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Recyclable Trifluoromethylation Reagents from Fluoroform

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Supporting Information

ABSTRACT: We present a strategy to rationally prepare CF_3^- transfer reagents at ambient temperature from HCF_3. We demonstrate that a highly reactive CF_3^- adduct can be synthesized from alkali metal hydride, HCF_3, and borazine Lewis acids in quantitative yield at room temperature. These nucleophilic reagents transfer CF_3^- to substrates without additional chemical activation, and after CF_3 transfer, the free borazine is quantitatively regenerated. These features enable syntheses of popular nucleophilic, radical, and electrophilic trifluoromethylation reagents with complete recycling of the borazine Lewis acid.

The trifluoromethyl functional group is widely used in medicinal chemistry to enhance the bioavailability, lipophilicity, and resistance to oxidative degradation of drug molecules, and these properties have led to its inclusion in many approved drugs.[1] Fluoroform (HCF_3, <$0.10/mol) is an attractive starting material for CF_3 installation reactions: it is nontoxic, widely available, and easily handled.[2] However, even though >0.5 million metric tons of HCF_3 are produced each year as a byproduct from PTFE manufacturing, it is not used as a CF_3 feedstock and is instead incinerated.[3]

Unlike methane, which is widely used as a source of the $-CH_3$ group,[4] the use of HCF_3 as a $-CF_3$ feedstock has presented significant challenges. Although HCF_3 has a large C−H bond dissociation enthalpy (107 kcal/mol),[5] its weak acidity (pK_a = 28)[6] renders deprotonation strategies for C−H bond activation tractable.[2,7] Unlike CH_3^-, which can be readily transferred to electrophilic substrates using organometallic reagents,[8] analogous $LiCF_3$ and $MgX(CF_3)$ are unstable because they irreversibly eliminate F^-, even at −80 °C.[9] However, CF_3^- can be stabilized through the formation of a Lewis acid (LA)−CF_3 adduct; this strategy forms the basis of all nucleophilic trifluoromethylation reagents.[10] The key challenge that limits the synthesis of LA−CF_3^- reagents from HCF_3 is poor compatibility between components of the reaction mixture. The LA and Brønsted base must coexist in solution prior to HCF_3 addition because the CF_3^- anion is extremely unstable. Furthermore, the base must not irreversibly react with the LA, and the LA must not promote CF_3^- defluorination (Figure 1).

Two primary strategies have emerged to provide compatible pairs of LAs and bases: the use of steric bulk to separate reactive Lewis acidic and basic centers,[11] and the use of Lewis pairs with mismatched strength to enable reversible adduct formation.[12] Recently, steric control has been used to activate HCF_3 using a mixture of bulky bases (potassium bis(trimethylsilyl)amide (KHMDS)[13] or phosphazene superbases)[14] and LAs such as $SiMe_3Cl$. The instability of the CF_3^- intermediate (−80 °C) requires the combination of KHMDS and electrophiles prior to addition of HCF_3, which presents an operational challenge. This strategy is limited by the expense of the required bases, cryogenic temperatures, and low generality.[2]

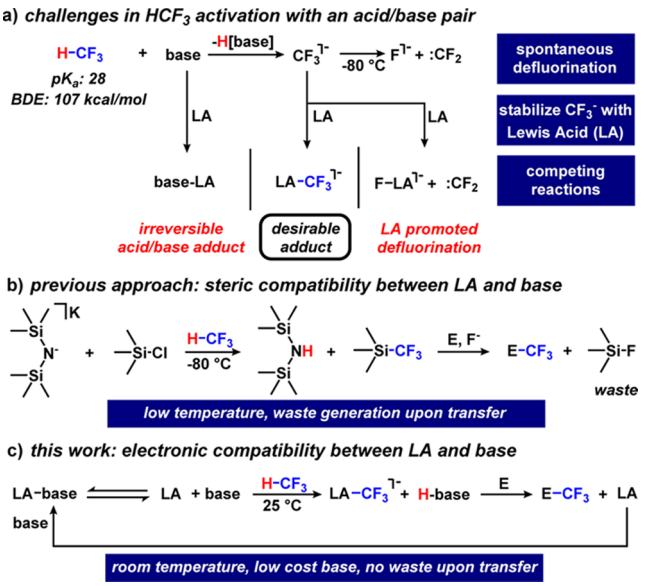

Figure 1. Challenges in HCF_3 activation (E = electrophile).

