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Iron-catalyzed selective oxidative arylation of phenols and biphenols

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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.

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,[14–16] exhibiting anti-allergic,[13,17] anti-oxidation,[18] and anti HIV-1[19] activities.

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

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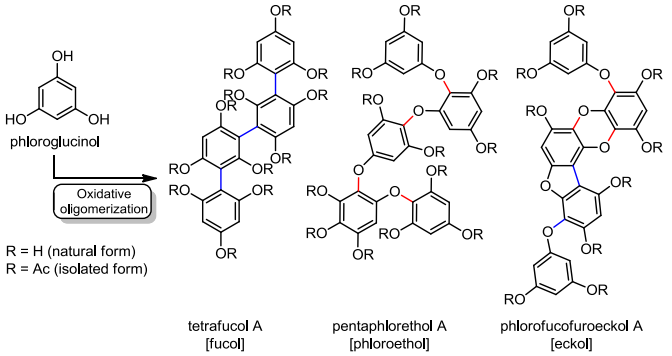


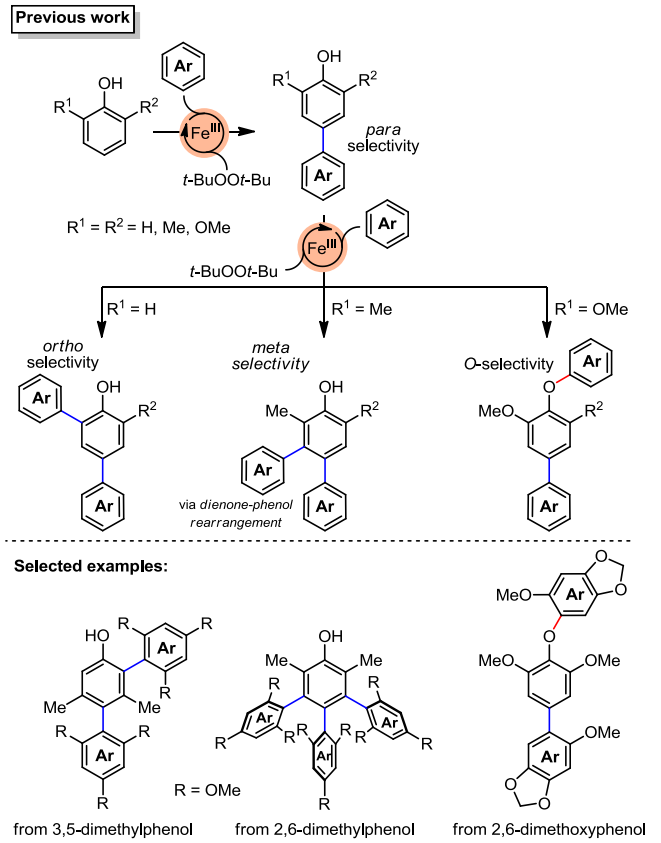
Fig. 1. Selected phlorotannins produced by oxidative oligomerization of phloroglucinol.

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] using *t*-BuOO*t*-Bu as the terminal oxidant.. 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.[40,49–54]

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.

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).



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

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]

The importance of HFIP in oxidative coupling reactions of