Photosensitized Dioxygen Enables Intermolecular Cyclopropanation of Alkenes Directly with Active Methylene Compounds

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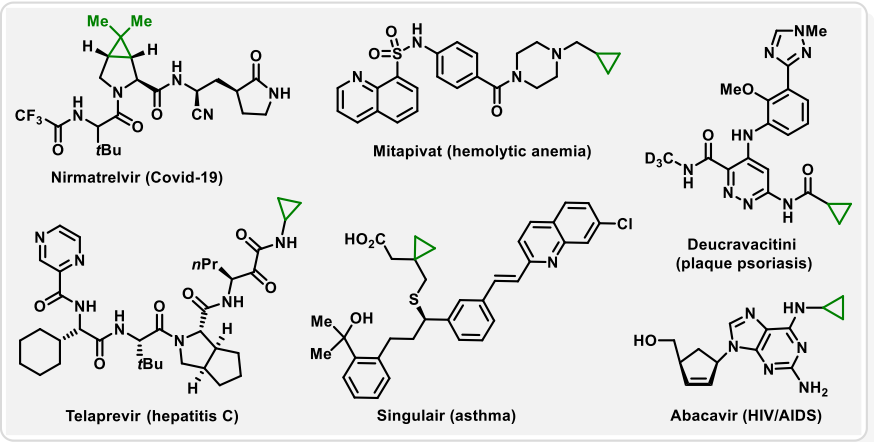
Summary: Cyclopropane, a versatile synthetic intermediate, is forged as a key structural feature in many preclinical, clinical and commercial drugs, and occur as a skeletal motif in numerous natural products. The most prolific technique for its synthesis is the metal-catalyzed reaction of an alkene with a diazoalkane, a highly energetic, reactive and explosive reagent requiring stringent safety precautions. The expedient construction of cyclopropyl ring on alkenes with convenient and innocuous reagents under nonhazardous conditions remains an ongoing challenge. Herein, we report a simple photoredox-catalyzed intermolecular cyclopropanation of unactivated alkenes with a diverse set of active methylene compounds that demonstrates striking conceptual and practical synthetic advances over the known methods. The reaction proceeds with a photoredox catalyst (PC*) excited under a blue LED light in air/O_2 and neutral reaction conditions in the presence of catalytic amounts of iodine, either in the form of added molecular I_2 or generated in situ from alkyl iodides. . The reaction demonstrates a remarkably broad scope on the applicability of 19 different active methylene compounds in 5 different clusters from the standpoint of synthetic tolerability, and tolerates a wide range of functional groups. Moreover, the reaction is also amenable for the cyclopropanation of alkenes in complex molecular architectures, pharmaceuticals and natural products. Mechanistic investigation through the isolation of a series

of intermediate products, probes, control experiments, UV-Vis and fluorescence studies indicate that photosensitized dioxygen plays a vital role in the generation of carbon-centered radicals for both the addition of active methylene compounds to alkenes and ring closure, and catalytically generated iodine recycles the PC.

Main Text: As a prominent member of strained cycloalkanes, cyclopropane is forged as a highly valuable and versatile intermediates in the synthesis of complex molecules and natural products.[1-3] Cyclopropyl moieties are also extensively featured as a pivotal design element in preclinical and clinical drug molecules[4] to achieve specific therapeutic goals, and a key motif in biologically active molecules[5] and natural products.[6,7] For example, the recently FDA-approved drugs, Nirmatrelvir (Paxlovid^{TM}) for Covid-19, Mitapivat (Pyrukynd) for hemolytic anemia, Deucravacitinib (Sotyktu) for plaque psoriasis, and 14 out of 200 top-selling small molecule commercial drugs,[4] including Singulair (asthma), Telaprevir (Hepatitis C) and Abacavir (HIV/AIDS) (Scheme 1), contain a cyclopropyl ring as a key element. The undertaking for cyclopropane-loaded drugs is on a continuous rise and, therefore, cyclopropanation is one of the most investigated strained ring forming reactions in organic synthesis. Yet, the carbonaceous triangle is also among the most difficult rings to create because of the ring and torsional strains, which destabilize the ring (by 17 kcal/mol) and cause it to ring-open during reactions.

