

Remote Giese Radical Addition by Photocatalytic Ring Opening of Activated Cycloalkanols

Noelia Salaverri,^a Benedetta Carli,^a Patricia B. Gratal,^a Leyre Marzo,^{a, b, *} and José Alemán^{a, b, c, *}

^a Organic Chemistry Department, Módulo 1, Universidad Autónoma de Madrid, 28049 Madrid, Spain

^b Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Madrid 28049, Spain

^c Center for Innovation in Advanced Chemistry (ORFEO-CINQA), Universidad Autónoma de Madrid, Madrid 28049, Spain
Phone: 914973875

E-mail: leyre.marzo@uam.es; jose.aleman@uam.es

Manuscript received: February 28, 2022; Revised manuscript received: March 23, 2022;

Version of record online: ■■■, ■■■



Supporting information for this article is available on the WWW under <https://doi.org/10.1002/adsc.202200220>

© 2022 The Authors. Advanced Synthesis & Catalysis published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Abstract: The application of proton coupled electron transfer (PCET) processes in organic synthesis has opened the door to new radical intermediates for synthesis such as alkyl radicals in remote positions to a ketone. Herein, we present the addition of these remote alkyl radicals to electron deficient double bonds under photoorganocatalyzed and very mild conditions. The method is not only applicable to deactivated double bonds, but monoactivated ones are also accessible using more stabilized alkyl radicals, and alkyl chains of any length can be introduced. The final products can be easily converted into more complex structures via a one-pot process, and the activating functional groups were transformed in the more versatile methyl esters. Mechanistic investigations support a mechanistic proposal based on a PCET process.

Keywords: Giese radical addition; PCET; Visible light; Photocatalysis

The activation of C–C bonds is a challenging task in organic synthesis due to their inertness and universality. However, its enormous synthetic potential is evidenced by the simplification of the synthetic routes for the construction of more complex molecules.^[1] The addition of transient alkyl radicals to electron deficient double bonds, known as the Giese reaction, is a well

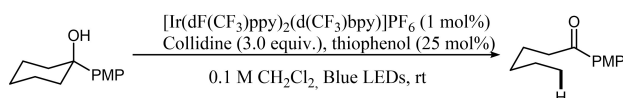
established transformation extensively described over the years.^[2]

In order to generate remote alkyl radicals,^[3] several methods have been developed, such as via metal mediated promoters^[4] or via photoredox catalysis.^[5] Among the photocatalytic methods, different approaches are applied to generate the alkyl radicals in remote positions.^[6] One of the approaches consists of the formation of an alkoxy radical and consecutive β–C–C bond scission,^[7] which has become a common strategy in the ring opening of strained and unstrained cycloalkanols. This method usually proceeds via a ligand to metal charge transfer (LMCT) process,^[8] or a proton coupled electron transfer (PCET).^[9] It allows the creation of new C-centered radicals in remote positions of ketones, regardless the size of the ring. The LMCT process was initially described by Zuo with CeCl₃ as photocatalyst in the amination or the formal cycloaddition of the remote alkyl radicals with alkenes.^[8a,b] Some years ago, Knowles described the proton coupled electron transfer (PCET) strategy as a redox neutral and an atom economical approach to activate alcohols (Figure 1A).^[9] This second strategy is based on the decrease of the activation barrier in the oxidation step upon coordination of the alcohol to the base, favoring this single electron transfer step (SET) that generates the alkoxy radical, followed by the β–C–C bond scission to afford the hydrogenated ketone. This method has been employed for the arylation,^[10a] halogenation^[10b] and allylation^[10c] of ketones in remote positions (Figure 1B).^[10] Based on our experience in the field of photocatalysis,^[11] here we present a general

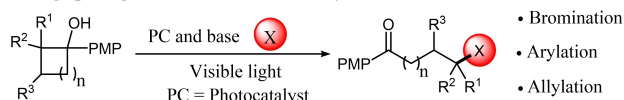
method to introduce remote transient alkyl radicals in electron deficient double bonds under very mild conditions with an organic-photocatalyst for the reaction (Figure 1C).

