Unlocking the Reactivity of Diazo Compounds on Red Light with the Use of Photochemical Tools

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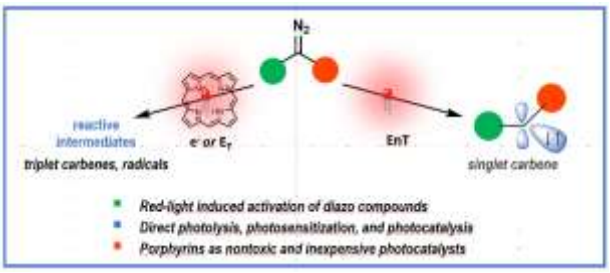
ABSTRACT: Photoinduced bioorthogonal reactions constitute a valuable class of chemical transformations that enable spatiotemporal control of biomacromolecules. Among them, those involving carbenes proved effective in various bioapplications, but they require ultraviolet or blue-light irradiation. Using lower energetic radiation, however, offers deeper penetration and diminishes photodamages. Thus, herein, we describe the photochemistry of structurally diversified diazo reagents under red light irradiation. Reactive intermediates can be generated via direct photolysis or taking advantage of porphyrin chemistry via photosensitisation and photoredox catalysis.

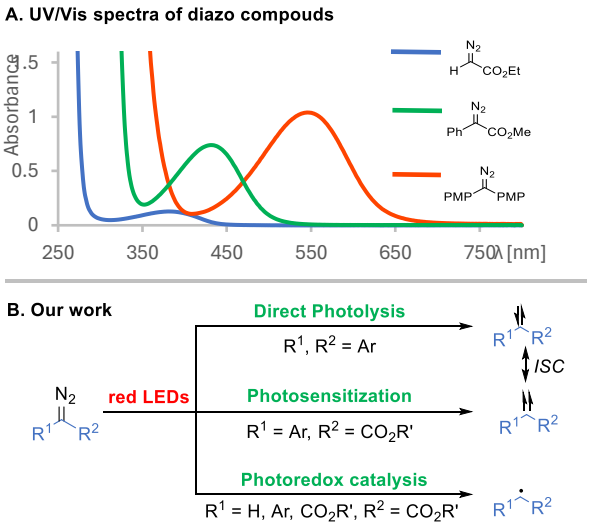


Bioorthogonal chemistry represents a collection of efficient chemical transformations that can proceed selectively in biological environments without perturbing the structure of delicate biomolecules and interfering with biochemical pathways.[1,2,3,4,5,6] Such perfectly designed approach enables specific labelling, bioconjugations and deconjugation-based cargo delivery, among which photoinduced bioorthogonal reactions constitute a valuable class ensuring spatiotemporal control of biomacromolecules.[7,8,9,10,11,12,13] Numerous photoactivated methods have been designed, yet most of them relate to tetrazole ligation or employ short-wavelength light emitting sources.[14,15,16] The phototoxicity of high energetic photons and low selectivity of UV-induced processes provide poor spatial control and make it inappropriate for application in biological systems. Therefore, switching to less energetic red or near-infrared (NIR) light, which efficiently penetrates various reaction media (including tissues), is a desirable solution. Along this line, tetrazole bioorthogonal chemistry was enabled on NIR radiation via two-photon excitation process or the use of upconversion of nanoparticles.[17,18] Rapid red light-mediated dihydrotetrazine oxidation in *vivo* was also reported.[19] Yet, red light-induced transformations in biorthogonal approaches are rare and call for extensive research.[20]

Diazoalkanes are versatile reactants for light-induced synthesis of small and complex structures,[21,22,23] as well as functionalizations of bioactive compounds.[24,25,26,27] In biological systems, they have been utilized in enzymatic enantioselective cyclopropanation, ring expansion, cyclopropenation, and insertion reactions.[28,29,30,31,32,33] So far, however, photolabeling approaches relying on carbene precursors are mostly limited to 3-aryl-3-(trifluoromethyl) diazirines that are activated on UV/violet light.[34,35,36]

Given the structural diversity of diazoalkanes, they can be directly activated not only by light from ultraviolet and visible regions but also by the less energetic red light or generate reactive intermediates in photocatalytic processes (Figure 1A). They have been indeed extensively explored under <500 nm light irradiation but the benefits arising from the application of low energetic photons, the exploration of red light-induced diazo chemistry is highly desirable. However, *before moving to complex biosystems, the photochemistry of diazo compounds under red light irradiation has to be established.*