Scheme 1. Marketed drugs containing a cyclopropyl ring

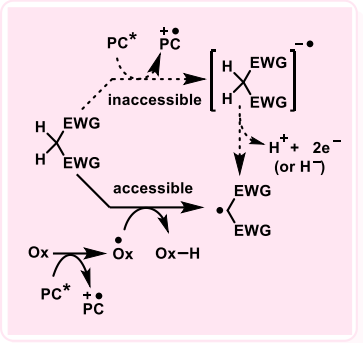


Among limited methods available for intermolecular cyclopropanation,[8], the most preferred and reliable method is the carbene insertion into alkenes.[9,10] This method is profoundly dependent on reactive carbene and metal-carbenoid intermediates [[M]=CR_2], in particular the donor-acceptor Rh-carbenoids,[9-11] derived from highly energetic and explosive diazoalkanes, which require stringent precautions for handling.[12,13] The metal-carbenoids are generally generated from diazomethane (CH_2N_2), $TMSCHN_2$, $PhCHN_2$, and α-diazocarbonyl compounds by decomposition upon transition-metal [M] catalysts,[8,14,15] and more recently under photoredox[16,17] and engineered enzymatic[18-21] conditions. Likewise, the classic Simmons-Smith and related reactions[22,23] demonstrate impressive ability to translate alkenes into cyclopropanes. Yet again, these reactions require a large excess of both unstable, and frequently difficult-to-access, 1,1- and 1,2-dihaloalkanes and highly reactive Et_2Zn or Zn/Cu to generate an adequate quantity of zinc carbenoids for satisfactory reactivity. Recently, emerging catalytic methods have sought to simplify cyclopropanation of alkenes with simple organic precursors.[24] However, these processes also pivot on the generation and exploitation of [M]=CR_2 intermediates,[25-28] and are generally applicable to styrene and 1,3-diene derivatives and often require specialized reagents and a few-step synthetic manipulations to arrive at reactive [M]=CR_2 intermediates in situ. Alternatively, the non-carbenoid approaches, such as the Johnson–Corey–Chaykovsky reaction[29] via a Michael addition-initiated ring closure[30,31] requires a careful molecular engineering to install a leaving

group at a precise reaction site either on Michael acceptors (α,β-unsaturated carbonyls) or Michael donors and a strong base, such as LDA, KHMDS, $NaNH_2$ or BuLi, to enolize the Michael donors for sufficient nucleophilicity. Additionally, the Kulinkovick reaction,[32-34] which converts terminal alkenes into cyclopropyl alcohols and amines, suffers fundamentally from functional group incompatibility and 1,2-addition reactions owing to the use of greater than stoichiometric amounts of titanium salts and alkyl Grignard reagents to generate sufficient quantity of titanacyclopropanes in situ as cyclopropanating reagents.

Evidently, the catalytic intermolecular construction of cyclopropyl rings on unactivated alkenes conveniently with simple, readily available, bench-stable and non-explosive chemicals that is also operationally straightforward and broadly applicable is an ongoing challenge in organic synthesis.[35-39] Herein, we disclose a simple photoredox approach for the intermolecular cyclopropanation of unactivated alkenes directly with active methylene compounds through a cooperativity of photosentized dioxygen (O_2) and alkyl halide via an electron relay system (Scheme 2). This new method offers a most convenient protocol with bench-stable chemicals under neutral reaction conditions in air/O_2 without requiring special safety and sensitivity precautions (such as stringent N_2 environment and glovebox). In addition, since hundreds of active methylene compounds with varied functional substituents are commercially available and an almost unlimited number of their analogs can be readily synthesized and stored for prolonged periods for use on demand, the current reaction provides a simplistic, practical, and broad-scope method for the intermolecular cyclopropanation of unactivated alkenes.

