

Reductive Cross-Coupling of Olefins via a Radical Pathway

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ABSTRACT: Olefins are widely available at low costs, which explains the usefulness of developing new methods for their functionalization. Here we report a simple protocol that uses a photoredox catalyst and an inexpensive thiol catalyst to stitch together two olefins, forming a new C–C bond. Specifically, an electron-poor olefin is reduced by the photoredox catalyst to generate, upon protonation, a carbon radical, which is then captured by a neutral olefin. This intermolecular cross-coupling process provides a tool for rapidly synthesizing sp^3 -dense molecules from olefins using an unconventional disconnection.

Olefins are ubiquitous motifs in petroleum-derived compounds, natural products, pharmaceuticals, and materials.¹ Therefore, developing methods for their direct functionalization is of high synthetic significance. One useful transformation is the intermolecular cross-coupling of two olefins, as it enables the rapid formation of new C–C bonds directly from these abundant feedstocks.² In this context, a reductive olefin cross-coupling has been reported³ recently based on a metal-hydride hydrogen atom transfer (MHAT)⁴ mechanism (Figure 1a). An iron catalyst promoted the formation of carbon radicals through MHAT activation of electron-rich olefins.³ These radicals were subsequently intercepted by electron-poor olefins in a classical Giese-type

reaction.⁵ Overall, this process enabled the combination of two olefins to produce valuable sp^3 -hybridized products.⁶

Herein, we report a novel method for the intermolecular reductive cross-coupling of two olefins based on a distinct mechanistic pattern (Figure 1b). Specifically, our strategy capitalizes on the generation of radicals from electron-poor olefins **1**. We surmised that **1** could be reduced by an excited photoredox catalyst (PC) to form a radical anion **I**, which upon protonation would deliver a carbon radical **II** adjacent to an electron-withdrawing group (EWG). This electrophilic radical **II** would be favorably poised⁷ to react with an electron-rich or neutral olefin **2** via radical addition. Eventually, the ensuing radical **III** would be reduced by a thiol catalyst via a hydrogen atom transfer (HAT)⁸ path to afford the desired olefin cross-coupling product **3**. This Communication details the realization of this idea. The resulting olefin cross-coupling method complements the previously reported protocol,³ as the same two olefins play opposite roles (compare Figure 1a and b). As a result, sp^3 -dense products **3** with different connectivity, arising from opposite disconnections, become available.⁹

Crucial to our reaction design was the ability to reduce electron-poor olefins **1** using a light-activated photoredox catalyst. The literature offers some studies demonstrating the feasibility of selectively reducing **1** to the corresponding radical anions of type **I**.¹⁰ While lending support to our mechanistic hypothesis, these methods were mainly limited to the reduction of specific olefins **1** or required UV light irradiation,¹⁰ or the resulting intermediate **I** reacted preferentially at the anion site via a polar pathway, rather than capitalizing on radical reactivity.¹¹ A few examples were reported where the radical intermediate **I** was intercepted by an olefin,¹² but mainly in an intramolecular fashion.¹³

