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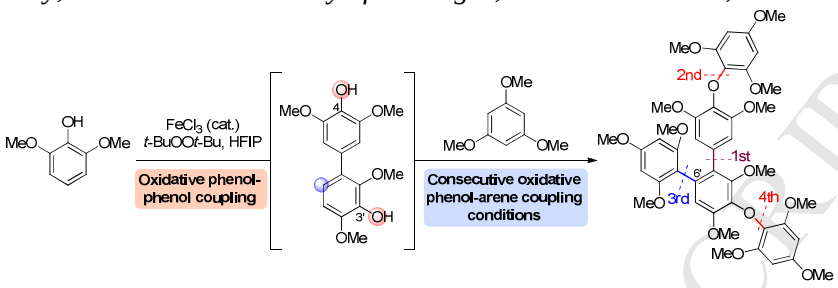

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ABSTRACT

The single-step synthesis of protected fucols and unnatural polyaryls by biomimetic oxidative cross-coupling between phenolic components and 1,3,5-trimethoxybenzene catalyzed by $FeCl_3$ in fluorinated solvents is reported. The regioselectivity (*ortho*, *meta* or *para*) and the chemoselectivity (C─C vs C─O) in this highly efficient transformation are controlled by the phenolic *ortho*-groups of the growing phenolic oligomer. The reaction scope was examined by coupling biphenol derivatives with the nucleophilic arene to afford large polyaryl compounds that are not easily accessible by other means. The versatility of the catalytic system in designing polyaryl frameworks was demonstrated by performing a sequential oxidative phenol-phenol and phenol-arene coupling reaction that afforded a single polyaryl product in high efficiency.

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1. Introduction

Since the historical synthesis of tropinone by Robinson[1,2] in 1917, exactly a century ago, biomimetic syntheses have been recognized as highly efficient and, very often, as the only possible route to complex natural products.[3-6] The success of biomimetic strategies depends mainly on an in-depth mechanistic understanding of the natural processes and on the ability of the synthetic chemist to develop highly selective conditions that imitate the reactions in nature. Of particular interest to us here is the oxidative coupling of phenols, an important biological process that provides plants and algae with a reliable method for preparing diverse chemical architectures from limited number of phenolic units with minimum energy loss. Although these transformations involve the generation of highly reactive radical species, in many cases the selectivity of these processes is enzymatically controlled, which enables highly efficient and stereospecific transformations that produce a single stereoisomer.[7-9]

In the synthesis of complex phenols, it is not always realized that the main advantage of bioinspired transformations is the extension beyond natural products to access new materials that are still unreachable by common synthetic tools. Phlorotannins,[10,11] for example, is a structurally diverse group of polyphenols, for which selective syntheses are still to be developed (Fig. 1). These compounds, which consist of oligomeric and polymeric phloroglucinol units, are produced in the cell walls of brown algae, and as such play a role in UV protection and defense against herbivores.[12] In some cultures, brown algae constitute a part of the human diet[13] and of traditional medicines[14] and are currently held to play extensive biological roles,[15,14,16] exhibiting anti-allergic,[17,13] anti-oxidation,[18] and anti HIV-1[19] activities.

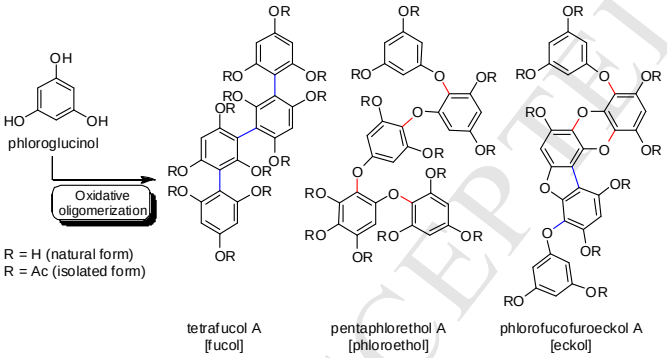
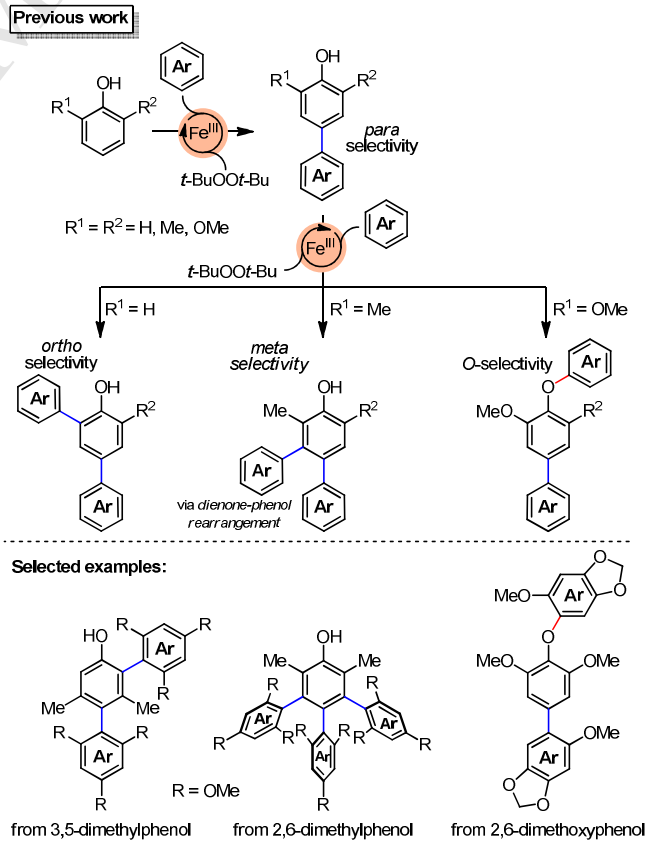


Fig. 1. Selected phlorotannins produced by oxidative oligomerization of phloroglucinol.

The phlorotannins are classified according to their coupling modes, namely, Ar–Ar or Ar–O–Ar. A crude extract of algal powder consists of phlorogluciol and mixtures of phenolic oligomers that have been condensed via biaryl bonds (fucols), diaryl ethers (phlorethols) or dibenzodioxin linkages (eckols).[20] In general, these compounds are sensitive under oxidation, basic and acid-catalyzed conditions and therefore have been isolated in their polyacetylated form (Fig. 1). It is therefore necessary to develop reliable synthetic methods for preparing phlorotannins for biological studies. In view of the complexity of these compounds, it is to be expected that synthetic approaches based on common cross-coupling chemistry[21,22] will not be facile and will require large number of synthetic steps; it is therefore likely that a biomimetic reaction will provide a superior pathway. However, the mechanisms and the factors that affect the selectivity of the oxidative polymerization processes that produce phlorotannins in algae are still unknown.[23] We therefore sought to probe this important process by developing a catalytic system that will serve as a model.

