# JOC*Article*

Facile Synthesis of TMS-Protected Trifluoromethylated Alcohols Using Trifluoromethyltrimethylsilane (TMSCF$_3$) and Various Nucleophilic Catalysts in DMF

G. K. Surya Prakash,* Chiradeep Panja, Habiba Vaghoo, Vijayalakshmi Surampudi, Roman Kultyshev, Mihirbaran Mandal, Golam Rasul, Thomas Mathew, and George A. Olah

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, 837 Bloom Walk, Los Angeles, California 90089-1661

gprakash@usc.edu
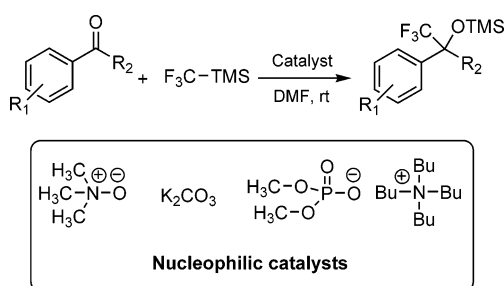
Organofluorine compounds are becoming increasingly important in different fields, such as material science, agro chemistry, and the pharmaceutical industry. Nucleophilic trifluoromethylation is one of the widely used methods to incorporate a trifluoromethyl moiety into organic molecules. We have carried out extensive studies to develop varieties of easily accessible nucleophilic catalysts to promote such reactions. TMS-protected trifluoromethylated alcohols were prepared from both aldehydes and ketones in excellent yields using catalytic amount of amine N-oxide. Carbonate and phosphate salts also showed efficient catalytic activity toward this reaction. These reactions were highly solvent dependent, and DMF was found to be the most suitable one among the various solvents studied. All these reactions proceeded under very mild conditions, giving clean products and avoiding the use of any fluoride initiators or expensive catalysts, and extremely water-free conditions. The mechanism for the reaction is discussed in detail. DFT calculations were performed on the possible reaction intermediates using the Gaussian 03 program at B3LYP/6-311+G* level to support the proposed mechanism.

Introduction

Fluorine, because of its unique electronic property and its size, quite often imparts specific beneficial properties to organic molecules.[1] Fluoroorganics have important applications in different fields, such as material science, agro chemistry, and the pharmaceutical industry.[2] Significant work has been carried out in past decade to incorporate a fluorinated moiety in organic molecules. TMSCF$_3$, which was first prepared by Ruppert et al.,[3] became the Ruppert−Prakash reagent,[4] after our group has extensively used[5] it as a versatile reagent to incorporate a trifluoromethyl group into organic compounds by nucleophilic activation. Fluoride sources, such as TBAF, TBAT, TMAF, or CsF, have been widely used as nucleophilic initiators for the trifluoromethylation reaction of different electrophiles for the past several years by different groups,[6] including our own.[3] However, the reactions are not catalytic with respect to the initiators used. Further, these initiators are very sensitive to moisture.

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.

(2) Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds. *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis, and Applications*; VCH: New York, 1988.

(3) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *24*, 2195.

(4) (a) Large-Radix, S.; Billard, T.; Langlois, B. R. *J. Fluorine Chem.* **2003**, *124*, 147. (b) Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873. (c) Also see: Thayer, A. M. *Chem. Eng. News* **2006**, June 5, p 15.
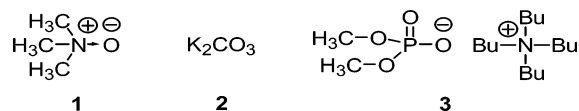
FIGURE 1. Nucleophilic catalysts containing oxygen.

