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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.[1] Many different synthetic approaches have been developed to form aryl C(sp^2)–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-free[6] 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 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(sp^2)–O bonds.[7b,8] 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,[9] it was envisaged that oxime anions **1** may readily form charge-transfer complexes[10] (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[11] 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.

Results and discussion

Our studies commenced by reacting aryl bromide $\mathbf{3a_{Br}}$ with a range of electronically diverse oximes (**9a–d** are representative) using KO*t*-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 ^{1}H, ^{13}C and ^{19}F 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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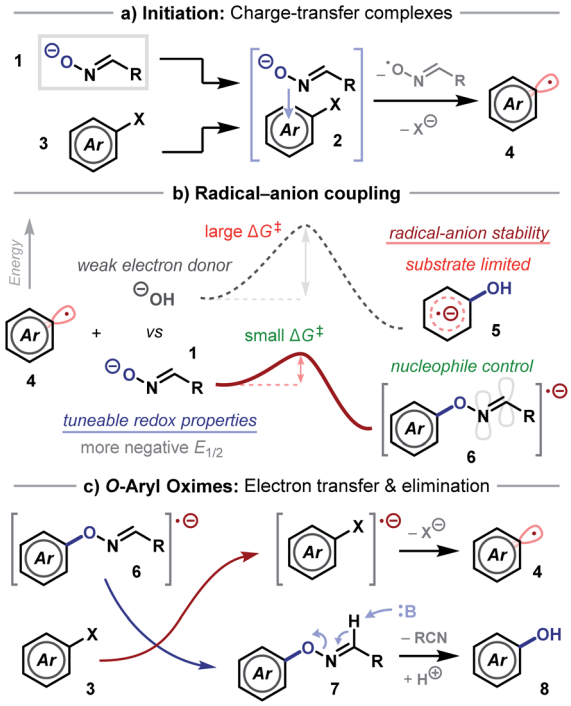
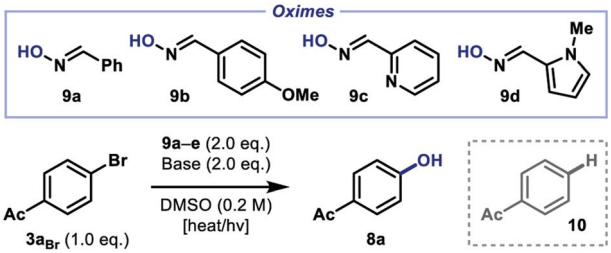


Scheme 1 Reagent and reaction design: (a) initiation; (b) radical–anion coupling; (c) reactivity of *O*-aryl oximes.

