Nucleophilic trifluoromethylation of carbonyl compounds and derivatives

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Dedicated to Professor Rosa Claramunt on the occasion of her 65th anniversary

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Abstract

This review highlights the main methods for the nucleophilic trifluoromethylation of aldehydes, ketones, esters, imines and their analogous compounds published in the literature in the last six years. The focus is on synthetically useful procedures and the work is organized according to the type of carbonyl compound subjected to the trifluoromethylation reaction.

Keywords: Nucleophilic trifluoromethylation, ketones, aldehydes, esters, imines

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1. Introduction

Fluorine is the most abundant halogen in the earth's crust,[1] and is widely used during lead optimization in drug discovery.[2,3,4] In fact, five of the new drugs approved last year by the FDA (Food and Drug Administration) contain a trifluoromethyl group. The special nature of fluorine inside a therapeutic or diagnostic small molecule candidate for a pharmaceutical compound imparts a variety of properties, which can enhance a number of pharmacokinetic and/or pharmacodynamic properties including increased membrane permeability, favourable protein-ligand interactions, improved metabolic stability, changes in physical properties, and selective reactivities with a profound effect on its bioactivity, stability and lipophilicity.[5-7]

Moreover, the effect of fluorine on the biological activity of agrochemicals such as herbicides, insecticides, fungicides, and plant growth regulators has earned fluorine a unique place in the toolbox of the agrochemical chemist, given that it represents about the 35 to 40% of the active ingredients in crop protection products.[8] Likewise, fluorine has been recognized as a key element in materials science. Fluorinated functional materials are emerging as important chemical tools to achieve improved performance and higher stability under a variety of conditions.[9]

Conventional synthetic methods are not always applicable to the preparation of organofluorine derivatives due to the unique characteristics of fluorine. Therefore, the synthetic access to fluorinated compounds was difficult in the past and largely restricted to the use as starting materials of a very limited amount of commercially available fluorinated building blocks[10] or simple synthetic fluorinated templates.[11,12] Taking into account that many biologically active compounds contain the trifluoromethyl group as the essential motif, the introduction of this moiety is a challenging topic, and the development of highly efficient methodologies for trifluoromethylation is of significant importance for wide fields of science and technology.

Trifluoromethylation of carbonyl derivatives is a valuable tool for the carbon-CF_3 bond construction. However, the trifluoromethyl group has been particularly difficult to install, in part because the reactive intermediates that are generated during trifluoromethylation reactions are unstable under the conditions necessary for the reactions to proceed. The harsh protocols typically required for these reactions can limit the substrates that can be used and/or cause side-product formation.

Excellent reviews of the nucleophilic trifluoromethylation of carbonyl compounds[13] including the asymmetric trifluoromethylation have been published. Here, we describe some of the seminal aspects of trifluoromethylation of carbonyl derivatives and carboxylic compounds covered by such reviews, and we mainly focus on publications that have appeared in the last years until the end of May 2013.

The following abbreviations / acronyms are used throughout this review:

DFT Density Functional Theory
DMDP Dihydroxymethyldihydroxypyrrolidine

IPr 1,3-Bis-(2′,6′-diisopropylphenyl)imidazol-2-ylidene
MW Microwave irradiation
PET Positron emission tomography
RPr Trifluoromethyltrimethylsilane, Ruppert–Prakash reagent
TASF Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB Tetra-n-butylammonium bromide
TBAF Tetra-n-butylammonium fluoride
TBAT Tetra-n-butylammonium difluorotriphenylsilicate
TBD 1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TDAE Tetrakis(dimethylamino)ethylene
TMAF Tetramethylammonium fluoride

In the 1980s, several nucleophilic trifluoromethylation reagents containing silicon were reported. For example, De Meijere and Hartkopf designed the trialkylsilyl(trifluoromethyl) diazenes **2** (Figure 1) as tailored reagents,[14] and following this work trifluoromethylsilicon compounds such as (trimethyl)trifluoromethylsilane **1**, (trichloro)trifluoromethylsilane **3** and (trimethoxy)trifluoromethylsilane **4** (Figure 1) were prepared by Ruppert's group.[15] However, at that time these compounds were not synthetically explored as efficient trifluoromethylating reagents. Finally, at the end of this decade Prakash and his coworkers reported the first nucleophilic trifluoromethylations of aldehydes and ketones using **1** ($TMSCF_3$, Ruppert-Prakash reagent, RPr) in the presence of TBAF.[16]

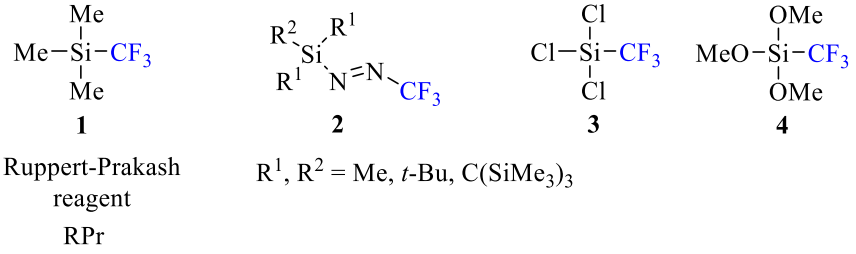
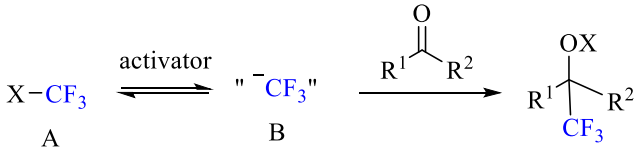


Figure 1

The most widely exploited route for nucleophilic trifluoromethylation involves the use of a CF_3 containing reagent A in combination with an activator to generate the anionic species B which can act as source of CF_3 carbanions in reactions with carbonyl compounds (Scheme 1).

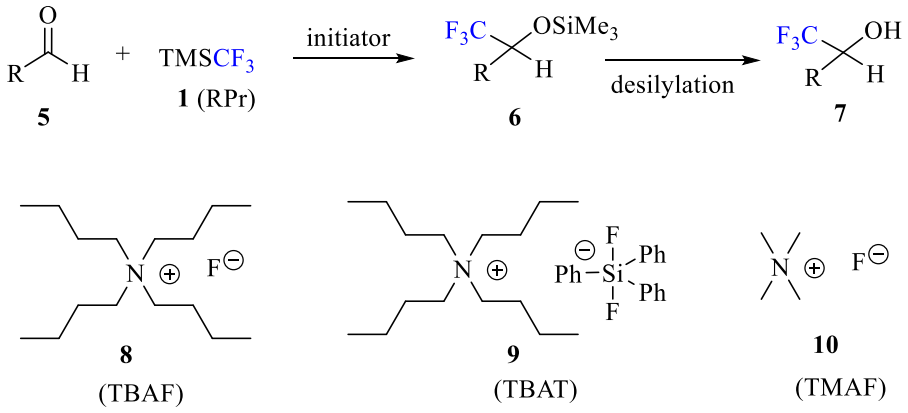


Scheme 1

According to this scenario, compounds bearing a CF_3 group on silicon,[17] sulfur,[18] or phosphorus,[19] as well as derivatives of trifluoroacetic acid,[20] fluoral,[21] and trifluoroacetophenone,[22] and other have been employed as efficient reagents for nucleophilic trifluoromethylation.

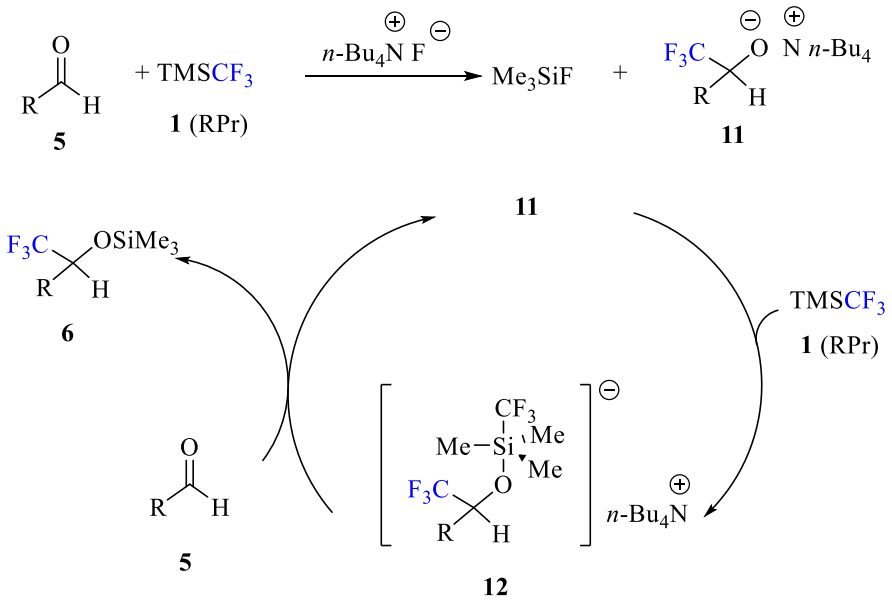
2. Trifluoromethylation of aldehydes

The trifluoromethylating reagent $TMSCF_3$, which was first prepared by Ruppert,[15] became the Ruppert-Prakash reagent **1** (RPr),[16] after this group has extensively used it as a versatile reagent to incorporate a trifluoromethyl group into organic compounds by nucleophilic activation.[17,23] $TMSCF_3$ itself does not react with carbonyl compounds **5**, and the trifluoromethide anion must be liberated by activation with an initiator (Scheme 2) to give the corresponding trifluoromethylated adducts **6**. Usually, fluoride anions, such as **8** (TBAF, tetra-*n*-butylammonium fluoride), **9** (TBAT, tetra-*n*-butylammonium triphenyldifluorosilicate), **10** (TMAF, tetramethylammonium fluoride) or CsF have been widely used as nucleophilic initiators for the trifluoromethylation of aldehydes. The initial addition step is usually followed by desilylation that gives the desired alcohol **7**.



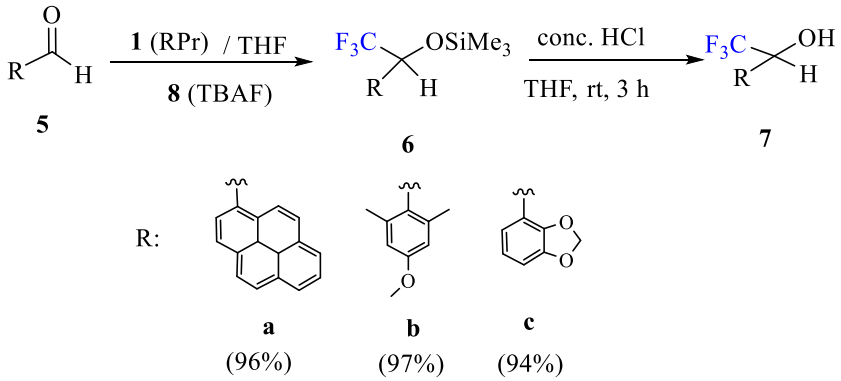
Scheme 2

Using this protocol a variety of aldehydes **5** reacted with $TMSCF_3$ and TBAF making the corresponding trifluoromethylated adducts easily accessible. Prakash and Yudin suggest that a catalytic amount of **8** (TBAF) in the reaction mixture initially gives Me_3SiF and an alkoxide adduct **11** (Scheme 3).[17] The reaction between **11** and **1** (RPr) leads to the formation of pentavalent complex **12** which transfers the trifluoromethyl group to the carbon of another molecule of carbonyl compound **5**.



Scheme 3

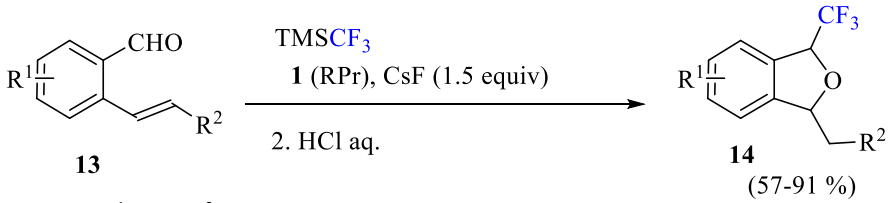
In a recent example, the reactions of **1** (RPr) (trimethyl)trifluoromethylsilane with various aldehydes, such as pyrenaldehyde **5a**, 2,6-dimethyl-*p*-anisaldehyde **5b**, and 2,3-(methylene-dioxy)benzaldehyde **5c** in the presence of a catalytic amount of **8** (TBAF) in THF led to the formation of the corresponding trifluoromethylated silyl ether derivatives **6a-c** in almost quantitative yields.[24] Acid hydrolysis of **6a-c** gave the novel trifluoromethylated alcohol derivatives **7a-c** in excellent isolated yields (Scheme 4).



Scheme 4

Other fluorinated activators have been used for the trifluoromethylation of aldehydes. For example, cinnamaldehyde was first trifluoromethylated using **1** (RPr) and catalytic amounts of CsF by Prakash *et al.*[16] Many other CsF-catalyzed processes have been used for the introduction of CF_3 group in aldehydes, which were first transformed to trifluoromethyl silyl ether

intermediates and afforded trifluoromethylated alcohols in excellent yields after acid hydrolysis.[13] This reaction can be applied to tandem processes as it has been shown in a novel synthetic route to biologically important trifluoromethylated phthalans.[25] Thus, a tandem nucleophilic addition/intramolecular oxa-Michael reaction, between *ortho*-formyl cinnamate derivatives or enones **13** (Scheme 5) and **1** (RPr) in the presence of cesium fluoride results in the formation of trifluoromethylated phthalans **14** in good yields.[26] Although the diastereomeric isomers of **14** are chromatographically inseparable, they can be clearly differentiated by their ^{19}F NMR spectrum, and according to the NOE measurement, the major isomer was assigned to be the *trans*-diastereoisomer in all cases.



