Radical–Anion Coupling Through Reagent Design: Hydroxylation of Aryl Halides

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ABSTRACT: The design and development of an oxime-based hydroxylation reagent, which can chemoselectively convert aryl halides (X = F, Cl, Br, I) into phenols under operationally simple, transition-metal-free conditions is described. Key to the success of this approach was the identification of a reducing oxime anion which can interact and couple with open-shell aryl radicals. Experimental and computational studies support the proposed radical-nucleophilic substitution chain mechanism.

Arene hydroxylation reactions are powerful enabling synthetic methods which are routinely used in the preparation of high-value pharmaceuticals, agrochemicals, polymers and natural products. Many different synthetic approaches have been developed to form aryl C(sp²)–OH bonds, but in terms of cost, operational simplicity and toxicity, nucleophilic aromatic substitution (S_{NAr}) represents one of the most attractive and frequently used methods. However, the broad application and selectivity of this approach is limited by the high basicity and low nucleophilicity of the hydroxide anion. Hydroxide surrogates have been developed to improve these aspects, but their reactivity is still mostly limited to aryl fluorides or chlorides bearing strong electron-withdrawing groups in either the *ortho* or *para* positions. The development of more general, transition-metal-free substitution reactions for arene hydroxylation is therefore a topic of significant importance with wide-reaching synthetic potential.

It has long been known that aryl halides that are not activated with strong electron-withdrawing groups can be substituted with a variety of different nucleophiles through the radical-nucleophilic substitution (S_{RN}1) chain mechanism. However, hydroxide anions do not participate in S_{RN}1 mechanisms since such processes are driven by electron transfer (ET) and hydroxide anions are poor electron donors. Consequently, the activation barrier for radical–anion coupling is insurmountably high. This is a general problem with oxygen nucleophiles as, to the best of our knowledge, there is no known oxygen-based anion which can engage in intermolecular coupling with aryl radicals to form new C(sp²)–O bonds. Our efforts in solving this limitation are outlined herein. In particular, we rationalised that oxime anions could not only be electronically tuned to initiate and favour an S_{RN}1 process, but also serve as hydroxide surrogates. Indeed, based on literature precedent with perfluoroalkyl iodides, it was envisaged that oxime anions 1 may readily form charge-transfer complexes (CTCs, 2) with aryl halides 3, which could be activated under mild conditions to promote the formation of aryl radical intermediates 4 (Scheme 1a). Radical–anion coupling could then be rendered kinetically favourable by employing a sufficiently reducing oxime anion (Scheme 1b). In addition, it was anticipated that the oxime π-system could also alleviate the need for the aromatic coupling partner to accommodate the unpaired electron in this coupling process (e.g. 5 vs 6), and therefore enable coupling with a broader range of substrates. Finally, ET from the coupled radical anions 6 to the aryl halides 3 could propagate a radical chain and afford O-aryl oxime intermediates 7 (Scheme 1c), which as demonstrated by Fier and Maloney can readily fragment under basic conditions to afford phenols 8.

In this paper, using the design rationale set out in Scheme 1, we report the development of an easily handled oxime-based nucleophile which can selectively substitute an array of electronically diverse arenes bearing every common halide (F, Cl, Br, I) to form phenols under operationally simple, transition-metal-free conditions. The proposed S_{RN}1 chain mechanism is supported by experimental and DFT computational studies.

Scheme 1. Reagent and reaction design: a) Initiation; b) Radical–anion coupling; c) Reactivity of O-aryl oximes.
Our studies commenced by reacting aryl bromide 3a into a range of electronically diverse oximes 9a-d with a 0.1 mmol of oxime 9a-d and 0.2 mmol of base (0.2 mmol) in DMSO (0.5 mL) under nitrogen. In all cases, we observed the formation of phenol 8a in modest to excellent yield, with electron-rich pyrrole-based oxime 9d proving optimal (75%, entry 4). Notably, strongly coloured solutions were observed in every reaction, which can indicate the formation of charge-transfer complexes (CTCs). To investigate this possibility further, the reaction using oxime 9d was irradiated with blue LEDs ($\lambda_{\text{max}} = 455$ nm) for 1 h, which gave phenol 8a in 65% yield instead of 38% yield in the dark or 44% yield when exposed to ambient light from the laboratory (entries 5–7). Interestingly, reactivity was also significantly inhibited by the addition of Galvinoxyl (1 equivalent), which reduced the yield of phenol 8a to 10% (entry 8). Compatibility with different bases was also demonstrated (KOH and Cs$_2$CO$_3$), but phenol 8a was obtained in diminished yields (entries 9–10). Decreasing the reaction concentration and the equivalents of the oxime also decreased the yield of 8a and led to the formation of the hydrodehalogenated product 10.