Figure 1. Red light-induced Reactions of Diazoalkanes

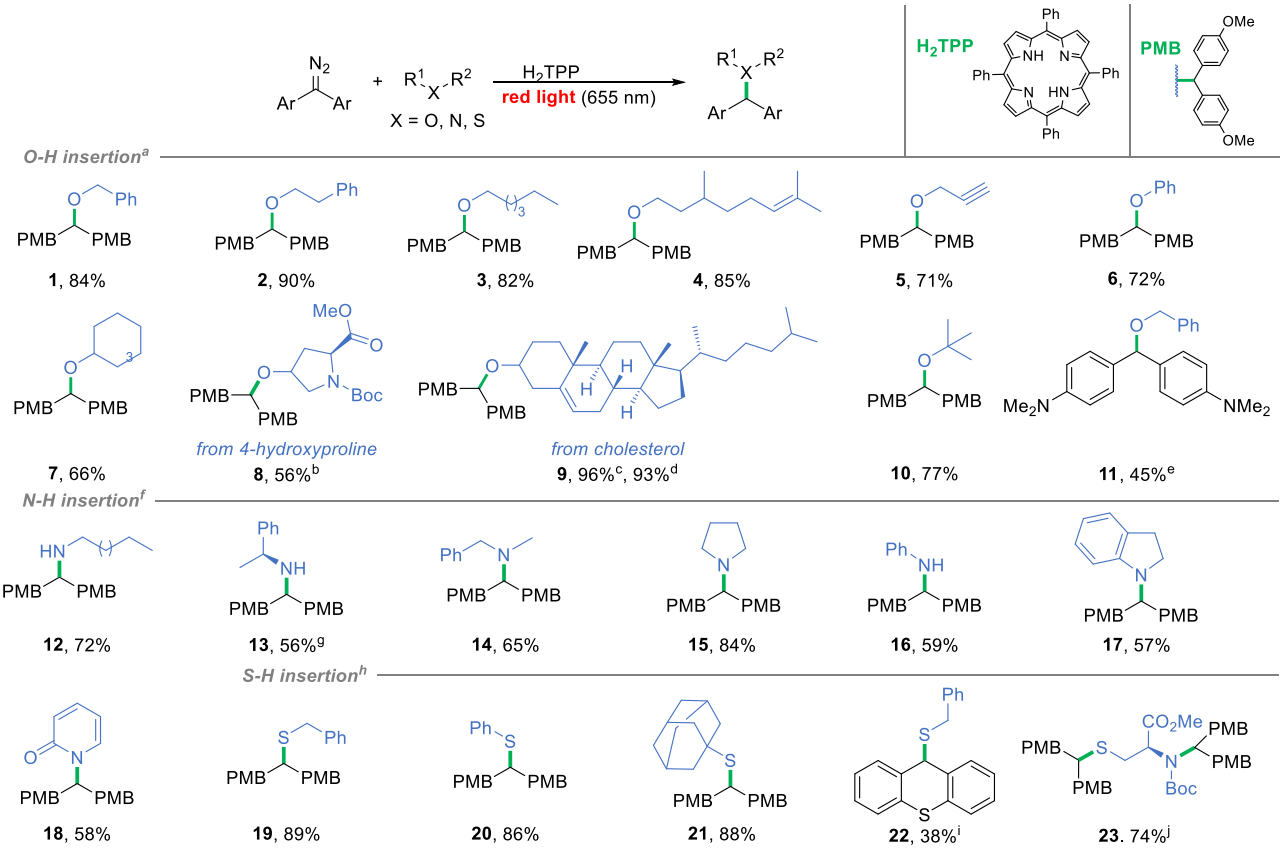


Driven by chemical curiosity, we wondered whether it is possible to unlock the potential of red light toward the generation of reactive species from structurally diversified diazo compounds utilizing various photochemical modes. While studying the photocatalytic activity of porphyrins under red-light illumination, we have found that they enable photoalkylation of aldehydes with α-diazoacetate.[37] Herein, we present our comprehensive experimental study on the red-light-induced photolysis, photosensitization as well as photoredox-driven generation of reactive intermediates from diazo reagents (Figure 1B).

PHOTOLYSIS - Direct photolysis of a diazo compound enables carbene generation with no need for a catalyst, which is highly appreciated in terms of biological applications. 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 λ_{max} toward the visible spectrum.[22,38,39] By increasing the donating character of the phenyl ring λ_{max} is shifted even

further and has a significant impact on the spin state of the carbene and the singlet-triplet splitting. For example, the local absorption maximum of electron-rich 4,4'-(diazomethylene)bis-(methoxybenzene) (**S1**) is within the green region (λ_{max} = 543 nm),[39] but it also weakly absorb red light. Given the ubiquity of free hydroxy-, amino- and thio- groups in molecules of biochemical importance, we focus on red light-induced photolysis of model diaryl diazoalkane **S1** in the presence of alcohols, amines, and thiols (Scheme 1). X-H (X = O, N, S). The insertion reactions gave the desired products and no consumption of substrate **S1** was detected in the dark, proving that light is a crucial factor. The method works well for primary alcohols of various chain lengths efficiently affording ethers **1-5**, with unactivated alkene and alkyne moieties remaining intact in case of products **4** (85%) and **5** (71%). Incorporation into the phenolic O-H bond, a tyrosine model, proved also successful, affording ether **6** in 72% yield. A slight decrease in reaction efficacy was observed for secondary and tertiary alcohols (ethers **7**, **8** and **10**), but cholesterol derive **9** formed almost quantitatively. On the other hand, irradiation of diaryl diazoalkane **S2** bearing amino groups at *para* positions (λ_{max} = 566 nm)[40]

