

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

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

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Wong T.H., Ma D., Di Sanza R., Melchiorre P. (2022). Photoredox Organocatalysis for the Enantioselective Synthesis of 1,7-Dicarbonyl Compounds. ORGANIC LETTERS, 24(8), 1695-1699 [10.1021/acs.orglett.2c00326].

Availability:

This version is available at: <https://hdl.handle.net/11585/897859> since: 2022-11-15

Published:

DOI: <http://doi.org/10.1021/acs.orglett.2c00326>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

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

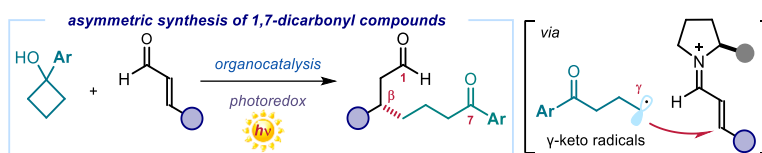
Thomas Hin-Fung Wong,^{a,b} Dengke Ma,^a Riccardo Di Sanza,^a and Paolo Melchiorre^{*,a,c}

^aICIQ - Institute of Chemical Research of Catalonia, Av. Països Catalans 16, 43007 Tarragona, Spain

^bDepartment of Analytical Chemistry and Organic Chemistry, University Rovira i Virgili, 43007 Tarragona, Spain

^cICREA - Catalan Institution for Research and Advanced Studies, Pg. Lluís Companys 23, 08010 Barcelona, Spain

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}

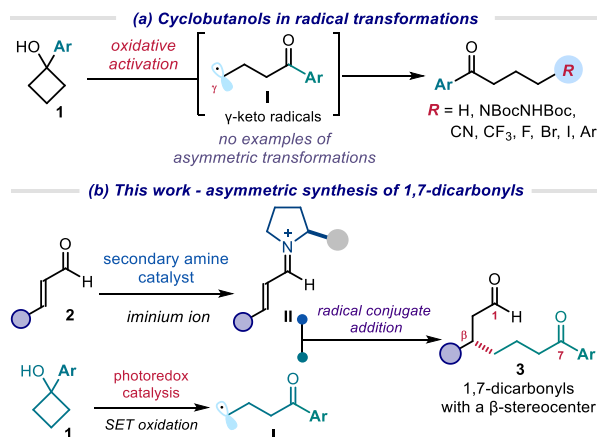


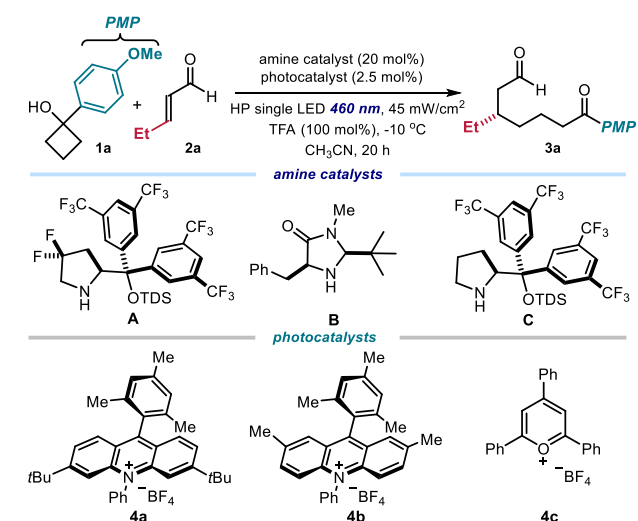
Figure 1. (a) Oxidative ring-opening of cyclobutanols **1** to afford γ -keto radicals **I** and the ensuing functionalization. (b) Design plan for the enantioselective catalytic synthesis of 1,7-dicarbonyl compounds via stereocontrolled iminium ion trap of primary radicals **I**.

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/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 ($\lambda_{\text{max}} = 460$ nm, 45 mW/cm²) 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 stereoselection, 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.

