogeneous catalysts for visible light mediated cross-dehydrogenative coupling reactions, solid materials attracted the interest of organic chemists. Typically, semi-conducting materials are applied [9], such as titanium dioxide, other transition metal oxides, cadmium, and zinc sulfide but also carbon nitride.

Before going into a detailed discussion on visible light photoredox catalyzed cross-dehydrogenative coupling reactions, the putative reaction mechanism will be briefly discussed. In a nutshell, the tertiary amine is first oxidized by the photoredox catalyst (photosensitizer, PS) and forms, after subsequent proton and electron transfer, the intermediate iminium ion which can then be trapped by a series of different nucleophiles (Figure 7.4).

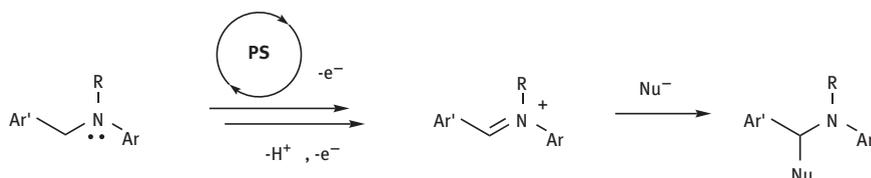


Figure 7.4: Photoredox catalyzed functionalization of tertiary amines.

The photochemical oxidation of tertiary amines dates back to the 1970s, when Whitten and co-workers examined the photophysical properties of Ru(II) polypyridyl complexes and the quenching of the excited species by either reductive quenching with tertiary amines [10] or oxidative quenching with viologens (e. g. paraquat) [11]. The putative reaction mechanism of photoredox catalyzed CDC transformations is depicted in Figure 7.5.

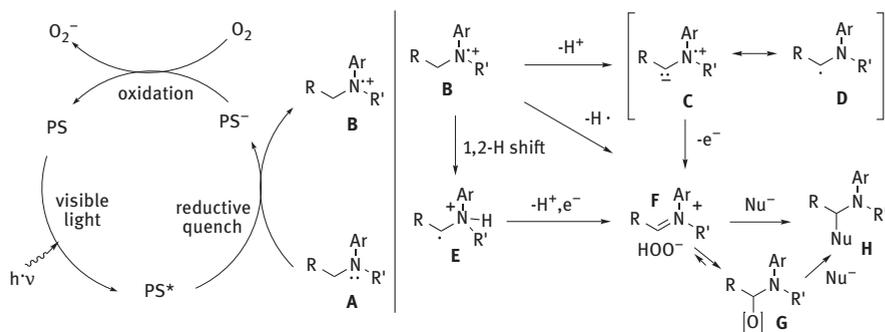


Figure 7.5: Photoredox oxidative functionalization of tertiary amines.

Irradiation with visible light generates the excited state of a photosensitizer PS^* , which can then undergo reductive quenching through single electron transfer from a tertiary amine **A** [12] to the photoexcited state. The reduced photosensitizer PS^- can then be reoxidized by molecular oxygen to the ground state PS of the photocatalyst under formation of a superoxide anion. More importantly, the tertiary amine **A** is oxidized to the amine radical **B** in this process. The amine radical **B** can now undergo different pathways that finally result in the formation of the iminium ion **F**. Mechanistically three different pathways are possible. First, a hydrogen atom abstraction, e. g. by the superoxide anion, from the neighbouring carbon centre is possible, which would result in the direct formation of the iminium ion **F**. Second, after deprotonation an intermediate zwitterion **C** is formed, which can be also represented by a carbon centred radical **D**, which, after a second single electron transfer, can undergo oxidation to the iminium ion **F**. Last, a 1,2-H shift would result in the formation of the carbon centred radical **E** bearing an adjacent quaternary ammonium ion. This carbon centred radical can now undergo deprotonation and single electron oxidation, which ultimately also results in the formation of the iminium ion **F**, which can react to the hemiaminal **G**. In the final reaction step iminium ion **F** is intercepted by a range of different nucleophiles to provide the cross-dehydrogenative coupling products **H**.

The intermediate iminium ion represents a highly attractive species for further transformations and, not surprisingly, different groups focused on performing a second catalytic transformation, in which the nucleophile needs activation by a metal/organocatalyst prior to the addition to the iminium ion (Figure 7.6). Nicewicz and MacMillan performed seminal work on the application of combined photoredox catalysis and organocatalysis in 2008 [13]. Yet, in the context of CDC, Rueping and co-workers were able to demonstrate for the first time a dual catalytic concept for the visible light mediated Mannich reaction [14] and alkylnylations [15]. To perform such dual catalytic transformations, the adaptation of both catalytic cycles is crucial as decomposition/inactivation of the second catalyst by the photoredox catalyst through redox chemistry is possible.