In the laboratory setting, oxidative phenol-phenol and phenol-arene coupling reactions, whether via electrochemical techniques,[24-30] hypervalent iodine chemistry,[31-34] inorganic peroxo compounds[35] or metal catalysis,[36-42] offer atom- and step-economic methods for preparing biaryls with good control over their chemo-, regio- and stereoselectivity. Recently, our group developed a system for selective oxidative coupling of phenols by a catalytic amount of $FeCl_3$ in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP),[33,43-48] in the presence of *t*-BuOO*t*-Bu. Under these general conditions, the selective oxidation of phenols yields phenoxyl radicals that, in turn, react with nucleophilic arenes or second phenolic coupling partners via radical-nucleophile coupling or radical-anion coupling mechanisms, respectively.[49,40,50-54]

As in the case in biological systems, the laboratory-synthesized product of oxidative coupling reactions may often preserve its phenolic unit(s), which expose(s) it to further oxidations. In most cases, these oxidations produce undesirable quinone or catechol side products that affect the overall efficiency of the process. However, under conditions that favor coupling, this process can be exploited as an efficient synthetic tool for preparing complex phenolic frameworks in a single operation.



Scheme 1. *ortho*-Directed consecutive oxidative cross-coupling of phenols and arenes by iron catalysis.

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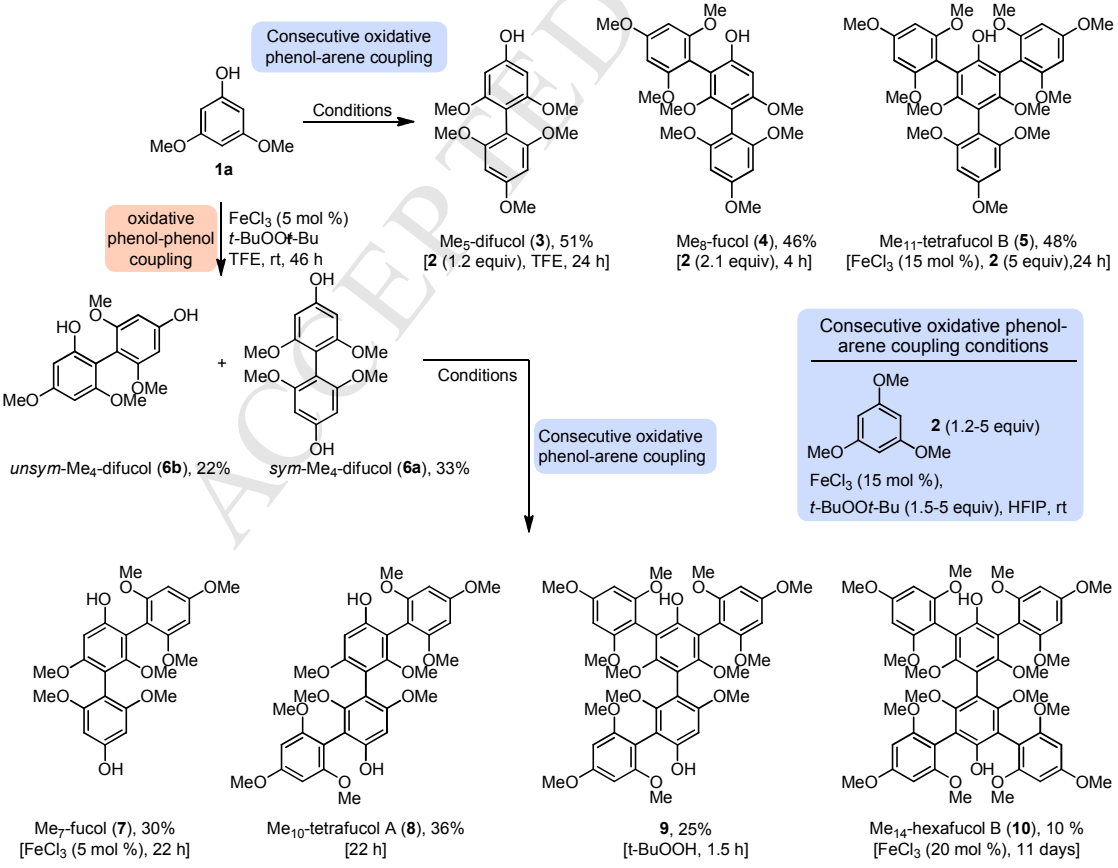
To accommodate this reactivity in target-oriented synthesis, it is necessary to characterize the factors that determine the chemo- and regioselectivity in each of the oxidative coupling steps. To this end, a structure-selectivity relationship study (that included EPR spectroscopy and kinetic studies) was performed by our group (Scheme 1).[55] That study revealed that the first step in the consecutive reaction between substituted phenols and nucleophilic arene is *para*-selective, while the selectivity in the following coupling steps is controlled by the identity of the *ortho*-substituents (R = H, Me or OMe, Scheme 1).[55] To further study the factors that control the selectivity in iron-catalyzed consecutive oxidative arylation of phenols, we set out to examine the reactivity of biphenols that have either two identical or two different phenolic units. Successful coupling of these biphenols opens the door for the preparation of larger and more complex natural and unnatural polyaryls.

In this article, the iron-catalyzed consecutive oxidative arylation of biphenols with phloroglucinol trimethyl ether (**2**, Scheme 2) is reported. This sequential reaction provides a highly selective method for preparing complex polyaryls that are not accessible by other means. In view of our previous observations that the phenolic *ortho*-groups control the regioselectivity and the chemoselectivity during the coupling steps, the scope of the reaction was examined for the preparation of protected phlorotannins and unnatural polyaryls. The power of this technology, which is concealed in obtaining multiple C–C and C–O bonds in a single event, was evaluated for the preparation of polyaryl **16** via one-pot oxidative phenol-phenol and biphenol-arene coupling reactions (scheme 3).

2. Results and discussion

One of the difficulties in developing multi-step processes relies in the ability to identify selective conditions for the production of each of the reaction intermediates. This is not a trivial challenge, as any change in one of the reaction parameters affects the kinetic profile of each of the coupling steps in a different manner. Therefore, we initiated the study by developing the tools that would aid us to identify the conditions for selective synthesis of each phenolic oligomer that is formed during the stages of the oxidative coupling. To achieve this objective, the kinetic profiles of the consecutive oxidative arylation were studied by HPLC, and the oxidation potentials of the phenolic intermediates were measured by cyclic voltammetry. This information was used to follow the progress of each arylation step as function of time under different conditions. With this data in hand, we were able to identify the particular conditions for preparing each phenol oligomer with a high degree of selectivity. For example, in the consecutive oxidative cross-coupling between 3,5-dimethoxyphenol (**1a**) and 1,3,5-trimethoxybenzene (**2**), the phenolic components have relatively high E_{ox} values (0.61 V – 0.82 V; Table 1).[49] Therefore, the rates of the oxidative coupling are relatively slow and selective conditions for preparing all three possible fucol oligomers **3**–**5** were identified (Scheme 2). Our kinetic studies implied that in 2,2,2-trifluoroethanol (TFE) the first arylation step is the rate-determining step, and therefore the concentration of Me_5-difucol **3** was expected to increase at the beginning of the reaction (Fig. 2A). Indeed, when the reaction was carried out in TFE [**2** (1.2 equiv)], arylphenol **3** was isolated in 51% yield.[51]



Scheme 2. Biomimetic oxidative oligomerization of protected fucol natural products. Conditions: phenol **1a** or biphenol **6a** (1 equiv), arene **2**

(1.2-7 equiv), $FeCl_3$ (15 mol %), *t*-BuOO*t*-Bu (1.5-7 equiv), HFIP or TFE (0.5 M), room temperature.

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Table 1. Oxidation potentials of selected compounds in HFIP.