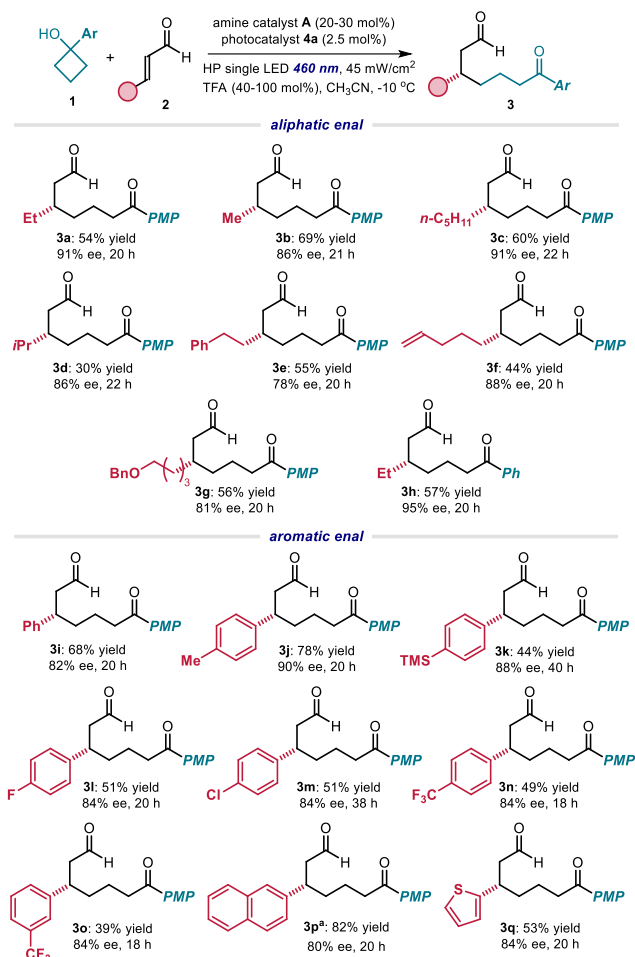
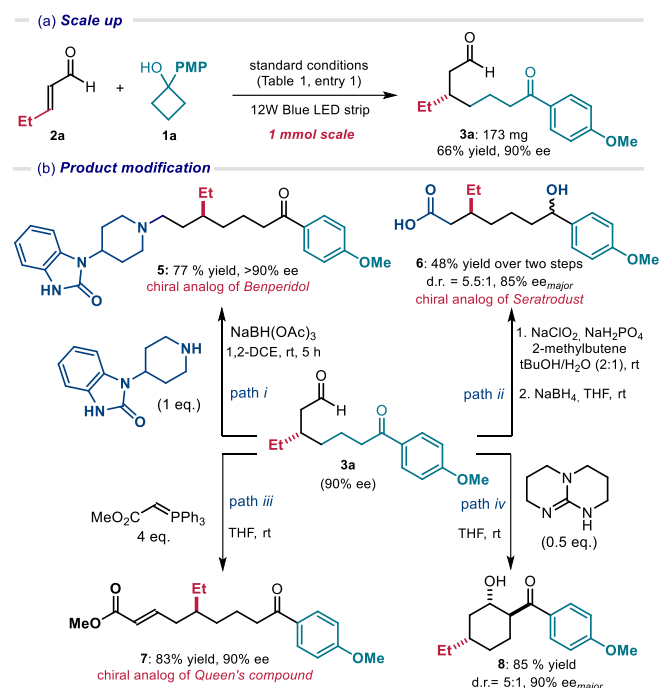


Figure 2. Substrate scope for the asymmetric synthesis of 1,7-dicarbonyl compounds **3**. Reactions performed on a 0.1 mmol scale using 3 equiv. of enal **2** in 0.2 mL of CH₃CN under illumination at 460 nm. Yields and enantiomeric excesses of the isolated products **3** are reported below each entry (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 CH₃CN:CH₂Cl₂ 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 *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** ($K_{SV} = 70.3 \text{ M}^{-1}$). Cyclic voltammetry established the thermodynamic feasibility of an SET oxidation of cyclobutanol **1a** ($E_{ox} = +1.56 \text{ V vs Ag/AgCl}$) by the excited **4a** ($E_{ox} = +2.08 \text{ V vs SCE}$).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

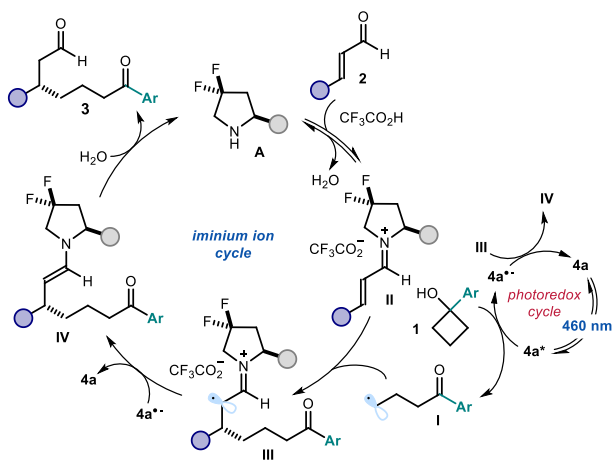


Figure 3. Proposed mechanism.

