Photochemical Organocatalytic Benzylation of Allylic C–H Bonds

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Emilien Le Saux,[†] Margherita Zanini,[†] and Paolo Melchiorre*[,†,‡]

[†]*ICIQ* – Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology, Avinguda Països Catalans 16, 43007 Tarragona, Spain

[‡]*ICREA* – Passeig Lluís Companys 23, 08010 Barcelona, Spain

Supporting Information Placeholder

ABSTRACT: We report a radical-based organocatalytic method for the direct benzylation of allylic C-H bonds. The process uses non-functionalized allylic substrates and readily available benzyl radical precursors and is driven by visible light. Crucial was the identification of a dithiophosphoric acid that performs two distinct catalytic roles, sequentially acting as a catalytic donor for the formation of photoactive electron donor-acceptor (EDA) complexes and then as a hydrogen atom abstractor. By mastering these orthogonal radical generation paths, the organic catalyst enables the formation of benzylic and allylic radicals, respectively, to then govern their selective coupling. The protocol was also used to design a three-component radical process, which increased the synthetic potential of the chemistry.

Benzyl and allyl groups are synthetically relevant fragments, so methods to directly join them are needed. However, developing a catalytic allylic benzylation strategy has proved difficult. Significant advances have been achieved in the context of metal-catalyzed allylic substitutions[1] (Figure 1a, *path i*). These methods required the use of hard 'unstabilized' benzylic nucleophiles and functionalized allylic substrates along with a metal catalyst (e.g. palladium[2], nickel,[3] iridium,[4] or rhodium[5]). Recently, radicals were used as surrogates of benzylic nucleophiles in a palladium-catalyzed allylic substitution,[6] securing milder reaction conditions (Figure 1a, *path ii*). However, all these metal-based methods rely on prefunctionalized allylic precursors bearing a suitable leaving group. A catalytic transformation that directly functionalizes allylic C-H bonds would provide a more straightforward approach to benzylic allylation chemistry, but this process has not yet been found.

Here we close this gap in synthetic methodology by developing a metal-free organocatalytic strategy to accomplish a direct allylic C–H benzylation. Our approach was motivated by recent studies that combined photoredox and thiol catalysis to perform direct C-H allylic functionalizations.[7,8] Single-electron transfer (SET) oxidation of a thiol catalyst led to a thiyl radical which, upon hydrogen atom transfer (HAT), could activate non-functionalized allylic substrates.[7] This approach generated allylic radicals that were successfully engaged in C(sp^3)-C(sp^2) and C(sp^3)-C(sp^3) bond formation.[8] However, the benzylation of allylic C-H bonds was not developed. Thiols can also catalyze other radical generation pathways. Specifically, we recently reported that sulfur anions, acting as catalytic donors, can readily form photoactive electron donor-acceptor (EDA) complexes[9] with a variety of radical precursors.[10] Excitation with visible light generated open-shell intermediates under mild conditions. We therefore surmised that the combination of these two mechanisms (EDA complex photochemistry and HAT activation) available to thiol catalysis could be leveraged to develop a direct allylic benzylation protocol (Figure 1b). Here we detail the realization of this idea.

