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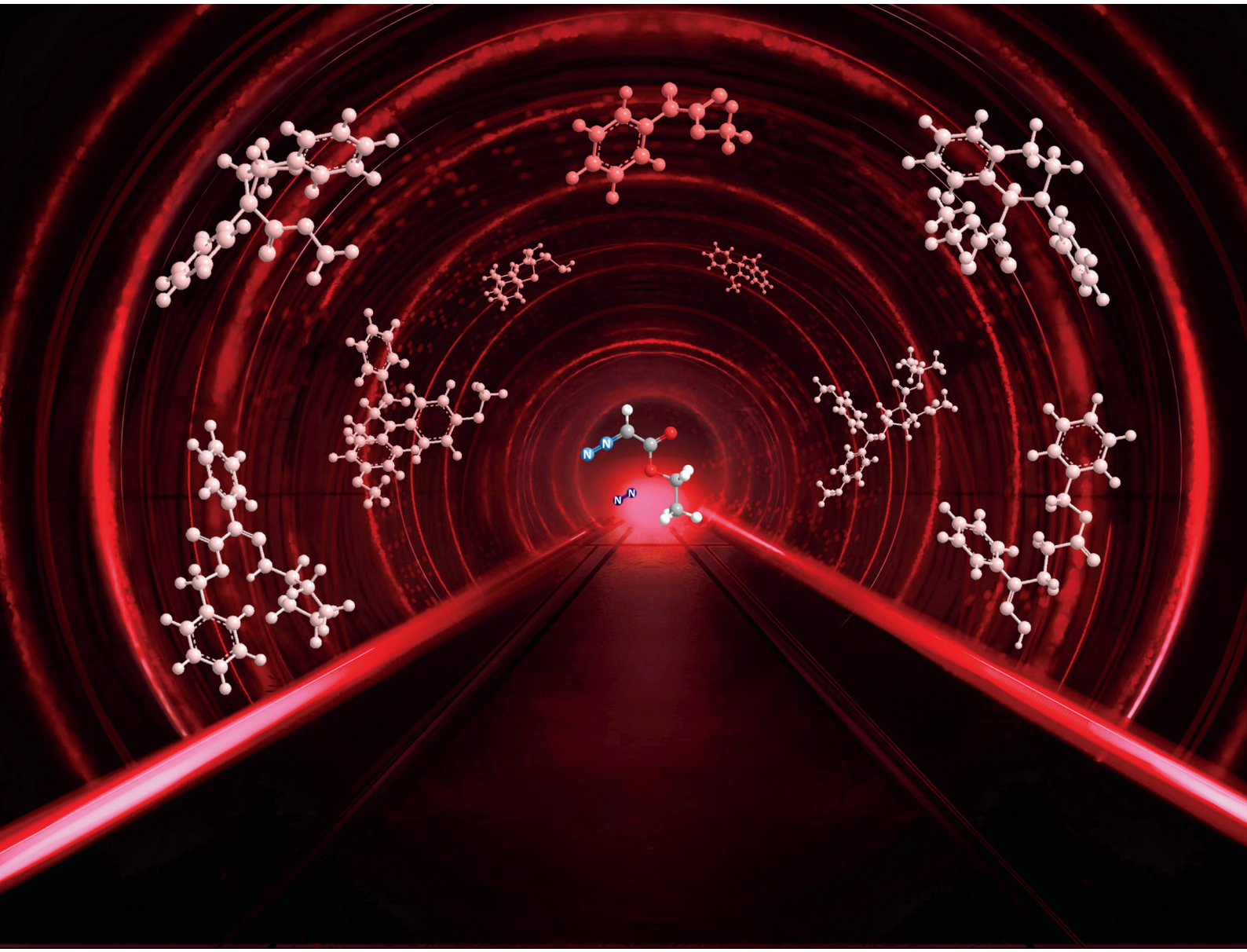

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# Unlocking the reactivity of diazo compounds in red light with the use of photochemical tools†

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**Structurally diversified diazoalkanes can be activated under red light irradiation relying on direct photolysis, photosensitization or photoredox catalysis.**

