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Progress on All Ends for Carbon–Carbon Bond Formation through Photoredox Catalysis**

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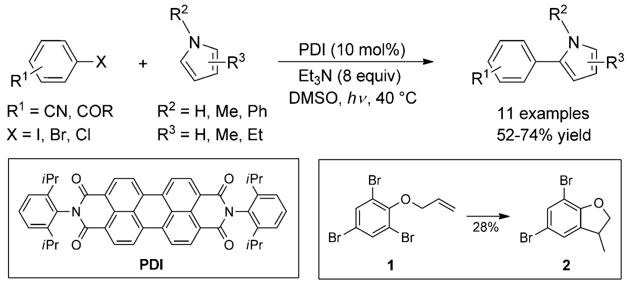
Carbon–carbon bond formation has become a fundamental tool in modern organic chemistry. Among the numerous procedures developed so far, transition-metal-catalyzed cross-coupling reactions offer interesting promises compared to the more conventional synthetic methods.[1] However, one problem of these methodologies can be the large activation energy needed for the transmetalation step. Thus, excess of base, high temperature, and stoichiometric amounts of Ag and Cu salts have been used to facilitate such steps, with the consequence of limited functional group tolerance and augmenting side reactions. Here, the use of photoredox catalysts in coupling reactions offers attractive possibilities, because such protocols take advantage of the visible-light-induced generation of radicals with unusual reactivities to trigger chemical reactions under mild conditions.[2]

As a recent example, König et al. reported a practical protocol for the C–C bond forming reactions between aryl halides and pyrroles using visible light and a metal-free photosensitizer (Scheme 1).[3] The key feature of this work was a perylene diimide (**PDI**) which is capable of absorbing two photons in one catalytic cycle, harvesting in this way enough energy to overcome the high reduction potential ($E°$) of aryl chlorides. Using optimized conditions, different substituted pyrroles were arylated providing the corresponding coupling products in good yields. The radical nature of this transformation was evidenced by the conversion of the oxoallyl substrate **1** to the corresponding 5-*exo* cyclization product **2**,[4] as well as with the use of TEMPO as a radical marker.



Scheme 1. Metal-free photocatalytic arylation of substituted pyrroles.

On the other hand, several photoredox processes have been successfully combined with coupling sequences (Figure 1).[5] In this methodology, visible-light irradiation of the photosensitizer (PS) generates the corresponding excited-state complex (PS*) with a sufficiently high reduction potential to induce oxidation by single-electron transfer (SET) of an organic substrate **4**, affording the alkyl radical **6**. Subsequent reaction between this reactive intermediate and substrate **3**, previously activated by a transition-metal complex or organocatalyst (Cat) acting in the coupling cycle, results in the formation of the desired coupling product **5** and a radical species of the catalyst. Finally, a second SET process between this radical and the oxidized form of the photosensitizer (PS⁺) regenerates both catalytically active species. New carbon–carbon bonds are formed in this transformation, and their stereoselective construction using prochiral substrates can be controlled by a suitable selection of chiral

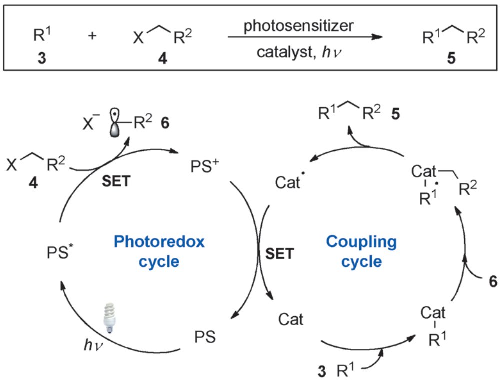


Figure 1. Dual catalysis: photoredox and carbon–carbon bond formation. PS, photosensitizer; Cat, transition metal or organocatalyst; R¹, organic substrate.

