Communication

Intermolecular Organophotocatalytic Cyclopropanation of Unactivated Olefins

David M. Fischer,[‡] Henry Lindner,[‡] Willi M. Amberg,[‡] and Erick M. Carreira*

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ABSTRACT: Intermolecular cyclopropanation of mono-, di-, and trisubstituted olefins with α-bromo-β-ketoesters and α-bromomalonates under organophotocatalysis is reported. The reaction displays broad functional group tolerance, including substrates bearing acids, alcohols, halides, ethers, ketones, nitriles, esters, amides, carbamates, silanes, stannanes, boronic esters, as well as arenes, and furnishes highly substituted cyclopropanes. The transformation may be performed in the presence of air and moisture with 0.5 mol % of a benzothiazinoquinoxaline as organophotocatalyst. Mechanistic investigations, involving Stern−Volmer quenching, quantum yield determination, and deuteration experiments, are carried out, and a catalytic cycle for the transformation is discussed.

Cyclopropanes are found in natural products, pharmaceuticals, agrochemicals, and fragrances and constitute useful synthetic building blocks.[1] Their high strain energy and unique bonding pattern makes them distinct, with reactivity not observed for other carbocycles.[2] A variety of classic cyclopropanation methods have been devised: metal-catalyzed reactions with diazoalkanes,[3] Simmons−Smith,[4] Kulinkovich,[5] as well as Corey−Chaykovsky[6] reactions, and carbanion alkylations.[7] Additional approaches employ noble metals or photocatalysis.[8] Herein, we report the first intermolecular organophotocatalyzed cyclopropanation of unactivated olefins with α-bromo-β-ketoesters and α-bromomalonates (Figure 1).

intermolecular • broad scope • single-step
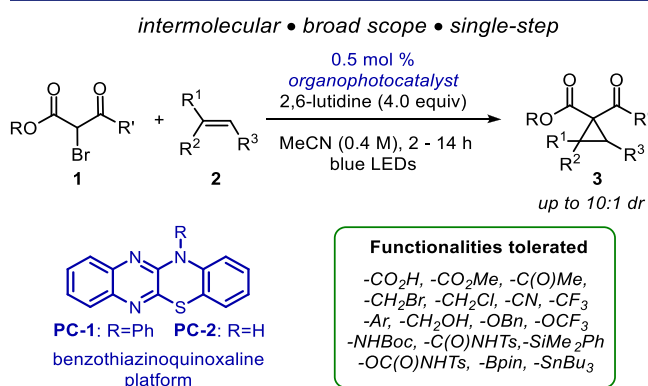
Figure 1. Intermolecular organophotocatalyzed cyclopropanation of unactivated olefins.

Photochemically driven transformations have recently been the focus of intense investigations.[9] Ir or Ru complexes as photocatalysts have enabled the application of visible-light photocatalysis in the service of synthesis. Parallel approaches, involving organophotocatalysts, have been investigated.[10] Polyaromatics have been used as dyes, and their application in organophotocatalysis is rapidly increasing.[11]
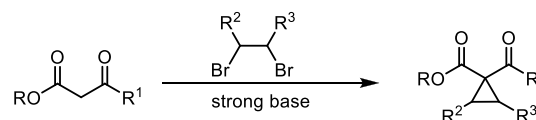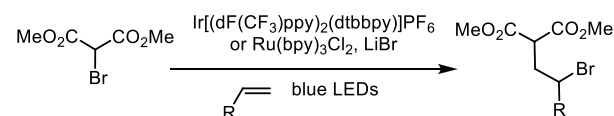
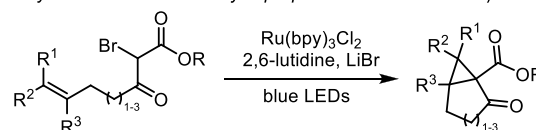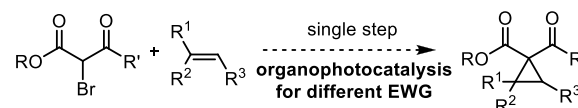**Figure 2.** Approaches toward γ-bromomalonates and cyclopropanes.

