Solvent-free synthesis of quaternary α-hydroxy α-trifluoromethyl diazenes: the key step of a nucleophilic formylation strategy†

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An efficient, scalable and operationally simple one-pot, 2-step strategy for the nucleophilic formylation of trifluoromethyl ketones is presented. The key step is an unprecedented diaza-carbonyl-ene reaction of formaldehyde tert-butyl hydrazone and trifluoromethyl ketones under solvent-free conditions. This reaction proved to be very fast, clean and high-yielding, affording densely functionalised α-hydroxy α-trifluoromethyl diazenes. The ensuing diazene-to-aldehyde transformation, avoiding protection/de-protection reactions and chromatographic purifications, and subsequent derivatizations in a one-pot fashion provide a direct entry to a variety of useful trifluoromethylated building blocks.

Introduction

Organofluorine compounds have attracted the interest of academia and industry from the viewpoint of their fruitful applications in pharmaceutical (approximately 20% of the market, including some of the most selling drugs)1 and materials sciences.2 Therefore, the development of synthetic methods for accessing new fluorinated compounds is an increasingly important issue in modern organic chemistry.3 In recent years, trifluoromethylated compounds have received considerable attention due to their unique chemical, physical and biological properties.4 In particular, trifluoromethyl carbinols and derivatives are present in a plethora of biologically active compounds. The selected examples shown in Scheme 1 include aminoalcohols I5 and II,6 α-hydroxy amides III and IV,7 the marketed anti-HIV agent efavirenz V,8 matrix metalloproteinase (MMP) peptidomimetic inhibitors such as VI,9 and the neurokinin 1 receptor antagonist CJ-17493 VII.10

Accordingly, two general approaches to the synthesis of such compounds have been developed. The first one is the nucleophilic trifluoromethylation of carbonyl compounds,11 and the second strategy is based on the addition of carbon nucleophiles to trifluoromethyl ketones.12 The retrosynthetic analysis of the selected targets suggests the use of α-hydroxy

†Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data and copies of NMR spectra. See DOI: 10.1039/c6gc00408c

Scheme 1 Retrosynthetic analysis of biologically relevant functionalized trifluoromethyl carbinols and derivatives.
α-trifluoromethyl aldehydes as common building blocks by virtue of the versatility of the formyl group. These intermediates might be conveniently built by employing trifluoromethyl ketones as electrophiles for the attack of α-trifluoromethyl hydrazones (Scheme 2, top). α-Trifluoromethyl diazene 7a in a modest 55% yield (after 20 days in CH₂Cl₂ at room temperature) along with small amounts of the hydrazo transfer by-product 6a. It was observed that the reaction rates are highly dependent on the reaction media (32% after 3 days (neat); 10 and 40% yields after 5 days in CH₃CN and H₂O, respectively). The anisyl-substituted derivative 3 showed no reactivity, while formaldehyde N-tert-butyl hydrazone 4, employed in a 1.5-fold excess, readily added to 1a in CH₂Cl₂ with complete C-selectivity, affording the desired α-hydroxy α-trifluoromethyl diazene 7a in 83% yield after 9 hours (entry 1, Table 1). Further optimization experiments were conducted in different solvents and the E-factor‡ was determined by 1H NMR.

Results and discussion

Preliminary experiments were performed with commercially available 2,2,2-trifluoroacetophenone (1a) as the model substrate. For comparative purposes, the reactivity of different simple formaldehyde hydrazones was analysed (Scheme 3). The simplest formaldehyde dimethylhydrazone 2 was very slowly added to the carbonyl compound (employed in a 2-fold excess) to afford the corresponding α-hydroxy α-trifluoromethyl-hydrazone 5a in a modest 55% yield (after 20 days in CH₂Cl₂ at room temperature) along with small amounts of the hydrazo transfer by-product 6a. It was observed that the reaction rates are highly dependent on the reaction media (32% after 3 days (neat); 10 and 40% yields after 5 days in CH₃CN and H₂O, respectively). The anisyl-substituted derivative 3 showed no reactivity, while formaldehyde N-tert-butyl hydrazone 4, employed in a 1.5-fold excess, readily added to 1a in CH₂Cl₂ with complete C-selectivity, affording the desired α-hydroxy α-trifluoromethyl diazene 7a in 83% yield after 9 hours (entry 1, Table 1). Further optimization experiments were conducted in different solvents and the E-factor‡ was determined by 1H NMR.