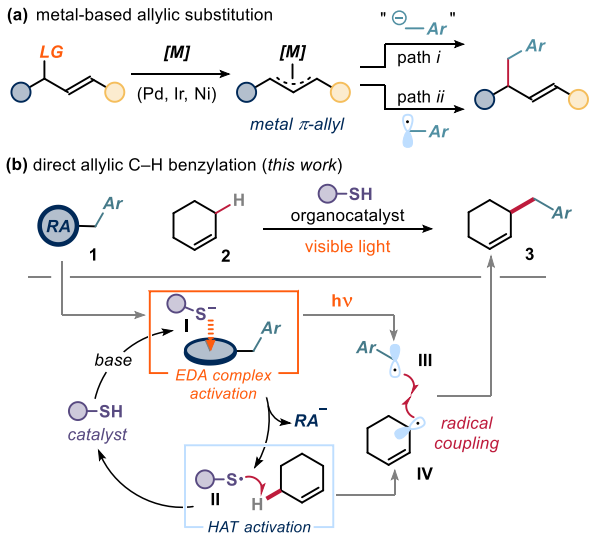
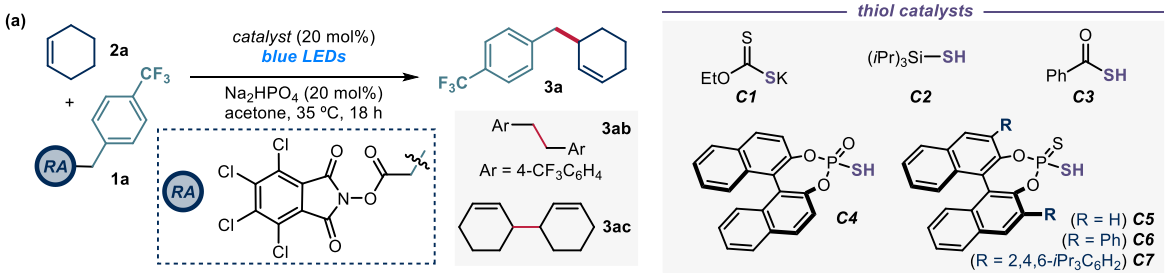


Figure 1. (**a**) Benzylation of allylic systems is generally achieved via metal-catalyzed allylic substitutions using prefunctionalized substrates and benzylic nucleophiles (path *i*) or radicals (path *ii*). (**b**) Proposed photochemical catalytic strategy for the direct allylic C–H benzylation based on an EDA complex/HAT activation sequence mastered by a thiol-based organocatalyst. RA: redox auxiliary, which drives EDA complex formation and acts as a fragmenting group.

The process is driven by visible light and uses readily available benzyl radical precursors **1** and non-functionalized allylic substrates **2**. Specifically, we used a thiol-based catalyst that performed two distinct roles: it first acted, upon deprotonation and formation of the thiolate **I**, as a catalytic donor for the formation of a photoactive EDA complex with the benzyl substrate **1**, decorated with a redox auxiliary (RA, blue circle in Figure 1b). Excitation with visible light induced an intracomplex SET, leading to a benzyl radical **III** and a thiyl radical **II**. The latter

intermediate then served as a hydrogen atom abstractor to activate the allylic substrate **2** via a HAT mechanism. By mastering these two orthogonal radical generation paths, the thiol organocatalyst promoted the formation of benzylic and allylic radicals **III** and **IV**, respectively, and then governed their selective coupling. The net process is the direct benzylation of allylic C-H bonds.

To test the feasibility of our strategy, we used tetrachlorophthalimide ester **1a** as the benzyl radical precursor (Figure 2a). This choice was motivated by the propensity of **1a** to engage in EDA complex formation acting as an acceptor.[11] Cyclohexene **2a** was selected as the C-H substrate since its allylic C-H bond dissociation energy (BDE, 83.2 kcal·mol^{-1})[12] makes it prone to HAT activation. Initial experiments were conducted in acetone using a blue LED (Figure 2b). A variety of thiol-based organocatalysts (20 mol%) were screened in the presence of an equimolar amount of Na_2HPO_4, which facilitated the formation of the thiolate donor of type **I**. We first tested the catalytic activity of potassium ethyl xanthate **C1** (entry 1), which we recently used as an effective catalytic donor for EDA complex activation.[10] The target cross-coupling product **3a** was generated in a yield as low as 15%, along with 7% of dimer **3ab**. The silane thiol **C2**, which was successfully used to activate allylic systems via a HAT pathway,[7] failed to promote the allylic benzylation, even in the presence of an external photoredox catalyst (entries 2 and 3). No reactivity was observed when using thiobenzoic acid **C3** as the catalyst (entry 4).[13] The thiophosphoric acid **C4**, which was used by Kanai in direct C-H allylic functionalization processes,[8d] delivered the target product **3a** in 22% yield along with 10% of dimer **3ab** (entry 5). This result prompted us to prepare the more electron-rich dithiophosphoric acid **C5** (estimated BDE, 83-86 kcal·mol^{-1}),[14] which offered better results, affording product **3a** in 41% yield together with 11% of **3ab** (entry 6). Bulkier catalysts **C6** and **C7** also proved effective, but did not offer significant improvements (entries 7-8). Control experiments (entries 9-11) established that the base, catalyst **C5**, and light were all essential for reactivity.