We sought to design a system for room-temperature HCF_3 activation using neutral, weak LAs to avoid irreversible reactions with bases and provide optimal stabilization of CF_3^-. Importantly, we hypothesized that a precisely tuned LA could be recyclable, impart high CF_3^- nucleophilicity to a LA−CF_3 adduct, and prevent F^- elimination from CF_3^- at room temperature. This represents a distinct concept in HCF_3 activation: no systematic approach for the selection of Lewis acids capable of providing these three desirable properties has been reported.

We targeted alkali metal hydride derived bases (NaH, $0.10/mol; KH, $35/mol) for HCF_3 deprotonation, and boron based LAs. A widely used solvent, dimethyl sulfoxide (DMSO), reacts with alkali hydrides to produce $KCH_2(SO)CH_3^-$ (pK_a = 35).[15] Because of the low expense of this strong, soluble base and its ability to deprotonate HCF_3, we selected it as an ideal basic partner.[16] Boron-based LAs were targeted because they have a wide range of Lewis acidities,[17] and can be easily prepared.

An appropriate LA must react reversibly with $KCH_2(SO)CH_3$ in order to enable HCF_3 deprotonation, while subsequently

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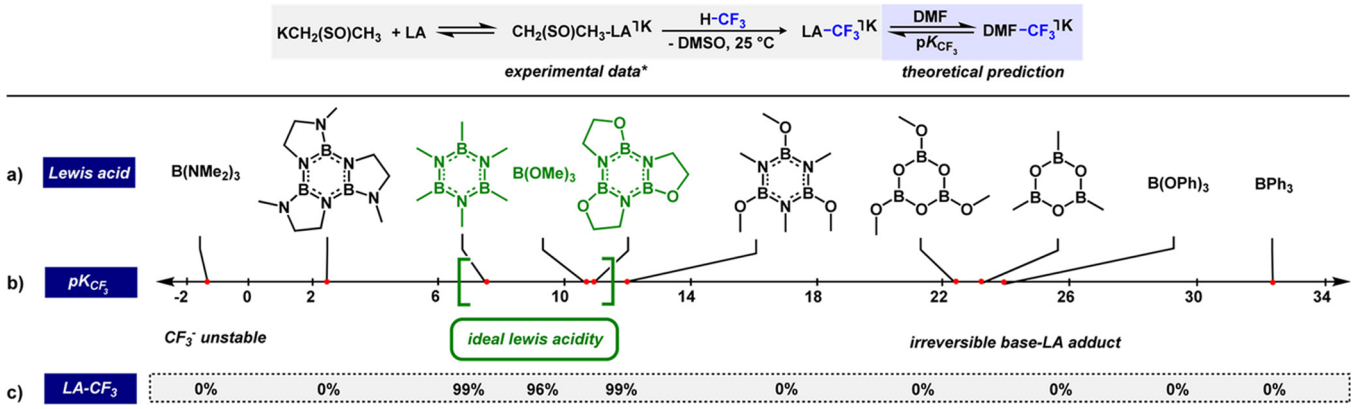

Figure 2. Development of LA−CF_3^- adducts from HCF_3. (a) LAs evaluated. (b) Calculated pK_{CF3} values of LAs (M062X/6-311++G(d,p)). (c) Yield of LA−CF_3^- adduct from HCF_3. *: HCF_3 was added to a 1:1 mixture of LA and $KCH_2(SO)CH_3$ (0.1 M), and the yield of LA-CF_3_ was quantified by $_{19}$F-NMR spectroscopy.

providing sufficient Lewis acidity to capture and stabilize CF_3^-. To select LAs with a wide range of strengths for experimental evaluation, the CF_3^- affinity of selected boron LAs was assessed computationally using density functional theory (DFT). The ΔG of the reaction between CF_3^- and a given LA was calculated at the M062X/6-311++G(d,p) level.[18] The scale was set to zero relative to the known adduct between dimethylformamide and CF_3,[7a] and the data were translated to provide predicted relative binding constants on a log scale (pK_{CF3}) as a unified metric of CF_3^- affinity. We used these data to select 13 LAs representing a 30 pK_{CF3} span for experimental evaluation in reactions between $KCH_2(SO)CH_3$, LAs, and HCF_3 (Figure 2).