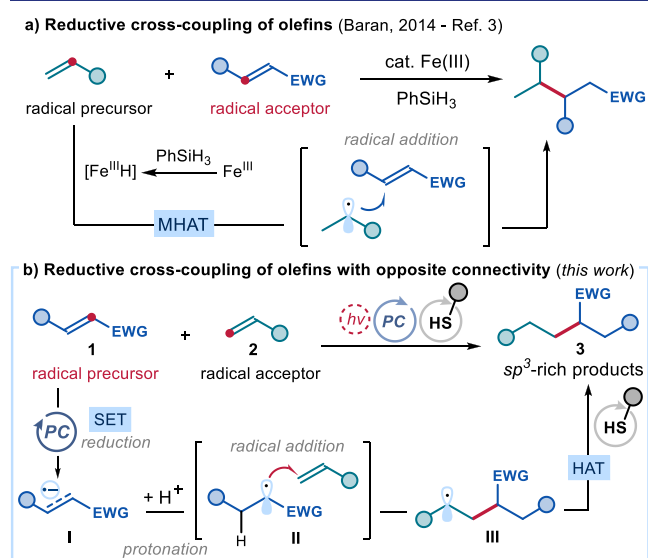


Figure 1. (a) Olefin cross-coupling strategy in which electron-rich olefins served as radical precursors. (b) The present strategy uses electron-poor olefins as radical precursors to afford sp^3 -rich products **3** with a different connectivity compared to the previous method. SET: single-electron transfer; HAT: hydrogen atom transfer; PC: photoredox catalyst; the purple dots indicate the substrates' reactive sites for C–C bond formation.

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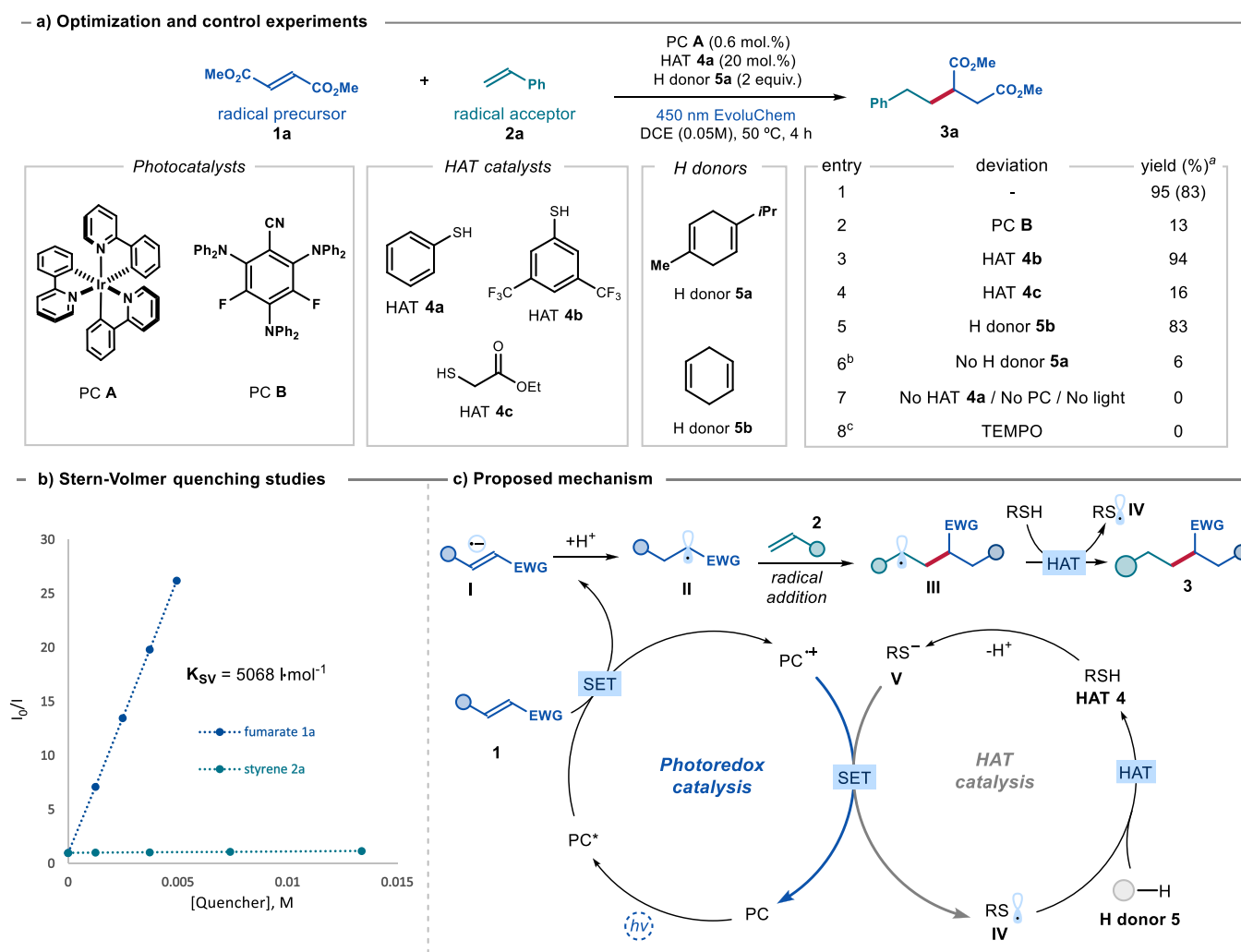


