Trifluoromethylated Vinylic and Aromatic Compounds from α-(Trifluoromethyl)allyl Alcohols

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Abstract: α-(Trifluoromethyl)allyl alcohols, easily available from α,β-unsaturated carbonyl compounds, are readily converted into γ-(trifluoromethyl)allyl thioethers, benzyl ethers, trifluoroacetates, and azides. A phenyl substituent at the γ-position to the hydroxyl function enhances their reactivity and the ease of S_N2' or S_N1' substitutions, whereas a phenyl ring at the α-position allows the BF_3-mediated synthesis of (trifluoromethyl)indenes. 4-Alkyl-4-methoxy-1-(trifluoromethyl)cyclohexa-2,5-dienols, readily available from 4-alkylphenols, are easily converted to 4-alkyl(trifluoromethyl)benzenes bearing a nucleophilic substituent (MeO, Cl) either on the ring or the benzylic position.

Key words: 1-(trifluoromethyl)allyl alcohols, 3-(trifluoromethyl)allyl compounds, (trifluoromethyl)arenes, (trifluoromethyl)indenes, allylic substitution

Introduction

Due to the unique properties of fluorine,[1] introduction of this element in organic substrates is well known to increase or modulate their biological properties, especially as far as target selectivity is concerned.[2] Among fluorinated substituents, the trifluoromethyl group is popular due to the liphophilicity it brings to organic molecules.[3] Surprisingly, however, very few products that contain a trifluoromethyl group on a vinylic position have been reported to exhibit biological activity. An exception is the preparation of fluorinated analogs of insect juvenile hormone JH-III (the activity of which was dramatically increased by a CF_3 group on carbon C-7)[4] and that of cyhalotrin (one of the best selling pyrethroids) and congeners.[5]

To date the most important work on the effect of triflouromethyl substitution has been done on the different stereoisomers of retinals trifluorinated either at carbons C-18 or C-19 and/or C-20.[6,7] Indeed, fluorine substitution greatly influences the conformational and spectroscopic properties of retinal,[7a,e] and therefore its interaction with opsin, as it can be seen from in vivo ^{19}F NMR.[8] Fluorinated retinoids also have been reported to be more efficient on mouse papilloma than non-fluorinated retinoids.[9] In a similar way, introduction of trifluoromethyl groups in carotenes enhances their oxidation potential[10] and probably influences their bio-activity. Also it was observed that 3-(trifluoromethyl)-2-buten-1-ol dramatically decreases the transfer of isopentenyl pyrophosphate by farnesyl pyrophosphate synthase and farnesyl transferase and thus behaves as a reversible inhibitor in the biosynthesis of isoprenoids.[11] A trifluoroprenyl moiety has also been introduced on anti-inflammatory pyrimidopurines and, again, induces better activity than a prenyl.[12] More recently, it has been reported that the introduction of trifluoromethyl substituents on the *meso*-positions of porphyrins modifies their absorption spectra in a way which opens promising opportunities in cancer photodynamic therapy.[13]

Terpenes and isoprenoids constitute a very wide class of natural compound that often exhibit biological activities. However, there are a small number of fluorinated isoprenoids, in contrast to the place of fluorine in other classes of compounds, which might be due to the lack of suitable reagents for the introduction of 4,4,4-trifluoro-2-butenyl moieties. γ-(Trifluoromethyl)allyl alcohols should be key tools for this purpose but they are not so easy to obtain. Three methods for their preparation have been reported. The first involves the Wittig-type synthesis of β-trifluoromethyl-α,β-unsaturated esters or ketones from trifluoroacetylated starting materials, followed by aluminum hydride reduction,[4a,b,6,7b,e,11a,12,14–16] however, the Wittig step is not totally stereoselective. The second approach starts from gaseous 1,1,1-trifluoropropyne (eventually generated in situ from liquid 2-bromo-1,1,1-trifluoropropene),[21] which is condensed with a carbonyl substrate, the resulting propargylic alcohol being further reduced in a stereoselective manner with Red-Al [(*E*)-isomer] or by hydrogenation over Lindlar's catalyst [(*Z*)-isomer].[17–21] The third route is based on β-metalation of α,α,α-trifluoropropenes, followed by condensation with an aldehyde.[22–26] This method has been also used to prepare β-(trifluoromethyl)allyl alcohols from 2-bromo-1,1,1-trifluoropropene.[30] The γ-(trifluoromethyl)allyl alcohols produced have been used in several fruitful transformations such as hydroxyl/halogen exchange followed by S_N2 substitution[12,14] or indium-mediated condensation on carbonyl compounds.[27] Several rearrangements of these substrates have also been studied (Wittig rearrangement,[20] Claisen rearrangement and its Johnson, Ireland or Eschenmoser modifications[19,20,23b,24,28,29]) as well as osmium-catalyzed dihydroxylation[21a] and S_N2' substitution of the corresponding acetates.[21b] All these transformations are highly stereoselective and lead to polyfunctionalized

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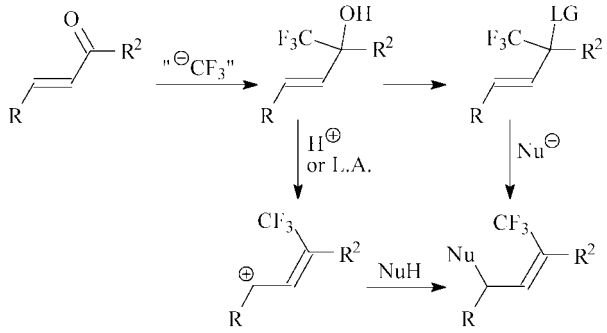
trifluoromethylated compounds such as polyols or carbohydrates.[21a]

α-(Trifluoromethyl)allyl alcohols are even far less described. Nevertheless, they could also be considered as valuable precursors of trifluoromethylated vinylic products via hydroxyl activation followed by S_N2' substitution. They have been prepared from 2-bromo-1,1,1-trifluoroacetone[31] or (trifluoromethyl)oxirane[32] via Wittig reactions. More recently, reductive titanium-mediated condensation of aldehydes with 2-bromo- and 2,2,2-tribromo-1,1,1-trifluoroacetone has been reported.[33] However, the regiospecific [1,2]-fluoride-catalyzed addition of (trifluoromethyl)trimethylsilane to α,β-unsaturated carbonyl compounds opens a general route to α-(trifluoromethyl)allyl alcohols.[34–36] For our part, we reported several times on the [1,2]-nucleophilic trifluoromethylation of α,β-unsaturated ketones, such as chalcone, di(benzylidene)acetone, or 4-methyl-4-methoxycyclohexa-2,5-dienone, using different reagents: fluoroform,[37] hemiaminals of fluoral,[38,39] trifluoromethanesulfinamides,[40] or *O*-trimethylsilyl-*N*-trifluoroacetyl-1,2-aminoalcohols.[41] Thus, we examined the hydroxyl substitution of the resulting α-(trifluoromethyl)carbinols under different conditions. Since CF_3 inhibits the development of a positive charge at the α-position, rearranged products were expected (Scheme 1).



Scheme 1 Substitution of α-(trifluoromethyl)allyl alcohols.

