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# Lewis acid activation of chiral 2-trifluoromethyl-1,3-oxazolidines. Application to the stereoselective synthesis of trifluoromethylated amines, α- and β-amino acids

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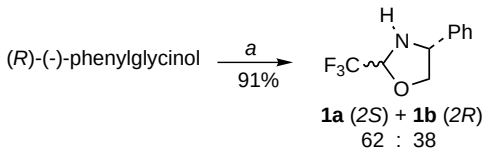
**Abstract**—The reaction of chiral 2-trifluoromethyl-1,3-oxazolidines with various silylated nucleophiles under Lewis acid activation provides a stereoselective route to functionalized α-trifluoromethylamines. This methodology was successfully applied to the diastereoselective synthesis of trifluoromethylated homoallylic and propargylic amines, trifluoromethylated α-amino nitrile, β-aminoketone and β-aminoester. The α-amino nitrile and the β-amino ester were converted into (+)-3,3,3-trifluoroalanine and (+)-4,4,4-trifluoro-3-aminobutanoic acid in a one-step procedure. 

Trifluoromethylated amines are important building blocks for the synthesis of bioactive compounds because of the unique electron withdrawing properties of the trifluoromethyl group.[1] The development of stereoselective methods for the synthesis of α-trifluoromethylated amines is then a current challenge in organofluorine chemistry.[2] Most of the existing stereoselective methods for their synthesis use reduction or organometallics addition to fluorinated imino- or enamino-compounds[3] or direct trifluoromethylation of a chiral sulfinylimine.[4] A stereoselective approach developed by Mikami et al. consists of lithium aluminum hydride reduction or organometallics reactions with (*R*)-phenylglycinol and fluoral derived oxazolidines and hemiacetals.[5] To achieve good yields and high stereoselectivity this method requires the separation of both oxazolidines diastereomer or the use of a large excess of organometallic reagent for the reaction on the hemiacetals. As a limitation, this reaction was only described for phenyl, benzyl and methyl group introduction. In order to investigate new potentialities of the use of 2-trifluoromethyl-1,3-oxazolidines toward the synthesis of enantiopure trifluoromethylamino compounds, we undertook the study of their Lewis acid-mediated reactions with silylated nucleophiles. This methodology will provide a stereoselective strategy for the introduction of various functionalized side chains. Although several examples of nucleophilic addition to trifluoromethyl-iminium ions and related reactions are described in the literature,[6] to our knowledge, no example is reported with silylated nucleophiles in the asymmetric series.

Chiral 2-trifluoromethyl-oxazolidines **1a**,**b** were readily prepared in high yield following the literature procedure[5a] starting from (*R*)-(−)-phenylglycinol (Scheme 1).




**Scheme 1.** Synthesis of 2-trifluoromethyl-1,3-oxazolidines. (a) Trifluoroacetaldehyde ethylhemiacetal, PPTS 0.1 equiv., toluene, Dean Stark distillation.

The use of (*R*)-(−)-phenylglycinol as a chiral auxiliary in the Strecker synthesis constitutes a highly stereoselective access to α-amino acids.[7] Because of the great interest of fluorine-containing amino acids,[8] we carried out the reaction of **1a**,**b** with trimethylsilyl cyanide promoted by Lewis acids (Table 1). The aminonitriles **2a**,**b** were obtained in high yield with $BF_3{\cdot}OEt_2$ (1.5 equiv.) or with a catalytic amount of TMSOTf as a diastereomeric mixture. The major diastereomer **2a**[9]

*Keywords*: fluorine; oxazolidines; iminium; asymmetric synthesis; amino acids.

