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Borazine-CF_3^- Adducts for Rapid, Room Temperature, and Broad Scope Trifluoromethylation

Jacob B. Geri, Michael M. Wade Wolfe, and Nathaniel K. Szymczak*

Abstract: *We present a strategy to use a fluoroform-derived borazine CF_3^- transfer reagent to effect rapid nucleophilic reactions in the absence of additives within minutes at 25 °C. Inorganic electrophiles spanning 7 groups of the periodic table can be trifluoromethylated in high yield, including transition metals used for catalytic trifluoromethylation. Organic electrophiles included (hetero)arenes, enabling C-H and C-X trifluoromethylation reactions. Mechanistic analysis supports a dissociative mechanism for CF_3^- transfer, and cation modification afforded a reagent with enhanced stability.*

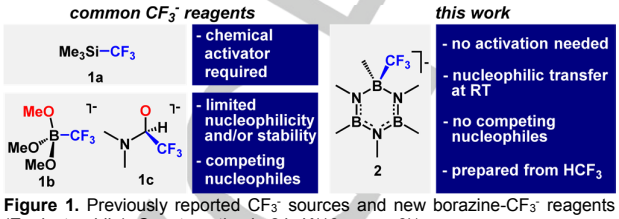


Figure 1. Previously reported CF_3^- sources and new borazine-CF_3^- reagents (E=electrophile). Countercation in **2** is K(18-crown-6)$^+$.

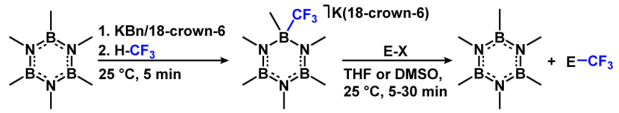
The trifluoromethyl (CF_3) group is indispensable in organic synthesis.[1] As the smallest fluoroalkyl group, it dramatically increases the bioavailability and metabolic stability of drug candidates without altering their steric profile. Nucleophilic trifluoromethylation reactions are particularly attractive; however, the trifluoromethyl anion (CF_3^-) is highly unstable.[2] While CF_3^- can be generated for *in-situ* use, it undergoes irreversible F^- elimination at -80 °C. Lewis acids can be employed to stabilize CF_3^-, but stabilization comes at the cost of attenuated CF_3^- nucleophilicity.[3] As a result, currently used CF_3^- reagents present a more limited reactivity scope than analogous Grignard and organolithium reagents.

The most commonly used CF_3^- transfer reagent, $SiMe_3CF_3$, uses a cationic Lewis acid (LA, $SiMe_3^+$) to stabilize CF_3^-. $SiMe_3CF_3$ is typically activated by a Lewis base (Nuc; e.g. F^-) to form $SiMe_3(Nuc)(CF_3)^-$ which can release CF_3^-; however, this intermediate is unstable above -60°C.[4] Therefore low temperatures or activation in the presence of substrate are used, but these conditions introduce operational challenges and/or decreased CF_3 transfer selectivity.[4c, 4d] An alternative approach that does not require an activator is the use of neutral LAs to generate anionic LA-CF_3^- adducts.[5] Unfortunately, previously employed LAs are either too strong ($B(OMe)_3$,[5b] BR_3[6]) or too weak (DMF),[7] resulting in either low CF_3^- nucleophilicity[8] or low thermal stability.[7, 9] $B(OR)_3CF_3^-$ and DMF-CF_3^- also present reactive oxyanion nucleophiles which can engage in competing reactions with oxophilic electrophiles.[5b, 7] A LA with optimal strength and no competing nucleophilic sites could enable the synthesis of potent and selective trifluoromethylation reagents.

