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Why Cyclopropanation is not involved in Photoinduced α-Alkylation of Ketones with Diazo Compounds?

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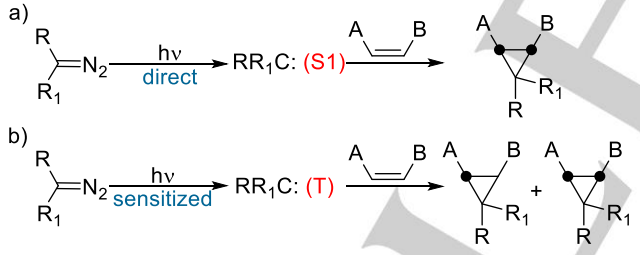
Abstract: Diazo compounds are widely used reagents in organic synthesis. Direct photolysis leads to singlet carbenes while in the presence of a photosensitizer carbenes in the triplet state are generated. However, their reactivity under light irradiation remains poorly understood. Herein, we report photocatalytic, direct alkylation of enamines, generated from ketones, with diazo esters in the presence of free base porphyrins acting as photoredox catalysts. Based on the experimental and theoretical studies, we propose a plausible mechanism involving generation of an enamine radical cation that subsequently reacts with diazo compounds thus excluding the controversial cyclopropanation-ring opening pathway.

Introduction

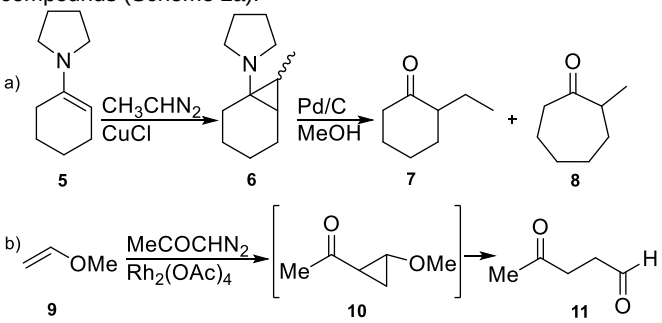
Diazo compounds are one of the most versatile chemical feedstocks and key components in numerous synthetic transformations, particularly in cyclopropanation, Wolf rearrangements, C-H or heteroatom-H insertions, and polymerization.[1] Over the last decade much effort has been also devoted to the reactivity of these compounds under light irradiation.[2] It was found that direct irradiation gives singlet carbenes while photosensitization generates carbenes in the triplet state (Scheme 1).[3] As a consequence, their reactions with olefins afford *cis*- or *cis*- and *trans*-cyclopropanes respectively.[4]



Scheme 1. The reactivity of diazo compounds under light irradiation.

Although these reactions have been extensively studied, little is known about the reactivity of diazo reagents towards carbonyl compounds under light irradiation. The reaction of dimethyl diazo malonate with carbonyl compounds in the presence/absence of benzophenone as a sensitizer furnishes a mixture of products. According to the mechanism, an ylide intermediate predominates upon direct irradiation while in the presence of a sensitizer insertion of a triplet carbene to the secondary C-H is also observed.[5] This clearly shows that the reaction pathway is determined by a competition between the singlet and triplet carbene formation. Recently, we have reported that in the presence of either porphyrin or $[Ru(bpy)_3]Cl_2$ as the photoredox catalyst, ethyl diazoacetate acts selectively as the alkylating agent of aldehydes (precisely enamines) affording products in high yields.[6a] Mechanistic studies confirmed the radical nature of the process that presumably involves the reaction of an enamine radical cation with a triplet carbene. Later, Meggers et al reported α-alkylation of 2-acyl imidazoles with diazo compounds in the presence of chiral Ru-photoredox catalyst and Rh-Lewis acid.[7] It was hypothesized that generated in situ $[Ru(bpy)_3]^+$ transfers an electron to diazo ester and after extrusion of nitrogen and protonation produces carbon-centred radicals. Interestingly, only Rh-enolate quenches the excited state of $[Ru(bpy)_3]^{2+}$.

As far as the reaction with enamines and enols is concerned, an alternative pathway - the cyclopropanation of enamines/enols followed by the ring-opening, should be considered. It is known that cyclopropanes bearing both electron-donating and withdrawing substituents are easily cleaved.[8] For example, the reaction of enamines with diazoethane in the presence of copper chloride leads to cyclopropylamines, which after cleavage under thermal hydrolysis furnish a mixture of alkylated carbonyl compounds (Scheme 2a).[9]



Scheme 2. Reactions involving cyclopropanation followed by ring-opening.

Moreover, copper and rhodium complexes catalyse the reaction of enamines with aryldiazoacetates leading to β-ketoesters in moderate yield via cyclopropanation/ring-opening pathway.[10] Similarly, the Rh(II)-catalysed reaction of α-diazoketones with vinyl ethers affords a cyclopropane derivative which subsequently undergoes the C-C bond cleavage yielding 1,4-dicarbonyl compounds (Scheme 2b).[11]

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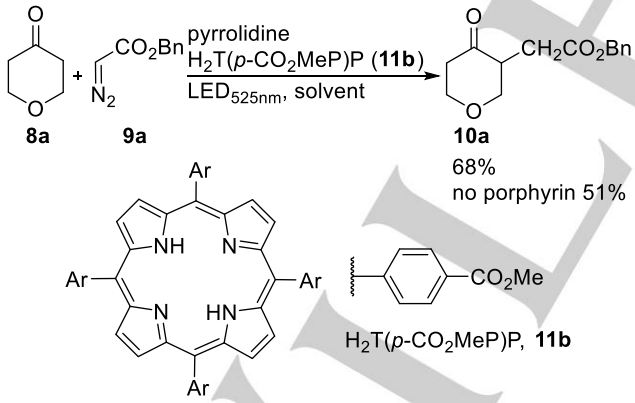
Differences in the proposed mechanisms for light-induced and metal-catalysed reactions involving diazo compounds arisen an important question – *If photocatalyzed reaction of enamines with diazo reagents proceed via the cyclopropanation/ring opening pathway?*

To answer this question we resolved to continue our studies on photocatalytic reactions involving diazo reagents. In addition to exploring mechanistic aspects, we wondered whether their reactivity could be shifted also toward α-functionalization of more-challenging ketones. Consequently, we have developed photoinduced alkylation of simple ketones with diazo compounds in the presence of a free-base porphyrin and a secondary amine is reported. Interestingly, for certain substrates the reaction proceeds in the absence of the porphyrin. Extensive mechanistic studies supported by DFT calculations enabled us to present a comprehensive view of the mechanism. *The reaction proceeds via the radical pathway and does not involve the assumed formation of a cyclopropane intermediate.*

Results and Discussion

Initial Studies

In the initial experiment 4-oxotetrahydropyran (**8a**) was reacted with benzyl diazoacetate (BDA, **9a**) in the presence of morpholine as an organocatalyst and free-base tetraphenylporphyrin (H_2TPP, **11a**) as a photoredox catalyst under our previously developed conditions (Scheme 3).[6b] The reaction led only to the recovery of the starting material. However, as the reactivity of enamines follows the order pyrrolidine > acyclic amine > piperidine > morpholine- derived enamines,[12] we assumed that for ketones, a more reactive enamine should be generated as an intermediate.



