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Review

Electrophilic polyfluoroalkylating agents based on sulfonate esters

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Abstract

This review surveys selected electrophilic polyfluoroalkylating reagents, polyfluoroalkyl alkane- and arenesulfonates, that have been used for the introduction of longer perfluorinated chains (C_nF_{2n+1}; $n \geq 4$) with methylene, ethylene or propylene spacers into the substrate. Polyfluoroalkyl mesylates, tosylates, triflates and nonaflates are described with their applications in various syntheses of polyfluorinated compounds.

Keywords: Polyfluoroalkyl; Perfluoroalkyl; Electrophilic polyfluoroalkylating agents; Polyfluoroalkylation; Sulfonate esters; Mesylates; Tosylates; Triflates; Nonaflates

Contents

1. Introduction

Highly fluorinated compounds (generally called *fluorous* compounds [1–4]) display properties which are utilized in catalysis, organic syntheses, separation techniques, biomedicinal field, electronics and materials chemistry [1–8].

High content of fluorine in a certain structure is generally achieved by connection of one or more polyfluoroalkyl chains to the substrate. Depending on the substrate, various reaction

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systems and reagents for introducing of polyfluoroalkyl chains can be chosen. In the case where the structure contains one or more nucleophilic functional groups suitable for substitution, polyfluoroalkylating electrophilic agents are utilized for introducing fluorinated chains.

When it is desirable to connect only polyfluorinated chain, $R_F(CH_2)_{1–3}$, without another functional groups or heteroatoms, there are exist only two types of polyfluorinated electrophilic agents, polyfluorinated halides and sulfonate esters. These agents are able to transfer polyfluoroalkyl chain, in which the perfluoroalkyl chain is insulated by a short nonfluorinated spacer [$R_F(CH_2)_n$–]. The length of the spacer and nucleophility of the substrate are decisive criteria for what kind of electrophilic agent will be suitable for the purpose. In the event that the nucleophility of the substrate is not sufficient, and depending on the length of the spacer between perfluorinated unit and reactive center, the corresponding polyfluoroalkyl halides can not be used. Either they do not react or the yields are very low. In these cases, polyfluoroalkyl sulfonate esters are irreplaceable. Utilization of sulfonate esters is sometimes the only possible way to connect polyfluoroalkyl chain to the substrate.

2. Description and reactivity of polyfluoroalkyl alkane- and arenesulfonates

Alkane- and arenesulfonates derived from polyfluorinated alcohols represent more reactive polyfluoroalkylating reagents in comparison to polyfluoroalkyl halides. Polyfluoroalkyl alkane- and arenesulfonates rank among highly activated alcohol derivatives. The structures of these sulfonates are shown in Fig. 1.

Thus, general formula of polyfluoroalkyl sulfonate esters is $R_F(CH_2)_nOSO_2G$, when G is CH_3, *p*-tolyl, CF_3 or C_4F_9. These agents have electrophilic character, inasmuch as the polyfluorinated part, $R_F(CH_2)_n$, as a electrophilic unit is generated after cleavage of the sulfonate GSO_2O– as the leaving group. The reactivity of the sulfonate esters depends on two factors, on the electronic properties of the group G and on the number of methylene units in the polyfluoroalkyl chain $(CH_2)_nR_F$. Both strongly influence the leaving ability of the sulfonate group.

The first factor is relative leaving group ability of sulfonate group GSO_2O– [9–11], which is expressed as k_{rel} in Table 1.

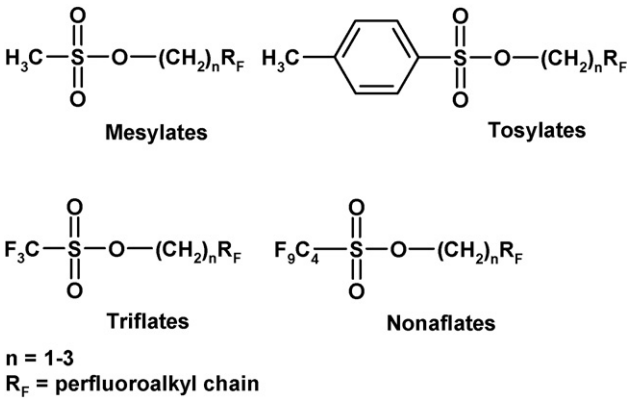


Fig. 1. Polyfluoroalkyl alkane- and arenesulfonates.

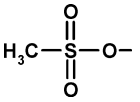
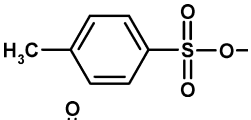
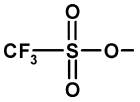
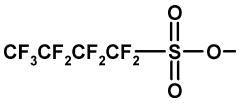
Direct systematic comparison of the different sulfonate groups GSO_2O– is not possible, since they have hitherto not been compared with regard to their leaving ability using the same conditions (solvent system and substrate).

Reactivity of nonfluorinated mesylates and tosylates is approximately the same, it depends on the concrete conditions of the reaction (substrate, solvent, steric hindrance). In case of (perfluoroalkane)sulfonate groups, triflate and nonaflate, leaving ability of the group dramatically increases (Table 1) [9–11]. The approximate order of reactivity is: *tosylates* ~ *mesylates* ≪ *triflates* < *nonaflates*.

Thus, polyfluoroalkyl tosylates should be the least reactive, but exact comparison of reactivity between polyfluoroalkyl mesylates and tosylates has not yet been accomplished. Mesylates have two advantages compared with tosylates, greater stability against hydrolysis and less steric hindrance for nucleophilic attack [12]. In some cases fluorinated mesylates are not suitable for polyfluoroalkylation due to very low reactivity [12]. In case of triflates, the situation is much clearer. Triflates are powerful fluoroalkylating agents (around 10,000 times more reactive than the corresponding tosylates) [13], whose reactivity does not decrease with perfluoroalkyl chain length increase [12]. Triflates are the most interesting group of activated polyfluoroalcohol derivatives due to high reactivity [12]. Nonaflates can be designated as the most reactive sulfonates.

The second factor that influences reactivity of the sulfonic ester is the electron-withdrawing forces of the perfluorinated chain which are against forces of the group G. The lower are electron-withdrawing forces of the perfluoroalkyl chain, the easier is the formation of the corresponding sulfonate anion and the greater reactivity of the whole sulfonate. The influence of the perfluorinated chain depends strongly on the length of the spacer between perfluorinated chain and sulfonate group. For identical sulfonic groups -SO_2G, the longer is the spacer, the lower will be the electron-withdrawing force of the perfluorinated group. In

Table 1
Relative leaving group ability of sulfonate group GSO_2O–

Leaving group	Common name	k_{rel} [a]	k_{rel} [b]
	Mesylate	1.00	1.00
	Tosylate	0.70	1.23
	Triflate	5.6×10^4	4.4×10^3
	Nonaflate	1.2×10^5	9.3×10^3

[a] Relative leaving group ability has not been measured under the same conditions; for details see original references [9,11].

[b] Relative rates of solvolysis of 1-phenylethan-1-yl esters in 80% EtOH/H_2O at 75 °C [10,11].

other words, a shorter spacer means a lower reactivity of the sulfonate. The reactivity of the sulfonates, depending on length of the spacer between sulfonate group and perfluorinated group, will increase in following order: *methylene* < *ethylene* < *propylene*.

