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Direct Synthesis of Polyaryls by Consecutive Oxidative Cross-Coupling of Phenols with Arenes

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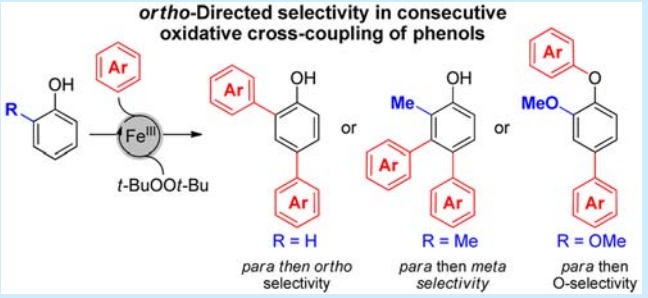
Supporting Information

ABSTRACT: A bioinspired iron-catalyzed consecutive oxidative cross-coupling reaction between a single phenolic unit and nucleophilic arenes was developed. This sustainable transformation offers a selective synthetic strategy for the preparation of complex polyaryl compounds directly from readily available phenols. With the aid of electron paramagnetic resonance spectroscopy, it was demonstrated that the groups *ortho* to the phenolic functionality (whether hydrogen, methyl, or methoxy) direct the regioselectivity (*ortho*, *para*, or *meta* via dienone−phenol rearrangement) and chemoselectivity (C−C coupling or C−O coupling) in this multistep process.

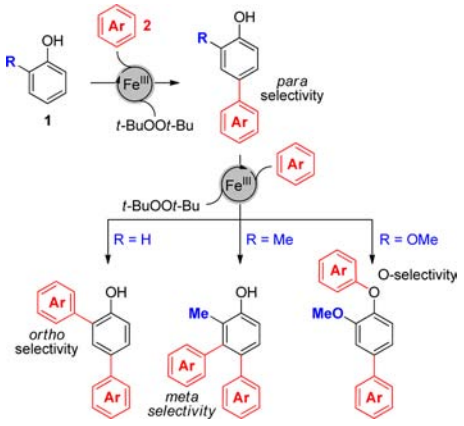


Polyphenols, oligomeric or polymeric compounds consisting of condensed phenolic building blocks,[1] are essential for plant growth and protection[1a,c] and serve as a source of bioactive materials.[2] Their synthesis in the plant kingdom involves a sequence of oxidative coupling events catalyzed by metalloenzymes and controlled by dirigent proteins.[3] In the laboratory, a variety of synthetic strategies and multistep approaches to access phenolic oligomers have been developed over the years.[1a,4] Nonetheless, the number of synthetic steps and, in many cases, the unimpressive overall yields have impeded biological and pharmacological studies.[2c] Therefore, the development of a reliable, selective, and efficient technology for synthesizing polyphenols in sufficient quantities remains an important unmet challenge,[2c,5] one that can perhaps be addressed by taking a bioinspired approach.

The past few years have witnessed the development of selective oxidative cross-coupling reactions between phenols and electron-rich arenes[6] that are based on hypervalent iodine chemistry,[6b,d] electrochemical techniques,[6c,7] or iron catalysis.[8] The reactions probably involve the coupling between phenoxyl radicals and nucleophilic arenes,[9] offering an efficient and direct entry to complex biaryl products. Fluorinated alcohols, such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), play a key role in these processes, as they extend the lifetime of the electrophilic species while diminishing undesirable side reactions such as homocoupling, Friedel−Crafts, or quinone formation reactions.[10] Previously, we have demonstrated that the coupling of 3,5-dimethoxyphenol with 1,3,5-trimethoxybenzene (**2a**, 1.3 equiv) in TFE afforded selectively biaryl Me_5-difucol in 51% isolated yield.[8a] In contrast, in HFIP with excess arene and terminal oxidant a biomimetic consecutive coupling took place to afford triaryl Me_8-fucol in 46% yield.[8a]

