

Combined Photocatalysis and Lewis Acid Catalysis Strategy for the Oxa-Pictet–Spengler Reactions of Ethers

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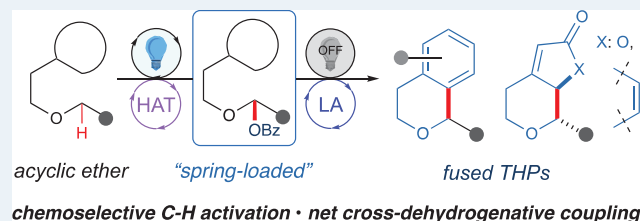
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ABSTRACT: Saturated oxygen-containing heterocycles are present in numerous natural products and biologically active compounds. While the oxa-Pictet–Spengler reaction conventionally serves as a traditional synthetic strategy for preparing arene-fused tetrahydropyrans (THPs), existing methods typically involve harsh conditions. Disclosed herein is the development of a mild photocatalytically triggered oxa-Pictet–Spengler reaction of ethers providing a synthetic approach to fused THP compounds. The tuned dual photo/hydrogen-atom transfer (HAT) catalysis enables site- and chemoselective C–H functionalization at the benzylic ether, which results in the formation of a benzoate acetal intermediate. The key intermediate is then exposed to subsequent Lewis acid catalysis, thus facilitating oxocarbenium ion generation and ring closure. Notably, this combination strategy successfully addresses concerns related to the overoxidation inherent in photocatalytic systems.

KEYWORDS: photocatalysis, C–H activation, oxocarbenium, oxa-Pictet–Spengler reaction, heterocycles



The prevalence of saturated heterocycles within the realm of biologically active molecules underscores their privileged status as essential chemical motifs.¹ Among these, cyclic ethers stand out for their abundance in natural products, many of which exhibit intriguing bioactivities.² Notably, fused tetrahydropyran (THP) structures recur in diverse compounds ranging from aromatic fused variations, like isochroman,³ to more complex saturated ring systems. Exemplary instances include compounds like trolliusol A,⁴ trichodermanone C,⁵ and plagiogryrin B⁶ (Figure 1A). A common approach for the synthesis of isochromans involves the oxa-Pictet–Spengler reaction of arenes,⁷ an intramolecular variant of the Friedel–Crafts reaction. In contrast to the prototypical Pictet–Spengler reaction,⁸ characterized by the formation of an easily accessible iminium ion intermediate, the traditional approach for the oxa-Pictet–Spengler requires strong acids and/or harsh conditions to generate oxocarbenium ions from the corresponding alcohol and aldehyde substrates (Figure 1B). While there exists historical precedent for transforming the corresponding acetate acetal into the oxocarbenium species, this pathway also typically entails the application of strongly acidic conditions.⁹ Noteworthy advancements have been reported in recent literature, including the development of an imidodiphosphate catalyst for an enantioselective version of the transformation.¹⁰

In alternative approaches, scientists have employed cross-dehydrogenative coupling (CDC) strategies in this field of chemistry.¹¹ As a demonstrative example, benzylic or allylic ethers can be directly oxidized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the mediator to generate the key oxocarbenium intermediate and enable subsequent inter¹²/intramolecular¹³ nucleophilic addition. However, the oxidizing

potential of DDQ limits its compatibility with various functionalities. Consequently, there exists a need for innovative alternatives, specifically those utilizing commercially available reagents under milder reaction conditions.

Photocatalysis has emerged as a potent strategy in synthetic organic chemistry that features mild photoexcitation processes and single-electron redox pathways.¹⁴ This technology has facilitated bond disconnections previously unattainable through traditional two-electron chemistry. Notably, C–H activation stands out as a robust strategy within photocatalysis eliminating the need for prefunctionalization or harsh conditions.¹⁵ In recent studies, several photocatalytic methods have been explored for the oxidation of benzylic ether to access oxocarbenium ions, which has proved invaluable for benzyl group deprotection and facilitating intermolecular nucleophilic addition.¹⁶ In many cases, researchers have commonly employed conditions that include a synergetic combination of visible light photocatalyst and bromotrichloromethane (BrCCl₃) as a terminal oxidant.¹⁷

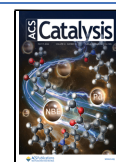
In our preliminary study, the BrCCl₃-mediated conditions were applied to a benzylic ether substrate harboring an additional nucleophilic aryl group, which resulted in the site-selective oxidation of the benzylic ether favorably over the