Thus, (perfluoroalkyl)methyl alcohol derivatives are least reactive. Only triflates and nonaflates prepared from them are enough reactive and therefore usable as electrophiles, whereas mesylates and tosylates are used rarely. 2-(perfluoroalkyl)ethyl alcohol based triflates succeed in many reactions in which mesylates and tosylates are not sufficiently reactive. In contrast, all types of sulfonate derivatives from 3-(perfluoroalkyl)propyl alcohols are sufficiently reactive.

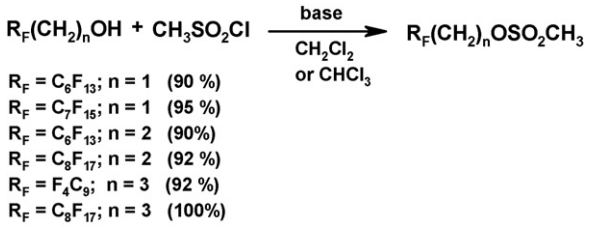
The perfluoroalkyl chain can be of various length; the most widely used are those with an even number of carbons, for example, perfluorobutyl, perfluorohexyl and perfluorooctyl. Perfluorodecyl and longer chains are not usually utilized, due to the high price of the corresponding starting materials and poor solubility in common organic solvents. For reagents with an odd number of perfluorinated carbons, only (perfluoroheptyl)-methyl triflate has been utilized, probably due to the restricted availability and higher price of other starting materials.

Generally, alkane- and arenesulfonates, as powerful alkylating agents, display high toxicity. As regards polyfluoroalkyl alkane- and arenesulfonates, any study about their toxicity has not been published yet. It is expected, that their toxicity will be similar to nonfluorinated ones.

3. Preparation of polyfluoroalkyl sulfonate esters

There exist many methods for the preparation of nonfluorinated sulfonate esters [11,14–19], but only a few synthetic procedures are used for polyfluoroalkyl sulfonate esters. The general procedure is based on the reaction of polyfluorinated alcohol with halo-derivative or anhydride of the corresponding sulfonic acid. For polyfluoroalkyl mesylates or tosylates, chlorides of the corresponding acids are most frequently used. For triflates, both chlorides and anhydrides are used. For the preparation of nonaflates, the fluoride of nonafluorobutanesulfonic acid was used. The reactions are carried out most frequently in dry dichloromethane or chloroform. Triethylamine, pyridine or aqueous sodium hydroxides are used as bases. The temperature range, in which components are added, varies from −40 to 20 °C. There exist two techniques of addition. The first is based on dropwise addition of the solution of chloride or anhydride of the sulfonic acid in chloroform into solution of polyfluorinated alcohol in dry triethylamine under cooling [12]. In the second, the compounds are added in reversed sequence. A solution of the alcohol in dichloromethane in the presence of a base is added to the cooled mixture of sulfonic acid anhydride in dichloromethane [20,21].

Although polyfluoroalkyl alkane- and arenesulfonates can be prepared and used in situ [22], in most cases, they are isolated and purified. The course of separation depends on the sulfonate. Thus, mesylates and tosylates can be extracted between water and chloroform following by washing with a solution of sodium hydrogen carbonate and brine [12]. For the more reactive sulfonates such as triflates or nonaflates, this work up technique is not recommended, but it has been successfully used for the separation extraction between aqueous and organic system [23,24]. Alternatively, they can be separated by simple filtration through a short column of silica gel and eluted with dichloromethane [12,20,21].



Scheme 1. Preparation of polyfluoroalkyl mesylates.

3.1. Preparation of polyfluoroalkyl methanesulfonates (mesylates)

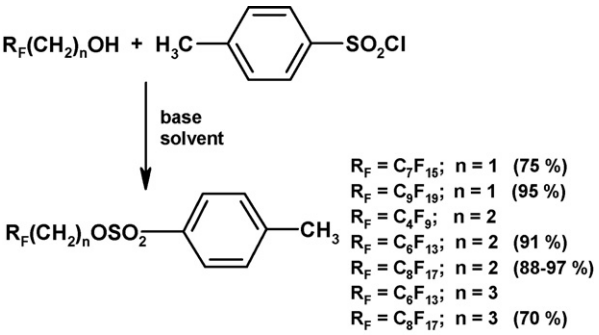
These have been synthesized from polyfluorinated alcohols by reaction with methanesulfonyl chloride, in chlorinated solvents such as chloroform or dichloromethane, in the presence of triethylamine [12,25–30], diisopropylethylamine [31–33] or pyridine [34] as a base. The individual components were added at 0 °C and then the mixture was warmed to room temperature. The yields of the reactions are high, greater than 90% (Scheme 1).

3.2. Preparation of polyfluoroalkyl p-toluenesulfonates (tosylates)

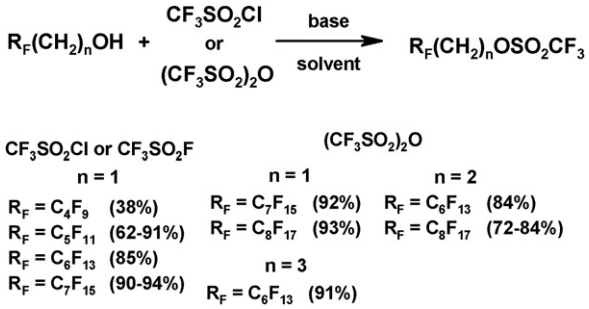
The preparation of polyfluoroalkyl tosylates from (perfluoroalkyl)methanols [12,35,36] 2-(perfluoroalkyl)ethanols [25,37–47] and 3-(perfluoroalkyl)propanols [48–52] is based on the reaction of the corresponding alcohols with tosyl chloride in the presence of triethylamine [25,39,40,45,47], pyridine [37–41,43,44,49,51,52] or sodium hydroxide [35,48,50] as a base. Chlorinated solvents, pyridine or acetone were used. Yields are in the range from 70% to 98% (Scheme 2).

3.3. Preparation of polyfluoroalkyl trifluoromethanesulfonates (triflates)

There are several methods for the preparation of triflates from (perfluoroalkyl)methanols. In the first method, a chloride



Scheme 2. Preparation of polyfluoroalkyl tosylates.



Scheme 3. Preparation of polyfluoroalkyl triflates.

[12,24,53,54] or fluoride [13,55,56] of the trifluoromethanesulfonic acid and polyfluorinated alcohol in the presence of triethylamine are used. The second method utilizes triflic anhydride [57–59] in the presence of pyridine. Both methods use chlorinated solvents, dichloromethane or chloroform. As a base, triethylamine or pyridine was used and reaction temperatures were about 0 °C (Scheme 3).