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)

AUTHOR INFORMATION

Corresponding Author

* **Paolo Melchiorre**: ICIQ Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; ICREA Catalan Institution for Research and Advanced Studies, 08010 Barcelona, Spain; orcid.org/0000-0001-8722-4602; Email: pmelchiorre@icmq.es

Authors

Thomas Hin-Fung Wong: ICIQ Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Department of Analytical Chemistry and Organic Chemistry, University Rovira i Virgili, 43007 Tarragona, Spain; orcid.org/0000-0002-5729-9619

Dengke Ma: ICIQ Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; orcid.org/0000-0001-5492-934X

Riccardo Di Sanza: ICIQ Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; orcid.org/0000-0002-5667-902X

Author Contributions

The manuscript was written through contributions of all authors.

ACKNOWLEDGMENT

Financial support was provided by Agencia Estatal de Investigación (PID2019-106278GB-I00), the MCIN/AEI/10.13039/501100011033 (CEX2019-000925-S)", and the European Research Council (ERC-2015-CoG 681840 - CATA-LUX). T.H.-F. Wong thanks the Secretariat of Universities and Research of the Ministry of Business and Knowledge of the Government of Catalonia and the European Social Fund for an FI Fellowship (2021FI-Boo304). D. Ma thanks the EU for a Horizon 2020 Marie Skłodowska-Curie Fellowship (H2020-MSCA-IF-2019 894795). Mr. Davide Spinnato (ICIQ) is acknowledged for his technical assistance to the quantum yield measurement. Dr. Martin Berger (ICIQ) is acknowledged for the helpful discussion on the preparation of the manuscript.

REFERENCES

- (a) Ren, R.; Zhu, C. Radical-Mediated Ring-Opening Functionalization of Cyclobutanols: A Shortcut to γ -Substituted Ketones. *Synlett* **2016**, 139. (b) Wu, X.; Zhu, C. Recent Advances in Ring-Opening Functionalization of Cycloalkanol by C–C σ -Bond Cleavage. *Chem. Rev.* **2018**, *18*, 587. (c) Morcillo, S. P. Radical-Promoted C–C Bond Cleavage: A Deconstructive Approach for Selective Functionalization. *Angew. Chem., Int. Ed.* **2019**, *58*, 14044. (d) Murakami, M.; Ishida, N. Cleavage of Carbon–Carbon σ -Bonds of Four-Membered Rings. *Chem. Rev.* **2021**, *121*, 264. (e) Yu, X.-Y.; Chen, J.-R.; Xiao, W.-J. Visible Light-Driven Radical-Mediated C–C Bond Cleavage/Functionalization in Organic Synthesis. *Chem. Rev.* **2021**, *121*, 506.
- (2) For selected examples: (a) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. Silver-Catalyzed Ring-Opening Strategy for the Synthesis of β - and γ -Fluorinated Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 10, 3490–3493. (b) Ren, R.; Zhao, H.; Huan, L.; Zhu, C. Manganese-Catalyzed Oxidative Azidation of Cyclobutanols: Regiospecific Synthesis of Alkyl Azides by C–C Bond Cleavage. *Angew. Chem., Int. Ed.* **2015**, *54*, 12692. (c) Yayla, H. G.; Wang, H.; Tarantino, K. T.; Orbe, H. S.; Knowles, R. R. Catalytic Ring-Opening of Cyclic Alcohols Enabled by PCET Activation of Strong O–H Bonds. *J. Am. Chem. Soc.* **2016**, *138*, 10794. (d) Guo, J.; Hu, A.; Chen, Y.; Sun, J.; Tang, H.; Zuo, Z. Photocatalytic C–C Bond Cleavage and Amination of Cycloalkanol by Cerium(III) Chloride Complex. *Angew. Chem., Int. Ed.* **2016**, *55*, 15319. (e) Jia, K.; Zhang, F.; Huang, H.; Chen, Y. Visible-Light-Induced Alkoxy Radical Generation Enables Selective C(sp³)–C(sp³) Bond Cleavage and Functionalizations. *J. Am. Chem. Soc.* **2016**, *138*, 1514. (f) Ren, R.; Wu, Z.; Xu, Y.; Zhu, C. C–C Bond-Forming Strategy by Manganese-Catalyzed Oxidative Ring-Opening Cyanation and Ethynylation of Cyclobutanol Derivatives. *Angew. Chem., Int. Ed.* **2016**, *55*, 2866. (g) Hu, A.; Chen, Y.; Guo, J.; Yu, N.; An, Q.; Zuo, Z. Cerium-Catalyzed Formal Cycloaddition of Cycloalkanol with Alkenes through Dual Photoexcitation. *J. Am. Chem. Soc.* **2018**, *140*, 13580. (h) Wang, D.; Mao, J.; Zhu, C. Visible light-promoted ring-opening functionalization of unstrained cycloalkanol via inert C–C bond scission. *Chem. Sci.* **2018**, *9*, 5805. (i) Wang, J.; Huang, B.; Shi, C.; Yang, C.; Xia, W. Visible-Light-Mediated Ring-Opening Strategy for the Regiospecific Allylation/Formylation of Cycloalkanol. *J. Org. Chem.* **2018**, *83*, 9696. (j) Zhao, R.; Yao, Y.; Zhu, D.; Chang, D.; Liu, Y.; Shi, L. Visible-Light-Enhanced Ring Opening of Cycloalkanol Enabled by Brønsted Base-Tethered Acyloxy Radical Induced Hydrogen Atom Transfer-Electron Transfer. *Org. Lett.* **2018**, *20*, 1228. (k) Huang, L.; Ji, T.; Rueping, M. Remote Nickel-Catalyzed Cross-Coupling Arylation via Proton-Coupled Electron Transfer-

