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Nucleophilic Trifluoromethylation of Carbonyl Compounds: Trifluoroacetaldehyde Hydrate as a Trifluoromethyl Source

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Abstract

A feasible nucleophilic trifluoromethylating protocol has been developed using trifluoroacetaldehyde hydrate as an atom economical trifluoromethyl source. The reaction was found to be applicable to the nucleophilic trifluoromethylation of a broad spectrum of carbonyl compounds with satisfactory yields in general. DFT calculations have been performed to provide mechanistic insight into the present and related reactions employing 2,2,2-trifluoro-1-methoxyethanol and hexafluoroacetone hydrate.

Introduction

Among various synthetic pathways, the nucleophilic trifluoromethylation of carbonyl compounds has provided a facile access to α -trifluoromethyl alcohols.^{1–4} Although TMSCF₃ (the Ruppert-Prakash reagent) is a versatile reagent capable of transferring the CF₃ group (Scheme 1-a),^{5,6} chemists have also strived for alternative nucleophilic trifluoromethylating reagents applicable to various synthetic purposes^{7–10} including direct deprotonation of trifluoromethane.⁴ In recent years, a series of nucleophilic trifluoromethylation reactions has been established based on the *in situ* formation of transient negatively charged species, which can release trifluoromethyl anion (CF₃[−]) along with a stable by-product (Scheme 1-b).¹¹ Langlois and others have demonstrated the direct trifluoromethylation of various electrophiles using trifluoromethane (CF₃H) in DMF via a trifluoromethylated hemiaminal derivative (CF₃[−]-DMF adduct analogue).^{12–19} Prakash *et al.* utilized phenyl trifluoromethyl sulfone (PhSO₂CF₃) and phenyl trifluoromethyl sulfoxide (PhSOCF₃) in nucleophilic trifluoromethylation reactions, which allowed the generation of CF₃[−] via pentavalent and tetravalent sulfur intermediates, respectively.²⁰ In line with this work, an alkoxide-induced trifluoromethylation was also reported by Beier and coworkers using diethyl trifluoromethylphosphate [(EtO)₂POCF₃].²¹ Recently, Colby *et al.* elegantly showed that hexafluoroacetone hydrate amidinate complex could also be exploited as a novel nucleophilic trifluoromethylating reagent.^{22–24} By releasing thermodynamically stable trifluoroacetate anion (CF₃CO₂[−]), such a reagent was able to incorporate the CF₃ moiety into various electrophiles. On the basis of these reactions, we envisaged that readily available trifluoroacetaldehyde hemiacetal derivatives (**1**) could enable nucleophilic trifluoromethylation by expelling formates as leaving groups. Compared with other similar reagents, the advantages of **1** lie in not only its high atom economy but also its maximum utilization of the CF₃ motif (Scheme 1-c).

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Supporting Information

¹⁹F and ¹H NMR spectra for all compounds, ¹³C NMR spectra and HRMS for new compounds: **3k** and **3s**. Details of theoretical calculations are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Results and Discussion

Our initial effort was focused on the trifluoromethylation of benzaldehyde (PhCHO, **2a**) using 2,2,2-trifluoro-1-methoxyethanol (**1a**) and 2,2,2-trifluoro-1-ethoxyethanol (**1b**). By treating **1a** and **1b** with potassium *tert*-butoxide (*t*-BuOK) in DMF, neither CF₃H nor the desired α -trifluoromethyl alcohol (**3a**) was observed after numerous attempts (Scheme 2). This could be ascribed to the plausible reverse addition of CF₃[−] to alkyl formates, which could significantly impede the trifluoromethylation of benzaldehyde (Scheme 2, Eq. 1).

Considering the essential low electrophilicity of formate anion (HCO₂[−]), trifluoroacetaldehyde hydrate (**1c**) was adopted in our further investigation to avoid the reverse CF₃[−]-by-product addition (Scheme 2, Eq. 2). According to ¹⁹F NMR spectroscopy, **3a** was obtained in 64% yield by treating **1c** (1.2 equiv.) with 6.0 equiv. of *t*-BuOK in DMF (Table 1, Entries 1–4). Further reaction condition screening was focused on alternative bases, reaction temperatures and the proportion of reagents; however, the yields did not improve (Table 1, Entry 5–11).

