Photochemical C–H acetalization of *O*-heterocycles utilizing phenylglyoxylic acid as the photoinitiator

Giorgos S. Koutouligenis¹ · Nikoleta Spiliopoulou¹ · Christoforos G. Kokotos¹

Received: 29 July 2021 / Accepted: 22 October 2021 / Published online: 9 November 2021

© The Author(s), under exclusive licence to European Photochemistry Association, European Society for Photobiology 2021

Abstract

A novel, mild, metal-free and easy-to-execute procedure for the C–H acetalization of *O*-heterocycles via visible light activation is presented, utilizing phenylglyoxylic acid as the photoinitiator. Biomass-derived *O*-heterocycles, like THF, can be employed, while primary, secondary alcohols and alcohols bearing a variety of functionalities were successfully employed, affording the desired acetals in high yields. Facile acidic deprotection was also performed.

Graphical abstract

Keywords Photoorganocatalysis · Photochemical C–H acetalization · Phenylglyoxylic acid · Photoinitiator

1 Introduction

A main problem that a synthetic chemist is faced with, during a synthetic sequence, is functional group manipulation. The most efficient and widespread solution to this problem constitutes the protection–deprotection strategy. Among the most important protecting groups for alcohols is the

tetrahydropyranyl (THP) group [1]. THP is a widespread protecting group for the hydroxy moiety that can be easily removed [1]. Along the same lines, the corresponding tetrahydrofuranyl (THF) ethers have also received attention as the protecting group [2]. THF ethers have the ability to be selectively cleaved in the presence of THP ethers, since THF ethers are more sensitive to acidic conditions [3].

Except from their importance as protecting groups, acetals can be found in numerous drugs against a variety of diseases with selected examples presented in Fig. 1. Having in mind that the acetal motif is required for the development of a certain type of drugs, the need to develop novel and straightforward techniques to synthesize this type of molecules has grown bigger over the years. The most common approach to insert the THF-acetal protection with an alcohol

Dedicated to Prof. Angelo Albini on the occasion of his 75th birthday.

✉ Christoforos G. Kokotos
ckokotos@chem.uoa.gr

¹ Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, 15784 Panepistimiopolis, Zografou, Greece

Fig. 1 Acetal-containing drugs

Scheme 1 Synthetic approaches toward the protection of alcohols such as THF ethers and our design

is via a metal-catalyzed process, like the use of CrCl_2 in THF at room temperature [4]. Chromium, like most metals, suffers from relatively high cost, high toxicity and of course sensitivity to aqueous conditions. A similar approach is the use of Mn and CCl_4 under heating [5]. Manganese compounds are reported to be less toxic than other heavy metal compounds, such as nickel or copper, but they are still considered to be toxic. Along the same lines, many synthetic routes to obtain 2-alkoxy-tetrahydrofurans have been described, including the use of other transition metals, such as copper [6, 7], iron [8, 9], rhenium [10], cerium [11], palladium [12], titanium [13], vanadium [14] and aluminum [15] (Scheme 1, A). Except from the use of metals, the synthesis of 2-alkoxy-tetrahydrofuran has also been reported with *n*-tetrabutylammonium peroxy-disulfate; however, excess of the reagents were used, limiting the green character of the method [16]. Two photocatalyzed iodine-based methods were recently developed by Toste [17] and Hashmi [18] (Scheme 1, B and C). Toste and coworkers described the use

of a chiral diaryliodonium phosphite to generate controlled diastereoselective *cis*- or *trans*-fused acetals (Scheme 1, B) [17]. More recently, Hashmi and coworkers showed that under visible light irradiation and using a dimeric gold complex lead to the formation of the desired acetals of tetrahydrofuran (Scheme 1, C) [18].

