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Review

Nucleophilic difluoromethylation and trifluoromethylation using tetrakis(dimethylamino)ethylene (TDAE) reagent

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Trifluoromethyl anion

ABSTRACT

In an effort to find new methodologies to introduce difluoromethylene and trifluoromethyl moieties into organic molecules of synthetic and biological interest, tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant of a series of good electron-acceptors such as bromodifluoromethyl heterocycles, chlorodifluoromethylated ketones as well as perfluoroalkyl iodides; the corresponding anions thus generated under very mild conditions, were successfully engaged in a number of intra- and intermolecular coupling reactions with a series of electrophiles (aldehydes, ketones, α-keto esters, *N*-tosyl aldimines, acyl chlorides, diol sulphates, disulfides, and diselenides). The corresponding adducts were usually obtained in moderate to good yields and the present method was found to be as good or even better as other most popular approaches. This paper gives an overview of our research efforts in this area as well as results from other groups.

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Contents

1. Introduction

Tetrakis(dimethylamino)ethylene (TDAE) was first discovered incidentally by Pruett et al. at the DuPont Company in 1950 [1] from the condensation of chlorotrifluoroethylene (CTFE) and dimethylamine (both gas), under pressure using an autoclave (Scheme 1). The compound was obtained as a pale green liquid and was found to be strongly luminescent in contact with air. Pruett et al. did not further examine the chemistry and properties of TDAE. The simple preparation of TDAE using CTFE and dimethylamine cannot be extended to higher homologs and other amines, presumably for steric reasons. Another general method to prepare analogues was later presented in the 1960s when Wanzlick et al. reported the synthesis of a series of 1,1′,3,3′-tetraphenyl-2,2′-biimidazolidinylenes (the cyclic analogues of TDAE) through the reaction of a diamine with ethyl orthoformate (Scheme 2) [2]. Later Winberg et al. (from DuPont) synthesized a long series of

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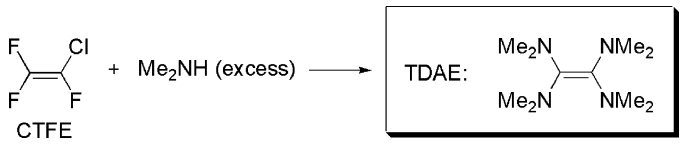
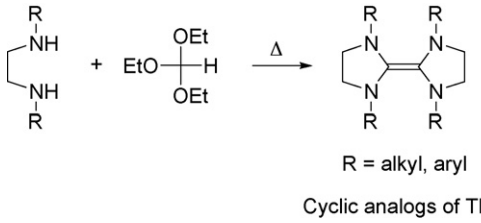
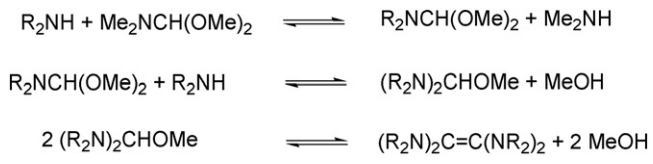


Scheme 1.



Scheme 2.



Scheme 3.

tetrakis(dialkylamino)ethylenes by variation of Wanzlick's method; in their approach the dimethyl acetal of *N*,*N*-dimethylformamide was simply heated with a secondary amine and the methanol and dimethylamine generated are removed by distillation (Scheme 3) [3].

TDAE is a very electron-rich tetraaminoethylene molecule with an ionizing potential close to zinc (6.12 eV). It is a powerful organic reducing agent as it can be seen from its oxidation potentials (Scheme 4); in CH_3CN electrochemical oxidation of TDAE occurs in two reversible one-electron oxidation steps, to $TDAE^{+}$ and $TDAE^{2+}$ at −0.78 V and −0.61 V *vs.* SCE (standard potentials, E^0) [4]. However in DMF, a two-electron reversible wave is observed at −0.62 V *vs.* SCE (standard potential, E^0). The superposition of the two one-electron steps points out that considerable conformational changes take place upon oxidation [4b], and this effect is enhanced in DMF.

It is a compound that reacts readily with oxygen, Lewis acids, strong bases and acids. It reacts easily with some oxidants such as Br_2, I_2 to make the corresponding dication salts, and can act as well as a carbon nucleophile. They are only two reviews describing the synthesis and chemical properties of tetraminoethylenes [5]. Since TDAE and their cyclic analogs were first discovered, there was only limited use of these reagents in organo-fluorine chemistry (and generally in organic synthesis) before we started our project in 1996. Carpenter [6] was the first to discover that TDAE can be used as a single electron transfer (SET) reagent in dehalogenation processes using $CF_3CCl_2CCl_3$ and $CF_3CCl_2CCl_2CF_3$ as substrates (Scheme 5). Pawelke [7a] then later found that at low temperatures, TDAE and CF_3I form a charge transfer complex which can act as a nucleophilic trifluoromethylating reagent in polar solvents; in such a way some trifluoromethyl-boron [$(CF_3)_3BNHEt_2$] and silicon compounds [$Me_2Si(CF_3)_2$ and the Ruppert–Prakash reagent CF_3SiMe_3) were obtained. The same author found [7b] also an interesting approach to prepare *N*-trifluoromethyl-dialkylamines, of general structure $R_2N–CF_3$, through the reduction of CF_2Br_2 in the presence of basic secondary amines R_2NH and a source of fluoride anion (Scheme 6).

Chambers et al. [8] employed TDAE in oligomerization and perfluoroalkylation processes (Scheme 7) using fluorinated olefins, such as hexafluoropropene (HFP). In these reactions TDAE should act as a carbon nucleophile producing a valuable fluoride source, soluble in organic solvents.

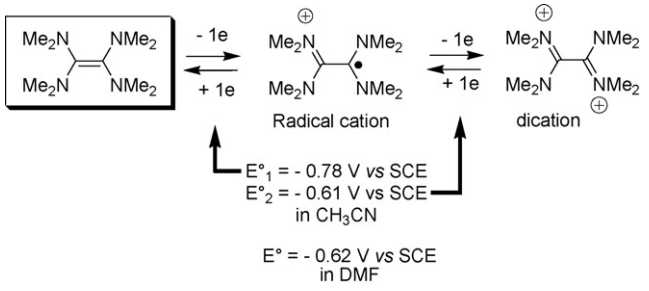
Besides these examples there was no other use of TDAE to promote any useful synthetic reactions with fluorinated compounds until we entered in this area in 1996.

2. Results and discussion

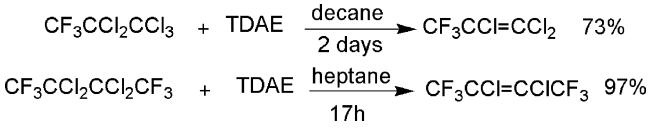
2.1. Halogenodifluoromethylated substrates

In a project directed to the synthesis and biological evaluation of novel difluoromethylene heterocyclic systems as potential anti-HIV-1 agents, we were looking for a valuable synthetic method to generate a difluoromethyl anion from the corresponding bromodifluoromethyl heterocyclic substrates and then intercept these species with a series of carbonyl electrophiles. 2-(Bromodifluoromethyl)benzoxazole **1** [9] was chosen as a model substrate because it was anticipated that it could be a good electron-acceptor and could be used to build novel benzoxazole–CF_2X–Ar structures (X = CHOH, CHF, CH_2, CO, CF_2) which have some structural analogy to a previously known non-nucleosidic reverse transcriptase inhibitor (NNRTI) from Merck [10] (Fig. 1).