Whereas the above mentioned results seemed to be satisfactory, its practicality was largely limited by the requirement of large excess of base. This was presumably due to the fact that commercial **1c** was a dihydrate CF₃CH(OH)₂·2H₂O.²⁵ To remove the excess amount of H₂O, CF₃CH(OH)₂ was treated with various amines expecting the formation of the corresponding salts similar to the hexafluoroacetone hydrate amidinate salts.²⁴ However, no solid complexes could be obtained by these means, probably due to the lower acidity of CF₃CH(OH)₂ compared with (CF₃)₂C(OH)₂. We further exploited 4 Å molecular sieves as a drying agent, which unfortunately absorbed majority of CF₃CH(OH)₂ along with water. After a brief screening, calcium chloride (CaCl₂) was shown to be an efficient drying agent allowing recovery of 95% **1c** with a composition of CF₃CH(OH)₂·½H₂O.²⁶ With such processed **1c** in hand, the required *t*-BuOK:**1c** ratio was reduced from 5:1 to 4:1 (Table 1, Entry 4, Table 2, Entries 4 and 5). The optimal reaction conditions were found by treating **1c** (1.5 equiv.) with *t*-BuOK (6.0 equiv.) in DMF at −50 °C for 30 min, followed by the addition of PhCHO (1.0 equiv.) (Table 2, Entries 5–7). Noticeably, despite the fact that THF and DMSO allowed the release of CF₃[−] from **1c**, the nucleophilic trifluoromethylation of benzaldehyde did not take place (Table 2, Entries 8 and 9).

With the optimal reaction conditions, the scope of substrates was investigated. As shown in Table 3, various aldehydes and ketones readily reacted. Aryl aldehydes bearing electron-donating substituents and halides were shown to participate in the reaction to afford products in good to excellent yields (Table 3, Entries 1–5, 8–11, and 13). However, other strong electron-withdrawing moieties, such as NO₂ and CF₃ groups, on the phenyl ring impeded the reaction (Table 3, Entries 6 and 7). In comparison with the significant electronic effects, the steric hindrance of substituents did not play a major role in the reactivity of the substrates (Table 3, Entries 5 and 9–11). As anticipated, the trifluoromethylation reaction with enolizable aldehydes was quite sluggish under such strong basic conditions (Table 3, Entry 14). Similar to aryl aldehydes, various benzophenone derivatives were also found to be reactive (Table 3, Entry 12, 14, 15). Bulky phenyl ketone (**2s**) also reacted to yield the corresponding product in excellent yield (Table 3, Entry 19). Intriguingly, although enolizable acetophenone was not a viable substrate in the present reaction, adamantan-2-one (**2t**) was smoothly trifluoromethylated, due to its low enolizability (Table 3, Entry 20).

To elucidate mechanistic aspects of the reaction, theoretical calculations were performed at the B3LYP/6-31+G(d,p) level in DMF^{27,28} using Gaussian 09 package.^{29,30} As shown in Scheme 3, trifluoroacetaldehyde hydrate **1c** preferentially underwent deprotonation in the presence of *t*-BuOK. Although further deprotonated intermediate **1c-K2** was slightly higher

in energy by +0.7 kcal/mol, ca. 60% of **1c-K** could still be deprotonated with 4 eq. of *t*-BuOK under the reaction conditions (Scheme 3, Eq. 2). It has also been found that salts **1c-K** and **1c-K₂** were thermodynamically unstable species tending to expel CF₃[−]. Since these processes involve a Gibbs free energy change of approximately −30 kcal/mol, the reversible addition of CF₃[−] to HCO₂K was rather unlikely to occur (Scheme 3, Eq. 4 and 5). In contrast, the products **3a-K** and *t*-BuOH were found to be more stable than the corresponding starting materials (**2a**, *t*-BuOK, and benzaldehyde) by −1.7 kcal/mol (Scheme 3, Eq. 6). This has not only provided a theoretical support for the success in isolating **3a**, but also agreed with the observed essential stability of **3a** in the presence of *t*-BuOK in DMF. Overall, the Gibbs energy change was calculated to be downhill by −52.2 kcal/mol, which is mainly due to the highly exothermic deprotonation and degradation processes (Scheme 3, Eq. 7). Noticeably, the analogous hydride transfer by releasing trifluoroacetate was also found to be an exothermic reaction, which was however slightly less thermodynamically favorable (Table 1, Entry 9 and Scheme 3, Eq. 8).