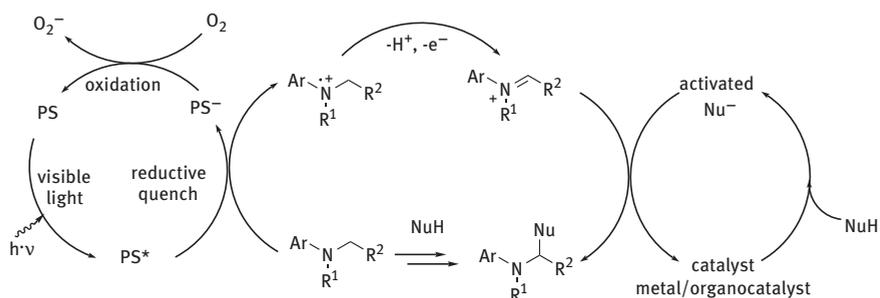


Figure 7.6: Oxidative functionalization of tertiary amines – dual catalytic systems.

Cross-dehydrogenative couplings have found widespread application in copper, iron, ruthenium and other transition metal catalyzed transformations [1]. Typically, they are performed at elevated reaction temperature and stoichiometric amounts of oxidants, e. g. *t*BuOOH or TEMPO are applied, which both clearly outline shortcomings of these methods. In the following section, we will concentrate on the development of visible light mediated photoredox catalyzed cross-dehydrogenative coupling reactions.

7.2 Aza-Henry reaction

In 2010, Stephenson and co-workers reported a visible light mediated photoredox catalyzed aza-Henry reaction (Figure 7.7) [6]. They were the first to demonstrate that $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (ppy = 2-phenyl-pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) can be used as a photoredox catalyst for the efficient aerobic oxidation of *N*-aryl-tetrahydroisoquinoline derivatives **1** followed by a subsequent aza-Henry reaction yielding the desired reaction products **3** in very high chemical yield. Remarkably, the reaction can be performed at room temperature using a standard household fluorescent bulb as the source of energy with only 1 mol% of catalyst loading and oxygen from air as the terminal oxidant. This seminal publication set the basis for the future developments in this field.

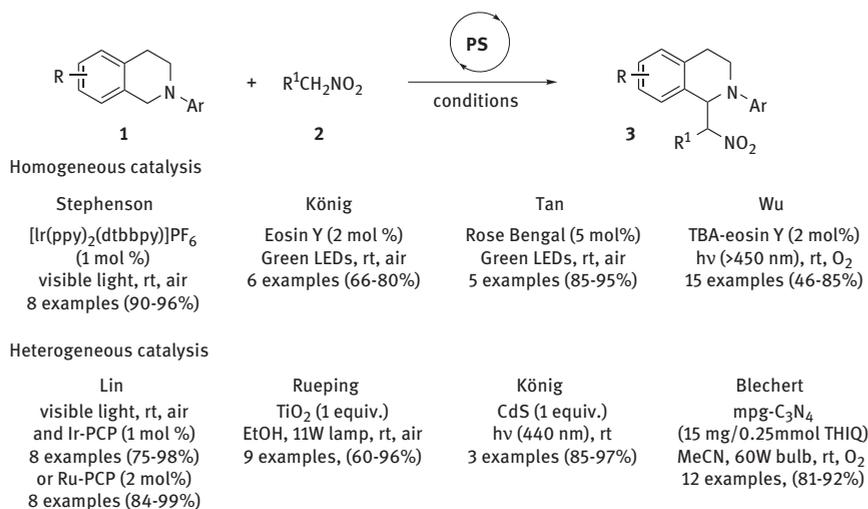


Figure 7.7: Visible light-mediated aza-Henry reaction.

The Tan, König, and Wu groups subsequently examined this transformation using organic dyes as photosensitizers [16–18]. Driven by the search for metal-free and a more economical way for photoredox catalysis Eosin Y, or Tetrabutylammonium

(TBA) Eosin Y, respectively, and Rose Bengal were identified as promising candidates. Again, oxygen or air can be used as the terminal oxidant. Green LEDs were used as the source of light in the case of Rose Bengal and Eosin Y while Wu and co-workers applied a 500 W high-pressure mercury lamp in the TBA-Eosin Y catalyzed oxidative aza-Henry reaction.

