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

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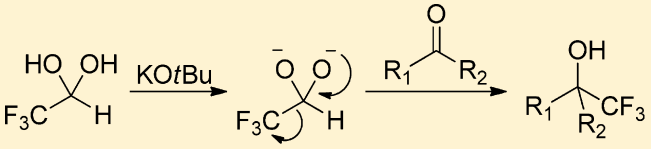
Supporting Information

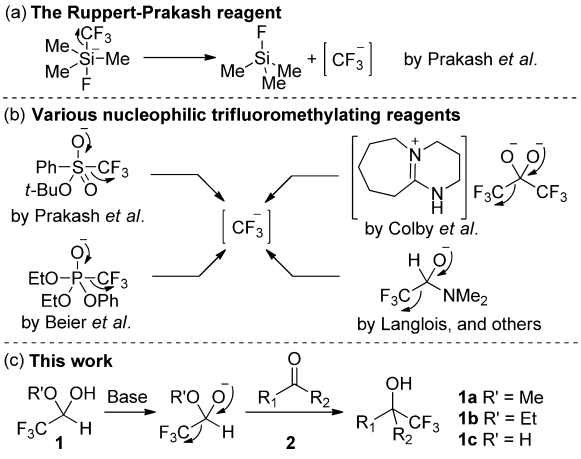
ABSTRACT: A feasible nucleophilic trifluoromethylating protocol has been developed using trifluoroacetaldehyde hydrate as an atom-economical trifluoromethyl source. The reaction was found to be applicable to the nucleophilic trifluoromethylation of a broad spectrum of carbonyl compounds with satisfactory 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 $TMSCF_3$ (the Ruppert−Prakash reagent) is a versatile reagent capable of transferring the CF_3 group (Scheme 1a),[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 (CF_3^-) along with a stable byproduct (Scheme 1b).[11] Langlois and others have demonstrated the direct trifluoromethylation of various electrophiles using trifluoromethane (CF_3H) in DMF via a trifluoromethylated hemiaminal derivative (CF_3^-−DMF adduct analogue).[12−19] Prakash et al. utilized phenyl trifluoromethyl sulfone ($PhSO_2CF_3$) and phenyl trifluoromethyl sulfoxide ($PhSOCF_3$) in nucleophilic trifluoromethylation reactions, which allowed the generation of CF_3^- via pentavalent and tetravalent sulfur intermediates, respectively.[20] In line with this work, an alkoxide-induced trifluoromethylation was also reported by Beier and co-workers using diethyl trifluoromethylphosphate [$(EtO)_2POCF_3$].[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 ($CF_3CO_2^-$), such a reagent was able to incorporate the CF_3 moiety into various electrophiles. On the basis of these reactions, we envisaged that ready 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 CF_3 motif (Scheme 1c).

Scheme 1. Generation of "CF_3^-" Synthon through the Release of Neutral or Negatively Charged Species



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 CF_3H nor the desired α-trifluoromethyl alcohol (**3a**) was observed after numerous attempts (Scheme 2). This could be ascribed to the plausible reverse addition of CF_3^- to alkyl formates, which could significantly impede the trifluoromethylation of benzaldehyde (Scheme 2, eq 1).

Considering the essential low electrophilicity of formate anion (HCO_2^-), trifluoroacetaldehyde hydrate (**1c**) was

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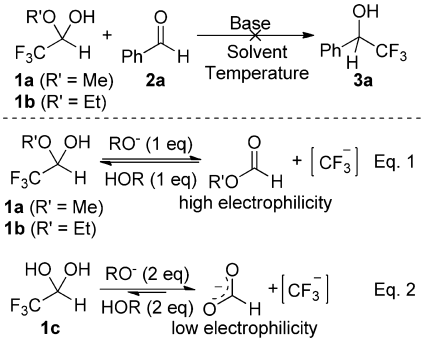
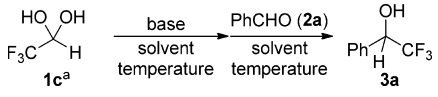
Scheme 2. Generation of CF_3^- from Different Trifluoroacetaldehyde Hemiacetal Derivatives



adopted in our further investigation to avoid the reverse CF_3^--byproduct addition (Scheme 2, eq 2). According to ^{19}F 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, entries 5−10).