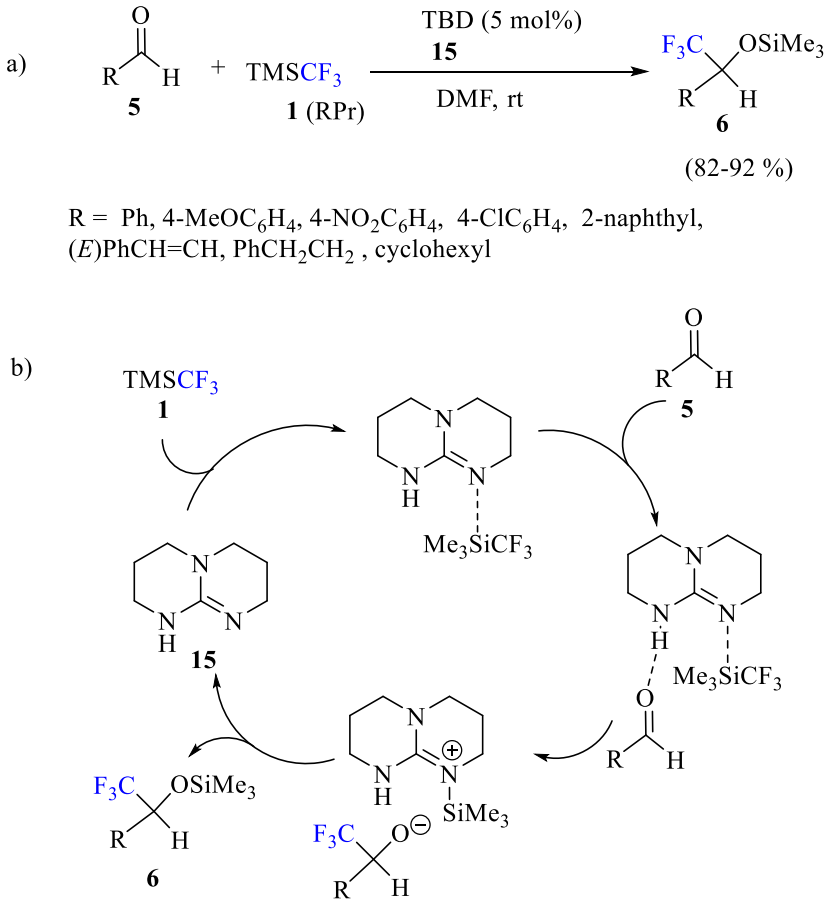
R^1 = H, R^2 = C_6H_5CO, 4-MeC_6H_4CO, 4-$MeOC_6H_4CO$, 3,4-$(MeO)_2C_6H_3CO$, 4-ClC_6H_4CO, MeO_2C, EtO_2C, n-BuO_2C, tBuO_2C, CN

R^1 = 4-NO_2, R^2 = EtO_2C

R^1 = 3,4-OCH_2O-, R^2 = EtO_2C

Scheme 5

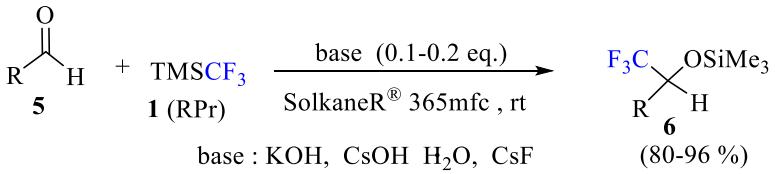
Nucleophilic trifluoromethylation of aldehydes with **1** ($TMSCF_3$, RPr) has also been studied using other non-fluorinated nucleophilic activators, such as, pyridine, $AsPh_3$, $SbPh_3$, Et_3N, *n*-Bu_2NH, Ph_3P or $P(tBu)_3$. These Lewis base catalyzed reactions proceed more slowly and the yields of the final products are lower than when fluoride ion is utilized.[13] Trimethylamine *N*-oxide as well as carbonate and phosphate salts such as K_2CO_3 and $(MeO)_2$-P(O)NBu_4 or lithium acetate also showed efficient catalytic activity in nucleophilic trifluoromethylation with $TMSCF_3$ (RPr) of aromatic, aliphatic and α,β-unsaturated aldehydes. All these reactions proceeded under very mild conditions. Selective trifluoromethylation of aldehydes over ketones can be achieved under *N*-heterocyclic carbene catalysis.[13] The superbase 1,5,7-triazabicyclo[4.4.0]dec-5-ene **15** (TBD, Scheme 6) acts as an efficient catalyst in trifluoromethylation of aldehydes using **1** (Scheme 6a).[27] Aromatic aldehydes, trans-cinnamaldehyde and aliphatic aldehydes **5** were treated with **1** (RPr) in DMF in the presence of 5 mol% of **15** affording the corresponding products **6** in good yields.



Scheme 6

The authors give a possible mechanism (Scheme 6b) in which first **15** (TBD) coordinates to the silicon atom of **1** ($TMSCF_3$, RPr) activating the C-Si bond. Hydrogen-bond activation of the carbonyl compound with the same molecule of TBD occurs next. Both the activated silylated nucleophile and carbonyl compound can then readily react to produce the adduct and silylated TBD. Finally, silyl transfer occurs to give the silylated adduct **6** with regeneration of TBD.

In these reactions coordinating solvents like THF are most suitable and solvents that contain acidic protons should be avoided. The hydrofluorocarbon SolkaneR 365mfc (1,1,1,3,3-pentafluorobutane) is a potentially useful alternative solvent for trifluoromethylation reactions,[28] since it has no impact whatsoever on the ozone layer, and it passed all the necessary toxicological tests successfully. Therefore SolkaneR 365mfc has been used as alternative solvent for the nucleophilic trifluoromethylation of aldehydes **5** (Scheme 7), in the presence of inorganic bases such as NaOH, KOH, CsOH and CsF. Solvolysis of **1** (RPr) by SolkaneR 365mfc *via* fluorophilic attraction might be responsible for this efficient transformation.



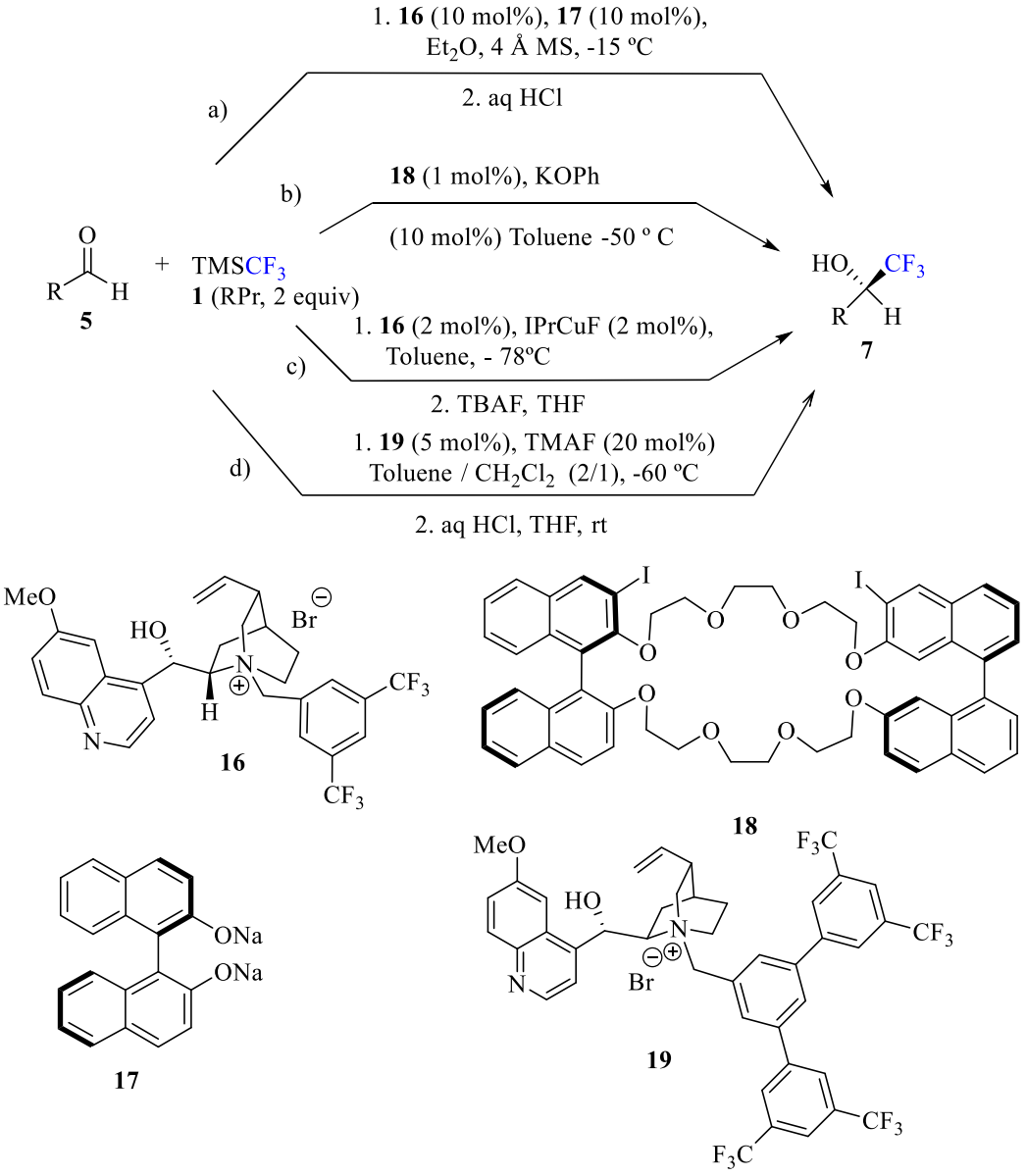
R = 1-naphthyl, 2-naphthyl, Ph, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, (*E*)PhCH=CH, $PhCH_2CH_2$

Scheme 7

A wide range of Lewis acids have been employed in nucleophilic trifluoromethylation with **1** ($TMSCF_3$, RPr). Shibata and co-workers reported the first Lewis acid-catalyzed trifluoromethylation reaction of aldehydes with $TMSCF_3$ in DMF.[29] The best results within acceptable reaction times for the nucleophilic addition to 2-naphthaldehyde in DMF, were obtained when TiF_4 (96%), $Ti(OiPr)_4$ (96%) and $MgCl_2$ (91%) were used.

The first enantioselective trifluoromethylation of carbonyl compounds was developed in 1994 by Iseki's and Kobayashi's groups[30] using chiral ammonium fluorides derived from *Cinchona* alkaloids as phase-transfer catalysts and **1** ($TMSCF_3$, RPr). Since 1999 other *N*-benzylquinidinium fluorides or bromides have been used as chiral ammonium salts in the enantioselective trifluoromethylation reaction of aromatic aldehydes.[13] For the same purpose, a chiral triaminosulfonium salt derived from diphenylpyrrolidine has been applied to the preparation of secondary alcohols through the trifluoromethylation of aldehydes, although in this case the enantiomeric excess did not exceed 52%.[31]

Feng *et al.* added BINOL/sodium salt **17** as co-catalyst to a derivative **16** (Scheme 8a, Table 1, entries 1 to 11).[32] This combination was able to furnish trifluoromethylated alcohols with higher enantiomeric excess (up to 71%).



Scheme 8

Shibata *et al.* proposed the use of chiral crown ethers **18** as catalysts for the addition of **1** (RPr) to carbonyl compounds (Scheme 8b, Table 1, entries 12 to 16).[33] Crown ethers **18** were easily synthesized from 3-iodobinaphthol and used together with catalytic potassium phenoxide, which acts as a Lewis base to activate **1** (RPr). Although these results are better than the first reported in the trifluoromethylation of aldehydes, they are slightly worse than Feng's group binary catalytic system.

Table 1. Catalyzed enantioselective trifluoromethylation of aldehydes **5** using **1** (RPr) and catalysts **16** and **18**

Entry	R	catalysts / activator	Yield (%)	*ee* (%)
1	Ph	**16** / **17** [a]	72	56
2	2-naphthyl		85	71
3	4-MeC_6H_4		87	60
4	3-ClC_6H_4		95	56
5	3,4-(OCH_2O)C_6H_3		95	46
6	thiophen-2-yl		68	45
7	3-MeC_6H_4		88	58
8	4-ClC_6H_4		72	50
9	4-PhC_6H_4		73	56
10	4-MeOC_6H_4		87	41
11	4-FC_6H_4		86	57
12	2-naphthyl	**18** / KOPh [b]	88	40
13	Ph		84	44
14	4-MeOC_6H_4		84	43
15	(*E*)-PhCH=CH		90	21
16	PhCH_2CH_2		72	24

[a] Reference 32. [b] Reference 33.

A general catalytic enantioselective trifluoromethylation of aromatic aldehydes using only 2 mol% of the (IPr)CuF [IPr = 1,3-bis(2´,6´-diisopropylphenyl)imidazol-2-ylidene] and quinidine derived quaternary ammonium salt **16** as the catalyst has been developed.[34] This process proceeds through [(IPr)CuCF_3] and (IPr)Cu-alkoxide to give the product **7** (Scheme 8c, Table 2, entries 1-21) and it transforms a wide range of aromatic aldehydes **5** to the corresponding products with high levels of enantiomeric excess.

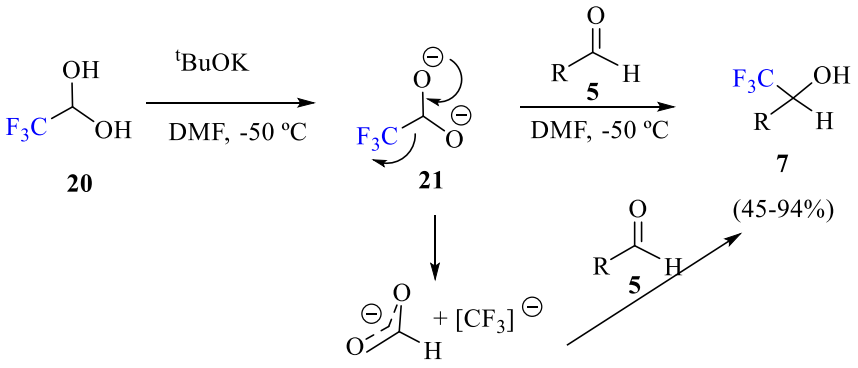
Recently, Shibata *et al.*[35] described the catalytic enantioselective trifluoromethylation reaction of aromatic aldehydes **5** using **1** (RPr) and a combination of sterically demanding *Cinchona* alkaloid-derived phase-transfer catalyst **19** with **10** (TMAF). The methodology provides medicinally important α-trifluoromethyl alcohols **7** with high chemical yields and moderate to good enantioselectivities (Scheme 8d, Table 2, entries 22-31).

