Oxidative Photocatalytic Homo- and Cross-Coupling of Phenols: Non-Enzymatic, Catalytic Method for Coupling Tyrosine

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Supporting Information Placeholder

ABSTRACT: The first, oxidative photocatalytic method for phenol-phenol homo-coupling and cross-coupling is described and isolated yields of up to 97% are obtained. Measured oxidation potentials and computed nucleophilicity parameters are consistent with a nucleophilic attack of one partner onto the oxidized radical form of the other partner. Understanding of this model permitted development of cross-coupling reactions between nucleophilic phenols/arenes and easily oxidized phenols in high selectivity and efficiency. A highlight of this method is that one equivalent of each coupling partner is utilized. Building on these findings, the first non-enzymatic, catalytic method for coupling tyrosine was developed.

INTRODUCTION

The biphenol scaffold is found in several biologically-active natural compounds (Chart 1).¹⁻⁷ Since the discovery that phenol oxidation is the key step in the synthesis of several of these natural products, chemists have explored analogous means to effect such transformations.⁸

Chart 1. Coupled Phenols Natural Products

While many stoichiometric phenol homo- and cross-couplings have been undertaken,⁸⁻¹¹ Uang and coworkers disclosed in 1999 one of the first catalytic reports of non-naphthol phenol homo-coupling using a vanadium catalyst under an oxygen atmosphere.¹² In 2011, the Waldvogel group revealed the homo-coupling of select phenols by utilizing a BDD anode in yields up to 83%.¹³ In 2014, we reported the use of a metal salen/an catalyst library to achieve highly selective homo- and cross-couplings of several alkyl and alkoxy substituted phenols,¹⁴ while Lumb and coworkers revealed a copper catalyzed aerobic oxidation of phenols.¹⁵ Finally, more-recent reports of

cross-coupling from Pappo and Kozlowski reveal selective, high-yielding phenol cross-couplings using iron porphyrin and chromium salen catalysts, respectively.^{16,17} While these advances in the field of oxidative coupling have facilitated the synthesis of a diverse array of ligands and natural products, they still require the use of high loadings of expensive transition metal catalysts, diamond electrodes, or stoichiometric oxidants that are not atom economical.^{5,13,18-20} In addition, many coupling patterns remain inaccessible, and couplings of mono-substituted phenols are especially challenging.

In particular, non-enzymatic catalytic methods for the direct oxidative *ortho-ortho* coupling of *L*-tyrosine have remained an elusive goal for chemists (Scheme 1). Many attempts have been made to

Scheme 1. Previous Approaches to Inter- and Intramolecular Tyrosine Coupling

effect such a coupling, as it would engender a biomimetic approach to the dityrosine motif found in several natural products, including mycocyclusin³ and RP-66453.⁴ However, most efforts have culminated in Suzuki type cross-couplings to forge the biaryl bond, as is the case in all efforts to generate mycocyclusin (Scheme 1a),^{3,21} a natural product that is also a key intermediate to the herquelines.^{22–24} Notably, Baran deployed an intramolecular oxidative coupling of tyrosine and *para*-hydroxyphenylglycine by employing a stoichiometric Cu^{III}-TMEDA complex (Scheme 1b).²⁵ In spite of these efforts, reports of intermolecular tyrosine coupling are limited. In 2001, Rieker and coworkers disclosed that superstoichiometric PIFA couples tyrosine in less than 40% isolated yield (Scheme 1c).²⁶ Additionally, they reported a 90% yield using horseradish peroxidase enzyme and H₂O₂, for which throughput was an issue.²⁶ Herein, we disclose a photocatalytic process to accomplish such couplings (Scheme 1d).

Our initial approach involved screening our library of oxidizing catalysts in the coupling of tyrosine and related phenols, but revealed no encouraging leads. Reasoning that these catalysts did not have sufficiently high oxidation potentials, we turned to photoredox catalysts, which have a wide range of reported oxidation potentials. By pairing a photoredox catalyst with a stoichiometric oxidant, the coupling of phenols should be feasible. While net-oxidative photoredox processes are less common,²⁷ we were encouraged by reports of the photo-crosslinking of tyrosine-residues in various polymers.²⁸ Although there was no direct evidence of tyrosine-tyrosine couplings, it appeared that tyrosine was within the oxidation range of known photocatalysts.^{28,29} Notably, in 2017, König³⁰ and Xia,³¹ respectively, disclosed the photocatalytic

cross-coupling of phenols with arenes and amines, respectively. In the former case, control of C-C vs C-O coupling was a challenge. In the latter case, a very electron-rich phenol was oxidized by persulfate and the amine was oxidized by the photocatalyst.^{30,31}

While there are limited examples of photocatalytic naphthol-phenol cross-couplings,³² to the best of our knowledge, there are no reports describing photocatalytic phenol-phenol cross- or homo- couplings. Challenges associated with such processes include identifying an appropriate oxidant that does not act on phenols directly, preventing decomposition of the products, controlling cross-selectivity by selective oxidation, and controlling regioselectivity.

RESULTS AND DISCUSSION

Reaction Optimization. Our strategy to explore this nascent field focused on Ru(bpy)₃Cl₂ and a persulfate oxidant.²⁸ Initial efforts in coupling *N*-AcTyOMe were unsuccessful, motivating us to screen a series of photocatalysts and oxidants with simpler phenols (eq 1). A selection of the results is outlined in Figure 1, and shows that oxygen was a highly effective oxidant with several photocatalysts. Other oxidants (DDQ, persulfates, peroxides) were also screened (not shown), but were less effective. Upon validation at larger scale, MesAcr⁺BF₄[−], 4CzIPN, and [Ru(bpm)₃](PF₆)₂, were identified as the best photocatalysts. We theorized that 2-*tert*-butyl-4-methoxyphenol proceeded in lower yield due to the low site nucleophilicity of the neutral compound at the putative reactive center. This phenol is readily oxidizable and, once acted on by the photocatalyst, will produce an electrophile. However, lacking an effective nucleophile as a coupling partner, this compound fails to dimerize.

MesAcr⁺BF₄[−] was identified as the most effective catalyst due to its ability to convert several phenols to their dimers in higher conversions with fewer oxidized byproducts (Table 1). An added

Figure 1. Photocatalyst screen with four phenolic substrates (see eq 1).

advantage of this photocatalyst is its lower cost compared to the transition metal catalysts. A solvent screen indicated that halogenated solvents gave good conversion ($\text{ClCH}_2\text{CH}_2\text{Cl}$, CH_2Cl_2), with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) providing the highest yields. Even so, the conditions shown in Table 1 also generated undesired side products **3** and **4**, the latter of which was confirmed with a crystal structure. Reasoning that lower oxygen concentrations would prevent over-oxygenation to **3** and formation of **4**, reactions under air were attempted. This change indeed curtailed the formation of these side products considerably and produced **2a** in 80% yield (vs 70% under O_2 , entry 1).

Table 1. Phenolic Coupling By-Products

entry	substrate	2	3	4
1		70%	5%	10%
2		65%	7%	5%
3		-	-	33%

When attempting to attain isolated yields of **2b** on larger scale without the internal standard, a significant decrease in yield was observed (Table 2, entry 2 vs 1). Thus, 4,4'-di-tert-butylbiphenyl was included in all subsequent reactions. Notably, reactions conducted without the photocatalyst but with the internal standard result in significant amounts of product in the case of **1b** (entry 3), suggesting the internal standard can act as a photocatalyst. Controls without light (entry 4) and without

MesAcr⁺BF₄⁻ or 4,4'-di-tert-butylbiphenyl (entry 5) confirmed that both light and a photocatalyst are needed.

Table 2. Biphenyl as a Photocatalyst

entry	x	y	light source	result
1	2	25	blue LEDs	45%
2	2	0	blue LEDs	25%
3	0	25	blue LEDs	30%
4	0	25	none	0%
5	0	0	blue LEDs	0%

Homo-coupling Scope. Substrates with 2,4-, 2,4,5-, or 3,4,5-substitution patterns exhibited high reactivity, affording dimers in isolated yields up to 76% (Figure 2, **2r**). Furthermore, the conditions were effective with aryl-substituted phenols. Notably, electron withdrawing arenes afforded higher conversions and yields than the electron donating counterparts (**2o** vs **2k**), which may arise from the electron withdrawing group giving rise to a more reactive radical intermediate. However, there was limited tolerance for bromo-substitution, as **2e** was achieved in only 16% isolated yield. Unfortunately, methoxy-substituted phenols, which are more easily oxidized, and substrates lacking a *para*-substituent proved untenable for dimerization as no significant yields (<5%) were achieved.

Mechanism. Previous reports proposed two distinct mechanisms for these types of photocatalytic reactions: nucleophilic attack onto an oxidized phenol as seen in Scheme 2, or the generation of a *para*-peroxy-quinol (**4**), followed by the nucleophilic attack of a phenol.^{30,31,33,34} Reactions run in the absence of O_2 afforded the same yield as catalyst loading, pointing away from a peroxy-quinol pathway, which requires O_2 to form. Further, when a 50:50 mixture of **1j** and **4a** were combined in the absence of light and photocatalyst, only homo coupling adduct **2j** was observed. These results diminish the likelihood of addition to the peroxy-quinol **4a**; rather, **4a** appears to be acting as an oxidant in a manner analogous to a peroxide. Overall, a pathway involving a radical-phenol addition appears most likely (Scheme 2). A test for peroxides after the completion of the reaction revealed the presence of a stoichiometric amount of hydrogen peroxide relative to the product, further supporting the mechanism proposed in Scheme 2. Finally, the introduction of an exogenous base to the system decreased the rate of reaction, indicat-

ing that a radical-anion coupling was not likely. One implication of the mechanism in Scheme 2 is that the coupling will proceed best when a monomer can be readily oxidized (**IV** to **V**) and can act as a nucleophile (**VI** to **VII**), which is consistent with the outcomes in Figure 2.

Figure 2. Scope of photocatalytic homo-coupling of phenols. (a) Solvent conditions: C₂H₄Cl₂; (b) Solvent conditions: C₂H₄Cl₂: HFIP (1:1); Yields in parentheses are based on recovery of starting material.

Scheme 2. Proposed Mechanism for the Photocatalytic Coupling of Phenols

Cross-coupling Scope. A further implication of the mechanism in Scheme 2 is that a cross-coupling should be feasible provided that one phenol is readily oxidized while the other possesses a reactive site that is more nucleophilic. Accordingly, the oxidation of the blue phenol (1) followed by nucleophilic attack by the red phenol (5) was proposed (Figure 3). A number of recent reports have centered on such cross-couplings;^{16,17,20,35–37} limitations include a reliance on an excess of one partner^{16,30,35–37} and/or poor selectivity due to competitive homo-coupling, as well as mixtures of *ortho*-vs *para*-coupled products.^{16,30,36}

The homo-coupling, described earlier in Figure 2, requires specific substitution patterns, which include an alkyl group at the *para*-position. In our recent report on chromium catalyzed phenolic couplings, we leveraged site nucleophilicity to predict the regioselectivity of coupling.¹⁷ The calculated values revealed that open *para*-positions are significantly more nucleophilic than open *ortho*-positions.¹⁷ Consequently, a high yielding cross-coupling can be induced by selecting one substrate without a *para*-substituent (red phenol). The poor homo-coupling of such substrates (see above) *and* the high nucleophilicity from the *para*-position both contribute to this outcome.

The cross-coupling was able to support a diverse array of di-, and tri-substitution patterns on the nucleophilic phenol partner (red phenol, Figure 3) . Remarkably, mono-substituted phenols (**6a-u**), which are difficult to couple due to multiple reactive sites and low oxidation potentials, were also tolerated.^{14,16,17} Notably, no homo-

coupling products were observed and only trace amounts (0-5%) of the *ortho-ortho* coupling were found in every instance but one (**6i-u**; 9% *ortho-ortho* vs 52% *ortho-para*). The greater site nucleophilicity of the para-position account for these differences. These results also accentuate the difference between the mechanisms proposed in this and recent reports.^{16,17} For instance, the coupling reported by Pappo in 2017 proceeds via a radical-radical pathway and therefore does not rely on site nucleophilicity.¹⁶

Figure 3. Scope of the photocatalytic phenol cross-coupling. Conditions: 2.0 mol % MesAc⁺BF₄⁻, 25 mol % 4,4'-di-tert-butylbiphenyl, HFIP, air, 35 °C, 48 h. Yields in parentheses are based on recovery of starting material. (a) Reaction stopped at 24 h. (b) *ortho-ortho* product recovered in 9% yield.

