Photoredox-Driven Three-Component Coupling of Aryl Halides, Olefins, and O_2

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Photoredox, Multicomponent Coupling, Catalysis, Sustainable

ABSTRACT: Modern organic synthesis requires methodologies that bring together abundant, feedstock chemicals in a mild and efficient manner. To aid in this effort, we have developed a multicomponent radical hydroxyarylation reaction that utilizes aryl halides, olefins, and O_2 as the reaction components. Crucial to this advance was an oxidative rather than reductive approach to aryl radical generation, which enables reaction tolerance to O_2. This methodology displays a broad functional group tolerance with a variety of functionalized aryl halides and a broad array of olefins. Development of this methodology enables rapid access to biologically relevant hydroxyaryl products from simple, commercially available starting materials.

Multicomponent coupling reactions, especially those that bring together simple and abundant feedstock chemicals under mild, functional group tolerant conditions, hold exceptional potential in creating molecular complexity, advancing sustainable synthesis, and generating chemical libraries.[1] Within this context, a catalytic photoredox-driven union of aryl halides, olefins, and O_2 to deliver the olefin hydroxyarylation product represents an important and previously unrealized transformation. The development of such a reaction enables rapid access to hydroxyaryl motifs that can be found in natural products, agrochemicals, and pharmaceutical agents (Figure 1, top).[2]

The conceptual challenge associated with this transformation is that the generation of aryl radical intermediates from aryl halides is classically considered a reductive process, and the reaction conditions are often incompatible with O_2 (Figure 1, middle).[3] Indeed, numerous photoredox reactions that operate in a reductive manifold frequently necessitate air-free conditions to achieve optimal yields. However, we recognized that the activation of silanols to generate a silyl radical intermediate capable of halogen atom transfer (XAT) operates under an oxidative manifold.[4]

Based on this observation, we hypothesized that these oxidative conditions would be compatible with aryl radical generation in the presence of O_2. Furthermore, we recognized that nucleophilic radicals are known to react with triplet O_2 and the differential nucleophilicity of a sp^2-aryl radical and a sp^3-alkyl radical could be utilized for sequencing bond formation in a multicomponent reaction.[5] We expected the less nucleophilic sp^2-radical to preferentially react with an olefin substrate, while the resulting more nucleophilic sp^3-radical is polarity-matched for subsequent capture by O_2, leading to clean and efficient multicomponent coupling.

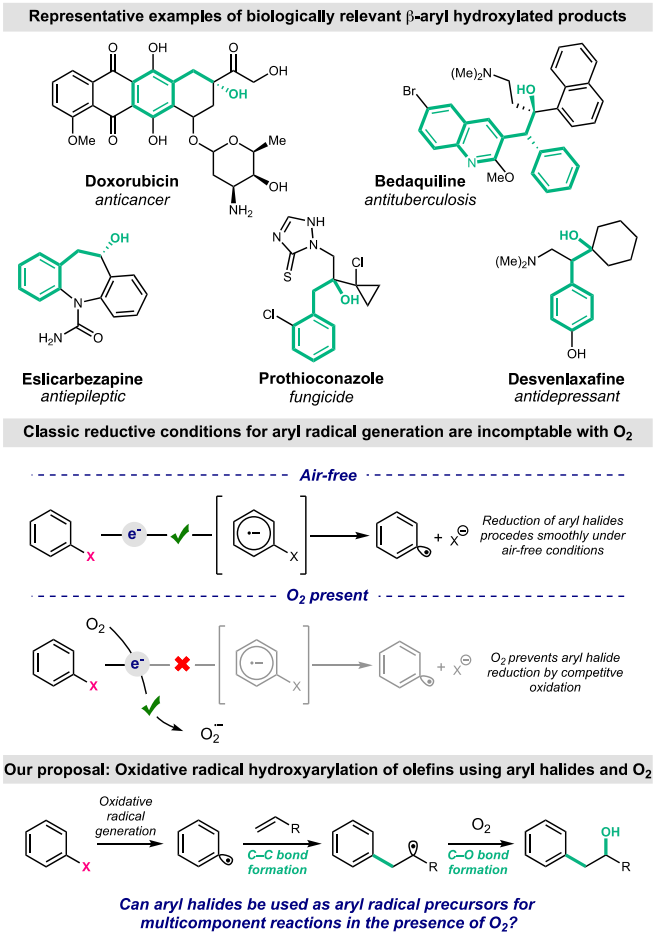


Figure 1. Rational for pursuing a multicomponent radical hydroxyarylation of olefins using aryl halides and O_2.

