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Phenylglyoxylic Acid: An Efficient Initiator for the Photochemical Hydrogen Atom Transfer (HAT) C-H Functionalization of Heterocycles

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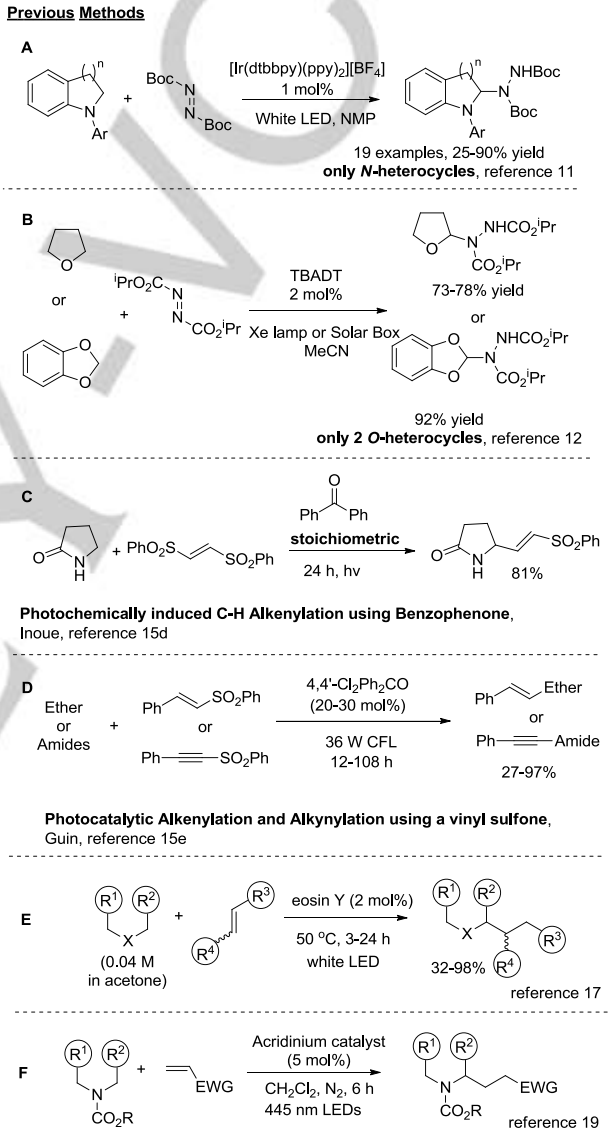
Abstract: C-H functionalization at the α position of heterocycles has become a rapidly growing area of research. Herein, we report a cheap and efficient photochemical method for the C-H functionalization of heterocycles. PhCOCOOH can behave as an alternative to metal-based catalysts and organic dyes and provides a very general and wide array of photochemical C-H alkylation, alkenylation and alkynylation, as well as C-N bond forming reaction methodologies. This novel, mild and metal-free protocol is successfully employed in the functionalization of a wide range of C-H bonds, utilizing not only *O*- or *N*-heterocycles, but also the less studied *S*-heterocycles.

Introduction

The introduction of novel reactivities and new platforms of activation is the ultimate goal in organic synthesis.[1] Photochemistry, the use of light to promote organic transformations, is a concept introduced in literature in 1912 and provides access to alternative activations compared to polar chemistry.[2] In recent years, photoredox catalysis has become a powerful strategy for the activation of small molecules.[3,4] Most examples rely on the use of metal-based catalysts (mainly Ru or Ir), having the advantage of tuning their electronic properties via ligand manipulation. Unfortunately, these complexes can be expensive, and some are not commercially-available. To address this problem, a number of organic dyes have been employed as photocatalysts, which in many cases provide similar reactivities. Photoorganocatalysis is a low-cost and environmentally friendly alternative.[5,6] However, each of these catalysts has certain limitations. For example, benzophenones have a long-lived triplet state, which allows a hydrogen atom transfer (HAT) process to occur. Nevertheless, a reverse hydrogen atom transfer (RHAT) is required, in order, for the catalyst, to be regenerated. Since this is usually a slow procedure, a faster dimerization of benzophenone to benzopinacol is usually observed. Quinones constitute an important category of photoinitiators, when



Scheme 1. Approaches for the selective photochemical C-H functionalization of heterocycles.

irradiated in the near UV. This family of catalysts is scarcely reported in photochemical reactions, while in the case of polyoxometalates, the use of toxic transition metals cannot be avoided. In addition, organic dyes, like Eosin Y,[7] are shown to be competent visible-light absorbing photochemical catalysts.

