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Frustrated Lewis pair meditated selective single fluoride substitution in trifluoromethyl groups

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ABSTRACT: Single fluoride substitution in trifluoromethylarenes is an ongoing synthetic challenge that often leads to 'over-reaction', where multiple fluorides are replaced. Development of this reaction would allow simple access to a vast range of difluoromethyl derivatives of current interest to pharmaceutical, agrochemistry and materials sciences. Using a catalytic Frustrated Lewis Pair approach, we have developed a generic protocol that allows a single substitution of one fluoride in trifluoromethyl groups with neutral phosphine and pyridine bases. The resulting phosphonium and pyridinium salts can be further functionalized via nucleophilic substitution, photoredox coupling and electrophilic transfer reactions allowing the generation of a vast array of difluoromethyl products.

Introduction:

Substituting a single fluorine atom in trifluoromethyl groups has been an enduring academic challenge. Apart from the carbon-fluorine (C–F) bond being the strongest carbon-element single bond known,[1] the bond dissociation energy of C–F bonds tends to decrease as *geminal* fluorine atoms are substituted (Figure 1, A), leading to over-reaction for carbon positions with more than one fluorine atom.[2] Indeed, a generic method for the nucleophilic substitution (a fundamental organic chemical transformation) of a single fluoride atom in trifluoromethyl groups remains unrealized. The ability to monoselectively functionalize aliphatic polyfluorides is an attractive proposition, as it would allow fast and convenient access to a number of fluorine containing motifs with high chemical diversity in the biologically relevant 3D chemical space.[3] Despite the synthetic potential of such a protocol, very few reports of monoselective C–F functionalization exist for benzotrifluorides, all of which are limited in their scope of benzotrifluorides and/or coupling partners. Specifically, *ortho*-silyl benzotrifluoride substrates have allowed kinetically controlled C–F functionalization in CF_3 groups (Figure 1, B),[4] Stephan reported controlled monohydrodefluorination of $PhCF_3$ using a silylium/phosphine adduct (Figure 1, C),[5] Single Electron Transfer (SET) approaches allow selective alkyldefluorination of electron poor benzotrifluorides using alkene or enone reagents (Figure 1, D),[6] and transition metal catalyzed monohydrodefluorination was exhibited on *para*-protected benzotrifluoride derivatives by Lalic (Figure 1, E).[7]

Recently, we reported a synthetic methodology that allowed selective single C–F bond activation in *gem*-difluorogroups.[8] The strategy was based on heterolytic cleavage and capture of carbocation and fluoride components of a C–F bond with a Frustrated Lewis Pair (FLP). Triaryl phosphine bases were employed in our FLP system, allowing subsequent Wittig couplings with aldehydes to provide fluoro-olefin products (Figure 1, F).

In theory, this concept could be extended to a wide variety of polyfluoride starting materials (including benzotrifluorides), given that any C–F bond on the captured cationic fragment would be 'deactivated' towards further fluoride abstraction. However, triaryl phosphoniums act as poor leaving groups from sp^3 carbon positions in traditional palladium coupling and nucleophilic substitution chemistries,[9] meaning that subsequent functionalization of intermediate phosphonium salts is limited.

