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Difluoromethane as Precursor to Difluoromethyl Borates

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Difluoromethane (CF_2H_2) is an ecologically-friendly refrigerant which holds promise as a source of CF_2H^-. However, its weak acidity (pK_a = 35-41) and low stability of the conjugate base has prevented its utilization as a chemical feedstock. In this manuscript, we use a Lewis pair approach to deprotonate CF_2H_2 and capture CF_2H^- as R_3B-CF_2H^- adducts. One reagent can be used as a base-free Suzuki reagent in palladium-mediated difluoromethylation, where CF_2H^- transfer is templated by precoordination to an azaborine derived R_3B-CF_2H^- reagent.

When incorporated into biologically active molecules, the difluoromethyl group acts as a metabolically stable lipophilic bioisostere of OH or SH groups.[1-3] As a result of these desirable properties, molecules containing -CF_2H groups are routinely investigated in drug development.[4-6] Many of the commonly used CF_2H transfer reagents (such as $SiMe_3CF_2H$ and $Zn(CF_2H)_2$) are prepared from halofluoromethanes (XCF_2H; X = Cl, Br, F) and their derivatives,[7-12] compounds with high ozone depleting potential.[13] In contrast, difluoromethane (CF_2H_2) would represent an attractive source of the difluoromethyl group if it could be deprotonated to reveal nucleophilic CF_2H^- fragments. It is nontoxic, has no ozone-depleting potential, and is already manufactured on a large scale as a refrigerant.[14] However, no approaches for nucleophilic difluoromethylation from difluoromethane have been reported.

Despite the attractive properties of CF_2H_2 as a source of CF_2H^-, challenges associated with deprotonation and capture have prevented its use as a chemical synthon. In addition to low acidity (gas phase proton affinity: 389 kcal/mol;[15] HCF_3: 376 kcal/mol),[16] free CF_2H^- is unstable to α-fluoride elimination.[17]

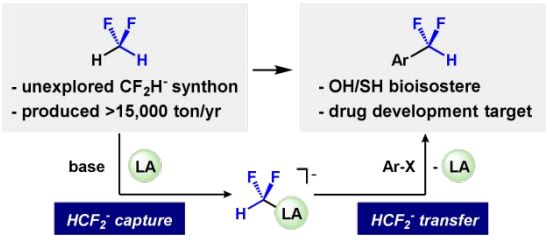

Figure 1. Conceptual outline of Lewis acid/base strategy to enable CF_2H^- capture/transfer from H_2CF_2.

Furthermore, if CF_2H^- is generated in the presence of a fluorophilic cation such as Li^+, immediate defluorination occurs.[17] If the Li is replaced with $[Cs(18\text{-crown-}6)_2]^+$, a cation with low F^- affinity, the corresponding $[CF_2H]^-$ is highly basic and readily deprotonates THF. For these reasons, CF_2H_2 has not been used to prepare synthetically useful CF_2H^- equivalents. These problems may be mitigated by deprotonating CF_2H_2 in the presence of a Lewis acid (LA) that can capture CF_2H^- as a LA-CF_2H^- adduct, and then later release CF_2H^- in a subsequent reaction. To realize this strategy, selection of an appropriate Brønsted base and Lewis acid is critical, because the Lewis acid and base must be strong enough to deprotonate CF_2H_2 and to stabilize CF_2H^- while also avoiding the formation of *inert* acid-base adducts.[18] We previously described a compatible Lewis acid / base approach that can resolve categorically similar issues with $ArCF_2H$ substrates;[19] the acid/base partners mediate CF_2Ph^- generation, capture, and release. In this communication, we report the direct synthesis of R_3B-CF_2H^- adducts from difluoromethane and their ability to serve as nucleophilic sources of CF_2H^-.

