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Photocatalytic Hydrodefluorination: Facile Access to Partially Fluorinated Aromatics

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Supporting Information

ABSTRACT: Polyfluorinated aromatics are essential to materials science as well as the pharmaceutical and agrochemical industries and yet are often difficult to access. This Communication describes a photocatalytic hydrodefluorination approach which begins with easily accessible perfluoroarenes and selectively reduces the C−F bonds. The method allows facile access to a number of partially fluorinated arenes and takes place with unprecedented catalytic activity using a safe and inexpensive amine as the reductant.

Partially fluorinated arenes are highly prized molecules in pharmaceutical and agricultural chemistry, and in materials science. A recent report found that 20−25% of all compounds in the drug pipeline contained fluorine,[1] including top selling drugs such as Diflunisal (**I**, Figure 1), Januvia (**II**), and antiviral Emtricitabine (**IV**). Fluorinated arenes are commonly found in agrochemicals (Teflubenzuron **III**), and fluorination is frequently used to modulate the properties of liquid crystals (**V**).

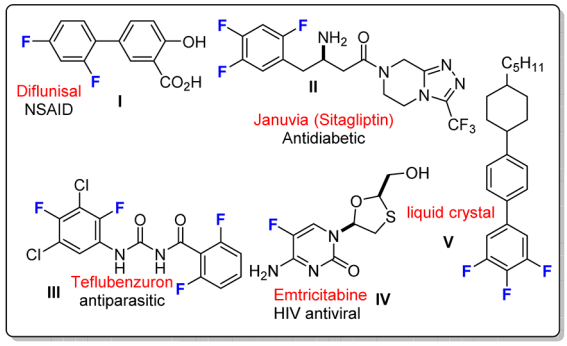
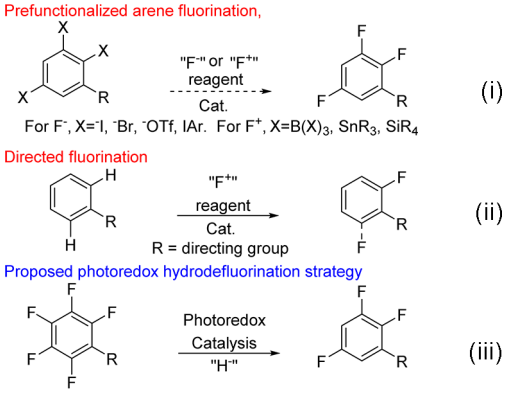


Figure 1. Some important partially fluorinated pharamaceuticals, agrochemicals and a liquid crystal.

Despite the value of these compounds their syntheses are often lengthy and rely on harsh methods such as the Balz−Schiemann reaction or the Halex process. In recognition of the need for more facile access to partially fluorinated arenes, catalytic fluorination of prefunctionalized arenes[2] and directed C−H fluorinations[3] have received considerable attention. Arguably, these methods are not well suited for the synthesis of polyfluorinated arenes because the starting materials would require multiple prefunctionalizations (i, Scheme 1) or uniquely arranged directing groups (ii). Herein we present photoredox catalysis of readily available perfluoroarenes (iii) as a new strategy to access partially fluorinated arenes.

Scheme 1. Comparison of Current and Proposed Strategy to Partially Fluorinated Arenes



Realization of a simple and robust hydrodefluorination (HDF) methodology has been a struggle.[4] HDF chemistry is inherently difficult for a number of reasons, including the relative inertness of the C−F bond to many insertion processes which, if successful, face problematic strong catalyst−F bonds, which often hamper catalyst turnover acting as a thermodynamic sink in the catalytic cycle. In attempts to develop a robust HDF catalytic system, a number of different types of catalysts have been investigated, including catalysts based on metal−hydrido complexes,[5] Rh,[6] Ni,[7] Pd,[8] and Au.[9] Furthermore, most methods use extremely fluorophilic reductants, such as pyrophoric Al-hydrides[10] or expensive Si-hydrides[11] to help alleviate this problem. We speculated that if we used a catalyst incapable of formation of M−F bonds, we might be able to circumvent these issues altogether and facilitate HDF with high catalytic turnover number (TON).

