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Radicals as Exceptional Electron-Withdrawing Groups: Nucleophilic Aromatic Substitution of Halophenols via Homolysis-Enabled Electronic Activation

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ABSTRACT: While heteroatom-centered radicals are understood to be highly electrophilic, their ability to serve as transient electron-withdrawing groups and facilitate polar reactions at distal sites has not been extensively developed. Here, we report a new strategy for the electronic activation of halophenols, wherein generation of a phenoxyl radical via formal homolysis of the aryl O–H bond enables direct nucleophilic aromatic substitution of the halide with carboxylate nucleophiles under mild conditions. Pulse radiolysis and transient absorption studies reveal that the neutral oxygen radical (O•) is indeed an extraordinarily strong electron-withdrawing group (σ_p^-(O•) = 2.79 vs. $\sigma_p^-(NO_2)$ = 1.27). Additional mechanistic and computational studies indicate that the key phenoxyl intermediate serves as an open-shell electron-withdrawing group in these reactions, lowering the barrier for nucleophilic substitution by more than 20 kcal/mol relative to the closed-shell phenol form of the substrate. By using radicals as transient activating groups, this homolysis-enabled electronic activation strategy provides a powerful platform to expand the scope of nucleophile-electrophile couplings and enable previously challenging transformations.

Over the last decade, a tremendous variety of radical-based synthetic technologies have been developed, introducing innovative approaches to bond construction and streamlining the synthesis of complex molecules.[1,2] While these transformations are diverse, free radical intermediates generally react through a small number of elementary steps, including addition to π-bonds or metal centers, fragmentation events, atom/group transfer, and radical-radical coupling (Fig. 1A). These elementary steps all feature bond formation or bond cleavage events that occur at the radical site. This stands in contrast to a common mode of reactivity observed in polar chemistry, where functional groups electronically influence reaction outcomes without directly engaging in chemical reactions themselves. For example, electron-donating and electron-withdrawing groups control the reactivity and selectivity of arene functionalization reactions at adjacent sites through electronic effects.[3] This analysis raises an interesting question as to whether open-shell functional groups, when sufficiently long-lived, might also serve as electronic activating groups and enable unconventional polar reactivity that extends beyond the classical bond-forming and bond-breaking reactions generally associated with free radical intermediates.[4]

In this regard, we were intrigued by the marked differences observed between the electronic properties of closed-shell and open-shell functional groups (Fig. 1B). Many heteroatom-centered functional groups such as alcohols, amines, thiols, and phosphines are considered either electron-rich or electron-neutral as indicated by Hammett substituent constants (σ) that are negative or close to zero.[3] In contrast, the corresponding radical forms of these functional groups are instead considered electron-deficient and thus electrophilic,[5] though this understanding is largely qualitative (vide infra). While these electrophilic radicals are known to participate in a broad range of addition, fragmentation, and group transfer reactions,[6–8] we hypothesized that they might also serve as unusually strong electron-withdrawing groups, activating substrates toward unorthodox forms of polar reactivity. Specifically, in the context of arene functionalization, we proposed that reversible homolysis of an aryl X–H bond could serve to activate electron-rich aryl halides toward substitution reactions with polar nucleophiles through transient polarity inversion.

To qualify this hypothesis, we first sought to quantify the degree of electron-withdrawing character that such radicals exhibit through comparison with existing Hammett substituent constants. We were encouraged by prior computational studies reported by Pratt and co-workers in which they propose that O• and NH• radicals exhibit strong electron-withdrawing abilities, roughly estimating Hammett constants σ_p of 2 and 1, respectively.[9,10] To obtain more precise values experimentally, we turned to pulse radiolysis, a technique that generates high-energy electron pulses for studying transient intermediates,[11,12] to measure the pK_a of semiquinone. The semiquinone radical is equivalent to a p-

