Lithium Acetate-catalyzed Trifluoromethylation of Carbonyl Compounds with (Trifluoromethyl)trimethylsilane

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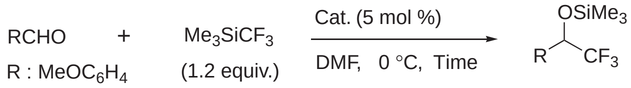
Trifluoromethylation of various aldehydes and ketones with (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of a Lewis base such as lithium acetate proceeded smoothly to afford the corresponding trifluoromethylated adducts in good to high yields.

(Trifluoromethyl)trimethylsilane ($TMSCF_3$) is generally used as a trifluoromethylating reagent because of its nucleophilic character exhibited toward a variety of electrophiles such as aldehydes, ketones,[1] esters,[2] and imines.[3] Although most of the trifluoromethylating reactions are carried out by using such strong bases as fluoride ion or metal alkoxides for the activation of $TMSCF_3$, there are only a few examples of other catalysts such as triethylamine and triethylamine *N*-oxide to be used for their effective promotion.[4]

In our previous papers, lithium 2-pyrrolidone and lithium acetate (AcOLi) were shown to be effectively employed as Lewis base catalysts for the activation of trimethylsilyl (TMS) enolate in aldol, Michael and Mannich-type reactions.[5] In order to demonstrate the utility of AcOLi in synthetic reactions as a Lewis base catalyst, trifluoromethylation of carbonyl compounds by activating carbon-silicon bond of $TMSCF_3$ with AcOLi, a mild and inexpensive Lewis base, was examined. In this communication, we would like to report a convenient method for trifluoromethylation of carbonyl compounds with $TMSCF_3$ by using weak Lewis base catalysts such as AcOLi under mild conditions.

In the first place, trifluoromethylation of 4-methoxybenzaldehyde with $TMSCF_3$ was tried in the presence of 5 mol % of AcOLi at 0 °C in DMF and the desired product was obtained in 98% yield within 10 min. The above reaction proceeded smoothly even when the amount of AcOLi was only 1 mol %. Acetates having such counter cations as sodium, potassium, or ammonium ion also worked effectively and afforded the desired products in high yields. Whereas lithium carboxylates worked as highly active Lewis base catalysts, lithium trifluoroacetate, a weak nucleophile, did not promote the reaction. In the absence of a catalyst the trifluoromethylated adduct was not detected. These results showed the capability of AcOLi to behave as an effective Lewis base catalyst in this trifluoromethylation.

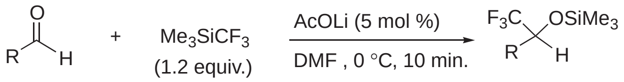
Table 1. Screening of various catalysts on trifluoromethylation

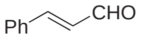
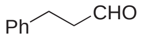
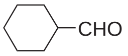


Entry	Cat.	Time /min.	Yield[a] /%
1	AcOLi	10	98 (97)[b]
2	AcOLi	10	97[c]
3	AcONa	10	96
4	AcOK	10	99
5	AcO-*n*NBu$_4$	10	97
6	*t*-BuCO$_2$Li	10	98
7	PhCO$_2$Li	10	96
8	CF$_3$CO$_2$Li	120	0
9	none	120	0

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield. [c]1 mol % of AcOLi was used.

Table 2. AcOLi-catalyzed trifluoromethylation of various aldehydes



Entry	Aldehyde	Yield[a]/%	Entry	Aldehyde	Yield[a]/%
1	4-Me$_2$NC$_6$H$_4$CHO	97	5		93
2	PhCHO	91	6		70
3	4-MeO$_2$CC$_6$H$_4$CHO	91	7		81
4	4-NO$_2$C$_6$H$_4$CHO	97			

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

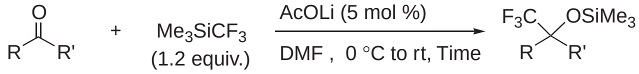
Next, trifluoromethylation of carbonyl compounds with $TMSCF_3$ were tried by using AcOLi catalyst in DMF (Table 2). Various aldehydes worked as good acceptors of $TMSCF_3$ under the above reaction conditions; both aromatic aldehydes having either electron-donating or -withdrawing group and aliphatic aldehydes alike reacted rapidly to afford the corresponding trifluoromethylated products in high yields.