Table 1 Optimization of the reaction of 1a and 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>α·β·γ</th>
<th>Yield (%)</th>
<th>E-factor (g/g)</th>
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<td>1</td>
<td>CH₂Cl₂</td>
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<td>10</td>
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<td>10</td>
<td>80</td>
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<tr>
<td>4</td>
<td>Toluene</td>
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<td>8.27</td>
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<tr>
<td>5</td>
<td>Et₂O</td>
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<td>10</td>
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<td>7.63</td>
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<tr>
<td>6</td>
<td>CH₃CN</td>
<td>6</td>
<td>10</td>
<td>90</td>
<td>6.69</td>
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<tr>
<td>7</td>
<td>H₂O</td>
<td>45</td>
<td>10</td>
<td>90</td>
<td>1.31</td>
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<td>8</td>
<td>—</td>
<td>20</td>
<td>10</td>
<td>&gt;99</td>
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<td>10</td>
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</table>

The E-factor is defined as the mass ratio of the waste to the desired product. For E-factors including solvents after chromatographic purifications or L-L extractions see the ESI.†
used as a descriptor of the environmental impact. Using CHCl₃ instead of CH₂Cl₂ provided full conversions in shorter reaction times, albeit yielding an 8 : 2 mixture of azocompound 7a and its tautomeric hydrazone form 8a, presumably induced by acid traces in the reaction media (entry 2). In general, lower reactivities were observed in hydrocarbons and ethereal solvents (entries 3–5), while conducting the reaction in a polar aprotic solvent such as CH₃CN had a positive effect, affording 7a in a higher yield (E-factor = 6.68, entry 6) and shorter reaction time (6 hours).

Next, we decided to explore the possibility of performing the reaction “on water”, exploiting the rate acceleration previously observed for FDAHs in reactions with α-keto esters.¹⁶e When pure water was used as the reaction medium, full conversion was observed in only 45 minutes, giving 7a in 90% isolated yield after simple L–L extraction with Et₂O, with an E-factor of 1.31§ (entry 7). Finally, we were delighted that the reaction carried out in the absence of a solvent²¹,²² proceeded cleanly and at a high rate, reaching completion in only 20 minutes. These conditions efficiently afforded analytically pure 7a in quantitative yield after removing the excess of hydrazone 4 under reduced pressure and without the need for chromatographic purification (E-factor = 0.18, entry 8). Finally, scaling-up from 0.5 to 6 mmol made the reaction proceed even faster, reaching completion in 10 minutes (entry 9). Under these optimal conditions, the reaction was performed with a 1 : 1 ratio of ketone 1a and reagent 4 to afford 7a without any further elaboration and, therefore, in a very high overall efficiency, quantified by an E-factor close to zero (entry 10).

The scope of the reaction was then explored with a range of trifluoromethyl ketones 1, including aromatic (1a–1d), heteroaromatic (1e), aliphatic derivatives (1f–1i) and the densely functionalized ethyl 3,3,3-trifluoropyruvate (1j), as outlined in Scheme 4. The collected data indicate that the reaction is highly efficient (5–300 minutes of reaction time) for all types of substrates, proceeding at room temperature to afford α-hydroxy α-trifluoromethyl diazenes 7 in quantitative yields (>99%) and high purity (>95% by NMR), without the need for chromatographic purification. The reaction rates correlate with stereoelectronic properties of the substrates, with the more reactive 1d (R = 4-F-C₆H₄), 1h (R = Me), and 1j (R = CO₂Et) reaching completion in less than 10 minutes. The solid ketone 1c, bearing an electron-rich aryl group, appeared as the most challenging substrate but, although requiring extra time for complete solubilisation, also afforded a satisfactory result. The mild and simple reaction conditions (room temperature, no need of oxygen and/or moisture exclusion) offer a practical way to scale-up the production (see pictures in the ESI†), as illustrated by a 10 gram (36 mmol) synthesis of 7a. Moreover, the simplicity of the solvent-free methodology allowed the development of some transformations of diazenes 7 into useful building blocks in a one-pot fashion. For example, applying an acid-catalysed isomerization reaction, α-hydroxy α-trifluoromethyl hydrazones 8 were obtained in high yields (Scheme 5).