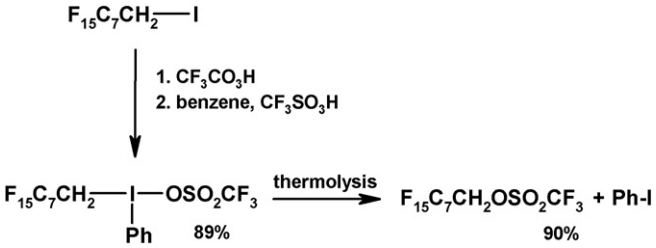
Preparation of 2-(perfluoroalkyl)ethyl triflates was first mentioned by Germain and Commeyras in 1981 [60]. They prepared 2-(perfluoroalkyl)ethyl triflate by means of an electrochemical method, anodic oxidation of 2-(perfluorohexyl)ethyl iodide in trifluoromethanesulfonic acid, in 98% yield. These esters are also mentioned in patents [61,62]. In 2001, it was described their synthesis on a laboratory scale [20,21] from the reaction of 2-(perfluoroalkyl)ethyl alcohols with the triflic anhydride (Scheme 3) in dichloromethane and hexane with pyridine as a base. The solution of the alcohol, dichloromethane/hexane and pyridine was slowly dropped to the stirred solution of triflic anhydride at −10 °C. When addition was complete, the mixture was slowly warmed to laboratory temperature. Esterification at laboratory temperature has been described earlier [22]. It is not necessary to separate and purify the triflate but it can be used immediately without further purification in the next reaction step [22].

3-(Perfluoroalkyl)propyl triflates are used only rarely. They are mentioned in a patent [63] and in two articles [64,65]. Their synthesis is based on the same principle as those with methylene or ethylene spacers. 3-(Perfluorohexyl)propanol is reacted with the triflic anhydride in the presence of a base in dichloromethane as a solvent. (Scheme 3).

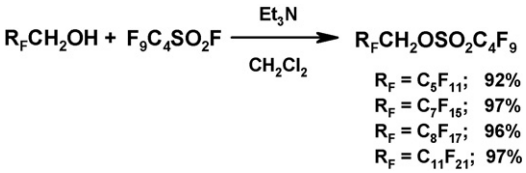
Reaction of (perfluoroheptyl)methyl iodide with trifluoroperoxyacetic acid followed by the reaction with benzene and triflic acid in 1,1,2-trichloro-1,2,2-trifluoroethane afforded [(perfluoroheptyl)methyl](phenyl)iodonium triflate, which was decomposed at 140–145 °C to produce (perfluoroheptyl)-methyl triflate in 90% yield [66,67] (Scheme 4).

3.4. Preparation of polyfluoroalkyl nonafluorobutanesulfonates (nonaflates)

The nonaflates have been prepared from (perfluoroalkyl)-methanols only. The preparation of the (perfluoroheptyl)methyl nonaflate utilizes the corresponding fluoride of the sulfonic acid. Thus, (perfluoroalkyl)methyl nonafluorobutanesulfonate, was



Scheme 4. Thermolysis of R_F(Ph)iodonium triflate.



Scheme 5. Preparation of polyfluoroalkyl nonaflates.

easily obtained by treating (perfluoroalkyl)methanols with a slight excess of $C_4F_9SO_2F$ in diethylether or dichloromethane in the presence of triethylamine [23,68,69] with high yields (Scheme 5).

Another method [70] describes esterification at −40 °C, when nonafluorobutanesulfonyl fluoride in dichloromethane is added to pentadecafluorooctan-1-ol in triethylamine. When addition was complete, the mixture was brought back to −15 °C and then worked up. However, in this case, the yield was lower, 49% only.

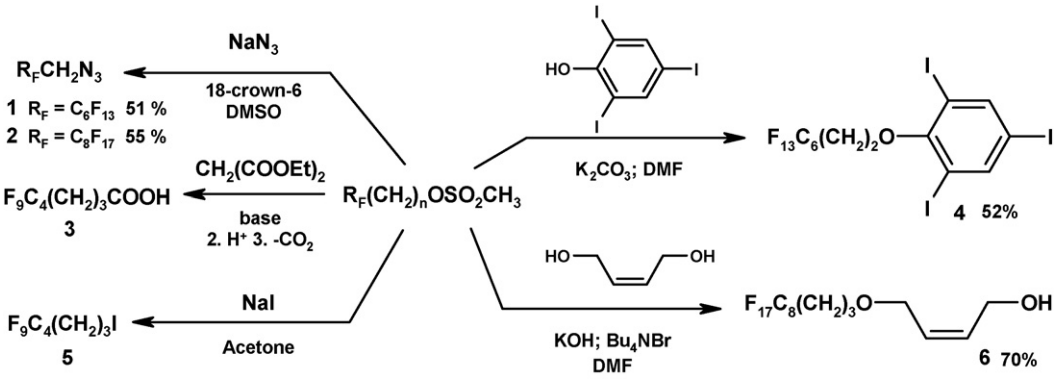
4. Synthetic utilization

4.1. Reactions of polyfluoroalkyl methanesulfonates

Polyfluoroalkyl mesylates were used for the preparation of polyfluorinated azides **1** and **2** [71]. Mesylates were reacted with sodium azide in dimethylsulfoxide in the presence of 18-crown-6-ether. Products **1** and **2** were formed in moderate yields 51 and 55%, respectively (Scheme 6). This azides were then used for construction of fluorinated [1–3] triazoles [71].

2-(Perfluoroalkyl)ethyl mesylate was used as a C-alkylating agent in the reaction with diethyl malonate. The final product **3** was a fluorinated acid [30] (Scheme 6). As an O-alkylating agent, it was used for alkylation of 2,4,6-triiodophenol. Reaction was carried out in the presence of potassium carbonate in DMF at 80 °C for 40 h. Yield of (polyfluoroalkyl)phenylether **4** was 52% [31–33] (Scheme 6).

3-(Perfluorobutyl)propyl mesylate was converted into the corresponding iodide **5** [28] under Finkelstein conditions, by reaction with sodium iodide in refluxing acetone with a yield of 87%. (Perfluorooctyl)propyl mesylate was reacted with cis-butene-1,4-diol under phase-transfer catalyst conditions (KOH, $Bu_4N^+Br^-$ in DMF) for 1 h at 70 °C and provided polyfluorinated alcohol **6** in 70% yield [27] (Scheme 6). This alcohol was used for the construction of fluorous-tagged sugars.



Scheme 6. Synthetic utilization of polyfluoroalkyl methanesulfonates.

4.2. Reactions of polyfluoroalkyl p-toluenesulfonates

(Perfluoroalkyl)methyl iodides **7–9** can be obtained by Finkelstein reaction of (perfluoroalkyl)methyl tosylate with sodium or potassium iodide in glycols [36,72] (Scheme 7). Because alkyl tosylates also form easily the corresponding bromides under Finkelstein reaction with lithium bromide, this can be utilized for the preparation of polyfluorinated bromides. Thus, reaction of 2-(perfluoroalkyl)ethyl tosylate with dry lithium bromide under reflux in acetone affords the desired bromides **10** and **11** in high, 91–93%, yield [41,44,46,47] (Scheme 7).

Facile polyfluoroalkylation of nitrogen in primary and secondary amines has found utilization in syntheses of polyfluorinated aza-macrocycles. Thus, fluorine-containing macrocycles **15** and **16** were prepared by means of nucleophilic substitution of the corresponding cyclic amines **12** and **13** and fluorinated tosylates [25,73]. The reaction was carried out in dioxane under reflux in the presence of sodium carbonate as a base (Scheme 8). Similar polyfluoroalkylation was accomplished with a di-azacrown unit **14**, but the products **17** and **18** were formed only in very low yield. Replacement of the tosylate with the corresponding mesylate failed to enhance the yield of the macrocycle. On the other hand, the corresponding triflate afforded desired bis(polyfluorolakylated) macrocycle **18** with higher, 53%, yields [74] (Scheme 8).