On the other hand, considerable advancement has been made during the past few years for the Lewis base catalyzed reactions, using silylated reagents.[7] Recently, trifluoromethylation has been studied using nucleophilic catalysts, such as tri-*tert*-butyl phosphine,[8] *N*-heterocyclic carbene (NHC),[9] and molecular sieves [10] in DMF or DMSO. Among the Lewis base catalysts, oxygen-containing nucleophiles are more efficient due to the high bond strength as well as the kinetic lability of the silicon−oxygen bond. Therefore, oxygen-containing nucleophiles are suitable initiators or catalysts in TMSCF₃ chemistry. Metal alkoxides[1] have been used in trifluoromethylation reactions using TMSCF₃, but due to their high basicity, they are not suitable in most cases. Hence, a search for milder oxygen-containing nucleophiles, which are catalytic in nature, less basic, cost-effective, and simple to use, has been carried out. Herein, we report our results obtained from our recent studies on nucleophilic trifluoromethylation with milder oxonucleophiles (Figure 1).

Results and Discussion

To validate our outlined approach, we have screened the reactivity of commercially available amine oxides, such as

(5) (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393. (b) Prakash, G. K. S.; Ramaiah, R. *Synlett* **1991**, 643. (c) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (d) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173. (e) Prakash, G. K. S.; Tongco, E. C.; Mathew, T.; Vankar, Y. D.; Olah, G. A. *J. Fluorine Chem.* **2000**, *101*, 199. (f) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2000**, *40*, 589. (g) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77. (h) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 589. (i) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847. (j) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718. (k) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (l) Mloston, G.; Prakash, G. K. S.; Olah, G. A.; Heimgartner, H. *Helv. Chim. Acta* **2002**, *85*, 1644. (m) Prakash, G. K. S.; Mandal, M.; Panja, C.; Mathew, T.; Olah, G. A. *J. Fluorine Chem.* **2003**, *123*, 61.

(6) (a) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (b) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572. (c) Petrov, V. A. *Tetrahedron Lett.* **2000**, *41*, 6959. (d) Li, N. S.; Tang, X. P.; Piccirilli, J. *Org. Lett.* **2001**, *3*, 1025. (e) Sevenard, D. V.; Kirsch, P.; Röschenthaler, G. V.; Movchun, V. N.; Kolomeitsev, A. A. *Synlett* **2001**, 379. (f) Benayoud, F.; Abouabdellah, A.; Richard, C.; Bonnet-Delpon, D.; Bēgue, J. P.; Levasseur, D.; Boutaud, O.; Schuber, F. *Tetrahedron Lett.* **2000**, *41*, 6367. (g) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635.

(7) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. (c) Denmark, S. E.; Coe, D. E.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (d) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K. T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (e) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (f) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (g) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2889. (h) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. I. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (i) Denmark, S. E.; Stavenger, R. A.; Wong, K. T. *J. Org. Chem.* **1998**, *63*, 918. (j) Denmark, S. E.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 9524. (k) Mukaiyama, T.; Nakagawa, T.; Fujisawa, H. *Chem. Lett.* **2003**, *32*, 56. (l) Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. *Chem. Lett.* **2004**, *33*, 1016.

(8) Mizuta, S.; Shibata, N.; Sato, T.; Fujimoto, H.; Nakamura, S.; Toru, T. *Synlett* **2006**, 267.

(9) Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 2193.

(10) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112.

SCHEME 1. CF₃ Transfer to Aldehydes Using Trimethylamine *N*-Oxide as a Catalyst in DMF
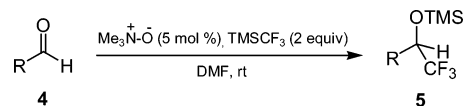
pyridine *N*-oxide, *p*-chloropyridine *N*-oxide, *N*,*N*-dimethylpyridine *N*-oxide, and trimethylamine *N*-oxide. During our earlier studies, we were able to develop an efficient catalytic method for the preparation of TMS-protected trifluoromethylated alcohols from a variety of aldehydes using trimethylamine *N*-oxide as a recoverable nucleophilic catalyst. This methodology is applicable for base-sensitive substrates. The work has been recently published.[5m]

In the previous methodology, our catalyst loading was too high. To overcome this problem, we began to investigate this reaction under different conditions. Finally, while trying to study the effect of solvent on the rate of the reaction, we found that DMF as a solvent has a very significant effect on the reaction rate (Scheme 1). The catalyst loading can be reduced 10-fold (from 50 to 5 mol %). For reactions in DMF, the amount of TMSCF₃ used can also be reduced further with substantial increase in product yields. We can even further reduce the loading of the catalyst to 2 mol %. However, more time is required to complete the reaction. Table 1 shows the results for the reaction of different aldehydes with TMSCF₃ using trimethylamine *N*-oxide as a catalyst and DMF as the solvent.