Photochemistry is a fast-growing field, which is known for many years, but the last 13 years has met with exponential development [19–25]. Usually transition metal-based catalysts are employed, but in the last decade, a significant number of researchers have focused their attempts on the use of small organic molecules as photocatalysts, a field called Photoorganocatalysis [26–33]. In recent years, our group has focused its interest on utilizing effectively a variety of photocatalysts–photoinitiators in many different chemical transformations [34–37]. We have developed a cheap, easy to operate photochemical protocol, where phenylglyoxylic acid acts as the photoinitiator under irradiation by common household lamps. During the last 7 years, this venture led to a plethora of successful organic transformations [34–37]. A photochemical synthesis of lactones via C–H activation of alcohols using phenylglyoxylic acid as the photoinitiator has been reported [34]. Recently, via this PhCOCOOH -mediated photochemical protocol, C–H functionalization at the α -position of heterocycles became possible, paving the way for the design of other synthetic pathways [36, 37]. In these cases, the THF radical was employed as the nucleophile, reacting with Michael acceptors or other electrophilic reagents. Herein, we turned our interest to the functionalization of *O*-heterocycles with nucleophiles. A two-step process, involving a photochemical α -chlorination and a nucleophilic substitution by alcohol, leads to the final acetal. The crucial point is the reversal in the reactivity of THF, which now acts as electrophile (Scheme 1, D).

2 Results and discussion

In the beginning, our design plan envisaged the use of THF both as the solvent and reagent, in a reaction with carbon tetrachloride, while phenylglyoxylic acid would be employed as the photoinitiator. Thus, our design postulated the in situ generation of 2-chlorotetrahydrofuran, utilizing CCl_4 in THF via visible light irradiation. After generation of the desired 2-chlorotetrahydrofuran, a one-pot reaction with the desired alcohol in catalytic acidic conditions was foreseen, leading to the corresponding protected alcohol. In addition, this methodology would provide an entry into transforming biomass-derived solvents (THF) in common chemical intermediates. Our initial concern was whether the photoorganocatalytic C–H activation of THF is possible or not. Based on our previous studies [36, 37], and as shown in Fig. 2, this postulation is possible.

Fig. 2 Reaction progress depending on the presence of the catalyst or its absence

When a solution of CCl_4 in THF was irradiated by household bulbs, without the presence of a photocatalyst, the conversion to the product was low (18%, 4 h). When phenylglyoxylic acid was employed as the photoinitiator in a solution of THF and CCl_4 , the reaction reached its completion (as indicated by GC–MS) after 4 h, under household bulb irradiation. This result highlights the pivotal role of the photoinitiator for the C–H activation event of THF.

We then postulated that the use of an acidic additive is of great importance for the reaction's equilibrium between the formed 2-chlorotetrahydrofuran and the corresponding oxocarbenium ion, to be susceptible to nucleophilic attack. Thus, a study of the acidic additive for the specific reaction was performed, to optimize the conditions, using benzyl alcohol (Table 1). A number of organic and inorganic acids, as well as Lewis acids were employed. 1,3-Benzodithiol-1-ium tetrafluoroborate (**4 h**) and (+)-camphorsulfonic acid (CSA) (**4c**), when used in 10 mol%, resulted in the best yields of the product (Table 1, entries 3 and 8 vs 1, 2, 4–7 and 9). In an effort to further improve the reaction yield, we increased the loading of the acidic additive from 10 mol% to 20 mol%, leading to a higher yield (Table 1, entry 10). Consequently, (+)-CSA was selected for carrying out the substrate scope. Finally, we considered the possibility of substituting CCl_4 with a less toxic halogen atom source, such as bromotrichloromethane (Table 1, entry 11) or carbon tetrabromide (Table 1, entry 12), but in both cases, slightly lower yields were obtained.

After identifying the optimum reaction conditions, a variety of alcohols were employed, to study the substrate scope and see the limitations of the method (Scheme 2). A number of substituted benzylic alcohols provided the corresponding products **3a–d** in good to excellent yields. Alcohols with aliphatic chains afforded products **3e–i** in moderate to good yields. Furthermore, secondary alcohols could be employed successfully to obtain **3j–l**, proving that this protocol is not limited to primary alcohols. Benzhydrol led to low yield (45%), probably due

Table 1 Screening of acidic additives for the reaction between 2-chlorotetrahydrofuran and benzyl alcohol^a

Entry	Additive	Additive (mol%)	Yield (%) ^b
1	TsOH (4a)	10	62
2	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4b)	10	70
3	(+)-CSA (4c)	10	80
4	<i>p</i> -NBA (4d)	10	61
5	HCl, 37% (4e)	10	62
6	TFA (4f)	10	72
7	ZnCl_2 (4 g)	10	43
8	$\text{C}_7\text{H}_5\text{BF}_4\text{S}_2$ (4 h)	10	77
9	TfOH (4i)	10	10
10	(+)-CSA (4c)	20	95
11	(+)-CSA (4c)	20	93 ^c
12	(+)-CSA (4c)	20	85 ^d