Entry	Compound	E_{ox} [V][a]
1	**1a**	0.69
2	**3**	0.61
3	**4**	0.73
4	**5**	0.82
5	**6a**	0.57
6	**6b**	0.62
7	**7**	0.57
8	**8**	0.71
9	**9**	0.71

[a]Cyclic voltammetry conditions: Phenol (3 mM), supporting electrolyte: tetrabutylammonium hexafluorophosphate (50 mM) in HFIP (5 mL) vs. Ag/0.01 M $AgNO_3$ in 0.1 M TBAP/CH_3CN, 50 mV s^{-1}.

The importance of HFIP in oxidative coupling reactions of phenols has been studied by number of groups,[26,27,34,32,29,33,56,57] including our group,[51,58,49] who demonstrated that HFIP has a significant acceleration effect in iron-catalyzed cross-dehydrogenative coupling (CDC) reactions[59-65] of phenols. Indeed, when the above reaction was carried out in HFIP (Fig. 2B), complete consumption of phenol **1a** was observed in 30 min (versus 80 min in TFE). Moreover, in this solvent, the coupling product arylpenol **3** (E_{ox} = 0.61 V, Table 1, entry 2) had a lower oxidation potential than the parent phenol **1a** (E_{ox} = 0.69, entry 1), and therefore it immediately reacted with a second arene unit, affording Me_8-fucol **4**. The oxidative coupling of the latter product **4** became the rate-determining step in HFIP, as it has the highest oxidation potential (E_{ox} of **4** = 0.73 V, entry 3). Product **4** was obtained in 46% yield when the reaction was limited to 4 h and 2.1 equiv of arene (Scheme 2).[51] To drive the third arylation step, higher loading of the iron catalyst (25 mol %), excess of arene (5 equiv) and prolonged reaction time were needed (Fig. 2C) affording Me_{11}-tetrafucol **5** in 48% (Scheme 2).

After establishing the methodology to optimize consecutive oxidative arylation of phenols, we went on to examine the reactivity of biphenols, since these compounds provide further opportunities for synthesizing large and more structurally complex polyaryls. Symmetrical Me_4-difucols **6a** and unsymmetrical Me_4-difucols **6b** (Scheme 2) were obtained in 33% and 22% yields, respectively, by the self-coupling of phenol **1a** [$FeCl_3$ (10 mol %), *t*-BuOO*t*-Bu, TFE, rt] under modified oxidative phenol-phenol coupling conditions (Scheme 2).[49] In theory, the consecutive oxidative cross-coupling reactions of arylphenols **6a** and **6b** with arene **2** could yield, respectively, either five or eleven different oligomers of different sizes. Indeed, as observed by HPLC analysis, the reaction of **6b** with arene **2** was not selective, and HPLC analysis revealed a complex reaction mixture. Despite intensive attempts, we were unable to achieve satisfying selectivity in this reaction. In contrast, the consecutive oxidative arylation of symmetrical biphenol **6a** with arene **2** was much more selective, and four (**7**, **8**, **9** and **10**, Scheme 2) out of the five possible oligomeric products were identified by HPLC and later isolated. The kinetic profile of this reaction suggested that the slow coupling steps are the second and the third arylations and the kinetics of the subsequent steps became much slower as the molecular structure grew (Fig. 2D). This observation was supported by the oxidation potential values of polyaryls **6a**, **7**, **8** and **9** (Table 1, entries 5, 7-9). On the basis of the kinetic profile, we were able to identify different conditions for obtaining oligomers **7**–**10**, yet in only moderate selectivity. When the iron-catalysed consecutive oxidative cross-coupling of biphenol **6a** was performed with a low loading of catalyst (5 mol %), Me_7-fucol (**7**) was isolated in only 30% yield. However, by increasing the loading of the redox catalyst ($FeCl_3$ 15 mol %), the second arylation took place, and Me_{10}-tetrafucol A[15,16] (**8**) was afforded in 36% yield. Under harsher reaction conditions that involved the use of *t*-BuOOH instead of *t*-BuOO*t*-Bu [$FeCl_3$ (5 mol %), 1.5 h], the third coupling step took place, affording polyphenol **9** in 25% yield, while the use of higher loading of the redox catalyst (20 mol %), excess of arene (7 equiv) and prolonged reaction time (11 days) afforded hexafucol B (**10**)[66] in 10% yield. Because of the structural similarity of compounds **7**–**10**, their separation from the reaction mixture by silica-gel chromatography is not a trivial task. Therefore, to obtain pure samples of the products, it was necessary to use preparative HPLC separation. Importantly, this work demonstrates that by changing between only four of the reaction parameters, namely, the loading of the redox catalyst, the oxidant type, the fluorinated alcohol solvent and the reaction time duration, it was possible to access a large number of fucol products. Unfortunately, our initial attempts to remove the protecting groups by common methods were unsuccessful, probably as result of the instability of the polyphenols in their free phenolic form, as discussed earlier.

An added – sometimes concealed – value in developing biomimetic catalytic system lies in the ability of the chemist to expand the use of the evolved chemistry, beyond naturally occurring substrates, to devise new synthetic opportunities to produce unique materials with novel properties. To exploit the knowledge acquired, we therefore instituted an examination of the consecutive oxidative cross-coupling reaction between unnatural biphenol derivatives and arenes. This reaction provides direct entry to large polyaryls that are not easily accessible by other means. The first step was to examine the factors that affect the selectivity in the reaction of biphenols according to the principles that were identified for substituted phenols (Scheme 1 and Fig. 3A).[55] For that purpose, a series of biphenols, including 4,4'-biphenol **11a** and compounds **11b**-**11g** (Fig. 3A), which had been prepared in a single step by iron- catalyzed oxidative phenol-phenol cross-coupling,[49] were reacted with arene **2** under our general conditions.