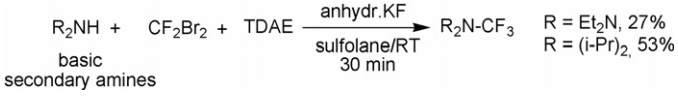
Attempts to generate the 2-(difluoromethyl)benzoxazole anion from exchange with *n*-BuLi in THF at −78 °C, resulted only in decomposition of the 2-(difluoromethyl)benzoxazole lithium derivative; therefore, use of the milder reagent, TDAE, was attempted. When one equivalent of TDAE was added dropwise to 2-(bromodifluoromethyl)benzoxazole and an excess of benzaldehyde (5 equiv.) in anhydrous DMF at −30 °C, a deep red color immediately developed, probably due to the formation of a charge transfer complex. The solution (which slowly became orange) was warmed up to room temperature and after 1 h at this temperature, was filtered (to remove the $TDAE^{2+}2Br^{-}$), hydrolyzed and worked-up. The corresponding alcohol adduct **2** was obtained in a 65% isolated yield, and the methodology could be extended to a series



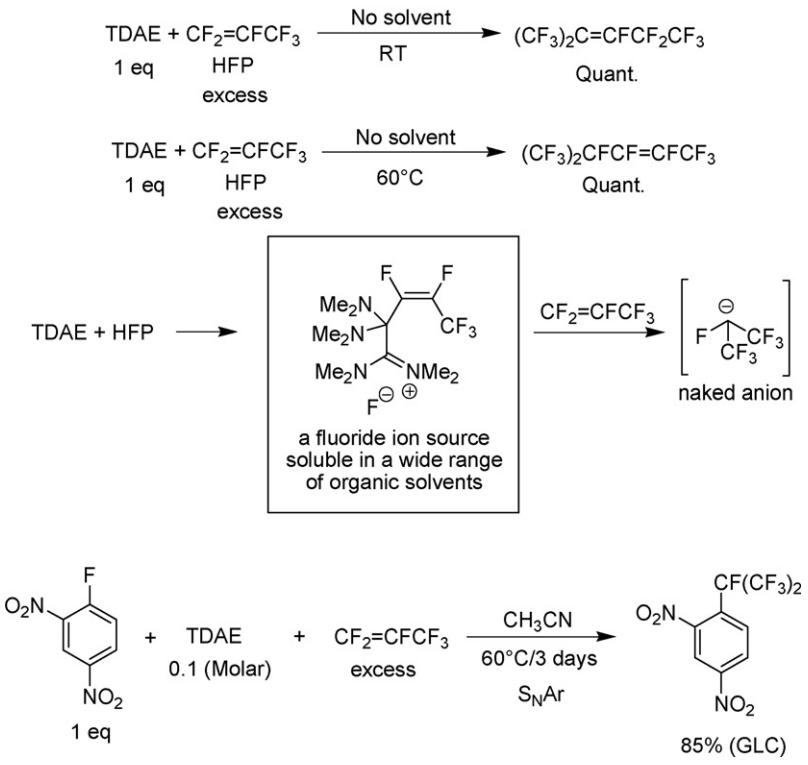
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

of aromatic, heterocyclic aldehydes as well as ketones, giving access to new alcohol adducts **3**–**11** in moderate to good yields [4,11] (Scheme 8). In addition 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole **12** [9] was also found to be a good substrate in such TDAE-mediated carbon–carbon-coupling reactions [11]. Electron-rich aldehydes were less reactive, their reactions being incomplete even after longer reaction times. The rather low yields with ketones could be explained by steric hindrance of the benzoxazole ring as well as the enolizable character of these ketones.

All the reactions appear to proceed via the formation of a charge transfer complex (deep red color) between **1** or **12** and the TDAE at low temperature (−20 °C). Upon raising the temperature, the solution gradually becomes orange and the complex gradually decomposes to generate the 2-(difluoromethyl)heterocyclic anion (and the $TDAE^{2+}$), and the putative anion is apparently stable enough to react with aromatic aldehydes and ketones. In all the experiments the $TDAE^{2+}2Br^{-}$ was recovered by simple filtration at the end of the reaction, demonstrating that the TDAE has been clearly oxidized.

A stepwise single electron transfer mechanism between the TDAE and the starting bromides **1** or **12** should occur in all the reactions (Scheme 9). Evidence of the 2-(difluoromethyl)benzoxazole radical as an intermediate in these reactions was demonstrated by the observation of the radical addition to 2,3-dihydrofuran, an electron-rich olefinic substrate (Scheme 10); TDAE should be added dropwise to a DMF solution of **1** and 2,3-dihydrofuran in order to detect the radical adduct **13** [11]. Unfortunately all the alcohol adducts obtained in this study were devoid of any anti-HIV-1 activity.

In a related HIV-1 project, we found that 2-(bromodifluoromethyl)benzoxazole **1** could be used in $S_{RN}1$ reactions with aromatic, heteroaromatic thiolates as well as heteroaryl phenolates [12]; some of the derived products were found to be active against the HIV-1 virus. However, the methodology was limited to commercially available heteroaryl-sulfur nucleophiles, but using heteroaryl-thiocyanates as electrophiles, we were able to prepare novel heteroaryl–CF_2SAr derivatives **14**–**16** that could complement our $S_{RN}1$ methodology (Scheme 11) [13].

Other bromodifluoromethyl derived compounds were also found to be reactive in the presence of TDAE and some electrophiles; for example reductive debromination of *N*-bromodifluoromethyl-1-4-dimethylaminopyridinium bromide **17** [14], 1-bromodifluoromethyl-2-methyl-benzimidazole **18** [15], 1-bromodifluoromethyl-3-methyl-imidazolium triflate **19** and 1-bromodifluoromethyl-2-phenyl-3-methyl-imidazolium triflate **20** [14] (Scheme 12).

Zhu et al. [16] were the first, after our work was published, to recognize as well the potential of TDAE to produce difluoromethyl anions from bromodifluoromethyl precursors. For example [16a] 5-bromodifluoromethyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid ethyl ester **25** could be used in nucleophilic addition to a series of aromatic aldehydes, and the corresponding alcohols were lactonized to give novel bicyclic *gem*-difluorinated 1*H*-pyrano[3,4-*d*][1,2,3]-triazol-4-one compounds in good yields. A representative example is given in Scheme 13; in addition to the desired alcohols, TDAE mediated dehydrofluorination products were also isolated.

