SYNLETT
Spotlight 241

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

(Trifluoromethyl)trimethylsilane ($TMSCF_3$) – Ruppert's Reagent: An Excellent Trifluoromethylation Agent

Compiled by Renato Saldanha Bastos

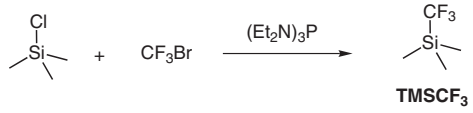
Renato Saldanha Bastos was born in Rio de Janeiro, Brazil in 1977. He received his Agronomy Engineering degree from Universidade Federal de Viçosa (UFV) in 2000 and his MSc in Soils and Plant Nutrition from the same University in 2003. He is currently working towards his PhD under the supervision of Professor Angelo da Cunha Pinto at the Universidade Federal do Rio de Janeiro (UFRJ). His research interests focus on the synthesis of substituted isatins, oximes and fluorinated analogues.

Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro (UFRJ), Avenida Athos da Silveira Ramos, Centro de Tecnologia, Bloco A, 6º andar. Ilha do Fundão, Cidade Universitária, Rio de Janeiro, CEP 21941-909, Brazil
E-mail: bastosrs@ufrj.br

Introduction

The trifluoromethyl group (also known as a pseudohalide) in a molecule may bring about remarkable differences to its physical, chemical and biological properties. Applications in medicinal, agrochemical and materials sciences have been developed.[1,2,3]

(Trifluoromethyl)trimethylsilane ($TMSCF_3$ or Me_3SiCF_3) was first synthesized by Ingo Ruppert in 1984.[4,5] The reaction involves the treatment of CF_3Br and Me_3SiCl in the presence of $(Et_2N)_3P$ (Scheme 1).



Scheme 1

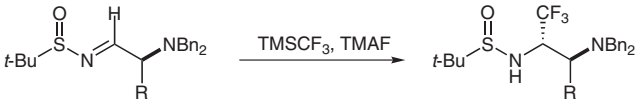
$TMSCF_3$ can be used as an efficient nucleophilic trifluoromethylating agent. Many electrophiles can accept the CF_3 group. It is generally necessary to use a fluoride source for reaction initiation. The fluoride ion acts as a nucleophile that attacks the trimethylsilane and facilitates the nucleophilic attack of the trifluoromethyl group on the eletrophilic center. Ruppert's reagent trifluoromethylation can also be initiated by different Lewis bases or carbenes.

Another important function of $TMSCF_3$ is the production of chiral trifluoromethylated alcohols when associated with chiral catalysts.

The reagent is a colorless liquid (bp 54–55 °C), commercially available as 0.5 M solution in THF, which can be handled at room temperature and in common laboratory glassware.

Abstracts

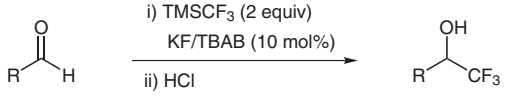
(A) The use of $TMSCF_3$ can be a convenient method for preparation of trifluoromethylated vicinal diamines using a stereoselective nucleophilic trifluoromethylation strategy.[6] Ruppert's reagent as the trifluoromethylation agent and tetramethylammonium fluoride (TMAF) as fluoride source can be used in the following examples.



R = Me, Pr, Bn, *t*-Bu, *i*-Bu, $(CH_2)_3NBn$

66–86% yield
de > 99:1

(B) The fluoride source is an important factor for improving the yield of a trifluoromethylation reaction. The use of KF, an inexpensive and commonly used fluoride source associated with tetrabutylammonium bromide (TBAB), has been shown to be an alternative procedure for initiating the trifluoromethylation reaction with the $TMSCF_3$.[7] In this example the KF/TBAB combination acts as catalyst for trifluoromethylation of aldehydes, ketones and imides in a variety of organic solvents.

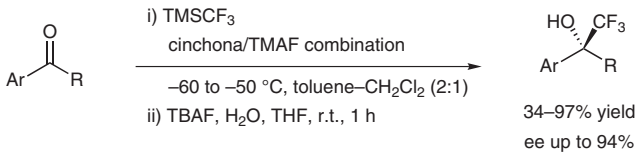


R = Ph, 1-Naph, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, *n*-heptyl

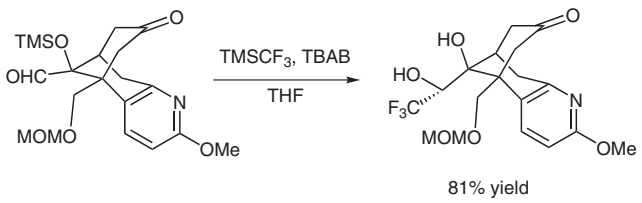
79–99% yield

SYNLETT 2008, No. 9, pp 1425–1426
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2008-1067022; Art ID: V24807ST