In connection with our interest in olefin functionalization[12] and photocatalysis,[13] we set out to develop approaches to substituted cyclopropanes. Simple cyclopropanes can be
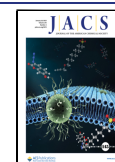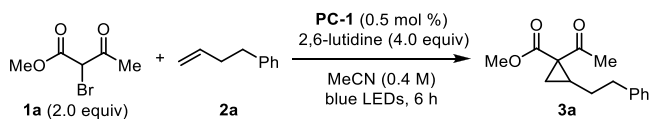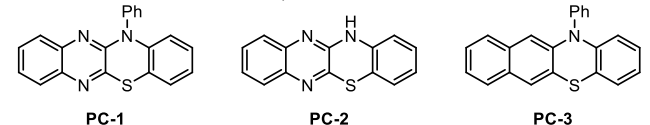
Table 1. Optimization of Reaction Conditions[a]

Entry	Deviation from std. conditions	Yield of 3a (%)[b]
1	10 mol % PC-3, 20 mol % LiBF₄ 2.0 equiv 2,6-lutidine, Ar	24
2	10 mol % PC-1, 20 mol % LiBF₄ 2.0 equiv 2,6-lutidine, Ar	43
3	none	97
4	Ar	98
5	Ru(bpy)₃Cl₂ instead of PC-1	6
6	PC-2 instead of PC-1	62
7	without PC-1	0
8	dark, 40 °C	0
9	without 2,6-lutidine	0

[a]Reaction temperature rises to 40 °C. [b]Yields obtained by ¹H NMR (mesitylene as internal standard).

synthesized alkylatively from β-ketoesters and *vic*-dibromides via γ-bromo-β-ketoesters.[7a,14] Stephenson has accessed γ-bromomalonates directly from olefins through intermolecular atom-transfer radical addition (ATRA) of α-bromomalonates with LiBr and Ru(bpy)₃Cl₂ or Ir[(dF(CF₃)-ppy)₂(dtbbpy)]PF₆ (Figure 2).[15] Tokuyama

subsequently examined intramolecular cyclopropanations of α-bromo-β-ketoesters in the presence of 2,6-lutidine, LiBr, and Ru(bpy)₃Cl₂.[16] However, direct intermolecular cyclopropanation of α-bromo-β-ketoesters with unactivated olefins remains elusive.

As part of a study on semipinacol rearrangements, Ohmiya and Nagao proposed reduction of bromomalonates by benzophenothiazine photocatalysts.[17] We hypothesized benzophenothiazines could also effect reduction of bromoketoesters, leading to cyclopropanation. However, when we subjected α-bromo-β-ketoester 1a and phenylbutene 2a to *N*-phenyl benzophenothiazine (PC-3) (10 mol %) and 20 mol % LiBF₄, along with 2.0 equiv 2,6-lutidine under an inert atmosphere in MeCN (0.4 M), cyclopropane 3a was isolated in merely 24% yield (Table 1, Entry 1). Our analysis of the UV−vis spectrum of PC-3 revealed poor absorbance ($\varepsilon_{446\ nm}$ < 100 M⁻¹ cm⁻¹).