The direct transformation of C-H to C-C or C-N bonds is one of the most ideal methodologies for constructing complex molecules with various potential applications in medicinal and bioorganic chemistry.[8] Heterocycles are present in

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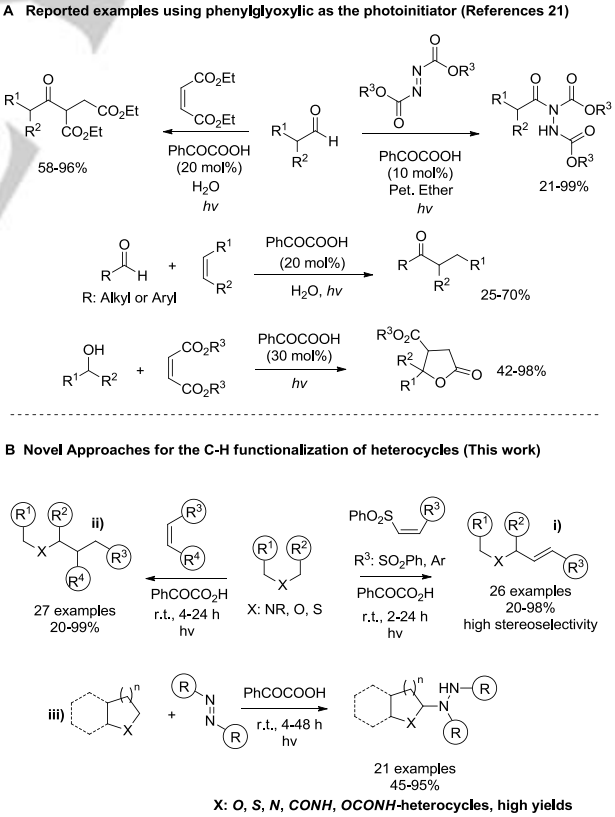
pharmaceuticals and bioactive molecules (35% of drugs feature a heterocycle). Also, heterocyclic scaffolds are found in plant-derived natural products and are ubiquitous in biological processes. Thus, researchers are constantly searching for novel functionalization methods.[9] Most of them are metal-catalyzed processes, while a handful of examples refer to metal-free C-H transformations. Although significant advances have been made, direct metal-catalyzed functionalization of heterocycles is still confronted by several challenges. For example, heteroatoms including N, S, and O can potentially coordinate strongly to transition metal catalysts, which can ultimately lead to catalyst poisoning/deactivation or C-H functionalization at undesired positions via chelation.

Dialkyl azodicarboxylates have been recognized as extremely useful electrophiles, due to their strong electron-withdrawing character and their vacant orbital.[10a-c] Early literature refers to scarce examples of reactions of dialkyl azodicarboxylates with ethers in various metal-catalyzed, radical-initiated or photochemical reactions.[10-12] In these reports, only *N*-heterocycles[11] (Scheme 1, **A**), and two examples with *O*-heterocycles[12] were presented (Scheme 1, **B**). Unfortunately, no *S*-heterocycles have been reported, while a unified solution is still absent.

Except from the C-N functionalization of heterocycles on the α position, the direct C-H alkenylation of heterocycles is also an important area of research. A number of protocols have been reported, based on peroxides/UV light, generation of radicals, aerobic/autooxidation and photoinitiation.[13] 1,2-Bis(phenylsulfonyl)ethylene is a commercially available reagent, which has been used for the addition of alkenyl functional groups.[14] A limited number of approaches for the functionalization of C-H bonds of heterocycles employing sulfones have been reported. Initially, Fuchs introduced alkynyl triflone reagents for the thermally-induced or photochemical (UV-light) radical alkynylation of tetrahydrofuranyl derivatives.[15a] The same year, Fuchs extended their method by incorporation of vinyl triflones as the alkenylation reagent via an AIBN-catalyzed process.[15b] Later, Inoue introduced a stoichiometric photocatalytic method employing benzophenone for the direct alkynylation[15c] and alkenylation[15d] of 2-pyrrolidinone (Scheme 1, **C**). Very recently, Paul and Guin took advantage of the main activation mode of benzophenone-derived triplets, in order to initiate a hydrogen atom transfer (HAT) process (Scheme 1, **D**).[15e] This method, although elegant and green is limited by the slow reverse HAT or reverse electron transfer/proton transfer, which has as an outcome the poor turnover of the photocatalyst, requiring high catalyst loadings and long reaction time.

In addition to the C-H alkenylation of heterocycles, the C-H alkylation has also received some attention. In 2005, Ochiai reported the alkylation of *O*-heterocycles, using *tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one.[16] Recently, Wu reported a method using a wide range of electron-deficient alkenes to afford the alkylation product of heterocycles.[17] The generation of the α-ethereal carbon radicals was achieved by a HAT process between excited Eosin Y, which was used as the photocatalyst, and THF, under white LED irradiation (Scheme 1, **E**).[17] Very recently, Barriault reported the photoredox-mediated catalytic generation of chlorine atoms and their ability to undergo hydrogen atom transfer reactions with a variety of cyclic and not cyclic alkanes and their addition to activated alkenes using an iridium-based catalyst.[18] Also, Nicewicz presented the alkylation of carbamate-protected amines, using an organic acridinium photoredox catalyst and 445 nm LEDs as the irradiation source (Scheme 1, **F**).[19] Finally, Vincent reported the benzophenone photocatalyzed Giese-type alkylations of C-H bonds using unsubstituted acrylates, acrylonitrile and methyl vinyl ketones as acceptors, in the presence of a catalytic amount of $Cu(OAc)_2$.[20]

We have recently developed a photochemical protocol that is easy to operate, employing cheap household lamps as the irradiation source and phenylglyoxylic acid, a cheap, organic, and commercially available molecule, as the initiator for the functionalization of aldehydes or alcohols (Scheme 2, **A**).[21] A fast and efficient visible-light metal-free hydroacylation of dialkyl azodicarboxylates, was developed,[21a] and extended in the synthesis of hydroxamic acids[21b] and amides,[21c] finding application in the synthesis of the drugs Vorinostat and Moclobemide. Then, a green and easy reproducible selective hydroacylation of both electron poor and electron rich alkenes was presented[21f, 21g] and an efficient photochemical protocol for the synthesis of γ-lactones,[21e] starting from diesters of maleic acid and alcohols.