The same group [16b,c] also studied the reactivity of ethyl 3-bromodifluoromethyl-3-benzyloxy-acrylate **29** as a potential CF_2 building block; the TDAE mediated reductive cleavage of **29** in the presence of heteroaryl aldehydes furnished the corresponding δ-

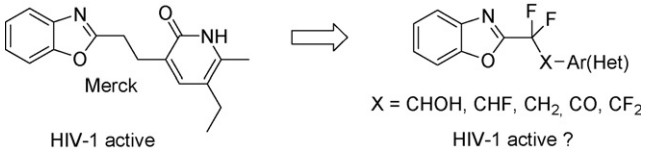
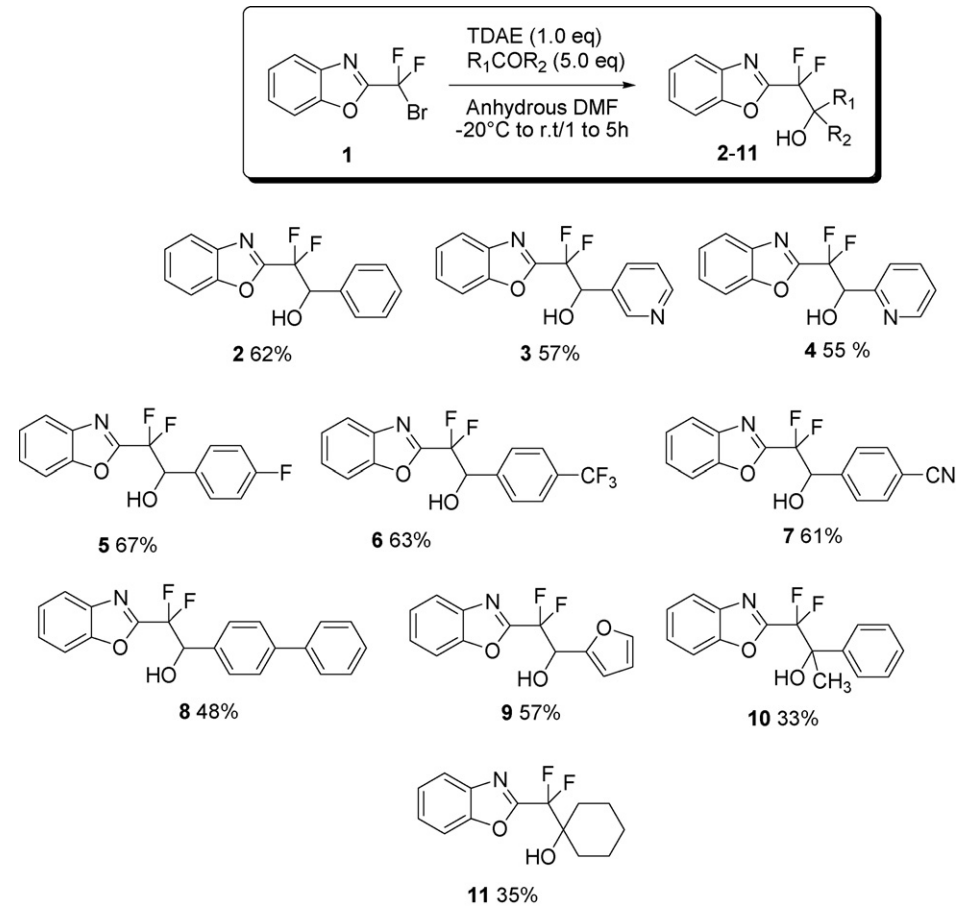
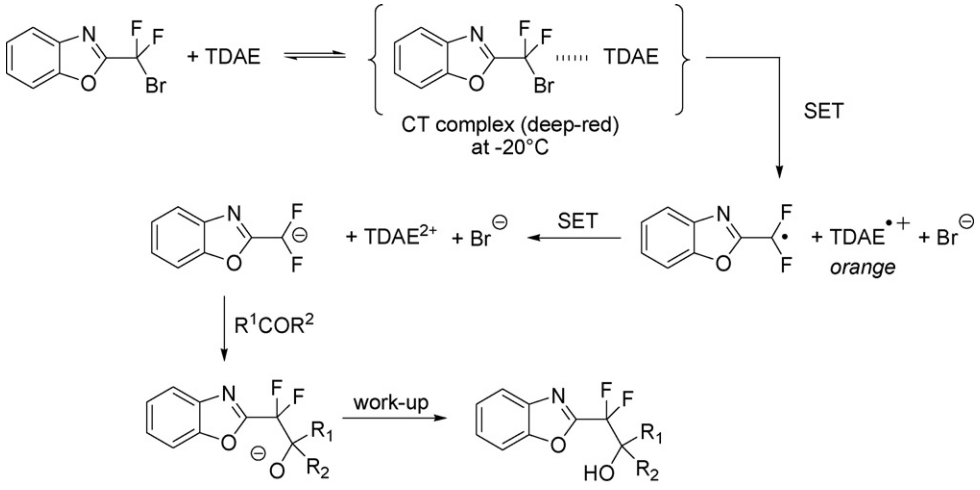


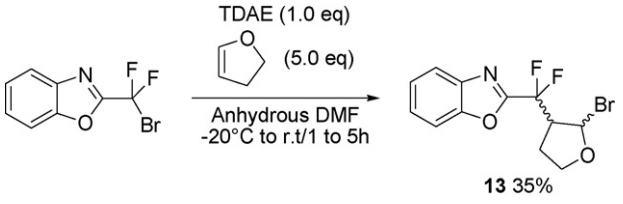
Fig. 1. Difluoromethylene benzoxazoles as potent HIV-1 inhibitors.



Scheme 8.



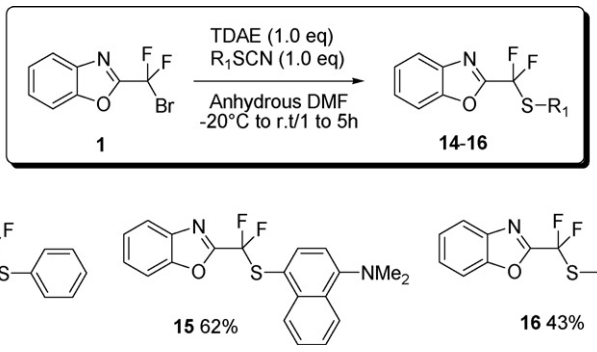
Scheme 9.



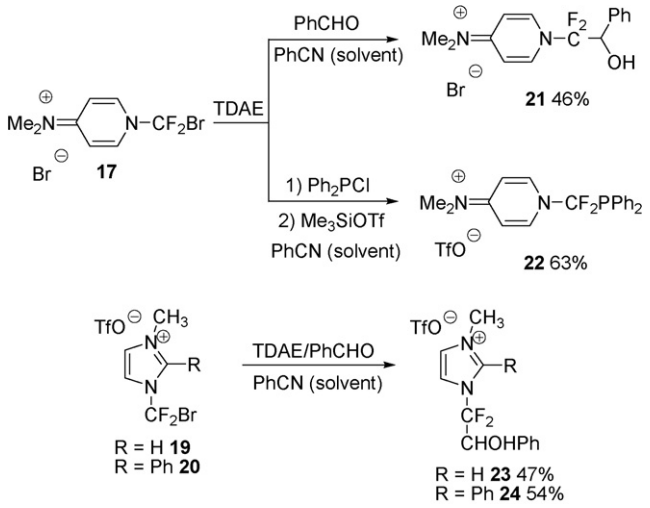
Scheme 10.

hydroxy esters **30** in moderate yields (Scheme 14). On the contrary using activated zinc the Reformatsky β-hydroxy esters were obtained. Using tosyl imines as electrophiles, *gem*-difluorinated δ-amino esters **31** were favoured over the α-addition products. Meanwhile the in situ formed β-amino esters lost one molecule of *p*-toluenesulfonamide to give the novel α-difluorovinyl substituted acrylates **32** as minor products under the basic conditions (Scheme 15).