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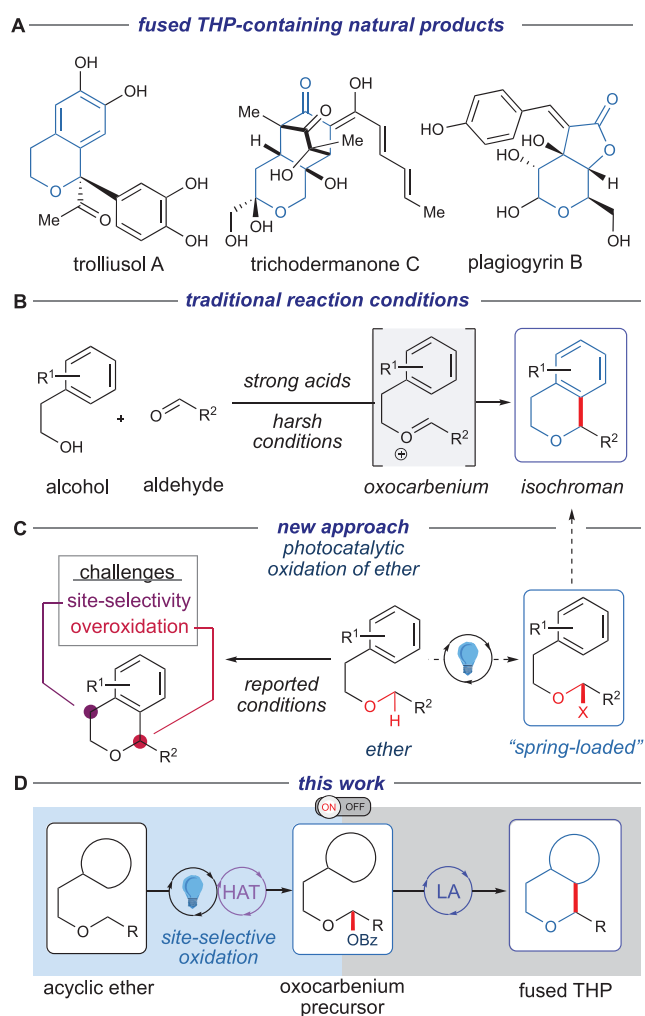


Figure 1. (A) Fused THP-containing natural products. (B) Traditional oxa-Pictet–Spengler reaction for isochromans. (C) Challenges of photocatalysis for this system and a blueprint of the new approach. (D) This work: site-selective photocatalytic oxidation of acyclic ether and mild Lewis acid-mediated oxa-Pictet–Spengler reaction.

other benzylic position (Figure 1C, left). The generated oxocarbenium intermediate underwent an oxa-Pictet–Spengler reaction to provide the desired isochroman. However, the desired product suffered from overoxidation because of the highly activated doubly benzylic position. This intriguing observation led to a meticulous exploration of alternative reagents that would provide the desired reaction selectivity. In this context, we envisaged that employing a different type of terminal oxidant could result in the formation of a more stable acetal intermediate. This spring-loaded intermediate would refrain from oxocarbenium ion formation until exposed to an acetal-activating reagent, thereby effectively mitigating the overoxidation concern (Figure 1C, right). As such, we envisioned that a combination of photocatalysis and hydrogen-atom transfer (HAT) catalysis¹⁸ would enable the introduction of a functional group at the ether α -position. Additionally, a Lewis acid-mediated oxocarbenium ion formation from the resulting intermediate would enable ring closure, thereby completing the mild oxa-Pictet–Spengler transformation (Figure 1D).

Table 1. Optimization of Reaction Conditions

entry	deviation from above conditions	yield (%) ^{a,b}
1	none	86 (82)
2	PC-2 instead of PC-1	18
3	PC-3 instead of PC-1	16
4	1.0 mol % of PC-1	72
5	TBPB instead of (BzO) ₂	9
6	A instead of <i>n</i> -BuSH	78
7	B instead of <i>n</i> -BuSH	64
8	C instead of <i>n</i> -BuSH	24
9	20 mol % of <i>n</i> -BuSH	75
10	MeCN instead of EtOAc	80
11	DCE instead of EtOAc	0
12	TFA instead of Bi(OTf) ₃	17