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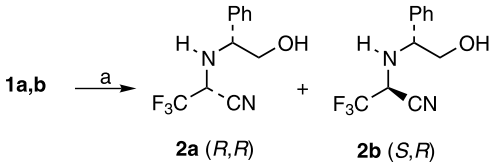
**Table 1.** Strecker reactions




(a) TMSCN (1.5 equiv.), Lewis acid, −78°C to rt, 12 h.

| Entry | **1a**:**1b** | Lewis acid | Yield (%)[a] | **2a**:**2b**[b] |
|---|---|---|---|---|
| 1 | 62:38 | $BF_3{\cdot}OEt_2$ (1.5 equiv.) | 91 | 83:17 |
| 2 | 87:13 | TMSOTf (0.1 equiv.) | 87 | 81:19 |
| 3 | 20:80 | TMSOTf (0.1 equiv.) | 84 | 83:17 |

[a] Isolated yields.

[b] Determined by $^{19}F$ NMR integration of the $CF_3$ signals of each diastereomer in the crude mixture. Both isomers can be separate by silica gel chromatography.

was separated by flash column chromatography. An interesting feature of this reaction is that the same diastereomeric ratio (**2a**:**2b** 83:17) was achieved irrespective of the starting oxazolidines **1a**:**1b** mixture (Table 1, entries 2 and 3). The major outcome of this observation is that the reaction can be performed from the diastereomeric mixture of oxazolidines avoiding a separation step.

These results strongly suggest the formation of an iminium as a key intermediate; the nucleophilic attack taking place at the less hindered *re* face. The (*R*,*R*) configuration of the major diastereomer **2a** was first assigned by comparison with literature NMR data[7c] in the non-fluorinated series relating a strong shielding effect of H-2 by the phenyl moiety in the major **2a** (*R*,*R*) isomer (Fig. 1).

Additional evidence of the (*R*,*R*) configuration of the major diastereomer was obtained by converting **2a** into an enantioenriched sample of (*R*)-(+)-3,3,3-trifluoroalanine and comparison of its optical rotation with literature data.[10] The removal of the chiral auxiliary and hydrolysis of the nitrile function of pure **2a** was effected using lead tetraacetate followed by HCl conc. treatment

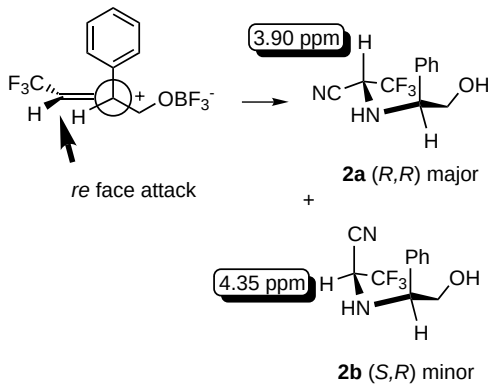
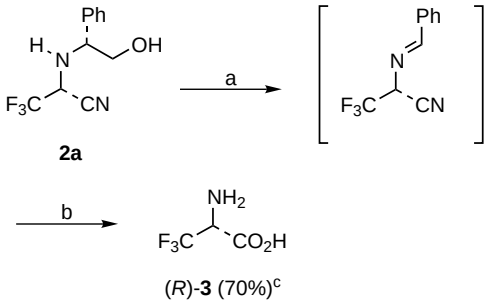



**Figure 1.**

and ion-exchange resin purification (Scheme 2). (*R*)-(+)-3,3,3-Trifluoroalanine **3** was obtained in 70% overall yield from **2a** and 65% ee ($[\alpha]_D^{20}$ +10.0 (*c* 0.76, MeOH) lit. data[10a] +15.4 (*c* 0.76, MeOH)). Although partial racemization occurred during the purification process on $H^+$ resin with 7% $NH_3$ elution,[11] we can assume that the configuration of **2a** is (*R*,*R*).




**Scheme 2.** Synthesis of (*R*)-(+)-3,3,3-trifluoroalanine. (a) $Pb(OAc)_4$, $CH_2Cl_2$:MeOH (2:1). (b) HCl conc., reflux, 4 h, $H^+$ resin. (c) Overall yield from **2a**.