Biographical Sketches

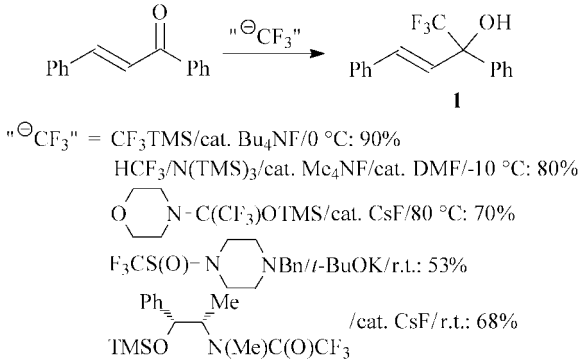
Sylvie Radix was born in Villefranche sur Saône (France) in 1971. As a former student of the Ecole Supérieure de Chimie Industrielle de Lyon, she joined Dr. B. R. Langlois' group at the University of Lyon in 1995, where she completed her Ph.D. degree on nucleophilic trifluoromethylation in 1998. After a one year postdoctoral stay with Prof. R. Grigg at Leeds University (UK), she spent one year at the University of Geneva in Prof. E. P. Kundig's group where she worked on dearomatization reactions mediated by chromium complexes. For two and a half years, she has held a position as a research assistant in medicinal chemistry in the Laboratoire de Chimie Thérapeutique at the Faculty of Pharmacy of Lyon.

Stéphanie Kucharski was born in Besançon (France) in 1974. She studied at the Ecole de Chimie, Physique et Electronique de Lyon from which she graduated in 1998. During her studies in chemistry, she spent a one year in Dr B. R. Langlois' laboratory, working on organofluorine chemistry. Now, she is involved in monetics and microchips cards.

Bernard R. Langlois was born near Paris (France) in 1947. After receiving his diploma from the 'Ecole Supérieure de Physique et Chimie Industrielles de Paris' in 1970, he entered the Rhône-Poulenc Co. where he worked, in different research centers (near Paris and Lyon), on organofluorine chemistry, from bench synthesis to development. In this context, he was involved in fluorinated aromatics and heterocycles, trifluoromethoxy-containing products, trifluoroacetic acid derivatives, triflic acid derivatives, and radical trifluoromethylation. In the meantime, he obtained a PhD degree from the University of Lyon in 1984 for research on difluorocarbene. In 1991, he moved to the University of Lyon where he was appointed as first-class Research Director by the CNRS. There, his research group is developing new methodologies for the introduction of fluorine-containing moieties in organic substrates. As far as possible, these methodologies are illustrated by the synthesis of potentially bioactive compounds.

To our knowledge, only two S_N2' substitutions of α-(trifluoromethyl)allyl sulfonates have been reported. The first is the quantitative Cu(I)-catalyzed and TMSCl-assisted reaction of butyl Grignard on (*E*)-3-benzyloxymethyl-1-(trifluoromethyl)allyl tosylate, which is not completely stereoselective.[21b] The second is the displacement of 1-(ω-phenylalkyl)-1-(trifluoromethyl)allyl mesylate by azide ions, the stereoselectivity of which is very dependent on the ω-phenylalkyl substituent.[42] As the latter substrate bears a monosubstituted vinyl group, it is not very indicative of the general reactivity of α-(trifluoromethyl)allyl sulfonates. Acid-catalyzed reactions of 1-phenyl-1-(trifluoromethyl)allyl alcohol have been briefly described twice. When treated with concentrated sulfuric acid in refluxing acetonitrile, hydrolysis and cyclization strongly compete with the expected Ritter reaction.[42] However, in warm methanesulfonic acid, cyclization occurs selectively, and 3-(trifluoromethyl)indene is obtained in medium yield.[43a] Again, this simple substrate provides limited information on the reactivity of more substituted allyl alcohols. Solvolysis, in acetic or trifluoroacetic acids, of 3-trifluoromethyl-3-indenyl tosylate, which is a very peculiar allyl sulfonate, has also been described and results in the isomerization to 1-trifluoromethyl-3-indenyl tosylate.[43b]

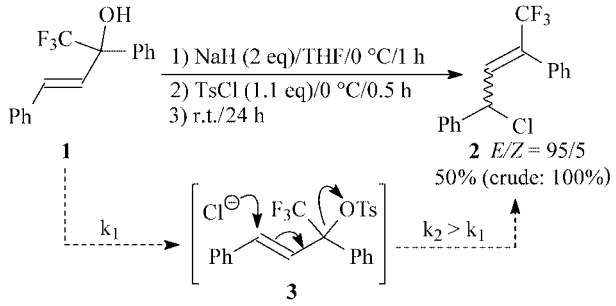
Thus, these rare and dispersed elements prompted us to study the reactivity of the α-(trifluoromethyl)allyl alcohols we had previously prepared. As we reported before, 1,3-diphenyl-1-(trifluoromethyl)allyl alcohol **1** can be easily obtained from chalcone and different nucleophilic trifluoromethylating agents (Scheme 2).[37–41]



Scheme 2 Nucleophilic trifluoromethylation of chalcone.

Substituent Effects

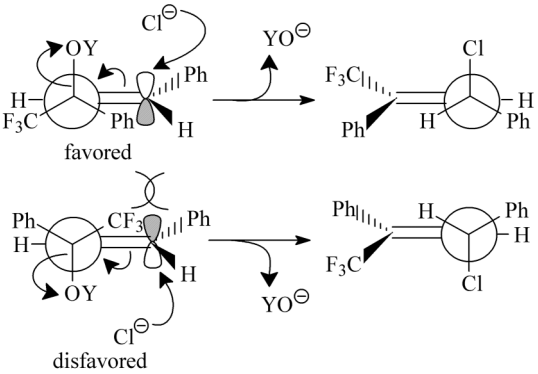
Initially, 1,3-diphenyl-1-(trifluoromethyl)allyl alcohol (**1**) was treated with tosyl chloride at room temperature after deprotonation with NaH at 0 °C. Surprisingly, the expected tosylate **3** was not obtained but γ-(trifluoromethyl)allyl chloride **2** was quantitatively formed with very high stereoselectivity (*E*/*Z*, 95:5). This indicates that the chloride ion generated along with **3** underwent a substitution reaction by a S_N2' process (Scheme 3). The less reactive mesyl chloride led to the same qualitative result as did triflyl chloride, which was far less chemoselective. This result indicates that **1** is much more reactive than its less conjugated analog 1-phenyl-1-(trifluoromethyl)allyl alcohol from which a mesylate has been isolated at room temperature.[42] The major isomer (*E*)-**2** has been isolated but appeared to be rather unstable over silica gel and exhibited a limited shelf-life (a few days at –18 °C). Nevertheless, its *E*-configuration has been unambiguously assigned by ^1H, ^{19}F, and ^{13}C NMR, and is in accordance with the literature,[44] as is the *Z*-configuration attributed to the minor isomer in the crude product.



Scheme 3 Formation of allyl chloride **2** from **1** and TsCl.

The preparation of **2** from **1** and the Vilsmeier reagent was also examined. Again, the *E*-isomer was formed quite exclusively but in a moderate yield (conv. **1**: 65%, crude yield **2**: 47%).

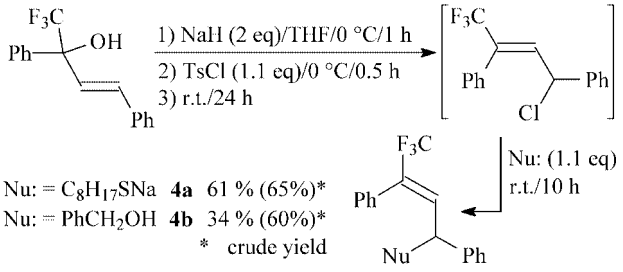
The high stereoselectivity observed during the S_N2' substitution of **3** by chloride can be rationalized as follows: as the CF_3 group is surrounded by an intense electrostatic field which develops strong repulsive interactions with any π-electron or negatively charged nucleophile, **3** probably adopts, in the transition state, a conformation which minimizes the repulsions with the electrons of the double bond and the incoming chloride and leads to the *E*-isomer (Scheme 4).



