Towards Enantioselective Nucleophilic Trifluoromethylation

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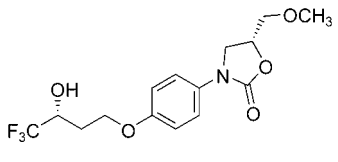
Abstract: Various trifluoroacetamides and trifluoromethanesulfinamides, derived from chiral silylated amino alcohols, have been synthesized with the goal of achieving enantioselective nucleophilic trifluoromethylation. The best results were obtained with (*R*)-phenylglycinol derivatives, but the *ee* values did not exceed 30%.

Keywords: amino alcohols · enantioselectivity · fluorination · nucleophilic addition

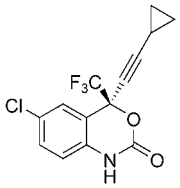
Introduction

Thanks to the intrinsic properties of fluorine, fluorinated organic compounds exhibit unique properties.[1] Among them, trifluoromethyl-substituted molecules constitute a particular class because of their specific properties, such as the high lipophilicity associated with this moiety. These compounds thus find wide application in the pharmaceutical field.[2] Many reliable methods for the introduction of CF_3 moieties into organic compounds have been reported in the last two decades,[3] and anionic trifluoromethylation has in recent years emerged as one of the most powerful strategies. Numerous reagents have been developed to overcome the great instability of the CF_3 anion and to allow nucleophilic trifluoromethylation.[4,5]

Recently, the emergence of drugs such as Befloxatone (antidepressant)[6] (**1**) and Efavirenz (anti-HIV)[7] (**2**), in which the CF_3 moiety is located at an asymmetric center, has underlined another important synthetic challenge: asymmetric trifluoromethylation.



Befloxatone (**1**)



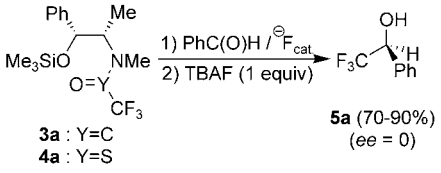
Efavirenz (**2**)

To obtain compounds containing trifluoromethylated asymmetric carbon moieties, the usual strategy is asymmetric reduction of or nucleophilic addition onto a trifluoroacetyl moiety.[8] In contrast, there are very few methods for the asymmetric nucleophilic addition of CF_3. The best enantiomeric excesses have been obtained from diastereoselective methods; that is, addition of CF_3SiMe_3 onto chiral sulfinimides.[9] Another strategy involved chiral trifluoromethylating reagents, achieved by activation of CF_3SiMe_3 with a chiral fluoride[10a] or a chiral Lewis base,[10b] both derived from quinquina alkaloids, but the *ee* values did not usually exceed 50%. Better enantiomeric excesses have sometimes been reached, with cinchonium fluoride and CF_3SiMe_3, but only with especially hindered carbonyl substrates.[10c]

We have recently described new efficient reagents for nucleophilic trifluoromethylation.[5] As some of them bear chiral centers, we focused our interest on their use in asymmetric reactions.

Results and Discussion

As examples, we have described the trifluoroacetamide **3a** and the trifluoromethanesulfinamide **4a** prepared from *O*-silylated ephedrine (Scheme 1). Both are able, under fluoride



3a : Y=C
4a : Y=S

5a (70-90%)
(*ee* = 0)

Scheme 1. Trifluoromethylation of benzaldehyde with **3a** or **4a**.

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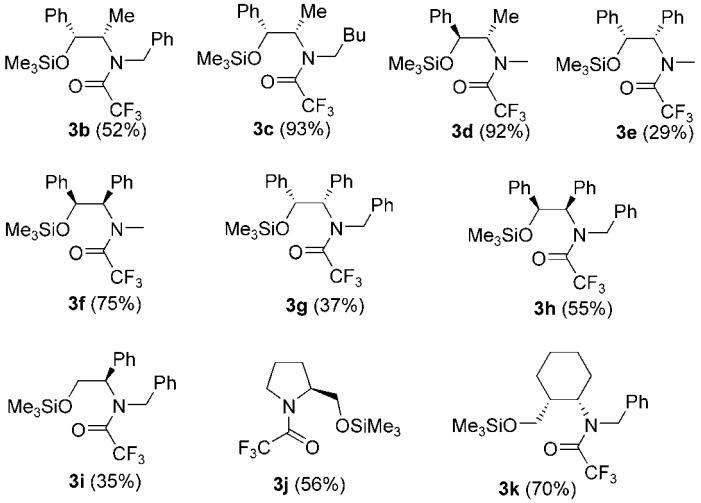
 DOI: 10.1002/chem.200400777

activation conditions, to trifluoromethylate carbonyl compounds.[5] Such reagents, which were obtained in optically pure forms (the two diastereomers of **4a** arising from the chirality at the sulfur atom were separated), seemed to be good candidates for asymmetric trifluoromethylation. However, their use in the trifluoromethylation of benzaldehyde did not give any enantiomeric enrichment of the resulting carbinol.

Faced with these disappointing results, we designed new trifluoroacetamides **3b–3k**, derived from various chiral



amino alcohols, with the goal of achieving stereoselective trifluoromethylation. The reagents **3b–3k** were prepared by the previously described procedure (global isolated yields are given in parentheses).[5a]

These new reagents were tested towards benzaldehyde under two different sets of conditions to evaluate their potential for stereoselective nucleophilic trifluoromethylation (Table 1).

With regard to the ephedrine derivatives, it appeared that increasing the size of the nitrogen substituent reduced the trifluoromethylation yield (Table 1, entries 1–3). As previously described,[5a] (*R*)-phenylglycinol derivative **3i** did not give rise to trifluoromethylation, but only to trifluoroacetyl group migration from nitrogen to oxygen.