^aPhenylglyoxylic acid (0.20 mmol), CCl_4 (1.00 mmol) in THF (3 mL) under CFL lamps irradiation for 4.5 h. Then, benzyl alcohol (**2a**) (1.00 mmol) and acidic additive (0.20 mmol) were added

^bYield of isolated product after column chromatography. TsOH: *p*-toluenesulfonic acid, $\text{BF}_3 \cdot \text{Et}_2\text{O}$: boron trifluoride diethyl etherate, (+)-CSA: (+)-camphorsulfonic acid, *p*-NBA: 4-nitrobenzoic acid, TFA: trifluoroacetic acid, $\text{C}_7\text{H}_5\text{BF}_4\text{S}_2$: 1,3-benzodithiol-1-ium tetrafluoroborate, TfOH: trifluoromethane sulfonic acid

^c BrCCl_3 was used instead of CCl_4

^d CBr_4 was used instead of CCl_4

Scheme 2 Scope of the photochemical C–H acetalization of THF

to its stereochemical hindrance. When (+)-menthol was employed, a 7:3 mixture of diastereomers of product **3l** was obtained.

During our investigation of the substrate scope, to expand the boundaries of the protecting group, we employed alcohols bearing a variety of functional groups, such as double and triple bond, amide, ester, ether, halogen and protected amines (Scheme 3). When 4-pent-en-1-ol was tested, the corresponding product **3m** was obtained in moderate yield (51%), but when cinammyl alcohol was used, an excellent yield of product **3n** (90%) was achieved. When propargyl alcohol was set in the reaction conditions, product **3o** was obtained in moderate yield (55%). A reason for this lower yield could be the volatility of the corresponding product. The presence of an ether group on the substrate in the reaction mixture is viable, since products **3p** and **3q** were isolated in good yields (67% and 75%, respectively). The exploration of 2-chlorotetrahydrofuran as a protecting group was also tested in the presence of *N*-protected amines or amides. The isolation of the products **3r** and **3s**, using 3-(*N*-Cbz)aminopropanol and 3-(*N*-Cbz)aminopropanol, respectively, showed that no difficulties were encountered (82% and 61%, respectively). In the same way, methyl 16-hydroxyhexadecanoate afforded product **3t** in good yield (70%) and 3-bromopropan-1-ol led to product **3u** in 72%. Protected amino acid Boc-*L*-Ser-OMe afforded the corresponding

Scheme 3 Scope of the photochemical C–H acetalization of *O*-heterocycles using alcohols bearing functional groups

product **3v** in moderate yield (53%) and as a mixture of diastereomers (1:1). Moreover, in an attempt to generalize this method, we tested its limits on other *O*-heterocycles (examples **3w–z**), affording the desired product in good yields.

As expected, the deprotection of THF-protected alcohol is quite straightforward and for the case of **3a** led to a quantitative yield (93%, 100% conversion) in 2 h, when **3a** was left stirring in HCl (1 N) at room temperature. To provide a greener alternative, the reaction mixture was set under sunlight (Scheme 4). The reaction proceeded as before and provided a quantitative conversion after 4.5 h. When sunlight irradiation was employed without adding the catalyst, no reaction occurred, verifying once again the need for a photoinitiator. Both experiments were performed in Athens, Greece [(37.97°N, 23.72°E) in 13/5/2021 from 11:00 to 15:30]. Moreover, to demonstrate the applicability of this method, a synthetically useful scale experiment (10 mmol) was performed, receiving the desired product in high yield (77% isolated yield). Also, the radical nature of this reaction was confirmed, since TEMPO or BHT was added in the reaction mixture and the product was not formed.

We next turned our attention on deciphering the reaction mechanism. Initially, UV–Vis experiments were performed [38]. The UV–Vis absorbance was measured for each of the reaction's components separately, utilizing concentrations close to the actual reaction conditions. It has been reported that the chemical interaction of an electron-rich molecule with an electron-poor compound can form a new complex, called electron donor–acceptor (EDA) complex, without the application of irradiation [39–42]. EDA complexes have been reported in literature since the 1950s [39–42], but only recently Melchiorre and others identified them as active intermediates in Photochemistry [43–47]. In the case we are examining herein, no difference at the UV absorbance was identified after mixing the reaction components, hinting that the reaction mechanism was not proceeding via an EDA

Scheme 4 Reaction under sunlight with and without catalyst and mechanistic experiments

Scheme 5 Proposed mechanism of the reaction

complex. Thus, the only compound that can absorb above 300 nm is PhCOCO2H.

