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S_NAr Catalysis Enhanced by an Aromatic Donor-Acceptor Interaction; Facile Access to Chlorinated Polyfluoroarenes

Sameera Senaweera and Jimmie D. Weaver

Department of Chemistry, Oklahoma State University, Stillwater, OK 74078

Abstract

Selective catalytic S_NAr reaction of polyfluoroaryl C–F bonds with chloride is shown. Stoichiometric TMSCl makes the reaction exergonic and allows catalysis, which involves ground state elevation of chloride, aromatic donor-acceptor interactions, and stabilization of the Meisenheimer complex. Traditional cross-coupling of the products is now possible and demonstrates the utility.

Graphical abstract

The use of TMSCl skews the thermodynamics of the Halex reaction, allowing catalysis and access to functionalized fluoroarenes.

Perfluoroarenes are widely available molecules and are typically synthesized via the halogen exchange process (Halex), which utilizes fluoride salts to substitute the corresponding poly- or perchloroarenes.¹ In fact, most commercially available mono- and dichlorofluoroarenes are byproducts of incomplete halogen exchange.² As a consequence, such molecules bear chlorine at the least activated position,³ typically *meta*- to an activating group. As a result, the corresponding *para*-chlorinated products are not accessible via partial Halex. However, if the synthetic strategy is reversed (retro-Halex), and chlorination of a perfluoroarene is performed, it takes place with the same regioselectivity.⁴ Consequently, the inaccessible chlorination patterns become accessible. Currently, attempts to perform such transformations use forcing conditions (i.e., refluxing sulfolane, bp = 285 °C).⁵ Catalysis of such

Correspondence to: Jimmie D. Weaver.

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transformations could reduce the extreme conditions and significantly increase the scope, allowing the retro-Halex to become synthetically useful.

The stoichiometric S_NAr of haloarenes is a well-studied class of reactions, typically requiring haloarenes with an activating group which can facilitate the reaction (scheme 1a).^{6, 7} It is believed⁸ that the electron withdrawing group stabilizes the negative charge buildup in the Meisenheimer intermediate, and polarizes the C–X bond, facilitating the addition of the nucleophile. Not surprisingly, strategies to catalyze S_NAr reactions and increase scope have long been sought.^{9–11} Transition metal activation of haloarene C–X bonds toward nucleophilic substitution is achieved via complexation of the π -cloud of the arene to a metal center, which polarizes the substrate.^{12, 13} In contrast, the quadrupole of perfluoroarenes is inverted,¹⁴ and thus, this activation is not feasible.^{6, 15} While S_NAr addition of a variety of traditional nucleophiles are prevalent in literature^{8, 16} the use of chloride as a nucleophile to displace a fluoride is rather limited and to the best of our knowledge, catalytic reactions to selectively substitute C–F with C–Cl are not known.¹⁷ In fact, in 2015, Sanford and co-workers revealed a mild S_NAr fluorination of heteroaryl chlorides and nitroarenes using anhydrous tetramethylammonium fluoride at room temperature, essentially the reverse of the desired reaction.⁷ Exploiting the principle of microscopic reversibility,¹⁸ we sought to develop the reverse reaction. Herein, we report conditions for the regioselective catalytic aromatic nucleophilic substitution of per- and polyfluoroarenes which undergo selective substitution of the C–F bond to give a C–Cl bond (scheme 1c).

We began with pentafluoropyridine and trimethylsilyl chloride (TMSCl) in THF at 80 °C.¹⁹ We speculated that the use of a chlorosilane would form a strong Si–F bond and serve as a thermodynamic driving force (i.e., bond dissociation energies, PhF 127 kcal/mol vs. PhCl 97 kcal/mol²⁰ and H₃SiCl 109 kcal/mol vs. H₃SiF 152 kcal/mol²¹). However, attempts at 80 °C and 150 °C failed to give any product. These results suggest that the chlorosilane is incapable of substitution on its own. However, Shipilov²² observed that hexaethylguanidium chloride can be used to substitute C–F bond with C–Cl bond, albeit as part of a complex mixture of products. Nonetheless, this work led us to consider the design of a catalyst that could facilitate transfer of the chloride.

