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A transition-metal-free & diazo-free styrene cyclopropanation†

Ana G. Herraiz [ab] and Marcos G. Suero *[a]

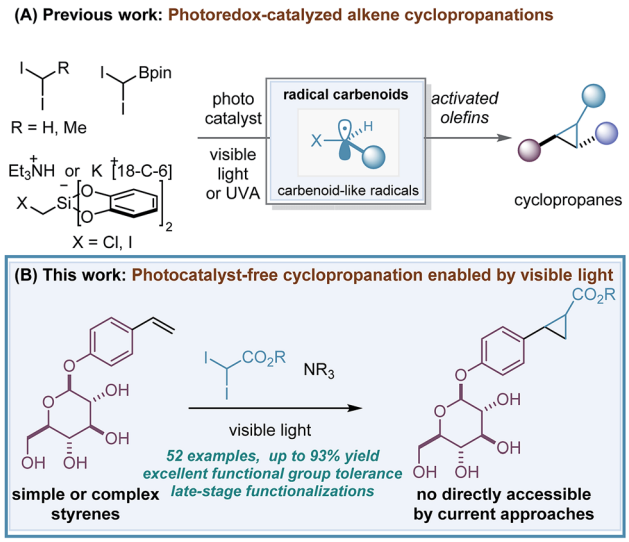
An operationally simple and broadly applicable novel cyclopropanation of styrenes using *gem*-diiodomethyl carbonyl reagents has been developed. Visible-light triggered the photoinduced generation of iodomethyl carbonyl radicals, able to cyclopropanate a wide array of styrenes with excellent chemoselectivity and functional group tolerance. To highlight the utility of our photocyclopropanation, we demonstrated the late-stage functionalization of biomolecule derivatives.

Introduction

Over the last few decades, one of the main challenges in the synthesis of cyclopropane rings[1] – a prevalent structural motif in pharmaceutical agents[2] and natural products[3] – has been to develop robust and general alkene cyclopropanations that avoid the use of explosive, highly toxic, pyrophoric or water-sensitive carbene transfer reagents (diazo reagents and organometallic carbenoids). However, although important advances have been made in this direction,[4] a major limitation remaining is the broad tolerance to functional groups and consequently, the cyclopropanation of complex molecules.[5]

In 2017, our group reported a new methodology for the stereoconvergent cyclopropanation of *E*/*Z* isomeric styrene mixtures and Michael acceptors[6] by means of photoredox catalysis (Scheme 1A).[7] The key to these studies was the use of the well-known $[Ru(bpy)_3][PF_6]_2$ photocatalyst and photoreducible diiodomethane[8] as a methylene source that enabled the generation of a carbenoid-like radical $(^{\bullet})CH_2I$ termed radical carbenoid, as a reactive cyclopropanating species. Although the method showed a broad functional group tolerance and excellent chemoselectivity, severe limitations in the styrene scope were found and an excess of diiodomethane (5 equivalents) had to be used. After this, firstly the group of Molander[9] and secondly the group of Li[10] reported two complementary redox-neutral cyclopropanations using photooxidizable bis(catecholato)iodomethylsilicate reagents and 4CzIPN or $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as photocatalysts. The Molander reaction was demonstrated in a wide variety of activated alkenes and showed an excellent functional group tolerance and chemoselectivity, however, the process was exclusively evaluated for methylene transfer *via* $(^{\bullet})CH_2I$. Moreover, Charette and co-workers developed a radical borocyclopropanation enabled by flow techniques, UVA light and xanthone as photocatalyst.[11] This reaction involved the generation of $(^{\bullet})CH(Bpin)I$ and provided valuable cyclopropylboronates as mixtures of diastereoisomers.[12]

The novel photoredox-catalyzed radical cyclopropanations represent a clear advance in the synthesis of cyclopropane rings and a more practical approach to strategies based on diazo reagents and metal-carbenoids.[13,14] However, it is clearly an underdeveloped methodology and challenges associated with alkene scope, reagent diversity or efficiency of the process (reagent equivalents) should be solved. In addition, the



Scheme 1 New radical cyclopropanations enabled by visible-light: a valuable alternative to methods employing diazo reagents or metal-carbenoids (A and B).