Equimolar quantities of $KCH_2(SO)CH_3$ and each LA were combined at room temperature in DMSO. HCF_3 was added (1 atm), and the formation of B−CF_3 adducts was assessed by ^{19}F-NMR spectroscopy. LAs with pK_{CF3} values above 11 exhibited irreversible coordination to $CH_2(SO)CH_3^-$, and did not react with HCF_3. LAs with pK_{CF3} values below 6 reacted with HCF_3, but were insufficiently Lewis acidic to stabilize the CF_3^- anion resulting from HCF_3 deprotonation (Figure 2c).[19]

Three LAs with intermediate pK_{CF3} values between 6 and 11 reacted with HCF_3 to provide B−CF_3 species in quantitative yield (Figure 3a). When either hexamethylborazine ($B_3N_3Me_6$), trimethyl borate ($B(OMe)_3$), or trisethyleneoxyborazine ($(BOC_2H_4N)_3$) were combined with 1 equiv $KCH_2(SO)CH_3$, followed by 1 equiv HCF_3 in DMSO solvent, the B−CF_3 adducts

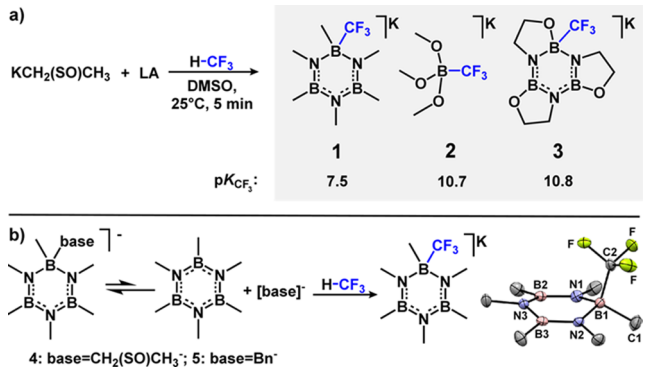

Figure 3. (a) Synthesis of **1**, **2**, and **3** from HCF_3. (b) HCF_3 activation by $B_3N_3Me_6$/base, ORTEP of **1**. Ellipsoids shown at 50% probability; B1−C2, 1.656(4) Å,; B1−C1, 1.627(4) Å; C1−B1−C2, 107.1(2). [K(18-crown-6)(THF)]$^+$ omitted for clarity.

were observed (**1**, **2**, and **3**) in quantitative conversion within 5 min at room temperature. These three LAs are easily obtained; $B(OMe)_3$ is a commodity chemical (<$1/mol),[20] and $B_3N_3Me_6$ and $(BOC_2H_4N)_3$ can be synthesized from simple starting materials (see SI for details).

Importantly, **2** is currently an expensive CF_3^- reagent with reported applications in nucleophilic trifluoromethylation and copper-catalyzed cross-coupling.[21] Solutions of **1** and **3** are oxygen-stable, decompose on exposure to moisture, and return the free borazine LAs upon thermal decomposition.