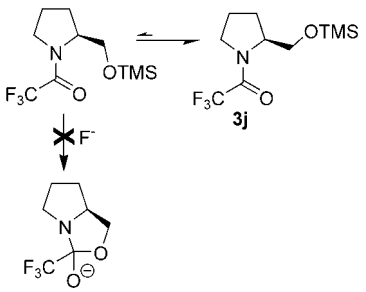
In the case of **3j** no reaction occurred, even with heating, and the starting reagent was recovered. It could be conjectured that the conformation of **3j** is not adapted to the intramolecular nucleophilic attack of the alcoholate, generated by desilylation, onto the trifluoroacetamide moiety (Scheme 2).

Abstract in French: *Une grande variété de trifluoroacétamides et de trifluorométhanesulfinamides, dérivés d'aminoalcools silylés chiraux, a été synthétisée afin de réaliser des trifluorométhylations anioniques énantiosélectives. Les meilleurs résultats ont été obtenus à partir de dérivés du (R)-phénylglycinol mais les excès énantiomériques n'excèdent pas 30 %.*

Table 1. Trifluoromethylation of benzaldehyde with **3**.

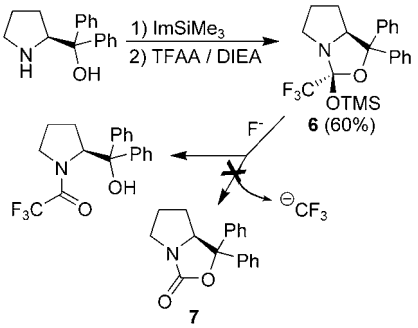
Entry	**3**	**5a**: Yield (*ee*) [%][a] method A[b]	method B[c]
1	**3a**	89 (0)	83 (4)
2	**3b**	32 (12)	71 (10)
3	**3c**	15[d] (n.d.)[e]	4[d] (n.d.)[e]
4	**3d**	83 (3)	86 (5)
5	**3e**	36 (0)	82 (0)
6	**3f**	46 (0)	72 (0)
7	**3g**	53 (0)	83[f] (0)
8	**3h**		86 (1)
9	**3i**	no trifluoromethylation	no trifluoromethylation
10	**3j**	no trifluoromethylation	no trifluoromethylation
11	**3k**	70 (0)	81[f] (1)

[a] Isolated yield: The *ee* values were determined by chiral HPLC (Chiralcel OJ-H column; hexane/*i*PrOH 19:1). [b] Method A: CsF (10 % mol) in DME (1,2-dimethoxyethane) for 24 h at room temperature [c] Method B: TBAT ($Bu_4N^+Ph_3SiF_2^-$; 10 mol %) in THF for 7 h. [d] Yield after six days. [e] n.d.: not determined. [f] Yield after 24 h.



Scheme 2. Conformer equilibrium of **3j**.

To circumvent this problem, we tried to synthesize an analogous reagent from α,α-diphenylprolinol, to favor the right conformer. However, the only product obtained during this synthesis was the bicyclic compound **6** (Scheme 3). Such a substrate, which is an isolated and stable form of the tetrahedral intermediate postulated for the mechanism of trifluoromethylation,[5a] could be an interesting reagent for our purpose, since it was obtained enantiomerically pure. Un-



Scheme 3. Formation and reactivity of **6**.

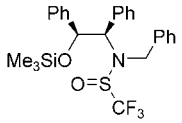
fortunately, no release of CF_3 through desilylation of **6** was observed, no doubt because the formation of the resulting constrained oxazolidinone **7** is not favorable.

From a stereoselective point of view, the results from **3a**–**3k** were rather disappointing, since the *ee* values of the resulting (trifluoromethyl)carbinol did not exceed 12% (Table 1, entry 2), the best result being obtained with the *N*-benzyl norephedrine derivative **3b**. Performing the reaction at lower temperatures (0°C or −78°C) clearly dramatically decreased the reaction kinetics, since only few percents of carbinol were obtained after several days.

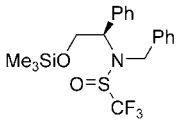
Nevertheless, these results seemed to demonstrate the importance of the nitrogen substituent, which must be larger than a methyl to produce some excess (Table 1, entry 2) but not so bulky as to suppress the yield dramatically (Table 1, entry 3). Furthermore, it seems that a five-membered cyclic intermediate should be more favorable to stereoselectivity than a six-membered one (Table 1, entry 11).

To improve these first encouraging results, we then focused our interest on analogous trifluoromethanesulfinamide derivatives. Indeed, such compounds not only each possess an additional chiral center, because of the chirality of the sulfur(IV) atom, but this atom bears the CF_3 moiety directly, so we supposed that such reagents should be better candidates for enantioselective trifluoromethylation.

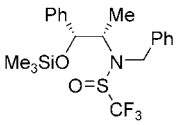
Consequently, various reagents were prepared (**4b**–**4g**), starting from diverse *vic*-amino alcohols, by a previously described procedure (global yields and diastereomeric excesses after purification are given in parentheses).[5b]



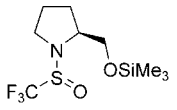
4b (68% *de* = 46%)



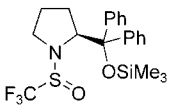
4c (46% *de* = 52%)



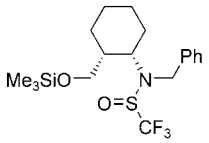
4d (37% *de* = 52%)



4e (20% *de* = 24%)



4f (75% *de* = 10%)



4g (41% *de* = 44%)

Generally these compounds were synthesized with low *de* values, but enriched fractions of one diastereomer were obtained after tedious chromatographic separation and then treated with benzaldehyde as above. Since the two fluorides (CsF, TBAT) had given almost the same results in the previous experiments, only CsF was used as activator here (Table 2).

As far as ephedrine derivatives are concerned, the presence of a chiral center bearing the CF_3 moiety did not seem to have a great influence from a stereoselective point of view. However, the best *ee* values did not arise from the same type of reagents as with trifluoroacetamides, the best enantioselectivity being obtained with **4c** and **4g**, whereas

Table 2. Trifluoromethylation of benzaldehyde with **4**.