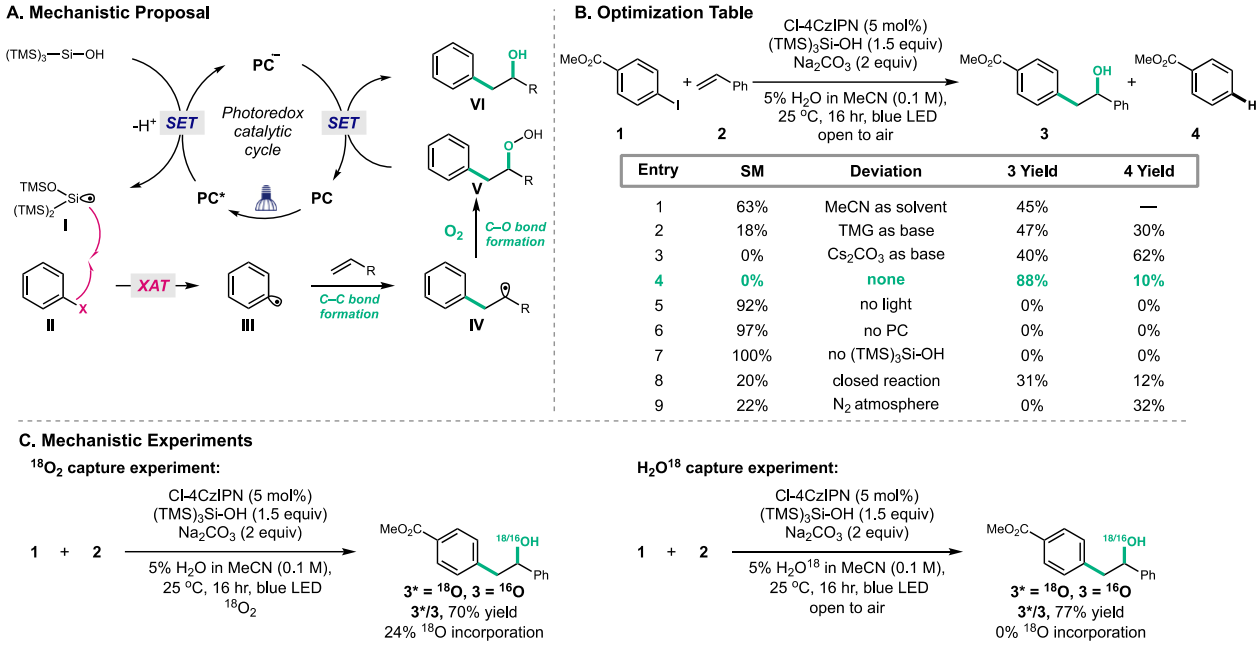


Figure 2. (A) Proposed mechanism for the formation of the observed hydroxyarylation products. (B) Optimization the hydroxyarylation of olefins with aryl halides and O_2. Conditions are as follows: **1** (0.1 mmol), **2** (0.3 mmol), Na_2CO_3 (0.2 mmol), $(TMS)_3SiOH$ (0.15 mmol), solvent (0.1 M), blue LEDs, and open to air at room temperature for 16 h. (C) Mechanistic experiments to support radical trapping of O_2 rather than radical-polar crossover and capture of H_2O^{18}.

Prior work in this area shows several examples of multicomponent olefin oxyarylation reactions, though these reactions require 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or metal-assisted trapping of the sp^3-radical intermediate.[6] To date, only a few reports have described aryl radical reactivity in the presence of O_2. Such reported reactions require aryl hydrazines,[7] aryl diazoniums,[8] or aryl boronates[6d,9] as aryl radical precursors, and are often combined with stoichiometric metal reductants, limiting their synthetic utility. Prior to this study, no catalytic multicomponent hydroxyarylation of olefins with aryl halides and O_2 has been reported.