Table 2. Catalyzed enantioselective trifluoromethylation of aldehydes **5** using **1** (RPr) and catalyst **16** and **19**

Entry	R	catalyst / activator	Yield (%)	*ee* (%)
1	2-naphthyl	**16** / IprCuF [a]	90	75
2	1-naphthyl		88	60
3	Ph		80	60
4	2-pyridyl		89	42
5	4-BrC_6H_4		81	57
6	3-BrC_6H_4		82	52
7	4-ClC_6H_4		83	51
8	3-ClC_6H_4		83	51
9	4-FC_6H_4		79	45
10	3-FC_6H_4		87	51
11	4-MeC_6H_4		88	68
12	4-PhC_6H_4		90	66
13	3-$PhOC_6H_4$		87	60
14	4-$MeOC_6H_4$		85	67
15	3-$MeOC_6H_4$		89	74
16	2-$MeOC_6H_4$		88	73
17	6-MeO-2-naphthyl		83	53
18	3,4-$(OCH_2O)C_6H_3$		92	81
19	3,4-$(OCH_2CH_2O)C_6H_3$		92	79
20	4-$(C_3H_5O)C_6H_4$		80	67
21	4-$C_2H_5SC_6H_4$		85	73
22	2-naphthyl	**19** / TMAF [b]	92	66
23	5-anthracyl		96	50
24	3,4-$O(CH_2)_2C_6H_3$		99	63
25	3-MeC_6H_4		72	63
26	3-$MeOC_6H_4$		82	70
27	3-ClC_6H_4		70	55
28	3-BrC_6H_4		73	58
29	4-MeC_6H_4		76	60
30	3,4-$Me_2C_6H_3$		86	56
31	3,4-$(MeO)_2C_6H_3$		94	50

[a] Reference 34. [b] Reference 35.

Stable hemiaminals of trifluoroacetaldehyde (fluoral) constitute powerful trifluoromethylating reagents giving good isolated yields of non-enolizable aldehydes even in heterocyclic series after activation by a stoichiometric strong base or catalytic cesium fluoride.[13] On the other hand, trifluoroacetaldehyde hydrate **20** was found to be applicable as a trifluoromethyl anion source to nucleophilic trifluoromethylation of aldehydes **5** (Scheme 9).[36] Actually, the reagent **20** is commercially available as a dihydrate $CF_3CH(OH)_2•2H_2O$, so the optimal reaction conditions were found by treating **20** (1.5 equiv) with tBuOK (6.0 equv) in DMF at –50 °C for 30 min, followed by the addition of aldehydes **5**. Aryl aldehydes bearing electron-donating substituents and halogens were shown to participate in the reaction to afford products in good to excellent yields. However, strong electron-withdrawing moieties such as NO_2 and CF_3 groups on the phenyl ring blocked the reaction. In comparison with the significant electronic effects, the steric hindrance of substituents did not play a major role in the reactivity of the substrates. DFT calculations have been performed to provide mechanistic insight into the present and related reactions employing 2,2,2-trifluoro-1-methoxyethanol and hexafluoroacetone hydrate. The authors envisaged that ready available trifluoroacetaldehyde hydrate **20** could enable nucleophilic trifluoromethylation by expelling formate as leaving group.

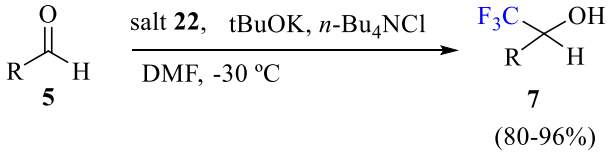


R= Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$Me_2NC_6H_4$, 3-MeC_6H_4 , 3-MeC_6H_4, 2,4,6-$(MeO)_3C_6H_2$, 2-naphthyl

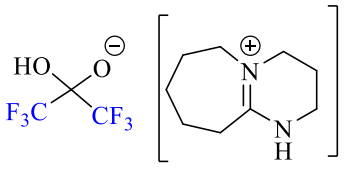
Scheme 9

Based on the previous trifluoroacetaldehyde hydrate, the corresponding hexafluoroacetone hydrate derivative **22** (Scheme 10) was prepared by treatement of an ethereal solution of hexafluoroacetone trihydrate with DBU. The powerful, new reagent amidinate salt **22** is a free flowing powder stable in air which, in basic conditions by using a combination of tetrabutylammonium chloride and tBuOK, promoted the generation of the CF_3 anion. It reacted with a series of aldehydes **5** to give their trifluoromethyl alcohols in good to excellent (80-96%) isolated yields (Scheme 10).[37] The new stable reagent is not hygroscopic and can be routinely weighed in air. The workup procedure for this synthetic method is notably advantageous, because the

byproducts of the reaction (i.e., tBuOH, tetrabutylammonium salts, and trifluoroacetate) are easily removed by an aqueous work-up.

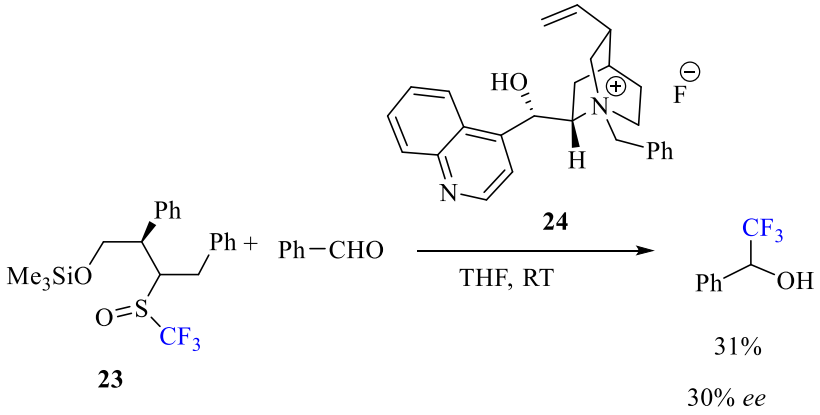


R= 4-$MeOC_6H_4$, 4-pyrrolidineC_6H_4, 4-Me_2N-naphthyl, 2-Br-3,4-$OCH_2OC_6H_2$, 3,4-$OCH_2CH_2OC_6H_3$, 4-$Me_2NC_6H_4$, 2,3,4-$(MeO)_3C_6H_2$



Scheme 10

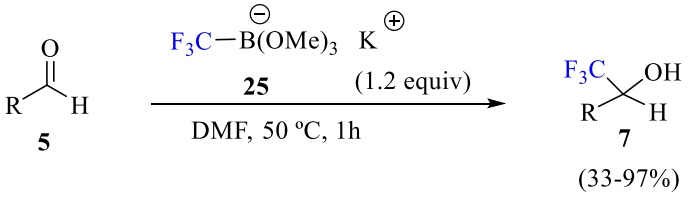
Compounds bearing a CF_3 group on sulfur, as well as, trifluoroacetic acid derivatives such as trifluoroacetamides, trifluoromethanesulfinamides, and α,α,α-trifluoroacetophenone also behave as efficient trifluoromethylating reagents for the nucleophilic trifluoromethylation of reactive aldehydes.[13] In addition, Langlois' group employed various chiral trifluoromethanesulfinamides such as chiral trifluoromethylating agents in order to get the same enantioselectivity. In this sense, **23** reacted with benzaldehyde in the presence of chiral ammonium fluoride **24** (Scheme 11) to give trifluoromethylated benzyl alcohol in 30% enantiomeric excess.[38]



Scheme 11

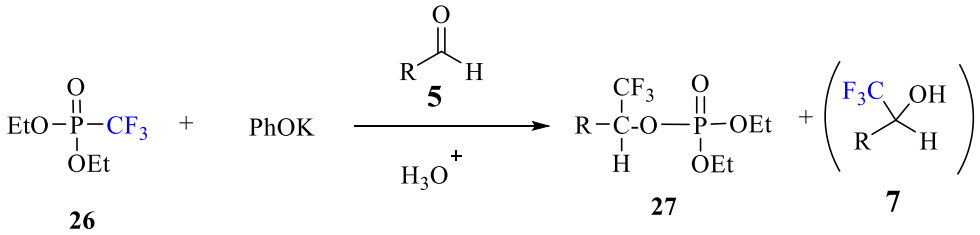
Potassium trialkoxy(trifluoromethyl)borates, prepared from trialkoxy borates and $TMSCF_3$/KF according to literature procedures[39] showed to behave as convenient reagents for

nucleophilic trifluoromethylation of non-enolizable aldehydes.[40] Benzaldehyde and other aromatic aldehydes as well as cinnamaldehyde, were treated with 1.2 equiv of salt **25** using DMF as the solvent followed by acidic work-up and furnished trifluoromethylated alcohols **7** in excellent yields (Scheme 12). The ester group of *p*-methoxycarbonylbenzaldehyde remained unaffected, and the desired alcohol **7** was formed as the sole product.



Scheme 12

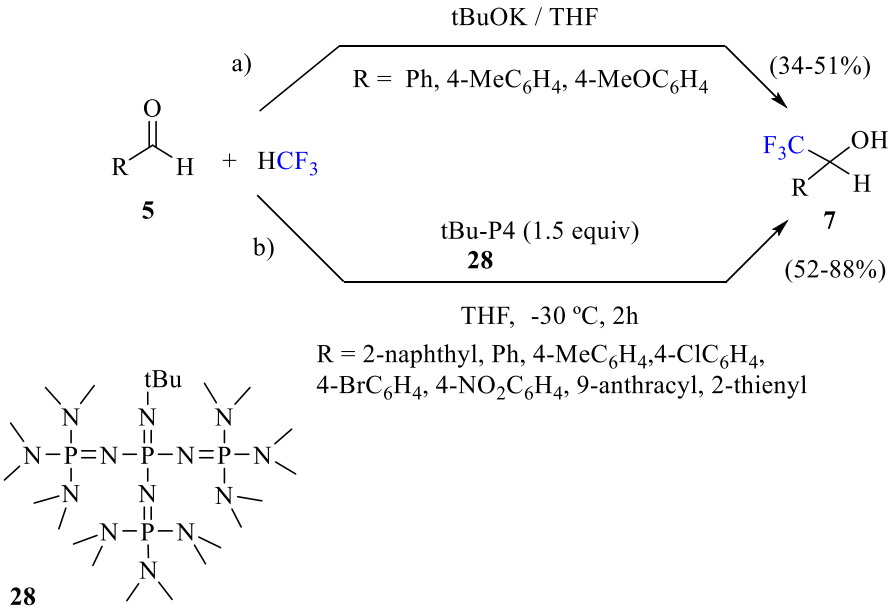
Diethyl trifluoromethylphosphonate **26** in the presence of alkoxide ions (potassium tert-butoxide or phenoxide) represents a new system for the nucleophilic trifluoromethylation of aryl and alkyl aldehydes (Scheme 13).[19] This new reagent was prepared by reaction of CF_3I with $P(OEt)_3$ under photolytic conditions. Addition of a nucleophilic reagent such as potassium phenolate to **26** would effect cleavage of the carbon–phosphorus bond to generate an unstable trifluoromethyl carbanion, which in the presence of aldehydes **5** provided the corresponding phosphates of trifluoromethyl carbinols **27** in good yields (60-72%) in some cases accompanied by small amounts of trifluoromethyl alcohols **7** (9-16%).



Scheme 13

Trifluoromethane HCF_3 has been reported[13] as a source of CF_3 anion because it can be deprotonated with common bases in DMF to produce a stable equivalent of the trifluoromethyl anion, a trifluoromethylating hemiaminolate species that reacts with nonenolizable aldehydes.

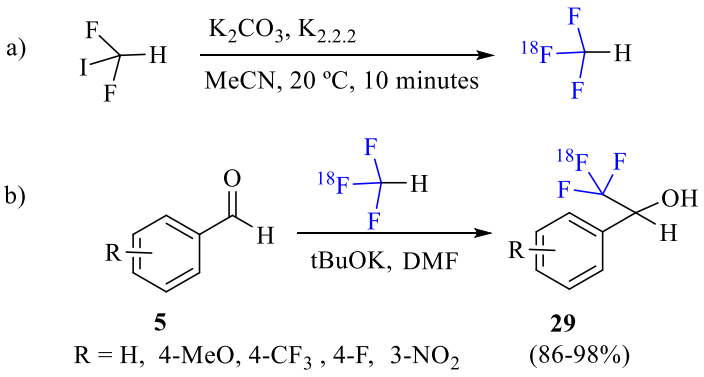
All the reported papers for trifluoromethylation by HCF_3 indicated the importance of required DMF. However, Prakash *et al.*[41] reported an excellent and elegant strategy without the help of DMF for direct nucleophilic trifluoromethylation with fluoroform (HCF_3) in the presence of tBuOK in THF, (34–51%, Scheme 14a).



Scheme 14

Recently, the direct trifluoromethylation of aldehydes using fluoroform in the presence of tBu-P4 superbase has been reported by Shibata's group.[42] Thus, the reaction of aromatic and heteroaromatic aldehydes **5** with HCF_3 and the extremely strong non metallic organo-superbase tBu-P4 **28** gives the corresponding α-trifluoromethyl alcohols **7** in good to high yields (52–88%, Scheme 14b). However, the reaction system is not applicable for the reaction of aliphatic aldehydes.

