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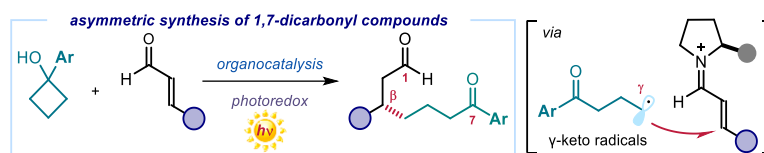
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Supporting Information Placeholder



ABSTRACT: We describe an asymmetric organocatalytic method to synthesize 1,7-dicarbonyl compounds containing a β -stereocenter. The chemistry relies on the formation of γ -keto radicals, generated upon oxidative ring-opening of cyclobutanols mastered by an organic photoredox catalyst. These non-stabilized primary radicals are stereoselectively intercepted by an iminium ion intermediate, formed upon activation of aliphatic and aromatic enals by a chiral secondary amine catalyst. This organocatalytic photoredox method served to prepare scaffolds found in natural products and drug molecules.

Cyclobutanols **1** have recently found wide synthetic application as versatile radical precursors.¹ Upon oxidative activation and strain-promoted ring opening, they offer access to γ -keto radicals **I**, which can be leveraged to realize the formal remote functionalization of carbonyl compounds (Figure 1a).^{1,2} The activation of cyclobutanols can be achieved using catalytic transition metals, stoichiometric oxidants, and photoredox catalysts. The resulting γ -keto radicals **I** have been used in a wide range of C-C bond forming processes (including alkylation,^{2g} formylation,²ⁱ allylation,²ⁱ vinylation,^{2e} alkylation,^{2e,f} and arylation^{2j}), and functional group introductions (i.e., amination,^{2b,d} halogenation,^{2a,h,j,l} cyanation,^{2f} and trifluoromethylation^{2m}). Yet, to the best of our knowledge, enantioselective methods for the stereocontrolled interception of γ -keto primary radicals **I** derived from cyclobutanols **1** have not been reported.³

In this study, we close this gap in asymmetric methodology by developing an organocatalytic strategy to accomplish the enantioselective trap of γ -keto primary radicals **I**, generated upon oxidative ring-opening of cyclobutanols **1** (Figure 1b). This exploration was motivated by our recent finding that a chiral iminium ion **II**, generated by activation of aliphatic and aromatic enals with a chiral secondary amine catalyst, could effectively intercept radicals with high stereocontrol.^{3d,4}