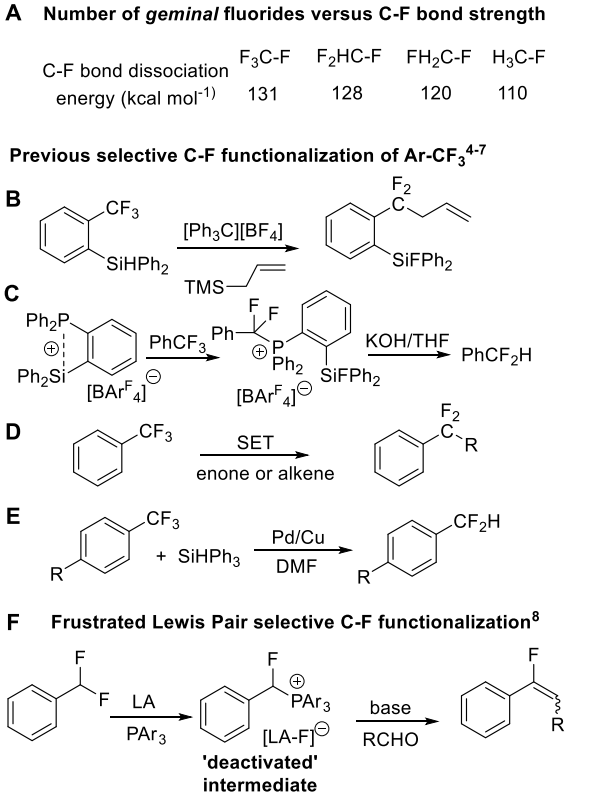
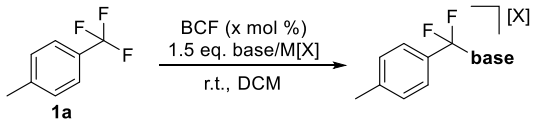


Figure 1. (A) Decreasing C–F bond strength with substitution of fluorine with hydrogen in tetrafluoromethane. (B-E) Known approaches to monoselective C–F functionalization. (F) Utilizing FLP reactivity to 'deactivate' fluorocarbon motifs towards further fluoride abstraction by Lewis acids to prevent 'over-reaction'.

To construct new carbon-element single bonds, we expanded our attention to other bases/leaving groups with established chemistry allowing single bond formation to sp^3 carbon centers. To this end, we found success in the use of 2,4,6-triphenylpyridine (TPPy). Pyridinium salts (in particular TPPy adducts) can undergo nucleophilic substitution but are also capable of cross coupling, reductive coupling and borylation chemistry, thus TPPy is a very attractive leaving group.[9] We document here, our efforts to apply FLP C–F activation methodology to more

Table 1. Selected optimization conditions for C–F activation.



entry	BCF loading	base	time	M[X]	Yield (%)
1[a]	150%	P(*o*-Tol)$_3$	24 h	-	<1
2[a]	20%	P(*o*-Tol)$_3$	24 h	Li[BF_4]	<1
3[a]	20%	P(*o*-Tol)$_3$	24 h	Li[$B(C_6F_5)_4$]	20
4	20%	P(*o*-Tol)$_3$	24 h	Me_3SiOTf	<1
5	20%	P(*o*-Tol)$_3$	24 h	Me_3SiNTf_2	70
6[a]	20%	P(*o*-Tol)$_3$	4 h	Me_3SiNTf_2	>95
7[a]	5%	P(*o*-Tol)$_3$	24 h	Me_3SiNTf_2	86
8[b]	20%	THT	24 h	Me_3SiNTf_2	<1
9[a]	20%	pyridine	24 h	Me_3SiNTf_2	<1
10	20%	lutidine	48 h	Me_3SiNTf_2	20
11[a]	150%	TPPy	24 h	-	<1
12	20%	TPPy	48 h	Me_3SiNTf_2	>95
13[b]	20%	TPPy	4 h	Me_3SiNTf_2	87
14	0%	TPPy	48 h	Me_3SiNTf_2	<1

[a] In DCE at 80 °C. [b] In DCE at 60 °C. BCF = tris(pentafluorophenyl)borane, THT = tetrahydrothiophene, TPPy = 2,4,6-triphenylpyridine.

challenging aromatic trifluoromethyl groups to generate difluoromethyl products.

Results and Discussion

Treatment of *p*-Tol–CF_3 (**1a**) with the FLP [$B(C_6F_5)_3$] (BCF) and P(*o*-Tol)$_3$ led to no reaction at room temperature, and less than 1% yield of the desired phosphonium salt after 24 h heating at 80 °C (Table 1, entry 1). However, removal of the abstracted fluoride from the reaction through precipitation of LiF or loss of Me_3SiF gas promoted the reaction and allowed for catalytic quantities of BCF to be used. Indeed, the use of Me_3SiNTf_2 was found to be effective even at room temperature, allowing high yields of the desired phosphonium salt [*p*-TolCF_2–P(*o*-Tol)$_3$][NTf_2] (**2a**) to be generated (Table 1, entries 5-7).