In identifying reducing photocatalysts with larger extinction coefficients in the blue-light range, a study of the cyclophosphinylation reaction of diaryl diynes caught our attention.[18] Therein, Xu examined and characterized dyes electro- and photochemically. Among these, the two benzothiazinoquinoxaline derivatives, PC-1 and PC-2, stood out based on their red-shifted absorption maxima, increased absorbance in the blue-light range ($\varepsilon_{446\ nm}$ > 3000 M⁻¹ cm⁻¹), and suitable reduction potential. We hypothesized they could be appropriate catalysts for cyclopropanation of unactivated olefins with α-bromo-β-ketoesters. To the best of our knowledge, they have not been further investigated as photocatalysts.
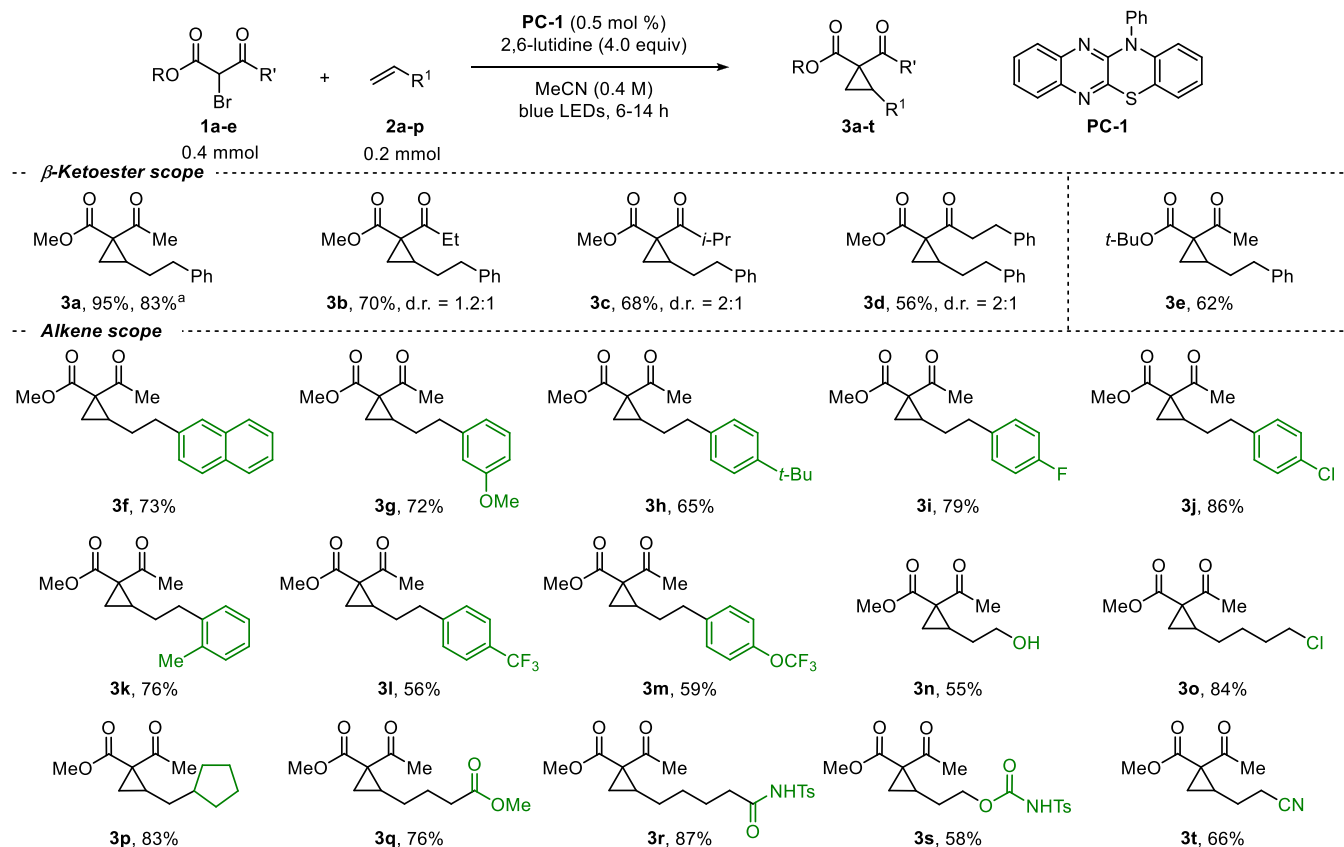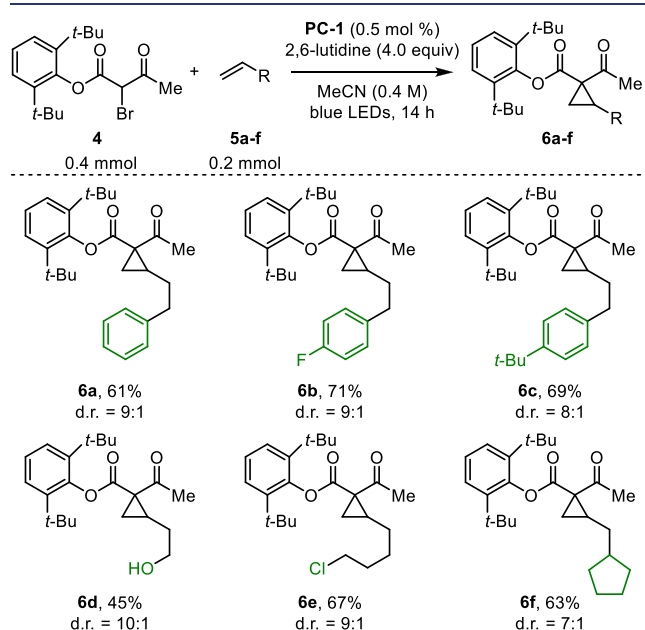

Figure 3. Substrate scope. d.r. = 1:1 (¹H NMR analysis of unpurified reaction mixture) unless otherwise indicated. [a]Conducted on 2.0 mmol scale.