(b)

entry	catalyst	yield **3a** (%)	yield **3ab** (%)	yield **3ac** (%)
1	**C1**	15	7	n.d.
2	**C2**	0	n.d.	n.d.
3	**C2** + Ir(ppy)$_3$	0	n.d.	n.d.
4	**C3**	0	n.d.	n.d.
5	**C4**	22	10	12
6	**C5**	45 (41)*	11	20
7	**C6**	37	12	10
8	**C7**	45	18	26
9	**C5** / no base	12	3	8
10	none	-	-	-
11	**C5** / no light	-	-	-

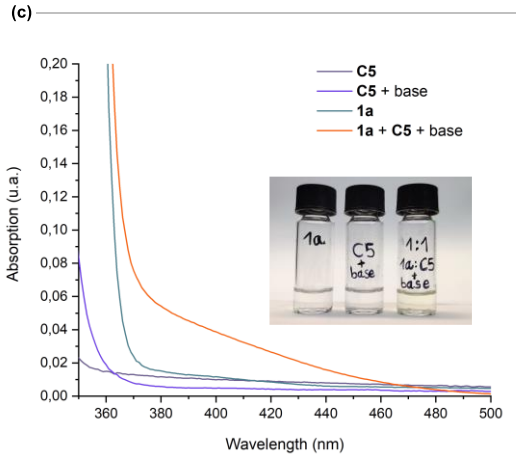


Figure 2. Initial explorations. (a) Model reaction and catalysts tested. **(b)** Optimization studies: reactions performed on a 0.1 mmol scale at 35 °C for 18 h under illumination by a blue LED strip (λ_{max} = 465 nm, 14 W) using 20 equiv. of **2a**. Yield determined by ^{1}H NMR analysis. *Yield of the isolated **3a**. **(c)** Optical absorption spectra, recorded in acetone in 1 mm path quartz cuvettes, of the separate reaction components and appearance of the colored EDA complex between catalyst **C5** and **1a**. [**1a**] = 0.10 M, [**C5**] = 0.02 M, [Na_2HPO_4] = 0.02 M. Ir(ppy)$_3$: tris[2-phenylpyridinato-C^2,N]iridium(III); n.d.: not determined.

We then performed investigations to gain mechanistic insights. The formation of an EDA complex was confirmed through UV/Vis spectroscopic analysis (Figure 2c). After mixing catalyst **C5** with ester **1a** in the presence of Na_2HPO_4, the solution developed a pale-yellow color, while its absorption spectrum showed a bathochromic displacement in the visible region. Overall, this evidence supports the formation of an EDA aggregation in the ground state. In addition, the homocoupling products **3ab** and **3ac** point to the formation of benzylic and allylic radicals during the process.

Adopting the conditions in Figure 2b, entry 6, we evaluated the scope of the photochemical allylic C-H benzylation of cyclohexene **2a** using tetrachloro-phthalimide esters **1**, easily derived from carboxylic acids, as benzyl radical precursors. Dithiophosphoric acid **C5** was used as the organocatalyst (20 mol%). Primary (product **3a**), secondary (**3b** and **3c**), and tertiary (**3d**) benzylic groups could be coupled with **2a** in moderate yields (Figure 3). We also used nonsteroidal anti-inflammatory drugs[15] bearing a carboxylic moiety as radical precursors, which allowed us to install the *indomethacin* (**3f**), *loxoprofen* (**3g**), and *flurbiprofen* (**3h-k**) scaffold within the allylation products.