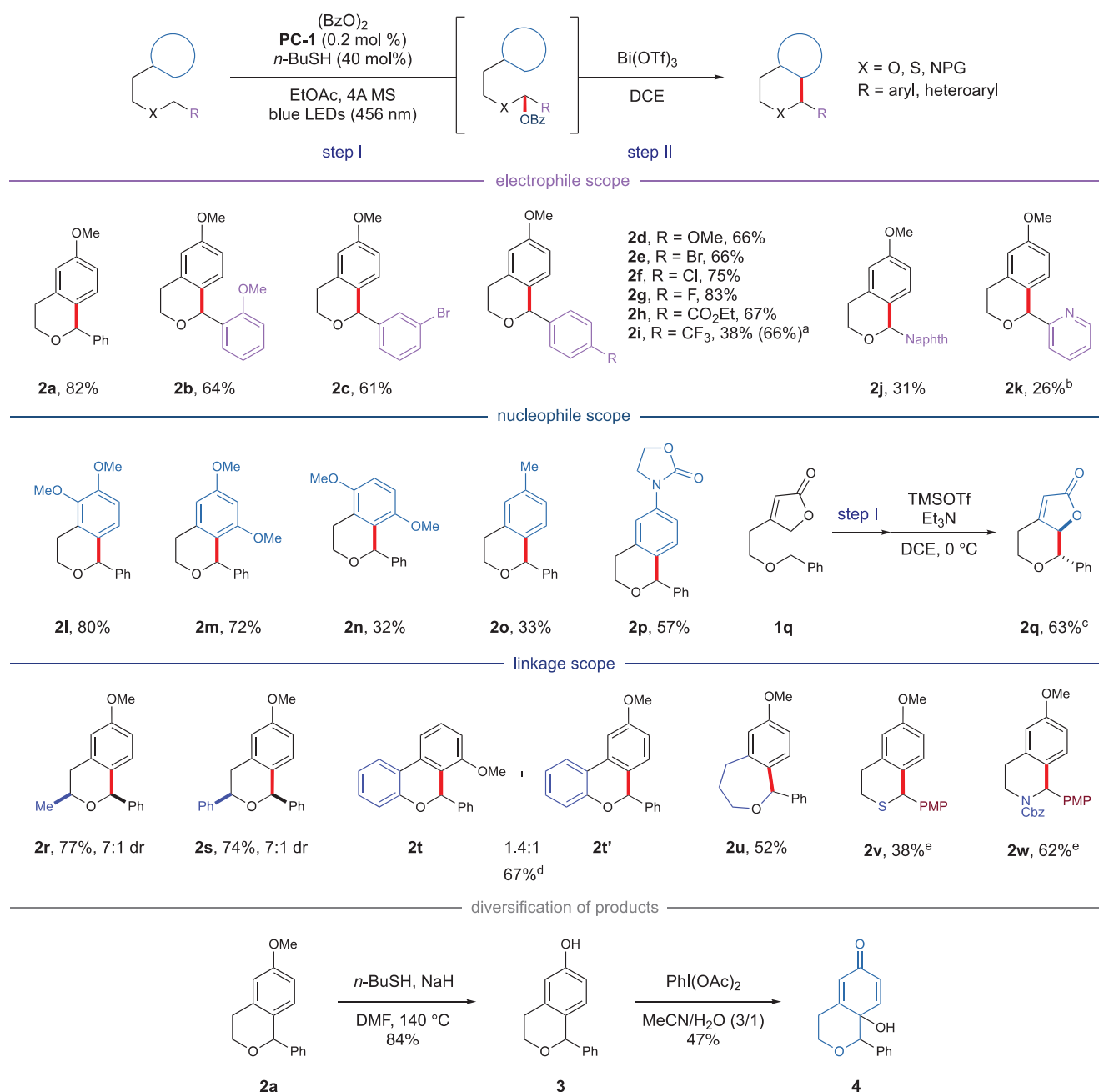
PC-1 PC-2 PC-3

(BzO)₂ TBPB A B C

^aReaction conditions unless otherwise indicated: **1a** (0.1 mmol), terminal oxidant (0.2 mmol; TBPB = *tert*-butylperbenzoate), **PC** (0.2 μ mol), and solvent (0.05 M; DCE = 1,2-dichloroethane) irradiated (456 nm) for 15 h. ^b¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard. Isolated yield given in parentheses.

In our reaction design, the employment of an appropriate terminal oxidant and a thiol-type HAT catalyst¹⁹ could site-selectively generate a radical at the benzylic ether position.²⁰ Concurrently, the oxidant-derived benzoate radical counterpart would couple to the ether radical to yield the crucial intermediate acetal. This benzoate acetal, while largely unreactive under the initial conditions, could subsequently be exposed to a Lewis acid catalyst to form the oxocarbenium species, thereby providing access to the ring-closure process.^{21a,16c,21b} We hypothesized that the strategic utilization of this spring-loaded acetal approach would effectively mitigate the overoxidation issue inherent in a photocatalytic oxa-Pictet–Spengler reaction.