We further explored transition states to achieve a continuous reaction pathway from **1c** to **3a-K** (Figure 1). As mentioned above, both **1c-K** and **1c-K₂** could irreversibly degrade to release CF₃H and HCO₂K. However, such fragmentation was more likely to proceed via **1c-K₂** intermediate due to the significantly lower barrier involving **TS2** than **TS1** (+6.5 kcal/mol v.s. +21.0 kcal/mol). Whereas **TS2'** was also located on the reaction pathway suggesting the possible hydride transfer and trifluoroacetate formation, it was substantially unfavorable compared with **TS2**. This is in good agreement with the fact that the trifluoromethyl transfer predominated in the present reaction. The calculation of analogous transition states involving lithium counteractions also showed that the C-CF₃ bond cleavage is kinetically preferred over hydride transfer by 9.1 kcal/mol (see SI), which rationalizes the observed trifluoroacetate formation (Table 1, Entry 9). Presumably, the nucleophilic addition involved the deprotonation of CF₃H by *t*-BuOK, which was predicted to have a small barrier of +9.3 kcal/mol. In spite of the endothermic deprotonation by +5.6 kcal/mol, the forward nucleophilic addition was both thermodynamically favored and kinetically facile due to a rather small activation barrier of +19.4 kcal/mol (compared with CF₃H). Apparently, both of these two factors facilitated the nucleophilic trifluoromethylation under the present reaction conditions.

In addition to the above mentioned studies, we also performed theoretical calculations to explore the mechanism of nucleophilic trifluoromethylations using trifluoroacetaldehyde hemiacetal (**1a**) and hexafluoroacetone hydrate (**5**). As shown in Figure 2-A, although the deprotonation of **1a** was thermodynamically feasible, the exothermicity of the subsequent CF₃ release was rather insignificant (−2.9 kcal/mol), indicating a facile reverse addition of “CF₃[−]” to methyl formate. This is indeed consistent with the observed low ability of trifluoroacetaldehyde hemiacetals to release the “CF₃[−]” anion. Moreover, the formations of trifluoroacetaldehyde (via methoxide release) and methyl trifluoromethylacetate (via hydride release) were found to be highly endothermic, suggesting that the low reactivity of **1a** was mainly due to the reversibility of the “CF₃[−]” release. Kinetically, the barrier to the nucleophilic trifluoromethylation of benzaldehyde was found to be fairly similar to nucleophilic trifluoromethylation of methyl formate (+21.5 kcal/mol versus +19.4 kcal/mol). Considering the overall Gibbs energy change from **1a-K** to **3a-K** was −4.6 kcal/mol, the interconversion between these two species was essentially reversible (Figure 2-C).

As shown in Figure 2-B, both the first and the second deprotonations of hexafluoroacetone hydrate (**5**) were highly exothermic due to the presence of geminal CF₃ groups. Although the release of the “CF₃[−]” anion were thermodynamically downhill from both deprotonated products (**5-K** and **5-K₂**), a significantly higher kinetic barrier was found during the course of CF₃ release from **5-K** (+24.6 kcal/mol versus +5.6 kcal/mol). This resembled the CF₃

release coordinate of **1c**, therefore implying that the primary kinetic driving force for CF₃ release was the formation of the highly ionic dipotassium salts **1c-K₂** and **5-K₂**. In contrast, **1a** could only form a monopotassium-containing species **1a-K**, which thus retarded to expel CF₃⁻. Noticeably, the nucleophilic trifluoromethylation using **5** was calculated to be thermodynamically more favorable than that using **1c** by ca. 13 kcal/mol. This was presumably due to the generation of by-product CF₃CO₂K, whose conjugate acid is more acidic than formic acid. Since both reactions involving **1c-K₂** and **5-K₂** were highly exothermic processes, the substantially irreversible nature of these two reactions was not altered by such relatively small difference in Gibbs free energy release.