Attempts using tetrahydrothiophene, pyridine or lutidine as the base partner gave poor conversion or failed to react with **1a** (Table 1, entries 8-10). However, the nitrogen donor base 2,4,6-triphenylpyridine[10] (TPPy) generated the desired TPPy pyridinium salt, **3a**, almost quantitatively at room temperature after 48 h (60% yield after 24 h) with catalytic loadings of BCF (Table 1, entry 12). Heating of reaction mixtures containing TPPy led to a faster conversion of **1a** to **3a** (Table 1, entry 13), however, it was found that **3a** decomposed at higher temperatures over time, compromising the reaction yield. Finally, running the reaction without any BCF catalyst failed to generate any **3a** (Table 1, entry 14). Although Me_3SiNTf_2 is a strong Lewis acid, previously reported hydrodefluorination reactions also failed when utilizing Me_3SiOTf.[11]

Phosphonium salt **2a** could be readily isolated via crystallization in 67% isolated yield. The ^{13}C NMR of **2a** confirms the substitution of a fluoride in **1a** by phosphorus with the benzylic carbon resonance at 121.3 ppm displaying one-bond couplings to both phosphorus and the remaining two fluorine atoms (td, $^1J_{CF}$ = 270.6 Hz, $^1J_{CP}$ = 90.0 Hz). The ^{19}F and ^{31}P NMR spectra of **2a** also support monoselective substitution, with a doublet signal δ_F -79.4 ($^2J_{FP}$ = 109.0 Hz) arising from the benzylic fluorines and a triplet signal at δ_P 31.8 ($^2J_{PF}$ = 109.0 Hz) due to the phosphonium center. A molecular structure of **2a** displays the

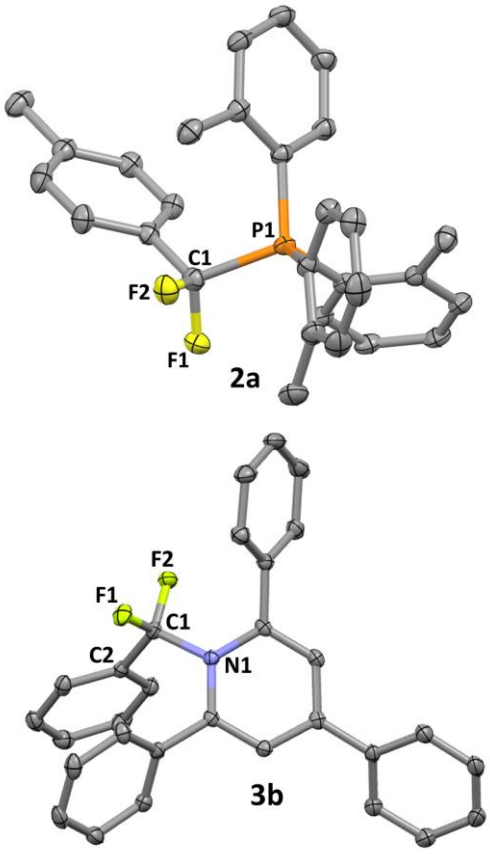


Figure 2. Molecular structures of [*p*-TolCF_2P(*o*-Tol)$_3$][NTf_2] (**2a**), [PhCF_2(TPPy)][NTf_2] (**3b**). Hydrogen atoms and anions omitted, thermal ellipsoids shown at 50%. See SI for crystallographic parameters.

connectivity in **2a** with P(*o*-Tol)$_3$ capturing the defluorinated [*p*-Tol–CF_2]$^+$ fragment at the benzylic position as expected (Figure 2).