Perfluoroarenes have a lowered LUMO compared to their hydrocarbon analogs[12] and offer a convenient mode of activation. It is established that addition of an electron into the LUMO[13] generates a radical anion[14] which undergoes fluoride extrusion[15] to generate a radical which abstracts an H-atom.[16] We posited that photoredox catalysis—which has not been explored for HDF of fluorinated arenes[17]—might have a distinct advantage over traditional methods in generating both the requisite radical anion as well as the H-atom source (eq 1, Scheme 2).[16a,d,e,18] Specifically, we speculated that tris[2-

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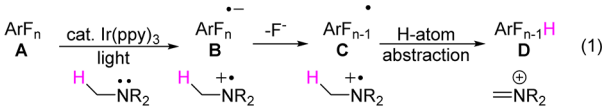
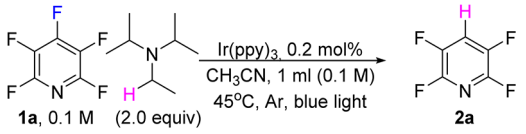
Scheme 2. Potential Mechanism



phenylpyridinato-C^2,*N*]iridium(III), [Ir(ppy)$_3$] could be used to facilitate outersphere electron transfer to generate a perfluororadical anion (**B**, Scheme 2) which results in fragmentation to give radical **C**[19] and a fluoride. Finally, **C** abstracts an H-atom from the amine radical cation[20] generated *in situ* giving **D** and an iminium.[21] Because the catalyst is a robust 18-electron complex and coordinatively saturated with 3-bidentate ligands, it avoids the problematic M−F bond which prevents decomposition and allows facile turnover. Additionally, we speculated this might alleviate the need for a fluorophilic reductant such as Al- or Si-hydride and allow us to use a simple and safer aliphatic amine as a reductant.

Thus, we began our investigation with using Ir(ppy)$_3$ (Ir(II)/(III), V = −2.20)[22] and pentafluoro pyridine (V = −2.12)[23] which provides a slight overpotential. We were pleased to find full conversion to 2,3,5,6-tetrafluoropyridine (**2a**) after 24 h (entry 1, Table 1). Remarkably, Ru(bpy)$_3$Cl$_2$ and Ru(bpm)$_3$Cl$_2$ [bpm = 2,2′-bipyrimidine] catalysts sluggishly afforded product (entries 2 and 3), despite a significant underpotential (V = −1.33, −0.91).[24] Control studies demonstrated the necessity of both catalyst and light (entry 5). The rate of the reaction did not appear to depend greatly on the equivalents of amine (entries 6 and 7) and reached completion using just 1.2 equiv of amine. There appears to be a rate dependency on catalyst concentration (entries 8−10).[25] Peculiarly, the reaction seems to have a pseudo-zero-order rate dependency on the substrate (entries 11−15).[25] Ultimately, using 0.1 M substrate, 1.1−3.3 equiv of Hünig's base, and 0.5 mol% photocatalyst, we began to evaluate the substrate scope.

