Lewis Base-catalyzed Trifluoromethylation of Aldimines with (Trifluoromethyl)trimethylsilane

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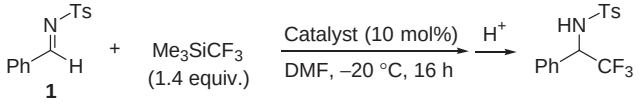
A catalytic trifluoromethylation of various aldimines with (trifluoromethyl)trimethylsilane in the presence of Lewis bases such as lithium acetate or benzoate proceeded smoothly to afford the corresponding trifluoromethylated adducts in good yields.

Trifluoromethylated compounds exhibit important functions due to their electronic properties and great potentials for biologically active drugs and agrochemicals. The introduction of a trifluoromethyl group into organic molecule is accomplished generally by treating (trifluoromethyl)trimethylsilane ($TMSCF_3$) with electrophiles such as aldehydes, ketones, and esters.[1] However, only a few examples have been reported on an effective trifluoromethylation of imines that are weak electrophiles toward $TMSCF_3$[2] and still less, a catalytic trifluoromethylation of imine.[3]

In our previous papers, the nitrogen- and oxygen-containing anions generated from amides, imides, carboxylic acids, or alcohols were shown to be effectively used as Lewis base catalysts for the activation of trimethylsilyl (TMS) enolate in aldol, Michael and Mannich-type reactions.[4] Further, trifluoromethylation of carbonyl compounds with $TMSCF_3$ was recently reported from our laboratory, which was carried out in the presence of lithium acetate (AcOLi) demonstrating usefulness of the acetate as a Lewis base catalyst.[5] In this communication, we would like to describe an effective method for trifluoromethylation of imines with $TMSCF_3$ under mild conditions by using a catalytic amount of Lewis base such as AcOLi.

In the first place, various Lewis base catalysts were examined by taking the reaction of *N*-tosylaldimines **1** with $TMSCF_3$ in the presence of 10 mol % of a catalyst at −20 °C in DMF as a model (Table 1). When the catalyst was absent, the trifluoromethylated adduct was not detected (Entry 1). On the other hand, several lithium carboxylates such as lithium benzoate, acetate and pivalate worked as effective Lewis base catalysts (Entries 3–6). It is noted here that lithium ion was an effective counter cation of the carboxylates for these reactions (Entries 7–9). Of these carboxylates, however, weakly nucleophilic lithium trifluoroacetate did not promote this reaction (Entry 2). While tifluoromethylation reactions did not proceed effectively when they were carried out in the presence of CsF or BnOLi (Entries 10 and 11).

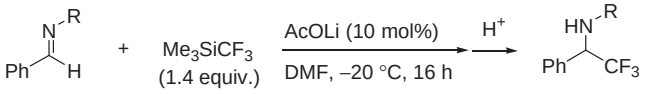
Table 1. Screening of various catalysts on trifluoromethylation



Entry	Catalyst	Yield[a] /%	Entry	Catalyst	Yield[a] /%
1	none	N.D.[b]	7	AcONa	86
2	CF_3CO_2Li	N.D.	8	AcOK	67
3	$PhCO_2Li$	94	9	AcO*n*-Bu_4	79
4	*t*-$BuCO_2Li$	87[b]	10	BnOLi	37[b]
5	AcOLi	93 (91)[c]	11	CsF	30[b]
6	AcOLi	95[b]			

[a]Each yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The reaction was carried out for 40 h. [c]Isolated yield.

Table 2. Effect of substituents on the nitrogen of aldimine



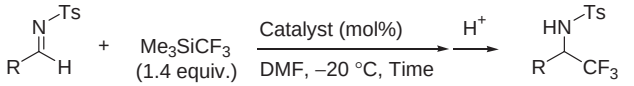
Entry	R	Yield[a] /%	Entry	R	Yield[a] /%
1	4-$MeC_6H_4SO_2$	93	4	$P(O)Ph_2$	75[b,c]
2	4-$ClC_6H_4SO_2$	82	5	Ph	N.D.
3	4-$NO_2C_6H_4SO_2$	93	6	Bn	N.D.

[a]Each yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]2.0 equiv. of $TMSCF_3$ were used. [c]The reaction was carried out at room temperature.

Lewis base-catalyzed trifluoromethylation was further examined by using other aldimines in the presence of a catalytic amount of AcOLi in DMF (Table 2). It was found then that the reactivity of this reaction depended on electrophilicities of the imines.[2g] When *N*-sulfonylimines and *N*-phosphinoylimines were used, the reactions proceeded smoothly under the same reaction conditions and the desired products were obtained in good yields (Entries 1–4). On the other hand, no desired products were detected when weak electrophiles such as *N*-phenylaldimine or *N*-benzylaldimine was used (Entries 5 and 6).