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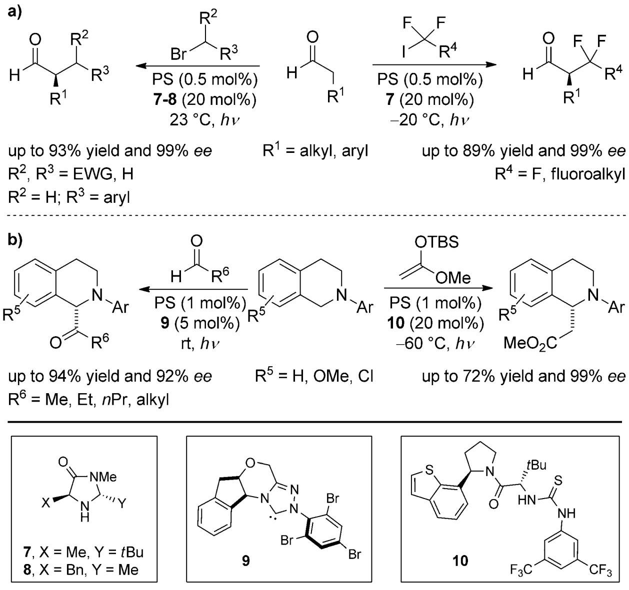
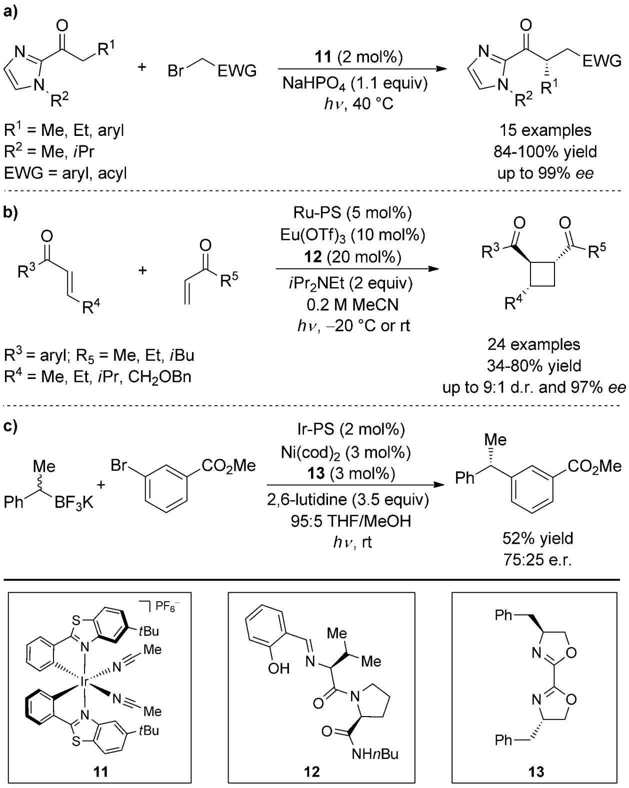
organocatalysts or ligands in case of metal-catalyzed processes.

Clearly, the application of such dual catalytic systems to asymmetric synthesis has attracted great interest in the last decade. For instance, MacMillan and co-workers have been able to generate chiral centers with high efficiency through enantioselective α-alkylation of prochiral aldehydes with alkyl and benzyl halides using [Ru(bpy)$_3$Cl$_2$] (bpy = 2,2′-bipyridin) or [Ir(ppy)$_3$] (ppy = 4-(1-pyrrolidinyl)pyridin) as photosensitizer and enantiopure imidazolidinones **7–8** as organocatalysts (Scheme 2 a).[6] The excited state of the photosensitizer promotes the formation of the alkyl radical from the bromide by single-electron transfer, which is added to the stereocontrolling enamine generated by reaction of the aldehyde with the chiral secondary amine. This reaction exhibits relatively broad scope and wide functional group tolerance and was later on applied to the α-trifluoro and perfluoroalkylation of aldehydes in good yields and excellent enantioselectivities (Scheme 2 a).[7] Likewise, the groups of Jacobsen and Rovis published different enantioselective applications following this photoredox-catalyzed methodology. More specifically, the α-acylation and alkylation of *N*-aryl tetrahydroquinolines by reaction with aldehydes or a silyl ketene acetal (Scheme 2 b).[8] The combination of catalytic amounts of [Ru(bpy)$_3$Cl$_2$] and chiral ligands such as the N-heterocyclic carbene **9** and thiourea **10** allows also to perform corresponding C–H functionalizations in an effective way. These transformations offer already today significant synthetic utility; however the development of more general and versatile applications using simple reaction conditions and easily available reagents is still demanded.