[a]*Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, Tarragona, 43007, Spain. E-mail: mgsuero@iciq.es*

[b]*Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, Calle Marcel. lí Domingo, 1, Tarragona, 43007, Spain*

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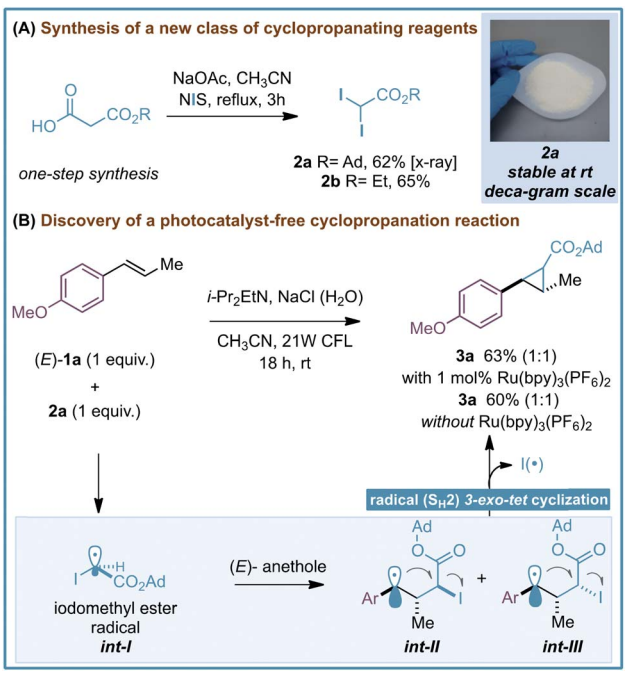
development of novel methodologies that avoid the use of precious Ru/Ir photocatalysts and permit late-stage functionalization of complex molecules would be highly appreciated. Here, we report the first general photocatalyst-free cyclopropanation of styrenes that use underexploited *gem*-diiodomethyl carbonyl compounds as cyclopropanating reagents and a simple compact fluorescence lamp (CFL) as a visible-light source (Scheme 1B). The process generates valuable cyclopropyl carboxylates that could be diversified by well-documented decarboxylative strategies.[15] Its excellent functional group tolerance and chemoselectivity have enabled access to cyclopropyl carboxylates that are not possible to obtain *in a direct manner* by current catalytic strategies relying on metal-carbene(carbenoid) (this is because of the preference of the latter species to react with more nucleophilic functionalities than a styrene double bond).

Results and discussion

During the development of our photoredox-catalyzed cyclopropanation, control experiments revealed that excluding the $[Ru(bpy)_3][PF_6]_2$ photocatalyst in the reaction resulted in a poor yield of the corresponding cyclopropanes (15–18% yield, 18 hours).[6] These interesting results encouraged us to question whether *gem*-diiodomethyl carbonyl reagents – activated alkyl iodides with more absorbance in the visible region – could provide an efficient photocatalyst-free cyclopropanation and deliver valuable carbonyl-substituted cyclopropane rings. Our investigations started by synthesizing 1-adamantanyl 2,2-diiodoacetate (**2a**) as a potential new cyclopropanating reagent (Scheme 2A). **2a** is a white solid that can be prepared on a 12 gram scale from 3-(adamantan-1-yloxy)-3-oxopropanoic acid and *N*-iodosuccinimide (NIS). Importantly, **2a** features great stability in comparison with the analogue ethyl 2,2-diiodoacetate (**2b**), which has to be stored in a freezer (<−20 °C) and in solution (0.5 M CH_3CN). Differential scanning calorimetry (DSC) studies were performed with reagent **2a** and did not show relevant exothermic decompositions, which are commonly found for diazo compounds (see ESI†).[16]

