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Regioselective oxidative arylation of fluorophenols

Congjun Yu,^[a] and Frederic W. Patureau*^[a]

In memory of our colleague, Prof. Dieter Enders (1946-2019)

Abstract: A metal free and highly regioselective oxidative arylation reaction of fluorophenols is described. The relative position of the fluoride leaving group (ie *ortho* or *para*) controls the 1,2 or 1,4 nature of the arylated quinone product, lending versatility and generality to this oxidative, defluorinative, arylation concept.

The quinone motif is ubiquitous in chemistry, material science, nanotechnology, and medicine.^[1] Due to their electron and hydrogen transport properties, quinone derivatives participate in various biological activities.^[2] For example, they act as membrane-bound compounds found in many living organism,^[3] and play a key role in cell respiration.^[4] In addition, they are embedded in many natural products, drugs,^[5] and materials.^[6] Among them, arylated quinones are particularly important (Figure 1). In material chemistry, they possess unique photochemical and electronic properties that make them useful in photosynthesis,^[7] as well as appealing structures for the dye industry.^[8] Thus, the efficient synthesis of aryl substituted quinones remains a strategic objective, especially in terms of arylation regioselectivity, a largely unaddressed challenge.



Figure 1. Natural products containing arylated quinones.

Some traditional methods to synthesize arylated quinones include pre-halogenation of the quinone core followed by a palladium-catalyzed cross-coupling,^[9] or utilizing diazonium salts as the aryl radical sources to functionalize the quinone.^[10] The latter methods however are neither step nor atom economical, and typically rely on sensitive/onerous palladium/phosphine catalysts. In 2011, Baran et al.^[11] reported boronic acids to be ideal radical sources to react with quinones in the presence of catalytic amounts of AgNO₃. Since then, several radical sources

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and catalysts were developed to achieve this reaction.^[12] Nevertheless, these methods are typically not regioselective. Indeed, the presence of a single R¹ functional group at the quinone core generates three inequivalent but similarly reactive electrophilic positions, usually leading to regioisomeric mixtures of diversely arylated coupling products. Cross dehydrogenative coupling (CDC) approaches were also developed with success,^[13] for example by You and co-workers. Nevertheless, these modern methods, while highly step and atom economical, do not solve any further the regioselectivity problem at the quinone. Herein, we propose to solve this problem for the 1,4 and the more challenging 1,2 quinones (Scheme 1).



Scheme 1. Synthesis of arylated quinones.

Since a few years, our research team has been focused on the development of new oxidant mediated CDCs.^[14] Indeed, the nature of the oxidant is particularly important in the context of CDCs because of its specific interactions with the substrates (and catalysts). Therefore, tuning its design can alter reactivity, and thus in some cases lead to new reaction concepts. Along this strategy, we were attempting to develop a cross dehydrogenative arylation method of phenols with notably hypervalent iodine oxidants, when we serendipitously came across the very regioselective arylated quinone **1c** depicted in Scheme 2. We then optimized the reaction conditions. It rapidly transpired that the reaction only operates with fluorophenols, wherein the fluoride is a leaving group.

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Scheme 2. Reaction optimization, yields determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard.

Moreover, the *ipso* arylation event does not occur. Instead, the arylation consistently occurs in *meta* position with respect to the fluoride leaving group (in the case of *para*-fluorophenols starting materials, see beneath for *ortho*-fluorophenols). Importantly, the arylation product is not observed when the fluoride leaving group

is replaced by chloride, bromide, or nitro. Furthermore, neither quinones nor hydroquinones deliver any arylation products, indicating that the latter structures are not reaction intermediates. In other words, the remote fluoride anion leaving group plays an essential enabling role in this arylation reaction. Different hypervalent iodine oxidants^[15] were otherwise tested in this reaction. lodosodilactone (I-8), a rare but trivial (non-fluorinated) hypervalent iodine reagent, performed best (80% yield of test coupling product 1c). Iodosodilactone I-8 was firstly synthesized and reported by Agosta^[16] in 1965. However, almost no reactions enabled by this iodine reagent were reported since then. In 2012, the Zhang group^[17] reported the single crystal structure of iodosodilactone I-8, showing an unusual planar shape which is unlike other typical aryl- λ^3 -iodanes (ie PIDA), with a typical T-shape structure. In any case, iodosodilactone I-8 can be prepared in large amount with high yield. Iodosodilactone I-8 is guite stable, it is neither air nor moisture sensitive, and can be stored for several months at room temperature without any detectable decomposition. Interestingly, the solvent has also a large impact on the reaction outcome. 1-Nitropropane, a cheap but also relatively rarely utilized solvent, outperforms other nitroalkanes and diverse usual organic solvents such as 1.2dichloroethane (DCE). With the best conditions in hand, we then explored the scope of this metal-free arylation reaction, for the synthesis of a variety of arylated 1,4-quniones (Scheme 3). For all the examples in which a para-fluorophenol was utilized as one of the building blocks, the arylation occurred exclusively at the 6-C-H-position. No 5-C-H arylation, nor ipso-(4-C-F)arylations were detected. Electron rich arylation coupling partners were found to be important in this reaction, anisoles reacting particularly well. It should moreover be noted that the C-H regioselectivity on the side of the anisole coupling partner is usually high, even if in some cases some minor (o/m/p) isomers could be detected.