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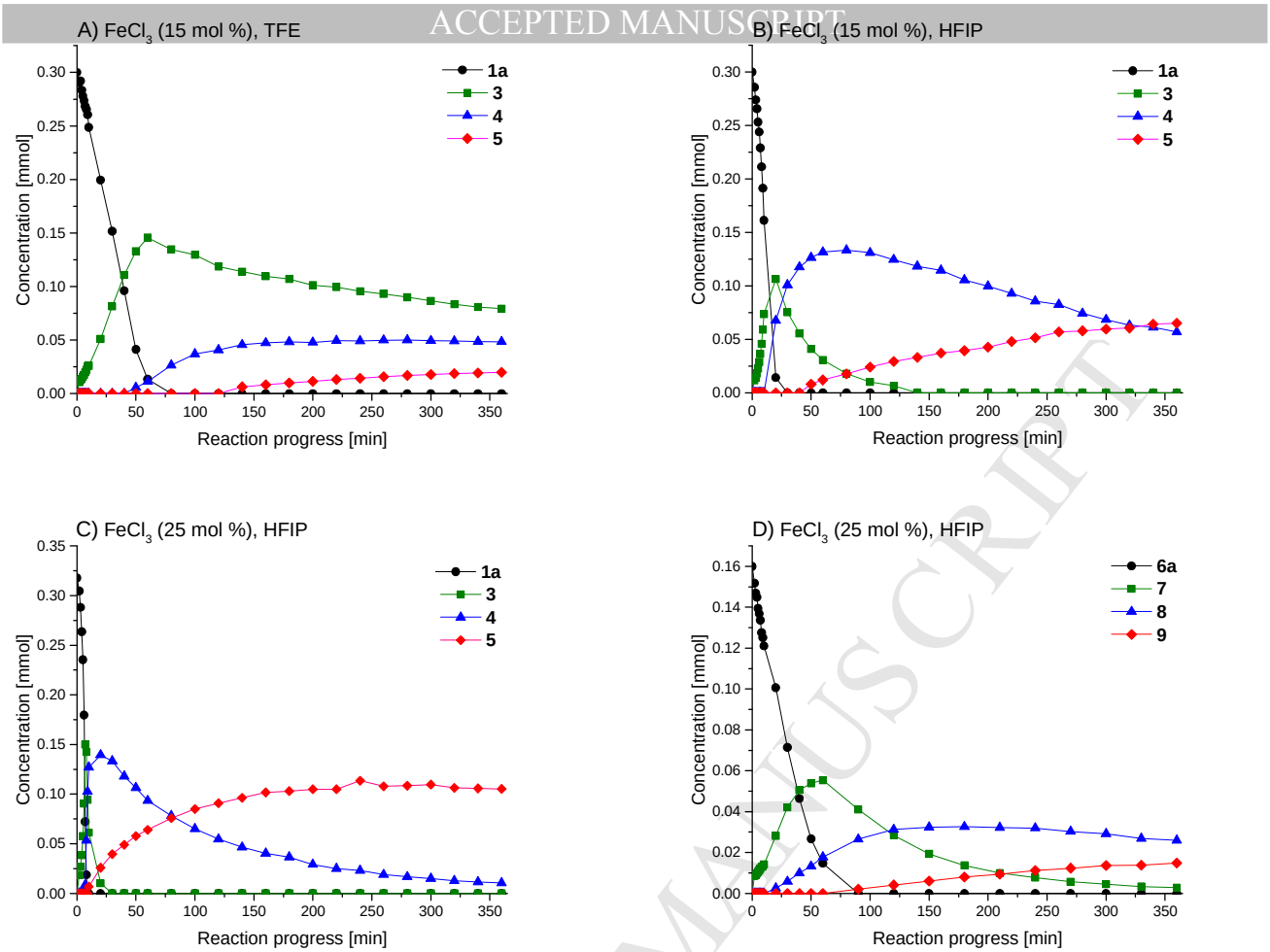

Fig. 2. Progress of the consecutive oxidative cross-coupling of phenol **1a** (A–C) or biphenol **6a** (D) with arene **2** under different reaction conditions. Conditions: A) phenol **1a** (1 equiv), arene **2** (5 equiv), $FeCl_3$ (15 mol %), *t*-BuOO*t*-Bu (5 equiv), TFE (0.5 M), room temperature; B) similar to A except HFIP instead of TFE; C) similar to A except $FeCl_3$ (25 mol %) and HFIP instead of TFE; D) biphenol **6a** (1 equiv), arene **2** (5 equiv), $FeCl_3$ (25 mol %), HFIP (0.5 M), room temperature. The reaction progress was analyzed by HPLC, with mesitylene as the internal standard.

The oxidative coupling of **11a** (four *ortho*-H groups, Fig. 3B) under our general conditions was sluggish and suffered from low conversion. Under these conditions [arene **2** (5 equiv), $FeCl_3$ (15 mol %), *t*-BuOO*t*-Bu (5 equiv), HFIP, 40 ^{o}C, 48 h], (3,3',5,5'-tetraaryl)biphenol **12** was isolated in a poor 18% yield. Replacing the terminal oxidant with *t*-BuOOH solved the conversion problem, yet, under the modified conditions product **12** was obtained together with its corresponding diphenoquinone by-product. The addition of a reduction step ($NaBH_4$) at the end of the process was rewarding, and polyaryl **12** was obtained in 70% yield, meaning that the average yield for the four coupling steps was 92%. Symmetrical biphenol **11b** (four *ortho*-OMe groups, Fig. 3) reacted, as expected, at the oxygen atoms of the 4 and 4'-phenolic groups to afford polyaryl **13** in 63% yield. On the other hand, the arylation of biphenol **11c**, which has two *ortho*-methoxy groups on one ring and two *ortho*-methyl groups on the second ring, took place at the oxygen atom of the 4-OH and the 2' and 6' *meta*-positions (*via dienone-phenol rearrangement*), affording polyaryl **14** in 46% yield. These results provided experimental evidence that biphenols follow a similar regio- and chemoselectivity trend to that of phenols and (4-aryl)phenols (Scheme 1),[55] suggesting that each *ortho*-group directs the selectivity only on its own phenolic ring and has no effect on the coupling of the second phenolic unit.

Further studies revealed that two non-equivalent phenolic units, as in biphenol **11d**, exhibit different coupling rates. The first oxidative cross-coupling of **11d** with arene **2** was highly selective at the oxygen atom of the 4-OH group (Fig. 3). The position of this phenolic group *para* to the biaryl bond provided the electronic requirement for the *O*-arylation, affording product **15** in 72% yield. Furthermore, the coupling at the 3'-OH group, which was found in the *meta*-position to the biaryl bond, was much slower and occurred only, but readily, after the arylation at the 6' position had taken place (40 ^{o}C), affording product polyaryl **16** in 56% yield. In our previous publication,[55] the unusual *meta*-coupling selectivity that had been observed for phenols with *ortho*-methyl substituents (Scheme 1) was explained by a two-step mechanism that involves oxidative coupling at the *ortho-ipso*-methyl carbon to generate a high-energy dienone intermediate, which undergoes a *dienone−phenol rearrangement*. This process directs the aryl group to the *meta*-position of the phenol. However, when the *meta*-position is blocked, as in biphenols **11e** and **11f**, the aryl migration is prevented, and therefore dienones **19** and **20** were obtained in 47% and 33% yields, respectively. Finally, the formation of polyaryl **21** from biphenol **11g** is an example that this rearrangement also takes place from the *para-ipso*-methyl group to the neighboring *meta*-position.