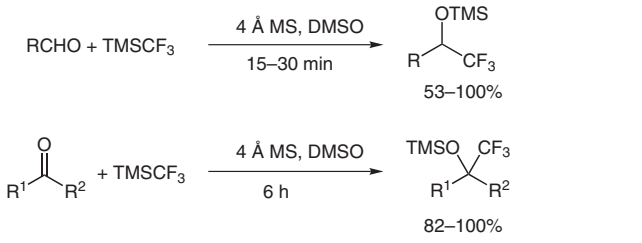
(C) Enantioselective trifluoromethylation is an interesting development for nucleophilic addition to ketones. This can be achieved using a combination of ammonium bromide of cinchona alkaloids with TMAF.[8]



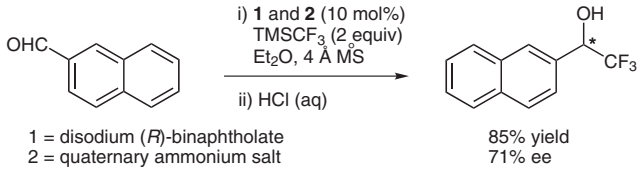
(D) The selective trifluoromethylation of carbonyls is uncommon. An interesting example of $TMSCF_3$ selectivity is the synthesis of a huperzine A analogue.[9] The synthetic route revealed the selective attack on the aldehyde in preference to the keto group.



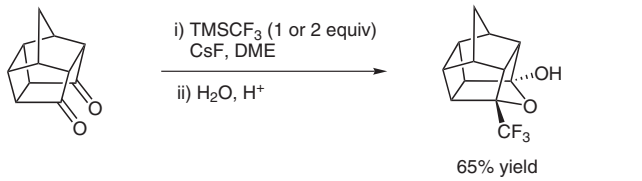
(E) $TMSCF_3$ can afford trifluoromethylated products without the presence of fluoride anions, which are strong bases. Using a combination of DMSO and 4 Å MS nucleophilic addition to a diverse range or carbonyl compounds was reported by Iwanami and Oriyama[10] to produce high yields of the trifluoromethylated adducts.



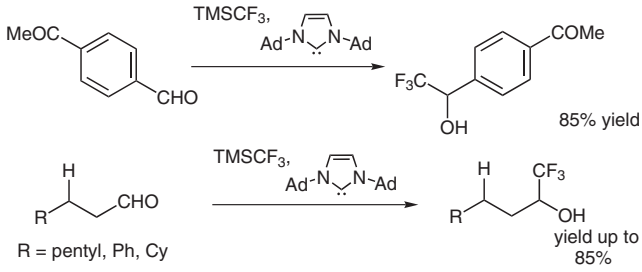
(F) Enantioselective trifluoromethylation with $TMSCF_3$ is always a big challenge. Zhao et al. used disodium (*R*)-binaphtholate (**1**) in combination with a chiral quaternary ammonium salt (**2**) to achieve high yield and enantiomeric excess for some aldehydes. 2-Naphthaldehyde afforded the best results. [11]



(G) $TMSCF_3$ can be used to afford hemiacetals by transannular cyclization from pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione ('cage' dione). The trifluoromethylation process proceeded stereoselectively and the CF_3 group is placed exclusively at the *exo* position.[12]



(H) A novel N-heterocyclic carbene (NHC) catalyzed trifluoromethylation using $TMSCF_3$ was proposed by Song et al. using 0.5–1 mol% catalyst.[13] This approach avoids the use of strong bases and was explored using a diverse range of carbonyl compounds. This catalyst may distinguish aldehydes from ketones and selectively trifluoromethylate also enolizable aldehydes.



References

(1) *Synthetic Fluorine Chemistry*; Olah, G. A.; Chambers, R. D.; Prakash, G. K. S., Eds.; John Wiley & Sons: New York, **1992**.
(2) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**.
(3) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, **2004**.
(4) Ruppert, I.; Schlich, K.; Volback, W. *Tetrahedron Lett.* **1984**, *25*, 2195.
(5) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
(6) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538.
(7) Mizuta, S.; Shibata, N.; Hibino, M.; Nagano, S.; Nakamura, S.; Toru, T. *Tetrahedron* **2007**, *63*, 8521.
(8) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707.
(9) Kaneko, S.; Nakajima, N.; Katoh, T.; Terashima, S. *Chem. Pharm. Bull.* **1997**, *45*, 43.
(10) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112.
(11) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822.
(12) Romaski, J.; Mlosto, G. *ARKIVOC* **2007**, *(vi)*, 179.
(13) Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 2193.