Scheme 3. Regioselective synthesis of arylated 1,4-quinones, isolated yields. [a] Trace amounts of different selectivities (*o/m/p*) at the anisole moiety. [b] lodosobenzene diacetate (PIDA, I-1) was utilized instead of iodosodilactone.

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Some interesting functional groups were otherwise well tolerated, such as halides (5c, 11c, 16c, 20c), an allyl ether (4c), an isoxazole heterocycle (18c), and even phenols (19-21c). In the latter cases, very important phenolic quinones could be constructed in a single step, which would be difficult to synthetize otherwise (for the relevance of such phenolic quinone structures, see for example Euonyquinone A, Figure 1). In addition to arylated 1,4-quinone products, arylated 1,2-quinones could be accessed as well, from ortho-fluorophenols substrates (Scheme 4). 1,2-Quinones are also ubiquitous in many natural products, drugs and materials.^[18] However, the regioselective arylation of 1,2-quinones is very challenging proposition.^[19] Interestingly, in this configuration, the ortho-fluorophenol building block must also carry a para-methoxy electron donating functional group. Moreover, the arylation regioselectivity has now changed from meta to para C-H arylation with respect to the fluoride leaving group, thus delivering 4,5-disubstituted-1,2quinones. While the isolated vields remain moderate (1e-9e), a large variety of anisole arvlation coupling partners were well tolerated. In spite of the mentioned limitations above, the operational simplicity of this approach may pave the way for future arylation methods of 1,2-quinones. Finally, we also explored and optimized a diarvlation method derived from these reaction conditions, with a single fluoride leaving group.^[20] Reoptimizing the hypervalent iodine oxidant (PIFA, I-2) as well as the reaction temperature (-20°C) afforded 2,6-diarylated-1,4quinones in promising yields (Scheme 5).



Scheme 4. Regioselective synthesis of arylated 1,2-quinones, isolated yields. [a] Trace amounts of different selectivities (o/m/p) at the anisole moiety.

Some mechanistic experiments were then performed. Firstly, a ¹⁹F NMR *in situ* measurement in a polytetrafluoroethylene (PTFE) tube was carried out. **I-1** (PIDA) was utilized as the oxidant in this experiment, under otherwise standard conditions, and the ¹⁹F NMR spectra were measured every 30 minutes after the reaction started. The rapid appearance of a characteristic *quartet* NMR signal was observed at around δ = +49 ppm (q, ³*J_F*. H = 7 Hz), calibrated in relation to benzotrifluoride (-63 ppm),^[21] increasing in time, which corresponds to the buildup of acetyl fluoride (AcF, see SI).^[22]

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Scheme 5. Regioselective synthesis of diarylated 1,4-quinones, isolated yields. [a] Trace amounts of different selectivities (o/m/p) at the anisole moiety.

This gives an indication as to the role and fate of the fluoride leaving group. Indeed, based on this observation, we propose that "pseudo-ketal"[23] intermediate int-II[24-26] is formed (Scheme 6, mechanistic proposal). The fluoride anion would then attack the adjacent carboxyl ester upon the remote nucleophilic attack of the arene coupling partner (intermediates int-III and int-IV). This would thereby release the oxygen atom towards the hydroquinone intermediate int-V, which would further oxidize under aerobic conditions to the final 1,4-quinone coupling product c. In support of this hypothesis, we furthermore noted that while the reaction still operates under carefully degassed condition (N₂), the isolated yield of product 1c then decreases to only 23% (see SI). Thus, these combined elements: 1) presence of AcF, and 2) reaction operating under N₂, arguably constitute solid evidence that the second oxygen atom does indeed come from the hypervalent iodine oxidant. In the case of orthofluorophenol building blocks, the corresponding reaction intermediate int-V' is in principle blocked at the quaternary carbon stage. We propose that this structure is unlocked by the 1,2-aryl migration to the neighboring most electrophilic carbon, yielding catechol intermediate int-VI' / int-VII', in turn oxidized under aerobic condition to the 1,2 quinone final coupling product e. Importantly, when meta- fluorophenol (h) was engaged as a substrate with either anisole or alternatively 1.4dimethoxybenzene, no coupling products were found. Finally, we propose the double arlyation products g of Scheme 5 to arise from a simple Brønsted acid catalyzed second arylation event (intermediate int-V"), followed by aerobic oxidation. This is in good agreement with the fact that the more electrophilic / acidic hypervalent iodine reagent I-2 performs particularly well in this double arylation method (Scheme 5 & 6). Moreover, it should be noted that in the absence of a second fluoride leaving group, the regioselectivity of this second arylation event is probably controlled by the steric impact of the first aryl group in combination with a very low reaction temperature (-20 °C).

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Scheme 6. Proposed mechanistic pathways

The versatility of this reaction was then examined with the late stage C—H "quinonation" of Etofenprox, an insecticide containing multiple ether functional groups as well as multiple Csp^2 —H bond candidates (Scheme 7). A single cross-coupling product was obtained in promising (for such a large structure) 42% yield, without further optimization.



Scheme 7. Late stage C—H "quinonation" of Etofenprox.

In summary, we have developed a regioselective oxidative arylation method of fluorophenols. The method directly provides highly regioselective arylated *para* and even *ortho* quinones, in contrast to the state of the art in this field. This high regioselectivity is dictated by the relative position of the fluoride leaving group, along the lines that we described herein. We anticipate that this method will impact the field of bioactive and material based quinones.

Acknowledgements

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Keywords: Regioselective arylation • Hypervalent iodine • CDC • Arylated quinone • fluorophenols

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