Scheme 2. Cooperative Electron Relay for α-H Abstraction

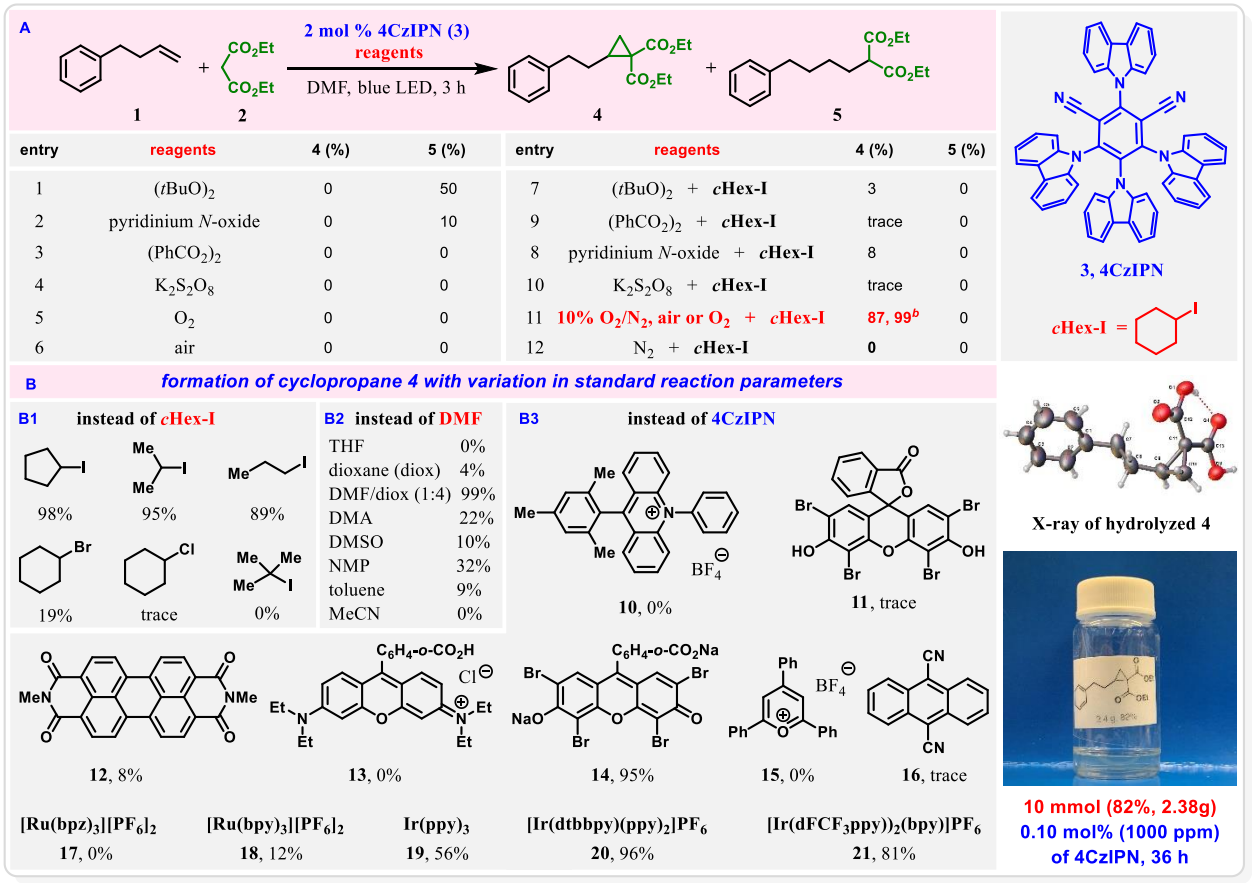


The direct cyclopropanation of alkenes with active methylene compounds requires the removal of two protons and two electrons (or H_2) through redox chemistry (Scheme 2). We envisioned that such a process could be mediated by an excited state photocatalyst (PC*) via stepwise electron transfer (ET) and the generation of α-carbon-centered radicals. Since the direct ET reduction of an active methylene group to remove a hydride might not be amenable from an acidic α-carbon center from a thermodynamic standpoint, we opted for the intermediacy of photoexcited oxidants to generate high energy radicals to function as radical relay for α-H abstraction. Accordingly, we initially examined a range of common peroxide oxidants with 4CzIPN as a photocatalyst (PC) under a blue LED light to generate intermediary radicals with anticipation to subsequently abstract α-H atom from an active methylene set (Scheme 3) (entries 1-6).[40,41] When 4-phenylbutene and diethyl malonate were taken as reactants, di-*tert*-butyl peroxide and pyridiunium *N*-oxide facilitated hydroalkylation with no cyclopropanation products observed (entries 1-2). Use of oxygen, a photosensitizable oxidant to generate a superoxide anion,[42] also didn't produce any cyclopropanated product (entry 5). However, we discovered that a combination of peroxide oxidants and alkyl iodides, such as cyclohexyl iodide (*c*Hex-I), began to furnish the cyclopropanated product **4** in observable amounts (entries 7-10). Remarkably, when O_2 was combined with *c*Hex-I, the photocatalytic reaction furnished the cyclopropanated product **4** in quantitative yield in 3 h (entry 11). The formation of the cyclopropyl ring was unambiguously established by a single crystal X-ray analysis of hydrolyzed product **4** as dicarboxylic acid. Control

experiments under N_2 and in the absence of alkyl iodide furnished no product (entries 5, 12), indicating that dioxygen and alkyl iodide were critical in the success of the reaction.

Further studies indicated that the reaction could be performed simply in air and even with only 10% O_2 in nitrogen (entry 11). Reactions could be conducted with 0.10 mol% (1000 ppm) of the photocatalyst in a small scale (0.10 mmol), which furnishes the product in quantitative yield in 3 h. Large scale (10 mmol) reactions could also be performed with 1000 ppm photocatalyst under the current reaction conditions albeit requiring a longer reaction time and with a slight decrease in the yield (82%, 2.38 g). Other alkyl iodides, except *tert*-alkyl iodide, could be used instead of cyclohexyl iodide (C1). Alkyl bromides and chlorides were not effective. The reaction proceeded most effectively in DMF or DMF/dioxane (1:4), and other polar and mid-polar solvents were either not effective or generated the cyclopropyl product **4** in low yields (C2). Next, we examined different organic and organometallic PC's with a range of redox ability for their efficacy. Among several common PC's examined (C3), Eosin Y sodium salt (**11**), $[Ir(dtbbpy)(ppy)_2][BF_4]$ (**20**) and $[Ir(dFCF_3ppy))_2(bpy)]PF_6$ (**21**) furnished the product **4** in high yields while $Ir(ppy)_3$ (**19**) was moderately effective.

Scheme 3. Reaction Parameter Optimization[a]



Reaction conditions: [a]Reactions were conducted in 0.10 mmol scale with 0.20 mmol diethyl malonate, unless stated otherwise, in 0.50 mL DMF at 440 nm blue LED (36 Watt Kessil lamp at 100% intensity) and ambient temperature (~35 °C controlled by fans) in 1 dram capped glass vials. Yields were determined by GC with trimethoxybenzene as a standard. [b]O_2, 5% O_2/N_2 and air were supplied through a balloon. 87% yield refers to the use of 10% O_2/N_2

Prompted by the unique roles of alkyl iodides and O_2 for catalytic turnover, we ventured to study the reaction mechanism. Analysis of solutions of PC, alkyl iodide and 4-phenylbutene (**1**) in DMF in different combinations by UV-Vis and fluorescence spectroscopies indicated that there was no interaction of alkyl iodide with either of the PC and alkene **1** (see SI for details). Independent reactions conducted with dodecyl and hexadecyl iodides under the standard catalytic conditions confirmed the formation alkyl formates (**22**, 65%; **23**, 72%) generated from the reaction