Other alkenes were suitable allyl radical precursors, including cyclopentene (product **3i**) and substituted cyclohexenes (**3j** and **3k**). Catalyst **C5** was also suitable for the activation of pyridinium salts **4**, a class of radical precursors prone to EDA complex formation acting as acceptors.[10,16] The phenylglycine-derived pyridinium salt afforded product **3l**. A list of unsuccessful substrates is reported in Figure S1 of the Supporting Information.

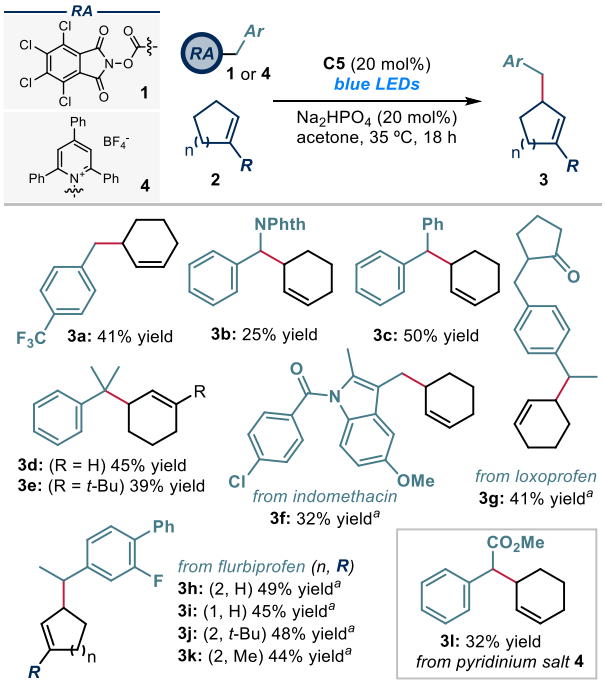


Figure 3. Substrate scope for the direct C-H allylic benzylation. Reactions performed on a 0.2 mmol scale. Yields refer to isolated products **3** (average of two runs per substrate). When applicable, *d.r.* is ≈1:1. [a] 0.1 mmol scale. *N*Phth: N-phthalimide.

One limitation of our system is that non-stabilized alkyl radicals did not deliver the desired cross-coupling products, although full consumption of the radical precursors (leading to the corresponding decarboxylation products) was observed. This lack of reactivity is congruent with the radical coupling step envisaged in our mechanistic proposal (Figure 1b), which requires the radical of type **III** to have enough kinetic stability (e.g. a benzylic radical) to engage in productive C-C bond formation with the allylic radical **IV**, according to the persistent radical effect (PRE).[17] Cognizant of this requirement, we sought to expand the synthetic utility of our strategy by intercepting non-stabilized alkyl radicals **V**, generated upon catalytic EDA activation of suitable radical precursors, with styrene derivatives **5** (Figure 4). The emerging benzylic radical **VI** would possess the persistent character needed for effective radical coupling with **IV**.

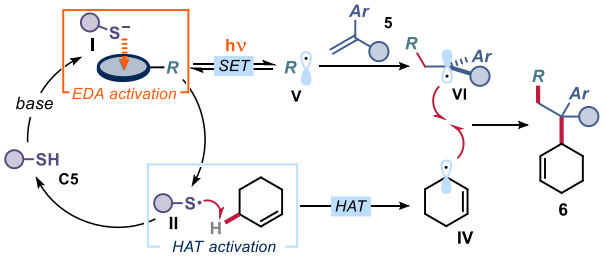


Figure 4. Implementing a three-component C-H allylic benzylation.