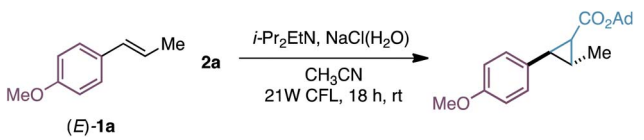
After this, we evaluated reagent **2a** (1 equiv.) for the cyclopropanation of (*E*)-anethole (**1a**) with and without the $[Ru(bpy)_3][PF_6]_2$ photocatalyst. We were delighted to find that both reactions led to the expected tri-substituted cyclopropane **3a** in moderate yields (63–60% yield, Scheme 2B) as an equimolar isomeric mixture of diastereoisomers. To explain the formation of **3a** we propose the initial generation of iodomethyl radical ester ***int-I*** as a cyclopropanating species. After this, an unbiased attack of the pyramidal sp^3-hybridized radical ***int-I*** on **1a** would generate benzylic radicals ***int-II*** and ***int-III***,[17] which would evolve to the corresponding cyclopropane **3a** by a radical homolytic substitution (S_H2) 3-*exo-tet* cyclization. Radical homolytic substitutions are common elementary steps in radical chemistry and in terms of frontier molecular orbitals, this cyclization involves the interaction between the high-energy singly occupied molecular orbital (SOMO) of the benzylic radical, and the lowest unoccupied molecular orbital (LUMO) of the C–I bond. A similar cyclization has been observed previously by Curran and Togo in cyclopropane synthesis using 1,3-dihaloalkanes and radical initiators/reductants.[18]

After these preliminary investigations, we evaluated other solvents, amines and visible-light sources and found that the best reaction conditions involve only 2 equiv. of reagent **2a**, i-Pr_2EtN (4 equiv.), CH_3CN (1 mL), an aqueous solution of NaCl (1.25 M, 0.5 mL) and degasification of the reaction mixture prior



Scheme 2 Synthesis of *gem*-diodomethyl carboxylate reagents **2a**,**b** (A) and discovery of a photocatalyst-free cyclopropanation. Ad = 1-adamantyl (B).

Table 1 Optimization studies[a]



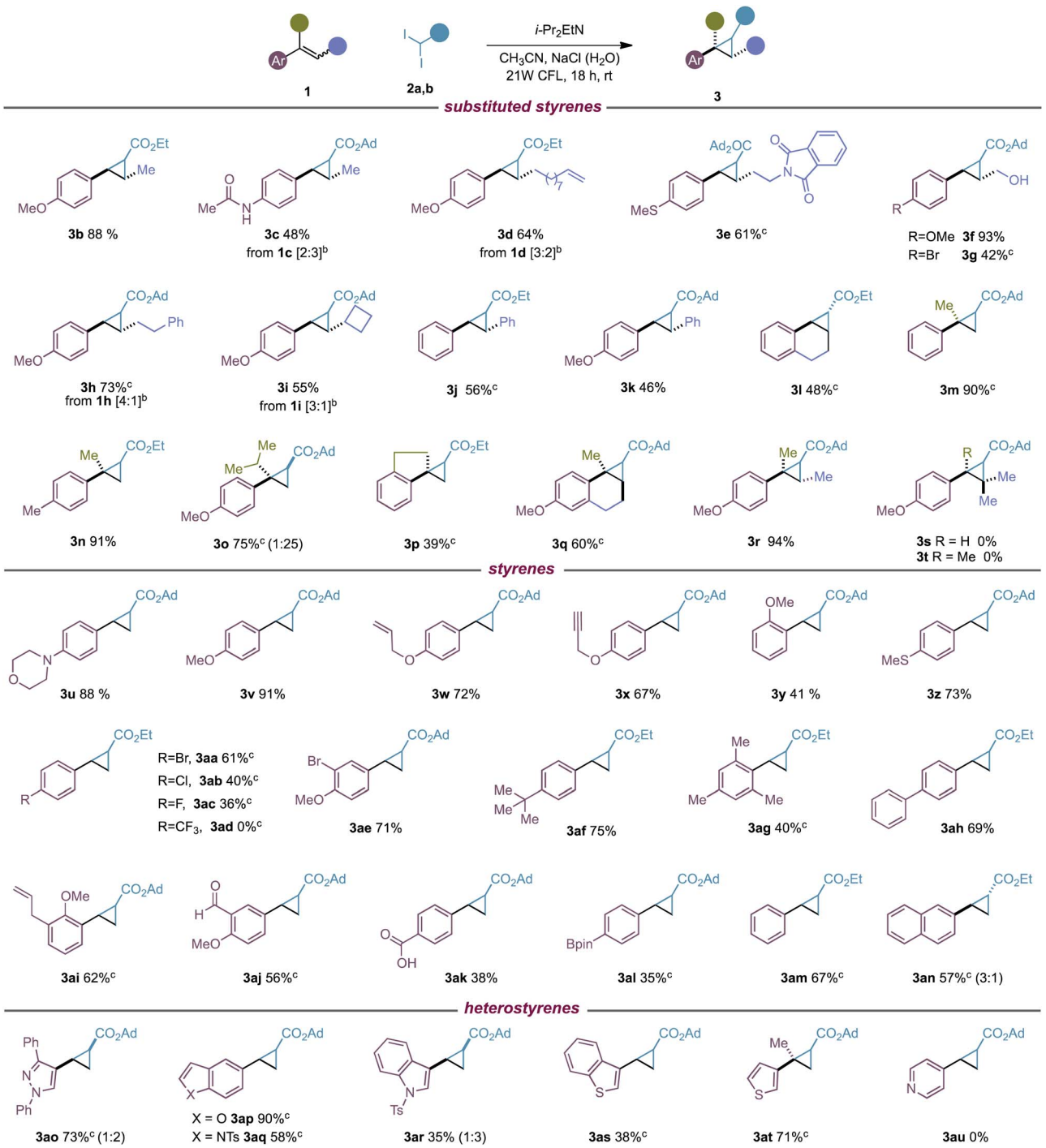
Entry	Deviation of the reaction conditions	Yield[b] **3a**, %
1	None	91[c](75)[d]
2	Without NaCl (H_2O)	17
3	Without NaCl	48
4	Under air	10
5	Without i-Pr_2EtN	0
6	In the dark	0