We recently reported the preparation of LA-CF_3^- adducts from fluoroform (HCF_3; an industrial waste product), using electronically matched LA/Brønsted base pairs (Figure 1).[10] A combined empirical/theoretical approach identified hexamethylborazine ($B_3N_3Me_6$) as one of the weakest LAs capable of stabilizing CF_3^- at 25 °C; the corresponding CF_3^- adduct, **2**, is highly nucleophilic. Unlike $SiMe_3CF_3/F^-$ (**1a**), $B(OMe)_3CF_3^-$ (**1b**), or DMF-CF_3^- (**1c**), **2** does not present competing nucleophilic centers, enabling reactions with hard electrophiles such as $SiMe_3Cl$, and the Lewis acid is recyclable. In this communication, we show that **2** is capable of rapid and highly general CF_3^- transfer to diverse transition metal, main group, and organic electrophiles, experimentally interrogate its mechanism, and present a variant with enhanced stability.

The reactivity profile for CF_3 transfer from a transition metal-CF_3 unit is dictated by the identity of the metal center.[11] Depending on the metal used, the CF_3 ligand can be used to form C-CF_3 bonds through direct nucleophilic transfer (Zn^{2+}),[12] radical substitution (Ag^+),[13] or reductive elimination (Cu^+,[14] Au^{3+},[15] Pd^{2+})[16]. We selected reactions with these metals to assess the transmetalation activity of **2**. $Zn(TMEDA)(Cl)_2$, $AgNO_3$, and Au(SiPr)Cl react with one equiv. **2** to afford M-CF_3 products (**3e**: 74%, **3c**: 44%, and **3d**: 15%) in under 10 minutes at 25 °C (Figure 2). While Ag, Au, and Zn –CF_3 complexes are useful CF_3 transfer reagents, only Cu and Pd complexes catalyze cross-coupling with CF_3^-.[4d, 5a] When treated with one equiv. **2** for 10 min, CuI and Pd(TMEDA)(*p*-tolyl)I reacted to afford $CuCF_3$ and $PdCF_3$ complexes in high yield (**3b**: 83% and **3a:** 98%). The obtained $CuCF_3$ reacts with (4-Ph)PhI to afford (4-Ph)PhCF$_3$ (66%).

Main group electrophiles in groups 13-15 are challenging substrates due to their high oxo/fluorophilicity.[17] **2** enabled the synthesis of $B(OMe)_3CF_3^-$, $SiMe_3CF_3$, $SnMe_3CF_3$,[18] and $PbMe_3CF_3$[19] from their corresponding halides in good to excellent yield (**3f**: 99%, **3g**: 96%, **3h**: 73%, and **3i**: 99% respectively) at 25 °C. Group 15 halides were also trifluoromethylated by **2**; when



transition metals (group 10-12)				
Pd(TMEDA)(p-Tol)–CF_3	Cu–CF_3	Ag–CF_3	Au(iPr)–CF_3	Zn(TMEDA)–$(CF_3)_2$
3a: (98%)	3b: (83%)	3c: (44%)	3d: (15%)	3e: (74%)

group 13	group 14			group 15	
$(MeO)_3B$–CF_3	Me_3Si–CF_3	Me_3Sn–CF_3	Me_3Pb–CF_3	Ph_2P–CF_3	Bi–$(CF_3)_2Cl$
3f: (80%)*	3g: (99%)	3h: (73%)	3i: (99%)	3j: (99%)	3k: (42%)

Figure 2. Reactions with inorganic electrophiles. TMEDA = tetramethylethylenediamine, iPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidine. X = Cl for substrates except for Pb; X=Br and Cu; X=I. Yield determined by ^{19}F-NMR. *: as reported in reference 8.

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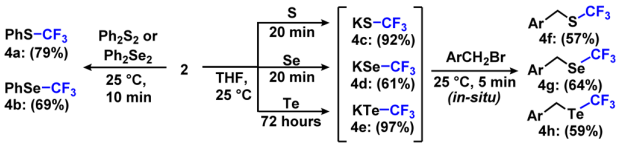

Figure 3. Reactions with organic and inorganic chalcogens.

were combined with **2**, PPh_2CF_3[20] (**3j**) and $Bi(CF_3)_2Cl$[21] (**3k**) were prepared in 99% and 42% yield.