To validate the announced formylation strategy, the subsequent one-pot diazene-to-aldehyde transformation from 7

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⁵Water amounts are normally not included in the E-factor; even though additional amounts of organic solvents are required in the subsequent L–L extractions.

⁶Solvent-free methodologies (ref. 21) are among the most promising strategies towards waste prevention and environmental protection, which also lead to milder conditions, very high volumetric productivity, increased safety and cost reduction (ref. 22).
was easily performed (Scheme 6). Thus, upon completion of the addition step, a simple treatment with HCl in a biphasic H₂O/Et₂O or H₂O/MTBE medium afforded the desired α-hydroxy α-trifluoromethyl aldehydes 9 in good yields with a high degree of purity (>95% estimated by ¹H NMR, see the ESI†).

Remarkably, the tert-butyl hydrazine was recovered (92–96%) as its hydrochloride salt and reused for the synthesis of 4, thus minimizing waste production in the formylation procedure.²⁰c Sensitive aldehydes 9 were directly used in subsequent reductive aminations or condensations with hydroxylamine to yield valuable trifluoromethylated β-aminoalcohols 10 and α-hydroxy aldoximes 11 in satisfactory overall yields for the three-step transformations. To again demonstrate the preparative utility of this methodology, the synthesis of 10a and 11a was performed on an 18 mmol scale without compromising the chemical yield.

Finally, the efficiency and simplicity of the present methodology are highlighted with 3-step protocols outlined in Scheme 7 for the synthesis of representative trifluoromethylated β-aminoalcohol hydrochloride 10a·HCl and α-hydroxy acids 12a and 12g in good overall yields, without the need for further chromatographic purifications of these products.

These α-hydroxy α-trifluoromethyl carboxylic acids 12 are valuable building blocks for target oriented synthesis, as illustrated with their transformation into amide III,⁷ᵃ,b and the formal synthesis of several biologically active α-hydroxy α-trifluoromethyl amides (Scheme 8).²⁴

Scheme 6 Synthesis of β-aminoalcohols 10 and α-hydroxy aldoximes 11. Overall yield for the three-step sequence.

Scheme 7 Chromatography-free synthesis of β-aminoalcohol hydrochloride 10a·HCl and α-hydroxy acids 12a and 12g.

Scheme 8 Synthesis of amide III and the formal synthesis of rac-VIII and ZM156854.

Experimental

Spectra were recorded at 300 or 500 MHz (¹H NMR); 75.5 or 125 MHz (¹³C NMR); and 470.6 MHz (¹⁹F NMR) with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ¹H and ¹³C respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminum backed plates (1.5 × 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light or by dipping the plates in solutions of KMnO₄, vanillin or phosphomolybdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. Formaldehyde hydra-
zones 2–4\textsuperscript{25} and not commercially available trifluoromethyl ketones 1\textsuperscript{26} were synthesized according to literature procedures.

General procedure for the synthesis of α-hydroxy α-trifluoromethyl diazenes 7

Freshly distilled formaldehyde tert-butylhydrozone 4 (0.75 mL, 6 mmol) was added to trifluoromethyl ketone 1 (6 mmol) at room temperature. The mixture was stirred for the time specified (Scheme 4, TLC monitoring) to afford pure diazene 7.

3-(tert-Butyldiazenyl)-1,1,1-trifluoro-2-phenylpropan-2-ol (7a).

