Photoredox Organocatalysis for the Enantioselective Synthesis of 1,7-Dicarbonyl Compounds

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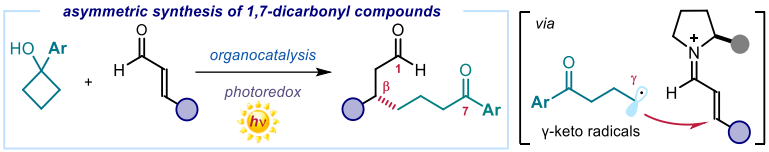
Supporting Information Placeholder



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] alkynylation,[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]

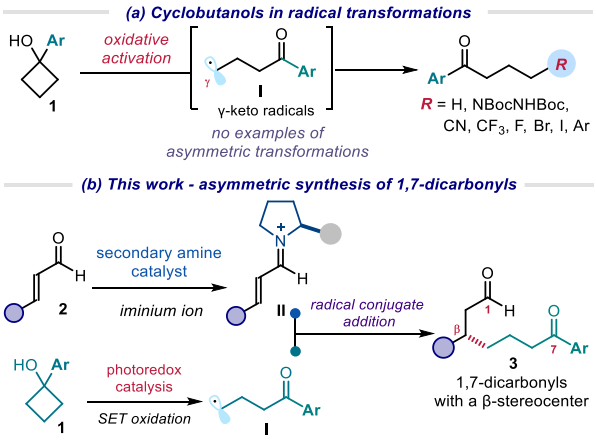


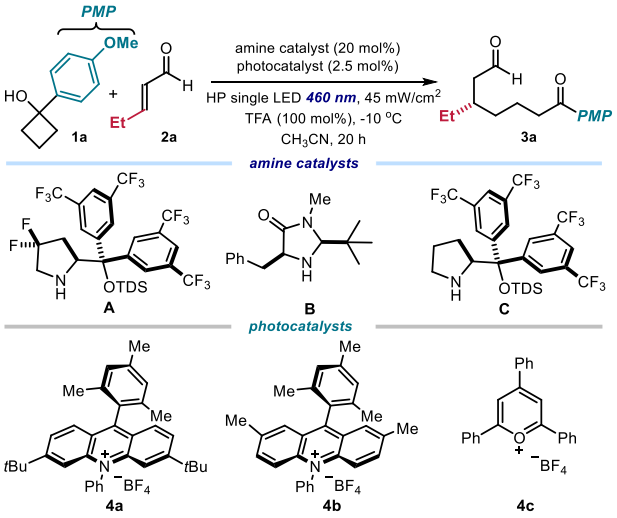
Figure 1. (a) Oxidative ring-opening of cyclobutanols **1** to afford γ-keto radicals **I** and the ensuing functionalization. (b) Design plan for the enantioselective catalytic synthesis of 1,7-dicarbonyl compounds via stereocontrolled iminium ion trap of primary radicals **I**.

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_{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_{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, λ_{max} = 460 nm) with an irradiance at 45 mW/cm², 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 (λ_{max} = 460 nm, 45 mW/cm²) at -10 °C. [b]Yield determined by ^{1}H 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: thexyldimethylsilyl; 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 form 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.