To examine the mechanism of CF_3 adduct formation, the reaction between $B_3N_3Me_6$ and $KCH_2(SO)CH_3$ was followed spectroscopically. The combination of equimolar $KCH_2(SO)$-CH_3 and $B_3N_3Me_6$ in DMSO afforded a homogeneous solution containing a single new species with C_s symmetry, as assessed by NMR spectroscopy. ^{1}H, ^{13}C, and ^{11}B-NMR spectra support the formation of a 1:1 Lewis pair between $KCH_2(SO)CH_3$ and $B_3N_3Me_6$ at room temperature (**4**). The ^{11}B-NMR spectrum exhibited a 2:1 set of resonances at +32.5 and −3.6 ppm. The resonance at −3.6 ppm is consistent with a tetrahedral boron center, whereas the broad resonance at 32.5 ppm ($\nu_{1/2}$ = 477 Hz) is minimally shifted from the free $B_3N_3Me_6$ (35.5), consistent with two planar boron centers.[22] The reversibility of $KCH_2(SO)$-CH_3 adduct formation with $B_3N_3Me_6$ was examined by variable temperature NMR spectroscopy. At 15 °C, the ^{1}H NMR spectrum exhibited resonances at 0.04 and −0.44 ppm for the B-CH_3 resonances. As the temperature was raised, the resonances broadened and coalesced at 35 °C; further increasing the temperature to 90 °C resulted in the appearance of resonances consistent with free $B_3N_3Me_6$ (Figure S23). Upon cooling, **4** was cleanly regenerated. The coalescence temperature of 35 °C was used to estimate a $\Delta G^{\ddagger} \approx 14$ kcal/mol.[23] These data are consistent with a dynamic exchange process between $CH_2(SO)$-CH_3^- and $B_3N_3Me_6$ at room temperature (Figure 3b).

The addition of 1 equiv HCF_3 to **4** immediately (<1 min) afforded **1** in 99% yield. NMR spectroscopy revealed a species similar to **4**, as assessed via ^{1}H, ^{11}B, ^{19}F, and ^{13}C NMR spectroscopy. A new resonance at −65.7 ppm ($^2J_{10B\text{-}19F}$ = 210 Hz) was observed in the ^{19}F NMR spectrum, consistent with a B−CF_3 adduct. Additionally, a new 2:1 set of resonances in the ^{11}B NMR spectrum at +33.1 and −5.7 ppm was observed along with two 2:1 sets of −CH_3 resonances in the ^{1}H and ^{13}C NMR spectra, representing desymmetrized N−CH_3 (^{1}H: 2.49, 2.45 ppm. ^{13}C: 34.73, 34.55 ppm.) and B-CH_3 (^{1}H: 0.08, −0.35 ppm.

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^{13}C: 4.31, 0.16 ppm.) units. The sharp peaks exhibited by this complex in the ^{1}H, ^{13}C, and ^{19}F NMR spectra suggest that although **4** equilibrates with free $KCH_2(SO)CH_3$, the formation of **1** is irreversible at room temperature.

Preparation of **1** in the less polar solvent tetrahydrofuran (THF) required adjustments to the base and the countercation. Potassium toluide (KTol) was selected as a base that can be prepared on large scales and in high (>95%) yield from KO*t*Bu, BuLi, and toluene at 25 °C.[24] The Lewis adduct between KTol, 18-crown-6,[25] and $B_3N_3Me_6$ (**5**) was characterized using NMR spectroscopy and X-ray crystallography. **5** possesses similar NMR spectra in comparison with **4**: C_s symmetry and diagnostic 2:1 sets of B-CH_3 and N−CH_3 resonances. The solid state structure of **5** revealed a tetrahedral boron center, containing two distinct B−C bond lengths for the B-CH_3 and B-CH_2Ph bonds (1.590(4) Å and 1.775(5) Å, respectively). The long B-CH_2Ph bond length[26] is consistent with a weak B−CH_2Ph bond. Similar to **4**, variable temperature ^{1}H NMR spectra of **5** exhibited dynamic behavior with broadening of the B−CH_3 peaks at 25 °C, which indicate reversible dissociation of the toluide base.

Solutions of **1** were prepared in THF by the addition of 1 equiv HCF_3 to **5**. **1** was obtained as a weighable solid in 95% yield, and was structurally characterized by X-ray crystallography (Figure 3b). The aromatic character of the borazine unit was disrupted by the inclusion of a tetrahedral boron center with a new B−CF_3 bond (C1−B1−C2: 107.1(2)°), and elongation of the proximal B−N bond distances (B1−N1, 1.550(3) Å; B1−N2, 1.549(3) Å) vs 1.44(3) in free borazine).[27] The B1−C2 (*C*F_3) bond (1.656(4) Å) is longer than the B1−C1 (*C*H_3) bond (1.627(4) Å), consistent with a weaker B−CF_3 bond. DFT analyses revealed a larger binding enthalpy of CH_3^- to $B_3N_3Me_6$ than that of CF_3^- by 8.5 kcal/mol (see SI). These structural and calculated metrics indicate that CF_3^- transfer should be preferred over CH_3^- transfer to electrophilic substrates.

