O_2 Activation

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Selective *Ortho*-Hydroxylation–Defluorination of 2-Fluorophenolates with a Bis(μ-oxo)dicopper(III) Species**

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Dedicated to Prof. Lawrence Que, Jr. on the occasion of his 65th birthday

Abstract: *The bis(μ-oxo)dicopper(III) species $[Cu^{III}_2(\mu\text{-}O)_2(m\text{-}XYL^{MeAN})]^{2+}$ (**1**) promotes the electrophilic ortho-hydroxylation–defluorination of 2-fluorophenolates to give the corresponding catechols, a reaction that is not accomplishable with a $(\eta^2{:}\eta^2\text{-}O_2)$dicopper(II) complex. Isotopic labeling studies show that the incoming oxygen atom originates from the bis(μ-oxo) unit. Ortho-hydroxylation–defluorination occurs selectively in intramolecular competition with other ortho-substituents such as chlorine or bromine.*

Fluorine forms the strongest single bond to carbon (bond dissociation energy up to 130 kcal mol^{-1}) and thus, C–F bonds are considered the most inert organic functionalities. This arises from the electronegativity of fluorine, which confers reinforcing ionic forces through the strong polarization of this bond.[1] Fluorinated organic compounds are renowned for their unique properties such as thermal stability, enhanced lipophilicity and ability to suppress metabolic detoxification, thus increasing the in vivo residence time.[2] Owing to these properties, fluorinated chemicals represent 20% of all pharmaceuticals and up to 30% of all agrochemicals.[3] In spite of their stability, the large-scale production and application of anthropogenic organofluorines have increasingly become subjects of debate due to the toxicity, global warming potential, ozone depletion, environmental persistence, and bioaccumulation of these compounds.[4] For this reason, the degradation of fluorinated organic compounds or activation and transformation of C–F bonds into more reactive functional groups is of current interest.[5]

In nature, several microbial enzymes can break C–F bonds,[6] and a wide range of fluorinated substrates including aliphatics (e.g. fluoroacetate, fluoropyruvate) and aromatics (e.g. fluorobenzoates, fluorophenols) can be defluorinated. Focusing on aromatics, the defluorination of fluorophenols usually occurs in aerobic organisms through the mediation of FAD-containing phenol hydroxylases, which convert 2-fluorophenols into catechols.[7] The oxidative dehalogenation of 4-fluorophenols has also been reported for cytochrome P450 and chloroperoxidase.[8]

Tyrosinase is a ubiquitous dicopper enzyme that catalyzes the *ortho*-hydroxylation of phenols to catechols and the subsequent oxidation to quinones using dioxygen as oxidant,[9] in an overall reaction analogous to that taking place in FAD-dependent phenol hydroxylases.[7] Tyrosinase operates via a $(\eta^2{:}\eta^2$-peroxo)dicopper(II) species (**P**), that undergoes electrophilic attack over the arene. However, in contrast to FAD-dependent hydroxylases, tyrosinase is incapable of hydroxylating 2-fluorophenols, which indeed are inhibitors of this enzyme.[10] Studies with model compounds have shown that the **P** species are usually in equilibrium with a highly electrophilic bis(μ-oxo)dicopper(III) species (**O**), which may open the door to novel oxidative reactivity hitherto not attained by the peroxide isomer. Herein, we indeed show that **O** species promote the defluorination of 2-fluorophenols to give the corresponding catechols, thus selectively transforming a C_{Ar}–F into a C_{Ar}–OH functional group. The reaction shows a remarkable selectivity, opening a bioinspired alternative to multistep transformations involving reactions that are most commonly associated with highly reactive organometallic compounds.[11]

$[Cu^{III}_2(\mu\text{-}O)_2(m\text{-}XYL^{MeAN})]^{2+}$ (**1**; Scheme 1) has been described as a thermally unstable compound, which can be generated at low temperatures (−90 °C) in acetone or THF by reaction of the dicopper(I) precursor $[Cu^{I}_2(m\text{-}XYL^{MeAN})]^{2+}$ with O_2.[12] It has been previously established that this compound can bind to phenolates and perform their *ortho*-hydroxylation, thus mimicking the reactivity exhibited by the dicopper enzyme tyrosinase.[13] Therefore, the activity of **1** resembles that found for other **P** and **O** type dicopper