After intensive optimization of the reaction conditions, 5 mol% of the [Mes-Acr]ClO₄ as photo-

A. Ring opening of unstrained cycloalkanols by PCET



B. Ring opening and functionalization of cycloalkanols



C. This work: Ring opening and remote Giese addition to Michael acceptors

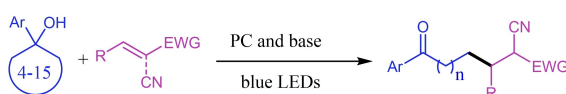


Figure 1. Generation and further functionalization of alkyl radicals in remote positions of ketones through PCET. A) PCET for the oxidative ring opening of cycloalkanols; B) remote allylation, halogenation and arylation of ketones; C) ring opening and remote radical addition to electron deficient double bonds.

Table 1. Optimization of the reaction conditions.^[a]

Entry	Deviation from standart conditions	Yield (%)
1	None	96
2	No light	n.r.
3	No PC	n.r.
4	No base	n.r.
5	In air	56
6	2,4,6-collidine as base	82
7	TBA ⁺ (Bu ₃ O)POO ⁻ as base	n.r.
8	CS ₂ CO ₃ as base	n.r.
9	3CzCIIPN as PC	n.r.
10	Ru(bpz) ₃ as PC	n.r.
11	[Ir(dF(CF ₃)ppy) ₂ (d(CF ₃)bpy)]PF ₆ as PC	99
12	2a (1.5 equiv.)	91

^[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Mes-Acr]ClO₄ (5 mol%), 2,6-lutidine (25 mol%), CH₂Cl₂ (1 mL), 455 nm LED, 20 °C.

catalyst, 25 mol% of 2,6-lutidine as base, in CH₂Cl₂ as solvent (0.1 M), at 20 °C under blue LED irradiation for 17 hours afforded the desired product **3a** in 96% yield (Table 1, entry 1). The photocatalytic nature of the reaction was confirmed when no conversion was obtained in the absence of light or photocatalyst (entries 2 and 3). The lack of reactivity in the absence of base evidenced the PCET process (entry 4). In the presence of air, the yield decreased to 56% but byproducts were not observed (entry 5). Other bases typically employed in PCET processes did not improve this result (entries 6–8). In addition, with other photocatalysts with lower oxidation power the reaction did not work except for the iridium catalyst, that afforded a slightly better yield (entries 9–11). However, we finally chose the cheaper organic photocatalyst instead of the transition metal catalyst. Therefore, we continued the optimization using the Fukuzumi's catalyst. Finally, decreasing the amount of Michael acceptor slightly decreased the yield of the process (entry 12).

With the optimal conditions in hand, we proceeded to study the scope of the reaction (Table 2). First, different cycloalkanols **1** were reacted with **2a**. Cycloalkanols of different sizes underwent this reactivity affording the final products in moderate to very good yields (**3a–f**). In addition, the reaction between **1a** and **2a** could be scaled up to 1 mmol with just a slight decrease in the reactivity (see SI for the set-up of this reaction, Figure S2). To further prove the robustness of the method other (hetero)arenes were employed instead of the PMP to form the initial (hetero)aryl radical cation. Thus, a furane, benzofurane or phenanthrene could be successfully oxidized to its radical cation to further generate the corresponding alkyl radical that afforded the final products **3g–i** in very good to excellent yields.^[12] Starting from five- or six-membered cyclic alcohols bearing a heteroatom (oxygen, sulfur or Boc-protected amine) in the β-position, a complete regioselectivity for the C–C bond scission α to the heteroatom is observed, forming the most stabilized alkyl radical and affording the final products in moderate to good yields (**3j–l**). Identical regioselectivity in the C–C bond scission step was observed when carrying out the reaction with α-substituted cycloalkanols, generating the most stabilized secondary alkyl radical that afforded a 1:1 mixture of the two possible diastereoisomers in good yield (**3m**). In addition, the transient alkyl radical could be also generated even when the arene was placed in a more distant position, obtaining **3n** in moderate yield as a 1:1 mixture of the two diastereoisomers. Next, a variety of deactivated double bonds **2** in their reaction with **1a** were evaluated (middle-Table 2). In addition to the nitrile, we could use as the second EWG an ester, a ketone, a sulfone or a second nitrile (**3o–q**), obtaining in all these cases a very good yield. In addition, the disulfonyl derivative also underwent this reactivity