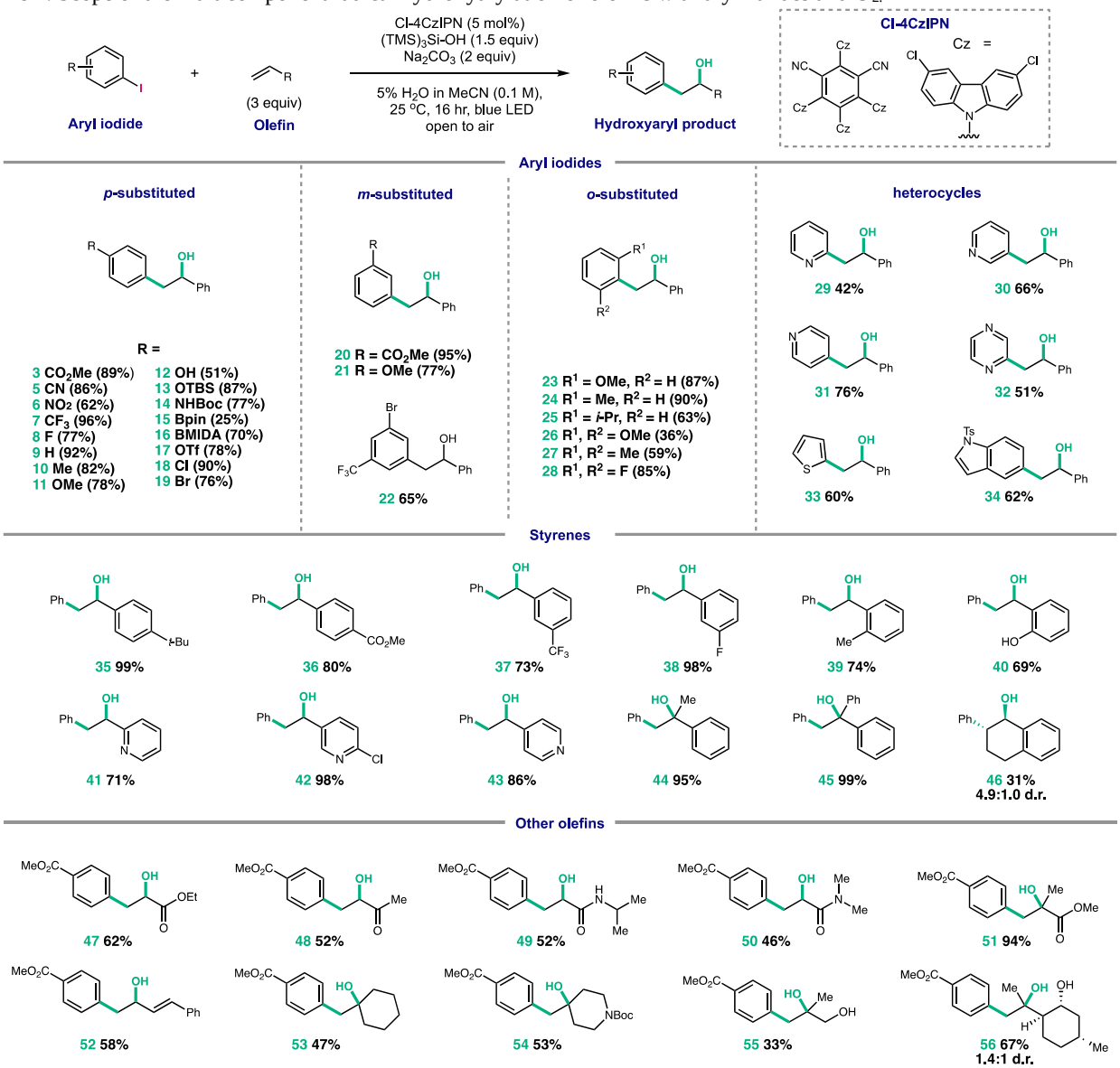
Our reaction design is depicted in Figure 2A. Oxidation of tris(trimethylsilyl)silanol ($(TMS)_3SiOH$) by a photocatalyst (PC) initiates a radical Brook rearrangement to silyl radical intermediate **I**. Polarity-matched halogen-atom transfer (XAT) between **I** and aryl halide **II** results in aryl radical **III**. Trapping of the aryl radical with an olefin forges a C–C bond and alkyl radical intermediate **IV**. This radical engages with triplet O_2 to form the C–O bond resulting in peroxy intermediate **V**. Previous radical aerobic hydroxyarylations require a stoichiometric reductant to convert **V** into the hydroxy product **VI**.[7] In our reaction design, we hypothesize the photocatalyst radical anion will reduce **V** to deliver the hydroxyarylated product **VI,** closing the catalytic cycle.