On the basis of this plan, we selected **1a** as a model substrate, which bears a benzylic ether moiety, along with another electron-rich aromatic ring on the other side. After screening reaction conditions, the desired isochroman product **2a** was isolated in 82% yield over two steps (86% NMR yield) when Ir-dF (**PC-1**), benzoyl peroxide [(BzO)₂], and 1-butanethiol were used under blue LED irradiation (456 nm) followed by bismuth triflate-mediated oxa-Pictet–Spengler

Table 2. Substrate Scope of Photo- and Lewis acid-catalyzed Oxa-Pictet–Spengler^f

^aStep I: 36 h. ^b $\text{Bi}(\text{OTf})_3$ (2.2 mmol), 24 h. ^cReacted at 0.3 mmol scale, step II: solvent removal *in vacuo*; TMSOTf (0.96 mmol), Et₃N (1.08 mmol), DCE (0.2 M), 0 °C, 4 h. ^dRatio determined by ¹H NMR analysis. ^eSulfide or amine (0.2 mmol), $(\text{BzO})_2$ (0.4 mmol), TPPT (0.4 μmol), and DCE (0.025 M), irradiated with 470 nm LEDs for 1 h; $\text{Bi}(\text{OTf})_3$ (20 μmol). ^fReaction conditions unless otherwise indicated: step I = ether (0.2 mmol), $(\text{BzO})_2$ (0.4 mmol), PC-1 (0.4 μmol), *n*-BuSH (80 μmol), and EtOAc (0.05 M) irradiated with 456 nm LEDs for 15 h; step II = solvent removal *in vacuo*, $\text{Bi}(\text{OTf})_3$ (20 μmol) and solvent (DCE, 0.025 M), 5 h. DCE = 1,2-dichloroethane, PMP = 4-methoxyphenyl, TMS = trimethylsilyl, TPPT = triphenylpyrylium tetrafluoroborate, and DMF = *N,N*-dimethylformamide.

(Table 1, entry 1). The use of other photocatalysts, such as PC-2 and PC-3, provided lower yields of the products (entries 2 and 3). Higher photocatalyst loading also lowered the desired reactivity, potentially because of the termination of the photocatalytic cycle resulting from radical–radical homocoupling of overgenerated benzoate radicals (entry 4). The replacement of the terminal oxidant $(\text{BzO})_2$ with *tert*-butyl perbenzoate led to a significant decrease in the yield (entry 5). A brief survey of thiol HAT catalysts showed that methyl thioglycolate was a viable alternative for this reaction system,

whereas secondary alkyl and aryl thiols were not suitable (entries 6–8). A reduction of the thiol catalyst loading to 20 mol % afforded 2a in a decent yield of 75% (entry 9). Switching the solvent from EtOAc to MeCN resulted in a comparable yield (entry 10), whereas the formation of the key intermediate acetal was not observed when the first step was performed in DCE (entry 11). Use of trifluoroacetic acid instead of $\text{Bi}(\text{OTf})_3$ also afforded the product, albeit in a low yield (entry 12).

[illegible]

We also investigated the mechanism of this transformation by starting with control experiments (Scheme 1A). The omission of irradiation or oxidant from the standard conditions led to no desired product, thereby suggesting that the reaction is a light-driven process and that benzoyl peroxide is essential for the desired reactivity. Interestingly, a lower yield of the product was obtained in the absence of a photocatalyst, whereas none of the reactivity was observed when both thiol catalyst and photocatalyst were omitted. This observation suggested that, in the presence of thiol catalyst, photoinduced homolytic cleavage of benzoyl peroxide generates two benzoate radicals, which can engage in hydrogen atom abstraction and radical coupling to furnish the acetal.²² A lower reaction efficiency was also observed in the absence of thiol catalyst, presumably because of photoinduced energy transfer from PC-1* to benzoyl peroxide, which led to homolytic cleavage (for the proposed mechanism, see the Supporting Information).²³ The omission of the Lewis acid in step II afforded none of the product. The reaction mixture after step I was investigated through NMR and ESI-HRMS analyses, which indicated that **5** is formed and stable in the absence of an activating agent, like Lewis acid. Furthermore, addition of one equivalent of TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] to the standard conditions also suppressed product formation (Scheme 1B), thereby suggesting a radical mechanism. Additionally, this reaction mixture contained adduct **6**, as