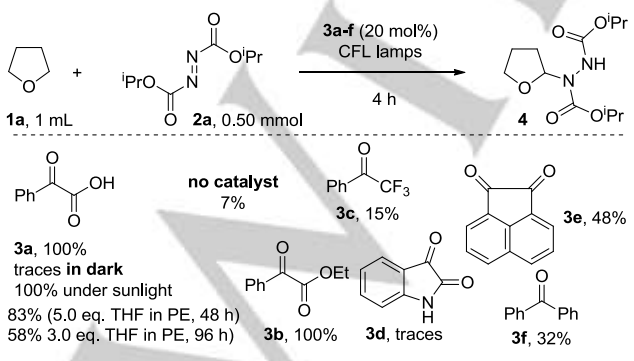


Scheme 2. HAT catalysis for the C-H functionalization mediated by phenylglyoxylic acid.

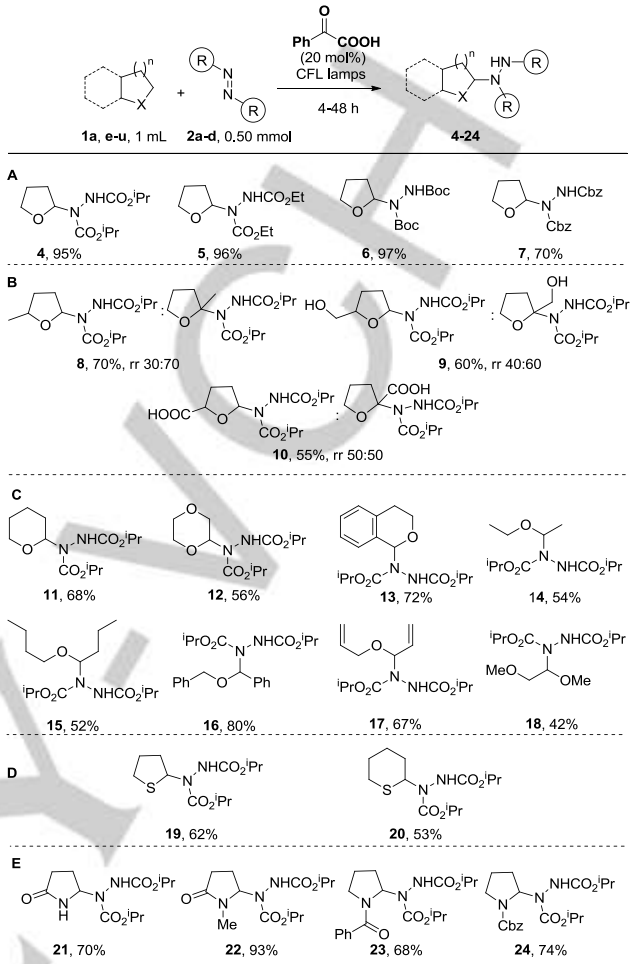
Our aim is to achieve the direct photochemical C-H functionalization of heterocycles as a promising approach with high atom- and step-economy (Scheme 2, **B**). Herein, we report our results on the mild alkenylation of C-H bonds, using phenylglyoxylic acid as the photoinitiator and *cis*-1,2-bis(phenylsulfonyl)ethylene (Scheme 2, **B**, *i*). In order to expand the potential of our protocol, we tested our photochemical protocol, not only in the reaction between a range of olefins and various heterocycles (Scheme 2, **B**, *ii*), but also in the successful formation of C-N bonds (Scheme 2, **B**, *iii*). In general, herein, we demonstrate that not only *O*- or *N*-, but also *S*-heterocycles can be activated via sustainable and green photochemistry, using a low-cost setup and providing comparable or better results to metal photocatalysis.

Results and Discussion

We initially investigated the reaction between THF (**1a**) and diisopropyl azodicarboxylate (DIAD, **2a**) (Scheme 3). A variety of aryl ketones (**3a-f**) were employed, and PhCOCOOH (**3a**) outperformed all, providing **4** in quantitative yield in short reaction time (4 h). In the absence of either the initiator or light, the reaction did not proceed. THF is used as the reagent and the solvent, since attempts to employ other solvents, in order to reduce the amount of THF, led to lower yields.[22] However, extending the reaction time, efficient yields of the product could be obtained, reducing the amount of THF (5 equivalents in Pet. Ether for 48 h, 83% yield or 3 equivalents in Pet. Ether for 96 h, 58% yield), providing a useful alternative for late-stage functionalization.[22] The reaction can also be driven by sunlight (25 September 2019, 10:00-14:00, Athens, Greece, 37.97° N, 23.72° E). No special precautions were taken to exclude air or moisture and reagent-grade THF was employed. Having established the optimum reaction conditions, we turned our attention into the exploration of the substrate scope (Scheme 4). First, a series of dialkyl azodicarboxylates were tested, affording products **4-7** in excellent yields (Scheme 4, **A**). Monosubstituted tetrahydrofurans at the α position led to a mixture of regioisomers (products **8-10**, Scheme 4, **B**). Moving from five-membered to six-membered ring *O*-heterocycles or using linear aliphatic ethers led to products **11-18** (Scheme 4,