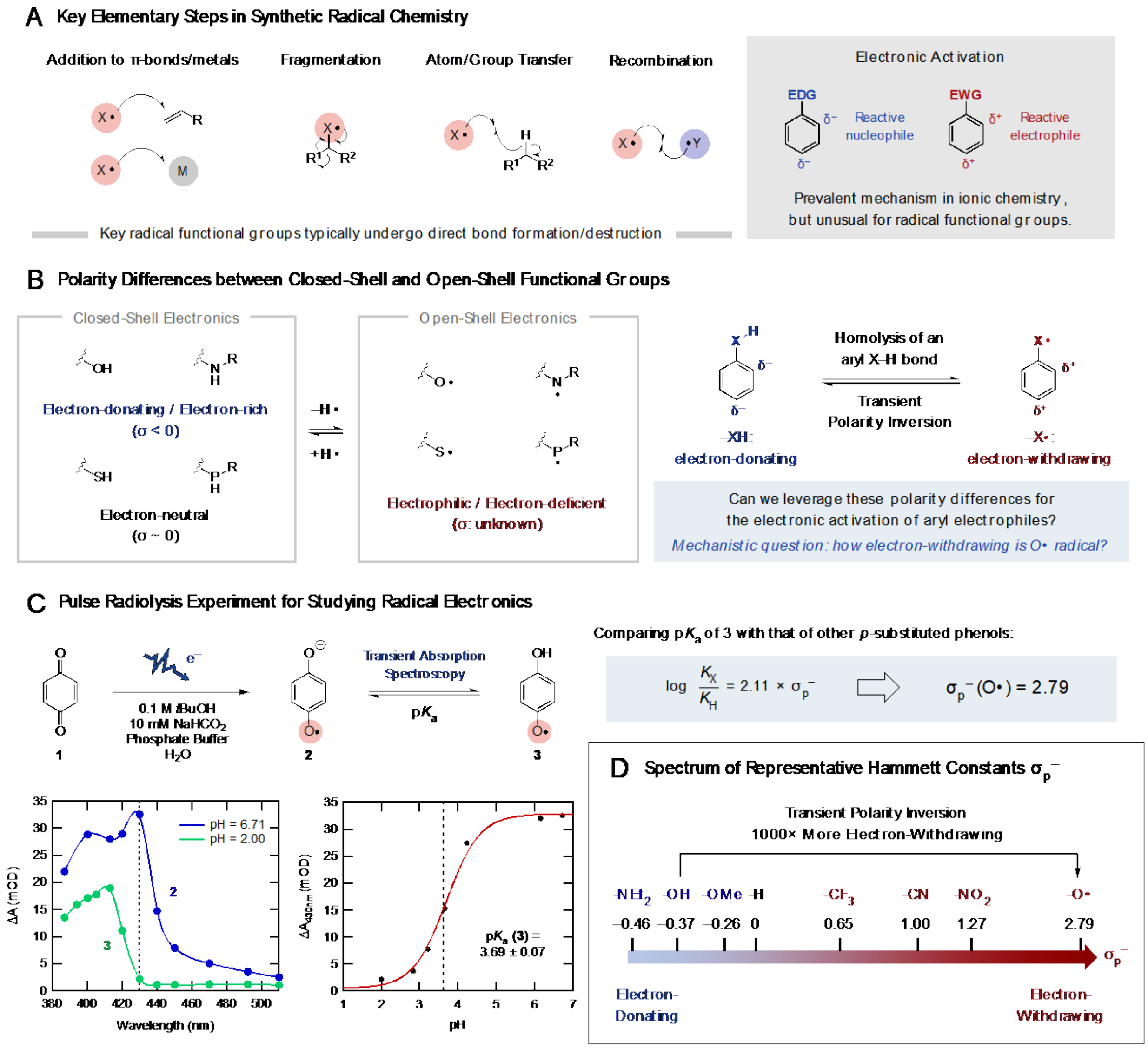

Fig. 1. **Background and motivation for developing a radical-mediated strategy for electronic activation of aryl halides.** (A) Key elementary steps in synthetic radical transformations and electronic activation as an orthogonal mechanism. (B) Polarity differences observed between heteroatom-centered closed-shell and open-shell functional groups. (C) Pulse radiolysis data for studying electronic properties of the phenoxyl radical. (D) A scale of extended Hammett substituent constants (σ_p^-).