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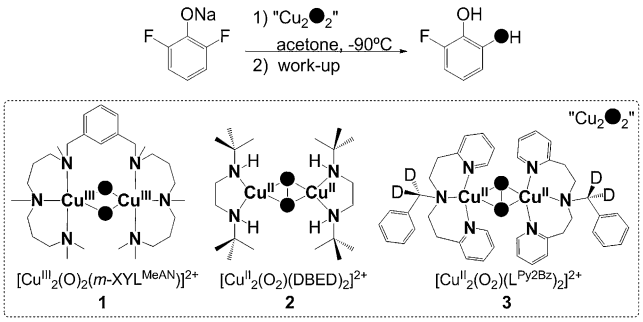
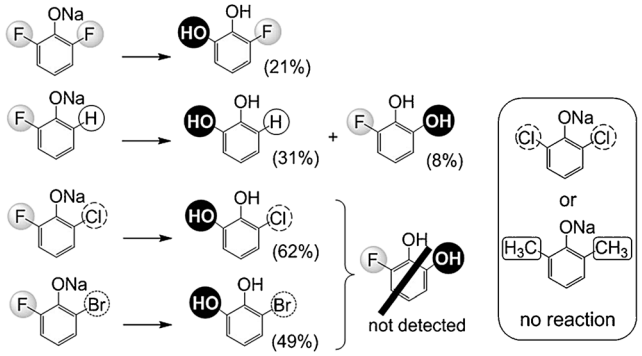


Scheme 1. *Ortho*-hydroxylation–defluorination reaction of sodium 2,6-difluorophenolate to give 3-fluorocatechol along with the schematic representation of Cu_2O_2 species **1**–**3**.

complexes.[14] The **P** species in tyrosinase has been shown to bind fluorophenolates, but the hydroxylation does not occur in *ortho*-substituted phenolates.[10] To our surprise, the reaction of **1** (2 mM) with 3 equiv sodium 2,6-difluorophenolate (Na(DFP)) at −90 °C caused the rapid decay of **1**, as shown by monitoring the reaction by UV/Vis spectroscopy. Following the complete decay of **1** and subsequent work-up, ^{1}H NMR and HPLC analyses evidenced that the reaction afforded 3-fluorocatechol in 21 % yield (with respect to **1**), indicating that *ortho*-hydroxylation and defluorination had taken place (Scheme 2). The yield was unaffected by the use



Scheme 2. Selective *ortho*-hydroxylation–defluorination reactions promoted by **1**. Reaction conditions: 1) **1**, sodium phenolate (3 equiv), acetone, −90 °C 2) acidic work-up. See the Supporting Information for further details.

of higher amounts of substrate (10 equiv) or by lowering the initial concentration of **1** (0.2 mM) (Table S1).

Isotope labeling experiments were performed by reacting Na(DFP) with ^{18}O-labeled **1** (generated by initial reaction of the dicopper(I) precursor with $^{18}O_2$, subsequent removal of the excess $^{18}O_2$, and placing the reaction under N_2) affording 3-fluorocatechol with 86 % ^{18}O label, thereby demonstrating that the oxygen atom incorporated into the catechol product originated from the Cu_2O_2 unit. Moreover, this dehalogenation reaction was regioselective for the *ortho* position of the phenolate, as no defluorination occurred upon reaction of **1** with 4-fluorophenolate (only 4-fluorocatechol was detected as product).

The *ortho*-defluorination reaction also occurred when unsymmetric phenolates bearing only one *ortho*-fluorine substituent were used as substrates. Thus, reaction of **1** with 3 equiv of sodium 2-fluorophenolate afforded 31 % of 1,2-dihydroxybenzene along with 8 % of 3-fluorocatechol (Scheme 2). Complex **1** proved to be highly selective in the defluorination of unsymmetric phenolates bearing other halogen substituents at the *ortho* position, such as sodium 2-chloro-6-fluorophenolate or sodium 2-bromo-6-fluorophenolate. Upon reaction with **1**, they both afforded exclusively 3-chlorocatechol and 3-bromocatechol in 62 % and 49 % yield, respectively (Scheme 2). Finally, no *ortho*-hydroxylation occurred upon reaction of **1** with phenolates bearing substituents in the *ortho* position different from fluorine or hydrogen. Thus, reaction with sodium 2,6-dichlorophenolate or sodium 2,6-dimethylphenolate only afforded the recovery of the starting material (Scheme 2). In conclusion, the *ortho*-C_{arene}–F bond is especially reactive against **O**, even in the presence of presumably weaker and/or more nucleophilic *ortho*-C_{arene}–R bonds. This result is especially remarkable, because the oxidative dehalogenation of C_{arene}–Br and C_{arene}–Cl bonds has been observed upon reacting binuclear copper(I) complexes with O_2,[15] whereas defluorination has never been reported for such systems.