Table 1 Reaction optimization studies

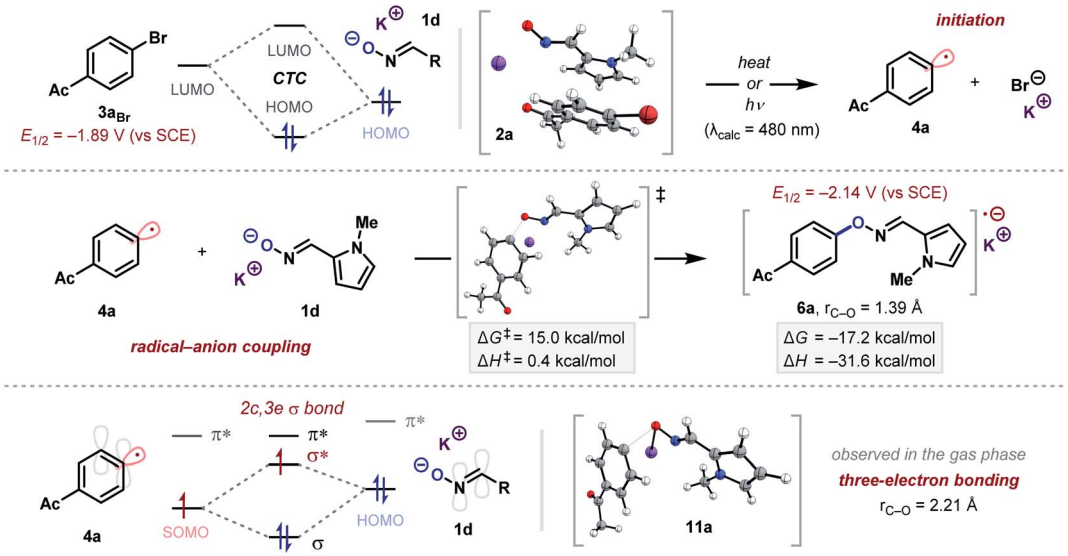


Entry[a]	Oxime	Temp./hv	Base	Time	Yield[b] 8a/%
1	**9a**	30 °C	KO*t*-Bu	16 h	52
2	**9b**	30 °C	KO*t*-Bu	16 h	45
3	**9c**	30 °C	KO*t*-Bu	16 h	38
4	**9d**	30 °C	KO*t*-Bu	16 h	75
5	**9d**	30 °C	KOH	16 h	38
6	**9d**	30 °C	Cs_2CO_3	16 h	25
7[c]	**9d**	450 nm	KO*t*-Bu	1 h	65
8[d]	**9d**	30 °C	KO*t*-Bu	1 h	38
9	**9d**	30 °C	KO*t*-Bu	1 h	44
10[e]	**9d**	30 °C	KO*t*-Bu	16 h	10
11[f]	**9d**	30 °C	KO*t*-Bu	16 h	<5
12[g]	**9d**	30 °C	KO*t*-Bu	16 h	49

[a] Reactions performed with 0.1 mmol of aryl bromide $\mathbf{3a_{Br}}$ and 0.2 mmol oxime **9a–d** with the stated base (0.2 mmol) in DMSO (0.5 mL) under nitrogen. [b] Determined by ^{1}H NMR spectroscopy against an internal standard (dibromomethane). [c] Under irradiation with 18 W blue LEDs (λ_{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 DPPH (1 equiv.). [g] Reaction performed in the presence of TEMPO (2 equiv.).

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 Cs_2CO_3), 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 (λ_{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 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 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 $S_{RN}1$ 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 $\mathbf{3a_{Br}}$), 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 (ΔG = −17.2 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 ∼4 kcal mol^{-1} (see the ESI† for details). The calculated redox potential of the coupled radical anion **6a** ($E_{1/2}$ = −2.14 *vs.* SCE) indicates that propagation of a radical chain by ET to aryl bromide $\mathbf{3a_{Br}}$ ($E_{1/2}$ = −1.89 *vs.* 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

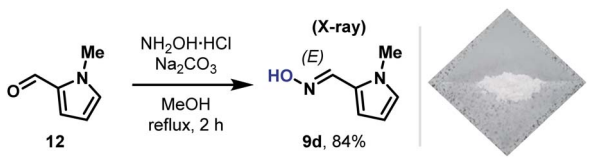


Scheme 2 Calculations and orbital illustrations to support the proposed radical–anion coupling mechanism.

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

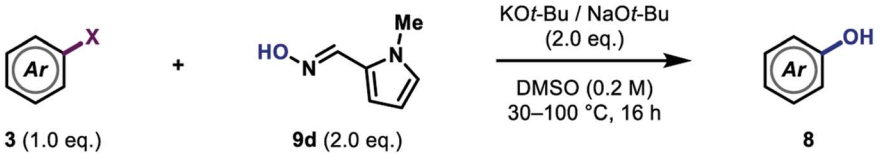
Importantly, oxime reagent **9d** is an easily handled white solid that is prepared on a gram-scale simply by condensing commercial aldehyde **12** with hydroxylamine in the presence of Na_2CO_3 (Scheme 3). To showcase the utility of designed reagent oxime **9d**, the scope of this new arene hydroxylation 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$_F$** 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 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 NaO*t*-Bu as the base. These harsher conditions may be required to overcome higher activation barriers associated with polar pathways (S_NAr or benzyne[16]) 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 **3r$_F$** 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).