Bioorthogonal chemistry represents chemical transformations that proceed selectively in biological environments without perturbing the structure of biomolecules or interfering with biochemical pathways.[1–6] Several photoactivated methods have been designed, yet most of them employ short-wavelength light emitting sources.[7–10] The phototoxicity of high energetic photons makes them inappropriate for biological applications. Therefore, switching to less energetic light is desirable. Along this line, tetrazole bioorthogonal chemistry was performed under NIR radiation *via* two-photon excitation or upconversion processes.[11,12] Dihydrotetrazine oxidation *in vivo* can also be achieved with less energetic photons.[13] Yet, red light-induced reactions even in synthetic chemistry call for in depth studies.[14]

Diazoalkanes are versatile reactants for photochemical synthesis of small/complex structures[15–17] and functionalization of bioactive compounds.[18–21] They have been utilized in enzymatic cyclopropanation, ring expansion, cyclopropenation, or insertion reactions.[22–27] So far, however, generation of carbenes in biological systems is mostly limited to diazirines that are activated in UV/violet light.[28–30] In view of benefits arising from the application of low energetic photons, red light-induced diazo chemistry is highly desirable. Given the structural diversity of diazoalkanes, they can be directly photolyzed or activated *via* photocatalytic processes under visible light (even red, Fig. 1A). We wondered whether it is possible to unlock the potential of red light toward the generation of reactive species from structurally diversified diazo compounds utilizing various photochemical modes. While studying the photocatalytic activity of porphyrins under red-light irradiation, we found that they catalyze photoalkylation of aldehydes with ethyl diazoacetate.[31] Herein, we present our comprehensive study on the red light-induced photolysis, photosensitization, and photoredox-driven generation of reactive intermediates from diazo reagents (Fig. 1B).

**Photolysis** – Direct photolysis of diazoalkanes enables carbene generation with no catalyst required. Although acceptor-only and acceptor/acceptor diazo compounds exhibit light absorption beyond the visible range, replacing H/one of the acceptor groups with an aryl substituent bathochromically shifts the $\lambda_{max}$ toward the visible spectrum.[16,32] By increasing the donating character of the phenyl ring, $\lambda_{max}$ is shifted even further (for –OMe, $\lambda_{max}$ = 543 nm),[33] and has an impact on the carbene spin state. Given the ubiquity of free hydroxy-, amino-, and thio-groups in natural compounds, we focused on red light-induced photolysis of diaryldiazoalkanes in the presence of alcohols, amines, and thiols (Scheme 1). The light-induced method works well for primary alcohols efficiently affording ethers **1–5**. Incorporation into the phenolic O–H bond, a

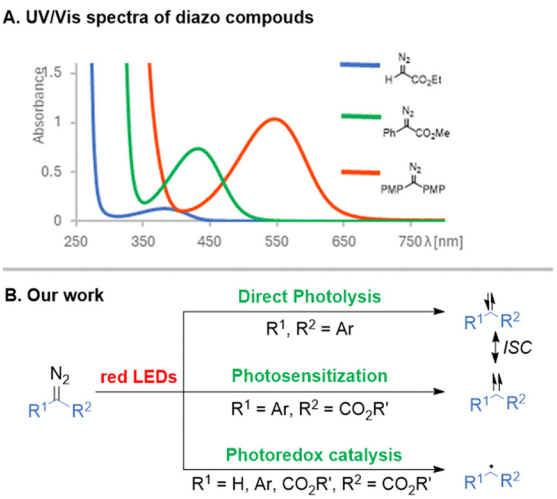


Fig. 1 Red light-induced reactions of diazoalkanes.