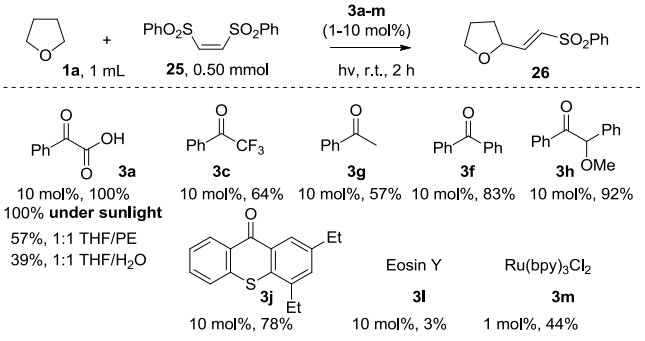
Scheme 3. Catalyst screening for the photochemical synthesis of **4**.



Scheme 4. Substrate scope of the photochemical C-H functionalization leading to a new C-N bond.

C). Then, *S*-heterocycles were successfully employed (**19** and **20**, Scheme 4, **D**). *N*-Heterocycles, which are present in drugs or are important for industrial processes, reacted smoothly leading to **21-24** in high yields, making this method suitable for late-stage functionalization of drugs (like the anti-diabetic Galvus[23a]) or enzyme inhibitors (like indolizidine 235b[23b]) containing heterocycles (Scheme 4, **E**). This constitutes, in our knowledge, the first successful unified solution for the introduction of C-N bonds to *O*-, *N*- and *S*-heterocycles.

These results gave us the opportunity to further try other types of radical acceptors. Initially, the photochemical reaction between THF (**1a**) and 1,2-bis(phenylsulfonyl)ethylene (**25**) was studied (Scheme 5). Among the promoters tested, PhCOCOOH provided the best results in short reaction time. Common catalysts, like Eosin Y or $Ru(bpy)_3Cl_2$ did not afford the product in high yields.[22] As before, attempts to employ other solvents and reduce the amount of THF as being simply the reagent led to lower yields.[22] However, as before, in substrates that are more precious, lower amount of heterocycles can be employed and similar yields can be



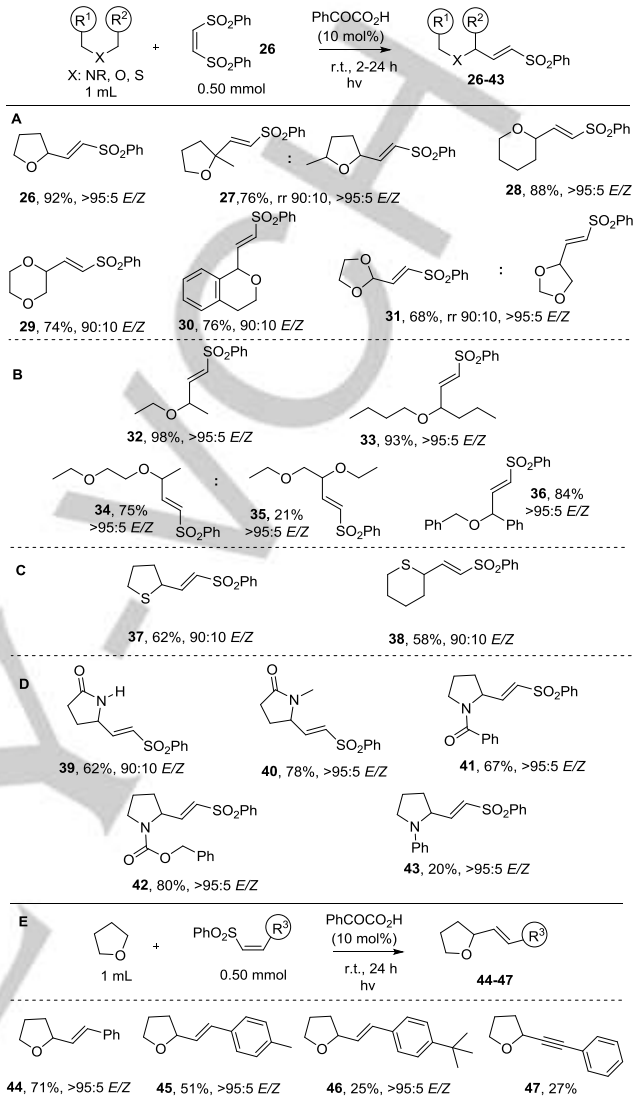
Scheme 5. Catalyst screening for the photochemical C-H alkenylation of THF.

obtained by extending the reaction time. The reaction can also be performed under sunlight.