Not only bromodifluoromethylated heterocyclic substrates were found to be useful starting materials in TDAE mediated

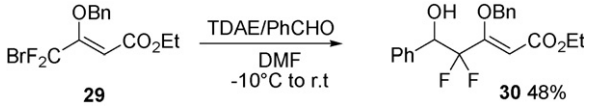


Scheme 11.



Scheme 12.

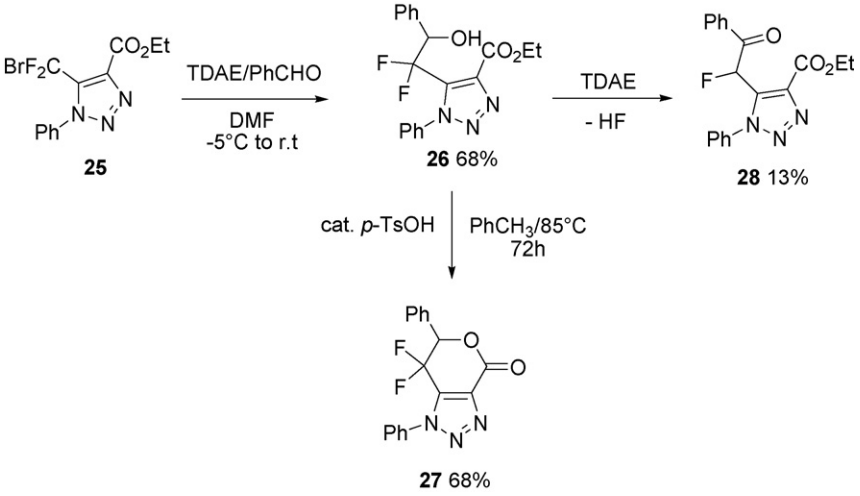
reactions; chlorodifluoromethylated ketones are also good partners [17–22], and TDAE was found to be useful in generating the corresponding difluoroacetyl anions. The methodology was found to be an alternative and milder approach to the classical Reformatsky reaction [23] that usually requires the use of catalysts or special activation. Electrophiles that were used with success were heteroaryl aldehydes [17–19], α-keto esters [20], *N*-tosyl aldimines [21] and thiocyanates [13]. Some specific examples are presented in Table 1. Adducts from the addition to α-keto esters are expected to have some interesting biological activities since 3,3,3-trifluoro-2-hydroxy-2-methyl propionic acid ethyl ester derivatives have been used for the synthesis of bioactive molecules [24], and the adducts using the chlorodifluoroacetylated dialkylhydrazone substrates are good candidates for chemical elaboration in order to yield difluoromethylene substituted β-amino alcohols.



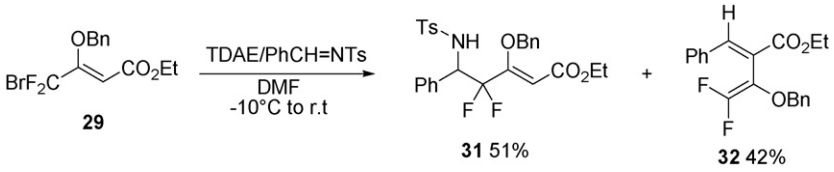
Scheme 14.

An interesting example is also the recent synthesis of novel fluorinated 4*H*-benzo[*h*]chromen-4-one and 4*H*-pyrano[3,2-*h*]quinoline-4-one derivatives [22], through a one-pot aldolization-intramolecular S_NAr process from the TDAE mediated reductive cleavage of *N*,*N*-dimethylamino-bis-halogenodifluoroacetyl substrates in the presence of heteroaryl aldehydes (Scheme 16). The final products are expected to have some interesting pharmacological properties as they do share some structural analogy to flavonoids that are known to possess a wide spectrum of biological activities.

A tentative mechanism for this reaction is depicted in Scheme 17. TDAE is able to promote the reduction of the two C–Cl bonds

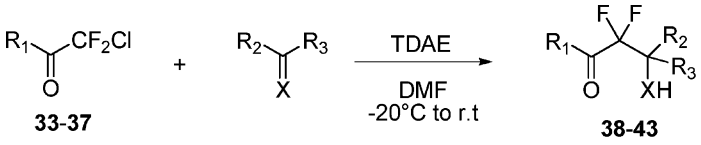


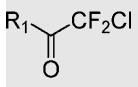
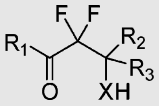
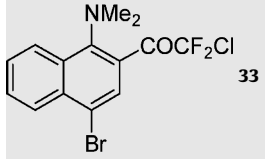
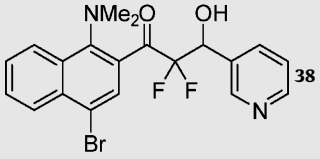
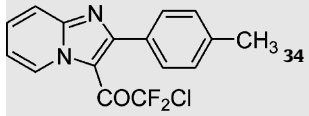
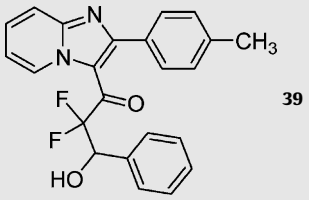
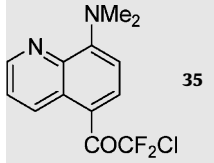
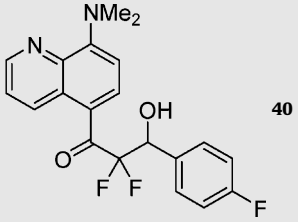
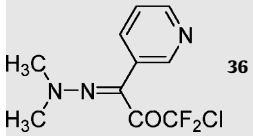
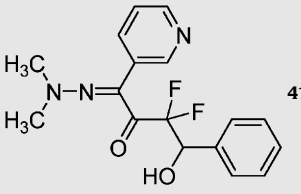
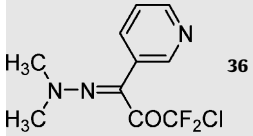
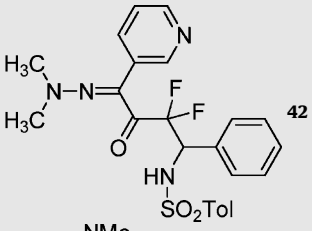
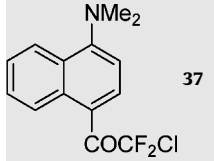
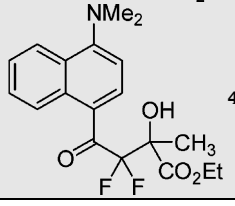
Scheme 13.

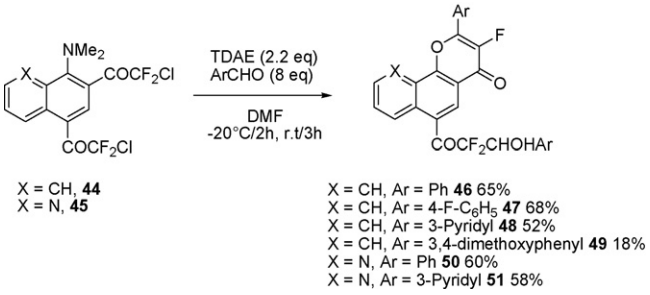


Scheme 15.