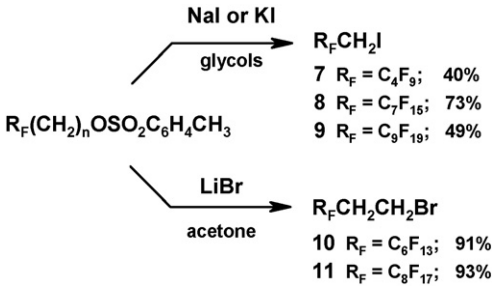
These macrocyclic ligands **15–18** with one or more fluorous ponytails have potential applications in metal ion separation involving a fluorous phase or supercritical carbon dioxide [25] or they can be used as highly hydrophobic ionophores which are useful in ion-selective transport of cations through liquid membranes [73]. They can be also used as phase-transfer catalysts [74].

Ethanolamine was *N*-monopolyfluoroalkylated by the reaction with 2-(perfluorohexyl)ethyl tosylate in refluxing 2-methylpropan-2-ol [37,38] with a yield of 58% (Scheme 9).

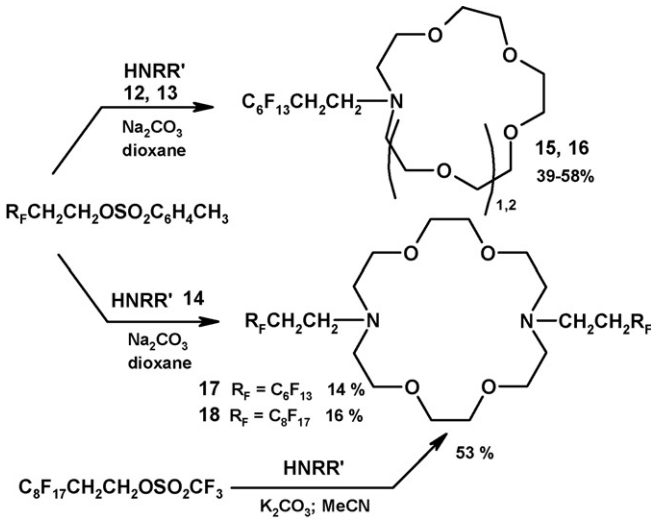
3-(Perfluoroalkyl)propyl tosylates were used for the preparation of 3-(perfluoroalkyl)propane thiols **19–21** [51] by reaction with thiourea in anhydrous ethanol under reflux for 20 h followed reaction with aqueous solution of sodium hydroxide at 70 °C for 2 h (Scheme 10).

(3-Perfluoroalkyl)propyl tosylates were also used as *N*-alkylating agents. 3-(Perfluorooctyl)propyl tosylate was reacted with 3-aminoethylpropanoate (**22**) [75] in the presence of potassium carbonate in acetonitrile. The reaction afforded polyfluorinated amine **23** in 83% yield, which served for construction of fluorous protecting group [75–77] (Scheme 11). Methyl-4-aminomethylbenzoate (**24**) was reacted under almost the same conditions, in the presence of potassium carbonate in acetonitrile and the monoalkylated product **25** was formed in 78% yield (Scheme 11).

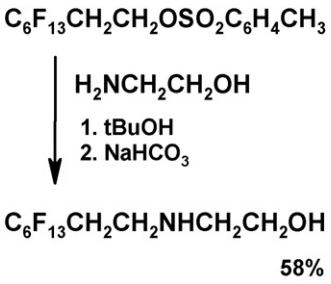
3-(Perfluorooctyl)propyl tosylate has been also used for the preparation of fluorophilic tri- and tetradentate nitrogen ligands



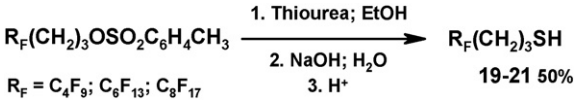
Scheme 7. Finkelstein reaction with polyfluoroalkyl tosylates.



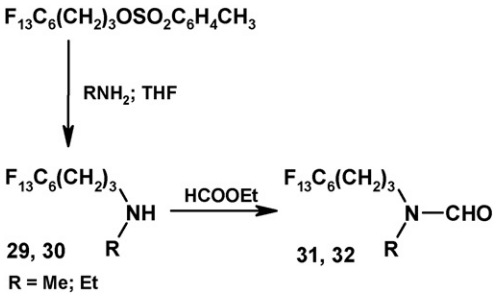
Scheme 8. Syntheses of polyfluorinated aza-macrocycles.



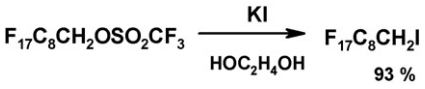
Scheme 9. *N*-monopolyfluoroalkylation of ethanolamine.



Scheme 10. Preparation of 3-(perfluoroalkyl)propyl thiols.



Scheme 12. Preparation of polyfluoroalkyl formamides.



Scheme 13. Preparation of (perfluorooctyl)methyl iodide.

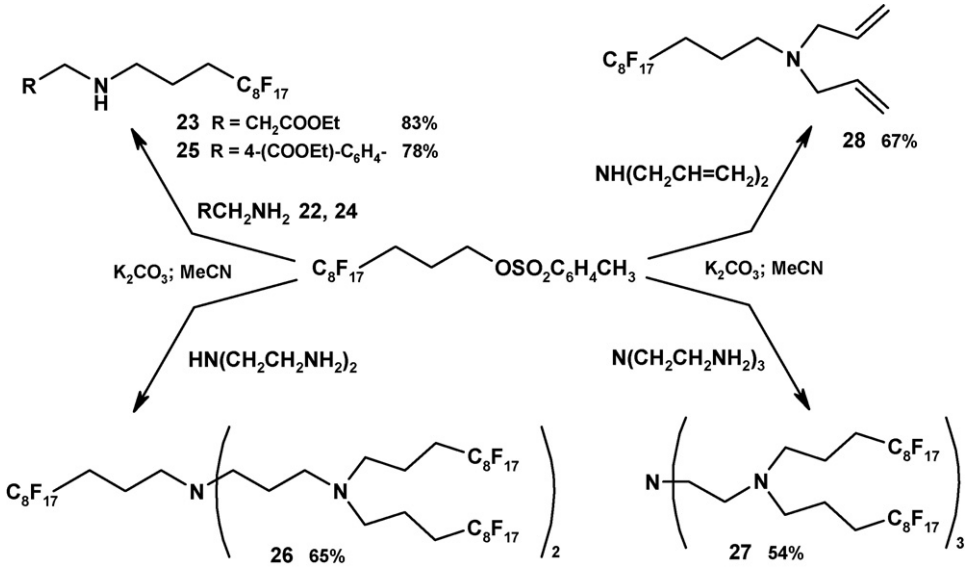
26 and **27** [48]. Refluxing acetonitrile and potassium carbonate were used as the reaction medium. In this case, nitrogen was substituted with two fluorinated chains and highly fluorinated tertiary tridentate and tetradentate amines **26** and **27** were obtained in 65 and 54% yield, respectively (Scheme 11). These ligands were used in the presence of copper(I) chloride for a fluorous variant of the cyclization of trichloroacetic acid ester to the corresponding lactone [48]. The secondary amine, diallyl amine, was polyfluoroalkylated by means of the tosylate [50] and tertiary polyfluorinated amine **28** was formed in 67% yield (Scheme 11). The amine was then transformed with methyl iodide into an ammonium salt, which was explored as a potential antimicrobial agent [50].