Scheme 1. Scope of Red Light-Induced Carbene Insertion into X-H Bonds



Reaction conditions: [a]diazo compound (0.2 mmol), alcohol (10 equiv.), MeCN (0.1 M), red LEDs (25 W), 135 min. [b]2.0 equiv. of diazo compound was used. [c]alcohol (0.1 mmol), diazo compound (5.0 equiv.), MeCN (0.03 M), red LEDs (25 W), 165 min. [d]alcohol (0.1 mmol), diazo compound (5.0 equiv.), DCM (0.1 M), red LEDs (25 W), 120 min. [e]alcohol (0.2 mmol), diazo compound (2.0 equiv.), THF (0.08 M), red LEDs (25 W), 60 min. [f]amine (0.2 mmol), diazo compound (2.0 equiv.), DCM_{dry} (0.1 M), [Ar], red LEDs (25 W), 135 min. [g]3.0 equiv. of diazo compound was used. [h]thiol (0.2 mmol), diazo compound (2.0 equiv.), DCM_{dry} (0.1 M), [Ar], red LEDs (25 W), 135 min. [i]4.0 equiv. of thiol was used. [j]0.1 mmol scale, 4.0 equiv. of diazo compound was used.

in the presence of benzyl alcohol led to product **11** although in a diminished yield (45%). It is noteworthy, when beneficial, a substrate ratio could be reversed and diazoalkane can be used in excess instead. Although experiments on O-H insertion revealed a negligible effect of moisture and air atmosphere on efficiency, dry and oxygen-free conditions were required for functionalizations of amines and thiols (for optimizations see SI). For reactions with both alkyl and aromatic amines, a slight decrease in yield was observed, in contrast with productive amine **15** formation (84%). *N*-hydroxy pyridine gave a mixture of O-H and N-H insertion products but, interestingly, upon isolation, a complete conversion to amide **18** occurred. The scope of tolerated thiols is also broad, even thiophenol and bulky adamantanethiol efficiently furnished products **20** and **21**.

Given the importance α-amino acids in biological systems, the feasibility of the developed method was examined with *N*-Boc protected cysteine methyl ester. Gratifyingly, insertion occurred on the amide N-H and S-H bonds simultaneously, affording product **23** in 74% yield.

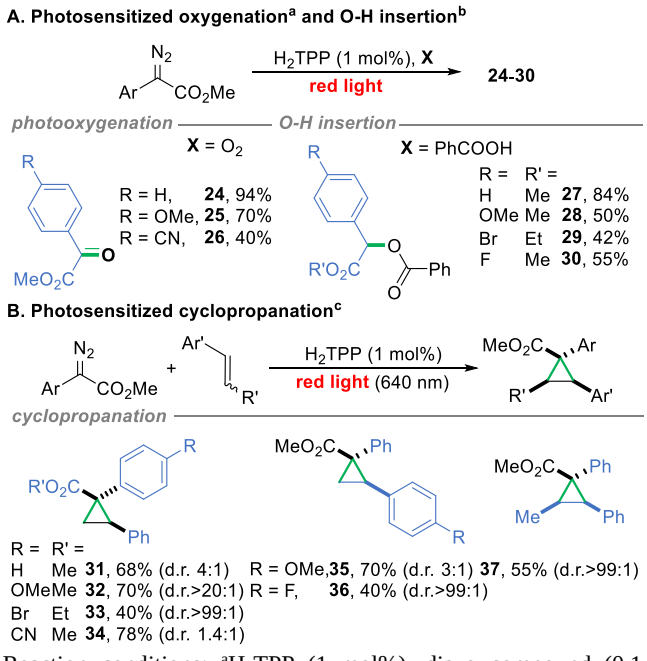
PHOTOSENSITIZATION - Most carbene precursors, including diazo compounds, do not, however, absorb red light (Fig. 1A), and to generate reactive species from these reagents photocatalytic approaches have to been employed. Among these, photosensitization with the use of a dye exhibiting a proper E_T

level gives access to triplet excited states via triplet-triplet energy transfer (EnT).[41,42] Again, due to absorption properties of commonly applied photocatalysts, already established methods are rather limited to violet/blue light, and expanding the approach to red light remains challenging. Along this line, only recently, a mild Ir-sensitized strategy to access triplet carbenes from diazirines and 1,3,4-oksadiazolines under blue light irradiation, as reported by MacMillan et al., and our group respectievly.[36,43]

Taking into consideration that porphyrins are sensitizers widely applied in photooxidations, photodynamic therapy and artificial photosynthesis,[37,45,46,47] we tested these red-light-absorbing organic dyes for photosensitization of diazo compounds. When aryldiazoesters ($E_T \approx 1.36$ eV/mol, 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_2TPP (E_T = 1.45 eV/mol)[48] and oxygen, β-ketoesters **24-26** formed (Scheme 2A). However, for more electrophilic aryl diazoalkane, a loss of selectivity was observed, yielding product **26** in a modest yield (40%). The experiment with the use of 1,3-diphenyl-1,3-dihydroisobenzofuran as the starting material resulted in the formation of endoperoxide and its subsequent dehydratation product,[48] evidencing generation of $^1O_2$ under developed conditions (see SI).