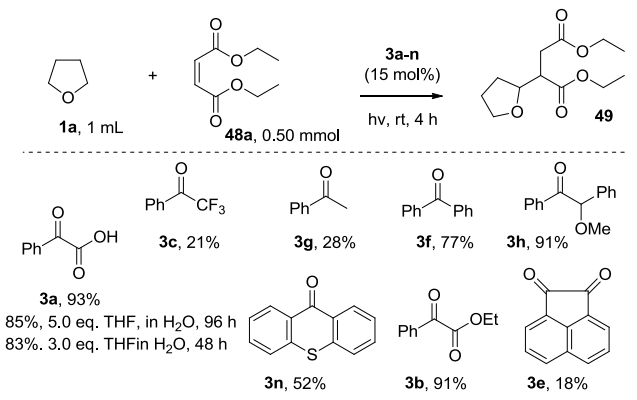
After establishing the optimum reaction conditions,[22] we explored the substrate scope (Scheme 6). Other tetrahydrofuranyl adducts, like 2-methyl-THF or dioxolane, reacted well leading to two regioisomers (9:1), in favor of the expected tertiary-substituted product in excellent diastereoselectivity. Moving from five-membered to six-membered heterocycles led to **28-30** (Scheme 6, **A**). Acyclic ethers were also functionalized in good to excellent yields (**32-36**). The only exception was diethoxyethane, which led to a 3:1 mixture of regioisomers (**34:35**) (Scheme 6, **B**). *S*-Heterocycles that are scarcely employed in C-H functionalization methods reacted smoothly leading to **37** and **38** (Scheme 6, **C**). Finally, this protocol can be extended to *N*-heterocycles (**39-43**), leaving open the potential of late-stage functionalization of drugs (Scheme 6, **D**).[23] Finally, we turned our attention into the alkene partner (**44-46**). Interestingly, this method can be extended to C-H alkynylation reaction (**47**) (Scheme 6, **E**).

Being successful in the C-H alkenylation of heterocycles, we moved on the C-H alkylation. We initially investigated the reaction between THF (**1a**) and diethyl maleate (**48a**) (Scheme 7). A variety of (activated) ketones were employed, and PhCOCOOH (**3a**) proved to be the best promoter, leading to the formation of **49** in 93% yield in short reaction time (4 h). Extending the reaction time, efficient yields of the product could be obtained, reducing the amount of THF (5 equivalents in H_2O for 48 h, 85% yield or 3 equivalents in H_2O for 96 h, 84% yield), providing a useful alternative for late-stage functionalization.[22]

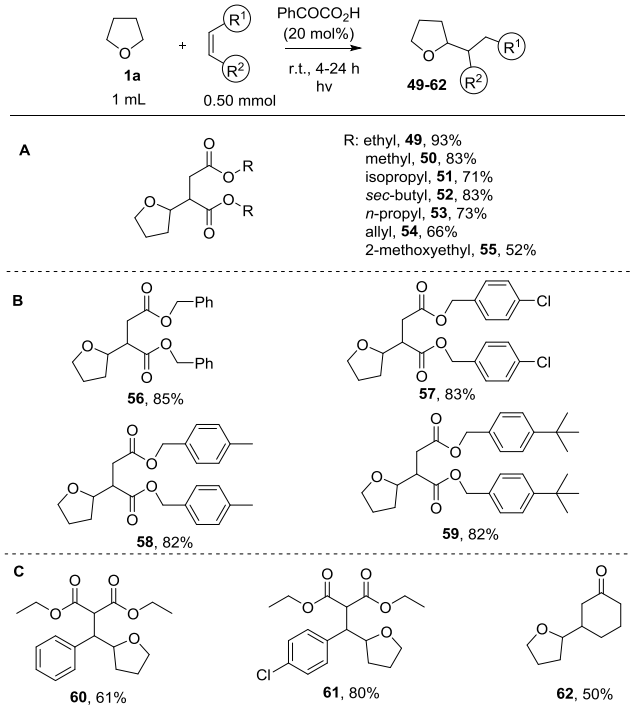
A variety of substituted electron-deficient olefins were tested and in all cases the products were isolated as mixture of diastereomers (Scheme 8). Alkyl-substituted electron-deficient olefins reacted smoothly leading to **49**-**55** in high yields (Scheme 8, **A**). This method can be extended to benzyl-substituted electron-deficient olefins (**56**-**59**) (Scheme 8, **B**). Finally, a range of different Michael acceptors were employed successfully, affording the desired products in good to excellent yields (**60**-**62**) (Scheme 8, **C**). Acrylate-type substrates (esters, amides or aldehydes) were also tested,



