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Introduction

Radical—anion coupling through reagent design: hydroxylation of aryl halides†

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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 highvalue pharmaceuticals, agrochemicals, polymers and natural products.1 Many different synthetic approaches have been developed to form aryl C(sp²)-OH bonds,² but in terms of cost, operational simplicity and toxicity, nucleophilic aromatic substitution (S_NAr)³ represents one of the most attractive and frequently used methods.⁴ 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.5 The development of more general, transition-metal-free6 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.⁷ 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



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.

Results and discussion

Our studies commenced by reacting aryl bromide $3a_{Br}$ with a range of electronically diverse oximes (9a–d are representative) using KOt-Bu in anhydrous DMSO (0.2 M) at 30 °C for 16 h

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[†] Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, computational details, and copies of ¹H, ¹³C and ¹⁹F NMR spectra for all compounds featured in this manuscript. CCDC 2102632 and 2102633. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc04748e

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Scheme 1 Reagent and reaction design: (a) initiation; (b) radicalanion coupling; (c) reactivity of O-aryl oximes.

under nitrogen (Table 1, entries 1-4). 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). The compatibility of oxime 9d with different bases was also demonstrated (KOH and Cs₂CO₃), but phenol 8a was obtained in diminished yields (entries 5 and 6). Notably, strongly coloured solutions were observed in every reaction, which can indicate the formation of CTCs. To investigate this possibility further, the reaction using oxime 9d was irradiated with blue LEDs ($\lambda_{max} = 455 \text{ nm}$) 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 7-9). However, under these photochemical conditions the yield of 8a was partially diminished by the formation of the hydrodehalogenated byproduct 10, which suggested that aryl radicals may be potential intermediates in this reaction. Indeed, reactivity was significantly inhibited by the addition of galvinoxyl or DPPH (1 equiv.) as electron accepting radical scavengers, which reduced the yield of phenol 8a to $\leq 10\%$ (entries 10 and 11). The addition of TEMPO had a relatively small effect on the yield of phenol 8a (entry 12, no trapped product was detected by high-resolution mass spectrometry but consumption of TEMPO was observed by EPR spectroscopy). However, it should be noted that the coupling of nitroxyl radicals with aryl radicals is known to be relatively slow in polar solvents.12

The acceleration of this reaction by light, its inhibition by galvinoxyl and DPPH, and the detection of hydrodehalogenated product **10** all strongly indicated that a radical chain mechanism consistent with an $S_{\rm RN}$ 1 reaction was in operation. UV/vis spectroscopic analysis of the reaction mixture and

Table 1 Reaction optimization studies



^{*a*} Reactions performed with 0.1 mmol of aryl bromide $3a_{Br}$ and 0.2 mmol oxime 9a-d with the stated base (0.2 mmol) in DMSO (0.5 mL) under nitrogen. ^{*b*} Determined by ¹H NMR spectroscopy against an internal standard (dibromomethane). ^{*c*} Under irradiation with 18 W blue LEDs ($\lambda_{max} = 450$ nm) and fan cooling. ^{*d*} Reaction performed in the dark. ^{*e*} Reaction performed in the presence of galvinoxyl (1 equiv.). ^{*f*} Reaction performed in the presence of TEMPO (2 equiv.).

computational studies both supported the formation of a 1:1 CTC 2a (formed between anion 1d and aryl bromide $3a_{Br}$), which may be activated with light or heat^{10c,d} 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.13 These studies suggest that radical-anion coupling is exergonic ($\Delta G = -17.2 \text{ kcal mol}^{-1}$) and there is only a modest activation barrier for radical-anion coupling ($\Delta G^{\ddagger} = 15.0$ kcal mol⁻¹), which is almost entirely entropic in nature ($\Delta H^{\ddagger} = 0.4$ kcal mol⁻¹). 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 (2c, 3e) σ bonded species **11a** in the gas phase.¹⁴ 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 $\sim 4 \text{ kcal mol}^{-1}$ (see the ESI[†] for details). The calculated redox potential of the coupled radical anion 6a ($E_{1/2} = -2.14 \text{ vs. SCE}$) indicates that propagation of a radical chain by ET to aryl bromide $3a_{Br}$ ($E_{1/2} = -1.89 \nu s$. SCE)15 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_NAr pathway was considered unlikely to proceed at 30 °C due to the



Scheme 2 Calculations and orbital illustrations to support the proposed radical-anion coupling mechanism

significant activation barrier calculated for the addition of the oxime anion ($\Delta G^{\ddagger} = 32.4 \text{ kcal mol}^{-1}$).