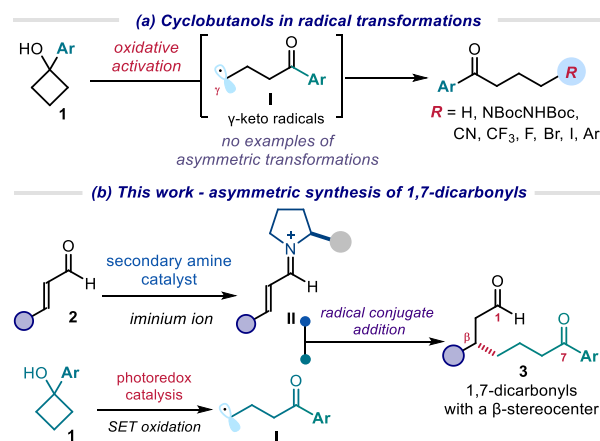


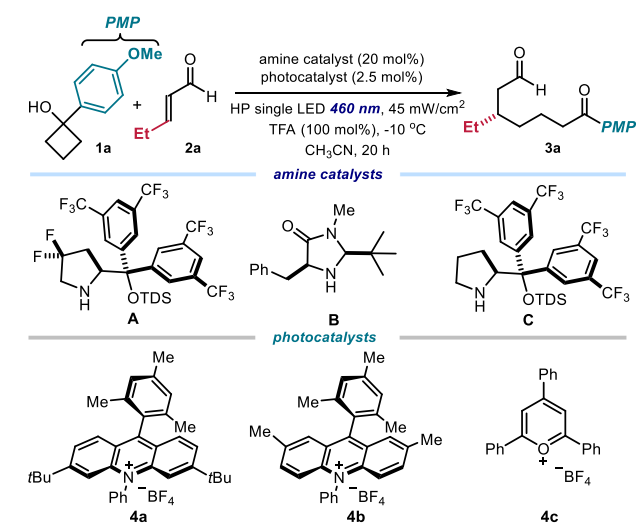
Figure 1. (a) Oxidative ring-opening of cyclobutanols **1** to afford γ -keto radicals **I** and the ensuing functionalization. (b) Design plan for the enantioselective catalytic synthesis of 1,7-dicarbonyl compounds via stereocontrolled iminium ion trap of primary radicals **I**.

Specifically, we wondered if, upon single-electron transfer (SET) oxidation and ring opening of cyclobutanol **1**, mastered by a light-activated photoredox catalyst, radical **I** could be effectively captured by the chiral iminium ion **II**. This is not a trivial target since non-stabilized primary radicals, such as **I**, are generally recalcitrant to asymmetric bond-forming processes,⁵ due to their high reactivity. If successful, our protocol would enable direct access to 1,7-dicarbonyl compounds **3** with a β -stereogenic center. 1,7-

Dicarbonyls are found in natural products and pharmaceutically relevant compounds, and they are useful intermediates to prepare bioactive molecules.⁶ While some methods are available for the synthesis of these scaffolds,⁷ they do not provide stereocontrolled entries into chiral 1,7-dicarbonyl compounds. Our proposed strategy, which combines photoredox catalysis and organocatalysis, can offer a direct asymmetric route to chiral 1,7-dicarbonyls.

We started our investigation using cyclobutanol **1a** ($E_{\text{ox}} = +1.56$ V vs Ag/AgCl) and pentenal **2a** as the model substrates (Table 1). We selected 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridinium tetrafluoroborate **4a** as the organic photocatalyst ($E_{\text{ox}} = +2.08$ V vs SCE),⁸ since it has the required redox potential to effectively activate **1a** via an SET oxidation. The experiments were conducted at -10 °C in CH_3CN under irradiation by a single high-power light-emitting diode (HP LED, $\lambda_{\text{max}} = 460$ nm) with an irradiance at 45 mW/cm^2 , as controlled by an external power supply. Trifluoroacetic acid (TFA, 1 equiv.) was used to secure the effective formation of the chiral iminium ion of type **II**.

Table 1. Optimization of the reaction conditions.^a



entry	amine	4	yield (%) ^b	ee (%) ^c
1	A	4a	65 (54)	91
2	B	4a	53	8
3	C	4a	30	5
4	A	4b	17	N.D.
5	A	4c	37	82
6 ^d	A	4a	15	57
7	A	none	0	-
8 ^e	A	4a	0	-
9	none	4a	12	0

^a Reactions performed on a 0.1 mmol scale for 20 h using 3 equiv. of **2a**, 20 mol% of aminocatalyst, 2.5 mol% of photocatalyst, and 100 mol% of TFA in 0.2 mL of CH_3CN under illumination by a single high-power (HP) LED ($\lambda_{\text{max}} = 460$ nm, 45 mW/cm^2) at -10 °C. ^b Yield determined by ^1H NMR analysis of the crude mixture using BnCl as the internal standard; yield of the isolated product **3a** is reported in brackets. ^c Enantiomeric excess of **3a**. ^d Reaction at ambient temperature. ^e Reaction in the dark. TDS: hexyldimethylsilyl; N.D.: not determined.