This three-component allylic benzylation procedure was successfully implemented using 10 mol% of organic catalyst **C5**, 5 to 10 equivalents of olefins **2**, and performing the reaction at 60 °C (Figure 5). The domino process offered a consistently higher yield than the direct allylic benzylation reported in Figure 3. This was due to a higher selectivity, since dimerization products were not detected. The process could be readily performed on a synthetically significant scale. For example, the reaction of cyclohexene **2a** with the glycine-derived pyridinium salt **4a** was conducted on a 1 mmol scale and delivered product **6a** (91% yield).

A variety of radical precursors, either phthalimide esters **1** or pyridinium salts **4**, could be used, offering the corresponding products in good to excellent yields (Figure 5a). Electron-poor radicals (products **6a-d**), non-stabilized primary (**6h-l**), secondary (**6e**), and tertiary (**6f-g** and **6m**) alkyl radicals were all amenable to this domino allylic benzylation process. Various heterocycles, including a pyrimidine (**6d**), a pyridine (**6k**), an oxetane (**6m**) and an azetidine (**6n**), could be installed in the final products. Moreover, complex biorelevant molecules bearing non-protected functional groups, such as *oleanolic acid* (**6o**), *dehydrocholic acid* (**6p**), and *indomethacin* (**6q**), were successfully functionalized. To increase the synthetic utility of our approach, we implemented a two-step telescoped sequence to form the tetrachloro-phthalimide ester **1** in situ and use it without further purification (Figure 5b). This one-pot strategy was successfully developed using cyclohexanecarboxylic acid, leading to product **6e** in 56% yield, and to functionalize *D-biotin*, obtaining adduct **6r** in 37% yield.

We next examined the scope of olefins **2** that could be employed as C-H allylic precursors (Figure 5c). While cyclopentene reacted smoothly to afford product **6s** in 75% yield, cyclooctene offered a moderate reactivity (**6t** formed in 39% yield). Interestingly, catalyst **C5** secured a high regioselectivity in the HAT activation of 1-substituted cyclohexenes (products **6u** and **6v**), promoting the formation of the less hindered allylic radical. Non-symmetrical C-H partners bearing a phthalimide functional group (**6x**) and a boronic ester (**6y**) were well tolerated. Noteworthy, the bulkier catalysts **C6** and **C7** greatly improved (**6x**) or even switched (**6y'** instead of **6y**) regioselectivity with respect to **C5**.[18] Our organocatalytic photochemical process was also suitable for the late-stage functionalization of *cholesterol*, which led to product **6z** in good yield. This coupling protocol was also useful to functionalize benzylic C-H bonds, including tetrahydronaphthalene (product **6aa**) and dihydroisobenzofuran (adduct **6bb**).

We eventually evaluated the styrene derivatives **5** suitable for this photochemical domino process using **2a** as the allylic precursor (Figure 5d). α-Aryl-styrene derivatives afforded the desired products in good to excellent yields (products **6cc-jj**). These results are congruent with the stabilization of the benzylic radical **VI**, emerging from the radical trap, which facilitates the radical coupling step (Figure 4). Interestingly, a benzodioxole and an aldehyde moiety, despite being sensitive to HAT activation, were left untouched (compounds **6dd** and **6ff**). A derivative of *fenofibrate*, a marketed fibrate medication, was equally suitable for the transformation, delivering product **6jj**. Styrenes (products **6oo** and **6pp**) and α-alkyl styrene derivatives (**6kk-nn**) offered reduced reactivity, but they were still competent substrates. In particular, a protected piperidine (**6mm**) and a boronic ester (**6nn**) could be installed in the final products from suitably adorned styrenes.