The TPPy salt **3a** was found to be stable in the reaction mixture at room temperature for a number of days, allowing spectroscopic and spectrometric characterization. ^{19}F NMR spectroscopy of **3a** revealed a signal at δ_F -55.5 arising from the benzylic fluorine atoms. The ^{13}C NMR spectrum revealed the benzylic carbon signal at δ_C 122.3 to be a triplet ($^1J_{CF}$ = 273 Hz), indicating a one-bond coupling to two fluorine atoms. Despite the apparent stability of **3a**, attempts to isolate and/or crystallize **3a** led only to decomposition products, however, evidence of its connectivity was obtained from the molecular structures of the related TPPy phenyl derivative **3b** derived from Ph–CF_3 (Figure 2), and from the transfer product **4k**, where pyridine displaced TPPy in **3a** (Figure 4). Interestingly, the N–CF_2 distance in **3b** is slightly elongated as compared to **4k** {N1–C1 (**3b**) = 1.521(2) Å *cf.* N1–C1 (**4k**) = 1.505(2) Å}, suggesting a slightly weaker N–CF_2 bond in **3b**.

A brief survey of substrates revealed that P(*o*-Tol)$_3$ could readily substitute a single fluoride in a range of trifluoromethyl groups (Figure 3). Electron donating groups as well as weakly withdrawing groups were well tolerated (**4a-d**). More challenging bis(trifluoromethyl)benzene substrates could also be activated, and selective activation in one or both of the trifluoromethyl groups could be controlled with suitable reaction temperatures. At 80 °C, monosubstitution dominated giving rise to

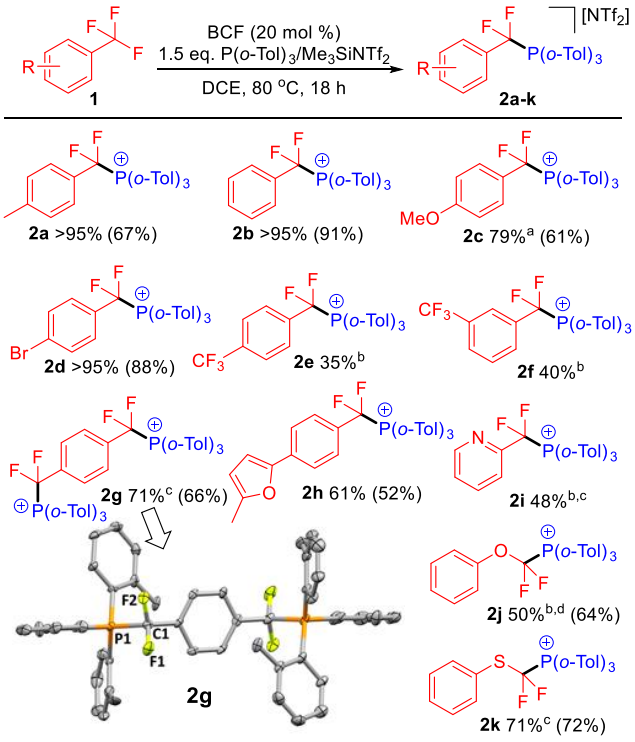


Figure 3. Benzotrifluoride scope for monoselective C–F functionalization using P(*o*-Tol)$_3$. Yields determined by ^{19}F NMR or ^{31}P NMR spectroscopy. Isolated yields from large scale reactions in brackets. [a] Conducted at 60 °C. [b] Conducted for 40 h. [c] In 1,2-DCB at 150 °C. [d] In 1,2-DCB at 100 °C.

products **2e** and **2f**, however, above 100 °C disubstitution became dominant, and the bisphosphonium product **2g** could be obtained in 71% yield.

Selective activation of 2-trifluoromethylpyridine under forcing conditions provided a mediocre 48% yield of **2i** due to catalyst inhibition by the starting material, however, the reaction was shown to better tolerate less basic heteroaromatics such as furan, with **2h** generated in 61% yield. Lastly, non-aromatic systems could also be monoselectively activated, with trifluoromethoxybenzene providing **2j** in 50% yield and **2k** generated in 71% yield from trifluoromethylthiobenzene.