SCF_3 and $SeCF_3$ are important functional groups in medicinal chemistry,[22] and SCF_3^-,[23] $SeCF_3^-$,[23] and $TeCF_3^-$[24] are useful synthons that must be prepared using **1a** at -60 °C. In contrast, **2** reacts with S, Se, and Te within 20 minutes at 25 °C to produce SCF_3^- (4c: 92%), $SeCF_3^-$ (4d: 61%), and $TeCF_3^-$ (4e: 97%); these anions were alkylated *in-situ* in 87% (**4f**), 68% (**4g**), and 59% (**4h**) combined yield. Additionally, dichalcogenides react with **2** to afford S- and Se-ethers (79% (**4a**), 69% (**4b**)). Because **2** is prepared from HCF_3, these reactions represent an economical route to R-SCF_3 and R-$SeCF_3$ moieties.

We repeated the above reactions using anionic CF_3 transfer reagents: analogous to **2**, these single reagent precursors require no optimization of exogenous additives. **1b**-**c** transfer CF_3^- to inorganic electrophiles, but the reactions are conducted at high temperature (**1b**)[5a] or under cryogenic conditions (**1c**).[5a, 9, 23] Efficiency was compared at 25°C (0.1 M) and yield measured after 10 min.[25] **1b** only provided trace product, and **1c** provided products in lower yield than **2** for all but 2 of 14 substrates (**3d**: 56%, **4d** 86%). We attribute the favorable reactivity of **2** to the combination of fast CF_3^- transfer and the absence of competing nucleophilic sites.

Rapid synthetic procedures are required in manipulations of ^{18}F ($t_{1/2}$=120 minutes).[26] We used the *in-situ* generation of the electrophilic trifluoromethylation reagent Togni I (**5a**) from HCF_3-derived **2** to showcase the speed with which HCF_3 can be used to deliver CF_3^+ equivalents to electron-rich substrates (Figure 4).[27] Preparation of **2** from HCF_3, CF_3^- transfer to form Togni I, and addition of 1-thio-β-D-glucose tetraacetate afforded **5b** in 32 minutes (43% combined yield, Figure 4). While the synthesis of $HC^{19}F_2{}^{18}F$[28] is challenging and there are numerous practical hurdles associated with manipulations of ^{18}F, the speed of our methodology combined with extremely rapid and selective CF_3^+ transfer from Togni I may enable electrophilic radiotrifluoromethylation reactions to be explored.

We next explored reactions between **2** and non-enolizable organic electrophiles (Figure 5a, 5b). CF_3^- addition reactions have been extensively studied with carbonyl substrates and were used to benchmark **2**. Substrates containing acyl chloride, isocyanate, aldehyde, ketone, ester, imine, and carbonate groups all afforded addition products in good yield (**6a**-**6k**: 29-87%). In contrast to reactions using **2**, **1b** provided <10% yield in all cases under identical conditions.

Nucleophilic aromatic addition/substitution (S_NAr) reactions offer unique, orthogonal reactivity patterns[11, 29] in comparison with cross-coupling[11] and radical substitution.[29b] However, S_NAr reactions with CF_3^- are not well described.[30] We hypothesized that the high nucleophilicity of **2** would support S_NAr reactivity. Indeed, we found that **2** can be used for metal-free C-F and C-

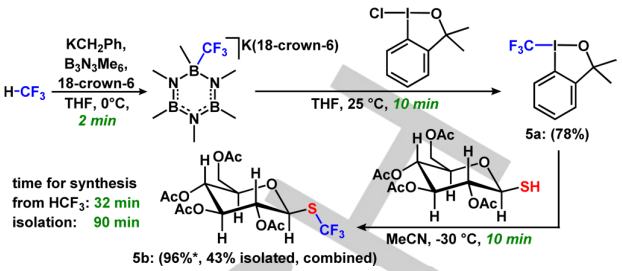

Figure 4. Rapid electrophilic trifluoromethylation from HCF_3. Isolated yield. *: yield determined by ^{19}F-NMR .

NO_2 aromatic trifluoromethylation (Figure 5f). **2** reacted with perfluorotoluene, 2-nitropyridine, and *p*-dinitrobenzene to afford **6l-n** in modest yield (27-42%). These reactions represent new general routes to Ar-CF_3 compounds.