We hypothesized that an appropriate Lewis pair for difluoromethane deprotonation / CF_2H^- capture must satisfy several key criteria. The base must be sufficiently strong to deprotonate CF_2H_2 and not contain fluorophilic cations such as Li^+ and Na^+. The Lewis acid must be sufficiently strong to stabilize CF_2H^- against α-fluoride elimination but weak enough

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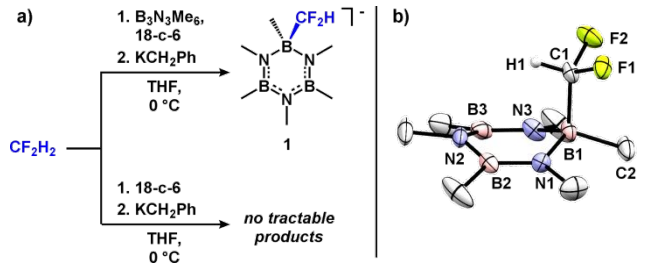

Figure 2. a) Synthesis of **1** from H_2CF_2. b) X-Ray crystal structure of **1**. K(18-c-6)(THF)$^+$ counterion omitted for clarity.

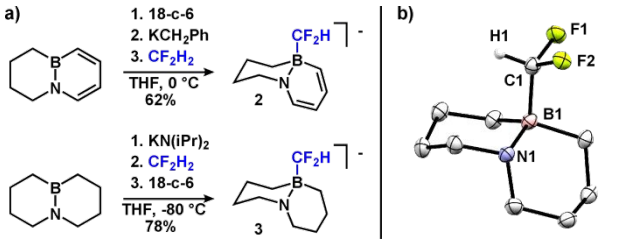

Figure 3. a) Synthesis of **2** and **3** from CF_2H_2. b) X-Ray structure of **3**. K(18-c-6)(THF) counterion omitted for clarity.

to release CF_2H^- nucleophiles. In addition to these requirements, the Lewis acid / base pairs must not quench their respective reactivity through the formation of irreversible adducts.[18] We selected KCH_2Ph as an initial base for experimental evaluation because of its high basicity (pK_a = 42 (DMSO)),[20] straightforward preparation,[21] and potassium counteraction. Hexamethylborazine ($B_3N_3Me_6$) was selected as the initial Lewis acid partner because it forms a reversible adduct with KCH_2Ph and is known to stabilize fluoroalkyl nucleophiles (CF_3^- and CF_2Ar^-).[19, 22, 23]

When CH_2F_2 gas was added to a deep red THF solution containing a 1:1:1 ratio of KCH_2Ph, $B_3N_3Me_6$, and 18-crown-6 at 0 °C, the solution became colorless after 90 minutes. ^{19}F NMR spectroscopy revealed the formation of a new species at -128.23 ppm exhibiting $^2J_{11B\text{-}19F}$ and $^1J_{1H\text{-}19F}$ coupling (32, 49 Hz) consistent with a B-CF_2H unit.[24] Trituration with pentane afforded a white solid in 95% yield, which was characterized by ^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR spectroscopy. The ^{1}H NMR spectrum revealed loss of symmetry of the $B_3N_3Me_6$ unit with four *–CH$_3$* resonances (2.51, 2.49, 0.05, -0.39 ppm), as well as a new *–CF$_2$H* resonance at 5.20 ppm with $^1J_{1H\text{-}19F}$ coupling (51 Hz). The ^{11}B-NMR spectrum revealed one broad (32.3 ppm) and one sharp resonance (-5.7 ppm) integrating in a 2:1 ratio. These data are consistent with a dearomatized $B_3N_3Me_6$ unit containing one tetrahedral and two planar boron atoms, enabling assignment of the isolated compound as K(18-crown-6)$B_3N_3Me_6(CF_2H)$ (**1**). Importantly, in the absence of $B_3N_3Me_6$, no tractable reaction products are observed.

Crystals suitable for X-Ray diffraction were obtained by allowing pentane to diffuse into a concentrated solution of **1** in THF at -35 °C. The solid-state structure revealed a CF_2H^- anion coordinated to a dearomatized $B_3N_3Me_6$ unit, capped with a K(18-crown-6)$^+$ cation (Figure 2b). The B-CF_2H bond is elongated relative to the other B-CH_3 bonds (1.640(5) vs 1.621(5), 1.612(7), 1.594(7) Å), consistent with lower bond strength (*vide infra*). The structure is largely homologous with other fluoroalkyl-borazine adducts K(18-crown-6)$B_3N_3Me_6$(*CF_3*) and K(18-crown-6)$B_3N_3Me_6$(*CF_2Ph*), which also exhibit elongated B-C distances of 1.656(4) and 1.670(6) Å.[19, 22]

