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.

Introduction

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_{Ar}) 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_{RN1}) chain mechanism.¶ However, hydroxide anions do not participate in S_{RN1} 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.⁷⁺ 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_{RN1} process, but also serve as hydroxide surrogates. Indeed, based on literature precedent with perfluoroalkyl iodides,⁸ it was envisaged that oxime anions 1 may readily form charge-transfer complexes⁹ (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,¹⁰ 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_{RN1} chain mechanism is supported by experimental and DFT computational studies.

Results and discussion

Our studies commenced by reacting aryl bromide 3a_{Bu} 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.

† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, computational details, and copies of {H, 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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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 CT complexes. To investigate this possibility
further, the reaction using oxime 9d was irradiated with blue
LEDs (λmax = 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 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 ≤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
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 mecha-
nism consistent with an SN₂ 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 3aBr),
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.¹³ These studies suggest that radical–anion
coupling is exergonic (ΔG = −17.2 kcal mol⁻¹)
and there is only a modest activation barrier for radical–anion
coupling (ΔH° = 15.0 kcal mol⁻¹), which is almost entirely
entropic in nature (ΔH° = 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 ~4 kcal mol⁻¹ (see the ESI† for
details). The calculated redox potential of the coupled radical
anion 6a (E1/2 = −2.14 vs. SCE) indicates that propagation of a
radical chain by ET to aryl bromide 3aBr (E1/2 = −1.89 vs.
SCE) 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 SN₂Ar pathway
was considered unlikely to proceed at 30 °C due to the

Table 1. Reaction optimization studies

| Entry | Oxime | Temp./hv | Base | Time | Yield | temp. 8a (%) |
|-------|-------|---------|------|------|-------|-------------|
| 1     | 9a    | 30 °C   | KOr-Bu | 16 h | 52    | 49          |
| 2     | 9b    | 30 °C   | KOr-Bu | 16 h | 45    |             |
| 3     | 9c    | 30 °C   | KOr-Bu | 16 h | 38    |             |
| 4     | 9d    | 30 °C   | KOr-Bu | 16 h | 75    |             |
| 5     | 9d    | 30 °C   | KOH   | 16 h | 38    |             |
| 6     | 9d    | 30 °C   | Cs₂CO₃| 16 h | 25    |             |
| 7     | 9d    | 450 nm  | KOr-Bu| 1 h  | 65    |             |
| 8     | 9d    | 30 °C   | KOr-Bu| 1 h  | 38    |             |
| 9     | 9d    | 30 °C   | KOr-Bu| 1 h  | 44    |             |
| 10    | 9d    | 30 °C   | KOr-Bu| 1 h  | 10    |             |
| 11    | 9d    | 30 °C   | KOr-Bu| 1 h  | 5     |             |
| 12    | 9d    | 30 °C   | KOr-Bu| 16 h | 49    |             |

¹ Reactions performed with 0.1 mmol of aryl bromide 3aBr and
0.2 mmol oxime 9a-d with the stated base (0.2 mmol) in DMSO (0.5
mL) under nitrogen. ¹ Determined by ¹H NMR spectroscopy against
an internal standard (dibromomethane). ¹ Under irradiation with
18 W blue LEDs (λmax = 450 nm) and fan cooling. ¹ Reaction
performed in the dark. ¹ Reaction performed in the presence of
galvinoxyl (1 equiv.). ¹ Reaction performed in the presence of DPPH (1
equiv.). ¹ Reaction performed in the presence of TEMPO (2 equiv.).
significantly activation barrier calculated for the addition of the oxime anion (ΔG°° = 32.4 kcal mol⁻¹).

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 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 yields, which demonstrates the compatibility of this reagent converted into the corresponding phenols in good to excellent 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 S₅Ar mechanistic switch or accelerate the rate of radical anion F bond fragmentation.³⁻⁴ The ortho-fluorine substituent of dihalogenated acetophenone 3r could also be selectively 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 (S₅Ar or benzynes⁶) or challenging ET initiation events (e.g. from the oxime anion to the arene). However, the ortho-fluorine substituent of dihalogenated biphenyl 3q could be easily and selectively substituted at 30 °C to afford the phenol in 78% yield. This remarkable reactivity may be due to the steric of the phenyl ring forcing the fluorine atom to bend out of plane, which could facilitate either a S₅Ar mechanistic switch or accelerate the rate of radical anion C-F bond fragmentation.³⁻⁴ The ortho-fluorine substituent of dihalogenated acetophenone 3r was also selectively substituted under these reaction conditions. Next, heteroaryl halides were studied (3s–w), and pleasingly activated pyridine 3s 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 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, etoricoxib 3y, iloperidone 3z, etoricoxib 3y, and blonanserin 3z 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 S₅Ar 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 polar⁴³ 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 observa-
tions, 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
SRN1 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) to the aryl
halide (Scheme 4b). The resultant aryl radical can then
interact with an oxime anion to form a weakly interacting
cluster that may be viewed as a 2c, 3e bonded species.
As this bond shortens, a delocalised radical anion (and a stan-
dard 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