The *gem*-difluorinated diarylprolinol silylether organocatalyst **A**, which we previously designed for the photoactivation of iminium ions,⁴ afforded the expected product **3a** with high enantioselectivity and good yield (Table 1, entry 1, 54% yield and 91% ee). Notably, catalyst **A** was uniquely competent for high stereoinduction, since other amine catalysts with an established profile in promoting asymmetric iminium-ion-mediated processes, including catalyst **B** and **C**, offered reduced catalytic activity and stereoselectivity (entries 2 and 3, respectively). Other photoredox catalysts (**4b-c**) were not suitable to efficiently promote the model reaction (entries 4-5). Temperature was also important in securing efficiency: when performing the model reaction catalyzed by **A** at ambient temperature, both yield and enantioselectivity of product **3a** dropped drastically (entry 6). We also performed control experiments: photocatalyst **4a** (entry 7) and light (entry 8) were found essential. A low reactivity was also observed in the absence of catalyst **A** (entry 9). For entries 7-9, decomposition of cyclobutanol **1a** was observed.⁹

Using the optimized conditions (Table 1, entry 1), we next explored the generality of the method for the asymmetric synthesis of chiral 1,7-dicarbonyl compounds **3** (Figure 2). We found that enals bearing a variety of saturated aliphatic substituents at the β position, including ethyl (product **3a**), methyl (**3b**), *n*-pentyl (**3c**), and isopropyl (**3d**) moieties, were suitable substrates. In all cases, the corresponding products were obtained in excellent enantioselectivity (86-91% ee), while the yields slightly decreased with increasing steric hindrance of the β substituent. Enals bearing a homobenzyl (adduct **3e**), a terminal olefin (**3f**), and a benzyl ether (**3g**) functionality were compatible with the reaction conditions. In addition to cyclobutanol **1a**, the less electron rich analogue bearing a phenyl substituent offered a similar reactivity, effectively leading to product **3h** in 57% yield and 95% ee. Attempts to intercept tertiary radicals, generated from suitable cyclobutanol precursors, met with failure. A list of unsuccessful substrates is reported in Figure S1 of the Supporting Information.

Aromatic enals were also competent substrates, although they required 30 mol% of catalyst **A** (optimization studies are detailed in Table S1 within the Supporting Information). Cinnamaldehyde was successfully transformed into product **3i** in 68% yield and 82% ee. Substituents on the phenyl ring of different electronic nature, including the electron-donating methyl (adduct **3j**) and electron-withdrawing fluorine (**3l**) group, had little effects on enantioselectivity. *Para*- and *meta*-trifluoromethyl-phenyl enals offered similar results (**3n** and **3o**), showing that the reaction system tolerates substituents at different positions of the aromatic ring. Aromatic enals bearing a trimethyl silyl (TMS, product **3k**) and a chlorine (**3m**), which can serve as synthetic handles for further modifications, could also be used. In addition to the basic phenyl ring, other aromatic systems, including naphthalene (**3p**) and thiophene (**3q**), were compatible with the protocol.