3-(Perfluoroalkyl)propyl tosylates, reacted with methyl- or ethylamine in THF in a pressure vessel at 20 °C, provided the corresponding (polyfluoroalkyl)alkylamines **29** and **30** [49,52,78]. Amines **29** and **30** were reacted with ethyl formate and gave *N*-alkyl-*N*-(polyfluoroalkyl)formamides **31** and **32**, that were used as fluorous solvents [52,78] (Scheme 12).

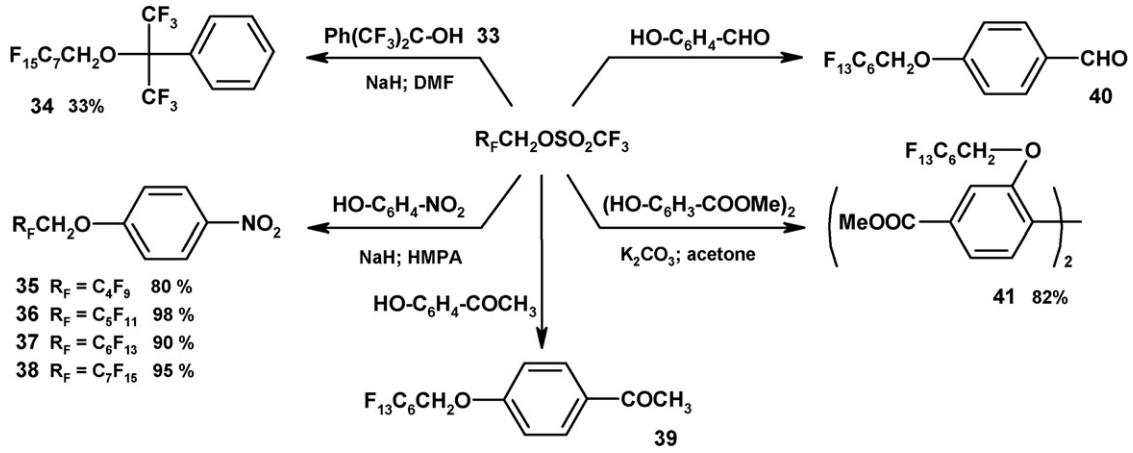
4.3. Reactions of polyfluoroalkyl trifluoromethanesulfonates

(Perfluorooctyl)methyl iodide was prepared from the corresponding triflate by Finkelstein reaction with potassium iodide in glycol under reflux in high 93% yield [57] (Scheme 13). The preparation is practicable on a multi-gramme scale.

(Perfluoroalkyl)methyl triflates were used as O-alkylating agents in the synthesis of new types of fluorinated ethers. A tertiary alcohol (1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol; **33**) was converted into the corresponding sodium salt using sodium hydride, then the salt was reacted with (perfluoroheptyl)methyl triflate. The product **34** was formed in 33% yield [58] (Scheme 14). *p*-Nitrophenyl[(perfluoroalkyl]methyl] ethers **35**–**38** with longer fluorinated chains must be synthesized by means of the corresponding triflates (corresponding tosylates and mesylates failed in this reaction) [12] (Scheme 14). These compounds were synthesized as part of a study of synthetic approaches to fluoroalkyl *p*-nitrophenyl ethers.



Scheme 11. Synthetic utilization of 3-(perfluorooctyl)propyl tosylate.



Scheme 14. Synthetic utilization of (perfluoroalkyl)methyl triflates.

(Perfluoroalkyl)methyl triflates were also used for the preparation of aryl-polyfluoroalkyl ethers **39**–**41**. These were intermediate in the preparation of new type of liquid crystals [79], thermotropic polyesters [80] or polyfluoroalkylated styrenes [81–83] (Scheme 14).

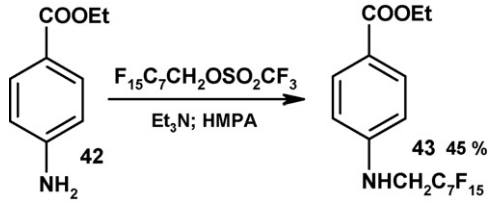
Polyfluoroalkyl triflate was used as an *N*-alkylating agent. Synthesis of polyfluorinated-derivative of Cetaben™ **43** was based on polyfluoroalkylation of 4-amino-ethylbenzoate with subsequent hydrolysis. Amino-derivative **42** was reacted with (perfluoroheptyl)methyl triflate in HMPA in the presence of triethylamine. The reaction afforded monoalkylated product **43** in 45% yield [24,53,54] (Scheme 15).

(Perfluorooctyl)methyl amine (**44**) can be prepared by reaction of gaseous ammonia with triflates. Dimethylformamide was used as a reaction medium, and only monoalkylated product **44** was formed in 75% yield after 2 h at 100 °C [84] (Scheme 16). Another way to obtain (perfluorooctyl)methyl amine (**44**) is via benzylamine [61]. (Perfluorooctyl)methyl triflate was reacted with benzylamine in THF under heating. After 3 h monopolyfluoroalkylated benzylamine **45** was formed in 93% yield and after hydrogenolysis, the desired amine **44** formed in 97% yield [61,85] (Scheme 16).

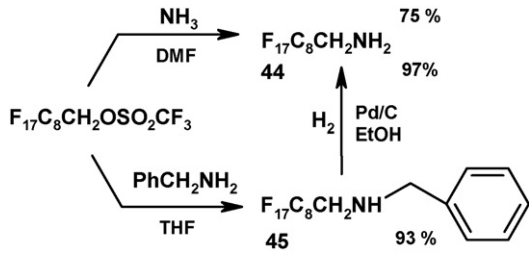
(Perfluoroheptyl)methyl triflate was utilized in the preparation of quarternary ammonium salts. Thus, its reaction with stilbazole-derivative **46** in *N*-methylpyrrolidinone at 50 °C for 18 h produced the corresponding *N*-polyfluoroalkylated compound **47** [86] in 16% yield (Scheme 17). Polyfluoroalkyl triflate, reacted with *N*,*N*-dimethyl-phenetylamine in boiling butanone, provided the corresponding quarternary ammonium salt **48** [87]. The reaction of methyl-(2-phenyloxy-ethyl) amine with polyfluoroalkyl triflate followed by alkylation with methyl triflate leads to a similar salt **49** [87] (Scheme 17). Quarternary ammonium salts **48** and **49** were tested as antimicrobial agents.

(Perfluorobutyl)methyl triflate was also used as C-alkylating agent in the reaction with 2-(3,3,3-trifluoropropyl)malonitrile in DMSO in the presence of potassium carbonate as a base [59]. The reaction ran at room temperature for 5 h (Scheme 18).