Entry	**4** (*de*) [%]	**5a**: yield (*ee*) [%][a]
1	**4a** (100)	73 (0)
2	**4b** (46)	64 (0)
3	**4c** (84)	65 (20)
4	**4d** (84)	68 (0)
5	**4e** (24)	3 (n.d.[b])
6	**4f** (100)	23 (1)
7	**4g** (84)	33 (17)

[a] Isolated yield: The *ee* values were determined by chiral HPLC (Chiralcel OJ-H column; hexane/*i*PrOH 19:1). [b] n.d.: not determined.

the corresponding trifluoroacetamides **3i** and **3k** had not induced any excess. In contrast, the 12% *ee* achieved with **3b** was not obtained with the corresponding sulfinamide **4d**. These results led to the postulation of a geometry of the reactive intermediates arising from trifluoromethanesulfinamides **4** different from that envisaged from trifluoromethylacetamides **3**, presumably because of the geometry of the sulfur atom.

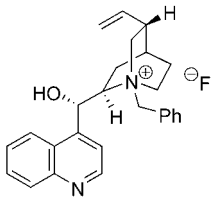
This hypothesis was also confirmed by the experiments with the (*R*)-phenylglycinol derivatives **3i** and **4c**, since the former did not release the trifluoromethyl group but underwent a transfer of the trifluoroacetyl moiety from nitrogen to oxygen,[5a] whereas the latter gave trifluoromethylation with 20% *ee*.

To improve the excess obtained with **4c**, the reaction was carried out under different sets of conditions (Table 3). Lower temperatures decreased the trifluoromethylation

Table 3. Trifluoromethylation with **4c** under various sets of conditions.

Entry	Temperature [°C]	Fluoride [%]	Yield [%]	*ee*
1	0	CsF	49	19
2	−78	CsF	0	–
3	RT	**8**	31	30
4	0	**8**	0	–

yield but did not modify the *ee* value (Table 3, entries 1, 2). The use of a chiral, but hindered, fluoride **8** to initiate the reaction increased the *ee* value slightly but decreased the yield (Table 3, entries 3, 4).



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With regard to enantioselectivity, the disappointing results obtained with reagents **3** and **4** led us to conclude that the various substituents in such reagents had only a moderate influence on the stereoselectivity of the reaction. The largest effect seemed to be that due to the nitrogen substituents, though the presence of too large a one decreased the reaction yield dramatically. This difficult choice between low yield and *ee* is not really consistent with the design of a useful and powerful stereoselective reagent for trifluoromethylation.

Attempts to model the transition states with **3** (cyclic Zimmermann–Traxler type or linear Mukaiyama type) seemed to confirm the weakness of the influence of the substituents other than the nitrogen one. In the case of sulfinamides **4**, the unknown geometry of the sulfur atom in the intermediate reactive species made the modeling more difficult.

Conclusion

Although the trifluoroacetamides and trifluoromethanesulfinamides arising from silylated amino alcohols constitute a family of powerful reagents for nucleophilic trifluoromethylation, their propensity to induce stereoselectivity seems to be limited, since the maximum achieved *ee* is 30%.

The design of a chiral reagent efficient for highly enantioselective nucleophilic trifluoromethylation appears to be a challenge that cannot be solved by the present strategy. Other strategies must be now envisaged, and we are now focusing our interest on these new routes.

Experimental Section

General: DME and THF were dried over Na/benzophenone and freshly distilled. CsF was dried at 300°C overnight and stored at 100°C. Benzaldehyde was freshly purified by distillation prior to use. Other reagents were used as purchased.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300, 75, and 282 MHz, respectively.

Chemical shifts are given in ppm relative to TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal references. Coupling constants are given in Hertz.

Flash chromatography was performed on silica gel 60 M (0.04–0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

Typical procedure: synthesis of 3a: A flame-dried three-necked vessel was successively charged, under nitrogen, with ephedrine (6.6 g, 40 mmol) and dichloromethane (40 mL). The resulting mixture was cooled to 0°C before addition of *N*-(trimethylsilyl)imidazole (6 mL, 41 mmol). The reaction medium was stirred at 0°C for 40 min and then allowed to warm to room temperature and kept stirring for 2 h. After this period, diisopropylethylamine (7.2 mL, 41.4 mmol) was added, and the mixture was again cooled to 0°C. A solution of trifluoroacetic anhydride (5.6 mL, 40 mmol) in CH_2Cl_2 (16 mL) was then added dropwise over 1.5 h. After this addition, the temperature was kept at 0°C for 10 min, then raised to room temperature. After stirring for 4 h, the reaction medium was washed with 6% aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by chromatography over silica gel.

***N*-Trifluoroacetyl-*O*-trimethylsilylephedrine (3a)**: (2 rotamers: 80/20; white solid). M.p. 51–52°C; ^{1}H NMR: δ = 7.25–7.38 (m, 5H), 5.01 and 4.84 (d, ^3J(H,H) = 4.4 Hz, 1H), 4.38 (qd, ^3J(H,H) = 6.9, ^3J(H,H) = 4.6 Hz, 0.8H), 4.07 (qqd, ^3J(H,H) = 6.8, ^5J(H,F) = 1.1, ^3J(H,H) = 4.6 Hz, 0.2H), 3.05 (q, ^5J(H,F) = 1.6 Hz, 3H); 1.26 and 1.19 (d, ^3J(H,H) = 6.6 and 7.1 Hz, 3H), 0.03 ppm (s, 9H); ^{13}C NMR: δ = 157.5 (q, ^2J(C,F) = 35.4 Hz), 141.9 and 141.6, 128.7 and 128.5, 128.3 and 127.9, 126.5 and 126.5, 117.0 and 116.9 (q, ^1J(C,F) = 287.6 and 288.1 Hz), 78.1 and 76.2, 59.0, 58.7 (q, ^4J(C,F) = 3.1 Hz), 32.2 (q, ^4J(C,F) = 3.8 Hz), 30.8, 12.8 and 10.2, 0.3 and 0.2 ppm; ^{19}F NMR: δ = −68.28 (0.2) and −70.57 ppm (0.8); elemental analysis calcd (%) for $C_{15}H_{22}F_3NO_2Si$: C 54.03, H 6.65, N 4.20, Si 8.42; found: C 53.75, H 6.58, N 4.21, Si 8.90.