1 is the first reported $R_3B\text{-}CF_2H^-$ adduct.[25] Organoboron –ate complexes of this type are the active form of commonly used Suzuki reagents in palladium-catalyzed cross coupling, and the known ability of K(18-crown-6)$B_3N_3Me_6(CF_3)$ and K(18-crown-6)$B_3N_3Me_6(CF_2Ph)$ to transfer fluoroalkyl anions to Pd(II) centers such as Pd(TMEDA)(Ph)I (TMEDA = tetramethylethylenediamine) suggested that **1** may be able to promote similar reactivity. Unfortunately, **1** did not react with Pd(TMEDA)(Ph)I even under forcing conditions (24 h, 80 °C in THF). The lack of reactivity and shorter B-CF_2H bond relative to analogous –CF_3^- and CF_2Ph^- adducts alluded to a stronger B-CF_2H bond preventing CF_2H transfer. We confirmed this hypothesis *in silico* and found that the calculated affinity of $B_3N_3Me_6$ for CF_2H^- (-33 kcal/mol) was 10 kcal higher than for CF_3^- (-23 kcal/mol) at the M062X/6-31g(d,p) level of theory.

One option to lower the kinetic barrier to CF_2H transfer is *via* pre-coordination to an adjacent ligand donor group. To implement this design principle for CF_2H^- transfer, we targeted two [6,6]-fused 1,2-azaborine rings that either contain (1,2,3,4-tetrahydro-[1,2]azaborinino[1,2-a][1,2]azaborinine)[26] or omit (octahydro-[1,2]azaborinino[1,2-a][1,2]azaborinine)[27] a nucleophilic π-system. Their calculated CF_2H^- affinity (M062X/6-31g(d,p)) is similar to $B_3N_3Me_6$ (-33 (**2**) and -34 (**3**) vs. -33 (**1**) kcal/mol) making these adducts suitable candidates to test our hypothesis. Adducts between these Lewis acids and CF_2H^- would present nucleophilic -C and/or -N nucleophilic sites proximal to the CF_2H^- group, and could serve to direct CF_2H^- transfer. When a solution of either of the [6,6]-fused 1,2-azaborine Lewis acids, KCH_2Ph, and 18-crown-6 was treated with CH_2F_2, CF_2H^- adducts analogous to **1** (K(18-crown-6)(**2**: 1,2,3,4-tetrahydro-[1,2]azaborinino[1,2-a][1,2]azaborinine)(CF_2H); **3**: K(18-crown-6)(octahydro-[1,2]azaborinino[1,2-a][1,2]azaborinine)(CF_2H)) were obtained as solids in 62% and 34% yield. The yield of **3** was increased to78% by substituting bulky $KN(^iPr)_2$[28] for KCH_2Ph.

^{19}F-NMR spectra of **2** exhibited two resonances (-127.10 and 131.96 ppm) with $^2J_{19F\text{-}19F}$, $^1J_{1H\text{-}19F}$, and $^2J_{11B\text{-}19F}$ coupling (311, 54, and 20 Hz), while the ^{11}B-NMR spectrum showed a sharp peak at -10.22 ppm. These data are consistent with a B-CF_2H unit containing diastereotopic fluorine units. **3** exhibited a single ^{19}F resonance (127.04 ppm, $^1J_{1H\text{-}19F}$, $^2J_{11B\text{-}19F}$ = 51 and 18 Hz), a sharp ^{11}B-NMR resonance at -12.4 ppm, and C_2-symmetric ^{1}H and ^{13}C NMR resonances. A single crystal of **3** was grown by allowing pentane to diffuse into a THF solution at -35 °C, and the solid state structure revealed that **3** exhibits a bent geometry of the azaborine unit, similar to that of the hydrocarbon decalin, capped by a B-CF_2H group. The B-CF_2H bond in **3** (1.633(3) Å) is within error of that in **1** (1.640(5) Å), and is consistent with their similar calculated CF_2H^- affinities and B-CF_2H bond lengths (1.633 and 1.638 Å).