It is generally accepted that there are two transition states (TS) associated with a S_NAr reaction. The first is the nucleophilic addition which leads to a sigma-complex known as the Meisenheimer intermediate, and the second TS being its decomposition. We speculated that formation of a frustrated ion pair^{23, 24} could increase the nucleophilicity of the chloride. We investigated different quaternary ammonium chloride salts that varied in steric size. Consistent with the above hypothesis, smaller ammonium chlorides gave little to no conversion, but using tetrabutylammonium chloride (Bu₄NCl), which was completely homogeneous at 80 °C, gave the best reactivity. Some limited success was observed using inorganic chlorides and other silanes.¹⁹ We expect that Bu₄NCl serves to increase the concentration of soluble reactive chloride.

After achieving moderate reactivity by destabilizing chloride, we turned our attention to activation of the fluoroarene. The negatively charged Meisenheimer complex is expected to

be electrostatically stabilized by the cation, while the neutral perfluoroarene would not. Thus, significant molecular reorganization must occur in the TS to take advantage of this stabilization. By preorganizing the perfluoroarene and catalyst, we hoped to reduce the entropic penalty, analogously to Zhang's elegant exploitation of this phenomenon.²⁵ If designed appropriately, this could bring the perfluoroarene into close proximity to the positively charged ammonium ion, and reduce the entropic cost during the TS. Simultaneously, it was expected that the nearby positive charge would better stabilize the buildup of negative charge in the Meisenheimer complex.

In order to test these ideas, we synthesized analogs of benzyltributylammonium chloride (BnNBu₃Cl). A catalyst screen was then performed in which the reaction progress was monitored at both early and late time points. If stabilization of the Meisenheimer intermediate²⁶ was the only important feature, then it could be expected that catalyst **1n** would have worked, but it did not, suggesting other features are also important in facilitating the entire reaction. Instead, the screen revealed that catalysts with the neutral (**1g**) and donating (**1e**, **1f**) arenes gave the superior results when compared to Bu₄NCl. In contrast, electron withdrawing groups on the benzyl fragment (**1a-1d**) retarded the rate. This is consistent with an aromatic donor-acceptor (DA) interaction. While a number of more exotic analogs were tested (**1h-1m**), of these only catalysts **1j** and **1m** offered comparable conversions to Bu₄NCl.

Catalyst loading experiments were performed (SI, Table 1, Entry 26 and 27), which indicated the relatively low catalyst turnover number (TON) of ~3. The low TON suggests either catalyst deactivation/decomposition, or potentially is the result of the involvement of more than one catalyst molecule during the catalytic cycle, requiring higher catalyst loading to achieve reasonable kinetics (*vide infra*). Characterization of the post-reaction mixture revealed benzyl chloride is formed in significant amounts, presumably from decomposition of the BnNBu₃Cl catalyst. Given the commercial availability and inexpensive nature of the catalyst, we used 0.4 equiv for the substrate screening to ensure reaction completion.

With optimum conditions in hand, we evaluated the scope of the reaction (Table 2). We were pleased to see good to excellent yields could be obtained starting with a variety of fluoroarenes. Traditionally, incomplete Halex sequences provides access to *meta*-chlorofluoroarenes (*vide supra*). We obtained the complimentary *para*-chlorofluoroarene products with excellent regioselectivity. Thus, this reaction provides access to new chemical space. The reaction works well with activated fluoroarenes (**2d-e**, **2g-h**). However, relatively unactivated fluoroarenes could also be engaged simply by elevating the temperature, (**2f** and **2k**). In fact, selective dichlorination of decafluorobiphenyl was achieved simply by increasing the amounts of TMSCl and BnNBu₃Cl (**2k**). It should be noted that the highly fluorinated nature of the products make them relatively volatile and can lead to difficult isolation. In order to isolate the products with high purity, it was necessary to develop an isolation method. This was accomplished via the decomposition of the remaining catalyst and selective extraction of the product.¹⁹ Thus, this method allows the isolation of pure products.