**Table 1. Reaction optimization studies**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime</th>
<th>Temp./hv</th>
<th>Base</th>
<th>Time</th>
<th>Yield of 8a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>16 h</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>16 h</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>16 h</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>9d</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>16 h</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>9d</td>
<td>450 nm</td>
<td>KOt-Bu</td>
<td>1 h</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>9d</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>1 h</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>9d</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>1 h</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>9d</td>
<td>30 °C</td>
<td>KOt-Bu</td>
<td>1 h</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>9d</td>
<td>30 °C</td>
<td>KOH</td>
<td>16 h</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>9d</td>
<td>30 °C</td>
<td>Cs$_2$CO$_3$</td>
<td>16 h</td>
<td>25</td>
</tr>
</tbody>
</table>

a Reactions performed with 0.1 mmol of aryl bromide 3a into and 0.2 mmol oxime 9a-d with the stated base (0.2 mmol) in DMSO (0.5 mL) under nitrogen. b Determined by $^1$H NMR spectroscopy against an internal standard (dibromomethane). c Under irradiation with 18 W blue LEDs ($\lambda_{\text{max}} = 455$ nm) and fan cooling. d Reaction performed in the dark. e Reaction performed in the presence of Galvinoxyl (1 equivalent).

The acceleration of this reaction by light, its inhibition by Galvinoxyl and the detection of hydrodehalogenated product 10 all strongly indicated that a radical chain mechanism consistent with an $S_{\text{N}1}$ reaction was in operation. UV/Vis spectroscopic analysis of the reaction mixture and computational studies both supported the formation of a 1:1 CTC 2a (formed between anion 1d and aryl bromide 3a$^t$), which may be activated with light or heat to promote the formation of aryl radical 4a (Scheme 2). The envisaged coupling of 4a with oxime anion 1d was also theoretically explored by DFT computational analysis. These studies suggest that radical–anion coupling is exergonic ($\Delta G^\ddagger = -17.2$ kcal/mol) and there is only a modest activation barrier for radical–anion coupling ($\Delta G^\ddagger = 15.0$ kcal/mol), which is almost entirely entropic in nature ($\Delta H^\ddagger = 0.4$ kcal/mol). Considering this, any attractive interaction between the oxime anion and aryl radical could dramatically accelerate the rate of coupling. Indeed, we observed the formation of a weak two-centre three-electron (2e,3c) d-bonded species 11a in the gas phase$^{12}$. In addition, when accounting for concentration effects, the large excess of the oxime anion relative to the radical-anion product will likely lower the activation barrier by ~4 kcal/mol (see the Supporting Information for details). The calculated redox potential of the coupled radical anion 6a ($E_{\text{1/2}} = -2.14$ vs SCE) indicates that propagation of a radical chain by ET to aryl bromide 3a$^t$ ($E_{\text{1/2}} = -1.89$ vs SCE)$^{13}$ would also be exergonic. The resultant neutral O-aryl oxime could then fragment under the basic reaction conditions to afford the observed phenol product. A polar $S_{\text{N}2}$ pathway was considered unlikely to proceed at 30 °C due to the significant activation barrier calculated for the addition of the oxime anion ($\Delta G^\ddagger = 32.4$ kcal/mol).
Importantly, oxime reagent 9d is an easily handled white solid that is prepared on a gram-scale simply by condensing commercial aldehyde 12 with hydroxylamine in the presence of Na$_2$CO$_3$ (Scheme 3). To showcase the utility of designed reagent oxime 9d, the scope of this new arene hydroxylation reaction was fully explored (Table 2). We first sought to determine if halides other than bromine could be substituted by examining a variety of para- and ortho-substituted aromatic carbonyl derivatives (3a–e). Pleasingly, these derivatives could all be converted into the corresponding phenols in good to excellent yields, which demonstrates the compatibility of this reagent with every common halide nucleofuge. However, of the meta-substituted carbonyl derivatives, only fluoride 3f could be efficiently substituted and that was at elevated temperature (60 °C), which may be due to a switch to a complementary polar SnAr mechanism. Benzonitrile and sulfone derivatives (3g–j) were also examined and the same reactivity pattern was observed: para-substituted derivatives (3g,i) reacted smoothly at 30 °C, whilst the meta-isomers (3h,j) required prolonged reaction times or heating at 60 °C. This reactivity pattern may directly correspond to the rate of radical-anion fragmentation, which is typically ortho > para > meta for aryl halides. More strongly electronically activated trifluoromethyl- and nitro-substituted aryl halides (3k–n) were all hydroxylated in typically excellent yields at 30 °C. Relatively unactivated 1-naphthyl and 4-biphenyl halides (3o,p) could also be substituted to afford the desired phenols in modest to excellent yields, although they generally required more forcing reaction conditions (100 °C) and the use of NaOt-Bu as the base. These harsher conditions may be required to overcome higher activation barriers associated with polar pathways (SnAr or benzyne) or challenging ET initiation events (e.g., from the oxime anion to the arene).

