PAPER

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/deprotection 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 **I**[5] 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

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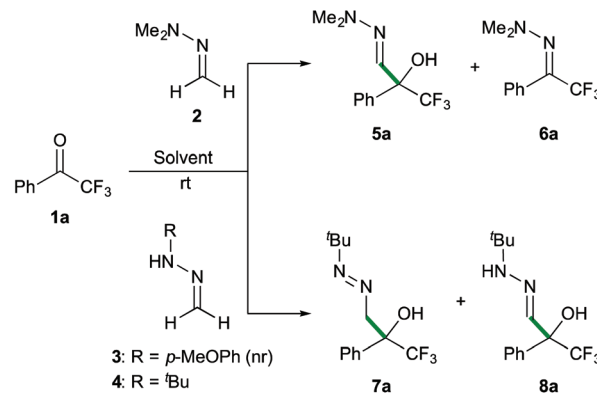
Scheme 1 Retrosynthetic analysis of biologically relevant functionalized trifluoromethyl carbinols and derivatives.
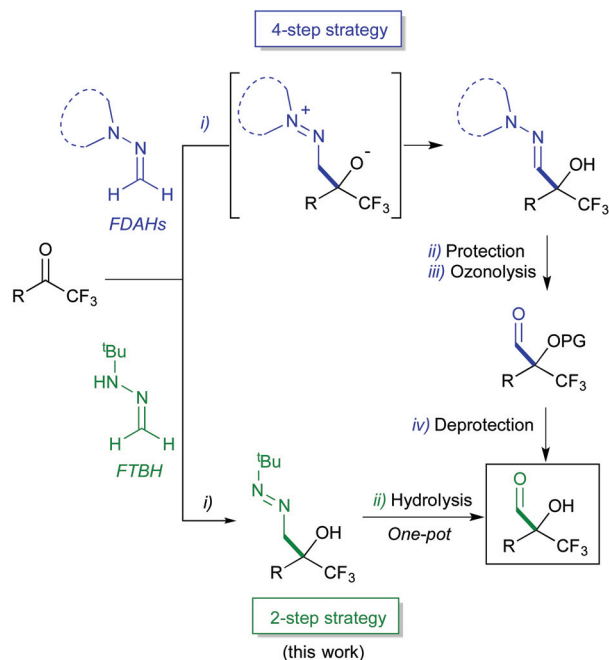
Scheme 2 Nucleophilic formylations of trifluoromethyl ketones employing formaldehyde hydrazones as d¹ reagents.

Scheme 3 Preliminary reactivity experiments.

Table 1 Optimization of the reaction of **1a** and **4** [a]

Entry	Solvent	T	**7a : 8a** [b]	Yield[c] (%)	E-factor[d] (g g^{-1})
1	CH_2Cl_2	9 h	10 : 0	83	12.08
2	$CHCl_3$	7 h	8 : 2	70	16.31
3	n-Hexane	31 h	10 : 0	80	6.49
4	Toluene	31 h	10 : 0	81	8.27
5	Et_2O	31 h	10 : 0	74	7.63
6	CH_3CN	6 h	10 : 0	90	6.69
7	H_2O	45 min	10 : 0	90	1.31
8	—	20 min	10 : 0	>99	0.18
9[e]	—	10 min	10 : 0	>99	0.18
10[e,f]	**—**	**20 min**	**10 : 0**	**>99**	**0.0004**

[a] Reactions performed on a 0.5 mmol scale (0.5 M) using **1a** (0.5 mmol) and **4** (0.75 mmol). [b] Determined by ¹H NMR. [c] Isolated yield after column chromatography (entries 1–6), after L–L extraction (entry 7), after removing the excess of hydrazone **4** under reduced pressure (entries 8 and 9). [d] E-factor = Waste (g)/**7a** (g); without considering potential recycling of **4** and solvents. [e] Reactions performed on a 6 mmol scale. [f] 1 : 1 **1a**/**4** molar ratio.

α-trifluoromethyl aldehydes as common building blocks by virtue of the versatility of the formyl group.[13] These intermediates might be conveniently built by employing trifluoromethyl ketones as electrophiles for the attack of d¹ reagents (Scheme 1). This approach, however, has been scarcely investigated.[14]

Our research team has intensively explored the nucleophilic reactivity of formaldehyde *N,N*-dialkylhydrazones (FDAHs),[15] which behave as formyl anion equivalents (d¹ synthons) in their reactions with a variety of electrophiles, including carbonyl compounds.[16] In particular, pyrrolidine derivatives spontaneously add to trifluoromethyl ketones affording α-hydroxy α-trifluoromethyl hydrazones (Scheme 2, top).[16a,b] This reaction, combined with hydroxyl protection and hydrazone cleavage by ozone, constitutes a convenient entry (3-steps) to both racemic or enantiomerically enriched α-alkoxy-α-trifluoromethyl aldehydes and derivatives thereof. More recently, we have exploited the superior reactivity of formaldehyde tert-butyl hydrazone (FTBH) with carbonyl compounds (α-keto esters,[17] isatins[18] and α-keto phosphonates)[19] as the key step of a formylation strategy. In the seeking of greener methodologies, herein we present a more concise one-pot, 2-step approach to α-hydroxy α-trifluoromethyl aldehydes employing FTBH (Scheme 2, bottom) based on the positive effect that solvent-free conditions have on the reaction rate of the first step, allowing subsequent transformations in a one-pot fashion.