Apart from typical homogeneous photosensitizers, the groups of Lin, Rueping, König, and Blechert and Wang developed protocols to perform visible light mediated cross-dehydrogenative couplings in the presence of heterogeneous photocatalysts [19–22].

The first to report on heterogeneous catalysts for the photochemical oxidative aza-Henry reaction were Lin and co-workers [19]. They developed porous-cross linked polymers bearing a bipyridine motif for binding of Ru(II) or Ir(III) based photoredox catalyst. The group of Blechert, Wang, and co-workers applied mesoporous-graphitic carbon nitride (mpg-C₃N₄) [22] while the groups of König [21] and Rueping [20] applied semi-conducting materials such as CdS or ZnO and TiO₂, in this visible light mediated transformation. Additionally, Rueping and co-workers demonstrated the recycling potential of the heterogeneous catalyst, which could be reused for at least five consecutive times. The advantage of these protocols is clearly the possibility of operationally facile catalyst recycling/reuse after simple filtration or centrifugation. Moreover, titanium dioxide or cadmium sulfide represent two of the economically most attractive catalysts, having low price and low molecular weight at the same time (TiO₂: 80 g/mol); the latter resulting in reasonable amounts of catalyst needed per reaction, although up to 1 equiv of catalyst is used.

The seminal publication by Stephenson and co-workers relies on the reductive quenching of the excited state of the photocatalyst [6]. The reduced photoredox catalyst is then reoxidized in the presence of oxygen to regenerate the ground state. In 2012, Stephenson and co-workers reported on the application of an alternative route for the formation of the iminium ion, which is crucial for CDC [23]. Bromo-trichloromethane acts as a stoichiometric oxidant, which finally leads to the formation of the iminium ion **4** (Figure 7.8). After subsequent addition of the nucleophile, the desired aza-Henry product **3** can be obtained in a dark reaction with excellent chemical yield without the need for further irradiation. Advantageous to this one-pot protocol is the controlled formation of the intermediate iminium ion **4**. Moreover, the reaction product cannot be oxidized by the photoredox catalyst, which

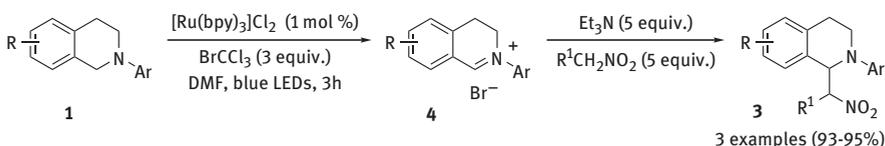


Figure 7.8: Two-step one-pot procedure for the aza-Henry reaction.

would lead to undesired side products. However, this protocol needs strict exclusion of oxygen and the reaction solution needs to be treated by three consecutive freeze-pump-thaw cycles to remove traces of oxygen, which is a limitation of this protocol.

Besides the oxidative CDC of *N*-aryl-tetrahydroisoquinoline derivatives, several groups concentrated on the oxidative aza-Henry reaction of aliphatic acyclic tertiary amines. In their publication from 2010, Stephenson and co-workers reported on the oxidative aza-Henry reaction of *N*-phenyl-pyrrolidine and nitromethane [6], yet the desired CDC product could only be isolated with 27 % yield; clearly showing up the limitations of the photochemical CDC. However, this clearly set up the stage for further improvement of this transformation, which further flourished by the application of organic dyes as shown by the Tan [16] and König [17] groups. Tan and co-workers were able to obtain the CDC product of *N,N*-dimethyl-aniline and nitromethane with a moderate 48 % chemical yield.

In 2012 Wang, Li, and co-workers advanced the application of aliphatic amines (Figure 7.9) [24]. 1,2-Bis-(*sec*-amino)-ethane undergoes, in the presence of visible light, an oxidative C–C bond cleavage resulting in a highly reactive iminium ion, which can be trapped with a series of β -aryl-nitro-ethanes or long-chain aliphatic nitroalkanes.