Table 1
TDAE mediated reductive cleavage of chlorodifluoromethylated ketones in the presence of electrophiles



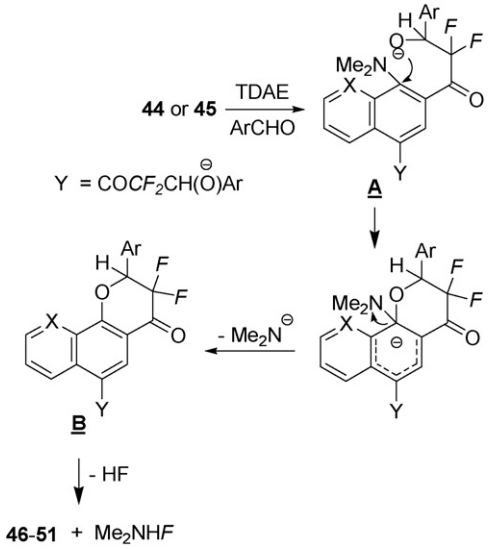
		Yield (%)
		
 **33**	 **38**	45
 **34**	 **39**	67
 **35**	 **40**	74
 **36**	 **41**	68
 **36**	 **42**	62
 **37**	 **43**	54



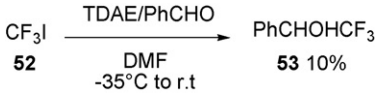
X = CH, **44**
X = N, **45**

X = CH, Ar = Ph **46** 65%
X = CH, Ar = 4-F-C_6H_5 **47** 68%
X = CH, Ar = 3-Pyridyl **48** 52%
X = CH, Ar = 3,4-dimethoxyphenyl **49** 18%
X = N, Ar = Ph **50** 60%
X = N, Ar = 3-Pyridyl **51** 58%

Scheme 16.

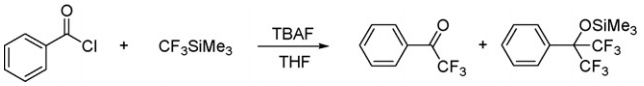


Scheme 17.



Scheme 18.

thus generating a bis-enolate, that can be trapped with the aldehyde (in excess) to yield the corresponding bis-alcoholate **A**; it subsequently undergoes an addition–elimination reaction yielding the difluoromethylene derivative **B** and the corresponding NMe_2 anion (N–O exchange reaction), which could act as a strong base and induces an H–F elimination, giving finally the fused derivatives **46**–**51**. Also an internal proton-transfer from the enolate may also occur.



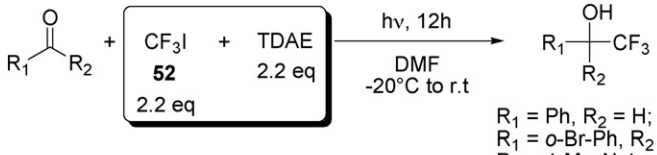
Scheme 20.

2.2. Trifluoromethyl iodide and perfluoroalkyl iodide as substrates

Among the numerous methods for incorporation of the trifluoromethyl group into organic compounds [25], one of the most useful involves the use of reagents that effectively generate unstable CF_3^- anion as an in situ species for the purpose of nucleophilic substrates such as aldehydes and ketones. Currently the use of the Ruppert–Prakash reagent (CF_3SiMe_3), because of its diversity of applicability, is generally considered to be the most effective reagent [26,27]. Other potential reagents have also been proposed in reactions with non-enolizable aldehydes and ketones [28]. Since we already demonstrated that bromodifluoromethylated heterocycles were good substrates in TDAE mediated nucleophilic addition reactions, it was a natural extension to determine whether a combination of TDAE and trifluoromethyl iodide **52** could be used to generate synthetically competent trifluoromethyl anions [29]. Initial results were, quite discouraging, because when TDAE was added to a solution of benzaldehyde and trifluoromethyl iodide in dry DMF at −35 °C and the solution allowed to warm with stirring to room temperature, although the reagents were totally consumed, the desired alcohol **53** was obtained in only poor yield (Scheme 18). Petrov also observed a similar result [30].

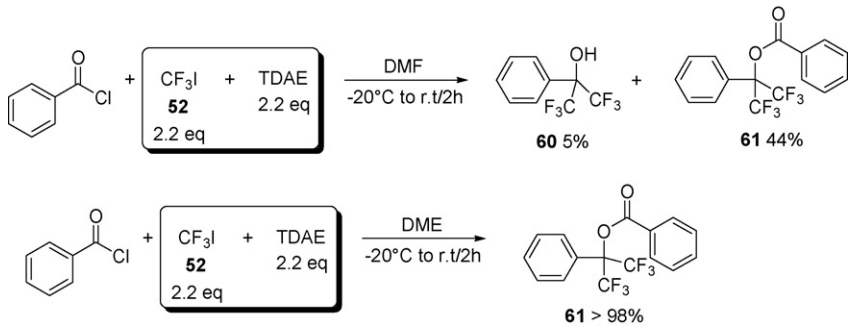
It was then found that when the same reaction was carried out at −20 °C, *under irradiation by a sun lamp*, the yield of **53** was remarkably improved up to 80%. Subsequent reactions carried out in this manner with a large number of aldehydes and ketones (selected examples are presented in Scheme 19) exhibited similar success. Although DMF is presently the preferred solvent, the reaction also gives good results when other solvents are used. For example, in the reaction with 1-naphthaldehyde, a 53% yield was obtained in 1,2-dimethoxyethane (DME), and a 72% isolated yield when DME/HMPA (1:1) was used.

In spite of the widespread application of the Ruppert–Prakash reagent (CF_3SiMe_3) as a nucleophilic trifluoromethylating agent, there was only one, brief mention of its reaction with acyl chlorides [31] when our TDAE project was ongoing. In this paper, it was claimed that the reaction of CF_3SiMe_3 with benzoyl chloride led to competitive single and double addition, to form the ketone and alcohol products, respectively (Scheme 20). However, neither yields nor experimental details were provided. Petrov observed that the reaction of benzoyl chloride with 1 equiv. of *i*-C_3F_7/TDAE yielded 56% of the corresponding ketone, whereas its reaction with 2 equiv. of C_2F_5I/TDAE led to a mixture

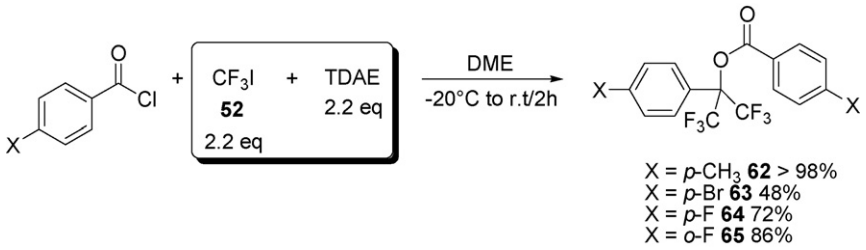


R_1 = Ph, R_2 = H; **53** 78%
R_1 = *o*-Br-Ph, R_2 = H; **54** 86%
R_1 = 4-Me_2N-1-naphthyl, R_2 = H; **55** 86%
R1 = 2-furanyl, R2 = H; **56** 78%
R_1 = 4-pyridyl, R_2 = H; **57** 73%
R_1 = *i*-C_3H_7, R_2 = H; **58** 48%
R_1 = Ph, R_2 = CH_3; **59** 18%

Scheme 19.



Scheme 21.



Scheme 22.

of ketone and alcohol products (33 and 17% yield, respectively) [30].