Results and discussion

Preliminary experiments were performed with commercially available 2,2,2-trifluoroacetophenone (**1a**) as the model sub-strate. 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-trifluoro-methyl-hydrazone **5a** in a modest 55% yield (after 20 days in CH_2Cl_2 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 CH_3CN and H_2O, 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 CH_2Cl_2 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‡[20] was

‡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 CHCl$_3$ instead of CH$_2$Cl$_2$ 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 CH$_3$CN 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 Et$_2$O, with an *E*-factor of 1.31§ (entry 7). Finally, we were delighted that the reaction carried out in the absence of a solvent¶[21,22] 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 substituents, with the more reactive **1d** (R = 4-F-C$_6$H$_4$), **1h** (R = Me), and **1j** (R = CO$_2$Et) 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 illus-
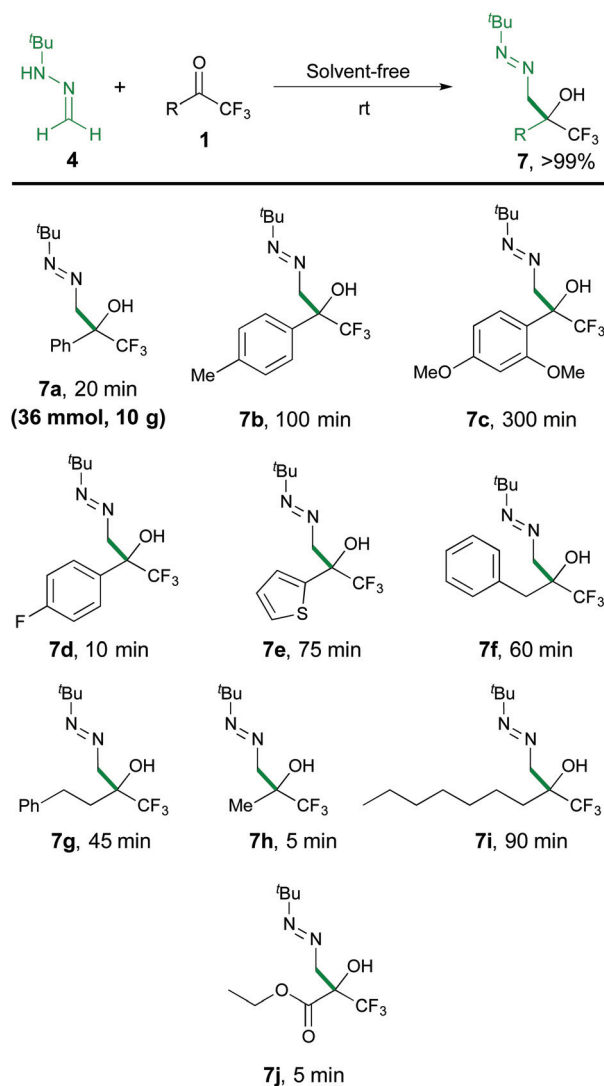
Scheme 4 Synthesis of diazenes **7**.

trated 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**[23] were obtained in high yields (Scheme 5).

To validate the announced formylation strategy, the subsequent one-pot diazene-to-aldehyde transformation from **7**
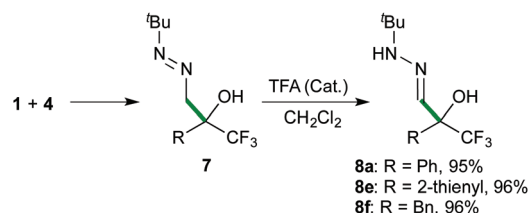
§ Water amounts are normally not included in the *E*-factor; even though additional amounts of organic solvents are required in the subsequent L–L extractions.

¶ Solvent-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).

Scheme 5 Synthesis of α-hydroxy α-trifluoromethyl hydrazones.
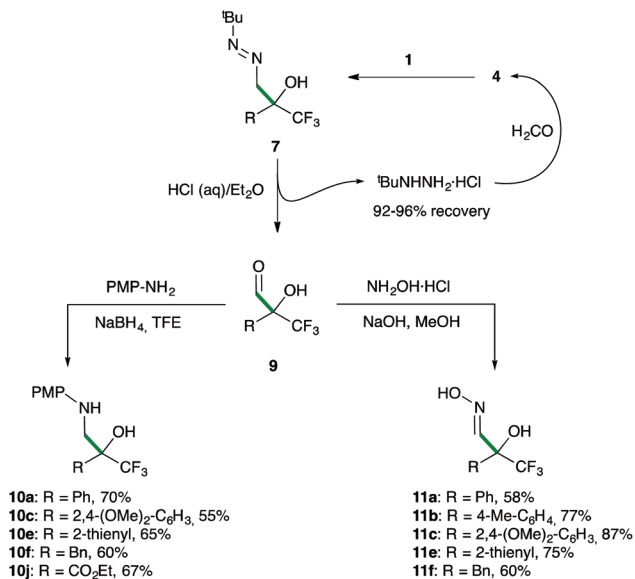
Scheme 6 Synthesis of β-aminoalcohols **10** and α-hydroxy aldoximes **11**. Overall yield for the three-step sequence.

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**.
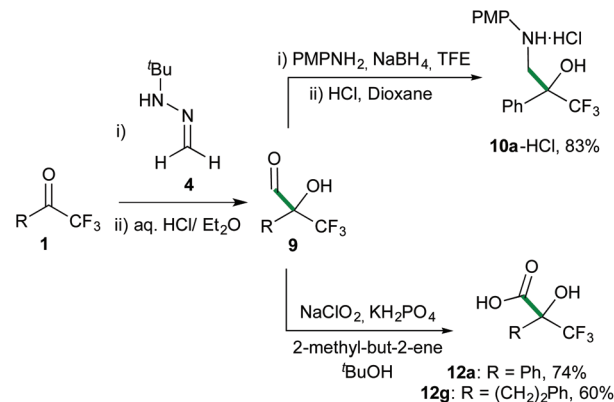
was easily performed (Scheme 6). Thus, upon completion of the addition step, a simple treatment with HCl in a biphasic H_2O/Et_2O or $H_2O/MTBE$ medium‖ afforded the desired α-hydroxy α-trifluoromethyl aldehydes **9** in good yields with a high degree of purity (>95% estimated by ^1H NMR, see the ESI†).

