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TTMPP-catalyzed trifluoromethylation of carbonyl compounds and imines with trifluoromethylsilane

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ABSTRACT

A highly basic phosphine, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), catalyzes trifluoromethylation using trifluoromethyltrimethylsilane to give the corresponding trifluoromethylated products in good to high yields, with both carbonyl compounds and imines.

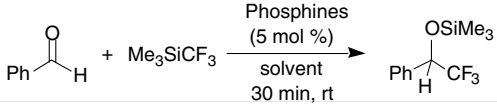
Trifluoromethylated compounds have received much attention due to their important applications as biologically active agents and liquid crystalline materials, which exhibit specific biological and physical features.[1] Among the various methodologies for introducing the trifluoromethyl group, Ruppert's reagent ((trifluoromethyl)trimethylsilane, $TMSCF_3$)[2] is a particularly useful reagent for introducing a trifluoromethyl unit due to its nucleophilic character. Prakash et al. found tetrabutylammonium fluoride (TBAF) to be an effective catalyst for the trifluoromethylation reaction of carbonyl compounds.[3] Following this pioneering work, other efficient activators, such as CsF,[4] amine,[5] phosphine,[6] amine oxide,[7] N-heterocyclic carbene,[8] lithium acetate,[9] quaternary ammonium phenoxide,[10] phosphete salts,[7b] molecular sieves-DMSO[11] and potassium carbonate,[7b] have been recently reported to realize high yields.

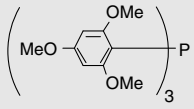
On the other hand, tris(2,4,6-trimethoxyphenyl)-phosphine (TTMPP)[12] is known to be a highly basic phosphine owing to its methoxy substitutions. Based on this property, some unique catalytic reactions have been reported.[13] We have also reported that TTMPP acts as a good catalyst in the aldol and imine aldol reaction of ester silyl enolate via O–Si bond activation.[14] In an effort to apply this phosphine to other useful reactions, trifluoromethylation using $TMSCF_3$ was examined. Here we report that TTMPP acts as a useful catalyst for the trifluoromethylation of both carbonyl compounds and imines.

Initially, trifluoromethylation of benzaldehyde with $TMSCF_3$ was examined in the presence of 5 mol % of TTMPP in THF at room temperature. The desired product was obtained in 95% yield within 30 min (Table 1, entry 1).

This reaction also proceeded smoothly when 1 mol % of TTMPP was used. The product was obtained in moderate to low yield when other phosphines were used instead of TTMPP (Table 1, entry 1 vs entries 8–11). This result clearly showed that the catalytic activity of TTMPP is much higher than the activity of other phosphines. DMF, DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) and acetonitrile were also effective solvents in thisTTMPP-catalyzed reaction. However, only trace amounts of product were obtained using Et_2O, toluene and CH_3OH.

Table 1
Optimization of the reaction conditions



Entry	Phosphine	Solvent	Yield[a] (%)
1	TTMPP	THF	95(85)[b]
2		DMF	96
3		DMPU	95
4		CH_3CN	80
5		Et_2O	0
6		Toluene	0
7		MeOH	0
8	TMPP[c]	THF	45
9	Ph_3P		Trace
10	nBu_3P		Trace
11	tBu_3P		Trace

[a] Yield was determined by ^1H NMR analysis using 1,1,2,2 tetrachloroethane as internal standard.
[b] Isolated yield.
[c] Tris(4-methoxyphenyl)phosphine.

In order to clarify the scope of this reaction, several aldehydes were examined in the presence of 5 mol % of TTMPP (Table 2).[15] Good results were obtained for both aromatics having an electron-donating or -withdrawing group and aliphatic aldehydes. Ketones also worked in this reaction (Table 3), although longer time was required to afford the corresponding product in THF. This problem was solved when DMF was used as the solvent. The reaction proceeded smoothly with various kinds of ketones in the presence of 5 mol % of TTMPP. 1,2-Adducts were obtained in good yields when α,β-unsaturated ketones were employed, and aliphatic

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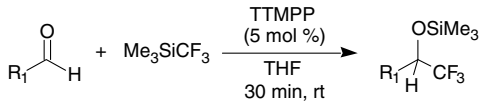
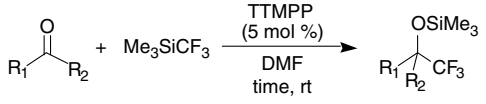
Table 2
TTMPP-catalyzed trifluoromethylation of various aldehydes



Entry	Aldehyde	Yield[a] (%)
1	C_6H_5CHO	85
2	4-$CH_3OC_6H_4CHO$	86
3	4-$NO_2C_6H_4CHO$	90
4	4-ClC_6H_4CHO	91
5	1-Naphthaldehyde	83
6	2-Naphthaldehyde	86
7	(*E*)-PhCH=CHCHO	90
8	$PhCH_2CH_2CHO$	85
9	*cyclo*-$C_6H_{11}CHO$	81
10	$C_8H_{17}CHO$	91
11	Furfural	82

[a] Isolated yield.