Table 2. Substrate scope of the reaction and Late Stage Functionalization of natural products.^[a]

Alcohols	
Ring sizes	
(Hetero)arenes	
β-heteroatoms	
α-substituted	
Michael acceptors	
EWG	
(Hetero)arenes	
Alkyl	
Limitations	
Late Stage Functionalization	

[a] Standard reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Mes-Acr]ClO₄ (5 mol%), 2,6-lutidine (25 mol%), CH₂Cl₂ (1 mL), 455 nm LED, 20 °C. [b] Reaction at 1 mmol scale of **1a**.

(**3r**) with 30% yield. Moreover, EWG-substituted arenes or electron deficient heteroarenes could be employed as the second activating group of the double bond **2**. Thus, with the strong electron withdrawing *p*-nitrobenzene *p*-nitrobenzene or the pyridine, the desired adducts were obtained in good yields (**3s**, **3u**), while with the less activating CF₃ allowed the synthesis of **3t** in moderate yield. Next, different arenes in the β-position of the Michael acceptor were studied (**3v–3ai**). In general, either electron donating or with-

drawing substituents in *ortho*, *meta* or *para* position were well tolerated, affording the final products in excellent yields, but lower yields were found with the use of strong electron donating group (*p*-methoxy, **3z**), or the mesityl substituent that presented a higher steric hindrance (**3ac**). Moreover, the reaction also tolerated the presence of heteroaryl substituents, obtaining higher yields with electron deficient heteroarenes such as the pyridine (**3ag**) than with the electron rich ones such as the furane or the thiophene (**3ah**, **3ai**).

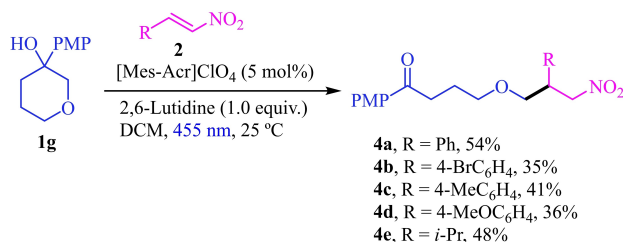
Primary, secondary or tertiary alkyl substituents were also employed, but the final products were obtained in moderate yields (**3aj–3al**). The reaction also presented some limitations related to the electron withdrawing groups that can activate the double bond. Thus, with a malonate, a diester, diketone, or a β -nitrilo phosphonate, the reaction did not work (bottom-left, Table 2). To further prove the applicability of the method in late-stage functionalization strategies, two natural products were subjected to these reaction conditions. Thus, the reaction was performed with a derivative of the hormone estrone and with the (*D*)-camphor, and in both cases the C–C bond scission step took place with a complete regioselectivity for the formation of the most stable radical, that is the most substituted one. The final products **3am** and **3an** were obtained in moderate yields as a 1:1 or 2:1 mixture of diastereoisomers, respectively.

In addition, we also explored the use of mono-activated double bonds. Thus, starting from the more stabilized α -alkoxy radical precursor **1g** under the standard reaction conditions the phenyl, *p*-bromo, *p*-methyl or *p*-methoxy nitro styrene, as well as the 3-methyl nitrobutene were successfully functionalized, albeit with moderate yields (Scheme 1, **4a–e**).