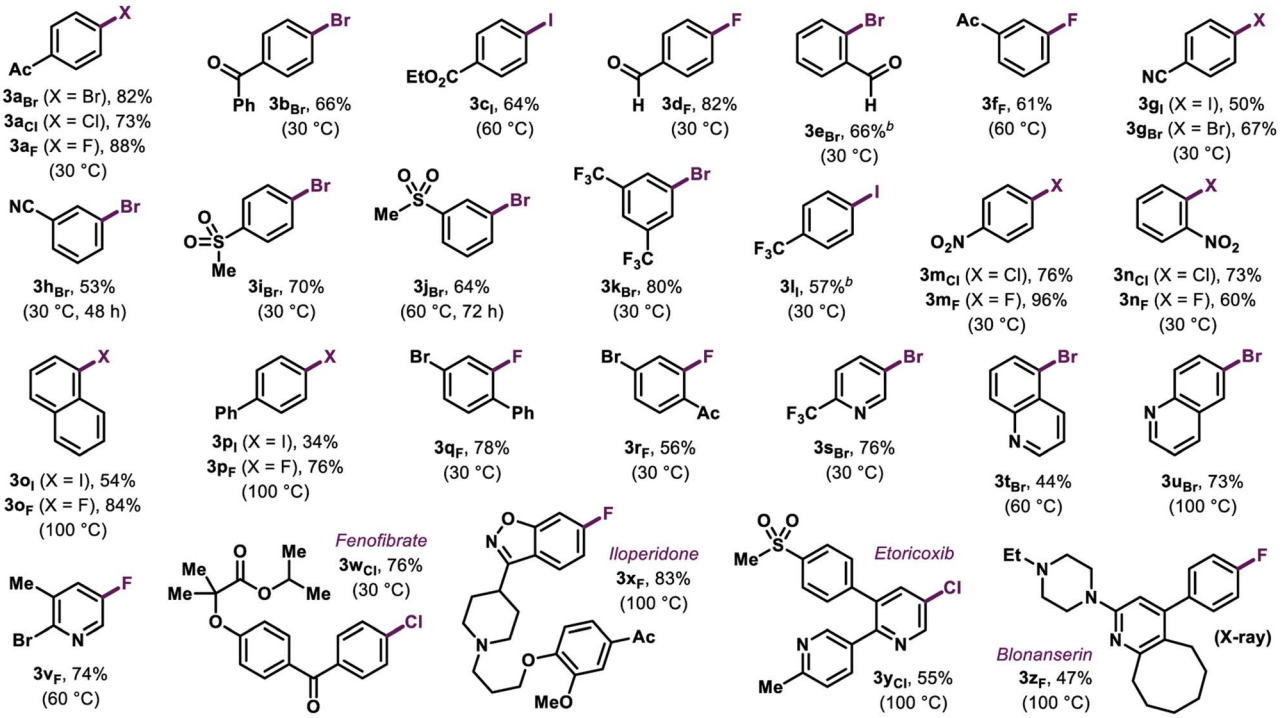
Intrigued by the reactivity and selectivity of some of the aryl fluorides, which could in theory also be substituted *via* a polar S_NAr pathway, their reactions were also studied in the presence of galvinoxyl (Scheme 4a). Interestingly, clear inhibition was observed for every example, which indicates 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 polar[19] and open-shell reactivity. In this



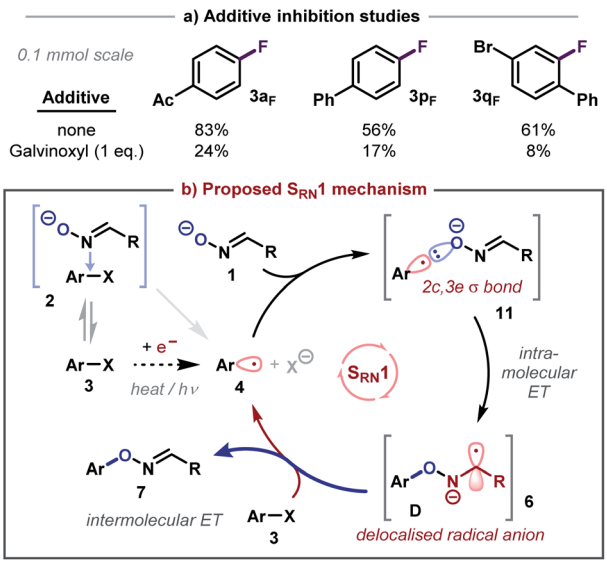
Scheme 3 Oxime synthesis.