Table 2  Scope of the aryl halide substitution protocol

| Ar   | X     | Molar  | 3 (1.0 eq.) | 9d (2.0 eq.) | KOt-Bu / NaOt-Bu | DMSO (0.2 M) | 30–100 °C, 16 h | 8          |
|------|-------|--------|-------------|--------------|-----------------|--------------|----------------|-------------|
| Ac   | Br    | 82%    | (30 °C)     |              |                 |              |                |             |
|      | Cl    | 73%    | (30 °C)     |              |                 |              |                |             |
|      | F     | 88%    | (30 °C)     |              |                 |              |                |             |
| NC   | Br    | 53%    | (30 °C, 48 h)|             |                 |              |                |             |
|      | Br    | 70%    | (30 °C)     |              |                 |              |                |             |
|      | F     | 64%    | (30 °C)     |              |                 |              |                |             |
|      | Cl    | 64%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 64%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 80%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 57%    | (30 °C)     |              |                 |              |                |             |
|      | Cl    | 76%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 76%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 44%    | (30 °C)     |              |                 |              |                |             |
|      | Br    | 73%    | (100 °C)    |              |                 |              |                |             |
|      | Cl    | 73%    | (100 °C)    |              |                 |              |                |             |
|      | Br    | 73%    | (100 °C)    |              |                 |              |                |             |
|      | Cl    | 57%    | (100 °C)    |              |                 |              |                |             |

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 SRN1 mechanism.
a polar S_NAr 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^3)-O bonds. We believe that the synthetic utility of this reagent is likely enhanced by its ability to substitute nucleofugues 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., L. 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.

Acknowledgements

The authors would like to thank the Wild Fund, the University of York, the Leverhulme Trust (for an Early Career Fellowship, ECF-2019-135, M. J. J.) and the Royal Society (Research Grant RGS/R1/201268) for financial support. We would also like to thank Prof. Peter O’Brien and Dr William P. Unsworth for helpful discussions.

