Tri-*tert*-butylphosphine is an Efficient Promoter for the Trifluoromethylation Reactions of Aldehydes, Ketones, Imides and Imines

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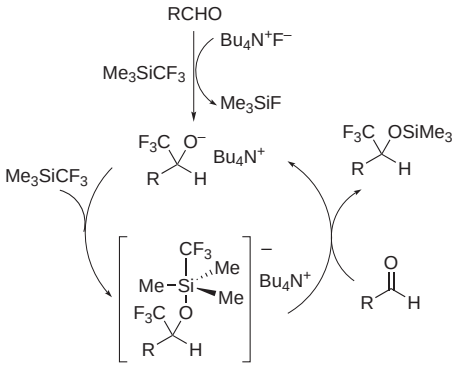
Abstract: A truly catalytic nucleophilic trifluoromethylation reaction of carbonyl compounds with Ruppert's reagent, Me_3SiCF_3, has been shown to be efficiently promoted by a P(*t*-Bu)$_3$–DMF system. Imines were also converted to the desired α-trifluoromethyl amines under similar reaction conditions.

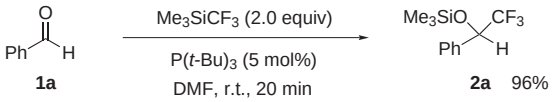
Key words: trifluoromethylation, fluorine, aldehydes, imines, Lewis bases

The synthesis of trifluoromethyl-containing organic compounds has attracted significant interest in the fields of pharmaceutical, agrochemical, and polymer chemistry since these compounds possess unique properties.[1] The construction of α-trifluoromethyl alcohol units exemplified by $CF_3C(OH)RR'$ is particularly important[2] as they frequently are a constituent of biologically active products such as Befloxatone[3] and Efavirenz.[4] Among various methodologies available for this purpose, nucleophilic trifluoromethylation reaction using Ruppert's reagent (Me_3SiCF_3) is a powerful method for introducing a CF_3 unit in synthetically useful carbonyl compounds.[5] After the initial discovery of trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3 by Prakash et al.[6] considerable attention has been devoted to the development of novel catalytic systems for this process. Most of the studies were performed with a wide variety of fluoride anions[7] such as tetrabutylammonium fluoride (TBAF) or cesium fluoride. Mechanistically, a fluoride anion is the initial catalyst in the reaction and the subsequent reactions would be catalyzed by an alkoxide intermediate generated in situ (Scheme 1). This autocatalyst system seems to impede application to an enantioselective reaction and therefore the development of a truly catalytic process of trifluoromethylation reaction is becoming a topic of interest in this area. Fuchikami et al. studied the trifluoromethylation reaction of aldehydes using a variety of Lewis bases.[8] Following this pioneering work, Prakash disclosed the importance of a truly catalytic process using trimethylamine *N*-oxide for the trifluoromethylation reaction.[9] The Lewis base-catalyzed trifluoromethylation reaction proceeds under a truly catalytic process, but these methodologies are not efficient enough as far as the chemical yields, catalyst loading and reaction time are concerned as compared to the methods involving a fluoride anion. Other catalysts such as alkoxides,[10a] acetates,[10b] carbenes[11] have also been reported for trifluoromethylation; however, they are presumably unsuitable for the base-labile substrates except for Mukaiyama's procedure.[10b] As a part of our research program for the development of novel methodologies in fluorine chemistry,[12] we herein report a mild catalytic system for trifluoromethylation reaction of a variety of substrates such as aldehydes, ketones, imides and imines using tri-*tert*-butylphosphine [P(*t*-Bu)$_3$].



Scheme 1 Mechanism of trifluoromethylation reaction with Me_3SiCF_3 in the presence of TBAF

Triphenylphosphine, PPh_3, is a widely used catalyst for trifluoromethylation reaction using Me_3SiCF_3.[8,13] The yields are relatively low and longer reaction time is required. Possible explanation for the low conversion is the poor nucleophilicity of PPh_3. As other phosphines have merely been studied in the trifluoromethylation reaction,[14] we became interested in performing the trifluoromethylation reaction using P(*t*-Bu)$_3$. First, the trifluoromethylation reaction of benzaldehyde (**1a**) was tried in DMF at room temperature using a catalytic amount of P(*t*-Bu)$_3$ (5 mol%, Scheme 2). Trifluoromethylated adduct **2a** was produced nicely in 96% yields within 20 minutes in contrast to the literature results (5 mol% of PPh_3: 60%, 24 h;[8] 5 mol% of P(*n*-Bu)$_3$:



Scheme 2

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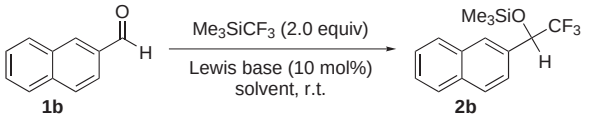
79%, 3 h[14]). This is of great interest because the sterically demanding P(*t*-Bu)$_3$ is believed to be unsuitable for Lewis base catalyzed reaction.[15]