Scheme 4 Stereoselectivity in the formation of **2**

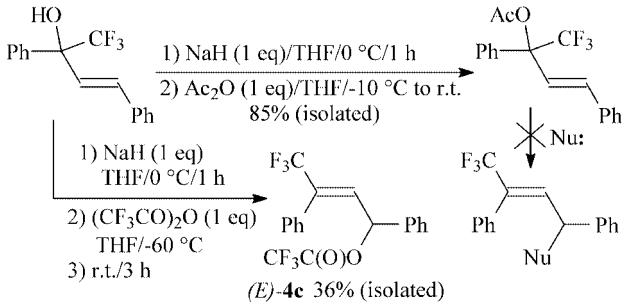
Due to its poor stability, **2** was then reacted in situ at room temperature with sodium *n*-octanethiolate or benzyl alcohol, through a stereospecific S_N2 process: allylic products **4a,b** were obtained in the same *E*/*Z* ratio (95:5) as **2**, as in-

dicated by the coupling constants between fluorine and the carbon at the β-position,[44] measured by ^{13}C NMR spectra. No product arising from a S_N2' substitution was detected (Scheme 5). In contrast, a complex mixture resulted from the action of benzylamine.



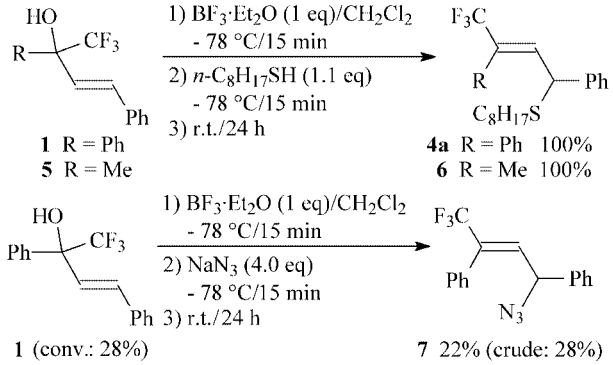
Scheme 5 Synthesis of **4a,b** from **2**.

To help elaborate further on the reactivity, **1** was then reacted with anhydrides in order to obtain allylic esters, which were expected to be more stable than **2**. Indeed, the corresponding acetate was obtained in good yield but did not undergo nucleophilic substitution with a range of nucleophiles [*i*-$PrNH_2$, $LiN(TMS)_2$, NaN_3, $C_8H_{17}SH$, CH_3SNa, KSCN, $C_4H_9Cu{\cdot}BF_3$], even at 80 °C. In contrast, trifluoroacetic anhydride did not provide the expected trifluoroacetate which was regio- and stereoselectively substituted, as soon as formed, by the trifluoroacetate anion to deliver the isomeric γ-(trifluoromethyl)allyl trifluoroacetate **4c** in pure *E*-configuration, as deduced from the $^3J_{CF}$ coupling constant (Scheme 6).



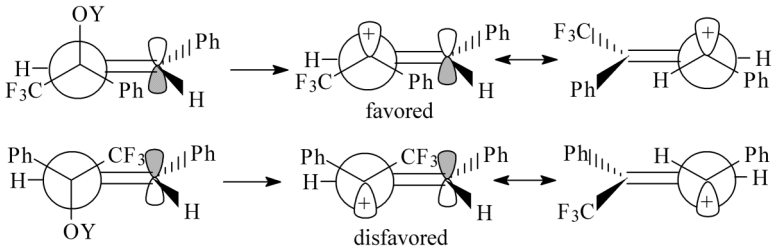
Scheme 6 Formation of **4c** from **1** and $(CF_3CO)_2O$.

Because of the poor nucleophilicity of the trifluoroacetate anion, it could be suspected that this substitution proceeded through a cationic intermediate and had a pronounced S_N1' character. In order to promote the formation of a cation, **1** was activated with $BF_3{\cdot}OEt_2$ prior to adding a nucleophile. Indeed, the hydroxyl group of **1**, as well as that of 1-methyl-1-(trifluoromethyl)cinnamyl alcohol **5**, was quantitatively substituted by octanethiol in a stereoselective S_N1' reaction to give **4a** and **6** (Scheme 7). The fact that **1** and **5** exhibited the same reactivity implies that the phenyl at the γ-position to CF_3 was able to stabilize the cationic intermediate more efficiently than the phenyl at the α-position. Again, pure *E*-products were obtained in both cases, as deduced from $^3J_{CF}$ coupling constants but also from a NOE ^1H-{^1H} experiment on compound **6**. The same stereoselectivity was observed with sodium azide but the yield of **7** was much lower, though the chemoselectivity was excellent; probably, the azide interacted competitively with boron trifluoride, as suggested by the limited conversion of **1**. Again, such a high stereoselectivity can be explained by the conformation of the intermediate carbocation which minimizes the repulsive interactions between the fluorine atoms and the π-electrons or the incoming nucleophile (Scheme 8).



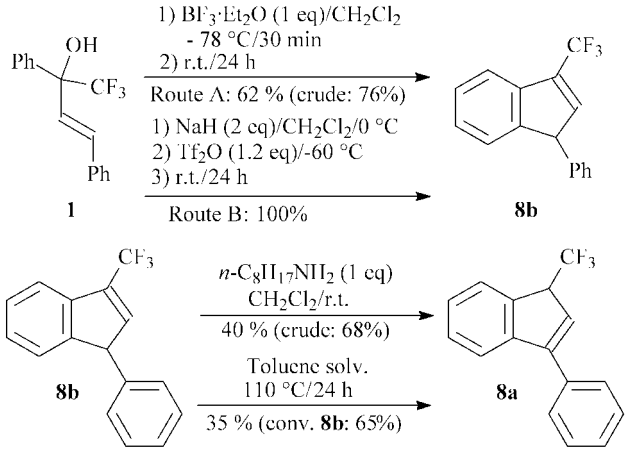
Scheme 7 BF_3-mediated substitution of **1** and **5** by nucleophiles.

Further nucleophiles were then tested; with *n*-octylamine, potassium thiocyanate, or sodium diethyl malonate, no substitution reactions occurred but 1-trifluoromethyl-3-phenylindene **8a** was formed in 20%, 85%, and 35% yields, respectively. Such a cyclization confirmed the occurrence of a carbocation. In order to elucidate the mechanism for the formation of **8a**, **1** was reacted with $BF_3{\cdot}OEt_2$ only. In this case, 3-trifluoromethyl-1-phenylindene **8b** was isolated in a good yield. Similarly, **8b** was also quantitatively formed from **1** and triflic anhydride (Scheme 9). Under the action of *n*-octylamine or upon



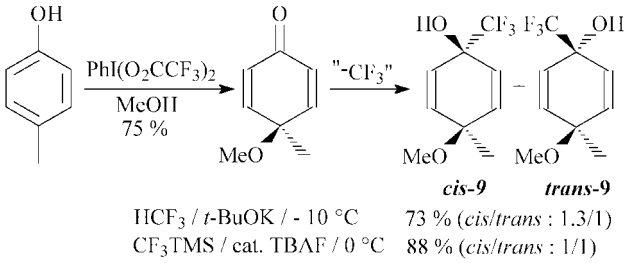
Scheme 8 Stereoselectivity of the S_N1' process.