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), i-$PrEt_2N$ (0.20 mmol), CH_3CN (1 mL), NaCl (1.25 M in H_2O, 0.5 mL). Reactions were degassed prior to irradiation. [b] ^{1}H-NMR yields calculated using 1,2-dimethoxyethane as the internal standard. [c] Yield of the isolated product adding additional **2a** (0.10 mmol, 1 equiv.) and i-$PrEt_2N$ (0.20 mmol, 2 equiv.) after 4 hours. [d] Yield of the isolated product using 1 gram of (*E*)-**1a** and 1 equiv. of **2a**. See the ESI for the evaluation of other solvents, amines, or visible-light sources.

to irradiation (91% yield, Table 1, entry 1). We were glad to find that these reaction conditions were also suitable for a 1 gram scale reaction using only 1 equiv. of **2a** (75% yield). However, poorer efficiency was observed when reactions were carried out without NaCl (H_2O) or H_2O (17–48% yield, entries 2 and 3)[19] or under air (10% yield, entry 4). No conversion to **3a** was observed without i-Pr_2EtN or the CFL (entries 5 and 6).

With the optimized reaction conditions in hand, we evaluated the scope of the new photocyclopropanation using 46 styrene derivatives and reagents **2a**, **b**.[20] As shown in Table 2, our protocol was effective for a variety of diversely substituted styrenes (**3b–r**),

Table 2 Scope of the styrene photocyclopropanation[a]



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), i-PrEt_2N (0.80 mmol), CH_3CN (2 mL), NaCl (1.25 M in H_2O, 1 mL); yields of the isolated product. Diastereomeric ratios were between 1 : 1 and 1.5 : 1 and determined by ^{1}H NMR analysis. [b] *E*/*Z*-alkene mixtures **1** are shown in brackets. [c] Reaction conditions **1** (0.40 mmol), **2** (0.20 mmol), i-PrEt_2N (0.40 mmol), CH_3CN (2 mL), NaCl (1.25 M in H_2O, 1 mL).