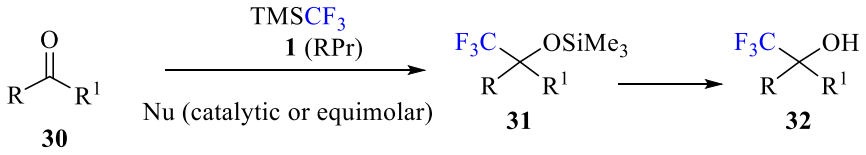
A new strategy towards [^{18}F]-trifluoromethyl-containing carbinols using [^{18}F]trifluoromethane has been developed.[43] In this case gaseous [^{18}F]-trifluoromethane is synthesized in a fast and efficient manner by reaction of difluoroiodomethane with [^{18}F]fluoride/kryptofix 2.2.2 ($K_{2.2.2}$) in acetonitrile in a satisfactory yield and in a reaction time of 10 minutes at room temperature (Scheme 15a). Various benzaldehydes **5** containing electron withdrawing and donating groups reacted in the presence of tBuOK in a moderate to high yield to give [^{18}F]-phenyl-2,2,2-trifluoromethanol derivatives **29** (Scheme 15b).



Scheme 15

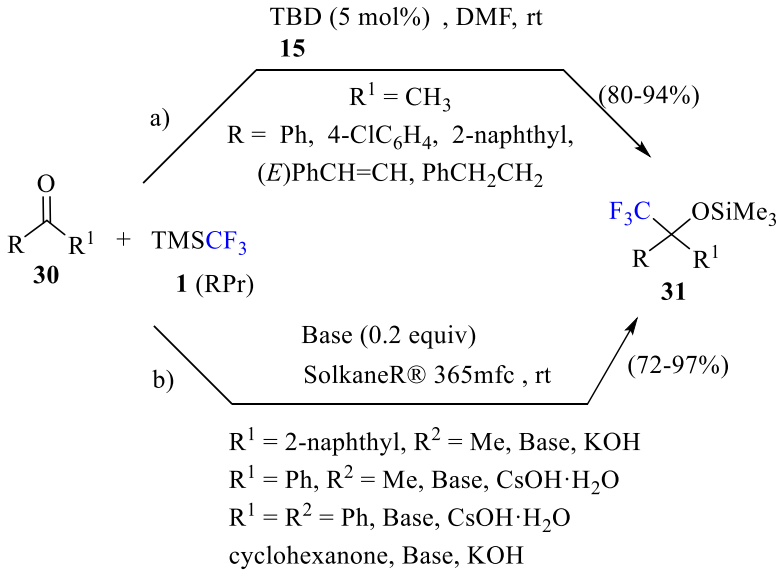
3. Trifluoromethylation of ketones

In a similar way to the aldehydes, the most widely exploited route for nucleophilic trifluoromethylation of ketones involves the use of a CF_3-containing reagent in combination with a suitable basic activator. General trifluoromethylation reaction between $TMSCF_3$ **1** (RPr) and ketones **30** proceeds according to Scheme 16,[13] whereby the trifluoromethylated alcohol in its trimethylsilylated form **31** is obtained upon the addition of an appropriate nucleophilic initiator to the reaction mixture. The initial addition step is usually followed by desilylation to give CF_3-substituted alcohols **32**.



Scheme 16

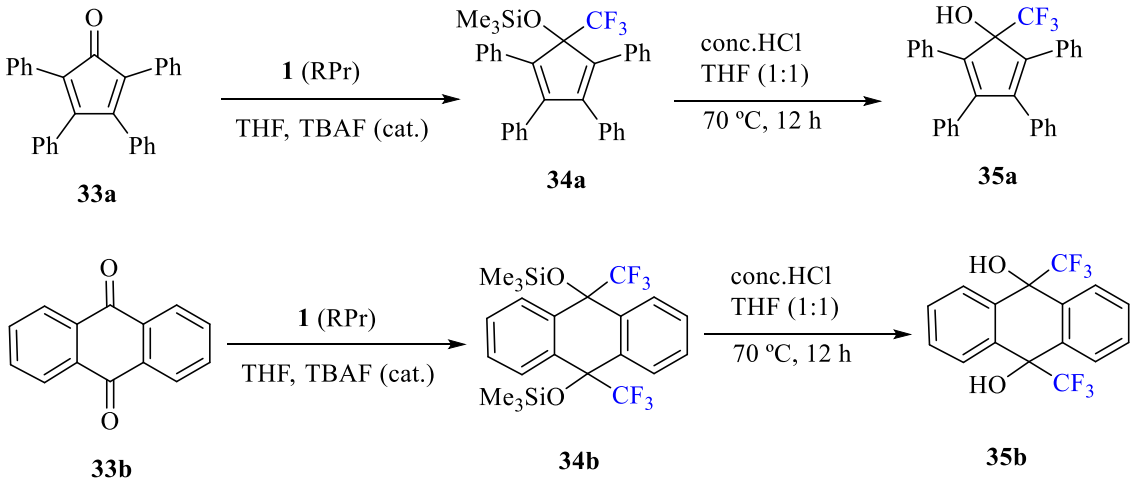
Typical initiator is a fluorine containing compound such as **8 (**TBAF) or CsF, but nucleophilic trifluoromethylation of ketones with **1** (RPr) have also been studied using other nucleophilic catalysts, such as, pyridine, $AsPh_3$ and $SbPh_3$, Et_3N, n-Bu_2NH, Ph_3P or P(t-Bu)$_3$, amine *N*-oxide, carbonate and phosphate salts.[13] For example, the reaction of various aryl methyl ketones **30** with **1** (RPr) in DMF in the presence of 5 mol% of **15** (TBD, Scheme 17 a) proceeded smoothly.[27] Longer reaction times were required in the case of aliphatic ketones compared to the reaction with aromatic ones.



Scheme 17

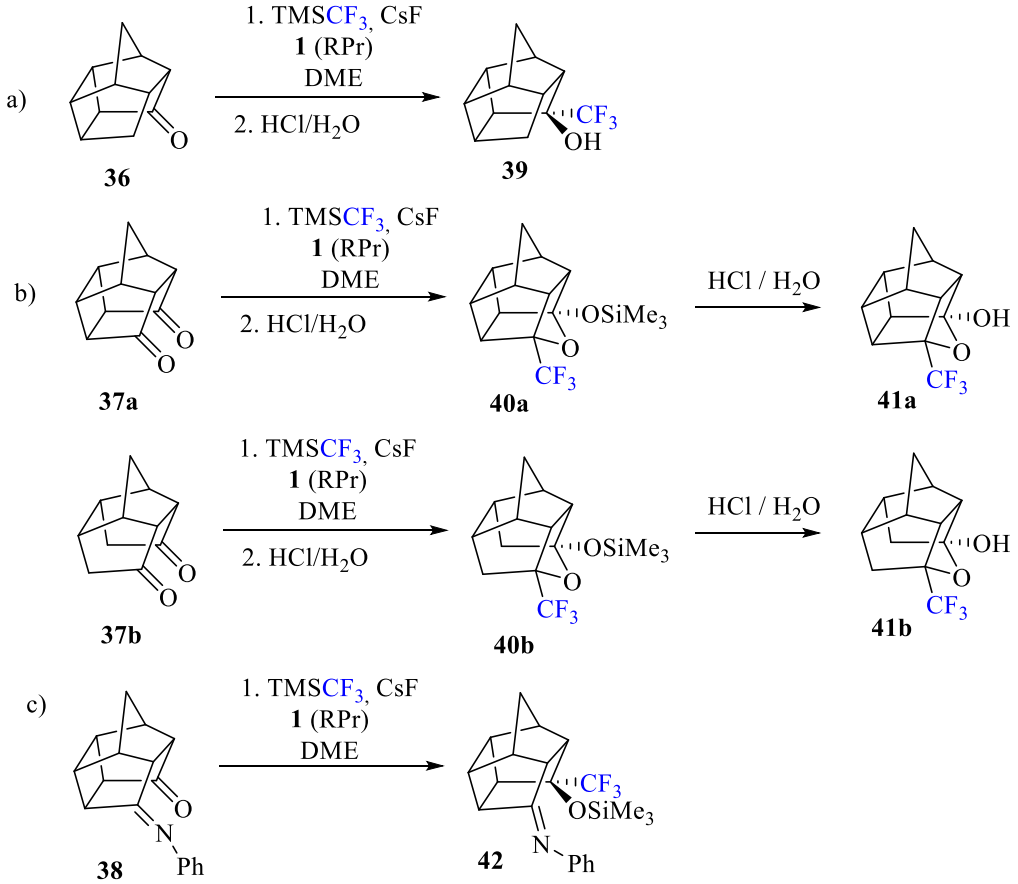
Moreover, as mentioned before, SolkaneR 365mfc has been used also as alternative solvent for the nucleophilic trifluoromethylation of ketones **30** (Scheme 17b) in the presence of inorganic bases such as NaOH, KOH, CsOH and CsF.[28]

The scope of trifluoromethylation process is very broad since simple ketones or α, *β*, and *γ*-dicarbonyl compounds reacted with **1** ($TMSCF_3$, RPr) in the presence of fluoride activator to give a variety of trifluoromethylated silyl eters and their corresponding tertiary alcohols, including allylic derivatives.[13] Singh and Shreeve have applied the reagent **1** (RPr) in the synthesis of some novel trifluoromethyl containing alcohol derivatives.[24] The reactions of **1** with various ketones, such as tetraphenylcyclopentadienone **33a**, 9,10-anthraquinone **33b**, in the presence of a catalytic amount of tetrabutylammonium fluoride in THF led to the formation of the corresponding trifluoromethylated silyl ether derivatives **34a**,**b** in almost quantitative yields. Acid hydrolysis of **34a**,**b** gave the trifluoromethylated alcohol derivatives **35a**,**b** in excellent isolated yields (Scheme 18).



Scheme 18

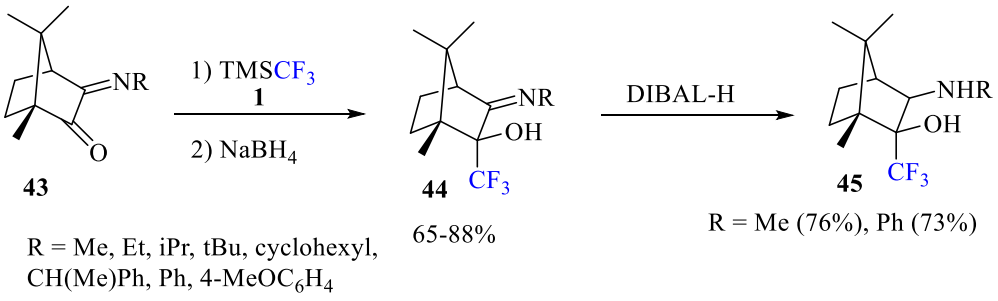
The trifluoromethylation of polycyclic ketones **36-38** using **1** (RPr) in the presence of dry CsF (Scheme 19) has been described.[44]



Scheme 19

Thus, the trifluoromethylation of the ketone **36** with **1** (RPr) in 1,2-dimethoxyethane (DME) in the presence of CsF led to a single product, which, after acidic hydrolysis, was identified as the trifluoromethylated alcohol **39**, with an *exo*-oriented trifluoromethyl group (Scheme 19, a). Under the same conditions, the corresponding diketones,**37a-b** were converted to the silylated acetals **40a-b** (Scheme 19b). In the case of the iminoketone **38** the addition of **1** occurred chemoselectively at the keto group yielding product **42** again with the CF_3 group in the exo position (Scheme 19c). In contrast to the reaction with the parent dione **37**, no cyclization *via* attack to the iminic carbon-nitrogen double bond was observed and the silylated adduct **42** was isolated as the only product.

Similarly, the chemoselective trifluoromethylation of the C=O group of α-imino ketones derived from camphorquinone **43** was performed with **1** (RPr).[45] The treatment with $NaBH_4$ underwent only desilylation (Scheme 20). The reduction of the C=N bond, leading to amino alcohols **45**, was achieved only by using diisobutylaluminium hydride (DIBAL-H) for the final step of the procedure.



43 **44** **45**

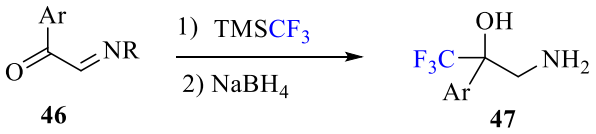
R = Me, Et, iPr, tBu, cyclohexyl, CH(Me)Ph, Ph, 4-$MeOC_6H_4$

65-88%

R = Me (76%), Ph (73%)

Scheme 20

Nevertheless, nucleophilic trifluoromethylation of acyclic α-imino ketones **46** derived from arylglyoxal, with **1** (RPr) offers a convenient access to the corresponding *O*-silylated β-imino-α-(trifluoromethyl) alcohols and then to the aminoalcohols **47** (Scheme 21),[46] after desilylation and selective reduction of the C=N bond with $NaBH_4$ all in "one pot" procedure.