With this mechanism in mind, we note that the activation of $(TMS)_3SiOH$ to form the halogen-abstracting silyl radical requires a highly oxidizing photocatalyst (E_p = +1.54 V vs. SCE)[4] so we chose metal-free photocatalyst Cl-4CzIPN ($E_{1/2}^{red}$ [*PC/PC$^{\bullet-}$] = +1.71 vs. SCE)[4a] to begin our studies. In our initial experiment, we investigated the reaction of 4-methyl iodobenzoate as the aryl radical precursor (**1**), styrene as the radical acceptor (**2**), and $(TMS)_3SiOH$ as the XAT reagent in the presence of photocatalyst Cl-4CzIPN, and sodium carbonate. Subjecting these reagents to irradiation by blue LEDs in a MeCN solution open to air produced hydroxyarylated product **3** in 45% yield, with starting material composing the rest of the reaction mass balance (Figure 2B, entry 1). In an effort to push the reaction to complete starting material consumption, we conducted experiments exploring base solubility, as base is required to generate the silyl radical abstractor. Organic base tetramethylguanidine (TMG) increased starting material consumption, though a large amount of hydrodehalogenation product **4** was observed (Figure 2B, entry 2). Similarly, cesium carbonate as base led to full consumption of starting material, but hydrodehalogenation outcompeted hydroxyarylation (Figure 2B, entry 3). Adding water as a cosolvent to the original conditions aided sodium carbonate solubility facilitating full starting material consumption and increasing hydroxyarylation yield to 88% with minimal hydrodehalogenation (10%, Figure 2B, entry 4). Control experiments revealed that light, photocatalyst, and XAT reagent are all necessary components for product formation (Figure 2B, entries 5-7).

To probe our hypothesis that C–O bond formation arises from O_2 capture, we conducted experiments investigating how the reaction atmosphere impacts product formation. Varying the optimized conditions so that the reaction is conducted in a closed reaction vessel rather than open to air reduced yield of **3** to 31% (Figure 2B, entry 8). Additionally, under an inert N_2 atmosphere, no **3** was observed. Conducting the experiment under an atmosphere of $^{18}O_2$ resulted in a 70% yield of **3** and **3*** with 24% $^{18}O_2$ incorporation giving strong evidence to support C–O bond formation resulting from O_2 capture. To rule out a potential mechanism where radical intermediate **IV** is oxidized to radical cation and C–O bond formation results nucleophilic addition of H_2O, we replaced the H_2O cosolvent with H_2O^{18}. No ^{18}O **3*** was detected by mass spectroscopy, giving further evidence that C–O bond formation arises from radical capture by O_2.

We next investigated the scope of the reaction, beginning with the scope of aryl iodides as aryl radical precursors. A variety of *para*-substituted electron-poor, -neutral, and -rich aromatics all reacted smoothly in good to excellent yields

Scheme 1. Scope of the multicomponent radical hydroxyarylation of olefins with aryl halides and O_2.[a]



[a]Conditions are as follows: Aryl halide (1 equiv), olefin (3 equiv), $(TMS)_3SiOH$ (1.5 equiv), Na_2CO_3 (2 equiv), 5% H_2O in MeCN (0.1 M), blue LEDs, and open to air at room temperature for 16 h.