detected by ESI-HRMS, which supported the intermediacy of the benzylic ether radical. Finally, a Stern–Volmer fluorescence quenching experiment was performed with the reaction components, and only benzoyl peroxide demonstrated significant quenching, thereby suggesting an oxidative quenching cycle (see the [Supporting Information](#)). From these experiments, we propose the following as the predominant mechanism ([Scheme 1C](#)). Benzoyl peroxide ($E_{\text{red}} = \sim -0.8$ V vs SCE)²⁴ can be reduced by excited PC-1* ($E_{1/2} \text{Ir}^{\text{III}*}/\text{Ir}^{\text{IV}} = -1.21$ V vs SCE)²⁵ to provide benzoate ion and benzoate radical. Then, oxidized photocatalyst PC-1* can generate thiyl radical from thiol HAT agent through proton-coupled electron transfer (PCET) to benzoate anion.²⁰ The thiyl radical can selectively abstract a hydrogen atom at the benzylic ether position of **1** to furnish benzylic ether radical **I**. Radical–radical cross-coupling between **I** and the benzoate radical provides key intermediate **II**, the acetal moiety of which is stable in the slightly acidic conditions because of the benzoic acid generated *in situ*. Radical–polar crossover of radical **I** may be also possible, and the benzoate anion could attack the resultant carbocation to afford acetal **II**. However, the absence of fully cyclized products during the photocatalyzed step disfavors the formation of carbocation intermediates. Additionally, the reaction proceeds efficiently in MeCN ([Table 1](#), entry 10), and Ritter reaction-type products are not observed under those conditions. In step II, bismuth-mediated elimination of the benzoate group of **II** affords oxocarbenium ion **III**, which smoothly undergoes an oxa-Pictet–Spengler reaction with the internal nucleophilic arene to furnish the final product **2**.

We have developed a two-step HAT/photocatalyzed oxa-Pictet–Spengler reaction of ethers. This mild protocol features a site-selective HAT at a benzylic ether position and subsequent radical cross-coupling with a benzoate radical to afford the key acetal intermediate. In the second step of the process, the intermediate undergoes an oxa-Pictet–Spengler reaction via oxocarbenium species in the presence of bismuth triflate. The exploitation of this spring-loaded strategy successfully mitigated the overoxidation issue inherent in photocatalytic oxa-Pictet–Spengler reactions. Notably, this methodology transforms acyclic ethers through cyclization under mild conditions, thereby efficiently providing access to isochromans, as well as other saturated cyclic core-fused THP products.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.4c01595>.

General information, experimental procedures, characterization of compounds, Stern–Volmer experiments data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Elliott, M. C.; Williams, E. Saturated oxygen heterocycles. *J. Chem. Soc., Perkin Trans.* **2001**, 1, 2303–2340. (b) Larrosa, I.; Romea, P.; Urpi, F. Synthesis of six-membered oxygenated heterocycles through carbon–oxygen bond-forming reactions. *Tetrahedron* **2008**, 64, 2683–2723. (c) Nibbs, A. E.; Scheidt, K. A. Asymmetric Methods for the Synthesis of Flavanones, Chromanones, and Azaflavanones. *Eur. J. Org. Chem.* **2012**, 2012, 449–462. (d) Pratap, R.; Ram, V. J. Natural and synthetic chromenes, fused chromenes, and versatility of dihydrobenzo[h]chromenes in organic synthesis. *Chem. Rev.* **2014**, 114, 10476–10526. (e) Cossy, J.; Guérinot, A. Natural Products Containing Oxygen Heterocycles—Synthetic Advances Between 1990 and 2015. In *Heterocyclic Chemistry in the 21st Century - A Tribute to Alan Katritzky*; Advances in Heterocyclic Chemistry, Vol. 119; Academic Press, 2016; pp 107–142.
- (2) Lu, Q.; Harmalkar, D. S.; Choi, Y.; Lee, K. An Overview of Saturated Cyclic Ethers: Biological Profiles and Synthetic Strategies. *Molecules* **2019**, 24, 3778.
- (3) Zhao, Z.; Kang, K.; Yue, J.; Ji, X.; Qiao, H.; Fan, P.; Zheng, X. Research progress in biological activities of isochroman derivatives. *Eur. J. Med. Chem.* **2021**, 210, 113073.
- (4) Li, D.-Y.; Wei, J.-X.; Hua, H.-M.; Li, Z.-L. Antimicrobial constituents from the flowers of *Trolius chinensis*. *J. Asian Nat. Prod. Res.* **2014**, 16, 1018–1023.
- (5) Marra, R.; Nicoletti, R.; Pagano, E.; DellaGreca, M.; Salvatore, M. M.; Borrelli, F.; Lombardi, N.; Vinale, F.; Woo, S. L.; Andolfi, A. Inhibitory effect of trichodermanone C, a sorbicillinoid produced by *Trichoderma citrinoviride* associated to the green alga *Cladophora* sp., on nitrite production in LPS-stimulated macrophages. *Nat. Prod. Res.* **2019**, 33, 3389–3397.
- (6) Murakami, T.; Tanaka, N.; Noguchi, T.; Saiki, Y.; Chen, C. Chemische und Chemotaxonomische Untersuchungen der Pterophyten. L. Chemische Untersuchungen der Inhaltsstoffe von *Plagiogyria matsumureana* MAKINO. *Chem. Pharm. Bull.* **1984**, 32, 1815–1821.
- (7) (a) Lherbet, C.; Soupaya, D.; Baudoin-Dehoux, C.; André, C.; Blonski, C.; Hoffmann, P. Bismuth triflate-catalyzed oxa- and thia-Pictet–Spengler reactions: access to iso- and isothio-chroman compounds. *Tetrahedron Lett.* **2008**, 49, 5449–5451. (b) Larghi, E. L.; Kaufman, T. S. Synthesis of Oxacycles Employing the Oxa-Pictet–Spengler Reaction: Recent Developments and New Prospects. *Eur. J. Org. Chem.* **2011**, 2011, 5195–5231.