Notably, SET selective C–F alkylation approaches do not tolerate aryl halides and furans, react poorly with electron rich benzotrifluorides and are completely inactive for non-aromatic CF_3 groups. Thus, the subsequent alkylation and hydrogenation of P(*o*-Tol)$_3$ positions (demonstrated below) is complementary to SET methodologies.

As described above, triaryl phosphines are poor leaving groups for S_N2 substitutions, and in general, controlled nucleophilic substitution of CF_3 groups is not possible using existing chemistries. In contrast, the nucleophilic substitution chemistry of alkylated 2,4,6-triphenylpyridiniums under mild conditions is well known.[9a-c] Thus, the ability to isolate selectively activated TPPy–CF_2R salts allows for the synthesis and storage of latent electrophilic CF_2R reagents. Conversely, the application of a two-step process (where TPPy–CF_2R salts are generated *in situ*) allows access to a number of S_N2 difluoromethyl products directly (Figure 4).

For instance, generation of *p*-Tol–$CClF_2$ (**4a**), *p*-Tol–$CBrF_2$ (**4b**) and *p*-Tol–CF_2I (**4c**) in high yields could be achieved through the treatment of *in situ* generated **3a** with nucleophilic

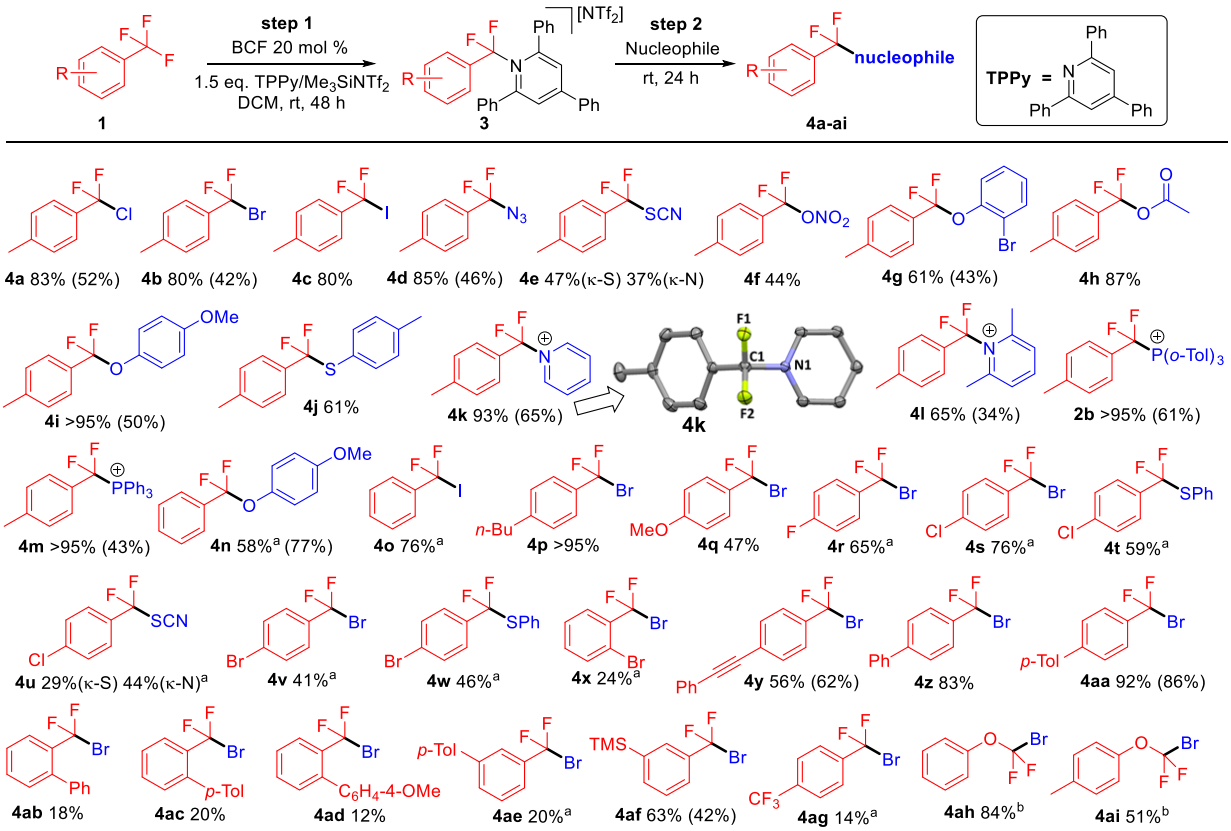


Figure 4. Scope for one-pot monoselective S_N2 functionalization of trifluoromethyl substrates. Note: the reaction in step 2 was typically complete in less than 1 hour, but final yields were determined at 24 h by ^{19}F NMR spectroscopy. Isolated yields from large scale reactions in brackets. [a] Step 1 performed at 60 °C in DCE. [b] Step 1 performed at 100 °C in 1,2-DCB.

tetraalkylammonium halides. CF_2X groups (X = Cl, Br, I) have established palladium cross coupling and redox chemistries allowing the formation of a range of difluoromethylene derivatives from such starting materials.[12]

Alkali metal inorganic salts were effective at displacing the TPPy group, with sodium azide, sodium thiocyanate, sodium nitrate, lithium (2-bromo)phenoxide, sodium acetate, lithium (4-methoxy)phenoxide and sodium *p*-tolyl sulfide generating products **4d-4j** in moderate to high yields.