Subjecting **1a** and **2a** to 10 mol % **PC-1**, 20 mol % LiBF$_4$, and 2.0 equiv 2,6-lutidine under argon in MeCN (0.4 M)


Figure 4. Substrate scope. d.r. determined by ^{1}H NMR analysis of unpurified reaction mixture.

(Table 1, Entry 2) gave cyclopropane **3a** in 43% yield. Reaction optimization (see SI) revealed the benefits of additional equivalents of base and, surprisingly, indicated that the presence of Li salt is detrimental. Catalyst loading was reduced to 0.5 mol % without decreasing product formation. Under optimized conditions (0.5 mol % **PC-1**, 4.0 equiv 2,6-lutidine in MeCN (0.4 M), Entry 3), **3a** was formed in 97% yield. Notably, in contrast to previous reports, this transformation is not sensitive to air, giving identical yields under ambient atmosphere (Entry 4). For comparison, when the reaction was conducted with Ru(bpy)$_3$Cl$_2$ under otherwise identical conditions, **3a** was produced in 6% yield (Entry 5). Photocatalyst **PC-2** also furnished the product, albeit in lower yield than **PC-1** (Entry 6). The reaction did not provide product in the absence of organophotocatalyst or light, and **2a** was fully recovered (Entries 7 and 8). Reaction without 2,6-lutidine led to formation of complex mixtures (Entry 9, see SI).

We investigated the substrate scope with α-bromo-β-ketoesters next (Figure 3). A variety of γ-substituted α-bromoacetoacetates were employed, including bromoacetoacetate along with ethyl, iso-propyl, and phenethyl ketones **1a−d**, affording cyclopropanes **3a−d** in 56−80% yield from 4-phenylbutene. tert-Butyl ester **1e** gave **3e** in 62% yield. Next, a collection of alkene substrates was examined. Naphthyl and anisole adducts **3f** and **3g** were isolated in 73% and 72% yield, respectively. Electron-poor and -rich aryl groups were tolerated, leading to **3h−m** in 56−86% yield. Primary alcohol **3n** and alkyl chloride **3o** were obtained in 55% and 84% yield, respectively. Notably, the transformation tolerates O−H protic functional groups, which under conditions involving carbenes instead favor O−H insertion.[19] **3p−t** were accessed in 58−87% yield.

The rather modest diastereoselectivity in the cyclopropanation prompted us to examine esters that may induce diastereocontrol. When 2,6-di-tert-butylphenyl ester **4** was
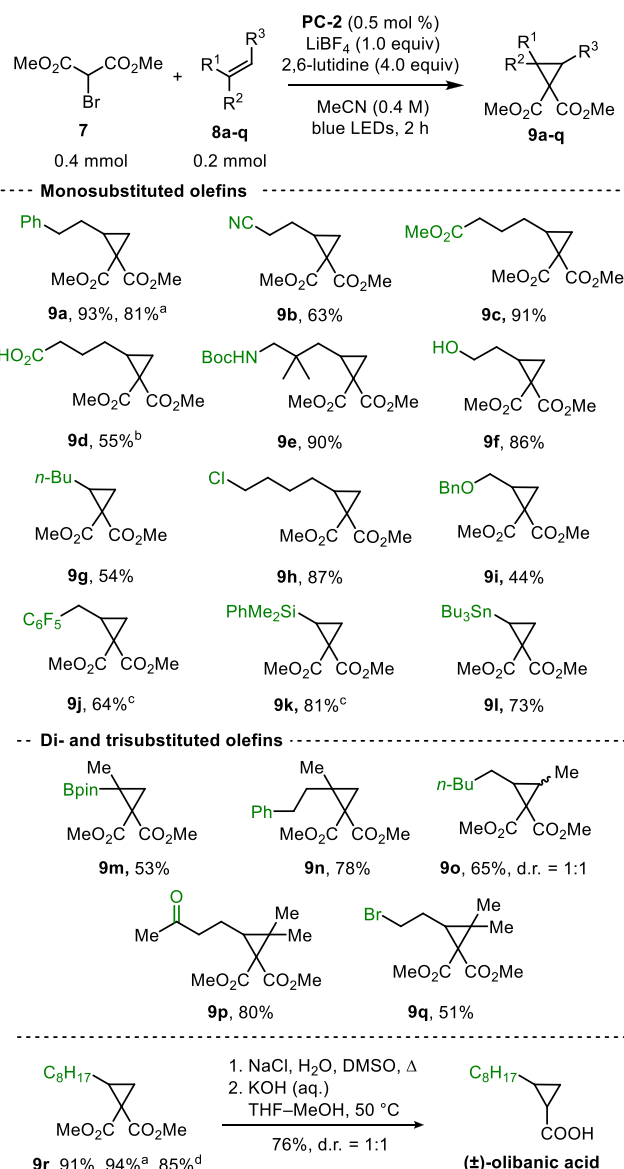
Figure 5. Substrate scope. ^{a}2.0 mmol scale. ^{b}Reaction conducted in sulfolane. ^{c}Reaction time = 8 h. ^{d}15 mmol scale with 0.1 mol % **PC-2**, 20 mol % LiBF$_4$, [1-decene] = 2 M.