- (8) (a) Cox, E. D.; Cook, J. M. The Pictet–Spengler condensation: a new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Yokoyama, A.; Ohwada, T.; Shudo, K. Prototype Pictet–Spengler Reactions Catalyzed by Superacids. Involvement of Dicationic Superelectrophiles. *J. Org. Chem.* **1999**, *64*, 611–617. (c) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet–Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538–8564.
- (9) (a) Mohler, D. L.; Thompson, D. W. Synthesis of isochromans via the titanium tetrachloride assisted cyclization of acetals of phenethyl alcohols. *Tetrahedron Lett.* **1987**, *28*, 2567–2570. (b) Giles, R. G. F.; Joll, C. A.; Sargent, M. V.; Tilbrook, D. M. G. Complementary diastereoselectivity in the intermolecular addition of titanium and magnesium naphtholates to asymmetric lactaldehydes. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 3029–3038. (c) Giles, R. G. F.; McManus, J. D. A novel titanium tetrachloride-induced rearrangement of an enantiopure 4-naphthylidioxolane. The possible role of titanium in the umpolung of tosyloxy and chlorine. *Tetrahedron Lett.* **2009**, *50*, 6361–6363.
- (10) Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B. Nitrated Confined Imidodiphosphates Enable a Catalytic Asymmetric Oxa-Pictet–Spengler Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 9429–9432.
- (11) (a) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335–344. (b) Girard, S. A.; Knauber, T.; Li, C. J. The cross-dehydrogenative coupling of C(sp³)-H bonds: a versatile strategy for C–C bond formations. *Angew. Chem., Int. Ed.* **2014**, *53*, 74–100.
- (12) (a) Cao, M.; Mao, Y.; Huang, J.; Ma, Y.; Liu, L. Cross-dehydrogenative coupling of secondary benzylic ethers with indoles and pyrroles. *Tetrahedron Lett.* **2019**, *60*, 1075–1078. (b) Feng, G.; Sun, C.; Xin, X.; Wan, R.; Liu, L. Cross-dehydrogenative coupling of 3,6-dihydro-2H-pyrans with 1,3-dicarbonyls and aryl moieties. *Tetrahedron Lett.* **2019**, *60*, 1547–1550. (c) Mao, Y.; Cao, M.; Pan, X.; Huang, J.; Li, J.; Xu, L.; Liu, L. Bimolecular oxidative C–H alkynylation of α -substituted isochromans. *Org. Chem. Front.* **2019**, *6*, 2028–2031. (d) Wang, Z.; Mao, Y.; Guan, H.; Cao, M.; Hua, J.; Feng, L.; Liu, L. Direct oxidative C(sp³)-H cyanation of secondary benzylic ethers. *Chin. Chem. Lett.* **2019**, *30*, 1241–1243.
- (13) Lee, A.; Betori, R. C.; Crane, E. A.; Scheidt, K. A. An Enantioselective Cross-Dehydrogenative Coupling Catalysis Approach to Substituted Tetrahydropyrans. *J. Am. Chem. Soc.* **2018**, *140*, 6212–6216.
- (14) (a) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012**, *77*, 1617–1622. (b) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (15) (a) Protti, S.; Fagnoni, M.; Ravelli, D. Photocatalytic C–H Activation by Hydrogen-Atom Transfer in Synthesis. *ChemCatChem*. **2015**, *7*, 1516–1523. (b) Chen, B.; Wu, L. Z.; Tung, C. H. Photocatalytic Activation of Less Reactive Bonds and Their Functionalization via Hydrogen-Evolution Cross-Couplings. *Acc. Chem. Res.* **2018**, *51*, 2512–2523. (c) Revathi, L.; Ravindar, L.; Fang, W.-Y.; Rakesh, K. P.; Qin, H.-L. Visible Light-Induced C–H Bond Functionalization: A Critical Review. *Adv. Synth. Catal.* **2018**, *360*, 4652–4698. (d) Li, Y.; Lei, M.; Gong, L. Photocatalytic regio- and stereoselective C(sp³)-H functionalization of benzylic and allylic hydrocarbons as well as unactivated alkanes. *Nat. Catal.* **2019**, *2*, 1016–1026. (e) Yang, Q.; Wang, Y.-H.; Qiao, Y.; Gau, M.; Carroll, P. J.; Walsh, P. J.; Schelter, E. J. Photocatalytic C–H activation and the subtle role of chlorine radical complexation in reactivity. *Science* **2021**, *372*, 847–852. (f) Zhang, Y.; Fitzpatrick, N. A.; Das, M.; Bedre, I. P.; Yayla, H. G.; Lall, M. S.; Musacchio, P. Z. A photoredox-catalyzed approach for formal hydride abstraction to enable C–H functionalization with nucleophilic partners (F, C, O, N, and Br/Cl). *Chem. Catal.* **2022**, *2*, 292–308. (g) Zhang, Y.; Sahoo, P. K.; Ren, P.; Qin, Y.; Cauwenbergh, R.; Nimmegeers, P.; SivaRaman, G.; Van Passel, S.; Guidetti, A.; Das, S. Transition metal-free approach for late-stage benzylic C(sp³)-H etherifications and esterifications. *Chem. Commun.* **2022**, *58*, 11454–11457. (h) Bellotti, P.; Huang, H. M.; Faber, T.; Glorius, F. Photocatalytic Late-Stage C–H Functionalization. *Chem. Rev.* **2023**, *123*, 4237–4352.