Scheme 3. Light-Induced reaction of ketones with BDA (**9a**).

Indeed, the use of pyrrolidine enabled the formation of α-alkylated product **10a** in reasonable yield (Scheme 3, Table 1, entry 2). Control experiments revealed that both light and pyrrolidine are essential as their exclusion halted the reaction completely (Table 1, entries 4-6). Surprisingly, the reaction gave product even in the absence of porphyrin **11b** (Table 1, entry 3).

Table 1. Initial Studies.[a]

Entry	Amine	Light	Cat. **11**	Yield[b] [%]
1	morpholine	LED_{525nm}	**a**	
2	pyrrolidine	LED_{525nm}	**b**	
3	pyrrolidine	LED_{525nm}	-	51
4	pyrrolidine	-	**b**	traces
5[c]	pyrrolidine	-	**b**	68
6	-	LED_{525nm}	**b**	0

[a] Reaction conditions: ketone (**8a**, 0.5 mmol), diazo ester (**9a**, 0.5 mmol), porphyrin **11a** or **11b** (1.0 mol%), amine (20 mol %), DMSO/buffer pH = 4.0, 9/1 (v/v) 5 mL, 8 h, rt. [b] Isolated yields. [c] Reaction was performed at 45°C.

To explain why the reaction proceeds regardless of the presence of a photocatalyst further experimental work was required.

Optimization studies

Photoredox catalysis enables introduction of functional groups (e. g. trifluoromethyl[13] benzyl,[14] alkyl[15]) at the α-position to the aldehyde moiety.[16] Due to lower reactivity of ketones, only few methods for the α-alkylation of ketones under light irradiation were reported though each possessing certain limitations.[17] In the presence of $Ru(bpy)_3Cl_2$ as a photoredox catalyst, enamines, generated in situ from a primary amine and β-ketocarbonyls, react with activated organic bromides giving functionalized β-ketoesters.[18] When enamine intermediates (from cyclic ketones or β-ketoesters) form with alkyl halides photoactive electron donor-acceptor (EDA) complexes, alkylation does not require any photocatalyst.[19] On the other hand, Meggers et al showed that with a photocatalyst absorbing light and at the same time activating the carbonyl group, certain carbonyl compounds can be functionalized with benzyl and phenacyl bromides.[20] Though stereoselective and high yielding, these catalytic procedures are limited to specifically designed either carbonyl compounds or alkylating reagents, or require the addition of co-catalysts. Hence, we resolved to optimize our newly developed method focusing on identifying the optimal reaction conditions giving product **10a** in high yields (for details see SI). Substituents present at the periphery of the porphyrin macrocycle have a strong impact on the redox properties,[21] therefore various porphyrins with electron-withdrawing and electron-donating substituents were tested (Figure 1).

All of them catalysed the model reaction of 4-oxotetrahydropyran (**8a**) with BDA (**9a**) giving the desired product **10a**, with free base porphyrin **11b** being the most effective.

Expectedly, only in the presence of primary and secondary amines the reaction furnished the desired product, reaching 68% for pyrrolidine (Table 2, entries 1-4). Tertiary amine NEt_3 did not catalyse the reaction, thus confirming the assumed role of an amine to form enamine in the catalytic cycle.

Further optimization studies comprised experiments with different diazo ester **9a**/ketone **8a** ratios in relation to

$H_2T(p\text{-}CO_2MeP)P$ (**11b**) as a photocatalyst and pyrrolidine as an organocatalyst. Importantly, the use of starting materials **8a**/**9a** in 1:1.2 molar ratio led to a significant increase in the reaction yield up to 83 % (Table 2, entry 7). In the case of 4-oxotetrahydropyran (**8a**) only mono-substituted product **10a** formed but alkylation of cyclohexanone (**8b**) led to a mixture of mono- **10b** and di-substituted **10bb** products.

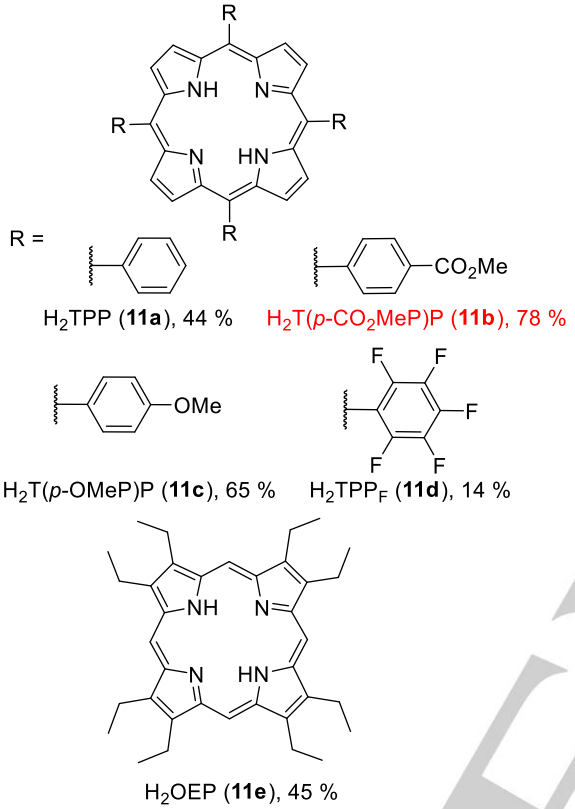


Figure 1. Porphyrins tested as photocatalysts in alkylation of ketone **8a**. Yields of product **10a**.