Enabled C–C Bond Cleavage. *J. Am. Chem. Soc.* **2020**, *142*, 3532. (l) Lu, Y.-C.; Jordon, H. M.; West, J. G. Rapid and scalable synthesis of fluoroketones via cerium-mediated C–C bond cleavage. *Chem. Commun.* **2021**, *57*, 1871. (m) Wu, S.; Li, J.; He, R.; Jia, K.; Chen, Y. Terminal Trifluoromethylation of Ketones via Selective C–C Cleavage of Cycloalkanols Enabled by Hypervalent Iodine Reagents. *Org. Lett.* **2021**, *23*, 9204.

(3) A few enantioselective catalytic methods have been reported using the parent cyclopropanols as radical precursors, see: (a) Woźniak, Ł.; Magagnano, G.; Melchiorre, P. Enantioselective Photochemical Organocascade Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 1068. (b) Wu, L.; Wang, L.; Chen, P.; Guo, Y.; Liu, G. Enantioselective Copper-Catalyzed Radical Ring-Opening Cyanation of Cyclopropanols and Cyclopropanone Acetals. *Adv. Synth. Catal.* **2020**, *362*, 2189. (c) Jiang, C.; Wang, L.; Zhang, H.; Chen, P.; Guo, Y.; Liu, G. Enantioselective Copper-Catalyzed Trifluoromethylation of Benzylic Radicals via Ring Opening of Cyclopropanols. *Chem* **2020**, *6*, 2407. (d) Le Saux, E.; Ma, D.; Bonilla, P.; Holden, C. M.; Lustosa, D.; Melchiorre, P. A General Organocatalytic System for Enantioselective Radical Conjugate Additions to Enals. *Angew. Chem., Int. Ed.* **2021**, *60*, 5357.

(4) For iminium-ion-based radical strategies in the absence of external photoredox catalysts, see: (a) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. Visible-light excitation of iminium ions enables the enantioselective catalytic β -alkylation of enals. *Nat. Chem.* **2017**, *9*, 868. (b) Mazzarella, D.; Crisenza, G. E. M.; Melchiorre, P. Asymmetric Photocatalytic C–H Functionalization of Toluene and Derivatives. *J. Am. Chem. Soc.* **2018**, *140*, 8439. (c) Berger, M.; Carboni, D.; Melchiorre, P. Photochemical Organocatalytic Regio- and Enantioselective Conjugate Addition of Allyl Groups to Enals. *Angew. Chem., Int. Ed.* **2021**, *60*, 26373.

(5) For a rare example of asymmetric addition of primary radicals to unsaturated carbonyls, see: (a) Sibi, M. P.; Nad, S. Enantioselective Radical Reactions: Stereoselective Aldol Synthesis from Cyclic Ketone. *Angew. Chem., Int. Ed.* **2007**, *46*, 9231. See also Ref. 3d. For an enzymatic system that triggers the trap of unstabilized primary radicals with electron-poor olefins, see (b): Clayman, P. D.; Hyster, T. K. Photoenzymatic Generation of Unstabilized Alkyl Radicals: An Asymmetric Reductive Cyclization. *J. Am. Chem. Soc.* **2020**, *142*, 15673.