TABLE 1. CF₃ Transfer to Aldehydes Using Trimethylamine *N*-Oxide as a Catalyst in DMF

entry	aldehydes (4a-i)	time (min)	products (5a-i)	yields (%)
a		12		87
b		8		89
c		8		90
d		12		88
e		24		90
f		24		86
g		12		88
h		12		82
i		12		76

TABLE 2. CF₃ Transfer to Ketones Using Trimethylamine *N*-Oxide as a Catalyst in DMF

entry	R₁	R₂	product	conv. (%)[a]	yield (%)[b]
a				74	62
b				75	51
c				100	80
d				100	90
e				96	84
f				80	69
g				80	81
h				83	50

[a] The rest is starting material. [b] Yields are calculated on the basis of conversion.

TABLE 3. Various Useful Nucleophilic Catalysts in Trifluoromethylation

entry	catalyst	time	conv. (%)
i	K₂CO₃	5 min	100
ii	Na₂CO₃	30 min	100
iii	Li₂CO₃	16 h	100
iv	CH₃COONa	20 min	100
v	HCOOAg	15 min	100
vi	KHCO₃	3 days	90
vii	NaHCO₃	3 days	80
viii	(NH₄)₂CO₃		

α,β-Unsaturated aldehyde (Table 1, **4i**) exclusively gives 1,2-addition product (Table 1, **5i**). Pyridine *N*-oxide can also act as a catalyst for this reaction. However, as shown in our previous study, trimethylamine *N*-oxide is found to be the most efficient amine *N*-oxide catalyst. In our earlier report, we mentioned that reactions of ketones do not progress under similar conditions. Present investigations on aromatic ketones containing an electron-withdrawing group showed substantial improvement when DMF was used as the solvent. However, reaction of ketones having an electron-donating group is sluggish toward this reaction. The results are shown in Table 2.

Encouraged by these results, we decided to explore this reaction further and perform the reaction by forming the amine

TABLE 4. Effect of Solvents in K₂CO₃-Catalyzed Reaction

entry	solvents	time	conv. (%)	yield (%)
i	DMF	5 min	100	86
ii	THF	overnight	60	
iii	THF + DMF (4:1)	10 h	100	80
iv	DCM	48 h	<5	
v	DCM + DMF (4:1)	1 h	100	78
vi	DMSO	5 min	100	78

TABLE 5. CF₃ Transfer to Aldehydes Using K₂CO₃ as a Catalyst in DMF

entry	aldehydes (**4a-k**)	time (min)	products (**5a-k**)	yields (%)
a		5		80
b		5		80
c		5		81
d		5		73
e		15		78
f		10		73
g		5		85
h		5		86
i		10		87
j		15		74
k		10		90

N-oxide catalyst in situ from the precursor amine. We first prepared the amine *N*-oxide in situ following the conventional procedure[11] using MCPBA and then performed the CF₃ transfer reaction in one pot. Interestingly, the reaction was found to be

TABLE 6. CF$_3$ Transfer to Ketones Using K$_2$CO$_3$ as a Catalyst in DMF

entry	R$_1$	R$_2$	catalyst (mol%)	TMSCF$_3$ (equiv)	time (h)	product	yield (%)
d	4-O$_2$N-C$_6$H$_4$	C$_6$H$_5$	10	1.5	1.5		85
g	4-Br-C$_6$H$_4$	C$_6$H$_5$	10	1.5	1.5		75
i	C$_6$H$_5$	C$_6$H$_5$	20	3.0	10		80
j	4-Cl-C$_6$H$_4$	C$_6$H$_5$	10	1.5	3		80
k	4-Br-C$_6$H$_4$	4-Br-C$_6$H$_4$	10	1.5	1		67
l	4-Ph-C$_6$H$_4$	C$_6$H$_5$	10	2.0	8		90
m	4-Me-C$_6$H$_4$	C$_6$H$_5$	20	3.0	24		76
n	4-MeO-C$_6$H$_4$	C$_6$H$_5$	20	3.0	24		67
o[a]	C$_6$H$_5$	—CH$_3$	10	1.5	3		67
p[a]	4-Cl-C$_6$H$_4$	—CH$_3$	10	1.5	3		85
q[a]	4-F$_3$C-C$_6$H$_4$	—CH$_3$	10	1.5	3		65