Conclusion

In conclusion, we have developed a novel nucleophilic trifluoromethylation of carbonyl compounds using trifluoroacetaldehyde hydrate **1c** as a CF₃⁻ precursor. The utilization of readily available trifluoroacetaldehyde hydrate has not only provided a facile synthetic access towards α -trifluoromethyl alcohols, but also allowed maximum utilization of the CF₃ moiety in the precursor (compared with hexafluoroacetone hydrate). Theoretical calculations have suggested that both trifluoroacetaldehyde hydrate deprotonation and subsequent CF₃ release from potassium salt **1c-K₂** were highly exothermic processes. These two steps contributed ca. +50 kcal/mol Gibbs free energy release as the actual driving force for the reaction. Further theoretical calculations of nucleophilic trifluoromethylations using trifluoroacetaldehyde hemiacetal **1a** and hexafluoroacetone hydrate **5** provided mechanistic rationalizations of their different reactivity from trifluoroacetaldehyde hydrate **1c**.

Experimental Section

General Methods

Unless otherwise mentioned, all the chemicals were purchased from commercial sources and used without further purification. Preparative thin layer chromatography or flash column chromatography were performed to isolate products with suitable eluent. ¹H, ¹³C, and ¹⁹F spectra were recorded on 400 MHz or 500 MHz NMR spectrometers. ¹H NMR chemical shifts were determined relative to CDCl₃ as the internal standard at δ 7.26 ppm. ¹³C NMR shifts were determined relative to CDCl₃ at δ 77.16 ppm. ¹⁹F NMR chemical shifts were determined relative to CFCl₃ at δ 0.00 ppm. Mass spectra were recorded on a high resolution mass spectrometer, in the EI, FAB or ESI modes.

Typical Procedure for Removal of Excess Water from Commercial Trifluoroacetaldehyde Hydrate **1c**

Commercial trifluoroacetaldehyde hydrate **1c** (5.00 g, 32.9 mmol) in 100 mL anhydrous Et₂O was added CaCl₂ (1.21 g, 11.0 mmol) in small portions with vigorous stirring. The mixture was stirred for 2 h and quickly subjected to suction filtration under air. The solvent of the filtrate was removed under reduced pressure to give partially dried product (4.11 g). The concentration of CF₃CHO in this sample was determined by ¹⁹F NMR spectrum with PhCF₃ as an internal standard, which indicated a formula of CF₃CH(OH)₂·½H₂O and > 95% yield. The newly prepared trifluoroacetaldehyde hydrate was transferred into a tightly sealed vial and stored in a glove box.

Typical Procedure for Nucleophilic Trifluoromethylation of Carbonyl Compounds

To a stirred solution of trifluoroacetaldehyde hydrate (**1c**, 1.5 mmol) in DMF (1.0 mL) at -50 °C, a solution of *t*-BuOK (673 mg, 6.0 mmol) in DMF (3.0 mL) was added dropwise over 5 min. The reaction was stirred for 30 min while maintaining the temperature at -50 °C. A solution of carbonyl compounds (**2**, 1.0 mmol) in DMF (1.0 mL) was then added into

the reaction mixture at $-50\text{ }^{\circ}\text{C}$ and stirred for 1 h. The reaction mixture was allowed to gradually warm up to room temperature before quenching with water. The resulting mixture was extracted with diethyl ether ($3\times 10\text{ mL}$). The combined organic phase was then washed with saturated NH_4Cl aqueous solution, water, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified with silica gel flash chromatography using pentane-diethyl ether as eluent.

1-Phenyl-2,2,2-trifluoroethanol (3a).²⁰—Colorless oil (146 mg, 83%). ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.37 (m, 5H), 5.00 (q, $J = 6.7\text{ Hz}$, 1H), 2.78 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.9 (d, $J = 6.7\text{ Hz}$, 3F).