Intrigued by these results, we set out to extend this biomimetic reaction (which in nature is limited to phloroglucinols) to unnatural phenols with the aim of offering entry to a novel class of polyaryl products. To this end, a selective iron-catalyzed consecutive oxidative cross-coupling reaction between a single phenolic unit and a number of arenes was developed (Scheme 1). Our structure−selectivity relationship study revealed that the first coupling is taking place at the available *para*/*ortho* positions, while the phenolic *ortho*-groups

Scheme 1. *ortho*-Directed Selectivity in Consecutive Oxidative Cross-Coupling between Phenols and Arenes



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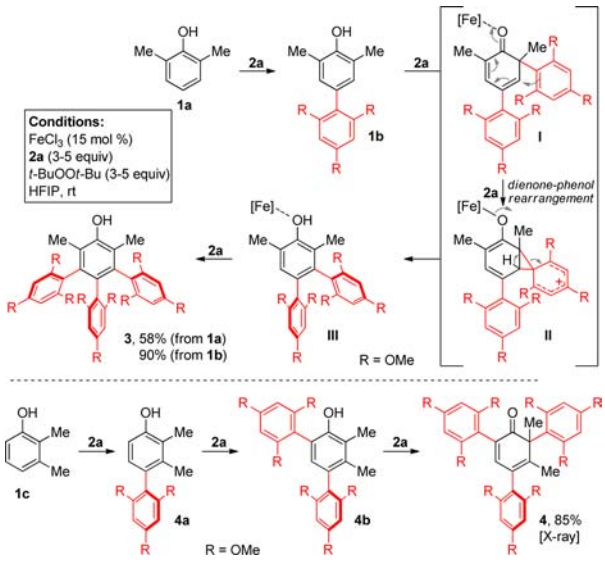
dictate the following coupling chemoselectivity (C−C coupling vs C−O coupling) and regioselectivity (*ortho*, *meta*). On the basis of this study, complex polyaryl compounds that are not accessible by common synthetic methods were prepared.

We began this investigation by studying the relationship between the structure of the phenolic components and their coupling selectivity under our general consecutive oxidative coupling conditions [phenol (1 equiv), arene (3−5 equiv), $FeCl_3$ (15 mol %), *t*-BuOO*t*-Bu (3−5 equiv), HFIP (0.5M), room temperature]. The reactivity of 2,6-dimethylphenol (**1a**) under oxidation conditions has been widely studied.[11] Nevertheless, under our conditions, a previously unreported cross-coupling selectivity was observed, with phenol **1a** undergoing cross-coupling with arene **2a** at both the *para* and the two *meta* positions to afford polyaryl **3** in 58% isolated yield. Since the electrophilic carbon sites in the phenoxyl radical are present at the *para* and *ortho* positions, it is unlikely that direct coupling will take place at the *meta* position (due to mechanistic restrictions). We thus postulated that, following the first *para*-arylation step (biaryl **1b**, Scheme 2), an oxidative addition step

Scheme 2. Consecutive Oxidative Cross-Coupling of *Ortho*-Methylated Phenols 1a and 1c



takes place at the *ipso*-methyl carbon to form a high energy dienone **I** intermediate.[6c] The latter undergoes a dienone−phenol rearrangement (via **II**) to install the aryl group at the neighboring *meta*-position (**III**).[12] Similar aryl migration, which is an acid-catalyzed process, has been proposed for the biosynthesis of various phenolic alkaloids.[13] To the best of our knowledge, this is the first report of such a process in intermolecular oxidative coupling reactions. To confirm the above-described putative order of events, aryl phenol **1b** was prepared by conventional Suzuki coupling (see Supporting Information). The reaction with arene **2a** afforded polyaryl **3** in 90% yield (Scheme 2), supporting the premise that the first coupling is *para* selective. The *ortho* addition step was confirmed by reacting 2,3-dimethylphenol (**1c**), which cannot undergo aryl migration, with arene **2a** (5 equiv) to afford dienone **4** as a single product in 85% yield (Scheme 2). The structure of the latter product was determined by 1D and 2D NMR and confirmed by X-ray diffraction.