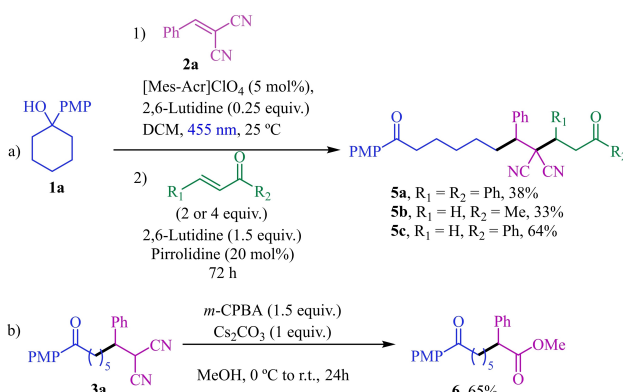
Then, taking advantage of the nucleophilic nature of the malononitrile moiety present in several of the

final products **3**, which is a nucleophile traditionally employed in organocatalysis, it was possible to further functionalize them through a consecutive one-pot Michael addition. Thus, starting from **1a** and **2a**, after the photocatalytic reaction was completed, chalcone, butanone or 1-phenyl propanone were added to the reaction mixture, together with 20 mol% of pyrrolidine and 1.5 equiv. of 2,6-lutidine. After 72 hours, the final products **5a–c** were obtained with moderate to good yields (Scheme 2a). In addition, to further prove the utility of the final products, it was possible to transform the malononitrile present in **3a**, into the versatile methyl ester group in very good yield by oxidative dehomologation with *m*-CPBA and Cs_2CO_3 (**6**, Scheme 2b).^[13]

Finally, the mechanism of the reaction was studied (Scheme 3). First, it was examined the formation of the hydrogen bond between the base and the alcohol **1a** by H-NMR. Upon increasing concentrations of 2,6-lutidine, the signal corresponding to the O–H that appears at 0.98 ppm in C_6D_6 , suffers a bathochromic shift, thus corroborating that the required interaction for the PCET event between the base and the alcohol was taking place (see SI).^[10a] Next, we examined which species is the one that interacts with the excited photocatalyst. The oxidation potential of the **1a** is 1.41 V vs SCE (see SI), thus, the photocatalyst is able to oxidize it. To confirm it, fluorescence quenching studies of the alcohol alone and a mixture of the alcohol and the base were carried out, observing in

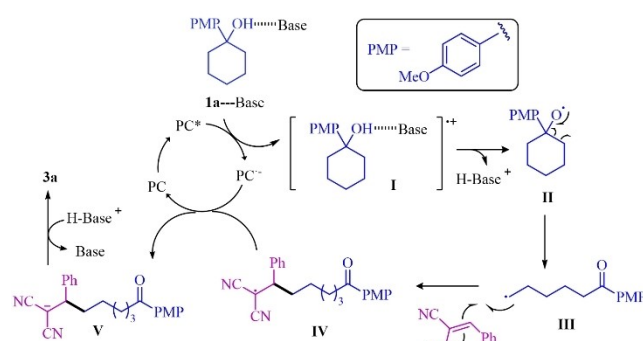


Scheme 1. Reaction between stabilized alkyl radicals and nitro olefines.

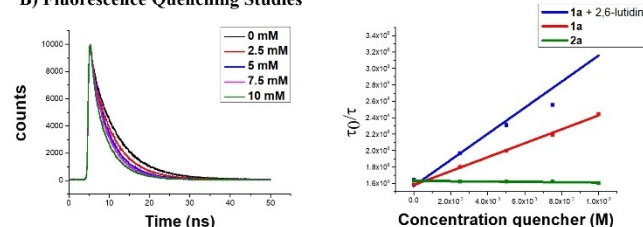


Scheme 2. One pot photo-organocatalyzed reactions and derivatization of compound **3a**.