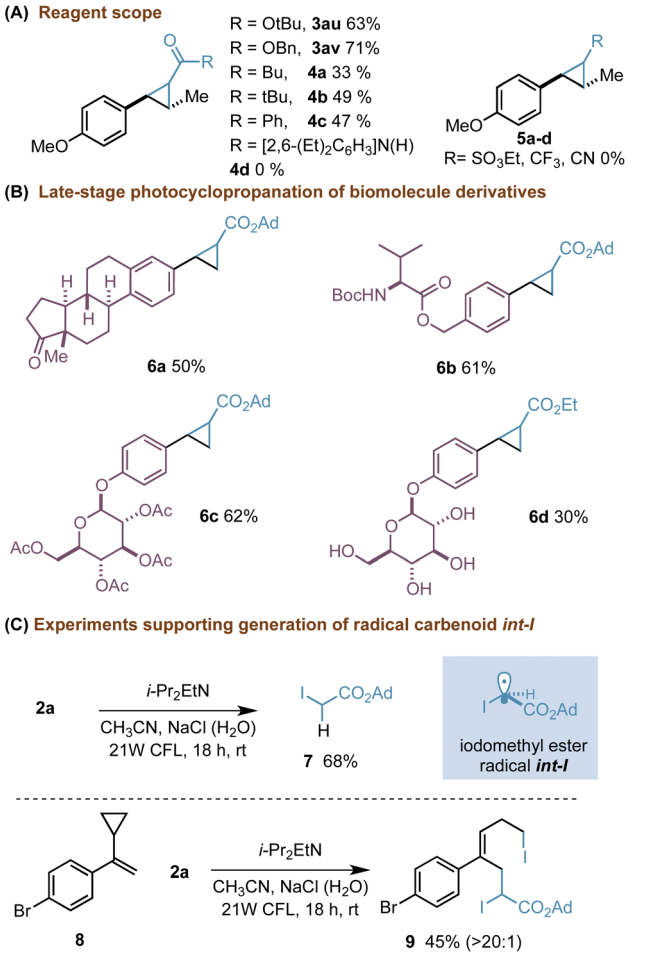
substituted at the β position with methyl (**3b**, **c**) or alkyl groups functionalized with an olefin (**3d**), phthalimide (**3e**), alcohol (**3f–g**) and phenyl (**3h**) or cyclobutyl rings (**3i**). We were glad to find that our photocyclopropanation worked well for stilbenes (**3j**, **k**), cyclic (**3l**, **q**) and α-substituted styrenes (**3m–q**), which failed in our previous photoredox cyclopropanation.[6a] In addition, whereas the more substituted acyclic and cyclic trisubstituted styrenes were well tolerated (**3q**, **r**), our process did not work for styrenes with a sterically demanding β carbon center (**3s**, **t**). It is worth highlighting that although the reaction generates mixtures of diastereoisomers at the α-carbonyl center, which are easily separable by column chromatography, the reaction proceeded with absolute stereoconvergence for *E*/*Z* isomeric mixtures of di and tri-substituted styrenes (**1c**, **d**, **h**, **i**, **r**).

We then decided to investigate the scope of terminal (hetero) styrenes (**3u–as**). These substrates provided poor conversion to the cyclopropane in our methylenation reaction,[6a] and instead open-chain dimeric products were found from the homocoupling of benzylic radical intermediates. We were delighted to find that the new photocatalyst-free cyclopropanation was able to cyclopropanate a broad variety of styrenes functionalized with amine (**3u**), alkoxide (**3v–x**), sulfide (**3z**), halogen (**3aa–ac**, **3ae**), alkyl (**3af**, **ag**), phenyl (**3ah**), allyl (**3ai**), aldehyde (**3aj**), carboxylic acid (**3ak**), pinacol boronic ester (**3al**), unsubstituted (**3am**) or naphthalene (**3an**) groups. Unfortunately, styrenes substituted with strong electron-withdrawing groups such as CF_3 did not yield the desired cyclopropane **3ad**. Furthermore, we observed that while our protocol was able to functionalize heterostyrenes containing imidazole (**3ao**), benzofurane (**3ap**), indole (**3aq**, **3ar**), benzothiophene (**3as**) and thiophene (**3at**), no cyclopropanation reaction was found for pyridine derivatives (**3au**).