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 ^{1}H or ^{19}F NMR spectroscopy against an internal standard (dibromomethane and 1-fluoronaphthalene, respectively).



Scheme 4 (a) Additional additive inhibition studies; (b) proposed $S_{RN}1$ 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 ET[20] from an anionic electron donor[21] (*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**.[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

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^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, ^{13}C and ^{19}F 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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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. Tlili, 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. Börgel, 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. Gurubrahamam, 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. Peñéñory, *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-Huyghes, 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 $S_{RN}1$ 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, I. D. Jurberg and M. W. Paixão, *ACS Catal.*, 2016, **6**, 1389–1407; (*b*) G. E. M. Crisenza, 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.

11 (*a*) P. S. Fier and K. M. Maloney, *Angew. Chem., Int. Ed.*, 2017, **56**, 4478–4482; (*b*) P. S. Fier and K. M. Maloney, *Org. Lett.*, 2017, **19**, 3033–3036.

12 (*a*) A. L. J. Beckwith, V. W. Bowry and K. U. Ingold, *J. Am. Chem. Soc.*, 1992, **114**, 4983–4992; (*b*) M. R. Heinrich, A. Wetzel and M. Kirschstein, *Org. Lett.*, 2007, **9**, 3833–3835.

13 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*) F. 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.

14 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**, 13533–13539.

15 H. G. Roth, N. A. Romero and D. A. Nicewicz, *Synlett*, 2016, **27**, 714–723.

16 Although no other regioisomers were observed, the possibility of benzyne 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. Idiris and C. R. Jones, *Org. Biomol. Chem.*, 2017, **15**, 9044–9056.

17 (*a*) A. B. Pierini and D. M. A. Vera, *J. Org. Chem.*, 2003, **68**, 9191–9199; (*b*) C. Costentin, M. Robert and J.-M. Savéant, *J. Am. Chem. Soc.*, 2004, **126**, 16051–16057; (*c*) N. Takeda, P. V. Poliakov, A. R. Cook and J. R. Miller, *J. Am. Chem. Soc.*, 2004, **126**, 4301–4309.

18 For examples of regio- and chemoselective radical anion C–F bond fragmentation, see: (*a*) D. E. Mashkantsev, I. V. Beregovaya and L. N. Shchegoleva, *J. Fluorine Chem.*, 2016, **188**, 171–176; (*b*) R. V. Andreev, I. V. Beregovaya and L. N. Shchegoleva, *J. Fluorine Chem.*, 2020, **234**, 109513.

19 For an example of an alternative polar pathway enabled by donor–acceptor interactions, see: S. Senaweera and J. D. Weaver, *Chem. Commun.*, 2017, **53**, 7545–7548.

20 C. Costentin, P. Hapiot, M. Médebielle and J. M. Savéant, *J. Am. Chem. Soc.*, 1999, **121**, 4451–4460.

21 (*a*) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402–7410; (*b*) D. A. Caminos, M. Puiatti, J. I. Bardagí and A. B. Peñéñory, *RSC Adv.*, 2017, **7**, 31148–31157; (*c*) G. Nocera and J. A. Murphy, *Synthesis*, 2020, **52**, 327–336.

22 For pioneering examples of 2c, 3e σ bonds in synthesis, see: (*a*) C. J. Evoniuk, G. D. P. Gomes, S. P. Hill, S. Fujita, K. Hanson and I. V. Alabugin, *J. Am. Chem. Soc.*, 2017, **139**, 16210–16221; (*b*) Q. Elliott, G. dos Passos Gomes, C. J. Evoniuk and I. V. Alabugin, *Chem. Sci.*, 2020, **11**, 6539–6555.

23 Due to the lower electron donating ability of phenolates relative to oxime anion **1d** we anticipate that radical–anion coupling with oxime anion **1d** will be substantially faster than with the phenolate products. This selectivity will be further enhanced by the relatively high concentration of the oxime anion.