It is well established that **O** species are usually in a nearly degenerate equilibrium with their corresponding **P** isomer.[16] Thus, it is not clear which one of the two isomers is the real executor of the phenol *ortho*-hydroxylation reaction. To determine the necessity of the bis(μ-oxo) core for the *ortho*-hydroxylation–defluorination reaction, we studied two **P** complexes that are known to promote the *ortho*-hydroxylation of phenolates. In particular, we chose the complexes $[Cu^{II}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)(DBED)_2]^{2+}$ (**2**)[14b,c] and $[Cu^{II}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)(L^{Py2Bz})_2]^{2+}$ (**3**),[14d] which have been previously described by the groups of Stack and Itoh, respectively (Scheme 1). Whereas for complex **3** only the **P** isomer is observed along the reaction with phenolates,[14d] for complex **2**, **P** converts into **O** upon phenolate coordination. In this respect, O is the real executor of the hydroxylation reaction.[14c] When **2** reacted with Na(DFP) (3 equiv), 3-fluorocatechol was obtained in 23 % yield (with respect to **2**). More interestingly, under analogous reaction conditions, **3** was unable to cleave the C–F bond and only trace amounts of catechol were observed (< 3 %, Table S1). Control experiments with $[Cu^{I}(MeCN)_4]CF_3SO_3$ as the copper source and O_2 as oxidant only afforded trace amounts of the defluorinated product. From these results it may be concluded that an **O** species is necessary to achieve this unprecedented *ortho*-hydroxylation–defluorination reaction of phenols by a Cu_2O_2 species.

A deeper insight into the mechanism of this *ortho*-hydroxylation–defluorination reaction was gained by means of low temperature UV/Vis spectroscopy. Acetone solutions of **1** at −90 °C exhibited an intense absorption band at 413 nm ($\varepsilon = 21\,000\ M^{-1}cm^{-1}$), which remained relatively stable at this temperature. Addition of 3 equiv of a particular phenolate led to an immediate color change from yellow to deep purple. This was readily evident in the UV/Vis spectrum, which showed the immediate formation of a novel species exhibiting two new bands in the range of 357–414 nm and 516–639 nm

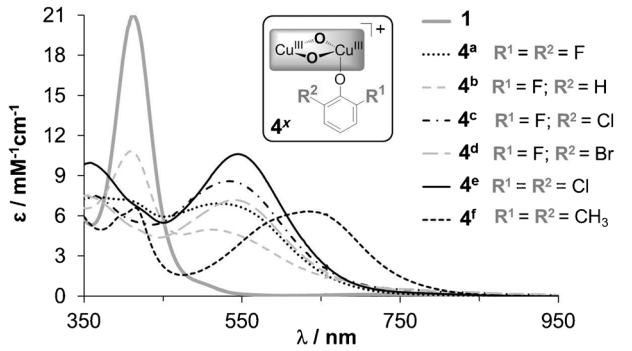


Figure 1. UV/Vis spectra of **1** and **4^x** in acetone at −90 °C. Compounds **4^x** were obtained by reaction of **1** with 3 equiv of the corresponding sodium phenolate.

depending on the nature of the phenolate (Figure 1 and S1). Previous rRaman studies on the purple intermediate resulting from the reaction of **1** with *p*-chlorophenolate[13] indicate that this species corresponds to the adduct that results from binding of the phenolate to the bis(μ-oxo) core of **1** (**4^x**, Figure 1). Cryospray mass spectrometry (CMS) at −90 °C was performed to further substantiate the proposed nature of **4^a**. The CMS spectrum of a freshly prepared sample of **4^a** is dominated by two intense peaks at *m*/*z* 783.2571 and *m*/*z* 763.3194 (Figure 2). Mass values and isotopic patterns of

