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Photoredox-catalyzed Cyclopropanation of Michael Acceptors

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Dedicated to Prof. Josefa Flórez González

Abstract: A new protocol for the catalytic cyclopropanation of α , β unsaturated carbonyl compounds with diiodomethane by means of photoredox catalysis has been successfully developed. The transformation is characterized by its mild conditions, functional group compatibility, and excellent selectivity profile.

Introduction

The cyclopropane ring is an important cyclic structural motif found in many natural products, medicines and crop protection agents.^[1] Over the past decades, the development of catalytic methodologies for the synthesis of these carbocycles has been an area of intense study.^[2] In particular, the simple methylene transfer into alkenes has provided the conceptual basis for the development of a range of useful methodologies involving iodomethylzinc carbenoids,[3] diazomethane[4] and sulfur or nitrogen ylides.^{[5],[6]} In contrast, it is rather surprising to see the scarcity of synthetic methods based on radical species.^[7] Recently, our group has introduced a novel reactivity concept based on the catalytic generation of radical carbenoid species by means of photoredox catalysis (Scheme 1).^[8] These radicals are substituted with an excellent leaving group and its reactivity is reminiscent of carbene species.



Scheme 1. Generation of radical carbenoids via SET process

By using this concept, we have developed a new alkene cyclopropanation reaction using commercial diiodomethane as methylene transfer reagent via photoredox catalysis (Scheme 2a).^[9] This process is characterized by its mild conditions, broad functional group compatibility, and excellent selectivity profile. lodomethyl radical carbenoid $ICH_2(\bullet)$ is the key intermediate photocatalytically generated that is able to cyclopropanate mixtures of E,Z-styrenes in a stereoconvergent manner. A benzyl radical has been proposed to explain the stereoconvergence phenomena and the ring-closing step (Scheme 2a).^[10] With the aim of expanding the scope of this radical cyclopropanation reaction, we questioned whether a related catalytic process could be developed for a, β-unsaturated

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carbonyl compounds. In this process, the nucleophilic iodomethyl radical would attack the C-C double bond generating an α -carbonyl radical intermediate, which might be able to conduct to the cyclopropane ring.[11] Herein, we report the successful development of new photocatalytic a cyclopropanation reaction of α,β-unsaturated carbonvl compounds using diiodomethane as methylene transfer reagent (Scheme 2b).





Scheme 2. Photocatalytic alkene cyclopropanation with diiodomethane.

Results and Discussion

We started our study using commercial (E)-chalcone (1a) as a model substrate (Table 1) and analogous reaction conditions developed previously for the cyclopropanation of styrene derivatives [Ru(bpy)₃(PF₆)₂ (1 mol %), CH₂I₂ (2.5 equiv), *i*-Pr₂EtN (5 equiv), Na₂S₂O₃ (5 equiv), CH₃CN/H₂O (4:1)]. It was highly gratifying to observe that the same reaction conditions were suitable for the cyclopropanation of 1a, and a 69% NMR yield of the expected trans-cyclopropane 3a was obtained as the only reaction product (Table 1, entry 1). In order to improve the efficiency of this process, we performed different experiments modifying the reaction variables. A dramatic decrease of yield was observed when no sodium thiosulfate and water were added (entry 2) or no degasification of the reaction mixture was carried out (entry 3). Further modification of the standard reaction conditions using alternative polar solvents (entry 4,5), visible-light sources (entry 6) or photocatalysts (entry 7-10) did not improve the efficiency of the process (see supporting information for further experiments).^[12]

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Table 1. Optimization Studies.[a]

1a	CH ₂ I ₂ CH ₂ I ₂ CH ₂ I ₂ CH ₃ CN, H ₂ O CH ₃ CN, H ₂ O	Jaa O
Entry ^[a]	Modification of the standard conditions	Yield [%] ^[b]
1	None	69
2	$Na_2S_2O_3$ and H_2O no added	35
3	Reaction mixture no degassed	17
4	DMSO instead CH ₃ CN	10
5	DMF instead CH ₃ CN	5
6	Blue LED strips instead of 21 W CFL	35
7	$Ir(ppy)_2(dtbbpy)PF_6$ instead $Ru(bpy)_3(PF_6)_2$	22
8	$Ir(ppy)_3$ instead $Ru(bpy)_3(PF_6)_2$	59
9	$Cu(dap)_2Cl$ instead $Ru(bpy)_3(PF_6)_2$	21
10	Eosin Y instead Ru(bpy) ₃ (PF ₆) ₂	42

[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.25 mmol), *i*-PrEt₂N (0.50 mmol), CH₃CN (4 mL), Na₂S₂O₃ (0.50 mmol), H₂O (1 mL). Reactions were degassed prior to irradiation. [b] NMR Yields calculated using 1,2-dimethoxyethane as internal standard. bpy = 2,2'-bipyridine. ppy = 2-phenylpyridine. dtbbpy = 4,4'-*bis*(1,1-dimethylethyl)-2,2'-bipyridine. dap = 2,9-*bis*(*para*-anisyl)-1,10-phenanthroline.