Figure 2. (a) Optimization studies and control experiments. Reactions performed on a 0.1 mmol scale using 1 equiv of styrene **2a** and 1.5 equiv of dimethyl fumarate **1a** under illumination by a blue LED (EvoluChem) at 450 nm. ^aYield of **3a** was determined by GC-FID analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. Yields of isolated **3a** are reported in parentheses (0.2 mmol scale). ^bUsing 2.0 equiv of thiophenol **4a**. ^cUsing 1.5 equiv of TEMPO. (b) Stern–Volmer luminescence quenching studies of Ir(ppy)₃ (PC **A**, 1.5 μM in DCE) with increasing amounts of dimethyl fumarate **1a** and styrene **2a** (excitation wavelength = 440 nm; emission recorded at 513 nm). (c) Proposed mechanism of the reductive cross-coupling of olefins.

We started our investigations by using dimethyl fumarate **1a** [$E(1a/1a^{\bullet-}) = -1.47 \text{ V vs SCE}$]¹⁴ as the radical precursor and styrene **2a** as the radical acceptor (Figure 2a). The experiments were performed in 1,2-dichloroethane (DCE) as the solvent in the presence of γ -terpinene **5a** as H donor¹⁵ (2.0 equiv) and thiophenol (20 mol %) as the HAT catalyst under irradiation by a blue LED ($\lambda_{\text{max}} = 450 \text{ nm}$). We initially tested the highly reducing iridium-based photoredox catalysts **A** [$E^*[\text{Ir(IV)}/\text{Ir(III)}^*] = -1.88 \text{ V vs SCE}$],¹⁶ as it had the required redox power to activate **1a**. The cross-coupling reaction of **1a** and **2a** proceeded smoothly, affording the target product **3a** in high yield (entry 1). The use of organic photocatalyst **B** led to a drastically reduced reactivity (entry 2). The screening of other HAT catalysts **4** (entries 3, 4) and H donors **5** (entry 5) confirmed that γ -terpinene **5a** and thiophenol **4a** offered the best results. We also used a stoichiometric amount of thiophenol **4a** to avoid the need of any additional H donor (entry 6), but product **3a** was obtained in low yield because of competitive thiol–ene and sulfa–Michael processes. Control experiments established that the presence of the H donor (γ -terpinene **5a**, entry 6), the HAT catalyst (thiophenol **4a**), light,

and photocatalyst **A** was essential for reactivity (entry 7). When the radical scavenger TEMPO was added under the optimal conditions (entry 8), the reactivity was completely inhibited, which was congruent with a radical path being operative.

To gain insight into the reaction mechanism, we conducted Stern–Volmer quenching studies. Irradiating a DCE solution of photoredox catalyst **A** at 440 nm revealed emission with a maximum at 513 nm (details in Section H1 of the Supporting Information). Measurements in the presence of increasing amounts of quenchers showed that dimethyl fumarate **1a** is a much more effective quencher than styrene **2a** (Figure 2b). This observation aligns with our mechanistic proposal in which the excited photocatalyst can effectively reduce electron-poor olefin **1** via single-electron transfer (SET), leading to the reactive radical anion of type **I** (Figure 2c). The ensuing radical anion **I** would then undergo protonation to give radical **II**, which can be intercepted by olefin **2**. The resulting radical **III** could then abstract a hydrogen atom from thiol **4**, leading to reductive olefin coupling product **3** and thiyl radical **IV**. Meanwhile, thiolate **V** [$E(\text{IV}/\text{V}) = -0.36 \text{ V vs } [\text{FC}^+/\text{FC}]$ in