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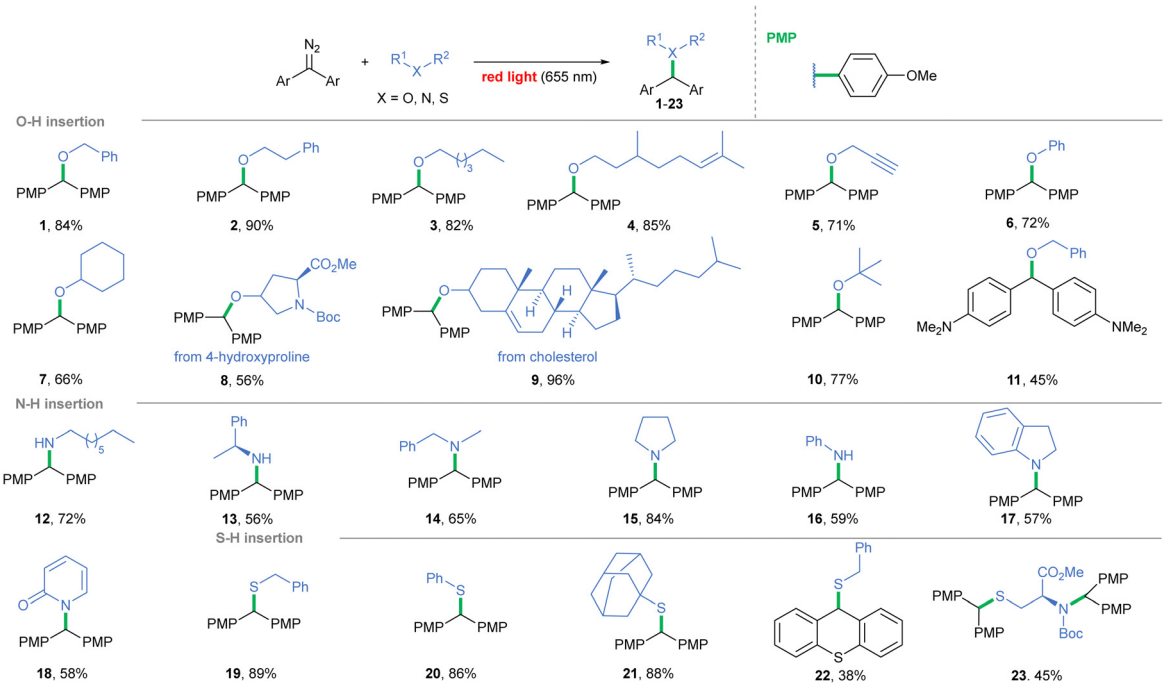
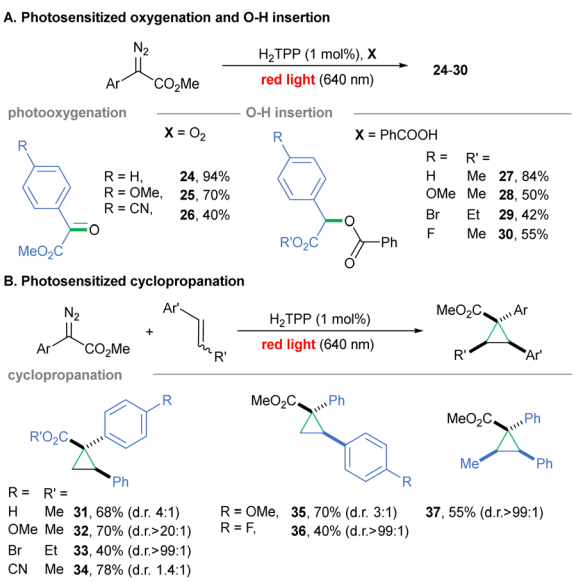



Scheme 1 Scope of red light-induced carbene insertion into the X–H bond.

tyrosine model, also proved successful (**6**, 72%). Secondary and tertiary alcohols were slightly less effective (**7**, **8** and **10**), but cholesterol derivative **9** formed almost quantitatively. On the other hand, irradiation of diaryl diazoalkane bearing amino groups at *p*-positions ($\lambda_{max}$ = 566 nm)[34] in the presence of benzyl alcohol led to product **11** in a diminished yield (45%). Noteworthily, when beneficial, the substrate ratio could be reversed and diazoalkane excess could be used instead. Benzyl and aromatic amines formed in a slightly diminished yield, in contrast with productive amine **15** formation (84%). 2-Hydroxypyridine gave a mixture of O–H and N–H insertion products but, upon isolation, full conversion to amide **18** occurred. The scope of tolerated thiols is broad, and even thiophenol and bulky adamantanethiol efficiently furnished products **20** and **21**. Furthermore, the feasibility of the method was examined with *N*-Boc protected cysteine ester, and insertion occurred on both the N–H and S–H bonds (**23**, 74%).