Using our usual conditions of 2.2 equiv. of CF_3I and TDAE in DMF at −20 °C (but no light), 5% of the alcohol adduct **60** was obtained, along with the benzoate ester **61** in 44% yield. Trying other solvents and conditions, it was quickly determined that DME was the preferred solvent for this reaction, with a quantitative yield of benzoate ester **61** being obtained in an overnight reaction at room temperature. Further optimization indicated that stirring at room temperature for 2 h was sufficient, and that, unlike in the earlier reported reaction with aldehydes and ketones [29], the reaction with benzoyl chloride was not enhanced by light (Scheme 21).

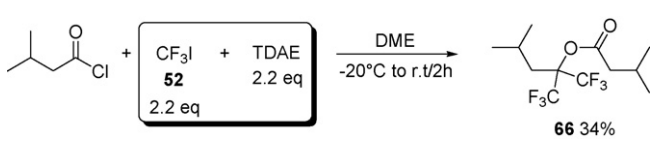
The high chemoselectivity exhibited in this reaction clearly indicates that the mechanistic sequence of steps in the reaction, involving initial CF_3 anion addition, loss of chloride anion, second addition of CF_3 anion, and finally acylation, must become progressively faster along the sequence, so that the ester **61** is essentially the only observed product of the reaction in DME when the stoichiometry is fulfilled. The reaction appears to be general for aroyl chlorides, as indicated by the examples given in Scheme 22, and preliminary results indicate that aliphatic acyl chlorides can be acceptable substrates. Thus, use of isobutyryl chloride in the reaction produced ester **66** as the only observable product in 34% yield (Scheme 23).

The obtained esters can be readily converted to the respective bis-trifluoromethyl-substituted alcohols by transesterification using methanolic NaOH (Scheme 24). These alcohols are known to be valuable starting monomers to produce trifluoromethylated polymers [32].

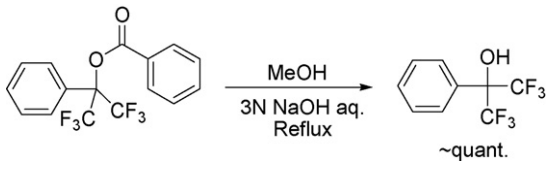
Trifluoromethylation of epoxides had not been reported by 2002 despite the fact that epoxides play an important role in organic synthesis, in part because of their structure and reactivity allows regio- and stereospecific carbon–carbon bond formation simultaneous with formation of an adjacent alcohol function. Nucleophilic trifluoromethylation of epoxides would provide a unique method for preparing chiral trifluoromethylcarbinols. CF_3I/TDAE-derived reagent did not undergo productive reaction with styrene oxide, either alone or in the presence of Lewis acids such as $TiCl_4$, BF_3 or BPh_3 (probably due to competitive reaction with TDAE), the reactions being examined in DMF and 1,2-dimethoxyethane. In 1988, Gao and Sharpless demonstrated that diol cyclic sulphates could be readily prepared from 1,2-diols [33], which themselves can be prepared via an asymmetric dihydroxylation of olefins [34]. Such cyclic sulphates are apparently more reactive than epoxides and have found much synthetic utility [35]. After an initial reaction of our CF_3I/TDAE reagent with cyclic sulphate **67**, under the usual conditions in DMF at −20 °C, resulted in formation of 8% of the desired product **68**, a quick optimization study revealed that THF is the best solvent (from among DMF, DME, CH_2Cl_2, and Et_2O) for this reaction, with a respectable 55% yield being obtained (Scheme 25).

The reaction proved to be general and highly regioselective, as indicated in Table 2, with the yields in each case being good but limited by intervention of a competing reaction of the sulphates with the inevitably present iodide ion.

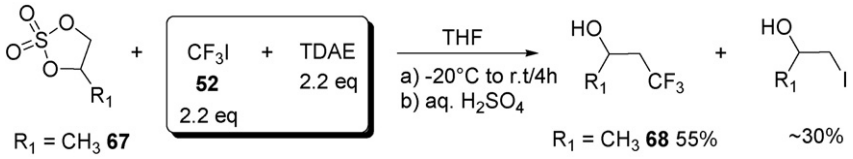
As indicated in Table 2, the yields of desired alcohol **68** could be enhanced by increasing the relative amount of CF_3I/TDAE reagent used in the reaction to 3 equiv., but additional increases did not



Scheme 23.



Scheme 24.



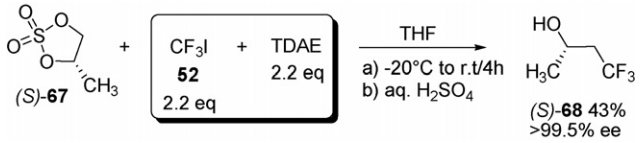
Scheme 25.

Table 2
Trifluoromethylation of cyclic sulfates[a]

Cyclic sulfate	Yields of products
69	**72** 45% + 55%
67	**68** 62% + not measured
67[b]	**68** 55% + 30%
67[c]	**68** 56% + not measured
69	**73** 49% + 33%
70	**74** 51% + 31%
71	**75** 50% + 40%

[a] In THF, using 2.2 equiv. each of CF_3I and TDAE; reagents were added at −20 °C, warmed to room temperature, and then stirred at room temperature for 4 h before hydrolysis with aqueous H_2SO_4.
[b] Using 3 equiv. each of CF_3I and TDAE.
[c] Using 5 equiv. each of CF_3I and TDAE.

prove to be beneficial. In an attempt to avoid the presence of competing iodide ion, the trifluoromethylation reaction was carried out using CF_3Br in the place of CF_3I, but there was no reaction either thermally or photochemically between CF_3Br and TDAE.



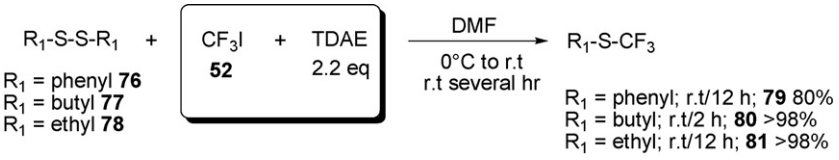
Scheme 26.

The stereospecificity of the ring-opening process was demonstrated by carring out the reaction using (*S*)-isomer **67**, whereupon (*S*)-**68** with an ee of >99.5% was obtained, as determined from the ^{19}F NMR spectrum of the (*R*)-2-methoxy-2-(trifluoromethyl)phenylacetate esters that were obtained from the alcohol mixture (Scheme 26). It is noteworthy to mention that utilizing either the CF_3SiMe_3-based methodologies [26,27] or other reagents [28] to trifluoromethylate sulphate **67** led to no detectable trifluoromethylated products. Thus the CF_3I/TDAE reagent has unique reactivity characteristics that allow this particular nucleophilic trifluoromethylation reaction to occur.

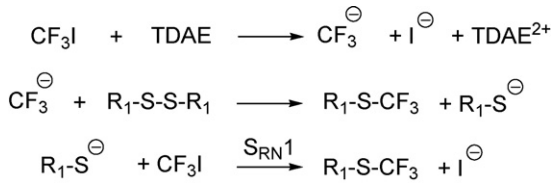
Thus far, the reaction has proved to be effective only for nucleophilic trifluoromethylation of 1,2-cyclic sulphates that bear at least one primary (CH_2) group. Reactions with sulphates derived from *meso*-2,3-butanediol, *meso*-1,2-cyclopentanediol, or *meso*-tartaric esters led to no detectable products containing the CF_3 group. Nor did the sulphate derived from 1,3-propanediol, which underwent strictly ring opening by iodide ion.