1-(4-Fluorophenyl)-2,2,2-trifluoroethanol (3b).³¹—Colorless oil (99 mg, 51%). ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.44 (m, 2H), 7.15-7.05 (m, 2H), 5.01 (q, $J = 6.6\text{ Hz}$, 1H), 2.74 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -79.2 (d, $J = 6.6\text{ Hz}$, 3F), -112.4 (m, 1F).

1-(4-Chlorophenyl)-2,2,2-trifluoroethanol (3c).^{20,32}—Colorless oil (122 mg, 58%). ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.33 (m, 4H), 5.01 (q, $J = 6.5\text{ Hz}$, 1H), 2.72 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -79.0 (d, $J = 6.5\text{ Hz}$, 3F).

1-(4-Bromophenyl)-2,2,2-trifluoroethanol (3d).³³—Colorless oil (143 mg, 56%). ^1H NMR (400 MHz, CDCl_3) δ 7.57-7.53 (m, 2H), 7.36-7.33 (m, 2H), 4.98 (dq, $J = 4.3, 6.6\text{ Hz}$, 1H), 2.83 (d, $J = 4.3\text{ Hz}$, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -79.0 (d, $J = 6.6\text{ Hz}$, 3F).

1-(4-Methylphenyl)-2,2,2-trifluoroethanol (3e).³³—Colorless oil (86 mg, 45%). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 7.9\text{ Hz}$, 2H), 7.23 (d, $J = 8.0\text{ Hz}$, 2H), 4.98 (q, $J = 6.7\text{ Hz}$, 1H), 2.56 (br, 1H), 2.38 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.9 (d, $J = 6.7\text{ Hz}$, 3F).

1-(4-Dimethylaminophenyl)-2,2,2-trifluoroethanol (3h).²⁴—Reddish solid (206 mg, 94%). ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, $J = 8.6\text{ Hz}$, 2H), 6.73 (d, $J = 8.8\text{ Hz}$, 2H), 4.88 (q, $J = 6.8\text{ Hz}$, 1H), 2.97 (s, 6H), 2.66 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.9 (d, $J = 6.8\text{ Hz}$, 3F).

1-(3-Methylphenyl)-2,2,2-trifluoroethanol (3i).⁴—Colorless oil (137 mg, 72%). ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.18 (m, 4H), 4.96 (q, $J = 6.7\text{ Hz}$, 1H), 2.68 (br, 1H), 2.39 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.8 (d, $J = 6.7\text{ Hz}$, 3F).

1-(2-Methylphenyl)-2,2,2-trifluoroethanol (3j).³⁴—Colorless oil (101 mg, 53%). ^1H NMR (400 MHz, CDCl_3) δ 7.66-7.56 (m, 1H), 7.34-7.19 (m, 3H), 5.31 (dq, $J = 6.6, 4.3\text{ Hz}$, 1H), 2.67 (d, $J = 4.5\text{ Hz}$, 1H), 2.39 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.2 (d, $J = 6.6\text{ Hz}$, 3F).

1-(2,4,6-Trimethoxyphenyl)-2,2,2-trifluoroethanol (3k).—White solid (186 mg, 70%). ^1H NMR (400 MHz, CDCl_3) δ 6.17 (d, $J = 11.6\text{ Hz}$, 2H), 5.44 (dq, $J = 11.8, 7.8\text{ Hz}$, 1H), 4.86 (d, $J = 11.8\text{ Hz}$, 1H), 3.83 (s, 6H), 3.80 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.6 (d, $J = 7.8\text{ Hz}$, 3F). ^{13}C NMR (125 MHz, CDCl_3) δ 162.1, 159.8, 125.3 (q, $J = 284.4\text{ Hz}$), 103.0, 91.4, 67.1 (q, $J = 33.4\text{ Hz}$), 56.1, 55.5. HRMS (EI-TOF): exact mass calcd for $\text{C}_{11}\text{H}_{13}\text{O}_4\text{F}_3\text{ [M}^+]$: 266.0760, Found : 266.0770.