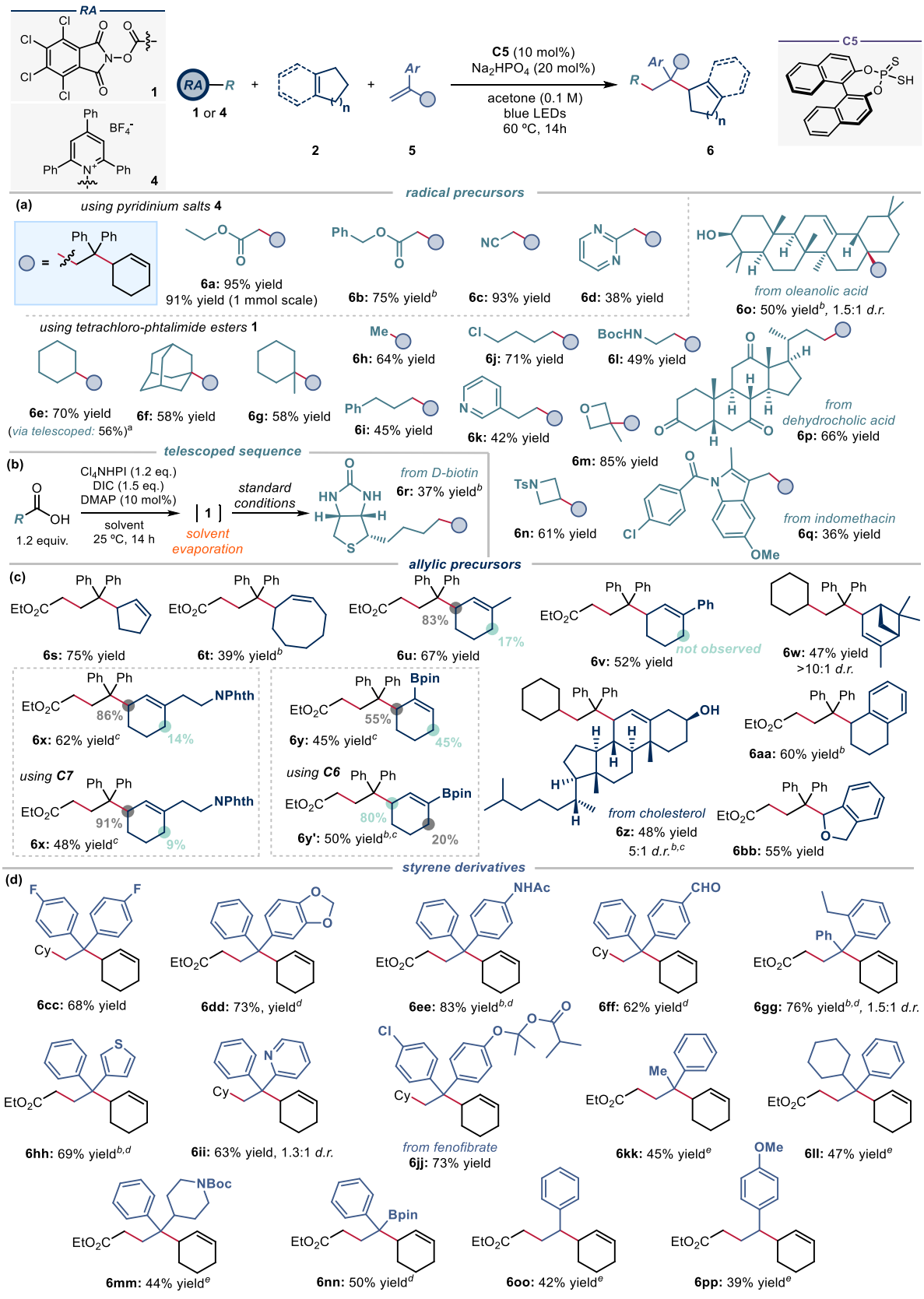


Figure 5. Photochemical organocatalytic three-component C-H allylic benzylation. Scope of (**a**) the radical precursors **1** and **4**, and (**b**) telescoped procedure; (**c**) scope of the allylic substrates **2** and (**d**) the styrene traps **5**. Reactions performed on a 0.1 mmol scale using 10 equiv. of **2** and 1 equiv. of **5**. Yields refer to isolated products **6** after purification (average of two runs). When applicable, *d.r.* was ≈1:1. [a] Using a one-pot telescoped procedure. [b] Yield determined by ^{1}H NMR analysis. [c] Using 5 equiv. of **3**. [d] Using 20 mol% of **C5**. [e] Using 20 mol% of **C5**, 20 equiv. of **2**, and 1 equiv. of Na_2HPO_4; Ts, tosyl; Boc, *tert*-butyloxycarbonyl; Bpin, pinacol boronic ester; Cy, cyclohexyl; DIC: *N*,*N*′-diisopropylcarbodiimide; Cl_4NHPI: *N*-(acyloxy)tetrachloro-phthalimide.

