# Oxidative Desulfurization-Fluorination: A Facile Entry to a Wide Variety of Organofluorine Compounds Leading to Novel Liquid-Crystalline Materials

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**Abstract:** The oxidative desulfurization-fluorination reaction of organosulfur compounds using an *N*-haloimide and a fluoride source is demonstrated to be an effective and mild fluorination method that allows us to synthesize in high yields with high chemoselectivity various types of *gem*-difluoro compounds, trifluoromethyl-substituted (hetero)-aromatics, trifluoromethyl ethers, and *N*-trifluoromethylanilines. Herein briefly summarized are the synthetic procedures as well as the scope and limitations of the reaction. The applicability of the reaction is demonstrated by the synthesis of a difluorinated glutamic acid and novel liquid-crystalline materials having an *N*-trifluoromethylamino, trifluoromethoxy, or 1,2-difluoroethylene group. The fluorine-containing liquid-crystalline materials are compared with the corresponding non-fluorinated materials in respect to phase transition behaviors and electro-optical properties and shown to be suitable for not only super twisted nematic (STN) but also for thin film transistor (TFT)-addressed liquid crystals displays.



## 1. Introduction

**Keywords:** desulfurization-fluorination; fluorine; fluorination; sulfur; synthetic methods; liquid crystals

Recent rapid progress in organofluorine chemistry has made it possible to produce many organofluorine compounds possessing unique and superb physical properties and biological activities.[1] Theoretical and experimental studies have demonstrated that these properties can be understood in terms of the isoelectronic structures of fluorine and oxygen, mimicking and blocking effects in the inhibition of enzymatic process, hydrogen-bond formation of the H···F type, and the large energy of a carbon-fluorine bond.[2] Accordingly, a diversity of novel materials, pharmaceuticals, and agrochemicals have been designed and synthesized.

Fluorine is rich in nature with the Clarke number of 625 ppm, existing mostly as $CaF_2$ and $Na_3AlF_6$. In contrast, naturally occurring organofluorine compounds

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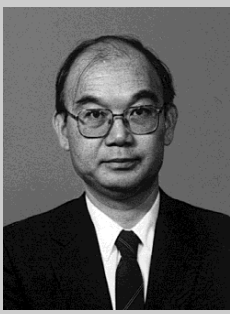


*Tamejiro Hiyama*, born in Osaka, Japan, in 1946, received his B. Eng. and M. Eng. degrees both from Kyoto University, Professor Hitosi Nozaki being the thesis advisor. After another year of graduate research, he was appointed Instructor in Department of Industrial Chemistry, Kyoto University, and continued to work with Professor Nozaki. Immediately after receiving the Doctor of Engineering degree in 1975 from Kyoto University, he joined the group of Professor Yoshito Kishi at Harvard University. After the postdoctoral year, he returned to Kyoto University and studied there until 1981, when he moved to Sagami Chemical Research Center as Research Fellow and Group Leader. There he was promoted to Senior Research Fellow in 1983 and then to Executive Research Fellow in 1988. In 1992, he joined the Research Laboratory of Resources Utilization, Tokyo Institute of Technology, as Professor of the Division of Newer Metal Resources. In April 1, 1997, he moved to the present position as Professor of Organic Material Chemistry. He is a recipient of Young Chemist Award of the Chemical Society of Japan, April, 1980. His current research interest include the development of new organometallic reagents for selective organic synthesis, organofluorine and organosilicon chemistry, synthesis of biologically active substances, design and synthesis of new functionality molecules and materials. He has published more than 300 original papers, 30 review articles and one book.

are very rare except for fluoroacetic acid, ω-fluorinated fatty acids, fluorocitrate, fluorothreonine, and fluorinated nucleoside.[3] Therefore, organofluorine compounds are available solely by organic synthesis.

There are two synthetic methods for organofluorine compounds: the *building block method* and the *fluorination method*.

The *building block method* uses fluorinated small organic molecules which are incorporated into target molecules by appropriate chemical transformations. Various kinds of building blocks have been developed and now commercially available.[4]

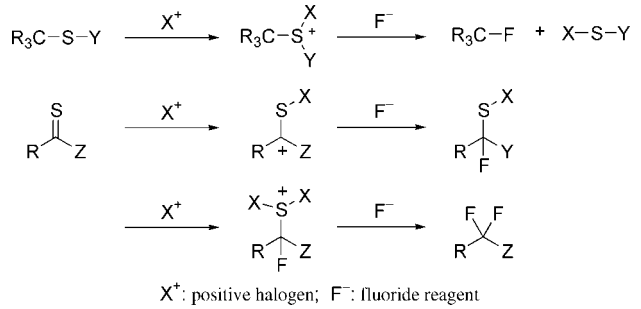
The *fluorination method* is concerned with introduction of fluorine into organic molecules using $F_2$, HF, $SF_4$, or reagents derived from these.[5] Because these fluorination reagents are usually extremely reactive and toxic, the reaction conditions should be carefully controlled by special skill using an appropriate apparatus.

For the synthesis of the requisite fluorinated target molecules, fluorination reaction should be 1) regio-, stereo-, and chemoselective enough to be applicable to complex organic molecules, 2) easy to manipulate, and 3) fast enough to complete quickly under mild conditions. Very often, the selectivity and reactivity contradict each other.

When a specific functional group in a substrate is activated electrophilically, selective fluorination can be achieved using a relatively mild nucleophilic fluorinating agent. For example, when a substrate is activated by a mild oxidant, fluoride ion can react with the substrate to form a C–F bond. According to this reaction design, oxidative fluorination, halo- (and thio-,

seleno-) fluorination of olefins,[6] deazo-fluorination,[7] and fluorination of alkynes[8] have been achieved. Fine tuning of the reactivities of a fluoride source and an oxidant depending on a substrate gives rise to the fluorinated target product in high yields.[9]

Recently, the authors have studied the oxidative fluorination of organosulfur compounds and found that a variety of organofluorine compounds can be readily prepared. The reaction is called *oxidative desulfurization-fluorination* and is reviewed herein with the emphasis on principle, scope, limitations, and applications. The synthetic potential of this methodology is demonstrated by the synthesis of fluorinated liquid crystalline materials whose properties also will be described. The basic concept is summarized in Scheme 1




**Scheme 1.** Oxidative desulfurization-fluorination of organosulfur compounds.

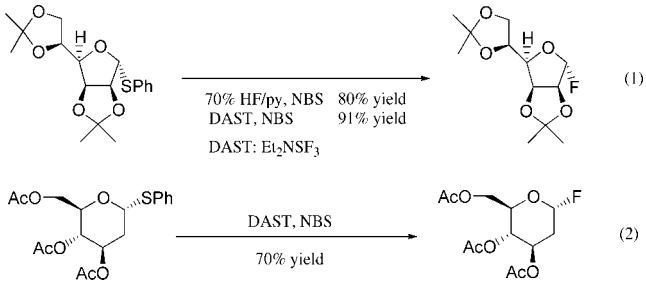
The positive halogen species $X^+$ attacks the sulfur atom to activate the C-S bond. Nucleophilic substitution with the fluoride species occurs to form the C-F bond. In the case of a substrate having a C=S double bond, double desulfurization-fluorination occurs to give difluoromethylene compounds. An advantage of this methodology is that the starting organosulfur materials are easily accessible.

The research described in this article was carried out at the Sagami Chemical Research Center and Tokyo Institute of Technology.

## 2. Fluorination Reactions

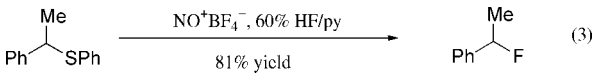
### 2.1 Fluorination of Sulfides and Thiols

Monofluorination results in the formation of fluoromethylene group –CHF– that is particularly essential in enzyme inhibitors and liquid-crystalline materials. This particular functional group has been introduced so far by 1) halogen-exchange,[10] 2) deoxygenation-fluorination of alcohols,[11] or 3) addition of HF to olefins.[12] For this purpose, the oxidative desulfurization-fluorination of sulfides and thiols is also effective. For example, fluorinated amino acids are prepared from the corresponding thiols with HF/$CF_3OF$ and/or HF/$F_2$,[13] reagents that need special care upon use. The combined use of 70% HF/pyridine (py) (Olah's reagent) and *N*-bromosuccinimide (NBS) or dialkylaminosulfur trifluoride (DAST) and NBS is conveniently used for fluorosugar synthesis starting from phenylthiosugars (Equation 1 and Equation 2).[14] The fluorosugars are versatile intermediates for *O*-glucosidation reaction.