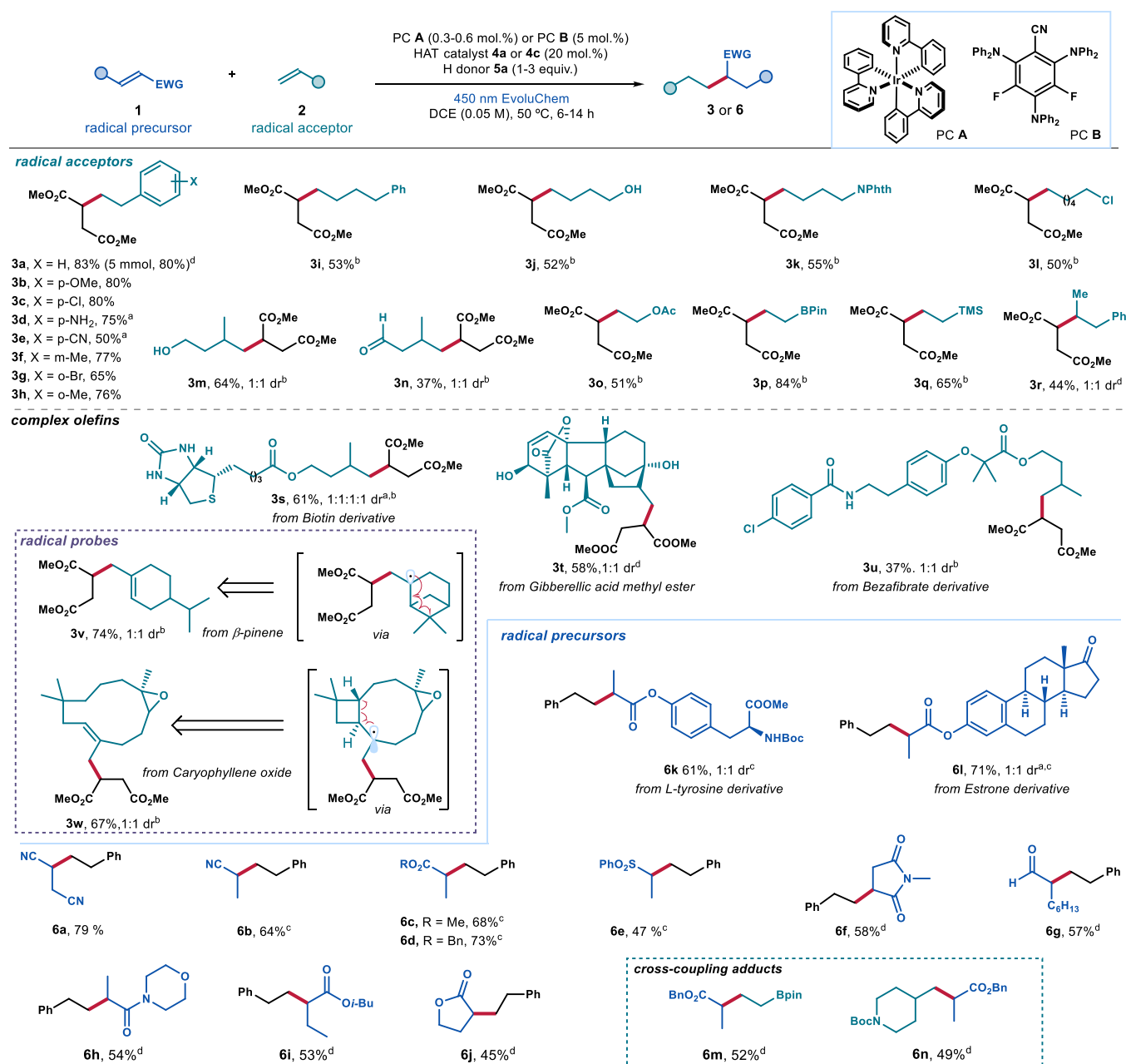


Figure 3. Photochemical reductive cross-coupling of olefins. Reactions performed on a 0.2 mmol scale at 50 °C using PC A (0.6 mol %), **4a** (20 mol %), γ -terpinene **5a** (2.0 equiv), **1** (1.5 equiv), and **2** (1.0 equiv). Yields refer to isolated products **3** and **6**. ^aYield was determined by ¹H NMR analysis of the crude mixture using dibromomethane as the internal standard. ^bPerformed using PC A (0.3 mol %), ethyl thioglycolate **4c** (20 mol %), γ -terpinene **5a** (1 equiv), **1** (1.0 equiv), and **2** (3.0 equiv). ^cPerformed using PC B (5.0 mol %), PhSH **4a** (20 mol %), 2,4,6-collidine (1 equiv), γ -terpinene **5a** (3 equiv), **1** (1.0 equiv), and **2** (3.0 equiv). ^dReaction performed under modified conditions; see the Supporting Information for details. Phth: phthalimide; Ac: acetyl; BPin: bis(pinacolato)boron; TMS: trimethylsilyl; Ph: phenyl; Bn: benzyl; *i*-Bu: isobutyl; Boc: *tert*-butoxycarbonyl.

DMSO for thiophenolate]¹⁷ could be oxidized by the oxidized photocatalyst ($E[\text{Ir(IV)/Ir(III)}] = 0.77 \text{ V vs SCE}$)¹⁶ to turn over the photocatalyst and generate the thiyl radical **IV**. This latter radical can abstract a hydrogen atom from H donor **5** to regenerate thiol catalyst **4**.

Using the conditions described in entry 1 of Figure 2a we then investigated the scope of the acceptor olefins using fumarate **1a** as the radical precursor (Figure 3). First, we demonstrated that the process was equally efficient on a 5 mmol scale, yielding 1.0 g of product **3a** (80% yield). Styrenes with different substitutions at the *ortho*-, *meta*-, and *para*-