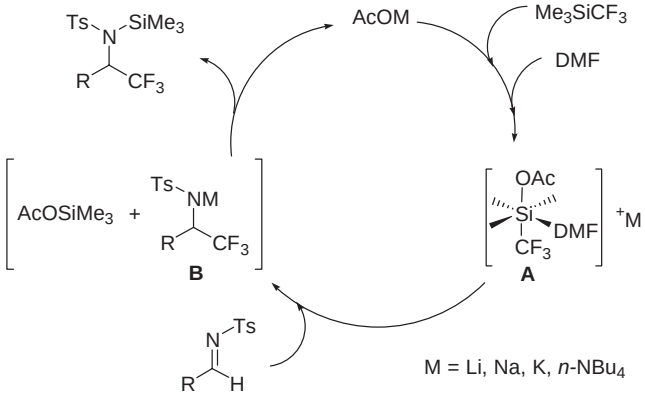
Next, the reaction of various *N*-tosylaldimines with $TMSCF_3$ was tried by using 10 mol % of AcOLi in DMF (Table 3). Aromatic aldimines having electron-donating or -withdrawing groups reacted smoothly to afford the trifluoromethylated adducts in good yields. Whereas aliphatic aldimines having no α-protons adjacent to the imino group reacted smoothly to afford the desired adduct in high yields, those with α-protons did not undergo the trifluoromethylation because of the competitive abstraction of α-proton that took place. Then, various Lewis bases were screened and reaction conditions were optimized in order to improve the yields. Consequently, the corresponding trifluoromethylated adducts were obtained in moderate to high yields when the reactions were carried out in the coexistence of an equimolar amount of PhOLi (Entries 12–14).

Table 3. Trifluoromethylation of various aldimines



Entry	R	Catalyst mol %	Time /h	Yield[a] /%
1	4-$MeOC_6H_4$	AcOLi (10)	40	83
2	4-MeC_6H_4	AcOLi (10)	40	82
3	4-ClC_6H_4	AcOLi (10)	16	93
4	4-BrC_6H_4	AcOLi (10)	16	80
5	4-$NO_2C_6H_4$	AcOLi (10)	16	92
6	2-Naphthyl	AcOLi (10)	16	92
7	2-Furyl	AcOLi (10)	16	86
8	4-Pyridyl	AcOLi (10)	16	89
9	*trans*-PhCH=CH	AcOLi (10)	16	78[b]
10	*t*-Bu	AcOLi (10)	40	90
11	*c*-C_6H_{11}	AcOLi (10)	40	trace
12	*c*-C_6H_{11}	PhOLi (100)	1	80[c,d]
13	*i*-Pr	PhOLi (100)	1	65[c,d]
14	$PhCH_2CH_2$	PhOLi (100)	1	35[c,d]

[a]Each yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]2.0 equiv. of $TMSCF_3$ were used. [c]The combined solution of imine and $TMSCF_3$ in DMF was added slowly to the DMF solution of PhOLi. [d]The reaction was carried out at 0 °C.



Scheme 1.

An assumed catalytic cycle of the present reaction is illustrated in Scheme 1. In the first step, Lewis base and DMF coordinate to the silicon atom of $TMSCF_3$ to form a hypervalent silicate **A**. The nucleophilicity of the silicate **A** is sufficient for the reaction with imines and it forms a *N*-lithiated **B** together with TMSOAc. Subsequent silylation of **B** by thus formed TMSOAc affords *N*-silyl amine along with the regeneration of the catalyst and to establish the catalytic cycle.

Thus, it is noted that a catalytic trifluoromethylation of various aldimines with $TMSCF_3$ by using Lewis base catalysts such as lithium acetate and lithium benzoate proceeded smoothly via the activation of carbon–silicon bond of $TMSCF_3$. This method can be quite effective since the reaction proceed smoothly by using a catalytic amount of a Lewis base. Further investigation on this reaction is now in progress.

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6 Typical experimental procedure is as follows (Table 1, Entry 5); to a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (1.0 mL) were added successively a solution of *N*-tosylbenzaldimine (103.7 mg, 0.4 mmol) in DMF (0.2 mL) and $TMSCF_3$ (87.3 μL, 0.56 mmol, 95% content) at −20 °C. The mixture was stirred for 16 h at the same temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the resulted residue was purified by preparative TLC to give the desired product (119.9 mg, 91%) as a white powder.

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