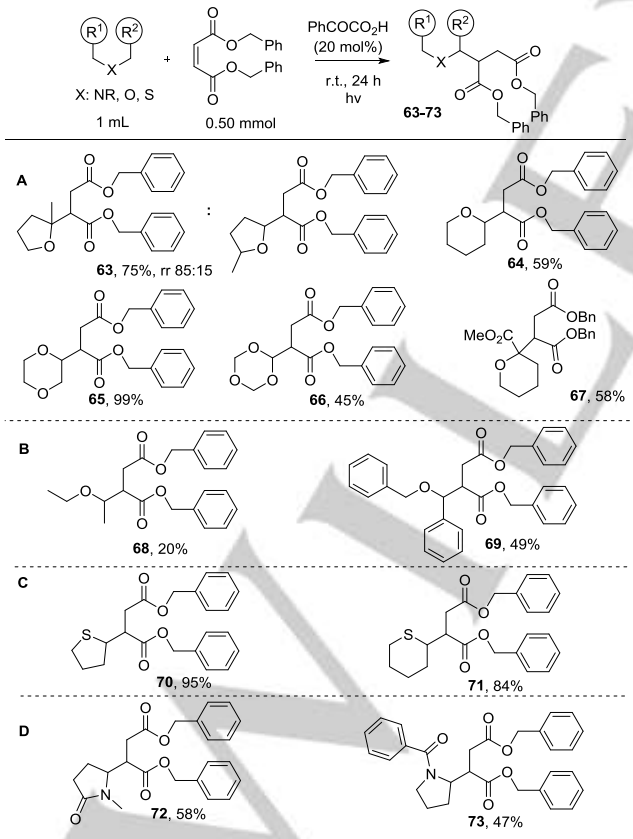
Scheme 6. Substrate scope of the photochemical C-H alkenylation of heterocycles.



Scheme 7. Catalyst screening for the photochemical synthesis of **49**.



Scheme 8. Substrate scope of the photochemical alkylation of THF.

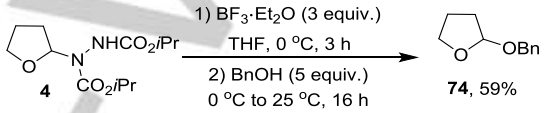


Scheme 9. Substrate scope of the photochemical alkylation of heterocycles.

however only polymerization products were observed.

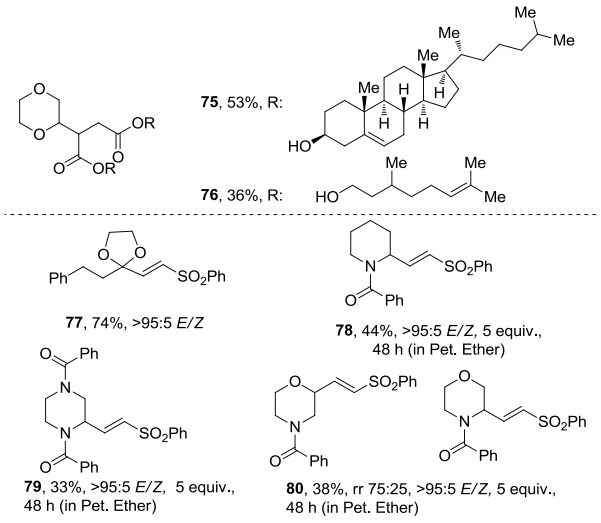
Next, we turned our attention into the heterocyclic partner (Scheme 9). 2-Methyl-THF reacted well leading to two regioisomers (**63**). Six-membered heterocycles and were successfully employed in the reaction, affording **64**-**67** in excellent yields (Scheme 9, **A**). The reaction was also carried out efficiently, when acyclic ethers were tested, leading to **68** and **69** (Scheme 9, **B**). *S*-Heterocycles were also successfully tested, affording **70** and **71** in high yields (Scheme 9, **C**). Finally, as before, *N*-heterocycles were functionalized successfully, affording the desired products in good yields (**72** and **73**) (Scheme 9, **D**).

N,*O*-Acetals are useful building blocks for further synthetic manipulations, for example via reactions with various ylides.[24] Nucleophilic substitution reaction at the α position of **4** by benzyl alcohol, in the presence of $BF_3.Et_2O$, led to protected alcohol **74** (Scheme 10).



Scheme 10. Example of further functionalization of addition product.

In an attempt to further enhance the applicability of our protocol, we employed it to the synthesis of addition products bearing natural abudant moieties and nitrogen bearing scaffolds, which are common in pharmaceutical products (Scheme 11). Initially, the reaction between dioxane and the fumarate esters of cholesterol and citronellol were performed leading to **75** and **76**. Also, a cyclic acetal derived from 3-phenyl-propanal led to **77** in high yield and excellent *E*/*Z*-selectivity. In order to expand the protocol on the use of *N*-containing heterocycles, which are more frequently encountered in pharmaceuticals, we employed the late-stage



Scheme 11. Examples with life abundant molecules, mixed heteroatom heterocycles and nitrogen containing heterocycles.

functionalization conditions (*N*-heterocycle 5.0 equivalents, 48 h), leading to products **78-80** in excellent yields.