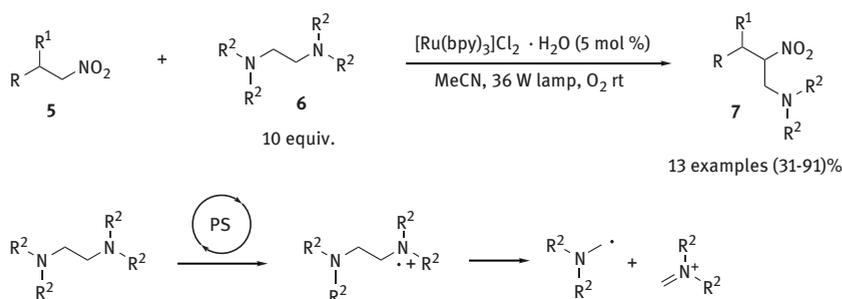


Figure 7.9: Photoredox catalyzed aza-Henry reaction with vicinal diamines.

Furthermore, they were able to demonstrate, that *O*-protected 2-dimethylamino-ethanol derivatives can be selectively functionalized at one of both methyl groups by means of photoredox catalysis.

As photoredox catalysis relies on the use of visible light, Lambert–Beer’s law has direct implications on the catalytic efficiency during scale-up processes. The micro-reactor technology provides a well-established platform to overcome this problem [25]. The high surface-to-volume ratio ensures efficient irradiation of the reaction solution and would thus allow the gram-scale synthesis of precious building blocks by photoredox chemistry.

Not surprisingly, the groups of Stephenson [26], Zeitler [27] and others [28] concentrated on the development of efficient continuous-flow visible light mediated photochemical transformations.

As already outlined before, Stephenson and co-workers had been able to successfully demonstrate the selective formation of the valuable iminium ion intermediate using bromo-trichloromethane as terminal oxidant [23]. They were able to demonstrate that this protocol is not only applicable to batch reactions, but that it can also be run in a continuous-flow microreactor (Figure 7.10) [26]. By generating the iminium ion in a microreactor, and adding this mixture to a flask containing the required nucleophile, the continuous-flow CDC reaction can be realized on a gram-scale. At the same time, Zeitler and co-workers reported on the application of $[\text{Ir}(\text{ppy})_2\text{bpy}]\text{PF}_6$ in the continuous-flow photocatalyzed aza-Henry reaction using the standard reaction protocol, in which the reductive quenching of the photoexcited state by the tertiary amine is the key (Figure 7.10) [27]. Comparable yields to the protocol of Stephenson and co-workers were obtained. Most interestingly, substrates, that proved poorly reactive for batch CDC reactions, could be efficiently subjected to CDC under continuous-flow conditions. In this manner CDC products of nitromethane with *N*-phenyl-pyrrolidin and *N,N*-dimethyl-*p*-methyl-anilin, respectively, could be isolated with good yields of 59 and 77 %, respectively. This nicely illustrates the potential of continuous-flow microreactors in photocatalyzed transformations.

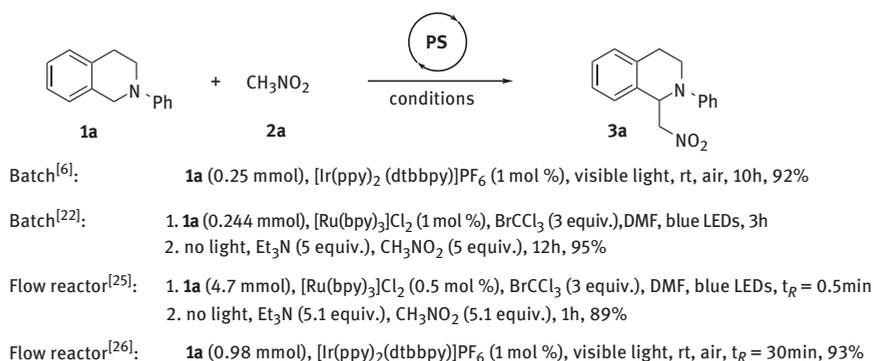


Figure 7.10: Comparison between photoredox catalyzed aza-Henry reaction in batch and flow modes.

7.3 Addition of malonates

After the work by Stephenson and co-workers, the area of visible light mediated photoredox catalyzed CDC reactions rapidly developed and a range of different nucleophiles have been investigated. The groups of König [17] and Wu [18] investigated the addition of malonates using organic dyes. Under otherwise the same reaction conditions as in the previously mentioned case, the desired CDC products **9** of *N*-aryl-tetrahydroisoquinolines **1** and malonates **8** could be obtained in moderate