Furthermore, reactions of known compounds proceed in similar or higher yields than other reports and use a 1:1

molar ratio of phenols, rather than an excess of one phenol. For example, the formation of **6e-u** with our prior reported Cr catalyst¹⁷ gave 50% yield, whereas the protocol herein provided 97% of the same product. The high yields, high selectivities, and absence of over-oxidation observed here for cross-coupling are supported by cyclic voltammetry data, which show that the blue phenol (e.g., **1u** = 0.78 eV) is more readily oxidized than the red phenol (e.g., **5e** = 1.29 eV) as well as the resultant product (**6e-u** = 0.83 eV).

Tyrosine Coupling. Our final endeavor aimed to achieve the direct catalytic coupling of tyrosine. Although tyrosine derivatives **2r-t** are reported in Figure 2, the *tert*-butyl group is necessary for the conversion. This group can be readily removed (eq 2), but is not ideal due to the decrease in step-economy.

When **1cc** was subjected to the photocatalytic conditions reported in Figure 2, only the *para*-peroxyquinol **4cc** was observed. A further HTE screen of photocatalysts was thus undertaken to determine if different photocatalysts could be more effective in producing dityrosine derivative **2cc**. This screen revealed that $\text{Ru}(\text{bpz})_3[\text{PF}_6]_2$ converts **1cc** to **2cc** while attenuating the formation of by-products. A larger scale reaction confirmed this result, affording a 40% isolated yield (73% brsm = based on recovered starting material). In this case, cyclic voltammetry revealed that the tyrosine dimer **2cc** (1.07 eV) was *more readily* oxidized than the tyrosine monomer (1.15 eV). In terms of the photocatalytic oxidation, the dimer essentially quenches the photocatalyst, accounting for lower conversions. Moreover, the reversibility of the dimer oxidation is low, indicating that decomposition may occur via over-oxidation.

Figure 4. Homo-coupling of *para*-substituted phenols. Conditions: 0.5 mol % $\text{Ru}(\text{bpz})_3[\text{PF}_6]_2$ 25 mol % 4,4'-di-*tert*-butylphenyl, HFIP, O_2 , 35 °C, 24 h. Yields in parentheses are

based on recovery of starting material.

CONCLUDING REMARKS

In summary, a photocatalytic method for coupling phenols was developed using $\text{MesAcr}^+\text{BF}_4^-$. Mechanism studies suggest that an oxidation of the phenol followed by the nucleophilic addition of a neutral phenol is a plausible pathway. This information was then leveraged to develop a cross coupling method with the same photocatalyst. The resultant process afforded a range of new compounds in high yields and selectivities, as well as known compounds with higher yields and selectivities. The method permitted more diverse substitution patterns on the nucleophilic coupling partner. Finally, the first non-enzymatic, catalytic coupling of tyrosine was achieved with a ruthenium photocatalyst.

ASSOCIATED CONTENT

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

Experimental protocols and spectroscopic data (pdf).

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Supporting Information for:

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General Considerations: When necessary, solvents and reagents were dried prior to use. THF was distilled from sodium benzophenone ketyl. Other solvents were purified with drying cartridges through a solvent delivery system. High throughput experiments were performed at the Penn/Merck High Throughput Experimentation Laboratory at the University of Pennsylvania. The screens were analyzed by HPLC by addition of an internal standard.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 254-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). When necessary, the column was pre-washed with 1% Et₃N in the eluent system. ¹H NMR spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance (CDCl₃ 7.26 ppm, DMSO-*d*₆ 2.50 ppm, acetone-*d*₆ 2.05 ppm, CD₂Cl₂ 5.32 ppm, MeOD-*d*₄ 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Decoupled ¹³C NMR spectra were recorded at 100 or 125 MHz. IR spectra were taken on an FT-IR spectrometer (ATR, Neat). Accurate mass measurement analyses were conducted via time-of-flight mass analyzer GCMS with electron ionization (EI) or via time-of-flight mass analyzer LCMS with electrospray ionization (ESI). The signals were measured against an internal reference of perfluorotributylamine for EI-GCMS and leucine enkephalin for ESI-LCMS. The instrument was calibrated and measurements were made using neutral atomic masses; the mass of the electron removed or added to create the charged species is not taken into account. Cyclic voltammograms were recorded using a glassy carbon working electrode immersed in a 0.02 M solution of tetra-*n*-butyl ammonium hexafluorophosphate with 0.001-0.002 M substrate and 0.001 M ferrocene as internal standard using a scan rate of 0.1 V/s.

Photochemistry Reactor:

Supplies:

- Blue LEDs: 39.4 inch strips, 470 nm Blue light, 32918 mcd/ft
- Power supply: 12 V DC CPS series Power supply -15 watt
- Connectors: LC2 Locking Male Connector CPS Adapter Cable
- Fan: 14 cm blade diameter, 19 cm overall diameter, 2 speed fan
- Five cylindrical glass jars: height 90 cm; diameter 90 cm
- Plastic sample vial rack
- Aluminum foil
- Glass disposal box

Reactor Setup: Carefully wrap two LED strips inside the glass jar. The LED strips should be wrapped as tightly as possible around the inside so there are no spaces between layers. Then wrap a layer of Aluminum foil around the glass jar. Place the device on a stir plate. Arrange the

other four glass jars in a square around the stir plate. Their centers should be 30 cm from each other. Next, cut the top 35 cm off of a glass disposal box, and place on top of the glass jars surrounding the plate. The

space at the bottom creates good ventilation to maintain temperature control. Place the fan in the hole on top of the glass disposal box. Attach the connectors to the power adapters and plug them into the nearest power source. Please allow at least one hour to pass for temperature equilibration after connecting to power source before running a reaction. **Warning:** Due to the high intensity of the light source it is highly recommended that impact resistant sunglasses be worn when placing a reaction in the photochemistry bay.

Preparation of phenol substrates:

5-Methyl-[1,1'-biphenyl]-2-ol (1d). 2-Bromo-4-methylphenol (967 μ L, 8.0 mmol, 1.0 equiv), phenylboronic acid (1.46 g, 12.0 mmol, 1.5 equiv), Cs_2CO_3 (6.52 g, 20.0 mmol, 2.5 equiv), and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (163 mg, 0.20 mmol, 2.5 mol%) were taken up in THF (53 mL) and H_2O (5.3 mL) under Ar. The reaction mixture was heated at reflux under Ar for 20 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of solvent and chromatography (5 to 10% EtOAc in hexanes) afforded a white solid (1.00 g) in 68% yield: ^1H NMR (500 MHz, CDCl_3) δ 7.50-7.46 (m, 4H), 7.41-7.37 (m, 1H), 7.07-7.06 (m, 2H), 6.89 (d, $J = 7.9$ Hz, 1H), 5.02 (br s, 1H), 2.32 (s, 3H). Spectral data were in agreement with those reported [*Org. Lett.* **2013**, 15, 984].

2-Hydroxy-4,5-dimethylbenzaldehyde. To a stirred suspension of 2,4-dimethylphenol (3.67 g, 30.0 mmol, 1.0 equiv) and MgCl_2 (4.29 g, 45.0 mmol, 1.5 equiv) in THF (150 mL) was added Et_3N (15.7 mL, 113 mmol, 3.75 equiv), followed by paraformaldehyde (6.08 g, 203 mmol, 6.75 equiv). The reaction mixture was heated at reflux under Ar for 16 h. After the resultant mixture was cooled to ambient temperature, the mixture was poured into 1 M HCl (aq) (100 mL) and the aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of solvent and chromatography (2 to 8% EtOAc in hexanes) afforded a pale yellow solid (4.12 g) in 92% yield: ^1H NMR (500 MHz, CDCl_3) δ 10.84 (s, 1H), 9.79 (s, 1H), 7.26 (s, 1H), 6.78 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H). Spectral data were in agreement with those reported [*Org. Lett.* **2017**, 19, 6280].

2,4,5-Trimethylphenol (1g). To a solution of 2-hydroxy-4,5-dimethylbenzaldehyde (3.76 g, 25.0 mmol, 1.0 equiv) in THF (100 mL) at 0 $^\circ\text{C}$ was added Et_3N (3.83 mL, 27.5 mmol, 1.1 equiv), followed by ethyl chloroformate (2.63 mL, 27.5 mmol, 1.1 equiv) dropwise. After stirring 1 h at 0 $^\circ\text{C}$, the reaction mixture was filtered to remove solid amine $\cdot$ HCl. The filtrate was added dropwise to a stirring solution of NaBH_4 (3.12 g, 82.5 mmol, 3.3 equiv) in H_2O (100 mL) at 0 $^\circ\text{C}$. After stirring 30 min at 0 $^\circ\text{C}$, the reaction mixture was warmed to rt for 2 h. The solution was diluted with H_2O , made acidic with 1 M HCl (aq), and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Removal of solvent and chromatography (4 to 10% acetone in hexanes) afforded a white solid (3.05 g) in 90% yield: ^1H NMR (500 MHz, CDCl_3) δ 6.88 (s, 1H), 6.58 (s, 1H), 4.40 (s, 1H), 2.19 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H). Spectral data were in agreement with those reported [*Beilstein J. Org. Chem.* **2018**, 2974].

1-(2-Hydroxy-4,5-dimethylphenyl)ethan-1-one. To a solution of 3,4-dimethylphenol (8.00 g, 65.5 mmol, 1.00 equiv), and CH₂Cl₂ (80 mL) was added AlCl₃ (26.2 g, 197 mmol, 3.00 equiv) in portions at 0 °C. Acetyl chloride (5.60 mL, 78.6 mmol, 1.20 equiv) was then added to the system dropwise. After 15 min, the reaction was complete as judged by TLC. The mixture was poured into ice water (250 mL) to quench. The aqueous layer was extracted with methylene chloride (75 mL x 3). The combined organic layer was washed with brine (200 mL), dried with Na₂SO₄, and concentrated. Recrystallization from hexanes (50 mL) afforded off-white crystals in 81% yield (8.74 g, 53.2 mmol): ¹H NMR (500 MHz, CDCl₃) δ 12.07 (s, 1H), 7.44 (s, 1H), 6.77 (s, 1H), 2.59 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Spectral data were in agreement with those reported [*Eur. J. Med. Chem.* **2019**, *175*, 114].

2-Ethyl-4,5-dimethylphenol (1h). To a stirring suspension of lithium aluminum hydride (830 mg, 22.0 mmol, 2.00 equiv) and THF (10 mL) was added a solution of 1-(2-hydroxy-4,5-dimethylphenyl)ethan-1-one (1.80 g, 11.0 mmol, 1.00 equiv) and THF (100 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 5 h. After completion, the reaction solution was quenched with H₂O (200 mL) at 0 °C and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL) and dried with Na₂SO₄. The resultant material was concentrated and used in the next step without further purification. After dissolution in C₆H₅Cl (45 mL), borane dimethyl sulfide (14.7 mL, 4.00 equiv, 44.0 mmol) was added dropwise with stirring at 0 °C under an inert atmosphere. After stirring for 15 min, the solution was heated to 80 °C. After 3 h, the solution was heated again to 130 °C and stirred for 18 hours. Thereafter, the solution was then cooled to room temperature, quenched with saturated Na₂CO₃ (100 mL), and extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried with Na₂SO₄, and concentrated. Chromatography (0-10% gradient of EtOAc in hexanes) afforded a white solid in 72% overall yield (1.23 g, 7.92 mmol): ¹H NMR (400 MHz, CDCl₃) δ 6.81 (s, 1H), 6.58 (s, 1H), 4.44 (s, 1H), 2.58 (q, *J* = 8.0 Hz, 2H), 2.185 (s, 3H), 2.177 (s, 3H), 1.22 (t, *J* = 8.0 Hz, 3H).

2-(2-Hydroxypropan-2-yl)-4,5-dimethylphenol. To a solution of 1-(2-hydroxy-4,5-dimethylphenyl)ethan-1-one (1.80 g, 11.0 mmol, 1.0 equiv) and dry THF (45 mL), was added a MeMgBr solution (3 M in THF, 14.6 mL, 43.8 mmol, 4.0 equiv) dropwise at 0 °C. The solution was then warmed to room temperature and stirred overnight. The solution was cooled to 0 °C and quenched with a saturated ammonium chloride solution (25 mL) and then H₂O (25 mL). The organic layer was extracted with diethyl ether (20 mL x 3), washed with brine (40 mL) and dried with Na₂SO₄. Concentration afforded a tan solid in 81% yield (1.60 g, 8.88 mmol): ¹H NMR (400 MHz, CDCl₃) δ 8.62 (br s, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 2.25 (br s, 1H), 2.19 (s, 3H), 2.17 (s, 3H), 1.66 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 153.5, 137.5, 128.2, 127.3, 126.5, 118.8, 76.1, 30.6, 19.5, 19.1; IR (film) 3358 (b), 2966, 1506, 1443, 1385, 1353, 1259, 1189, 1132, 1045, 889, 785, 765, 735, 508 cm⁻¹; HRMS (EI-TOF) *m/z* = 180.1150 calcd for C₁₁H₁₆O₂ [M]⁺, found 180.1156.