(6) (a) Paquette, L. A.; Collado, I.; Purdie, M. Total Synthesis of Spinosyn A. 2. Degradation Studies Involving the Pure Factor and Its Complete Reconstitution. *J. Am. Chem. Soc.* **1998**, *120*, 2553. (b) Vanhaecke, T.; Papeleu, P.; Elaut, G.; Rogiers, V. Trichostatin A-like hydroxamate histone deacetylase inhibitors as therapeutic agents: toxicological point of view. *Curr. Med. Chem.* **2004**, *11*, 1629. (c) de Figueiredo, R. M.; Berner, R.; Julis, J.; Liu, T.; Türp, D.; Christmann, C. Bidirectional, organocatalytic synthesis of lepidopteran sex pheromones. *J. Org. Chem.* **2007**, *72*, 640. (d) Lecerf-Schmidt, F.; Haudecoeur, R.; Peres, B.; Queiroz, M. M. F.; Marcourt, L.; Challal, S.; Queiroz, E. F.; Taiwe, G. S.; Lomberget, T.; Le Borgne, M.; Wolfender, J.-L.; De Waard, M.; Robins, R. J.; Boumendjel, A. Biomimetic synthesis of Tramadol. *Chem. Commun.* **2015**, *51*, 4451.

(7) Methods for the synthesis of racemic 1,7-dicarbonyls: (a) Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. A facile

synthesis of 1,7-dicarbonyl compounds via three-component Michael addition reactions. *Tetrahedron Lett.* **2004**, *45*, 2649. (b) Huang, Z.; Xu, J. One-pot synthesis of symmetric 1,7-dicarbonyl compounds via a tandem radical addition–elimination–addition reaction. *RSC Adv.* **2013**, *3*, 15114–15120. (c) Xu, C.-M.; Yang, L.; Huang, D.-F.; Niu, T.; Fu, Y.; Hu, Y.-L. Preparation of Diketones via the Reaction of Bisorganozinc Iodides and Benzoyl Chlorides. *Chin. J. Org. Chem.* **2010**, *30*, 1240. (d) Tachinami, T.; Nishimura, T.; Ushimaru, R.; Noyori, R.; Naka, H. Hydration of Terminal Alkynes Catalyzed by Water-Soluble Cobalt Porphyrin Complexes. *J. Am. Chem. Soc.* **2013**, *135*, 50. (e) Sarkar, S.; Banerjee, A.; Yao, W.; Patterson, E.V.; Ngai, M.-Y. Photocatalytic Radical Aroylation of Unactivated Alkenes: Pathway to β -Functionalized 1,4-, 1,6-, and 1,7-Diketones. *ACS Catal.* **2019**, *9*, 10358. For the preparation of racemic 1,8-dicarbonyls, see: (f) Ji, M.; Wu, Z.; Zhu, C. Visible-light-induced consecutive C–C bond fragmentation and formation for the synthesis of elusive unsymmetric 1,8-dicarbonyl compounds. *Chem. Commun.* **2019**, *55*, 2368. See also Ref 7c.

(8) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. Acridinium-Based Photocatalysts: A Sustainable Option in Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7244.

(9) The cyclobutanol substrate is affected by the acidic conditions required to elicit iminium ion formation. We observed decomposition of cyclobutanol **1a** upon stirring with 1 eq. of TFA for 20 hours.

(10) Moerlein, S. M.; Banks, W. R.; Parkinson, D. Production of fluorine-18 labeled (3-N-methyl) benperidol for PET investigation of cerebral dopaminergic receptor binding. *Int. J. Rad. Appl. Instrum. A.* **1992**, *43*, 913.

(11) (a) Shiraiishi, M.; Kato, K.; Terao, S.; Ashida, Y.; Terashita, Z.; Kito, G. Quinones. 4. Novel eicosanoid antagonists: synthesis and pharmacological evaluation. *J. Med. Chem.* **1989**, *32*, 2214. (b) Wouters, J.; Durant, F.; Masereel, B. Antagonism of the TXA₂ receptor by seratrodist: a structural approach. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2867.

(12) Butler, C. G.; Callow, R. K.; Johnston, N. C. The isolation and synthesis of queen substance, 9-oxodec-trans-2-enoic acid, a honeybee pheromone. *Proc. Royal Soc. B.* **1962**, *155*, 417.

(13) Ghobril, C.; Sabot, C.; Mioskowski, C.; Baati, R. TBD-Catalyzed Direct 5- and 6-enolexo Aldolization of Ketoaldehydes. *Eur. J. Org. Chem.* **2008**, 4104.

(14) Crystallographic data for compound **8** (*minor* diastereoisomer) has been deposited with the Cambridge Crystallographic Data Centre, accession number CCDC 2144951.

(15) (a) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. Mechanistic Studies in Photocatalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 3730. (b) Cismesia, M. A.; Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 5426.

(16) (a) Lovering, F.; Bikker, J.; Humblet, J. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752. (b) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515.