The third reagent for oxidative fluorination is $ArIF_2$, whose fluorination is considered to proceed in an $S_Ni$ fashion with inversion of configuration.[15]

Reagents consisting of $NO^+[BF_4]^-$ and 60% HF/py (Equation 3)[16] or CsF and $FSO_3Me$[17] are also employed for the fluorination of sulfides.




When alkyl aryl sulfides, Ar–S–R, are treated with these reagents, the arylthio group ArS is substituted by F to give rise to fluoroalkanes F–R.

The authors have developed the oxidative desulfurization-fluorination reaction using a combination of tetrabutylammonium dihydrogen trifluoride ($TBAH_2F_3$) and 1,3-dibromo-5,5-dimethylhydantoin (DBH). A fluoro-Pummerer rearrangement[18] is found to take place to give the corresponding 1-fluoroalkyl sulfides selectively (Figure 1).[19] Fluoromethyl sulfides are obtained from aryl methyl sulfides bearing an electron-donating or electron-withdrawing group in the aryl moiety. The corresponding fluoro(methylthio)acetate results from the reaction with ethyl (methylthio)acetate.

The fluoride reagent $TBAH_2F_3$ can be easily prepared from aqueous HF, $KHF_2$, and tetrabutylammonium fluoride (TBAF)[20] and is currently available from Acros Organics as a dichloromethane solution. $TBAH_2F_3$ is more stable than the HF/py complex:[21] no trace of HF elimination or loss of fluorination

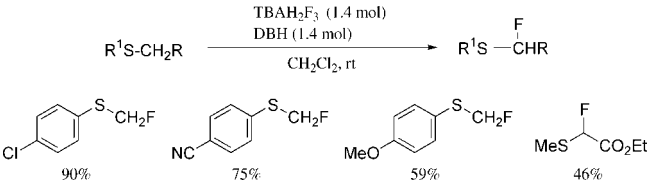


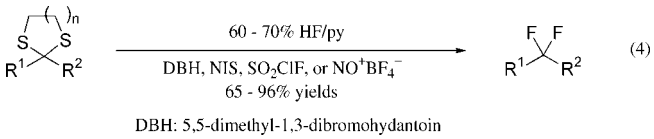

**Figure 1.** Fluoro-Pummerer rearrangement of sulfides.

power is observed during storage at room temperature. The fluoride reagent is easy to manipulate. For example, all the reactions can be carried out in ordinary glassware.

Electrochemical oxidation can replace the use of an oxidant. Thus, electrochemical oxidative fluorination of alkyl aryl sulfides[18a] induces the fluoro-Pummerer rearrangement smoothly, particularly when an electron-withdrawing group is substituted at the α-position in an alkyl group. Diastereoselective fluorination also is feasible.[18b,18c]

## 2.2 Fluorination of Dithioacetals

There are many biologically active synthetic agents that contain a difluoromethylene (–$CF_2$–) group.[22] Such *gem*-difluoro compounds are prepared by treatment of aldehydes or ketones with $SF_4$, DAST, or a similar reagent. The *gem*-difluorination can be more easily performed starting with dithioacetals, for which a reagent system consisting of HF/py and an oxidant such as DBH, NBS,[24] $SO_2ClF$,[25] or $NO^+[BF_4]^-$ [16] is preferable to the HF/$CF_3OF$ combination (Equation 4).[23]




(4)

The *gem*-difluorination is sometimes accompanied by a side reaction: aromatic ring halogenation takes place especially when DBH is used as an oxidant, and an acid-sensitive functional group does not tolerate these reaction conditions.

The authors have found that such *gem*-difluorination can be conveniently carried out with $TBAH_2F_3$ under milder conditions. Functional groups like oxirane, OH, and a C=C double bond are compatible (Figure 2).[26]

The strategy is applied to the synthesis of difluoroglutamic acid (Scheme 2).[26b]

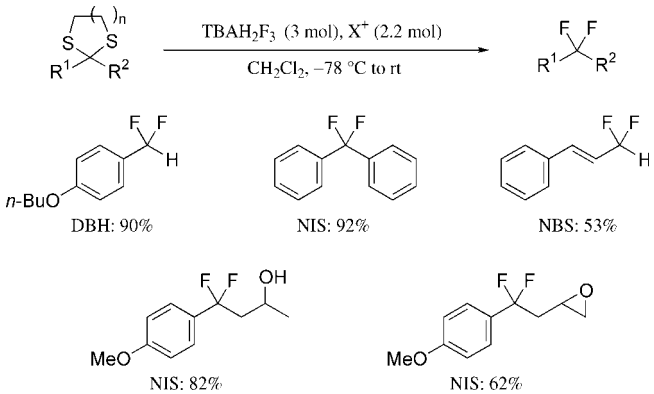
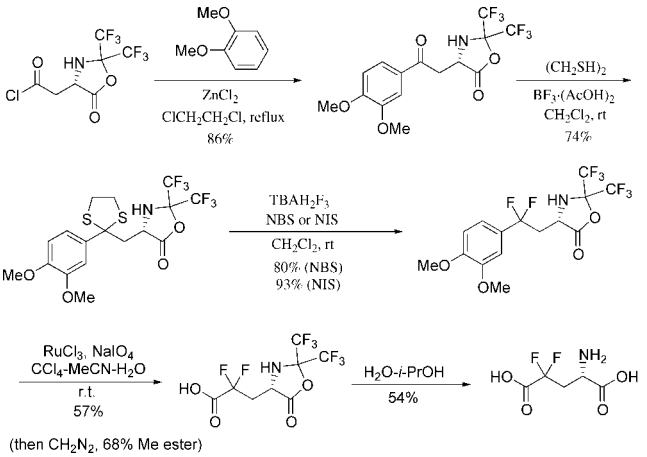
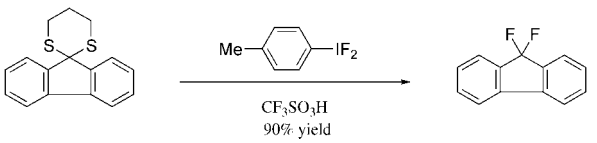



**Figure 2.** *gem*-Difluorination.



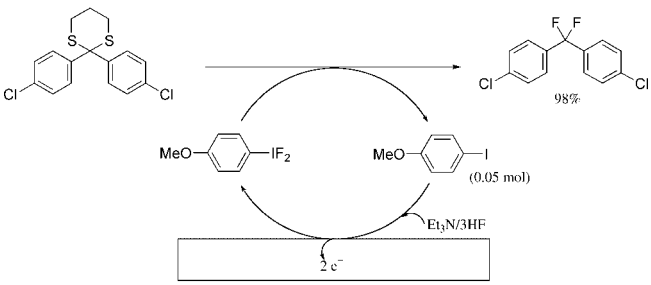

**Scheme 2.** Synthesis of difluoroglutamic acid from aspartic acid.

The same transformation is achievable with *p*-(difluoroiodo)toluene (Equation 5). Dithioacetals derived from aliphatic ketones are less efficiently converted into the corresponding *gem*-difluorination products.[27]




(5)

The electrochemical oxidation of *p*-iodoanisole proceeds in the presence of a fluoride ion and gives *p*-(difluoro)iodoanisole, which can mediate the difluorination of dithioacetals (Scheme 3).[28]




**Scheme 3.** Electrochemical fluorination of dithioacetals.

Using 70% HF/py or 80% HF/melamine (HF/mel), *gem*-difluorination of dithioacetals derived from perfluoroalkyl ketones is also possible and gives rise to perfluoroalkyl-substituted aromatic compounds (Figure 3).[29] Since the starting ketones are available from perfluoroalkanoic acids by reaction with arylmagnesium reagents, the net transformation allows the perfluoroalkylation of aromatic compounds.