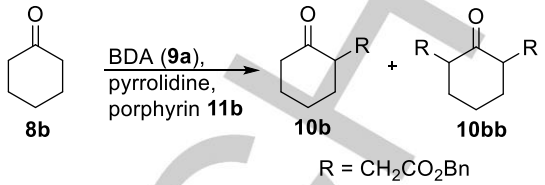
Table 2. Optimization studies.[a]

Entry	**8a**/**9a** [equiv.]	Amine	Yield[c] [%]
1	1/1	morpholine	21
2	1/1	piperazine	21
3	1/1	NEt_3	0
4	1/1	pyrrolidine	71
5[b]	1/1	pyrrolidine	74
6[b]	1.2/1	pyrrolidine	65
7[b]	1/1.2	pyrrolidine	83

[a] Reaction conditions: ketone (**8a**, 0.5 mmol), BDA (**9a**, 0.5 mmol), porphyrin (**11b**, 1.0 mol%), amine (20 mol%), DMSO/buffer pH 4.0 = 9:1 (v/v) 5 mL, $LEDs_{525nm}$, 7 h. [b] Reaction finished after 5 h, LED_{525nm}. [c] Isolated yields.

Consequently, the conditions predominantly yielding either mono- or di-product were defined (Table 3, for details see SI).

Table 3. Optimization studies.[a]



Entry	**9a** [eq.]	Amine [mol%]	Time [h]	**10b**[b] [%]	**10bb**[b] [%]
1[c]	1	20	5	-	-
2[d]	1	20	5	10	2
3	1.2	20	5	30	30
4[e]	1	20	5	48	20
5	3	40	7	10	80

[a] Reaction conditions: ketone (**8b**, 0.25 mmol, 1 equiv.), BDA (**9a**, X equiv.), photocatalyst (**11b**, 1.0 mol%), pyrrolidine (X mol%), DMSO/buffer pH = 4.0, 9:1 (v/v) 5 mL, LED_{525nm}, 5 h, rt. [b] Isolated yields. [c] Without light. [d] Without photocatalyst. [e] Ketone (**8b**, 0.25 mmol, 1 equiv.), BDA (**9a**, X equiv.), photocatalyst (**11b**, 1.0 mol%), pyrrolidine (X mol%), DMSO/buffer pH 7.0 = 9:1 (v/v) 2.5 mL, LED_{525nm}, 5 h, rt.

Reaction scope and limitations

Under the developed conditions the scope and limitations of the α-functionalisation of ketones were explored employing two sets of conditions (with and without porphyrin **11b**) for mono-alkylated product (Figure 2). **Method A** for mono-product: ketone (0.5 mmol), pyrrolidine (20 mol%), diazo ester (1.2 equiv.), $H_2T(p\text{-}CO_2MeP)P$ (**11b**, 1 mol%) a DMSO/buffer mixture (9/1 (v/v), 5 mL, buffer pH = 4, *c* = 0.1 M), 5 h, LED_{525nm}, rt. (**Method A' – same as A but without photocatalyst added)**. Additionally, α-difunctionalisation of ketones was explored employing two sets of conditions (with and without porphyrin): **Method B** for di-product: ketone (0.25 mmol), pyrrolidine (40 mol%), diazo ester (3 equiv.), $H_2T(p\text{-}CO_2MeP)P$ (**11b**, 1 mol%) a DMSO/buffer mixture (9/1 (v/v), 2.5 mL, buffer pH = 7, c = 0.1 M), 7 h, LED_{525nm}, rt (Figure 3, for optimization see SI).

Dialkylated products were only obtained in porphyrin-catalysed reaction (Chart 3). In general, ketones that easily form enamines were reactive under the developed conditions.[22] The mono-alkylation reaction of ketones with various diazo esters (CO_2Bn (**9a**), CO_2Et (**9b**), CO_2t-Bu (**9c**), $CO_2CH_2CH_2Ph$ (**9d**), $CO_2CH_2(p\text{-}OMePh)$ (**9e**)) gave products in decent yields. However, the reaction with $N_2CHCO_2CH_2(p\text{-}NO_2Ph)$ (**9f**) proved difficult under developed conditions presumably due to the strong electron-withdrawing character of the NO_2 group.[23] The desired product **10m** was even obtained from the aliphatic ketone – acetone, but acetophenone remains unreacted as with pyrrolidine it did not generate enamine.

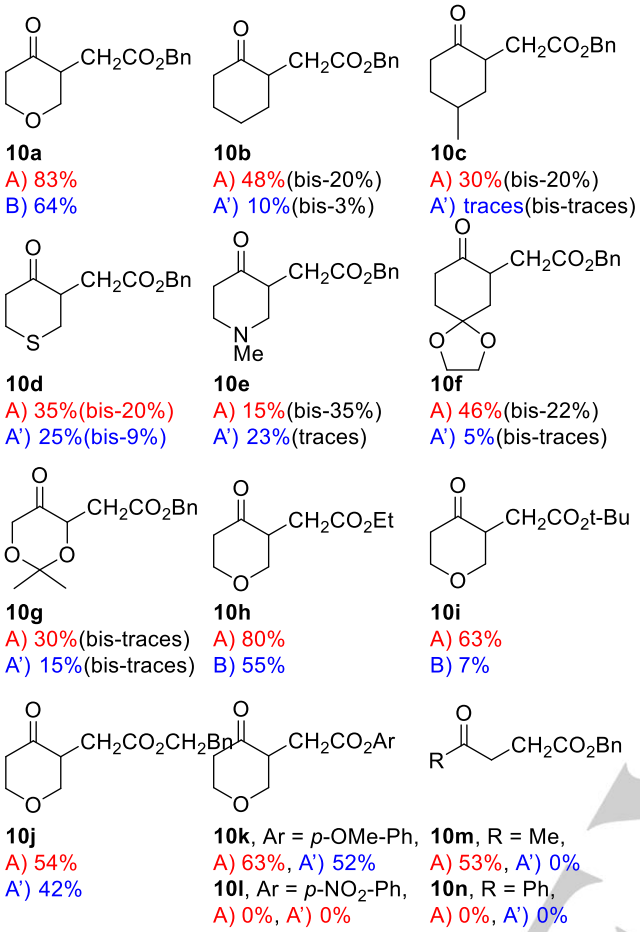


Figure 2. Scope and limitations – mono-alkylated products.