Since porphyrins are well-known $^1O_2$ sensitizers,[44,45] maintaining oxygen-free conditions was crucial to prevent competitive oxidation pathways in consecutive O-H insertion (Scheme 2A) and cyclopropanation (Scheme 2B) (for details see SI). The insertion into O-H carboxylic bonds works for various aryldiazoesters leading to products **27-30**.

Scheme 2. Red Light-induced Photosensitized Transformations of Diazo Compounds



Reaction conditions: [a]H_2TPP (1 mol%), diazo compound (0.1 mmol), DCM_{dry} (0.1 M), [O_2], red LEDs (3 W, 660 nm), 1 h. [b]H_2TPP (1 mol%), diazo compound (0.1 mmol), benzoic acid (2.0 equiv.), DCM_{dry} (0.1 M), [Ar], red LEDs (40 W, 640 nm), 16 h. [c]H_2TPP (1 mol%), diazo compound (0.1 mmol), styrene (10.0 equiv.), DCM_{dry} (0.1 M), [Ar], red LEDs (40 W), 16 h.

Both the increase and decrease in electron density on the phenyl ring affects the efficacy of the reaction, compared to the high yield observed for the product bearing an unsubstituted phenyl moiety (**27**, 84%). In contrast, electron-poor aryl diazoalkane reached the highest productivity of the cyclopropanation reaction that afforded cyclopropane **34** in 90%. The method is suitable for both electron-rich and -poor styrenes, with a better outcome in the case of *para*-methoxy-styrene-derived product **35** (70%). A modest yield was observed when the internal olefin was subjected to reaction conditions leading to cyclopropane **37** (55%). α-Diazo esters, diazomalonates, and aryl diazoketones possessing higher E_T values than porphyrin (E_T =1.63 eV/mol for ethyl diazoactetate, calculated using SMD(DCM)/M06/6-311++g(d,p)//B3LYP-D3/6-31g(d))) cannot, in principle, be activated under the developed conditions.

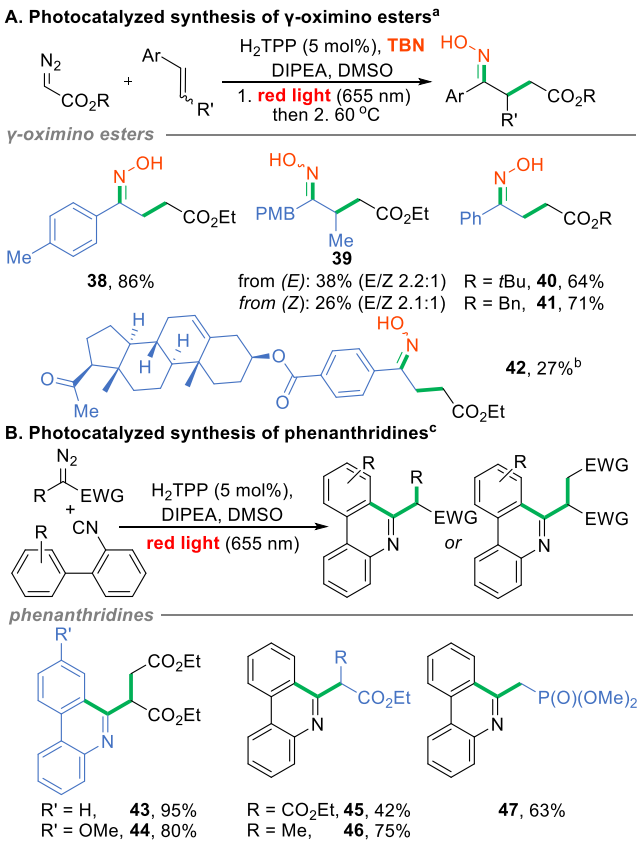
Intuitively, the reaction rate for diazoalkane transformation depends on the carbene rate formation, which if EnT-mediated, should occur slower than via direct photolysis. In that manner, comparative kinetics studies on catalyst-free, blue light-induced and H_2TPP-sensitized red light-mediated cyclopropanation with the use of methyl phenyl diazoacetate and styrene, revealed full consumption of diazoalkane in 0.5 h via direct photolysis, while the photosensitization protocol requires overnight irradiation (see SI).

PHOTOREDOX CATALYSIS - To unlock the red-mediated reactivity of yet unconquered α-diazo esters, we screened the possibilities offered by photoredox catalysis. These acceptor-only type of diazoalkanes are reduced to alkyl radicals via the photon coupled electron transfer event (PCET) in oxidative quenching or the photocatalyst recovery step of the (E_{RED} = -1.28 V vs SCE for EDA).[49] In this view, numerous blue light-induced methodologies utilizing diazoesters as surrogates of alkyl radicals for organic transformations were reported.[49,50,51,52,53,54]