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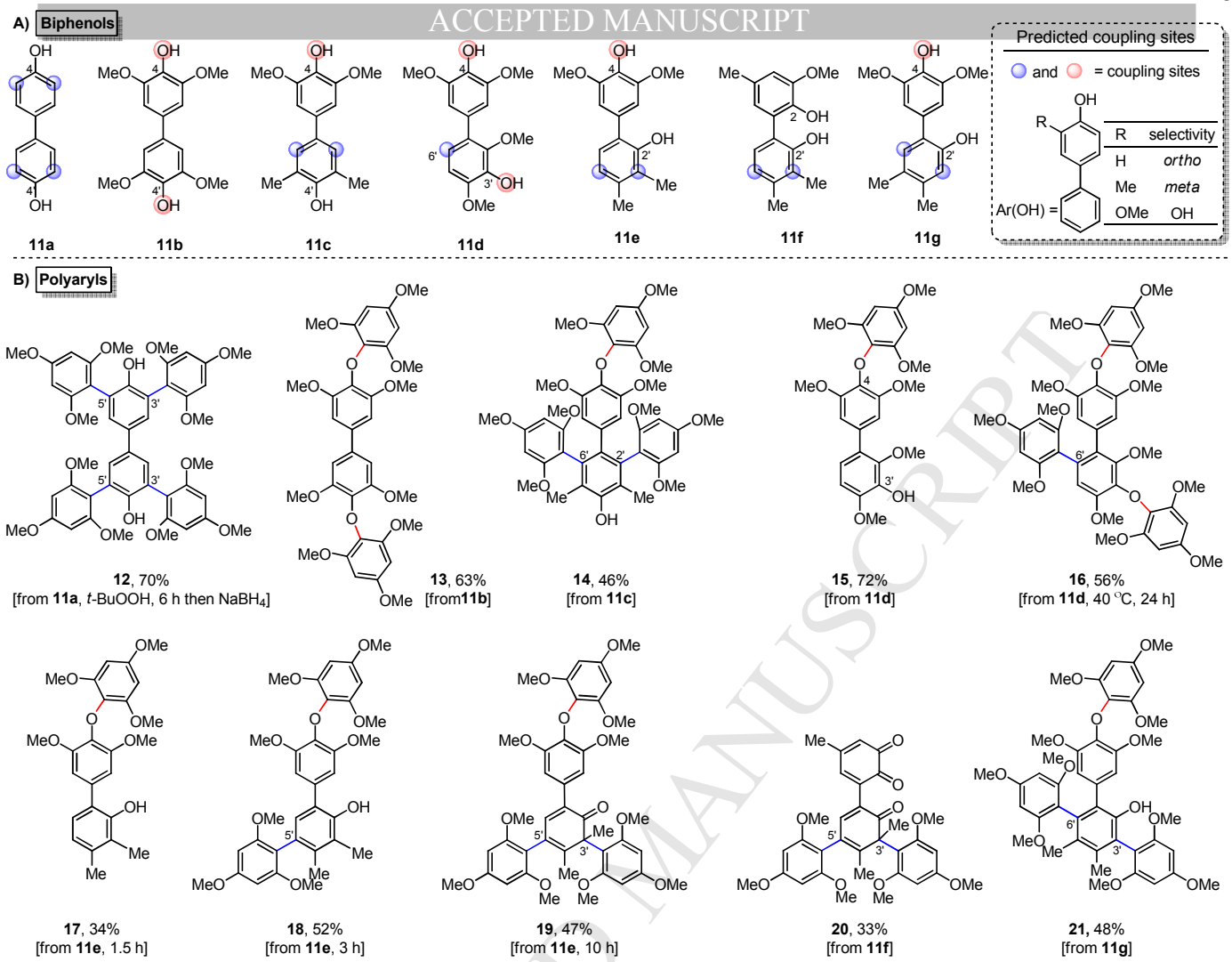
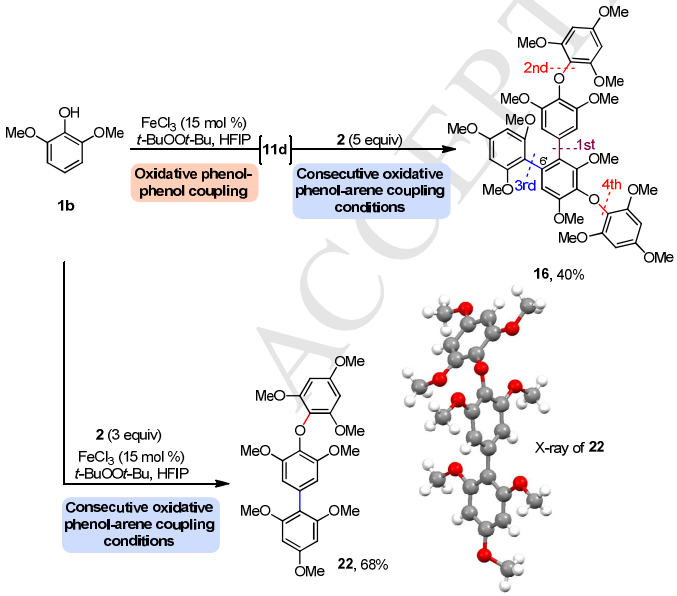


Fig. 3. Consecutive oxidative cross-coupling reaction of unnatural biphenols **11a-g**. General conditions: biphenol **11** (1 equiv, 0.5 M), arene **2** (3-5 equiv), $FeCl_3$ (15 mol %), *t*-BuOO*t*-Bu (3-5 equiv), HFIP, room temperature.



Scheme 3. Selective syntheses of polyaryls **16** and **22** by oxidative phenol-phenol and phenol-arene coupling reactions.

To demonstrate the versatility of the Fe(III)/*t*-BuOO*t*-Bu/HFIP catalytic system in catalysing different types of oxidative coupling reactions, a one-pot sequential oxidative phenol-phenol and phenol-arene coupling reaction of phenol **1b** (Scheme 3) was performed. In this process, the first step involved oxidative homocoupling of phenol **1b** to produce the biphenol **11d** intermediate. The addition of arene **2** at this stage advanced the consecutive reaction between the biphenol and three arene units, affording polyaryl **16** in 40% yield. Overall, this sequential reaction afforded two biaryl and two diaryl ether bonds in a single highly selective operation. In contrast, when phenol **1b** and arene **2** were mixed together at the beginning of the reaction, only the consecutive oxidative phenol-arene coupling reaction took place, affording triaryl ether **22** in 68% yield (X-ray).[55]

3. Conclusions

In summary, the biomimetic iron-catalyzed consecutive oxidative cross-coupling of phenolic components was applied for preparing protected phlorotannin natural products and unnatural polyaryl frameworks that are not easily accessible by other means. We demonstrated that it is possible to achieve selectivity in this multicomponent process by adjusting between four of

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the reaction parameters, namely, the catalyst loading, the peroxide, the fluoroalcohol solvent, and the reaction time. In addition, by reacting a variety of biphenols, it was confirmed that the coupling regioselectivity (*ortho*, *meta* or *para*) and the chemoselectivity (C–C vs C–O coupling) in biphenol derivatives is controlled, as in phenols, by the phenolic *ortho*-groups. Finally, a sequential oxidative phenol-phenol and phenol-arene coupling reaction was performed, emphasizing the power of the chemistry for preparing natural products and their unnatural analogous. We intend to expand the consecutive oxidative cross-coupling reaction to other classes of phenolic units and to apply this efficient strategy for preparing natural and unnatural polyphenols that are needed for drug discovery.[67]

4. Experimental section

4.1. General information

All reagents were of reagent grade quality, purchased commercially from Sigma-Aldrich, Alfa-Aesar, or Fluka, and used without further purification. $FeCl_3$ anhydrous 98% purchased from Strem Chemicals. Purification by column chromatography was performed on Merck chromatographic silica gel (40–63 μm). TLC analyses were performed using Merck silica gel glass plates 60 F254. NMR spectra were recorded on Bruker DPX400 or DMX500 instruments; chemical shifts, given in, are relative to Me_4Si as the internal standard or to the residual solvent peak. HRMS data were obtained using a Thermoscientific LTQU XL Orbitrap HRMS equipped with APCI (atmospheric-pressure chemical ionization). HPLC analysis was carried out on Agilent 1260 instrument equipped with a G4212-60008 photodiode array detector, ES-MS Advion Expression unit and an Agilent reverse phase ZORBAX Eclipse plus C18 3.5 μm column (4.6 X 100 mm).