2-Isopropyl-4,5-dimethylphenol (1i). To a solution of 2-(2-hydroxypropan-2-yl)-4,5-dimethylphenol (1.27 g, 7.06 mmol, 1.0 equiv) and dry CH₂Cl₂ (17 mL) was added Et₃SiH (2.81 mL, 17.6 mmol, 2.5 equiv) followed by trifluoroacetic acid (2.16 mL, 28.2 mmol, 4.0 equiv) at 0 °C. After stirring for 14 hours at rt, water (40 mL) was added and the solution was stirred for another 2 h. Extraction with CH₂Cl₂ (20 mL x 3), washing with brine (40 mL), concentration, and chromatography (10% EtOAc in Hexanes) afforded a white solid in 80% yield (928 mg, 5.65 mmol): ¹H NMR (500 MHz, CDCl₃) δ 6.93 (s, 1H), 6.56 (s, 1H), 4.39 (s, 1H), 3.14 (septet, *J* = 7.0 Hz, 1H), 2.19 (s, 3H), 2.18 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 150.7, 135.0, 131.6, 128.8, 127.7, 116.9, 26.9, 23.0, 19.5, 19.2; IR (film) 3195 (b), 2960, 2934, 2868, 1514, 1452, 1415, 1342, 1267, 1185, 1039, 800 cm⁻¹; HRMS (EI-TOF) *m/z* = 164.1201 calcd for C₁₁H₁₆O [M]⁺, found 164.1187.

2-(tert-Butyl)-4,5-dimethylphenol (1j). To a solution of 3,4-dimethylphenol (4.0 g, 32.7 mmol, 1.0 equiv) and CH₂Cl₂ (150 mL) was added *tert*-butanol (6.8 mL, 72.0 mmol, 2.2 equiv) followed by the dropwise addition of concentrated H₂SO₄ (3.5 mL, 65.4 mmol, 2.0 equiv). After stirring at 50 °C for 24 h, the solution was quenched with saturated NaHCO₃ (100 mL) and extracted with EtOAc (100 x 3 mL). The combined organic layers were washed with brine (100 mL) and dried with Na₂SO₄. Chromatography afforded a white solid in 70% yield (4.05 g, 22.7 mmol): ¹H NMR (500 MHz, CDCl₃) δ, 7.01 (s, 1H), 6.48 (s, 1H), 4.51 (s, 1H), 2.18 (s, 3H), 2.17 (s, 3H), 1.39 (s, 9H). Spectral data were in agreement with those reported [*Synthesis* **1989**; 1989(1): 25].

4'-Methoxy-4,5-dimethyl-[1,1'-biphenyl]-2-ol (1k). 2-Bromo-4,5-dimethylphenol (1.61 g, 8.0 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (2.43 g, 16.0 mmol, 2.0 equiv), and Pd(PPh₃)₄ (462 mg, 0.40 mmol, 5 mol%) were taken up in toluene (40 mL) under Ar. A solution of Na₂CO₃ (16.0 mL, 2.0 M in H₂O:MeOH [4:1], 32.0 mmol, 4.0 equiv) was added and the reaction mixture was heated at reflux under Ar for 21 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na₂SO₄. Chromatography (10 to 20% EtOAc in hexanes) afforded a light yellow solid (1.61 g) in 88% yield: *R*_f = 0.29 (10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.03-7.01 (m, 3H), 6.80 (s, 1H), 5.04 (s, 1H), 3.86 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.2, 150.4, 137.3, 131.2, 130.3, 129.6, 128.7, 125.2, 117.0, 114.7, 55.5, 19.7, 18.9; IR (film) 3371, 3020, 2940, 2920, 1605, 1500, 1452, 1263, 1240, 1176, 1019, 1008, 836, 807 cm⁻¹; HRMS (EI-TOF) *m/z* = 228.1150 for C₁₅H₁₆O₂ [M]⁺, found 228.1154.

4,5-Dimethyl-[1,1'-biphenyl]-2-ol (1l). 2-Bromo-4,5-dimethylphenol (1.61 g, 8.0 mmol, 1.0 equiv), phenylboronic acid (1.46 g, 12.0 mmol, 1.5 equiv), and Pd(PPh₃)₄ (185 mg, 0.16 mmol, 2 mol%) were taken up in toluene (40 mL) under Ar. A solution of Na₂CO₃ (16.0 mL, 2.0 M in H₂O:MeOH [4:1], 32.0 mmol, 4.0 equiv) was added and the reaction mixture was heated at reflux under Ar for 20 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na₂SO₄. Chromatography (30 to 50% CH₂Cl₂ in hexanes) afforded a colorless oil (994 mg) in 63% yield: *R*_f = 0.37 (10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.52-7.48 (m, 4H), 7.42-7.38 (m, 1H), 7.05 (s, 1H), 6.83 (s, 1H), 5.08 (s, 1H), 2.30 (s, 3H), 2.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 150.3, 137.8, 137.4,

131.2, 129.3, 129.2, 128.8, 127.6, 125.5, 117.1, 19.7, 18.9; IR (film) 3520, 3430, 3025, 2920, 1625, 1600, 1575, 1484, 1443, 1399, 1297, 1235, 1178, 1125, 763, 699, 688 cm^{-1} ; HRMS (EI-TOF) m/z = 198.1045 for $\text{C}_{14}\text{H}_{14}\text{O}$ $[\text{M}]^+$, found 198.1041.

4'-Fluoro-4,5-dimethyl-[1,1'-biphenyl]-2-ol (1m). 2-Bromo-4,5-dimethylphenol (1.21 g, 6.0 mmol, 1.0 equiv), 4-fluorophenylboronic acid (1.68 g, 12.0 mmol, 2.0 equiv), K_2CO_3 (3.32 g, 24.0 mmol, 4.0 equiv), and $\text{Pd}(\text{PPh}_3)_4$ (347 mg, 0.30 mmol, 5 mol%) were taken up in THF (30 mL) and H_2O (15 mL) under Ar. The reaction mixture was heated at reflux under Ar for 24 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Chromatography (30 to 50% CH_2Cl_2 in hexanes) afforded a colorless oil (914 mg) in 70% yield: R_f = 0.41 (40% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.45-7.42 (m, 2H), 7.15 (apparent triplet, J = 8.4 Hz, 2H), 6.99 (s, 1H), 6.78 (s, 1H), 4.85 (s, 1H), 2.27 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.4 (d, J = 245.4 Hz), 150.3, 137.9, 133.4 (d, J = 3.1 Hz), 131.3, 130.9 (d, J = 8.0 Hz), 129.0, 124.6, 117.2, 116.1 (d, J = 21.1 Hz), 19.7, 18.9; IR (film) 3540, 3400, 2970, 2925, 2860, 1625, 1600, 1575, 1496, 1454, 1296, 1221, 1179, 1158, 1124, 837, 820 cm^{-1} ; HRMS (EI-TOF) m/z = 216.0950 for $\text{C}_{14}\text{H}_{13}\text{FO}$ $[\text{M}]^+$, found 216.0941.

3'-Fluoro-4,5-dimethyl-[1,1'-biphenyl]-2-ol (1n). 2-Bromo-4,5-dimethylphenol (1.21 g, 6.0 mmol, 1.0 equiv), 4-fluorophenylboronic acid (1.68 g, 12.0 mmol, 2.0 equiv), K_2CO_3 (3.32 g, 24.0 mmol, 4.0 equiv), and $\text{Pd}(\text{PPh}_3)_4$ (347 mg, 0.30 mmol, 5 mol %) were taken up in THF (30 mL) and H_2O (15 mL) under Ar. The reaction mixture was heated at reflux under Ar for 24 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Chromatography (30 to 50% CH_2Cl_2 in hexanes) afforded a colorless oil (914 mg) in 67% yield (865 mg, 4.0 mmol): ^1H NMR (400 MHz, CDCl_3) δ 7.42 (m, 1H), 7.25 (d, J = 6.92 Hz, 1H), 7.19 (dt, J = 9.8, 2.24 Hz, 1H), 7.06 (td, J = 8.32, 1.88 Hz, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 4.89 (s, 1H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2 (d, J = 245.0 Hz), 150.2, 139.9 (d, J = 7.9 Hz), 138.2, 131.2, 130.4 (d, J = 9.1 Hz), 129.1, 124.7 (d, J = 2.8 Hz), 124.3 (d, J = 1.9 Hz), 117.5, 116.2 (d, J = 21.5 Hz), 114.2 (d, J = 20.0 Hz), 19.6, 18.8; IR (film) 3410 (b), 2915, 1582, 1479, 1191, 1156, 1119, 868, 774 cm^{-1} ; HRMS (EI-TOF) m/z = 216. 0950 calcd for $\text{C}_{14}\text{H}_{13}\text{FO}$ $[\text{M}]^+$, found 216. 0955.

4,5-Dimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol (1o). 2-Bromo-4,5-dimethylphenol (1.61 g, 8.0 mmol, 1.0 equiv), 4-(trifluoromethyl)phenylboronic acid (3.04 g, 16.0 mmol, 2.0 equiv), and $\text{Pd}(\text{PPh}_3)_4$ (462 mg, 0.40 mmol, 5 mol%) were taken up in toluene (40 mL) under Ar. A solution of Na_2CO_3 (16.0 mL, 2.0 M in H_2O :MeOH [4:1], 32.0 mmol, 4.0 equiv) was added and the reaction mixture was heated at reflux under Ar for 19 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4 . Chromatography (5 to 10% EtOAc in hexanes) afforded a white solid (777 mg) in 37% yield: R_f = 0.28 (10% EtOAc in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, J = 8.0 Hz, 2 H), 7.63 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 6.78 (s, 1H), 4.85 (s, 1H), 2.29 (s, 3H), 2.26 (s, 3H); ^{13}C NMR

(125 MHz, CDCl₃) δ 150.3, 141.5, 138.6, 131.4, 129.6, 129.5 (q, J = 32.2 Hz), 129.4, 125.9 (q, J = 3.6 Hz), 124.4 (q, J = 270.0 Hz), 124.3, 117.6, 19.7, 18.8; IR (film) 3550, 2975, 2925, 1610, 1505, 1460, 1315, 1303, 1161, 1123, 1107, 1064, 843 cm⁻¹; HRMS (EI-TOF) m/z = 266.0918 for C₁₅H₁₃F₃O [M]⁺, found 266.0904.

4'-Methoxy-5-methyl-[1,1'-biphenyl]-2-ol (1p). 2-Bromo-4-methylphenol (967 μ L, 8.0 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (1.82 g, 12.0 mmol, 1.5 equiv), and Pd(PPh₃)₄ (185 mg, 0.16 mmol, 2 mol%) were taken up in toluene (40 mL) under Ar. A solution of Na₂CO₃ (16.0 mL, 2.0 M in H₂O:MeOH [4:1], 32.0 mmol, 4.0 equiv) was added and the reaction mixture was heated at reflux under Ar for 20 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na₂SO₄. Chromatography (5 to 10% EtOAc in hexanes) afforded a yellow resin (836 mg) in 49% yield: ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, J = 8.7 Hz, 2H), 7.06-7.01 (m, 4H), 6.88 (d, J = 7.6 Hz, 1H), 5.07 (s, 1H), 3.86 (s, 3H), 2.32 (s, 3H). Spectral data were in agreement with those reported [*Bioorg. Med. Chem.* **2014**, 22, 6908].

5-Methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol (1q). 2-Bromo-4-methylphenol (967 μ L, 8.0 mmol, 1.0 equiv), 4-(trifluoromethyl)phenylboronic acid (2.28 g, 12.0 mmol, 1.5 equiv), Cs₂CO₃ (6.52 g, 20.0 mmol, 2.5 equiv), and Pd(dppf)Cl₂·CH₂Cl₂ (163 mg, 0.20 mmol, 2.5 mol%) were taken up in THF (53 mL) and H₂O (5.3 mL) under Ar. The reaction mixture was heated at reflux under Ar for 20 h. After cooling to ambient temperature, the resulting mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na₂SO₄. Chromatography (5 to 10% EtOAc in hexanes) afforded an off-white solid (925 mg) in 46% yield: R_f = 0.15 (5% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.11-7.10 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 4.92 (s, 1H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 150.2, 141.5, 131.0, 130.7, 130.4, 129.7 (q, J = 32.6 Hz), 129.6, 126.8, 126.0 (q, J = 3.6 Hz), 124.3 (q, J = 272.0 Hz), 116.2, 20.6; IR (film) 3300, 3025, 2925, 2910, 1625, 1495, 1400, 1320, 1201, 1153, 1107, 1066, 1016, 841, 607 cm⁻¹; HRMS (EI-TOF) m/z = 252.0762 for C₁₄H₁₁F₃O [M]⁺, found 252.0772.