subjected to reaction conditions, product cyclopropane **6a** was obtained in 61% yield and 9:1 d.r. The use of **4** constituted a general solution to render the cyclopropanation studied herein diastereoselective (Figure 4), and cyclopropanes **6b−f** were obtained in 45−71% yield and 7:1 to 10:1 d.r. It had previously been shown that 2,6-di-tert-butylphenyl cyclopropanoates may be saponified to remove the auxiliary.[20]

We set out to explore the generality of the cyclopropanation reaction. When dimethyl bromomalonate (**7**) and **2a** were subjected to conditions optimized for α-bromo-β-ketoesters, only γ-bromomalonate (the ATRA product) was observed (see SI). Intriguingly, upon addition of 10 mol % LiBF$_4$, cyclopropane product **9a** was obtained in 40% yield. Gratifyingly, use of 0.5 mol % **PC-1**, 1.0 equiv LiBF$_4$, and 4.0 equiv 2,6-lutidine in MeCN afforded cyclopropane **9a** in 82% yield. Interestingly, contrary to bromoketoesters, use of **PC-2** instead of **PC-1** led to product formation in higher yield (95%). The use of other Li salts gave analogous results. However, use of n-Bu$_4$NBF$_4$ gave only the ATRA product (see
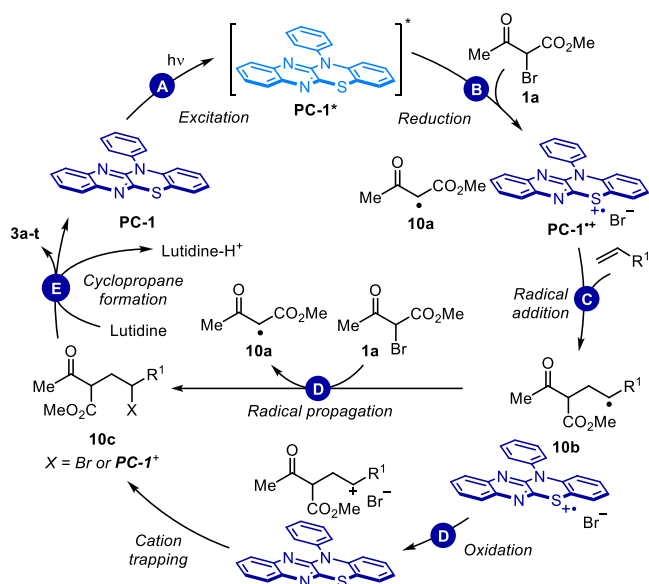
Figure 6. Mechanistic proposal. Lutidine = 2,6-lutidine.

SI). In contrast to previous results with α-bromo-β-ketoesters **1a–e**, these findings implicate an important and beneficial role for Li$^+$ with bromomalonates.