Unsubstituted heteroarenes can form σ-complexes with strong nucleophiles, and subsequent oxidation/rearomatization can be an attractive C-H functionalization strategy.[31] Unsubstituted triazine, pyrimidine, and quinazoline compounds selectively reacted with **2** at the 4- position to furnish σ-adducts (Figure 6b), which were oxidized to CF_3-substituted products (**6o-q**). Notably, 5-bromo-2-chloropyrimidine afforded **6r** in 49% yield as the sole product. In 4-Cl substituted quinazolines or triazines, treatment with **2** afforded geminal bistrifluoromethylated amides (**6s-u**). The anionic σ-adducts were functionalized at the nitrogen atom by introducing an electrophile (e.g. H_2O, benzyl bromide) to isolate dearomatized heterocyclic products. To demonstrate this selectivity, **6v** was prepared in 60% yield over three steps in one pot. These 4- selective trifluoromethylations of heteroarenes complement *meta*- selective radical C-H trifluoromethylations.[32] We hypothesized that **2** could enable selective addition reactions with pyridines if they were first activated by LAs. Using only the steric bulk of the activating LA to control selectivity, quinoline-LA adducts reacted with **2** to afford σ-adducts at either the 2- (BF_3) or 4- ($B(C_6F_5)_3$) position. These reactions proceeded with high (85%; 93%) selectivity with commercially available LAs, in contrast with a previous method that relied on larger $B(C_6F_4CF_3)_3$ for 4- selective trifluoromethylation.[33] Oxidation afforded the C-H trifluoromethylated products (**6w**: 27%; **6x**: 61%). This methodology expands the scope of 2- selective trifluoromethylation reactions beyond pyridine N-oxides,[34] enabling the inclusion of oxidizable functionalities such as an allylic thioether (**6y,** 37%).[35] Overall, the broad scope of **2** showcases the utility of a highly nucleophilic reagent that does not require exogenous activators.[36]

To interrogate whether CF_3^- transfer occurs through an associative or dissociative pathway, we determined the rate law for CF_3 transfer from **2** to representative electrophiles (E= **7, 8**). In an associative mechanism, the rate dependence for both **2** and E would be 1st order with a negative $\Delta S^{\ddagger}$. In a dissociative mechanism, the rate dependence for **2** and E would be 1st/zero order, with a positive $\Delta S^{\ddagger}$. Orders consistent with a dissociative mechanism were observed in CF_3^- transfer to **7**/**8**, with a positive $\Delta S^{\ddagger}$ (+12(3) e.u.) value for **7**.

In addition to establishing the rate law for CF_3 transfer, we also found that thermal decomposition of **2** followed second order