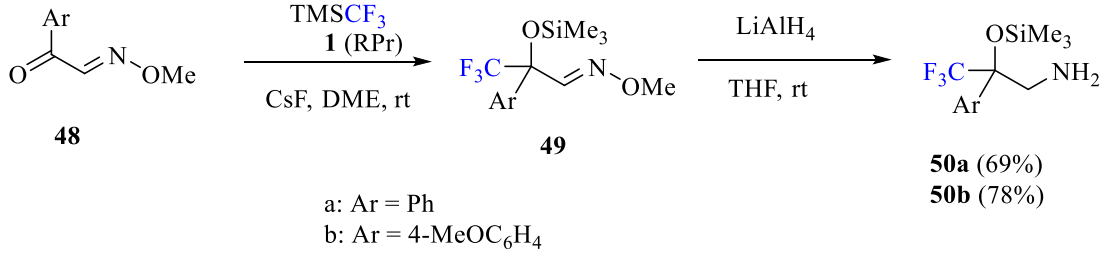
46 **47**

a: Ar = 4-$NO_2C_6H_4$, R = tBu (91%)
b: Ar = 4-$MeOC_6H_4$, R = *i*Pr (92%)

Scheme 21

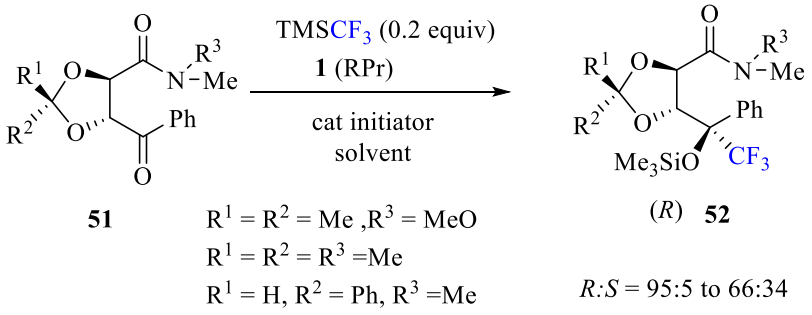
Another example of the preparation of amino alcohols with a primary amino group *via* nucleophilic trifluoromethylation of properly selected arylglyoxalimines **48** has been described.[47]

The nucleophilic trifluoromethylation was carried out using an equimolar amount of **1** (RPr) in dimethoxyethane and in presence of catalytic amounts of CsF (Scheme 22). β-Amino-α-trifluoromethyl alcohol derivatives **50** were obtained *via* sequential nucleophilic trifluoromethylation of selected α-imino ketones **48** derived from arylglyoxals, and subsequent removal of the MeO substituent located at the nitrogen atom.



Scheme 22

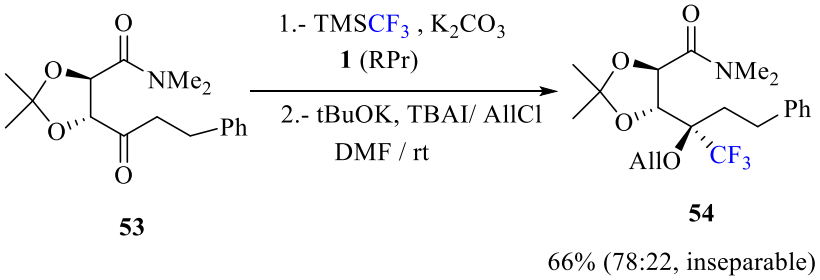
Portella and coworkers have described a highly diastereoselective nucleophilic mono(trifluoromethylation) of a tartaric acid-base diketone using **1** (RPr). The process was extended to the asymmetric synthesis of functionalized amides **52** (Scheme 23). The key step involves the diastereoselective addition of RPr to a tartaric acid derived ketoamide **51**.[48] Despite the preparation of **52** in fair yields (Scheme 23), this methodology might be applied to a variety of compounds covering aliphatic, aromatic, and heteroaromatic series, although the overall process is generally more effective in the aromatic series.



Scheme 23

This nucleophilic trifluoromethylation of a tartaric acid derived ketoamide has been used as key step in the synthesis of the four stereoisomers of 2-(trifluoromethyl) tetrahydronaphthalene-1,2-diols and/or their 2-*O*-allyl derivatives.[49] According to the "one-pot" procedure depicted in Scheme 24, the *O*-allyl trifluoromethylated compound **54** was first synthesized from ketoamide **53** prepared from the bis(dimethylamide) of tartaric acid. As previously observed, the trifluoromethylation step with aliphatic ketones is less diastereoselective than it was with

aromatic ones, which is advantageous because gives access to the whole set of stereoisomers. Unfortunately, the separation of the diastereomers of **54** proved to be difficult and a stepwise procedure had to be carried out to obtain each diastereomer separately.

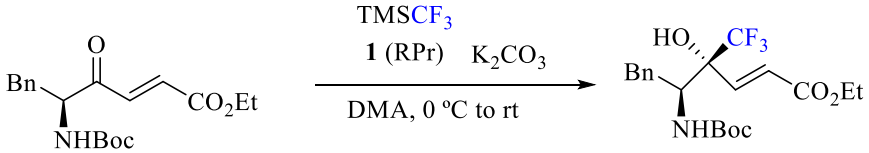


53 **54**

66% (78:22, inseparable)

Scheme 24

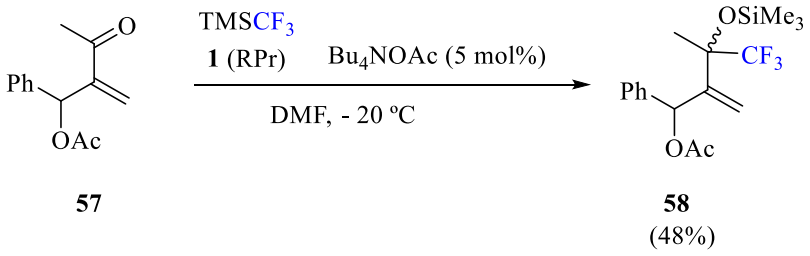
Besides ketoamides, ketoesters **55** also reacted in a selective way through the keto group with **1** (RPr, 2 equiv) in the presence of K_2CO_3 (10 mol %) to give the allyl alcohol **56** in 59% yield with 77% *de* within 12 h (Scheme 25) as described by Kobayashi's group.[50]



55 **56**

Scheme 25

In a similar process, acylated Baylis-Hillman adducts **57** with a ketone group (Scheme 26) underwent nucleophilic attack by CF_3 anion at the C=O bond.[51] The trifluoromethyl alcohol derivative **58** was obtained as a mixture of two diastereoisomers and Michael addition products were not observed.



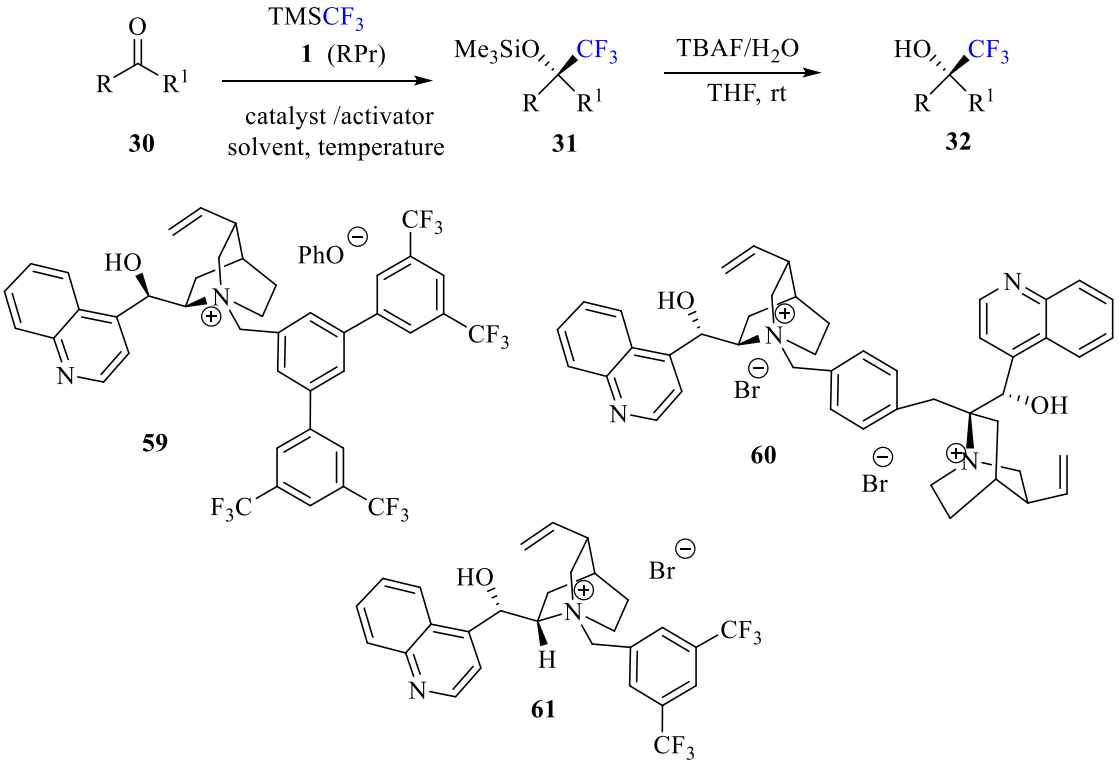
57 **58**

(48%)

Scheme 26

The catalytic enantioselective nucleophilic trifluoromethylation of carbonyl derivatives is certainly one of the most important strategies for the synthesis of optically active trifluoromethylated alcohols.[52] The combination of chiral catalysts with achiral species has proved to be a powerful tool in the construction of chiral non-racemic trifluoromethylated molecules. Using chiral ammonium salts derived from *cinchona* alkaloids the trifluoromethylation of ketones **30** gives the corresponding trifluoromethylated alcohols **32** (Scheme 27).

Mukaiyama *et al*. developed a *cinchona* alkaloid derivative **59** with phenoxide as counteranion (Scheme 27)[53] based on the fact that metal alkoxides are efficient nucleophilic initiators of the Ruppert–Prakash reagent **1**. Therefore, they demonstrated that this cinchonidine-derived quaternary ammonium phenoxide **59** could catalyze the asymmetric trifluoromethylation of ketones and with **1** efficiently, affording the desired products in high yields and with up to 87% *ee* (Scheme 27, Table 3, entries 1-11).



Scheme 27

Shibata's group developed a new derived *cinchona* alkaloid **60**, being the best one for the trifluoromethylation of a wide range of aromatic ketones (Scheme 27, Table 3, entries 12-30) and using tetramethylammonium fluoride **10** (TMAF) as an initiator.[54] Using this methodology quaternary trifluoromethylated alcohols were obtained with good to excellent yields and enantioselectivities up to 94%.

More recently, in 2009, Feng *et al.* reported[55] the use of sodium hydride as an additive to the *Cinchona* alkaloid derivative **61** to catalyze the trifluoromethylation of ketones with moderate to excellent yields and moderate to good enantioselectivities (Scheme 27, Table 3, entries 31-35). In this catalytic system, NaH might serve as the efficient Lewis base to activate **1** (RPr), and the amount of NaH has a great influence on the enantioselectivity of the reaction.

Table 3. Catalyzed enantioselective trifluoromethylation of ketones **30** with **1** (RPr)

Entry	R	R^1	catalyst /activator solvent, temperature	Yield (%)	*ee* (%)
1	3-$O_2NC_6H_4$	Me		98 [e]	87
2	2-$O_2NC_6H_4$	Me	**59** (10 mol%)	93 [e]	71
3	4-$O_2NC_6H_4$	Me	Toluene/CH_2Cl_2 (7:3)	97 [e]	73
4	3-$O_2NC_6H_4$	Et	−78 ºC [a]	99 [e]	64
5	1-naphthyl	Me		91 [e]	51
6	2-naphthyl	Me		95 [e]	77
7	3-BrC_6H_4	Me		97 [e]	61
8	3-NCC_6H_4	Me		90 [e]	71
9	3-$MeOC_6H_4$	Me		90 [e]	59
10	3-pyridyl	Me		90 [e]	46
11	4-pyridyl	Me		93 [e]	60
12	naphthyl	Me		87 [f]	85
13	6-Me-2-naphthyl	Me		74 [f]	88
14	6-MeO-2-naphthyl	Me		74 [f]	87
15	4-BrC_6H_4	Me		81 [f]	86
16	3-BrC_6H_4	Me		73 [f]	71
17	4-$MeOC_6H_4$	Me		84 [f]	89
18	4-ClC_6H_4	Me		71 [f]	87
19	4-FC_6H_4	Me	1.- **60** (10 mol %) / **10** (TMAF, 10 mol%), Toluene/CH_2Cl_2 (2:1), −60 ºC 2.- TBAF/H_2O, THF, rt [b]	96 [f]	87
20	4-MeC_6H_4	Me		94 [f]	88
21	3-ClC_6H_4	Me		80 [f]	74
22	(*E*)PhCH=CH	Me		85 [f]	70
23	$PhCH_2CH_2$	Me		37 [f]	10
24	4-BrC_6H_4	Et		84 [f]	93
25	Ph	Et		65 [f]	82
26	Ph	Pr		83 [f]	76
27	1-indanone			34 [f]	74
28	1-tetralone			75 [f]	94
29	6-MeO-tetralone			82 [f]	86
30	1-benzosuberone			53 [f]	73

Table 3 (continued)

31	2-naphthyl	Me		96 [f]	81
32	3-ClC_6H_4	Me	**61** (5 mol %)/ /NaH (50 mol %)	96 [f]	68
33	4-ClC_6H_4	Me	iPr_2O, –20 ºC [c]	83 [f]	61
34	4-$O_2NC_6H_4$	Me		64 [f]	50
35	(*E*)-PhCH=CH	Me		31 [f]	59
36	Ph	Me	1.- **18** (1 mol %) / KOPh (10 mol %),	66 [f]	38
37	2-naphthyl	Me	Toluene, –50 ºC	91 [f]	34
			2.- TBAF/H_2O, THF, rt [d]		

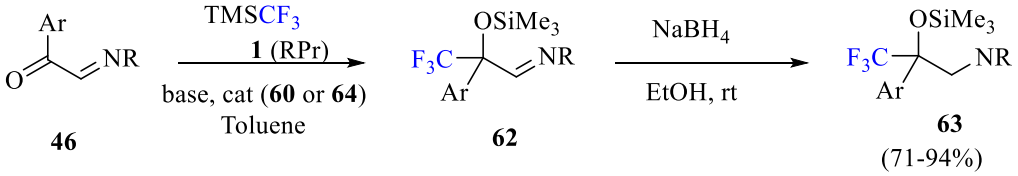
. [a] Reference 53. [b] Reference 54. [c] Reference 55. [d] Reference 33. [e] Obtained compounds **31.** [f] Obtained compounds **32**.