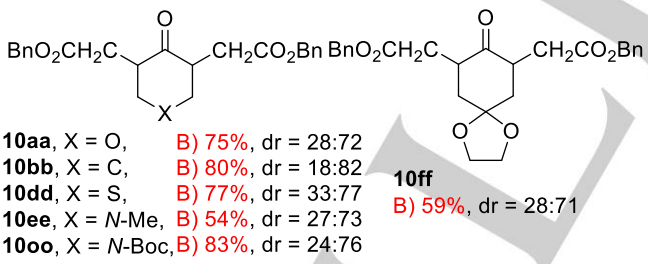
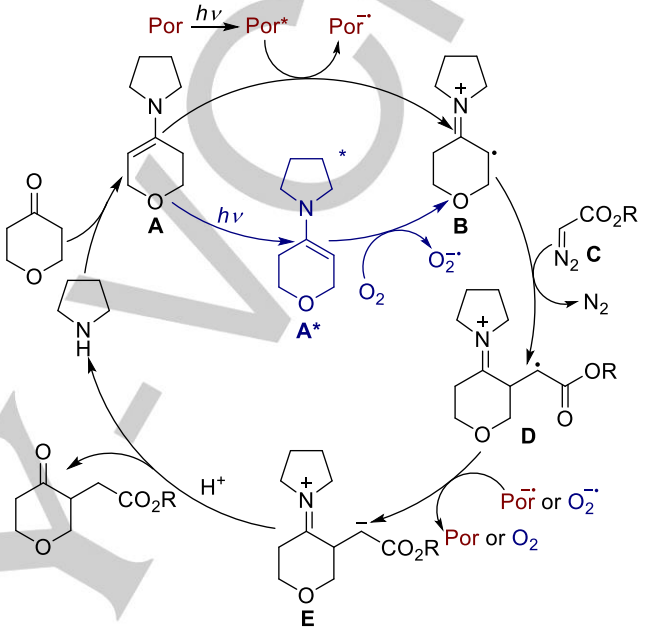


Figure 3. Scope and limitations – dialkylated products.

In the dialkylation reaction, a variety of six-membered carbo- and heterocycles furnished products in high yields and with diastereoselectivity up 4 : 1. Interestingly, *N*-Boc-piperidone (**10o**) underwent the exclusive formation of 2,5-dialkylated product (**10oo**).

Mechanistic investigations

As stated by prof. König, '*Photoredox reactions with visible light have been used in a broad range of transformations, though the mechanism needs to be fully understood to design better catalytic systems*'[24] we resolved to perform detailed mechanistic studies. The model reaction of 4-oxotetrahydropyran (**8a**) with BDA (**9a**) using pyrrolidine as an organocatalyst afforded products regardless of the presence of the porphyrin though in various yields. Consequently, based on the CV, radical trapping, EPR, UV-Vis experiments supported by theoretical calculations, two plausible mechanistic pathways are proposed (Scheme 4).

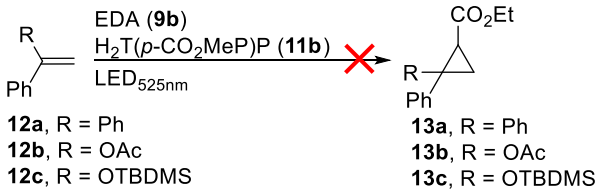


Scheme 4. Proposed mechanisms for light-induced functionalization of ketones with BDA.

In both reaction pathways I and II, the initial step involves the reaction of the ketone with pyrrolidine leading to enamine **A** (detected by ^{1}H NMR and ESI-MS analyses, see SI). Under light irradiation, it (0.49 V vs SCE, MeCN)[25] is oxidized to radical cation **B** by $H_2T(p\text{-}CO_2MeP)P$ in the excited state (**11b**, E_{red}*[Por*/Por$^{\bullet-}$] = 1.03 V vs SCE, DMSO), if present (pathway I). Otherwise, it is enamine **A** that absorbs light and in the exited state is assumed to be oxidized by oxygen (pathway II, 0.99 V vs SCE, solvent). Subsequently, radical cation **B** reacts with protonated diazo reagent **C** with the simultaneous extrusion of nitrogen. The resultant adduct **D** undergoes reduction to betaine **E** through a PET process with the regeneration of the photocatalyst or is reduced by $O_2^{\bullet-}$. The catalytic cycle ends with the hydrolysis of the imine (in acidic conditions) affording the desired product **10** and regenerating the amine. In addition, chain propagation reactions may likely be also involved as the quantum yield of the reaction is 20% when the porphyrin is added, and 7% when there is no photocatalyst in the reaction mixture.[26]

In the following sections we discuss the experiments supporting the proposed mechanistic pathways.

Verification of cyclopropane - ring opening mechanism. As an alternative pathway, cyclopropanation of an enamine followed by ring-opening was considered. Kuehne and King reported that the reaction of enamines with diazoethane in the presence of copper chloride gives cyclopropylamines.[9] To ascertain the involvement of a cyclopropane intermediate or the formation of regioisomeric products, the progress of the reaction was monitored by ^{1}H NMR, but we were not able to detect either of them (for details see SI). As cyclopropanes bearing both electron-donating and electron-withdrawing groups are easily cleaved,[8] their detection in the reaction mixture might be difficult. Therefore, olefins (**12a-c**) - common substrates for cyclopropanation were subjected to our model, porphyrin-catalysed reaction conditions. They remained unreactive (were recovered), thus supporting the lack of the cyclopropane-intermediate pathway in the considered reaction mechanism (Scheme 5).



12a, R = Ph
12b, R = OAc
12c, R = OTBDMS

13a, R = Ph
13b, R = OAc
13c, R = OTBDMS

Scheme 5. Verification of cyclopropane-intermediate mechanism.

Intrigued by the question why cyclopropanation is not observed in the alkylation of ketones, theoretical studies were pursued. The potential energy surface (PES) was scanned for both the enamine and imine cationic radical (Figure 4). Furthermore, two parameters were studied at the M062x/6-31G(d) level of theory – the angle (α) between the newly formed C-C bond (blue-red dotted) and the cyclohexyl ring (blue) and the dihedral angle (Θ) between the mentioned bond and the ester moiety (red).[27] In each case the potential energy surface is the same with respect to its shape implying a spontaneous process in which once formed, cyclopropane should stay as the final product. As in our case only the alkylated derivative is observed, so the lack of cyclopropanation is supported. It is known that in acidic solutions diazo acetates are protonated.[28] In our reaction proceeding at pH = 4, EDA (**9b**) should be protonated and as such reacts with radical cation **B** forming intermediate **D**. This, already bears two hydrogen atoms at the α-position to the ester group, and therefore is not able to form cyclopropane intermediate.