Neutral nucleophiles could also displace TPPy in **3a**. Pyridine and lutidine displaced TPPy to generate salts **4k** and **4l** in 93% and 65% yields respectively. When using pyridine or lutidine under C–F functionalization conditions (Table 1, entries 9-10), **4k** could not be generated, and **4l** could only be generated in 20% yield. Phosphonium salts **2a** and **4m** could be generated almost quantitatively from addition of P(*o*-Tol)$_3$ or PPh_3 respectively to **3a**. Although **2a** could be accessed directly using P(*o*-Tol)$_3$ as a base in step 1 (Figure 3), the displacement of TPPy by less sterically encumbered phosphines allows access to a greater range of phosphonium salts, including those containing unhindered phosphines.

Expanding the reaction to other trifluoromethylarenes allowed an assessment of functional group tolerance and effect on the reaction. Benzotrifluoride (**1b**) provided near quantitative conversion to the TPPy salt **3b**, which could be isolated via crystallization in 53% yield. The high NMR yield of this reaction demonstrated that in the presence of TPPy Friedel-Crafts alkylation was not a dominant side-reaction. Treating *in situ* generated **3b** with lithium (4-methoxy)phenoxide or TBAI generated products **4n** and **4o**. Longer alkyl chains (n-butyl) in the para position gave outstanding results with **4p** being generated in over 95% yield.

Introducing the more donating group –OMe at the *para* position provided **4q** in a moderate yield of 47%. In this reaction, it was found that consumption of the trifluoromethylarene starting material occurred very quickly, but the intermediate TPPy salt was less stable and partially decomposed before TBAB could be introduced. In contrast, using P(*o*-Tol)$_3$ as the base in the C–F activation step yielded phosponium salt **2c** in 79% (Figure 3), resulting from the higher stability of the phosphonium salt as compared to the TPPy salt.

Fluoro-, chloro- and bromo-groups at the *para* position slowed the rate of C–F activation, and generally required gentle heating for step 1 to be completed in a reasonable timeframe. In contrast to donating groups, TPPy salts with electron deficient benzylic groups were found to have higher thermal stability, with little decomposition after prolonged mild heating, thus the slower reaction rates could be overcome by running step 1 at 60 °C. Employing 2-bromo-trifluoromethylbenzene, led to a final yield of 24% for **4x** representing steric encumbrance to the FLP C–F activation step. The yield of **4x** could be improved to 48% with a longer reaction time for step 1 (see SI).