position afforded the olefin cross-coupling products **3b–3h** with good to excellent yields. Nonactivated terminal olefins bearing aliphatic substituents were suitable for this process, affording the corresponding products **3i–3n** in good yields. A variety of functional groups were tolerated well, including a free alcohol (adducts **3j** and **3m**), a halogen atom (product **3l**), and an aldehyde (**3n**). Electron-rich and heteroatom-functionalized olefins were also reactive, affording products **3o–3q**.

While terminal disubstituted olefins offered good yields (adducts **3m, 3n**, **3s–3w**), internal olefins exhibited reduced reactivity. For example, *trans*- β -methylstyrene afforded product

3r in 44% yield (see Figure S4 in the Supporting Information for a list of substrates that proved to be unreactive or poorly reactive). The higher reactivity of terminal olefins allowed us to chemoselectively functionalize a derivative of the gibberellic acid (adduct 3t), leaving the internal double bond unaffected. Our methodology was also suitable for the late-stage functionalization of natural products and their derivatives bearing an olefin moiety. For example, a biotin and a bezafibrate derivative reacted smoothly to provide adducts 3s and 3u, respectively. When β -pinene or caryophyllene oxide were reacted, the ring-opening products 3v and 3w, respectively, were obtained in good yields. This observation supports the involvement of a radical of the type III (Figure 2c) as an intermediate in the process.