*4.2. General procedure for the synthesis of Me_4-difucols **(6a)** and **(6b)***

To a solution of $FeCl_3$ (8.1 mg, 10 mol %), 3,5-dimethoxyphenol (154 mg, 1 mmol) in TFE (1 ml, 0.5M), di-*t*-butylperoxide (0.75 mmol) was added drop-wise at room temperature. Then stirring was continued for 48 hours. After complete consumption of the limiting starting material (indicated by TLC and HPLC), the volatiles were removed under reduced pressure and the crude residue was purified by column chromatography (silica gel 40-60 μm) to afford the pure product.

*4.2.1 Sym-Me_4-difucol **(6a)***

The crude residue was purified over silica-gel column chromatography (ethyl acetate/hexane, 2:3) to afford compound **6a** (46 mg, 33% yield) as a pale brown solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 2H), 6.04 (s, 4H), 3.52 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 157.9, 103.1, 92.2, 55.2; HRMS (ESI): *m/z* calcd for $C_{16}H_{18}O_6$ $[M+Na]^+$ 329.0996, found 329.0998.

*4.2.2 Unsym-Me_4-difucol **(6b)***

The crude residue was purified over silica-gel column chromatography (ethyl acetate/hexane, 2:3) to afford compound **6b** (22 mg, 22% yield) as an off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.59 (s, 1H), 6.04 (s, 2H), 6.01 (s, 2H), 3.69 (s, 3H), 3.53 (s, 3H), 3.52 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 159.2, 158.8, 158.0, 156.6, 103.3, 102.8, 93.7, 92.1, 89.8, 55.3, 55.2, 54.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{18}O_6$ $[M+Na]^+$ 329.0996, found 329.0990.

*4.3. General procedure for the synthesis of biphenols **(11b-11d)** and **(11g)***

Compounds: 3,3',5,5'-tetramethoxy-[1,1'-biphenyl] -4,4'-diol (**11b**), 3,5-dimethoxy-3',5'-dimethyl-[1,1'-biphenyl]-4,4'-diol (**11c**), 2,3',4,5'-tetramethoxy-[1,1'-biphenyl]-3,4'-diol (**11d**), 3',5'-dimethoxy-4,5-dimethyl-[1,1'-biphenyl]-2,4'-diol (**11g**) were prepared according to the procedure reported previously by our group[49]

*4.4. General procedure for the synthesis of biphenols **(11e-11f)***

To a solution of $FeCl_3$ (10 mol %), phenol (1 equiv, 0.25 mmol) and 2,3-dimethylphenol (3 equiv, 0.75 mmol) in HFIP (0.5M), *t*-butyl hydroperoxide (1.5 equiv, 0.38 mmol) was added drop-wise with constant stirring at 0 ºC. Then stirring was continued at room temperature for 24 hours. After complete consumption of the limiting starting material (indicated by TLC and HPLC), the volatiles were removed under reduced pressure and the crude residue was purified by column chromatography (silica gel 40-60 μm) to afford the pure product.

*4.4.1 3',5'-dimethoxy-3,4-dimethyl-[1,1'-Biphenyl]-2,4'-diol **(11e)***

The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:4) to afford compound **11e** (13.0 mg, 20% yield) as a gray solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.63 (s, 2H), 5.58 (s, 1H), 5.40 (s, 1H), 3.90 (s, 6H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 147.7, 137.8, 134.4, 128.5, 126.5, 125.5, 123.0, 121.7, 105.8, 56.4, 20.1, 11.9; HRMS (ESI): m/z calcd for $C_{16}H_{18}O_4$ [M+Na]+ 297.1097, found 297.1099.

*4.4.2 3'-methoxy-3,4,5'-trimethyl-[1,1'-Biphenyl]-2,2'-diol **(11f)***

The crude residue was purified by column chromatography (ethyl acetate/hexane 1:9) to afford the compound **11f** (35.4 mg, 56% yield) as a brownish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.72 (s, 2H), 6.12 (s, 1H), 6.03 (s, 1H), 3.93 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 146.4, 139.5, 138.0, 130.4, 127.4, 124.7, 124.1, 123.9, 122.4, 122.2, 110.9, 56.1, 21.2, 20.1, 12.1; HRMS (ESI): m/z calcd for $C_{16}H_{18}O_3$ [M+H]+ 259.1329, found 259.1328.

4.5. General procedure for the Biomimetic oxidative oligomerization of protected fucols

General Method A: To a stirred solution of the 3,5-dimethoxyphenol/Me_4-difucol (1.0 equiv), 1,3,5-trimethoxybenzene (3-7 equiv) and $FeCl_3$ (5-20 mol %) in HFIP (0.5 M), di-*t*-butylperoxide (3-7 equiv, respectively to the arene) was added drop-wise at room temperature. Upon completion of the consecutive reaction, as indicated by TLC and HPLC analysis, the volatiles were removed under reduced

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pressure. The crude residue was purified by silica-gel column chromatography affording pure polyaryl products.

General Method B: To a stirred solution of the *sym*-Me_4-difucol (1.0 equiv), 1,3,5-trimethoxybenzene (6 equiv) and $FeCl_3$ (15% mol %) in HFIP (0.5 M), *t*-butyl hydroperoxide (6 equiv, respectively to the arene) was added drop-wise at room temperature. Upon completion of the consecutive reaction, as indicated by TLC and HPLC analysis, the volatiles were removed under reduced pressure. The crude residue was purified by silica-gel column chromatography affording pure polyaryl product.

*4.5.1 Me_5-difucol (**3**) and Me_8-fucol (**4**)* were prepared according to the procedure reported previously by our group.[51]

*4.5.2 Me_{11}-tetrafucol B (**5**)*
3,5-dimethoxyphenol (**1a**, 38 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (**2**, 210 mg, 1.25 mmol) were reacted according to method A with $FeCl_3$ (6.1 mg, 15 mol %) for 24 h. The crude residue was purified by column chromatography (DCM/acetone, 24:1) to afford compound **5** (78 mg, 48% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 4H), 6.22 (s, 2H), 5.04 (s, 1H), 3.82 (s, 9H), 3.74 (s, 18H), 3.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 160.6, 159.5, 159.3, 158.2, 152.6, 113.3, 110.1, 107.0, 104.9, 92.1, 91.8, 60.3, 56.4, 56.2, 55.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{40}O_{12}$ $[M+Na]^+$ 675.2412, found 675.2408.

4.5.3 Me_7-fucol (7)
Biphenol **6a** (46 mg, 0.15 mmol) and 1,3,5-trimethoxybenzene (**2**, 76 mg, 0.45 mmol) were reacted according to method A with $FeCl_3$ (1.2 mg, 5 mol%) for 22 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 3:2) and then over preparative HPLC chromatography (Phenomenex Luna C18, 21.2 X 250 mm, 10 micron, CH_3CN-H_2O) to afford compound **7** (21 mg, 30% yield) as an off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.58 (s, 1H), 6.24 (s, 1H), 6.23 (s, 2H), 6.06 (s, 2H), 3.79 (s, 3H), 3.62 (s, 6H), 3.55 (s, 9H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 158.9, 158.8, 158.7, 157.9, 157.3, 155.5, 107.5, 107.3, 105.5, 103.9, 94.9, 92.3, 91.1, 58.9, 55.4, 55.3, 55.1, 55.0; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}O_9$ $[M+K]^+$ 511.1365, found 511.1356.