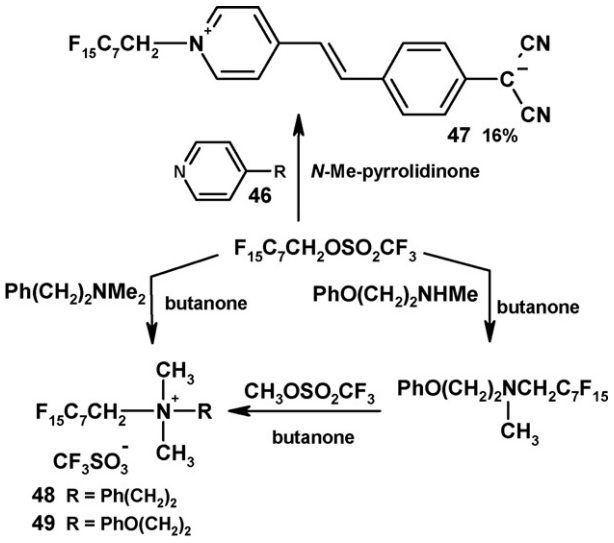
2-(perfluoroalkyl)ethyl iodides were used for the preparation of bis-substituted cyclopentadienes bearing two fluorophilic chains, but due to the low reactivity of these iodides, the product



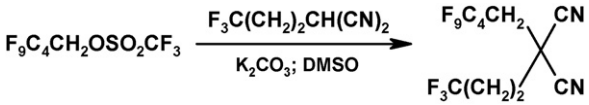
Scheme 15. Synthesis of polyfluorinated-derivative of Cetaben™.



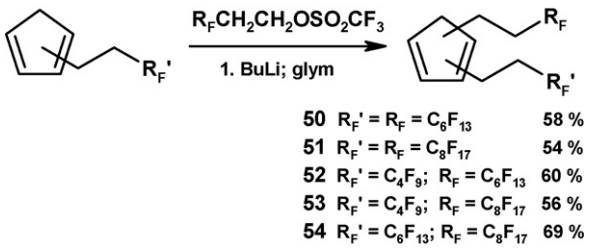
Scheme 16. Preparation of (perfluorooctyl)methyl amine.



Scheme 17. (Perfluoroheptyl)methyl triflate as *N*-alkylating agent.



Scheme 18. Preparation of bis(polyfluoroalkylated) malonitrile.



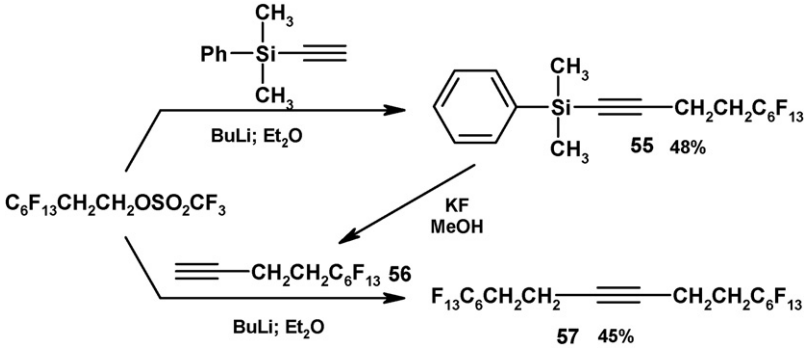
Scheme 19. Preparation of bis(polyfluoroalkylated) cyclopentadienes.

50–54 was formed only in a yield of 5%. Therefore 2-(perfluoroalkyl)ethyl triflates were chosen as better electrophiles. These gave the target bis-polyfluoroalkylated products **50–54** in a yield of 50–60% [21,88] (Scheme 19). The ligands were used for the preparation of fluorophilic ferrocenes and rhodium complexes.

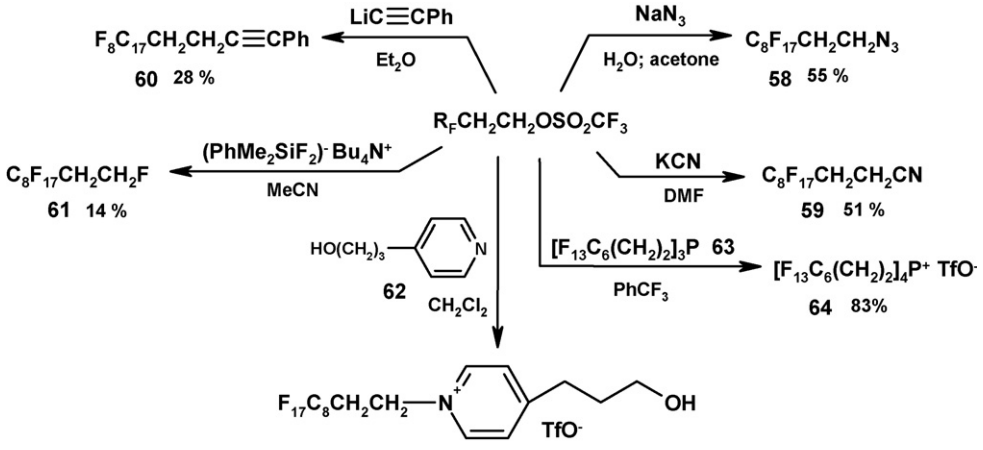
In another application polyfluoroalkyl triflate was used for the preparation of polyfluoroalkylated acetylenes **55–57** [89,90]. In the first step, a silylated terminal polyfluoroalkylated acetylene **55** was prepared from the lithium salt of ethynyl(phenyl)dimethylsilane with 2–(perfluoroalkyl)ethyl triflate. After desilylation with potassium fluoride, a terminal polyfluorinated acetylene **56** was obtained. Analogous lithiation of this acetylene **56** followed by the reaction with fluoroalkyl triflate afforded [bis(perfluorohexyl)ethyl]acetylene (**57**) [89,90] (Scheme 20). In all cases, polyfluoroalkyl triflate is a requirement, because the corresponding iodide was unreactive. Both fluorous acetylenes **56** and **57** resemble normal acetylenes in reactivity and are thus potential building blocks.

With strong nucleophiles such as azide or cyanide, polyfluoroalkyl triflates undergo substitution and the corresponding polyfluorinated azide **58** and cyanide **59** was obtained in moderate yield 55 and 51%, respectively [20,21]. With lithium phenylacetylide or tetrabutylammonium difluorodimethylphenylsilicate, polyfluorinated phenylacetylene **60** and fluoride **61** were formed in low yields, 28 and 14%, respectively. This reflects that triflate can be successfully reacted even with nucleophiles of moderate strength [20,21] (Scheme 21). 2–(Perfluoroalkyl)ethyl triflate was used for the *N*-alkylation of 3-(4-pyridyl)propan-1-ol (**62**). Reaction was carried out in dichloromethane [62] (Scheme 21). It was used in the reaction as P-alkylating agent with tris(polyfluoroalkyl) phosphine **63** providing the corresponding phosphonium salt **64** in 83% yield [91] (Scheme 21).

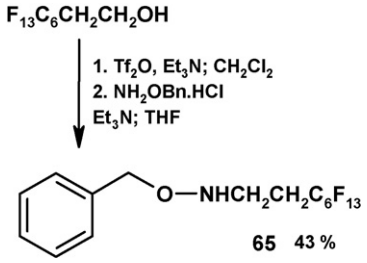
Polyfluoroalkyl triflates can be generated in the reaction mixture and used for the next step without further isolation and



Scheme 20. Preparation of polyfluoroalkylated acetylenes.