(**3**-**19**, 78-96%). Notably, unprotected phenol **12** was compatible (51%), though increased yields could be obtained with phenol protection (**13**, 87%). Protected aniline **14** reacted smoothly as well in 77% yield. Given the selectivity for aryl iodides, we explored the reaction tolerance for aromatic substituents that could be utilized for orthogonal reactivity. Pinacol boronate (Bpin)-substituted arene produced a mixture of hydroxyarylated product **15** in 25% yield and hydroxyarylated phenol **12** in 40% yield where **12** is likely arising from oxidation and hydrolysis of the aryl-Bpin under photoredox conditions.[10] Switching from Bpin to the less redox sensitive *N*-methyliminodiacetic acid (MIDA) substituted borane increased yield to 70% of **16**. Electrophilic cross-coupling handles TfO-, Cl-, and Br-substituted arenes were tolerated and products were obtained in good yields (**17**-**19,** 76-90%). Expanding beyond *para*-substituted arenes, -*meta*-substitution was well tolerated with electron-rich, -poor, and reactive handles all producing good yields (**20**-**22**, 65-95%). Additionally, *ortho*-substitution was well tolerated with both mono- and di-substituted arenes (**23**-**28**, 36-90%). Previous hydroxyarylations have limited utility in functionalizing heteroaryl species.[7-9] Under our XAT conditions, pyridines could be functionalized at the 2-, 3-, and 4-positions in moderate yields (**29**-**31**, 42-76%). Additional heterocycles such as pyrazine **32**, thiophene **33**, and indole **34** all produced hydroxyarylated products in 51-62% yields.

With the aryl iodide scope established, we investigated the range of olefin radical acceptors applicable to our conditions. We began by exploring styrene substitution and its effect on hydroxyarylation yield. Electron-poor, -neutral, and -rich, styrenes substituted at *ortho*-, *meta*-, *and para*-positions all gave

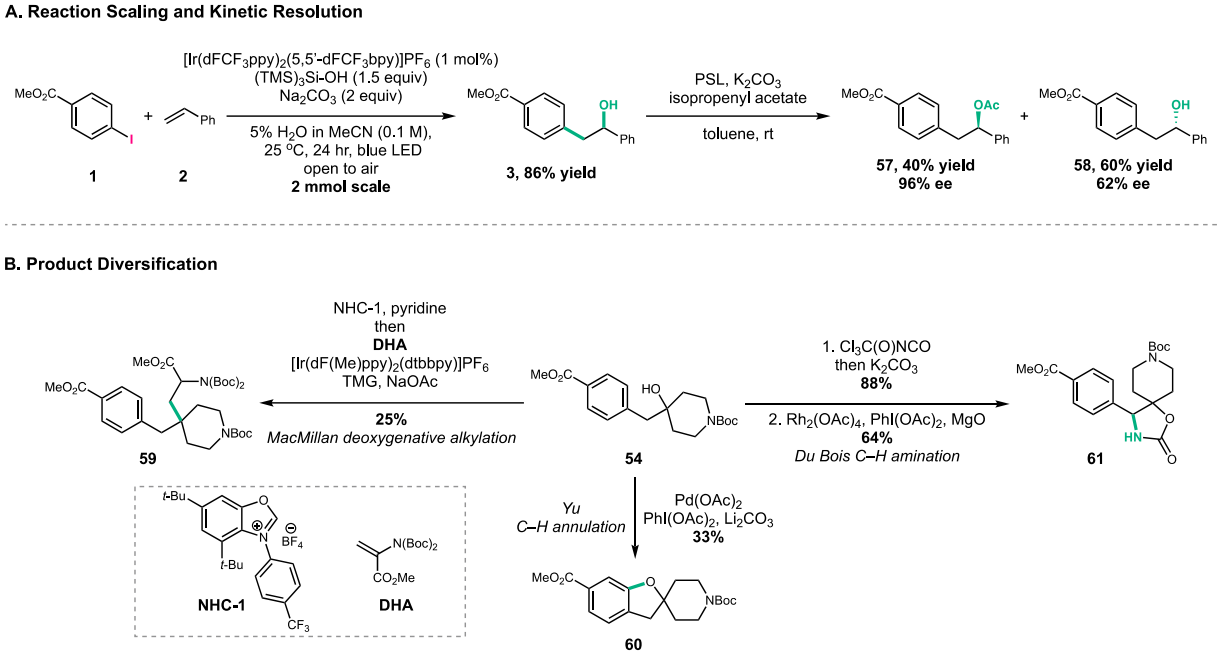


Figure 3. (A) Rapid access to enantioenriched 1,2-diarylalcohols on mmol scale. (B) Diversification of aliphatic alcohol **54** hydroxyaryl product.