Next, we wanted to understand the mechanism and phenomena which lead to the catalysis and specifically the observed rate enhancement when BnNBu_3Cl was used compared to NBu_4Cl . We postulated that an aromatic interaction between the perfluoroarene and the catalyst's arene moiety, along with the electrostatic interactions between the Meisenheimer intermediate and charged ammonium of the catalyst are responsible for the superior performance. Based on the compilation of evidence, including UV-Vis, NMR, and kinetic experiments, we propose the following mechanism for the catalytic retro-Halex of perfluoroarenes (Scheme 2).²⁵ First, chloride transfer from the catalyst to TMSCl generates the active chloride source, $\text{Me}_3\text{SiCl}_2^-$ (**4b**). Favorable aromatic DA interactions lead to complexation of the fluoroarene with the BnNBu_3Cl catalyst, which bring the catalyst and substrate in close proximity. NMR titration experiments indicate the formation of both a 1:1 complex as well as a 2:1 complex (BnNBu_3Cl :perfluoroarene). Initial rate analysis indicates the reaction is greater than second order in catalyst concentration, which is consistent with the necessary high catalyst loading. Via preorganization, the catalyst molecules facilitate the formation of the Meisenheimer complex (**4c**) upon chloride transfer from $\text{Me}_3\text{SiCl}_2^-$. Next, TMSCl assisted extrusion²⁷ of fluoride generates the chlorofluoroarene (**2a**) which is associated with the ammonium cation. The catalytic cycle is completed by displacement of **2a** with another substrate molecule.

To support the idea of an aromatic DA interaction, we carried out an NMR titration experiment using pentafluoropyridine and BnNBu_3Cl .²⁵ Interestingly, we observed up-field shifts of the fluorines signals with increasing BnNBu_3Cl concentration up to about 0.85 equiv., consistent with shielding of the fluorines on pentafluoropyridine, presumably, as a result of an interaction with electron rich phenyl ring of BnNBu_3Cl (Fig. 1b). However, between 0.85-2.0 equivalents, the fluorine signals moved down-field. Finally, after 2 equivalents of BnNBu_3Cl , the ^{19}F chemical shifts become constant. These results are consistent with initial formation of a 1:1 and then a 1:2 complex between the fluoroarene and the catalyst, which results in more deshielding of the fluorines.

The observation of a 1:2 perfluoroarene: BnNBu_3Cl complex in the NMR is consistent with a kinetic analysis which indicate a rate law that is 2.3 order with respect to the catalyst. This supports a transition state involving two catalyst molecules.

Preorganization of the transition state was further examined by UV-Vis spectroscopy. When an aromatic DA interaction occurs, the HOMO-LUMO gap becomes smaller²⁸ resulting in a new red shifted absorption band which may be observed via UV-Vis spectroscopy.²⁵ Such an experiment was carried out by mixing pentafluoronitrobenzene (PFNB) and BnNBu_3Cl (1:1 and 1:2 molar ratio) and $\text{PFNB}:\text{BnNBu}_3\text{Cl}:\text{TMSCl}$ (1:2:2 molar ratio) in DCM. Comparison of these mixtures with the spectra of the individual components revealed the emergence of a red shifted absorption band at 370-380 nm, consistent with a formation of a DA complex.^{19, 25, 28} Overlap of PFNB's absorption band with the newly formed band obscures identification of the maximum absorption wavelength (λ_{max}). However, the first derivative analysis allows identification of the new red-shifted λ_{max} of both the 1:1 and 2:1 catalyst:PFNB complexes (Fig. 1a). The observation of two different λ_{max} values also supports the formation of two distinct types of complexes.

We next investigated the nature of the silane in the reaction.¹⁹ To individuate effects from each reaction component, we evaluated all possible combinations for ¹⁹F and ¹H NMR spectral deviation. Fluorinated catalyst **1d** was used with pentafluoropyridine so that ¹⁹F NMR could be used to monitor the changes to both reaction components. A concentration dependent change >1 ppm of the ¹⁹F catalyst signal was observed upon mixing **1d** and TMSCl in a 1:1 mol ratio. Meanwhile, the ¹H methyl signal of TMS signal undergoes an up-field shift (~0.4 ppm in ¹H NMR) when compared to TMSCl (Fig. 1c). Thus, we propose that upon mixing the chloride catalyst and TMSCl, a penta-coordinated silicate (Me₃SiCl₂⁻) is formed. Further evidence for this species was obtained by HRMS and ¹H-DOSY experiments, both of which confirmed the mass of this anion. Furthermore, we have observed that the BnNBu₃Cl salt goes from being partially to completely soluble upon addition of the TMSCl at room temperature in THF. This may facilitate the reaction by simultaneously providing chloride and a TMSCl that can immediately facilitate the fluoride extrusion step.²⁷