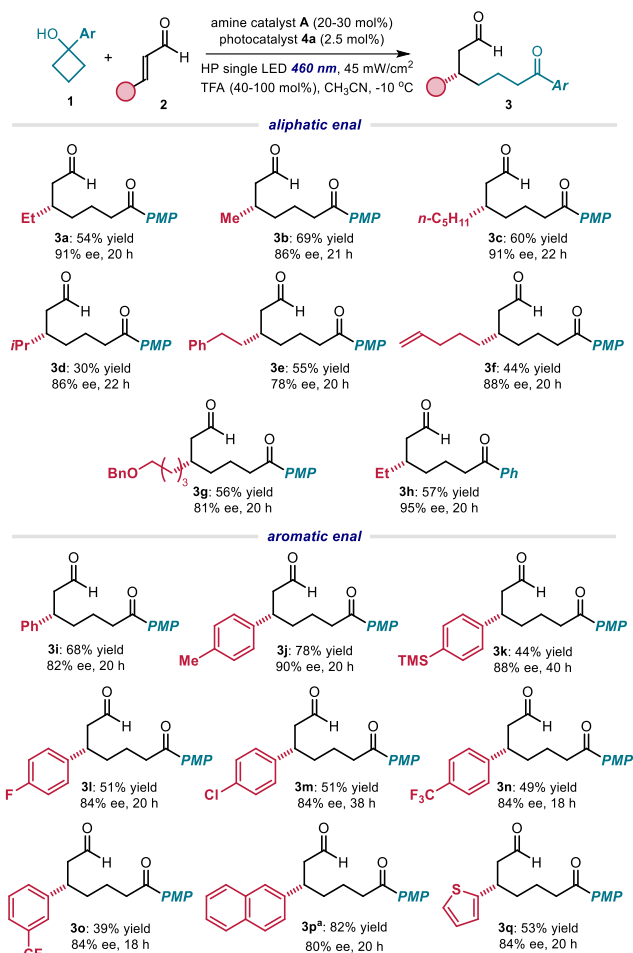
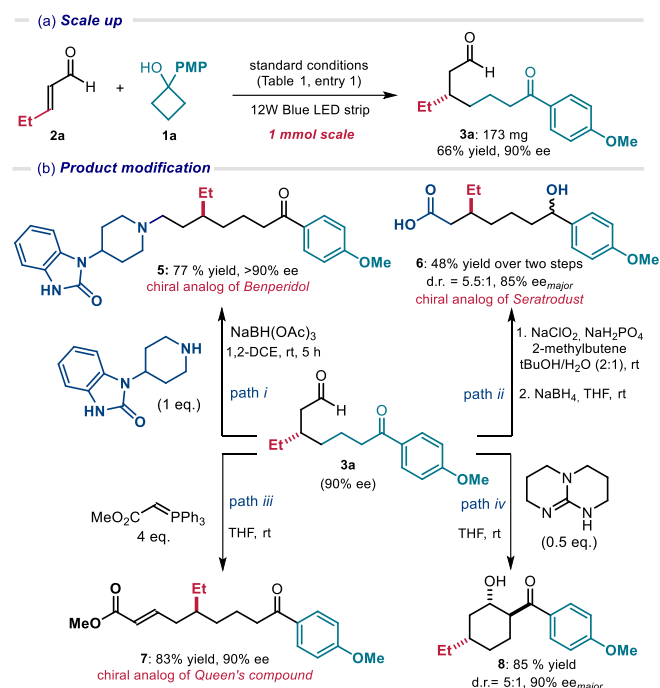


Figure 2. Substrate scope for the asymmetric synthesis of 1,7-dicarbonyl compounds **3**. Reactions performed on a 0.1 mmol scale using 3 equiv. of enal **2** in 0.2 mL of CH_3CN under illumination at 460 nm. Yields and enantiomeric excesses of the isolated products **3** are reported below each entry (average of two runs per substrate). For aliphatic enal, 20 mol% of aminocatalyst **A** and 100 mol% of TFA were used; for aromatic enal, 30 mol% of aminocatalyst **A** and 40 mol% of TFA were used. ^a Using 5 mol% of photocatalyst **4a** in a $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$ mixture (4:1) as solvent. PMP = *p*-methoxy phenyl.

To examine the utility of the method, we performed the model reaction on a 1 mmol scale, which offered product **3a** in synthetically useful amount (Scheme 1a, **3a** formed in 66% yield and 90% ee, 173 mg). We then sought to convert adduct **3a** into analogues of straight-chain pharmacophores through functional group interconversion (Scheme 1b). Firstly, a reductive amination with 1-(4-piperidiny)-1,3-dihydro-2H-benzimidazol-2-one smoothly afforded the chiral adduct **5** bearing an (*S*)-2-ethyl-7-oxoheptamine skeleton without erosion of enantiopurity (path i). Product **5** is an analogue of *Benperidol*, a neuroleptic used as selective ligand for dopaminergic D₂-receptors.¹⁰ In addition, after redox manipulation (path ii), the two carbonyl groups within **3a** could be selectively altered to achieve a 7-hydroxylheptanoic acid **6**, an intermediate in the preparation of asthma medication *Seratroduct*.¹¹ The dicarbonyl skeleton in **3a** could also be diversified through a Wittig-olefination (path iii), which afforded the 1,9-dicarbonyl product **7**