Verification of a radical mechanism. In accordance with the proposed mechanism reactive radicals are formed and indeed the addition of TEMPO (a radical scavenger) stopped the reaction completely. The reaction involves reactive species both in triplet and singlet excited states as the addition of either benzoquinone[29] or cycloheksan-1,3-dien[30] (singlet and triplet exited states quenchers) stopped model reactions (with and without porphyrin) completely (for details see SI). Two radical species as TEMPO adducts **14**, **15** were detected by MS further evidencing the involvement of radical **B** (Scheme 6). Adduct **15**

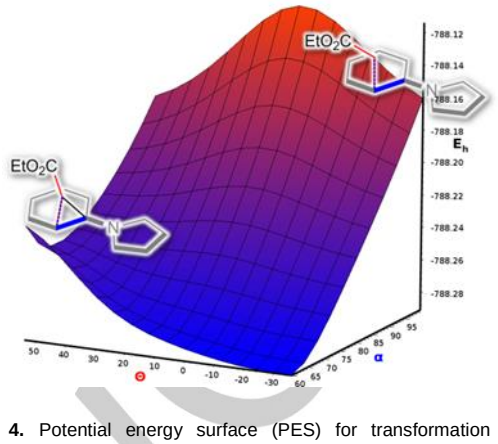
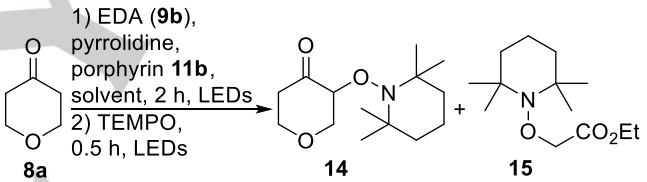


Figure 4. Potential energy surface (PES) for transformation of mono-substituted enamine to cyclopropane.

could originate from carbenes generated from direct or photosensitized photolysis of EDA (**9b**) but current data suggest that in our case, they are rather not involved in the C-C bond forming reaction. In addition, in the presence of water, triplet carbenes may abstract hydrogen atom and the hydroxyalkyl radicals generated may induce the decomposition of EDA by chain processes.[3]



Scheme 6. TEMPO trapping.

Additionally, the use of two different spin traps (PBN and DMPO) in EPR experiments allowed for the detection of two paramagnetic species **B** and **D**, thus supporting the proposed radical mechanism. In the presence of PBN, the EPR spectrum recorded for the reaction of 4-oxotetrahydropyran (**8a**) with EDA (**9b**) catalysed by porphyrin **11b** and pyrrolidine, is the superposition of two very similar components (triplets of doublets with hyperfine splitting constants: a_N = 1.49 mT, $a_{H\,\beta}$ = 0.44 mT and a_N = 1.51 mT, $a_{H\,\beta}$ = 0.41 mT), of relative intensity 53 and 47%, respectively (Figure 5a). Their hyperfine splitting constants suggest the presence of carbon-centred radicals, as they are similar to values obtained for PBN-benzoyl radical adduct in DMSO solution (a_N = 1.45 mT and a_H = 0.47 mT). When the reaction was conducted in the presence of DMPO (Figure 5b) two components are also seen, the dominating one (90% of total intensity) with hyperfine splitting constants of 1.47 mT (a_N) and 2.16 mT ($a_{H\beta}$) and a second one with a_N = 1.60 mT and a_H = 2.46 mT. In this case, both components also indicate the formation of carbon-centred radicals, as the value of $a_{H\beta}$ is higher than that of a_N.

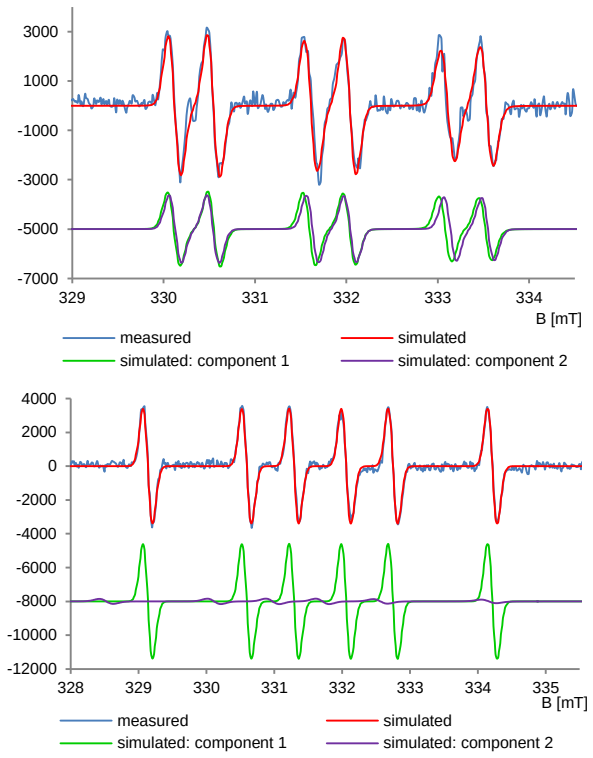


Figure 5. EPR spectra for the mixture of 4-oxotetrahydropyran (**8a**), pyrrolidine, EDA (**9b**), porphyrin **11b** in DMSO/buffer: a) with PBN, b) DMPO. Reaction conditions: 4-oxotetrahydropyran (**8a**, 1 equiv., 0.25 mmol), pyrrolidine (0.2 equiv.), EDA (**9b**, 1 equiv.), porphyrin **11b** (1 mol%), DMSO/buffer pH = 4 (5 mL, 9/1 (v/v), mixture), spin trap PBN/DMPO after 10 min of irradiation with green LED.

In the EPR spectrum registered after the visible light irradiation of a mixture of porphyrin **11b**, pyrrolidine, and 4-oxotetrahydropyran (**8a**) (no EDA added) in the presence of PBN a triplet of doublets is observed. The best fit is obtained for two very similar components (hyperfine splitting constants: aN = 1.51 mT, aH β = 0.33 mT and aN = 1.50 mT, aH β = 0.35 mT). The spectrum is very similar to the one measured for the whole reaction, differing only with respect to intensity thus strongly supporting the formation of radical **B**.