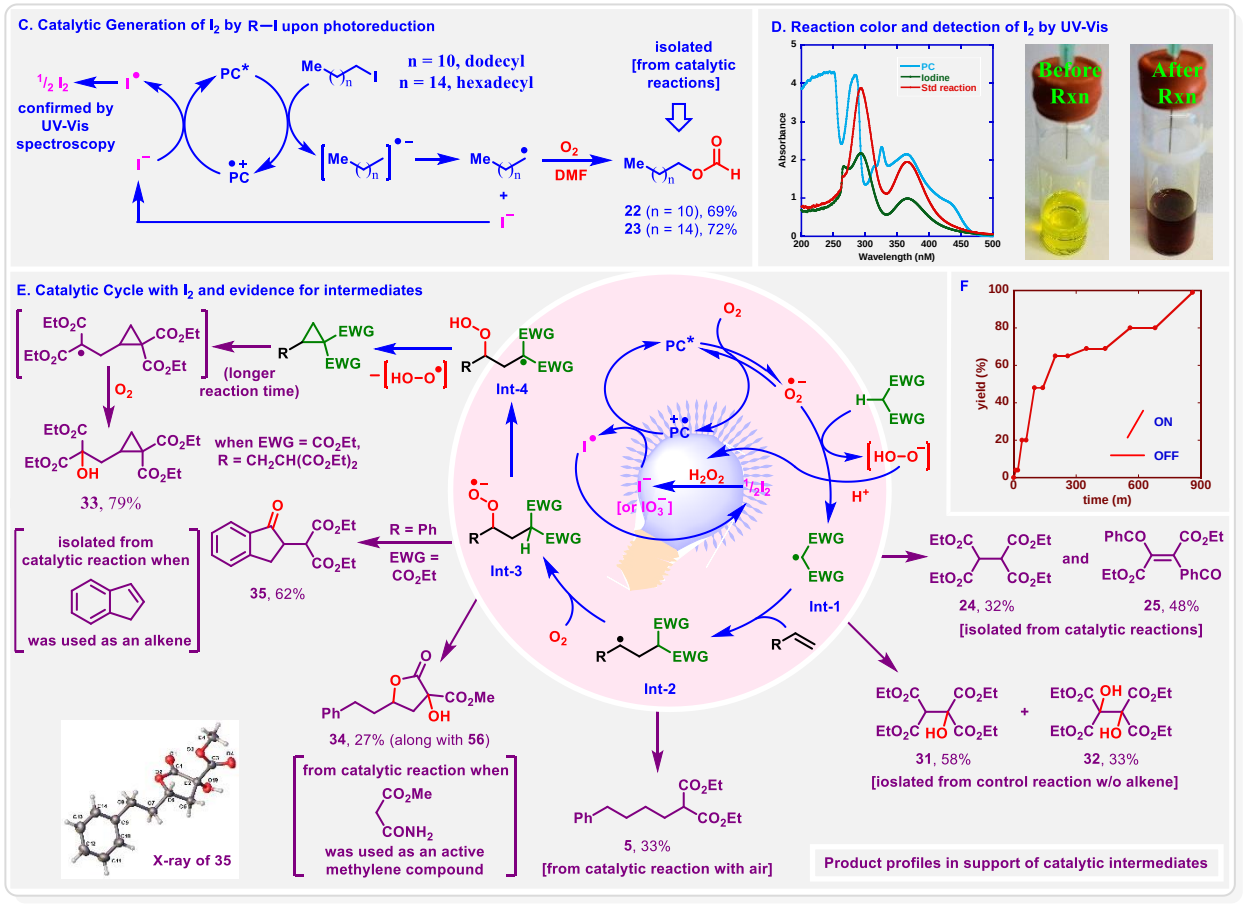
of alkyl radicals with O_2 in DMF along with the cyclopropyl product **1** and unreacted alkyl iodides in 78-85% and 23-32%, respectively (Scheme 4C). Since reaction solutions usually turned reddish brown during reaction, we further analyzed reaction mixtures by UV-Vis spectrometer and confirmed the generation of I_2 (Scheme 4D). These experiments suggested that alkyl radicals are not involved in the reduction of PC radical cations for catalytic turnover. Rather iodide (I^-) or iodate (IO_3^-), generated from the hydrolysis or the oxidation of I_2, furnish the required electrons to PC radical cations.[43,44] In order to further confirm the role of I_2, we conducted the standard catalytic reaction by replacing *c*Hex-I with 5 mol% I_2. Pleasingly, the reaction generated the cyclopropyl product **4** in 99%, 89% and 83% yields under O_2, air and 10% O_2 in N_2 in 3 h (Scheme 5G).

We propose a catalytic cycle for the cyclopropanation reaction based on above findings, and a series of additional experiments and characterization of 13 different products (Scheme 4E) supporting the existence of various catalytic intermediates as outlined in Scheme 4. We anticipate that dioxygen is first photosensitized by PC* to superoxide ion ($O2^{\bullet-}$), which abstracts α-H from active methylene compounds to generate α-C-radicals. We have confirmed the formation of these α-C radicals by the isolation of their saturated dimer **24** and alkene dimer **25** as side products from catalytic reactions. Since both the cyclopropyl product **4** and the alkene dimer **25** could also arise from carbene intermediates, we designed an intramolecular competition experiment in which diethyl α-allyl malonate bearing a methine (α-C-H) group was reacted with di-*tert*-butyl malonate containing a methylene (α-CH_2) group (Scheme 5H). The reaction yielded a 1:1 mixture of the expected cyclopropyl product **26** along with another cyclopropyl product **27** derived from the innate methine group, indicating that carbene intermediates are not generated in the reaction. In the absence of alkene, the α-C radicals undergo radical dimerization followed by further oxidation to generated mono- and dihydroxylated products (**31**, **32**). Additionally, when a reaction of diethyl α-allyl malonate with diethyl malonate was allowed to continue longer, α-hydroxylated cyclopropyl