Next, we investigated the functional group tolerance of this cyclopropanation (Figure 5). One previous report for the cyclopropanation of terminal olefins with diethyl bromomalonate uses a heterogeneous, porous, polymeric photocatalyst.[21] We showcase that the transformation with organophotocatalyst **PC-2** is tolerant of a wide range of functionalities, terminal, 1,1-disubstituted, 1,2-disubstituted, and trisubstituted olefins. To this end cyclopropanes **9a–k** were obtained in 44–93% yield. Vinyl stannane **8l** and vinyl boronic pinacol ester **8m** were converted to cyclopropanes **9l** and **9m** in 73% and 53% yield, respectively, giving cyclopropanes that could be elaborated via metal-catalyzed cross-coupling reactions.[22] Next, effects of alkene substitution patterns were investigated. 1,1-Disubstituted olefin **8n** gave **9n** in 78% yield. E- and Z-oct-2-ene separately furnished **9o** in 64–65% yield and 1:1 d.r. Trisubstituted olefins were well tolerated, with **9p** and **9q** isolated in 80% and 51% yield, respectively. **9r** was accessed from 1-decene in 91–94% yield and converted to the natural products cis- and trans-olibanic acid in 72% overall yield. Finally, **9a** was also produced on a 2.0 mmol scale in 81% yield, and **9r** was prepared on a 15 mmol scale in 85% yield.

To gain an understanding of the mechanism of this transformation, a series of experiments were conducted after devising a mechanistic construct (Figure 6). Initial investigations focused on the absorbance characteristics of **PC-1** and **PC-2** (Figure 7, A).

Both photocatalysts show strong absorption in the blue-light range, with absorbance maxima of 412 and 414 nm, respectively. The UV–vis spectra of **PC-1** and **PC-2**, with concentrations corresponding to 0.5 mol % catalyst loading (c = 1 mM), showed absorbance above 3.0 (no transmittance detected) for $\lambda < 457$ nm. The blue LEDs employed in the transformation emit >90% of light between 410 and 510 nm. Thus, almost the entire spectrum of wavelengths emitted by the blue LED photoreactor can be absorbed by **PC-1** or **PC-2** (Figure 7, A). Next, the fate of the excited-state photocatalyst was examined (Figure 7, B). Stern–Volmer relationship

studies showed fluorescence quenching by α-bromo-β-ketoester **1a**, while no quenching by 2,6-lutidine or **2a** was observed. Combining those results with cyclic voltammetry (CV) measurements of **PC-1** ($E^*_{1/2}(PC^{\bullet+}/PC^*) = -1.43$ V vs SCE) and α-bromo-β-ketoester **1a** ($E_{p/2}$ (B/B$^{\bullet-}$) $= -1.03$ V vs SCE), we concluded that reduction of **1a** is feasible, leading to C-centered radical **10a** (Figure 6). When the reaction was carried out in the presence of 1.0 equiv of TEMPO, no product formation was observed (Figure 7, C), which is consistent with proposed radical pathways and previous studies on ATRA.[15a,23] Two possible mechanistic pathways can be devised following addition of **10a** to the olefin. First, radical propagation via bromide abstraction by secondary alkyl radical **10b** would form secondary alkyl bromide **10c** (X = Br) and another β-ketoester radical **10a** (Figure 6, D). Alternatively, oxidized photocatalyst **PC-1**$^{\bullet+}$ ($E_{1/2}(PC^{\bullet+}/PC) = 1.06$ V vs SCE) may effect oxidation of **10b** ($E_{1/2}(C^+/C^\bullet) = 0.47$ V vs SCE)[15b,24] to a carbocation which could then be trapped by bromide or **PC-1**. Previously, it has been suggested that thiazine photocatalysts may form adducts with cations.[17b,25]
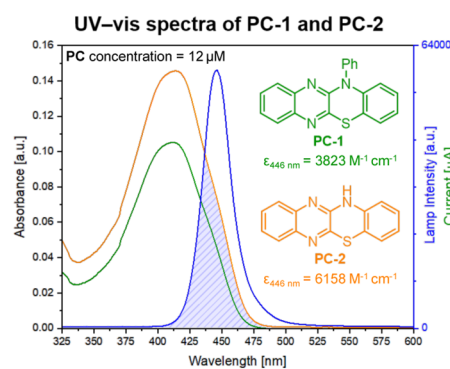
Atom-transfer radical additions leading to γ-bromomalonates have been proposed to proceed via radical propagation in previous studies.[15a,23] As discussed by Yoon, a light-on-light-off experiment is insufficient to assess radical chain processes,[23] prompting us to determine the quantum yield.

For the reaction with bromoketoester **1a** and phenylbutene **2a** (1.0 mmol scale), after 120 min, 8% conversion (see SI) of alkene was observed, and the quantum yield was calculated as $\Phi = 0.012$, which is consistent with a closed photoredox catalytic cycle (Figure 7, D).