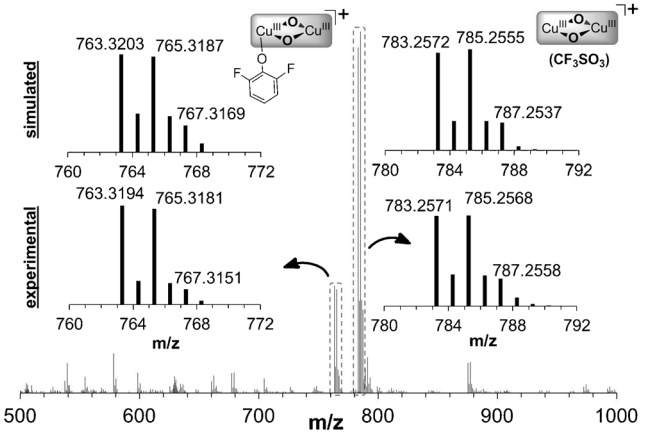


Figure 2. Spectra of cryospray mass spectrometry (CMS) experiments at −90 °C corresponding to the reaction of **1** with 3 equiv of Na(DFP) in acetone.

these peaks are consistent with their formulation as $\{[Cu^{III}_2(\mu\text{-}O)_2(m\text{-}XYL^{MeAN})](OTf)\}^+$ and $\{[Cu^{III}_2(\mu\text{-}O)_2(C_6H_3F_2O)(m\text{-}XYL^{MeAN})]\}^+$. In agreement with this interpretation, collision-induced dissociation experiments conducted over the *m*/*z* 763.3 species produced a new peak at *m*/*z* 634.3 corresponding to the loss of a phenolate ligand (*m*/*z* 129.0; Figure S3). This experiment further confirmed the nature of **4^a** as a phenolate-bound **O** species.

Kinetic analysis indicated that the formation of **4^x** was too fast to be studied by conventional benchtop UV/Vis spectroscopic techniques but its decay was substantially slower followinga first-order process that could be adjusted to a single exponential. The decay rates of complexes **4$^{g–k}$**, obtained by reaction of **1** with 10 equiv of the appropriate *para*-substituted sodium 2-fluorophenolates, were studied by UV/Vis spectroscopy and they were fitted to a single exponential function by nonlinear regression methods. Interestingly, plotting the logarithm of the rate of decay (k_{obs}) against the corresponding Hammett *meta*-substituent constants (σ^+) afforded a linear correlation ($R^2 = 0.98$) that gave a negative slope ($\rho = -2.4$) (Figure 3) indicating that the reaction

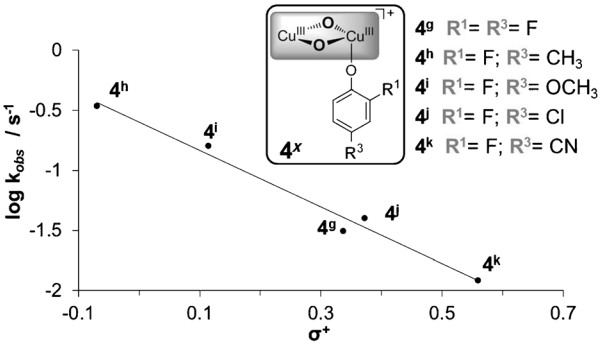


Figure 3. Hammett plot for the thermal decay of **4$^{g–k}$** at −90 °C in acetone.

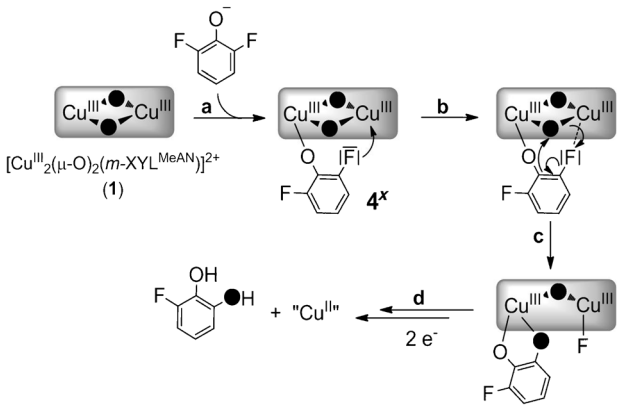
occurred through an electrophilic attack on the aromatic ring of the phenolate. Remarkably, the hydroxylation reaction of nonfluorinated phenolates catalyzed by tyrosinase and some model compounds is also of electrophilic nature, and exhibits ρ values that are similar to the value found for this *ortho*-hydroxylation–defluorination reaction.[13,14,17] This data provides strong experimental support that the reaction of **1** with Na(DFP) entails an initial binding of the phenolate moiety to one of the copper centers, and then proceeds through an electrophilic attack of one of the oxo ligands at the *ortho*-C_{arene}–F site, akin to that occurring in the hydroxylation of phenolates.