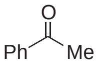
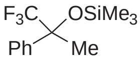
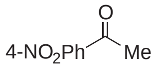
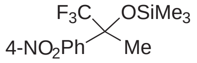
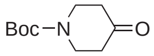
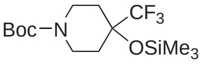
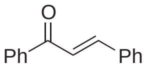
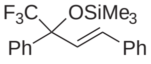
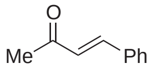
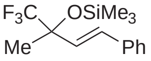
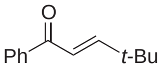
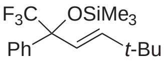
Ketones also worked as good acceptors of this reaction (Table 3), and 1,2-addition products were obtained in good yields when α,β-unsaturated ketones were employed. However, 1,4-addition product was not detected in each case (Entries 4–6).

The effect of solvents was examined by taking the reaction of 4-methoxybenzaldehyde and $TMSCF_3$ in the presence of AcOLi or tetrabutylammonium acetate (AcON*n*-Bu$_4$) as a model reaction. The reaction proceeded smoothly in DMF or in DMSO when AcOLi was used as a catalyst. As shown in Table 4, it proceeded smoothly in various other solvents as well when a catalytic amount of AcON*n*-Bu$_4$ was used. Although the difference between the reactivity of AcOLi and that of AcON*n*-Bu$_4$ is not yet clearly explained, the reaction is considered to proceed via two different mechanisms.

Assumed catalytic cycle of the present reaction is illustrated in Scheme 1. In the first place, a Lewis base catalyst coordinates to silicon atom of $TMSCF_3$ to form a hypervalent silicate **A**. For the next step, two different pathways may be considered: that is,

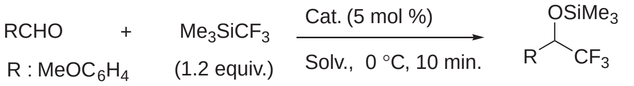
Table 3. AcOLi-catalyzed trifluoromethylation of various ketones



Entry	Ketone	Time /h	Product	Yield[a]/%
1		2		84[c]
2		1		95
3		1		80 (96)[b]
4		1		97 (97)[b]
5		2		97[c]
6		4		91[d]

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The result using AcON*n*-Bu$_4$ in THF was shown in parentheses. [c]1.5 equiv. of TMSCF$_3$ were used. [d]2.0 equiv. of TMSCF$_3$ were used.

Table 4. Effect of solvents on trifluoromethylation

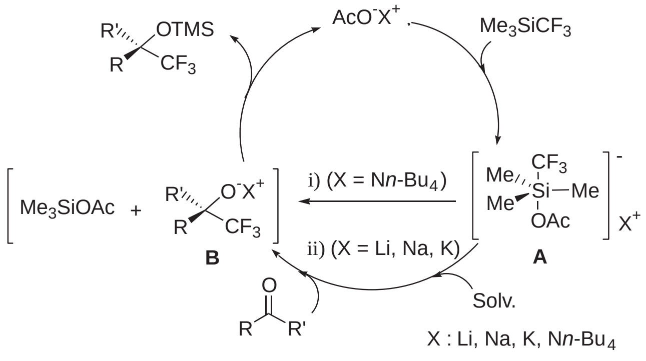


Entry	Solvent	Yield[a]/% AcOLi	Yield[a]/% AcON*n*-Bu$_4$
1	THF	0	96
2	CH_2Cl_2	0	95
3	AcOEt	0	99
4	Toluene	0	98
5	DMF	98	97
6	DMSO	96[b]	95[b]
7	CH_3CN	0	70

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The reaction was carried out at room temperature.

i) when an ammoniun ion was used as a counter cation, the nucleophilicity of the silicate **A** is sufficient to react with carbonyl compounds to form alkoxide **B** and TMSOAc. On the other hand, ii) when alkaline metal ions such as Li, Na, or K were used, the nucleophilicity of the silicate is enhanced by further coordination of strongly electron-donating solvent such as DMF or DMSO for the attack of carbonyl compounds to form **B** and TMSOAc. Subsequent silylation of **B** by thus formed TMSOAc afforded *O*-silyl ether along with the regeneration of the catalyst to establish a catalytic cycle.

Thus, it is noted that AcOLi works as an effective Lewis base catalyst in trifluoromethylation that proceeds via the activation of carbon–silicon bond of TMSCF$_3$. This method is quite practical since it only needs such a mild, readily available and inexpensive Lewis base catalyst, namely, AcOLi. Further study on this reaction is now in progress.



Scheme 1.

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