We noted that LiBF$_4$ was necessary to effect cyclopropanation with α-bromomalonates, whereas it was detrimental in the reaction with α-bromo-β-ketoesters. For the latter, addition of LiBF$_4$ resulted in lower yields (34% vs 95%, see SI) and increased decomposition of **1a**. To effect cyclopropanation, enolization of intermediate **10c** by the base (2,6-lutidine) is necessary (Figure 6, E). We hypothesize enolization of intermediate malonate (pK_a = 13) is facilitated by Lewis acidic Li$^+$, which is not required for enolization of intermediate acetoacetate **10c** (pK_a = 11). To study enolization of **10c**, deuteration experiments were conducted in d_3-MeCN with 1.0 equiv of D$_2$O (Figure 7, E). Dimethyl methylmalonate and methyl methylacetoacetate were chosen as models for **10c**. Equilibration (66% deuterium incorporation) in the presence of LiBF$_4$ and 2,6-lutidine was complete in 9 and 5 min for malonates and acetoacetates, respectively. In the absence of LiBF$_4$, only acetoacetates reached equilibrium, albeit only after 2 h. These experiments support formation of an enolate under reaction conditions and account for the difference in reactivity observed between malonates, which require Li$^+$, and acetoacetates, which do not. Additionally, in the presence of base, bromoketoester **1a** undergoes decomposition, while no such effect was observed for bromomalonates. We suggest that with Li$^+$ a larger fraction of starting material **1a** is enolized, leading to increased decomposition. Thus, a fine balance between sufficient enolization of intermediate **10c** to effect cyclization and minimal enolization of starting material **1a** is required (Figure 7, E).

In conclusion, we have developed an intermolecular cyclopropanation of unactivated alkenes with α-bromomalonates and, for the first time, α-bromo-β-ketoesters under organophotocatalytic conditions. The transformation shows broad functional group tolerance and is amenable to terminal

Step A *Experiment: UV–vis Absorbance*

UV–vis spectra of PC-1 and PC-2

PC concentration = 12 μM

PC-1
$\varepsilon_{446\ nm}$ = 3823 $M^{-1}\ cm^{-1}$

PC-2
$\varepsilon_{446\ nm}$ = 6158 $M^{-1}\ cm^{-1}$

- λ_{max}(**PC-1**) = 412 and λ_{max}(**PC-2**) = 414 nm
- Blue LEDs emit > 90% of light between 410 and 510 nm

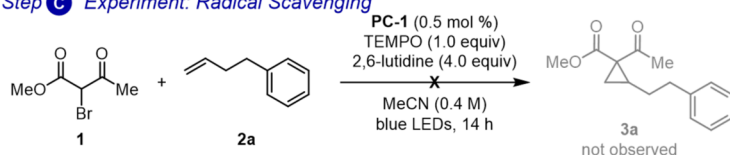**Step B** *Experiment: Cyclic Voltammetry and Stern–Volmer Quenching of PC-1* by Reagents*

CV of PC-1 and PC-2
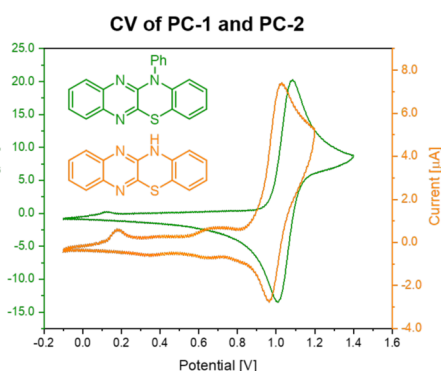
- $E_{1/2}^{*}$ (V vs SCE) (**PC-1**) = −1.43
- $E_{1/2}^{*}$ (V vs SCE) (**PC-2**) = −1.49

Stern–Volmer Relationship for PC-1 vs [1a], [2a] and [2,6-lutidine]

y = 1.005 + 7.997x
R^2 = 0.9845
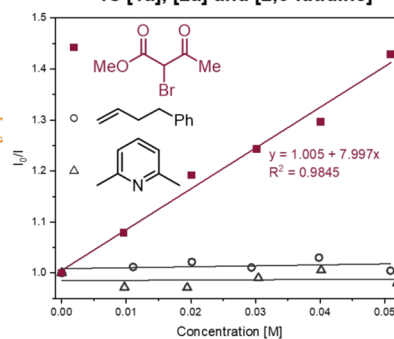
- 2,6-Lutidine and **2a** have no effect on fluorescence
- Photocatalytic reduction of **1a** by **PC-1*** is feasible