***N*-Trifluoroacetyl-*N*-benzyl-*O*-trimethylsilylephedrine (3b)**: (2 rotamers: 80/20; yellow oil). ^{1}H NMR: δ = 7.40–7.00 (m, 10H), 5.25 (d, ^3J(H,H) = 7.9 Hz, 0.8H), 5.05 (d, ^2J(H,H) = 15.4 Hz, 0.2H), 4.99 (d, ^3J(H,H) = 3.6 Hz, 0.2H), 4.73 (d, ^2J(H,H) = 15.4 Hz, 0.2H), 4.50 (d, ^2J(H,H) = 15.4 Hz, 0.8H; H_{3a}), 4.20 (m, 0.2H), 3.50–3.30 (m, 1.6H), 1.28 (d, ^3J(H,H) = 6.7 Hz, 2.4H), 1.19 (d, ^3J(H,H) = 6.7 Hz, 0.6H), 0.02 (s, 7.2H), 0.01 ppm (s, 1.8H); ^{13}C NMR: δ = 157.6 (q, ^2J(C,F) = 35.1 Hz), 142.6, 141.6, 137.8, 135.6, 129.1, 129.0, 128.8, 128.6, 128.4, 128.1, 127.49, 127.45, 127.0, 126.9, 126.8, 126.6, 117.2 (q, ^1J(C,F) = 287.8 Hz), 117.0 (q, ^1J(C,F) = 288.3 Hz), 79.0, 74.4, 63.8, 59.4 (q, ^4J(C,F) = 3.4 Hz), 52.8 (q, ^4J(C,F) = 3.5 Hz), 48.1, 14.1, 12.9, 0.4, 0.0 ppm; ^{19}F NMR: δ = −68.00 (0.20), −69.50 ppm (0.80); elemental analysis calcd (%) for $C_{21}H_{26}F_3NO_2Si$: C 61.59, H 6.40, N 3.42, Si 6.86; found: C 61.71, H 6.45, N 3.31, Si 6.74.

***N*-Trifluoroacetyl-*N*-pentyl-*O*-trimethylsilylephedrine (3c)**: (2 rotamers: 80/20; yellow oil). ^{1}H NMR: δ = 7.40–7.20 (m, 5H), 5.25 (d, ^3J(H,H) = 8.0 Hz, 0.8H), 4.83 (d, ^3J(H,H) = 4.5 Hz, 0.2H), 4.00 (qd, ^3J(H,H) = 4.5, ^3J(H,H) = 6.6 Hz, 0.2H), 3.57 (m, 0.2H), 3.37 (bq, ^3J(H,H) = 6.6 Hz, 0.8H), 3.05 (td, ^2J(H,H) = 15.2, ^3J(H,H) = 7.3 Hz, 0.8H), 2.46 (td, ^2J(H,H) = 15.2, ^3J(H,H) = 7.3 Hz, 0.8H), 1.78 (m, 0.2H), 1.50 (d, ^3J(H,H) = 6.6 Hz, 2.4H), 1.40–1.00 (m, 6.6H), 0.91 (t, ^3J(H,H) = 6.8 Hz, 0.6H), 0.83 (t, ^3J(H,H) = 7.2 Hz, 2.4H), 0.02 (s, 1.8H), 0.01 ppm (s, 7.2H); ^{13}C NMR: δ = 157.1 and 156.9 (q, ^2J(C,F) = 35.4 Hz), 142.5, 141.7, 128.6, 128.3, 128.2, 128.1, 126.6, 126.5, 117.0 and 116.6 (q, ^1J(C,F) = 286.7 Hz; CF_3), 78.6, 74.4, 60.8, 58.9 (q, ^4J(C,F) = 3.2 Hz), 29.8, 29.1, 29.0, 28.9, 22.7, 22.52, 22.49, 22.4, 14.3, 14.1, 0.29, 0.27 ppm; ^{19}F NMR: δ = −68.33 (0.20), −70.60 ppm (0.80); elemental analysis calcd (%) for $C_{19}H_{30}O_2F_3NO_2Si$: C 58.58, H 7.76, N 3.60, Si 7.21; found: C 58.65, H 7.94, N 3.7, Si 6.83.

***N*-Trifluoroacetyl-*N*-methyl-*O*-trimethylsilylpseudoephedrine (3d)**: (2 rotamers: 60/40; white solid). Mp: 60–61°C; ^{1}H NMR: δ = 7.38–7.33 (m, 5H), 4.78 (d, ^3J(H,H) = 7.5 Hz, 0.6H), 4.63 (br s, 0.6H), 4.56 (dq, ^3J(H,H) = 8.2, ^6J(H,F) = 1.2 Hz, 0.4H), 4.10 (dqq, ^3J(H,H) = 8.2, ^3J(H,H) = 6.8, ^4J(H,F) = 1.2 Hz, 0.4H), 3.08 (q, ^4J(H,F) = 6.8 Hz, 1.8H), 2.97 (s, 1.2H), 1.11 (d, ^3J(H,H) = 6.8 Hz, 1.8H), 1.04 (d, ^3J(H,H) = 6.8 Hz, 1.2H), 0.01 (s, 5.4H), −0.04 ppm (s, 3.6H); ^{13}C NMR: δ = 158.2 and 157.3 (q, ^2J(C,F) = 34.9 Hz), 141.9 and 141.8, 128.9 and 128.6, 128.6 and 128.2, 127.5 and 127.3, 117.3 (q, ^1J(C,F) = 287.7 Hz), 117.1 (q, ^1J(C,F) = 288.3 Hz), 76.3 and 76.1, 59.2 (q, ^4J(C,F) = 2.9 Hz), 58.0 (br s), 31.0 (br s), 28.4, 14.9, and 13.6 (C_3), −0.1 and −0.12 ppm; ^{19}F NMR: δ = −67.87 (0.40), −70.69 ppm (0.60); elemental analysis calcd (%) for $C_{15}H_{22}F_3NO_2Si$: C 54.03, H 6.65, N 4.20, Si 8.42; found: C 54.09, H 6.46, N 4.37, Si 8.28.