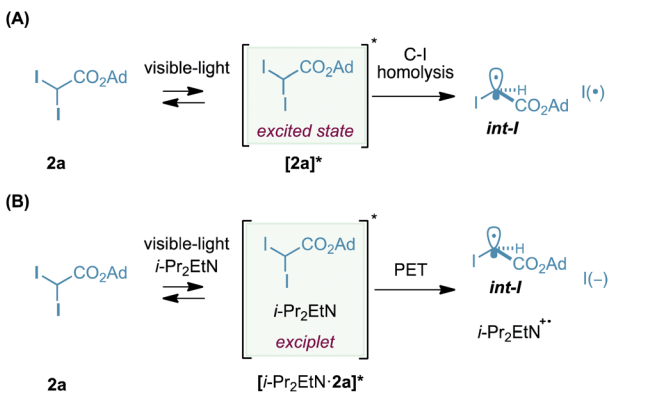
The excellent functional group tolerance and chemoselectivity observed towards the styrene double bond are in sharp contrast to current catalytic methods that cyclopropanate styrenes involving electrophilic metal-carbenes from diazoacetates. These methods may suffer from chemo- and site-selectivity in challenging substrates bearing additional alkenes (**3d**, **w**, **ai**),[21] or functionalities able to intercept the corresponding metal-carbene intermediate such as alcohol (**3f**, **g**),[22] aldehyde (**3aj**),[23] alkyne (**3x**),[24] carboxylic acid (**3ak**)[25] or sulfide (**3e**, **z**) groups.[26]

On the other hand, although our process was successfully extended to other *gem*-diiodomethyl esters (**3au**, **av**) or ketone reagents (**4a–c**, Scheme 3A), the corresponding analogues substituted with amides (**4d**) or other electron-withdrawing groups did not provide the expected cyclopropane ring (**5a–c**). The synthetic potential of our photocyclopropanation was further illustrated with the late-stage functionalization of biomolecule derivatives (Scheme 3B). Our process was able to functionalize styrenes derived from estrone (**6a**), L-valine (**6b**) and β-D-glucose pentaacetate (**6c**).[27] In addition, we were delighted to find that the process could also work with the unprotected glucose derivative (**6d**).[28] This final example clearly highlights the potential of our methodology to be applicable in alternative complex scenarios.[29]

Moreover, we wanted to prove the formation of radical ***int-I***.[30] Firstly, an experiment carried out without styrene resulted in the isolation of iodoacetate **7** (Scheme 3C). Its formation can be explained involving abstraction of a hydrogen atom with ***int-I***. An additional experiment carried out with the classic cyclopropyl radical probe **8** also supports the formation of ***int-I*** as an intermediate by forming an atom-transfer radical addition (ATRA) product **9**.



Scheme 3 Reagent scope (A), late-stage functionalization (B) and radical trapping experiments (C). Diastereomeric ratios of cyclopropanes were between 1 : 1 and 1.5 : 1 and determined by ^{1}H NMR analysis.



Scheme 4 Mechanistic hypotheses for the photogeneration of int-I (A and B).

Finally, our current hypotheses for the photogeneration of radical carbenoid ***int-I*** are depicted in Scheme 4. Considering that our reagent **2a** absorbs in the visible region (tail of absorption: 460 nm at 0.1 M, see ESI†), we believe that one of the possible scenarios could involve the photogeneration of the excited state [**2a**]* and its evolution to ***int-I*** and I(˙) by homolysis (Scheme 4A).[31] In this particular case, i-Pr_2EtN might be acting as a quencher of the iodine species, I(˙) or I_2, formed during the reaction.[32] Recently, the group of Aggarwal hypothesized a homolytic cleavage of the C–I bond in α-iodo ketones by visible light as a suitable pathway for the generation of electrophilic alkyl radicals, analogous to ***int-I***.[33]

On the other hand, another possible scenario involves the formation of a short-lived exciplet [i-Pr_2EtN·**2a**]* that undergoes photoinduced electron transfer and generates ***int-I***.[34] Exciplet analogues have been proposed recently in the generation of radicals from inactivated alkyl iodides.[35]

The quantum yield measured for the model photocyclopropanation of (*E*)-**1a** with **2a** was found to be 1.5 ($\lambda = 410$ nm in CH_3CN/H_2O, using potassium ferrioxalate as the actinometer), suggesting that if a radical-chain is operating, it is very inefficient. At this point, this result does not allow us to discriminate between one of the two mechanistic hypotheses depicted in Scheme 4.

Conclusions

In summary, we have developed a robust, scalable, and safe photochemical cyclopropanation reaction with *gem*-diiodomethyl carbonyl reagents. Our new cyclopropanation features an excellent functional group tolerance that permitted the functionalization of a broad range of functionalized styrenes and biomolecules.

Conflicts of interest

A patent application describing the results presented in this manuscript has been filled.

Acknowledgements

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