Aryl trifluoromethyl thioethers continue to attract much interest within pharmaceutical and agrochemical companies. This interest derives from the recognized potential of the SCF_3 group to have positive influence on biological activity. Diverse methods have been reported for the synthesis of aryl trifluoromethyl thioethers [25]. The first is the classic $S_{RN}1$ reaction of aryl thiolates with CF_3I or CF_3Br. This method first reported by Yaguploskii using CF_3I and UV irradiation in 1977 [36], by Wakselman and Tordeux using CF_3Br in 1984 [37], along with later variations [38,39], has proved to be generally useful when using aryl thiolates but less efficient when using alkanethiolates [40]. The CF_3I/TDAE reagent proves to be an excellent choice for the conversion of aryl and alkyl disulfides into their trifluoromethyl thioethers. The reaction is very fast, and only 2 h of stirring at room temperature was sufficient to give a quantitative yield (Scheme 27).

However, it occurred to us that this same CF_3I that we are using to generate the trifluoromethyl anion could also be a substrate for reaction, via the $S_{RN}1$ mechanism, *with the thiolate coproduct*, thus



Scheme 27.



Scheme 28.

potentially enabling both halves of the disulfide to be used in a one-pot reaction, where the CF_3I would be used productively in two different reactions, both of which lead to the same desired product (Scheme 28).

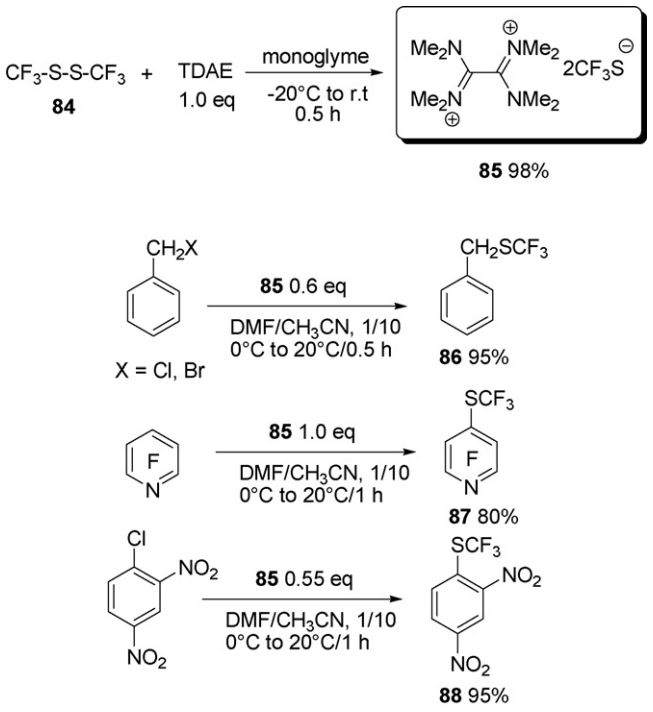
Indeed, when a total of 5 equiv. of CF_3I are used, while maintaining the quantity of TDAE at 2.2 equiv., yields of trifluoromethylthioether reached as high as 200%, based on the number of equivalents of disulfide, with both diaryl and dialkyl disulfide (Scheme 29).

We also demonstrated that the CF_3I was reduced faster than the disulfides excluding a possible TDAE mediated $S_{RN}1$ reaction from the direct reduction of the disulfides with TDAE. It is in contrast to an earlier observation [41], that TDAE could effectively reduce CF_3–S–S–CF_3 **84** to yield a novel stable trifluoromethyl sulphide anionic salt stabilized with TDAE dication, $TDAE^{2+}$, $2CF_3S^-$ **85** that was characterized by X-ray analysis and cyclic voltammetry; also several reactions show the synthetic utility of this anionic reagent (Scheme 30).

Developing methods to prepare trifluoromethylamines and, in particular *chiral* trifluoromethylamines [42–44], which had previously only been synthesized from precursors (i.e., ketones) already bearing a trifluoromethyl group, are of great interest for the pharmaceutical industry [45]. Prakash and co-workers have demonstrated [42–44] that the use of CF_3SiMe_3 proved to be very effective for the nucleophilic trifluoromethylation of *N*-tosyl aldimines and *N*-(2-methyl-2-propane-sulfinyl)imines (Scheme 31), with the latter reactions exhibiting excellent diastereoselectivity.

As we already knew that nucleophilic difluoromethylation of *N*-tosyl aldimines was effective [21], it was of interest to use our CF_3I/TDAE reagent in nucleophilic addition to *N*-tosyl aldimines and *N*-tolyl sulfinimines, and compare with the current methodology. When a series of *N*-tosyl imines, **89**–**96**, was allowed to react with the trifluoromethyl anion derived from CF_3I/TDAE in the usual manner, very good yields of the trifluoromethylated adducts **97**–**104** were obtained, as exemplified in Scheme 32.

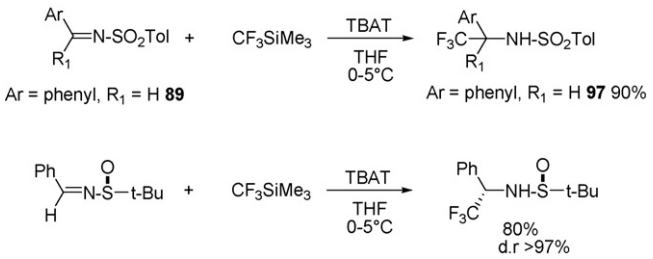
The reaction is quite effective for aromatic *N*-tosylaldimines **89**–**95** and still satisfactory for the benzophenone *N*-tosylimine **96**. Unfortunately, the analogous reactions with imines bearing aliphatic substituents on the imine carbon did not produce the desired adducts. *N*-*p*-Tolylsuflinimines easily prepared from the respective aldehydes or ketones and commercially available (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate [46] are more convenient chiral auxiliaries to make than are *N*-*tert*-butylsulfinimines [43], and were used as enantiopure sulfinimines (Scheme 33).



Scheme 30.

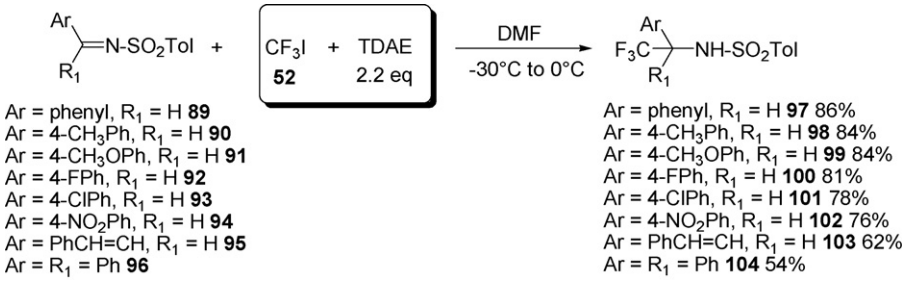
When nucleophilic trifluoromethylation of *p*-toluenesulfinimides **105**–**112** was carried out, very good yields and diastereoselectivities were observed for a wide variety of substrates (Scheme 34), including, in this case, one derived from an aliphatic aldehyde **119**. The best diastereoselectivity was obtained with *p*-toluenesulfinimide **112** derived from 1-naphthyl, probably for steric reasons.