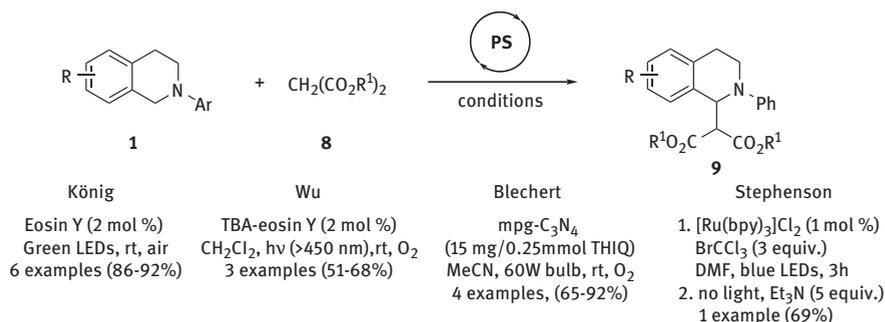


Figure 7.11: Addition of malonates to photogenerated iminium ions.

to very good yields using molecular oxygen as terminal oxidant (Figure 7.11). Blechert, Wang and co-workers applied mpg-C₃N₄ as heterogeneous recyclable catalyst [22a]. Remarkably, the reaction can be performed both neat and in solution. Stephenson and co-workers realized this transformation by preformation of the iminium ion with bromo-trichloromethane and subsequent dark reaction with malonates [23].

7.4 Mannich reaction

In early 2011 Rueping and co-workers reported in their seminal publication on the successful merger of organocatalysis and photoredox catalysis for the CDC reaction of *N*-aryl-tetrahydroisoquinolines **1** and linear aliphatic methyl-ketones **10** (Figure 7.12) [14]. L-proline was found to be a good catalyst for an efficient ketone addition to intermediate iminium ions. As outlined in the introduction to this chapter, the adaptation of both catalytic cycles is crucial. This was achieved by adjusting the reaction rate of the photoredox catalytic cycle to the organocatalytic transformation by variation of the light source. Later, the groups of Wu [18] and Tan [16] subsequently investigated this transformation using organic dyes (Rose Bengal and TBA-eosin Y). In addition, the groups of Blechert and Wang [22] as well as König [29] and Rueping [20], investigated the heterogeneous photoredox catalysis with mpg-carbon nitride, cadmium sulfide and titanium dioxide, respectively (Figure 7.12). In the case of Rose Bengal and CdS as photosensitizer, cyclohexanone can be used as nucleophile. A direct approach to the Mannich products can be alternatively achieved by the addition of silyl-enol-ethers **12**. In this context Stephenson demonstrated the addition of the silyl-enol-ether derived from acetone and 2-silyloxy-tetrahydrofuran (Figure 7.13) [23]. Moreover, Xia and co-workers were able to show that silyl-enol-ethers derived from a range of different acetophenons can be subjected to visible-light mediated CDC transformations (Figure 7.13) [30].

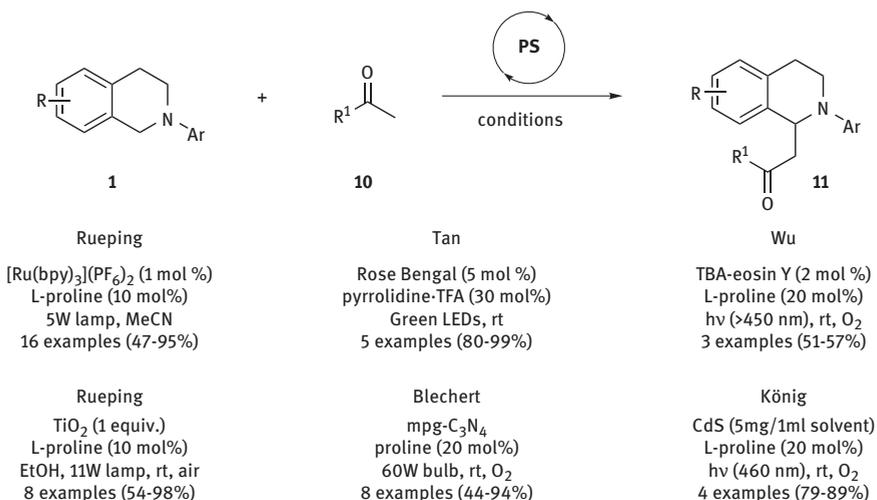


Figure 7.12: Dual catalytic systems for the Mannich reaction.