3-tert-Butyltyrosine was formed by using a procedure from the reported literature in quantitative yield (19.6 g, 82.8 mmol): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.02 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.31-3.28 (m, 1H), 3.08 (dd, J = 12.0, 4.0 Hz, 1H), 2.74-2.71 (m, 1H), 1.33 (s, 9H). Spectral data were in agreement with those reported [*Org. Biomol. Chem.*, 2009, 7, 3119–3127].

Methyl-3-tert-butyltyrisinoate was formed by using a procedure from the reported literature in 53 % yield (3.9 g, 15.5 mmol): ¹H NMR (400 MHz, CDCl₃) δ 7.03 (s, 1H), 6.86 (d, J = 6.0 Hz, 1H), 6.55 (d, J

= 6.0 Hz, 1H), 5.30 (s, 1H), 3.73 (m, 4H), 3.04-2.99 (m, 1H), 2.85-2.79 (m, 1H), 1.38 (s, 9H). Spectral data were in agreement with those reported [*Org. Biomol. Chem.*, 2009, 7, 3119–3127].

Methyl N-Ac-3-tert-Butyltyrisinoate (1r). To a stirring solution of methyl-3-*tert*-butyltyrisinoate (3.00 g, 11.95 mmol, 1.0 equiv), CH₂Cl₂ (100 mL), and water (20 mL), was added Na₂CO₃ (1.39 g, 13.10 mmol, 1.1 equiv), followed by acetyl chloride (1.10 mL, 15.50 mmol, 1.3 equiv) at rt. After stirring for 30 min at rt, the solution was heated to reflux and stirred for another 30 min. The solution was then cooled to rt and extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were washed with brine (50 mL) and dried with Na₂SO₄. The resultant off-white solid was further purified by chromatography (25% hexanes in EtOAc) to afford **1f** as a white solid in 68% yield (2.38 g, 8.12 mmol): ¹H NMR (400 MHz, CDCl₃) δ 6.94 (d, *J* = 1.6 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.90 (d, *J* = 7.4 Hz, 1H), 4.87-4.82 (m, 1H), 3.74 (s, 3H), 3.09-3.00 (m, 2H), 1.99 (s, 3H), 1.38 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 170.1, 154.1, 136.2, 127.9, 127.4, 126.6, 116.6, 53.4, 52.4, 37.3, 34.5, 29.5, 23.1; IR (film) 3255 (b), 2950, 1619 (s), 1575, 1423, 1268, 1220, 1170, 736 cm⁻¹; HRMS (EI-TOF) *m/z* = 293.1627 calcd for C₁₆H₂₃NO₅ [M]⁺, found 293.1638.

Methyl N-Cbz-3-tert-Butyltyrisinoate (1s). To a solution of methyl-3-*tert*-butyltyrisinoate (2.00 g, 7.96 mmol, 1.0 equiv), Na₂CO₃ (885 mg, 8.35 mmol, 1.05 equiv), CH₂Cl₂ (32 mL), and water (5 mL) was added benzyl chloroformate (1.2 mL, 8.35 mmol, 1.05 equiv) at rt. After stirring for 3 h at rt, the solution was quenched with 1 N HCl (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL) and dried with Na₂SO₄. The resultant off-white solid was further chromatographed (33% EtOAc in hexanes) to afford **1g** as a white solid in 74% yield (2.37 g, 5.89 mmol): ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.32 (m, 5H), 6.97 (s, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 1H), 5.34 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.68-4.63 (m, 1H), 3.73 (s, 3H), 3.05 (m, 2H), 1.38 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 155.8, 153.7, 136.22, 136.18, 128.6, 128.2, 128.1, 128.0, 127.5, 126.9, 116.7, 67.1, 55.0, 52.4, 37.7, 34.5, 29.5; IR (film) 3370, 3321 (b), 2945, 1697 (s), 1256, 1214, 1052, 617 cm⁻¹; HRMS (EI-TOF) *m/z* = 385.1889 calcd for C₂₂H₂₇NO₅ [M]⁺, found 385.1897.

Methyl N-Boc-3-tert-Butyltyrisinoate (1t). Compound **1t** was formed using a procedure from the literature in 57% yield (2.01 g, 5.70 mmol): ¹H NMR (400 MHz, CDCl₃) δ 6.96 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.33 (br s, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 4.55 (m, 1H), 3.71 (s, 3H), 3.00 (d, *J* = 4.8 Hz, 2H), 1.43 (s, 9H), 1.38 (s, 9H). Spectral data were in agreement with those reported [*Org. Biomol. Chem.*, 2009, 7, 3119–3127].

Homo-coupling of phenols

General procedure for the photooxidative coupling of phenols (Procedure A).

To an 8 mL glass vial with an open top cap charged with phenol **1** (500 μmol, 1.0 equiv), 4,4'-di-*tert*-butylbiphenyl (33.4 mg, 125 μmol, 0.25 equiv), and MesAcr⁺BF₄⁻ (4.0 mg, 125 μmol, 0.02 equiv) was added solvent (1.0 mL) at room temperature. The cap was then pierced with a 16 gauge x 1.5 inch needle and the solution was irradiated with blue LEDs. After stirring for 12-24 h, the solvent was removed. The materials was then chromatographed (0-10% gradient of EtOAc in hexanes unless otherwise noted).

3,3'-Di-*tert*-butyl-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (2a**)**. Using procedure A, **1a** (82.0 mg, 500 μmol, 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 18 h to afford a white solid in 70% yield (57.0 mg, 175 μmol): ¹H NMR (400 MHz, CDCl₃) δ 7.14 (s, 2H), 6.89 (s, 2H), 5.16 (s, 2H), 2.31 (s, 6H), 1.43 (s, 18 H). Spectral data were in agreement with those reported [*Angew. Chem. Int. Ed.* **2019**, 58, 2120–2124].

3,3',5,5'-Tetra-*tert*-Butyl-[1,1'-biphenyl]-2,2'-diol (2b**)**. Using Procedure A, **1b** (103.2 mg, 500 μmol, 1.0 equiv) was homo-coupled in 1,2-dichloroethane over 24 h to afford a white solid (42.1 mg, 103 μmol) in 41% yield (70% based on recovered starting material): ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, *J* = 1.9 Hz, 2H), 7.13 (d, *J* = 2.2 Hz, 2H), 5.22 (br s, 2H), 1.46 (s, 18H), 1.34 (s, 18H). Spectral data were in agreement with those reported [*J. Am. Chem. Soc.* **2014**, 136, 7662].

3,3',5,5'-Tetramethyl-[1,1'-biphenyl]-2,2'-diol (2c). Using Procedure A, **1c** (61.1 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 14 h to afford a white solid (20.5 mg, 85 μmol) in 34% yield (54% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 7.00 (s, 2H), 6.87 (s, 2H), 5.06 (br s, 2H), 2.28 (br s, 12H). Spectral data were in agreement with those reported [*Chem. Comm.* **2017**, 53, 9616].

5,5''-Dimethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2d). Using procedure A, **1d** (92.1 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 12 h. Chromatography (10% Et_2O /hexanes) afforded a white solid (31.3 mg, 85 μmol) in 34% yield (55% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 7.56 (d, $J = 7.7$ Hz, 4H), 7.47 (t, $J = 7.6$ Hz, 4H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.17-7.16 (m, 4H), 5.67 (s, 2H), 2.39 (s, 6H). Spectral data were in agreement with those reported [*Organometallics* **2015**, 34, 4102].

3,3'-Dibromo-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (2e). Using procedure A, 2-bromo-4-methylphenol (93.6 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 14 h. Chromatography (8 to 10% Et_2O in hexanes) afforded an off-white solid (15.1 mg, 41 μmol) in 16% yield (33% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 7.35 (s, 2H), 7.01 (s, 2H), 5.78 (s, 2H), 2.31 (s, 6H). Spectral data were in agreement with those reported [*Chem. Comm.* **2017**, 53, 9616].

4,4',5,5',6,6'-Hexamethyl-[1,1'-biphenyl]-2,2'-diol (2f). Using procedure A, **1f** (68.0 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 18 h to afford a white solid in 61% yield (41.0 mg, 152 μmol): ^1H NMR (400 MHz, CDCl_3) δ 6.74 (s, 2H), 4.48 (s, 2H), 2.31 (s, 6H), 2.16 (s, 6H), 1.92 (s, 6H). Spectral data were in agreement with those reported [*J. Am. Chem. Soc.* **2019**, 141, 10016–10032].

3,3',5,5',6,6'-Hexamethyl-[1,1'-biphenyl]-2,2'-diol (2g). Using procedure A, **1g** (68.1 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,2-dichloroethane over 24 h to afford a light yellow solid (31.9 mg, 118 μmol) in 47% yield (56% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 7.00 (s, 2H), 4.54 (s, 2H), 2.24 (s, 12H), 1.86 (s, 6H). Spectral data were in agreement with those reported [*Chem. Eur. J.* **2011**, *17*, 14164].

3,3'-Diethyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (2h). Using procedure A, **1h** (75.0 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,2-dichloroethane over 18 h to afford a tan solid in 62% yield (46.5 mg, 156 μmol): R_f = 0.56 (10% EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.03 (s, 2H), 4.56 (s, 2H), 2.65 (q, J = 7.5 Hz, 4H), 2.26 (s, 6H), 1.87 (s, 6H), 1.24 (s, J = 7.52 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.4, 133.9, 131.0, 128.6, 127.6, 120.1, 23.0, 19.8, 16.1, 14.2; IR (film) 3488, 2962, 2929, 1443, 1203, 1161, 1082, 1055, 882 cm^{-1} . HRMS (EI-TOF) m/z = 298.1933 calcd for $\text{C}_{22}\text{H}_{30}\text{O}_2$ $[\text{M}]^+$, found 298.1920.

3,3'-Di-iso-propyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (2i). Using procedure A, **1i** (82.0 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 18 h to afford a white solid in 65% yield (77% brsm) (53.0 mg, 162 μmol): R_f = 0.63 (10% EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.08 (s, 2H), 4.60 (s, 2H), 3.28 (septet, J = 6.9 Hz, 2H), 2.27 (s, 6H), 1.86 (s, 6H), 1.26 (d, J = 7.0 Hz, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.9, 133.7, 132.0, 128.6, 128.1, 120.2, 27.1, 22.7 (d, conformers), 20.0, 16.1; IR (film) 3525, 2959, 2924, 1444, 1281, 1207, 1159, 1093, 1038, 883 cm^{-1} ; HRMS (EI-TOF) m/z = 326.2264 calcd for $\text{C}_{22}\text{H}_{30}\text{O}_2$ $[\text{M}]^+$, found 326.2261.

3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (2j). Using procedure A, **1j** (89.0 mg, 500 μmol , 1.0 equiv) was homo-coupled in a mixture of 1,1,1,3,3,3-hexafluoro-2-propanol and 1,2-dichloroethane (2:1) over 24 h to afford a white solid in 50% yield (65% brsm) (44.0 mg, 152 μmol): ^1H

NMR (500 MHz, CDCl₃) δ 7.13 (s, 2H), 4.80 (s, 2H), 2.25 (s, 6H), 1.82 (s, 6H), 1.40 (s, 9H). Spectral data were in agreement with those reported [*Chem. Eur. J.* **2006**, *12*, 7482-7488].

4,4'''-Dimethoxy-4',5',5'',6''-tetramethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2k). Using procedure A, **1k** (114.2 mg, 500 μ mol, 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 22 h. Chromatography (60 to 90% CH₂Cl₂ in hexanes) afforded a white solid (40.3 mg, 89 μ mol) in 36% yield (72% based on recovered starting material), with a trace impurity ($\sim$ 5%) of the *para*-peroxy adduct of the dimeric product: R_f = 0.27 (75% CH₂Cl₂ in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, J = 8.7 Hz, 4H), 7.20 (s, 2H), 6.98 (d, J = 8.7 Hz, 4H), 4.87 (s, 2H), 3.85 (s, 6H), 2.32 (s, 6H), 1.98 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 158.9, 148.5, 136.0, 132.0, 130.5, 130.4, 129.3, 125.3, 121.7, 114.0, 55.4, 20.0, 16.5; IR (film) 3475, 3390, 2930, 2840, 1605, 1511, 1452, 1440, 1284, 1235, 1174, 1148, 1131, 1032, 825, 549 cm⁻¹; HRMS (EI-TOF) m/z = 454.2144 for C₃₀H₃₀O₄ [M]⁺, found 454.2155.