(O•)-substituted phenol and its pK_a value can thus be used to calculate the Hammett constant σ_p^- for the O• radical (Fig. 1C).[13] Previous pulse radiolysis studies of the semiquinone radical have demonstrated its markedly enhanced acidity with pK_a values measured as 3.9 (± 0.2),[14] 4.0,[15] and 4.1.[16] While encouraging, these values were deemed unsuitable for the accurate determination of σ_p^-(O•) as these experiments used solvent-quantities of *tert*-butanol as a hydroxyl radical scavenger.[17] In our pulse radiolysis studies, the semiquinone radical was generated in aqueous buffer solutions containing benzoquinone **1** and minimal concentrations of *tert*-butanol (0.1M) and sodium formate (10mM) (see SI for details). The UV-Vis absorption features of the generated semiquinone radical anion **2** and the neutral semiquinone radical **3** were observed at pH 6.71 and 2.00, respectively. By tracing the absorption at 430 nm in buffer solutions with varied pH, the relative concentrations of **2** and **3** were measured. This titration curve was fitted with the Henderson-Hasselbalch equation to provide a pK_a of 3.69 (± 0.07) for **3**, which is significantly more acidic than the parent phenol (pK_a = 10.0)[18] and lower than the previously reported pK_a values. This corresponds to a σ_p^-(O•) value of 2.79 (vs. σ_p^-(NO2) = 1.27), supporting our hypothesis that the electron-withdrawing effects of heteroatom-centered radicals are exceptionally strong (Fig. 1D).

Encouraged by this result, we decided to test the synthetic applications of homolysis-enabled electrophile activation by designing a protocol for the nucleophilic aromatic substitution (S_NAr) of fluorophenols (Fig. 2A). Nucleophilic aromatic substitution is one of the best-studied and widely

