Photoredox Catalysis

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A Stereoconvergent Cyclopropanation Reaction of Styrenes

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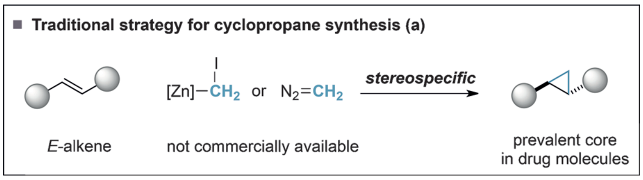
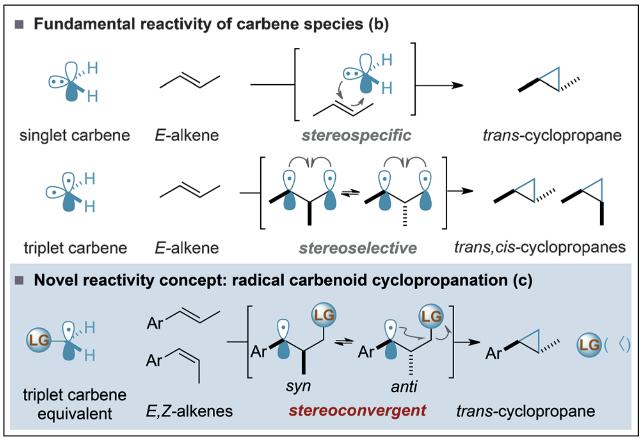
In memory of José Barluenga Mur

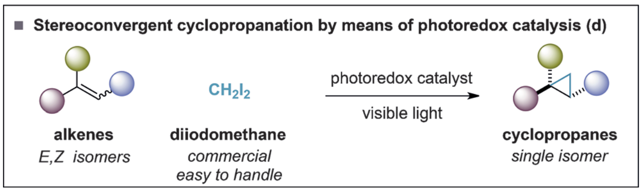
Abstract: *The first stereoconvergent cyclopropanation reaction by means of photoredox catalysis using diiodomethane as the methylene source is described. This transformation exhibits broad functional group tolerance and it is characterized by an excellent stereocontrol en route to trans-cyclopropanes regardless of whether E- or Z-styrene substrates were utilized.*

The catalytic transfer of a methylene group to alkene molecules for the synthesis of cyclopropane cores is a longstanding challenge in chemical synthesis.[1] At present, classical methods rely on the use of well-defined iodomethylzinc reagents[2] or diazomethane,[3] which possess problems with efficiency, availability, and safety [Eq. (a)].[4] Although reliable control of the stereochemistry is achieved, these processes remained confined to the utilization of isomerically pure alkenes. Taking into consideration the inherent difficulties for accessing stereodefined substituted alkenes, the means to design a stereoconvergent cyclopropanation using *E,Z*-alkene mixtures with easy to handle and commercially available methylene sources would be highly appreciated. Despite the potential advantages, it is rather surprising that such strategies remains largely underdeveloped,[5] probably owing to the need for a new reactivity principle by using less-conventional carbene precursors.



It is well established that the electronic configuration of carbenes determines their reactivity and reaction outcome [Eq. (b)].[6] While singlet methylene carbene reacts with *E*-alkenes to give *trans*-cyclopropanes in a stereospecific manner, triplet methylene reacts to isomeric cyclopropane mixtures through a pre-existing equilibrium of the two corresponding biradical species.[6b] Taking this into account, we wondered whether a stereoconvergent cyclopropanation could be within reach using a synthetic equivalent of a triplet carbene containing a radical adjacent to an appropriate leaving group [Eq. (c)].[7] We hypothesized that such radical carbenoid species[8] might lead to stabilized radical intermediates that would be in equilibrium through a simple C–C bond rotation, thus leading to the most stable *trans*-configured cyclopropane. Herein, we report the successful development of such a method using simple CH_2I_2 as the methylene source by means of visible-light photoredox catalysis [Eq. (d)].





Macmillan and Stephenson, among others, have shown that photoredox catalysis allows the generation of transient carbon-centered radicals from activated halide compounds involving a single-electron reduction process.[9] Additionally, Guo recently described a photoredox cyclopropanation that involves a double single-electron reduction of dibromomalonates and generation of α-bromomalonate carbanion intermediates.[5d] However, this method is unable to transfer a simple methylene group. We envisioned that our cyclopropanation reaction mechanism using CH_2I_2 (**2**) would proceed as depicted in Scheme 1. Irradiation of the widely-used ruthenium catalyst $[Ru(bpy)_3]^{2+}$ (**4**; bpy = 2,2′-bipyridine) with visible light would convert to the long-lived