heating, this compound was isomerized into the more conjugated indene **8a** (Scheme 9). As previously mentioned, 3-(trifluoromethyl)indene, a simpler analog of **8b**, was prepared formerly, but under more drastic conditions, by cyclization of 1-phenyl-1-(trifluoromethyl)allyl alcohol with Brönsted acids such as sulfuric acid in boiling acetonitrile (yield: 7%)[42] or warm methanesulfonic acid (yield: 53%).[43]



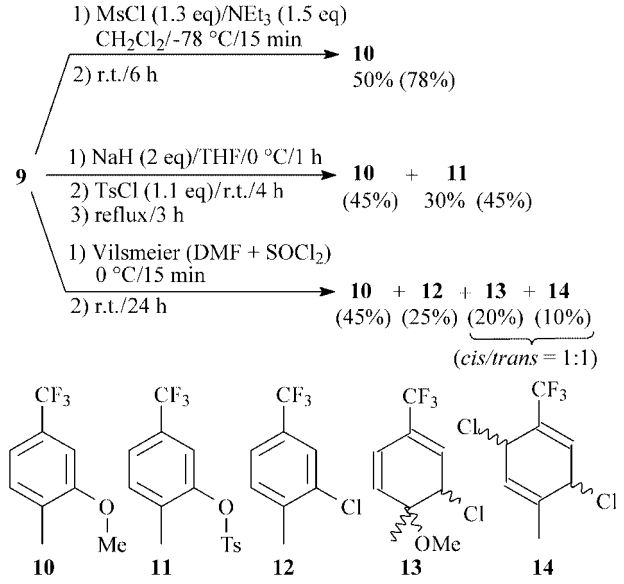
Scheme 9 Formation of **8a** and **8b**.

Next we turned our attention to cyclic α-(trifluoromethyl)allyl alcohols since we previously described the trifluoromethylation of 4-methyl-4-methoxycyclohexa-2,5-dienone. This substrate, easily available from the oxidation of *p*-cresol with iodine(III) in the presence of methanol, was reacted with trifluoromethane under basic conditions and afforded the *bis*-allylic alcohol **9** as a mixture of stereoisomers in which the *cis*-isomer was preponderant.[37] Better yields were obtained with CF_3TMS but without stereoselectivity (Scheme 10).



Scheme 10 Preparation of alcohol **9**.

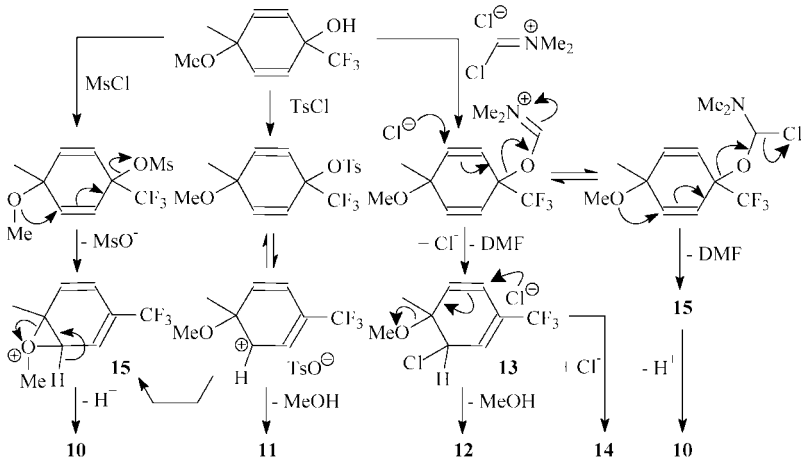
As **1**, *cis*/*trans* **9** was reacted with mesyl chloride, tosyl chloride, and Vilsmeier's reagent. 4-Methyl-3-methoxy(trifluoromethyl)benzene **10** was selectively obtained with mesyl chloride and no incorporation of chloride was observed. In the other cases, **10** remained the major product but the side-products depended on the reagent employed (Scheme 11). Globally, formation of **10** and **12** from *p*-cresol formally corresponds to a three-step substitution of a phenolic group by trifluoromethyl, along with additional methoxylation or chlorination.



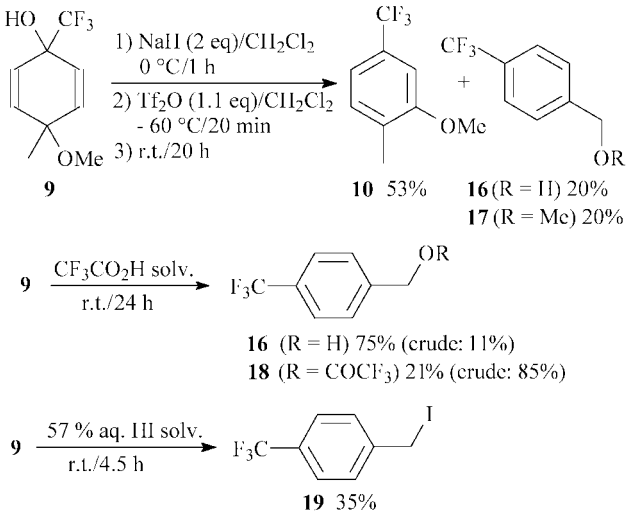
Scheme 11 Aromatization of **9**.

Compound **10** obviously resulted from an intramolecular substitution of the hydroxyl moiety of **9**, after its transformation into a leaving group. Due to the chemoselectivity observed with mesyl chloride, a concerted intramolecular S_N2' process must be considered. As no chlorine was incorporated, this substitution probably occurred after chloride had diffused away from the molecule. In contrast, the poorly nucleophilic tosylate anion was incorporated to deliver **11** when tosyl chloride was used; it could be suspected that, in this case, an intermediate carbocation was generated by solvolysis, after diffusion of the chloride anion. This hypothesis is consistent with the higher sensitivity of tosylates towards solvolysis, compared with that of mesylates. The generated cation would then interact either with TsO^- in a solvent cage or with the methoxy substituent. As far as the Vilsmeier's reagent was concerned, it could be suggested that, after reaction of the hydroxyl group, the generated chloride remained in a close vicinity of the iminium moiety, because of a possible equilibrium with a covalent species, and could thus compete with the methoxy group. These different possibilities are summarized in Scheme 12.

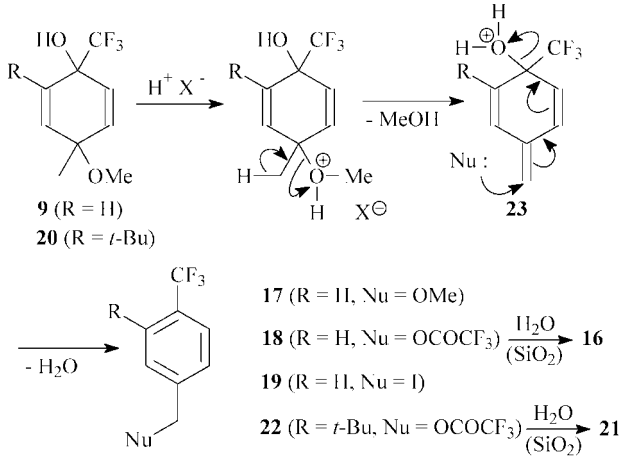
When **9** was treated with triflic anhydride, **10** was also formed, as expected, but along with 4-(trifluoromethyl)benzyl alcohol (**16**) and its methyl ether **17** (Scheme 13). As these side-products could be related to the generation of triflic acid, **9** was also reacted with trifluoroacetic acid (used as solvent): again, **16** was isolated along with its trifluoroacetate **18** (**18** was almost the unique product detected in the crude mixture but was extensively hydrolyzed during chromatography). In the same way, stirring **9** in hydroiodic acid led to 4-(trifluoromethyl)benzyl iodide **19** (Scheme 13). 1-Trifluoromethyl-2-*tert*-butyl-4-methyl-4-methoxycyclohexa-2,5-dienol (**20**), obtained in the same way as **9**,[37] was also stirred in trifluoroacetic acid and delivered 3-*tert*-butyl-4-



Scheme 12 Intra and intermolecular substitutions of **9**.