As mentioned before for the trifluoromethylation of aldehydes, Shibata proposed the use of chiral crown ethers as catalysts for the addition of **1** (RPr) to carbonyl compounds (Scheme 27, Table 3, entries 36 and 37).[33] Crown ethers **18** have been used together with catalytic potassium phenoxide, which acts as a Lewis base to activate $TMSCF_3$. Although these results are better than the first reported in the trifluoromethylation of aldehydes, they are slightly worse than Feng's group binary catalytic system.

A new, simple and promising method for the enantioselective synthesis of β-amino-α-(trifluoromethyl) alcohols has been developed.[56] Chemoselective addition of **1** (RPr) to the carbonyl group of α-imino ketones **46** in the presence of enantiomerically pure bromides **60** and **64** (15 mol%), derived from *Cinchona* alkaloids, and potassium fluoride or carbonate, followed by reduction, afforded *O*-silylated β-aminoalcohols **63** in very good yields and with moderate *ee* values (Scheme 28).

Similar to aryl aldehydes, various benzophenone derivatives were also found to be reactive to the nucleophilic trifluoromethylation using trifluoroacetaldehyde hydrate **20** (1.5 equiv) with tBuOK (6.0 equiv) in DMF at −50 °C for 30 min, followed by the addition of ketone **30** (1.0 equiv).[36] Bulky phenyl ketones also reacted to yield the corresponding products **32** in excellent yield. Although enolizable acetophenone was not a viable substrate in the present reaction, adamantan-2-one was smoothly trifluoromethylated because of its low enolizability (Scheme 29a).

A new reagent, the amidinate salt of hexafluoroacetone hydrate **22** (Scheme 29b) has been used also for the conversion of a series of ketones to their trifluoromethyl alcohols **32** in good to excellent (78-94%) isolated yields.[37]

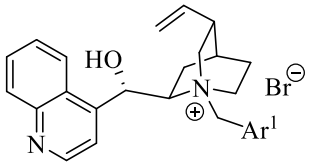


46 **62** **63** (71-94%)

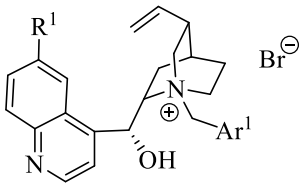
base = KF or K_2CO_3 *ee* : 18-71%

Ar = Ph, 4-$MeOC_6H_5$, 4-NO_2-C_6H_5, benzofuran-2-yl, 7-Et-benzofuran-2-yl

R = tBu, iPr



64a-c

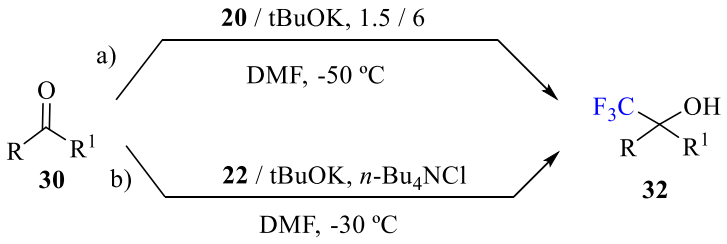


64d-f

a: Ar^1 = Ph
b: Ar^1 = anthracen-9-yl
c: Ar^1 = 3,5-$(CF_3)_2$-C_6H_3

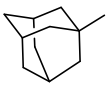
d: Ar^1 = anthracen-9-yl, R^1 = H
e: Ar^1 = 3,5-$(CF_3)_2$-C_6H_3, R^1 = H
f: Ar^1 = 3,5-$(CF_3)_2$-C_6H_3, R^1 = OMe

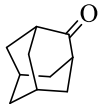
Scheme 28



a) procedure R = Ph, R^1= Ph, 4-$NO_2C_6H_4$, (45-96%)

R = R^1 = 4-$MeOC_6H_4$ (80%)



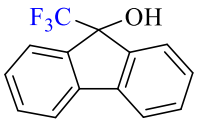


(95%)

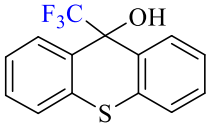
b) procedure

R = R^1 = Ph (94%)

R = R^1 = 4-$MeOC_6H_4$ (94%)



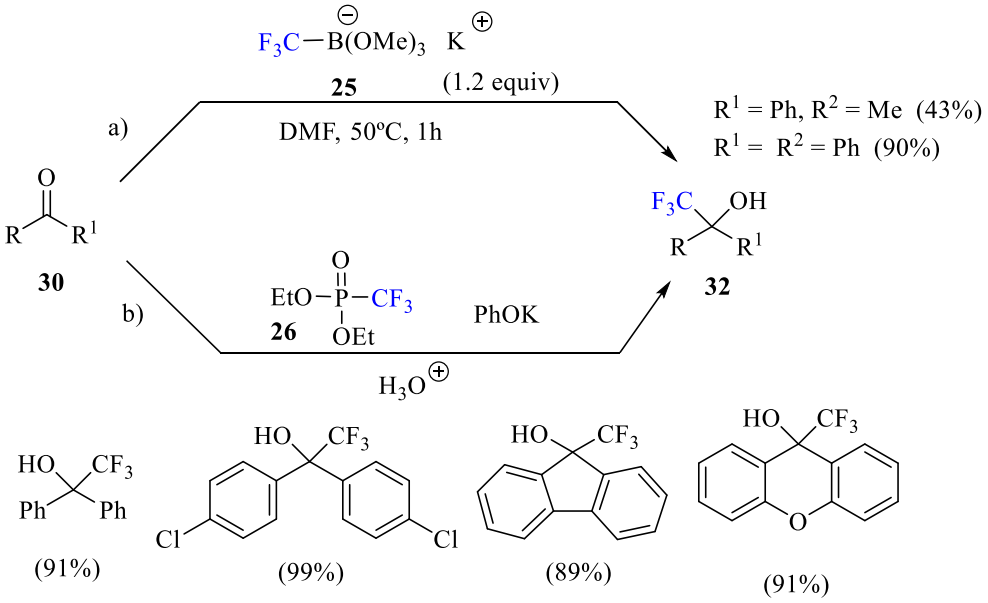
(88%)



(78%)

Scheme 29

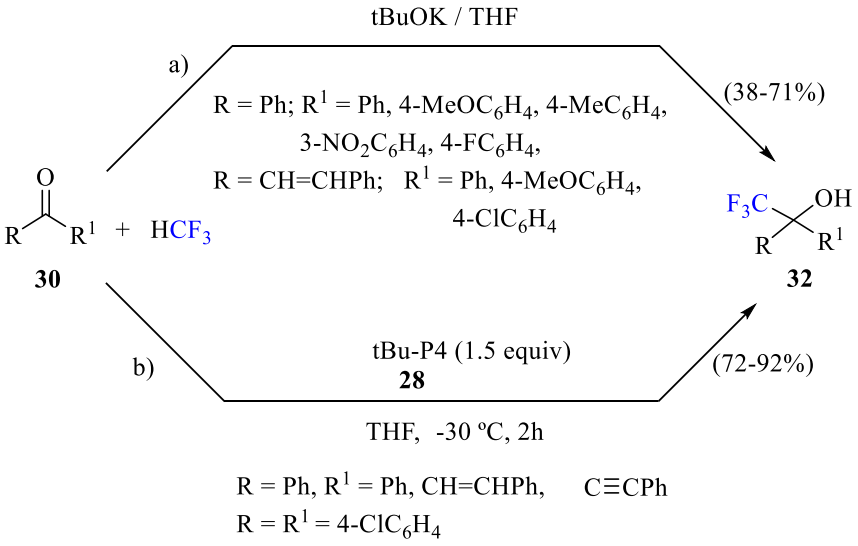
Trifluoroacetophenone, phenyl trifluoromethyl sulfone or sulfoxide, a variety of novel trifluoroacetamides and trifluoromethanesulfinamides derived from *O*-silylated aminoalcohols can be used as nucleophilic trifluoromethylating reagents towards non-enolizable ketones by action of potassium *tert*-butoxide.[13] Likewise, potassium trimethoxy(trifluoromethyl)borate **25** (Scheme 30, a) is shown to behave as convenient reagent for nucleophilic trifluoromethylation of ketones **30** to give CF_3-substituted alcohols **32** in good yields.[40]



Scheme 30

Diethyl trifluoromethylphosphonate **26** in the presence of alkoxide ions (potassium tert-butoxide or phenoxide) represents a new system for the nucleophilic trifluoromethylation of ketones.[19] In the presence of potassium tert-butoxide, non-enolizable ketones **30** provide the corresponding trifluoromethyl carbinols **32** in high yields (Scheme 30, b).

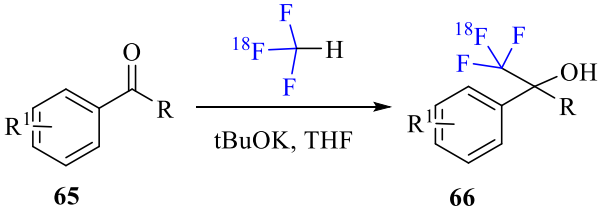
Trifluoromethane (fluoroform) as a source of CF_3 anion has been used also for nucleophilic trifluoromethylation of ketones and as has been seen for aldehydes.[13] More recently, the trifluoromethylation of ketones and chalcones using HCF_3 in the presence of KHMDS has been accomplished by Prakash *et al.*[41] in moderate to good yields (38-81%, Scheme 31a)



Scheme 31

In a similar form, the HCF_3/ tBu-P4 base **28**/THF system (without the presence of DMF) is also applicable for the trifluoromethylation of ketones.[42] Cinnamyl-substituted ketone chalcone, alkynyl-substituted ketone, and benzophenones **30** were suitable substrates for this transformation (Scheme 31, b) and were efficiently converted into α-trifluoromethyl alcohols **32** in high yields. However, as in the case of aldehydes, the reaction system is not applicable for the reaction of aliphatic ketones.

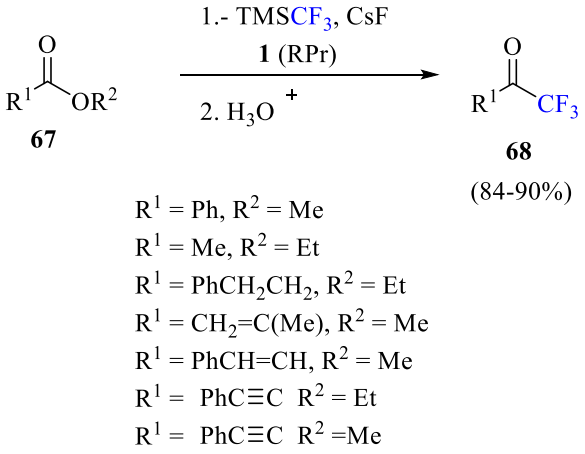
[^{18}F]Trifluoromethane is used also in the reaction with ketones forming [^{18}F]trifluoromethyl carbinols **66** in good yields.[43] Reaction with substituted benzophenones **65** (Scheme 32, R = Ph) provided the expected products in excellent yields (Scheme 32). In the case of acetophenones **65** (Scheme 32, R = Me), enolate formation was expected under the applied reaction conditions, which would lead to a decreased availability of reactive ketones. Indeed, higher base and precursor concentrations were required to obtain the products in satisfactory yields (Scheme 32). Substrate degradation, as was observed using UV-HPLC, caused by the strong basic conditions probably led to low yields.



Scheme 32

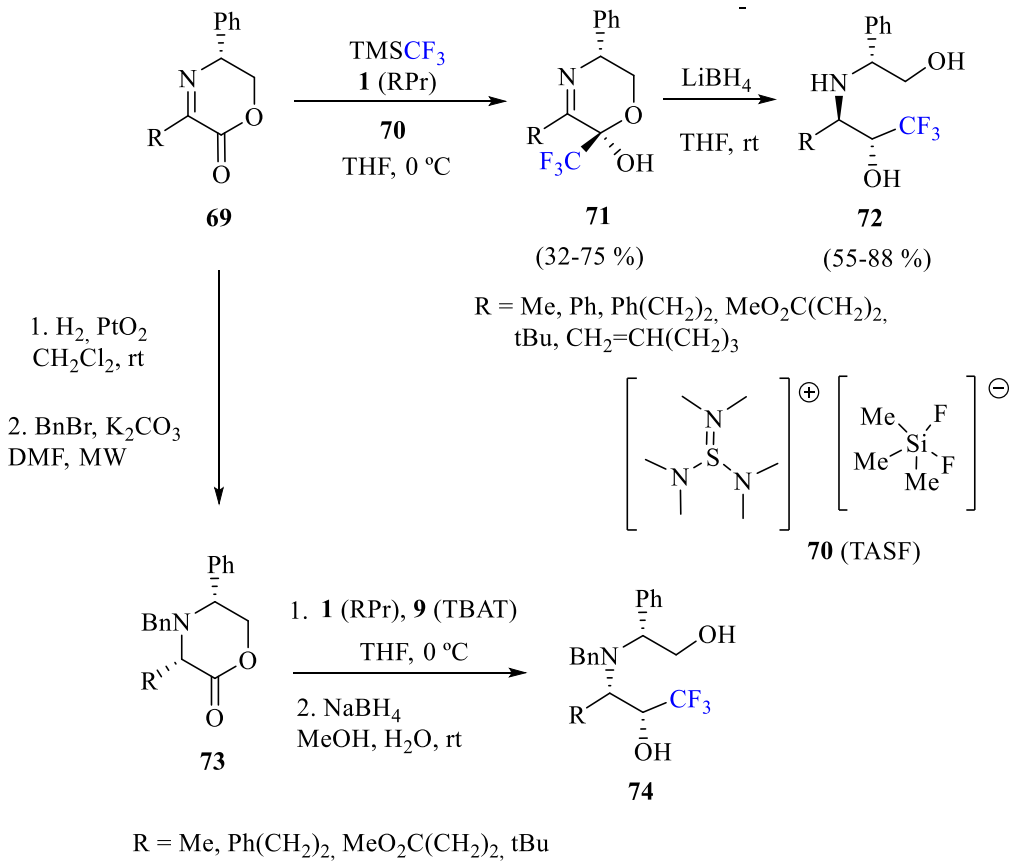
4. Trifluoromethylation of esters

Previous reports have described the poor reactivity of trifluoromethyl anion towards esters,[17,57] because simple esters are not sufficiently electrophilic to react with **1** ($TMSCF_3$, RPr) even when stoichiometric amounts of fluoride are used to promote the process. CsF is a very good initiator for the trifluoromethylation of esters with **1** (RPr). At room temperature (25 °C) with cesium fluoride, carboxylic esters **67** were found to react to give the silyl ether intermediates, which afforded the trifluoromethyl ketones **68** after hydrolysis (Scheme 33).[57]