(1*S*,2*R*)-*N*-Trifluoroacetyl-*N*-methyl-*O*-trimethylsilyl-1,2-diphenylethanol (3f): (2 rotamers: 90/10; white solid). M.p. 106°C; ^{1}H NMR: δ = 7.60–7.00 (m), 5.74 (d, ^3J(H,H) = 7.5 Hz, 0.9H), 5.51 (d, ^3J(H,H) = 7.5 Hz, 0.9H), 5.39 (d, ^3J(H,H) = 6.2 Hz, 0.1H), 5.21 (d, ^3J(H,H) = 6.2 Hz, 0.1H), 3.05 (s, 0.3H), 2.89 (t, ^5J(H,F) = 1.7 Hz, 2.7H), 0.04 (s, 0.9H), 0.02 ppm (s, 8.1H); ^{13}C NMR: δ = 157.4 (q, ^2J(C,F) = 35.5 Hz), 157.3 (q, ^2J(C,F) = 35.1 Hz), 141.0, 140.8, 136.1, 135.9, 130.3, 129.8, 129.0, 128.8, 128.7, 128.64, 128.58, 128.5, 127.3, 127.1, 116.8 (q, ^1J(C,F) = 288.3 Hz), 117.1 (q, ^1J(C,F) = 288.1 Hz), 74.91, 74.86, 66.2 (q, ^4J(C,F) = 2.7 Hz), 65.8, 32.7 (q, ^4J(C,F) = 3.8 Hz), 32.4, 0.4, 0.3 ppm; ^{19}F NMR: δ = −66.61 (0.10), −70.43 ppm (0.90); elemental analysis calcd (%) for $C_{20}H_{24}F_3NO_2Si$: C 60.74, H 6.12, N 3.54, Si 7.10; found: C 60.47, H 6.25, N 3.75, Si 6.93.

(1*S*,2*R*)-*N*-Trifluoroacetyl-*N*-benzyl-*O*-trimethylsilyl-1,2-diphenyl-ethanol (3h): (2 rotamers: 95/5; yellow oil). ^{1}H NMR: δ = 7.40–7.17 (m, 13H), 7.15–7.14 (m, 2H), 5.96 (d, ^3J(H,H) = 8.9 Hz, 1H), 4.30 (d, ^1J(H,H) = 15.9 Hz, 1H), 4.21 (d, ^3J(H,H) = 8.9 Hz, 1H), 3.95 (d, ^1J(H,H) = 15.9 Hz, 1H), 0.26 ppm (s, 9H); ^{13}C NMR: δ = 158.1 (q, ^2J(C,F) = 35.1 Hz), 142.2, 137.8, 134.5, 130.7, 129.02, 128.99, 128.6, 128.5, 128.4, 128.3, 127.4, 127.2, 116.8 (q, ^1J(C,F) = 288.5 Hz), 73.4, 71.8, 53.0 (q, ^4J(C,F) = 3.6 Hz), 0.09 ppm; ^{19}F NMR: δ = −66.62 (0.05), −69.07 ppm (0.95); elemental analysis calcd (%) for $C_{26}H_{28}F_3NO_2Si$: C 66.22, H 5.98, N 2.97, Si 5.96; found: C 66.38, H 6.02, N 2.86, Si 5.87.

(*R*)-*N*-Trifluoroacetyl-*N*-benzyl-*O*-trimethylsilylphenylglycinol (3i): (2 rotamers: 50/50; yellow oil). ^{1}H NMR: δ = 7.00–7.50 (m, 10H), 5.36 (br. t,

^3J(H,H) = 6.7 Hz, 0.5 H), 4.96 (br. dd, ^3J(H,H) = 8.0, ^3J(H,H) = 6.3 Hz, 0.5 H), 4.69 (d, ^2J(H,H) = 15.1 Hz, 0.5 H), 4.67 (s, 2 H), 4.43 (dd, ^2J(H,H) = 10.4, ^3J(H,H) = 8.0 Hz, 0.5 H), 4.27 (d, ^2J(H,H) = 15.1 Hz, 0.5 H), 3.94–4.12 (m, 1.5 H), 0.12 and 0.11 ppm (s, 9 H); ^{13}C NMR: δ = 158.6 and 158.1 (q, ^2J(C,F) = 34.9 Hz), 137.1, 136.6, 135.9, 135.8, 129.3, 129.0, 128.9, 128.61, 128.58, 128.45, 128.42, 128.2, 128.0, 127.6, 117.4 and 117.1 (q, ^1J(C,F) = 288.2 Hz), 61.9, 62.2, 61.2 (q, ^4J(C,F) = 2.6 Hz), 61.4, 51.5 (q, ^4J(C,F) = 3.5 Hz), 47.5, −0.3, −0.5 ppm; ^{19}F NMR: δ = −66.55 (0.5), −68.69 ppm (0.5); elemental analysis calcd (%) for $C_{20}H_{24}F_3NO_2Si$: C 60.74, H 6.12, N 3.54, Si 7.10; found: C 60.62, H 6.23, N 3.61, Si 6.85.

