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TETRAHEDRON: *ASYMMETRY*

A synthesis of (*S*)-α-(fluorodiphenylmethyl)alkylamines by HF–pyridine treatment of 4-alkyl-5,5-diphenyl-oxazolidinones

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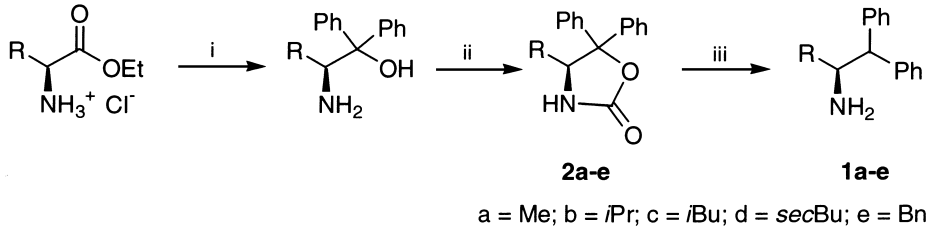
Abstract

Treatment of enantiomerically pure (*S*)-4-alkyl-5,5-diphenyl-oxazolidinones, themselves derived from appropriate amino acids, with HF–pyridine (Olah's reagent) generated a range of (*S*)-α-(fluoro-diphenylmethyl)alkylamines. These compounds represent a novel range of fluorinated chiral amines.

We recently described the synthesis of a range of novel (*S*)-α-(diphenylmethyl)alkylamines **1a**–**e** from a variety of (*S*)-amino acids[1,2] as shown in Scheme 1. The key step in the route is the final one where the oxazolidinones **2a**–**e**, when treated under standard hydrogenation conditions, delivered amines **1a**–**e**, as a consequence of *O*-benzyl cleavage and subsequent decarboxylation.



Scheme 1. Reagents: (i) PhMgBr (5 equiv.), Et_2O, 40–50%; (ii) triphosgene, Et_3N, 80–90%; (iii) H_2, Pd/C, (3 atm), MeOH/AcOH, 70%

We now report that treatment of the oxazolidinones **2a**–**d**[3] and **4**[4] with HF–pyridine (Olah's reagent)[5,6] results in a decarboxylative hydrofluorination reaction to generate the corresponding fluorinated amines **3a**–**d** and **5** (Table 1). The general route to the fluorinated amines is outlined in Scheme 2.

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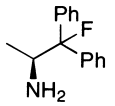
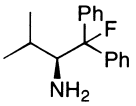
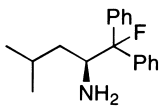
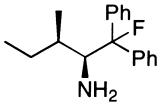
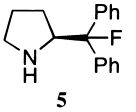
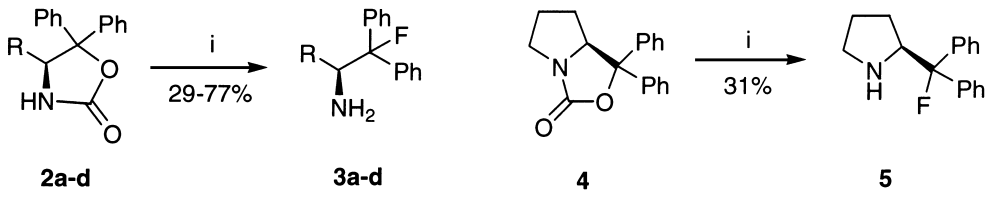
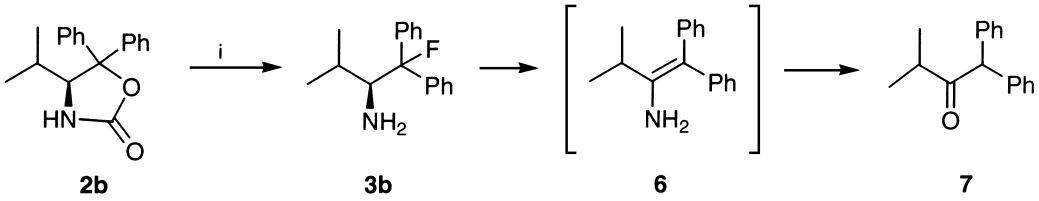
Table 1
Physical properties and spectroscopic data for the (*S*)-fluorinated amines **3a–d** and **5**