[a] Silylenol ether (5−10%) of the corresponding ketones was obtained.

complete within a few minutes. To rationalize this significant rate acceleration, we performed several control reactions and found that K$_2$CO$_3$ (which was used as a base) was responsible for the rate enhancement.

After a thorough literature search, we found a recent report by Yan et al.[12] where K$_2$CO$_3$ had been used as a catalyst in a "cyano-silylation" reaction. In the case of CF$_3$ transfer, there were some initial reports[13] of using carbonate salts as initiators with trifluoromethyltriethylsilane in DMF with limited applica-

tion. However, the efficiency of carbonates as catalysts for CF$_3$ transfer from TMSCF$_3$ in DMF has not been explored much. Therefore, we decided to revisit this arena and studied the trifluoromethylation reaction using different carbonate and bicarbonate salts as catalysts. The results are shown in Table 3.
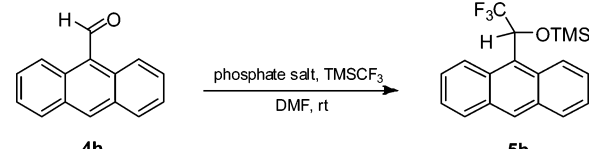
Reactions are found to be quantitative in the presence of catalysts **i**−**v** listed in Table 3. However, proton-containing catalysts (**vi**−**viii**) show low efficiency (no reaction was observed for (NH$_4$)$_2$CO$_3$, Table 3, entry **viii**). Recently, the use of lithium acetate as a catalyst in similar reactions has been

(11) (a) O'Neil, I. A.; Miller, N. D.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1995**, 617. (b) O'Neil, I. A.; Miller, N. D.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1995**, 619.

(12) Bin, H.; Yan, L.; Xiaoming, F.; Guolin, Z. *Synlett* **2004**, *10*, 1776.

(13) Nelson, D. W.; O'Reilly, N. J.; Speier, J.; Gassman, P. G. *J. Org. Chem.* **1994**, *59*, 8157 and references therein.

TABLE 7.   Phosphate Salts as Nucleophilic Catalysts

entry	phosphate	amount (mol%)	time	TMSCF$_3$ (equiv)	yield (%)
i	K$_3$PO$_4$	5	2 h	1.5	86
ii	K$_2$HPO$_4$·3H$_2$O	5	30 min	1.5	85
iii	KH$_2$PO$_4$	5	16 h	1.5	80
iv	(OMe)$_2$P(O)(O$^-$)($^+$NBu$_4$)	2	5 min	1.2	92

SCHEME 2.   CF$_3$ Transfer to Aldehydes Using K$_2$CO$_3$ as a Catalyst in DMF
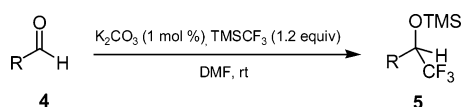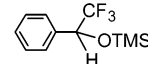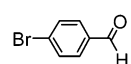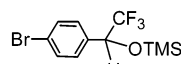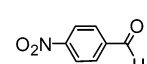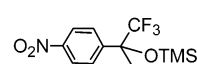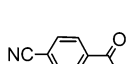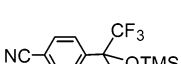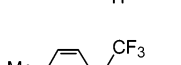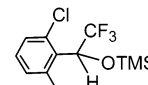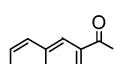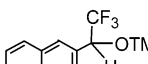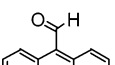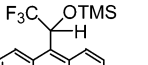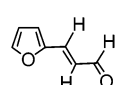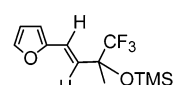
discussed by Mukayama and co-workers.[14] Since K$_2$CO$_3$ gave the best result (Table 3, entry **i**), we decided to explore its role in the CF$_3$ transfer reactions in different solvent systems.