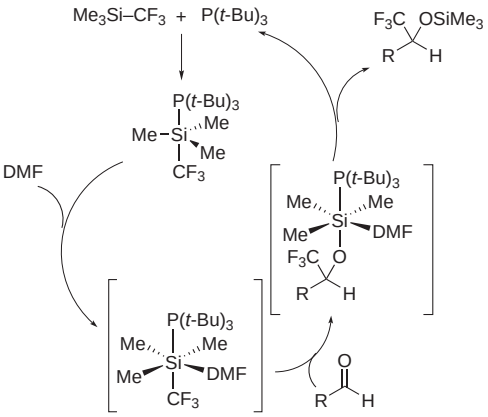
Table 1 Reaction of 2-Naphthaldehyde with Me_3SiCF_3 in the Presence of Lewis Base



Run	Lewis Base	Solvent	Time (h)	Yield (%)[a]
1	P(*t*-Bu)$_3$	DMF	0.5	99
2	P(*n*-Bu)$_3$	DMF	0.5	99
3	P(*n*-octyl)$_3$	DMF	0.5	99
4	P(cyclohexyl)$_3$[b]	DMF	24	16
5	PPh_3	DMF	17	16
6	O=PPh_3	DMF	5	78
7	O=P(*n*-Bu)$_3$	DMF	16	3
8	–	DMF	24	22
9	P(*t*-Bu)$_3$	HMPA	0.5	86
10	P(*t*-Bu)$_3$	DMA	1	99
11	P(*t*-Bu)$_3$	DMSO	0.5	94
12	P(*t*-Bu)$_3$	MeCN	24	Trace
13	P(*t*-Bu)$_3$	CH_2Cl_2	24	Trace
14	P(*t*-Bu)$_3$	THF	24	Trace
15	P(*t*-Bu)$_3$	Et_2O	24	Trace

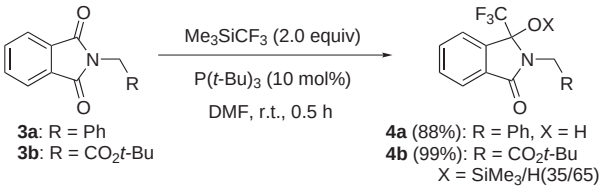
[a] Isolated yield.
[b] Commercially available toluene solution (25%) was used.

We began our investigation by thoroughly screening commercially available phosphines as a promoter (10 mol%) for the trifluoromethylation of 2-naphthaldehyde (**1b**) with Me_3SiCF_3 and were convinced P(*t*-Bu)$_3$ to be quite effective in this process giving the adduct **2b** quantitatively (run 1, Table 1). Optimal yields were also obtained using P(*n*-Bu)$_3$ and tri-*n*-octylphosphine at ambient temperature for this substrate **1b**, but P(cyclohexyl)$_3$ did not act effectively (runs 2–4). It is interesting to note that O=PPh_3 is also an effective catalyst for the reaction, but PPh_3 and O=P(*n*-Bu)$_3$ reacted much more slowly giving only traces of the product (runs 5–7). In a control experiment, very low conversion was observed in the absence of P(*t*-Bu)$_3$ even after 24 hours stirring at room temperature (run 8). Variation of solvents showed that polar aprotic solvents such as DMF, HMPA, *N*,*N*′-dimethylacetamide (DMA), as well as DMSO significantly accelerated the reaction (runs 9–15). The results collected here suggest that the combination of P(*t*-Bu)$_3$ and the polar aprotic solvent play an important role to accelerate the reaction. They both may coordinate to the silicon species to render the Me_3SiCF_3 more reactive via a hypervalent intermediate.[10b] The truly catalytic scenario for the P(*t*-Bu)$_3$–DMF-induced reaction can be presented in Scheme 3.



Scheme 3 Trifluoromethylation mechanism with Me_3SiCF_3 in the presence of P(*t*-Bu)$_3$–DMF

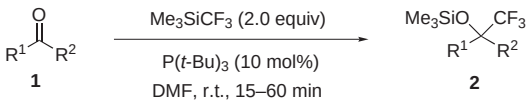
We next focused on expanding the scope of the methodology using a variety of carbonyl compounds under optimized conditions (Table 2). The trifluoromethylation of substituted aryl aldehydes proceeded readily both with electron-rich and electron-poor aromatics in almost quantitative yields of the corresponding trifluoromethylated silyl ethers within one hour at room temperature (entries 1–13). Aliphatic aldehydes also gave good yields of products (entries 14, 15). Selective 1,2-addition occurred in the trifluoromethylation of *trans*-cinnamylaldehyde to furnish *trans*-α-trifluoromethyl allylic alcohol as trimethylsilyl ether (entry 16).[7f] Ketones were reactive under the conditions without any trouble of competing aldolization (entries 17, 18). Cyclic five-membered imides (**3a**,**b**) were also trifluoromethylated with Me_3SiCF_3 in high yields under P(*t*-Bu)$_3$ catalyst to furnish trifluoromethylated *N*,*O*-ketals (**4a**,**b**)[16] as an alcohol or a mixture of corresponding alcohol and trimethylsilyl ether (Scheme 4).