Table 1. Optimization of Reaction Conditions

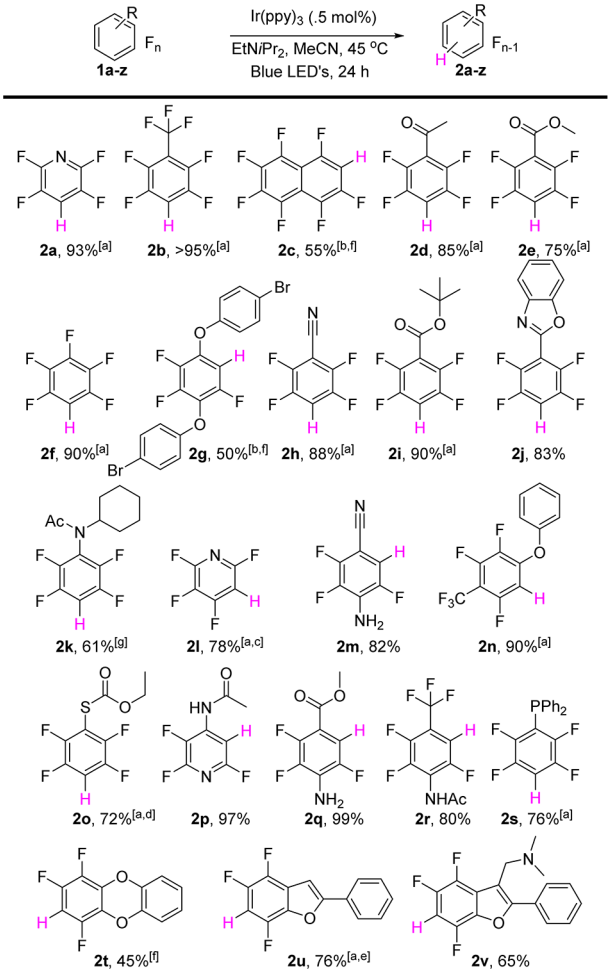


entry	modification of conditions	conversion	time, h
1	none	100%[a]	24
2	Ru(bpy)$_3$ instead of Ir(ppy)$_3$	37%[a]	24
3	Ru(bpm)$_3$ instead of Ir(ppy)$_3$	2−3%[a]	24
4	without degassing	0%[a]	24
5	no catalyst or in dark	0%[a]	24
6	1.2 equiv of amine	32/100%[a]	0.5/22.5
7	2.0 equiv of amine	35/100%[a]	0.5/22.5
8	0.05 mol% catalyst	5/12%[b]	0.5/1
9	0.125 mol% catalyst	25/43%[b]	0.5/1
10	0.25 mol% catalyst	47/82%[b]	0.5/1
11	0.075 M substrate conc	0.015/0.050 mmol **2a**[b]	0.5/6
12	0.10 M substrate conc	0.018/0.063 mmol **2a**[b]	0.5/6
13	0.15 M substrate conc	0.017/0.044 mmol **2a**[b]	0.5/6
14	0.20 M substrate conc	0.022/0.058 mmol **2a**[b]	0.5/6
15	0.35 M substrate conc	0.032/0.070 mmol **2a**[b]	0.5/6

[a]Determined by GC. [b]Determined by ^{19}F NMR.

Under these conditions a number of perfluoroarenes underwent smooth HDF (Table 2). Importantly, the reaction

Table 2. Scope of the Photocatalytic HDF



[a]^{19}F NMR yield. [b]65 °C, 72 h. [c]From 3-Cl tetrafluoropyridine. [d]Contains 10% di-HDF product. [e]Contains 9% regioisomer. [f]Incomplete conversion: **2c**, 57% conv.; **2g**, 70% conv.; **2t**, 60% conv. [g]36 h.

tolerates a number of functional groups including CF$_3$ (**2b**, **2n**, and **2r**), ketones (**2d**), esters (**2e**, **2i**, and **2q**), nitriles (**2h**, **2m**), oxazoles (**2j**), and aliphatic amines[26] (**2v**). The inherent selectivity can be overcome by starting with a chloride (**2l** vs **2a**). Perfluoroarenes substituted with electron releasing amino, alcohol, or thiol groups proved to be sluggish or unselective substrates. However, in conjunction with appropriate functional groups the sluggish substrates underwent facile reaction. For instance, symmetrical ether (**2g**) provides the mono-HDF product. Alternatively, electronic modulation of substrates can activate them toward HDF. Thiols become active after formation of the thiocarbonate (**2o**) and similarly amines are activated by acylation (**2k**). Other ring functionality can also serve to activate substrates with electron releasing groups (**2m**, **2n**, **2p**, **2q**, and **2r**). Dibromide **2g** demonstrates the propensity to undergo HDF rather than C−Br reduction.[27] Highly fluorinated phosphines, which are an important class of ligand for several catalytic processes,[28] also undergo HDF allowing facile fine-tuning of the electronics. Fused arenes, which are important in materials science applications,[29] undergo smooth HDF (**2t**, **2u**, and **2v**).

Under these conditions several substrates can undergo di- or even tri-HDF events to afford products that would be difficult

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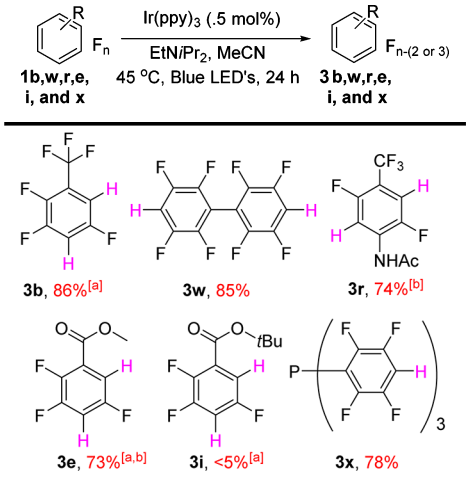
Table 3. Di- and Tri-HDF



[a] ^{19}F NMR yield. [b] 42 h.