Scheme 33

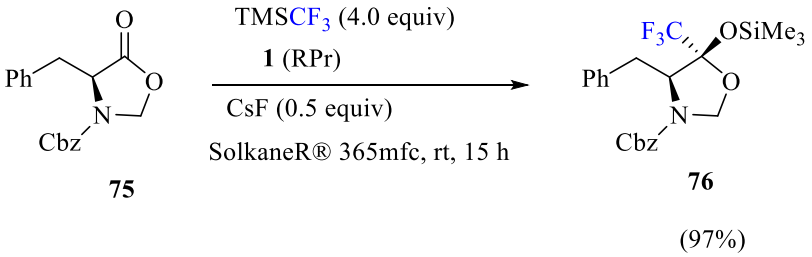
Reactions of various keto esters, *N*-protected amino esters, a variety of amino acid derived *N*-substituted oxazolidin-5-ones and benzylated mono- and bicyclic imides with **1** (RPr) in the presence of catalytic amounts of cesium fluoride led to the formation of the respective CF_3-adducts.[13] Fustero *et al.* have developed an efficient method for preparing both *anti*- and *syn*-α-amino-β-trifluoromethyl alcohols.[58] The method involves the addition of **1** (RPr) to optically pure 5,6-dihydro-2*H*-1,4-oxazin-2-ones **69** (Scheme 34) to afford the corresponding trifluoromethyl imino lactols **71**. Various fluoride sources were evaluated but finally good yields were achieved with tris(dimethylamino)sulfonium difluorotrimethylsilicate **70** (TASF). The stereoselective reduction of imino lactols **71** with $LiBH_4$ produced *anti*-amino diols **72** as the major isomers with good selectivity.



Scheme 34

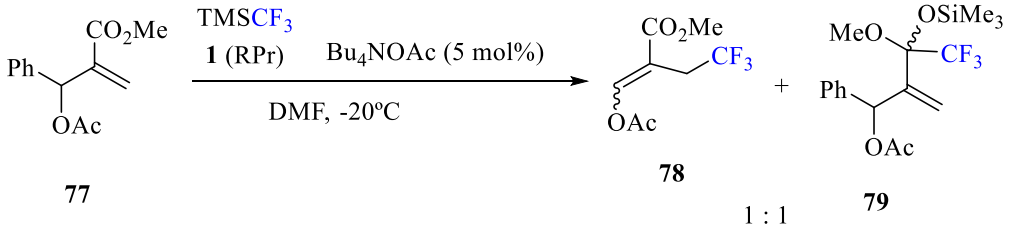
For the preparation of the corresponding *syn* diastereoisomers **74** the starting substrates **69** were first hydrogenated and the amino group was protected with BnBr to yield **73** (Scheme 34). The addition of **1** (RPr) to these amino lactones was more effective when using **9** (TBAT) as activator. Further reduction with $NaBH_4$ produced *syn*-diols **74** with excellent diastereoselectivity (> 97:3). Using the same methodology this group has described the preparation of optically pure fluorinated quaternary piperidines from the quiral iminolactone derived from (*R*)-phenylglycinol. The addition of **1** (RPr) with tris(dimethylamino)sulfonium difluorotrimethylsilicate **70** (TASF) as fluoride source followed by iodoamination and migration of the CF_3 group allowed access to derivatives of α-trifluoromethylpipecolic acid.[59]

As already indicate above for the nucleophilic trifluoromethylation of carbonyl compounds, SolkaneR 365mfc (1,1,1,3,3-pentafluorobutane) is a good alternative solvent for trifluoromethylation reactions of esters.[28] In SolkaneR 365mfc, the reaction of oxazolidin-5-one **75** with **1** (RPr) and with CsF proceeded quite nicely to afford **76** in 97% yield (Scheme 35).



Scheme 35

Trifluoromethylation of Baylis-Hillman adducts **77** with an ester group was performed using **1** (RPr) in the presence of Bu_4NOAc and using DMF as solvent (Scheme 36).[51] However, an inseparable mixture of Michael addition product **78** and derivative **79** (both as isomeric mixtures) was obtained with low yield (30%).

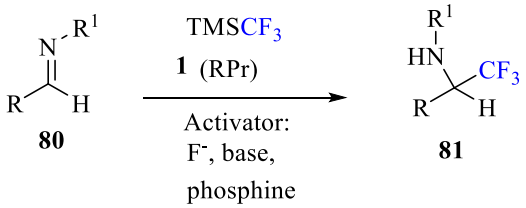


Scheme 36

Analogously to carbonyl compounds (*vide supra*), nucleophilic trifluoromethylation of formate esters and methylbenzoate using HCF_3 and KHMDS in toluene or THF (without using DMF) has been described by Prakash and col.[41] Although, trifluoromethylated derivatives were obtained in low yields.

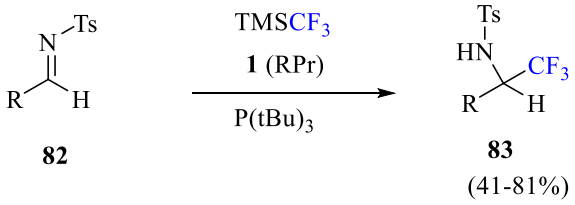
5. Trifluoromethylation of imines and their analogues

Trifluoromethylation of imines using nucleophilic reagents has been reviewed and gives access to α-trifluoromethylated amines, including asymmetric derivatives.[60] As it happens with carbonyl compounds (see previous sections), the most used reagent towards this end is the Ruppert-Prakash **1** (RPr) which can be activated in different ways (Scheme 37).



Scheme 37

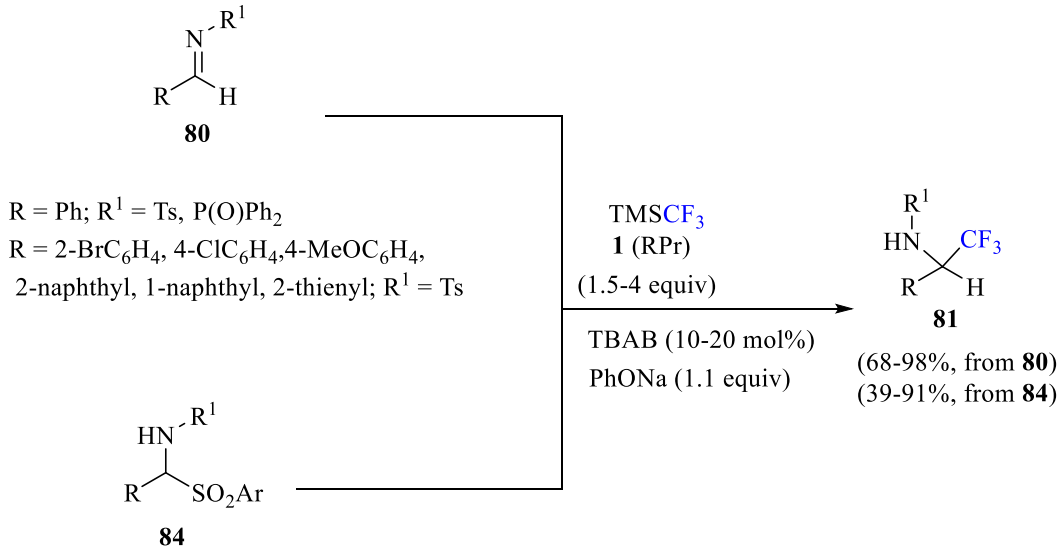
Similarly, the trifluoromethylation of tosylimines **82** has been accomplished by the use of **1** (RPr) and phosphine $P(tBu)_3$ as an activator in DMF (Scheme 38).[61]



R = Ph, 4-$NO_2C_6H_4$, 2-naphthyl, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 38

Typically, Lewis base activation, usually performed with fluoride anion, is required in stoichiometric or overstoichiometric amounts and only few methods are catalytic but these are limited to very reactive substrates, such as azirines, or require solvents like DMF and provide low efficiency. Recently, a new protocol for the catalytic trifluoromethylation of imines has been disclosed, using a phase transfer methodology with tetra-*N*-butyl ammonium bromide (TBAB, 20 mol%) and sodium phenoxide as stoichiometric promoter (Scheme 39).[62]

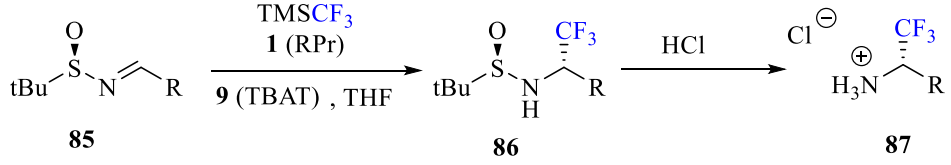


Ar = Ph; R = cyclohexyl; R^1 = SO_2-4-$MeOC_6H_4$, SO_2Mes, Cbz
Ar = R = Ph; R^1 = Cbz
Ar = 4-MeC_6H_4; R = cyclohexyl; R^1 = Ts, $P(O)Ph_2$
Ar = 4-MeC_6H_4; R = $(CH_3)_2CH$, $Ph(CH_2)_2$, $CH_3(CH_2)_2$; R^1 = Ts

Scheme 39

Thus, the combination of 1.5 equivalents of **1** (RPr) and 10 mol% TBAB as catalyst and 1.1 equivalents of PhONa produced the trifluoromethylation of imines **80** in good yields (Scheme 39). In the case of unbranched aldehydes, competing tautomerization to the corresponding enamides was avoided thanks to a slight modification of the protocol, involving the *in situ* generation of the imines at low temperature from the corresponding α-amido sulfones **84**, although sacrificing additional equivalents of **1** (RPr) and PhONa (Scheme 39). Therefore, this procedure allowed the obtainment of the adducts in satisfactory yields, even with imines derived from aldehydes (Scheme 39). Furthermore, a variety of protecting groups can be used and tolerated, including sulfonyl, diphenylphosphinoyl and carbobenzyloxy groups.

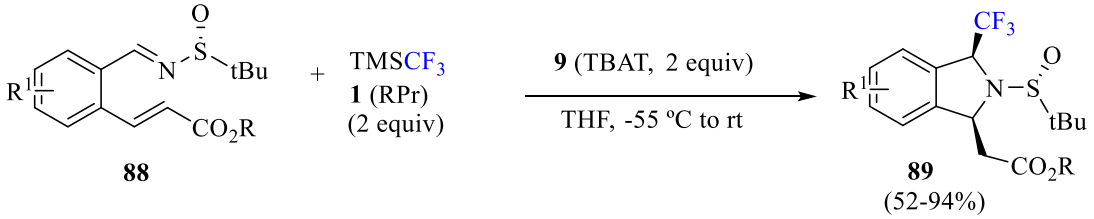
The diastereoselective approach was achieved by Prakash and co-workers, using a chiral auxiliary and leading to chiral α-trifluoromethylated amines.[63] The reactivity and stereoselectivity of the reaction are dependent on the fluoride source. Thus, chiral sulfinyl imines **85** reacted with **1** (RPr) in the presence of **9** (TBAT)[64] in THF to give high diastereoselectivities and yields of the trifluoromethylated products **86**, which can be hydrolyzed to the chiral amine salts **87** with high enantioselectivities (Scheme 40). The same group extended the method to the asymmetric synthesis of trifluoromethylated allylic amines[65] and vicinal ethylenediamines.[66]



85 **86** **87**

Scheme 40

Another diastereoselective application of this addition including concomitant cyclization leading to trifluoromethylated isoindolines **89** has been disclosed recently (Scheme 41).[67] This is a tandem nucleophilic addition/intramolecular aza-Michael reaction initiated also by **9** (TBAT) and provides good yields and diastereoselectivities either with electron-rich or electron-poor aromatic rings.



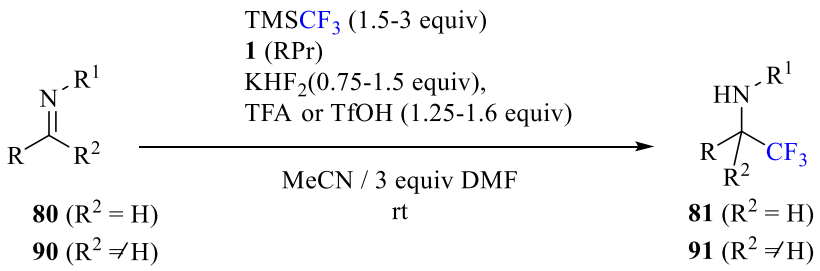
88

89
(52-94%)
dr: 24/1 to 99/1

R = Et; R^1 = H, 4-MeO, 4,5-OCH_2O-, 4-Me, 4F, 4-CF_3, 4-NO_2
R = iPr; R^1 = H
R = tBu; R^1 = H

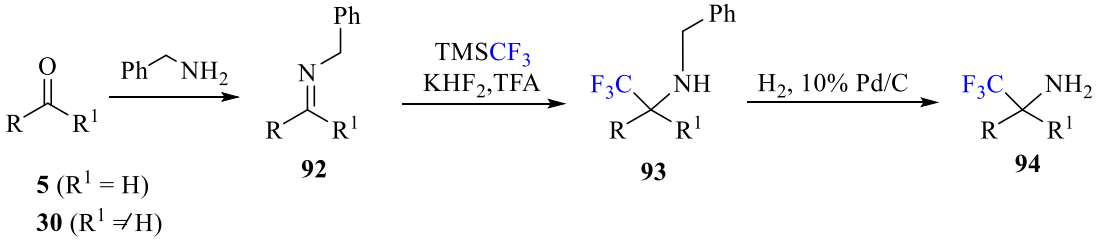
Scheme 41

Alkylimines are unreactive when treated with **1** (RPr) under conventional basic conditions. Therefore, a strategy to increase the reactivity of alkyl imines which involves the use of protic solvents has been developed. Indeed, it was found that HF generated *in situ* from TFA or triflic acid and potassium hydrodifluoride was able to activate the reaction between alkylimines and **1** (RPr). This is a general method applicable to aldimines **80** and ketimines **90** as well and the corresponding amines **81** or **91** are obtained with good yields (Scheme 42).[68]



Scheme 42

This approach has been employed in a three-step synthesis of trifluoromethylamines **94** from aldehydes **5** or ketones **30** without the need to isolate or purify the intermediates **92** or **93**, thus providing a high yielding methodology (Scheme 43).[69]



R = Me; R^1 = Et
R = R^1 = Et
R = Me; R^1 = CH_2OCH_3
R = H; R^1 = tBu
R = Me; R^1 = cyclopropyl
R - R^1 = $-(CH_2)_3-$
R = H; R^1 = cyclopentyl
R = H; R^1 = cyclohexyl
R - R^1 = $-(CH_2)_5-$
R - R^1 = $-(CH_2)_2O(CH_2)_2-$

Scheme 43

Besides the well-known **1** (RPr) reagent, several other reagents for nucleophilic trifluoromethylation of both the carbonyl and the imine group have been disclosed.[60] The list includes the addition product of *N,N*-dimethyltrimethylsilylamine with 2,2,2-trifluoroacetophenone **95**, the reagent **96** derived from CF_3I and tetrakis(dimethylamino)ethylene (TDAE) and potassium trimethoxy(trifluoromethyl)borate **25** (Figure 2).