 **3a** yield: 77 % m.p. 45.5 °C	$[\alpha]_D^{25}$ = -26.7 (MeOH, c=0.8). δ_H 7.45-7.16 (10H, m, Ar), 3.82 (1H, dq, J= 25.60 and 6.40 Hz, C**H**-NH_2), 1.65 (2H, s, N$\mathbf{H_2}$), 1.03 (3H, d, J= 6.80 Hz, C$\mathbf{H_3}$). δ_C 142.5 (d, J= 22.0 Hz, ***i***-Ar), 142.3 (d, J= 22.0 Hz, ***i***-Ar), 128.9 (d, J= 1.6 Hz, **m**-Ar), 128.6 (d, J= 1.2, **m**-Ar), 127.9 (d, J= 1.1 Hz, **p**-Ar), 127.6 (d, J= 1.6 Hz, **2C p**-Ar), 125.4 (d, J= 9.9 Hz, **o**-Ar), 124.8 (d, J= 10.3 Hz, **o**-Ar), 100.0 (d, J= 181.3 Hz, Ph_2**C**F), 53.0 (d, J= 22.4 Hz, **C**H-NH_2), 16.97 (**C**H_3). δ_F -174.9 (d, J= 24.46 Hz). m/z (CI): 230 (79 %), 210 (83 %). ν_{max} (cm^{-1}) 2983, 1740, 1597, 1491, 1447, 1376, 1200, 967, 850, 762, 696, 650. $C_{15}H_{16}NF$. Calculated: C 78.57, H 7.03, N 6.11, F 8.28. Found: C78.10, H 7.01, N 6.05.
 **3b** Yield: 29 % m.p. 49.7 °C	$[\alpha]_D^{25}$=-18.9 (MeOH, c=2.1). δ_H 7.44-7.15 (10H, m, Ar), 3.50 (1H, d, J= 32.00 Hz, C**H**-NH_2), 1.80 (1H, m, $(CH_3)_2$**CH**), 1.46 (2H, s, N$\mathbf{H_2}$), 0.94 (3H, d, J= 7.2 Hz, C$\mathbf{H_3}$), 0.83 (3H, dd, J= 6.8 and 2.0 Hz, C$\mathbf{H_3}$). δ_C 143.0 (d, J= 22.4, ***i***-Ar), 142.8 (d, J= 23.5 Hz, ***i***-Ar), 128.6 (d, J= 1.5 Hz, ***m***-Ar), 128.4 (d, J= 1.9 Hz, ***m***-Ar), 127.4 (d, J= 1.1 Hz, ***p***-Ar), 127.1 (d, J= 1.1 Hz, ***p***-Ar), 124.9 (d, J= 10.3 Hz, ***o***-Ar), 124.2 (d, J= 10.2 Hz, ***o***-Ar), 102.9 (d, J= 182.8, Ph_2**C**F), 61.0 (d, J= 20.5 Hz, **C**H-NH_2), 27.9 (Me_2**C**H), 22.9 (**C**H_3), 15.9 (d, J= 6.1 Hz, **C**H_3). δ_F -173.7 (d, J= 31.99 Hz). m/z (CI) 258 (16 %), 238 (100 %). ν_{max} (cm^{-1}) 2963, 1597, 1492, 1447, 1188, 1033, 890, 744. $C_{17}H_{20}NF$. Calculated: C 79.34, H 7.83, N 5.44, F 7.38. Found: C 79.08, H 7.82, N 5.31.
 **3c** Yield: 61 % m.p. 84 °C	$[\alpha]_D^{25}$= -48.8 (MeOH, c= 1.2). δ_H 7.50-7.26 (10H, m, Ar), 3.72 (1H, ddd, J= 26.0, 10.4 and 2.0 Hz, C**H**-NH_2), 1.85 (1H, m, $(CH_3)_2$**CH**), 1.51 (2H, s, N$\mathbf{H_2}$), 1.35 (1H, m, C$\mathbf{H_2}$), 1.18 (1H, m, C$\mathbf{H_2}$), 0.87 (6H, t, J= 6.4 Hz, ($\mathbf{CH_3}$)$_2$CH). δ_C 142.5 (d, J= 21.2 Hz, ***ipso***-Ar), 142.1 (d, J= 21.3 Hz, ***ipso***-Ar), 128.6 (d, J= 1.5 Hz, ***m***-Ar), 128.4 (d, J= 1.7 Hz, ***m***-Ar), 127.5 (d, J= 1.2 Hz, ***p***-Ar), 127.3 (d, J= 1.2 Hz, ***p***-Ar), 125.1 (d, J= 9.9 Hz, ***o***-Ar), 124.7 (d, J= 9.9 Hz, ***o***-Ar), 105.4 (d, J= 184.7 Hz, Ph_2**C**F), 55.3 (d, J= 22.4 Hz, **C**H-NH_2), 39.9 ($(CH_3)_2$**C**H), 24.9 (**C**H_3), 24.1 (**C**H_3), 21.02 (**C**H_2). δ_F -174.1 (d, J= 30.12 Hz). m/z (EI): 251 (5%), 208 (26 %), 194 (8 %). HRMS (CI, MH^+) found 272.1812. $C_{18}H_{22}NF$ requires 272.1815. ν_{max} (cm^{-1}) 2943, 1743, 1589, 1492, 1448, 1381, 1047, 993, 899, 772, 744, 692.
 **3d** Yield: 53 % m.p. 76.9 °C	$[\alpha]_D^{25}$ = -32.3 (MeOH, c= 0.6). δ_H 7.45-7.16 (10H, m, Ar), 3.82 (1H, dd, J= 25.60 and 6.40 Hz, C**H**-NH_2), 1.65 (2H, s, N$\mathbf{H_2}$), 1.03 (3H, J= 6.80 Hz, C$\mathbf{H_3}$). δ_C 143.0 (d, J= 20.1 Hz, ***ipso***-Ar), 142.8 (d, J= 20.1 Hz, ***ipso***-Ar), 128.6 (d, J= 1.5 Hz, ***m***-Ar), 128.4 (d, J= 1.9 Hz, ***m***-Ar), 127.4 (d, J= 1.2 Hz, ***p***-Ar), 127.2 (d, J= 1.2 Hz, ***p***-Ar), 125.0 (d, J= 10.3 Hz, ***o***-Ar), 124.3 (d, J= 9.9 Hz, ***o***-Ar), 103.0 (d, J= 183.2 Hz, Ph_2**C**F-), 61.8 (d, J= 20.4 Hz, **C**H-NH_2), 35.1 (CH_3**C**H-), 22.5 (d, J= 6.5 Hz, CH_3**C**H_2-), 18.8 (**C**H_3-CH), 12.3 (**C**H_3CH_2-). δ_F -174.9 (d, J= 24.46 Hz). HRMS (CI, MH^+) found 272.1814. $C_{18}H_{22}NF$ requires 272.1815. ν_{max} (cm^{-1}) 2963, 1745, 1448, 1366, 1258, 1217, 1019, 795, 746, 695.
 **5** Yield: 31 % oil	$[\alpha]_D^{25}$ = -8.1 (MeOH, c 7.4). δ_H 7. 47-7.16 (10H, m, Ar), 4.14 (1H, dt, J= 28.40 and 7.20 Hz, C**H**), 3.02-2.95 (1H, m, C$\mathbf{H_2}$-NH), 2.85-2.77 (1H, m, C$\mathbf{H_2}$-NH), 1.81-1.20 (5H, m, N**H** and C$\mathbf{H_2}$). δ_C 143.1 (d, J= 23.5 Hz, ***ipso***-Ar), 142.6 (d, J= 23.5 Hz, ***ipso***-Ar), 128.6 (d, J= 1.1 Hz, ***m***-Ar), 128.5 (d, J= 1.1 Hz, ***m***-Ar), 127.9 (d, J= 1.1 Hz, ***p***-Ar), 127.7 (d, J= 1.1 Hz, ***p***-Ar), 125.7 (d, J= 8.8 Hz, ***o***-Ar), 125.0 (d, J= 8.8 Hz, ***o***-Ar), 100.0 (d, J= 181.3 Hz, Ph_2**C**F), 64.3 (d, J= 21.7 Hz, **C**H-NH), 47.4 (**C**H_2-NH), 26.5 (d, J= 3.4 Hz, **C**H_2-CH), 25.9 (**C**H_2). δ_F -171.0 (d, J= 27.47 Hz). m/z (CI) 256 (76 %), 236 (100 %); HRMS (C1, MH^+) found 256.1499. $C_{17}H_{18}NF$ requires 256.1502.