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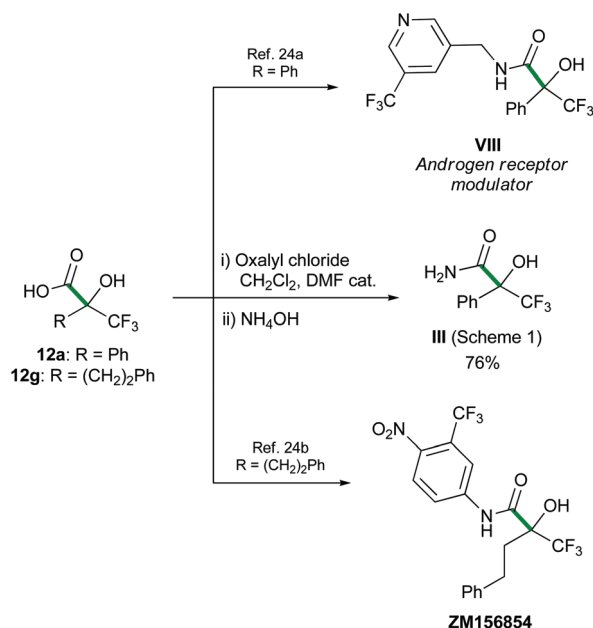
Finally, the efficiency and simplicity of the present methodology are highlighted with 3-step protocols outlined in Scheme 7 for the synthesis of representative trifluoromethylated β-aminoalcohol hydrochloride **10a**-HCl and α-hydroxy acids **12a** and **12g** in good overall yields, without the need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

‖ For products **9** of relatively low volatility, Et_2O can be replaced by less hazardous MTBE, as illustrated for **9c** (see crude ^1H-NMR in the ESI†).

Experimental

Spectra were recorded at 300 or 500 MHz (^1H NMR); 75.5 or 125 MHz (^{13}C NMR); and 470.6 MHz (^{19}F NMR) with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^1H and ^{13}C 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 $KMnO_4$, 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**[25] and not commercially available trifluoromethyl ketones **1**[26] were synthesized according to literature procedures.

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

Freshly distilled formaldehyde *tert*-butylhydrazone **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%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.63–7.54 (m, 2H), 7.46–7.30 (m, 3H), 4.52 (s, 1H), 4.43 (d, 1H, J = 14.2 Hz), 4.36 (dd, 1H, J = 0.4, 14.2 Hz), 1.12 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 136.3, 128.6, 128.3, 126.4, 124.8 (q, $J_{C,F}$ = 285.6 Hz), 76.6 (q, $J_{C,F}$ = 28.7 Hz), 69.9, 68.7, 26.4. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.01 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{13}$H$_{18}$F$_3$N$_2$O [M + H]$^+$ 275.1366, found 275.1356.

3-(*tert*-Butyldiazenyl)-1,1,1-trifluoro-2-(*p*-tolyl)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%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.46 (d, 2H, J = 8.2 Hz), 7.19 (d, 2H, J = 8.2 Hz), 4.52 (s, 1H), 4.41 (d, 1H, J = 14.2 Hz), 4.32 (d, 1H, J = 14.2 Hz), 2.35 (s, 3H), 1.13 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 138.5, 133.3, 129.0, 126.3, 124.8 (q, $J_{C,F}$ = 285.6 Hz), 76.5 (q, $J_{C,F}$ = 28.8 Hz), 70.0, 68.8, 26.5, 21.1. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.07 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{14}$H$_{20}$F$_3$N$_2$O [M + H]$^+$ 289.1522, found 289.1521.

3-(*tert*-Butyldiazenyl)-2-(2,4-dimethoxyphenyl)-1,1,1-trifluoropropan-2-ol (7c). Following the general procedure starting from **1c** (1.47 g, 6 mmol), diazene **7c** was obtained as a pale yellow oil (2.01 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.43 (d, 1H, J = 8.6 Hz), 6.53–6.48 (m, 2H), 5.68 (d, 1H), 4.51 (d, 1H, J = 14.3 Hz), 4.38 (d, 1H, J = 14.3 Hz), 3.85 (s, 3H), 3.81 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 161.1, 158.7, 131.2, 125.3 (q, $J_{C,F}$ = 287.3), 115.8, 104.8, 99.4, 77.5 (q, $J_{C,F}$ = 28.3 Hz), 70.0, 68.1, 55.8, 55.3, 26.5. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.29 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{15}$H$_{21}$F$_3$N$_2$O$_3$Na [M + Na]$^+$ 357.1396, found 357.1388.

3-(*tert*-Butyldiazenyl)-1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol (7d). Following the general procedure starting from **1d** (0.85 mL, 6 mmol), diazene **7d** was obtained as a pale yellow oil (1.75 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.62–7.51 (m, 2H), 7.13–7.02 (m, 2H), 4.41 (d, 1H, J = 14.1 Hz), 4.35 (d, 1H, J = 14.1 Hz), 1.12 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 162.8 (d, $J_{C,F}$ = 247.7 Hz), 132.1 (d, $J_{C,F}$ = 3.1 Hz), 128.5 (dd, $J_{C,F}$ = 8.2, 1.1 Hz), 124.6 (q, $J_{C,F}$ = 286.0 Hz), 115.2 (d, J = 21.5 Hz), 76.3 (q, $J_{C,F}$ = 28.6 Hz), 69.7, 68.9, 26.4. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.32 (s, CF$_3$), [(−113.35)–(−113.44) m, 1F]. HRMS (ESI): m/z calcd for C$_{13}$H$_{17}$F$_4$N$_2$O [M + H]$^+$ 293.1272, found 293.1261.

3-(*tert*-Butyldiazenyl)-1,1,1-trifluoro-2-(thiophen-2-yl)propan-2-ol (7e). Following the general procedure starting from **1e** (0.76 mL, 6 mmol), diazene **7e** was obtained as a pale yellow

oil (1.68 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33 (dd, 1H, J = 1.17, 5.13 Hz), 7.13–7.07 (m, 1H), 7.01 (dd, 1H, J = 3.82, 5.09 Hz), 4.82 (s, 1H), 4.40 (d, 1H, J = 14.3 Hz), 4.35 (d, 1H, J = 14.3 Hz), 1.13 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 140.2, 127.1, 126.3, 125.8, 124.1 (q, $J_{C,F}$ = 285.8 Hz), 70.0 (q, $J_{C,F}$ = 28.5 Hz), 68.9, 26.4. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.25 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{11}$H$_{16}$F$_3$N$_2$OS [M + H]$^+$ 281.0930, found 281.0920.