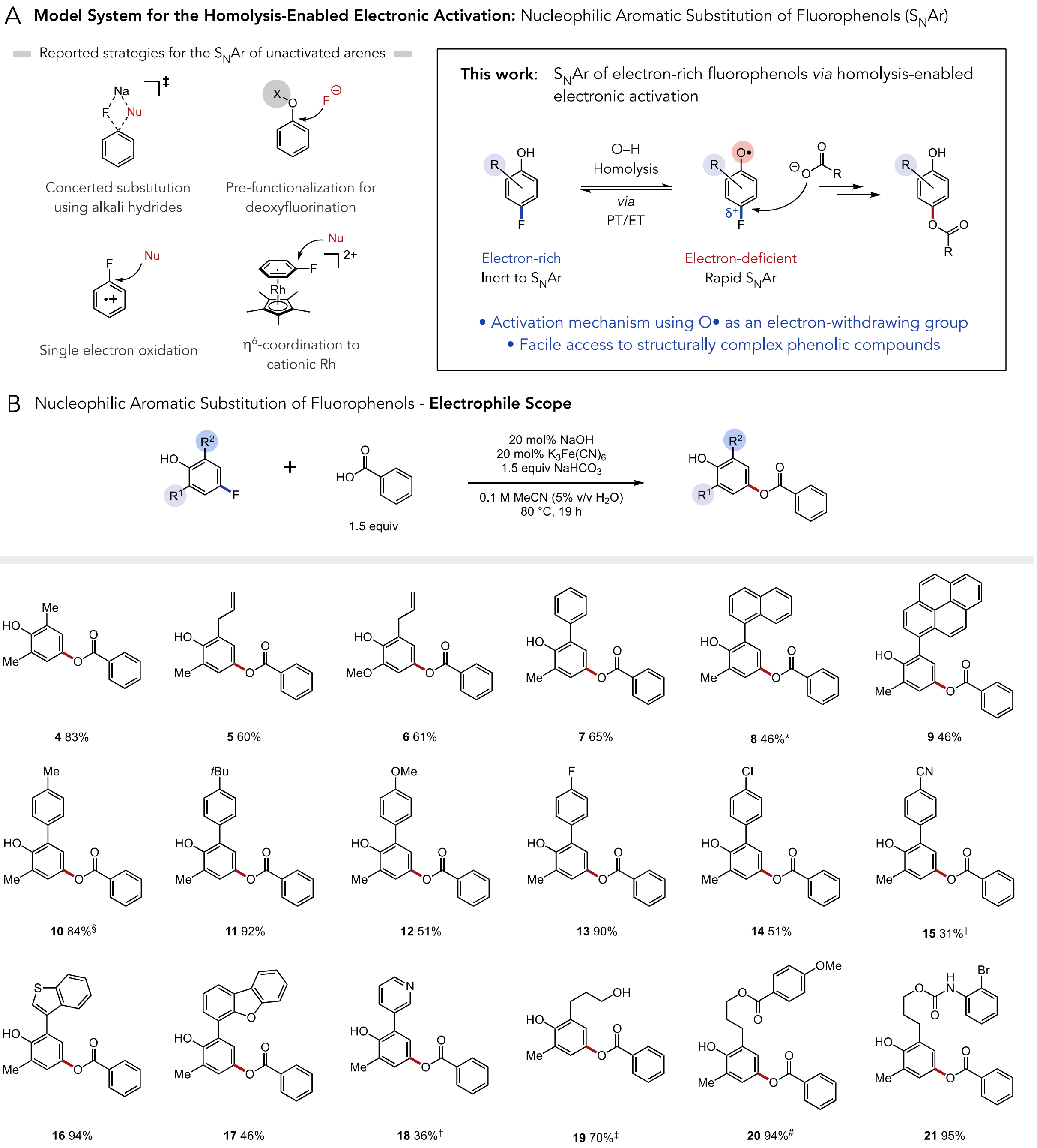

Fig. 2. **Nucleophilic aromatic substitution (S$_N$Ar) of fluorophenols and electrophile scope.** (A) Previous reports on the S$_N$Ar of unactivated arenes and S$_N$Ar of fluorophenols as a model system to evaluate the synthetic potential of homolysis-enabled electronic activation. (B) Electrophile scope of S$_N$Ar enabled by O–H bond homolysis. Reactions were run at 0.50 mmol scale. *40 mol% NaOH and 40 mol% $K_3Fe(CN)_6$. §Reaction was run at 0.37 mmol scale. †40 mol% NaOH and 40 mol% AgOTf instead of $K_3Fe(CN)_6$. ‡Reaction from a fluorophenol electrophile with a TBS-protected pendent alcohol provides 52% of TBS-deprotected product with 18% of product with TBS-group intact (combined isolated yield of 70%). #Reaction was run at 0.40 mmol scale.

applied reaction classes in organic chemistry.[19,20] However, due to the high kinetic barriers associated with dearomatization, S$_N$Ar typically requires the use of electron-deficient arene electrophiles together with strong nucleophiles such as alkoxides or thiolates. This limitation has drawn the interest of many laboratories in recent years, and a number of elegant methods have been developed to achieve S$_N$Ar of unactivated electrophiles, including the use of alkali hydrides for concerted substitution,[21,22] the development of pre-functionalization reagents for deoxyfluorination,[23,24] the application of single electron oxidation,[25–27] and η^6-coordination with a rhodium catalyst.[28] However, direct S$_N$Ar with many electron-rich arenes remains a general challenge. With a σ_p^-(OH) value as low as –0.37,[3] fluorophenols are prohibitively electron-rich to serve as electrophiles in S$_N$Ar reactions. Yet, we questioned whether this limitation might be overcome when the phenol is transiently transformed via reversible oxidation into its corresponding phenoxyl form, whose enhanced electrophilicity could enable efficient substitution reactions with polar nucleophiles. If successful, this method could provide facile access to complex phenol derivatives, which are common structures in biologically active molecules,[29] directly from simple starting materials. Therefore, with this goal in mind, we set out to devise a system where upon homolytic activation of a phenolic O–H bond, the O• radical may serve as a strong electron-withdrawing group and transiently render the arene ring electrophilic. The relatively long lifetimes of phenoxyl radicals may then accommodate the slower polar nucleophilic substitution step.[30,31]

Over the past decade, our group and others have studied and employed light-driven strategies for the homolysis of O–H bonds in a variety of synthetic contexts.[32] Given our prior work in this area, we began our optimization by treating 2,6-dimethyl-4-fluorophenol with 2 mol% $[Ru(bpy)_3](PF6)_2$ in acetonitrile under blue light irradiation with a range of nucleophiles. Gratifyingly, a combination of benzoic acid and sodium bicarbonate furnished the desired substitution product **4** in 17% yield (Fig. S1). Encouraged by this result, we questioned whether different methods for O–H bond homolysis might be more efficient, especially since phenoxyl radicals can be generated using a variety of mild oxidants.[33,34] Once generated, this long-lived phenoxyl may undergo polar substitution, and the nascent product-derived phenoxyl radical can then abstract an H-atom from another molecule of the fluorophenol substrate ($k \sim 10^5\ M^{-1}\ s^{-1}$ for phenol O–H/O• self-exchange)[35] to propagate a radical chain (vide infra). Indeed, we found that 2,6-dimethyl-4-fluorophenol, benzoic acid, and sodium bicarbonate in the presence of catalytic amounts of sodium hydroxide base and the mild oxidant potassium ferricyanide at 80 °C in aqueous acetonitrile[31] afforded the desired cross-coupled product **4** in 76% yield (for optimization details, see Table S1). In control experiments, the starting material is fully recovered from reactions run in the absence of the oxidant, while diminished yields are observed when either sodium hydroxide or sodium bicarbonate are omitted.