Scheme 4

The scope of this reaction was explored with respect to imines **5a**–**e** (Table 3).[17] When the *p*-toluenesulfonylimine **5a** was subjected to the reaction with Me_3SiCF_3 at room temperature under optimized conditions, the α-trifluoromethyl amine **6a** was produced in very low yield (entry 1). Pleasingly, an increased loading of P(*t*-Bu)$_3$ to 100 mol% in DMF at room temperature gave **6a** in 63% yield. Reasonable to good yields of several α-trifluoromethyl amines **6b**–**e** were obtained under the same conditions (entries 3–6).

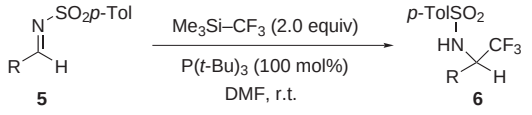
Table 2 Trifluoromethylation Reaction of Aldehydes and Ketones with Me_3SiCF_3 Catalyzed by P(*t*-Bu)$_3$



Entry	1	R^1	R^2	2	Yield (%)[a]
1	**1a**	Ph	H	**2a**	99
2	**1b**	2-Naphthyl	H	**2b**	99
3	**1c**	1-Naphthyl	H	**2c**	95
4	**1d**	4-$MeOC_6H_4$	H	**2d**	92
5	**1e**	4-ClC_6H_4	H	**2e**	96
6	**1f**	2-ClC_6H_4	H	**2f**	99
7	**1g**	4-BrC_6H_4	H	**2g**	94
8	**1h**	4-$NO_2C_6H_4$	H	**2h**	94
9	**1i**	3-$NO_2C_6H_4$	H	**2i**	91
10	**1j**	2-$NO_2C_6H_4$	H	**2j**	97
11	**1k**	4-MeC_6H_4	H	**2k**	80
12	**1l**	2-MeC_6H_4	H	**2l**	76
13	**1m**	2, 4-$(Me)_2C_6H_3$	H	**2m**	87
14	**1n**	*n*-C_7H_{15}	H	**2n**	62
15	**1o**	$PhCH_2CH_2$	H	**2o**	79
16	**1p**	*trans*-PhCH=CH	H	**2p**	94
17	**1q**	Ph	Me	**2q**	84[b]
18	**1r**	*c*-C_6H_{10}		**2r**	81

[a] Isolated yield.
[b] Me_3SiCF_3 (4.0 equiv) was used.

Table 3 Trifluoromethylation of Sulfonylimines **5** with Me_3SiCF_3 in the Presence of P(*t*-Bu)$_3$

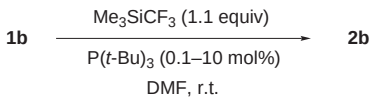


Entry	5	R	Time (h)	6	Yield (%)[a]
1[b]	**5a**	Ph	24	**6a**	Trace
2	**5a**	Ph	19	**6a**	63
3	**5b**	4-$NO_2C_6H_4$	4	**6b**	41
4	**5c**	2-Napthyl	22	**6c**	73
5	**5d**	4-ClC_6H_4	22	**6d**	75
6	**5e**	4-BrC_6H_4	19	**6e**	80

[a] Isolated yield.
[b] P(*t*-Bu)$_3$ (10 mol%) was used.

In summary, we have developed an efficient Lewis base catalyzed trifluoromethylation reaction using P(*t*-Bu)$_3$.[18] The reaction is applicable to a range of substrates with a variety of versatile functional groups. The synthetic advantage of the present reaction is the rapid conversion of carbonyl compounds to trifluoromethyl ethers in contrast to the known Lewis base catalyzed methods.[8,9] Furthermore, since a variety of chiral trialkylphosphines are readily available, this would provide useful flexibility for asymmetric trifluoromethylation reaction. It is noteworthy that the catalyst loading from the conversion of **1b** to **2b** could be lowered to 1 mol% and 0.1 mol% producing **2b** in excellent yields after 0.5 hours without compromising the conversion (1000 catalyst turnovers, Table 4). Expansion of the scope of the reaction and applications to asymmetric trifluoromethylation reaction catalyzed by chiral trialkylphosphines are currently under investigation.

Table 4 Variation of Catalyst Loading



Run	P(*t*-Bu)$_3$ (mol%)	Time (h)	Yield (%)[a]
1	10	0.5	97
2	1	0.5	97
3	0.1	0.5	94

[a] Isolated yield.

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(18) **Typical Experimental Procedure.**
Tri-*tert*-butylphosphine [P(*t*-Bu)$_3$, 3.9 mg, 0.019 mmol]) was placed in a round-bottomed flask under N_2. Dry DMF (0.25 mL) and 2-naphthaldehyde (**1b**, 30 mg, 0.19 mmol) were added. To the stirred solution, Me_3SiCF_3 (57 μL, 0.38 mmol) was added at r.t. The mixture was stirred at r.t. for 0.5 h; the reaction was concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane to afford **2b** in 99% yield.