Although $KB(OMe)_3CF_3$ (**2**) has been previously shown to facilitate nucleophilic CF_3^- transfer reactions, these proceed only under forcing reaction conditions.[28] Because nucleophilic CF_3^- transfer necessitates the cleavage of a B−CF_3 bond, we hypothesized that CF_3^- reagents stabilized by weaker LAs may exhibit superior nucleophilicity. **1** has a pK_{CF3} value 3.2 units lower than **2**, indicating that $B_3N_3Me_6$ is a weaker LA than $B(OMe)_3$. The addition of $B(OMe)_3$ to **1** afforded **2** in 80% yield, which is consistent with the difference in the calculated CF_3^- affinity of $B_3N_3Me_6$ and $B(OMe)_3$ (Figure 4b). When **1** was allowed to react with benzophenone, the corresponding trifluoromethylcarbinol was generated in 72% yield in 30 min at room temperature. In contrast, **2** provided only 2% yield under identical conditions; this implicates that **1** has a higher nucleophilicity than **2** (Figure 4a).

The observation that $B_3N_3Me_6$ can be released upon thermal decomposition of **1** suggests that the free LA may be regenerated, recovered, and reused after CF_3^- transfer. CO_2 was selected as an initial substrate to test this hypothesis. The addition of 4 atm CO_2 to **1** in DMSO afforded trifluoroacetate ($CO_2CF_3^-$) in 93% isolated yield (Figure 4b). $B_3N_3Me_6$ was recovered in 95% isolated yield by extraction into pentane; the recovery of the free LA after CF_3 transfer is a unique attribute of this system. Transformations with high atom economy using **1** should be advantageous[29] in comparison with $SiMe_3CF_3$/CsF,[10a] KB-$(OMe_3)CF_3$, or DMF/KOtBu/HCF_3,[16] which generate stoichiometric waste ($SiMe_3F$) or require low temperatures (−80 °C).

The high cost of trifluoromethylation reagents stems largely from their multistep syntheses from CF_3Br or CF_3I.[10a,30] The regeneration of the $B_3N_3Me_6$ LA in the reactions noted above suggested that these popular reagents could be prepared from HCF_3 using $B_3N_3Me_6$ as a recyclable component, thereby reducing the reaction inputs to base, HCF_3, and the direct precursor (Figure 5). Reagents used to install the CF_3 group can be divided between their use for CF_3^-,[31] CF_3·,[32] and CF_3^+ transfer.[33] The most important of these is $SiMe_3CF_3$, the precursor to almost all other trifluoromethylation reagents.[10a] We used the preparation of this compound to demonstrate the *in situ* recyclability of $B_3N_3Me_6$ on a large scale.

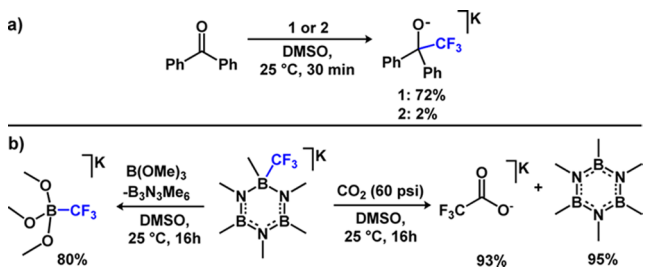

Figure 4. (a) Relative reactivity of **1** and **2** in nucleophilic trifluoromethylation of benzophenone. (b) CF_3^- transfer between **1** and $B(OMe)_3$; synthesis of $CF_3CO_2^-$ from HCF_3 and subsequent recovery of $B_3N_3Me_6$.