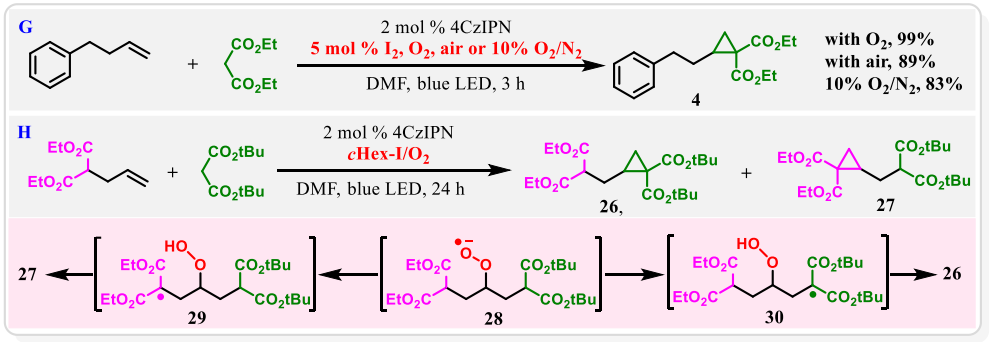
product **33** was generated, suggesting that the superoxide ion ($O2^{\bullet-}$) or the radical anions are capable of abstracting α-H from active methylene compounds (such as in Int-1, Int-3 and Int-4).

The α-C-radicals then undergo addition to alkenes to form secondary C-radicals, which subsequently react with dioxygen to generate peroxy radical anions. The radical addition steps for the formation of Int-2 and Int-3 are supported by the isolation of hydroalkylation product **5** from the standard reaction under reduced O_2 concentration (air), and a hydroxylactone **34** via deaminative oxidation when malonamide was used. In addition, a reaction of indene with diethyl malonate generated an oxo-product **35** further confirming the existence of Int-3 in solution. The radical anions (Int-3) then abstract the intramolecular α-H to generate α-C radicals, which then subsequently undergo radical 1,3-substitution with the peroxide to create the cyclopropyl ring. The possibility for radical chain propagation was eliminated based on the on-off experiment in which the product was formed only when the reaction was exposed to blue LED (Scheme 5F).

Scheme 4. Proposed Catalytic Cycle along with Additional Product Profiles for Mechanism



Scheme 5. Catalytic reaction with I_2 and internal competition study

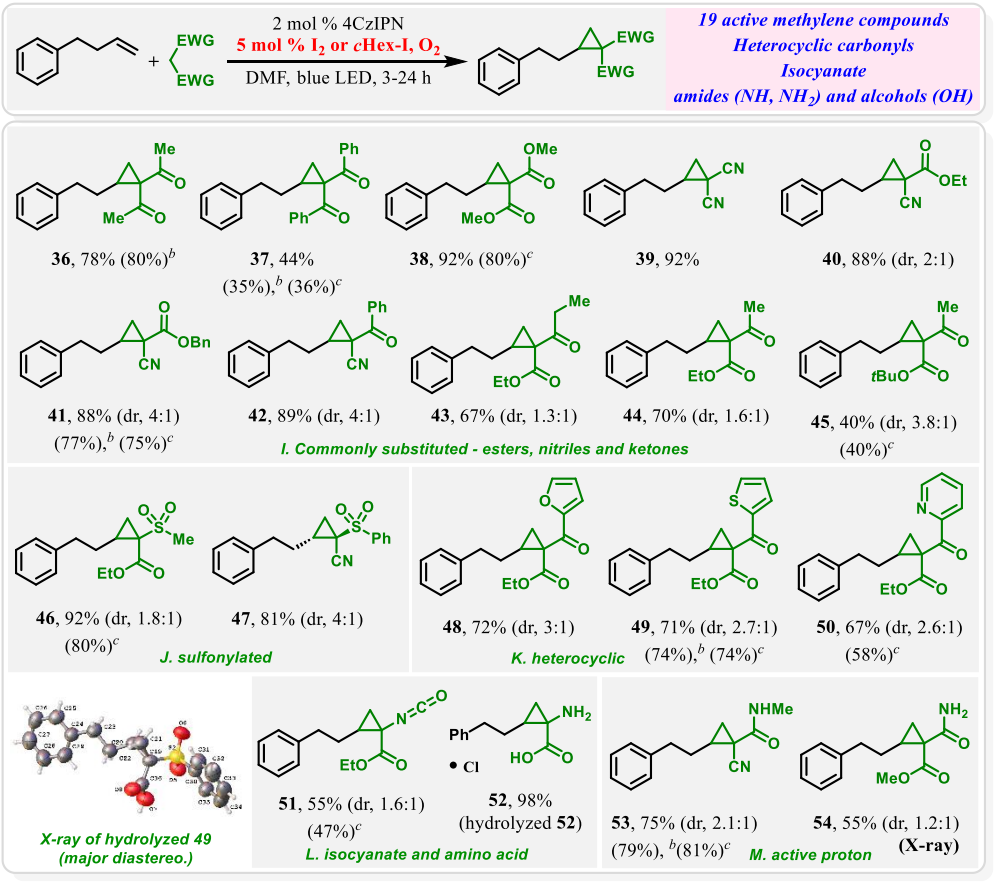


With optimized reaction conditions, we explored the scope of the cyclopropanation reaction with regard to the active methylene compounds in the presence of both stoichiometric *c*Hex-I and catalytic I_2 and in air and O_2 (Scheme 6). The reaction under both catalytic protocols demonstrated a remarkably broad scope on the applicability of the active methylene compounds,