Mechanistic studies

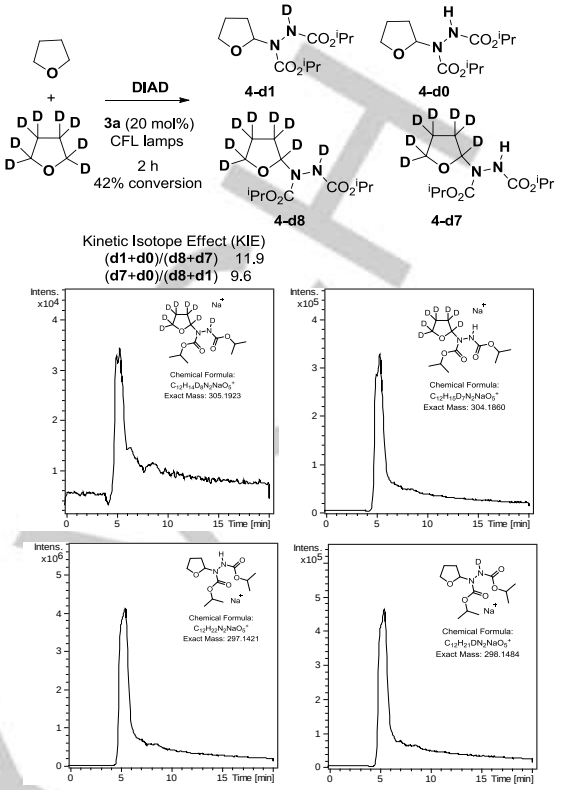
Mechanistic experiments were performed to elucidate the reaction mechanism. In all three cases, our major target was to understand the type of interaction between phenylglyoxylic acid and the rest of the mixture, THF and the radical trap. Starting from fluorescence quenching studies.[22] After irradiation of phenylglyoxylic acid (1 mM in MeCN) at 360 nm, its fluorescence was measured at 402 nm and in all cases the quenching of phenylglyoxylic acid by increasing amounts of added THF and radical traps are both trivial, except for the case of diethyl maleate (**48a**), where the quenching is due to the *Z/E* isomerization of the double bond, induced by the excited keto acid. All these indicate that the initial radical is not formed by the excited phenylglyoxylic acid, but by another radical species which is not yet present.

Next, UV-Vis experiments were performed.[22] The association of an electron-rich molecule with an electron-acceptor can lead to the formation of an aggregate, called electron donor-acceptor (EDA) complex. EDA complexes are known in literature since the 1950s,[25] but only recently Melchiorre and others have identified them as active species in photochemical reactions.[5d] An EDA complex is usually recognized, when upon addition of the two components, an increase in the UV absorbance of the mixture is observed. Upon mixing phenylglyoxylic acid, with DIAD in THF or with **25** in THF or with **48a** in THF, no noticeable increase in the UV absorbance was observed, excluding the possibility of an EDA complex formation, in all three cases.[22]

Next, we studied the photochemical reaction by NMR spectroscopy. Previous studies on the photochemistry of phenylglyoxylic acid propose that excited triplet state of phenylglyoxylic acid in iPrOH decomposes upon irradiation to the dimerization product (diphenyltartaric acid),[26a] whereas in water the photodecomposition leads to benzaldehyde.[21g,26b-d] The process was monitored by ^{13}C- and ^{1}H-NMR spectroscopy and our observations state that excited phenylglyoxylic acid, in THF, photodecomposes both to benzaldehyde and to diphenyltartaric acid.[22] The products of the photodecomposition are observed both in the spectra from the irradiation of phenylglyoxylic alone and of the reaction mixture.[22] According to literature precedents[26] and our own observations,[21g] this means that excited $PhCOCO_2H$ is decomposing both to benzoyl radical and ketyl radical, which are responsible for the initiation of the process.

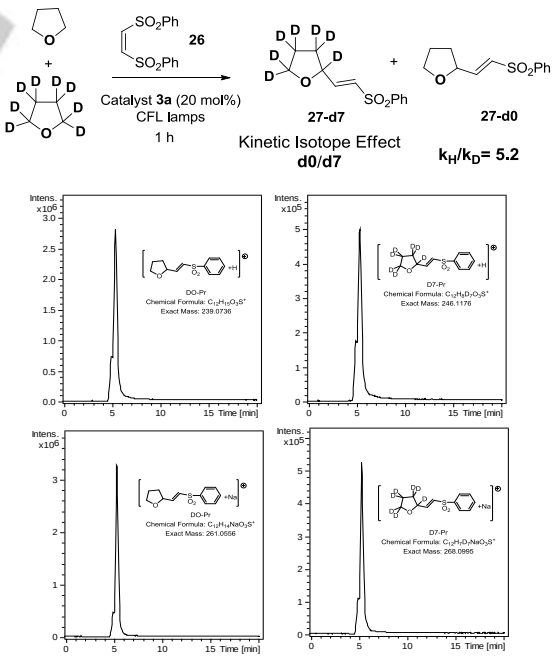
The radical nature of the reaction was also confirmed with the use of radical traps (BHT and TEMPO), where no product was formed.[22] More specifically, when the reaction mixture with TEMPO was irradiated, in the presence of phenylglyoxylic acid in THF, an adduct (THF-TEMPO) was identified, which confirms the generation of the α-THF radical.[22]

Moreover, in order to shed more light in the reaction mechanism, a kinetic isotope effect (KIE) experiment was performed (Figure 1). Since we have a long interest in



Extracted Ion Chromatograms at A) m/z 305.1923, B) m/z 304.1860, C) m/z 297.1421 and D) 298.1484

Figure 1. KIE of the C-N bond forming methodology.