2-Benzyl-3-(*tert*-butyldiazenyl)-1,1,1-trifluoropropan-2-ol (7f). Following the general procedure starting from **1f** (0.91 mL, 6 mmol), diazene **7f** was obtained as a pale yellow oil (1.73 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.38–7.27 (m, 5H), 3.92 (d, 1H, J = 14.4 Hz), 3.71 (dd, 1H, J = 0.4, 14.4 Hz), 3.29 (d, 1H, J = 14.2 Hz), 3.00 (d, 1H, J = 14.2 Hz), 1.17 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 134.1, 131.2, 128.3, 127.3, 125.9 (q, $J_{C,F}$ = 297.2 Hz), 75.4 (q, $J_{C,F}$ = 27.0 Hz), 68.5, 68.3, 38.5, 26.4. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.64 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{14}$H$_{20}$F$_3$N$_2$O [M + H]$^+$ 289.1522, found 289.1512.

2-[(*tert*-Butyldiazenyl)methyl]-1,1,1-trifluoro-4-phenylbutan-2-ol (7g). Following the general procedure starting from **1g** (1.01 mL, 6 mmol), diazene **7g** was obtained as a pale yellow oil (1.81 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35–7.17 (m, 5H), 4.03 (d, 1H, J = 14.4 Hz), 3.97 (d, 1H, J = 14.4 Hz), 2.97–2.73 (m, 2H), 2.25–1.99 (m, 2H), 1.23 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 141.2, 128.7, 128.3, 126.2, 126.0 (q, $J_{C,F}$ = 286.8 Hz), 77.2, 75.1 (q, $J_{C,F}$ = 27.8 Hz), 68.7, 35.3, 28.9, 26.6. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.95 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{15}$H$_{22}$F$_3$N$_2$O [M + H]$^+$ 303.1679, found 303.1679.

3-(*tert*-Butyldiazenyl)-1,1,1-trifluoro-2-methylpropan-2-ol (7h). Following the general procedure starting from **1h** (0.52 mL, 6 mmol), diazene **7h** was obtained as a pale yellow oil (1.27 g, 99%). ^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ 3.93 (d, 1H, J = 13.7 Hz), 3.81 (d, 1H, J = 13.7 Hz), 1.44 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, CD$_2$Cl$_2$): δ 125.9 (q, $J_{C,F}$ = 284.3 Hz), 73.4 (q, $J_{C,F}$ = 28.5 Hz), 70.7, 68.3, 26.3, 20.0 (d, $J_{C,F}$ = 1.0 Hz). ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −81.14 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_8$H$_{15}$F$_3$N$_2$O [M + H]$^+$ 213.1209, found 213.1206.

2-[(*tert*-Butyldiazenyl)methyl]-1,1,1-trifluorononan-2-ol (7i). Following the general procedure starting from **1i** (1.14 mL, 6 mmol), diazene **7i** was obtained as a pale yellow oil (1.78 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.95 (d, 1H, J = 14.2 Hz), 3.89 (d, 1H, J = 14.2 Hz), 3.69 (s, 1H), 1.89–1.68 (m, 2H), 1.63–1.38 (m, 2H), 1.37–1.23 (m, 8H), 1.21 (s, 9H), 0.88 (t, 3H, J = 7.0 Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 126.0 (q, $J_{C,F}$ = 286.7 Hz), 75.3 (q, $J_{C,F}$ = 27.7 Hz), 68.7, 68.5, 33.3, 31.7, 29.9, 29.0, 26.5, 22.6, 22.4, 14.0. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.98 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{14}$H$_{28}$F$_3$N$_2$O [M + H]$^+$ 297.2148, found 297.2145.

Ethyl 2-[(*tert*-butyldiazenyl)methyl]-3,3,3-trifluoro-2-hydroxypropanoate (7j). Following the general procedure starting from **1j** (0.77 mL, 6 mmol), diazene **7j** was obtained as a colorless oil (1.62 g, 99%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.40 (d, 1H, J = 13.9 Hz), 4.38 (q, 1H, J = 7.1 Hz), 4.37 (q, 1H, J = 7.1 Hz), 4.03 (d, 1H, J = 13.9 Hz), 1.34 (t, 3H, J = 7.15 Hz), 1.17 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 168.6, 122.9 (q, $J_{C,F}$ = 286.2 Hz), 76.7 (q, $J_{C,F}$ = 29.2 Hz), 68.5, 68.0, 63.8, 26.7, 14.0. ^{19}F NMR

(470.6 MHz, CDCl$_3$): δ −77.49 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{10}$H$_{17}$F$_3$N$_2$O$_3$Na [M + Na]$^+$ 293.1083, found 293.1081.

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 CH$_2$Cl$_2$ (10 mL) was added to a solution of diazene **7** (1 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. A saturated NaHCO$_3$ solution (15 mL) was added and the organic phase was separated. The remaining aqueous phase was extracted with Et$_2$O (3 × 10 mL), and the combined organic layer was dried over anhydrous MgSO$_4$, 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: 72–75 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.66–7.58 (m, 2H), 7.45–7.35 (m, 3H), 7.34 (s, 1H), 5.04 (s, 1H), 1.20 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 136.3, 132.7 (d, $J_{C,F}$ = 1.7 Hz), 128.6, 128.4 (d, $J_{C,F}$ = 0.6 Hz), 126.2 (d, $J_{C,F}$ = 1.7 Hz), 124.4 (q, $J_{C,F}$ = 286.2 Hz), 75.2 (q, $J_{C,F}$ = 29.2 Hz), 54.1, 28.3. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.18 (s, CF$_3$). HRMS (CI): m/z calcd for C$_{13}$H$_{17}$F$_3$N$_2$O [M]$^+$ 274.1293, found 274.1289.