The bidentate nature of K$_2$CO$_3$ makes it different and unique from other well-known monodentate initiators or catalysts used so far for CF$_3$ transfer reactions. We performed the trifluoromethylation reactions with a catalyti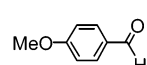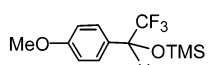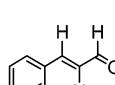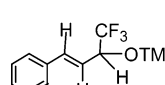c amount of K$_2$CO$_3$ using different solvent systems (Table 4). DMF, in this case also, appeared to be the most efficient solvent (Table 4, entry **i**). The high dielectric constant of DMF may be playing an important role in stabilizing the reaction transition state, which in turn makes the reaction more facile. Thus, we found that DMSO also behaves similarly toward this reaction (Table 4, entry **vi**).

Both aldehydes and ketones undergo this reaction, giving only the trimethylsilyl-protected trifluoromethylated alcohols, and no deprotected alcohols were observed. Scheme 2 and Tables 5 and 6 illustrate the scope of this reaction using K$_2$CO$_3$ as the catalyst. Aldehydes containing both electron-withdrawing as well as electron-donating groups undergo CF$_3$ transfer efficiently (Table 5). In the case of ketones, significant variation was observed (Table 6, entries **m** and **n**). Furthermore, enolizable ketones (Table 6, entries **o**–**q**) were found to give small amounts of silylenol ethers as byproducts.

To overcome the enolization problem associated with enolizable ketones in the presence of the basic catalyst, we began to explore the catalytic efficiency of less basic salts, such as nitrate, sulfate, or phosphates. Phosphate salts were found to be very effective catalysts for the CF$_3$ transfer reaction, keeping the enolization to a minimum (Table 9, entries **o**–**q**). We probed the catalytic activity of the mono-, di-, and tribasic potassium phosphates for the trifluoromethylation reaction of 9-anthraldehyde (**4h**) in DMF, and the results are shown in Table 7. The diphosphate was found to be more reactive, may be due to its water of crystallization, which helps to increase its solubility in DMF (Table 7, entry **ii**). So far, to our best knowledge, phosphate salts have not been used as catalysts in trifluoromethylation reactions. Subsequently, we looked for metal-free

(14) (a) Mukaiyama, T.; Kawano, Y.; Fujisawa, H. *Chem. Lett.* **2005**, *34*, 88. (b) Kawano, Y.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 422. (c) Kawano, Y.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 894. (d) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 304.

TABLE 8.   CF$_3$ Transfer to Aldehydes Using Phosphate (3) as a Catalyst in DMF

entry	aldehydes (4a-k)	time (min)	products (5a-k)	yields (%)
a		5		77
b		5		70
c		5		75
d		5		80
e		15		85
f		5		87
g		5		90
h		5		92
i		10		91
j		15		87
k		10		86

phosphate catalysts, which could be more useful in different synthetic applications, where metal salts are less preferred.

We anticipated that the phosphate catalyst (**3**), which is prepared easily following the literature procedure,[15] would be a suitable candidate as an effective nucleophilic catalyst due to its enhanced solubility in DMF. Catalyst **3** turned out to be excellent and gave very promising results for the trifluoromethylation reaction. The results for the reaction with aldehydes (Scheme 3) and ketones are summarized in Tables 8 and 9, respectively. The amount of the silylenol ethers formed from enolizable ketones using phosphate catalyst **3** is less compared to that obtained from the K$_2$CO$_3$-catalyzed reaction (Table 9, entries **o**–**q**).

Mechanism

We have already discussed the mechanism of trifluoromethylation using trimethylamine *N*-oxide as a catalyst in our

(15) Phan, M. R.; Poulter, C. D. *J. Org. Chem.* **2001**, *66*, 6705.