At this point, we aimed to improve the reaction yield, which remained moderate for most substrates (Table S1, Scheme 2). By definition, the observed *ortho*-hydroxylation–defluorination reaction does not involve a neat gain or loss of electrons, but experimentally it is observed that the oxidation state of copper changes from +3 to +2 at the end of the reaction. We speculated that the source of the electrons, which reduce the metal center, could originate from a reaction with a second Cu_2O_2 unit releasing O_2, from an oxidative degradation of the ligand, or from a combination of both. Since the *m*-XYL^{MeAN} ligand was recovered intact after the complete decay of **4^x**, substoichiometric reactions most likely originate from an intermolecular reaction with a second Cu_2O_2 unit. Following this reasoning, the addition of a reducing agent was envisioned to provide the necessary electrons from an external source, thus facilitating the reaction and increasing the yields. Indeed this strategy has been previously successfully applied for the intramolecular oxidative aromatic dechlorination by a **P** species.[15b] Unfortunately, in the present case, the addition of $[Cu^I(MeCN)_4]CF_3SO_3$, sodium ascorbate, or zinc dust as reducing agent caused the rapid

decomposition of **1**, which was previously reported for other **O** species.[14e] However, we observed that **2** (which is a **P** species in the absence of a phenolate substrate) could be generated in the presence of sodium ascorbate. Most remarkably, whereas the reaction of **2** in acetone at −90 °C with sodium 2-chloro-6-fluorophenolate and sodium 2-bromo-6-fluorophenolate afforded 41 % of 3-chlorocatechol and 34 % of 3-bromocatechol, respectively, the presence of sodium ascorbate (2 equiv with respect to **2**) raised the yields to 83 % in both cases.

From all these results a mechanistic picture of the *ortho*-hydroxylation–defluorination can be drawn. 2-fluorophenolates bind rapidly to one of the copper(III) centers in **1** to afford $\mathbf{4}^{x}$ (step a, Scheme 3), which evolves through a first-order intramolecular process, in which the bis(μ-oxo) core performs an electrophilic attack on the aromatic ring (step c). This attack is translated to a selective *ortho*-hydroxylation–defluorination reaction. It is especially remarkable that the reaction occurs exclusively at the *ortho*-fluorine atom, even in the presence of competing substituents with weaker C–X bonds (X = Cl, Br) at the other *ortho* position of the phenolate (Scheme 2). This selectivity may be tentatively reasoned by the establishment of a putative interaction between an unpaired pair of electrons of the *ortho*-fluorine atom and the adjacent copper(III) center, so that the carbon atom of the C–F bond becomes properly oriented to be attacked by the bis(μ-oxo) core (step b, Scheme 3). Coordination bond interactions between a lone pair of electrons from fluorine ligands with copper(III) centers have not been reported, but such interactions are well-established for other metals such as alkaline and alkaline earth metals, Ag, Pd, Pt, Ru, or Ir, among others.[18] An electrophilic attack on the aromatic ring (step c, Scheme 3) affords the catecholate product. In the absence of a reducing agent, the $2e^-$ reduction of the copper centers from oxidation state +3 to +2 is achieved by an intermolecular decomposition involving a second Cu_2O_2 complex (step d, Scheme 3).

In conclusion, this work constitutes the first example of an *ortho*-hydroxylation–defluorination reaction of phenolates with oxygen as a sacrificial oxidant by means of a synthetic metal complex. This reaction finds precedent in FAD-dependent hydroxylase enzymes in biological systems. It constitutes a fascinating transformation from a basic chemical point of view not only because of the strength of the C–F bond but also because of the rather unusual selectivity properties it exhibits.[19] Even though product yields are still far from practical for synthetic purposes, this work points towards the involvement of **O** species in the *ortho*-hydroxylation of 2-fluorophenolates by cleaving the C–F bond, thus obtaining the corresponding catechol. Moreover, this reaction is also interesting from the perspective of environmental science, because it enables the transformation of the inert C–F bonds of common persistent pollutants into a more reactive C–OH unit. Studies regarding the catalytic version of this transformation are currently underway in our lab.



Scheme 3. Proposed mechanism of the *ortho*-hydroxylation–defluorination reaction of 2-fluorophenolates promoted by **1**.

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[19] The origin of the remarkable selectivity is currently explored by means of computational DFT analyses.

