This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Visible Light Induced Cyclopropanation of Dibromomalonates with Alkenes via Double-SET by Photoredox Catalysis

Yanbin Zhang, a,e Rong Qian, a,e Xingliang Zheng, b Yi Zeng, b Jing Sun, a Yiyong Chen, a Aishun Ding a and Hao Guo a,e

We report herein a visible light induced generation of carbanion via Double-SET and its application in cyclopropanation of alkenes. This new synthetic approach to cyclopropane derivatives was conducted under mild conditions, using sunlight in the open air, showing the features of environmentally benign and easiness to handle.

Visible light photoredox catalysis (VLPC) has a rich history in organic chemistry. Research on using solar energy to achieve new photocatalysis strategies is of continuous interest for chemists. Thanks to the creating contributions from MacMillan, a,b Yoon, c Stephenson, a,d and other researchers, a VLPC has attracted much attention of chemists. A large number of outstanding works in this field a,e have proved that visible light is mild, environmentally benign, and infinitely available. Most importantly, visible light induced transformations are highly tolerant and selective, since undesired side reactions of UV-sensitive compounds can be minimized or even avoided. Upon the irradiation of visible light, photoredox catalysts can be easily turned into photoexcited state which is readily available for both oxidative and reductive quenching. e This feature makes VLPC a powerful tool for the generation of reactive radical intermediate via Single Electron Transfer (SET) process. However, till now, the application of VLPC is still quite limited to radical formation and subsequent transformations. b,c,d,e,f,g,h,i,k,l,n Reports on carbocation or carbanion generation and following bonds formation are rare. Thus, studies to extend the application of VLPC and develop non-radical-limited visible light photoreactions are highly desired.

It has been reported that benzyl bromide can be reduced into carbanion PhCH2 – via Double-SET under the catalysis of Ru(bpy)3 2+ (Scheme 1). h It is also known that bromomalonate 1 can be converted into a carbon-centered radical via SET under the catalysis of Ru(bpy)3 2+ (Scheme 2). h Considering that two strong electron withdrawing groups were attached on the carbon center of this radical, it might be able to be reduced into malonate carbanion. i,j,k We hypothesized that a second SET to the in situ formed radical intermediate might result in such a malonate carbanion (Scheme 2).

Based on the above idea, a cyclopropanation via intermolecular Michael addition and subsequent intramolecular nucleophilic substitution was designed. k A prospective mechanism for this Double-SET transformation is shown in Scheme 3. Under the visible light irradiation, Ru(bpy)3 2+ accepts a photon to reach the excited state Ru(bpy)3 10+ . e This high energy species is able to grab a single electron from the amine to form the highly reducing Ru(bpy)3 6+. Then the first SET to the dibromomalonate 2 leads to the electron-deficient bromomalonate radical 5 and regenerates Ru(bpy)3 2+. k Next, a similar catalytic circle processes the second SET to the carbon-centered radical 5 and results in the desired bromomalonate carbanion 6. Its Michael addition to an electron-deficient alkene 3 will afford a new carbanion 7 which undergoes intramolecular nucleophilic substitution to produce a cyclopropane derivative 4 as the final product. The base might have two effects: donating electrons and trapping the in situ formed HBr.

Close attention should be paid to several key features in the above dual-catalysis design plan. First of all, the carbamation 6 should be easily available from the reducing of corresponding radical 5 and reactive enough for Michael addition. Secondly, very strong electron-withdrawing groups should be attacked at the α-position of the Michael addition acceptor, so that the in situ formed carbanion 7 will...
be highly nucleophilic for the following transformation. Thirdly, the steric hindrance at α-position should be very little to enable the three-membered ring formation process.