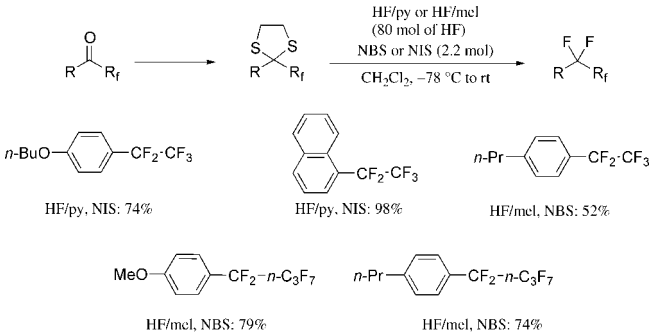



**Figure 3.** Synthesis of perfluoroalkyl-substituted aromatic compounds.

## 2.3 Oxidative Desulfurization-Fluorination of Dithioester and Orthothioester

*Fluorination methods* known for trifluoromethylarenes are the reaction of arenecarboxylic acids with $SF_4$,[30] halogen exchange of trichloromethylarenes,[31] Friedel-Crafts alkylation/halogen exchange of aromatics with $CCl_4$/HF,[32] and *oxidative desulfurization-fluorination* of arenedithiocarboxylic acid with $XeF_2$.[33] The *building block method* is also available.[34]

The *oxidative desulfurization-fluorination* reaction also gives trifluoromethylarenes. The starting materials are (hetero)arenedithiocarboxylates **1**, which upon treatment with $TBAH_2F_3$ and DBH, give trifluoromethyl-substituted aromatic compounds **2** as shown in Table 1.[35]

For this transformation, 70% HF/py is also effective; however, extreme care should be taken during handling, reaction, and work-up. It is worthy of note that when NBS or NIS is employed along with $TBAH_2F_3$ in lesser amounts, difluoro(methylthio)-methylated (hetero)arenes **3** are produced.[35a] The difluorination products **3** are intermediates of the trifluoromethylation. In fact, the trifluoromethylated compounds **2** are obtained by treatment of **3** with $TBAH_2F_3$/DBH (Equation 6).[35a]

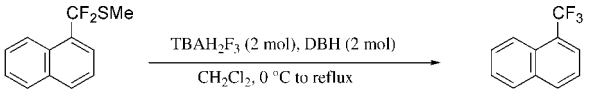
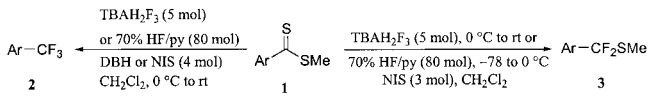


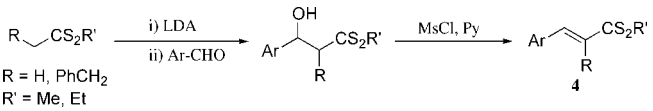

**Table 1.** Oxidative desulfurization-fluorination of methyl arenecarbodithioates **1**.




| Ar−$CF_3$ yield/% | Ar | Ar−$CF_2$SMe yield/% |
|---|---|---|
| 63 ($TBAH_2F_3$, DBH)<br>79 (HF/py, DBH)<br>63 (HF/py, NIS) | | 61 ($TBAH_2F_3$, NIS) |
| 52 ($TBAH_2F_3$, DBH) | | 86 ($TBAH_2F_3$, NIS) |
| 71 ($TBAH_2F_3$, DBH) | Me, O, Me | not performed |
| 69 (HF/py, DBH) | N | 71 (HF/py, NIS) |
| 79 (HF/py, DBH) | N | 61 (HF/Py, NIS) |

The substrates, methyl (hetero)arenedithiocarboxylates **1**, are readily accessible by sequential treatment of the corresponding (hetero)arenemagnesium halides with $CS_2$ and MeI.[35a] Because a $CS_2$Me group is in this way introduced electrophilically, the net transformation is regarded as *electrophilic trifluoromethylation*.

In a similar way, α,β-unsaturated dithiocarboxylates are conveniently converted into the corresponding 3,3,3-trifluoropropenes. The starting materials are conveniently prepared by the cross-aldol reaction of aromatic aldehydes and lithium enolates derived from dithiocarboxylates followed by dehydration (Scheme 4).[35a]




**Scheme 4.** Synthesis of α,β-unsaturated carbodithioates.

The trifluorination of α,β-unsaturated dithiocarboxylates is smoothly carried out with $TBAH_2F_3$ (6 mol) and NIS (12 mol), and various kinds of 3,3,3-trifluoropropenes substituted by an aryl group are readily prepared, except for $NO_2$-substituted ones, which afford difluorination products (Figure 4).[35a]

When the amounts of NIS and $TBAH_2F_3$ are reduced, the yield of **5** decreases, giving the thiocarboxylate RCH=CHC(O)SR as a by-product. DBH or NBS in lieu of NIS and HF/py in lieu of $TBAH_2F_3$ result in the formation of a complex mixture of unidentified products.[35a]

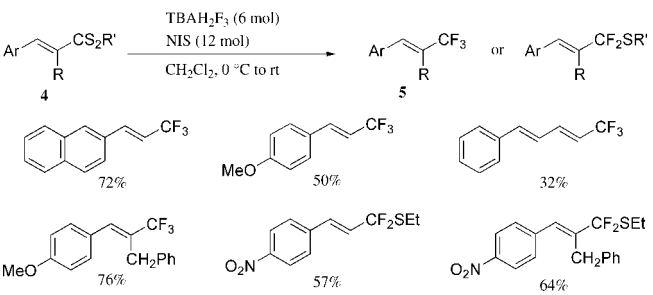
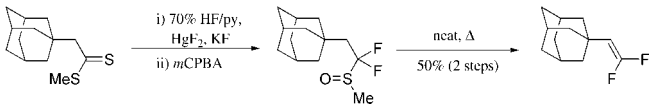



**Figure 4.** Trifluorination or difluorination of α,β-unsaturated dithiocarboxylates.

Since the *building block method* has limitations in the preparation of 3,3,3-trifluoropropene derivatives,[33] this method is considered to be a potent alternative.

In contrast, methyl dithiocarboxylates $RCS_2Me$, upon treatment with 70% HF/py, $HgF_2$ and KF, give the difluorination products $RCF_2SMe$, which are converted into *gem*-difluoro olefins *via* oxidation and thermolysis (Scheme 5).[36]




**Scheme 5.** *gem*-Difluoroolefin synthesis from a dithiocarboxylate.

Aromatic orthothioesters show a reactivity similar to that of dithioesters. For example, trifluoromethylarenes are obtained by treatment with 70% HF/py and DBH (Figure 5).[37] Ring bromination is an accompanying reaction when the substrate has an electron-donating alkoxy group.

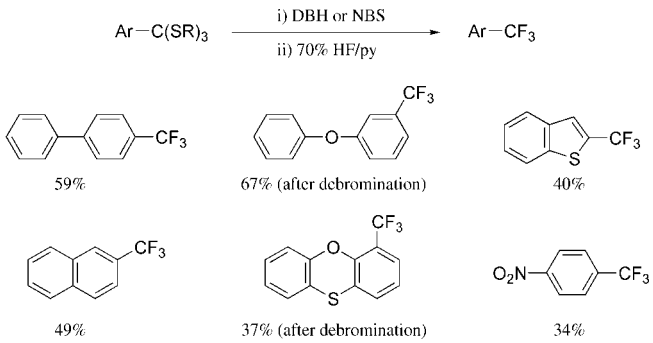



**Figure 5.** Oxidative desulfurization-fluorination of orthothioesters.

Upon treatment of aliphatic orthothioesters **6** with $TBAH_2F_3$ and DBH, difluorination followed by β-bromination occurs to give $RCXBrCF_2SMe$ **7a** (X = H) or **7b** (X = Br) depending on the kind of R (Figure 6).[38]

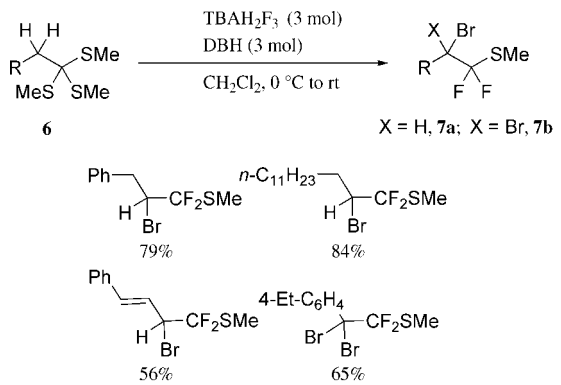
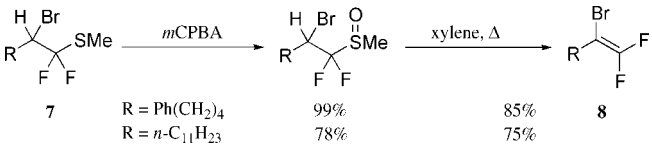



**Figure 6.** Brominative fluorination of orthothioesters.

Products of type **7a** are transformed to olefins **8** by the oxidation-thermolysis sequence (Scheme 6). Subsequent metalation of **8** followed by reaction with an electrophile affords various 1,1-difluoroalkenes.[33]




**Scheme 6.** Synthesis of 2-bromo-1,1-difluoro-1-alkenes.

When tris(methylthio)ethanol derivatives **9** are treated with $TBAH_2F_3$ and DBH, difluorination and oxidation takes place to give difluoro(methylthio)methyl ketones **10** (Figure 7).[38] Substrates **9** are easily prepared from aldehydes RCHO and $LiC(SMe)_3$. When NIS and/or HF/py were used as the component of the reagent, no trifluoromethylation occurred even under forcing conditions. The hydroxy group in a substrate containing a pyridine ring remains unchanged. Treatment of **9** with DAST causes fluorination and rearrangement of a methylthio group to afford difluorination products **11** (Figure 8).[19]