Recently, we have proved that free-base porphyrins are suitable photo-oxidants and photo-reductants for red light-mediated organic transformations.[37] Therefore, we harnessed their photoredox abilities to tune already reported blue light-induced protocols for radical-based transformations of α-diazoesters to apply them on red illumination instead. Our studies were initiated with the redesign of the photocatalyzed synthesis of γ-oximino esters, originally performed by Li and coworkers on blue light with the use of $Ru(bpy)_3(PF_6)_2$ catalyst and α-diazoester, styrene and TBN as starting materials.[49] Extensive 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 when full conversion of alkene was observed (see SI). The optimized 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**). When a *cis*-isomer was used instead, a lower efficacy was achieved. Due to solubility problems, the synthesis of pregnenolone-derived ester **42** was less efficient, even at a prolonged irradiation time. 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)[37] 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 amino-pyridinium salts.[55]

Scheme 3. Diazo Compounds as Radical Precursors in Red Light-mediated Photocatalyzed Transformations



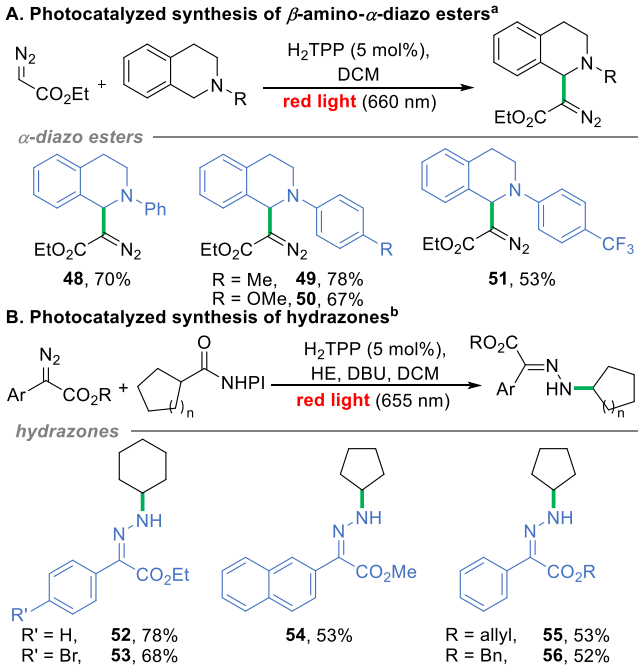
Reaction conditions: [a]H_2TPP (5 mol%), olefin (0.2 mmol), diazo compound (2.0 equiv.), TBN (2.0 equiv.), DIPEA (3.0 equiv.) DMSO (0.05 M), [Ar], red LEDs (25 W) for 20 h then 60 °C for 17 h. [b]irradiation for 66 h then 60 °C for 17 h, DMSO/MeCN (1:1, 0.33 M). [c]H_2TPP (5 mol%), isocyanate (0.2 mmol), diazo compound (5.0 equiv.), DIPEA (1.0 equiv.), $DMSO_{dry}$ (0.2 M), [Ar], red LEDs (25 W), 18 h. TBN = *t*-butyl nitrite.

Next, we examined an analogous PCET-based approach for the phenanthridine formation utilizing isocyanobiphenyls and diazoalkanes.[56] Proper optimization of the red light- mediated protocol enabled efficient synthesis of heterocycles **43-47** (Scheme 3B) with better productivity or at least comparable to the Xuan methodology. Importantly, diazoalkanes of different type - acceptor-only, acceptor/acceptor and alkyldiazo ester - are well tolerated.

Finally, there are several valuable 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 irradiation, such transformations were studied. Given that sole H_2TPP is not able to photoreduce EDA, meaning the diazo functionality should remain intact, we tested H_2TPP as a photooxidant of diversely substituted tetrahydroisoquinolines under red light irradiation in the presence of EDA similarly to the reaction developed by Zhou and coworkers.[57] In fact, desired products **48-51** with intact diazo moiety 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.[58] Replacing these dyes with H_2TPP enabled the reaction of aryldiazo esters with NHPI reagents under red light irradiation. A wide range of donor/acceptor diazoalkanes reacted under the developed conditions to give hydrazones **52-56** (Scheme 4B). None of the red light-induced protocols described herein proceed even residually without the porphyrin catalyst added.

Scheme 4. Diazo Compounds as Radical Acceptors in Red Light-mediated Photocatalyzed Transformations



Reaction conditions: [a]H_2TPP (5 mol%), tetrahydroisoquinoline (0.2 mmol), diazo compound (3.0 equiv.), DCM (0.2 M), red LEDs (3 W), 48 h. [b]H_2TPP (5 mol%), diazo compound (0.2 mmol), NHPI ester (1.5 equiv.), HE (1.2 equiv.), DBU (2.3 equiv.), DCM_{dry} (0.1 M), [Ar], red LEDs (25 W), 18 h. NHPI = *N*-hydroxyphthalimide. HE = Hantzsch ester.

In summary, in this study we demonstrate that modern photochemistry provides tools for red light-driven activation of structurally diversified 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. In this manner, carbenes react with naturally abundant moieties, free hydroxy-, amino-, and thio-groups. If this pathway is not possible, we induce transformations of diazo compounds taking advantage of porphyrins, nature-inspired dyes, which are 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 photocatalytically through porphyrin-mediated photoredox processes, by undergoing reduction to alkyl radicals or by serving as radical acceptors. The developed methods are either catalyst-free or take place in the presence of nontoxic organic dye under low-energy irradiation. Therefore, three-modes of activation of

diazo compounds under red-light irradiation have been unlocked giving the possibility of their adaptation to biorthogonal chemistry.