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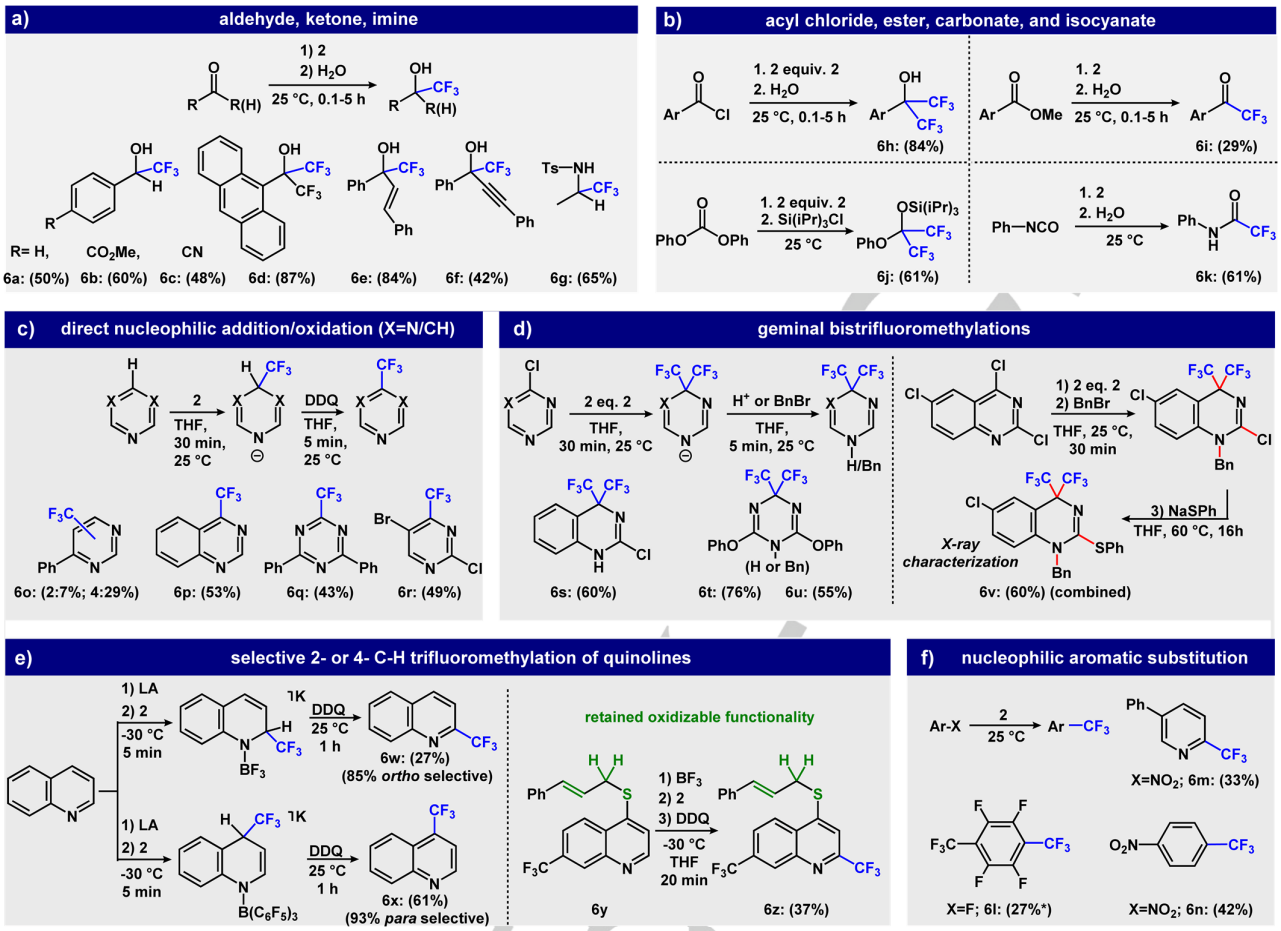

Figure 5. a) CF_3^- addition to C=O and C=N compounds. b) CF_3^- addition to acyl chloride, ester, carbonate, and isocyanate compounds. c) Nucleophilic aromatic substitution. (*: yield determined by ^{19}F-NMR) d) Direct nucleophilic addition/oxidation. e) Geminal bistrifluoromethylations. f) 2- or 4- C-H trifluoromethylation of quinolines.

kinetics, suggesting that an encounter between $[K(18\text{-crown-6})]^+$ and CF_3^- units promote CF_3^- defluorination.[2] This is supported by the presence of an intermolecular K-F interaction in the solid state structure of **2**, which elongates a single C-F bond.[10] Accordingly, cation Lewis acidity was found to directly influence the stability of **2**. Encapsulation of K^+ with 2 equiv 18-crown-6 improved the solution half-life at 60 °C (0.2 M) from 7 min to 18 min. Replacing K^+ in **2a** with less Lewis acidic Cs^+ provided even higher stability (180 min). The latter variant exhibits high stability at 25 °C, with a daily decomposition rate of 1% in solution (0.2 M THF) and 3% as a solid, and showed *no* decomposition after one month at -30 °C. The higher stability of **2b** is consistent with the absence of Cs-CF_3 interactions in its solid state structure.