In summary, the *oxidative desulfurization-fluorination* of arenedithioester or areneorthothioesters af-

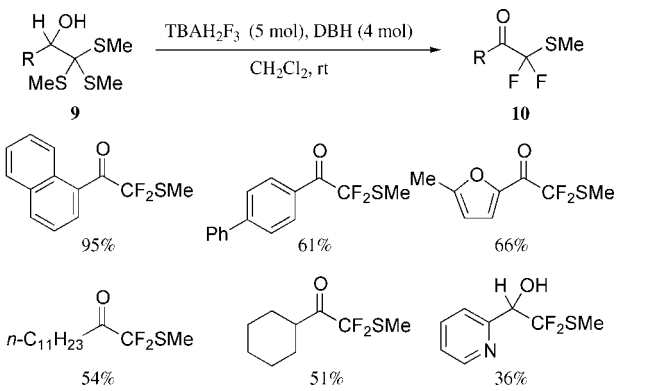



**Figure 7.** Oxidative desulfurization-fluorination of 2,2,2-tris(methylthio)ethanols.

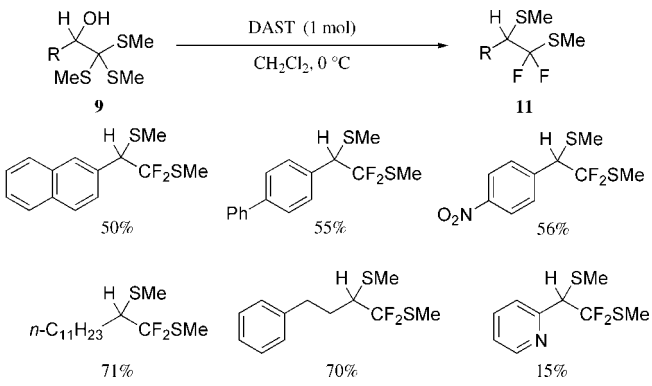



**Figure 8.** Fluorination of 2,2,2-tris(methylthio)ethanols with DAST.

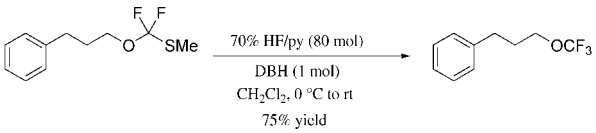
fords trifluoromethylarenes with all C–S bonds being converted into C–F bonds, whereas the same reaction with aliphatic orthothioesters results in brominative difluorination.

### 2.4 Synthesis of Trifluoromethyl Ethers from Dithiocarbonates

Trifluoromethyl ethers are a very important class of compounds particularly in materials, agrochemical, and pharmaceutical sciences owing to their high chemical and thermal stabilities as well as their lipophilicity and gas solubility.[1] Aryl trifluoromethyl ethers are prepared usually by 1) halogen exchange reaction of aryl trichloromethyl ethers with $SbF_3$/$SbCl_5$ [39] or HF,[40] 2) trichloromethylation/halogen exchange of phenols with $CCl_4$/HF,[41] or 3) oxidative fluorination of fluorodithioformates or chlorodithioformates with $SF_4$ [42] or $MoF_6$.[43] Alkyl trifluoromethyl ethers are available by 1) addition of $CF_3OF$ to alkenes,[44] 2) trifluoromethylation of alcohols with *O*-trifluoromethylbenzofuranium salts,[45] or 3) fluorination of alkyl fluoroformates.[46] These reactions are, however, often hard to control and require toxic reagents thus being disfavored. Some building blocks containing a trifluoromethoxy group, though commercially available, are in general expensive and inconvenient.

The *oxidative desulfurization-fluorination* of dithiocarbonates using 70% HF/py and DBH gives trifluoromethyl aryl and alkyl ethers in good yields after purification by silica-gel column chromatography (Table 2)[47]. The starting dithiocarbonates are easily prepared by treatment of phenols or alcohols with $CS_2$ and MeI. Ring bromination frequently occurs when the substrates lack an electron-withdrawing group in the phenolic moiety. This side reaction is suppressed by using a smaller amount of HF/py. When $TBAH_2F_3$ and NBS are employed, a novel class of compounds, difluoro(methylthio)methyl ethers **14**, are isolated as the sole products.

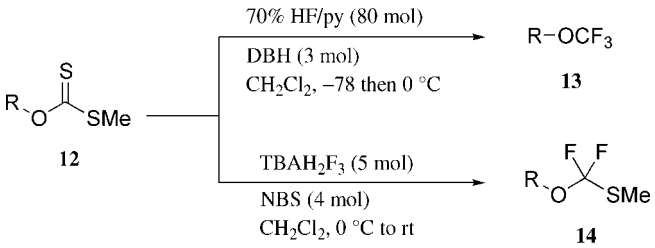
The isolated difluorinated products can be converted into trifluoromethyl ethers **13**. Thus, **14** are considered to be precursors of **13** (Equation 7).[47]



(7)

When dithiocarbonates derived from secondary and tertiary alkanols or benzylic alcohols are treated with 70% HF/py and NBS, fluorination instead of the formation of trifluoromethyl ethers takes place to give alkyl or benzylic fluorides **15**.[47] NIS also promotes the fluorination efficiently without ring halogenation.

**Table 2.** Oxidative desulfurization-fluorination of dithiocarbonates **12**.




| R | Yield (%) of **13** | Yield (%) of **14** |
|---|---|---|
| 4-Pr-$C_6H_4$- | -[a] | 58 |
| | 81[b] | |
| | 60[c] | |
| 4-$PhCH_2O$-$C_6H_4$- | 56[d] | 43 |
| 4-Br-$C_6H_4$- | 62 | 43 |
| 3-MeOC(O)-$C_6H_4$- | 76 | 32 |
| 4-Br-$C_6H_4$-$CH_2CH_2$- | 81[b] | 19 |
| $PhCH_2CH_2CH_2$- | 75[e] | 15 |
| *n*-$C_{16}H_{33}$- | 95 | 9 |

[a] Accompanied by aromatic bromination.

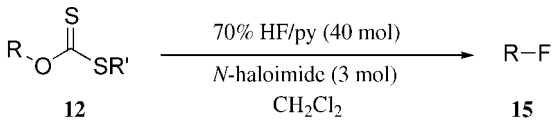
[b] HF/py (40 mol) was used.

[c] HF/py (20 mol) was used.

[d] Yield of 2-Br-4-$CF_3O$-$C_6H_3$-$OCH_2Ph$, DBH (4 mol) was used.

[e] 4-Br-$C_6H_4$-$CH_2CH_2CH_2$-$OCF_3$ was isolated.

**Table 3.** Synthesis of alkyl fluorides **15** from xanthates of secondary or benzylic alcohols.

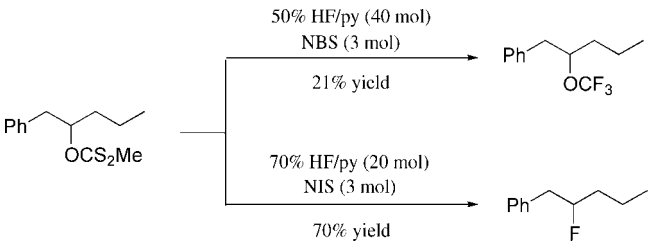



| Dithiocarbonate **12** | *N*-Halo imide | Product **15** | Yield (%) of **15** |
|---|---|---|---|
| Ph, $OCS_2Me$ | NIS | Ph, F | 48 |
| Ph, $OCS_2iPr$ | NIS | Ph, F | 78 |
| Ph, $OCS_2Ph$ | NIS | Ph, F | 42 |
| $OCS_2Me$ | NIS | F | 48 |
| $OCS_2Me$ | NIS | F | 78 |
| Br, $OCS_2Me$ | DBH | Br, F | 43 |
| Ph, $OCS_2Me$ | DBH | Ph, F | 94 |

The group R′ in R′SC(S)OR has little effect on the reactivity: all of dithiocarbonates (R′ = Me, *i*-Pr, and Ph) give the R–F **15**. DBH is shown to be the best oxidant for the fluorination of dithiocarbonates R′SC(S)OR (R = benzylic) (Table 3).

Depending on the structure of the starting compounds **12**, trifluoromethyl ethers **13** or fluorides **15** are produced selectively. The reaction is assumed to proceed through carbocationic intermediates in contrast to the similar reaction with *p*-TolIF$_2$.[48] Hereby fluorides **15** are produced irrespective of the starting material, the reaction is possibly proceeding through an S$_N$*i* mechanism.