Author Contributions

All authors have given approval to the final version of the manuscript.
‡ KŁ, PK, and KO, contributed equally.

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REFERENCES

1. Sletten, E. M.; Bertozzi, C. R. Bioorthogonal chemistry: Fishing for selectivity in a sea of functionality. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998.
2. Bertozzi, C. R. A decade of bioorthogonal chemistry. *Acc. Chem. Res.* **2011**, *44*, 651–653.
3. Bird, R. E.; Lemmel, S. A.; Yu, X.; Zhou, Q. A. Bioorthogonal Chemistry and Its Applications. *Bioconjug. Chem.* **2021**, *32*, 2457–2479.
4. Scinto, S. L.; Bilodeau, D. A.; Hincapie, R.; Lee, W.; Nguyen, S. S.; Xu, M.; am Ende, C. W.; Finn, M. G.; Kathrin Lang, K.; Lin, Q.; Pezacki, J. P.; Prescher, J. A.; Robillard, M. S.; Fox, J. M. Bioorthogonal chemistry. *Nat. Rev. Methods Prim.* **2021**, 1.
5. Devaraj, N. K. The Future of Bioorthogonal Chemistry. *ACS Cent. Sci.* **2018**, *4*, 952–959.
6. Jia, S.; Sletten, E. M. Spatiotemporal Control of Biology: Synthetic Photochemistry Toolbox with Far-Red and Near-Infrared Light. *ACS Chem. Biol.* **2022**, *17*, 3255–3269.
7. Lim, R. K. V.; Lin, Q. Photoinducible bioorthogonal chemistry: A spatiotemporally controllable tool to visualize and perturb proteins in live cells. *Acc. Chem. Res.* **2011**, *44*, 828–830.
8. Li, J.; Kong, H.; Zhu, C.; Zhang, Y. Photo-controllable bioorthogonal chemistry for spatiotemporal control of bio-targets in living systems. *Chem. Sci.* **2020**, *11*, 3390–3396.
9. Zhu, C.; Kou, T.; Kadi, A. A.; Li, J.; Zhang, Y. Molecular platforms based on biocompatible photoreactions for photomodulation of biological targets. *Org. Biomol. Chem.* **2021**, *19*, 9358–9368.
10. Fairbanks, B. D.; Macdougall, L. J.; Mavila, S.; Sinha, J.; Kirkpatrick, B. J.; Anseth, K. Bowman, S. N. Photoclick Chemistry: A Bright Idea. *Chem. Rev.* **2021**, *121*, 6915–6990.
11. Arora, A.; Singh, K. Click Chemistry Mediated by Photochemical Energy. *ChemistrySelect* **2022**, *7*, e20220054.
12. Kumar, G. S.; Lin, Q. Light-Triggered Click Chemistry. *Chem. Rev.* **2021**, *121*, 6991–7031.
13. Boase, N. R. B. Shining a Light on Bioorthogonal Photochemistry for Polymer Science. *Macromol. Rapid Commun.* **2020**, *41*, 1–21.
14. Song, W.; Wang, Y.; Qu, J.; Madden, M. M.; Lin, Q. A photoinducible 1,3-dipolar cycloaddition reaction for rapid, selective modification of tetrazole-containing proteins. *Angew. Chem. Int. Ed.* **2008**, *47*, 2832–2835.
15. Song, W.; Wang, Y.; Qu, J.; Lin, Q. Selective functionalization of a genetically encoded alkene-containing protein via 'photoclick chemistry' in bacterial cells. *J. Am. Chem. Soc.* **2008**, *130*, 9654–9655.
16. An, P.; Lewandowski, T. M.; Erbay, T. G.; Liu, P.; Lin, Q. Sterically Shielded, Stabilized Nitrile Imine for Rapid Bioorthogonal Protein Labeling in Live Cells. *J. Am. Chem. Soc.* **2018**, *140*, 4860–4868.
17. Yu, Z.; Ohulchanskyy, T. Y.; An, P.; Prasad, P. N.; Lin, Q. Fluorogenic, two-photon-triggered photoclick chemistry in live mammalian cells. *J. Am. Chem. Soc.* **2013**, *135*, 16766–16769.
18. Lederhose, P.; Chen, Z; Muller, R; Blinco, J. P.; Wu, S; Barner-Kowollik, C. Near-Infrared Photoinduced Coupling Reactions Assisted by Upconversion Nanoparticles. *Angew. Chem. Int. Ed.* **2016**, *55*, 12195–12199.
19. Wang, C; Zhang, H.; Zhang, T; Zou, X; Wang, H; Rosenberger, J. E.; Vannam, R; Trout, W. S.; Grimm, J. B; Lavis, L. D.; Thorpe, C; Jia, X; Li, Z, Fox, J. M. Enabling in Vivo Photocatalytic Activation of Rapid Bioorthogonal Chemistry by Repurposing Silicon-Rhodamine Fluorophores as Cytocompatible Far-Red Photocatalysts. *J. Am. Chem. Soc.* **2021**, *143*, 10793–10803.
20. Sellet, N.; Cormier, M.; Goddard, J. P. The dark side of photocatalysis: Near-infrared photoredox catalysis for organic synthesis. *Org. Chem. Front.* **2021**, *8*, 6783–6790.