Scheme 21. Synthetic utilization of 2-(perfluoroalkyl)ethyl triflates.



Scheme 22. Preparation of polyfluorinated benzyloxyamine.

purification [22] as is shown in Scheme 22. A fluorinated alcohol was converted into the corresponding triflate, which was immediately reacted with *O*-benzylhydroxylamine. The reaction afforded polyfluorinated *O*-benzylhydroxylamine **65** in a moderate, 43%, yield (Scheme 22). This amine **65** was then used for synthesis of *N*-polyfluoroalkyl hydroxamates [22].

3-(Perfluorohexyl)propyl triflate was used as an O-alkylating agent in the synthesis of fluorous building blocks. Methyl gallate was converted into the sodium salt with sodium hydride in THF and then reacted with 3-(perfluoroalkyl)propyl triflate. Tris(polyfluoroalkylated) gallate **66** was obtained in 80% yield [64]. Fluorous gallate **66** was then converted into the corresponding benzylalcohol and benzaldehyde (Scheme 23). 3-(Perfluorooctyl)propyl triflates was used in preparation of polyfluoroalkylated bisphosphonate **67** [65]. Methylene bis(diethyl phosphonate) was converted into the corresponding salt by reaction with potassium *tert*-butoxide in toluene and reacted with polyfluoroalkyl triflate. Monopolyfluoroalkylated bisphosphonate **67** [65] was obtained in 42% yield (Scheme 23).

4.4. Reactions of polyfluoroalkyl nonaflates

In the chemistry of fluorous ligands, (perfluoroheptyl)-methyl nonaflate was utilized as the agent for polyfluoroalkylation of bisoxazolines. In the first step, bisoxazoline **68** was lithiated with butyllithium and then alkylated with nonaflate [92]. The reaction afforded (perfluoroheptyl)methyl-bisoxazoline **69** in 67% yield (Scheme 24), but connection of the second (perfluoroheptyl)methyl chain by this means failed. The fluorous oxazoline **69** was used as a ligand in palladium-catalyzed alkylation [92].

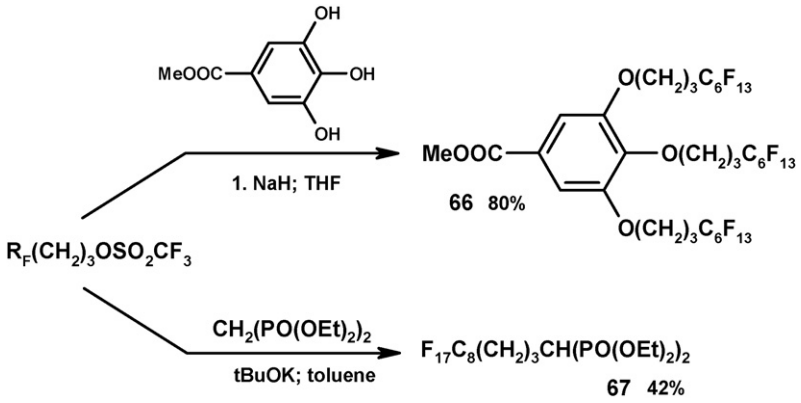
Scheme 24. Polyfluoroalkylation of bisoxazoline-derivative.

Polyfluoroalkyl nonaflate as a O-alkylating agent was used for polyfluoroalkylation of hydroxy groups in various types of structures. Synthesis of another type of fluorous oxazoline **71**, with four polyfluoroalkyl chains, utilizes polyfluoroalkyl nonaflate in last step [93]. Substitution of **70** was carried out in dimethylformamide in the presence of cesium carbonate. The product **71** was formed in 66% yield (Scheme 25). The fluorine content of the ligand **71** is 59.3%, and this ligand was used for asymmetric alkylations [93].

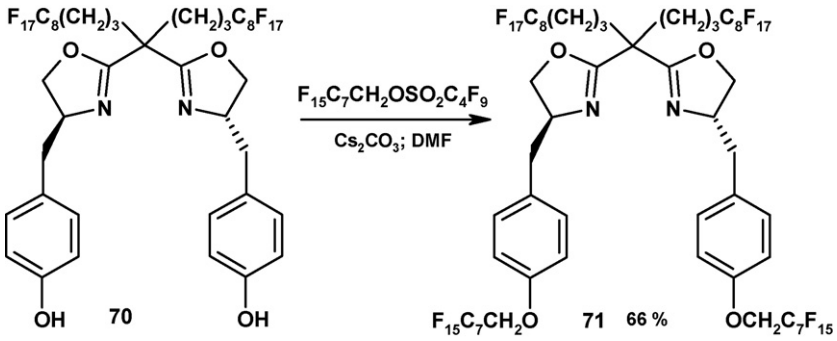
For substitution of 4′-methoxybiphenyl-4-ol (**72**) by (perfluoroheptyl)methyl chain, the corresponding polyfluoroalkyl nonaflate was used [70]. The reaction was carried out in the presence of potassium carbonate, to convert phenol **72** into a potassium salt, in dimethylformamide. The product **73** was formed in good, 74%, yield (Scheme 26). This 4′-methoxy-4-(polyfluorooctyloxy)biphenyl was prepared as part of a study of polyphilic materials [70].

In other applications, (perfluoroheptyl)methyl nonaflate was used for alkylation of tris(4-hydroxyphenyl)phosphine (**74**) [94], tris(4-hydroxyphenyl)phosphine oxide (**75**) [95] and tris(3,5-dihydroxyphenyl)phospine oxide (**76**) [96]. The reactions were carried out in dimethylformamide as a solvent with potassium or cesium carbonate and afforded the desired polyfluorinated ligands **77–79** in 32–75% yields (Scheme 27). The phosphine oxides **77–79** were converted into the corresponding phosphanes, which were used as a ligand for the preparation of metallocomplexes for fluorous biphasic catalysis [96].

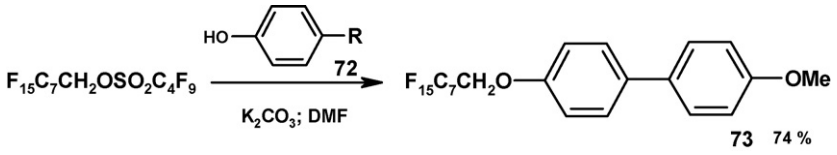
In the synthesis of an enantiopure fluorous 1,2-diphenyl-1,2-ethanediamine **81** bearing four fluorous ponytails and having 62.2% fluorine content, it was necessary to use a polyfluoroalkylating agent with as short a spacer as possible. Therefore, (perfluoroheptyl)methyl nonaflate was employed [97,98].



Scheme 23. 3-(Perfluoroalkyl)propyl triflates as O- and C-alkylating agents.