19 in total categorized in 5 different clusters from the standpoint of synthetic tolerability, and generated a suite of 1,1-dicarbonylcyclopropanes. Initially, we examined the reactivity of the most common active methylene compounds bearing esters, ketones and nitriles with the same or different functional integrity on the two termini of the methylene sets (**36**-**45**) (I). The reactions with methylene sets bearing different functionalities, such as cyanoesters, ketoesters and ketonitriles (**40**-**45**), proceeded with moderate to good diastereoselectivity to generate trisubstituted cyclopropanes (dr, up to 4:1). The diastereoselectivity could also be increased (1.6:1 to 3.8:1) by replacing Et in **44** with t-Bu in **45**. The reaction also displayed high efficacy with sulfonylated methylene sets and afforded the trisubstituted sulfonylcyclopropane products (**46**-**47**) in high yields and good diastereoselectivity (J). An X-ray analysis of the hydrolyzed product of the major disastereomer of sulfonyl cyclopropane **47** revealed that the larger groups, the sulfonyl and the alkyl, were disposed in an anti-fashion along the cyclopropyl plane confirming steric control for diastereoselectivity. The reaction parameters were also amenable for the introduction of carbonylated heterocycles on cyclopropyl cores as demonstrated by the formation of products from active methylene sets bearing furanyl, thiophenyl and pyridyl rings along with esters (**48**-**50**) with moderate to good diastereoselectivity (K). Most importantly, the method also tolerates with competence some of the most sensitive functional groups. For example, isocyanate (L) can be readily introduced into cyclopropane rings (**51**), an important building block in pharmaceutical and medicinal chemistry to introduce cyclopropyl amides (anticancer drug Lenvatinib[45]) and cyclopropyl urea anologs[46,47] (NPR-A agonist[48]), for which no direct method exists currently, and is synthesized in three steps commencing with the cyclopropanation of acrylic esters with diazomethane. In addition, the isocyanate cyclopropane **51** could be readily hydrolyzed to obtain cyclopryl amino acid **52** in quantity yield. 1° and 2° amides containing active hydrogens are also compatible for the cyclopropanation of alkenes (M), which generate cyclopropyl carboxamides (**53**-**54**) in excellent yields with moderate diastereoselectivity. The products of the current process, such as 1,1-dicarbonyl- and 1-carbonyl-1-sulfonylcyclopropanes,

are known to function as inhibitors against a range of biological targets including BACE inhibitors for Alzheimer's disease[49,50,51] and, therefore, represent significant design elements in drug discovery.

Scheme 6. General Scope on Active Methylene Compounds[a]