2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanol (3m).²⁰—White solid (129 mg, 57%). ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J = 0.5\text{ Hz}$, 1H), 7.81-7.73 (m, 3H), 7.49-7.40 (m, 3H),

5.06 (dq, $J = 6.7, 4.2$ Hz, 1H), 2.76 (d, $J = 4.2$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.6 (d, $J = 6.7$ Hz, 3F).

2,2,2-Trifluoro-1,1-diphenylethanol (3p).²⁰—Colorless oil (227 mg, 90%). ^1H NMR (400 MHz, CDCl_3) δ 7.58-7.53 (m, 4H), 7.43-7.37 (m, 6H), 3.06 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -74.3 (s, 3F).

2,2,2-Trifluoro-1,1-bis(4-methoxyphenyl)ethanol (3q).²⁴—Colorless oil (250 mg, 80%). ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, $J = 8.6$ Hz, 4H), 6.89-6.85 (m, 4H), 3.80 (s, 6H), 3.03 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -75.1 (s, 3F).

2,2,2-trifluoro-1-(4-nitrophenyl)-1-phenylethanol (3r).²⁰—Colorless oil (134 mg, 45%). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (t, $J = 11.5$ Hz, 2H), 7.68 (dd, $J = 17.5, 8.5$ Hz, 2H), 7.54-7.51 (m, 2H), 7.45-7.35 (m, 3H), 3.26 (s, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -74.7 (s, 3F).

1-Adamantan-1-yl-2,2,2-trifluoro-1-phenylethanol (3s)—White solid (298 mg, 96%). ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.30 (m, 5H), 2.52 (s, 1H), 2.02 (s, 3H), 1.76 (dd, $J = 49.5, 12.2$ Hz, 6H), 1.61 (dd, $J = 38.1, 12.2$ Hz, 6H). ^{19}F NMR (376 MHz, CDCl_3) δ -66.8 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 136.2, 128.1, 127.1 (q, $J = 290.1$ Hz), 127.9 (br), 127.3 (br), 127.2 (br), 82.4 (q, $J = 25.4$ Hz), 39.8, 36.71, 36.68, 28.5. HRMS (EI-TOF): exact mass calcd for $\text{C}_{18}\text{H}_{19}\text{F}_3$ $[\text{M}-\text{H}_2\text{O}]^+$: 292.1433, Found : 292.1439.

2-(Trifluoromethyl)adamantan-2-ol (3t).²⁰—White solid (209 mg, 95%). ^1H NMR (400 MHz, CDCl_3) δ 2.29-2.21 (m, 2H), 2.14-2.04 (m, 4H), 1.90 (s, 1H), 1.89-1.80 (m, 2H), 1.80-1.70 (m, 4H), 1.64-1.54 (m, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -75.7 (s, 3F).

Theoretical Calculations

Theoretical calculations were performed at the B3LYP/6-31+G(d,p) level in DMF using Gaussian 09 package.^{29,30} Solvent effects were included implicitly through the self-consistent reaction field approach, as implemented in the default Polarizable Continuum Model (PCM) in Gaussian 09.^{27,28} Thermal and entropic corrections for PCM-optimized structures were obtained by frequency analysis at the B3LYP/6-31+G(d,p) level. The frequency analyses confirmed that all considered ground state structures were true minima on the PES. All transition states were also identified and validated using vibrational frequency analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Calculated reaction coordinate from 1c to 3a-K.

Figure 2. Calculated reaction coordinate of nucleophilic trifluoromethylation of aldehyde using trifluoroacetaldehyde hemiacetal (**1a**) and hexafluoroacetone hydrate (**5**).

(a) The Ruppert-Prakash reagent **(b) Various nucleophilic trifluoromethylating reagents** **(c) This work** **Scheme 1.**

Generation of “CF₃⁻” synthon through the release of neutral or stable species.

Scheme 2. Generation of CF_3^- from different trifluoroacetaldehyde hemiacetal derivatives.

Scheme 3.

Calculated thermodynamics of the nucleophilic trifluoromethylation reaction using **1c** and the related reactions.

Table 1

Reaction condition optimization using **1c** [$\text{CF}_3\text{CH}(\text{OH})_2 \cdot 2\text{H}_2\text{O}$] as a CF_3^- precursor.