After the UV–Vis studies, mechanistic ^1H - and ^{13}C -NMR experiments were performed [38]. Having in mind our previous mechanistic studies in methanol [34], H_2O [35], and THF [36, 37], and the experiments we rerun herein, we can conclude that the main photodecomposition product of phenylglyoxylic acid in THF is its dimer (diphenyltartaric acid) and in a smaller quantity is benzaldehyde. These two photodecomposition products of PhCOCO2H can be observed both in the spectra of the irradiation of the photoinitiator and of the reaction mixture. Taking into consideration our previous results [34–37] and the data from these NMR mechanistic studies of the reaction, we can conclude that PhCOCO2H photodecomposes mainly to a ketyl radical and less to a benzoyl radical in THF. These radicals are responsible for the initiation of the studied process.

Putting all these data together, the proposed mechanism of this photochemical C–H acetalization reaction is shown below (Scheme 5). Initially, upon irradiation, phenylglyoxylic acid is excited to the singlet state **I** and via intersystem crossing (ISC) to its triplet state **II**. Then, the excited PhCOCO2H is decomposed mainly to phenyltartaric acid via ketyl radical **IV** and to a lesser extent to benzaldehyde via benzoyl radical **III**. Ketyl radical **IV** or benzoyl radical **III** can then abstract a hydrogen atom from THF, which acts as a HAT donor, leading to α -THF radical **V**, which initiates the process. α -THF radical **V** reacts with a molecule of CCl_4 to afford the desired intermediate **1a** or its corresponding oxocarbenium ion (in equilibrium with **1a** via an acid-catalyzed pathway) and radical **VI**. Radical **VI** can then sustain the radical propagation via reaction with THF (leading to **V** and CHCl_3 , whose presence was detected in small amounts by GC–MS). Alternatively, radical **VI** can decompose in the presence of air to chlorine radical **VII** [48, 49], and this can

also sustain the propagation with THF [50] (leading to **V** and HCl , whose presence was also detected by GC–MS). CHCl_3 can also break down to HCl in the presence of irradiation and air [51]. Once all CCl_4 is consumed, the acid-catalyzed process pushes the equilibrium toward the oxocarbenium ion, which quickly reacts with the nucleophilic alcohol, leading to product formation. We postulate that the acid additive acts via weakening the C–Cl bond of **1a** via hydrogen bonding between the lone pair of the chloride and the acidic proton $[\text{OC} \cdots \text{Cl} \cdots \text{H} - \text{A}]$.

3 Conclusions

In conclusion, a novel metal-free photochemical C–H activation of THF and in general *O*-heterocycles was developed. Utilizing phenylglyoxylic acid (cheap and small organic molecule) as the photoinitiator and sunlight irradiation (or household bulb irradiation), a facile derivatization of the biomass-derived solvent THF into protected alcohols was described. Formation of the 2-chlorotetrahydrofuran via the HAT process was described. A plethora of alcohols bearing various functionalities were employed successfully, leading to products in high yields. Furthermore, mechanistic studies were performed to propose a viable reaction mechanism.

4 Experimental section

4.1 General remarks

Chromatographic purification of products was accomplished using forced-flow chromatography on Merck® Kieselgel 60 F_{254} 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminum-backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, ninhydrin or potassium permanganate stains. Melting points were determined on a Buchi® 530 hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a Finnigan® Surveyor MSQ LC–MS spectrometer. HRMS spectra were recorded on Bruker® Maxis Impact QTOF spectrometer. ^1H - and ^{13}C -NMR spectra were recorded on Varian® Mercury (200 MHz and 50 MHz, respectively) or an Avance III HD Bruker 400 MHz (400 MHz and 100 MHz, respectively), and are internally referenced to residual solvent signals. Data for ^1H -NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal), coupling constant and assignment. Data for ^{13}C -NMR are reported in terms of chemical shift (δ ppm). Mass spectra and conversions of the reactions were recorded on a Shimadzu® GCMS-QP2010 Plus Gas

Chromatograph Mass Spectrometer utilizing a MEGA® column (MEGA-5, F.T.: 0.25 μ m, I.D.: 0.25 mm, L: 30 m, T_{max}: 350 °C, Column ID# 11,475). A Varian® Cary 50 UV–Vis spectrophotometer was used for the UV–Vis data.