Scheme 2. Selected examples of asymmetric photoredox catalysis.

During the last months, notable advancements in asymmetric photoredox catalysis have been published, raising new perspectives for light-induced coupling processes. Whereas previously known examples focused on the use of photosensitizers and catalysts separately, Meggers and co-workers reported the application of a chiral iridium complex playing both roles which allowed to carry out the formation of a carbon–carbon bond in an enantioselective fashion (Scheme 3 a).[9] More specifically, they showed that the octahedral iridium(III) complex **11** coordinated by two achiral bidentate ligands, which confers metal-centered chirality, triple acts as catalytic, photoredox, and chiral center to perform the α-alkylation of acyl imidazoles with benzyl and phenacyl bromides. The irradiation of the reaction mixture with visible light at 40 °C in the presence of 2 mol% of the metallic complex **11** and Na$_2$HPO$_4$ (1.1 equiv) as base, gave rise to a wide range of 2-substituted products in high yields and enantioselectivities. In this case both photoredox and coupling catalytic cycles are connected through an intermediate Ir^{III} enolate complex, while the chirality generating key step constitutes the exergonic addition of a photoreductively generated electrophilic radical to the electron-rich metal-coordinated enolate.



Scheme 3. New developments in asymmetric photoredox catalysis.

In addition, the group of Yoon recently developed a complementary methodology to generate chiral centers using photoredox processes (Scheme 3 b).[10] In this case, the asymmetric [2+2] photocycloaddition of α,β-unsaturated ketones to obtain the corresponding cyclobutanes is achieved with the combination of [Ru(bpy)$_3$Cl$_2$] and a stereocontrolling Lewis acid as catalytic system. The latter cocatalyst comprises the chiral Schiff base ligand **12** and Eu(OTf)$_3$. By irradiation with visible light at room temperature or −20 °C in the presence of *i*Pr$_2$NEt as base, three stereogenic centers are formed in good diasteromeric ratio, obtaining the major isomer in excellent enantiomeric excess. Here, the crucial activation step of the cycloaddition involves the one-electron reduction of a Lewis acid-activated aryl enone by a Ru^{I} species generated by irradiation of $[Ru(bpy)_3]^{2+}$ in the presence of a donor amine.

Finally, Molander and co-workers recently reported a reaction catalyzed by two transition metals for the photoredox cross-coupling of secondary organoboron reagents with aryl bromides (Scheme 3c).[11] Interestingly, the reaction of the racemic (1-phenylethyl)trifluoroborate with methyl 3-bromobenzoate using $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ as photosensitizer and $[Ni(cod)_2]$/bisoxazole **13** (cod = cyclooctadienyl) as chiral coupling catalyst, provided the corresponding 1,1-diarylethane in moderate yield as a mixture of enantiomers in a promising ratio of 75:25. This encouraging experiment showed that the stereoconvergent synthesis of enantioenriched compounds using photocatalysis is possible by means of suitable selection of reaction conditions and chiral ligands.

In conclusion, we summarized the recent developments in the area of asymmetric carbon–carbon bond formation using combined photoredox catalysis and coupling reactions. As shown by the work of Meggers et al. it is possible to use one catalyst, for example, a chiral iridium complex, working at the same time as chiral catalyst and photosensitizer. Noteworthy, these reactions open new avenues for asymmetric catalysis whereby light is used as green energy source.

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