With these optimized reaction conditions established, we proceeded to examine the generality of our S$_N$Ar protocol with respect to the phenolic electrophile component on a preparative scale, using benzoic acid as a model nucleophile (Fig. 2B). With the success of the model substrate (**4**, 83% yield), we were gratified to find that variation of the ortho substituents on the phenol was accommodated under these reaction conditions with phenols containing allyl, phenyl, naphthyl, and pyrenyl groups (**5–9**, 46–61% yield) furnishing the desired products in moderate to good efficiencies. In particular, this protocol also tolerates electron-donating substituents on the phenol electrophile (**6**, 61% yield), a notable contrast to traditional S$_N$Ar strategies. Phenols with electronically diverse phenyl substituents (**10–15**, 31–90% yield) were all viable coupling partners and underwent nucleophilic substitution in good to excellent yields. Substitution occurred exclusively at the position para to the O–H group even in the presence of other fluoro- and chloroarenes. Heterocyclic moieties, such as benzothiophene (**16**, 94% yield), dibenzofuran (**17**, 46% yield), and pyridine (**18**, 36% yield), were all tolerated in the substitution reaction. In the case of phenols with electron-deficient substituents (i.e., **15** and **18**), diminished reactivity was observed, presumably due to the higher oxidation potentials of these substrates and the limited stability of the phenoxyl intermediates with electron-withdrawing substituents. To overcome these constraints, silver triflate, a stronger oxidant relative to potassium ferricyanide ($E^\circ_{1/2}$ = 0.04 V ($Ag^{+/0}$)[36] and –0.17 V ($Fe^{III/II}$) vs. $Fc^{+/0}$) (Fig. S4)[36], was employed to allow access to synthetically viable yields of product. Finally, this coupling protocol operates in the presence of pendent silyl-protected alcohols (**19**, 70% yield), esters (**20**, 94% yield), and carbamates (**21**, 95% yield) in excellent efficiencies, accommodating a wide variety of polar functionalities. However, fluorophenols without ortho substituents did not provide the desired products, likely due to competitive dimerization of the phenoxyl radicals ($k \sim 10^7$–$10^9\ M^{-1}\ s^{-1}$, see SI for details).[37,38]

We next investigated the scope of the nucleophile in the substitution reaction using 4-fluoro-2,6-dimethylphenol as the electrophilic coupling partner (Fig. 3). Electron-rich (**22–24**, 62–85% yield) and electron-deficient (**25–28**, 75–78% yield) aryl carboxylates can be introduced to provide access to diverse benzoate derivatives in good yields. Notably, halide substituents at the ortho, meta, and para positions of the benzoate nucleophile are well tolerated under mild reaction conditions, allowing for downstream functionalization of the cross-coupled products. Moreover, substituted naphthoate (**29**, 67% yield), nicotinate (**30**, 54% yield), and benzothiophene carboxylate (**31**, 35% yield) proved to be competent nucleophiles in our S$_N$Ar protocol. Our C–O bond-forming strategy was also successfully applied to the derivatization of medicinally active compounds bexarotene (**32**, 59% yield) and ataluren (**33**, 77% yield). In addition to aryl carboxylates, alkyl carboxylates (**34–39**, 30–91% yield), from simple acetate to α-branched carboxylates to sterically bulky dicyclohexylacetate, were all amenable substrates in the reaction. Carboxylates containing ketones (**40**, 73% yield), azabicycles (**41**, 86% yield), and disulfides (**42**, 63% yield) were coupled with the model phenol without difficulty. Notably, a range of protected amino acids (**43–50**, 59–87% yield) was compatible in the substitution reaction, undergoing selective C–O bond formation at the C-terminus or, in the case of glutamate **50**, at the side chain carboxylate. This protocol is highly selective for coupling at the free carboxylate group, and the resulting products exhibit no epimerization (see SI). Finally, 4-chloro-2,6-dimethylphenol was also found to be an effective electrophile in this protocol, undergoing smooth coupling with a number of aryl and alkyl carboxylates (**4**, **25**, **32**, **36**, and **47**) (Fig. 4A). As chlorophenols are readily accessible substrates, this finding broadens the synthetic versatility of this radical cross-coupling method.