Importantly, oxime reagent 9d is an easily handled white solid that is prepared on a gram-scale simply by condensing commercial aldehvde 12 with hydroxylamine in the presence of Na₂CO₃ (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 metasubstituted carbonyl derivatives, only fluoride $3f_F$ could be efficiently substituted and that was at elevated temperature (60 °C), which may be due to a switch to a complementary polar S_NAr 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.^{7b} More strongly electronically activated trifluoromethyl- and nitrosubstituted aryl halides (3k-n) were all hydroxylated in typically excellent yields at 30 °C. Relatively unactivated 1-naphthyl



Scheme 3 Oxime synthesis.

and 4-biphenyl halides (30, p) could also be substituted to afford the desired phenols in modest to excellent yields, although they generally required more forcing reaction conditions (100 $^{\circ}$ 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 (S_NAr or benzyne¹⁶) or challenging ET initiation events (e.g. from the oxime anion to the arene). However, the ortho-fluorine substituent of dihalogenated biphenyl 3q_F could be easily and selectively substituted at 30 °C to afford the phenol in 78% yield. This remarkable reactivity may be due to the sterics of the phenyl ring forcing the fluorine atom to bend out of plane, which could facilitate either a S_NAr mechanistic switch or accelerate the rate of radical anion C-F bond fragmentation.^{17,18} The ortho-fluorine substituent of dihalogenated acetophenone 3rF was also selectively substituted under these reaction conditions. Next, heteroaryl halides were studied (3s-v), and pleasingly activated pyridine 3s_{Br} could be hydroxylated in excellent yield at 30 °C. Unactivated bromo quinolines 3t, u could also be substituted to afford the corresponding phenols in 44-73% yield. Interestingly, as previously observed for dihalogenated arenes, the fluorine atom of pyridine $3v_F$ could also be selectively substituted. Finally, the wider synthetic utility of oxime reagent 9d was demonstrated through the functionalization of aryl halide containing drugs; pleasingly, fenofibrate $3w_{Cl}$, iloperidone $3x_F$, etoricoxib $3y_{Cl}$ and blonanserin $3z_F$ were all successfully hydroxylated (47-83% yield).

Intrigued by the reactivity and selectivity of some of the aryl fluorides, which could in theory also be substituted *via* a polar S_NAr 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 polar¹⁹ and open-shell reactivity. In this

Table 2 Scope of the aryl halide substitution protocol^a



^{*a*} Reactions performed on a 0.30 mmol scale in 1.5 mL of DMSO. Substituted halogens highlighted. ^{*b*} Yield of volatile compound determined by ¹H or ¹⁹F NMR spectroscopy against an internal standard (dibromomethane and 1-fluoronaphthalene, respectively).



Scheme 4 (a) Additional additive inhibition studies; (b) proposed ${\rm S}_{\rm RN}{\rm 1}$ mechanism.

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^{7c} S_{RN} 1 chain is initiated by either the formation and activation of a CTC, or a slow thermal (concerted) dissociative ET²⁰ from an anionic electron donor²¹ (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, $3e \sigma$ bonded species 11.²² 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.23 However, the contribution of

(00)

a polar $S_{\ensuremath{N}\xspace}\xspace$ Ar pathway for some substrates cannot be completely excluded.

Conclusions

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 $C(sp^2)$ –O bonds. We believe that the synthetic utility of this reagent is likely enhanced by its ability to substitute nucleofuges 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.

Data availability

Experimental procedures, characterisation data, computational details, and copies of ¹H, ¹³C and ¹⁹F NMR spectra for all compounds featured in this manuscript are provided in the ESI.[†]

Author contributions

Conceptualisation, supervision and writing – M. J. J.; investigation and methodology – A. J. G., P. U., W. O. W., G. S., I. O., A. C. W., V. C., M. J. J.; all authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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