With these conditions in hand, we next turned our attention to assessing the scope of this radical cyclopropanation reaction by varying the aromatic substituent at C1 (Table 2). We found that electron-rich aromatic rings led to excellent yields (3b-c) in comparison for electron-poor ones (3d,e). Although full conversion is accomplished for the latter substrates, cyclopropane decomposition is clearly observed under the reaction conditions.^[13] In this sense, we later extensively explored the substrate scope at the C3 position keeping an electron-rich aromatic group at C1 position. We found that the process worked well for aromatic rings substituted with alkyl (3f), alkoxide (3g,h), amino (3i), halogen (3j), ciano (3k), CF₃ (3l) or aldehyde groups (3m). Additionally, substrates bearing five- and six-membered ring heterocycles (3n-r) worked well and no products from a Minisci-type C-H bond iodomethylation were observed.^[14] It is noteworthy the excellent site-selectivity profile observed for the cyclopropanation of the conjugated alkene moiety versus other functionalities such us alkyl-substituted alkenes (3h), nitriles (3k,o) or aldehyde groups (3m), that might undergo methylene transfer by using classic protocols. Additionally, we were delighted to find that the efficiency of the cyclopropanation reaction was not decreased for trisubstituted chalcones (3s) or for substrates bearing an alkyl group at C3 position instead of an aromatic ring (3t).[15]

Table 2. Cyclopropanation reaction of chalcone substrates.^[a]



[a] Reaction conditions: **1** (0.40 mmol), **2** (1.00 mmol), *i*-PrEt₂N (2.00 mmol), CH₃CN (10 mL), Na₂S₂O₃ (2.00 mmol), H₂O (1.5 mL), Reactions were degassed prior to irradiation. [b] Reaction carried out with 1 gram of (*E*)-**1c**. PMP = *para*-methoxyphenyl.

This new cyclopropanation reaction was also amenable for isomeric E/Z mixtures of chalcones **1a,c,j** and permitted the steroconvergent synthesis of the desired *trans*-cyclopropane **3a,c,j** with total stererocontrol (Scheme 3). These results highlights a unique feature of this radical cyclopropanation reaction based on the novel radical carbenoid species $ICH_2(\bullet)$.



Scheme 3. Stereoconvergent chalcone cyclopropanation.

Later, we believed that alternative Michael acceptors could be cyclopropanated by using the process developed for the chalcone derivatives. We were pleased to find that α , β -unsaturated aldehydes (**4a**), methyl ketones (**4b**),^[16] amides (**4c**) or simple alkyl-substituted enones (**4d**) were suitable substrates for the synthesis of the corresponding cyclopropanes **5a–d**

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cyclopropanation reaction.^[17]

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groups (β-nitrostyrene) were not suitable for this radical



Scheme 4. Catalytic cyclopropanation of α,β-unsaturated carbonyls.

Finally, we wondered whether the catalytic concept depicted in Scheme 1 for radical carbenoid generation, could be generalized by using alternative *gem*-diiodoalkanes. This generalization would allow access to complex cyclopropane cores using a simple and novel catalytic approach. Preliminary studies have revealed that commercially available 1,1-diiodoethane (6) worked well under the same reaction conditions developed in Table 1 and produced tri-substituted cyclopropane 7 in 69% isolated yield as a mixture of diastereoisomers (Scheme 5). This result suggested the involvement of a new radical carbenoid species 8, whose reactivity is analogous to the iodomethyl radical carbenoid $ICH_2(\bullet)$.



Scheme 5. Cyclopropanation with 1,1-diiodoethane (6).

Conclusions

In summary, we have successfully developed a new cyclopropanation reaction of α , β -unsaturated carbonyl compounds with CH₂I₂ by means of photoredox catalysis. Notable features of this process are the mild reaction conditions and excellent selectivity profile. The process involves the catalytic generation of radical carbenoid species, which are able to transfer a CH₂ in a stereocontrolled manner. Additionally, we were able to transfer for the first time, a CH(Me) group by using commercial 1,1-diiodoethane.

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Keywords: photoredox catalysis • carbenoid • cyclopropanation • radical • cyclopropane

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- [13] An experiment carried out with chalcone 1e during 30 hours, provided cyclopropane 3e in 22% NMR yield. This result clearly suggested cyclopropane decomposition under the reaction conditions. We believe that an unproductive cyclopropane ring-opening could be occurring through a one-electron reduction of the carbonyl group to the corresponding radical anion. This photoredox process has been exploited by Yoon and co-workers for a [3+2] cycloaddition of aryl cyclopropyl ketones: Z. Lu, M. Shen, T. P. Yoon, J. Am. Chem. Soc. 2011, 133, 1162.
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- [17] Although our original working hypothesis was based on the formation of an α -carbonyl radical intermediate (Scheme 2b), we cannot rule out the formation of a benzyl radical intermediate in substrates bearing an aromatic ring in β position.

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A new protocol for the cyclopropanation of α,β -unsaturated carbonyl compounds with simple diiodomethane has been developed by means of photoredox catalysis. The process involves the phocatalytic generation of iodomethyl radical, a novel carbenoid species able to transfer a CH₂ group to a wide variety of Michael acceptors in a stereocontrolled manner.