TOSOH

TOSOH F-TECH, INC.

Trifluoromethylating Reagents

CF_3-TMS

(Trifluoromethyl)trimethylsilane

$CF_3Si(CH_3)_3$

Tosoh F-Tech Inc. developed a process for the large-scale production of (Trifluoromethyl)trimethyl-silane (CF_3-TMS, Ruppert's Reagent) which will become a first choice for the introduction of CF_3 groups in pharmaceutical and electronics industries. The specification of CF_3-TMS is shown in Table 1. CF_3-TMS is a nucleophilic trifluoromethylating reagent and in this review we introduce the character of CF_3-TMS and summarize the synthesis of CF_3 group containing compounds via nucleophilic trifluoromethylation reactions utilising CF_3-TMS.

Table 1 The specification of CF_3TMS

	Specification
Appearance	Clear Liquid
Purity	>99.0% (GC%)
Water	< 500ppm (Karl Fischer Method)

1) Physical Properties

CF_3-TMS is a stable clear liquid. However, it generates $CF_3^-$with a catalytic amount of F^- ion. Since CF_3-TMS is highly flammable (Flash Point <-20°C), it should be stored cool and in a well ventilated area and kept away from heat, sparks and open fire. The physical properties are shown in Table 2.

Table 2 Physical properties of CF_3TMS

Chemical Structure	$CF_3Si(CH_3)_3$
CAS Number	81290-20-2
Appearance	Clear Liquid
Molecular Weight	142.2
Boiling Point	57°C
Specific Density	0.9626 at 20°C
Refractive Index	1.3304 at 20°C
Flash Point	-32°C (Tag closed cup)
Auto ignition Point	>260°C

2) Trifluoromethylation

The Si-CF3 bond is weak due to the high electron withdrawing property of the CF3 group and it is easily cleaved with catalytic amount of F^- ion. This generates $CF3^-$ as the nucleophile which attacks the electrophilic carbon. Aldehydes and ketones are very susceptable to nucleophilic attack by CF_3-TMS. Esters and amides show less reactivity. The following reactions are typical for CF_3-TMS with different substrates.

2-1) Aldehydes and ketones

CF_3-TMS reacts quantitatively with aldehydes and ketones in the presence of catalytic amount of F^- to give corresponding alcohols.[1)]

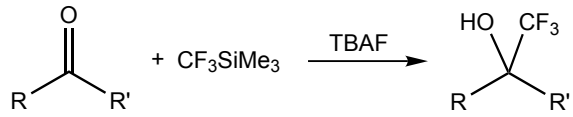
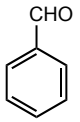
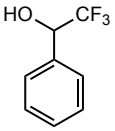
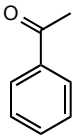
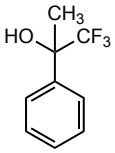
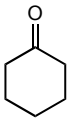
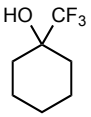
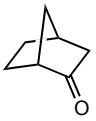
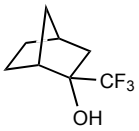
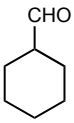
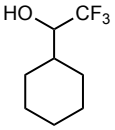


Table 3 Trifluoromethylation of aldehyde and ketones

Substrate	Product	Yield(%)
		85
		74
		77
		92
		80

2-2) Enone

Trans enones react with CF_3-TMS in the presence of catalytic amount of Cesium Fluoride to give trifluoromethylated allylic alcohols.[2)]

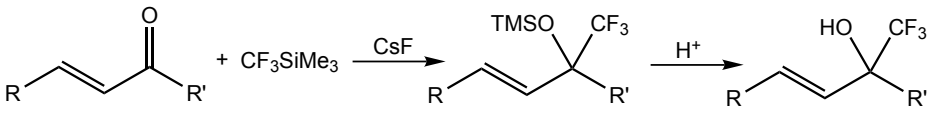


Table 4 Trifluoromethylation of enones

R	R'	Yield(%)
Ph	CF_3	93
Ph	Ph	95
CH_3	C_2H_5	68
Ph	CH_3	72

2-3) Ester

Esters react with CF_3-TMS the presence of stoichiometric amount of F^- to give corresponding trifluorom ethylketones.[3)]

