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COMMUNICATION

Visible Light Induced Cyclopropanation of Dibromomalonates with Alkenes via Double-SET by Photoredox Catalysis

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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 benigness and easiness to handle.

Visible light photoredox catalysis (VLPC) has a rich history in organic chemistry.[1] Research on using solar energy to achieve new photocatalysis strategies is of continuous interest for chemists. Thanks to the creating contributions from MacMillan,[2] Yoon,[3] Stephenson,[4] and other researchers,[5] VLPC has attracted much attention of chemists. A large number of outstanding works in this field[2-5] 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.[6] This feature makes VLPC a powerful tool for the generation of reactive radical intermediate via Single Electron Transfer (SET) process.[7] However, till now, the application of VLPC is still quite limited to radical formation and subsequent transformations.[2-5] Reports on carbocation or carbanion generation and following bonds formation are rare.[8] 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 $PhCH_2^-$ via Double-SET under the catalysis of $Ru(bpy)_3^{2+}$ (Scheme 1).[8]
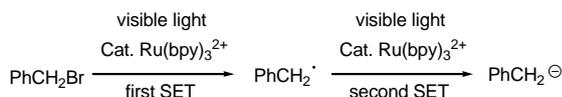
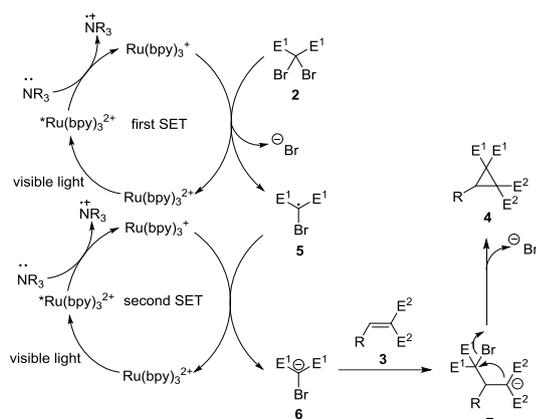**Scheme 1.** The reduction of $PhCH_2Br$ into carbanion $PhCH_2^-$ via Double-SET

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).[9] 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.[10] We hypothesized that a second SET to the in situ formed radical intermediate might result in such a malonate carbanion (Scheme 2).
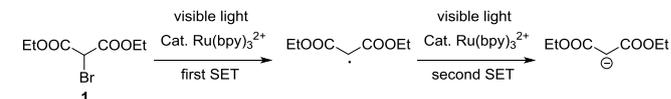
Scheme 2. The formation of carbanion via hypothesized Double-SET

Based on the above idea, a cyclopropanation via intermolecular Michael addition and subsequent intramolecular nucleophilic substitution was designed.[11] 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 $Ru(bpy)_3^{2+}*$.[6a] This high energy species is able to grab a single electron from the amine to form the highly reducing $Ru(bpy)_3^+$.[6b] Then the first SET to the dibromomalonate **2** leads to the electron-deficient bromomalonate radical **5** and regenerates $Ru(bpy)_3^{2+}$.[12] 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[11,13] 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 carbanion **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 attached at the α-position of the Michael addition acceptor, so that the in situ formed carbanion **7** will

Scheme 3. The prospective mechanism

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

Entry	Light source	Catalyst [Ru]	Time (h)	Isolated yield (%)
1[b]	dark	--	32	16
2[b]	dark	1 mol%	30	21
3[b]	visible light	--	18	23
4[b]	visible light	1 mol%	5	94
5[c]	visible light	1 mol%	5	92
6[c]	sunlight	1 mol%	4	97

[a] All reactions were carried out using **2a** (0.2 mmol), **3a** (0.4 mmol), and Pr$^i_2$NEt (0.4 mmol) in deaerated methanol (10 mL) at rt. [b] The reaction was carried out under argon atmosphere. [c] The reaction was carried out under air atmosphere.

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. **3**, 2 equiv. Pr$^i_2$NEt, 1 mol% Ru(bpy)$_3$Cl$_2$·6H$_2$O, methanol, visible light, and rt) and Condition B (2 equiv. **3**, 2 equiv. Pr$^i_2$NEt, 1 mol% Ru(bpy)$_3$Cl$_2$·6H$_2$O, methanol, sunlight, and rt) were applied for the following studies.[14]

With the optimal conditions in hand, we investigated the scope of this photocyclopropanation with a series of dibromomalonate derivatives and alkenes. Reactions under Conditions A and B gave similar results (Table 2). Firstly, the electronic effect of substituents on the phenyl ring of the alkenes 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.[11] 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). Finally, electron-rich alkene **3t**, aliphatic alkene **3u**, and 2-methylenemalononitrile **3v** were applied under Condition A. No cyclopropanes were formed (Scheme S1 in ESI). In all the above cases, no reduced **3** was formed.