Scheme 13 (Trifluoromethyl)benzyl derivatives from **9**.



Scheme 14 Mechanism of formation of **18, 19, 22**.

(trifluoromethyl)benzyl alcohol **21** along with its trifluoroacetate **22** (yield **21**+**22**: 57%).

As the electron-withdrawing effect of CF_3 decreased the basicity of the hydroxyl function at the α-position, the methoxy group was the most basic site in compound **9** and was probably protonated selectively; subsequently, methanol was eliminated to provide the quinol methide **23**. Then, the less basic hydroxy group could be activated by protonation and water substituted, through a S_N2' substitution, by the conjugated base of the acid or another nucleophile such as methanol (Scheme 14).

In conclusion, this study shows that α-(trifluoromethyl)allyl alcohols, which are easily available by nucleophilic trifluoromethylation of α,β-unsaturated carbonyl compounds, constitute fruitful synthetic tools, especially for preparing (trifluoromethyl)vinyl moieties or γ-(trifluoromethyl)allyl thiols, amines, alcohols, ethers, etc.... A phenyl ring at the γ-position to the hydroxyl function greatly enhances their reactivity and therefore the ease of S_N2' or S_N1' substitutions, whereas a phenyl ring at the α-position allows the synthesis of (trifluoromethyl)indenes, which can lead to interesting Cp-like ligands, as suggested by Gassman et al. [43,45] 4-Methyl-4-methoxy-1-(trifluoromethyl)cyclohexa-2,5-dienol, as well as its 2-*tert*-butylated analog, also constitute attractive examples of α-(trifluoromethyl)allyl alcohols which allow the mild preparation, in three steps from 4-methylphenol or 2-*tert*-butyl-4-methylphenol, of 4-(trifluoromethyl)toluenes bearing another substituent (MeO, Cl, I, $OCOCF_3$) on the ring or at the benzylic position. Formally, these transformations correspond to a three-step substitution of a phenolic group by trifluoromethyl, along with an additional 'electrophilic-like' substitution by a nucleophilic species, either on an aromatic or benzylic carbon. It would be interesting to optimize this synthetic sequence since no exchange of OH for CF_3 is known until now and, on the other hand, few realistic accesses to aromatics bearing both a methyl group and trifluoromethyl one are available. Moreover, such a sequence can be probably subjected to a large synthetic diversity since the methyl group could be replaced by a longer alkyl chain and methanol could be replaced, in the oxidation step, by other nucleophiles such

as various alcohols, carboxylic acids, hydrogen bromide or nitrogen-containing compounds. Finally, *ipso*-substitution of the *tert*-butyl of **22** by an electrophile could be envisaged.

Prior to use, THF was distilled over sodium-benzophenone then stored over 3 Å molecular sieves under N_2. Other reagents were used as received. Starting compounds **1**, **5**, **9**, **20** have been described in our previous articles.[37–41] TLC analyses were carried out on Kieselgel 60F 254 deposited on aluminum plates, detection was carried out by UV (254 nm), phosphomolybdic acid (10% in ethanol) or ninhydrine (1% in ethanol). Flash chromatography was performed on silica gel Geduran SI 60. Uncorrected melting points were determined in capillary tubes. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$. ^{1}H NMR spectra were recorded at 200MHz or 300 MHz and ^{13}C NMR spectra at 50 or 75 MHz. The substitution pattern of the different carbons were determined by a 'DEPT 135' sequence. ^{19}F NMR spectra were recorded at 188 MHz. Chemical shifts (δ) are given in ppm with TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) used as internal references. Coupling constants are given in Hz. Crude yields were determined by ^{19}F NMR with $PhOCF_3$ (δ_F = –58.3 ppm) used as standard. GC was carried out on an apparatus fitted with a semi-capillary column [length: 15 m, Φ: 0.53 mm, film thickness (DB1): 1 μm] and a catharometric detector. Mass spectrometry, coupled with gas chromatography, was carried out under electron impact at 70 eV.

4-Chloro-2,4-diphenyl-1,1,1-trifluoro-2-butene (2)
NaH (4 mmol) was added, as a 60% dispersion in oil (160 mg), to a solution of **1** (556 mg, 2 mmol) in THF (5 mL), cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then *p*-TsCl (210 mg, 1.1 mmol) was added. Stirring was continued at 0 °C for 30 min then at r.t. for 24 h. The reaction medium was hydrolyzed with H_2O (5 mL) then extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), then H_2O (5 mL), and dried over Na_2SO_4. After filtration, the solvent was evaporated under vacuum at r.t. Column chromatography over silica gel (PE–Et_2O, 90:10) gave a pale yellow oil (297 mg, 50%) the NMR analysis of which indicated the presence of two isomers (*E*/*Z* 95:5).

***E*-Isomer (*E*)-2**
^{1}H NMR (300 MHz): δ = 5.30 (d, 1 H, *J* = 10.6 Hz, CHCl), 6.78 (qd, 1 H, *J* = 10.6, 1.6 Hz, CH=), 7.20–7.35 (m, 7 H, ArH), 7.36–7.51 (m, 3 H, ArH).

^{13}C NMR (75 MHz): δ = 70.31 (C4), 123.17 (q, *J* = 273 Hz, CF_3), 126.21, 131.38, 131.98, (q, *J* = 30.1 Hz, C2), 136.63 (q, *J* = 5.3 Hz, C3), 141.44 (q, *J* = 1.1 Hz, C_{arom}), 128.60, 128.84, 129.04, 129.68.

^{19}F NMR (188 MHz): δ = –66.52 (br s).

MS: *m*/*z* (%) = 296 (M^{+}•), 262, 261 (M – Cl), 191, 183 (100), 133, 115, 77.

***Z*-Isomer (*Z*)-2**
^{1}H NMR (300 MHz): δ = 6.05 (d, 1 H, *J* = 10.6 Hz, CHCl), 6.40 (qd, 1 H, *J* = 10.6, 1.0 Hz, CH=), 7.20–7.35 (m, 7 H, ArH), 7.36–7.51 (m, 3 H, ArH).

^{19}F NMR (188 MHz): δ = –57.10 (br s).

Because of their limited shelf-life, (*E*)-**2** and (*Z*)-**2** have not been submitted to elementary analysis.

(*E*)- 2,4-Diphenyl-4-octylthio-1,1,1-trifluoro-2-butene (4a)
A solution of sodium *n*-octanethiolate in THF (1 mL) was prepared from *n*-octanethiol (95 μL, 0.55 mmol) and NaH (44 mg of a 60% suspension in oil, 1.1 mmol) at 0 °C for 1 h, then added at r.t. to a solution of **2**, prepared in situ from **1** (0.5 mmol) following the above-described procedure. The reaction medium was stirred at r.t. for 10 h then treated as described for **2**. Column chromatography over silica gel (PE) gave **4a** (132 mg, 65%) as a colorless oil.