(*S*)-*N*-Trifluoroacetyl-*O*-trimethylsilyl-2-pyrrolidinemethanol (3j): (2 rotamers: 90/10; yellow oil). ^{1}H NMR: δ = 4.22 (brm, 1 H), 3.80 (dd, ^2J(H,H) = 10.3, ^3J(H,H) = 5.5 Hz, 1 H); 3.70 (dd, ^2J(H,H) = 10.3, ^3J(H,H) = 2.9 Hz, 1 H), 3.65 (m, 2 H), 2.25–1.80 (m, 4 H), 0.13 (s, 8.1 H), 0.11 ppm (s, 0.9 H); ^{13}C NMR: δ = 156.2 and 155.9 (q, ^2J(C,F) = 36.6 Hz), 116.8 and 116.7 (q, ^1J(C,F) = 287.5 Hz), 63.6 (q, ^5J(C,F) = 1.3 Hz), 61.6, 60.7, 59.6 (q, ^4J(C,F) = 2.4 Hz), 48.0, 47.8 (q, ^4J(C,F) = 3.5 Hz), 28.7, 26.8, 24.9 (q, ^5J(C,F) = 1.0 Hz), 20.9, −0.4, −0.5 ppm; ^{19}F NMR: δ = −70.91 (0.10), −73.02 ppm (0.90); elemental analysis calcd (%) for $C_{10}H_{18}F_3NO_2Si$: C 44.59, H 6.74, N 5.20, Si 10.43; found: C 44.47, H 6.83, N 5.36, Si 10.22.

(1*R*,2*S*)-*N*-Trifluoroacetyl-*O*-trimethylsilyl-2-benzylamino-cyclohexanemethanol (3k): (2 rotamers: 70/30; colorless oil). ^{1}H NMR: δ = 7.41–7.22 (m, 3 H), 7.21–7.14 (m, 2 H), 5.12 (d, ^2J(H,H) = 15.8 Hz, 0,3 H), 4.80 (d, ^2J(H,H) = 18.1 Hz, 0.7 H), 4.66 (d, ^2J(H,H) = 18.1 Hz, 0.7 H), 4.40 (d, ^2J(H,H) = 15.8 Hz, 0.3 H), 4.22 (m, 1 H), 3.80 (m, 2 H), 2.41 (brs, 0.7 H), 2.16 (brs, 0.3 H), 2.04–1.66 (m, 3 H), 1.64–1.12 (m, 5 H), 0.15 ppm (s, 9 H); ^{13}C NMR: δ = 158.2 (q, ^1J(C,F) = 35.1 Hz), 158.1 (q, ^1J(C,F) = 34.9 Hz), 138.4, 137.7, 129.0, 128.9, 127.7, 127.3, 126.7, 126.1, 117.3 (q, ^1J(C,F) = 287.1 Hz), 116.9 (q, ^1J(C,F) = 288.9 Hz), 61.7, 61.5, 60.7, 59.7 (q, ^4J(C,F) = 2.7 Hz), 49.8 (q, ^4J(C,F) = 3.8 Hz), 49.0, 43.1, 38.8, 29.5, 28.6, 27.6, 26.7, 26.6, 25.5, 21.03, 21.0, −0.3 ppm; ^{19}F NMR: δ = −68.67 (0.30), −69.21 ppm (0.70); elemental analysis calcd (%) for $C_{19}H_{28}F_3NO_2Si$: C 58.89, H 7.28, N 3.61, Si 7.25; found: C 59.07, H 7.33, N 3.88, Si 7.13.

Synthesis of *N*-trifluoromethanesulfinyl-*O*-trimethylsilylephedrine (4a)

[CF_3SO^+] solution: A flame-dried three-necked vessel was successively charged, under nitrogen, with potassium triflinate (CF_3SO_2K, 3.5 g, 20 mmol), dichloromethane (60 mL), and $POCl_3$ (935 μL, 10 mmol). The reaction medium was stirred at room temperature for 40 min.

Synthesis: A flame-dried three-necked vessel was successively charged, under nitrogen, with ephedrine (1.65 g, 10 mmol) and dichloromethane (47 mL). The resulting mixture was cooled to 0 °C before addition of *N*-(trimethylsilyl)imidazole (1.5 mL, 10.2 mmol). The reaction mixture was stirred at 0 °C for 20 min and was then allowed to warm to room temperature and kept stirring for 2 h. After this period, diisopropylethylamine (3.5 mL, 20 mmol) was added and the mixture was again cooled to 0 °C. The [CF_3SO^+] solution was then added over 1 h. After the addition, the temperature was kept at 0 °C for 10 min, then raised to room temperature. After stirring for 24 h, the reaction mixture was washed with 6% aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by chromatography over silica gel.

***N*-Trifluoromethanesulfinyl-*O*-trimethylsilylephedrine (4a)**: (Colorless oil/*de* = 20%). ^{1}H NMR: δ = 7.23–7.35 (m, 5 H), 4.85 (d, ^3J(H,H) = 3.9 Hz, 0.6 H), 4.68 (d, ^3J(H,H) = 5.7 Hz, 0.4 H), 3.70 (dq, ^3J(H,H) = 5.7, ^3J(H,H) = 7.0 Hz, 0.4 H), 3.58 (dq, ^3J(H,H) = 3.9, ^3J(H,H) = 7.0 Hz, 0.6 H), 2.84 (q, ^5J(H,H) = 1.4 Hz, 1.8 H), 2.70 (q, ^5J(H,H) = 1.8 Hz, 1.2 H), 1.32 (d, ^3J(H,H) = 7.0 Hz, 1.2 H), 1.22 (d, ^3J(H,H) = 7.0 Hz, 1.8 H), 0.06 (s, 5.4 H), 0.04 ppm (s, 3.6 H); ^{13}C NMR: δ = 141.8, 141.4, 128.7, 128.6, 128.4, 128.1, 127.0, 126.8, 124.5 (q, ^1J(C,F) = 343.1 Hz), 124.5 (q, ^1J(C,F) = 341.6 Hz), 77.9, 77.0, 64.5 (brs), 62.8, 29.1, 26.6, 13.9, 13.2, 0.34, 0.32 ppm; ^{19}F NMR: δ = −75,03 (0.6), −75.27 ppm (0.4); elemental analysis calcd (%) for $C_{14}H_{22}F_3NO_2SSi$: C 47.57, H 6.27, N 3.96, S 9.07, Si 7.95; found: C 47.69, H 6.56, N 3.91, S 9.40, Si 8.20.