TABLE 9. CF$_3$ Transfer to Ketones Using Phosphate (3) as a Catalyst in DMF

| entry	R$_1$	R$_2$	catalyst (mol%)	TMSCF$_3$ (equiv)	time (h)	product	yield (%)
d			5	1.5	1		87
e			10	1.5	1		81
g			5	1.5	1		94
i			10	2.5	16		65
l			10	2.0	12		74
m			20	2,5	24		65
n			20	2.5	24		55
o[a]		—CH$_3$	5	1.5	2		70
p[a]		—CH$_3$	5	1.5	1		85
q[a]		—CH$_3$	5	1.5	0.5		72

[a] Silylenol ether (1−6%) of the corresponding ketones was obtained.

SCHEME 3. CF$_3$ Transfer to Aldehydes Using Phosphate (3) as a Catalyst in DMF
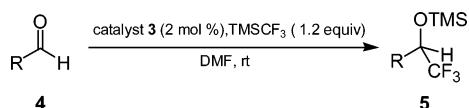
previous publication.[5m] A possible mechanism for the bidentate, potassium carbonate catalyzed reaction is shown in Scheme 4. It is important to note that free alcohol was never obtained even after using an excess of the catalysts, which itself supports the true catalytic (vide supra) nature of the reaction. As indicated in Scheme 4, we can envision route "**a**", wherein only a single anionic center is involved in the attack of TMSCF$_3$ to form the trigonal bipyramidal intermediate **i**. This intermediate **i** can form the hexavalent intermediate **ii** by further expanding the valency of silicon, which has a low-lying empty d orbital. Our theoretical study on intermediate **ii** supports such a possibility. Subsequently, either the pentavalent (**i**) or the hexavalent intermediate (**ii**) can undergo attack by the aldehydes or ketones to form the second set of intermediates (**iii** and **iv**), which can then decompose to give the product and regenerate the catalyst. Alternatively, both the anionic centers in the catalyst can simultaneously attack two molecules of TMSCF$_3$ to give rise to a double trigonal bipyramidal intermediate (**v**), wherein the carbonate can occupy the axial positions of both the trigonal bipyramids. Intermediate **v** can further react with two molecules of carbonyl compounds to give the intermediate **vi** from which trifluoro-

SCHEME 4.   Possible Mechanism with Potassium Carbonate as Catalyst
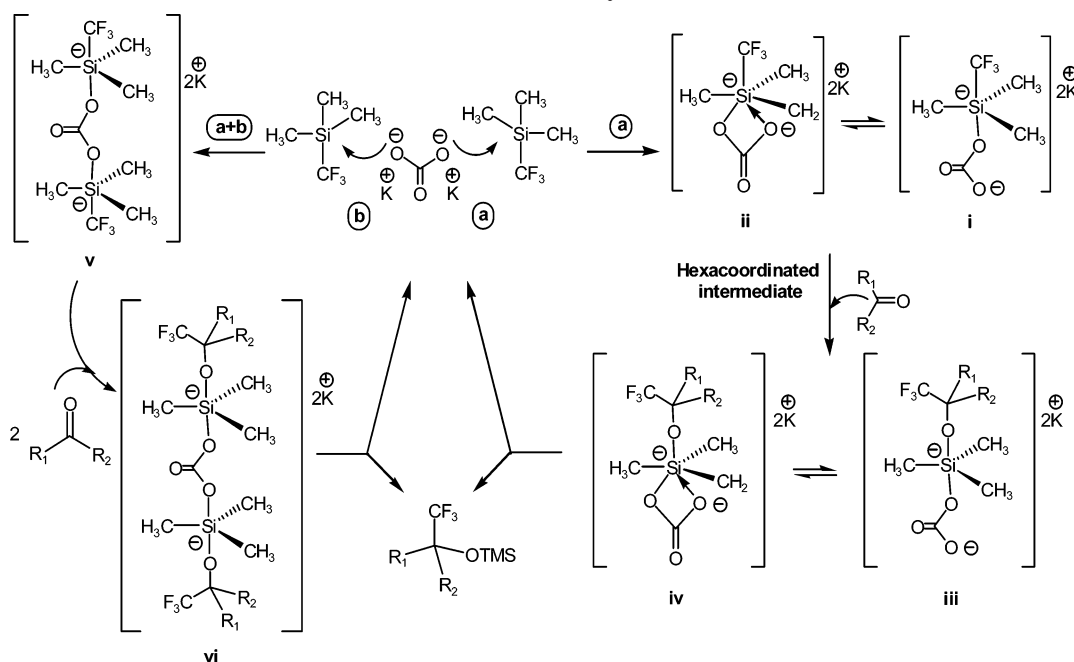
methylated product is formed with regeneration of the catalyst. This path is illustrated in Scheme 4 through route "**a+b**". Calculations on intermediate **v** also support the possibility of such a complex formation. The reaction can proceed via any one of the routes described above or by a combination of both the routes.