with a δ stereogenic center. This structure resembles the backbone of the Queen substance, a honeybee pheromone.¹² Lastly (path iv), a Lewis base-catalyzed intramolecular aldol reaction¹³ led to the cyclohexanol scaffold **8**, decorated with three stereogenic centers, with good yield and diastereoselectivity. The relative configuration of the major diastereoisomer of **8** was assigned by means of NMR studies, as detailed in section J of the Supporting information, while the absolute configuration of the minor isomer of **8** was unambiguously assigned by X-ray crystallographic analysis.¹⁴

Scheme 1. Synthetic applications



To glean insight into the mechanism, we conducted Stern-Volmer fluorescence quenching experiments (details in section F of the Supporting Information). We found that cyclobutanol **1a** efficiently quenched the fluorescence of the excited photocatalyst **4a** ($K_{\text{SV}} = 70.3 \text{ M}^{-1}$). Cyclic voltammetry established the thermodynamic feasibility of an SET oxidation of cyclobutanol **1a** ($E_{\text{ox}} = +1.56 \text{ V}$ vs Ag/AgCl) by the excited **4a** ($E_{\text{ox}} = +2.08 \text{ V}$ vs SCE).⁸ Based on these investigations, we propose the mechanism detailed in Figure 3. The light-activated photocatalyst **4a** would activate cyclobutanol **1a** through SET oxidation to afford the γ -keto radical **I**. This non-stabilized primary radical is then captured by the chiral iminium ion **II** in a stereocontrolled fashion. The emerging α -iminyl radical cation **III** is quenched by the reduced photocatalyst **4a**⁻, thus closing the photoredox catalytic cycle. Hydrolysis of the ensuing enamine **IV** leads to the desired chiral 1,7-dicarbonyl compound **3** while turning over the chiral amine catalyst **A**. We measured a quantum yield (Φ) for the model reaction as low as 0.04. This value is consistent with our mechanistic proposal, suggesting that a radical chain propagation, if present, is not a dominant path.¹⁵

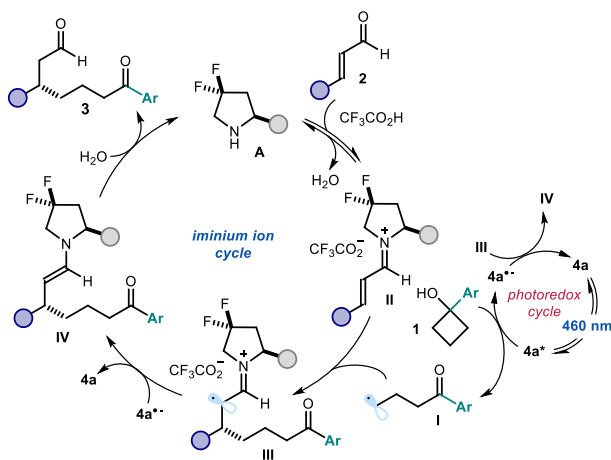


Figure 3. Proposed mechanism.

In summary, we have developed a catalytic enantioselective method that offers a rare entry into chiral 1,7-dicarbonyl compounds. The chemistry requires visible light, an organic photocatalyst, and a chiral secondary amine catalyst. Key for success is the stereocontrolled trap of non-stabilized primary radicals, generated upon oxidative ring opening of cyclobutanols. Synthetic elaboration of the 1,7-dicarbonyl products served to easily prepare chiral analogues of known bioactive molecules.¹⁶

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data (PDF)
X-ray crystallographic data for the minor diastereoisomer of product **8** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

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