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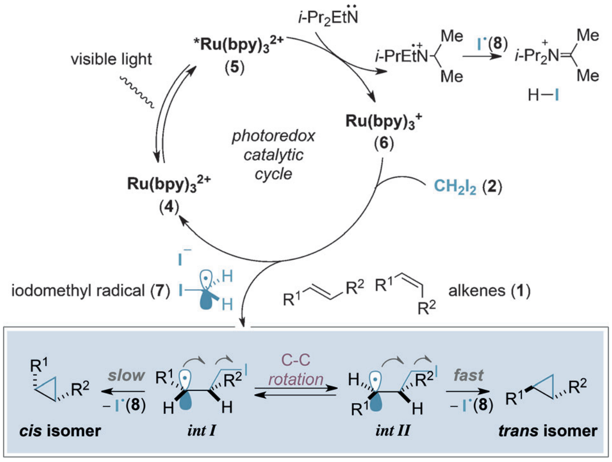
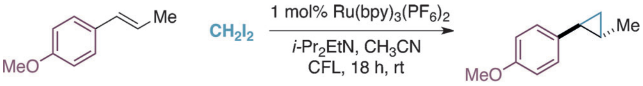


Scheme 1. Working hypothesis.

photoexcited state *[Ru(bpy)$_3$]$^{2+}$ (**5**; $E_{1/2}{}^{(II)*/(I)} = 0.77$ V vs. SCE), which is reduced to [Ru(bpy)$_3$]$^+$ (**6**) with *N*,*N*-diisopropylethylamine by a well-established SET process. The Ru^I intermediate is a strong reductant ($E_{1/2}{}^{(II)/(I)} = -1.33$ V vs. SCE) and would donate an electron to CH$_2$I$_2$ ($E_{red} = -1.44$ V vs. SCE),[10] thereby generating a transient anion radical [CH$_2$I$_2$]$^{-\bullet}$, which evolves into iodomethyl radical (**7**).[11] Addition to *E*,*Z*-alkenes **1** would conduct to intermediates ***int I*** and ***int II***, which would be in equilibrium through a C−C bond rotation. Finally, a cyclization step would take place by homolytic substitution preferentially on intermediate ***int II***, in which both R^1 and R^2 groups are in a favorable relative *anti* orientation.[12] Our envisaged cyclopropanation was initially evaluated using (*E*)-anethole (**1a**) as the alkene substrate. To our delight, in a first round of experiments we identified that the cyclopropanation reaction took place with 59% yield of desired *trans*-cyclopropane **3a** as a single diastereoisomer by using 1 mol% Ru(bpy)$_3$(PF$_6$)$_2$ (**4**), diiodomethane (**2**; 2.5 equiv), *N*,*N*-diisopropylethylamine (5 equiv), acetonitrile (0.1 M) and a 21 W compact fluorescent lamp (CFL) as visible light source (Table 1, entry 1).

Table 1: Optimization studies.[a]



(*E*)-**1a** or E/Z-**1a** (1:2) **2** **3a**

Entry	Alkene **1a**	Additive	Yield **3a** [%][b]
1	*E*	–	59
2	*E*	Na$_2$S$_2$O$_3$,H$_2$O	76(85)[c]
3	*E*	Na$_2$S$_2$O$_3$,H$_2$O	0[d]
4	*E*	Na$_2$S$_2$O$_3$,H$_2$O	0[e]
5	*E*	Na$_2$S$_2$O$_3$,H$_2$O	45[f]
6	*E*/*Z*	Na$_2$S$_2$O$_3$,H$_2$O	79

[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.25 mmol), *i*-PrEt$_2$N (0.50 mmol), CH$_3$CN (1 mL); Na$_2$S$_2$O$_3$ (0.50 mmol), H$_2$O (0.4 mL). Reactions were degassed prior to irradiation. [b] GC/MS yields calculated using acetophenone as internal standard. [c] Yield of isolated product using 1 gram of (*E*)-**1a**. [d] Reaction carried out without *i*-Pr$_2$EtN. [e] Reaction carried out in the dark. [f] Reaction mixture not degassed.