In contrast, use of 50% HF/py or 70% HF/py/KHF$_2$ affords trifluoromethyl ethers **13** from the dithiocarbonates derived from secondary alcohols.[47a,49] Thus, either trifluoromethyl ethers **13** or fluorides **15** can selectively be prepared by acidity control of the fluoride reagent (Scheme 7). The oxidative desulfurization-fluorination is an exclusive method for the synthesis of secondary alkyl trifluoromethyl ethers from the corresponding secondary alcohols, though yields remain yet to be improved.




**Scheme 7.** Synthesis of secondary alkyl fluorides or trifluoromethyl ethers from dithiocarbonates.

Recently, BrF$_3$ was shown to be applicable to the synthesis of primary alkyl trifluoromethyl ethers through the *oxidative desulfurization-fluorination*.[50] Although the mechanism still remains to be clarified, BrF$_3$ or BrF[51] is suggested for the active species in this transformation. Since a haloimide reagent can be replaced by PhI(OCOCF$_3$)$_2$ for the trifluoromethylation, cooperation of both an oxidant and a fluoride reagent appears to be essential.

## 2.5 Oxidative Desulfurization-Fluorination of Thionoesters and Thionocarbonates

Thionoesters **16**, that are easily prepared from the corresponding esters with the Lawesson reagent ([4-MeOC$_6$H$_4$P(=S)S]$_2$),[52] upon treatment with TBAH$_2$F$_3$ and NBS, give α,α-difluoroalkyl ethers **17** (Figure 9).[53] Although ethers **17** appear to be sensitive to moisture, the purification can be easily performed by flash silica-gel chromatography. The same transformation is achieved with BrF$_3$ [54] or DAST,[55] which sometimes cause troubles in experimental operations. The direct fluorination of esters leading to **17** is achieved under harsh conditions.[56]

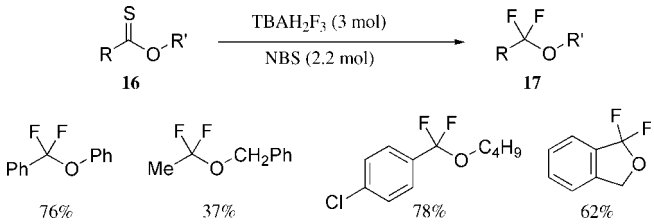



**Figure 9.** Synthesis of α,α-difluoro ethers by oxidative desulfurization-fluorination.

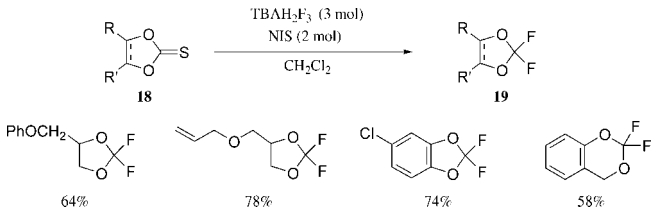



**Figure 10.** Synthesis of carbonyl fluoride acetals by oxidative desulfurization-fluorination.

In a similar way, fluorocarbonyl acetals **19** are available from thionocarbonates **18** (Figure 10).[53] This approach is useful for the preparation of 2,2-difluoro-1,3-benzodioxolanes, a characteristic structural moiety found in some potent pharmaceuticals and agrochemicals.

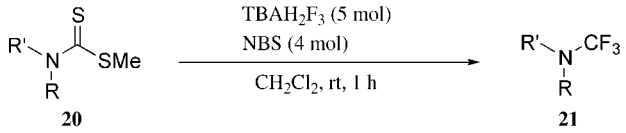
## 2.6 Synthesis of Trifluoromethylamines from Dithiocarbamates

Recorded synthetic methods for *N*-trifluoromethylamines are 1) fluorination of *N*-formamides or *N*-trichloromethylamines with SF$_4$, SbF$_3$, DAST, or anhydrous HF,[57–61] 2) fluoromethylation of secondary amines with CF$_2$Br$_2$ and tetrakis(dimethylamino)ethylene,[62] 3) electrochemical fluorination of alkylamines,[63] and 4) trifluoromethylation of amines with an *O*-(trifluoromethyl)dibenzofuranium salt.[64] However, very often these reactions are avoided because 1) the reagents are relatively toxic, corrosive, and/or explosive, 2) special apparatus is sometimes needed, and 3) scope and limitations of each reaction are not well-studied.

The authors have found that *N*-trifluoromethylamines **21** are readily prepared by *oxidative desulfurization-fluorination* of dithiocarbamates **20** (Table 4).[65]

The starting dithiocarbamates **20** are a well-known class of compounds and are prepared in high yields by sequential treatment of amines with a base, CS$_2$, and MeI. The *oxidative desulfurization-fluorination* of **20** using TBAH$_2$F$_3$ and NBS affords *N*-trifluoromethylamines **21** in high yields. Among the various fluoride sources (TBAH$_2$F$_3$, 70% HF/py, and 3 HF/

**Table 4.** Synthesis of *N*-trifluoromethylamines.



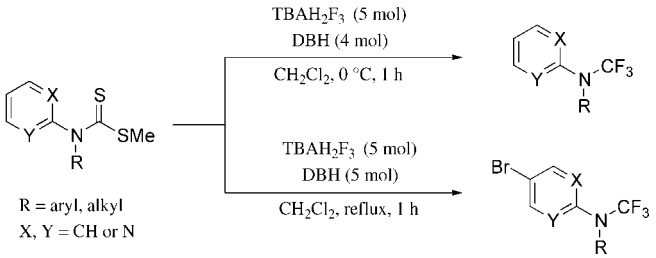

**20** **21**

| R | R' | Yield (%) of **21** |
|---|---|---|
| Ph | Ph | 78 |
| 4-MeO-$C_6H_4$- | $PhCH_2$- | 99 |
| | | 38[a] |
| 4-Cl-$C_6H_4$- | $PhCH_2$- | 88 |
| 4-NC-$C_6H_4$- | $PhCH_2$- | 78 |
| | | 99[b] |
| | | 97[c] |
| | | 99[d] |
| MeO-$C_6H_4$- | Me- | 90 |
| $O_2N$-$C_6H_4$- | Me- | 68 |
| | | 96[b] |
| 3-Me-$C_6H_4$- | 3-Me-$C_6H_4$- | 48 |
|  | | 76 |
| $PhCH_2$- | $PhCH_2$- | 86 |
| $PhCH_2$- | Pr- | 84 |

[a] NBS (1.5 mol) was used.
[b] DBH (4 mol) was used.
[c] 70% HF/py (1 mL/mmol) was used.
[d] 3 HF/$Et_3N$ (0.2 mL/mmol) was used.

$NEt_3$), $TBAH_2F_3$ is the reagent of choice because it allows the use of ordinary glassware. No difluorination products are isolable. Use of a smaller amount of either of the two reagents gives a mixture of *N*-trifluoromethylamine **21** and substrate **20**.

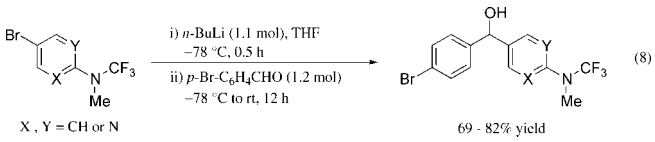
The trifluoromethylation reaction is applicable to a wide range of substrates: aromatic, heteroaromatic, and aliphatic amines can be converted into the corresponding *N*-trifluoromethylamines. Aryl(trifluoromethyl)amines are stable to moisture, whereas dialkyl(trifluoromethyl)amines are highly susceptible to hydrolysis. Thus, work-up and isolation of dialkyl(trifluoromethyl)amines are effected by filtration, concentration, and distillation under reduced pressure.



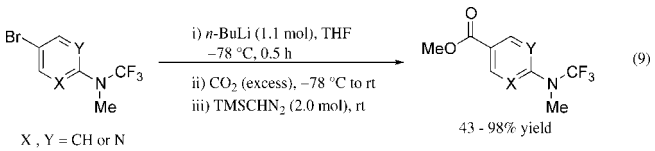

**Scheme 8.** Synthesis of trifluoromethylamines.

When DBH is used in lieu of NBS for the fluorination of (heteroaryl)dithiocarbamates, trifluoromethylation is attained at room temperature, whereas ring-bromination at the *p*-position is an accompanying reaction at the reflux temperature of $CH_2Cl_2$ (Scheme 8).[65] This side reaction is suppressed by use of NBS.