3-[2-(*tert*-Butyl)hydrazono]-1,1,1-trifluoro-2-(thiophen-2-yl)-propan-2-ol (8e). Following the general procedure, α-hydroxy hydrazone **8e** was obtained as a yellow oil (0.27 g, 96%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34 (dd, J = 0.8, 5.1 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.04 (dd, J = 3.9, 5.1 Hz, 1H), 5.23 (s, 1H), 1.20 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 140.2, 131.5 (d, $J_{C,F}$ = 1.1 Hz), 127.2, 126.0, 125.3 (d, $J_{C,F}$ = 1.7 Hz), 123.9 (q, $J_{C,F}$ = 286.1 Hz), 74.8 (q, $J_{C,F}$ = 30.8 Hz), 54.2, 28.3. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.30 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{11}$H$_{16}$F$_3$N$_2$OS [M + H]$^+$ 281.0930, found 281.0920.

2-Benzyl-3-[2-(*tert*-butyl)hydrazono]-1,1,1-trifluoropropan-2-ol (8f). Following the general procedure, α-hydroxy hydrazone **8f** was obtained as a white solid (0.28 g, 96%); mp: 62–64 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25–7.16 (m, 5H), 6.88 (s, 1H), 4.30 (s, 1H), 3.21 (d, 1H, J = 14.2 Hz), 3.02 (d, 1H, J = 14.2 Hz), 0.96 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 134.0, 132.4 (d, $J_{C,F}$ = 0.7 Hz), 130.7, 128.0, 126.9, 77.2, 75.2 (q, $J_{C,F}$ = 28.0 Hz), 53.9, 38.7, 28.0. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.95 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{14}$H$_{20}$F$_3$N$_2$O [M + H]$^+$ 289.1522, found 289.1511.

General procedure for the one-pot synthesis of α-hydroxy α-trifluoromethyl aldehydes 9

Freshly distilled formaldehyde *tert*-butylhydrazone **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**. Subsequently, aq. HCl (30 mL, 6 M) was added to a solution of

diazene **7** (6 mmol) in Et$_2$O (55 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred until consumption of the starting material (TLC monitoring, approx. 6 h). The organic phase was separated and the aqueous phase was extracted with Et$_2$O (2 × 30 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure (35 mmHg, 5 °C) to afford α-hydroxy aldehyde **9** (purity > 95% estimated by ^{1}H-NMR). This material was used in subsequent transformations without further purification. **9c** was synthesized employing MTBE as the solvent, which was removed under reduced pressure (15 mmHg, 15 °C).

General procedure for the synthesis of β-aminoalcohols 10

p-Methoxyphenylaniline (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. NaBH$_4$ (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/CH$_2$Cl$_2$) to afford products **10**.

1,1,1-Trifluoro-3-[(4-methoxyphenyl)amino]-2-phenylpropan-2-ol (10a). Following the general procedure, β-aminoalcohol **10a** was obtained as a brown solid (1.31 g, 70%); mp: 53–55 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.69–7.59 (m, 2H), 7.50–7.39 (m, 3H), 6.83–6.74 (m, 2H), 6.72–6.64 (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). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 153.9, 141.2, 136.5, 128.9, 128.5, 126.3, 125.4 (q, $J_{C,F}$ = 285.4 Hz), 116.6, 114.8, 74.8 (q, $J_{C,F}$ = 27.6 Hz), 55.6, 51.5. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.28 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{16}$H$_{17}$F$_3$NO$_2$ [M + H]$^+$ 312.1206, found 312.1195.

2-(2,4-Dimethoxyphenyl)-1,1,1-trifluoro-3-[(4-methoxyphenyl)amino]propan-2-ol (10c). Following the general procedure, β-aminoalcohol **10c** was obtained as a brown oil (1.22 g, 55%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.43–7.34 (m, 1H), 6.83–6.72 (m, 2H), 6.71–6.60 (m, 2H), 6.59–6.50 (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). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 161.3, 159.4, 152.7, 142.1, 130.8, 125.5 (q, $J_{C,F}$ = 287.8 Hz), 115.1, 114.7, 105.3, 99.8, 77.3 (q, $J_{C,F}$ = 28.2 Hz), 55.9, 55.6, 55.2, 48.4 (d, $J_{C,F}$ = 1.3 Hz). ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.84 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{18}$H$_{21}$F$_3$NO$_4$ [M + H]$^+$ 302.1417, found 372.1408.

1,1,1-Trifluoro-3-[(4-methoxyphenyl)amino]-2-(thiophen-2-yl)-propan-2-ol (10e). Following the general procedure, β-amino-alcohol **10e** was obtained as a brown solid (1.24 g, 65%); mp: 41–43 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 (dd, 1H, J = 5.1, 1.2 Hz), 7.18 (d, 1H, J = 3.3 Hz), 7.07 (dd, 1H, J = 5.1, 3.6 Hz), 6.81–6.72 (m, 2H), 6.72–6.64 (m, 2H), 3.87 (d, 1H, J = 13.5 Hz), 3.75 (s, 3H), 3.60 (d, 1H, J = 13.5 Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 154.0, 140.9, 140.7, 127.4, 126.6, 125.6, 124.7 (q, $J_{C,F}$ = 1.3 Hz), 123.8 (q, $J_{C,F}$ = 285.7 Hz), 116.7, 114.9, 74.8 (q, $J_{C,F}$ = 29.9 Hz), 55.7, 52.2. ^{19}F NMR (470.6 MHz, CDCl$_3$):

δ −79.39 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{14}$H$_{15}$F$_3$NO$_2$S [M + H]$^+$ 318.0770, found 318.0759.