^{1}H NMR (300 MHz): δ = 0.88 (t, 3 H, *J* = 6.8 Hz, CH_3), 1.20–1.43 (m, 12 H, CH_2), 2.32 (t, 2 H, *J* = 6.8 Hz, CH_2S), 4.41 (d, 1 H, *J* = 10.9 Hz, CHS), 6.66 (dq, 1 H, *J* = 10.9, 1.5 Hz, CH=), 7.25–7.44 (m, 10 H, ArH).

^{13}C NMR (50 MHz): δ = 14.14, 22.70, 28.86, 29.16, 29.19, 29.45, 31.45, 31.86, 46.43 (C4), 123.37 (q, *J* = 273 Hz, CF_3), 127.70, 127.85, 128.63, 129.02, 129.84, 130.96 (q, *J* = 30.0 Hz, C2), 131.44, 135.75 (q, *J* = 5.5 Hz, C3), 139.21.

^{19}F NMR (188 MHz): δ = –66.00 (br s).

MS: *m*/*z* (%) = 406 (M^{+}•), 261 (M – RS), 221, 191, 183 (100), 133, 69 (CF_3), 43, 41.

Anal. Calcd for $C_{24}H_{29}F_3S$: C, 70.9; H, 7.2. Found: C, 70.6; H, 7.4.

(*E*)-4-Benzyloxy-2,4-diphenyl-1,1,1-trifluoro-2-butene (4b)
The same procedure used was repeated except that the solution of thiolate was replaced by pure benzyl alcohol (57 μL, 0.55 mmol). Column chromatography with PE–Et_2O (98:2) gave **4b** (50 mg, 27%) as a colorless oil.

^{1}H NMR (300 MHz): δ = 4.34 (s, 2 H, CH_2), 4.80 (d, 1 H, ***J*** = 9.2 Hz, CHO), 6.61 (d, 1 H, ***J*** = 9.2 Hz, CH=), 7.21–7.38 (m, 15 H, ArH).
^{13}C NMR (50 MHz): δ = 70.21 (CH_2), 76.82 (C4), 123.10 (q, *J* = 273 Hz, CF_3), 126.78, 127.75, 127.86, 128.33, 128.37, 128.51, 128.81, 128.89, 129.64, 131.49, 132.50 (q, *J* = 30.3 Hz, C2), 135.86 (q, *J* = 5.3 Hz, C3), 137.70, 139.62.

^{19}F NMR (188 MHz): δ = –66.95 (br s).

Anal. Calcd for $C_{23}H_{19}F_3O$: C, 75.0; H, 5.2. Found: C, 75.2; H, 5.0.

(*E*)-2,4-Diphenyl-1,1,1-trifluoro-4-trifluoroacetoxy-2-butene (4c)
NaH (160 mg of a 60% suspension in oil, 4 mmol) was added to a solution of **1** (556 mg, 2 mmol) in THF (5 mL), cooled to 0 °C. The resulting mixture was stirred at 0 °C for 1 h then cooled to –10 °C, then a solution of Tf_2O (390 μL, 2 mmol) in THF (5 mL) was added within 15 min. After stirring at r.t. for 3 h, usual work up and column chromatography with PE–Et_2O (80:20) gave **4c** (270 mg, 36%) as an orange oil.

^{1}H NMR (300 MHz): d = 6.20 (d, 1 H, *J* = 9.2 Hz, CHO), 6.67 (qd, 1 H, *J* = 9.2, 1.6 Hz, CH=), 7.21–7.48 (m, 10 H, ArH).
^{13}C NMR (50 MHz): δ = 76.35 (C4), 114.5 (q, *J* = 275 Hz, CF_3CO_2), 124.5 (q, *J* = 286 Hz, CF_3), 126.96, 128.80, 129.21, 129.37, 129.62, 130.32, 130.79 (q, *J* = 5.5 Hz, C3), 135.58 (q, *J* = 30.9 Hz, C2), 135.71, 156.22 (q, *J* = 42.8 Hz, CF_3CO).

^{19}F NMR (188 MHz): δ = –67.65 (br s, CF_3), –75.48 (s, CF_3CO_2).

MS: *m*/*z* = 374 (M^{+}•), 305 (M – CF_3), 261, 260 (100, M – CF_3CO_2), 191, 183, 133, 105, 77, 69 (CF_3), 51.

Anal. Calcd for $C_{18}H_{12}F_6O_2$: C, 57.8; H, 3.2. Found: C, 57.5; H, 3.4.

1-Phenyl-3-Trifluoromethylindene (8b)
To a solution of **1** (139 mg, 0.5 mmol) in CH_2Cl_2 (1.5 mL), cooled to 0 °C, was added NaH (42 mg of a 60% suspension in oil, 1 mmol). The resulting mixture was stirred at 0 °C for 1 h then cooled to –60 °C, then a solution of Tf_2O (100 μL, 0.6 mmol) in CH_2Cl_2 (5 mL) was added within 15 minutes. After warming to r.t., the reaction medium was stirred for 24 h, followed by the usual work-up. Column chromatography with PE–Et_2O (95:5) afforded **8b** (130 mg, 100%) as a colorless oil.

^{1}H NMR (300 MHz): d = 4.69 (dq, 1 H, *J* = 2.2, 2.2 Hz, C*H*Ph), 6.99 (dq, 1 H, *J* = 2.2, 2.2 Hz, C*H*=), 7.06 (m, 2 H, ArH), 7.22–7.37 (m, 6 H, ArH), 7.54 (dq, 1 H, *J* = 7.7, 1.1 Hz, H4). ^{13}C NMR (50 MHz): d = 53.40 (C1), 120.80 (C4), 122.39 (q, *J* = 270 Hz, CF_3), 124.43 (C7), 126.85 (C6), 127.37 (C5), 127.48, 127.88, 128.97, 134.50 (q, *J* = 34 Hz, C3), 136.94, 138.06 (C3a), 140.80 (q, *J* = 5 Hz, C2), 147.89.
^{19}F NMR (188 MHz): δ = –64.54 (br s).

MS: *m*/*z* = 260 (100, $M^{+\cdot}$), 240, 192, 191 (100, M – CF_3), 165, 94, 82.

Anal. Calcd for $C_{16}H_{11}F_3$: C, 73.8; H, 4.3. Found: C, 73.6; H, 4.4.

BF_3-Mediated Substitution of 1 and 5 by Nucleophiles; General Procedure

To a solution of **1** (139 mg, 0.5 mmol) or **5** (108 mg, 0.5 mmol) in CH_2Cl_2 (2 mL, HPLC grade), cooled to –78 °C, was added $BF_3{\cdot}Et_2O$ (65 μL, 0.5 mmol). After stirring for 15 min at –78 °C, the nucleophile was added and stirring was continued at the same temperature for 15 min before warming to r.t. Unless stated otherwise, the reaction mixture was stirred at r.t. for 24 h, followed by the usual work-up. The organic residue was purified by column chromatography.

(*E*)-2,4-Diphenyl-4-octylthio-1,1,1-trifluoro-2-butene (4a)

From **1**, $BF_3{\cdot}Et_2O$, and *n*-octanethiol (95 μL, 0.55 mmol). Column chromatography with PE gave **4a** (203 mg, 100%) as a colorless oil.

(*E*)-4-Azido-2,4-diphenyl-1,1,1-trifluoro-2-butene (7)

From **1**, $BF_3{\cdot}Et_2O$, and sodium azide (130 mg, 2.0 mmol). Column chromatography with PE–Et_2O (90:10) gave **7** (33 mg, 22%) as a yellow oil.