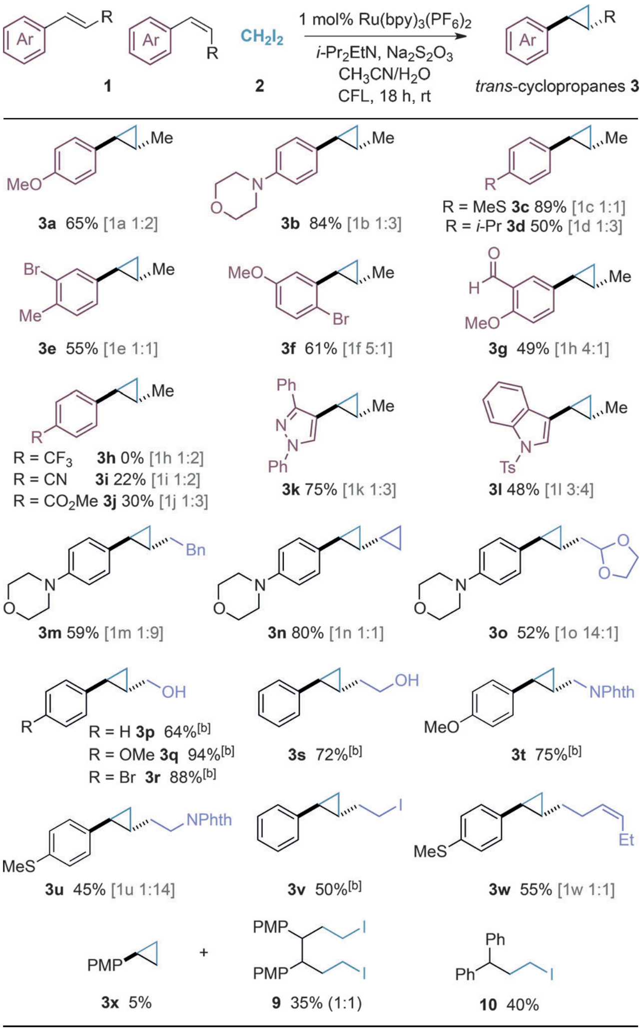
During the course of these studies, we recognized the possibility of I$_2$/I$_3^-$ formation species, which are known to quench the photoexcited state *[Ru(bpy)$_3$]$^{2+}$ (**5**) and would be detrimental for the progress of the reaction.[13] In this sense, we were pleased to find that by adding water and sodium thiosulfate as a suitable iodine quencher to the reaction mixture, the yield of **3a** successfully increased up to 76% (entry 2).

These conditions were adapted for a larger scale reaction using 1 gram of (*E*)-anethole (**1a**) without compromising the efficiency of the process (85% yield, entry 2). Control experiments showed that *i*-Pr$_2$EtN (entry 3) and visible light (entry 4) are essential for this reaction, and also the necessity of degassing the reaction mixture prior to irradiation (entry 5).[14] More importantly, we found what *E*/*Z*-mixtures of **1a** (*E*/*Z*, 1:2) resulted in the exclusive formation of **3a**, thus demonstrating the feasibility of conducting a stereoconvergent cyclopropanation reaction.[15] Additional control experiments showed that (*Z*)-**1a** to (*E*)-**1a** or *cis*-**3a** to *trans*-**3a** isomerizations did not occur during the course of the reaction and UV light (300 nm) does not promote the cyclopropanation as previously described by Kropp for alkyl-substituted alkenes (see the Supporting Information).[11a–c]

Having the optimized reaction conditions in hand, we next investigated the scope of this cyclopropanation by examining a wide range of styrenes **1a**–**x**. As shown in Table 2, this process was successfully applied in substrates functionalized with electron-donating and electron-withdrawing groups (**3b**–**j**) and also with heterocycles (**3k**,**l**).

We noticed that styrenes bearing electron-rich substituents converted to the corresponding cyclopropane in a more efficient manner (**3a**–**c**). It is possible that the nucleophilic character of the benzyl radical ***int II*** plays an important role in the cyclization event (Scheme 1, R^1 = Ar). In fact, no product (**3h**) or low yield (**3i**,**j**) was observed for styrenes bearing moderate/strong electron-withdrawing groups, and alkene decomposition was observed. Having established that the electronics of the aromatic moiety have a direct impact in the outcome of the cyclopropanation reaction, we next evaluated the alkyl substitution for alkenes **1m**–**w**. This procedure was successfully applied to a wide range of alkyl groups functionalized with aromatic rings (**3m**), cycloalkanes (**3n**), acetals (**3o**), alcohols (**3p**–**s**), imides (**3t**,**u**), alkyl iodides (**3v**), or alkenes (**3w**). The excellent level of efficiency for this radical cyclization is notable because no other reaction products have been observed for substrates bearing embedded nucleophiles, which could potentially intercept a benzylic radical intermediate (Table 2; **3m**,**s**,**w**), as well as for substrate **1v** bearing a C−I bond, which could participate in a competitive cyclization for the synthesis of a cyclobutane analogue. However, only cyclopropane **3v** was observed as only product of the reaction. The excellent functional group tolerance of this radical cyclopropanation is illustrated in substrates bearing tertiary amines (**3b**,**m**–**o**) or sulfides (**3c**,**u**,**w**), which generally react with iodomethylzinc reagents generating the corresponding ylide.[16] Furthermore, directing groups were not needed to ensure site-selectivity for a substrate bearing two reactive alkenes (**3w**). Remarkably, only the alkene conjugated with the aromatic group was selectively cyclo-