We propose that this reaction proceeds via a radical chain mechanism that is initiated through a stepwise proton transfer/electron transfer (PT/ET) reaction of the base and Fe(III) oxidant with substrate a to generate a key phenoxyl radical intermediate **b** (Fig. 4B). Transient absorption spectroscopy data support that this phenoxyl radical, when generated from laser photolysis experiments, is indeed sufficiently long-lived to allow for

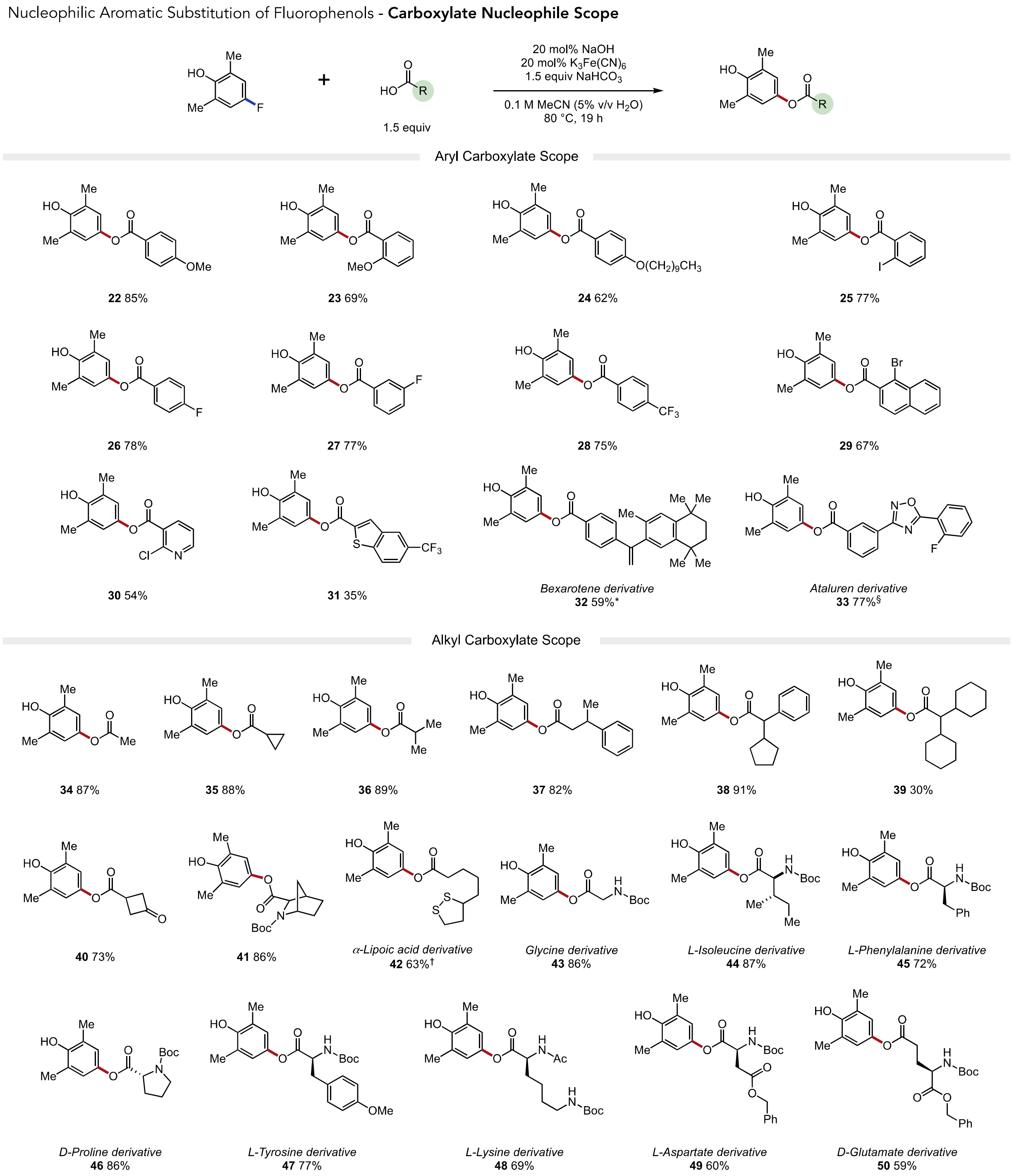

Fig. 3. **Nucleophile scope.** Reactions were run at 0.50 mmol scale. *Reaction was run at 0.20 mmol scale. §Reaction was run at 0.25 mmol scale. †40 mol% NaOH and 40 mol% $K_3Fe(CN)_6$.