On the other hand, monobasic phosphate catalyzed reactions can proceed in a similar fashion as described for the trimethylamine *N*-oxide catalyzed reaction. With tri- and dibasic phosphates (Table 7, entries **i** and **ii**), we can think of similar mechanisms as mentioned for the potassium carbonate catalyzed reaction. Use of bidentate or tridentate catalysts can open up new possible mechanistic pathways for the trifluoromethylation reactions using TMSCF₃.

To rationalize the various mechanistic pathways, we performed DFT calculations at the B3LYP/6-311+G* level for complexation of TMSCF₃ with CO_3^{2-}.
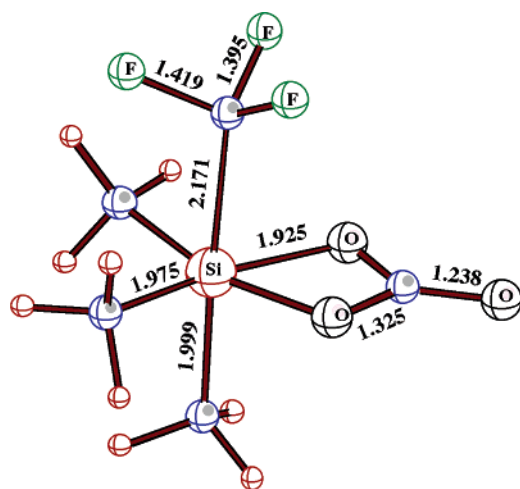
ii, C_s (E = -1010.94598 Hartrees)

FIGURE 2. B3LYP/6-311+G* calculated structure of **ii**.

Calculations of the Structure of the Complex of TMSCF₃ and CO_3^{2-}

Calculations were performed using the Gaussian 03 program.[16] The geometry optimizations and vibrational frequency calculations were performed at the B3LYP/6-311+G* level. Complexation of TMSCF₃ with CO_3^{2-} leads to **ii**, which was found to be a stable minimum at the B3LYP/6-311+G* level (Figure 2). The complexation energy was found to be 63.7 kcal/mol at the B3LYP/6-311+G*//B3LYP/6-311+G* + ZPE (zero-point vibrational energy, scaled by a factor of 0.96) level. The C_s symmetry structure **ii** contains a six-coordinate silicon atom involving four carbon and two oxygen atoms. The Si−O bond distance of **ii** is 1.925 Å. The Si−C (CF₃) bond length of **ii** is 2.171 Å, 0.172 Å longer than the Si−C (axial CH₃) bond, indicating relatively more nucleophilic character of the CF₃ group compared to the CH₃ group.