With these considerations in mind, diethyl 2,2-dibromomalonate 2a and 2-benzylidenemalononitrile 3a were chosen as the model substrates to examine this new cyclopropanation protocol. To our delight, the reaction underwent smoothly under our initial attempt. Then a series of control reactions were examined. Without light, neither with nor without the catalyst, this reaction proceeded slowly to give very low yields of the cyclopropane 4aa after full conversion of the starting material 2a (entries 1 and 2, Table 1). Under the irradiation of visible light and in the absence of catalyst, a similar low yield of 4aa was formed (entry 3, Table 1). When irradiated by visible light and in the presence of 1 mol% of the photocatalyst, the reaction speed dramatically increased, affording 4aa in 94% isolated yield (entry 4, Table 1). Notably, this reaction could be carried out in air, yielding 4aa in almost the same excellent yield (entry 5, Table 1). As the time was shortened to approximately 5 hours, it enables this transformation to be conducted under sunlight. Indeed, higher efficiency and better yield were observed (entry 6, Table 1). So Condition A (2 equiv. Pr3NNEt, 1 mol% Ru(bpy)3Cl2·6H2O, methanol, visible light, and rt) and Condition B (2 equiv. Pr3NNEt, 1 mol% Ru(bpy)3Cl2·6H2O, methanol, sunlight, and rt) were applied for the following studies.44

With the optimal conditions in hand, we investigated the scope of this photocyclopropanation with a series of dibromomalonate derivatives and alkynes. Reactions under Conditions A and B gave similar results (Table 2). Firstly, the electronic effect of substituents on the phenyl ring of the alkynes was studied carefully. With strong electron-withdrawing groups, such as methoxycarbonyl (entry 1, Table 2), trifluoromethyl (entry 2, Table 2), and nitro (entries 3-5, Table 2), the corresponding cyclopropane derivatives were formed in good to excellent yields. Excellent yields were also obtained for weak electron-withdrawing groups substituted substrates, like fluorine (entry 6, Table 2) and chlorine (entry 7, Table 2), and weak electron-donating groups, like alkyl (entries 9-13, Table 2) and phenyl (entry 14, Table 2). For substrates bearing strong electron-donating groups, like alkoxy (entries 15-18, Table 2) and acetoxy (entry 19, Table 2), the yields decreased slightly. The electronic effect of the substrate strongly suggested a carbanion intermediated mechanism.45 Then other dibromides 2b and 2c were applied in the photocyclopropanation of 3a, which gave the desired products 4ba and 4ca in excellent isolated yields, respectively (entries 20 and 21, Table 2).

Mechanistically, a set of reactions were performed to investigate the stereochemistry of this cyclopropanation. As shown in Scheme 4, under the standard conditions, reactions of 2a with either Z-8 or E-8 gave the same trans-product 9 in nearly the same yield. Notably, no cis-9 was formed in either case. To check whether there was an isomerization of Z-8 into E-8 under this reaction conditions, the un consumed reactant Z-8 and E-8 were recovered. Careful 1H NMR analysis proved that there was no change in their double bond configuration in the recovered starting material. These results suggest a free bond rotation occurred at the cyclization procedure, which fits well with our designed reaction pathway via Michael addition and subsequent intramolecular nucleophilic attraction.

Although the above results fitted well with our initially proposed mechanism as shown in Scheme 3, some other possibilities of reaction pathways should also be considered. (For further discussion, see ESI)

In summary, we have developed a visible light induced generation of carbanion to achieve cyclopropanation of dibromomalonates with...
Further investigations on the applications of this system to new reactions for organic synthesis are in progress in our group.

We greatly acknowledge the financial support from Shanghai Rising-Star Program (14QA1400500), National Basic Research Program of China (973 Program, 2012CB720300), National Nature Science Foundation of China (21274023, 21102016, and 21102157), Shanghai Scientific and Technological Innovation Project (13520711500), and Development and Innovation of Instrument Functions, CAS (No. Y27YQ11110G).

Notes and references

52, 11701-11703; (g) D. P. Hari and B. König, Angew. Chem., Int. Ed. 2013, 52, 4734-4743.


14 For a detailed description of experimental procedure, please see ESI.