Under porphyrin-free conditions, the mixture of ketone (**8a**), EDA (**9b**) and pyrrolidine, in the presence of PBN, a two-component EPR spectrum is observed (aN = 1.51 mT, aH β = 0.40 mT, I = 62% and aN = 1.38 mT, aH β = 0.24 mT, I = 38%) (Figure 6). The first component is the same as one of the components in the EPR spectrum of a reaction mixture (compare with Figure 5b) and corresponds to a carbon-centred radical. The second component is similar to the one present in the Fenton reaction (hydrogen peroxide and ferrous sulphate) in the DMSO:buffer mixture and it can be assigned to PBN-CH_3 or PBN-OH adducts thus suggesting the presence of superoxide anion radical formed in the reaction with molecular oxygen.

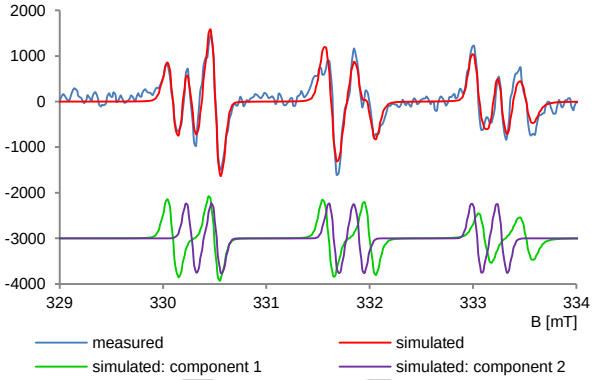


Figure 6. EPR spectra of the mixture of 4-oxotetrahydropyran (**8a**), pyrrolidine, EDA (**9b**) in DMSO/buffer with PBN. Reaction conditions: ketone **8a** (1 equiv., 0.25 mmol), pyrrolidine (0.2 equiv.), EDA (**9b**, 1 equiv.) DMSO/buffer pH = 4 (5 mL, 9/1 (v/v) mixture), spin trap PBN after 10 min of irradiation with LED.

The same pattern, but with a significantly lower total intensity, is also observed in the absence of EDA (**9b**).

Furthermore, to confirm the formation of the oxygen derived radical, the reaction of 4-oxotetrahydropyran (**8a**) with pyrrolidine was conducted in aerated conditions, under green light irradiation. In these conditions only one component is seen in the EPR spectrum with PBN, with a_N = 1.39 mT and $a_{H\,\beta}$ = 0.23 mT – which is also observed as a minor one in the spectrum of 4-oxotetrahydropyran (**8a**), pyrrolidine, and EDA (**2b**) system in degassed solvent. When DMPO was used as a spin trap with the mixture of 4-oxotetrahydropyran (**8a**), EDA (**9b**), and pyrrolidine was irradiated with green light, the dominating component (90% of total intensity) is the same as in the presence of the porphyrin (a_N = 1.47 mT, $a_{H\,\beta}$ = 2.16 mT), arising from the carbon-centred radical (**B**). In accordance with the proposed mechanism reactive radicals are formed. EPR measurements proved the formation of two different carbon-centred radicals, which after analysing simulated hyperfine splitting constants of spin adducts can be assigned to radical cation **B** and radical cation **D**. Additionally, no signal from a carbene radical was found in the reaction mixture or background reactions.

Stern-Volmer analysis. Expectedly, NMR experiments confirm that enamine forms under developed conditions (see SI). The quenching rates (k_q) for each of the reaction components were measured using standard Stern−Volmer analyses. Only enamine **A** (k_q = 4.1 x 10^{10} [$M^{-1}s^{-1}$]) strongly quenches the luminescence of porphyrin **11b** while for EDA (**9b**) (k_q = 4.5 x 10^9 [$M^{-1}s^{-1}$]), ketone **8a** (k_q = 1.2 x 10^8 [$M^{-1}s^{-1}$]), and pyrrolidine (k_q ~ 8.2 x 10^7 [$M^{-1}s^{-1}$])[31] quenching rates are much smaller (Figure 7). This is in contrast to the reaction with aldehydes where the highest quenching rate was measured for EDA (**9b**)[6a] thus suggesting differences in the mechanistic pathways.

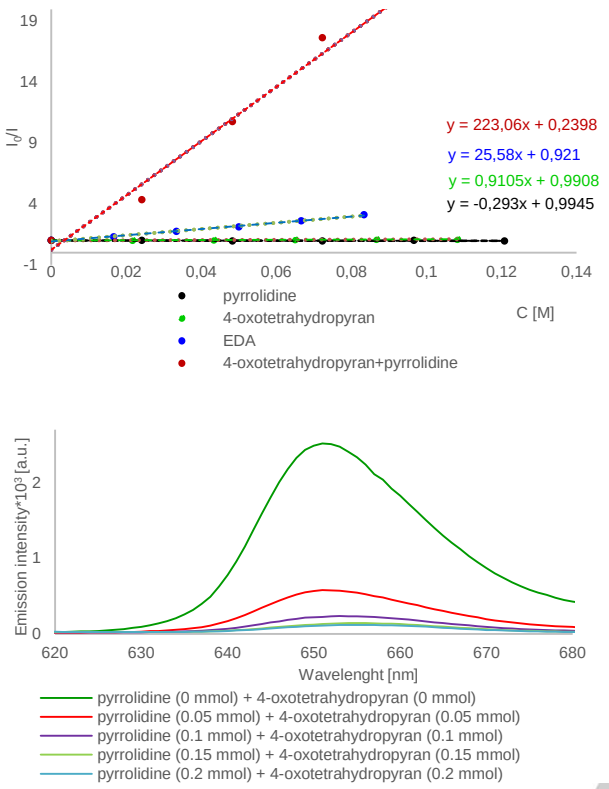


Figure 7. **Up:** Stern−Volmer quenching experiment for $H_2T(p\text{-}CO_2MeP)P$ (**11b**). Experimental conditions: for pyrrolidine, EDA (**9b**), enamine (formed in situ), and 4-oxotetrahydropyran (**8a**) samples were prepared by adding the solutions of substrates (2.5 x 10^{-3} M) to $H_2T(p\text{-}CO_2MeP)P$ (**11b**) in DMSO (total volume 2 mL) and degassed with Ar. The concentration of $H_2T(p\text{-}CO_2MeP)P$ (**11b**) in DMSO was 7.2 × 10^{-7} M. **Down:** Fluorescence quenching of $H_2T(p\text{-}CO_2MeP)P$ (**11b**) (7.2 × 10^{-7} M in DMSO) upon titration with pyrrolidine and 4-oxotetrahydropyran (**8a**).