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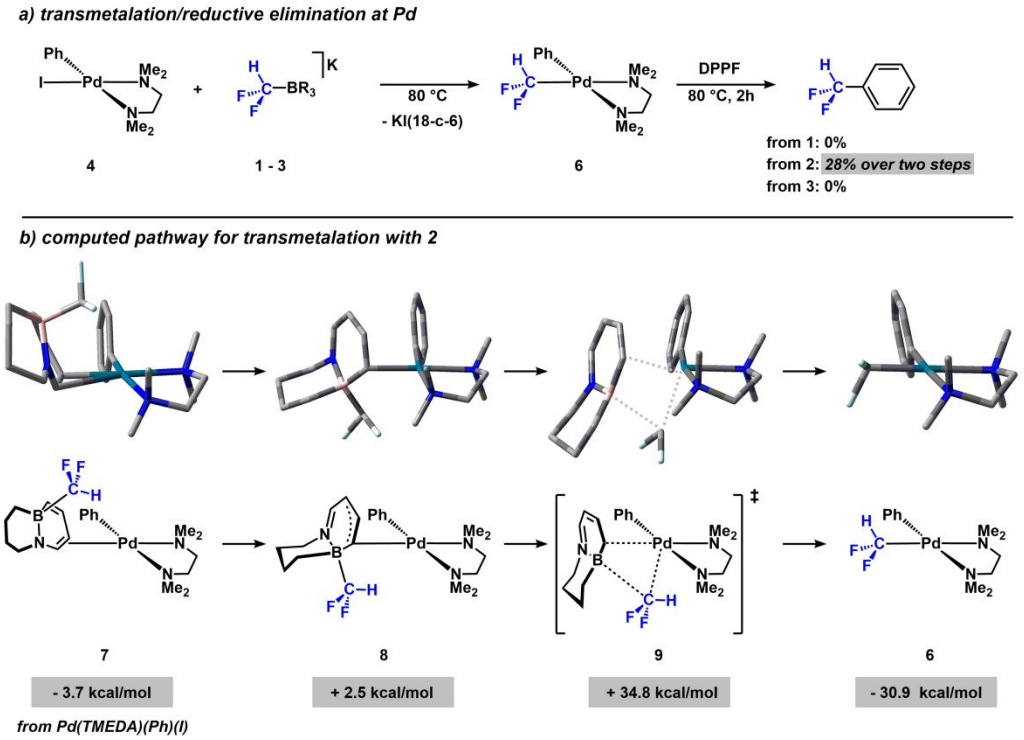

Figure 4. a) Transmetalation of **1-3** to Pd(TMEDA)(Ph)I and subsequent reaction with 1,1'-bis(diphenylphosphino)ferrocene (DPPF). b) Computed pathway for transmetalation using **2** (M06L2X/6-31g(d,p). Hydrogen atoms omitted for clarity.

To assess whether pre-coordination could provide a more kinetically accessible pathway for CF_2H^- transmetalation, we evaluated the reactivity of **2** and **3** with Pd(TMEDA)(Ph)I. Heating a mixture of **2** and 1.5 equivalents Pd(TMEDA)(Ph)I (**4**) at 80 °C afforded a 1:1 ratio of Pd(TMEDA)$(CF_2H)_2$ (**5**)[29] and Pd(TMEDA)(CF_2H)(Ph) (**6**)[30] in 55% combined yield as identified by ^{19}F-NMR spectroscopy. Addition of two equiv. DPPF, followed by heating to 80 °C for 2 h triggered reductive elimination of difluoromethylbenzene in 28% combined yield over both steps.[31] In contrast, **3** or **1**, which do not contain a nucleophilic π-system, afforded Pd(TMEDA)$(CF_2H)_2$ in only trace quantities; further reaction with DPPF did not yield $PhCF_2H$.