Mechanistically, a set of reactions were performed to gain more information. Firstly, radical scavenger TEMPO was added to this reaction system. The addition of 1 equiv. of TEMPO resulted in a slightly decreased yield. Further increase the amount of TEMPO to 5 equiv. led to similar results. In both cases, no obvious changes in the reaction speed were observed. Next, 5 equiv. of BHT was used instead of TEMPO, similarly, no inhibition was observed (Scheme S2 in ESI). Considering that no obvious feature of free radical was observed, since O$_2$ in air, TEMPO, or BHT could not significantly affect this transformation, radical species might not be involed in the rate-determing step.[15,16] This might mean that the reduction of carbon radical into carbanion proceeds at an extremely rapid rate. Then a dark reaction after irradiation for 5 minutes was also carried out yielding only 29% of **4aa**, which ruled out a radical chain mechanism, since it gave a similar yield of **4aa** with the reaction under Condition A without light (Scheme S3 in ESI).

Next, alkenes **8** with different configurations were employed 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 unconsumed reactant **Z-8** and **E-8** were recovered. Careful ^{1}H 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 occured 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

Table 2. The photocyclopropanation under Condition A[a] or B[b].
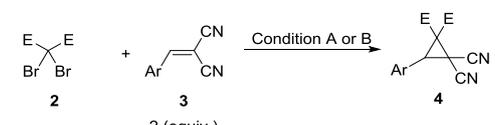
Entry	2 (E)	3 (Ar)	4	Condition A		Condition B	
				Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	2a (COOEt)	3b (4-COOMeC$_6$H$_4$)	4ab	4	98	4	98
2	2a (COOEt)	3c (4-CF$_3$C$_6$H$_4$)	4ac	4	96	2.5	98
3	2a (COOEt)	3d (4-NO$_2$C$_6$H$_4$)	4ad	2	92	2	91
4	2a (COOEt)	3e (3-NO$_2$C$_6$H$_4$)	4ae	2	84	2	81
5	2a (COOEt)	3f (2-NO$_2$C$_6$H$_4$)	4af	2	85	2	84
6	2a (COOEt)	3g (4-FC$_6$H$_4$)	4ag	3	95	3	97
7	2a (COOEt)	3h (4-ClC$_6$H$_4$)	4ah	3.5	95	3	95
8	2a (COOEt)	3a (C$_6$H$_5$)	4aa	5	92	4	97
9	2a (COOEt)	3i (4-MeC$_6$H$_4$)	4ai	2.5	95	2	96
10	2a (COOEt)	3j (3-MeC$_6$H$_4$)	4aj	3	95	3	95
11	2a (COOEt)	3k (2-MeC$_6$H$_4$)	4ak	2.5	96	3	98
12	2a (COOEt)	3l (4-EtC$_6$H$_4$)	4al	3	94	3	95
13	2a (COOEt)	3m (4-Pr^{i}C$_6$H$_4$)	4am	2.5	96	2.5	96
14	2a (COOEt)	3n (4-PhC$_6$H$_4$)	4an	4	89	4.5	90
15	2a (COOEt)	3o (4-MeOC$_6$H$_4$)	4ao	5	70	4	85
16	2a (COOEt)	3p (3-MeOC$_6$H$_4$)	4ap	3	85	3	85
17	2a (COOEt)	3q (2-MeOC$_6$H$_4$)	4aq	3	80	3	79
18	2a (COOEt)	3r (4-EtOC$_6$H$_4$)	4ar	4	81	4	81
19	2a (COOEt)	3s (4-AcOC$_6$H$_4$)	4as	4	77	4	77
20	2b (COOMe)	3a (C$_6$H$_5$)	4ba	3	96	3	95
21	2c (COOPr^i)	3a (C$_6$H$_5$)	4ca	4	93	4	93

[a] All reactions were carried out using 2 (0.2 mmol), 3 (0.4 mmol), and Pr$^i_2$NEt (0.4 mmol) in deaerated methanol (10 mL) under 23W household lamp at rt under air atmosphere. [b] All reactions were carried out using 2 (0.2 mmol), 3 (0.4 mmol), and Pr$^i_2$NEt (0.4 mmol) in deaerated methanol (10 mL) under sunlight at rt under air atmosphere. [c] Isolated yield.
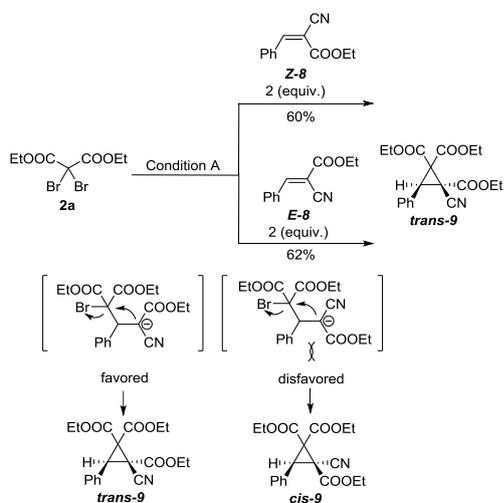
Scheme 4. Cyclopropanation of two stereoisomeric alkenes **Z-8** and **E-8**

alkenes by VLPC, which provides a novel catalytic protocol for the synthesis of multisubstituted cyclopropane derivatives under mild conditions. The high yield of this transformation shows broad synthetic application prospects. A carbanion pathway with Double-SET has been proposed to explain the mechanism of this reaction. Further investigations on the applications of this system to new reactions for organic synthesis are in progress in our group.

Notes and references

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Electronic Supplementary Information (ESI) available: [A picture for the setup of this reaction, experimental procedures, and characterization data for all compounds.]. see DOI: 10.1039/c000000x/

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