(1*S*,2*R*)-N-Trifluoromethanesulfinyl-*N*-benzyl-*O*-trimethylsilyl 1,2-diphenyl-ethanol (4b): (Yellow oil/*de* = 60%). ^{1}H NMR: δ = 7.47–6.92 (massif, 10 H), 5.32 (d, ^3J(H,H) = 5.1 Hz, 0.8 H), 5.21 (d, ^3J(H,H) = 6.4 Hz, 0.2 H), 4.54–4.40 (m, 1 H), 4.37–4.21 (m, 1.8 H), 4.09 (d, ^2J(H,H) = 15.3 Hz, 0.2 H), 0.04 (s, 7.2 H), −0.1 ppm (s, 1.8 H); ^{13}C NMR: δ = 141.2, 140.8, 136.8, 136.6, 135.5, 135.2, 130.4, 130.0, 129.7, 129.6, 129.2, 129.1, 128.9, 128.81, 128.75, 128.7, 128.57, 128.55, 128.43, 128.40, 128.38, 128.2, 127.8, 124.9 (q, ^1J(C,F) = 343.0 Hz), 124.7 (q, ^1J(C,F) = 341.0 Hz), 77.0, 76.0, 69.6, 69.3, 48.6, 48.4, 0.5, 0.2 ppm; ^{19}F NMR: δ = −73.16 (0.20), −73.56 ppm (0.80); elemental analysis calcd (%) for $C_{25}H_{28}F_3NO_2SSi$: C 61.07, H 5.74, N 2.85, S 6.52, Si 5.71; found: C 61.17, H 5.67, N 2.73, S 6.44, Si 5.68.

(*R*)-*N*-Trifluoromethanesulfinyl-*N*-benzyl-*O*-trimethylsilylphenylglycinol (4c): (Yellow oil/dia. Maj.). ^{1}H NMR: δ = 7.43–7.18 (m, 10 H), 4.54 (d, ^2J(H,H) = 15.4 Hz, 1 H), 4.53 (bdd, ^3J(H,H) = 8.9, ^3J(H,H) = 5.6 Hz, 1 H), 4.23 (d, ^2J(H,H) = 15.4 Hz, 1 H), 4.01 (dd, ^2J(H,H) = 10.9, ^3J(H,H) = 8.9 Hz, 1 H), 3.86 (dd, ^2J(H,H) = 10.9, ^3J(H,H) = 5.6 Hz, 1 H), 0,14 ppm (s, 9 H); ^{13}C NMR: δ = 137.5, 135.9, 129.3, 129.2, 128.99, 128.93, 128.5, 128.3, 127.1 (q, ^1J(C,F) = 342.0), 65.1, 63.7, 47.5, 0.4 ppm; ^{19}F NMR: δ = −74.09 ppm; elemental analysis calcd (%) for $C_{19}H_{24}F_3NO_2SSi$: C 54.92, H 5.82, N 3.37, S 7.72, Si 6.76; found: C 54.68, H 6.07, N 3.13, S 7.89, Si 6.53.

(1*R*,2*S*)-*N*-Trifluoromethanesulfinyl-*N*-benzyl-*O*-trimethylsilylephedrine (4d): (Yellow oil/*de* = 80%). ^{1}H NMR: δ = 7.49–7.09 (m, 10 H), 4.88 (d, ^3J(H,H) = 3.0 Hz, 0.9 H), 4.72 (d, ^2J(H,H) = 15.6 Hz, 0.9 H), 4.56 (d, ^2J(H,H) = 14.9 Hz, 0.1 H), 4.54 (d, ^3J(H,H) = 6.0 Hz, 0.1 H), 4.24 (d, ^2J(H,H) = 15.6 Hz, 0.9 H), 4.07 (d, ^2J(H,H) = 14.9 Hz, 0.1 H), 3.56 (m, 0.1 H), 3.36 (qd, ^3J(H,H) = 3.0, ^3J(H,H) = 7.1 Hz, 0.9 H), 1.42 (d, ^3J(H,H) = 7.0 Hz, 0.3 H), 1.20 (d, ^3J(H,H) = 7.2 Hz, 2.7 H), 0.15 (s, 8.1 H), 0.00 ppm (s, 0.9 H); ^{13}C NMR: δ = 141.7, 136.1, 129.3, 129.1, 128.5, 128.4, 128.0, 126.8, 124.8 (q, ^1J(C,F) = 340.9 Hz), 74.9, 61.2, 47.8, 14.0, 0.5 ppm; ^{19}F NMR: δ = −73.30 (0.10), −75.73 ppm (0.90); elemental analysis calcd (%) for $C_{20}H_{26}F_3NO_2SSi$: C 55.92, H 6.10, N 3.26, S 7.46, Si 6.54; found: C 56.01, H 5.89, N 3.40, S 7.27, Si 6.38.

(*S*)-*N*-Trifluoromethanesulfinyl-*O*-trimethylsilyl-2-pyrrolidinemethanol (4e): (Yellow oil/*de* = 0%). ^{1}H NMR: δ = 3.88 (m, 2 H), 3.62 (m, 2 H), 3.28 (m, 0.5 H), 3.07 (m, 0.5 H), 2.17–1.70 (m, 4 H), 0.15 (s, 4.5 H), 0.11 ppm (s, 4.5 H); ^{13}C NMR: δ = 126.6 (q, ^1J(C,F) = 338.5 Hz), 124.2 (q, ^1J(C,F) = 337.0 Hz), 65.9, 65.5, 64.0, 61.5, 46.6, 43.8, 28.7, 26.0, 24.6, 23.1, 0.45, 0.45 ppm; ^{19}F NMR: δ = −74.03 (0.50), −75.20 ppm (0.50); elemental analysis calcd (%) for $C_9H_{18}F_3NO_2SSi$: C 37.35, H 6.27, N 4.84, S 11.08, Si 9.71; found: C 37.51, H 6.36, N 5.03, S 10.95, Si 9.37.