Table 1. Reaction Condition Optimization Using 1c $[CF_3CH(OH)_2{\cdot}2H_2O]$ as a CF_3^- Precursor

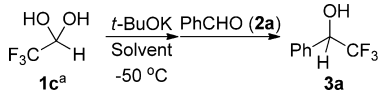


entry	solvent	base	T (°C)	hydrate/base/PhCHO	yield[b] (%)
1	DMF	*t*-BuOK	−30	1.2:3.6:1.0	0[b]
2	DMF	*t*-BuOK	−30	1.2:4.8:1.0	33
3	DMF	*t*-BuOK	−30	1.2:6.0:1.0	64
4	DMF	*t*-BuOK	−30	1.2:7.2:1.0	21
5[d]	DMF	*t*-BuOK	−30	1.2:6.0:1.0	0[c]
6	DMF	*t*-BuOK	rt	1.2:3.6:1.0	47
7	DMF	*t*-BuOK	rt	1.2:4.8:1.0	0
8	DMF	*t*-BuONa	rt	1.2:3.6:1.0	17
9	DMF	*t*-BuOLi	rt	1.2:3.6:1.0	0[e]
10	DMF	NaH	rt	1.2:3.6:1.0	0

[a] $CF_3CH(OH)_2{\cdot}2H_2O$. [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 CF_3CO_2K.

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 $CF_3CH(OH)_2{\cdot}2H_2O$.[25] To remove the excess amount of H_2O, $CF_3CH(OH)_2$ 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 $CF_3CH(OH)_2$ compared with $(CF_3)_2C(OH)_2$. We further exploited 4 Å molecular sieves as a drying agent, which unfortunately absorbed the majority of $CF_3CH(OH)_2$ along with water. After a brief screening, calcium chloride ($CaCl_2$) was shown to be an efficient drying agent allowing recovery of 95% **1c** with a composition of $CF_3CH(OH)_2{\cdot}^1/_2H_2O$.[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, and 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 CF_3^- from **1c**, the nucleophilic trifluoromethylation of benzaldehyde did not take place (Table 2, entries 8 and 9).

Table 2. Reaction Condition Optimization Using 1c $[CF_3CH(OH)_2{\cdot}^1/_2H_2O]$ 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] $CF_3CH(OH)_2{\cdot}^1/_2H_2O$. [b] ^{19}F NMR yield was determined using $PhCF_3$ as an internal standard. [c] Only CF_3H was observed.

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 NO_2 and CF_3 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, entries 16−18). 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 because of 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 equiv of *t*-BuOK under the reaction conditions (Scheme 3, eq 2). It has also been found that salts **1c-K** and **1c-K$_2$** were thermodynamically unstable species tending to expel CF_3^-. Since these processes involve a Gibbs free energy change of approximately −30 kcal/mol, the reversible addition of CF_3^- to HCO_2K 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 benzalde-

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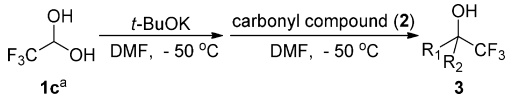
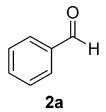
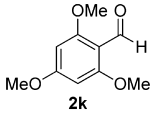
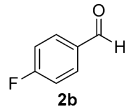
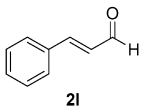
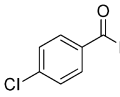
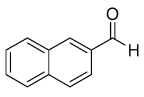
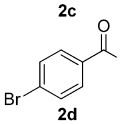
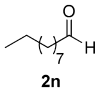
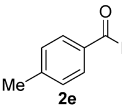
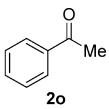
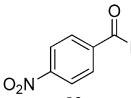
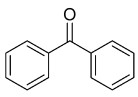
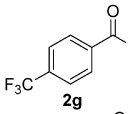
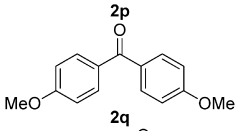
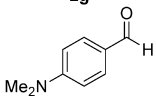
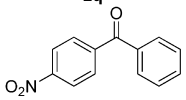
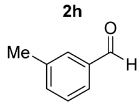
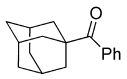
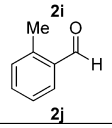
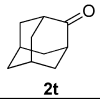
Table 3. Nucleophilic Trifluoromethylation of Carbonyl Compounds 2 with Trifluoroacetaldehyde Hydrate 1c [$CF_3CH(OH)_2 \cdot {}^1/_2H_2O$]

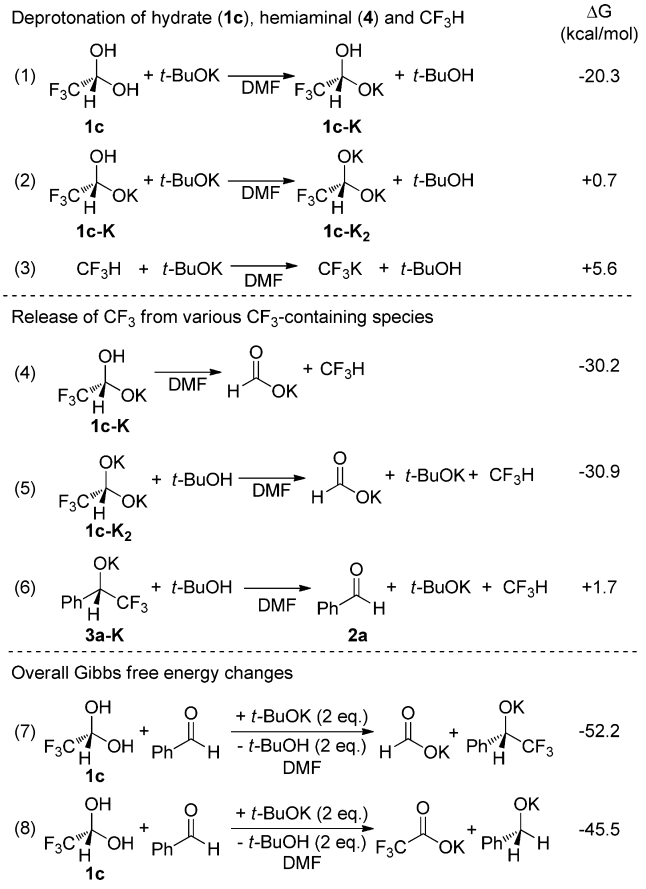


entry	Substrates	yield (%)[b]	entry	Substrates	yield (%)[b]
1	 **2a**	89/83	11	 **2k**	77/70
2	 **2b**	65/51	12	 **2l**	0/-[c]
3	 **2c**	64/58	13	 **2m**	65/57
4	 **2d**	64/56	14	 **2n**	0/-[c]
5	 **2e**	48/45	15	 **2o**	0/-[c]
6	 **2f**	0/-[c]	16	 **2p**	>99/90
7	 **2g**	0/-[c]	17	 **2q**	91/80
8	 **2h**	97/94	18	 **2r**	-[d]/45
9	 **2i**	82/72	19	 **2s**	>99/96
10	 **2j**	57/53	20	 **2t**	>99/95

[a] $CF_3CH(OH)_2 \cdot {}^1/_2H_2O$. [b] ^{19}F NMR yield/isolated yield. ^{19}F NMR yield was determined using $PhCF_3$ as an internal standard. [c] Not isolated. [d] ^{19}F NMR yield not determined due to significant ^{19}F NMR signal line broadening.

hyde) 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).

Scheme 3. Calculated Thermodynamics of the Nucleophilic Trifluoromethylation Reaction Using 1c and Related Reactions



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 CF_3H and HCO_2K. However, such fragmentation was more likely to proceed via the **1c-K2** intermediate due to the

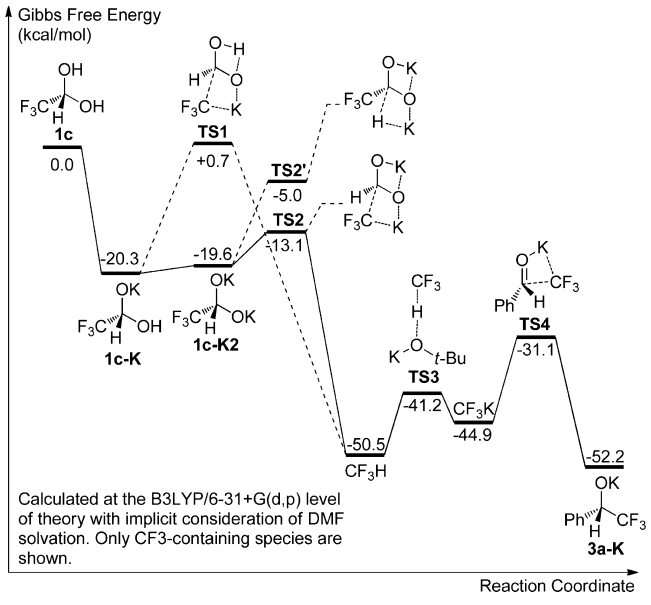


Figure 1. Calculated reaction coordinate from **1c** to **3a**–**k**.

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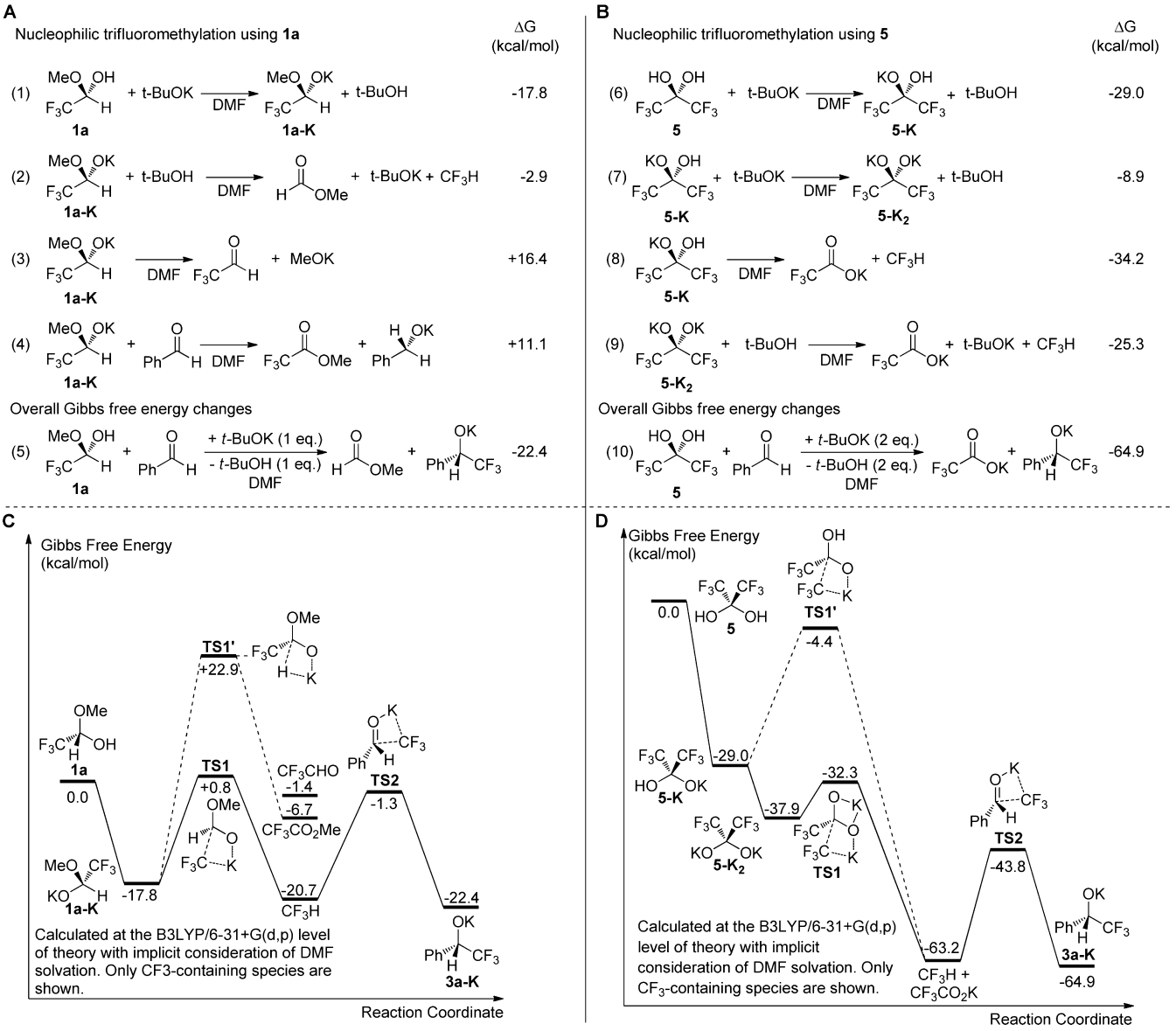

Figure 2. Calculated reaction coordinate of nucleophilic trifluoromethylation of aldehyde using trifluoroacetaldehyde hemiacetal (**1a**) and hexafluoroacetone hydrate (**5**).

significantly lower barrier involving **TS2** than **TS1** (+6.5 kcal/mol vs. +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 countercations also showed that the C−CF_3 bond cleavage is kinetically preferred over hydride transfer by 9.1 kcal/mol (see the Supporting Information), which rationalizes the observed trifluoroacetate formation (Table 1, entry 9). Presumably, the nucleophilic addition involved the deprotonation of CF_3H 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 CF_3H). 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 show in Figure 2A, although the deprotonation of **1a** was thermodynamically feasible, the exothermicity of the subsequent CF_3 release was rather insignificant (−2.9 kcal/mol), indicating a facile reverse addition of "CF_3^-" to methyl formate. This is indeed consistent with the observed low ability of trifluoroacetaldehyde hemiacetals to release the "CF_3^-" 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 "CF_3^-" release. Kinetically, the barrier to the nucleophilic trifluoromethylation of benzaldehyde was found to be fairly similar to nucleophilic trifluoromethylation of methyl

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formate (+21.5 kcal/mol versus +19.4 kcal/mol). Considering the overall Gibbs free energy change from **1a-K** to **3a-K** was −4.6 kcal/mol, the interconversion between these two species was essentially reversible (Figure 2C).

As shown in Figure 2B, both the first and the second deprotonations of hexafluoroacetone hydrate (**5**) were highly exothermic due to the presence of geminal CF_3 groups. Although the release of the "CF_3^-" anion were thermodynamically downhill from both deprotonated products (**5-K** and **5-K_2**), a significantly higher kinetic barrier was found during the course of CF_3 release from **5-K** (+24.6 kcal/mol versus +5.6 kcal/mol). This resembled the CF_3 release coordinate of **1c**, therefore implying that the primary kinetic driving force for CF_3 release was the formation of the highly ionic dipotassium salts **1c-K_2** and **5-K_2**. In contrast, **1a** could only form a monopotassium-containing species **1a-K**, which thus retarded to expel CF_3^-. 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 byproduct CF_3CO_2K, whose conjugate acid is more acidic than formic acid. Since both reactions involving **1c-K_2** and **5-K_2** 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 CF_3^- precursor. The utilization of readily available trifluoroacetaldehyde hydrate has not only provided a facile synthetic access toward α-trifluoromethyl alcohols but also allowed maximum utilization of the CF_3 moiety in the precursor (compared with hexafluoroacetone hydrate). Theoretical calculations have suggested that both trifluoroacetaldehyde hydrate deprotonation and subsequent CF_3 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 eluents. ^{1}H, ^{13}C, and ^{19}F spectra were recorded on 400 or 500 MHz NMR spectrometers. ^{1}H NMR chemical shifts were determined relative to $CDCl_3$ as the internal standard at δ 7.26 ppm. ^{13}C NMR shifts were determined relative to $CDCl_3$ at δ 77.16 ppm. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ 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. To commercial trifluoroacetaldehyde hydrate **1c** (5.00 g, 32.9 mmol) in 100 mL of anhydrous Et_2O was added $CaCl_2$ (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 CF_3CHO in this sample was determined by its ^{19}F NMR spectrum with $PhCF_3$ as an internal standard, which indicated a formula of $CF_3CH(OH)_2 \cdot {}^1/_2H_2O$ and >95% yield. The newly prepared trifluoroacetaldehyde hydrate was transferred into a tightly sealed vial and stored in a glovebox.

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 was added dropwise a solution of *t*-BuOK (673 mg, 6.0 mmol) in DMF (3.0 mL) 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 °C and stirred for 1 h. The reaction mixture was allowed to gradually warm to room temperature before quenching with water. The resulting mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phase was then washed with saturated NH_4Cl aqueous solution and 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%); ^{1}H NMR (400 MHz, $CDCl_3$) δ. 7.55−7.37 (m, 5H), 5.00 (q, J = 6.7 Hz, 1H), 2.78 (br, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.9 (d, J = 6.7 Hz, 3F).

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

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

*1-(4-Bromophenyl)-2,2,2-trifluoroethanol (**3d**):*[33] colorless oil (143 mg, 56%); ^{1}H 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 Hz, 1H), 2.83 (d, J = 4.3 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.0 (d, J = 6.6 Hz, 3F).

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

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

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

*1-(2-Methylphenyl)-2,2,2-trifluoroethanol (**3j**):*[34] colorless oil (101 mg, 53%); ^{1}H 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 Hz, 1H), 2.67 (d, J = 4.5 Hz, 1H), 2.39 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.2 (d, J = 6.6 Hz, 3F).

*1-(2,4,6-Trimethoxyphenyl)-2,2,2-trifluoroethanol (**3k**):* white solid (186 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J = 11.6 Hz, 2H), 5.44 (dq, J = 11.8, 7.8 Hz, 1H), 4.86 (d, J = 11.8 Hz, 1H), 3.83 (s, 6H), 3.80 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.6 (d, J = 7.8 Hz, 3F); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 159.8, 125.3 (q, J = 284.4 Hz), 103.0, 91.4, 67.1 (q, J = 33.4 Hz), 56.1, 55.5; HRMS (EI-TOF) exact mass calcd for $C_{11}H_{13}O_4F_3$ [M^+] 266.0760, found 266.0770.

*2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanol (**3m**):*[20] white solid (129 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 0.5 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%); ^{1}H 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).

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*2,2,2-Trifluoro-1,1-bis(4-methoxyphenyl)ethanol (**3q**):*[24] colorless oil (250 mg, 80%); ^{1}H 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%); ^{1}H 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), 7.4527.35 (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%); ^{1}H 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 $C_{18}H_{19}F_3$ $[M - H_2O]^+$ 292.1433, found 292.1439.

*2-(Trifluoromethyl)adamantan-2-ol (**3t**):*[20] white solid (209 mg, 95%); ^{1}H 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 the 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{19}F and ^{1}H NMR spectra for all compounds. ^{13}C 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.

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Notes

The authors declare no competing financial interest.

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