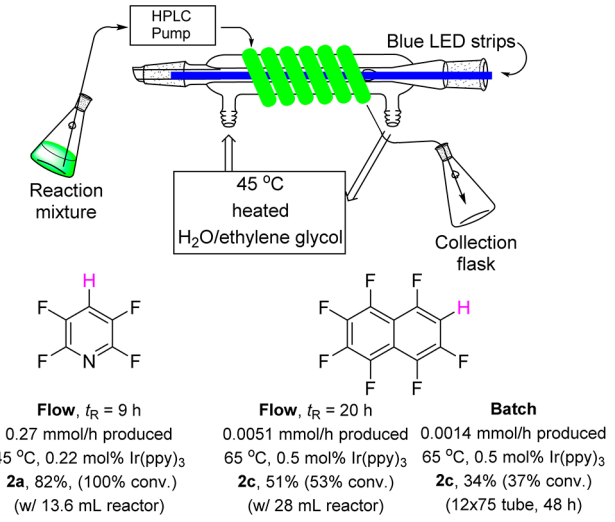
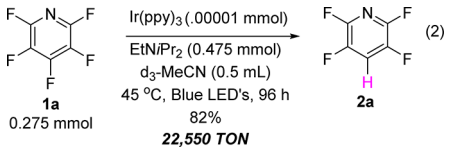


Figure 2. HDF in a flow reactor.

to access by other means. Conveniently, in most cases[30] the difference in rate constants for mono- and di-reduction is substantial and selectivity can be controlled by the equivalents of amine used as well as close monitoring of the reaction. Octafluorotoluene undergoes *ortho*,*para* di-reduction, leaving the benzylic fluorines intact (**3b**, Table 3). While decafluorobiphenyl gives symmetric 4,4′ reduction in excellent yield (**3w**). Interestingly, removal of the first fluorine of **1r** occurs ortho to the CF_3 group, the second HDF event occurs meta to give a 2,5-di-H arene (**3r**). While the regioselectivity of the HDF event is primarily dictated by the electronics of the perfluorarene,[16a,31] the rate difference in the di-HDF of the methyl (**3e**) and *tert*-butyl esters (**3i**) is substantial and suggests that there is a steric contribution.[14b,35] Finally, perfluorotriphenyl phosphine undergoes smooth conversion to the tri-HDF product (**3x**) which allows direct synthesis from commercially available phosphine.

We next investigated the robustness of the photocatalyst by evaluating the TON using pentafluoropyridine (**1a**, eq 2).



Aliquots (7 total) of **1a** and Hünig's base were repeatedly added over the 4 day period.[25] To our delight, the catalyst proved remarkably resilient and never ceased to produce product. Eventually the rate of a byproduct formation began to increase at which time an internal standard was added and a yield of 82% was obtained to give an unprecedented TON of 22,550.[4,10,32]

HDF products are important building blocks for a number of different applications. As such, obtaining larger quantities of these products will be necessary. Consequently, we wanted to investigate the feasibility of our method to be converted to a flow method. Thus, utilizing a homemade flow reactor, essentially like the one previously described by Gagné (Figure 2).[33] The reaction mixture was pumped by an HPLC pump into perfluoroalkoxy tubing which was wrapped around a condenser.[25] Within the condenser were outward facing blue LED strips. The temperature was controlled by passing a mixture of water and ethylene glycol via a recirculating heater/chiller through the condenser. Pentafluoropyridine (**1a**, Figure 2) underwent smooth conversion, producing **2a** at a rate of 0.27 mmol/h (978 mg/24 h). Octafluoronapthalene (**1c**), which is a sluggish substrate that never reaches full conversion under standard conditions was also subjected to the flow reactor. While full conversion was never reached even in under flow conditions, we did see a 3.75× rate enhancement in product formation (**2c**, flow vs batch), which is likely due, in part, to the diminished path length of the light.[33,34] These results suggest the method is convertible to flow and larger quantities of HDF product could be obtained when desired.