- (16) (a) Liu, Z.; Zhang, Y.; Cai, Z.; Sun, H.; Cheng, X. Photoredox Removal of p-Methoxybenzyl Ether Protecting Group with Hydrogen Peroxide as Terminal Oxidant. *Adv. Synth. Catal.* **2015**, *357*, 589–593. (b) Xiang, M.; Meng, Q. Y.; Li, J. X.; Zheng, Y. W.; Ye, C.; Li, Z. J.; Chen, B.; Tung, C. H.; Wu, L. Z. Activation of C–H Bonds through Oxidant-Free Photoredox Catalysis: Cross-Coupling Hydrogen-Evolution Transformation of Isochromans and β -Keto Esters. *Chem.—Eur. J.* **2015**, *21*, 18080–18084. (c) Xia, Q.; Wang, Q.; Yan, C.; Dong, J.; Song, H.; Li, L.; Liu, Y.; Wang, Q.; Liu, X.; Song, H. Merging Photoredox with Bronsted Acid Catalysis: The Cross-Dehydrogenative C–O Coupling for sp(3) C–H Bond Peroxidation. *Chem.—Eur. J.* **2017**, *23*, 10871–10877. (d) Ahn, D. K.; Kang, Y. W.; Woo, S. K. Oxidative Deprotection of p-Methoxybenzyl Ethers via Metal-Free Photoredox Catalysis. *J. Org. Chem.* **2019**, *84*, 3612–3623. (e) Cavedon, C.; Sletten, E. T.; Madani, A.; Niemeyer, O.; Seeberger, P. H.; Pieber, B. Visible-Light-Mediated Oxidative Debenzylation Enables the Use of Benzyl Ethers as Temporary Protecting Groups. *Org. Lett.* **2021**, *23*, 514–518. (f) Wan, T.; Capaldo, L.; Laudadio, G.; Nychev, A. V.; Rincón, J. A.; García-Losada, P.; Mateos, C.; Frederick, M. O.; Nuño, M.; Noël, T. Decatungstate-Mediated C(sp³)-H Heteroarylation via Radical-Polar Crossover in Batch and Flow. *Angew. Chem., Int. Ed.* **2021**, *60*, 17893–17897. (g) Liang, K.; Li, X.; Wei, D.; Jin, C.; Liu, C.; Xia, C. Deprotection of benzyl-derived groups via photochemically mesolytic cleavage of C–N and C–O bonds. *Chem.* **2023**, *9*, 511–522.
- (17) (a) Tucker, J. W.; Narayanan, J. M.; Shah, P. S.; Stephenson, C. R. Oxidative photoredox catalysis: mild and selective deprotection of PMB ethers mediated by visible light. *Chem. Commun.* **2011**, *47*, 5040–5042. (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. Visible-light photoredox catalysis in flow. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144–4147. (c) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. Visible Light Mediated Activation and O-Glycosylation of Thioglycosides. *Org. Lett.* **2013**, *15*, 30–33. (d) Lu, P.; Hou, T.; Gu, X.; Li, P. Visible-Light-Promoted Conversion of Alkyl Benzyl Ether to Alkyl Ester or Alcohol via α -sp³ C–H Cleavage. *Org. Lett.* **2015**, *17*, 1954–1957. (e) Xiang, M.; Meng, Q.-Y.; Gao, X.-W.; Lei, T.; Chen, B.; Tung, C.-H.; Wu, L.-Z. Reactivity and mechanistic insight into the cross coupling reaction between isochromans and β -keto esters through C–H bond activation under visible light irradiation. *Org. Chem. Front.* **2016**, *3*, 486–490. (f) Otake, Y.; Williams, J. D.; Rincón, J. A.; de Frutos, O.; Mateos, C.; Kappe, C. O. Photochemical benzylic bromination in continuous flow using BrCCl₃ and its application to telescoped p-methoxybenzyl protection. *Org. Biomol. Chem.* **2019**, *17*, 1384–1388. (g) Talukdar, R. Tracking down the brominated single electron oxidants in recent organic red-ox transformations: photolysis and photocatalysis. *Org. Biomol. Chem.* **2020**, *18*, 8294–8345. (h) Guan, Q.; Zhou, L.-L.; Dong, Y.-B. Construction of Nanoscale Covalent Organic Frameworks via Photocatalysis-Involved Cascade Reactions for Tumor-Selective Treatment. *Adv. Ther.* **2022**, *5*, 2100177.
- (18) (a) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056–2071. (b) Capaldo, L.; Quadri, L. L.; Ravelli, D. Photocatalytic hydrogen atom transfer: the philosopher’s stone for late-stage functionalization? *Green Chem.* **2020**, *22*, 3376–3396. (c) Cao, H.; Tang, X.; Tang, H.; Yuan, Y.; Wu, J. Photoinduced intermolecular hydrogen atom transfer reactions in organic synthesis. *Chem. Catal.* **2021**, *1*, 523–598. (d) Capaldo, L.; Ravelli, D.; Fagnoni, M. Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration. *Chem. Rev.* **2022**, *122*, 1875–1924.