A) Mechanism Proposal



B) Fluorescence Quenching Studies



Scheme 3. Mechanistic proposal and fluorescence quenching studies.

both cases an efficient quenching of the excited photocatalyst (Scheme 3b and SI).

Thus, and in accordance to previous literature reports,^[9a] upon visible light irradiation, the photocatalyst reaches the excited state from where it oxidizes the *p*-methoxyphenyl ring, forming the radical cation intermediate **I** (Scheme 3a). Then, concerted electron transfer and deprotonation by the base takes place, forming the alkoxy radical **II** that evolves through the β -C–C bond scission to form the alkyl radical **III**. This alkyl radical reacts with **2a**, forming the radical intermediate **IV**. After oxidation of the radical anion of the photocatalyst to reduce **IV** closes the catalytic cycle and affords the anionic intermediate **V**, yielding after protonation **3a**. A quantum yield of 0.03 was found, suggesting that no significant radical chain is taking place under these photocatalytic conditions.

To sum up, a methodology to introduce alkyl radicals generated in remote position of ketones into electron deficient double bonds has been described. A broad variety of alcohols underwent this reactivity to form primary and secondary alkyl radicals, or radicals in α position to a heteroatom. In addition, cycloalkanols of different sizes afforded good results being possible to introduce alkyl radicals of any length. Similarly, a large variety of aryl or alkyl substituted deactivated double bonds underwent the reaction with good results, and also monoactivated double bonds could be functionalized with the more stabilized α -alkoxy radical. Moreover, the final products could be further functionalized through a one-pot reaction, or under oxidative conditions to transform the activating groups in the more versatile methyl esters. Finally, a PCET type mechanism is proposed and supported by mechanistic studies.

Experimental Section

General procedure A for the photocatalytic reaction

A dry vial equipped with a magnetic stir bar was charged with the corresponding alcohol (0.1 mmol, 1.0 equiv.), corresponding alkene (0.2 mmol, 2.0 equiv.), 2,6-lutidine (3 μ L, 0.025 mmol, 0.25 equiv.), 9-mesityl-10-methylacridinium perchlorate [$\text{Acr}^+\text{-Mes}$] (2 mg, 0.005 mmol, 5 mol%) and 1.0 mL of DCM (0.1 M). Degasification of the reaction mixture was performed via freeze-pump-thaw cycling (3×10 min under vacuum). Then, the reaction mixture was irradiated and stirred in the photo-reactor setup under 465 nm LED for 17 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel) to provide the product.

Acknowledgements

Financial support was provided by the Spanish Government (RTI2018-095038 – B–I00, PID2019-110091GB–I00), “Comunidad de Madrid”, and European Structural Funds (S2018/

NMT-4367) and proyectos sinérgicos I+D (Y2020/NMT-6469) and Comunidad Autónoma de Madrid (PEJD-2019-PRE/AMB-16640 and S11/PJI/2019-00237). N. S. thanks MINECO for a FPU predoctoral fellowship and L. M thanks CAM for an “Atracción de Talento Investigador” contract (2017-T2/AMB-5037).