^{1}H NMR (300 MHz): δ = 5.02 (d, 1 H, *J* = 9.9 Hz, CHN), 6.57 (dq, 1 H, *J* = 9.9, 1.5 Hz, CH=), 7.25–7.29 (m, 4 H, ArH), 7.39–7.50 (m, 6 H, ArH).

^{13}C NMR (50 MHz): δ = 61.93 (C4), 122.84 (q, *J* = 274 Hz, CF_3), 126.79, 128.73, 128.83, 129.10, 129.35, 129.75, 130.61, 132.68 (q, *J* = 5.3 Hz, C3), 134.20 (q, *J* = 29.8 Hz, C2), 137.17.

^{19}F NMR (188 MHz): δ = –67.01 (br s).

MS: *m*/*z* = 303 ($M^{+\cdot}$), 275 (M – N_2), 274, 261 (M – N_3), 206, 192, 183 (100), 151, 133, 103, 77, 51.

Anal. Calcd for $C_{16}H_{12}F_3N_3$: C, 63.4; H, 4.0; N, 13.9 Found: C, 63.1; H, 4.2; N, 14.1.

(*E*)-2-Methyl-4-octylthio-4-phenyl-1,1,1-trifluoro-2-butene (6)

From **5**, $BF_3{\cdot}Et_2O$, and *n*-octanethiol (95 μL, 0.55 mmol). Column chromatography with PE–Et_2O, (80:20) gave **6** (172 mg, 100%) as a colorless oil.

^{1}H NMR (300 MHz): δ = 0.88 (t, 3 H, *J* = 6.6 Hz, CH_3CH_2), 1.10–1.45 (m, 12 H, CH_2), 1.90 (s, 3 H, CH_3C=), 2.38 (t, 2 H, *J* = 7.4 Hz, CH_2S), 4.70 (d, 1 H, *J* = 10.3 Hz, CHS), 6.34 (dq, 1 H, *J* = 10.3, 1.5 Hz, CH=), 7.21–7.37 (m, 5 H, ArH).

^{13}C NMR (50 MHz): δ = 10.95 (q, *J* = 1.1 Hz, *C*H_3C=), 14.12 (*C*$H_3$$CH_2$), 22.74, 24.69, 29.16, 29.23, 29.30, 31.92, 34.18, 45.96 (C4), 124.07 (q, *J* = 273 Hz, CF_3), 125.63 (q, *J* = 30 Hz, C2), 127.76, 128.88, 133.25 (q, *J* = 6.0 Hz, C3), 139.53.

^{19}F NMR (188 MHz): δ = –69.78 (br s).

NOE ^{1}H-{^{1}H}: irradiation of methyl group (δ =1.90) enhanced (+3.5%) the signal corresponding to the proton on C-4 (δ = 4.70).

Anal. Calcd for $C_{19}H_{27}F_3S$: C, 66.2; H, 7.9 Found: C, 66.4; H, 7.8.

3-Phenyl-1-(trifluoromethyl)indene (8a)

From **1**, $BF_3{\cdot}Et_2O$, and KSCN (194 mg, 2.0 mmol). Reaction time: 3 h. Column chromatography with PE–Et_2O (95:5) gave **8a** (111 mg, 85%) as a white solid; mp 49–51 °C.

^{1}H NMR (200 MHz): d = 4.27 (qd, 1 H, *J* = 9.3, 2.1 Hz, H1), 6.45 (d, 1 H, *J* = 2.2 Hz, H2), 7.30–7.72 (m, 9 H, ArH).

^{13}C NMR (50 MHz): δ = 52.63 (q, *J* = 29 Hz, C1), 121.17 (C4), 124.69 (q, *J* = 2.9 Hz, C2), 124.82 (q, *J* = 1.5 Hz, C7), 126.12 (q, *J* = 278 Hz, CF_3), 126.32 (C6), 127.74, 128.42 (C5), 128.51, 128.89, 134.54, 138.68 (q, *J* = 2.0 Hz, C7a), 144.14 (C3a), 149.32 (C3).

^{19}F NMR (188 MHz): δ = –67.80 (d, *J* = 9.3 Hz).

MS: *m*/*z* = 260 ($M^{+\cdot}$), 191, 165, 95, 83.

Anal. Calcd for $C_{16}H_{11}F_3$: C, 73.8; H, 4.3. Found: C, 74.0; H, 4.2.

1-Phenyl-3-(Trifluoromethyl)indene (8b)

From **1** and $BF_3{\cdot}Et_2O$. Reaction time: 4 h. Column chromatography with PE–Et_2O (95:5) gave **8b** (81 mg 62%) as a colorless oil.

Isomerization of 8b into 8a

Octylamine (260 mg, 1 mmol) was added at r.t. to a solution of **8b** (260 mg, 1 mmol) in CH_2Cl_2 (3 mL, HPLC grade). The mixture was stirred for 1 h then underwent the usual work-up procedure. Column chromatography with PE–Et_2O (95:5) afforded **8a** (104 mg, 40%).

3-Methoxy-4-methyl(trifluoromethyl)benzene (10)
Reaction of 9 and Methanesulfonyl Chloride

Compound **9** (208 mg, 1 mmol) was treated with MsCl for 6 h at r.t., following the procedure used for the synthesis of **2** from **1** and *p*-TsCl. Column chromatography with PE–Et_2O (80:20) gave **10** (95 mg, 50%) as a colorless oil.

^{1}H NMR (300 MHz): δ = 2.25 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.85 (d, 1 H, *J* = 8.5 Hz, H5), 7,37 (q, 1 H, *J* = 0.7 Hz, H2), 7.42 (dq, 1 H, *J* = 8.5, 0.7 Hz, H6).

^{13}C NMR (75 MHz): δ = 16.21 (CH_3), 55.47 (OCH_3), 109.47 (C5), 122.34 (q, *J* = 32.3 Hz, C1), 124.33 (q, *J* = 4.0 Hz, C2), 124.60 (q, *J* = 271 Hz, CF_3), 127.33 (C4), 127.44 (q, *J* = 3.5 Hz, C6), 160.17 (C3).

^{19}F NMR (188 MHz): δ = –61.46 (s).

MS: *m*/*z* = 190 (100%, $M^{+\cdot}$), 175 (M – CH_3), 159 (M – OCH_3), 145, 121 (M – CF_3), 109, 91, 77.

Anal. Calcd for $C_9H_9F_3O$: C, 56.8; H, 4.8. Found: C, 57.0; H, 4.5.

2-Methyl-5-(trifluoromethyl)phenyl *para*-Toluenesulfonate (11)
Reaction of 9 with *p*-TsCl

Compound **9** (208 mg, 1 mmol) was treated with *p*-TsCl for 3 h in refluxing THF, following the procedure used for the synthesis of **2** from **1** and *p*-TsCl. Column chromatography with PE–Et_2O (80:20) allowed the separation of **10** from **11** and gave **11** (99 mg, 30%) as a white solid.

^{1}H NMR (300 MHz): δ = 2.17 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 7.17 (s, 1 H, H6), 7.26–7.41 (m, 4 H, H3,4,2′,6′), 7.65 (d, 2 H, *J* = 8.1 Hz, H3′,5′).

^{13}C NMR (50 MHz): δ = 16.50 (CH_3), 21.72 (CH_3), 119.71 (q, *J* = 3.8 Hz, C6), 123.37 (q, *J* = 272 Hz, CF_3), 123.66 (q, *J* = 3.8 Hz, C4), 128.48 (C3′), 128.97 (q, *J* = 33 Hz, C5), 130.01 (C2′), 132.12 (C3), 132.60 (C2), 136.26 (C4′), 145.98 (C1′), 148.15 (C1).