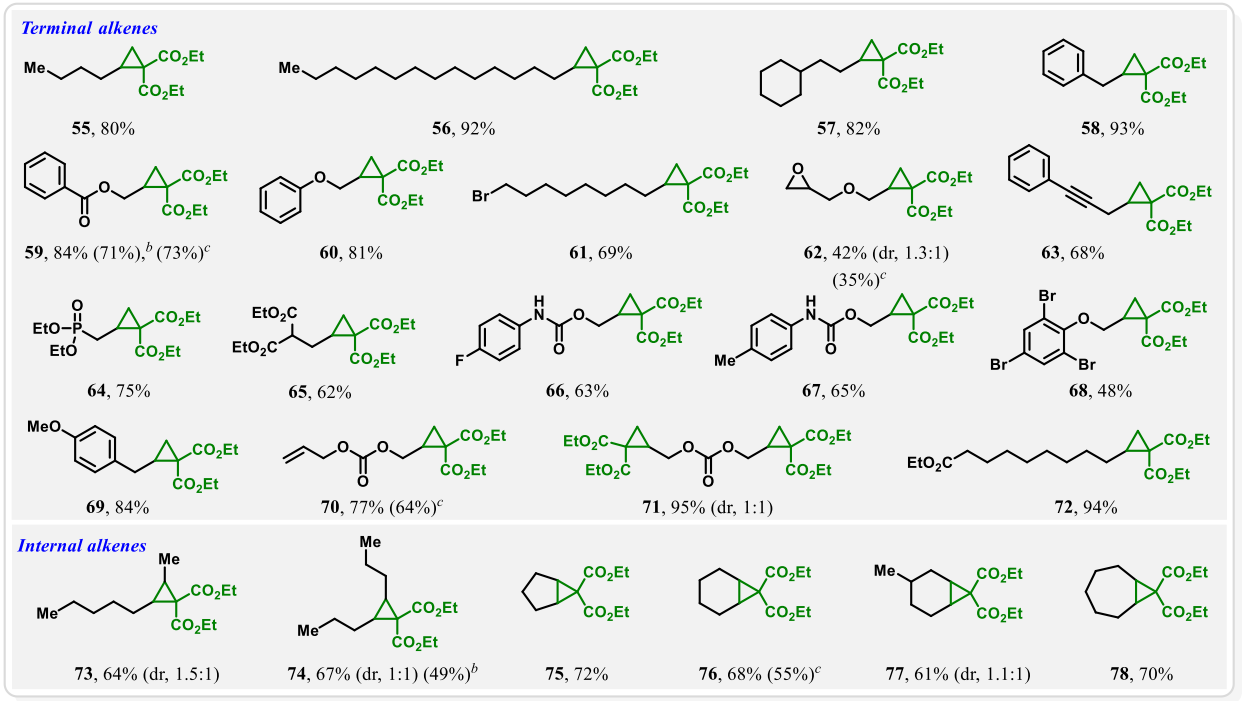


Reaction conditions: [a]Reactions were conducted in 1.0 mmol scale, unless stated otherwise, in 5.0 mL DMF at 440 nm blue LED (36 Watt Kessil lamp at 100% intensity) and ambient temperature (~35-40 °C controlled by fans) under O_2 in 6 dram capped glass vials. Reported yields are for isolated products. dr was determined by ^{1}H NMR. Yields in parenthesis are for 0.10 mmol scale with 5 mol % I_2. [b]Under air in 3 h. [c]Under O_2 in 3 h.

Next, we examined the scope of the cyclopropanation reaction on alkenes taking diethyl malonate as a representative active methylene compound (Scheme 7). The reaction proceeds

efficiently with terminal alkenes containing acyclic and cyclic alkyl, and aryl backbones, and tolerates various functional groups, such as ester, carbonate, carbamate, epoxide, ether, alkyne, alkyl bromide and aryl bromide (**55**-**72**). Moreover, alkenes bearing active hydrogens on α-carbons, such as phosphates (**64**) and malonate esters (**65**), and on amide nitrogen, like secondary carbamates (**66**-**67**), are also excellent substrates for cyclopropanation. The reaction can be controlled for monocyclopropanation on substrates containing two alkenes (**70**) and is also applicable for dicyclopropanation on both alkenes (**71**) further highlighting the synthetic utility for selective cyclopropanation. This method also works well for the cyclopropanation of more sterically challenging linear and cyclic disubstituted internal alkenes, which generated tetrasubstituted cyclopropyl products (**73**-**78**).[52]

Scheme 7. General Scope on Alkenes and Functional Group Compatibility[a]