(19) Bao, X.; Yu, W.; Wang, G. Thiols as Powerful Atom Transfer Catalyst: Opportunities in Photoredox-Mediated Reactions. *Adv. Synth. Catal.* **2023**, 365, 2299–2309.

(20) (a) Hager, D.; MacMillan, D. W. Activation of C-H bonds via the merger of photoredox and organocatalysis: a coupling of benzylic ethers with Schiff bases. *J. Am. Chem. Soc.* **2014**, 136, 16986–16989.

(b) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. A General Strategy for Organocatalytic Activation of C–H Bonds via Photoredox Catalysis: Direct Arylation of Benzylic Ethers. *J. Am. Chem. Soc.* **2014**, 136, 626–629.

(21) (a) Gil-Negrete, J. M.; Perez Sestelo, J.; Sarandeses, L. A. Transition-Metal-Free Cross-Coupling of Indium Organometallics with Chromene and Isochroman Acetals Mediated by $\text{BF}_3\cdot\text{OEt}_2$. *Org. Lett.* **2016**, 18, 4316–4319. (b) Wang, Z.; Niu, K.; Liu, Y.; Song, H.; Wang, Q. Electrochemical $\alpha\text{-C}(\text{sp}^3)\text{-H/O-H}$ cross-coupling of isochromans and alcohols assisted by benzoic acid. *Chem. Commun.* **2022**, 58, 10949–10952.

(22) To examine the possibility of intermediary disulfide or BzO-SBu being a HAT driver, we mixed thiol and benzoyl peroxide. However, formation of such intermediates was not observed by NMR spectroscopy, which suggested that thiol assists homolytic cleavage of benzoyl peroxide under light irradiation through an as yet undetermined mechanism.

(23) Oxidation of benzoate ion by the photocatalyst and HAT by benzoate radical would be also possible: Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. Visible-Light-Promoted Activation of Unactivated $\text{C}(\text{sp}^3)\text{-H}$ Bonds and Their Selective Trifluoromethylthiolation. *J. Am. Chem. Soc.* **2016**, 138, 16200–16203.

(24) Santa Cruz, T.; Akins, D.; Birke, R. L. Chemiluminescence and energy transfer in systems of electrogenerated aromatic anions and benzoyl peroxide. *J. Am. Chem. Soc.* **1976**, 98, 1677–1682.

(25) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **2005**, 17, 5712–5719.