Tolerance of non-aromatic unsaturated hydrocarbon groups was demonstrated with the generation of **4y** (56% yield) featuring a phenyl acetylide group in the *para* position. Placement of aryl groups in the benzotrifluoride *para* position resulted in high yields of desired brominated products **4z** and **4aa**, however, aryl groups in the *ortho* position led to very low yields of desired brominated products. Closer inspection revealed step 1 to be almost quantitative in these reactions, but subsequent nucleophilic substitution of the TPPy occurred very slowly. A molecular structure of the intermediate **3s** (see SI) revealed this stability likely arises from π-π stacking between the eclipsed *ortho* aryl and the pyridinium groups.[13]

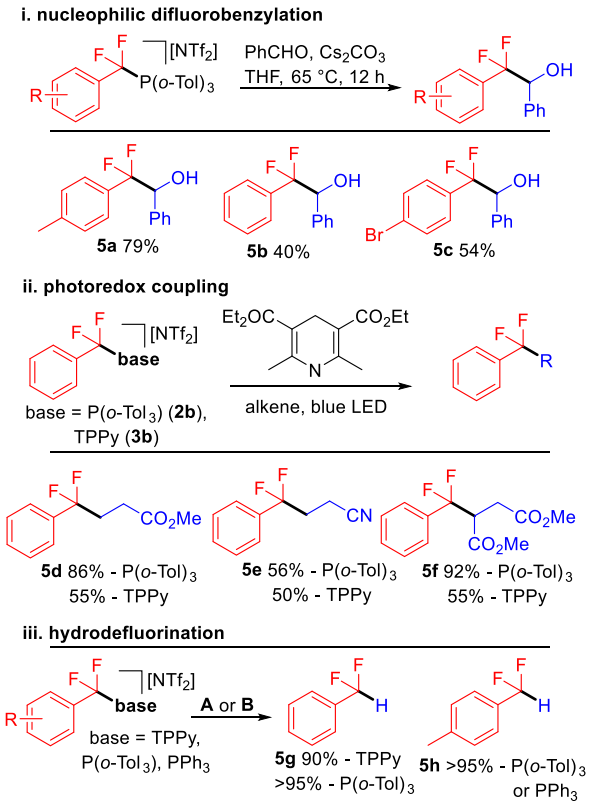


Figure 5. C–C and C–H bond forming reactions for pyridinium and phosphonium salts. See SI for detailed conditions. Conditions: **A** for TPPy: PhC(O)Ph, $NaSC_6H_4$-4-F, DCE, r.t., 16 h. **B** for P(*o*-Tol)$_3$/PPh_3: KOH (5 equiv.), THF, r.t. 1 h. Yields determined by ^{19}F NMR spectroscopy.

Strongly electron withdrawing groups such as CF_3 deactivated the benzotrifluoride substrates, with 1,4-bis(trifluoromethyl)benzene only generating the selectively brominated product **4ag** in 14% yield.

Lastly, C–F activation of non-aromatic trifluoromethyl groups in trifluoromethoxybenzene and 4-trifluoromethoxytoluene to generate products **4ah** and **4ai** in good yield demonstrated the ability to enable selective nucleophilic substitution in non-aromatic CF_3 groups for the first time. Controlled direct access to α,α-difluoro ethers from trifluoromethyl ethers is not possible using any other approach, and they are of increasing interest to agrochemical and pharmaceutical sciences due to their high lipophilicity.[14]

Both phosphonium and pyridinium salts have been reported to facilitate C–C bond formation via photoredox coupling[9d-o] and nucleophilic transfer reactions.[15] Applying previously reported protocols for C–C bond formation with phosphonium and pyridinium salts allowed us to demonstrate the ability of this methodology to readily access carbon substituted difluoride products (Figure 4).

For example, benzaldehyde was reacted with phosphonium salts **2a**, **2b** and **2d** to generate products **5a-c**, where the difluorobenzyl group underwent nucleophilic transfer to benzaldehyde (Figure 5, i). This selective coupling is unique to our methodology.