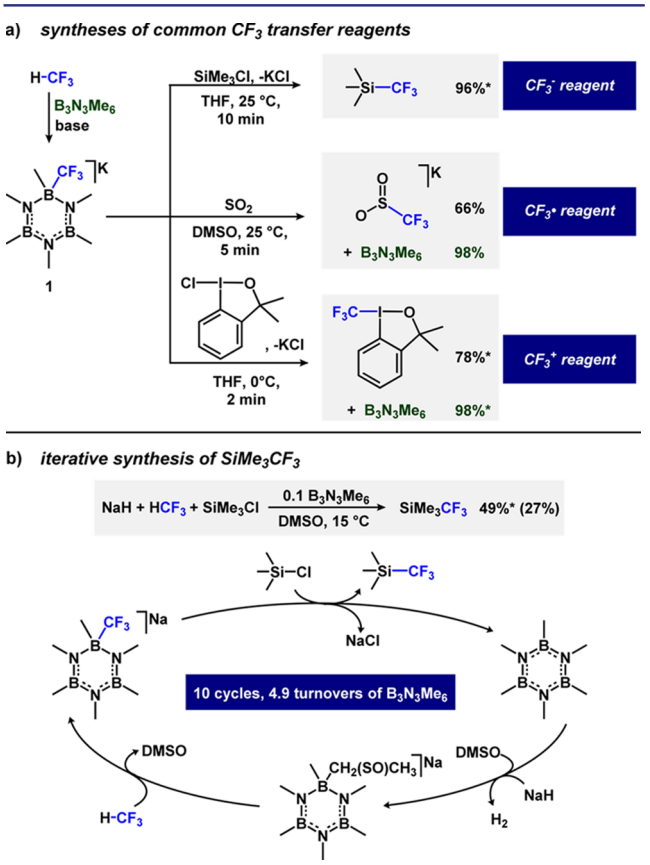

Figure 5. (a) Synthesis of $SiMe_3CF_3$, KSO_2CF_3, and Togni I from HCF_3. *: yield measured *in situ* by ^{19}F-NMR spectroscopy. (b) Iterative synthesis of $SiMe_3CF_3$ with in situ $B_3N_3Me_6$ recycling; $NaCH_2(SO)CH_3$ made *ex situ*.

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Through ten cycles of an iterative addition/distillation protocol, we achieved ~5 turnovers with respect to $B_3N_3Me_6$ to obtain 34 mmol $SiMe_3CF_3$ after distillation without the need for separation or purification of the borazine LA. The only consumed reagents were NaH, $SiMe_3Cl$, and HCF_3. The radical $CF_3\cdot$ reagent KSO_2CF_3[32] was also prepared in 66% isolated yield by treating SO_2 with **1** (98% recovery of $B_3N_3Me_6$). Finally, the hypervalent iodonium-CF_3 reagent Togni I,[33] a widely used CF_3^+ reagent, was synthesized in 78% chemical yield and with 98% regeneration of $B_3N_3Me_6$ by treating the appropriate iodaoxole with **1**. We expect that direct access to these well-established nucleophilic, radical, and electrophilic reagents from HCF_3 may increase access to the CF_3 group in existing large-scale processes.

In summary, we have developed a predictive design concept that led to the preparation of several trifluoromethylation reagents from HCF_3. One of these, **1**, exhibited high nucleophilicity at room temperature. After CF_3^- transfer, the free LA was quantitatively regenerated. We exploited this property to present an iterative synthesis of $SiMe_3CF_3$ on a large scale from NaH, HCF_3, and $SiMe_3Cl$ as the only consumed reagents with repeated *in situ* reuse of the LA. This methodology provides direct access to other common trifluoromethylating reagents from HCF_3, including $K(B(OMe)_3CF_3$, KSO_2CF_3, KCO_2CF_3, and Togni reagent I. Finally, we introduce borazines as a class of tunable, weak LAs for synthetic applications. The rational selection of compatible LAs and bases for efficient nucleophilic trifluoromethylation using HCF_3 is a design strategy that may also be applied to other unstable anions to promote other difficult nucleophilic functionalizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05408.

Crystallographic information for **1** and **5** (CIF)
Synthetic details, characterization (PDF)

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Notes

The authors declare the following competing financial interest(s): We have a patent pending on content relating to this manuscript.

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