In summary, we have introduced photocatalytic HDF as a viable method to access polyfluorinated arenes and an alternative to current HDF strategies in which we demonstrated the importance of avoiding the metal-F bond for catalytic turnover. One desirable outcome is the use of safer and less expensive amine reductant than the traditional Al- and Si-H's. Importantly, we have demonstrated that with a single catalyst we can perform mono-HDF, di-HDF, and even tri-HDF on a number of different types of arenes to give facile access to polyfluorinated aromatic rings, a task for which selective fluorination is poorly suited. Finally, we have demonstrated that the chemistry is amenable to flow methods, suggesting that it could be used to make sizable quantities of polyfluorinated arenes in a convenient, safe, and cost-effective manner. Given the ease with which the requisite perfluoroarenes can be prepared via S_NAr chemistry, we believe this method has great potential to help in a number of research areas.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012. (b) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 5602. (c) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134. (d) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552. (e) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292. (f) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (g) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.

(3) (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (b) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081. (c) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.

(4) Lentz, D.; Braun, T.; Kuehnel, M. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328.

(5) (a) Edelbach, B. L.; Fazlur Rahman, A. K.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **1999**, *18*, 3170. (b) Arndt, P.; Spannenberg, A.; Baumann, W.; Burlakov, V. V.; Rosenthal, U.; Becke, S.; Weiss, T. *Organometallics* **2004**, *23*, 4792.

(6) (a) Aizenberg, M.; Milstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 8674. (b) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359.

(7) (a) Archibald, S. J.; Braun, T.; Gaunt, J. A.; Hobson, J. E.; Perutz, R. N. *J. Chem. Soc., Dalton Trans.* **2000**, 2013. (b) Fischer, P.; Götz, K.; Eichhorn, A.; Radius, U. *Organometallics* **2012**, *31*, 1374.

(8) Breyer, D.; Braun, T.; Kläring, P. *Organometallics* **2012**, *31*, 1417.

(9) Zhan, J.-H.; Lv, H.; Yu, Y.; Zhang, J.-L. *Adv. Synth. Catal.* **2012**, *354*, 1529.

(10) For an example of an Al-H reductant, see: Jäger-Fiedler, U.; Klahn, M.; Arndt, P.; Baumann, W.; Spannenberg, A.; Burlakov, V. V.; Rosenthal, U. *J. Mol. Catal. A: Chem.* **2007**, *261*, 184.

(11) For an example of an R_3Si-H reductant, see: Reade, S. P.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2009**, *131*, 1847.

(12) Gant, K. S.; Christophorou, L. G. *J. Chem. Phys.* **1976**, *65*, 2977.

(13) (a) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; McGrady, J. E.; Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333. (b) Sun, A. D.; Love, J. A. *Dalton Trans.* **2010**, *39*, 10362. (c) Edelbach, B. L.; Kraft, B. M.; Jones, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 10327. (d) Kiplinger, J. L.; Richmond, T. G. *J. Am. Chem. Soc.* **1996**, *118*, 1805. (e) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373.

(14) (a) Yim, M. B.; Wood, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 2053. (b) Shchegoleva, L. N.; Bilkis, I. I.; Schastnev, P. V. *Chem. Phys.* **1983**, *82*, 343. (c) Shoute, L. C. T.; Mittal, J. P. *J. Phys. Chem.* **1993**, *97*, 379−384.

(15) (a) Rossi, R. A. *Acc. Chem. Res.* **1982**, *15*, 164. (b) Freeman, P. K.; Srinivasa, R. *J. Org. Chem.* **1987**, *52*, 252.

(16) (a) Selivanova, G. A.; Reshetov, A. V.; Beregovaya, I. V.; Vasil'eva, N. V.; Bagryanskaya, I. Y.; Shteingarts, V. D. *J. Fluorine Chem.* **2012**, *137*, 64. (b) Laev, S. S.; Gurskaya, L. Y.; Selivanova, G. A.; Beregovaya, I. V.; Shchegoleva, L. N.; Vasil'eva, N. V.; Shakirov, M. M.; Shteingarts, V. D. *Eur. J. Org. Chem.* **2007**, *2007*, 306. (c) Jones, W. D. *Dalton Trans.* **2003**, *2003*, 3991. (d) Krasnov, B. I.; Platonov, V. E. *Russ. J. Org. Chem.* **2001**, *37*, 517. (e) Laev, S. S.; Shteingarts, V. D. *J. Fluorine Chem.* **1998**, *91*, 21. (f) Krasnov, V. I.; Platonov, V. E.; Beregovaya, I. V.; Shohegoleva, L. N. *Tetrahedron* **1997**, *53*, 1797.