Following the general procedure starting from 1a (0.84 mL, 6 mmol), diazene 7a was obtained as a pale yellow oil (1.64 g, 99%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.69 (d, J = 8.2 Hz), 7.19 (d, J = 8.2 Hz), 4.52 (s, 1H), 4.41 (d, J = 14.2 Hz), 4.32 (d, J = 14.2 Hz), 2.35 (s, 3H), 1.13 (s, 9H). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): δ 138.5, 133.3, 129.0, 126.3, 124.8 (q, J\textsubscript{CF} = 285.6 Hz), 76.5 (q, J\textsubscript{CF} = 28.8 Hz), 70.0, 68.8, 26.5. \textsuperscript{19}F NMR (470.6 MHz, CDCl\textsubscript{3}): δ −78.01 (s, CF\textsubscript{3}). HRMS (ESI): m/z calecd for C\textsubscript{13}H\textsubscript{18}F\textsubscript{3}N\textsubscript{2}O\textsuperscript{+} [M+H]+ 275.1366, found 275.1356.

3-(tert-Butyldiazenyl)-1,1,1-trifluoro-2-(p-toly1)propan-2-ol (7b).

Following the general procedure starting from 1b (0.91 mL, 6 mmol), diazene 7b was obtained as a pale yellow oil (1.73 g, 99%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.46 (d, J = 8.2 Hz), 7.19 (d, J = 8.2 Hz), 4.52 (s, 1H), 4.41 (d, J = 14.2 Hz), 4.32 (d, J = 14.2 Hz), 2.35 (s, 3H), 1.13 (s, 9H). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): δ 138.5, 133.3, 129.0, 126.3, 124.8 (q, J\textsubscript{CF} = 285.6 Hz), 76.5 (q, J\textsubscript{CF} = 28.8 Hz), 70.0, 68.8, 26.5. \textsuperscript{19}F NMR (470.6 MHz, CDCl\textsubscript{3}): δ −78.01 (s, CF\textsubscript{3}). HRMS (ESI): m/z calecd for C\textsubscript{13}H\textsubscript{18}F\textsubscript{3}N\textsubscript{2}O\textsuperscript{+} [M+H]+ 275.1366, found 275.1356.

3-(tert-Butyldiazenyl)-1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol (7c).

Following the general procedure starting from 1c (1.47 g, 6 mmol), diazene 7c was obtained as a pale yellow oil (1.64 g, 6 mmol), diazene 7d was obtained as a pale yellow oil (1.64 g, 99%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.30 (m, 3H), 4.52 (s, 1H), 4.43 (d, J = 14.2 Hz), 4.36 (dd, J1, J2 = 0.4, 14.2 Hz), 1.12 (s, 9H). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): δ 136.3, 128.6, 128.3, 126.4, 124.8 (q, J\textsubscript{CF} = 285.6 Hz), 76.6 (q, J\textsubscript{CF} = 28.7 Hz), 69.9, 68.7, 26.4. \textsuperscript{19}F NMR (470.6 MHz, CDCl\textsubscript{3}): δ −79.29 (s, CF\textsubscript{3}). HRMS (ESI): m/z calecd for C\textsubscript{13}H\textsubscript{18}F\textsubscript{3}N\textsubscript{2}O\textsuperscript{+} [M+H]+ 275.1366, found 275.1356.
General procedure for the ‘one-pot’ synthesis of α-hydroxy α-trifluoromethyl hydrazones 8

Freshly distilled formaldehyde tert-butylhydrazone 4 (0.13 mL, 1 mmol) was added to trifluoromethyl ketone 1 (1 mmol) at room temperature. The mixture was stirred for the time specified (Scheme 4, TLC monitoring) to afford pure diazene 7. Subsequently, a solution of TFA (0.1 mmol) in CH2Cl2 (10 mL) was added to a solution of diazene 7 (1 mmol) in CH2Cl2 (0.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. A saturated NaHCO3 solution (15 mL) was added and the organic phase was separated. The remaining aqueous phase was extracted with Et2O (3 x 10 mL), and the combined organic layer was dried over anhydrous MgSO4, filtered and concentrated to afford pure α-hydroxy hydrazone 8.