4',5',5'',6''-Tetramethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2l). Using procedure A, **1l** (99.2 mg, 500 μ mol, 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 14 h. Chromatography (5% acetone in hexanes) afforded an off-white solid (55.1 mg, 140 μ mol) in 56% yield: R_f = 0.35 (5% acetone in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.62 (d, J = 7.2 Hz, 4H), 7.45 (t, J = 7.7 Hz, 4H), 7.34 (t, J = 7.4 Hz, 2H), 7.25 (s, 2H), 4.90 (s, 2H), 2.34 (s, 6H), 2.01 (s, 6H). Spectral data were in agreement with those reported [*Org. Lett.* **2003**, *5*, 3831].

4,4'''-Difluoro-4',5',5'',6''-tetramethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2m). Using procedure A, **1m** (108.1 mg, 500 μ mol, 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 15 h to afford an off-white solid (71.3 mg, 165 μ mol) in 66% yield: R_f = 0.54 (10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.59-7.55 (m, 4H), 7.20 (s, 2H), 7.11 (apparent triplet, J = 8.7 Hz, 4H), 4.81 (s, 2H), 2.32 (s, 6H), 1.98 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 162.2 (d, J = 246.2), 148.5, 136.6, 134.0 (d, J = 3.3 Hz), 132.3, 131.0 (d, J = 8.0 Hz), 129.6, 124.9, 121.4, 115.3 (d, J = 21.2 Hz),

20.0, 16.6; IR (film) 3500, 3390, 2920, 2850, 1605, 1510, 1443, 1215, 1158, 1025, 831, 803, 730, 535 cm^{-1} ; HRMS (EI-TOF) $m/z = 430.1744$ for $\text{C}_{28}\text{H}_{24}\text{F}_2\text{O}_2$ $[\text{M}]^+$, found 430.1758.

3,3'''-Difluoro-4',5',5'',6''-tetramethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2n). Using procedure A, **1n** (108 mg, 500 μmol , 1.0 equiv) was homo-coupled over 18 h to afford a tan solid in 60% yield (65 mg, 300 μmol): $R_f = 0.44$ (10% EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.33 (m, 6H), 7.25 (s, 2H), 7.05-7.00 (m, 2H), 4.86 (s, 2H), 2.33 (s, 6H), 1.99 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.8 (d, $J = 243.0$ Hz), 148.5, 140.1 (d, $J = 8.1$ Hz), 137.0, 132.2, 129.7 (d, $J = 8.4$ Hz), 129.6, 124.8 (d, $J = 2.7$ Hz), 124.5 (d, $J = 2.00$ Hz), 121.3, 116.3 (d, $J = 21.7$), 113.9 (d, $J = 20.9$ Hz), 19.8, 16.5; IR (film) 3516 (br), 2910, 1615, 1584, 1390, 1269, 1246, 1193, 1172, 1120, 787, 698 cm^{-1} . HRMS (EI-TOF) $m/z = 430.1774$ calcd for $\text{C}_{28}\text{H}_{24}\text{F}_2\text{O}_2$ $[\text{M}]^+$, found 430.1761.

4',5',5'',6''-Tetramethyl-4,4'''-bis(trifluoromethyl)-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2o). Using procedure A, **1o** (133.1 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 14 h. Chromatography (4% acetone in hexanes) afforded an off-white solid (92.4 mg, 174 μmol) in 70% yield: $R_f = 0.23$ (5% acetone in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.76 (d, $J = 8.2$ Hz, 4H), 7.69 (d, $J = 8.4$ Hz, 4H), 7.29 (s, 2H), 4.87 (s, 2H), 2.37 (s, 6H), 2.03 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.7, 141.7, 137.5, 132.5, 130.1, 129.7, 129.2 (q, $J = 32.2$ Hz), 125.3 (q, $J = 3.6$ Hz), 124.5, 124.4 (q, $J = 272.0$ Hz), 121.2, 20.0, 16.7; IR (film) 3510, 2925, 1615, 1445, 1390, 1323, 1152, 1107, 1067, 1017, 839 cm^{-1} ; HRMS (EI-TOF) $m/z = 530.1680$ for $\text{C}_{30}\text{H}_{24}\text{F}_6\text{O}_2$ $[\text{M}]^+$, found 530.1685.

4,4'''-Dimethoxy-5',5''-dimethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2p). Using procedure A, **1p** (107.2 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 18 h. Chromatography (5 to 10% EtOAc in hexanes) afforded an off-white solid (35.5 mg, 83 μmol) in 33% yield (55% based on recovery of starting material): $R_f = 0.18$ (10% EtOAc in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.49 (d, $J = 8.7$ Hz, 4H), 7.13 (m, 4H), 7.00 (d, $J = 8.7$ Hz, 4H), 5.67 (s, 2H), 3.86 (s,

6H), 2.38 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.2, 147.6, 131.2, 131.1, 130.6, 130.5, 130.0, 129.1, 125.0, 114.3, 55.5, 20.7; IR (film) 3260, 2930, 1605, 1575, 1511, 1457, 1290, 1246, 1215, 1201, 1178, 1024, 833, 783, 577 cm^{-1} ; HRMS (EI-TOF) m/z = 426.1831 for $\text{C}_{28}\text{H}_{26}\text{O}_4$ $[\text{M}]^+$, found 426.1831 (same as calcd).

5',5''-Dimethyl-4,4'''-bis(trifluoromethyl)-[1,1':3',1'':3'',1'''-quaterphenyl]-2',2''-diol (2q). Using procedure A, **1q** (126.1 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 15 h. Chromatography (3 to 5% EtOAc in hexanes) afforded an off-white solid (62.6 mg, 125 μmol) in 50% yield (61% based on recovery of starting material: R_f = 0.33 (5% EtOAc in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.71 (m, 8H), 7.18 (m, 4H), 5.45 (s, 2H), 2.40 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.8, 141.6, 131.9, 131.8, 131.2, 130.0, 129.7 (q, J = 32.5 Hz), 128.2, 125.6 (q, J = 3.7 Hz), 124.4 (q, J = 272.0 Hz), 124.2, 20.7; IR (film) 3505, 2920, 1615, 1475, 1403, 1324, 1166, 1100, 1068, 1018, 837, 830, 601 cm^{-1} ; HRMS (EI-TOF) m/z = 502.1367 for $\text{C}_{28}\text{H}_{20}\text{F}_6\text{O}_4$ $[\text{M}]^+$, found 502.1361.

Dimethyl-3,3'-(5,5'-di-tert-butyl-6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)(2S,2'S)-bis(2-acetamidopropanoate) (2r). Using procedure A, **1r** (147 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 18 h. Chromatography (75% EtOAc in hexanes) afforded a white solid in 76% yield (111 mg, 189 μmol): ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 7.10 (s, 2H), 6.90 (s, 2H), 4.66 (br s, 2H), 3.31 (s, 6H), 3.10- 3.17 (m, 2H), 2.93-2.89 (m, 2H), 1.93 (s, 6H), 1.43 (s, 18 H); ^{13}C NMR (100 MHz, acetone- d_6) δ 172.8, 170.0, 152.8, 137.6, 131.0, 139.0, 128.6, 125.3, 54.4, 52.3, 38.4, 35.4, 30.1, 22.7; IR (film) 3307 (br), 2952, 1741, 1637, 1436, 1202, 1174, 1127 cm^{-1} ; HRMS (EI-TOF) m/z = 607.3022 calcd for $\text{C}_{32}\text{H}_{44}\text{N}_2\text{NaO}_8$ $[\text{M}+\text{Na}]^+$, found 607.2995.

Dimethyl-3,3'-(5,5'-di-tert-butyl-6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)(2S,2'S)-bis(2-((benzyloxy)carbonyl)amino)propanoate) (2s). Using procedure A, **1s** (193 mg, 500 μmol , 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 24 h. Chromatography (33% EtOAc in hexanes) afforded a white foam in 44% yield (85.0 mg, 111 μmol): ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 7.27-7.24 (m, 10H), 7.13 (s, 2H), 6.91 (s, 2H), 5.01 (s, 4H), 4.46-4.42 (m, 2H), 3.70 (s, 6H), 3.08-3.05 (m, 2H), 2.92-2.86 (m, 2H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 158.3, 152.5, 139.4, 138.0, 137.7, 131.3, 129.7, 129.4, 128.9, 128.7, 128.4, 67.6, 57.1, 52.8, 38.4, 35.9, 30.4; IR (film) 3342, 2953, 1704 (s), 1515, 1435, 1345, 1235, 124, 1177, 1056, 1026, 696 cm^{-1} ; HRMS (EI-TOF) m/z = 791.3534 calcd for $\text{C}_{44}\text{H}_{52}\text{N}_2\text{NaO}_{10}$ $[\text{M}+\text{Na}]^+$, found 791.3520.

Dimethyl 3,3'-(5,5'-di-*tert*-butyl-6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)(2*S*,2'*S*)-bis(2-((*tert*-butoxycarbonyl)amino)propanoate) (2t). Using procedure A, **1t** (176 mg, 500 μ mol, 1.0 equiv) was homo-coupled in 1,1,1,3,3,3-hexafluoro-2-propanol over 24 h. Chromatography (33% EtOAc in hexanes) afforded a white foam in 62% yield (109 mg, 155 μ mol): ^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 7.12 (s, 2H), 6.93 (s, 2H), 4.38 (br s, 2H), 3.72 (s, 6H), 3.08-3.05 (m, 2H), 2.91-2.86 (m, 2H), 1.49 (s, 18H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 157.7, 152.5 (d, conformers), 139.5 (d, conformers), 131.2, 129.8 (d, conformers), 128.6 (d, conformers), 128.1, 80.6, 56.1, 52.7, 38.4 (d, conformers), 35.9, 30.0, 28.7; IR (film) 3444 (br), 2956, 1699, 1435, 1364, 1236, 1200, 1161, 1058 cm^{-1} ; HRMS (ESI-TOF) m/z = 701.4013 calcd for $\text{C}_{38}\text{H}_{57}\text{N}_2\text{O}_{10}$ $[\text{M}+\text{H}]^+$, found 701.4008.

Further substrates for cross coupling of phenols

2-Isopropyl-4-methoxyphenol (1w). To a solution of 1-(2-hydroxy-5-methoxyphenyl)ethan-1-one (1.83 g, 11.0 mmol, 1.00 equiv) and dry THF (45 mL) stirring at 0 $^{\circ}\text{C}$ under an Ar atmosphere was added a 3 M MeMgBr in THF (14.7 mL, 44.0 mmol, 4.00 equiv). The solution was warmed to rt and stirred overnight. The solution was cooled to 0 $^{\circ}\text{C}$ and quenched with NH_4Cl (40 mL) and H_2O (50 mL). After extracting with Et_2O (30 mL x 3), the combined organic layers were washed with brine (50 mL) and dried with Na_2SO_4 . Concentration afforded the intermediate 2-(2-hydroxypropan-2-yl)-4-methoxyphenol. Thereafter, to a solution of the intermediate (1.50 g, 9.03 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added Et_3SiH (3.6 mL, 22.6 mmol, 2.50 equiv,) and trifluoroacetic acid (2.8 mL, 36.14 mmol, 4.00 equiv) at 0 $^{\circ}\text{C}$. After stirring for 14 h at rt temperature, H_2O (30 mL) was added and the solution was stirred for another 2 h. After extracting with CH_2Cl_2 (30 mL x 3), the combined organic layers were washed with brine (50 mL) Chromatography (10 % EtOAc in hexanes) afforded 2-isopropyl-4-methoxyphenol in 30% yield (445 mg, 2.68 mmol) as a clear oil : ^1H NMR (400 MHz, CDCl_3) δ 6.77 (d, J = 2.9 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.61 (dd, J = 8.6, 2.9 Hz, 1H), 4.42 (s, 1H), 3.77 (s, 3H), 3.18 (septet, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz). Spectral data were in agreement with those reported [*PNAS*, **2018**, *115* (19), 4939-4944].

5-Methoxy-[1,1'-biphenyl]-2-ol (1x). To a stirring solution of 4-methoxy phenol (7.0 g, 56.4 mmol, 1.00 equiv) and CH_2Cl_2 (85 mL) was added Br_2 (2.93 mL, 58.6 mmol, 1.04 equiv) dropwise at 0 $^{\circ}\text{C}$. After stirring 2 h, the solution was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL) and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (60 mL) and dried with $\text{Na}_2\text{S}_2\text{O}_4$. Concentration afforded the intermediate 2-bromo-4-methoxyphenol (10.8 g, 53.2 mmol), which was used directly in the next step. To a flask charged with the intermediate (1.02 g, 5.00 mmol, 1.00 equiv), phenylboronic acid (914 mg, 7.50 mmol, 1.50 equiv), $i\text{-Pr}_2\text{NH}$ (1.33 mL, 10.0 mmol, 2.0 equiv) and palladium acetate (11.2 mg, 0.05 mmol, 0.01 equiv) under Ar was added degassed water (5 mL). The solution was then stirred at 100 $^{\circ}\text{C}$ for 2 h. The solution was quenched with 1 N HCl (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried with $\text{Na}_2\text{S}_2\text{O}_4$, and purified via chromatography (0-25% gradient of EtOAc in hexanes) to afford a clear oil in 56 % yield over two

steps (667 mg, 3.33 mmol): ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.48 (m, 4H), 7.43-7.38 (m, 1H), 6.29 (d, $J = 8.3$ Hz, 1H), 6.85-6.82 (m, 2H), 4.93 (br s, 1H) 3.80 (s, 3H). Spectral data were in agreement with those reported. [*Chem. Commun.*, **2016**, 52, 10529-10532].