**Photosensitization** - Most carbene precursors, including diazo compounds, do not, however, absorb red light (Fig. 1A), and for their activation photocatalytic approaches are required. Among these, photosensitization with the use of a dye of proper $E_T$ level gives access to triplet excited states *via* triplet–triplet energy transfer (EnT).[35,36] Only recently, mild Ir-sensitized strategies to access triplet carbenes from diazirines and 1,3,4-oksadiazolines under blue light irradiation were proposed by MacMillan and our group,[30,37] but approaches relying on red light remain challenging. Porphyrins are sensitizers widely applied in photooxidation, photodynamic therapy and artificial photosynthesis.[38–41] We tested these red-light-absorbing organic dyes for photosensitization of diazoalkanes. When aryldiazoesters ($E_T \approx 133$ kJ mol$^{-1}$, calculated using SMD(DCM)/M06/6-311++g(d,p)//B3LYP-D3/6-31g(d)), were irradiated with red light in the presence of $H_2$TPP ($E_T$ = 138 kJ mol$^{-1}$)[42] and oxygen, β-ketoesters **24–26** formed (Scheme 2A).

For more electrophilic aryl diazoalkane, a loss of selectivity was observed (**26**, 40%). Since porphyrins are well-known $^1O_2$ sensitizers,[38,39] maintaining oxygen-free conditions was crucial to prevent competitive oxidation pathways in consecutive O–H insertion (Scheme 2A) and cyclopropanation (Scheme 2B, see ESI†). The insertion into O–H carboxylic bonds works for



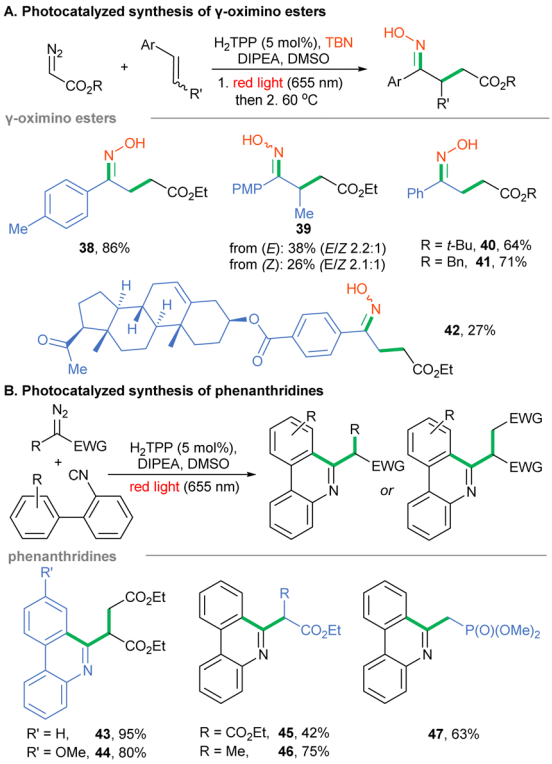

Scheme 2 Red light-induced photosensitized transformations of diazo compounds.

various aryldiazoesters leading to products **27–30**. Electron-poor aryldiazo ester reached the highest cyclopropanation productivity (**34**, 90%). The method is suitable for both electron-rich and -poor styrenes, with a better outcome for *p*-methoxy-styrene-derived product **35** (70%). A modest yield was observed when the internal olefin was subjected to the reaction conditions giving cyclopropane **37** (55%). α-Diazo esters, diazomalonates, and aryldiazoketones possessing higher $E_T$ values than porphyrin (calculated $E_T$ = 158 kJ mol$^{-1}$ for EDA) cannot, in principle, be activated under the developed conditions. Intuitively, the reaction rate for diazoalkane transformation depends on the carbene rate formation, which for the red light-mediated EnT-approach occurs slower than *via* direct photolysis under blue light (see ESI†).

**Photoredox catalysis** – To unlock the red-light mediated reactivity of yet unconquered α-diazo esters, we screened the possibilities offered by photoredox catalysis. These acceptor-only types of diazoalkanes are reduced to alkyl radicals *via* proton coupled electron transfer (PCET, $E_{RED}$ = −1.28 V *vs.* SCE for EDA).[43] In this view, numerous blue light-induced methodologies utilizing diazoesters as surrogates of alkyl radicals have been reported.[43–48] Recently, we have proved that porphyrins are suitable photo-oxidants and photo-reductants for red light-mediated organic transformations.[31] Therefore, we harnessed their photoredox abilities to tune already reported blue light-induced, radical-based transformations of α-diazoesters and applied them on red illumination instead. Our studies were initiated with the redesign of the photocatalyzed synthesis of γ-oximino esters, originally performed by Li under blue light with the use of α-diazoester, styrene and TBN as starting materials.[43] Optimization studies substantially shortened the reaction time (reported on blue: 60 h) to 37 h by thermally accelerating the isomerization of the nitroso compound to the final product **38** (see ESI†). Our method works well for various α-diazoesters giving esters **38**, **40** and **41** in yields comparable to those reported by Li (Scheme 3A). A slight yield decrease was observed for *trans*-anethole, though with a similar *E*/*Z* ratio (product **39**). Due to solubility problems, the synthesis of pregnenolone-derived ester **42** was less efficient. For the Ru-catalyzed reaction a key step relies on the reduction of diazo ester by the photocatalyst in the excited state. In our case, as the reduction potential of the porphyrin in the excited state (−0.91 *vs.* SCE)[31] is higher than that of EDA (−1.28 V *vs.* SCE), we assume that the excited porphyrin oxidizes DIPEA, thus generating a strongly reducing porphyrin radical anion, similar to the mechanism reported for the generation of radicals from aminopyridinium salts.[49]