4.2 General procedure for the photochemical acetalization of O-heterocycles

Phenylglyoxylic acid (30 mg, 0.20 mmol) was placed in a normal glass tube followed by carbon tetrachloride (153 mg, 1.00 mmol) and O-heterocycle (3 mL). The reaction mixture was left stirring under light irradiation (2 × 85 W household lamps) for 4.5 h. After the reaction was completed (as indicated by GC–MS), the reaction mixture was removed from light irradiation and (+)-camphorsulfonic acid (46 mg, 0.20 mmol) was added, followed by the addition of freshly distilled or purified alcohol (1.00 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo and the crude product was purified using flash column chromatography (Pet. Eth.–EtOAc 8:2 or Pet. Eth.–EtOAc 5:5 or Pet. Eth.–EtOAc 3:7).

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s43630-021-00126-7>.

Acknowledgements The authors gratefully acknowledge the Hellenic Foundation for Research and Innovation (HFRI) for financial support through a grant, which is financed by 1st Call for H.F.R.I. Research Projects to Support Faculty Members and Researchers and the procurement of high-cost research equipment grant (grant number 655). G. S. K. would like to thank Stavros Niarchos Foundation (SNF) for financial support through a PhD Fellowship grant. N. S. would like to thank the Hellenic Foundation for Research and Innovation (HFRI) for financial support through a doctoral by the Hellenic Foundation for Research and Innovation (HFRI) through a PhD Fellowship grant (Fellowship Number: 721).

Declarations

Conflict of interest The authors declare no conflict of interest.