Step C *Experiment: Radical Scavenging*

PC-1 (0.5 mol %)
TEMPO (1.0 equiv)
2,6-lutidine (4.0 equiv)
—X→
MeCN (0.4 M)
blue LEDs, 14 h

1 + 2a → 3a *not observed*

Step D *Experiment: Quantum Yield Determination*

- Carried out on 1.0 mmol scale under standard conditions
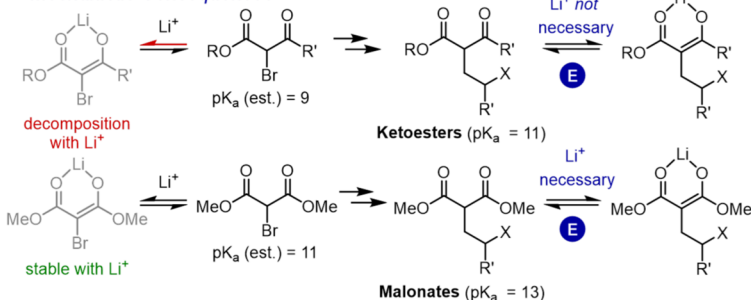- Quantum yield : **Φ = 0.012**
- Φ < 1 supports a closed catalytic cycle

Step E *Experiment: Deuterium Exchange* ┈┈┈→ *Mechanistic Consequences*

D_2O + MeCN (0.4 M) 40 °C, additive, time to equilibrium ⇌ HOD +
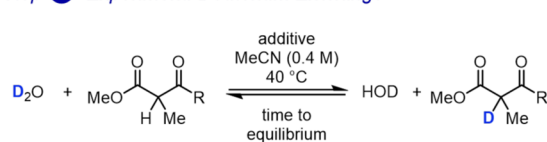
	None	LiBF$_4$ (50 mol%)	2,6-lutidine (4.0 equiv)	2,6-lutidine (4.0 equiv) and LiBF$_4$ (50 mol%)
R = OMe	> 16 h	> 16 h	> 16 h	9 min
R = Me	> 4 h	> 4 h	2 h	5 min

- Malonates and esters exchange α–H under reaction conditions
- Formation of an enolate is feasible in the transformation

pK_a (est.) = 9   **Ketoesters** (pK_a = 11)   *Li$^+$ not necessary* E

pK_a (est.) = 11   **Malonates** (pK_a = 13)   *Li$^+$ necessary* E

decomposition with Li$^+$ / stable with Li$^+$

- Lithium-assisted enolization of starting materials leads to decomposition for bromoketoesters, but is crucial for malonates in intermediate **10c**

Figure 7. Mechanistic investigations. **A**, UV–vis absorbance of **PC-1** and **PC-2** in MeCN (12 μM). **B**, Cyclic voltammetry and Stern–Volmer relationship between **PC-1*** and **1a**, **2a**, and 2,6-lutidine; fluorescence spectra recorded in MeCN (12 μM **PC-1**). **C**, Radical scavenger experiment carried out with 1.0 equiv of TEMPO. **D**, Quantum yield determined on 1.0 mmol scale; 8% conversion after 120 min. **E**, Equilibrium involving β-dicarbonyl compounds and D$_2$O (1.0 equiv) in d_3-MeCN (0.4 M) at 40 °C.

as well as highly substituted olefins. We demonstrated that structurally similar substrates, α-bromomalonates and α-bromo-β-ketoesters, show distinctly different behavior in this transformation. While Li$^+$ is beneficial for α-bromomalonates, it is not only superfluous for α-bromo-β-ketoesters but, in fact, detrimental. Salient features of the transformation are its air tolerance and the successful application of benzothiazinoquinoxalines **PC-1** and **PC-2** as organophotocatalysts. More broadly, further exploration of this remarkable class of modular photocatalysts may lead to novel reaction discovery.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c11680.

Experimental details; NMR and CV data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Erick M. Carreira − *Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zurich, Switzerland;* Ⓞ orcid.org/0000-0003-1472-490X; Email: carreira@ethz.ch

Authors

David M. Fischer − *Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zurich, Switzerland;* Ⓞ orcid.org/0000-0001-6960-0969

Henry Lindner − *Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zurich, Switzerland;* Ⓞ orcid.org/0000-0001-9251-2887

Willi M. Amberg − *Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zurich, Switzerland;* Ⓞ orcid.org/0000-0002-7053-5815

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