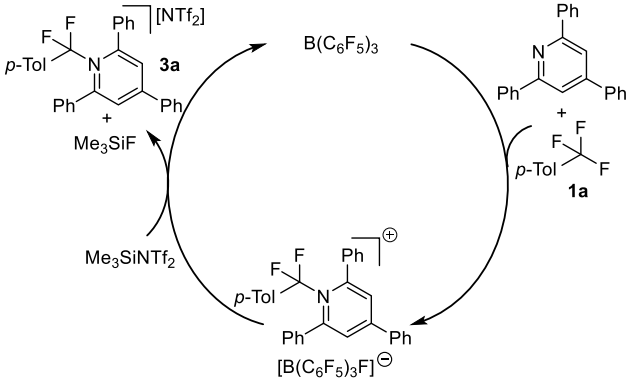


Figure 6. Plausible mechanism for catalytic generation of **3a**.

Redox coupling reactions are well reported for phosphonium and TPPy salts. To provide proof-of-principle for C–C redox couplings, phosphonium salt **2b** and TPPy salt **3b** were subject to reported redox coupling conditions[12i] using Hantzsch ester as the reductant (Figure 5, ii). With Michael acceptors, both salts produced good yields of the desired products **5d-f**, however, under these conditions, the phosphonium salt **2b** outperformed the pyridinium salt **3b**. The general applicability of reported redox couplings using phosphonium and pyridinium salts to difluoromethyl substrates is under ongoing investigation.

Finally, formal hydrodefluorination to difluoromethyl groups (hydroxyl biosteres)[16] was demonstrated from both phosphonium and TPPy salts with both nucleophilic transfer and redox coupling conditions enabling the formation of **5g** and **5h** in excellent yields (Figure 5, iii).

Given that phosphonium/pyridinium C–C and C–H couplings are reported to tolerate aromatic halides and furans, and perform well for electron rich aromatic and non-benzylic positions, couplings from phosponium/pyridinium difluoromethyl salts are complimentary to reported SET mediated defluoroalkylations.[6]

Mechanistically, a possible reaction pathway for the generation of **3a** is illustrated in Figure 6. We suspected that fluoride abstraction is performed by BCF, and that Me_3SiNTf_2 acts to regenerate BCF from $[BF(C_6F_5)_3]^-$, driving the reaction forward via the formation of Me_3SiF gas. To test this hypothesis, $Cs[BF(C_6F_5)_3]$ was reacted with an equivalent of Me_3SiNTf_2 at room temperature and found to quickly (< 10 minutes) generate $Cs[NTf_2]$, BCF and Me_3SiF (see SI). Additionally, small concentrations of $[BF(C_6F_5)_3]^-$ are observed during and after the reaction, and the reaction was found to be inactive in the absence of BCF (using conditions from Table 1, entry 14) implying that BCF is indeed the fluoride abstraction agent (*c.f.* direct transfer to Me_3SiNTf_2). Similar findings were found for previously reported catalytic pseudohalodefluorination.[17]

Conclusion

We have developed an effective synthetic protocol to selectively activate and functionalize a single fluoride position in both aromatic and non-aromatic trifluoromethyl groups via phosphonium and pyridinium salts. This protocol allows for a wide variety of post functionalization, including the first instance of nucleophilic substitution in non-customized benzotrifluorides, photoredox coupling and electrophilic transfer reactions. In general, the pyridinium salts allow facile S_N2 functionalization as well as photoredox couplings. In contrast, the phosphonium salts are more robust, but only support photoredox couplings and difluorobenzyl nucleophilic transfers.

ASSOCIATED CONTENT

The Supporting Information, including experimental details, is available free of charge on the ACS Publications website. Crystal X-ray crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk): CCDC 1944140, 1944141, 1944142, 1944143 and 1963332 for compounds **3b**, **3s**, **4k**, **2a** and **2g** respectively.

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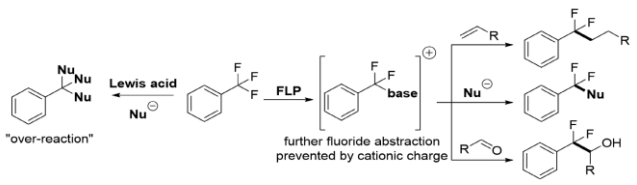
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