Scheme 2. (i) HF–pyridine

These reactions were typically carried out over 30 h. Shorter periods of time resulted in unreacted oxazolidinones. If the reactions are left to stir for extended periods the products become susceptible to elimination. For example, in the case of oxazolidinone **2b** extended treatment generated ketone **7**[7] which was isolated after 4 days stirring at ambient temperature. This presumably arose after HF elimination from **3b** to generate the intermediate enamine **6**. Hydrolysis on work-up would then afford ketone **7** as illustrated in Scheme 3.



Scheme 3. (i) HF–pyridine, 4 days, aq. work-up

It was important to determine if the fluorinated amines **3a–d** and **5** were enantiomerically pure and that no racemisation had occurred during the HF–pyridine reaction. To this end fluorinated amine **3a** was prepared as a *racemate* and was then treated with (*S*)-α-methoxyphenylacetic acid **8** as a chiral solvating agent to generate the corresponding salt in solution. Fig. 1 illustrates a comparison of the selected regions of the ^{1}H NMR spectra of the diastereoisomeric salts generated from (*S*)-α-methoxyphenylacetic acid **8** and either (*RS*)-**3a** or (*S*)-**3d**. It is clear that a single diastereoisomeric salt is generated in the latter case and within the level of detection there is no indication of any racemisation. The ^{1}H NMR spectrum of the analogous salt of amine **3d** was also judged to be enantiomerically pure. Thus, we are confident that the fluorination reactions outlined in Scheme 2 are not susceptible to racemisation.

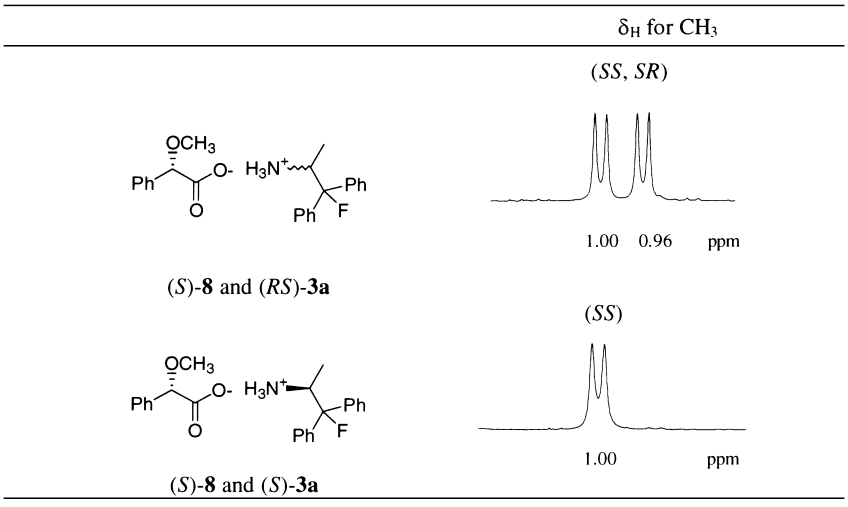


Figure 1. Selected regions of the ^{1}H NMR spectra of the salts (*S*)-α-methoxyphenylacetic acid **8** and (*RS*)-**3a** or (*S*)-**3a**

These compounds can be made in both enantiomeric series starting from the appropriate amino acids and they offer a range of new fluorinated chiral amines for applications in asymmetric synthesis and as components for combinatorial libraries.

Experimental. Preparation of **3a**–**d** and **5**: A suspension of the oxazolidinones (3–5 mM) **2a**–**d** and **4**[1,2] in 70% HF–pyridine (10–15 ml) was stirred for 31 h at ambient temperature in a teflon vessel (bottle) and then the reaction mixture was cooled to 0°C and quenched with aqueous KOH (7 M) until the solution was basic (pH 13–14). The organics were then extracted into Et_2O (four times), dried over $MgSO_4$ and concentrated under reduced pressure. Conc. HCl solution (1 ml) was added and the resultant suspension was dissolved in water and the aqueous layer washed with Et_2O (20 ml×3). The residual aqueous solution was then made basic (pH 13–14) by addition of NaOH pellets, and the amines **3a**–**d** and **5** were extracted into Et_2O (20 ml×3). The compounds could be further purified by chromatography over silica gel.

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