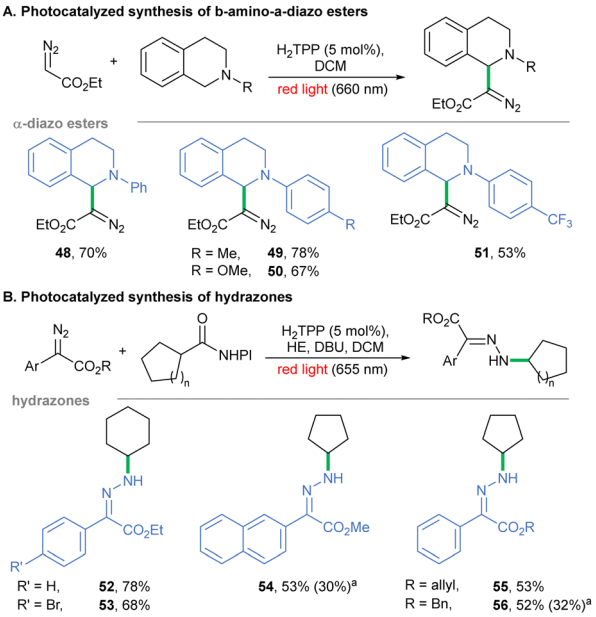
Next, we examined an analogous PCET-based approach toward phenanthridines utilizing isocyanobiphenyls and diazoalkanes.[50] Scheme 3B shows the optimization of the red light-mediated protocol-enabled synthesis of heterocycles **43–47** with better productivity or comparable to the Xuan methodology. Finally, there are methodologies involving diazo reagents in which the diazo moiety remains intact or does not generate reactive intermediates. To fill the picture of the photochemistry of diazo compounds under red-light




Scheme 3 Diazo compounds as radical precursors in red light-mediated photocatalyzed transformations.

irradiation, such transformations were studied. Given that sole $H_2TPP$ is unable to photoreduce EDA, we tested $H_2TPP$ as a photo-oxidant of diversely substituted tetrahydroisoquinolines in the presence of EDA and red light, similar to Zhou's report.[51] In fact, products **48–51** were obtained in decent yields (Scheme 4A). Furthermore, diazo compounds have been shown to react with radicals generated under photochemical conditions, including alkyl radicals generated from NHPI esters in the presence of Rose Bengal on yellow LEDs.[52] We performed this transformation with the $H_2TPP$ catalyst instead, under red light irradiation. A wide range of donor/acceptor diazoalkanes reacted under the developed conditions to give hydrazones **52–56** (Scheme 4B).

In summary, this study demonstrates that photochemistry provides tools for red light-driven activation of various diazo compounds. A proper structural modification of diazoalkane results in a bathochromic shift of the absorption maxima allowing for direct photolysis under low-energetic, red-light irradiation. If this pathway is not possible, we induce transformations of diazo compounds taking advantage of nature-inspired dyes, established as safe and effective for photodynamic therapy and artificial photosynthesis. The triplet energy level of the porphyrin excited state is sufficient for productive EnT to aryl-diazo esters giving access to triplet carbenes. Other diazoalkanes may be activated through porphyrin-mediated photoredox processes by undergoing reduction to alkyl radicals or by serving as radical acceptors. Therefore, three-modes of




Scheme 4 Diazo compounds as radical acceptors in red light-mediated photocatalyzed transformations. [a]Reaction set under blue light irradiation (25 W, 455 nm).

activation of diazo compounds under red-light irradiation have been unlocked.

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## Conflicts of interest

There are no conflicts to declare.

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