The presence of a bromo functionality allows for the introduction of a variety of functional groups (Equation 8 and Equation 9).[65]

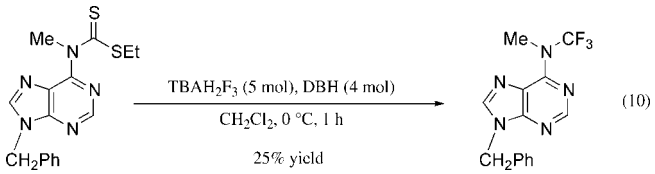



(8)




(9)

The applicability of the *oxidative desulfurization-fluorination* is demonstrated by a facile synthesis of a trifluoromethyl-substituted nucleoside base from the corresponding dithiocarbamate (Equation 10).[65]




(10)

Diphenyl(trifluoromethyl)amine is disclosed to have a redox potential similar to that of diphenyl ether, manifesting that a $CF_3$ group endows an amino group with resistance against oxidation.

A perfluoroalkyl group can also be introduced to secondary amines, taking advantage of the *oxidative desulfurization-fluorination*. Although perfluoroalkylamines, components of artificial blood, are available by electrochemical fluorination, tertiary amines with a single perfluoroalkyl group are hardly accessible.[2] Tertiary mono(perfluoroalkyl)amines can be synthesized by treatment of perfluoroalkanethio-

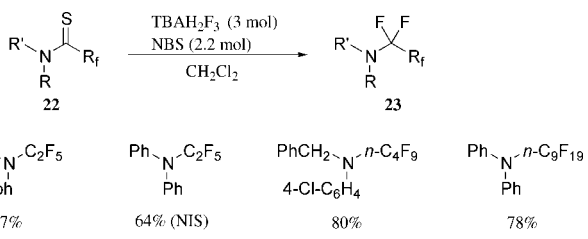



**Figure 11.** Preparation of perfluoroalkylamines **23**.

amides **22** with $TBAH_2F_3$ and NBS (Figure 11).[66] Substrates **22** are prepared from perfluoroalkanamides and $P_2S_5$, or alternatively, the Lawesson reagent. Perfluoroalkyl(aryl)amines having an electron-donating group on the aryl group are susceptible to hydrolysis but are isolable provided that special care is taken during the isolation.

## 3. Synthesis and Electro-Optical Properties of Novel Fluorine-Containing Liquid Crystals

Recently, STN (*super**t**w*isted *n*ematic for passive matrix) and TFT (*t*hin *f*ilm *t*ransistor for active matrix) mode displays have been rapidly becoming important in flat panel displays.[67] Owing to the new technology, large size portable color displays with low-voltage and high-speed addressing are now commercialzed. More recently, twisted nematic (TN) TFT-mode, in-plane switching TFT-mode, and vertical alignment TFT-mode are evolving, and thus a great demand is growing for new types of LC materials.[68] 4-Cyano-4′-pentylbiphenyl and its analogues, which are utilized widely for passive matrix LC displays (LCDs), are not applicable to the TFT-mode LCD due to low voltage holding ratio of the materials.

In general, fluorine-substituted LCs are gifted with a high voltage holding ratio and a low threshold voltage as well as high chemical and thermal stabilities. Accordingly, novel fluorine-containing LC materials have attracted much attention in the recent development of LC materials,[1,69] and various types of fluorine-containing LCs with high positive or negative dielectric anisotropy have been designed and synthesized.

Syntheses of fluorine-containing LCs are carried out starting with commercially available fluorinated building blocks. This synthetic strategy is very often hampered by the inaccessibility of the requisite fluorinated building blocks. In addition, the fluorine functionality induces unusual reactivity and prevents conventional synthetic transformations.[1] An alternative method is fluorination using very reactive and/or toxic reagents and thus is rarely employed.

As discussed in Section 2, *oxidative desulfurization-fluorination* is a convenient approach for the synthesis of organofluorine compounds. We have applied the reaction to the syntheses of novel LC materials having a fluorine functional group such as an *N*-trifluoromethylamino, trifluoromethoxy, or 1,2-difluoroethylene group. In this section, we briefly summarize the synthesis and electro-optical properties of such LCs.[67,70]

### 3.1 Synthesis and Electro-Optical Properties of *N*-Trifluoromethylamino-Substituted Liquid Crystals

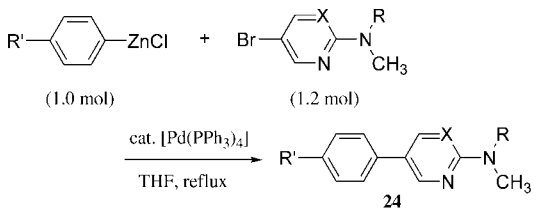
LC materials with an amino group show smectic C ($S_C$) phases in a wide range of temperatures.[71] Due to their strong basicity and low resistance to oxidation, however, amines are not appropriate materials. In contrast, the trifluoromethyl group on an amine nitrogen enhances resistance to oxidation and reduces basicity and nucleophilicity. As described in Section 2.6, (*p*-bromoaryl)trifluoromethylamines are produced in high yields under forcing conditions. The bromine functionality can advantageously be utilized for the synthesis of *N*-trifluoromethylamino-substituted LCs **24** through the palladium-catalyzed cross-coupling reaction using arylzinc reagents.[72] The yields isolated as well the as phase transition behaviors of **24** as observed with a polarizing microscope and differential scanning calorimeter (DSC) are summarized in Table 5.

[Methyl(trifluoromethyl)amino]pyridines exhibited smectic A ($S_A$) phases, whereas the corresponding 2-(dimethylamino)pyridines lost the LC phases. Thus, a trifluoromethylamino group appears to induce liquid crystallinity. The corresponding pyrimidines showed only simple melting points.[72a]

A cross-coupling reaction with organosilane reagents[73] was also effective for the preparation of trifluoromethylamino-substituted heterobiaryls (Equation 11).

The trifluoromethylamino-substituted LCs serve as versatile additives for ferroelectric LCs (FLCs). For example, 2-[methyl(trifluoromethyl)amino]-5-(4-octyloxyphenyl)pyridine when added to an FLC host mixture improved both the range of the chiral $S_C$

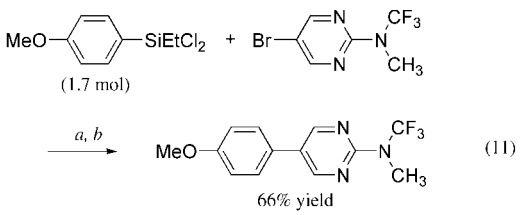
**Table 5.** Synthesis of trifluoromethylamino-substituted heterobiaryls.




| R' | X | R | Yield (%) | Phase transition temp.[a] (°C) |
|---|---|---|---|---|
| $n$-$C_3H_7O$ | CH | $CF_3$ | 58 | Cr 66 $S_A$ 93 Iso |
| $n$-$C_6H_{13}O$ | CH | $CF_3$ | 67 | Cr 53 $S_A$ 70 Iso |
| $n$-$C_8H_{17}O$ | CH | $CF_3$ | 20 | Cr 51 $S_A$ 62 Iso |
| $n$-$C_3H_7O$ | CH | $CH_3$ | 39 | Cr 104 Iso |
| $n$-$C_3H_7O$ | N | $CF_3$ | 45 | Cr 94 Iso |
| $n$-$C_3H_7O$ | N | $CH_3$ | 48 | Cr 106 Iso |

[a] DSC on 2nd heating.
Cr: Crystal. Iso: Isotropic liquid. $S_A$: Smectic A phase.

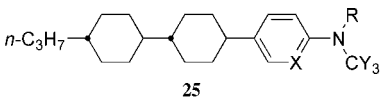
($S_C$*) phase and the rate of response to an electric field.[72a]




*a*: KF (9 mol), DMF, 60 °C, 3 h,
*b*: $Pd(OAc)_2$ (8 mol %), P(*o*-Tol)$_3$ (8 mol %), DMF, 120 °C, 18 h

We have also prepared compounds **25**, all having a cyclohexyl(cyclohexyl)benzene mesogen, and summarize their phase transition temperatures in Table 6.[72a] Compounds **25** mainly exhibit smectic B ($S_B$) phases in a wide range of temperatures and are effective additives for STN-LC materials in reducing threshold voltage ($V_{th}$). In addtion, compounds **25** were shown to be thermally and chemically stable and miscible with nematic host LCs for STN-mode displays. Accordingly, the trifluoromethylamino-substituted LCs are suitable additives for both STN and FLC materials

**Table 6.** Phase transition temperatures of trifluoromethylamino-substituted liquid crystals.




**25**

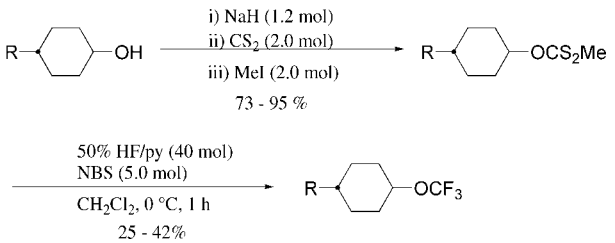
| X | Y | R | Phase transition temp. (°C) |
|---|---|---|---|
| CH | F | Me | < 20 $S_B$ 173 Iso[a] |
| CH | F | Et | Cr 35 $S_B$ 141 Iso[b] |
| N | F | Me | Cr 62 $S_X$ 73 $S_B$ 120 N 121 Iso[b] |
| CF | F | Me | Cr 62 $S_B$ 101 Iso[a] |
| CH | H | Me | Cr 59 $S_B$ 189 Iso[a] |

[a] Examined by a polarizing microscope.
[b] Measured by DSC on 2d heating.
$S_X$: higher order smectic phase.