3-[2-(tert-Butyl)hydrazono]-1,1,1-trifluoro-2-phenylpropan-2-ol (8a)

Following the general procedure, α-hydroxy hydrazone 8a was obtained as a white solid (0.26 g, 95%); mp: 72 °C. 1H NMR (300 MHz, CDCl3): δ 7.76–7.58 (m, 2H), 7.45–7.35 (m, 3H), 7.34 (s, 1H), 5.04 (s, 1H), 1.20 (s, 9H). 13C NMR (75.5 MHz, CDCl3): δ 136.3, 132.7, 126.8, 128.4 (d, JCF = 0.6 Hz), 126.2 (d, JCF = 1.7 Hz), 124.4 (q, JCF = 286.2 Hz), 75.2 (q, JCF = 29.2 Hz), 54.1, 28.3. 19F NMR (470.6 MHz, CDCl3): δ −78.18 (s, CF3). HRMS (CI): m/z calcd for C13H17F3N2O [M]+ 274.1293, found 274.1289.

General procedure for the synthesis of β-aminoaocohols 10

p-Methoxyphenylalanine (0.73 g, 6 mmol) was added to a solution of crude aldehyde 9 (6 mmol) in TFE (15 mL). The mixture was stirred at 30 °C for 20 minutes. NaBH4 (0.28 g, 7.2 mmol) was then added and the reaction was stirred vigorously until hydrogen evolution ceased (approx. 30 min). The mixture was filtered through a Celite pad, concentrated and the residue was purified by flash chromatography (pentane/CH2Cl2) to afford products 10.

1,1,1-Trifluoro-3-[4-methoxyphenylamino]-2-phenylpropan-2-ol (10a). Following the general procedure, β-aminoaocohol 10a was obtained as a brown solid (1.31 g, 70%); mp: 53–55 °C. 1H NMR (300 MHz, CDCl3): δ 7.69–7.59 (m, 2H), 7.50–7.39 (m, 3H), 6.83–6.74 (m, 2H), 6.72–6.62 (m, 2H), 4.25 (s, 1H), 3.94 (d, 1H, J = 13.8 Hz), 3.75 (s, 3H), 3.61 (dd, 1H, J = 13.8, 0.4 Hz), 3.10 (s, 1H). 13C NMR (75.5 MHz, CDCl3): δ 153.9, 141.2, 136.5, 128.9, 128.5, 126.3, 125.4 (q, JCF = 285.4 Hz), 116.6, 114.8, 74.8 (q, JCF = 27.6 Hz), 55.6, 51.5. 19F NMR (470.6 MHz, CDCl3): δ −78.28 (s, CF3). HRMS (ESI): m/z calcd for C14H21F3NO4 [M + H]+ 312.1206, found 312.1195.

2-(2,4-Dimethylphenyl)-1,1,1-trifluoro-3-[4-methoxyphenylamino]-2-phenylpropan-2-ol (10c). Following the general procedure, β-aminoaocohol 10c was obtained as a brown oil (1.22 g, 55%). 1H NMR (300 MHz, CDCl3): δ 7.43–7.34 (m, 1H, 6.83–6.72 (m, 2H), 6.71–6.60 (m, 2H), 5.88 (s, 1H), 3.89 (s, 3H), 3.83 (d, 1H, J = 13.4 Hz), 3.82 (s, 3H), 3.77 (d, 1H, J = 13.4 Hz), 3.75 (s, 3H). 13C NMR (75.5 MHz, CDCl3): δ 161.3, 159.4, 152.7, 142.1, 130.8, 125.5 (q, JCF = 287.8 Hz), 115.1, 114.7, 105.3, 99.8, 77.3 (q, JCF = 28.2 Hz), 55.9, 55.6, 55.2, 48.4 (d, JCF = 1.3 Hz). 19F NMR (470.6 MHz, CDCl3): δ −79.84 (s, CF3). HRMS (ESI): m/z calcd for C16H15F3NO4 [M + H]+ 302.1417, found 301.1401.
δ = -79.39 (s, CF3). HRMS [ESI]: m/z calcd for C14H15F3NO2S [M + H]+ 389.0916, found 389.0914.