References

- Greene, T. W., & Wuts, P. G. M. (1999). *Protective Groups in Organic Synthesis*. Vol. 3 (Eds.: John Wiley & Sons, Inc.). Wiley-Interscience, New York. 49.
- For a book see: (a) Greene, T. W., & Wuts, P. G. M. (1999). *Protective Groups in Organic Synthesis*. Vol. 3 (Eds.: John Wiley & Sons, Inc.). Wiley-Interscience, New York. 57.
- Barks, J. M., Gilbert, B. C., Parsons, A. F., & Upeandran, B. (2000). An efficient and extremely mild method for protecting alcohols as 2-tetrahydrofuranyl ethers. *Tetrahedron Letters*, 41(32), 6249–6252. [https://doi.org/10.1016/S0040-4039\(00\)01045-5](https://doi.org/10.1016/S0040-4039(00)01045-5)
- Baati, R., Valleix, A., Mioskowski, C., Barma, D. K., & Falck, J. R. (2000). A convenient synthesis of 2-tetrahydrofuranyl ethers. *Organic Letters*, 2(4), 485–487. <https://doi.org/10.1021/ol991332f>
- Falck, J. R., Li, D. R., Bejot, R., & Mioskowski, C. (2006). An economic and practical synthesis of the 2-tetrahydrofuranyl ether protective group. *Tetrahedron Letters*, 47(29), 5111–5113. <https://doi.org/10.1016/j.tetlet.2006.05.081>
- Kumar, G. S., Pieber, B., Reddy, K. R., & Kappe, O. C. (2012). Copper-catalyzed formation of C–O bonds by direct α -C–H bond activation of ethers using stoichiometric amounts of peroxide in batch and continuous-flow formats. *Chemistry a European Journal*, 18(20), 6124–6128. <https://doi.org/10.1002/chem.201200815>
- Barve, B. D., Wu, Y.-C., El-Shazly, M., Korinek, M., Cheng, Y.-B., Wang, J.-J., & Chang, F.-R. (2015). Copper-catalyzed selective C–O bond formation by oxidative α -C(sp³)-H/O–H coupling between ethers and salicylaldehydes. *Tetrahedron*, 71(15), 2290–2297. <https://doi.org/10.1016/j.tet.2015.02.035>
- Behbahani, F. K., & Farahani, M. (2011). Anhydrous FePO₄ as a cost-effective and recyclable catalyst for tetrahydropyranlation and tetrahydrofuranlation of alcohols and phenols. *Letters in Organic Chemistry*, 8(6), 431–435. <https://doi.org/10.2174/157017811796064485>
- Barve, B. D., Wu, Y.-C., El-Shazly, M., Korinek, M., Cheng, Y.-B., Wang, J.-J., & Chang, F.-R. (2014). Iron-catalyzed oxidative direct α -C–H bond functionalization of cyclic ethers: selective C–O bond formation in the presence of a labile aldehyde group. *Organic Letters*, 16(7), 1912–1915. <https://doi.org/10.1021/ol5004115>
- Sittiwong, W., Richardson, M. W., Schiaffo, C. E., Fischer, T. J., & Dussault, P. H. (2013). Re₂O₇-catalyzed reaction of hemiacetals and aldehydes with O-, S-, and C-nucleophiles. *Beilstein Journal of Organic Chemistry*, 9, 1526–1532. <https://doi.org/10.3762/bjoc.9.174>
- Maione, A. M., & Romeo, A. (1987). Cerium (IV)-mediated synthesis of tetrahydrofuranyl ethers. *Synthesis*, 3, 250–251. <https://doi.org/10.1055/s-1987-27903>
- Troisi, L., Granito, C., Ronzini, L., Rosato, F., & Videtta, V. (2010). An economic and efficient tetrahydrofuranlation of alcohols, imines and alkynes. *Tetrahedron Letters*, 51(46), 5980–5983. <https://doi.org/10.1016/j.tetlet.2010.09.014>
- Durán-Peña, M. J., Botubol-Ares, J. M., Hanson, J. R., Hernández-Galán, R., & Collado, I. G. (2015). Unexpected mild protection of alcohols as 2-O-THF and 2-O-THP ethers catalysed by Cp₂TiCl reveal an intriguing role of the solvent in the Single-Electron Transfer reaction. *European Journal of Organic Chemistry*, 6333–6340. <https://doi.org/10.1002/ejoc.201500869>
- Das, B., Krishnaiah, M., Reddy, V. S., & Laxminarayana, K. (2007). Vanadium(III) chloride (VCl₃): Efficient reagent for the introduction of tetrahydrofuran-based acetal protecting groups for alcohols. *Helvetica Chimica Acta*, 90(11), 2163–2166. <https://doi.org/10.1002/hlca.200790223>
- Williams, D. B. G., Simelane, S. B., M. Lawton, M., & Kinfe, H. H. (2010). Efficient tetrahydropyranyl and tetrahydrofuranyl protection/deprotection of alcohols and phenols with Al(OTf)₃ as catalyst. *Tetrahedron*, 66(25), 4573–4576. <https://doi.org/10.1016/j.tet.2010.04.053>
- Jung, J. C., Choi, H. C., & Kim, Y. H. (1993). Direct facile tetrahydrofuranlation of alcohols through radical coupling with (Bu₄N)₂S₂O₈. *Tetrahedron Letters*, 34(22), 3581–3584. [https://doi.org/10.1016/S0040-4039\(00\)73641-0](https://doi.org/10.1016/S0040-4039(00)73641-0)
- Ye, B., Zhao, J., Zhao, K., McKenna, J. M., & Toste, F. D. (2018). Chiral diaryliodonium phosphate enables light driven diastereoselective α -C(sp³)-H Acetalization. *Journal of the American Chemical Society*, 140(26), 8350–8356. <https://doi.org/10.1021/jacs.8b05962>
- Xiaojia, S., Lumin, Z., Zuozuo, W., Matthias, R., Abdullah, M. A., & Hashmi, A. S. K. (2020). Visible light-induced α -C(sp³)-H acetalization of saturated heterocycles catalyzed by