Trifluoromethylamines are shown to have much better liquid crystallinity and electro-optical properties than the corresponding methylamines.[72a] Thus, the trifluoromethylamino-substituted LCs will find wide applications as a stable component of LCD materials.

### 3.2 Syntheses and Electro-Optical Properties of Liquid Crystals having a Trifluoromethoxy Polar Functional Group

As we described in Section 2.4, trifluoromethyl ethers derived from primary and secondary alcohols in addition to phenols are readily obtained by *oxidative desulfurization-fluorination* of the corresponding dithiocarbonates.[47,49] In view of the facts that LCs with a 4-(trifluoromethoxy)phenyl mesogen exhibit low viscosity and high voltage holding ratio and thus are widely used as a switching element of TFT-LCDs[74] and also that LCs with a cyclohexane mesogen show smaller birefringence than those with a benzene mesogen,[75] we considered that LCs with a (trifluoromethoxy)cyclohexane mesogen would exhibit much better physical and electro-optical properties and synthesized trifluoromethoxy-substituted cyclohexane-type LCs according to the route shown in Scheme 9.[76]




**Scheme 9.** Synthesis of trifluoromethoxycyclohexane-type liquid crystals.

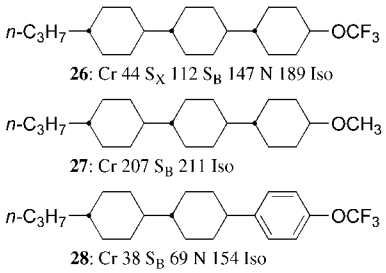
An example is compound **26** which showed an N phase from 147 to 189 °C on heating, whereas methoxycyclohexane **27** exhibited only an $S_B$ phase in a narrow range of temperature.[76b] Furthermore, compound **26** had a high nematic-to-isotropic transition temperature as compared with trifluoromethoxybenzene **28**. These results indicate that a trifluoromethoxycyclohexane mesogen appears to stabilize the N phase.

We next compared **26**, **27**, and **28** as an additive for nematic LC materials.[76b] Each was added at 20 wt % to a host nematic mixture, and nematic-isotropic temperature ($T_{NI}$), dielectric anisotropy ($\Delta\varepsilon$), $V_{th}$, birefringence ($\Delta n$), and response time ($\tau$) of the resulting mixture were measured in a TN cell. Rising switching time ($\tau_r$) and decay switching time ($\tau_d$) were measured as the electro-optical response from 100% to 10% and from 0% to 90%, respectively, to estimate $\tau$. The values $\tau$ were obtained when $\tau_r$ became equal to $\tau_d$ at a properly applied voltage. The results are summarized in Table 7. Trifluoromethoxycyclohexane **26** induced a larger $\Delta\varepsilon$ value than methoxycyclohexane **27**. In general, when $V_{th}$ becomes smaller, $\Delta\varepsilon$ becomes larger. However, both $V_{th}$ and $\Delta\varepsilon$ were reduced with **26** as compared with **28**. Thus, a trifluoromethoxycyclohexane mesogen contributes to the reduction of $V_{th}$ of the host mixture. Furthermore, **26** improved the $T_{NI}$ and $\Delta n$ of the host. Thus, **26** is obviously a better additive than **28** that is currently utilized for TN-displays.

We next studied the possibility of **26** as an additive for TFT-addressed LCDs, adding **26** to a TFT mixture

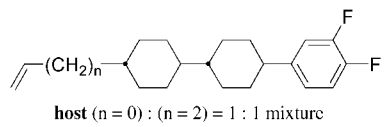
to observe that the nematic phase range expanded and response time was improved without decrease of voltage holding ratio as summarized in Figure 12.[76b] The $T_{NI}$ of the resulting **26**/TFT mixture was not lowered at all upon heating at 80 °C for 10 h or under UV irradiation. Accordingly, LCs with the trifluoromethoxycyclohexane mesogen are shown to be very stable against heat and light.

**Table 7.** Electro-optical properties of trifluoromethyl ethers (added at 20 wt % to the host liquid crystal).




| | $T_{NI}$/°C[a] | $\Delta\varepsilon$[b] | $\Delta\varepsilon$[c] | $V_{th}$/V[d] | $\Delta n$[e] | $\tau$/ms[f] |
|---|---|---|---|---|---|---|
| **host** | 116.7 | 4.8 | --- | 2.14 | 0.090 | 25.3 |
| **26** | 130.2 | 4.7 | 4.3 | 2.10 | 0.084 | 37.0 |
| **27** | 137.3 | 3.4 | -2.2 | 2.43 | 0.084 | 44.1 |
| **28** | 122.4 | 5.1 | 6.5 | 2.19 | 0.089 | 32.0 |

[a] Nematic-to-isotropic transition temperature.
[b] Dielectric anisotropy.
[c] Extrapolated from $\Delta\varepsilon$.
[d] Threshold voltage.
[e] Birefringence.
[f] Response time.




**host** (n = 0) : (n = 2) = 1 : 1 mixture

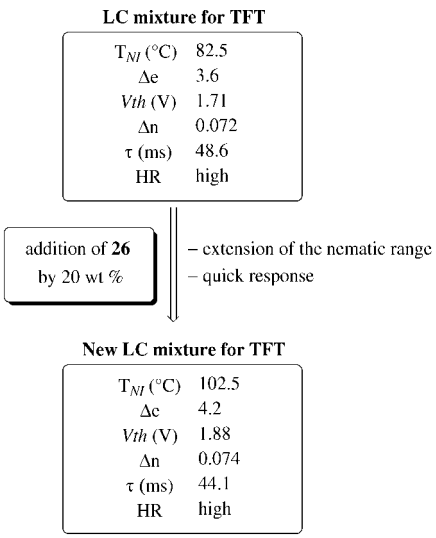
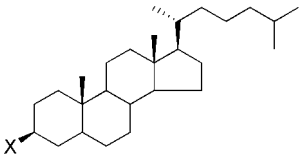



**Figure 12.** Materials for TFT-addressed twisted nematic LC displays.

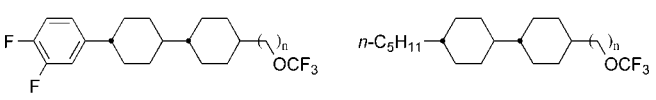



**30**: X = $OCF_3$, **31**: X = $OCH_3$

**Figure 13.** Chiral dopants for TN- and TFT-TN-LC displays.

We further studied the possibility of a trifluoromethoxy-substituted LCs as a chiral dopant for TN-LCDs (Figure 13).[76b] Cholesteryl nonanoate (**29**) is currently used as a chiral dopant for STN-LCDs. We prepared 3β-trifluoromethoxycholestane (**30**) and 3β-methoxycholestane (**31**), mixed each at 1 wt % with a TN-host mixture consisting of 4-alkoxyphenyl 4-alkylcyclohexane-1-carboxylates, and measured helical pitches of each mixture at 25 °C. The pitch of the mixture including **29**, **30**, or **31** was 15.9, 15.9, or 39.2 μm, respectively. Thus, a trifluoromethoxy group in a chiral dopant acts as a polar functionality clearly better than a methoxy group. Because LCs containing a cyano or alkyloxycarbonyl group bring a striking decrease in voltage holding ratio, ester **29** is seemingly inappropriate for TFT-LCDs. To confirm this hypothesis, we mixed **29** or **30** (2 wt %) to an LC mixture for TFT-LCDs and measured the voltage holding ratios of the resulting mixture: **29** reduced the value from 97.5% to 97.0% at 80 °C; **30** held at 97.4%. The helical pitch of both the mixtures was 8.0 μm at 25 °C. Therefore, compound **30** is concluded to be an excellent chiral dopant for not only STN-LCDs but also TFT-TN-LCDs.