*4.5.4 Me_{10}-tetrafucol (**8**)*
Biphenol **6a** (46 mg, 0.15 mmol) and 1,3,5-trimethoxybenzene (**2**, 76 mg, 0.45 mmol) were reacted according to method A with $FeCl_3$ (3.6 mg, 15 mol%) for 22 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 3:2) and then over preparative HPLC chromatography (Phenomenex Luna C18, 21.2 X 250 mm, 10 micron, CH_3CN-H_2O) to afford compound **8** (35 mg, 36% yield) as a brown oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 2H), 6.26 (s, 2H), 6.24 (d, *J* = 2.2 Hz, 2H), 6.21 (d, *J* = 2.2 Hz, 2H), 3.79 (s, 6H), 3.65 (s, 6H), 3.59 (s, 6H), 3.54 (s, 6H), 3.03 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.1, 158.9, 158.8, 158.7, 157.4, 155.5, 108.2, 107.4, 105.5, 95.0, 91.0, 90.9, 58.9, 55.4, 55.3, 55.10 (x 2C); HRMS (ESI): *m/z* calcd for $C_{34}H_{38}O_{12}$ $[M+Na]^+$ 661.2256, found 661.2246.

*4.5.5 Compound (**9**)*
Biphenol **6a** (31 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 101 mg, 0.60 mmol) were reacted according to method B with $FeCl_3$ (2.4 mg, 15 mol%) for 1.5 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 3:2) and then over preparative HPLC chromatography (Phenomenex Luna C18, 21.2 X 250 mm, 10 micron, CH_3CN-H_2O) to afford compound **9** (21 mg, 25% yield) as a brown oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 6.55 (s, 1H), 6.28 (s, 1H), 6.27 (d, *J* = 2.3 Hz, 2H), 6.22 (d, *J* = 2.3 Hz, 2H), 6.21 (s, 2H), 3.79 (s, 6H), 3.79 (s, 3H), 3.70 (s, 6H), 3.66 (s, 3H), 3.58 (s, 6H), 3.53 (s, 6H), 3.09 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.3, 160.0, 159.1, 158.8, 158.7, 157.3, 155.5, 153.3, 112.6, 110.2, 108.8, 107.5, 105.6, 105.3, 94.7, 91.6, 91.4, 90.9, 59.0, 58.9, 55.6 (x 2C), 55.3, 55.1, 55.0; HRMS (ESI): *m/z* calcd for $C_{43}H_{48}O_{15}$ $[M+Na]^+$ 827.2885, found 827.2867.

*4.5.6 Me_{14}-hexafucol B (**10**)*
Biphenol **6a** 46 mg, 0.15 mmol) and 1,3,5-trimethoxybenzene (**2**, 176 mg, 1.05 mmol) were reacted according to method A with $FeCl_3$ (4.8 mg, 20 mol%) for 11 days. The crude residue was purified by column chromatography (ethyl acetate/hexane, 3:2) and then over preparative HPLC chromatography (Phenomenex Luna C18, 21.2 X 250 mm, 10 micron, CH_3CN-H_2O) to afford compound **10** (14 mg, 10% yield) as a brown oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.25 (s, 8H), 3.79 (s, 15H), 3.60 (s, 24H), 3.16 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 159.0, 157.2, 153.3, 113.7, 110.3, 105.3, 91.4, 59.2, 55.5, 55.1; HRMS (ESI): *m/z* calcd for $C_{52}H_{58}O_{18}$ $[M+Na]^+$ 993.3515, found 993.3522.

4.6. General procedure for the Consecutive Oxidative Cross-Coupling of Biphenols with Arenes

General method C: To a stirred solution of the phenol/biphenol derivative (1.0 equiv), 1,3,5-trimethoxybenzene (3-5 equiv) and $FeCl_3$ (15 mol %) in HFIP (0.5 M), di-*t*-butylperoxide (3-5 equiv, respectively to the arene) was added drop-wise at room temperature. Upon completion of the sequential oxidative cross-coupling reaction, as indicated by TLC and HPLC analysis, the volatiles were removed under reduced pressure. The crude residue was purified by silica-gel column chromatography affording pure polyaryl products.

General method D: To a stirred solution of the biphenol derivative (1.0 equiv), 1,3,5-trimethoxybenzene (3-5 equiv) and $FeCl_3$ (15 mol %) in HFIP (0.5 M), di-*t*-butylperoxide (3-5 equiv, respectively to the arene) was added drop-wise at room temperature and the stirring was continued at 40 ^{0}C.
Upon completion of the consecutive reaction, as indicated by TLC and HPLC analysis, the volatiles were removed under reduced pressure. The crude residue was purified by silica-gel column chromatography affording pure polyaryl products.

General method E: To a stirred solution of biphenol (1.0 equiv), 1,3,5-trimethoxybenzene (6 equiv) and $FeCl_3$ (15 mol %) in HFIP (0.5 M) at 0 ºC was added drop-wise *t*-butyl hydroperoxide (6 equiv. respectively to the arene). The reaction was further stirred at room temperature until full consumption of the biphenol starting material. $NaBH_4$ (1.1 equiv) was added in one portion and the mixture stirred for 3 h. The reaction was quenched with 1 *N* HCl aq. sol. and extracted with dichloromethane (3 X 10 mL). The combined organic phase was dried over $MgSO_4$, the volatiles removed under reduced pressure and the crude residue purified by silica-gel column chromatography affording pure polyaryl product.

*4.6.1 Compound **12***
Biphenol **11a** (19 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 101 mg, 0.60 mmol) were reacted according to method E for 6 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 7:3) to afford compound **12** (59 mg, 70% yield) as red solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 4H),

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6.25 (s, 8H), 5.31 (s, 2H), 3.83 (s, 12H), 3.72 (s, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.9, 150.7, 132.4, 130.1, 121.3, 108.7, 91.5, 56.2, 55.4; HRMS (ESI): *m/z* calcd for $C_{48}H_{50}O_{14}$ $[M]^+$ 850.3195, found 850.3191.

*4.6.2 Compound **13***

Biphenol **11b** (34 mg, 0.11 mmol) and 1,3,5-trimethoxybenzene (**2**, 56 mg, 0.33 mmol) were reacted according to method C for 24 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford compound **13** (44 mg, 63% yield) as a yellowish solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 4H), 6.14 (s, 4H), 3.77 (overlapped, 18H), 3.73 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.3, 151.8, 137.5, 135.8, 131.9, 105.5, 92.4, 57.1, 56.7, 55.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{38}O_{12}$ $[M+K]^+$ 677.0000, found 677.2015.

*4.6.3 Compound **14***

Biphenol **11c** (27 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 84 mg, 0.50 mmol) were reacted according to method C for 10 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford compound **14** (36 mg, 46% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 2H), 6.06 (s, 2H), 5.97 (s, 4H), 4.70 (s, 1H), 3.76 (s, 6H), 3.74 (s, 3H), 3.59 (s, 12H), 3.50 (s, 6H), 3.37 (s, 6H), 1.98 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 158.1, 155.2, 152.1, 150.9, 149.7, 136.7, 136.6, 135.8, 132.6, 131.7, 122.3, 111.5, 108.3, 92.6, 90.0, 56.7, 56.6, 55.5, 55.2, 13.5; HRMS (ESI): *m/z* calcd for $C_{43}H_{48}O_{13}$ $[M+Na]^+$ 795.2987, found 795.2990.