Our kinetic studies revealed that the consecutive reactions of isomers **1a** and **1c** with arene **2a** have different kinetic profiles (Figure 1). The oxidative coupling of phenol **1a** (E_{ox} = 0.54 V

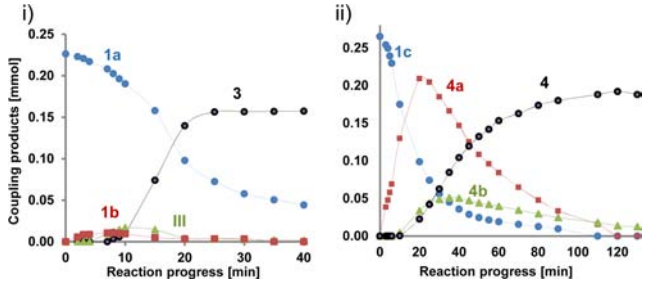
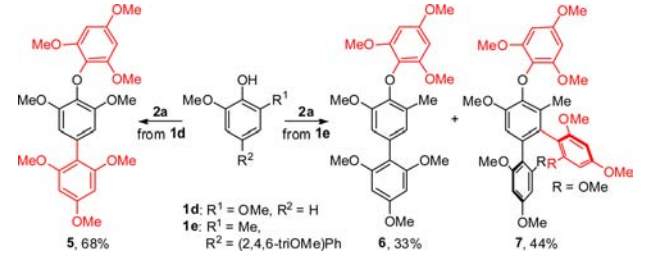


Figure 1. Kinetic profiles of the consecutive oxidative cross-coupling for phenol **1a** (i) and phenol **1c** (ii) with arene **2a**.

in HFIP vs $Ag/AgNO_3$) generates biaryl **1b** (E_{ox} = 0.34 V), which has a lower oxidation potential than its parent phenol and therefore reacts rapidly with a second arene to form compound **III**. The concentrations of **1b** and **III** remain low during the entire process, thus the *rate-determining step* for this consecutive coupling is probably the oxidative coupling of phenol **1a**.[11b,15] In contrast, phenol **1c** (E_{ox} = 0.55 V) has a lower oxidation potential than coupling aryl phenol **4a** (E_{ox} = 0.60 V), and therefore, the concentration of the latter builds up to an appreciable level before it decays, suggesting that the initial reactant is more reactive than the biaryl intermediate **4a**. The fact that the two isomers (**1a** and **1c**) display different kinetic profiles suggests that the consecutive oxidative coupling follows a substrate-controlled mechanism.

Next, we studied the effect of *o*-methoxy group(s) on the multicoupling selectivity. In contrast to the coupling of 3,5-dimethoxyphenol with *o*-hydrogen and *o*-cresol derivatives **1a**−**1c**, the coupling of 2,6-dimethoxyphenol (**1d**) with arene **2a** exhibited a different chemoselectivity (Scheme 3). While the first coupling was *para* selective, the second oxidative coupling took place at the phenolic oxygen atom, affording triaryl ether **5** in 68% yield.[16]

Scheme 3. Consecutive Oxidative Cross-Coupling of 2-Methoxyphenols 1d and 1e (under General Conditions)



To obtain a better understanding of the structure−selectivity relationships for different phenols, an EPR spectroscopy investigation of key phenoxyl radicals was carried out. On the basis of the study of Pedulli and Guerra,[17] persistent phenoxyl radicals **1b-rad**, **1d-rad**, **1e-rad**, and **1f-rad** were generated in situ in the EPR spectrometer by continuous UV photolysis of *t*-BuOO-*t*-Bu in deoxygenated toluene/HFIP (7:3) solutions. The relevant proton hyperfine coupling constants (hfcs, *a*) are given in Figure 2. The EPR studies revealed that in the presence of HFIP the spin-density distributions of phenoxyl