2-Benzyl-1,1-trifluoro-3-[(4-methoxyphenyl)amino]propan-2-ol (10f). Following the general procedure, β-aminoalcohol 10f was obtained as a brown oil (1.17 g, 60%). 1H NMR (500 MHz, CDCl3): δ 7.93–7.90 (m, 3H), 7.85 (s, 1H), 7.48 (d, 2H, J = 8.2 Hz), 7.24 (d, 2H, J = 8.2 Hz), 2.43 (s, 3H), 1.28 (s, 3H). 13C NMR (75.5 MHz, CDCl3): δ 147.0, 139.3, 131.7, 129.2, 126.2, 124.1 (q, JCF = 285.2 Hz), 75.5 (q, JCF = 29.9 Hz), 21.0. 19F NMR (470.6 MHz, CDCl3): δ = 79.27 (s, CF3). HRMS [ESI]: m/z calcd for C16H15F3NO4S [M + Na]+ 336.0750, found 336.0753.

2-(2,4-Dimethoxyphenyl)-3,3,3-trifluoro-2-hydroxypropional oxime (11e). Following the general procedure, α-hydroxy aldoxime 11e was obtained as a colorless oil (1.01 g, 75%). 1H NMR (500 MHz, CDCl3): δ 7.84 (s, 1H), 7.71 (s, 1H), 7.39 (d, 1H, J = 5.1, 1.2 Hz), 7.21–7.18 (m, 1H), 7.07 (dd, 1H, J = 5.1, 3.7 Hz), 4.47 (s, 1H). 13C NMR (75.5 MHz, CDCl3): δ 146.2, 137.9, 127.4, 127.0, 126.3 (d, JCF = 0.5 Hz), 123.4 (q, JCF = 286.1 Hz), 75.0 (q, JCF = 11.6 Hz). 19F NMR (470.6 MHz, CDCl3): δ = -78.79 (s, CF3). HRMS [ESI]: m/z calcd for C10H10F3NO2S [M + Na]+ 256.0556, found 256.0552.

Hydroxylamine hydrochloride (0.50 g, 7.2 mmol) and sodium hydroxide (0.30 g, 7.2 mmol) were sequentially added to a solution of crude aldehyde 9 (6 mmol) in MeOH (45 mL). The mixture was stirred at room temperature overnight. The mixture was then diluted with water (15 mL) and the organic phase was extracted with CH2Cl2 (2 × 30 mL) and Et2O (2 × 30 mL). The combined organic layer was dried (MgSO4), filtered and concentrated. The product was purified by flash chromatography (1:1 cyclohexane/AcOEt) to afford α-hydroxy aldoximes 11.

3,3,3-Trifluoro-2-hydroxy-2-phenylpropanal oxime (11a). Following the general procedure, α-hydroxy aldoxime 11a was obtained as a white solid (0.76 g, 58%); mp: 62–68 °C. 1H NMR (300 MHz, CDCl3): δ 7.93 (s, 1H), 7.47–7.36 (m, 3H), 4.21 (s, 1H). 13C NMR (75.5 MHz, CDCl3): δ 137.4, 129.3, 128.7, 126.3 (d, JCF = 0.6 Hz), 123.9 (q, JCF = 288.3 Hz). 19F NMR (470.6 MHz, CDCl3): δ = -168.1 (d, JCF = 1.1 Hz), 153.1, 141.1, 122.9 (q, JCF = 288.3 Hz), 115.8, 114.7, 77.8 (q, JCF = 28.6 Hz), 64.0, 53.7, 46.5 (d, JCF = 1.2 Hz), 13.8. 15N NMR (470.6 MHz, CDCl3): δ = 77.26 (s, CF3). HRMS [ESI]: m/z calcd for C8H6F2NO2Na [M + Na]+ 250.0932, found 250.0931.