Notes and references

1 Z. Rappoport, The Chemistry of Phenols, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2003, ISBN: 978-0-471-49737-0.
2 For selected examples of different arene hydroxylation strategies, see: (a) K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, J. Am. Chem. Soc., 2006, 128, 10694–10695; (b) A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann and M. Beller, Angew. Chem., Int. Ed., 2009, 48, 7595–7599; (c) A. Tili, N. Xia, F. Monnier and M. Taillefer, Angew. Chem., Int. Ed., 2009, 48, 8725–8728; (d) S. Bracegirdle and E. A. Anderson, Chem. Commun., 2010, 46, 3454; (e) C. Zhu, R. Wang and J. R. Falck, Org. Lett., 2012, 14, 3494–3497; (f) K. Ohkubo, A. Fujimoto and S. Fukuzumi, J. Am. Chem. Soc., 2013, 135, 5368–5371; (g) S. Xia, L. Gan, K. Wang, Z. Li and D. Ma, J. Am. Chem. Soc., 2016, 138, 13493–13496; (h) J. Börjel, L. Tanwar, F. Berger and T. Ritter, J. Am. Chem. Soc., 2018, 140, 16026–16031; (i) L. Yang, Z. Huang, G. Li, W. Zhang, R. Cao, C. Wang, J. Xiao and D. Xue, Angew. Chem., Int. Ed., 2018, 57, 1968–1972; (j) R. Sang, S. E. Korkis, W. Su, F. Ye, P. S. Engl, F. Berger and T. Ritter, Angew. Chem., Int. Ed., 2019, 58, 16161–16166; (k) Y. M. Cai, Y. T. Xu, X. Zhang, W. X. Gao, X. B. Huang, Y. B. Zhou, M. C. Liu and H. Y. Wu, Org. Lett., 2019, 21, 8479–8484.
3 (a) J. F. Bunnett and R. E. Zahler, Chem. Rev., 1951, 49, 273–412; (b) F. Terrier, Modern Nucleophilic Aromatic Substitution, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2013, ISBN: 9783527656141; (c) S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba and J. A. Murphy, Angew. Chem., Int. Ed., 2019, 58, 16368–16388.
4 (a) D. G. Brown and J. Boström, J. Med. Chem., 2016, 59, 4443–4458; (b) D. G. Brown and J. Boström, J. Med. Chem., 2016, 59, 4443–4458.
5 For related hydroxide surrogate substitution reactions, see: (a) A. P. Krapcho and D. Waterhouse, Synth. Commun., 1998, 28, 3415-3422; (b) J. F. Rogers and D. M. Green, Tetrahedron Lett., 2002, 43, 3585-3587; (c) J. I. Levin and M. T. Du, Synth. Commun., 2002, 32, 1401-1406; (d) P. S. Fier and K. M. Maloney, Org. Lett., 2016, 18, 2244-2247; (e) Y. Zhou, J. Chem. Res., 2017, 41, 591-593; (f) M. Reitti, R. Gurubrahnam, M. Walther, E. Lindstedt and B. Olofsson, Org. Lett., 2018, 20, 1785-1788.
6 (a) C.-L. Sun and Z.-J. Shi, Chem. Rev., 2014, 114, 9219–9280; (b) W. Liu, J. Li, C. Huang and C. Li, Angew. Chem., Int. Ed., 2020, 59, 1786-1796.
7 (a) J. F. Bunnett and J. K. Kim, J. Am. Chem. Soc., 1970, 92, 7463–7464; (b) R. A. Rossi, A. B. Pierini and A. B. Peñéñoy, Chem. Rev., 2003, 103, 71–168; (c) A. Studer and D. P. Curran, Nat. Chem., 2014, 6, 765-773.
8 (a) C. Amatore, J. Badoz-Lambling, C. Bonnel-Hughes, J. Pinson, J. M. Saveant and A. Thiebault, J. Am. Chem. Soc., 1982, 104, 1979–1986; (b) M. T. Baumgartner, A. B. Pierini and R. A. Rossi, Tetrahedron Lett., 1992, 33, 2323–2326; (c) J. M. Saveant, J. Phys. Chem., 1994, 98, 3716–3724.
9 For an example of an S_NAr reaction with oxime anions and alkyl radicals initiated by the photochemical activation of a CTC, see: Z. Chen, H. Liang, R. Chen, L. Chen, X. Tang, M. Yan and X. Zhang, Adv. Synth. Catal., 2019, 361, 3324–3330.
10 (a) C. G. S. Lima, T. de M. Lima, M. Duarte, J. D. Jurberg and M. W. Paixão, ACS Catal., 2016, 6, 1389–1407; (b) G. E. M. Crisenzia, D. Mazzarella and P. Melchiorre, J. Am. Chem. Soc., 2020, 142, 5461–5476; (c) M. A. Fox, J. Younathan and G. E. Fryxell, J. Org. Chem., 1983, 48, 3109–3112; (d) S. V. Rosokha and J. K. Kochi, New J. Chem., 2002, 26, 851–860.
All calculations were performed using the ORCA 4.2.0 software package: (a) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, 2, 73–78; (b) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2018, 8, e1327; Unless stated otherwise, calculations were carried out using the ωB97X-D3(BJ) functional with the ma-def2-TZVP basis set and the CPCM continuum solvation model (DMSO); (c) S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, 132, 154104; (d) S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, 32, 1456–1465; (e) A. Najibi and L. Goerigk, *J. Chem. Theory Comput.*, 2018, 14, 5725; (f) W. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, 7, 3297; (g) J. Zheng, X. Xu and D. G. Truhlar, *Theor. Chem. Acc.*, 2011, 128, 295–305; (h) M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.*, 2003, 24, 669–681.

Dielectric continuum solvation models are known to obscure weak radical–anion interactions. For example, see: A. Cardinale, A. A. Isse, A. Gennaro, M. Robert and J.-M. Savéant, *J. Am. Chem. Soc.*, 2002, 124, 13333–13339.

Although no other regioisomers were observed, the possibility of benzylene intermediates in some reactions cannot be excluded. For relevant work, see: (a) A. E. Goetz and N. K. Garg, *Nat. Chem.*, 2013, 5, 54–60; (b) Y. Dong, M. I. Lipschutz and T. D. Tilley, *Org. Lett.*, 2016, 18, 1530–1533; (c) F. I. M. Idris and C. R. Jones, *Org. Biomol. Chem.*, 2017, 15, 9044–9056.