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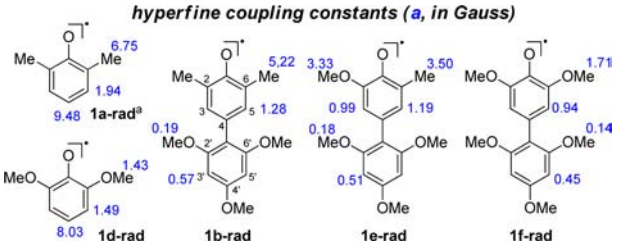

Figure 2. Room-temperature (T = 295 K) hyperfine coupling constants (a, in Gauss) for selected phenoxyl radicals and aryl phenoxyl radicals in a toluene/HFIP (7:3 v/v) mixture. The EPR spectra and hfc values for additional phenols are given in the Supporting Information. (a) Measured in benzene, ref 14.

radicals having *o*-methyl and *o*-methoxy groups are different. The spectra of phenoxyl radical **1d-rad** and aryl phenoxyl radical **1f-rad** showed that much of the electron-spin density is located between the oxygen atoms (the hfcs with the hydrogen of the *o*-methoxy groups are 1.43 and 1.71 G, respectively). In contrast, the large a values that were measured for the H_{meta} in aryl phenoxyl radical **1b-rad** (1.28 G) in comparison to the values observed for aryl phenoxyl radical **1f-rad** (0.94 G) imply that the spin density of phenoxyl radicals with *o*-methyl substituents is located mainly on the ring. The spin density transfer from the phenolic ring to the aryl group in aryl phenoxyl radicals **1b-rad** and **1f-rad** constitutes spectroscopic evidence that the aryl group contributes significantly to the stabilization of the oxidized intermediate. Moreover, the large *a*-values for the *para*-hydrogen atom in phenoxyl radicals **1a−rad** and **1d−rad** (9.48 and 8.03 G, respectively) and the high spin density in aryl phenoxyl radicals **1b−rad** (at C-2,6) and **1f−rad** (at the oxygen atoms) are in agreement with the selectivity that was found for their reactions with arene **2a**.

In light of the above findings, we postulated that EPR spectroscopy can be exploited as a tool to predict the selectivity in the oxidative coupling of substituted phenols. To examine this premise, we synthesized 2′,3,4′,6′-tetramethoxy-5-methyl-[1,1′-biphenyl]-4-ol (**1e**) by a multistep synthesis (see the Supporting Information) and recorded its EPR spectrum. The high a values for the hydrogen atoms of aryl phenoxyl radical **1e−rad** in both the *o*-methyl and *o*-methoxy groups (3.50 and 3.33 G) provided evidence of high spin density at the *ipso*-methyl carbon and at the phenoxyl group. Therefore, it was to be expected that the two coupling modes, namely, C−C and C−O, would compete. Indeed, the reaction of biaryl **1e** under our reaction conditions afforded a mixture of triaryl ether **6** (C−O coupling) and tetraaryl ether **7** (C−C and C−O) in 33% and 44% yields, respectively (Scheme 3).

The scope of the consecutive oxidative cross-coupling reaction was examined, and the relationship between the identity of the *ortho* groups and the coupling selectivity was confirmed (Figure 3). Phenols with hydrogen substitution at the *ortho* positions, such as *p*-cresol and 3,5-dimethylphenols, underwent coupling at the *ortho* and *para* positions to afford biaryls **8** and triaryl **10** in 41% and 35% yields, respectively. The arylations of *o*-cresol took place at C-3, C-4, and C-6 to afford polyaryl **16** in 32% yield. On the other hand, the bulky *tert*-butyl group in 2-*tert*-butylphenol prevented oxidative addition at its *ipso*-carbon, and the triaryl **9** was isolated in 44% yield. To further investigate the aryl migration step, a range of 4-aryl-2,6-dimethylphenols, differing in electronic delocalization across the biaryl bond, were prepared (see the Supporting