Cross-Coupling of Phenols

General procedure for the photooxidative phenol/phenol and phenol/arene cross-couplings (Procedure B):

To an 8 mL glass vial with an open top cap charged with phenol **1** (500 μmol , 1.00 equiv), 4,4'-di-*tert*-butylbiphenyl (33.4 mg, 125 μmol , 0.25 equiv), and MesAcr $^+\text{BF}_4^-$ (4.0 mg, 125 μmol , 0.02 equiv) was added 1,1,1,3,3,3-hexafluoro-2-propanol (1.0 mL) at room temperature followed by compound **5** (500 μmol , 1.00 equiv). The cap was then pierced with a 16 gauge x 1.5 inch needle and the solution was irradiated with blue LEDs. After stirring for 48 h, the solvent was removed. The material was then chromatographed (0-25% gradient of EtOAc in hexanes).

3,3'-Di-*tert*-butyl-5-methoxy-[1,1'-biphenyl]-2,4'-diol (6a-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butylphenol (75.1 mg, 500 μmol , 1.00 equiv) over 48 h to afford a white solid in 56% yield (91.0 mg, 0.277 mmol, 74% brsm): ^1H NMR (400 MHz, CD_2Cl_2) δ 7.32 (d, $J = 1.8$ Hz, 1H), 7.15 (dd, $J = 8.0$ Hz, 2.1 Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 2.7$ Hz, 1H), 5.19 (m 2H), 3.76 (s, 3H), 1.44 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.7, 153.0, 145.7, 137.8, 137.7, 129.70, 129.65, 128.9, 128.3, 117.7, 113.5, 112.3, 56.1, 35.4, 35.1, 29.71, 29.65; IR (film) 3540, 3395, 2954, 1198, 1176, 1153, cm^{-1} ; HRMS (EI-TOF) $m/z = 328.2038$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$ $[\text{M}]^+$, found 328.2043.

3,3',5'-Tri-*tert*-butyl-5-methoxy-[1,1'-biphenyl]-2,4'-diol (6b-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μmol , 1.00 equiv) was coupled with 2,6-di-*tert*-butylphenol (103 mg, 500 μmol , 1.00 equiv) to afford a tan solid in 45% yield (86.5 mg, 225 μmol 87% brsm): $R_f = 0.61$ (10 %

EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.22 (s, 2H), 6.88 (d, $J = 3.0$ Hz, 1H), 6.65 (d, $J = 3.0$ Hz, 1H), 5.33 (s, 1H), 5.22 (s, -OH), 3.78 (s, 3H), 1.47 (s, 18H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.9, 152.5, 145.5, 137.3, 137.1, 129.9, 128.3, 126.3, 113.3, 112.1, 55.9, 35.2, 34.7, 30.4, 29.7; IR (film) 3640, 3538, 2954, 1598, 1469, 1450, 1426, 1211, 1150, 1060, 764 cm^{-1} ; HRMS (EI-TOF) $m/z = 384.2664$ calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3$ $[\text{M}]^+$, found 384.2662.

3',5'-Di-*tert*-butyl-5-methoxy-3-methyl-[1,1'-biphenyl]-2,4'-diol (6b-v). Using procedure B, 2-methyl-4-methoxyphenol (69.1 mg, 500 μmol , 1.00 equiv) was coupled with 2,6-di-*tert*-butylphenol (103 mg, 500 μmol , 1.00 equiv) to afford a tan solid in 27% yield (46 mg, 134 μmol): $R_f = 0.42$ (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.24 (s, 2H), 6.70 (d, $J = 2.9$ Hz, 1H), 6.64 (d, $J = 3.0$ Hz, 1H), 5.33 (s, 1H), 5.03 (s, 1H), 3.78 (s, 3H), 2.30 (s, 3H), 1.47 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 153.0, 145.0, 137.1, 129.0, 128.3, 125.9, 125.5, 115.8, 112.8, 56.0, 34.7, 30.4, 16.7; IR (film) 3590, 3545, 2955, 1465, 1422, 1198, 776 cm^{-1} ; HRMS (EI-TOF) $m/z = 342.2195$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3$ $[\text{M}]^+$, found 342.2191.

3-(*tert*-Butyl)-3',5'-diisopropyl-5-methoxy-[1,1'-biphenyl]-2,4'-diol (6c-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μmol , 1.00 equiv) was coupled with arene 2,6-di-*iso*-propylphenol (89.2 mg, 500 μmol , 1.00 equiv) to afford a tan oil in 44% yield (78.0 mg, 219 μmol 62% brsm): ^1H NMR (500 MHz, CDCl_3) δ 7.12 (s, 2H), 6.89 (d, $J = 3.0$ Hz, 1H), 6.63 (d, $J = 3.0$ Hz, 1H), 5.21 (s, 1H), 4.90 (s, 1H), 3.79 (s, 3H), 3.21 (septet, $J = 6.9$ Hz, 2H), 1.44 (s, 9H), 1.30 (d, $J = 6.9$ Hz, 12H). Spectral data were in agreement with those reported [*Tetrahedron*. **2019**, 75, 2004-2011].

3,3'-Di-*tert*-butyl-5-methoxy-5'-methyl-[1,1'-biphenyl]-2,4'-diol (6d-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-6-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a tan solid in 76% yield (131 mg, 382 μmol , 89% brsm): $R_f = 0.30$ (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, $J = 1.5$ Hz, 1H), 7.10 (d, $J = 1.5$ Hz, 1H), 6.89 (d, $J = 3.0$ Hz, 1H), 6.63 (d, $J = 3.0$ Hz, 1H), 5.22 (s, 1H), 4.92 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.7, 152.6, 145.4, 137.4, 137.0,

129.6, 129.3, 128.9, 126.5, 124.2, 113.4, 111.9, 55.9, 35.2, 34.9, 29.9, 29.7, 16.2; IR (film) 3521, 2954, 1481, 1425, 1400, 1217, 1199, 1186, 1151, 1090, 1049, 777, 768, 760 cm^{-1} ; HRMS (EI-TOF) $m/z = 342.2195$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3$ $[\text{M}]^+$, found 342.2212.

3,5'-Di-*tert*-butyl-5-methoxy-2'-methyl-[1,1'-biphenyl]-2,4'-diol (6e-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a tan solid in 97% yield (165 mg, 483 μmol): $R_f = 0.21$ (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.13 (s, 1H), 6.89 (d, $J = 3.0$ Hz, 1H), 6.64 (s, 1H), 6.53 (d, $J = 3.0$ Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 3.76 (s, 3H), 2.05 (s, 3H), 1.42 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.3, 152.4, 145.7, 137.1, 156.5, 134.7, 129.8, 128.6, 128.0, 118.7, 113.4, 111.9, 55.8, 35.1, 34.5, 29.8, 29.6, 19.1; IR (film) 3524, 3402, 3958, 1600, 1433, 1397, 1386, 1363, 1317, 1242, 1193, 1138, 1049 cm^{-1} ; HRMS (EI-TOF) $m/z = 342.2195$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3$ $[\text{M}]^+$, found 342.2208.

5'-(*tert*-Butyl)-3-isopropyl-5-methoxy-2'-methyl-[1,1'-biphenyl]-2,4'-diol (6e-w). Using procedure B, 2-*iso*-propyl-4-methoxyphenol (83.1 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a white solid in 82% yield (135 mg, 483 μmol): $R_f = 0.24$ (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.14 (s, 1H), 6.82 (d, $J = 3.0$ Hz, 1H), 6.64 (s, 1H), 6.54 (d, $J = 3.0$ Hz, 1H), 5.17 (s, 1H), 4.63 (s, 1H), 3.80 (s, 3H), 3.33 (septet, $J = 6.9$ Hz, 1H), 2.08 (s, 3H), 1.42 (s, 9H), 1.30-1.27 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.4, 152.9, 144.3, 136.3, 135.8, 134.6, 129.5, 128.0, 127.9, 118.7, 112.2, 112.0, 55.9, 34.5, 29.8, 27.6, 22.8, 22.6, 19.1; IR (film) 3545, 2959, 1610, 1461, 1437, 1399, 1388, 1362, 1338, 1266, 1194, 1175, 1143, 1111, 1088, 1041, 908, 851, 779, 763, 732 cm^{-1} ; HRMS (EI-TOF) $m/z = 328.2038$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$ $[\text{M}]^+$, found 328.2038 (same as calcd).

5'-(*tert*-Butyl)-5-methoxy-2',3-dimethyl-[1,1'-biphenyl]-2,4'-diol (6e-v). Using procedure B, 2-methyl-4-methoxyphenol (69.0 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a tan solid in 54% yield (81.0 mg, 271 μmol): $R_f = 0.12$ (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.10 (s, 1H), 6.72 (d, $J = 2.9$ Hz, 1H), 6.64 (s, 1H), 6.52 (d, $J = 3.0$ Hz, 1H), 4.90 (s, 1H), 4.56 (s, 1H), 3.76 (s, 3H), 2.29 (s, 3H), 2.08 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.3, 152.7, 145.3, 136.3, 134.6, 129.4, 127.9, 127.8, 125.1, 118.7, 116.0, 113.0, 55.9, 34.5, 29.8, 19.2, 16.6; IR (film) 3505, 3400, 2918, 1609, 1510, 1471, 1440, 1399, 1388, 1363,

1339, 1255, 1192, 1173, 1154, 1099, 1052, 854, 771 cm^{-1} ; HRMS (EI-TOF) m/z = calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$ $[\text{M}]^+$, found 300.1725.

5-(*tert*-Butyl)-5'-methoxy-2-methyl-[1,1':3',1''-terphenyl]-2',4'-diol (6e-x). Using procedure B, 2-phenyl-4-methoxyphenol (100 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a white solid in 62% yield (112.0 mg, 309 μmol): R_f = 0.09 (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.16 (s, 1H), 6.89 (d, J = 3.1 Hz, 1H), 6.71 (d, J = 3.1 Hz, 1H), 6.64 (s, 1H), 4.84 (s, 1H), 4.76 (s, 1H), 3.81 (s, 3H), 2.14 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 156.2, 153.8, 145.7, 140.0, 136.3, 134.2, 131.6, 131.5, 130.3, 129.6, 128.94, 128.85, 127.6, 118.7, 116.4, 115.4, 55.9, 34.9, 30.0, 19.5; IR (film) 3520, 2955, 1463, 1428, 1398, 1387, 1359, 1343, 1258, 1199, 1175, 1120, 1046, 854, 786, 769, 753 745, 581 cm^{-1} ; HRMS (EI-TOF) m/z = 362.1883 calcd for $\text{C}_{24}\text{H}_{26}\text{O}_3$ $[\text{M}]^+$, found 362.1883 (same as calcd).

5'-(*tert*-Butyl)-3-methoxy-2',5-dimethyl-[1,1'-biphenyl]-2,4'-diol (6e-y). Using procedure B, 2-methoxy-4-methylphenol (69.0 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a yellow oil in 30 % yield (45.0 mg, 150 μmol , 92% brsm): R_f = 0.06 (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.10 (s, 1H), 6.70 (s, 1H), 6.58 (s, 2H), 5.43 (s, 1H), 4.82 (s, 1H), 3.92 (s, 3H), 2.33 (s, 3H), 2.12 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.6, 146.4, 140.6, 135.7, 133.5, 129.4, 129.1, 128.9, 128.1, 123.7, 118.1, 110.7, 56.1, 34.4, 29.9, 21.3, 19.4; IR (film) 3510, 2955, 1486, 1463, 1399, 1388, 1316, 1256, 1215, 1182, 1152, 1125, 1063, 732 cm^{-1} ; HRMS (EI-TOF) m/z = 300.1725 calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$ $[\text{M}]^+$, found 300.1730.