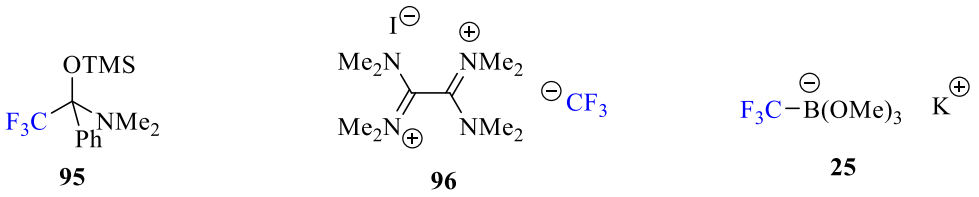
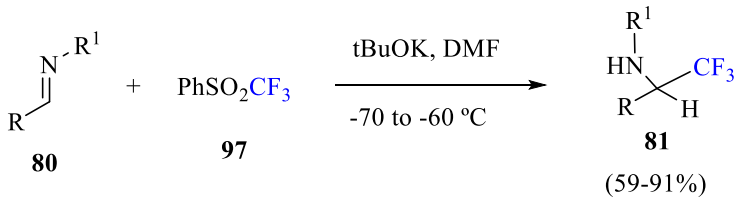


Figure 2

It is noteworthy that the reagent **96** is effective in the addition to both *N*-tosyl aldimines and *N*-tolyl sulfinimines. In the later case, the diastereoselectivities while good (*dr* up to 94:6), fall short of those observed by Prakash in the trifluoromethylation of (2-methyl-2-propane)sulfinaldimines.[63]

Trifluoromethyl phenyl sulfone **97** can also be used to trifluoromethylate imines **80**, including phenyl and sulfinyl derivatives, in the presence of tBuOK to provide the corresponding amines **81** with good yields (Scheme 44).[70] It is remarkable that starting from a homochiral sulfinimine, the reaction is highly diastereoselective (*dr*: 98:2).



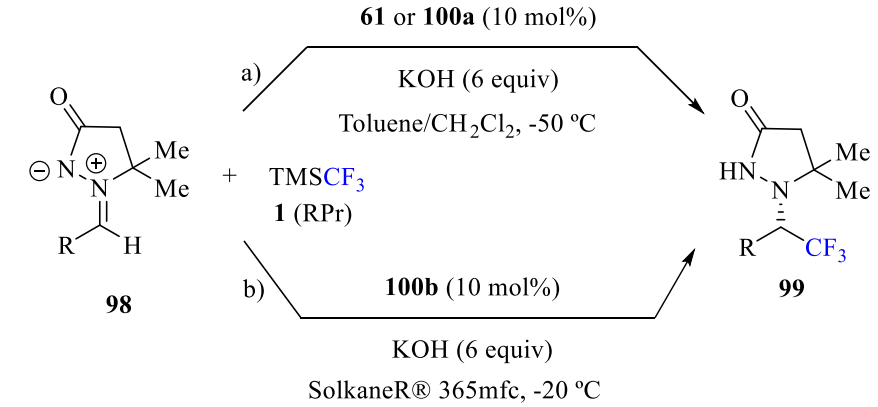
R^1 = Ph; R = 4-FC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_4$
R^1 = tBuSO; R = (*E*)C(Ph)=CH-Ph

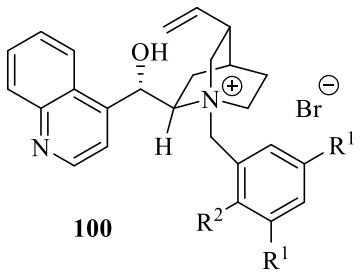
Scheme 44

Cationic electrophiles, such as nitrones and iminium salts, would be expected to interact efficiently with nucleophilic trifluoromethylating reagents, as carbonyls and imines do. Indeed, this strategy has been used to improve the reactivity of alkylimines and hydrazones. For instance, the dimethyliminium salt derived from benzaldehyde rapidly reacted with the anionic potassium trimethoxy(trifluoromethyl)borate nucleophile **25** yielding the corresponding α-trifluoro-methylated amine. In this case, however, the reaction was not more efficient compared to the reaction with benzaldehyde itself.[40]

Iminium[71] or hydrazonium complexes,[72,73] obtained by treatment with Lewis acids also reacted towards **1** (RPr), therefore providing a strategy oriented to overcome the low reactivity of the precursors alkyl imines and hydrazones. This idea has been employed to develop the first enantioselective trifluoromethylation of imine equivalents. Indeed, up to 2009 only classical diastereoselective approaches for the stereoselective trifluoromethylation of imines or their equivalents using chiral auxiliaries had been reported,[63,65,66,74,75] and there were no examples of

enantioselective variants. Then, as reported by Shibata, azomethine imines **98** derived from pirazolidinones (hydrazonium derivatives) were made to react with **1** (RPr) in the presence of 10% of a chiral quaternary ammonium bromide (cinchoninium salt) **61** or **100a** and KOH to successfully give trifluoromethylated amines **99** in good yield and enantiomeric excesses (Scheme 45, a).[76] Improved reaction conditions were achieved recently (Scheme 45b) using environmentally benign Solkane solvent at -20ºC and a novel iododerivative of cinchoninium salt **100b** as catalyst.[77]





100

a: R^1 = *t*-Bu, R^2 = H

b: R^1 = H, R^2 = I

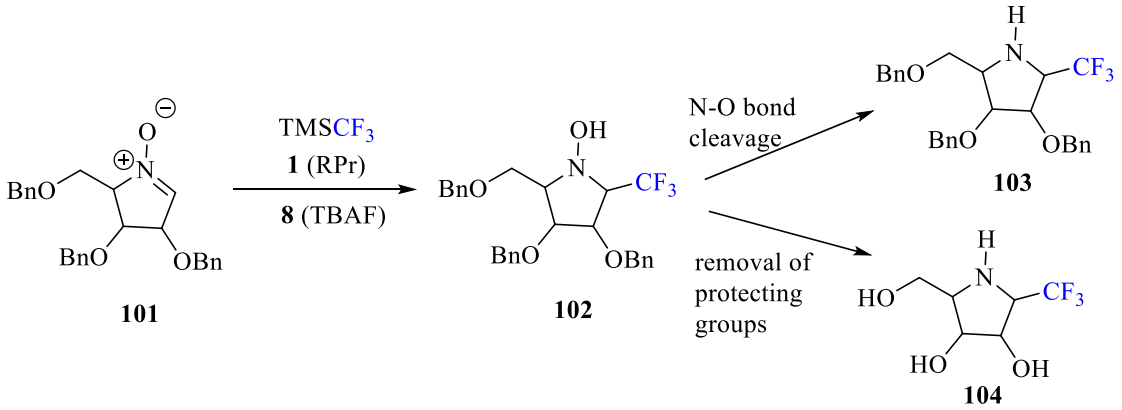
using **61**: R = Ph, 2-MeC_6H_4, 6-MeO-2-naphthyl
(86-94 %, *ee* = 88-90%)

using **100a**: R = 3-MeC_6H_4, 4-MeC_6H_4, 3-MeOC_6H_4, 4-MeOC_6H_4, 4-iPrC_6H_4, 4-tBuC_6H_4, 3,4-$Me_2C_6H_3$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 1-naphthyl, 2-naphthyl, CH=CHPh, cyclohexyl
(72-95%, *ee* = 71-98%)

using **100b**: R = Ph, 3-MeOC_6H_4, 4-MeOC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-iPrC_6H_4, 4-tBuC_6H_4, 4-FC_6H_4
(65-99%, *ee* = 74-96%)

Scheme 45

Finally, nitrones derived from carbohydrates have been reduced through nucleophilic addition with RPr reagent **1**. In this way trifluoromethylated pyrrolidine derivatives were obtained in a stereoselective way with average yields (Scheme 46).[78] The resulting pyrrolidines were further transformed by cleavage of the N-O bond and removal of protecting groups to give trifluoromethylated analogues of the natural product 6-deoxy-DMDP.



Scheme 46

6. Conclusions

Recent developments in nucleophilic trifluoromethylation reactions of carbonyl and imine derivatives are outlined. During the last six years several methods and strategies have been developed, nowadays representing reliable methodologies for the preparation of CF_3-substituted alcohols or amines. It is noteworthy that recent advances in fluorination technology give access to radiolabelled ^{18}F-containing derivatives ready to be used in positron emission tomography (PET).

However, despite the remarkable advances, there are still important limitations to these new approaches. In particular, the nucleophilic trifluoromethylation of carboxylic acid derivatives, such as esters or acyl halides and the asymmetric introduction of trifluoromethyl group are challenging problems that remain to be addressed. Further development of new methodologies is necessary for preparation of chiral trifluoromethylated molecules to be increasingly used in pharmaceutical and agrochemical industry.

7. Acknowledgements

Financial support from the Dirección General de Investigación del Ministerio de Ciencia e Innovación (CTQ2012-34323) and by Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV, UFI-QOSYC 11/12) is gratefully acknowledged.

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Gloria Rubiales was born in Aranda de Duero (Burgos, Spain). She was graduated in Chemistry from the University of Valladolid and received her Ph.D. degree in Chemistry from the University of the Basque Country under the supervision of Prof. Claudio Palomo and Prof. Fernando Cossío. She has worked at the University of the Basque Country as Assistant Professor and Associate Professor. Since 1995 she was appointed as an Associate Professor in Organic Chemistry at the same University, where she is working in Dr. Palacios's group. Her current research interest is focused on the development of new methodology in organic synthesis of

heterocyclic compounds containing phosphorus, nitrogen and fluorine substituents, as well as on the design and development of Enzyme Inhibitors, Molecular Modeling and Computational Chemistry.

Concepción Alonso was born in Vitoria-Gasteiz, Spain, in 1968. She received her B.Sc. degree in Chemistry from the University of Valladolid in 1991, and Ph.D. degrees in Chemistry from the University of Basque Country in 1998, the latter under the supervision of Prof. Francisco Palacios. She stayed for two years at the University of California at Davis as a postdoctoral fellow under the supervision of Prof. Mark J. Kurth. After her return to Spain she has been working as a postdoctoral fellow and as research associate with Prof. Francisco Palacios at the University of Basque Country. And she became Associate Professor in 2012 in Organic Chemistry at the same University. Her research has been focused in the development of new reactions and methods for the synthesis of small organophosphorus molecules by solid-phase and combinatorial chemistry. Nowadays, her current interest is focused in the development of new methodologies in organic synthesis of heterocyclic compounds containing phosphorus, nitrogen and fluorine susbtituents.

Eduardo Martinez de Marigorta was born in 1961 in Vitoria-Gasteiz. He graduated in Chemistry in 1984 and received his Ph. D. at the University of Basque Country under the guidance of Dr. Esther Domínguez on the chemistry of isoquinolines and protoberberines. In 1991-92 and 1996 he worked with Dr. Ian Fleming at the University of Cambridge on the use of silyl anions in synthesis. By the end of 1996 he joined the Faculty of Pharmacy and Dr. Palacios'

group at the University of Basque Country where he is now Associate Professor of Organic Chemistry. His research interests include the chemistry of fluorine and phosphorus containing compounds and their applications to the conventional and solid-phase synthesis of cyclic and acyclic compounds.

Francisco Palacios was born in Vitoria, Spain (1951). He graduated in Chemistry in the University of Zaragoza and he received his PhD degree in the University of Oviedo in 1977 under the supervision of Prof. José Barluenga. After two years (1979-1981) of Post Doctoral work with Prof. Dr. Rolf Huisgen in the Organic Chemistry Institute of the Ludwig University (Munich, Germany) working on Cycloaddition Reactions, he came back to the University of Oviedo as Assistant Professor and he became Associate Professor in 1983 in the same University. Since 1991 he has been full Professor of Organic Chemistry in the University of the Basque Country (Faculty of Pharmacy). He has held Visiting Professorships at the Ecole Nationale Superière de Chimie of Montpellier (France, 2003) and at the Department of Chemistry of the University of Coimbra (Portugal, 2005, 2006, 2008, 2010, 2011). His research interests are organic synthesis, organophosphorus chemistry, fluorine chemistry, heterocyclic chemistry, cycloaddition reactions, design and development of enzyme inhibitors and solid-phase synthesis.