21. Yang, Z.; Stivanin, M. L.; Jurberg, I. D; Koenigs, R. M. Visible light-promoted reactions with diazo compounds: A mild and practical strategy towards free carbene intermediates. *Chem. Soc. Rev.* **2020**, *49*, 6833–6847.
22. Durka, J.; Turkowska, J.; Gryko, D. Lightening Diazo Compounds? *ACS Sustain. Chem. Eng.* **2021**, *9*, 8895–8918.
23. Ciszewski, Ł. W.; Rybicka-Jasińska, K.; Gryko, D. Recent developments in photochemical reactions of diazo compounds. *Org. Biomol. Chem.* **2019**, *17*, 432–448.
24. Davies, H. M. L.; Denton, J. R. Application of donor/acceptor-carbenoids to the synthesis of natural products. *Chem. Soc. Rev.* **2009**, *38*, 3061–3071.
25. Ge, S.S; Chen, B; Wu, Y.Y; Long, Q-S; Zhao, Y.L; Wanga, P.Y; Yang, S. Current advances of carbene-mediated photoaffinity labeling in medicinal chemistry. *RSC Adv.* **2018**, *8*, 29428–29454.
26. Harada, S. Development of Novel Methodology Using Diazo Compounds and Metal Catalysts. *Chem. Pharm. Bull.* **2021**, *69*, 1170–1178.
27. Mix, K. A.; Aronoff, M. R.; Raines, R. T. Diazo Compounds: Versatile Tools for Chemical Biology. *ACS Chem. Biol.* **2016**, *11*, 3233–3244.
28. Liu, Z.; Arnold, F. H. New-to-nature chemistry from old protein machinery: carbene and nitrene transferases. *Curr. Opin. Biotechnol.* **2021**, *69*, 43–51.
29. Wittmann, B. J.; Knight, A. M.; Hofstra, J. L.; Reisman, S. E.; Kan, S. B. J.; Arnold, F. H. Diversity-Oriented Enzymatic Synthesis of Cyclopropane Building Blocks. *ACS Catal.* **2020**, *10*, 7112–7116.
30. Mao, R; Wackelin, D. J.; Jamieson, C. S.; Rogge, T; Gao, S; Das, A; Taylor, D. M.; Houk, K. N.; Arnold, F.H. Enantio- and Diastereoenriched Enzymatic Synthesis of 1,2,3-Polysubstituted Cyclopropanes feom (Z/E)-Trisubstituted Enol Acetates *J. Am. Chem. Soc.* **2023**, *145*, 16176–16185.
31. Miller, D. C.; Lal, R. G.; Marchetti, L. A.; Arnold, F. H. Biocatalytic One-Carbon Ring Expansion of Aziridines to Azetidines via a Highly Enantioselective [1,2]-Stevens Rearrangement. *J. Am. Chem. Soc.* **2022**, *144*, 4739–4745.
32. Chen, K.; Huang, X.; Jennifer Kan, S. B.; Zhang, R. K.; Arnold, F. H. Enzymatic construction of highly strained carbocycles. *Science* **2018**, *360*, 71–75.
33. Zhang, R. K.; Chen, K.; Huang, X; Wohlschlager, L.; Renata, H.; H. Arnold, F. H. Enzymatic assembly of carbon–carbon bonds via iron-catalysed sp 3 C–H functionalization. *Nature* **2019**, *565*, 67–72.
34. Blencowe, A.; Hayes, W. Development and application of diazirines in biological and synthetic macromolecular systems. *Soft Matter* **2005**, *1*, 178–205.
35. Huth, S. W.; Oakley, J. V.; Seath, C. P.; Geri, J. B.; Trowbridge, A. D.; Parker, D. L.; Jr, Rodriguez-Rivera, F. P.; Schwaid, A. G.; Ramil, C.; Ryu, K. A.; White, C. H.; Fadeyi, O. O.; Oslund, R. C.; MacMillan, D. W. C. µMap Photoproximity Labeling Enables Small Molecule Binding Site Mapping. *J. Am. Chem. Soc.* **2023**, *145*, 16289–16296.
36. Geri, J. B.; Oakley, J. V.; Reyes-Robles, T.; Wang, T.; McCarver, S. J.; White, C. H.; Rodriguez-Rivera, F. P.; Parker, D. L.; Jr, Hett, E. C.; Fadeyi, O. O.; Oslund, R. C.; MacMillan, D. W. C. Microenvironment mapping via Dexter energy transfer on immune cells. *Science* **2020**, *367*, 1091–1097.
37. Rybicka-Jasińska, K.; Wdowik, T.; Łuczak, K.; Wierzba, A. J.; Drapała, O.; Gryko, D. Porphyrins as Promising Photocatalysts for Red-Light-Induced Functionalizations of Biomolecules. *ACS Org. Inorg. Au* **2022**, *2*, 422–426.
38. Jurberg, I. D.; Davies, H. M. L. Blue light-promoted photolysis of aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112–5118.
39. Jana, S.; Pei, C.; Empel, C.; Koenigs, R. M. Photochemical Carbene Transfer Reactions of Aryl/Aryl Diazoalkanes—Experiment and Theory *Angew. Chem. Int. Ed.* **2021**, *60*, 13271–13279.