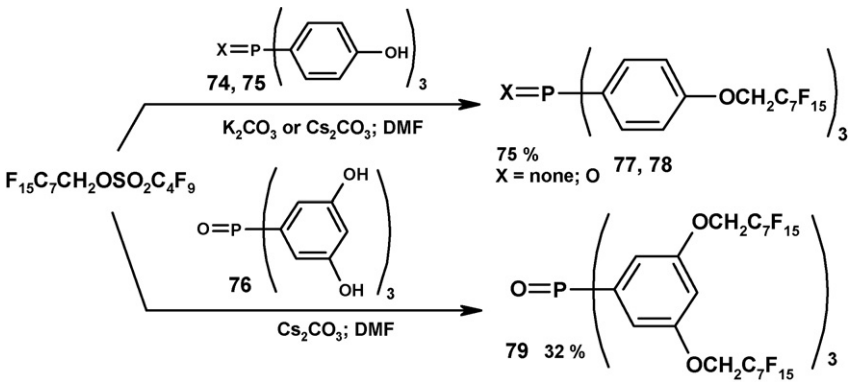
Scheme 25. Preparation of fluorous bisoxazoline-derivative.



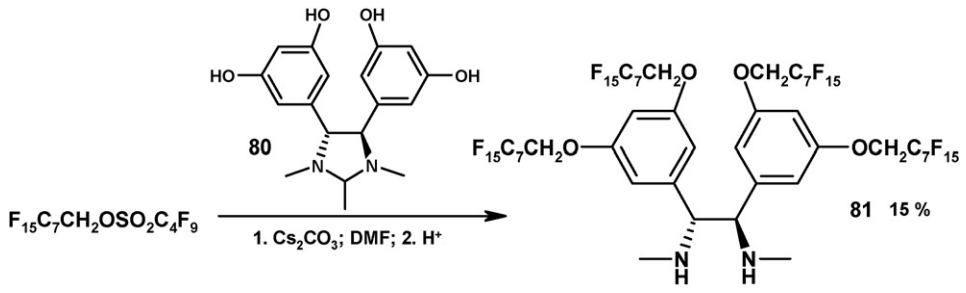
Scheme 26. Preparation of 4′-methoxy-4-(polyfluorooctyloxy)biphenyl.

Tetraol **80** was reacted with the nonaflate and cesium carbonate in dimethylformamide. The desired product **81** was obtained in 15% yield after deprotection in acid medium (Scheme 28). It can be used as a ligand for fluorous biphasic catalysis.

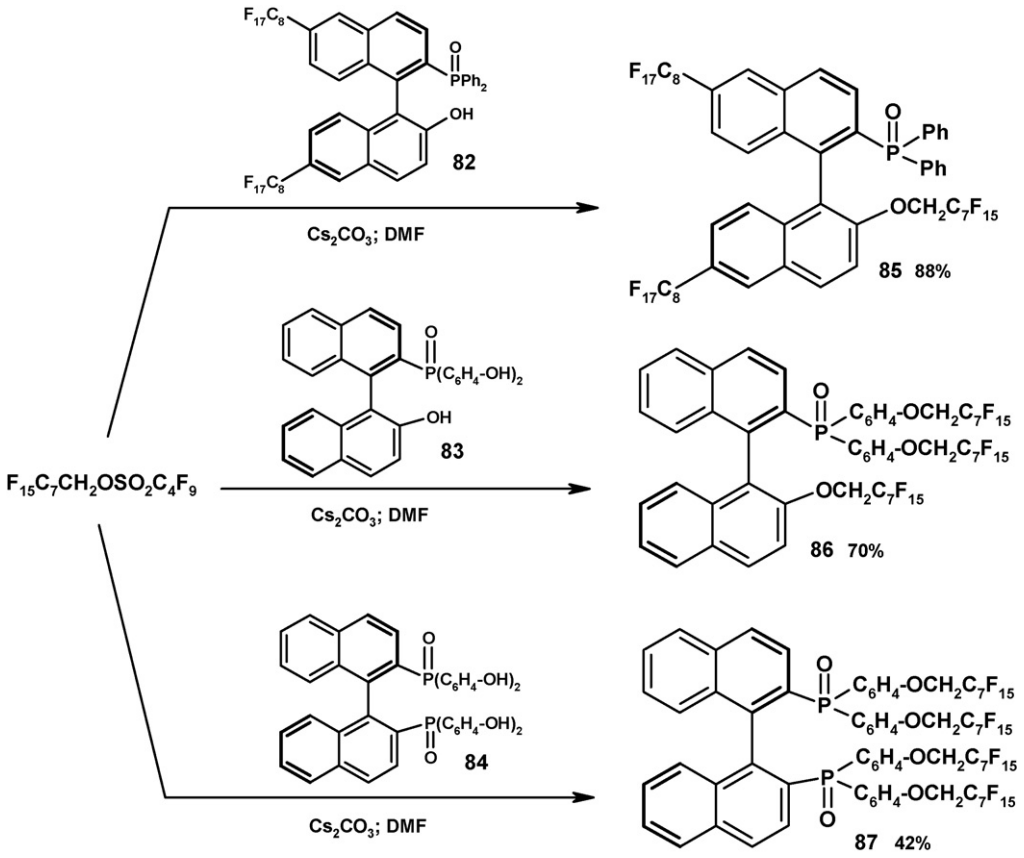
Chiral fluorous analogues of the ligand 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyl (MOP), have been prepared. Polyfluoroalkylation at oxygen of **82** and **83** was accomplished by means of nonaflate [99–101] under almost the same reaction conditions as described above. Polyfluoroalkylation affords the desired products **85** and **86** in high, 88 and 70%, yield, respectively (Scheme 29). In this manner, chiral phosphine ligand **87** based on binaphthyl derivatives (BINAP) have been synthesized from **84** in 42% yield [100,101] (Scheme 29). The binaphthyls **85**–**87** were then converted into the corresponding phosphines, which have been used in both the palladium-catalyzed asymmetric substitution of 1,3-diphenylprop-2-en-1-yl acetate with various nucleophiles and asymmetric Heck reaction of 2,3-dihydrofuran with various aryl triflates [99–101].



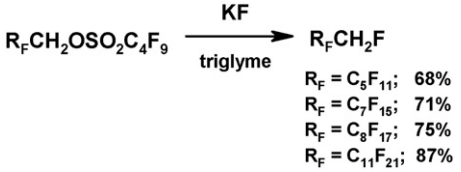
Scheme 27. (Perfluoroheptyl)methyl nonaflate as O-alkylation agent.



Scheme 28. Preparation of fluorous 1,2-aryl-1,2-ethanediamine.



Scheme 29. Preparation of chiral fluorous phosphine ligands.



Scheme 30. Preparation of 1*H*,1*H*-perfluoroalkanes.

(Perfluoroalkyl)methyl nonaflates were converted into the corresponding fluorides by the reaction with potassium fluoride in triglyme at 170–200 °C [68,69] (Scheme 30).

5. Conclusions

Polyfluoroalkyl alkane- and arenesulfonates have predominant positions among all types of polyfluoralkylating agents due to their high reactivity. These polyfluoralkylating agents are irreplaceable in many synthetic procedures. As highlighted in this review, polyfluoroalkyl alkane- and arenesulfonates are widely used for the preparation of various types of structures.

From their wide utilization is clear, that polyfluoroalkyl alkane- and arenesulfonates will be still a focus of interest of chemists concerned with the preparation of new types of recyclable fluorous protecting groups and tags, scavengers and fluorophilic catalysts, as well as liquid crystals, special fluorosurfactants, etc. Electrophilic polyfluoroalkylating agents based on sulfonate esters can be applied in particular in small-scale and discovery oriented research.

Acknowledgements

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