Table 2. Scope of the aryl halide substitution protocol

![Scheme 2. Calculations and orbital illustrations to support the proposed radical–anion coupling mechanism](image)

![Scheme 3. Oxime synthesis](image)
Reactions performed on a 0.30 mmol scale in 1.5 mL of DMSO. Substituted halogens highlighted.

Yield of volatile compound determined by $^1$H or $^{19}$F NMR spectroscopy against an internal standard (dibromomethane and $^{1}$-fluoronaphthalene, respectively).

Intrigued by the reactivity and selectivity of some of the aryl fluorides, which could in theory also be substituted via a polar S$_{N}$Ar pathway, their reactions were also studied in the presence of Galvinoxyl (Scheme 4a). Interestingly, clear inhibition was observed for every example, which indicates that these reactions are at least partially radical in nature. Alternatively, it is possible that Galvinoxyl may disrupt CTC formation, which can theoretically facilitate both polar and open-shell reactivity. In this regard, it should also be noted that the formation of strongly coloured reaction mixtures was observed for almost every substrate described in Table 2, which suggests that CTC formation with oxime reagent 9d could be a general process.

Thus, considering these results and our previous observations, it is reasonable to assume that many of the substitution reactions described herein likely proceed via an open-shell mechanism. We therefore propose that an electron-catalysed S$_{N}$1 chain is initiated by either the formation and activation of a CTC, or a slow thermal (concerted) dissociative ET from an anionic electron donor (e.g. the oxime anion 1) to the aryl halide 3 (Scheme 4b). The resultant aryl radical 4 can then interact with an oxime anion 1 to form a weakly interacting cluster that may be viewed as a 2c,3e σ bonded species 11. As this bond shortens, a delocalised radical anion 6 (and a standard 2c,2e bond) is then formed by intramolecular ET from species 11 into a nearby π* orbital (on either the oxime or the aryl ring). Radical anion 6 then reduces another equivalent of 3 through intermolecular ET to regenerate aryl radical 4 and release the coupled product 7, which fragments in situ to afford the observed phenol product. However, the contribution of a polar S$_{N}$Ar pathway for some substrates cannot be completely excluded.

Scheme 4. a) Additional additive inhibition studies; b) Proposed S$_{N}$1 mechanism.
In summary, we have reported the design and development of a new oxime-based hydroxylation reagent, which can be used to chemoselectively convert aryl halides into phenols under remarkably simple, transition-metal-free conditions. These reactions are proposed to primarily proceed via the unprecedented intermolecular coupling of an oxygen-based anion with aryl radicals to form new C(sp²)–O bonds. We believe that the synthetic utility of this reagent is likely enhanced by its ability to substitute nitrile oxides through complementary polar pathways. It is hoped that these findings will facilitate the rational design of other such anionic reagents and enable new unconventional retrosynthetic strategies to be realised.

ASSOCIATED CONTENT
Supporting Information Experimental procedures, characterisation data, computational details, and copies of 1H, 13C and 31P NMR spectra for all compounds featured in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org

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REFERENCES


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<th>Additive</th>
<th>Ac</th>
<th>Br</th>
<th>F</th>
<th>Me</th>
<th>Ph</th>
<th>n-pentyl</th>
<th>3,5-dimethylphenyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>83%</td>
<td>56%</td>
<td>61%</td>
<td>56%</td>
<td>61%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galvinoxyl (1 eq.)</td>
<td>24%</td>
<td>17%</td>
<td>8%</td>
<td>24%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.1 mmol scale

a) Additive inhibition studies

b) Proposed S N 1 mechanism

[Diagram]

[Diagram]

[Diagram]


(14) Although no other regioisomers were observed, the possibility of benzene intermediates in some reactions cannot be excluded. For relevant work, see: (a) Goetz, A. E.; Garg, N. K. Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model. *Nat. Chem.* **2013**, *5*(1), 54–60.


(b) Elliott, Q.; dos Passos Gomes, G.; Evoniuik, C. J.; Alabugin, I. V. Testing the Limits of Radical-Anionic CH-Amination: A 10-Million-Fold Decrease in Basicity Opens a New Path to...
\[ \text{Ar}_X \quad + \quad \text{Me}^\text{HO}^+ \quad \overset{\text{Base, DMSO}}{\rightarrow} \quad \text{Ar}_\text{OH} \]

\( X = \text{F, Cl, Br, I} \)