40. Humphreys, R. W. R.; Arnold, D. R. Substituent effects on the zero-field splitting parameters of diarylmethylene. Evidence for merostabilization in appropriately substituted diphenylmethylenes. *Can. J. Chem.* **1979**, *57*, 2652–2661.
41. Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem* **2020**, *6*, 1888–1903.
42. Strieth-Kalthoff, F., James, M. J., Teders, M., Pitzer, L. & Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.* **2018**, *47*, 7190–7202.
43. Orłowska, K.; Santiago, J. V.; Krajewski, P.; Kisiel, K.; Deperasińska, I.; Zawada, K.; Chaładaj W.; Gryko, D.UV Light Is No Longer Required for the Photoactivation of 1,3,4-Oxadiazolines. *ACS Catal*. **2023**, *13*, 1964–1973.
44. Costa e Silva, R.; da Silva, L. O.; de Andrade Bartolomeu, A.; Brocksom, T. J.; de Oliveira, K. T. Recent applications of porphyrins as photocatalysts in organic synthesis: Batch and continuous flow approaches. *Beilstein J. Org. Chem.* **2020**, *16*, 917–955.
45. Kou, J.; Dou, D.; Yang, L. Porphyrin photosensitizers in photodynamic therapy and its applications. *Oncotarget* **2017**, *8*, 81591–81603.
46. Gust, D.; Moore, T. A.; Moore, A. L. Solar fuels via artificial photosynthesis. *Acc. Chem. Res.* **2009**, *42*, 1890–1898.
47. Seely, R. The energetics of electron-transfer reactions of chlorophyll and other compounds *Photochem. Photobiol.* **1978**, *27*, 639-654.
48. Entradas, T.; Waldron, S.; Volk, M. The detection sensitivity of commonly used singlet oxygen probes in aqueous environments. *J. Photochem. Photobiol. B Biol.* **2020**, *204*, 111787-111798.
49. Liu, Y.; Zhu, K.; Zhao, J.; Li, P. Photocatalytic Regioselective Difunctionalization of Alkenes with Diazo Compounds and tert-Butyl Nitrite: Access to γ-Oximino Esters. *Org. Lett.* **2022**, *24*, 6834–6838.
50. Li, F.; Zhu, S.; Koenigs, R. M. Photocatalytic 1,2-oxo-alkylation reaction of styrenes with diazoacetates. *Chem. Commun.* **2022**, *58*, 7526–7529.
51. Ciszewski, Ł. W.; Durka, J.; Gryko, D. Photocatalytic Alkylation of Pyrroles and Indoles with α-Diazo Esters. *Org. Lett.* **2019**, 21, 7028–7032.
52. Huang, X.; Webster, R. D.; Harms, K.; Meggers, E.; Asymmetric Catalysis with Organic Azides and Diazo Compounds Initiated by Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2016**, *138*, 12636–12642.
53. Su, Y-L.; Liu,G.X.; De Angelis, L.; He, R.; Al-Sayyed, A.; Schanze, K. S.; Hu, W-H.; Qiu, H.; Doyle, M.P. Radical Cascade Multicomponent Minisci Reactions with Diazo Compounds. *ACS Catal*. **2022**, *12*, 1357–1363.
54. Su, Y. L.; Liu, G. X.; Liu, J. W.; Tram, L.; Qiu, H.; Doyle, M. P. Radical-Mediated Strategies for the Functionalization of Alkenes with Diazo Compounds. *J. Am. Chem. Soc.* **2020**, *142*, 13846–13855.
55. Goliszewska, K.; Rybicka-Jasińska, K.; Clark, J. A.; Vullev, V. I.; Gryko, D. Photoredox Catalysis: The Reaction Mechanism Can Adjust to Electronic Properties of a Catalyst. *ACS Catal.* **2020**, *10*, 5920–5927.
56. Ye, H. B.; Zhou, X. Y.; Li, L.; He, X. K.; Xuan, J. Photochemical Synthesis of Succinic Ester-Containing Phenanthridines from Diazo Compounds as 1,4-Dicarbonyl Precursors. *Org. Lett.* **2022**, *24*, 6018–6023.
57. Xiao, T.; Li, L.; Lin, G.; Mao, Z. W.; Zhou, L. Metal-free visible-light induced cross-dehydrogenative coupling of tertiary amines with diazo compounds. *Org. Lett.* **2014**, *16*, 4232–4235.
58. Chan, C. M.; Xing, Q.; Chow, Y. C.; Hung, S. F.; Yu, W. Y. Photoredox Decarboxylative C(sp3)-N Coupling of α-Diazoacetates with Alkyl N-Hydroxyphthalimide Esters for Diversified Synthesis of Functionalized N-Alkyl Hydrazones. *Org. Lett.* **2019**, *21*, 8037–8043.