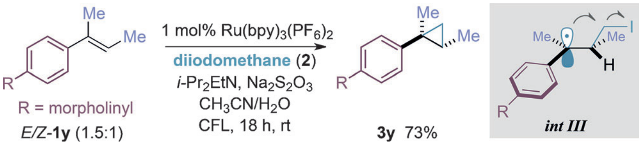
Table 2: Sterereoreoconvergent cyclopropanation.[a]



[a] See the Supporting Information for experimental details; yields are of isolated product. *E*/*Z*-alkene mixtures **1** are shown in brackets; reactions were degassed prior to irradiation; additional **2** (2.5 equiv) and $Na_2S_2O_3$ (5 equiv) were added after 2 hours of reaction. [b] *E* isomer was used. NPhth = phthalimide. PMP = *para*-methoxyphenyl.

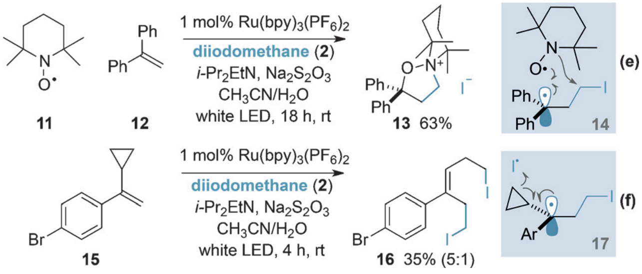
propanated. In contrast to these results, unsubstituted styrenes provided a mixture of cyclopropanes (**3x**) and a dimeric product (**9**), and α-substituted styrenes conducted to open-chain iodoalkanes (**10**).

After this, we investigated whether mixtures of isomeric trisubstituted alkenes could be suited substrates for affecting an otherwise analogous stereoconvergent cyclopropanation. We anticipated that the extension to these substrates would be far from trivial, as the critical C−C bond rotation prior to cyclization was expected to be rather problematic. Gratifyingly, this was not the case and **3y** was cleanly obtained from **1y** (E/Z = 1.5:1) with high efficiency and as a single diastereoisomer, representing a rare example of a stereoconvergent reaction with trisubstituted olefin mixtures (Scheme 2).[5a,17] At present, we believe these results suggest the involvement of ***int III***, in which the aromatic and corresponding methyl group are in a relative *anti* orientation.



Scheme 2. Stereoconvergent cyclopropanation of trisubstituted alkene **1y**.

Finally, we provided compelling evidence for the formation of radical **7**. While the addition of TEMPO to a reaction mixture containing CH_2I_2 did not afford the TEMPO-CH_2I adduct, the presence of one equivalent of 1,1-diphenylethene (**12**) allowed for the formation of a cyclic ammonium iodide salt **13** in 63% yield [Scheme 3, Eq. (e)]. Its formation is explained through the initial coupling of radical **7** with alkene **12** and the generation of a tertiary radical **14**, which couples with TEMPO via radical–radical coupling/cyclization. The radical nature of **7** was further confirmed using the cyclopropyl radical probe **15** [Scheme 3, Eq. (f)]. Formation of alkene **16** suggested the involvement of cyclopropylmethyl radical **17** prior to the ring-opening reaction.[18]



Scheme 3. Mechanistic experiments.

In summary, we have described the first stereoconvergent cyclopropanation reaction of styrenes with CH_2I_2 by means of photoredox catalysis. The transformation is characterized by its mild conditions, broad functional group compatibility, and excellent selectivity profile. We have experimentally demonstrated that the process involves a triplet carbene equivalent able to transfer a CH_2 group to a wide range of *E*,*Z*-alkene mixtures in a stereocontrolled manner.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenoids · catalysis · cyclopropanation · photoredox catalysis · radicals

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Communications

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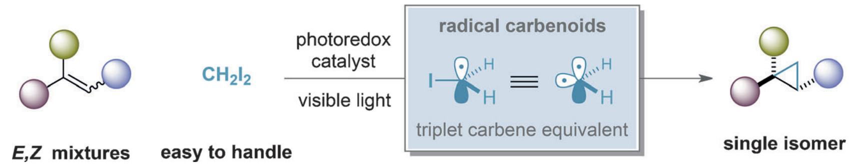

Photocatalytic approach: A stereoconvergent cyclopropanation reaction by means of photoredox catalysis using diiodomethane as the methylene source is described. This transformation exhibits broad functional group tolerance and is characterized by excellent stereocontrol en route to *trans*-cyclopropanes regardless of whether *E*- or *Z*-styrene substrates were utilized.