Next, we assessed the electron-poor olefins capable of reacting with styrene 2a in our olefin cross-coupling protocol (Figure 3, lower panel). We found that fumaronitrile could serve as a radical precursor, yielding product 6a in a high yield. By using photocatalyst B in combination with a weak base (2,4,6-collidine, 1 equiv), we achieved enhanced reactivity with less activated electron-poor olefins. Under these slightly modified conditions (refer to Section H4 in the Supporting Information for the proposed mechanism), acrylonitrile, acrylates, and vinylsulfone underwent smooth reactions, yielding the corresponding products 6b–6e in moderate to good yields. Additionally, other electron-poor olefins, such as *N*-methyl maleimide, an enal, and an acrylamide, also generated olefin cross-coupling products 6f–6h in decent yields. The protocol was also effective for internal and cyclic acrylates, affording adducts 6i and 6j. Furthermore, acrylates derived from biorelevant molecules successfully participated in our coupling method (products 6k and 6l). To demonstrate the versatility of the methodology, we investigated cross-coupling reactions between two less activated substrates, leading to the formation of adducts 6m and 6n in moderate yield. In general, the main byproduct of this protocol is the reduction product of electron-poor olefins I, the formation mechanism of which is discussed in Section G2 of the Supporting Information.

We then conducted further mechanistic investigations using benzyl acrylate. First, a radical probe experiment was performed with cyclopropyl-containing styrene 7, resulting in the formation of the ring-opening product 8 in good yield (Figure 4a). This outcome suggested the generation of a radical from the electron-poor olefin, followed by its trapping by styrene 7.¹⁸ When D₂O was introduced into the reaction, the deuterated product 6d-D was obtained in 52% yield (Figure 4b). NMR analysis revealed 70% deuterium incorporation at the β position of the acrylate moiety and 30% incorporation at the benzylic position. This finding is consonant with the SET reduction of the electron-poor olefin, forming the radical anion of type I. Protonation then occurs at the β carbon,^{10c} leading to the formation of the more stabilized radical II. Radical addition to styrene then forms radical intermediate III, which can be deuterated through HAT with deuterated thiophenol, which can be generated *in situ* via D₂O exchange.

In summary, we have developed a light-driven protocol that uses mild conditions and readily available catalysts for the reductive cross-coupling of olefins, providing sp³-rich products with distinct connectivity. Central to this transformation was the photoredox-enabled generation of radicals through the reduction of electron-poor olefins. These substrates were

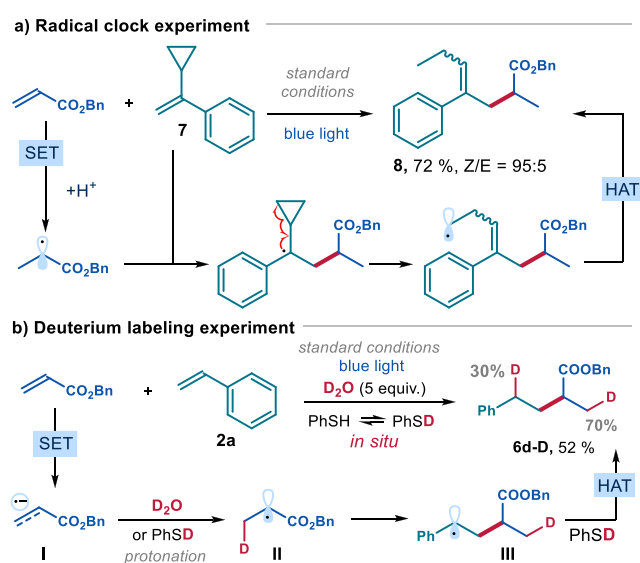


Figure 4. (a) Radical clock experiment. (b) Deuterium labeling experiment. Reactions performed on a 0.2 mmol scale using PC B (5.0 mol %), PhSH 4a (20 mol %), 2,4,6-collidine (1 equiv), γ -terpinene 5a (3 equiv), and 3 equiv of 7 or 2a in DCE (0.05 M) for 14 h.

readily coupled with various styrenes and other readily available neutral olefins. A notable feature of this method is its high tolerance for functional groups, which we harnessed for the late-stage modification of biorelevant compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c11285>.

Details of experimental procedures and full characterization data and copies of NMR spectra (PDF)

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W.Z. and I.A.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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