The $BF_3{\cdot}OEt_2$-promoted reaction of the diastereomeric mixture of oxazolidines **1a**,**b** was then extended to various silylated nucleophiles (Scheme 3).[12] The reactions with allyltrimethylsilane, bis-trimethylsilylacetylene, an enoxysilane and a ketene silyl acetal proceeded in good yields. Bis-trimethylsilylacetylene proved to be the less reactive and 4 days reflux in $CH_2Cl_2$ were necessary to ensure a good transformation of **1a**,**b**. The control of the stereoselectivity increases from bis-trimethylsilyl-acetylene (54:46), allyltrimethylsilane (70:30), ketene silyl acetal (84:16) to become almost complete for the enoxysilane.[13] This high stereoselectivity may be attributed to a Lewis acid coordination of the oxygen atom of the enoxysilane. It should be noticed that in contrast to related reactions[6d] no elimination of the amino group occurred. As for the Strecker-type reaction, the configurations of the major **4a**, **6a** and **7a** diastereomers are assumed to be (*R*,*R*) resulting from the addition on the less hindered *re* face of the iminium. This was confirmed for **7a** giving (*R*)-(+)-3-amino-4,4,4-trifluorobutanoic acid **8**[14] in 90% yield after removal of the chiral auxiliary and hydrolysis of the ester function in a one-pot procedure.

Further studies on the stereoselective synthesis of bioactive α-trifluoromethyl amino compounds are now in progress.

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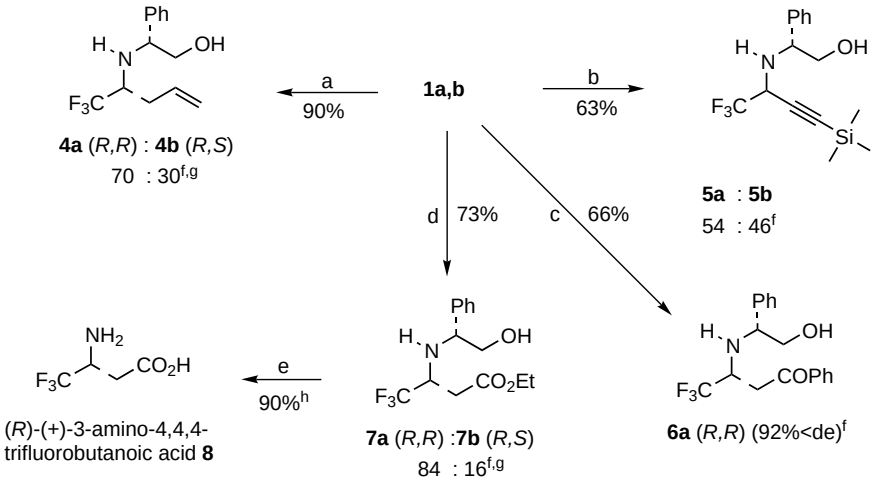


**Scheme 3.** Reactions of **1a**,**b** with various silylated nucleophiles. (a) AllylTMS, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$. (b) Bis-trimethylsilyl-acetylene, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$, reflux 4 days. (c) $H_2C{=}C(OTMS)Ph$, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$. (d) $H_2C{=}C(OTMS)OEt$, $CH_3CH_2CN$, $BF_3{\cdot}OEt_2$, 1 h 30 min reflux. (e) $Pb(OAc)_4$, $CH_2Cl_2$:MeOH (2:1) then HCl conc., reflux, 4 h, $H^+$ resin. (f) Determined by $^{19}F$ NMR integration of the $CF_3$ signals of each diastereomer in the crude mixture. (g) A pure fraction of both isomers was obtained after silica gel chromatography separation. (h) Overall yield from a pure sample of **7a**.