Presumably, these differences result from the fact that enamines formed from cyclic ketones and pyrrolidine are easier to oxidize[32] than enamines generated from aldehydes and morpholine.[33]

The main reaction pathway involves the oxidation of enamine **A** to the radical cation. Free-base porphyrins can act as both reducing and oxidizing agents, and the driving force for the electron transfer relates to the standard potential of oxidation of the donor the standard potential of the acceptor, and the energy of excited state. In the excited state reduction potential of $H_2T(p\text{-}CO_2MeP)P$ (**11b**, 1.03 V vs SCE, DMSO) is high enough to oxidize enamine **A** (0.49 V vs SCE, MeCN) to radical cation **B**. Moreover, the Rehm−Weller formalism allows for estimating the thermodynamic driving force, $-\Delta G_{PET}^{(0)}$, for PET between the enamines and porphyrins in the excited-state, ($-\Delta G_{PET}^{(0)} \approx -0.6$ V). Because of the irreversible electrochemical oxidation of enamines and the solvents used (DMSO/buffer), we do not have exact values for their oxidation potentials.

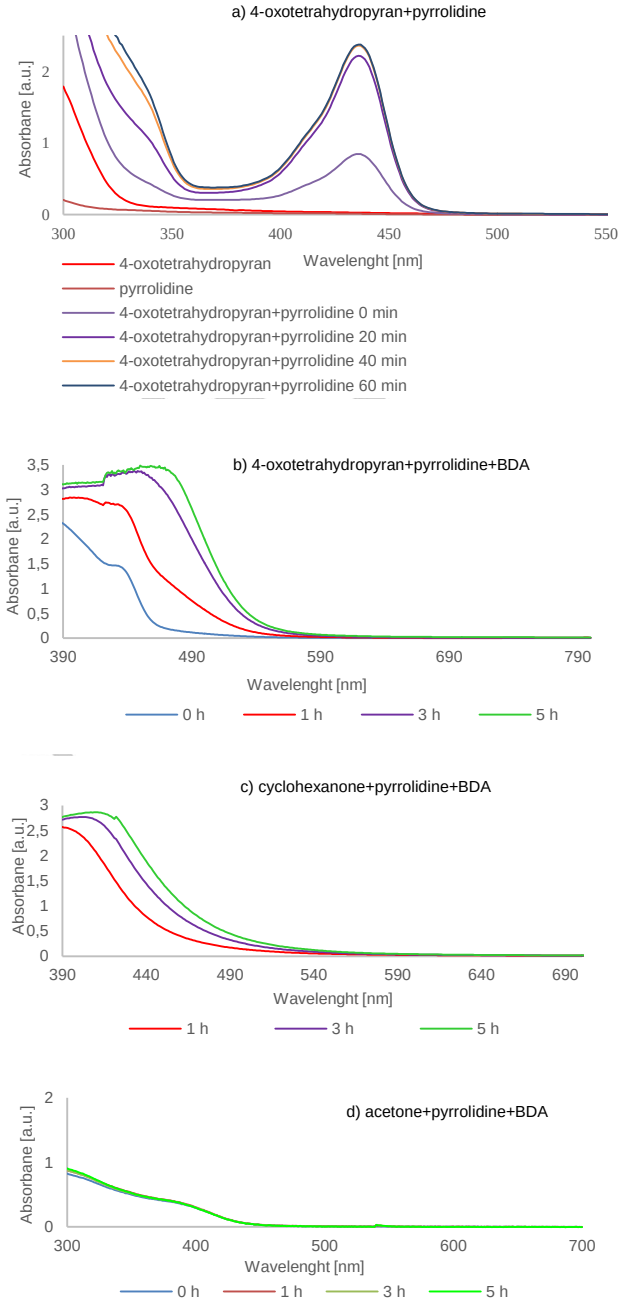
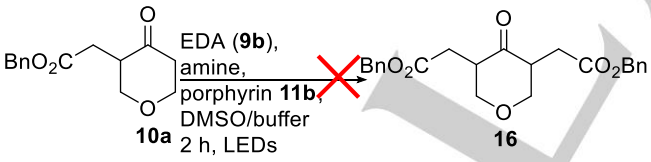


Figure 8. UV-Vis Experiment. Reaction conditions: a) control experiments: 1) ketone (**8a**) (0.25 mmol, DMSO/buffer pH = 4, 1.5 mL, 9/1 (v/v) mixture); 2) pyrrolidine (20 mol%), DMSO/buffer pH = 4 (1.5 mL, 9/1 mixture); 3) ketone (**8a**) (0.25 mmol), pyrrolidine (20 mol%), DMSO/buffer pH = 4 (1.5 mL, 9/1 v/v mixture) measured in 0, 20, 40, 60 min after mixing. b) ketone (**8a**, 0.25 mmol), pyrrolidine (20 mol %), BDA (**9a**, 0.25 mmol), DMSO/buffer pH = 4, 1.5 mL, 9/1 (v/v) mixture), LED_{525nm}. c) cyclohexanone (**8b**, 0.25 mmol), pyrrolidine (20 mol%), BDA (**9a**, 0.25 mmol), DMSO/buffer pH = 4, 1.5 mL, 9/1 (v/v) mixture), LED_{525nm}. d) acetone (**8m**, 0.25 mmol), pyrrolidine (20 mol%), BDA (**9a**, 0.25 mmol), DMSO/buffer pH = 4, 1.5 mL, 9/1 (v/v) mixture), LED_{525nm}.

For acetonitrile, the voltammograms show peak potentials about 0.49 V vs SCE for oxidation of enamines. Therefore, for PET initiated from the singlet excited state of the porphyrins, ΔG most likely assumes negative values, making it thermodynamically favourable.