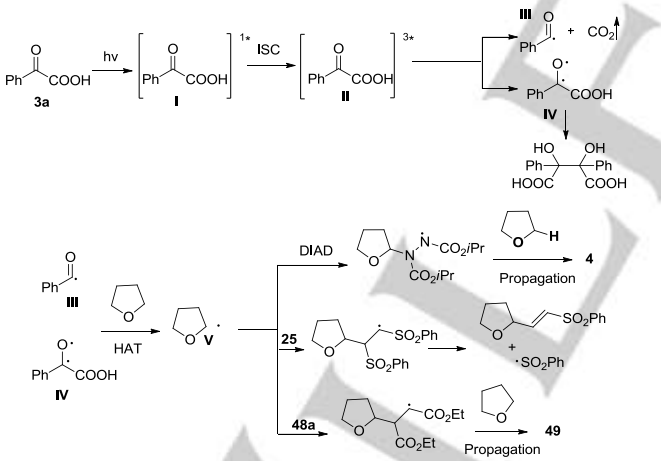
Extracted Ion Chromatograms at A) m/z 239.0736, B) m/z 246.1176, C) m/z 261.0556 and D) 268.0995

Figure 2. KIE of the C-H alkenylation methodology.

studying reaction mechanisms with the use of High Resolution Mass Spectrometry (HRMS),[27] the KIE was measured both by NMR and HRMS.[22] Treatment of DIAD with THF and *d8*-THF, provided products **4-*d*0**, **4-*d*1**, **4-*d*7** and **4-*d*8**. Also, treatment of **26** with THF and *d*8-THF, led to sulfonyl alkenes **27-*d*0** and **27-*d*7**. The KIE was determined, (Figure 2).

In a recent report, Yoon employed the quantum yield measurement as a mechanistic tool.[28] Using potassium ferrioxalate as the actinometer,[28,29] we calculated the quantum yield for all the cases, more specifically, THF and DIAD (Φ = 44), THF and **25** (Φ = 39), THF and **48a** (Φ = 85), indicating a chain propagation mechanism in all cases.

Taking all these data into account, a mechanism is proposed (Scheme 12). In THF, phenylglyoxylic acid (**3a**) is excited to singlet state **I** and via intersystem crossing (ISC) to triplet state **II** and is photodecomposed to both phenyltartaric acid and benzoyl radical **III** via homolytic cleavage of the activated C-C bond of triplet excited form.[21g,22,26] When a HAT donor is present (THF), ketyl (**IV**) or benzoyl (**III**) radical abstracts a hydrogen atom from THF, leading to the first alpha tetrahydrofuranyl (α-THF) radical **V**, which initiates the process. Addition of this initial α-THF radical **V** to the radical acceptor, affords new radical species, which via a radical propagation mechanism (quantum yield measurement) affords the desired product. In the case of the C-H alkenylation, the propagation occurs from the phenylsulfonyl radical, generated after the elimination. This reaction does not require any precaution from air, since the energy transfer quenching from oxygen of the radicals generated by PhCOCOOH is a slower process from the HAT process.[21g,22]



Scheme 12. Proposed reaction mechanism.

Conclusions

In conclusion, a novel, metal-free photochemical C-H functionalization of heterocycles was developed. This method relies on a small organic molecule (phenylglyoxylic acid) and cheap household lamps or sunlight. Herein, a unified fast, simple, photoorganocatalytic protocol for the C-H activation of *O*-, *S*- and *N*-heterocycles was demonstrated, leading to products in good to high yields. These results can offer a new and alternative route in Photocatalysis.

Experimental Section

In a glass vial with a screw cap, phenylglyoxylic acid (15 mg, 0.10 mmol) and dialkyl azodicarboxylate (0.50 mmol) or 1,2-bis(phenylsulfonyl)ethylene (**26**) (154 mg, 0.50 mmol) or Michael acceptor (0.50 mmol) were dissolved in ether/heterocycle (1 mL). The vial was sealed with a screw cap and left stirring under household bulb irradiation (2 x 85W household lamps) for 2-96 hours. After completion of the reaction, the solvent was removed *in vacuo* and the product was purified by flash silica chromatography

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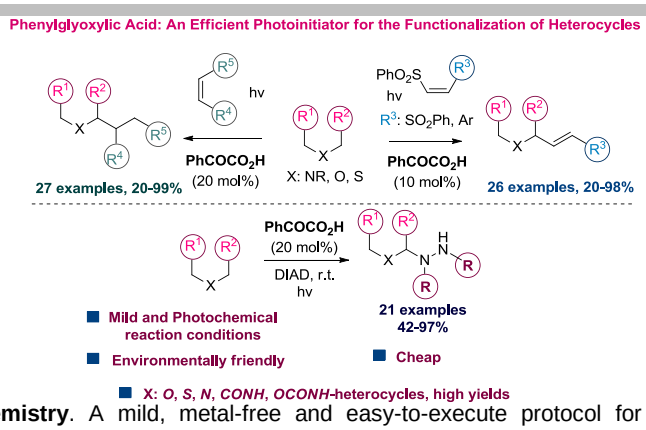

Photochemistry. A mild, metal-free and easy-to-execute protocol for the C-H functionalization of *O*-, *S*- and *N*-heterocycles.

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Phenylglyoxylic Acid: An Efficient Initiator for the Photochemical Hydrogen Atom Transfer (HAT) C-H Functionalization of Heterocycles