In addition to the fundamental interest in the development of S_NAr catalysis, this chemistry has the potential to be a straightforward method to access starting materials for coupling reactions that would be difficult or impossible with the fluoroarene starting materials. To demonstrate utility, Suzuki and Sonogashira coupling reactions were performed, which proceeded smoothly to **5a** and **5b** in good yields. In contrast to pentafluoropyridine which undergoes substitution with lithiates,²⁹ **2a** undergoes halogen-lithium exchange, and gives smooth addition to benzaldehyde to give **5c**, and could be used as a method to access fluorinated analogs of bioactive molecules.

In conclusion, we have demonstrated the first selective catalytic S_NAr of C–F bonds of perfluoroarenes with a Cl⁻. BnNBu₃Cl was determined to be the best chloride transfer catalyst and importantly provides insights into potential strategies that can facilitate otherwise impossible S_NAr reactions. This reaction is characterized by ground state elevation of the chloride and its conversion to a silicate, transition state preorganization by aromatic DA interaction between the substrate and catalyst, a Coulombic interaction that stabilizes the Meisenheimer complex, and the use of TMSCl to facilitate the breakdown of the intermediate. These strategies are general and thus provide future direction for S_NAr catalysis. Here, we demonstrated the feasibility of catalyzing the retro-Halex reaction and have shown how it can provide access to new chlorofluoroarenes. Furthermore, we demonstrated how these can immediately be used with more traditional chemistry to access derivatized multifluorinated arenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(a, a') UV-Vis spectra indicating formation of a DA complex. (b) ¹⁹F NMR spectra of the titration between pentafluoropyridine and BnNBu₃Cl. (c) Formation of Me₃SiCl₂⁻ observed by ¹H NMR

a) Classical S_NAr

EWG = electron withdrawing group

b) Transition metal assisted S_NAr **c) This work** **Scheme 1. Strategies of S_NAr with fluoroarenes**

Scheme 2. Plausible mechanism of catalytic S_NAr

Scheme 3. Synthetic utility of chlorodefluorinated products

i. **A**, 1.2 equiv, Pd(OAc)₂ 5 mol%, PPh₃ (10 mol%), K₂CO₃(aq) (2.7 equiv), DME (0.75 M), sealed vial, 80°C, Ar, overnight, **70%**^f

ii. **B**, 1.2 equiv, Pd(pph)₂Cl₂ 2 mol%, Cs₂CO₃ (1 equiv), tBu₃P (4 mol%), DBU (10 mol%), DMF (0.3 M), MW reactor, 150 °C, 10 min, **80%**

iii. BuLi (1.2 equiv), THF (0.5 M), -78 °C and then, **C**, 1.2 equiv, **62%**^f

^f Starting from pentafluoropyridine, over both steps

Table 1
Catalyst screen for the chlorination reaction^a

R =	
 1a , 1%, 37%	 1b , 3 %, 54%
 1c , 4%, 68%	 1d , 4%, 50%
 1e , 7%, 85%	 1f , 8%, 88%
 1g , 11%, 95%	 Bu₄NCl , 7%, 69%
 1h , 8%, 51% ^b	 1i , 7%, 48% ^b
 1j , 19%, 81% ^b	 1k , 2%, 36% ^b
 1l , 7%, 56% ^b	 1m , 20%, 82% ^b
 1n , NR, NR ^b	

^a%convesion detrmined after 1 h, 20 h by ¹⁹F NMR

^b%convesion detrmined after 3 h, 20 h by ¹⁹F NMR

Table 2
Reaction scope for the catalytic chlorination

^aNMR yield (isolated yield after workup in paranthesis),

^bUsed BnNBu₃Cl (1.0 equiv) and TMSCl (2.0 equiv),

^cUsed BnNBu₃Cl (0.5 equiv) and TMSCl (2.0 equiv),

^dUsed BnNBu₃Cl (0.8 equiv) and TMSCl (2.0 equiv),

^eUsed BnNBu₃Cl (1.0 equiv) and TMSCl (2.4 equiv)