(17) For an example of a photochemical defluorination of an electron-rich monofluoroarene, see; Dichiarante, V.; Fagnoni, M.; Albini, A. *Green Chem.* **2009**, *11*, 942.

(18) Laev, S. S.; Shteingarts, V. D. *J. Fluorine Chem.* **1999**, *96*, 175.

(19) Experiments suggesting the intermediacy of a radical were performed; see SI for details.

(20) Using *d*-MeCN gives no deuterium incorporation into the product while use of deuterium-labeled dicyclohexyl-d_5-ethylamine gives 32% deuterium incorporation into the mono-HDF product. These results suggest that either α-C-H of the amine radical cation can serve as the H-atom source. See SI for details.

(21) We believe iminium ions are initially formed and serve as the fluoride counterion. However, we have not been able to isolate these salts. Under rigorously anhydrous conditions we have observed bis(diisopropylammonium) hexafluorosilicate precipitating from solution when reactions are run in borosilicate tubes. Presumably this comes from fluoride etching silicon from the tube walls and hydrolysis of the ethyl group of the iminium. In reactions run under less rigorous conditions, we believe advantageous water leads to hydrolysis of the iminium prior to silicon etching to afford secondary amine HF salts. See SI for details and crystal structure.

(22) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

(23) Beletskaya, I. P.; Artamkina, G. A.; Mil'chenko, A. Y.; Sazonov, P. K.; Shtern, M. M. *J. Phys. Org. Chem.* **1996**, *9*, 319.

(24) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.

(25) For details, see the Supporting Information.

(26) Conceivably, access to the less reactive ortho position is possible by using the amino group as a temporary blocking group which adds with similar preferences. After the HDF reaction is complete, the amino group can be converted to the fluorine via diazotization.

(27) A small amount ∼7% of hydrodebromination product was observed. This was observed previously: Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2012**, *4*, 854.

(28) (a) K. Morita, D.; A. David, S.; Tumas, W.; K. Morita, D.; R. Pesiri, D.; H. Glaze, W. *Chem. Commun.* **1998**, 1397. (b) Hirai, T.; Hamasaki, A.; Nakamura, A.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5510.

(29) For a recent example, see; Zhang, J.; Chen, W.; Rojas, A. J.; Jucov, E. V.; Timofeeva, T. V.; Parker, T. C.; Barlow, S.; Marder, S. R. *J. Am. Chem. Soc.* **2013**, *135*, 16376.

(30) Of the substrates tried, the rate differences between the first and sequential reductions were sufficiently different to be able to isolate the desired HDF product. Two exceptions were tri(pentafluorophenyl) phosphine (**1x**) and the decafluorobiphenyl (**1w**).

(31) We believe the addition of the electron occurs at the LUMO which resembles primarily π^* and that fragmentation then occurs upon crossover to the lowest lying C−F σ^* orbital. For a better explanation of this process, see; ref 16a. In the case of **1l** (Ar-Cl), presumably the C−Cl σ^* is lower in energy and hence fragmention occurs at this carbon. Alternatively, it is possible that the C−Cl σ^* orbital is low enough in energy that it is the LUMO in which case the π^* orbital may not be involved at all.

(32) Lv, H.; Cai, Y.-B.; Zhang, J.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3203.

(33) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140.

(34) (a) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (b) Neumann, M.; Zeitler, K. *Org. Lett.* **2012**, *14*, 2658. (c) Lu, H.; Schmidt, M. A.; Jensen, K. F. *Lab Chip* **2001**, *1*, 22.

(35) The structure of the radical anion is not planar. Consequently, substitutions can destabilize the structure of the radical anion. Destabilization of the radical anion would be expected to increase the barrier to formation of the requisite radical anion. For a more thorough study of the structure of the radical anion of hexafluorobenzene, see ref 14b.