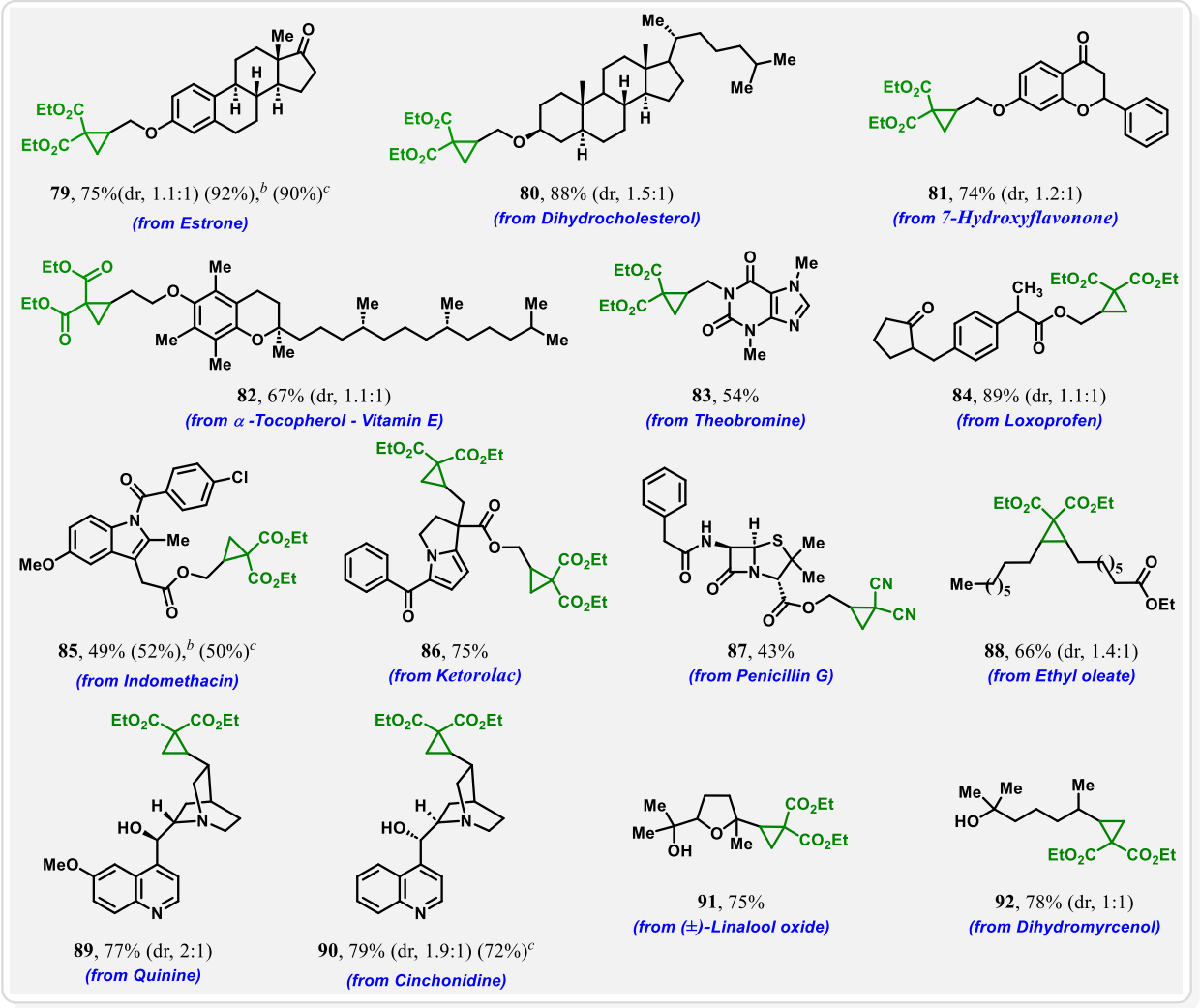


Reaction conditions: [a]Reactions were conducted in 1.0 mmol scale, unless stated otherwise, in 5.0 mL DMF at 440 nm blue LED (36 Watt Kessil lamp at 100% intensity) and ambient temperature (~35-40 °C controlled by fans) under O_2 in 6 dram capped glass vials. Reported

yields are for isolated products. dr was determined by ^{1}H NMR. Yields in parenthesis are for 0.10 mmol scale with 5 mol % I_2. [b]Under air in 3 h. [c]Under O_2 in 3 h.

We also examined the scope of the reaction on complex pharmaceuticals and natural products bearing alkenes (Scheme 8). The alkenes in *O*-allylated steroids estrone (**79**) and dihydrocholesterol (**80**), and *O*-allylated 7-hydroxyflavonone (**81**) and α-tocopherol (vitamin E) (**82**) generated cyclopropanated products in good to excellent yields. *N*-allylated alkaloid heterocycle theobromine (**83**), and *O*-allylated nonsteroidal anti-inflammatory drugs (NSAIDs) loxoprofen (**84**) and indomethacin (**85**) were similarly cyclopropanated with diethyl malonate. The *C*- and *O*-diallylated NSAID ketorolac (**86**) was efficiently converted to a product with two trisubstituted cyclopropyl rings. Drugs, such as penicillin G (**87**), containing acidic NH and sensitive β-lactam ring were also tolerated. The naturally occurring internal alkene in the fatty acid ester ethyl oleate (**88**) also furnished tetrasubstituted cyclopropyl product in good yield. Additional innate alkenes in aliphatic and heterocyclic natural products bearing a free hydroxy group, such as alkaloids quinine (**89**) and cinchonidine (**90**), and terpenes linalool oxide (**91**) and dihydromyrcenol (**92**), underwent efficient cyclopropanation without interference from the unprotected alcohols present in the molecular backbones.

Scheme 8. Scope on Drugs and Natural Products-Derived Alkenes[a]



Reaction conditions: [a]Reactions were conducted in 1.0 mmol scale, unless stated otherwise, in 5.0 mL DMF at 440 nm blue LED (36 Watt Kessil lamp at 100% intensity) and ambient temperature (~35-40 °C controlled by fans) under O_2 in 6 dram capped glass vials. Reported yields are for isolated products. dr was determined by ^{1}H NMR. Yields in parenthesis are for 0.10 mmol scale with 5 mol % I_2. [b]Under air in 3 h. [c]Under O_2 in 3 h.

In summary, we have developed a simple visible light photoredox protocol for intermolecular cyclopropanation of unactivated alkenes with active methylene compounds. The cyclopropanation is enabled by a photoredox catalyst excited under blue LED in ambient conditions with air/O_2 in the presence of *c*Hex-I or 5 mol% I_2, barring requirements of stringent

safety and precautionary protocols for this class of reaction. Mechanistic studies and the isolation of intermediate products indicate that the reaction proceeds via cooperative electron relay between PC* and dioxygen to abstract α-H from active methylene compounds and that exogenous or in situ-generated catalytic I_2 is required for catalytic turnover. The reaction demonstrates a remarkably broad scope with the participation of 19 different active methylene compounds bearing a diverse set of functionality, works for terminal and internal alkenes, and tolerates a great variety of synthetically important, and often challenging, functional groups. A broader synthetic applicability was also demonstrated by the cyclopropanation of alkenes in complex molecules including pharmaceuticals and natural products. We anticipate that the development of this method creates a new dimension in the field of cyclopropanation, and will inspire further global research.

Acknowledgement: We gratefully acknowledge the NIH NIGMS (R35GM133438) and The Pennsylvania State University (PSU) for support of this work. We thank Dr. Hemant Yennawar at the Pennsylvania State University for the X-ray crystallographic analysis of compounds **4**, **32** and **37**. The X-ray instrument was funded by the NIH SIG S10 grants (1S10OD028589-01 and 1S10RR023439-01).

Author Contributions: R. G. conceived of and directed the project and prepared the manuscript. R. G. and D. P. P. designed the experiments. D. P. P. performed experiments. D. P. P., A. P., R. K. T. and S. M. collected and analyzed data.

Competing Interest: The authors declare no conflict of interest.

Additional Information: The supporting data for the findings of this study are available within the manuscript and its supplementary information. The X-ray crystallographic data for compound **4** (deposition No. 2224825), and hydrolyzed products of compounds **32** (deposition No. 2224826)

and **37** (deposition No. 2224828) are available from the Cambridge Crystallographic Data Center (CCDC).

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