3,3,3-Trifluoro-2-hydroxy-2-p-tolylpropanal oxime (11b). Following the general procedure, α-hydroxy aldoxime 11b was obtained as a white solid (1.08 g, 77%); mp: 66–68 °C. 1H NMR (500 MHz, CDCl3): δ 7.92 (s, 1H), 7.88 (s, 1H), 7.48 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.2 Hz), 4.23 (s, 1H), 2.83 (s, 3H). 13C NMR (75.5 MHz, CDCl3): δ 147.3, 139.3, 131.7, 129.2, 126.2, 124.1 (q, JCF = 285.2 Hz), 75.5 (q, JCF = 29.9 Hz), 21.0. 19F NMR (470.6 MHz, CDCl3): δ = 79.27 (s, CF3). HRMS [ESI]: m/z calcd for C16H15F2NO4S [M + Na]+ 308.0914, found 308.1102.

Synthesis of β-aminoalcohol hydrochloride 10a-HCl. p-Methoxyphenylalanine (0.37 g, 3 mmol) was added to a solution of crude aldehyde 9a (3 mmol) in TFE (7.5 mL). The mixture was stirred at 30 °C for 20 min. After this time, NaBH4 (0.14 g, 3.6 mmol) was added and the reaction was stirred vigorously until the end of hydrogen evolution (approximately 30 minutes). The solvent was removed under reduced pressure and the crude was dissolved in CH2Cl2 (5 mL). The mixture was filtered through silica and Celite pad (height: 1 cm), and washed with a mixture of pentane/CH2Cl2 (2:1, 10 mL). Solvents were removed under reduced pressure and the product was dissolved in dry Et2O (15 mL). HCl (1 M in dioxane, 3.8 mL) was added and the mixture was stirred at room temperature until the appearance of a white solid (approximately 1 h). The solid was filtered and washed with Et2O (2 mL) to afford the pure amine hydrochloride 10a-HCl (0.72 g, 83%). 1H NMR (300 MHz, DMSO-d6): δ 7.69–7.60 (m, 2H), 7.44–7.33 (m, 3H), 7.02 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.70 (br s, 2H), 4.01 (d, 1H, J = 13.4 Hz), 3.77 (d, 1H, J = 13.4 Hz), 3.68 (s, 3H). 13C NMR (75.5 MHz, CDCl3): δ 156.9, 134.9, 133.4, 128.9, 128.2, 127.1, 125.0 (q, JCF = 285.3 Hz), 121.8, 114.5, 75.2 (q, JCF = 27.8 Hz), 55.5, 53.0. 19F NMR (470.6 MHz, CDCl3): δ = -77.07 (s, CF3). HRMS [ESI]: m/z calcd for C16H15F2NO4S [M+H]+ 312.1300, found 312.1200.
General procedure for the synthesis of α-hydroxy acids 12

A solution of NaClO₂ (20 mmol) and KH₂PO₄ (18 mmol) in H₂O (70 mL) was added dropwise to a solution of crude aldehyde 9 (6 mmol) in ⁴BuOH (70 mL) and 2-methyl-but-2-ene (60 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The solvents were removed under reduced pressure and the residue was treated with 2 M NaOH and extracted with Et₂O. The aqueous layer was acidi- fied to pH 1 (2 M HCl) and extracted with EtOAc. The combined organic layer was dried (MgSO₄), filtered and the solvent was removed under reduced pressure to afford pure α-hydroxy acid.

3,3,3-Trifluoromethyl-2-phenylpropanoic acid (12a). Following the general procedure, 12a was obtained as a white solid (0.98 g, 74%). Characterization data are in agreement with those reported in the literature.²⁷

2-Hydroxy-4-phenyl-2-(trifluoromethyl)butanoic acid (12g). Following the general procedure, α-hydroxy acid 12g was obtained as a white solid (0.89 g, 74%); mp = 83–85 °C.

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Notes and references