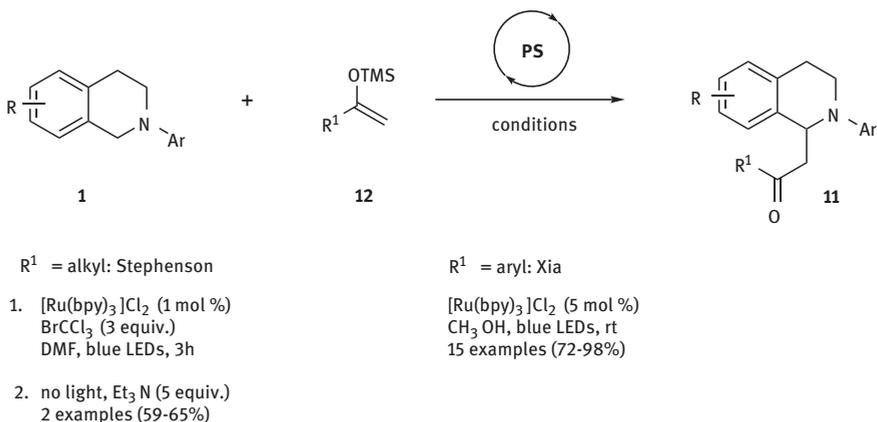


Figure 7.13: Photoredox catalyzed addition of silyl-enol-ethers to iminium ions.

7.5 Allylation

The controlled formation of the intermediate iminium ion can also be applied to subsequently perform efficient allylation reactions. Stephenson and co-workers reported on the addition of (2-methyl-allyl)-trimethylsilane to photochemically generated iminium ions [23].

7.6 Cyanation of tertiary amines

The Strecker reaction is one of the best-studied transformations to yield α -amino acids [31]. Valuable α -amino nitriles can be obtained through the addition of cyanide to an iminium ion. Not surprisingly, different groups reported their work on the addition of cyanide to an iminium ion, generated through photoredox catalysis. Different sources of cyanide can be applied, e. g. KCN in the presence of AcOH, or TMSCN and malodinitrile, which both liberate HCN in the presence of water (Figure 7.14). Rueping and co-workers reported their findings on the photoredox catalyzed Strecker reaction using homogeneous Ir(III) complexes as well as heterogeneous titanium dioxide as catalyst [20, 32]. Moreover, they were able to demonstrate, that under the cyanation conditions, *N,N*-dialkyl-anilines can be subjected to photoredox catalyzed CDC reactions. The groups of König [17] and Tan [33] reported on the application of organic dyes for this transformation.

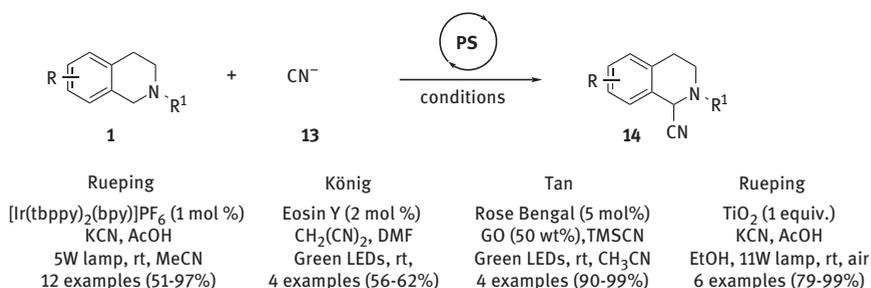


Figure 7.14: α -Cyanation of tetrahydroisoquinolines.

7.7 Alkynylation

The intermediate iminium ion can alternatively be trapped in metal-catalyzed transformations. The groups of Rueping and Stephenson developed protocols to realize the combination of photoredox- and metal catalysis (Figure 7.15). Stephenson and co-workers relied on the initial formation of the iminium ion by employing bromo-trichloromethane as the terminal oxidant [23]. In a subsequent dark reaction, the copper catalyst and alkyne are added and the propargylic amines can be obtained in a one-pot procedure. Rueping and co-workers relied on a cascade reaction sequence [15]. The propargylic amines can be obtained via the reductive quenching pathway and, through careful optimization of reaction parameters, the interplay of both catalysts can be achieved. In addition, the authors were able to demonstrate that also *N*-glyciny-ester derivatives **15** can be subjected to the alkynylation reaction.