However, in the porphyrin-free reaction, it is enamine **A** that absorbs light and in the excited state (**A***) is oxidized presumably by molecular oxygen. It is consistent with the observation that the enamine generated in situ from 4-oxotetrahydropyran (**8a**) and pyrrolidine absorbs visible light at the maximum 437 nm with its absorption increasing over time (Figure 8) (for details see SI). However, for enamines (from cyclohexanone (**8b**) and acetone (**8m**), for details see SI) the new absorption band is not present which is in agreement with the fact that these ketones afford products only in the porphyrin-catalysed reaction. Thus, in porphyrin-free reactions the absorption of visible light by enamine is crucial for the product formation. The mechanism for the porphyrin-free reaction assumes oxidation of excited enamine **A*** by molecular oxygen. Indeed, the yield increases when the reaction was exposed to the air, opposite to the reaction with the porphyrin. This photocatalyst is able to generate singlet oxygen and/or reactive oxygen species ROS which by reacting with both the catalyst and substrates diminished the reaction yield (Figure 6). Furthermore, the addition of $K_2S_2O_8$ as an oxidant (1.85 V vs SCE, MeCN)[34] to the degassed porphyrin-free reaction caused an increase in the reaction yield from traces to 25%. Hence, we concluded that *molecular oxygen can oxidize enamine **A** in the excited state to radical cation **B** if the porphyrin is not present.*

Next, we focused on elucidating whether the second alkylation occurs before or after the hydrolysis of iminium **E** to the desired mono-alkylated product. To this end, we subjected mono-alkylated ketones **10a** and **10l** to the developed reaction conditions, however no conversion was observed (Scheme 7). As a result, we concluded that dialkylated ketones form if iminium **E** directly undergoes second oxidation-alkylation sequence faster than hydrolysis to the mono-alkylated product.



Scheme 7. Alkylation of product **10a**.

Theoretical studies. For catalytic cycle steps including porphyrin in the excited state we have been able to conduct calculations using only a very small basis set (B3LYP/6-31G[35] and M06-2X/6-31G[36]). Thus, for all reactions in the presence of porphyrin as a catalyst the data obtained from the small basis set calculations are taken into account while the values for reactions without porphyrin were obtained with the 6-311++G(2d,2p) basis set.

The oxidation of the enamine by triplet oxygen seems to be not allowed thermodynamically ($\Delta G_{B3LYP/6\text{-}311++G(2d,2p),\ DMSO}$ = +27.02 kcal/mol, $\Delta G_{M06\text{-}2X/6\text{-}311++G(2d,2p),\ DMSO}$ = +35.40 kcal/mol). Conversely, the obtained Gibbs energies tentatively indicate that singlet oxygen spontaneously oxidize enamine **A** ($\Delta G_{B3LYP/6\text{-}311++G(2d,2p),\ DMSO}$ = -11.72 kcal/mol, $\Delta G_{M06\text{-}2X/6\text{-}311++G(2d,2p),\ DMSO}$ = -2.30 kcal/mol). Hence, the most probable path for porphyrin-free reaction is the oxidation of enamine **A** by singlet oxygen. Even more preferred would be – according to the calculated Gibbs energy values – the oxidation of enamine **A*** in the excited state, as these values are negative for both triplet ($\Delta G_{M06\text{-}2X/6\text{-}311++G(2d,2p),\ DMSO}$ = -60.29 kcal/mol) and singlet ($\Delta G_{M06\text{-}2X/6\text{-}311++G(2d,2p),\ DMSO}$ = -97.99 kcal/mol) oxygen.

For the reaction of porphyrin in the excited state (Por*) with enamine **A**, the values of Gibbs energy are also negative ($\Delta G_{M06\text{-}2X/6\text{-}31G,\ DMSO}$ = -7.55 kcal/mol) indicating that the oxidation of enamine **A** to radical cation **B** is favoured thermodynamically. The consequent reduction of radical adduct **D** by porphyrin radical anion is also favourable ($\Delta G_{M06\text{-}2X/6\text{-}31G,\ DMSO}$ = -29.12 kcal/mol).

For the reduction of radical cation **D** by $O_2^{\bullet-}$, the B3LYP functional gives negative value (ΔGB3LYP/6-31G, DMSO = -22.93 kcal/mol). However, by applying M06-2X and a larger basis set functional positive value was obtained (ΔGM06-2X/6-311++G(2d,2p), DMSO = +8.95 kcal/mol). This might indicate why in the absence of the porphyrin this step is less favoured thermodynamically and is in agreement with the decreased yields in porphyrin-free reaction in comparison to photocatalysed reaction.

Conclusions

Developed, photoinduced α-alkylation of ketones with diazo esters gives access to mono- and dialkylated products. For ketones forming enamines that absorb visible light the reaction does not require the addition of the photocatalyst though yields are diminished.

Extensive mechanistic studies supported by theoretical calculations provide sufficient data to corroborate the proposed radical mechanism. The reaction does not involve expected cyclopropanation of enamine instead enamine radical cation **B** reacts with diazo acetate leading to iminium radical.

These findings demonstrate venues in both diazo compound chemistry and its utility in photoredox catalysis.

Experimental Section

General procedure for α-mono-functionalization of ketones – method A:

To a 10 mL vial equipped with stir bar a photocatalyst (1 mol%) was added and dissolved in a mixture of DMSO and buffer pH 4 (mixture 9:1, 5 mL). The vial was sealed and purged with argon for 5 min. Then the ketone (0.5 mmol), pyrrolidine (0.2 equiv., 0.1 mmol) and diazo ester (1.2 equiv., 0.6 mmol) were added. The reaction mixture was stirred under light irradiation (LED_{525nm}, 25 ℃) for 5 h. The light was turned off and the reaction mixture was diluted with Et_2O, and washed with 1N HCl. The aqueous phase was extracted with Et_2O three times. The combined organic phases were washed with saturated $NaHCO_{3aq}$, brine, dried over

$MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using silica gel (hexanes/Et_2O).

General procedure for α-di-functionalization of ketones – method B:

To a 10 mL vial equipped with stir bar a photocatalyst (1 mol%) was added and dissolved in a mixture of DMSO and buffer pH 7 (mixture 9:1, 5 mL). The vial was sealed and purged with argon for 5 min. Then ketone (1 equiv., 0.25 mmol), pyrrolidine (0.4 equiv., 0.1 mmol) and EDA (3 equiv., 0.75 mmol) were added. The reaction mixture was stirred under light irradiation (LED_{525nm}, 25 ℃) for 7 h. The light was turned off, the reaction mixture was diluted with Et_2O, and washed with 1N HCl. The aqueous phase was extracted with Et_2O three times. The combined organic phases were washed with saturated $NaHCO_{3aq}$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using silica gel (hexanes/Et_2O).

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Keywords: diazo compounds • photoredox catalysis • alkylation of ketones • porphyrins

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Layout 1:

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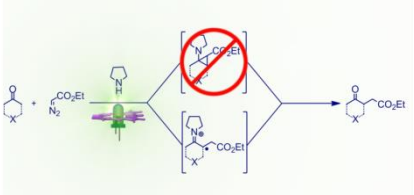

Photoredox Catalysis

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Why Cyclopropanation is not involved in Photoinduced α-Alkylation of Ketones with Diazo Compounds?