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9. Data for **2a**. Colorless liquid; $[\alpha]_D^{20}$ +203 (*c* 0.76, $CHCl_3$); $^1H$ NMR $\delta$ 2.06 (s, 1H), 2.87 (d, $^3J_{HH}=13.4$, 1H), 3.65 (dd, $^2J_{HH}=10.7$, $^3J_{HH}=9.5$, 1H), 3.82 (dd, $^2J_{HH}=10.7$, $^3J_{HH}=3.8$, 1H), 3.90 (dq, $^3J_{HH}=13.4$, $^3J_{HF}=6.7$, 1H), 4.13 (dd, $^3J_{HH}=9.5$, $^3J_{HH}=3.8$, 1H), 7.18–7.41 (5H); $^{19}F$ NMR $\delta$ −74.2 (d, $^3J_{HF}=6.7$); $^{13}C$ NMR $\delta$ 50.9 (q, $^2J_{CF}=34.5$), 62.5, 66.9, 113.4, 121.6 (q, $^1J_{CF}=281.3$), 126.8 (2C), 127.5 (2C), 129.2, 136.3; IR (neat) 3338, 3020, 2934, 1216, 1150; MS *m*/*z* 245 (M+1, 49), 227 (5), 218 (65), 213 (100). Anal. calcd for $C_{11}H_{11}N_2OF_3$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.23; H, 4.52; N, 11.13%.
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11. 3,3,3-Trifluoroalanine is poorly stable at pH >6. Its partial racemization had already been reported by Zanda et al., see Ref. 10d.
12. Data for **4a**: Colorless liquid; $^1$H NMR $\delta$ 2.29–2.48 (m, 4H), 3.00 (qdd, $^3J_{HF}=7.6$, $^3J_{HH}=3.8$, $^3J_{HH}=1.5$, 1H), 3.55 (m, 1H), 3.67 (dd, $^3J_{HH}=7.3$, $^2J_{HH}=4.2$, 1H), 4.01 (dd, $^3J_{HH}=8.0$, $^2J_{HH}=4.2$, 1H), 5.11 (dd, $^3J_{HH}=16.3$, $^2J_{HH}=1.5$, 1H), 5.13 (dq, $^3J_{HH}=9.1$, $^2J_{HH}=^4J_{HH}=1.5$, 1H), 5.52 (ddt, $^3J_{HH}=16.3$, $^3J_{HH}=9.1$, $^3J_{HH}=2.3$, 1H), 7.23–7.27 (5H); $^{19}$F NMR $\delta$ −74.8 (d, $^3J_{HF}=7.6$); $^{13}$C NMR $\delta$ 33.9, 55.6 (q, $^2J_{CF}=27.6$), 63.3, 67.0, 119.5, 128.0 (2C), 128.1 (2C), 128.2 (q, $^1J_{CF}=282.6$), 128.7, 132.9, 139.5; IR (neat) 3355, 3084, 2930, 2875, 1264; MS *m*/*z* 260 (M+1, 35), 242 (9), 228 (86), 131 (100). Anal. calcd for $C_{13}H_{15}NOF_3$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.08; H, 6.23; N, 5.02%. Compound **5a**: Colorless liquid; $^1$H NMR $\delta$ 0.13 (s, 9H), 2.00–2.40 (m, 2H), 3.62 (dd, $^2J_{HH}=10.9$, $^3J_{HH}=7.6$, 1H), 3.76 (dd, $^2J_{HH}=10.9$, $^3J_{HH}=4.4$, 1H), 3.92 (q, $^3J_{HF}=6.5$, 1H), 4.01 (dd, $^3J_{HH}=7.6$, $^3J_{HH}=4.4$, 1H), 7.31–7.41 (m, 5H); $^{19}$F NMR $\delta$ −75.3 (d, $^3J_{HF}=6.5$); $^{13}$C NMR $\delta$ −0.48, 51.8 (q, $^2J_{CF}=32.5$), 