2-Benzyl-1,1,1-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%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39–7.30 (m, 5H), 6.70–6.63 (m, 2H), 6.37–6.30 (m, 2H), 3.71 (s, 3H), 3.44 (d, 1H, J = 14.1 Hz), 3.27 (d, 1H, J = 13.9 Hz), 3.18 (dd, 1H, J = 14.1, 0.6 Hz), 2.87 (d, 1H, J = 13.9 Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 153.5, 141.6, 134.2, 132.1, 128.0, 127.3, 126.5 (q, $J_{C,F}$ = 287.2 Hz), 116.0, 114.7, 73.2 (q, $J_{C,F}$ = 26.3 Hz), 55.6, 48.2, 38.0 (d, J = 1.4 Hz). ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −80.21 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{15}$H$_{20}$F$_3$NO$_2$ [M + H]$^+$ 326.1338, found 326.1350.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-{[(4-methoxyphenyl)amino]methyl}propanoate (10j). Following the general procedure, β-aminoalcohol **10j** was obtained as a brown oil (1.23 g, 67%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.81–6.74 (m, 2H), 6.70–6.63 (m, 2H), 4.33 (dq, 1H, J = 10.7, 7.2 Hz), 4.21 (dq, 1H, J = 10.7, 7.2 Hz), 3.84 (d, 1H, J = 13.2 Hz), 3.75 (s, 3H), 3.46 (d, 1H, J = 13.2 Hz), 1.27 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 168.8 (d, $J_{C,F}$ = 1.1 Hz), 153.1, 141.1, 122.9 (q, $J_{C,F}$ = 288.3 Hz), 115.8, 114.7, 77.8 (q, $J_{C,F}$ = 28.6 Hz), 64.0, 55.7, 46.5 (d, $J_{C,F}$ = 1.2 Hz), 13.8. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −77.26 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{13}$H$_{17}$F$_3$NO$_4$ [M + H]$^+$ 308.1104, found 308.1102.

General procedure for the synthesis of α-hydroxy aldoximes 11

Hydroxylamine hydrochloride (0.50 g, 7.2 mmol) and sodium hydroxide (0.29 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 CH$_2$Cl$_2$ (2 × 30 mL) and Et$_2$O (2 × 30 mL). The combined organic layer was dried (MgSO$_4$), filtered and concentrated. The product was purified by flash chromatography (3 : 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: 62–64 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.97 (d, J = 0.3 Hz, 1H), 7.66–7.56 (m, 3H), 7.47–7.36 (m, 3H), 4.21 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 147.3, 134.7, 129.3, 128.7, 126.3 (d, $J_{C,F}$ = 0.6 Hz), 123.9 (q, $J_{C,F}$ = 288.0 Hz), 75.4 (q, $J_{C,F}$ = 29.6 Hz). ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.24 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_9$H$_8$F$_3$NO$_2$Na [M + Na]$^+$ 242.0399, found 242.0390.

3,3,3-Trifluoro-2-hydroxy-2-(p-tolyl)propanal oxime (11b). Following the general procedure, α-hydroxy aldoxime **11b** was obtained as a white solid (1.08 g, 77%); mp: 66–68 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.95 (s, 1H), 7.85 (s, 1H), 7.48 (d, 2H, J = 8.2 Hz), 7.24 (d, 2H, J = 8.2 Hz), 4.23 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 147.5, 139.3, 131.7, 129.2, 126.2, 124.1 (q, $J_{C,F}$ = 285.2 Hz), 75.5 (q, $J_{C,F}$ = 29.9 Hz), 21.0. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.27 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{10}$H$_{10}$F$_3$NO$_2$Na [M + Na]$^+$ 256.0556, found 256.0548.

2-(2,4-Dimethoxyphenyl)-3,3,3-trifluoro-2-hydroxypropanal oxime (11c). Following the general procedure, α-hydroxy aldoxime **11c** was obtained as a white solid (1.46 g, 87%); mp = 150–152 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.55 (s, 1H), 8.12 (s, 1H), 7.63 (d, 1H, J = 8.5 Hz), 6.66–6.56 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.81 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 162.0, 158.5, 147.6, 130.1, 124.9 (q, $J_{C,F}$ = 286.3), 116.6, 105.2, 99.3, 75.4 (q, $J_{C,F}$ = 30.3 Hz), 55.5, 54.9. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.59 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{11}$H$_{13}$F$_3$NO$_4$ [M + H]$^+$ 280.0791, found 280.0785.

3,3,3-Trifluoro-2-hydroxy-2-(thiophen-2-yl)propanal oxime (11e). Following the general procedure, α-hydroxy aldoxime **11e** was obtained as a colorless oil (1.01 g, 75%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.84 (s, 1H), 7.71 (s, 1H), 7.39 (dd, 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). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 146.2, 137.9, 127.4, 127.0, 126.3 (d, $J_{C,F}$ = 0.5 Hz), 123.4 (q, $J_{C,F}$ = 286.1 Hz), 75.0 (q, $J_{C,F}$ = 31.6 Hz). ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −78.30 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_7$H$_6$F$_3$NO$_2$Na [M + Na]$^+$ 247.9964, found 247.9959.

2-Benzyl-3,3,3-trifluoro-2-hydroxypropanal oxime (11f). Following the general procedure, α-hydroxy aldoxime **11f** was obtained as a colorless oil (0.84 g, 60%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.50 (s, 1H), 7.43 (s, 1H), 7.33–7.23 (m, 3H), 7.22–7.16 (m, 2H), 3.55 (s, 1H), 3.22 (d, 1H, J = 14.0 Hz), 3.09 (d, 1H, J = 14.0 Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 146.4, 132.8, 130.8, 128.3, 127.4, 124.4 (q, $J_{C,F}$ = 286.4 Hz), 75.3 (q, $J_{C,F}$ = 28.5 Hz), 38.6. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −79.85 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{10}$H$_{10}$F$_3$NO$_2$Na [M + Na]$^+$ 256.0056, found 256.0552.

Synthesis of β-aminoalcohol hydrochloride 10a-HCl

p-Methoxyphenylaniline (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 minutes. After this time, NaBH$_4$ (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 CH$_2$Cl$_2$ (5 mL). The mixture was filtered through silica and Celite pad (height: 1 cm), and washed with a mixture of pentane/CH$_2$Cl$_2$ (2/1, 10 mL). Solvents were removed under reduced pressure and the product was dissolved in dry Et$_2$O (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 Et$_2$O (2 mL) to afford the pure amine hydrochloride **10a-HCl** (0.72 g, 83%). ^{1}H NMR (300 MHz, DMSO-d^6): 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). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 156.9, 134.9, 133.4, 128.9, 128.2, 127.1, 125.0 (q, $J_{C,F}$ = 285.3 Hz), 121.8, 114.5, 75.2 (q, $J_{C,F}$ = 27.8 Hz), 55.5, 53.0. ^{19}F NMR (470.6 MHz, CDCl$_3$): δ −77.07 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{16}$H$_{17}$F$_3$NO$_2$$^+$ [M$^+$] 312.1206, found 312.1198.