*4.6.4 Compound **15***

Biphenol **6a** (31 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 51 mg, 0.30 mmol) were reacted according to method C for 5 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 2:3) to afford compound **15** (34 mg, 72% yield) as a brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, J = 8.6 Hz, 1H), 6.76 (s, 2H), 6.71 (d, J = 8.6 Hz, 1H), 6.15 (s, 2H), 5.74 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 3.74 (s, 6H), 3.72 (s, 6H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.3, 151.6, 147.0, 144.7, 138.8, 137.0, 132.2, 132.1, 128.0, 120.3, 107.1, 105.8, 92.4, 60.5, 56.9, 56.7, 56.4, 55.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}O_9$ $[M+Na]^+$ 495.1631, found 495.1632.

*4.6.5 Compound **16***

Biphenol **11d** (31 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 84 mg, 0.50 mmol) were reacted according to method D for 24 h. The crude residue was purified by column chromatography; (ethyl acetate/hexane, 3:2) to afford compound **16** (45 mg, 56% yield) as a pale brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.37 (s, 2H), 6.16 (s, 2H), 6.08 (s, 2H), 5.98 (s, 2H), 3.77 (s, 3H), 3.75 (overlapped, 6H), 3.74 (overlapped, 9H), 3.59 (s, 6H), 3.56 (s, 6H), 3.50 (s, 6H), 3.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 158.3, 155.5, 155.3, 152.2, 152.0, 150.5 (x 2C), 149.0, 140.4, 136.3, 132.6, 132.3, 132.0, 129.8, 128.3, 112.7, 111.3, 108.7, 93.0, 92.5, 90.4, 60.2, 56.8, 56.6, 56.5, 55.6, 55.6, 55.5, 55.3; HRMS (ESI): *m/z* calcd for $C_{43}H_{48}O_{15}$ $[M+Na]^+$ 827.2891, found 827.2909.

*4.6.6 Compound **17***

Biphenol **11e** (27 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 51 mg, 0.30 mmol) were reacted according to method C for 1.5 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 3:7) to afford compound **17** (15 mg, 34% yield) as a green oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.71 (s, 2H), 6.24 (s, 2H), 5.55 (s, 1H), 5.42 (s, 1H), 3.89 (s, 6H), 3.87 (s, 3H), 3.73 (s, 6H), 2.27 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.7, 149.4, 147.7, 137.6, 134.3, 129.8, 128.9, 125.9, 124.9, 123.0, 112.0, 106.0, 90.7, 56.5, 55.9, 55.5, 17.1, 12.8; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}O_7$ $[M+H]^+$ 441.1908, found 441.1900.

*4.6.7 Compound **18***

Biphenol **11e** (27 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 51 mg, 0.30 mmol) were reacted according to method C for 3 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 2:3) to afford compound **18** (31 mg, 52% yield) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.66 (s, 2H), 6.24 (s, 2H), 6.15 (s, 2H), 5.50 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.73 (s, 12H), 3.72 (s, 6H), 2.27 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 158.7, 155.7, 152.3 (x 2C), 149.3, 137.6, 137.0, 131.8 (x 2C), 129.5, 125.9, 124.8, 122.9, 112.1, 107.1, 92.3, 90.7, 56.8, 56.8, 55.9, 55.6, 55.5, 17.1, 12.7; HRMS (ESI): *m/z* calcd for $C_{34}H_{38}O_{10}$ $[M+Na]^+$ 629.2357, found 629.2366.

*4.6.8 Compound **19***

Biphenol **11e** (27 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 84 mg, 0.50 mmol) were reacted according to method C for 10 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford compound **19** (36 mg, 47% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.85 (s, 2H), 6.20 (d, J = 2.1 Hz, 1H), 6.18 (d, J = 2.1 Hz, 1H), 6.12 (s, 2H), 6.11 (s, 2H), 3.84 (s, 3H), 3.79 (s, 6H), 3.76 (s, 3H), 3.71 (s, 15H), 3.69 (s, 6H), 1.80 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 160.7, 159.9, 158.9, 158.6, 155.6, 155.1, 152.5, 151.0, 143.9, 137.4, 131.5, 130.5, 120.9, 120.8, 113.5, 111.3, 107.6, 92.3, 91.9, 91.0, 59.2, 57.2, 56.8, 56.1, 55.9, 55.7, 55.6, 55.5, 55.3, 25.2, 17.8; HRMS (ESI): *m/z* calcd for $C_{43}H_{48}O_{13}$ $[M+Na]^+$ 795.2987, found 795.2991.

*4.6.9 Compound **20***

Biphenol **11f** (26 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 51 mg, 0.30 mmol) were reacted according to method D for 72 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford compound **20** (19 mg, 33% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.86 (s, 1H), 6.65 (s, 1H), 6.23 (s, 2H), 5.46 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.69 (s, 6H), 3.60 (s, 6H), 2.34 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 167.0 (x 2C), 160.7, 158.6, 152.3, 148.8, 138.4, 137.7, 135.0, 132.2, 131.1, 129.6, 128.9, 127.1, 121.1, 112.4, 111.3, 100.1, 91.0, 56.1, 56.0, 55.9, 55.5, 21.7, 17.2, 13.2; HRMS (ESI): *m/z* calcd for $C_{33}H_{34}O_9$ $[M+Na]^+$ 597.2095, found 597.2093.

*4.6.10 Compound **21***

Biphenol **11g** (27 mg, 0.10 mmol) and 1,3,5-trimethoxybenzene (**2**, 84 mg, 0.50 mmol) were reacted according to method C for 24 h. The crude residue was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford compound **21** (37 mg, 48% yield) as an off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 6.27 (s, 2H), 6.08 (s, 2H), 6.00 (s, 2H), 4.86 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.76 (s, 6H), 3.75 (s, 3H), 3.61 (s, 6H), 3.59 (s, 6H), 3.54 (s, 6H), 2.01 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.4, 159.0, 158.1, 155.4, 152.1, 151.2, 148.3, 136.5, 136.3, 132.7, 132.2, 131.8, 127.6, 126.0, 119.6, 111.9, 108.2, 107.8, 92.4, 91.2, 90.1, 56.6 (x 2C), 56.1, 55.5 (x 2C), 55.4, 55.2, 17.6,

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16.9; HRMS (ESI): *m/z* calcd for $C_{43}H_{48}O_{13}$ $[M+Na]^+$ 795.2987, found 795.2993.

*4.7. General procedure for one-pot sequential oxidative coupling for the formation of compound **16***

To a solution of $FeCl_3$ (6 mg, 15 mol %), 2,6-dimethoxyphenol (77 mg, 0.5 mmol) in HFIP (0.5 ml, 0.5M), di-*t*-butylperoxide (0.38 mmol) was added drop-wise at room temperature. Then stirring was continued for 24 hours. After the formation of the biphenol **11d** as indicated by TLC and HPLC, 1,3,5-trimethoxybenzene (**2**, 210 mg, 1.25 mmol) and di-*t*-butylperoxide (1.25 mmol) were added drop-wise at room temperature. Then the stirring was continued at 40 ^{0}C upon completion of the consecutive reaction the volatiles were removed under reduced pressure and the crude residue purified by silica-gel column chromatography to afford compound **16** (78 mg, 40% yield) as a yellow solid.

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