subsequent reactions ($t_{1/2}$ = 690 μs, see Fig. S2-3). The electron-poor oxygen center then electronically activates the arene ring for the subsequent nucleophilic substitution event with a carboxylate nucleophile formed from *in situ* deprotonation of the corresponding acid. The resulting intermediate phenoxyl **c** undergoes rapid hydrogen atom exchange with another molecule of a to provide the desired cross-coupled product and **b** (ΔE_{calc} = -0.45 kcal/mol for the hydrogen atom exchange, *vide infra*),[35] the latter of which goes on to propagate the radical chain. Consistent with our proposed mechanism, we observed that chain propagation in this reaction does not depend on the mechanism of chain initiation. The desired S_NAr reaction was observed with a variety of radical initiation methods, such as ferrocenium oxidant with tert-butoxide base, diphenyl picryl hydrazyl, Gomberg's dimer, and 1,1′-azobis(cyclohexanecarbonitrile) (Fig. 4C). Additionally, low temperature (10 K) electron paramagnetic

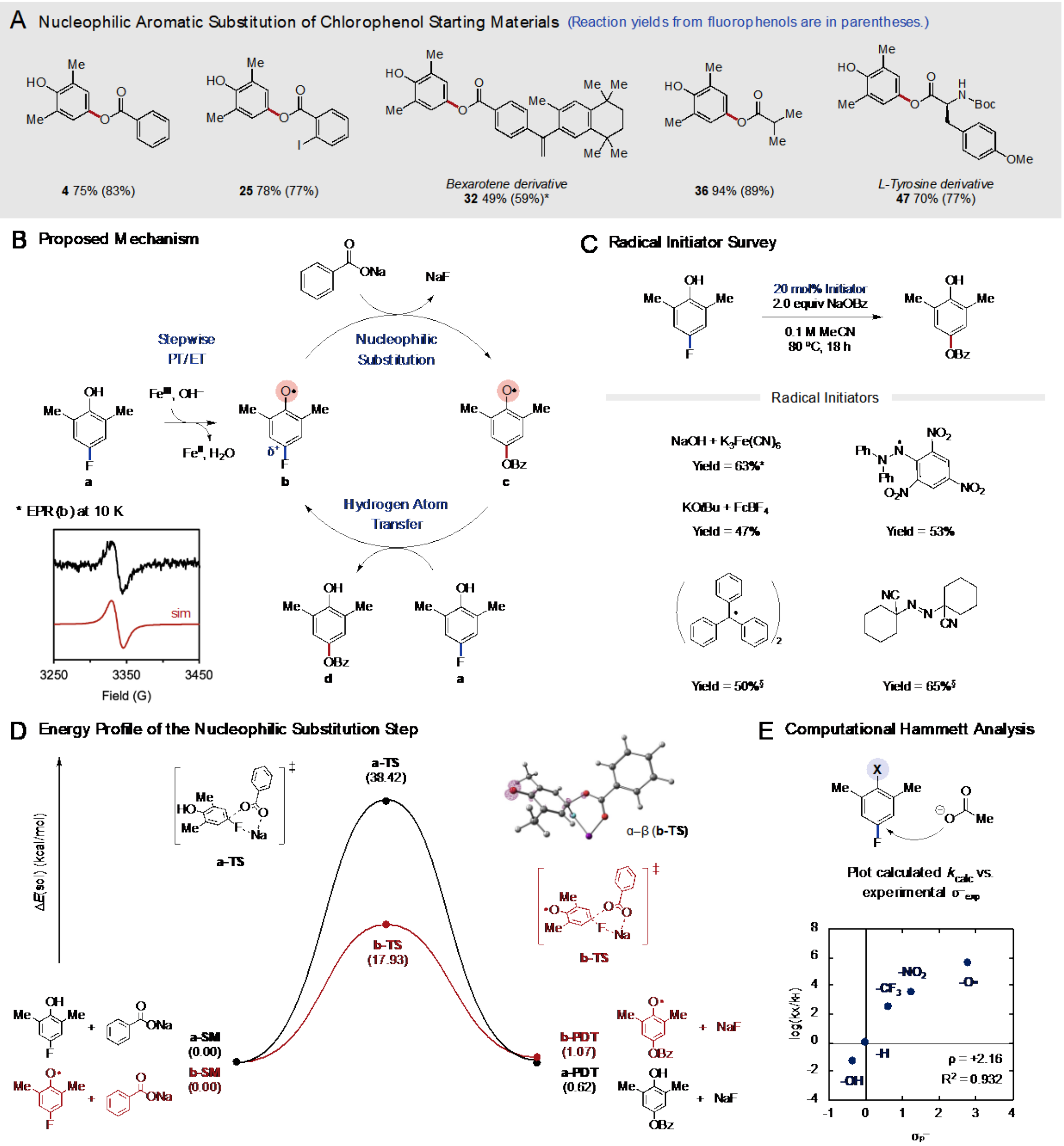

Fig. 4. **SNAr of chlorophenol substrates and mechanistic studies.** (A) SNAr reactions of chlorophenol substrates. Reaction yields obtained from the corresponding fluorophenols are shown in parentheses. *Reaction was run at 0.20 mmol scale. (B) Proposed mechanism for the SNAr reaction of halophenols. Inset: (black) electron paramagnetic resonance (EPR) spectrum of the radical intermediate **b** at 10 K. (red) simulation done with the g_{eff} value of 2.0049. (C) SNAr reactivity data under various radical initiation methods. Fc: Ferrocenium. *5% v/v water for solubility. §10 mol% initiator. (D) Computed energy profile of the nucleophilic substitution step from electrophiles **a** and **b**. DFT calculations carried out using Gaussian 16 at UM11/6-311++G(d,p)/CPCM(MeCN) level of theory. The overall thermochemistry for the nucleophilic substitution is close to thermoneutral when calculated, though the driving force may derive from the precipitation of sodium fluoride byproduct (see SI for details). (E) Hammett analysis of closed- and open-shell aryl fluorides obtained from calculated kinetic barriers and experimental Hammett constants.

resonance experiments were carried out to probe the key radical intermediate **b** (Inset, Fig. 4B and Fig. S3). Indeed, the mixture of phenol a, sodium hydroxide, and potassium ferricyanide generates an organic radical with a g-factor of 2.0049, consistent with reported values for substituted phenoxyl radicals.[39]

We then carried out computational analysis to gain insight into the key nucleophilic substitution step. Density functional theory calculations (UM11/6-311++G(d,p)/CPCM(MeCN)) on the nucleophilic substitution of parent phenol **a** and activated radical **b** suggest that both electrophiles undergo SNAr through concerted mechanisms[22,40] and similar transition state geometries (**a-TS** and **b-TS**, Fig.