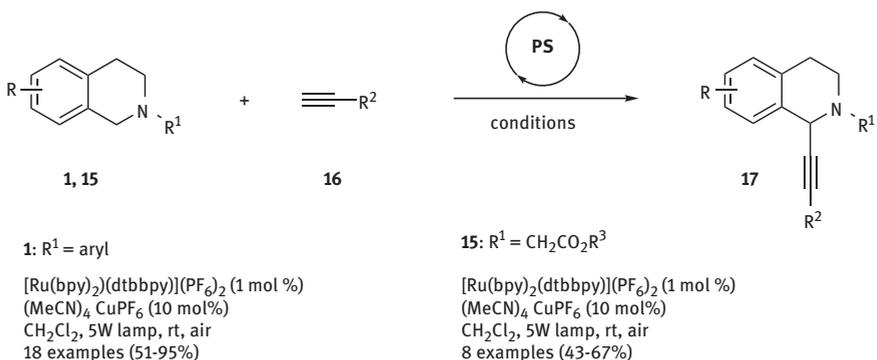


Figure 7.15: Dual catalysis – combining photoredox and metal catalysis for the alkylation of THIQ.

7.8 [3+2] cycloaddition reaction

The application of *N*-glycinyll esters or derivatives thereof, opens up the field of visible light mediated cross-dehydrogenative couplings toward annulation reactions. Oxidation of the tetrahydroisoquinoline core furnishes an iminium ion. In case of *N*-glycinyll-esters, the adjacent C–H bond can be easily deprotonated, resulting in the formation of an azomethine ylide, which is an ideal precursor for [3 + 2] cycloaddition reactions [34]. The groups of Rueping and Xiao reported on their findings on photochemically triggered [3 + 2] cycloaddition reactions, allowing the construction of tri- and tetracyclic systems (Figure 7.16) [35, 36].

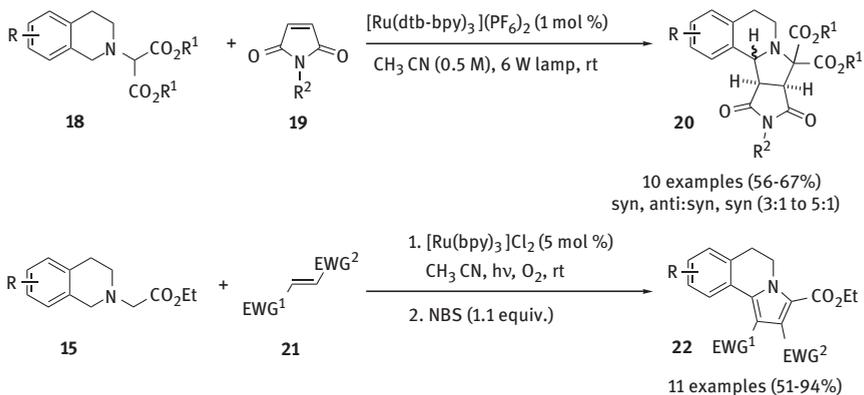


Figure 7.16: Photoredox catalyzed cycloaddition reactions.

7.9 Acylation

In 2012, DiRocco and Rovis reported on an interesting application combining both photoredox and NHC catalysis (Figure 7.17) [37]. Interestingly, the authors reported on the beneficial influence of *m*-dinitrobenzene, an oxidant that was found to be crucial for catalytic turnover, although the reaction was performed without exclusion of oxygen, which is typically sufficient for good turnover. Photochemical oxidation of *N*-aryl-tetrahydroisoquinolines **1** furnishes an iminium ion, which can be acylated with a range of different aliphatic (mostly linear) aldehydes **23** after the Umpolung reaction with the chiral NHC **25** to give products in moderate to high chemical yield and excellent enantioselectivity.

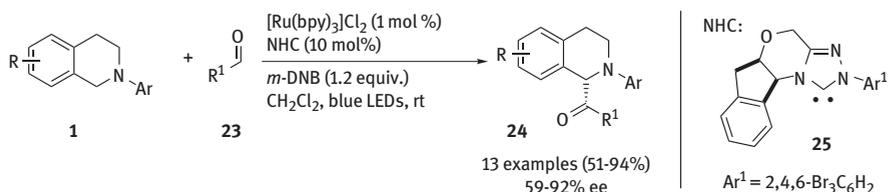


Figure 7.17: Dual catalytic system – asymmetric α -acylation of tertiary amines.

7.10 C-heteroatom (C–P, C–O, C–N) bond formation

The CDC protocols furthermore enable the efficient synthesis of C–P bonds (Figure 7.18). Rueping and co-workers demonstrated that photochemical oxidation of *N*-aryl-tetrahydroisoquinolines with $[\text{Ir}(\text{ppy})_2\text{bpy}]\text{PF}_6$ furnishes iminium ions that can be readily reacted with a range of different phosphonates [38]. At the same time, König and co-workers reported on the application of Eosin Y in the oxidative phosphorylation reaction [17]. Furthermore, it was shown that ZnO can be used as an efficient heterogeneous photoredox catalyst [20].