5'-(*tert*-Butyl)-3,5-dimethoxy-2'-methyl-[1,1'-biphenyl]-2,4'-diol (6e-z). Using procedure B, 2,4-dimethoxyphenol (77.0 mg, 500 μmol , 1.00 equiv) was coupled with 2-*tert*-butyl-5-methylphenol (82.0 mg, 500 μmol , 1.00 equiv) to afford a yellow oil in 25% yield (38.0 mg, 123 μmol , 57% brsm): R_f = 0.03 (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.11 (s, 1H), 6.60 (s, 1H), 6.51 (d, J = 2.8 Hz, 1H), 6.30 (d, J = 2.8 Hz, 1H), 5.17 (s, 1H), 4.76 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 2.13 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 152.8, 147.2, 137.1, 135.8, 133.6, 129.5, 129.0, 128.0, 118.2, 106.5, 98.5, 56.2, 55.9, 34.4, 29.8, 19.3; IR (film) 3454, 2956, 1613, 1465, 1426, 1400, 1388, 1203, 1153, 1061, 786 cm^{-1} ; HRMS (EI-TOF) m/z = 316.1675 calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4$ $[\text{M}]^+$, found 316.1676.

3-(*tert*-Butyl)-5'-isopropyl-5-methoxy-2'-methyl-[1,1'-biphenyl]-2,4'-diol (6f-u) Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 2-*iso*-propyl-5-methylphenol (75.1 mg, 500 μ mol, 1.00 equiv) to afford a yellow oil in 85% yield (140 mg, 426 μ mol): R_f = 0.23 (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.08 (s, 1H), 6.89 (d, J = 3.1 Hz, 1H), 6.72 (s, 1H), 6.52 (d, J = 3.0 Hz, 1H), 4.74 (s, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 3.19 (septet, J = 6.9 Hz, 1H), 2.06 (s, 3H), 1.42 (s, 9H), 1.27-1.24 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 152.4, 145.7, 137.2, 136.3, 132.9, 129.1, 128.50, 128.48, 117.4, 113.4, 112.0, 55.9, 35.1, 29.6, 27.1, 22.8, 22.7, 19.3; IR (film) 3525, 3362, 2959, 1435, 1405, 1325, 1247, 1221, 1208, 1179, 1164, 1142, 1052, 1024, 848 cm^{-1} ; HRMS (EI-TOF) m/z = 328.2038 calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$ $[\text{M}]^+$, found 328.2047.

3-(*tert*-Butyl)-5-methoxy-2',5'-dimethyl-[1,1'-biphenyl]-2,4'-diol (6g-u) Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 2,5-dimethylphenol (61.0 mg, 500 μ mol, 1.00 equiv) to afford a tan oil in 71% yield (106 mg, 353 μ mol 92% brsm): ^1H NMR (400 MHz, CDCl_3) δ 7.03 (s, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.74 (s, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.01 (br s, 1H), 4.72 (s, 1H), 3.77 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H), 1.42 (s, 9H). Spectral data were in agreement with those reported [J. Am. Chem. Soc. **2017**, 139, 13404–13413].

3-(*tert*-Butyl)-5-methoxy-2',3'-dimethyl-[1,1'-biphenyl]-2,4'-diol (6h-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 2,3-dimethylphenol (61.0 mg, 500 μ mol, 1.00 equiv) over 24 h to afford a tan resin in 57% yield (85.0 mg, 283 μ mol 86% brsm): ^1H NMR (400 MHz, CDCl_3) δ 7.00 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.02 (br s, 1H), 4.67 (s, 1H), 3.76 (s, 3H), 2.24 (s, 3H), 2.07 (s, 3H), 1.42 (s, 9H). Spectral data were in agreement with those reported [J. Am. Chem. Soc. **2017**, 139, 13404–13413].

3-(*tert*-Butyl)-5-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-2,4'-diol (6i-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 3,5-dimethylphenol (61.0 mg, 500 μ mol, 1.00 equiv) over 24 h to afford a clear resin in 52% yield (77.0 mg, 283 μ mol 86% brsm): ^1H NMR (500 MHz, CDCl_3) δ 6.87 (d, J = 3.0 Hz, 1H), 6.66 (s, 2H), 6.40 (d, J = 3.0 Hz, 1H), 4.66 (s, 1H), 4.51 (s, 1H), 3.75 (s, 3H), 2.01 (s, 6H), 1.40 (s, 9H). The *ortho-ortho* product, **3-(*tert*-butyl)-5-methoxy-4',6'-dimethyl-[1,1'-biphenyl]-2,2'-diol (6i'-u)**, was also collected as a clear resin in 9% yield (14 mg, 45.0 μ mol): ^1H NMR (500 MHz, CDCl_3) δ 6.96 (d, J = 2.9 Hz, 1H), 6.75 (m, 2H), 6.51 (d, J = 3.0 Hz, 1H), 4.84 (s, 1H), 4.72 (s, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.04 (s, 3H), 1.41 (s, 9H). Spectral data were in agreement with those reported [*J. Am. Chem. Soc.* **2017**, 139, 13404–13413].

3-(*tert*-Butyl)-5-methoxy-2',3',6'-trimethyl-[1,1'-biphenyl]-2,4'-diol (6j-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 2,3,5-trimethylphenol (68.0 mg, 500 μ mol, 1.00 equiv) to afford a yellow oil in 60% yield (94.0 mg, 300 μ mol, 90% brsm): R_f = 0.14 (10 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.89 (d, J = 3.0 Hz, 1H), 6.63 (s, 1H), 6.41 (d, J = 3.0 Hz, 1H), 4.92 (s, 1H), 4.55 (s, 1H), 3.76 (s, 3H), 2.20 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.6, 152.7, 145.6, 138.5, 137.2, 136.4, 127.8, 127.7, 120.9, 114.7, 113.1, 111.6, 55.8, 35.1, 29.5, 20.3, 17.3, 12.0; IR (film) 3517, 3404, 2954, 1434, 1405, 1322, 1298, 1250, 1209, 1157, 1038, 1056, 1034, 852 cm^{-1} ; HRMS (EI-TOF) m/z = 314.1882 calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$ $[\text{M}]^+$, found 314.1888.

3-(*tert*-Butyl)-5-methoxy-2',3',5'-trimethyl-[1,1'-biphenyl]-2,4'-diol (6k-u). Using procedure B, 2-*tert*-butyl-4-methoxyphenol (90.1 mg, 500 μ mol, 1.00 equiv) was coupled with 2,3,6-trimethylphenol (68.0 mg, 500 μ mol, 1.00 equiv) to afford a yellow oil in 60% yield (94.0 mg, 300 μ mol, 80% brsm): R_f = 0.15 (10 % EtOAc in hexanes): ^1H NMR (400 MHz, CDCl_3) δ 6.92 (s, 1H), 6.88 (d, J = 3.0 Hz, 1H), 6.50 (d, J = 3.0 Hz, 1H), 4.72 (s, 1H), 4.69 (s, 1H), 3.75 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.4, 152.3, 145.7, 137.1, 135.2, 130.2, 129.1, 128.1, 123.0, 121.0, 113.3, 111.9, 55.8, 35.1, 29.6, 16.8, 15.9, 12.4; IR (film) 3434, 2950, 1469, 1432, 1211, 1052, 777 cm^{-1} ; HRMS (EI-TOF) m/z = 314.1882 calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$ $[\text{M}]^+$, found 314.1882 (same as calcd).

2',4',5'-Trimethoxy-3,5-dimethyl-[1,1'-biphenyl]-2-ol (6l-c). Using procedure B, 2,4-dimethylphenol (61.0 mg, 500 μmol , 1.00 equiv) was coupled with 1,2,4-trimethoxy benzene (74.6 μL , 500 μmol , 1.00 equiv) to afford a tan solid in 38% yield (54.0 mg, 187 μmol , 77% brsm): R_f = 0.50 (20 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.98 (s, 1H), 6.89 (s, 1H), 6.84 (s, 1H), 6.65 (s, 1H), 6.19 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.62, 149.57, 149.52, 144.3, 131.1, 129.5, 128.9, 126.0, 125.3, 119.0, 115.4, 98.4, 57.5, 56.5, 56.2, 20.6, 16.5; IR (film) 3479, 2921, 1518, 1466, 1435, 1393, 1204, 1175, 1029, 854, 769 cm^{-1} ; HRMS (EI-TOF) m/z = 288.1362 calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4$ $[\text{M}]^+$, found 288.1373.

3-Ethyl-2',4',5'-trimethoxy-5,6-dimethyl-[1,1'-biphenyl]-2-ol (6l-h). Using procedure B, 2-ethyl-4,5-dimethylphenol (61.0 mg, 500 μmol , 1.00 equiv) was coupled with 1,2,4-trimethoxy benzene (74.6 μL , 500 μmol , 1.00 equiv) to afford a tan solid in 38% yield (77% brsm) (54.0 mg, 187 μmol): R_f = 0.55 (20 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.98 (s, 1H), 6.69 (s, 2H), 4.78 (s, 1H), 3.98 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.70-2.63 (m, 2H), 2.25 (s, 3H), 1.94 (s, 3H), 1.26 (t, J = 7.52, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.8, 149.7, 149.0, 143.7, 133.5, 129.9, 127.8, 127.0, 124.2, 115.3, 115.1, 98.3, 56.7, 56.5, 56.2, 23.1, 19.9, 16.9, 14.3; IR (film) 3485, 2935, 1506, 1456, 1204, 1168, 1040, 1027 cm^{-1} ; HRMS (EI-TOF) m/z = 316.1675 calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4$ $[\text{M}]^+$, found 316.1678.

3-(tert-butyl)-2',4',5,5'-tetramethoxy-[1,1'-biphenyl]-2-ol (6l-u). Using procedure B, phenol 2-tert-butyl-4-methoxyphenol (93.0 mg, 500 μmol , 1.00 equiv) was coupled with 1,2,4-trimethoxy benzene (74.6 μL , 500 μmol , 1.00 equiv) to afford a brown solid in 85% yield (147.0 mg, 425 μmol): ^1H NMR (400 MHz, CDCl_3) δ 6.92 (d, J = 3.0 Hz, 1H), 6.86 (s, 1H), 6.65 (s, 2H), 6.07 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 1.45 (s, 9H). Spectral data were in agreement with those reported [*Eur. J. Org. Chem.* **2017**, 2194-2204].

2',4',5,5'-Tetramethoxy-3-methyl-[1,1'-biphenyl]-2-ol (6l-v). Using procedure B, 2-methyl-4-methoxyphenol (69.0 mg, 500 μ mol, 1.00 equiv) was coupled with 1,2,4-trimethoxy benzene (74.6 μ L, 500 μ mol, 1.00 equiv) to afford a brown solid in 92% yield (140.0 mg, 460 μ mol): ^1H NMR (400 MHz, CDCl_3) δ 6.86 (s, 1H), 6.75 (d, $J = 2.7$ Hz, 1H), 6.66 (s, 2H), 6.11 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 2.32 (s, 3H). Spectral data were in agreement with those reported [*Eur. J. Org. Chem.* **2017**, 2194-2204].

5-(tert-Butyl)-2',4',5'-trimethoxy-3-methyl-[1,1'-biphenyl]-2-ol (6l-aa). Using procedure B, 2-methyl-4-tert-butylphenol (82.0 mg, 500 μ mol, 1.00 equiv) was coupled with 1,2,4-trimethoxy benzene (74.6 μ L, 500 μ mol, 1.00 equiv) to afford a white solid in 32% yield (53.0 mg, 161 μ mol, 80% brsm): $R_f = 0.55$ (20 % EtOAc in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.19 (d, $J = 2.0$ Hz, 1H), 7.10 (d, $J = 2.3$ Hz, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 6.21 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.34 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.7, 149.6, 149.5, 144.2, 143.0, 127.5, 125.5, 125.4, 124.8, 119.3, 115.8, 98.3, 57.3, 56.6, 56.2, 34.1, 31.7, 16.8; IR (film) 3430 (br), 2955, 1508, 1484, 1460, 1440, 1336, 1250, 1222, 1202, 1172, 1161, 1027, 822 cm^{-1} ; HRMS (EI-TOF) $m/z = 330.1831$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4$ $[\text{M}]^+$, found 330.1817.

Para-Substituted Phenol Homo-coupling

Methyl acetyl-L-tyrosinate (1cc). Compound 1cc was generated following a literature protocol in 57% yield (1.87 g, 7.89 mmol): ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 7.00 (d, $J = 8.2$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 2H), 4.58 (m, 1H), 3.67 (s, 3H), 3.02 (dd, $J = 13.9, 5.7$ Hz, 1H), 2.85 (dd, $J = 13.9, 8.6$ Hz, 1H), 1.91 (s, 3H). Spectral data were in agreement with those reported [*Org. Biomol. Chem.*, 2009, **7**, 3119–3127].

General procedure for the photooxidative coupling of 4-substituted phenols (Procedure C).