4D). The reaction of radical electrophile **b**, however, is much more facile with a kinetic barrier more than 20 kcal/mol lower than that of **a**. In addition, the spin density plot of **b-TS** shows that the radical character is concentrated on the phenoxyl oxygen atom, distal to the site of substitution, which suggests that the phenoxyl is functioning primarily as an electron-withdrawing group with insignificant spin delocalization at the reactive site. Additionally, the kinetic barrier for S_NAr was calculated with a variety of closed-shell aryl fluorides and was compared to that of **b** (Fig. 4E). Hammett analysis obtained from calculated rate constants and experimental Hammett constants shows a linear correlation between the closed-shell functional groups and the O• radical. The strong Hammett correlation suggests that all the electrophiles in the study react through a common two-electron-based S_NAr mechanism. These results also further validate the value of σ_p^-(O•) obtained from our pulse radiolysis study. Together, these computational insights support the view that a transient radical substituent can promote nucleophilic substitution at a distal reaction site by acting as an exceptionally strong electron-withdrawing group.

In summary, we have described a mode of reactivity that leverages the neutral O-radical as a strong electron-withdrawing group for the electronic activation of otherwise inert aryl electrophiles. The feasibility of this strategy was established through pulse radiolysis studies, and its practicality was demonstrated by the development of a synthetic protocol for S_NAr of electron-rich halophenols. Mechanistic and computational results further support the conclusion that homolytic activation of a polar protic bond enables aryl electrophile activation through transient polarity inversion. Given the diversity of known heteroatom-centered radicals and our relatively limited understanding of their electronic effects, we believe that there are opportunities to extend the physical and synthetic studies discussed above beyond the phenoxyl systems studied here.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data; spectroscopic data for transient absorption studies; coordinates and energies for DFT calculation (PDF)

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Author Contributions

N.Y.S. and R.R.K. conceptualized the project. All authors contributed to the planning of experiments and interpretation of results. R.R.K and M.J.B directed the research. N.Y.S., M.J.B., E.T., and A.R. conducted the experiments. N.Y.S. and E.T. wrote the manuscript with input from all the authors.

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