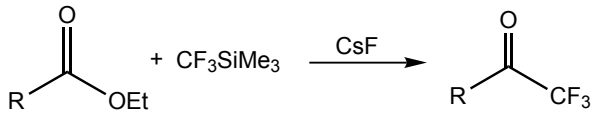
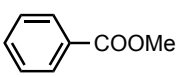
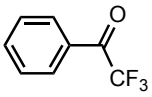
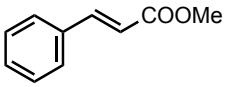
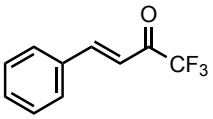
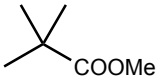
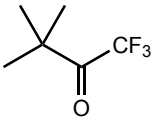
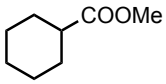
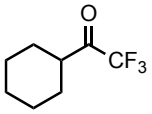
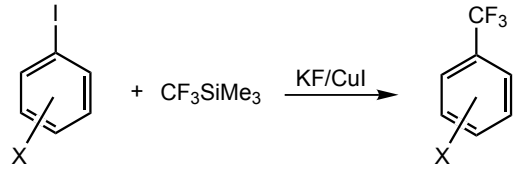


Table 5 Trifluoromethylation of esters

Substrate	Product	Yield(%)
		95
		85
		68
		72

2-4) Aromatics

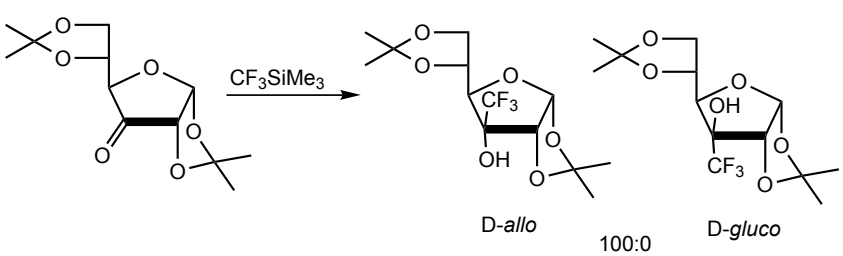
The transient trifluoromethylcopper species is generated *in situ* from CF_3-TMS in the presence of cuprous iodide and potassium fluoride; reaction with aryl iodies gives trifluoromethylated aryl compounds.[4)]



2-5) Miscellaneous

Trifluoromethylation of carbohydrates

Trifluoromethylation of 3-oxo-glucose proceeds with CF_3-TMS and gives the L-*allo* in 100% selectivity, although CF_3MgBr gives the L-*allo* and D-*gluco* in the ratio of 75:25, respectively.[5)]



Preparation of trifluoromethyl-cycloalkenones

Oxidation with PCC of tertiary alcohols obtained from trifluoromethylation of conjugated cycloenones give trifluoromethyl-cycloalkenones.[6)]

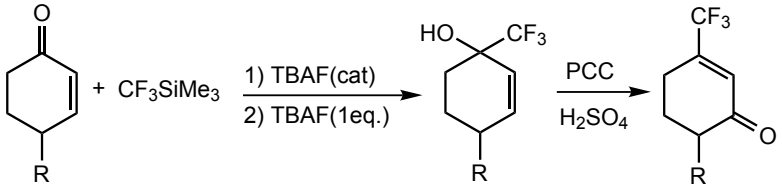
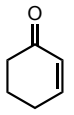
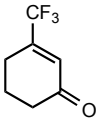
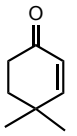
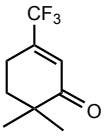
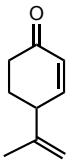
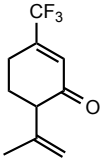
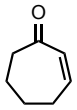
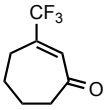
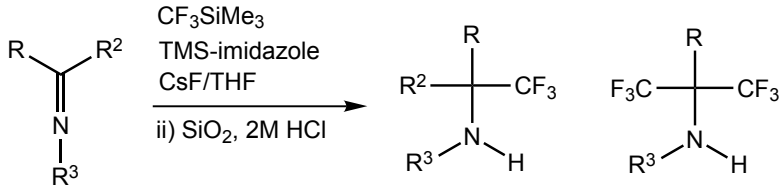