- a dimeric gold complex. *Organic Letters*, 22(15), 5844–5849. <https://doi.org/10.1021/acs.orglett.0c01924>
19. Prier, C. K., Rankic, D. A., & MacMillan, D. W. C. (2013). Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chemical Reviews*, 113(7), 5322–5363. <https://doi.org/10.1021/cr300503r>.
 20. Scubi, K. L., Blum, T. R., & Yoon, T. P. (2016). Dual catalysis strategies in photochemical synthesis. *Chemical Reviews*, 116(17), 10035–10074. <https://doi.org/10.1021/acs.chemrev.6b00018>
 21. Kärkäs, M. D., Porco, J. A., Jr., & Stephenson, C. R. J. (2016). Photochemical approaches to complex chemotypes: applications in natural product synthesis. *Chemical Reviews*, 116(17), 9683–9747. <https://doi.org/10.1021/acs.chemrev.5b00760>
 22. Cambie, D., Bottecchia, C., Straathof, N. J. W., Hssel, V., & Noel, T. (2016). Applications of continuous-flow photochemistry in organic synthesis, material science and water treatment. *Chemical Reviews*, 116(17), 10276–10341. <https://doi.org/10.1021/acs.chemrev.5b00707>
 23. Hopkinson, M. N., Tlahuext-Aca, A., & Glorius, F. (2016). Merging visible light photoredox and gold catalysis. *Accounts of Chemical Research*, 49(10), 2261–2272. <https://doi.org/10.1021/acs.accounts.6b00351>
 24. Ravelli, D., Protti, S., & Fagnoni, M. (2016). Decatungstate anion for photocatalyzed “window ledge” reactions. *Accounts of Chemical Research*, 49(10), 2232–2242. <https://doi.org/10.1021/acs.accounts.6b00339>
 25. Schwarz, J., & König, B. (2018). Decarboxylative reactions with and without light—a comparison. *Green Chemistry*, 20, 323–361. <https://doi.org/10.1039/C7GC02949G>
 26. Fagnoni, M., Dondi, D., Ravelli, D., & Albini, A. (2007). Photocatalysis for the formation of the C–C bond. *Chemical Reviews*, 107(6), 2725–2756. <https://doi.org/10.1021/cr068352x>.
 27. Ravelli, D., Fagnoni, M., & Albini, A. (2013). Photoorganocatalysis. What for? *Chemical Society Reviews*, 42, 97–113. <https://doi.org/10.1039/C2CS35250H>
 28. Romero, N. A., & Nicewicz, D. A. (2016). Organic photoredox catalysis. *Chemical Reviews*, 116(17), 10075–10166. <https://doi.org/10.1021/acs.chemrev.6b00057>
 29. Ravelli, D., Protti, S., & Fagnoni, M. (2016). Carbon–carbon bond forming reactions via photogenerated intermediates. *Chemical Reviews*, 116(17), 9850–9913. <https://doi.org/10.1021/acs.chemrev.5b00662>
 30. Silvi, M., & Melchiorre, P. (2018). Enhancing the potential of enantioselective organocatalysis with light. *Nature*, 554, 41–49. <https://doi.org/10.1038/nature25175>
 31. Sideri, I. K., Voutyritsa, E., & Kokotos, C. G. (2018). Photoorganocatalysis, small organic molecules and light in the service of organic synthesis: the awakening of a sleeping giant. *Organic and Biomolecular Chemistry*, 16, 4596–4614. <https://doi.org/10.1039/C8OB00725J>.
 32. Theodoropoulou, M. A., Nikitas, N. F., & Kokotos, C. G. (2020). Aldehydes as powerful initiators for photochemical transformations. *Beilstein Journal of Organic Chemistry*, 16, 833–857. <https://doi.org/10.3762/bjoc.16.76>
 33. Nikitas, N. F., Gkizis, P. L., & Kokotos, C. G. (2021). Thioxanthone: a powerful photocatalyst for organic reactions. *Organic and Biomolecular Chemistry*, 19, 5237–5253. <https://doi.org/10.1039/D1OB00221J>
 34. Kaplaneris, N., Bisticha, A., Papadopoulos, G. N., Limnios, D., & Kokotos, C. G. (2017). Photoorganocatalytic synthesis of lactones via a selective C–H activation-alkylation of alcohols. *Green Chemistry*, 19(18), 4451–4456. <https://doi.org/10.1039/C7GC01903C>
 35. Voutyritsa, E., & Kokotos, C. G. (2020). Green metal-free photochemical hydroacylation of unactivated olefins. *Angewandte Chemie International Edition*, 59(4), 1735–1741. <https://doi.org/10.1002/anie.201912214>
 36. Papadopoulos, G. N., Kokotou, M. G., Spiliopoulou, N., Nikitas, F. N., Voutyritsa, E., Tzaras, D. I., Kaplaneris, N., & Kokotos, C. G. (2020). Phenylglyoxylic acid: An efficient initiator for the photochemical hydrogen atom transfer C–H functionalization of heterocycles. *ChemSuschem*, 13(22), 5934–5944. <https://doi.org/10.1002/cssc.202001892>