The alkali metal dependence on the decomposition of **2** suggested that Lewis acids could also be used to facilitate dissociative CF_3^- transfer. We hypothesized that the $B_3N_3Me_6(CF_3)$-cation interaction would labilize the B-CF_3 bond by reducing electron density at the carbon atom of CF_3^-. Reagents **2** and **2b**, in which a cation-fluorine interaction is either present or absent, allowed us to clearly interrogate this hypothesis. In nucleophilic CF_3^- transfer to aldehyde **7**, **2** was 3x faster than **2b**, indicating that the cation likely assists in rate-determining CF_3^- dissociation. This mechanistic insight suggested that **2b** could be activated by the addition of exogenous Lewis acids: addition of 5 equiv. $K[B(C_6F_5)_4]$ to **2b** lead to a >40x increase in rate with no reduction in yield. This provides a complementary strategy to SiR_3CF_3 reagents; activity is enhanced by addition of cationic, rather than anionic, activators.

In summary, we have demonstrated that a recyclable and fluoroform-derived CF_3^- reagent promotes broad-scope trifluoromethylation at 25 °C. **2** is an excellent transmetalation reagent, rapidly trifluoromethylating 18 different elements in high yield. The reagents promote CF_3^- transfer reactions with diverse organic electrophiles including carbonyl/imine and (hetero)aromatic compounds. CF_3^- transfer follows a cation-assisted dissociative mechanism, which enabled the design of a weighable solid reagent with enhanced shelf-stability that could be activated with exogenous K^+.

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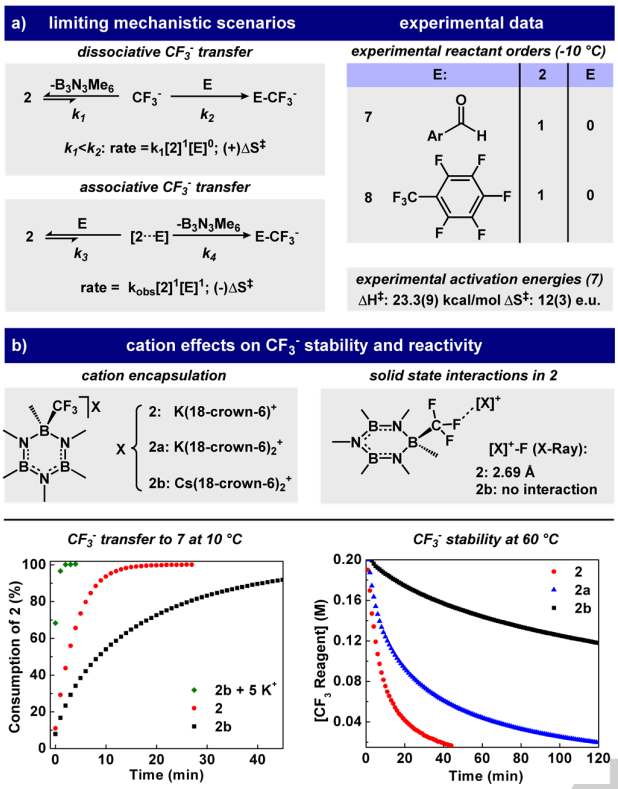

Figure 6. a) Possible mechanisms for CF_3^- transfer. b) Cation effects on CF_3^- stability/reactivity. In **7**, Ar=4-F -Ph.

Experimental Section

General experimental details and characterization data for all of the reported compounds are included in the Supporting Information.

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Keywords: Fluorine • Reaction Mechanisms • Boron • Nucleophilic Substitution • Waste Prevention

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[36] **2** is comparable or better than **1a**/activator for the described reactions with arenes (see SI). We note that reactions using **1a** require screening base additives to ensure compatibility and solubility: with **2**, these are not required.

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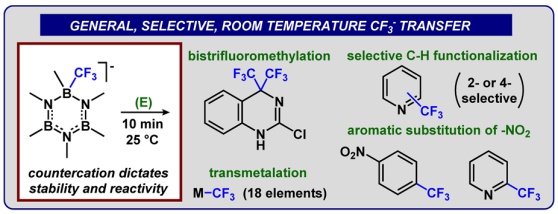

A fluoroform-derived reagent facilitates the nucleophilic trifluoromethylation of a broad array of inorganic and organic electrophiles at room temperature. The scope includes 18 inorganic elements, nucleophilic aromatic substitution, and CF_3^- addition to carbonyl and imine compounds. Kinetic analysis supports a dissociative mechanism, and an enhanced-stability reagent is presented.

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