Table 6 Prepparation of trimethyl-cycloalkenones

Substrate	Product	Yield(%)
		28
		25
		34
		20

Reaction with imines

The reaction of imines with CF_3-TMS in the presence of CsF and TMS-imidazole gave the following products in moderate yields.[7)]



R=Ph etc.
R^2=H etc.
R^3=Ph etc.

Preparation of trifluoromethyl acetamides

In situ treatment of trifluoromethylated alcohols in acetonitril with excess H_2SO_4 and acetic acid give trifluoromethylated amides.[8)]

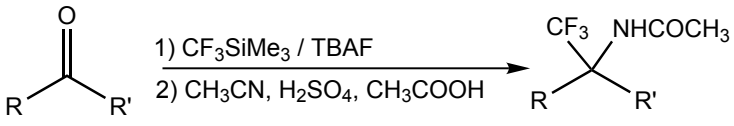
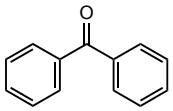
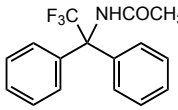
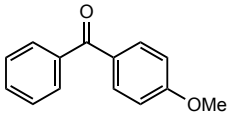
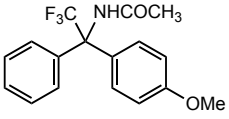
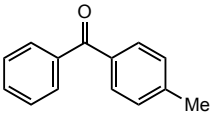
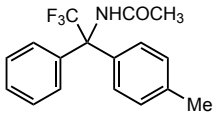
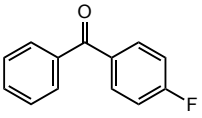
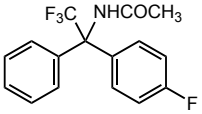
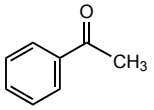
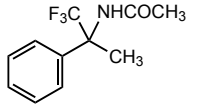


Table 7 Prepparation of trimethyl-cycloalkenones

Substrate	Product	Yield(%)
		68
		66
		81
		57
		54

3) Summary

1. Tosoh F-Tech, Inc. developed an industrial production process of CF_3-TMS which is a versatile trifluoromethylating agent for a wide variety of functional group.
2. The high chemo and regio selectivity and mild reaction conditions of F^- catalyzed trifluoromethylation allow reactions with complex substrates without significant formation of side products.
3. The methodology provides easy acces to novel pharmaceutical and electronic compounds carrying a CF3 group.

4) Literature

1) G.K.S. Prakash, R. Krishnamurti, G.A.Olah, *J.Am.Chem.Soc*., **111,** 393(1989)

2) R.P. Singh, R.L. Kirchmeier, J.M. Shreeve, *Org. Lett.* **1**, 1047(1999)

3) J. Wiedemann, T. Heiner, G. Mloston, G.K.S. Prakash, G.A. Olah, *Angew.Chem. Int.Ed*.,**37**, 820(1998)

4) T. Fuchikami, M.Urata, *JP 1991-218325*

5) S. Lavaire, R. Plantier-Royon, C. Portella, *Tetrahedron Asymmetry*, **9**, 213(1998)

6) G.K.S. Prakash, E.C.Tango,T. Mathew, Y.D. Venkar, G.A.Olah, *J.Fluorine Chem*., **101**, 199(2000)

7) J.C. Blazejewski, E. Anselm, M.P. Wilmshurst, *Tetrahedron Lett*., **40**, 5475(1999)

8) E.C.Tango, G.K.S. Prakash, G.A.Olah, *Synlett* **1997**, 1193