 37. Voutyritsa, E., Garreau, M., Kokotou, M. G., Triandafillidi, I., Waser, J., & Kokotos, C. G. (2020). Photochemical functionalization of heterocycles with EBX reagents: C–H alkynylation versus deconstructive ring cleavage. *Chemistry A European Journal*, 26(63), 14453–14460. <https://doi.org/10.1002/chem.202002868>
 38. For more information about the mechanistic experiments, see supporting information.
 39. Mulliken, R. S. (1952). Molecular compounds and their spectra. III. The interaction of electron donors and acceptors. *The Journal of Physical Chemistry*, 56(7), 801–822. <https://doi.org/10.1021/j150499a001>.
 40. Gould, I. R., & Farid, S. (1996). Dynamics of bimolecular photoinduced electron-transfer reactions. *Accounts of Chemical Research*, 29(11), 522–528. <https://doi.org/10.1021/ar950053z>
 41. Farid, S., Dinnocenzo, J. P., Merkel, P. B., Young, R. H., & Shukla, D. (2011). Bimolecular electron transfers that follow a Sandros-Boltzmann dependence on free energy. *Journal of the American Chemical Society*, 133(13), 4791–4801. <https://doi.org/10.1021/ja104536j>
 42. Farid, S., Dinnocenzo, J. P., Merkel, P. B., Young, R. H., Shukla, D., & Guirado, G. (2011). Reexamination of the Rehm-Weller data set reveals electron transfer quenching that follows a Sandros-Boltzmann dependence on free energy. *Journal of the American Chemical Society*, 133(30), 11580–11587. <https://doi.org/10.1021/ja2024367>
 43. Arceo, E., Jurberg, I. D., Álvarez-Fernández, A., & Melchiorre, P. (2013). Photochemical activity of a key-donor-acceptor complex can drive stereoselective catalytic α -alkylation of aldehydes. *Nature Chemistry*, 5, 750–756. <https://doi.org/10.1038/nchem.1727>
 44. Arceo, E., Bahamonde, A., Bergonzini, G., & Melchiorre, P. (2014). Enantioselective direct α -alkylation of cyclic ketones by means of photo-organocatalysis. *Chemical Science*, 5(6), 2438–2442. <https://doi.org/10.1039/C4SC00315B>
 45. Nappi, M., Bergonzini, G., & Melchiorre, P. (2014). Metal-free photochemical aromatic perfluoroalkylation of α -cyanoaryllacetates. *Angewandte Chemie International Edition*, 53(19), 4921–4925. <https://doi.org/10.1002/anie.201402008>
 46. Kandukuri, S. R., Bahamonde, A., Chatterjee, I., Jurberg, I. D., Escudero-Adán, E. C., & Melchiorre, P. (2015). X-Ray characterization of an electron donor-acceptor complex that drives the photochemical alkylation of indoles. *Angewandte Chemie International Edition*, 54(5), 14851489. <https://doi.org/10.1002/anie.201409529>
 47. Spell, M. L., Devenaux, K., Bresnahan, C. G., Bernard, B. L., Sheffield, W., Kumar, R., & Ragains, J. R. (2016). A visible-light-promoted *O*-glycosylation with a thioglycoside donor. *Angewandte Chemie International Edition*, 55(22), 6515–6519. <https://doi.org/10.1002/anie.201601566>
 48. Pavlik, J. O., Plooard, P. I., Somersall, A. C., & Guillet, J. E. (1973). Photochemistry of ketones in carbon tetrachloride solution. *Canadian Journal of Chemistry*, 51, 1435–1440. <https://doi.org/10.1139/v73-216>.
 49. Kuchmii, S. Y., Kulik, S. V., Korzhak, A. V., Beious, A. I., & Kryukov, A. I. (1989). Photochemical and photocatalytic reactions of carbon tetrachloride with alcohols. *Theoretical and Experimental Chemistry*, 25, 627–632. <https://doi.org/10.1007/BF00534442>.

50. Begum, S., & Subramanian, R. (2014). Reaction of chlorine radical with tetrahydrofuran: a theoretical investigation on mechanism and reactivity in gas phase. *Journal of Molecular Modeling*, 20, 2262–2273. <https://doi.org/10.1007/s00894-014-2262-0>.
51. Liang, F., Yanai, M., Suzuki, Y., & Tsuda, A. (2020). Photo-on-demand synthesis of chloroformates with a chloroform solution containing an alcohol and its one-pot conversion to carbonates and carbamates. *Organic Letters*, 22, 3566–3569. <https://doi.org/10.1021/acs.orglett.0c01013>.