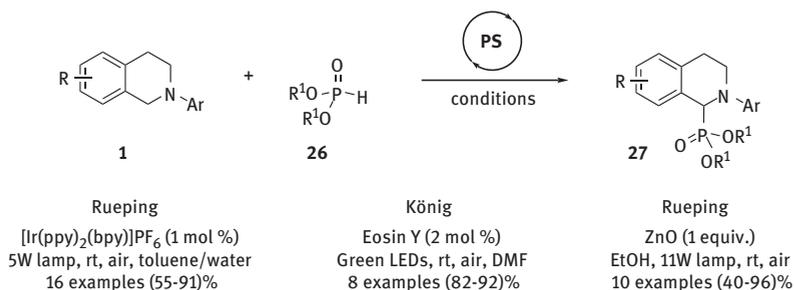


Figure 7.18: Visible light mediated oxidative phosphorylations of amines.

Xiao and co-workers recently demonstrated the efficient application of different oxygen and nitrogen-centred nucleophiles. Yet, protocols that have been developed so far only concentrate on intramolecular cyclization reactions. In a first report, Xiao and co-workers described an interesting functionalization of *N*-benzyl-*N'*-tosyl-ethylene-diamines (Figure 7.19) [39]. Photochemical oxidation of the benzylamine furnishes the reactive intermediate iminium ion that is trapped in a diastereoselective cyclization reaction by the second nitrogen atom. This protocol allows the formation of valuable tetrahydroimidazoles **29**.

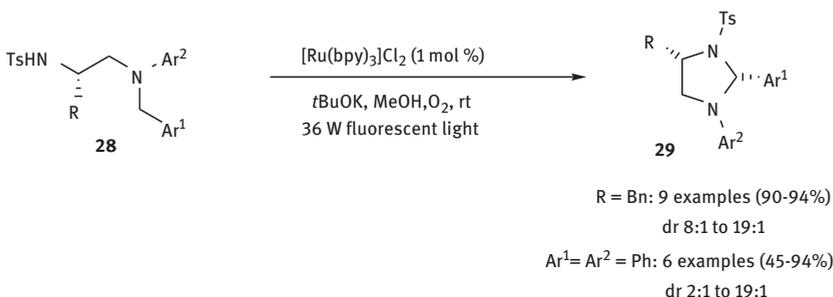


Figure 7.19: Photoredox catalyzed synthesis of tetrahydroimidazoles.

Later, Xiao and co-workers reported on the cyclization reaction of tetrahydroisoquinoline derivatives **30** bearing a proximal alcohol or sulfonated amine functional group, which can intramolecularly add to the photochemically generated iminium ions (Figure 7.20) [40]. Furthermore, the authors were able to demonstrate that this transformation can be conducted under metal free conditions by using Eosin Y as well as on gram-scale with an iridium complex as photosensitizer.

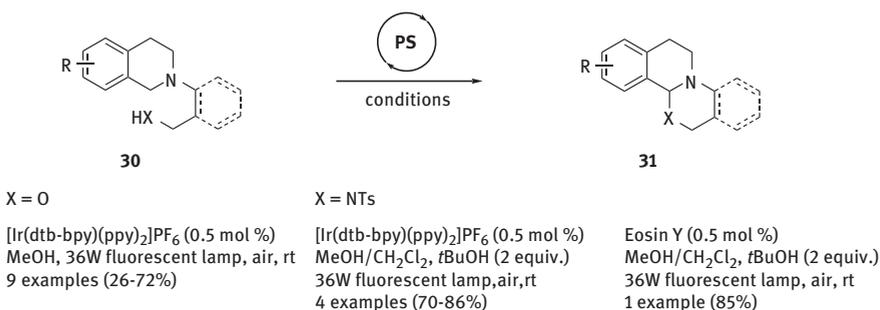


Figure 7.20: Visible light photoredox catalyzed intramolecular additions.

7.11 Conclusion

In summary, visible light photoredox catalyzed cross-dehydrogenative coupling reactions have been extensively investigated over the past years, showing significant improvements in both the application of visible light in organic synthesis and the development of sustainable methods for the coupling of non-prefunctionalized building blocks. In this chapter a range of different methods for the functionalization of tertiary amines have been presented; yet, this strategy will continue growing to further exploit the benefits of CDC coupling reactions under photochemical reaction conditions.

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