General procedure for the synthesis of α-hydroxy acids 12

A solution of NaClO$_2$ (20 mmol) and KH$_2$PO$_4$ (18 mmol) in H$_2$O (70 mL) was added dropwise to a solution of crude aldehyde **9** (6 mmol) in ^{t}BuOH (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 Et$_2$O. The aqueous layer was acidified to pH 1 (2 M HCl) and extracted with EtOAc. The combined organic layer was dried (MgSO$_4$), filtered and the solvent was removed under reduced pressure to afford pure α-hydroxy acid.

3,3,3-Trifluoro-2-hydroxy-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, 60%); mp = 83–85 °C. ^{1}H NMR (500 MHz, acetone-d^6): δ 8.57 (s, 1H), 7.35–7.07 (m, 5H), 2.89 (dt, J = 4.6, 12.8 Hz, 1H), 2.54 (dt, J = 4.6, 12.8 Hz, 1H), 2.34 (dt, J = 4.6, 12.8 Hz, 1H), 2.15 (dt, J = 4.6, 12.8 Hz). ^{13}C NMR (125 MHz, acetone-d^6): δ 169.6, 140.8, 128.5, 128.3, 126.1, 124.4 (c, $J_{C,F}$ = 286.7 Hz), 77.3 (c, $J_{C,F}$ = 28.2 Hz), 34.2. ^{19}F NMR (470.6 MHz, acetone-d^6): δ −78.80 (s, CF$_3$). HRMS (ESI): m/z calcd for C$_{11}$H$_{11}$F$_3$O$_3$ [M + Na]$^+$ 271.0845, found 271.0849.

Synthesis of α-hydroxy α- trifluoromethyl amide III

Oxalyl chloride (0.2 mL, 2.16 mmol) and a drop of DMF were subsequently added to a stirred solution of the acid **12a** (264 mg, 1.2 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 3 h, slowly warming to rt, then NH$_3$ (28% in water, 40 mL) was added. The resulting solution was stirred at rt for 6 h, diluted with water (40 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with brine (100 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (1:1 cyclohexane/AcOEt) to afford α-hydroxy amide **III** as a white solid (0.2 g, 76%). Characterization data are in agreement with those reported in the literature.[27]

Conclusions

In summary, the high diaza–ene reactivity of formaldehyde *tert*-butyl hydrazone (FTBH) with trifluoromethyl ketones under solvent-free conditions afforded analytically pure α-hydroxy α-trifluoromethyl diazenes in a quantitative way. From these products, operationally simple diazene-to-aldehyde transformations and subsequent derivatizations in a 'one-pot' fashion provide a simple and environmentally friendly entry to trifluoromethylated β-aminoalcohols, α-hydroxy aldoximes and α-hydroxy acids.

Acknowledgements

Notes and references

1 A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15.

2 (*a*) T. Hiyama, in *Organofluorine Compounds: Chemistry Applications*, Springer, New York, 2000; (*b*) P. Kirsch, in *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2004; (*c*) R. D. Chambers, in *Fluorine in Organic Chemistry*, Blackwell, Oxford, 2004; (*d*) T. Yamazaki, T. Taguchi and I. Ojima, in *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, Chichester, 2009; (*e*) V. A. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Wiley, Hoboken, New Jersey, 2009; (*f*) C. Isanbor and D. ÓHagan, *J. Fluorine Chem.*, 2006, **127**, 303; (*g*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*h*) M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070; (*i*) D. ÓHagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*j*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*k*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*l*) D. O'Hagan, *J. Fluorine Chem.*, 2010, **131**, 1071.

3 (*a*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1 and references cited therein; (*b*) G. Valero, X. Company and R. Rios, *Chem. – Eur. J.*, 2011, **17**, 2018; (*c*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470.

4 (*a*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455; (*b*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475 and references therein. (*c*) H. Kawai and N. Shibata, *Chem. Rec.*, 2014, **14**, 1024.

5 Cholesteryl ester transfer protein inhibitor **I**: M. A. Massa, D. P. Spangler, R. C. Durley, B. S. Hickory, D. T. Connolly, B. J. Witherbee, M. E. Smith and J. A. Sikorski, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1625.

6 Non-steroidal selective glucocorticoid receptor agonist **II**: H. A. Barnett, D. M. Coe, T. W. J. Cooper, T. I. Jack, H. T. Jones, S. J. f. Macdonald, I. M. McLay, N. Rayner, R. Z. Sasse, T. J. Shipley, P. A. Skone, G. I. Somers, S. Taylor, I. J. Uings, J. M. Woolven and G. G. Weingarten, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 158.

7 Anesthetic and anti-convulsant **III**: (*a*) I. Choudhury-Mukherjee, H. A. Schenck, S. Cechova, T. N. Pajewski, J. Kapur, J. Ellena, D. S. Cafiso and M. L. Brown, *J. Med. Chem.*, 2003, **46**, 2494; (*b*) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S. –H. Ko, J. P. Stables, M. K. Patel and M. L. Brown, *Bioorg. Med. Chem.*, 2004, **12**, 979. Pyruvate dehydrogenase kinase inhibitor **IV**: (*c*) T. D. Aicher, R. C. Anderson, G. R. Bebernitz, G. M. Coppola, C. F. Jewell,

D. C. Knorr, C. Liu, D. M. Sperbeck, L. J. Brand, R. J. Strohschein, J. Gao, C. C. Vinluan, S. S. Shetty, C. Dragland, E. L. Kaplan, D. DelGrande, A. Islam, X. Liu, R. J. Lozito, W. M. Maniara, R. E. Walterand and W. R. Mann, *J. Med. Chem.*, 1999, **42**, 2741.