good to excellent yields resulting in a variety of benzylic hydroxylated products (**35**-**46**, 74-99%). Again, phenol protection was not required (**40**, 69%) and heterocycles, such as, 2-, 3-, and 4-vinyl pyridines, all reacted in good to excellent yields (**41**-**43**, 71-96%). Investigating substitution of the styrene olefin revealed α-substituted styrenes gave excellent yields (**44** and **45**, 95% and 99%, respectively), likely associated with the increased stability of a tertiary-substituted radical intermediate. Conversely, β-substitution reduced hydroxyarylated product yield (**46**, 31%), likely due to additional steric demands at the site of aryl radical addition to the olefin. Expanding beyond styrenes, we investigated the reactivity of Michael acceptors and their ability to generate synthetically useful α-hydroxy carbonyl compounds. Acrylates, enones, and acrylamides were all competent with α-substitution of the olefin again increasing yield (**47**-**51**, 46-94%). Aryl radical addition to a conjugated diene formed the secondary allylic alcohol **52** in 58% yield. Additionally, unactivated 1,1-disubstitued olefins reacted to give a variety of tertiary alcohols. Cylohexane **53**, medicinally relevant piperidine **54**, β-hydroxy alcohol **55**, and functionalized chiral pool substrate **56** (from (-)-isopulegol) were all obtained in moderate yields (33-67%).

To further demonstrate the applicability of this methodology in complex molecule synthesis, we conducted experiments to perform this reaction on scale. Early on in our studies, we observed decreased yield moving from optimization scale (0.1 mmol) to substrate scope scale (0.5 mmol, Table S1). This effect was largely associated with stir rate, where we observed smooth "vortexing" of the reaction mixture throughout the reaction time was crucial for optimal and reproducible yields. Scaling from 0.5 mmol to 2 mmol also required slight tuning of the reaction conditions (Table S2). Though the organic photocatalyst Cl-4CzIPN provided good and reproducible yields on scales $\leq$0.5 mmol, its poor solubility in MeCN/H_2O became an issue when scaling the reaction, presumably due to reduced light penetration. Alternatively, photocatalyst [Ir(dFCF$_3$ppy)$_2$(5,5'-dCF$_3$bpy)]PF$_6$ has similar oxidizing properties to Cl-4CzIPN ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.68 V vs. SCE)[11] and an improved solubility profile in our reaction solvent. With this photocatalyst and a slightly longer reaction time, we scaled the hydroxyarylation reaction to 2 mmol without appreciable decrease in yield (86%, Figure 3A). With access to mmol quantities of hydroxyaryl product **3**, we subjected **3** to enzyme-catalyzed kinetic resolution. Using commercially available *Pseudomonas stutzeri* lipase, enantioenriched benzylic alcohols could be accessed in just two steps from **1** and **2** (Figure 3A).[12]

Additionally, we highlight the ability to diversify the alcohol products into a range of medicinally relevant motifs. Using a deoxygenative alkylation protocol reported by MacMillan et al., **54** could be transformed into quaternary carbon containing unnatural amino acid **59** (25% yield, Figure 3B).[13] The free hydroxyl group of **54** could be utilized for a Yu C–H annulation to deliver spirocyclic benzofuran/piperidine heterocycle **60** in 33% yield.[14] Finally, functionalization of the benzylic site through Du Bois C–H amination produced synthetically useful oxazolidinone **61** (Figure 3B).[15] In all cases, the yields reported represent reactions run using the originally reported conditions. No attempts to optimize for this particular substrate were made, highlighting the ability to diversify without the need for significant extra experiments.

In summary, we present the first example of a hydroxyarylation of alkenes using aryl halides and O_2. Our methodology has significant potential for industrial impact given it utilizes abundant, feedstock chemicals, displays a diverse substrate scope, and is operationally simple to set up. In addition to our methodology providing rapid access to biologically relevant hydroxyaryl scaffolds, these products can undergo a variety of transformations to build molecular complexity and introduce new motifs. Investigations to develop new reactions using our O_2 tolerant oxidative aryl radical generation conditions are ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and spectra.

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support for this work was provided by the National Institutes of Health (GM129495), and NMR data were collected on instruments obtained with support from the National Science Foundation (CHE-1521620). We thank Jack C. Sharland and the Huw M. L. Davies Lab at Emory University for providing some styrene starting materials. We thank AiLing Yu and the Cora E. MacBeth lab at Emory University for assistance with the $^{18}O_2$ experiment. We thank Meito Sangyo for providing PSL for the kinetic resolution experiment.

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