^{19}F NMR (188 MHz): δ = –63.08 (s).

Anal. Calcd for $C_{15}H_{13}F_3O_3S$: C, 54.5; H, 4.0. Found: C, 54.1; H, 4.2.

Reaction of 9 with the Vilsmeier's Reagent
Compound **9** (208 mg, 1 mmol) was treated with chloromethylene-*N*,*N*-dimethyliminium chloride for 24 h at r.t., following the procedure used for the synthesis of **2** from **1** and *p*-TsCl. Column chromatography with PE–Et_2O (80:20) gave **10** along with an inseparable mixture of 3 chlorinated products (**12**, **13**, **14**) which were characterized by ^{19}F NMR and gas chromatography coupled with mass spectroscopy.

3-Chloro-4-methyl(trifluoromethyl)benzene (12)
^{19}F NMR (188 MHz): δ = –63.12 (s).

MS: *m*/*z* =196 (M^+·), 194 (M^+·), 177 (M – F), 175 (M – F), 159 (100, M – Cl), 127 (M – F_3), 125 (M – CF_3), 89.

2-Chloro-1-methoxy-1-methyl-4-trifluoromethyl-3,5-cyclohexadiene (13)
2 diastereomers.

^{19}F NMR (188 MHz): δ = –68.73 (s).

MS: *m*/*z* = 226 (M^+·), 191 (M – Cl), 175, 159, 91, 77, 43 (100).

1,4-Dichloro-2-methyl-5-trifluoromethyl-2,5-cyclohexadiene (14)
2 diastereomers.

^{19}F NMR (188 MHz): δ = –76.73 (s), –77.34 (s).

MS: *m*/*z* = 230 (M^+·), 213 (M – F), 211 (M – F), 197 (M – Cl), 195 (M – Cl), 159, 91 (100).

4-(Trifluoromethyl)benzyl Derivatives; General Procedure
Trifluoroacetic acid or 57% aqueous hydroiodic acid (0.5 mL) was added to **9** or **20** (1 mmol) at r.t. The reaction medium was stirred at this temperature until the substrate was completely consumed as indicated by GPC. After addition of Et_2O (10 mL), the crude medium was neutralized with 8% aqueous $NaHCO_3$. After decantation, the aqueous phase was extracted again with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL) then H_2O (5 mL), and dried over Na_2SO_4. After evaporation of the solvent at room temperature under reduced pressure, the residue was separated and purified over silica gel.

Reaction of 9 with Trifluoroacetic Acid
Column chromatography with PE–Et_2O (80:20) gave **18** (57 mg, 21%) as a colorless oil and further elution with Et_2O (100%) gave **16** (130 mg, 75%) as a yellowish oil.

4-(Trifluoromethyl)benzyl Trifluoroacetate (18)
^1H NMR (300 MHz): δ = 5.41 (s, 2 H, CH_2), 7.51 (d, 2 H, *J* = 8.1 Hz, H2,6), 7.67 (d, 2 H, *J* = 8.1 Hz, H3,5).

^{13}C NMR (75 MHz): δ = 68.41 (CH_2), 114.47 (q, *J* = 285 Hz, CF_3CO_2), 123.82 (q, *J* = 272 Hz, CF_3), 125.93 (q, *J* = 3.7 Hz, C3,5), 128.62 (C2,6), 131.46 (q, *J* = 32.7 Hz, C4), 137.13 (q, *J* = 0.9 Hz, C1), 157.27 (q, *J* = 42.7 Hz, CF_3CO_2).

^{19}F NMR (188 MHz): δ = –63.30 (s, CF_3), –75.30 (s, CF_3CO_2).

MS: *m*/*z* = 272 (M^+·), 253 (M – F), 203 (M – CF_3), 175, 159 (100), 145, 109, 89, 69 (CF_3), 63.

Anal. Calcd for $C_{10}H_6F_6O_2$: C, 44.1; H, 2.2. Found: C, 44.3; H, 2.4.

4-(Trifluoromethyl)benzyl Alcohol (16)
^1H NMR (300 MHz): δ = 2.13 (br s, 1 H, OH), 4.75 (s, 2 H, CH_2), 7.46 (d, 2 H, *J* = 7.9 Hz, H2,6), 7,61 (d, 2 H, *J* = 7.9 Hz, H3,5).

^{13}C NMR (50 MHz): δ = 64.46 (CH_2), 123.85 (q, *J* = 270 Hz, CF_3), 125.48 (q, *J* = 3.8 Hz, C3,5), 126.86 (C2,6), 129.81 (q, *J* = 32.3 Hz, C4), 144.78 (C1).

^{19}F NMR (188 MHz): δ = –62.90 (s).

MS: *m*/*z* = 176 (M^+·), 157 (M – F), 145 (M – CH_2OH), 127, 107 (M – CF_3), 79 (100), 77, 69 (CF_3), 50.

These data were in complete accordance with those of a commercial authentic sample (from Aldrich Co.) and elementary analysis has not been carried out.

3-*tert*-Butyl-4-(trifluoromethyl)benzyl Alcohol (21)
Compound **20** was reacted with CF_3CO_2H as described above. Column chromatography with PE–Et_2O (80:20) followed by Et_2O (100%) gave **21** (57 mg, 40%) as a yellowish oil.

^1H NMR (300 MHz): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.20 (br s, 1 H, OH), 4.74 (s, 2 H, CH_2), 7.29 (d, 1 H, *J* = 8.1 Hz, H6), 7.63 (s, 1 H, H2), 7,71 (d, 1 H, *J* = 8.1 Hz, H5).

^{13}C NMR (50 MHz): δ = 32.06 [q, *J* = 3.4 Hz, $C(CH_3)_3$], 36.64 (CMe_3), 64.75 (CH_2), 124.07 (C6), 125.16 (q, *J* = 274 Hz, CF_3), 127.02 (C2), 127.38 (q, *J* = 30.5 Hz, C4), 128.74 (q, *J* = 7.4 Hz, C5), 144.19, C3), 149.63 (q, *J* = 1.6 Hz, C1).

^{19}F NMR (188 MHz): δ = –53.27 (s).

MS: *m*/*z* = 232 (M^+·), 217 (M – CH_3), 197, 147, 91, 77, 57, 41 (100), 29.

Anal. Calcd for $C_{12}H_{15}F_3O$: C, 62.1; H, 6.5. Found: C, 61.9; H, 6.8.

4-(Trifluoromethyl)benzyl Iodide (19)
Compound **9** was reacted with HI as described above. Column chromatography with PE–Et_2O (80:20) gave **19** (100 mg, 35%) as a reddish oil.

^1H NMR (200 MHz): δ = 4.47 (s, 2 H, CH_2), 7.49 (d, 2 H, *J* = 8.4 Hz, H2,6), 7.57 (d, 2 H, *J* = 8.4 Hz, H3,5).

^{13}C NMR (75 MHz): δ = 33.50 (CH_2), 124.04 (q, *J* = 296 Hz, CF_3), 125.79 (q, *J* = 3.8 Hz, C3,5), 129.03 (C2,6), 130.02 (q, *J* = 20.1 Hz, C4), 143.27 (q, *J* = 1.3 Hz, C1).

^{19}F NMR (188 MHz): δ = –63.06 (s).

MS: *m*/*z* 286 (M^+·), 159 (100, M – I), 140, 109, 89.

Anal. Calcd for $C_8H_6F_3I$: C, 33.6; H, 2.1. Found: C, 33.3; H, 2.3.

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