Because LCs containing an ω-methoxyalkyl moiety show high Δε, broad nematic phases, and low viscosity as well as high voltage holding ratios,[77] we envisaged that replacement of the methoxy group by a trifluoromethoxy group would improve the properties. Thus, we prepared ω-trifluoromethoxyalkyl-substi-




**32**: N phase n = 1 - 5 **33**: $S_B$ phase n = 1 - 5

**Figure 14.** Structures of ω-trifluoromethoxycyclohexane-type LCs.

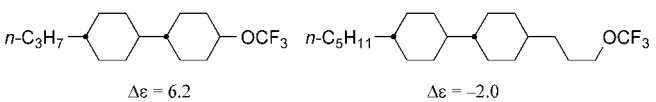


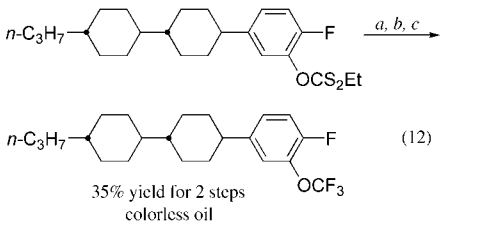

**Figure 15.** Dielectric anisotropy of trifluoromethyl ether-type LCs.

tuted LCs **32** and **33** and examined their phase transition behaviors (Figure 14).[76b] Different mesophases were observed depending mainly on the structure of the mesogen: **32** and **33** showed N and $S_B$ phases, respectively. Those with a longer alkyl chain had higher mesomorphic-isotropic transition temperatures.[76b]

The electro-optical properties of the LCs were found to be independent of the length of the alkyl chain except for the $\Delta\varepsilon$ values. As readily seen in Figure 15, a trifluoromethoxy group connected directly to a cyclohexane mesogen induces a positive $\Delta\varepsilon$.

### 3.3 Synthesis and Properties of 3-Substituted Phenyl Trifluoromethyl Ethers

It is also possible to introduce a trifluoromethoxy group into a lateral position of a mesogen.[78] Use of 80% HF/mel[79] for *oxidative desulfurization-fluorination* of the corresponding dithiocarbonate was essential: 70% HF/py gave complex mixtures. Under these reaction conditions, trifluoromethylation as well as bromination of the phenyl ring took place. Debromination was easily performed by treatment with *n*-BuLi followed by protonation (Equation 12).



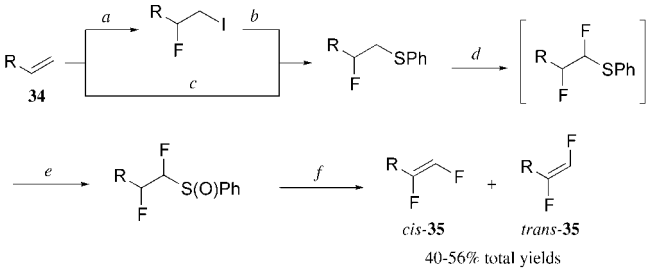

*a*: HF/mel (70 mol), DBH (5 mol), $CH_2Cl_2$, 0 °C, 30 min
*b*: *n*-BuLi (2 mol), THF, −78 °C, 10 min
*c*: $H_2O$

Although the 3-trifluoromethoxy-substituted benzenes did not exhibit a mesophase, they did prove to be versatile additives for reducing $V_{th}$ and $\Delta n$ of LC materials.

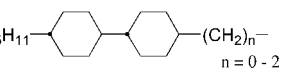
### 3.4 Synthesis and Electro-Optical Properties of Liquid Crystals with a *vic*-Difluoro-Olefinic Moiety

In order to evaluate the fluorine effect, fluorinated functional materials need to be well-compared with non-fluorinated functional materials. For this purpose, the direct transformation of a C–H bond in the parent materials to a C–F bond should be straightforward. In view of the observations that LCs containing an ω-alkenyl side chain are known to show low viscosity and $V_{th}$ and high voltage holding ratio[80] and that LCs with a *vic*-difluoro-olefinic functionality in a connecting part of mesogens exhibit low viscosity and high polarity,[81] we envisaged that LCs having an ω-*vic*-difluoroalkenyl group might exhibit properties favorable for LCDs. We thus developed a convenient method for the synthesis of LC materials having a *vic*-difluoro-olefinic moiety from the corresponding terminal olefins.[82] The route is shown in Scheme 10 which involves 1) thio-fluorination[5b] of **34** (or, alternatively, halo-fluorination[5a] followed by sulfide substitution), 2) fluoro-Pummerer rearrangement to give α,β-difluoroalkyl phenyl sulfides,[19] 4) oxidation of the sulfides to sulfoxides, and 5) thermolysis of the resulting sulfoxides. The isomers *cis*-**35** and *trans*-**35** thus synthesized were easily separated by flash column chromatography on silica gel.

The phase transition behaviors of those compounds were compared with those of the parent olefins **34**.[82] The fluorine-introduction effect was obvious. For example, *cis*-**35a** showed nematic phase at higher temperatures than **34a**, whereas the temperature range of the nematic phase in *trans*-**35** was reduced, and the $T_{NI}$ was lowered (Figure 16).

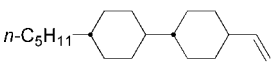



*a*: $TBAH_2F_3$ (3 mol), NIS (1 mol), $CH_2Cl_2$, rt
*b*: PhSH (1.2 mol), NaH (1.1 mol), THF, 0 °C to rt
*c*: 70% HF/py (10 mol), *N*-PhS-phthalimide (1 mol), $CH_2Cl_2$, rt
*d*: $TBAH_2F_3$ (3 mol), DBH (1 mol), $CH_2Cl_2$, rt, 30 min
*e*: *m*CPBA (1.1 mol), $CH_2Cl_2$, −30 °C, 3 h
*f*: *o*-xylene, 170 °C

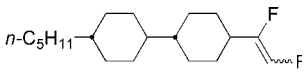
R = 


**Scheme 10.** Synthesis of *vic*-difluoro-olefins from terminal olefins.

To examine the electro-optical properties of compounds *cis*-**35a**, *trans*-**35a**, and **34a**, each of those compounds was mixed at 20 wt % with the **host** (cf.




**34a**: Cr -8 $S_B$ 52 N 63 Iso




*cis*-**35a**: Cr 20 $S_B$ 22 N 70 Iso
*trans*-**35a**: Cr 34 $S_B$ 38 N 41 Iso

**Figure 16.** Phase transition behavior of *vic*-difluoro-olefins.

**Table 8.** Electro-optical properties of *vic*-difluoro-olefins.

| Compounds (20 wt% in **host**) | $T_{NI}$ (°C) | $\Delta\varepsilon$ | $\Delta\varepsilon'$ (extrpltd) | $V_{th}$ (V) | $\Delta n$ | π/ms (Cell Voltage/V) |
|---|---|---|---|---|---|---|
| **host** | 116.7 | 4.8 | --- | 2.14 | 0.090 | 25.3 (5.1) |
| **34a** | 102.8 | 3.6 | −1.2 | 2.29 | 0.081 | 22.4 (5.3) |
| *cis*-**35a** | 105.1 | 4.2 | 1.8 | 1.99 | 0.081 | 33.3 (4.3) |
| *trans*-**35a** | 97.7 | 3.3 | −2.7 | 2.16 | 0.081 | 31.2 (4.7) |

Table 7), and the properties of the resulting mixtures were measured and are summarized in Table 8.[82] Compound *trans*-**35a** exhibited a $\Delta\varepsilon$ similar to that of the parent olefin **34a**, probably because the dipole moments of the two C–F bonds compensate each other. In contrast, *cis*-**35a** showed a $\Delta\varepsilon$ higher than that of **34a**. Whereas the mixing of **34a** at 20 wt % raised the $V_{th}$ of the host mixture, addition of both *cis*-**35a** and *trans*-**35a** reduced the $V_{th}$. Since all the compounds reduced equally $\Delta n$s, the fluorine effect on $\Delta n$ was not obvious. Both *cis*-**35a** and *trans*-**35a** were thermally stable, as no decomposition was detected upon heating their xylene solutions at 170 °C for 24 h.

As we have described above, activation of a leaving group in a substrate by an electrophilic oxidant facilitates the nucleophilic substitution by a weakly nucleophile fluoride ion. This reaction design suggests that not only organosulfur compounds but also nitrogen compounds can be employed as the substrates for fluorination. According to this synthetic methodology, a variety of organofluorine compounds will be available for testing the biological and/or electro-optical profiles required for spceecific drugs and/or materials in the 21st century.

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