(*S*)-*N*-Trifluoromethanesulfinyl-*O*-trimethylsilyl-1,1-diphenyl-2-pyrrolidinemethanol (4f): (Yellow oil/dia. maj.). ^{1}H NMR: δ = 7.52–7.27 (m, 10 H), 4.89 (dd, ^3J(H,H) = 9.2, ^3J(H,H) = 4.0 Hz, 1 H), 3.69 (m, 1 H), 2.16 (m, 1 H), 2.09–1.87 (m, 2 H), 1.55 (m, 1 H), 0.95 (m, 1 H), −0.19 ppm (s, 9 H); ^{13}C NMR: δ = 142.5, 141.8, 130.03, 129.98, 128.6, 128.3, 128.0, 127.5, 124.3 (q, ^1J(C,F) = 336.5 Hz), 83.4, 73.3, 43,1, 28.6, 26.0, 2.0 ppm; ^{19}F NMR: δ = −73.78 ppm; elemental analysis calcd (%) for $C_{21}H_{26}F_3NO_2SSi$: C 57.12, H 5.93, N 3.17, S 7.26, Si 6.36; found: C 57.29, H 5.72, N 3.33, S 6.92, Si 6.69.

(*S*)-*N*-Trifluoromethanesulfinyl-*O*-trimethylsilyl-1,1-diphenyl-2-pyrrolidinemethanol (4f): (Yellow oil/dia. Min.). ^{1}H NMR: δ = 7.56–7.29 (m, 10 H), 4.87 (dd, ^3J(H,H) = 8.9, ^3J(H,H) = 2.7 Hz, 1 H), 3.16 (m, 1 H), 2.54 (m, 1 H), 2.20 (ddd, ^3J(H,H) = 17.1, ^3J(H,H) = 8.9, ^2J(H,H) = 13.5 Hz, 1 H), 1.97 (m, 1 H), 1.56 (m, 1 H), 0.81 (dddd, ^3J(H,H) = 17.1, ^2J(H,H) = 12.5, ^3J(H,H) = 8.3, ^3J(H,H) = 6.1 Hz, 1 H), −0.13 ppm (s, 9 H); ^{13}C NMR: δ = 142.4, 141.6, 130.2, 129.9, 128.7, 128.5, 128.1, 127.8, 125.4 (q, ^1J(C,F) = 346.5 Hz), 83.7, 68.9, 45.8, 28.2, 23.6, 2.0 ppm; ^{19}F NMR: δ = −72.33 ppm; elemental analysis calcd (%) for $C_{21}H_{26}F_3NO_2S$-Si: C 57.12, H 5.93, N 3.17, S 7.26, Si 6.36; found: C 56.99, H 5.85, N 3.26, S 7.36, Si 6.51.

(1*R*,2*S*)-*N*-Trifluoromethanesulfinyl-*O*-trimethylsilyl-2-benzylaminocyclohexanemethanol (4g): (Colorless oil/*de* = 20%). ^{1}H NMR: δ = 7.45–7.24 (m, 5 H), 4.67 (d, ^2J(H,H) = 15.6 Hz, 0.6 H), 4.66 (d, ^2J(H,H) = 15.8 Hz, 0.4 H), 4.35 (d, ^2J(H,H) = 15.8 Hz, 0.4 H), 4.24 (d, ^2J(H,H) = 15.6 Hz, 0.6 H), 3.91 (dd, ^3J(H,H) = 6.0, ^2J(H,H) = 12.0 Hz, 0.4 H), 3.70 (m, 1.6 H), 3.37 (m, 1 H), 2.15 (m, 0.4 H), 2.03 (m, 0.6 H), 1.97–1.59 (m, 5 H), 1.49–1.11 (m, 3 H), 0.16 ppm (s, 9 H); ^{13}C NMR: δ = 135.8, 135.7, 129.3, 129.2, 128.7, 128.6, 128.4, 128.2, 124.7 (q, ^1J(C,F) = 342.0 Hz), 124.5 (q, ^1J(C,F) = 340.9 Hz), 60.9, 60.8, 60.6, 60.1, 47.3, 46.8, 39.3, 38.7,

28.9, 28.8, 28.0, 26.9, 26.49, 26.41, 21.5, 21.1, −0.2 ppm; ^{19}F NMR: δ = −74.40 (0.40), −75.24 ppm (0.60); elemental analysis calcd (%) for $C_{18}H_{28}F_3NO_2SSi$: C 53.04, H 6.92, N 3.44, S 7.87, Si 6.89; found: C 53.13, H 7.06, N 3.71, S 7.74, Si 7.05.

Typical procedure for trifluoromethylation with 3 or 4 and CsF: Dried CsF (15 mg, 0.1 equiv) was added to a solution of **3** or **4** (1 mmol) and the electrophile (1 mmol) in DME (1 mL). After 24 h, the crude product was desilylated with TBAF in THF (1 M, 1 mL) for 1 h and extracted with pentane and brine. The organic phase was dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude products were purified by chromatography over silica gel.

Typical procedure for trifluoromethylation with 2 and TBAT: A solution of tetrabutylammonium triphenyldifluorosilicate (TBAT, 54 mg, 0.1 equiv) in THF (0.5 mL) was added dropwise over 15 min to a stirred solution of **3** or **4** (1 mmol) and the electrophile (1 mmol) in THF (1 mL). After 6 h, the crude mixture was desilylated with TBAF in THF (1 M, 1 mL) for 1 h, and then extracted with pentane and brine. The organic phase was dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude products were purified by flash chromatography over silica gel.

Acknowledgement

We thank the CNRS and Rhodia Co. for financial support and Rhodia - Co. for a generous gift of potassium triflinate.

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Received: July 29, 2004
Published online: December 15, 2004