References

- a) L. Soullart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410; b) Z. Nairouk, M. Cormier, I. Marek, *Nat. Chem. Rev.* **2017**, *1*, 0035.
- a) B. Giese, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753; b) B. Giese, J. A. González-Gómez, T. Witzel, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 69; c) G. S. C. Srikanth, S. L. Castle, *Tetrahedron* **2005**, *61*, 10377; d) W. Zhang, *Tetrahedron* **2001**, *57*, 7237.
- a) *Radical Reactions in Organic Synthesis* (Ed.: Samir Z. Zard, Oxford Chemistry Masters, Oxford University Press 2003); b) J. T. M. Correia, V. A. Fernandes, B. T. Matsuo, J. A. C. Delgadode, W. C. Souza, M. W. Paixão, *Chem. Commun.* **2020**, *56*, 503; c) S. Crespi, M. Fagnoni, *Chem. Rev.* **2020**, *120*, 9790; d) Y. Sumida, H. Ohmiya, *Chem. Soc. Rev.* **2021**, *50*, 6320.
- a) H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490; b) R. Ren, H. Zhao, L. Huan, C. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12692; c) R. Ren, Z. Wu, Y. Xu, C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 286.
- Some selected reviews: a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; c) E. Meggers, *Chem. Commun.* **2015**, *51*, 3290; d) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898; e) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035; f) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075; g) A. F. Garrido-Castro, M. C. Maestro, J. Alemán, *Tet. Lett.* **2018**, *59*, 1286; h) T. Rigotti, J. Alemán, *Chem. Commun.* **2020**, *56*, 11169.
- A 1,5-hydrogen atom transfer (HAT) from heteroatomic radical can be an alternative strategy. However, these methods are limited to the formation of the alkyl radical in the δ -position to the heteroatom. For some reviews in the heteroatom HAT see: a) X. Wu, C. Zhu, *CCS* **2020**, *2*, 813; b) X. Wu, C. Zhu, *Chem. Commun.* **2019**, *55*, 9747; c) W. Guo, Q. Wang, J. Zhu, *Chem. Soc. Rev.* **2021**, *50*, 7359–7377.
- a) S. P. Morcillo, *Angew. Chem. Int. Ed.* **2019**, *58*, 14044; b) X. Wu, C. Zhu, *Chin. J. Chem.* **2019**, *37*, 171.
- a) J.-J. Guo, A. Hu, Y. Chen, J. Sun, H. Tang, Z. Zuo, *Angew. Chem. Int. Ed.* **2016**, *55*, 15319; b) A. Hu, Y. Chen, J.-J. Guo, N. Yu, Q. An, Z. Zuo, *J. Am. Chem. Soc.* **2018**, *140*, 13580; c) T. Xue, Z. Zhang, R. Zeng, *Org. Lett.* **2022**, *24*, 977; d) W. Liu, Q. Wu, M. Wang, Y. Huang, P. Hu, *Org. Lett.* **2021**, *23*, 8413.
- a) H. G. Yayla, H. Wang, K. T. Tarantino, H. S. Orbe, R. R. Knowles, *J. Am. Chem. Soc.* **2016**, *138*, 10794;

- b) E. Ota, H. Wang, N. L. Frye, R. R. Knowles, *J. Am. Chem. Soc.* **2019**, *141*, 1457.
- [10] a) L. Huang, T. Ji, M. Rueping, *J. Am. Chem. Soc.* **2020**, *142*, 3532; b) D. Wang, J. Mao, C. Zhu, *Chem. Sci.* **2018**, *9*, 5805; c) J. Wang, B. Huang, C. Shi, C. Yang, W. Xia, *J. Org. Chem.* **2018**, *83*, 9696; d) T. Kikuchi, K. Yamada, T. Yasui, Y. Yamamoto, *Org. Lett.* **2021**, *23*, 4710.
- [11] Some recent contributions: a) A. F. Garrido-Castro, A. Gini, M. C. Maestro, J. Alemán, *Chem. Commun.* **2020**, *56*, 3769; b) M. J. Cabrera, S. Cembellín, A. Halim-Salem, M. Berton, L. Marzo, A. Miloudi, M. C. Maestro, J. Alemán, *Green Chem.* **2020**, *22*, 6792; c) R. I. Rodríguez, L. Mollari, J. Aleman, *Angew. Chem. Int. Ed.* **2021**, *60*, 4555; d) R. I. Rodríguez, M. Sicignano, J. Alemán, *Angew. Chem. Int. Ed.* **2022**, DOI: 10.1002/anie.202112632.
- [12] Other oxidable functional groups such as the phenyl ring were studied but no conversion was obtained due to their higher oxidation potential.
- [13] A. Gontala, S. K. Woo, *Adv. Synth. Catal.* **2020**, *362*, 3223.
-