These experiments highlight ring unsaturation as a key structural element that can be used to direct CF_2H^- transfer and suggests that precoordination of the R_3B-CF_2H^- adduct may facilitate transmetalation. We assessed this hypothesis using a combined experimental / theoretical approach. Combination of **2** and **4** at 25 °C afforded a deep red species (**7**) with new NMR resonances. Titration of **2** with **4** identified **7** as a 1:1 adduct of **2** and **4**. Alternative reagents **3** and **1**, which lack a nucleophilic π-system, did not form observable adducts when combined with **4**. Heating **7** at 80 °C for 2 hours afforded Pd(TMEDA)(CF_2H)(Ph) (**6**), establishing **7** as an intermediate formed prior to CF_2H^- transfer. ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC spectra allowed a partial structural assignment for **7**. Notably, ^{1}H-NMR resonances associated with the sp^2 C-H groups in the azaborine fragment (C1-H:4.89, C2-H: 4.85, C3-H: 4.07, C4-H: 7.86) are significantly shifted with respect to those found in unbound **2**, suggesting a Pd-π interaction in **7**. To augment the assignment, DFT analyses were used to identify two structural isomers of **7** as energetic minima, in which the closest Pd-C contact is at either the C3 or C1 position. Of these two isomers, the isomer with Pd-C3 coordination was more stable by -1.3 kcal/mol and the calculated NMR shifts[32] more closely resembled the experimental values ((C1-C4)-H: 5.40, 5.01, 3.15, 8.20 vs. 2.58, 7.63, 5.29, 6.26), allowing us to assign the connectivity of **7** as depicted in Figure 4.

An associative mechanism for CF_2H^- transmetalation from **2** to **4** *via* **7** was then computationally evaluated (M06L2X/6-31g(d,p)). In the first step, I^- is displaced by **2** to form the observed prereactive complex **7** in an exothermic process (-3.8 kcal/mol). Rotation of the ring positions the CF_2H^- group in close proximity to the Pd(II) center (**8**: +1.3 kcal/mol). CF_2H^- transfer occurs through β-alkyl elimination (transition state **9**) to form

product **6** and the free azaborine Lewis acid with a net barrier of 34.7 kcal/mol. These computational and experimental data support our hypothesis that an associative mechanism for CF_2H^- transmetalation to Pd(II) is operative for reagent **2**.

In conclusion, we have developed the first strategy to repurpose CF_2H_2, widely available refrigerant, into a $–CF_2H^-$ building block. A compatible Lewis acid/base pair approach enabled the preparation of a family of three boron-CF_2H^- adducts (**1**-**3**) following difluoromethane deprotonation. Of these reagents, only **2** can transmetalate CF_2H^- to palladium(II), a challenging transformation which has not been demonstrated using B-CF_2H^- sources.[29, 30, 33, 34] We identified that templated coordination through the π-system of **2** is required to facilitate $–CF_2H^-$ transfer, and used the resulting difluoromethylpalladium complex to prepare $PhCF_2H$. We anticipate that this conceptual approach to difluoromethane activation and transfer may be applied to other reactive nucleophiles and that difluoromethylborate adducts will find applications in organic synthesis through further optimization.

Acknowledgments

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Conflicts of interest

We have submitted a patent application regarding chemistry similar to that described in this work.

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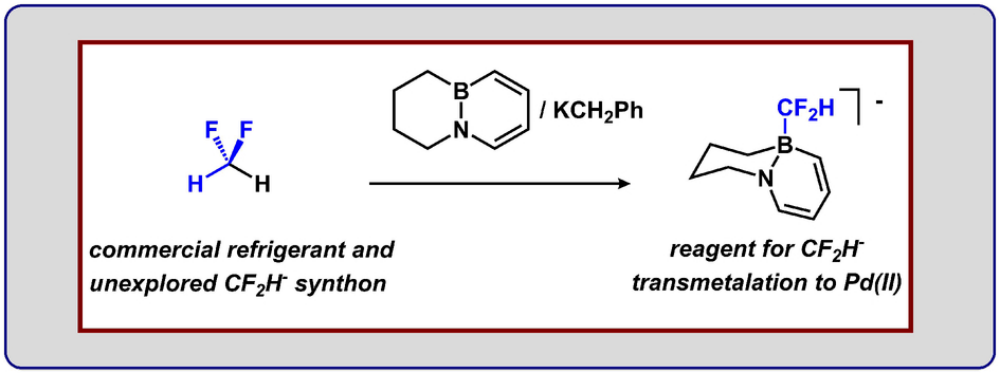

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