In summary, we have developed a radical-based organocatalytic system that permits the direct benzylation of allylic C-H bonds. The process uses non-functionalized allylic substrates and readily available benzyl radical precursors and is driven by visible light. Crucial was the identification of a dithiophosphoric acid catalyst that activated both substrates by mastering a sequence of EDA complex activation and H atom abstraction. The protocol's functional group tolerance enabled the functionalization of a variety of biologically relevant compounds and the design of a three-component radical process.

ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures and full characterization data and copies of NMR spectra (PDF). The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*pmelchiorre@iciq.es

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Crawley, M. L. Allylic Substitution Reactions. *Stereoselective Synthesis 3*; de Vries, J. G.; Evans, P. A.; Molander, G. A., Eds.; Science of Synthesis; Thieme; Stuggart, 2011; pp 403−442. (b) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev*. **2019**, *119*, 1855−1969.

(2) (a) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. Palladium-Catalyzed Asymmetric Allylic Alkylations of Polynitrogen-Containing Aromatic Heterocycles. *J. Am. Chem. Soc.* **2011**, *133*, 12439–12441. (b) Zhang, J.; Stanciu, C.; Wang, B.; Hussain, M. M.; Da, C.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. Palladium-Catalyzed Allylic Substitution with (η^6 -Arene–CH_2Z)$Cr(CO)_3$-Based Nucleophiles. *J. Am. Chem. Soc.* **2011**, *133*, 20552–20560. (c) Sha, S. C.; Zhang, J.; Carroll, P. J.; Walsh, P. J. Raising the pK_a Limit of "Soft" Nucleophiles in Palladium-Catalyzed Allylic Substitutions: Application of Diarylmethane Pronucleophiles. *J. Am. Chem. Soc.* **2013**, *135*, 17602–17609. (d) Shen, Y.; Dai, Z.-Y.; Zhang, C.; Wang, P.-S. Palladium-Catalyzed Allylic Alkylation via Photocatalytic Nucleophile Generation. *ACS Catal.* **2021**, *11*, 6757−6762.

(3) Sha, S. C.; Jiang, H.; Mao, J.; Bellomo, A.; Jeong, S. A.; Walsh, P. J. Nickel-Catalyzed Allylic Alkylation with Diarylmethane Pronucleophiles: Reaction Development and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2016**, *55*, 1070–1074.

(4) Moon, P. J.; Wei, Z.; Lundgren, R. J. Direct Catalytic Enantioselective Benzylation from Aryl Acetic Acids. *J. Am. Chem. Soc.* **2018**, *140*, 17418–17422.

(5) Pal, D.; Wright, T. B.; O'Connor, R.; Evans, P. A. Regio- and Diastereoselective Rhodium-Catalyzed Allylic Substitution with Unstabilized Benzyl Nucleophiles. *Angew. Chem., Int. Ed.* **2021**, *60*, 2987–2992.

(6) (a) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. Decarboxylative Allylation of Amino Alkanoic Acids and Esters via Dual Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 13606–13609. (b) Zhang, H. H.; Zhao, J. J.; Yu, S. Enantioselective Allylic Alkylation with 4-Alkyl-1,4-Dihydro-Pyridines Enabled by Photoredox/Palladium Cocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16914–16919.

(7) Cuthbertson, J. D.; MacMillan, D. W. C. The Direct Arylation of Allylic sp^3 C-H Bonds via Organic and Photoredox Catalysis. *Nature* **2015**, *519*, 74–77.