8   (a) J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, L. Logue, G. L. Trainor, P. S. Anderson and S. K. Erickson-Viitanen, *J. Med. Chem.*, 2000, **43**, 2019; (b) M. E. Pierce, L. P. Rodney, L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C.-Y. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer and P. J. Reider, *J. Org. Chem.*, 1998, **63**, 8536; (c) E. J. J. Grabowski, *Chirality*, 2005, **17**, S249; (d) M. M. Bastos, C. C. P. Costa, T. C. Bezerra, F. C. Da Silva and N. Boechat, *Eur. J. Med. Chem.*, 2016, **108**, 455.

9   M. Sani, D. Belotti, R. Giavazzi, W. Panzeri, A. Volonterio and M. Zanda, *Tetrahedron Lett.*, 2004, **45**, 1611.

10   S. Caron, N. M. Do, J. E. Sieser, P. Arpin and E. Vazquez, *Org. Process Res. Dev.*, 2007, **11**, 1015.

11   Recent review: (a) G. Rubiales, C. Alonso, E. Martínez de Marigorta and F. Palacios, *ARKIVOC*, 2014, **ii**, 362. Selected examples: (b) J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee and C. H. Senanayake, *Org. Lett.*, 2005, **7**, 2193; (c) G. K. S. Prakash, Z. Zhang, F. Wang, S. Munoz and G. A. Olah, *J. Org. Chem.*, 2013, **78**, 3300.

12   Selected examples: (a) R. Motoki, M. Kanai and M. Shibasaki, *Org. Lett.*, 2007, **9**, 5079; (b) F. Tur and J. M. Saá, *Org. Lett.*, 2007, **9**, 5079; (c) G. Blay, I. Fernández, A. Monleón, José R. Pedro and C. Vila, *Org. Lett.*, 2009, **11**, 441; (d) C. Palacio and S. J. Connon, *Org. Lett.*, 2011, **13**, 1298; (e) N. Duangdee, W. Harnying, G. Rulli, J.–M. Neudörfl, H. Gröger and A. Berkessel, *J. Am. Chem. Soc.*, 2012, **134**, 11196.

13   M. B. Smith, in *March, Jerry, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley-Interscience, New York, 6th edn, 2007.

14   Some examples: (a) P. Bravo, M. Frigerio and G. Resnati, *J. Org. Chem.*, 1990, **55**, 4216; (b) A. Dondoni, A. Boscarato, P. Formaglio, J.-P. Bégué and F. Benayoud, *Synthesis*, 1995, 654.

15   Reviews: (a) R. Fernández and J. M. Lassaletta, *Synlett*, 2000, 1228; (b) R. Brehme, D. Enders, R. Fernández and J. M. Lassaletta, *Eur. J. Org. Chem.*, 2007, 5629.

16   Diastereoselective 1,2 additions to trifluoromethyl ketones: (a) R. Fernández, E. Martín-Zamora, C. Pareja, J. Vázquez, E. Díez, A. Monge and J. M. Lassaletta, *Angew. Chem., Int. Ed.*, 1998, **37**, 3428; (b) C. Pareja, E. Martín-Zamora, R. Fernández and J. M. Lassaletta, *J. Org. Chem.*, 1999, **64**,

8846. α-Alkoxy-(amino)aldehydes: (c) R. Fernández, E. Martín-Zamora, C. Pareja and J. M. Lassaletta, *J. Org. Chem.*, 2001, **66**, 5201. Simple aldehydes: (d) R. Fernández, E. Martín-Zamora, C. Pareja, M. Alcarazo, J. Martín and J. M. Lassaletta, *Synlett*, 2001, 1158. Racemic 1,2-additions to α-keto esters: (e) A. Crespo-Peña, E. Martín-Zamora, R. Fernández and J. M. Lassaletta, *Chem. – Asian J.*, 2011, **6**, 2287. Enantioselective 1,4-additions to α-hydroxyenones: (f) D. Monge, E. Martín-Zamora, J. Vaźquez, M. Alcarazo, E. Álvarez, R. Fernańdez and J. M. Lassaletta, *Org. Lett.*, 2007, **9**, 2867; (g) R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernańdez and J. M. Lassaletta, *Org. Lett.*, 2007, **9**, 3303.

17   A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2012, **134**, 12912.

18   D. Monge, A. Crespo-Peña, E. Martín-Zamora, E. Álvarez, R. Fernández and J. M. Lassaletta, *Chem. – Eur. J.*, 2013, **19**, 8421.

19   I. Serrano, D. Monge, E. Álvarez, R. Fernández and J. M. Lassalettta, *Chem. Commun.*, 2015, **51**, 4077.

20   (a) R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233; (b) A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1; (c) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273; (d) R. A. Sheldon, *Green Chem.*, 2012, **41**, 1437.

21   (a) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; (b) K. Tanaka, in *Solvent-Free Organic Synthesis*, Wiley-VCH, Weinheim, 2003.

22   A. Loupy, *Top. Curr. Chem.*, 1999, **206**, 153.

23   For an example of the C-coupling of aryl bromides with *N-tert*-butyl hydrazones, see: A. Takemiya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 14800.

24   (a) Y. Kim, R. S. Meissner, H. J. Mitchell, J. J. Perkins, M. A. Rossi and J. Wang, *US* 2009/0275515A1; (b) P. Wang, L.-W. Feng, L. Wang, J.-F. Li, S. Liao and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 4626.

25   (a) Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada and N. Yoshikawa, *J. Org. Chem.*, 1988, **53**, 129; (b) J.-S. M. Lehn, S. Javed and D. M. Hoffman, *Inorg. Chem.*, 2007, **46**, 993.

26   Trifluoromethyl ketones **1** were prepared by Grignard reagent addition to 2,2,2-ethyltrifluoroacetate: (a) For characterization of trifluoromethyl ketone **1g** see: K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota and J. Ichiwaka, *Chem. – Eur. J.*, 2011, **17**, 12175. For characterization of trifluoromethyl ketone **1i** see: E. Massolo, M. Benaglia, M. Orlandini, S. Rossi and G. Celentano, *Chem. – Eur. J.*, 2015, **21**, 3589.

27   H. A. Schenck, P. W. Leukowski, I. Choudhury-Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel and M. L. Brown, *Bioorg. Med. Chem.*, 2014, **12**, 979.