The perfluoroalkyl anion reagents created by mixing C_2F_5I and n-C_4F_9I with TDAE were also effective in their nucleophilic reactions with aldehydes, ketones, *N*-tosyl imines, disulfides and diselenides as exemplified in Scheme 35 (selected examples) [47].

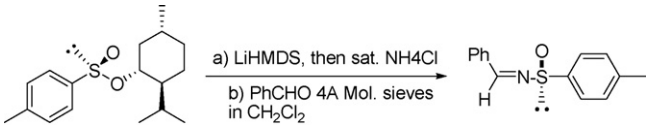


Scheme 31.

Scheme 29.

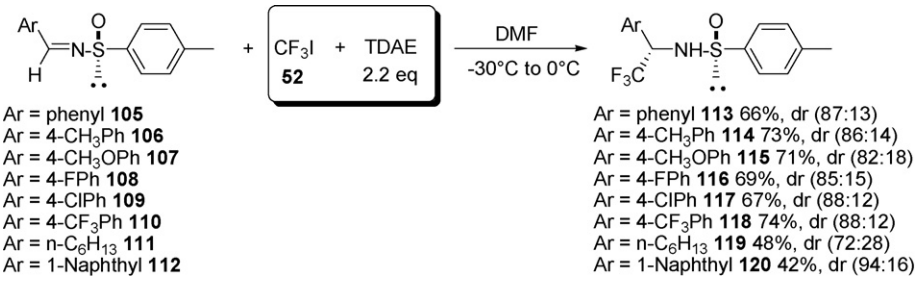


Scheme 32.

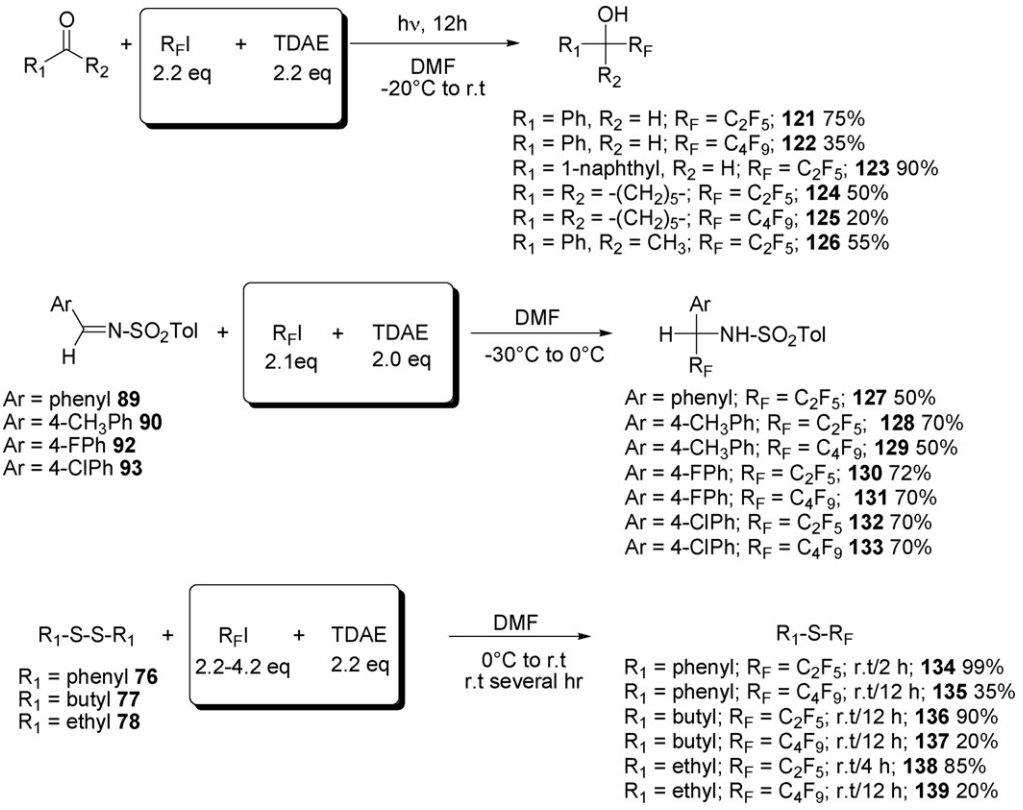


Scheme 33.

As observed with CF_3I [29], irradiation was also found to be beneficial in the aldehyde and ketones reactions. Nucleophilic pentafluoroethylation was found to be generally useful as was the case for trifluoromethylation, but when one tries to use *n*-C_4F_9I in the reaction, yields for the most part diminish, sometimes significantly.



Scheme 34.



Scheme 35.

3. Conclusion

The tetrakis(dimethylamino)ethylene (TDAE) reagent has been found to be a very useful reagent to promote nucleophilic difluoromethylation and trifluoromethylation reactions. A series of good electron-acceptors and electrophiles have been used with success in these reactions; the approach complements the existing methods to introduce a difluoromethylene and trifluoromethyl moieties into organic molecules and has some advantages because of its simplicity, mildness and sometimes very particular reactivity. One remaining question to be addressed is the effect of light for the perfluoroalkylation of aldehydes and ketones, since such activation was not needed with other electrophiles and also using bromodifluoromethyl heterocycles and chloro-difluoromethylated ketones as substrates. In order to provide an answer to that problem, we have carried out some additional experiments with CF_3I and 1-naphthaldehyde as electrophile. As reported in our initial communication in 2001 [29], non-enolizable aldehydes and ketones are excellent substrates for trifluoromethylation using the reagent created when a two equivalents of TDAE are added to two equivalents of CF_3I at −30 °C in DMF solvent in the presence of an equivalent of aldehyde or ketone. The TDAE was the last component to be added and upon its addition the solution immediately developed an orange-red color. The reaction mixture was then stirred at −20 °C for 10 min and irradiation by sun lamp begun as the reaction warmed to RT over a period of 1 h, after which the mixture was stirred at RT overnight with continued irradiation. In this particular reaction, the yields of products were found to be significantly diminished in the absence of irradiation. For example, the yield for the reaction with 1-naphthaldehyde with irradiation was 93%, whereas without light it was only 69%. If the reaction with 1-naphthaldehyde was stopped when the reaction reached RT, only 6% of product was formed, *thus indicating that the reaction was largely occurring at RT.* If the 1-naphthalehyde was held out of the reaction and only added once the orange-red solution had reached 0 °C, the yield of product was almost unchanged, which indicated substantial stability of the in situ trifluoromethyl anion "reagent", whatever it is, at 0 °C. Subsequently, it was found that the reaction mixture did not need to be irradiated for the entire duration of the reaction, but only for about 30 min to 1 h, during the warm up to RT, after which the reaction can simply be stirred at room temperature for another 4–8 h. Additional experiments are under way to fully understand this particular effect as well as to rationalize more deeply the mechanism of the TDAE reaction. In addition work is now under progress to develop a catalytic version of the TDAE approach as well as to extend the methodology to new substrates and electrophiles. It is worth mentioning that the TDAE mediated nucleophilic reaction approach is not restricted to fluorinated substrates, as witnessed by the fact that, for example, aromatic and heterocyclic benzylic substrates can also be used in the reaction with aldehydes, ketones, α-keto esters, α-ketolactams and ketomalonates [48].

Acknowledgments

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