To an 8 mL glass vial with an open top cap charged with phenol **1** (500 μmol , 1.00 equiv), 4,4'-di-*tert*-butylbiphenyl (33.4 mg, 125 μmol , 0.25 equiv), and $\text{Ru}(\text{bpz})_3(\text{PF}_6)$ (8.7 mg, 125 μmol , 0.02 equiv) was added solvent (1.0 mL) at rt. The atmosphere was removed and replaced with O_2 (3 x). After irradiating with stirring for 12 h with blue LEDs, the solvent was removed and the compound chromatographed.

5,5'-Dimethyl-[1,1'-biphenyl]-2,2'-diol (2bb) Using procedure C, 4-methylphenol (54 mg, 500 μmol , 1.00 equiv) was homo-coupled in 12 h. Chromatography (10 % EtOAc in hexanes) afforded a yellow resin in 28% yield (15 mg, 70 μmol , 41 % brsm): ^1H NMR (400 MHz, CDCl_3) δ 7.11 (d, $J = 8.3$ Hz, 2H), 7.06 (s, 2H), 6.92 (d, $J = 8.2$ Hz, 2H), 5.38 (s, 2H), 2.32 (s, 3H). Spectral data were in agreement with those reported [*Green Chemistry*, **2014**, 16(5), 2807-2814].

Dimethyl 3,3'-(6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)(2*S*,2'*S*)-bis(2-acetamidopropanoate) (2cc) Using procedure C, **1cc** (119 mg, 500 μmol , 1.00 equiv) was homo-coupled over 12 h. Chromatography (10-100% EtOAc in hexanes) to afford a yellow resin in 40% yield (73 % brsm) (47.2 mg, 100 μmol): ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 7.06-7.04 (m, 4H), 6.85 (d, $J = 8.0$ Hz, 2H), 4.67-4.63 (m, 2H), 3.70 (s, 6H), 3.11-3.06 (m, 2H), 2.96-2.90 (m, 2H), 1.92 (s, 6H); ^{13}C NMR (100 MHz, $\text{MeOD}-d_4$) δ 172.3, 171.8, 152.8, 132.1, 129.0, 128.1, 125.9, 116.0, 54.2, 51.3, 36.3, 20.9; IR (film) 3283 (br), 2953, 1739 (s), 1659 (s), 1540, 1221 cm^{-1} . HRMS (EI-TOF) $m/z = 473.1924$ calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}]^+$, found 473.1931.

General Procedure for High Throughput Experimentation (HTE)

The following procedure is a representative of the HTE screening. The solutions of catalysts (0.125 μmol , 50 μL) in $\text{ClC}_2\text{H}_4\text{Cl}$ were dosed into the 96-well plate reactor vials and the solvent evaporated overnight under an N_2 atmosphere. Solutions of phenol (25 μmol , 50 μL) and 4,4'-di-*tert*-butylbiphenyl (6.25 μmol , 50 μL) in solvent were dosed into the 96-well plate reactor vials. The reaction plate was then purged and continuously back-filled with oxygen using a desiccator fixed with a T-valve for 3-5 min. The plate was

sealed and stirred at 35 °C for 12 h while being irradiated with blue LEDs. After cooling to ambient temperature, the vials were diluted with a solution of biphenyl (2.5 μmol, 500 μL) in MeCN and then sealed. The contents were shaken for 15 min. A centrifuge was then used to force the insoluble matter to the bottom of the reaction vial. To a separate 96-well LC plate with 1 mL vials were added 700 μL of MeCN, and then 40 μL of the diluted reaction mixtures. The mixture was then analyzed using Agilent Chemstation on an UPLC -MS modified with a 96-well plate auto-sampler. Acquity X-Select C18 2.4 μm; 50mm x 2.1mm; 1 mL/min; MeCN:H₂O: 0.5% Formic Acid; gradient: 5% MeCN to 99% in 2.40 mins; Detection wavelength: 191-400 nm. ESI pos/neg; nebulizer: 700 L/hr; cone gas: 30 L/hr; source 150 °C; desolvation 450 °C. Area ratios are based on total wavelength chromatograph (TWC), which integrates a peak over the range of 191-400 nm.

Retention times (min) of starting material and products for optimization screen (Fig. 1 in manuscript)

1a R_t = 1.32, **2a** R_t = 1.70, **1c** R_t = 1.06, **2c** R_t = 1.36, **1g** R_t = 1.12, **2g** R_t = 1.44, **1u** R_t = 1.22, **2u** R_t = 1.56 biphenyl internal standard R_t = 1.39.

Retention times (min) of starting material and products for tyrosine screen

1cc R_t = 0.78, **2cc** R_t = 0.87 biphenyl internal standard R_t = 1.39.

Table S1. HTE screen results for optimization reaction

		Pdt/IS ratio			
		2- <i>tert</i> -Butyl-4-methoxyphenol	2,4-Dimethylphenol	2,4,5-Trimethylphenol	2- <i>tert</i> -Butyl-4-methylphenol
Photocatalysts	2,7- <i>t</i> -Bu-MesAcr ⁺ BF ₄ ⁻	0.226089162	1.390717085	2.582228119	1.791634698
	MesAcr ⁺ BF ₄ ⁻	0.208822131	1.323476778	1.848257451	1.414756159
	4-(3,6-di- <i>t</i> -bu-Cz)IPN Cat	0.240925587	1.255092935	1.829090642	1.627248342
	4CzIPN	0.15166798	0.659694945	0.446918202	0.398744417
	2,4,6-Triphenylpyrylium BF ₄ ⁻	0.070378834	0.485464438	0.608758351	0.761987107
	Eosin Y	0.094855331	0.300369604	0.177891645	0.141968044
	[Ru(bpy) ₃](PF ₆) ₂	0.263539278	1.121029161	0.100090174	0.038332472
	[Ru(bpm) ₃](PF ₆) ₂	0.450233993	1.625475479	1.548356304	0.818490316
	[Ru(bpz) ₃](PF ₆) ₂	0	0.211874897	0.937575714	0.112427823
	[Ir{dF(Me) ₂ ppy} ₂ (dtbbpy)]PF ₆	0.481541471	1.169308367	2.776294927	1.625922922
	[Ir{dF(CF ₃)ppy} ₂ (dtbpy)]PF ₆	0.536780874	3.098759878	3.152414154	1.460250366
	Ir(ppy) ₃	0.444415973	1.841958571	2.440633193	1.230387468

Table S2. HTE screen results for Tyrosine Coupling

		Tyrosine Pdt/IS ratio			
		<i>i</i> -PrOH	Acetonitrile	Acetone	HFIP
Photocatalysts	2,7- <i>t</i> -Bu-MesAcr ⁺ BF ₄ ⁻	0.056547407	0.149814833	0	0.358079987
	MesAcr ⁺ BF ₄ ⁻	0.035673902	0.088284037	0.038256697	0.2863929
	4-(3,6-di- <i>t</i> -bu-Cz)IPN Cat	0.05603297	0	0.216073136	0
	4CzIPN	0.099565881	0.118540087	0.072433821	0.288307863
	2,4,6-Triphenylpyrylium BF ₄ ⁻	0	0	0	0.784651564

	Eosin Y	0.091240731	0.16177764	0.10094579	0.725593829
	[Ru(bpy) ₃](PF ₆) ₂	0	0.049496915	0	0.50334406
	[Ru(bpm) ₃](PF ₆) ₂	0	0	0	0
	[Ru(bpz) ₃](PF ₆) ₂	0	0.148418897	0.10452353	0.892753455
	[Ir{dF(Me) ₂ ppy} ₂ (dtbbpy)]PF ₆	0.102917308	0.130723699	0.110669424	0.307836102
	(Ir[dF(CF ₃)ppy] ₂ (dtbpy))PF ₆	0.077547464	0.111924931	0.068762599	0.51463928
	Ir(ppy) ₃	0	0.039496277	0.107091866	0

100 MHz ^{13}C NMR Spectrum 2-(2-hydroxypropan-2-yl)-4,5-Dimethylphenol in CDCl_3

500 MHz ^1H NMR Spectrum of **1i** in CDCl_3

125 MHz ^{13}C NMR Spectrum of 1i in CDCl_3

500 MHz ^1H NMR Spectrum of 2-bromo-4,5-dimethylphenol in CDCl_3

100 MHz ^{13}C NMR Spectrum of 1n in CDCl_3

400 MHz ^1H NMR Spectrum of Methyl-*ortho*-*t*-Bu-tyrosinoate in CDCl_3

500 MHz ^1H NMR Spectrum of substrate 2g in CDCl_3

400 MHz ^1H NMR Spectrum of 2h in CDCl_3

500 MHz ^1H NMR Spectrum of substrate 2j in CDCl_3

400 MHz ^1H NMR Spectrum of 1s in $\text{MeOD-}d_4$

400 MHz ^1H NMR Spectrum of 2-isopropyl-4-methoxyphenol in CDCl_3

100 MHz ^{13}C NMR Spectrum of 6d-u in CDCl_3

100 MHz ^{13}C NMR Spectrum of 6e-w in CDCl_3

100 MHz ^{13}C NMR Spectrum of 6l-h in CDCl_3

Cyclic voltammogram of 1u

Cyclic voltammogram of 5e

Cyclic voltammogram for 6e-u

Cyclic voltammogram for 2cc

X-ray Structure Determination of Compound 4cc

Compound **4cc**, C₁₂H₁₄NO₅, crystallizes in the monoclinic space group P2₁ (systematic absences 0k0: k=odd) with a=8.3518(7)Å, b=9.1518(8)Å, c=9.0312(9)Å, β=112.947(3)°, V=635.67(10)Å³, Z=2, and d_{calc}=1.318 g/cm₃. X-ray intensity data were collected on a Bruker D8QUEST [1] CMOS area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073Å) at a temperature of 100K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 1468 frames were collected with a crystal to detector distance of 50.0 mm, rotation widths of 0.5° and exposures of 3 seconds:

scan type	2θ	ω	φ	χ	Frames
ω	12.50	188.87	126.22	54.72	374
ω	12.50	188.87	277.82	54.72	374
φ	13.39	189.33	0.00	54.72	720

Rotation frames were integrated using SAINT [2], producing a listing of unaveraged F² and σ(F²) values. A total of 11093 reflections were measured over the ranges 6.62 ≤ 2θ ≤ 50.754°, -9 ≤ h ≤ 10, -10 ≤ k ≤ 11, -10 ≤ l ≤ 10 yielding 2309 unique reflections (R_{int} = 0.0255). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS [3] (minimum and maximum transmission 0.7251, 0.7452). The structure was solved by direct methods - ShelXT [4]. Refinement was by full-matrix least squares based on F² using SHELXL-2018 [5]. All reflections were used during refinement. The weighting scheme used was w=1/[σ²(F_o²) + (0.0365P)² + 0.1380P] where P = (F_o² + 2F_c²)/3. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0295 and wR2=0.0685 for 2232 observed reflections for which F > 4σ(F) and R1=0.0311 and wR2=0.0692 and GOF =1.103 for all 2309 unique, non-zero reflections and 175

variables. The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.17 and -0.22 e/Å³.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP representation of the molecule with 50% probability thermal ellipsoids displayed.

Figure 1. ORTEP drawing of the title compound with 50% thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 4cc

Empirical formula	C ₁₂ H ₁₄ NO ₅
Formula weight	252.24
Temperature/K	100
Crystal system	monoclinic
Space group	P2 ₁
a	8.3518(7) Å
b	9.1518(8) Å
c	9.0312(9) Å
β	112.947(3)°
Volume	635.67(10) Å ³
Z	2
d _{calc}	1.318 g/cm ³
μ	0.103 mm ⁻¹
F(000)	266.0
Crystal size, mm	0.32 × 0.2 × 0.15
2θ range for data collection	6.62 - 50.754°
Index ranges	-9 ≤ h ≤ 10, -10 ≤ k ≤ 11, -10 ≤ l ≤ 10
Reflections collected	11093
Independent reflections	2309[R(int) = 0.0255]
Data/restraints/parameters	2309/1/175
Goodness-of-fit on F ²	1.103
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0295, wR ₂ = 0.0685
Final R indexes [all data]	R ₁ = 0.0311, wR ₂ = 0.0692
Largest diff. peak/hole	0.17/-0.22 eÅ ⁻³
Flack parameter	0.0(3)

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- [4] SHELXT v2014/4: Sheldrick, G.M., Acta Cryst., A, 71, 3-8 (2015).
- [5] SHELXL-2018/3: Sheldrick, G.M., Acta Cryst., A, 71, 3-8 (2015).
- [6] Olex2: Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., Puschmann, H., J. Appl. Cryst., 42, 339-341 (2009)

Calculated site nucleophilicity data found below. The method used to calculate these parameters can be found in our previous report: *J. Am. Chem. Soc.* **2019**, 141, 25, 10016-10032.

N_i , eV
[charge]

Overall and site-specific nucleophilicities