$\text{HO}-\text{C}(\text{OH})(\text{F}_3)-\text{H}$ 1c^a		base	solvent	temperature	PhCHO (2a)	solvent	temperature	hydrate:base:PhCHO	yield (%) ^b
1	DMF	<i>t</i> -BuOK		-30				1.2:3.6:1.0	0 ^b
2	DMF	<i>t</i> -BuOK		-30				1.2:4.8:1.0	33
3	DMF	<i>t</i> -BuOK		-30				1.2:6.0:1.0	64
4	DMF	<i>t</i> -BuOK		-30				1.2:7.2:1.0	21
5 ^d	DMF	<i>t</i> -BuOK		-30				1.2:6.0:1.0	0 ^c
6	DMF	<i>t</i> -BuOK		r.t.				1.2:3.6:1.0	47
7	DMF	<i>t</i> -BuOK		r.t.				1.2:4.8:1.0	0
8	DMF	<i>t</i> -BuONa		r.t.				1.2:3.6:1.0	17
9	DMF	<i>t</i> -BuOLi		r.t.				1.2:3.6:1.0	0 ^e
10	DMF	NaH		r.t.				1.2:3.6:1.0	0

^a $\text{CF}_3\text{CH}(\text{OH})_2 \cdot 2\text{H}_2\text{O}$;

^b ^{19}F NMR yield was determined using PhCF_3 as an internal standard;

^c Only CF_3H was observed;

^d Base was added dropwise to a solution of hydrate **1c** and **2a** in DMF at -30 °C;

^e **1c** was found to convert to $\text{CF}_3\text{CO}_2\text{K}$.

Table 2

Reaction condition optimization using **1c** [$\text{CF}_3\text{CH}(\text{OH})_2 \cdot \frac{1}{2}\text{H}_2\text{O}$] as a CF_3^- precursor.

entry	solvent	hydrate:base:PhCHO	yield (%) ^b
1	DMF	1.2:4.8:1.0	66
2	DMF	1.2:4.2:1.0	62
3	DMF	1.2:3.6:1.0	64
4	DMF	1.2:3.0:1.0	61
5	DMF	1.5:6.0:1.0	89
6	DMF	1.8:7.2:1.0	77
7	DMF	2.0:8.0:1.0	83
8	THF	2.0:8.0:1.0	0 ^c
9	DMSO	2.0:8.0:1.0	0 ^c

^a $\text{CF}_3\text{CH}(\text{OH})_2 \cdot \frac{1}{2}\text{H}_2\text{O}$

^b ^{19}F NMR yield was determined using PhCF_3 as an internal standard.

^cOnly CF_3H was observed.

Table 3

Nucleophilic trifluoromethylation of carbonyl compounds **2** with trifluoroacetaldehyde hydrate **1c** [$\text{CF}_3\text{CH}(\text{OH})_2 \cdot \frac{1}{2}\text{H}_2\text{O}$].

entry	Substrates	yield (%) ^b
1	 2a	89/83
2	 2b	65/51
3	 2c	64/58
4	 2d	64/56
5	 2e	48/45
6	 2f	0/- ^c
7	 2g	0/- ^c

entry	Substrates	yield (%) ^b
8	 Me_2N $\mathbf{2h}$	97/94
9	 Me $\mathbf{2i}$	82/72
10	 Me $\mathbf{2j}$	57/53
11	 OMe $\mathbf{2k}$	77/70
12	 $\mathbf{2l}$	0/- ^c
13	 $\mathbf{2m}$	65/57
14	 $\mathbf{2n}$	0/- ^c
15	 $\mathbf{2o}$	0/- ^c
16	 $\mathbf{2p}$	>99/90

entry	Substrates	yield (%) ^b
17	2q	91/80
18	2r	^d /45
19	2s	>99/96
20	2t	>99/95

^aCF₃CH(OH)₂·1/2H₂O;

^b¹⁹F NMR yield/isolated yield. ¹⁹F NMR yield was determined using PhCF₃ as an internal standard.

^cNot isolated.

^d¹⁹F NMR yield not determined due to significant ¹⁹F NMR signal line broadening.