(8) (a) Vu, M. D.; Das, M.; Guo, A.; Ang, Z. E.; Dokić, M.; Soo, H. Sen; Liu, X. W. Visible-Light Photoredox Enables Ketone Carbonyl Alkylation for Easy Access to Tertiary Alcohols. *ACS Catal.* **2019**, *9*, 9009–9014. (b) Fan, X-Z.; Rong, J-W.; Wu, H-L.; Zhou, Q.; Deng, H-P.; Tan, J.D.; Xue, C-W.; Wu, L-Z.; Tao, H-R.; Wu, J. *Angew. Chem., Int. Ed*. **2018**, *57*,8514 –8518. (c) Jia, J.; Kancherla, R.; Rueping, M.; Huang, L. Allylic C(sp3)-H Alkylation via Synergistic Organo- And Photoredox Catalyzed Radical Addition to Imines. *Chem. Sci.* **2020**, *11*, 4954–4959. (d) Tanabe, S.; Mitsunuma, H.; Kanai, M. Catalytic Allylation of Aldehydes Using Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 12374–12381. (e) Nakashima, T.; Ohmatsu, K.; Ooi, T. Mannich-Type Allylic C-H Functionalization of Enol Silyl Ethers under Photoredox-Thiol Hybrid Catalysis. *Org. Biomol. Chem.* **2021**, *19*, 141–145.

(9) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. Synthetic Methods Driven by the Photoactivity of Electron Donor–Acceptor Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 5461–5476.

(10) de Pedro Beato, E.; Spinnato, D.; Zhou, W.; Melchiorre, P. A General Organocatalytic System for Electron Donor−Acceptor Complex Photoactivation and Its Use in Radical Processes. *J. Am. Chem. Soc.* **2021**, *143*, 12304−12314.

(11) Bosque, I.; Bach, T. 3-Acetoxyquinuclidine as Catalyst in Electron Donor–Acceptor Complex-Mediated Reactions Triggered by Visible Light. *ACS Catal.* **2019**, *9*, 9103–9109.

(12) Khursan, S. L.; Mikhailov, D. A.; Yanborisov, V. M.; Borisov, D. I. AM1 Calculations of bond dissociation energies. Allylic and benzylic C–H bonds. *React. Kinet. Catal. Lett.* **1997**, *61*, 91–95.

(13) Kobayashi, F.; Fujita, M.; Ide, T.; Ito, Y.; Yamashita, K.; Egami, H.; Hamashima, Y. Dual-Role Catalysis by Thiobenzoic Acid in Cα-H Arylation under Photoirradiation. *ACS Catal.* **2021**, *11*, 82–87.

(14) The BDE value of **C5** was estimated by means of DFT calculations and comparison with calculated BDEs for S-H bonds reported in the literature: Denisov, E.; Chatgilialoglu, C.; Shestakov, A.; Denisova, T. Rate constants and transition-state geometry of reactions of alkyl, alkoxyl, and peroxyl radicals with thiols. *Int. J. Chem. Kinet.* **2009**, *41*, 284-293. See section E4 in the Supporting Information for computational details.

(15) Kovačević, A. B.; Silva, S. M. C.; Doktorovová, S. Lipid nanoparticles as carriers for delivery of anti-inflammatory drugs. In *Emerging Nanotechnologies in Immunology*; Shegokar, R.; Souto, E. B., Eds.; Micro and Nano Technologies; Elsevier, 2018; pp 103-133.

(16) (a) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced Deaminative Borylation of Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 10700−10704. (b) Sandfort, F.; Strieth-Kalthoff, F.; Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Borylation of Aliphatic Amines Enabled by Visible Light Excitation of an Electron Donor−Acceptor Complex. *Chem. Eur. J.* **2018**, *24*, 17210−17214.

(c) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single Electron Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 5697−5701.

(17) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74–108.

(18) Further details on the correlation between the catalysts' steric hindrance and the regioselectivity are reported in section E3 of the Supporting information.

Proposed graphical abstract: