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Nucleophilic trifluoromethylation with CF_3H/LiHMDS: probing the nucleophilic reactivity of $LiCF_3$ species

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The nucleophilic trifluoromethylation involving trifluoromethyllithium ($LiCF_3$) species has been an open question since Haszeldine attempted to prepare $LiCF_3$ in 1949. Indeed, $LiCF_3$ has been used for electrophilic difluoromethylene transfer processes (*via* elimination of fluoride ions) since 2010. Herein, we demonstrated that by using a polar solvent such as dimethylformamide (DMF) or hexamethylphosphoramide (HMPA) as the lithium chelator, the *in situ* deprotonation of fluoroform (HCF_3) with lithium hexamethyldisilazide (LiHMDS) could generate a tamed $LiCF_3$ species that is sufficiently persistent to undergo nucleophilic trifluoromethylation reaction. The nucleophilic reactivity of $LiCF_3$ species was probed with several electrophiles, including arylsulfonyl fluorides, diaryl ketones, and silyl chlorides. The synthetic utility of this method is demonstrated with the efficient synthesis of highly valuable triflones that are otherwise difficult to synthesize from HCF_3 using potassium or sodium bases. This work not only showcases a new protocol for the utilization of fluoroform (an industrial waste with high global warming potential) as the trifluoromethylation reagent, but also provides intriguing insights into the harnessing of nucleophilic reactivity of the transient $LiCF_3$ species.

nucleophilic trifluoromethylation, trifluoromethyllithium, fluorinated carbanion, negative fluorine effect, fluorinated carbenoid

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Organofluorine compounds have attracted attention in the fields of pharmaceuticals, agrochemicals and materials owing to the unique properties of fluorine substituents [1]. In this context, various synthetic methods have been well developed for the efficient incorporation of fluorine atoms or fluorinated moieties into organic molecules [2]. Among them, fluoroalkylation involving the transfer of a fluorinated carbanion or fluorocarbenoid is a pivotal strategy for synthesizing fluorinated organic molecules [2i,j]. However, as a consequence of the low thermal stability of the α-fluoro carbanions in the presence of Group I and Group II metal cations as well as its intrinsic low nucleophilicity towards a certain electrophile [3,4], the α-fluorine substitution on the carbanionic center often demonstrates an unfavorable effect on the carbanion's nucleophilic reaction (negative fluorine effect, NFE) [3e-g,4b-d]. More α-fluorine substituents on the carbanionic center can result in lower yield of the desired nucleophilic fluoroalkylation reaction [3d,e,g]. Moreover, the NFE is more striking when Li^+ is present as the countercation and lithium α-fluorocarbenoids have been regarded as the "beast" in carbenoid chemistry [5] due to the facile elimination of LiF to form carbene species. By using removable activation groups, nucleophilic mono- and difluoromethylation have been achieved with *in situ* generated functionalized monofluoromethyllithium [6] and difluoromethyllithium species [7,8], respectively. In 2018, the

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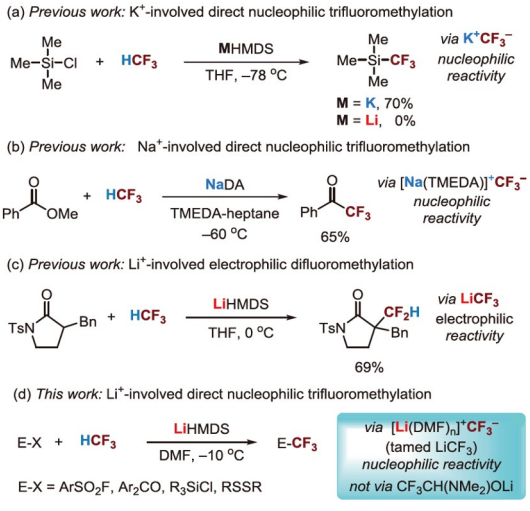
direct nucleophilic monofluoromethylation with lithium fluorocarbenoid $LiCH_2F$ was developed by *in situ* lithiation of ICH_2F with MeLi-LiBr in an ethereal solvent system at –78 °C [5b]. However, lithium trifluorocarbenoid $LiCF_3$ readily undergoes decomposition to more stable difluorocarbene and LiF even at –100 °C [2i,9], and therefore has been recognized as "notoriously" unstable species [9g]. Since Haszeldine's first attempt to generate $LiCF_3$ from iodotrifluoromethane and elemental lithium in 1949, there has been no report on the efficient capture of $LiCF_3$ [10].

On the other hand, nucleophilic trifluoromethylation is commonly conducted with the stable organosilicon reagent $TMSCF_3$ (Ruppert–Prakash reagent) [11a] in the presence of a Lewis base initiator, proceeding through a pentacoordinate silicate as the active reaction intermediate [11]. More recently, the trifluoromethanide anion (CF_3^-) derived from R_3SiCF_3 reagent was experimentally observed [12]; however, little attention has been paid to the possibility of $LiCF_3$-involved nucleophilic trifluoromethylation although lithium salts have been used as the initiators [13,14]. Fluoroform (HCF_3) is also a nucleophilic trifluoromethylation reagent when coupled with a base [15,16]. Since 2012, fluoroform (HCF_3) has been tamed for direct nucleophilic trifluoromethylations in common solvents such as THF, ether and toluene by the appropriate choice of a base with K^+ (Scheme 1a) [10d,16], Na^+ (Scheme 1b) [16,17] or organocation [16,18] as the countercation. However, the use of Li^+ as the countercation under similar conditions failed to afford nucleophilic trifluoromethylation product (Scheme 1a) [10d]. Indeed, Li^+-induced defluorination of CF_3^- readily takes place and has been well utilized in difluoromethylene transfer reactions (electrophilic reactivity) [19]. In 2012, Mikami and coworkers demonstrated that HCF_3 was capable of electrophilic difluoromethylation of lithium enolates (Scheme 1c) [19b] and the involvement of the electrophilic reaction of $LiCF_3$ with the lithium enolates was supported by computational studies [19g]. This reaction mode has been applied to the difluoromethylation of a series of carbon nucleophiles, silyl anions, and boryl anions [19]. Given the wide availability of lithium reagents in organic synthesis, it is highly valuable to develop nucleophilic trifluoromethylation that is compatible with Li^+, as well as to probe the nucleophilic reactivity of the trifluoromethylating species generated under such conditions.

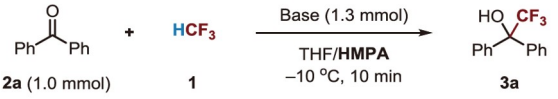


Scheme 1 Metal countercation effect on the reactivity of CF_3^- and the modulation of this effect. NaDA, sodium diisopropylamide.

In 2013, a detailed computational study by Luo, Qu and coworkers investigated the effect of alkali metal cations on direct nucleophilic trifluoromethylation using fluoroform [20]. This work showed that, compared to the corresponding Na- and K-containing species, $LiCF_3$ has a slightly decreased nucleophilic reactivity but significantly increased instability. Based on these calculations [20] and Prakash's report on the low-temperature NMR characterization of CF_3^- with the $[K(18\text{-crown-6})]^+$ cation [12a], we envisioned that nucleophilic trifluoromethylation reaction with a tamed $LiCF_3$ would become possible when the Li-F interaction is alleviated with a strong lithium chelator to mitigate the unproductive $LiCF_3$ decomposition. Considering the extremely low stability of $LiCF_3$ itself, it may be particularly challenging to tame the pregenerated $LiCF_3$ species. We speculated that efficient nucleophilic trifluoromethylation would be more feasible when $LiCF_3$ was generated in the presence of an effective lithium chelator and reacted with a proper electrophile *in situ*. Herein, we report our success on nucleophilic trifluoromethylations employing tamed $LiCF_3$ that is *in situ* generated by deprotonation of HCF_3 with lithium hexamethyldisilazide (LiHMDS) in the presence of hexamethylphosphoramide (HMPA) or dimethylformamide (DMF) as the lithium chelators (Scheme 1d). Of note, we found that the tamed $LiCF_3$ generated in DMF readily undergoes direct nucleophilic trifluoromethylation reactions with a series of electrophiles. The uniqueness and practicality of this method are demonstrated with the efficient synthesis of highly valuable triflones that are otherwise difficult to synthesize from HCF_3 using potassium or sodium bases.

Our investigation started with the examination of the generation of tamed $LiCF_3$ using HMPA [21] as the lithium chelator and the nucleophilic trifluoromethylation reaction with the tamed $LiCF_3$ (Table 1). The experiment was initially performed by dissolving HCF_3 (**1**, 1.0 equiv) in HMPA as the solvent and employing sterically hindered LiHMDS (1.0 M in THF, 1.3 equiv) as a base in the presence of the non-enolizable ketone Ph_2CO (**2a**, 1.0 equiv) as an electrophile (Table 1, entry 1). LiHMDS was slowly added to the reaction over 10 minutes at –10 °C, which was kept for an additional 10 minutes. After quenching with aqueous HCl, ^{19}F NMR analysis of the reaction mixture showed a new peak corresponding to the desired trifluoromethylcarbinol **3a** (75% yield). When excess HCF_3 but a reduced amount of HMPA

Table 1 Initial experiments and optimization[a)]



Entry	**1** (mmol)	Base	THF (mL)	HMPA (mL)	**3a** (%)[b)]
1	1.0	LiHMDS[c)]	0	2.5	75
2	9.5[d,e)]	LiHMDS	2.0	0.23[f)]	61
3	12.0[e,g)]	^{t}BuOLi	2.0	2.5	1
4	3.0[h)]	^{t}BuOLi	0	5	59
5	1.0	LiHMDS	2.0	0	0
6	1.0[e,i)]	LiHMDS	2.0	0	0

a) Reaction conditions: for entries 1-3, 5, and 6, a THF solution of the base (1.0 M) was used; for entry 4, an HMPA solution of the base (0.67 M) was used. b) The yield was determined by ^{19}F NMR spectroscopy analysis using $PhOCF_3$ as an internal standard. c) The addition of LiHMDS in THF was begun as soon as the reaction tube containing HMPA, HCF_3 and Ph_2CO was immersed into the cold bath at –10 °C. d) **1** (0.5 mmol) in HMPA was first added. e) The reaction was conducted under the atmosphere of **1** (1 atm. in a 200-mL balloon). f) The amount of HMPA equals 1.3 mmol g^{-1}) **1** (3.0 mmol) in HMPA was first added, 10 °C, 1 h. h) ^{t}BuOLi (2.0 equiv), rt, 1 h. i) **1** (1.0 mmol) in THF was first added.

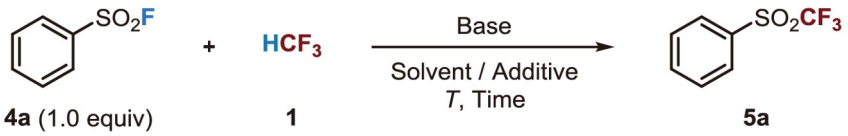
(1.3 equiv) were used, **3a** was still obtained in 61% yield (Table 1, entry 2). With HMPA as the additive or the sole solvent, the use of lithium *tert*-butoxide (^{t}BuOLi) instead of LiHMDS also enabled the trifluoromethylation reaction (Table 1, entries 3 and 4), implying the formation of *in situ* generated trifluoromethylating species. The ineffective reaction observed in THF-HMPA at -10 °C is probably due to the weak ionization ability of ^{t}BuOLi (entry 3). However, control experiments with either stoichiometric or a large excess of HCF_3 in the absence of HMPA did not provide any detectable amount of the desired product **3a** (Table 1, entries 5 and 6). When 1.0 equiv of HCF_3 was employed, most of HCF_3 was consumed. These results demonstrate that CF_3^- generated in the presence of Li^+ can be synthetically useful providing that its tendency to decomposition is reduced by changing the coordination environment of Li^+.

Encouraged by the preliminary success of the trifluoromethylation of Ph_2CO, we moved to explore if the tamed $LiCF_3$ could be employed for the trifluoromethylation of other electrophiles. Sulfonyl fluorides are readily available sulfonylation reagents [22] and have been used for the synthesis of highly valuable trifluoromethyl sulfones (triflones) *via* reactions with relatively expensive $TMSCF_3$ reagent under the activation with a fluoride salt [23]. However, the trifluoromethylation of sulfonyl fluorides with cost-effective HCF_3 is rare. It was only in 2015 that Shibata and co-workers reported such a transformation using an expensive organic super-base as the catalyst in combination with stoichiometric amount of tris(trimethylsilyl)amine in THF or DMF as solvent [23c]. In the report, it was shown that the use of potassium bases instead of the organic super-base led to no triflones [23c]. In this context, we investigated the possibility of the trifluoromethylation of sulfonyl fluorides with tamed $LiCF_3$ by employing benzenesulfonyl fluoride ($PhSO_2F$, **4a**) as the model substrate (Table 2).

Under similar conditions for trifluoromethylation of Ph_2CO with LiHMDS, either the combination of 1.0 equiv of HCF_3 (**1**) and excess HMPA or the combination of excess HCF_3 (**1**) and 1.0 equiv of HMPA could deliver $PhSO_2CF_3$ (**5a**), albeit in low yield (Table 2, entries 1 and 2). A control experiment in the absence of HMPA gave no **5a**, again demonstrating the importance of a strong Li^+ chelator for successful nucleophilic trifluoromethylation (Table 2, entry 3). However, the use of more HMPA tended to promote the undesired reaction of $PhSO_2F$ (**4a**) with LiHMDS, thus decreasing the yield of **5a**. To improve the reaction efficiency, we surveyed the effect of other lithium-coordinating additives/solvents and lithium bases by using excess HCF_3 (Table 2, entries 4-7). We found that employing DMF instead of THF-HMPA could increase the yield of **5a** to 60% (Table 2, entry 5). When LiHMDS was replaced with LiOMe or LiTMP, no reaction was observed, most probably due to the side reaction between LiOMe (or LiTMP) and $PhSO_2F$, respectively (Table 2, entries 6 and 7). Further optimization of the reaction conditions showed that the use of a slightly more excessive amount of LiHMDS and 1.0 equiv of HCF_3 would bring about a higher yield (Table 2, entry 9). Screening of the reaction temperature revealed that -10 °C was optimal (Table 2, entry 9 vs entries 10-12). A comparison of the effect of alkali metal cation showed that Na^+ and K^+ were inferior to Li^+ (Table 2, entries 13 and 14), indicating that Li^+ can be used as a unique countercation to promote nucleophilic trifluoromethylation.

With the optimal reaction conditions in hand (Table 2, entry 9), we further examined the scope of this nucleophilic trifluoromethylation reaction concerning different sulfonyl fluorides (Scheme 2). Generally, a variety of arylsulfonyl fluorides with either electron-donating (**5b-5d**, **5j** and **5k**) or electron-withdrawing groups (**5e-5i**) on the *para*-position of the benzene ring reacted smoothly to give the corresponding triflones in moderate yields. The *meta*- and *para*-halogenated substrates showed similar reactivity to the *ortho*-substituted ones (**5l-5o**). The naphthalenesulfonyl fluorides were also viable substrates, with the derivatives bearing an electron-donating substituent participating in trifluoromethylation in higher yields than the non-substituted ones (**5p-5r**). The optimized reaction conditions also proved to be efficient for aryl bis(sulfonyl fluoride) **4s**, resulting in the formation of the corresponding bis(trifluoromethyl sulfone) **5s** in 49% yield. Furthermore, substrates bearing heterocycle moieties on the aryl ring were also compatible, providing the desired products in 51%-73% yields (**5t-5v**).

Table 2 Optimization of the reaction conditions of nucleophilic trifluoromethylation of $PhSO_2F$ with HCF_3[a)]



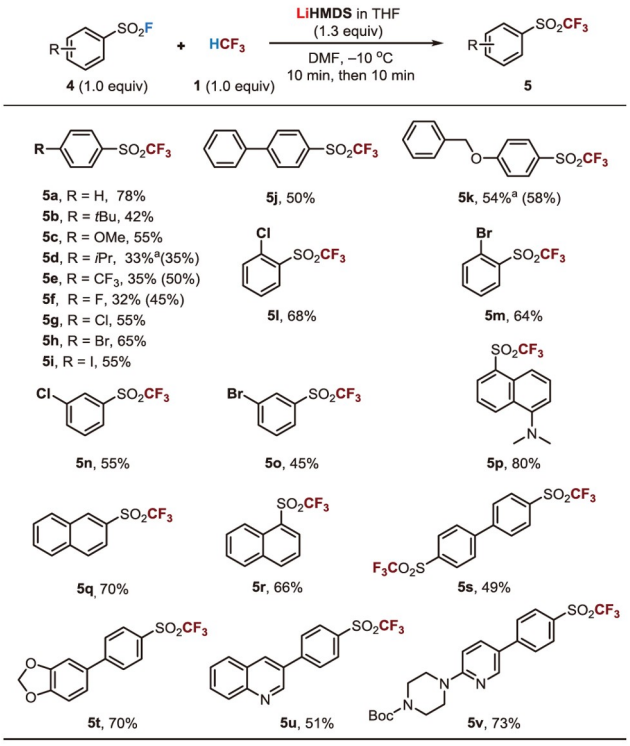
4a (1.0 equiv) **1** **5a**

Entry[a)]	**1** (equiv.)	Base (equiv.)	Solvent/Additive	T (°C)	Time (min)	Yield (%)[b)]	Conversion of **4a** (%)[b)]
1	1.0	LiHMDS in THF (1.1)	THF/HMPA[c)]	-10	10	13	82
2	9.5[d,e)]	LiHMDS in THF (1.1)	THF/HMPA[f)]	-10	10	38	71
3	10[e,g)]	LiHMDS in THF (1.1)	THF	-10 to rt	360[h)]	0	34
4	10[e,g)]	LiHMDS in THF (1.1)	DME	-10 to rt	360[h)]	2	34
5	10[e,g)]	LiHMDS in THF (1.1)	DMF	-10 to rt	360[h)]	60	82
6	10[e,g)]	solid MeOLi (1.1)	DMF	-10 to rt	360[h)]	trace	28
7	10[e,g)]	LiTMP in THF (1.1)	DMF	-10	10	1	30
8	10[e,g)]	LiHMDS in THF (1.3)	DMF	-10 to rt	360[h)]	72	93
9	**1.0**	**LiHMDS in THF (1.3)**	**DMF**	**-10**	**10**	**80**	**>99**
10	1.0	LiHMDS in THF (1.3)	DMF	-20	10	73	>99
11	1.0	LiHMDS in THF (1.3)	DMF	-30	10	71	>99
12	1.0	LiHMDS in THF (1.3)	DMF	0	10	57	97
13	1.0	NaHMDS in THF (1.3)	DMF	-10	10	58	93
14	1.0	KHMDS in THF (1.3)	DMF	-10	10	44	>99

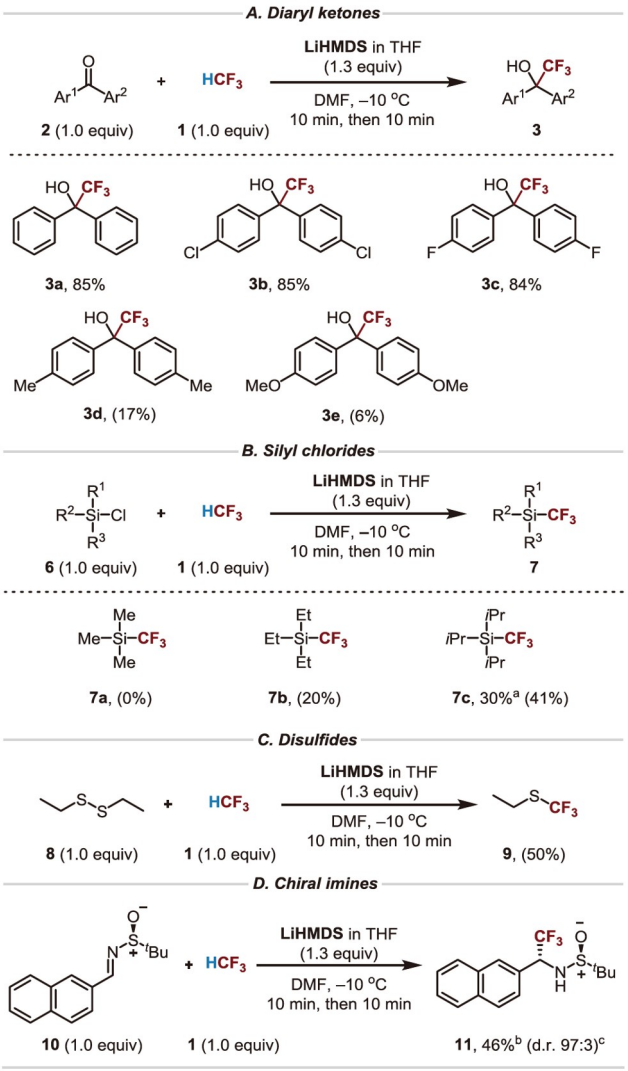
a) Reaction conditions: **4a** (1.0 mmol), **1** (1.0 mmol), solvent (2.0 mL), base (1.0 M in THF, 1.1-1.3 mmol), -10 °C to rt, 10 min to 6 h; for details, see the Supporting Information. b) Determined by ^{19}F NMR spectroscopy analysis using benzotrifluoride or trifluoromethoxybenzene as an internal standard. c) THF (2.0 mL)/HMPA (1.0 mL). d) **1** (0.5 mmol) was first added. e) Under the atmosphere of **1** (1 atm. in a 200 mL-balloon). f) THF (2.0 mL)/HMPA (0.2 mL, 1.0 mmol). g) A solution of **1** (1.0 mmol) was first added. h) -10 °C, 1 h; then rt, 5 h. DME, 1,2-dimethoxyethane.

Subsequently, we investigated the trifluoromethylation of electrophiles other than sulfonyl fluorides with tamed $LiCF_3$ generated in DMF (Scheme 3). Diaryl ketones, bearing electron-neutral and electron-deficient aryl groups, were trifluoromethylated in high yields (**3a-3d**). However, electron-rich diaryl ketones, such as di-*p*-tolylmethanone and bis-(4-methoxyphenyl)methanone, gave the desired products in low yields probably due to their low electrophilicity. Nevertheless, aromatic aldehydes such as 2-naphthaldehyde failed to undergo the desired transformation due to their ready condensation reaction with LiHMDS to form aldmines [24]. It is notable that when HMPA was used as the sole solvent, the use of lithium *tert*-butoxide (^{t}BuOLi) instead of LiHMDS as the base enabled the trifluoromethylation reaction of 2-naphthaldehyde, giving the desired trifluoromethylation product in 40% yield. Although trimethylsilyl chloride (TMSCl) was not a suitable electrophile because of its high reactivity towards LiHMDS (**7a**) (for detail, see the Supporting Information), sterically hindered silyl chlorides were applicable for capturing CF_3^- (**7b** and **7c**), with the sterically bulky triisopropylsilyl chloride (TIPSCl) giving $TIPSCF_3$ (**7c**) in 41% yield. Furthermore, we found that diethyldisulfide, which is less reactive towards LiHMDS than diphenyldisulfide, could take part in the trifluoromethylation with moderate yield (**9**). It is noteworthy that the buffering of the reaction system by the external addition of hexamethyldisilazane (HMDS) is not necessary [10f]. Importantly, the stereoselective trifluoromethylation of chiral *tert*-buylsufinylimine **10** was achieved in moderate yield with high stereocontrol (d.r. 97:3) (Scheme 3D). The relative configuration of sulfinamide **11** was determined by comparing its ^{19}F and ^1H NMR data with those previously reported in literature [25]. The diastereoselectivity can be rationalized by a non-chelation-controlled addition step to give the Cram products, which is consistent with the strong chelation of lithium cation by DMF.

Finally, mechanistic studies of the nucleophilic trifluoromethylation reactions with tamed $LiCF_3$ generated from HCF_3/LiHMDS in DMF were carried out (Scheme 4). The trifluoromethylation reactions using HCF_3 in DMF could proceed through *in situ* deprotonation of HCF_3 followed by trapping of CF_3^- by DMF to produce a reservoir of trifluoromethylating hemiaminolate species [10e,26], and thus both the Grignard-type and the Barbier-type reactions in

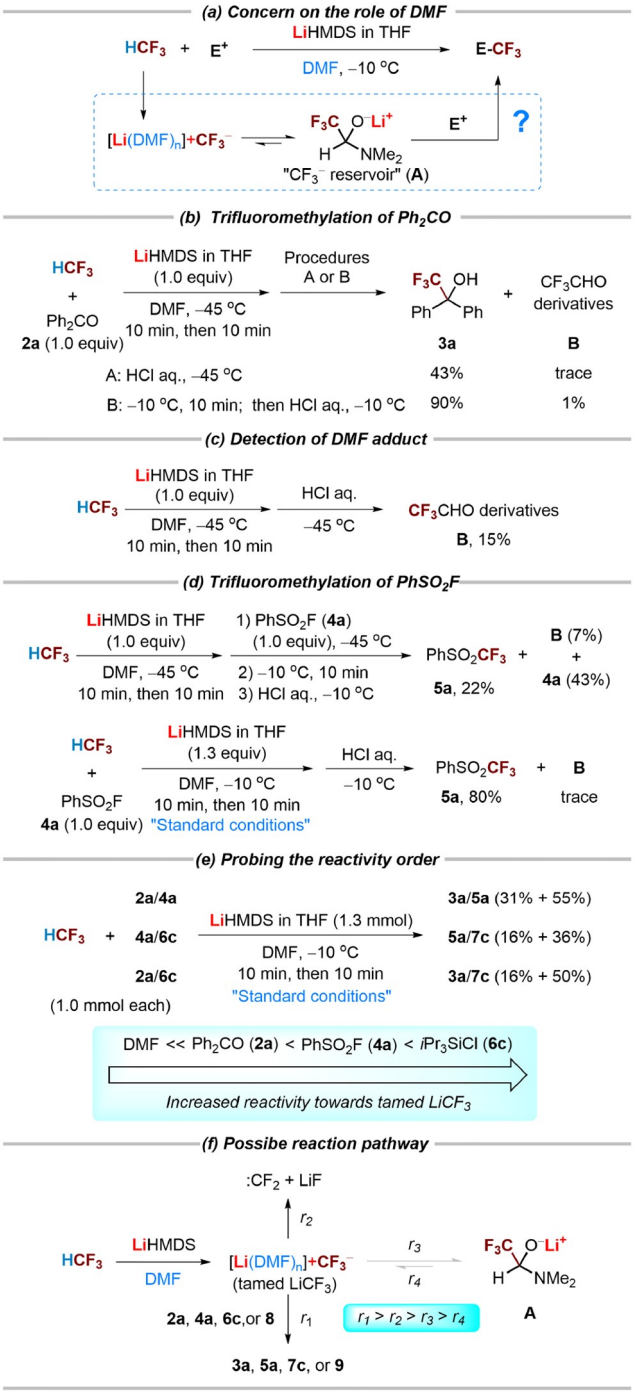


Scheme 2 Substrate scope of arylsulfonyl fluorides. Reaction conditions: **4** (1.0 mmol), **1** (1.0 mmol), solvent (2.5 mL), LiHMDS (1.0 M in THF, 1.3 mmol), –10 °C, 10 min. Isolated yields. Yields determined by ^{19}F NMR analysis with $PhOCF_3$ as an internal standard are shown in the parentheses. a) Contaminated by unreacted **4**.



Scheme 3 Nucleophilic trifluoromethylation of other electrophiles with HCF_3/LiHMDS in DMF: **1** (1.0 mmol), solvent (2.5 mL), LiHMDS (1.0 M in THF, 1.3 mmol), –10 °C, 10 min. Isolated yields. Yields determined by ^{19}F NMR analysis with $PhOCF_3$ as an internal standard are shown in the parentheses. a) The reaction was performed on 15-mmol scale. b) The reaction was performed on 0.5-mmol scale. c) Determined by ^{19}F NMR analysis of the crude reaction mixture.

DMF had been considered as indirect trifluoromethylation process [10f,9d]. Therefore, we studied the potential reservoir role of DMF in our reactions (Scheme 4a). Initially, we tried to detect the $LiCF_3$-DMF adduct **A** at -10 °C according to reported procedures using potassium bases [26a]. However, ^{19}F NMR analysis of the crude mixture after acidic quenching indicated that trifluoromethylated hemiaminaloate **A** was formed in very low yields (13±1%, $n = 4$). To eliminate the possible influence of the reverse-addition reaction, we decided to quench the capture reaction at a lower temperature before the completion of the deprotonation process. By using the trifluoromethylation of Ph_2CO at -45 °C as a probe (Scheme 4b), we found a suitable time point to quench the capture reaction (at -45 °C, 10 mins after the addition of LiHMDS). However, quenching the capture reaction at -45 °C before the completion of deprotonation still led to a much lower yield of CF_3CHO derivatives (15%) (Scheme 4c), as compared with the reaction of Ph_2CO (43%). Moreover, we noticed that no matter whether the trifluoromethylation of Ph_2CO was quenched during (Scheme 4b, Procedure A) or near completion of the process (Scheme 4b, Procedure B), only a trace amount of the CF_3CHO derivatives were detected. These results indicate that in our reaction system, Ph_2CO is much more reactive than DMF, and DMF is not a good trapper of CF_3^-. It is interesting to note that under similar conditions (-10 °C in DMF), the $LiCF_3$ species is less efficient than the KCF_3 species [26c] for the trifluoromethylation of DMF, indicating that the $LiCF_3$ species is more labile than the KCF_3 species. Indeed, we failed to detect $LiCF_3$ species in DMF when the deprotonation of HCF_3 with LiHMDS was conducted at temperatures ranging from -40 °C to -10 °C. Then we probed the possible contribution of the DMF adduct **A** on the trifluoromethylation of $PhSO_2F$ (Scheme 4d). The addition of 1.0 equiv of $PhSO_2F$ into the CF_3-capture system at -45 °C followed by proceeding the reaction under the standard conditions led to the formation of $PhSO_2CF_3$ in a much lower yield than the reaction under the "standard" conditions (22% *vs*. 80%). In



Scheme 4 Mechanistic studies. All the yields were determined by ^{19}F NMR analysis with $PhOCF_3$ as an internal standard. For experimental details, see the Supporting Information. r_1, r_2, r_3, and r_4 refer to the reaction rate of the indicated step.

the former case, the CF_3CHO derivatives were still detected in a substantial amount, implying that the $LiCF_3$-DMF adduct **A**, if any, is a less reactive trifluoromethylator than the directly formed tamed $LiCF_3$. Indeed, the addition of $PhSO_2F$ after a prolonged capture stage led to only a trace amount of $PhSO_2CF_3$ (Section 4.4 in the Supporting Information). At last, the reactivity order of Ph_2CO (**2a**), $PhSO_2F$ (**4a**) and TIPSCl (**6c**) was evaluated by competition experiments (Scheme 4e), showing that **6c** is the most reactive and **2a** is the least reactive. In the competition reaction between **2a** and **6c**, the somewhat higher yield of **7c** than the reaction with only **6c** probably arose from further deprotonation of HCF_3 by the base released from the activation of the side product $^{i}Pr_3Si\text{-}N(TMS)_2$ by the alcoholate of **3a**. Indeed, in this case, **3a** was detected mainly in the form of a silyl ether. Together with DMF, their reactivity towards tamed $LiCF_3$ increases in the following order: DMF << Ph_2CO (**2a**) < $PhSO_2F$ (**4a**) < TIPSCl (**6c**).

The above-mentioned results suggest that the trifluoromethylation of diarylketones, arylsulfonyl fluorides and silyl chlorides employing tamed $LiCF_3$ in DMF is likely a direct nucleophilic trifluoromethylation process, where DMF mainly serves as a lithium chelator to stabilize CF_3^- rather than a CF_3^- reservoir. The possible mechanism of our reaction in DMF is depicted in Scheme 4f. First, the *in situ* deprotonation of HCF_3 by LiHMDS affords CF_3^- in the form of $[Li(DMF)_n]^+CF_3^-$, a tamed $LiCF_3$ with higher stability than $LiCF_3$ itself. Such a tamed $LiCF_3$ is still prone to decomposition as demonstrated by the low yield of the DMF-capturing reaction ($r_2 > r_3$, in Scheme 4f). Then the tamed $LiCF_3$ undergoes CF_3^- transfer reaction with electrophiles, which is faster than that of the decomposition of the tamed $LiCF_3$ ($r_1 > r_2$, in Scheme 4f). This reaction prefers highly reactive electrophiles. However, to facilitate the desired trifluoromethylation reaction, the electrophiles should be less reactive towards hexamethyldisilazide anion than towards CF_3^-. Since DMF is not a good trapper of tamed $LiCF_3$ ($r_2 > r_3$, in Scheme 4f), the contribution of the $LiCF_3$-DMF adduct **A** on the trifluoromethylation reaction is minimal, if any ($r_4 < r_3$, in Scheme 4f).

In conclusion, we have developed the direct nucleophilic trifluoromethylation reaction with a combination of HCF_3 and a lithium base such as LiHMDS in the presence of HMPA or DMF. The reaction proceeds through the deprotonation of HCF_3 by the lithium base followed by the transfer of CF_3^- from tamed $LiCF_3$ that is stabilized by HMPA or DMF. The reactivity of the tamed $LiCF_3$ was probed with a series of electrophiles including DMF, non-enolizable ketones, arylsulfonyl fluorides, and silyl chlorides. It was found that the nucleophilic trifluoromethylation reaction with tamed $LiCF_3$ in DMF is a direct CF_3^- transfer process. This work not only showcases a new protocol for the utilization of the industrial waste fluoroform as the trifluoromethylation reagent, it also provides intriguing insights into the harnessing of nucleophilic reactivity of the transient $LiCF_3$ species.

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