63.4, 66.4, 91.8, 97.4, 123.8 (q, $^1J_{CF}=281.5$), 127.3, 127.8, 128.8, 139.4; IR (neat) 3334, 3031, 2961, 2182, 1253, 1138; MS *m*/*z* 316 (M+1, 7), 284 (100), 214 (5), 121 (71). Anal. calcd for $C_{15}H_{20}NOF_3Si$: C, 57.12; H, 6.39; N, 4.44. Found: C, 56.95; H, 6.03; N, 4.14%. Compound **6a**: Colorless liquid; $[\alpha]_D^{20}$ −27 (*c* 1.12, $CHCl_3$); $^1$H NMR $\delta$ 1.78 (m, 2H), 3.24 (dd, $^2J_{HH}=12.5$, $^3J_{HH}=2$, 1H), 3.33 (d, $^2J_{HH}=12.5$, 1H), 3.58 (dd, $^2J_{HH}=11.3$, $^3J_{HH}=7.9$, 1H), 3.79 (dd, $^2J_{HH}=11.3$, $^3J_{HH}=3.8$, 1H), 4.04 (qd, $^3J_{HF}=7.2$, $^3J_{HH}=2$, 1H), 4.07 (dd, $^3J_{HH}=7.9$, $^2J_{HH}=3.8$, 1H), 7.23–7.27 (5H), 7.49 (dd, $^3J_{HH}=7.3$, $^3J_{HH}=5.2$, 2H), 7.62 (tt, $^3J_{HH}=5.2$, $^4J_{HH}=1.2$, 1H), 7.95 (dt, $^3J_{HH}=7.3$, $^4J_{HH}=1.2$, 2H); $^{19}$F NMR $\delta$ −74.9 (d, $^3J_{HF}=7.2$); $^{13}$C NMR $\delta$ 38.6, 54.0 (q, $^2J_{CF}=28.6$), 62.4, 67.0, 126.5 (q, $^1J_{CF}=274.7$), 127.3, 127.7, 128.2, 128.6, 128.8, 133.9, 136.2, 140.4, 196.9; IR (neat) 3349, 3030, 2928, 1686, 1266; MS *m*/*z* 338 (M+1, 44), 320 (13), 306 (69), 186 (100). Anal. calcd for $C_{18}H_{18}NO_2F_3$: C, 64.09; H, 5.38; N, 4.15. Found: C, 64.13; H, 5.59; N, 3.90%. Compound **7a**: Colorless liquid; $[\alpha]_D^{20}$ −16 (*c* 0.76, $CHCl_3$); $^1$H NMR $\delta$ 1.27 (t, $^3J_{HH}=7.3$, 3H), 2.53 (dd, $^2J_{HH}=16.2$, $^3J_{HH}=8.4$, 1H), 2.73 (dd, $^2J_{HH}=16.2$, $^3J_{HH}=4.4$, 1H), 3.57 (dd, $^2J_{HH}=11.0$, $^3J_{HH}=8.2$, 1H), 3.70 (m, 1H), 3.72 (dd, $^2J_{HH}=11.0$, $^3J_{HH}=3.4$, 1H), 4.00 (dd, $^3J_{HH}=8.2$, $^3J_{HH}=3.4$, 1H), 4.18 (q, $^3J_{HH}=7.3$, 2H), 7.20–7.40 (5H); $^{19}$F NMR $\delta$ −75.5 (d, $^3J_{HF}=8.1$); $^{13}$C NMR $\delta$ 13.9, 34.5, 54.7 (q, $^2J_{CF}=28.5$), 61.3, 62.3, 67.1, 125.9 (q, $^1J_{CF}=283.5$), 127.3, 127.8, 128.5, 140.0, 170.9; IR (neat) 3345, 3064, 2984, 1735, 1268; MS *m*/*z* 306 (M+), 274, 259, 104 (100). Anal. calcd for $C_{14}H_{18}NO_3F_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.08; H, 5.89; N, 4.48%.
13. The other diastereomer could not be discriminated from other minor side products in the crude mixture.
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