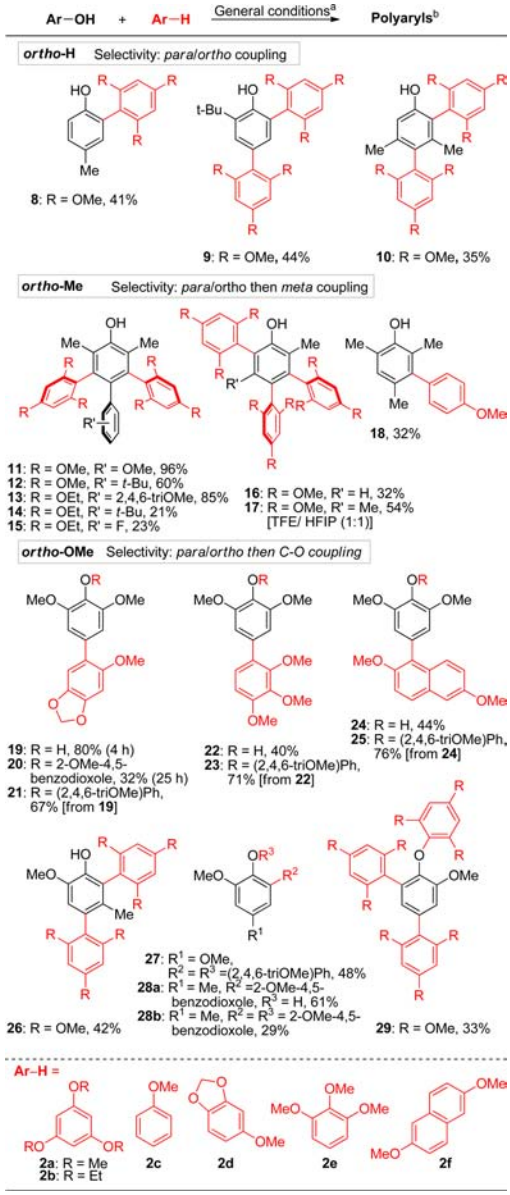

Figure 3. Scope of the consecutive oxidative cross-coupling. (a) General conditions: Ar-OH (1 equiv), Ar-H (3−5 equiv), $FeCl_3$ (15 mol %), *t*-BuOO-*t*-Bu (3−5 equiv), HFIP, rt. (b) Isolated yields.

Information) and reacted with arene **2a** or **2b** to afford polyaryls **11**−**15** as single products in different isolated yields (21%−96%). Other nucleophiles were also examined, and arenes **2c**−**2f** were found to be less reactive than arene **2a**; that is, their reactions with 2,6-dimethoxyphenol (**1d**) were confined with a single oxidative coupling step, affording biaryls **19**, **22**, and **24** in 80%, 40%, and 44% yields, respectively. These three aryl phenols further reacted with arene **2a** to afford triaryl ethers **21**, **23**, and **25** in 67%, 71%, and 76% yields, respectively.

In summary, we have developed a strategy for synthesizing complex polyaryl compounds by a consecutive oxidative cross-coupling reaction between a single phenolic unit and a number of arenes. Our structure−selectivity relationship studies revealed unique regioselectivity and chemoselectivity that derive from the identity of the phenolic *ortho* groups. An EPR study of the key persistent phenoxyl radicals showed a correlation between the distribution of the high spin density, which is a structure-related property, and the coupling

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selectivity. Finally, our biomimetic consecutive oxidative cross-coupling reaction answers the current need[2c] for a reliable, selective and efficient technology for preparing polyaryls and natural polyphenols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02064.

X-ray data for compound **4** (CIF)
Full experimental procedures, characterization data, and NMR spectra (PDF)
EPR experimental data (PDF)

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Notes

The authors declare no competing financial interest.

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