Table 3
TTMPP-catalyzed trifluoromethylation of various ketones



Entry	Ketone	Time (h)	Yield[a] (%)
1	$C_6H_5COCH_3$	0.5	88
2[b]		14	84
3	4-$ClC_6H_4COCH_3$	0.5	85
4	4-$CF_3C_6H_4COCH_3$	0.5	87
5	$C_6H_5COC_2H_5$	0.5	80
6	(*E*)-C_6H_5CH=$CHCOCH_3$	0.5	92
7	(*E*)-C_6H_5CH=$CHCOC_6H_5$	0.5	75
8	$C_6H_5CH_2CH_2COCH_3$	4	84
9	Cyclohexanone	12	78
10	$C_5H_{11}COC_2H_5$	22	76

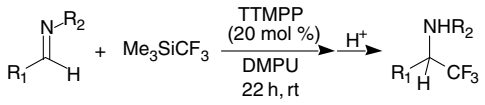
[a] Isolated yield.
[b] In THF.

ketones also worked well, although longer reaction times were required compared to the reaction with aromatic ketones.

In addition, imines were examined in this TTMPP-catalyzed trifluoromethylation. Compared to carbonyl compounds, a lot fewer examples have been reported.[16] Especially, examples of the catalytic versions are still scarce.[17] In the present study, we screened solvents and aldimines and found that the corresponding trifluoromethylated amine was obtained in good yield using *N*-tosylaldimine in DMPU.[18] Although the catalytic activity is not satisfactory, reasonable to good yields of several α-trifluoromethylated aromatic amines were obtained under the same conditions (Table 4, entries 8–11). N-Unactivated imines also worked well (Table 4, entries 6, 12 and 13). The product was not obtained when other phosphines such as triphenylphosphine, tributylphosphine and tri-*tert*-butylphosphine were used instead of TTMPP (Table 4, entry 1 vs entries 3–5). Again, the superiority of TTMPP was confirmed from these results.

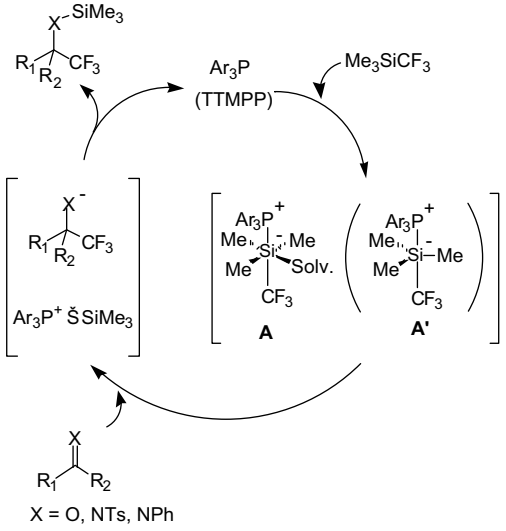
Although the mechanism of this reaction is not clear, a possible mechanism is illustrated in Scheme 1. First, TTMPP coordinates the silicon atom of the $TMSCF_3$ to form activated hexa-coordinated or penta-coordinated silicon species **A** (**A**′) and the C–Si bond is activated. Next, the nucleophilicity of the CF_3 group is enhanced and it readily reacts with an electrophile to produce the alkoxide or amino ion and silylphosphonium salt. Finally, immediate silylation occurs to give the silylated adduct with regeneration of TTMPP. In this reaction, a unique solvent effect was observed. The origin of

Table 4
TTMPP-catalyzed trifluoromethylation of various imines



Entry	R_1	R_2	Yield (%)
1	Ph	Ts	71
2[a]			45
3			Trace[b]
4			0[c]
5			0[d]
6[a]		Ph	74
7		$PhCH_2$	Trace
8	4-$CH_3OC_6H_4$	Ts	48
9	4-ClC_6H_4		77
10	4-BrC_6H_4		70
11	4-$NO_2C_6H_4$		60
12[a]	4-$CH_3OC_6H_4$	Ph	35
13[a]	4-ClC_6H_4		58

[a] In DMF.
[b] P(*t*Bu)3 was used instead of TTMPP.
[c] P(*n*Bu)3 was used instead of TTMPP.
[d] PPh3 was used instead of TTMPP.



Scheme 1. Proposed mechanism.

this effect is thought to be dependence of the reactivity of **A** (**A**′) on the solvent.

In summary, we disclose that TTMPP acts as an efficient catalyst in trifluoromethylation using $TMSCF_3$ as a trifluoromethylating agent. Wide range of aldehydes and ketones have been shown to undergo trifluoromethylation in generally excellent yield. The catalytic activity of TTMPP is found to be much higher than the activity of other phosphines, such as triphenylphosphine, tributylphosphine and tri-*tert*-butylphosphine. Imines are also worked in this catalytic reaction. Further investigation along these lines, including stereoselective reactions, is currently underway.

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15. *General experimental procedure for the trifluoromethylation of carbonyl compounds*: To a solution of appropriate carbonyl compound (1 mmol) and TTMPP (0.05 mmol) in solvent (1 mL), $TMSCF_3$ (1.5 mmol) was added at room temperature. The reaction was monitored by TLC. Then, the mixture was quenched with water and extracted with ether (2×25 mL). The combined extracts were washed with water and brine, and then dried over Na_2SO_4. The solvent was removed on an evaporator to leave crude product, which was purified by column chromatography on silica gel (AcOEt/hexane = 1:5) to give the corresponding product.
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18. *General experimental procedure for the trifluoromethylation of imine*: To a solution of appropriate imine (1 mmol) and TTMPP (0.20 mmol) in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (1 mL), $TMSCF_3$ (2.0 mmol) was added at room temperature. The reaction was monitored by TLC. After 22 h, the mixture was quenched with water and extracted with AcOEt (2×25 mL). The combined extracts were washed with water and brine, and then dried over Na_2SO_4. The solvent was removed on an evaporator to leave crude product, which was purified by preparative TLC to afford the desired product.