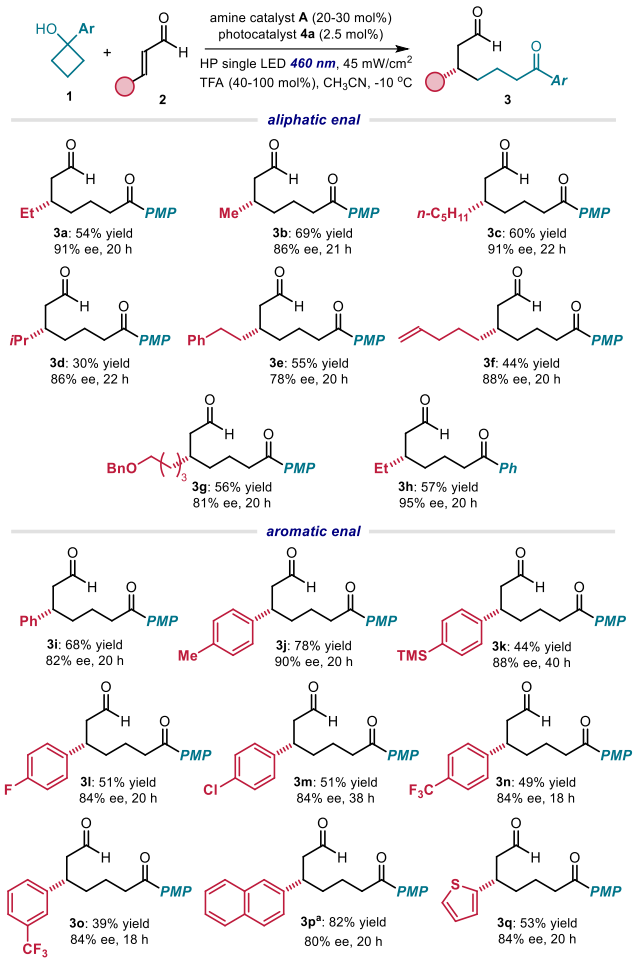
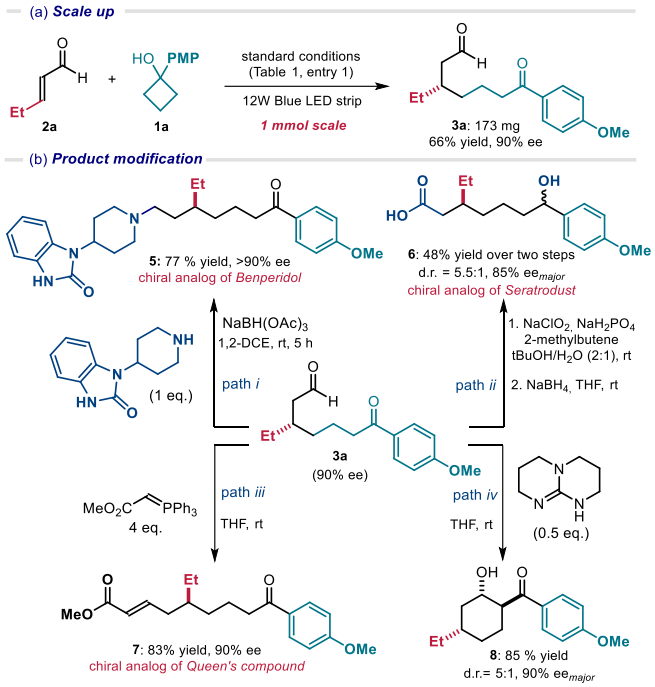


Figure 2. Substrate scope for the asymmetric synthesis of 1,7-dicarbonyl compounds **3**. Reactions performed on a 0.1 mmol scale using 3 equiv. of enal **2** in 0.2 mL of CH_3CN under illumination at 460 nm. Yields and enantiomeric excesses of the isolated products **3** are reported below each entry (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 CH_3CN:CH_2Cl_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-piperidinyl)-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 *Seratrodust*.[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 reaction[13] 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_{SV}= 70.3 M^{-1}). Cyclic voltammetry established the thermodynamic feasibility of an SET oxidation of cyclobutanol **1a** (E_{ox}= +1.56 V vs Ag/AgCl) by the excited **4a** (E_{ox}=+2.08 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**$^{\bullet-}$, 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]

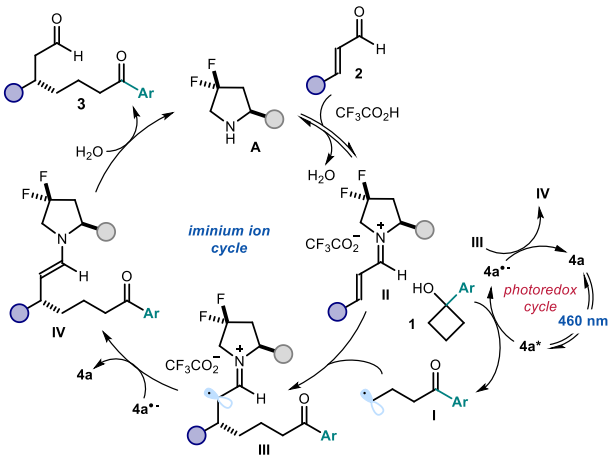


Figure 3. Proposed mechanism.

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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