NBO charges[17] of the structure **ii** were also calculated. In **ii**, the CO_3^{2-} group as a whole bears −1.46 of charge, which indicates that −0.54 of charge was transferred from CO_3^{2-} to the TMSCF₃ group upon complexation. In **ii**, the CF₃ group as a whole bears −0.61 charge, and the CH₃ on average −0.51 of charge. This again indicates the relatively more nucleophilic nature of the CF₃ group compared to the CH₃ group.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford CT, 2004.
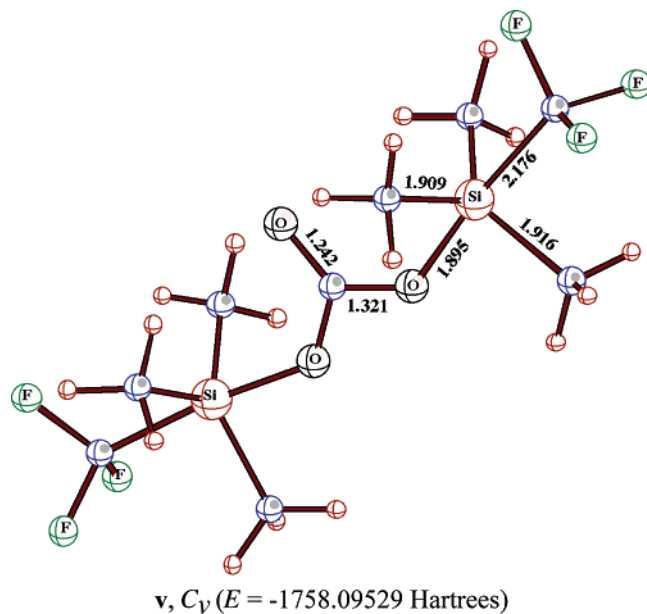
v, C_V (E = -1758.09529 Hartrees)

FIGURE 3. B3LYP/6-311+G* calculated structure of **v**.

Further complexation of **ii** with another molecule of TMSCF$_3$ leads to **v**, which was also found to be a stable minimum at the B3LYP/6-311+G* level (Figure 3). The complexation energy was found to be 44.2 kcal/mol at the B3LYP/6-311+G*// B3LYP/6-311+G* + ZPE level. The C_{2v} symmetry structure **v** contains two five-coordinate silicon atoms. The Si−O bond distance in **v** is 1.895 Å. The Si−C (CF$_3$) bond length in **v** is 2.176 Å, about 0.26 Å longer than the Si−C (CH$_3$) bond, indicating relatively more nucleophilic character of the CF$_3$ group compared to the CH$_3$ group. NBO charges of the structure **v** were also calculated. In **v**, the CO$_3$$^{2-}$ group as a whole bears −1.45 of charge, which indicates that −0.55 of charge was transferred from CO$_3$$^{2-}$ to two TMSCF$_3$ groups upon complexation.

(17) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

Conclusions

In summary, a new generation of nucleophilic catalysts has been explored for the facile trifluoromethylation reaction of carbonyl compounds. Trimethylamine *N*-oxide has been used successfully as an effective catalyst in the nucleophilic trifluoromethylation reactions, and its catalytic property has been improved further by using DMF as a solvent. The reactions with carbonates and phosphates are fast, insensitive to moisture, and very clean in nature. TMS-protected alcohols were obtained as sole products in high yields in most of the cases. Further, DFT calculations were performed on the possible reaction intermediates using the Gaussian 03 program at B3LYP/6-311+G* level to support the possible mechanism of the trifluoromethylation reaction.

Experimental Section

General Procedure for the Addition of TMSCF$_3$ to Aldehyde/ Ketone under Nucleophilic Catalysis in DMF. Aldehyde/ketone (1 mmol) and TMSCF$_3$ (neat) in dry DMF (3 mL) were placed in a 25 mL round-bottom flask (or a 30 mL vial). To this solution was added nucleophilic catalyst, and the mixture was stirred vigorously at room temperature. Completion of the reaction was monitored by TLC and GCMS. The reaction mixture was then poured in brine solution (15 mL) and extracted with diethyl ether (3 × 30 mL). Combined organic layers were finally washed with brine solution, dried over anhydrous Na$_2$SO$_4$, and then solvent was removed under reduced pressure. The crude product was further purified by chromatography (using 9:1 hexanes/ethyl acetate solvent system) to afford pure TMS-protected alcohols.

Supporting Information Available: Experimental procedure, spectral data, and copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra of the TMS-protected trifluoromethylated alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060835D