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

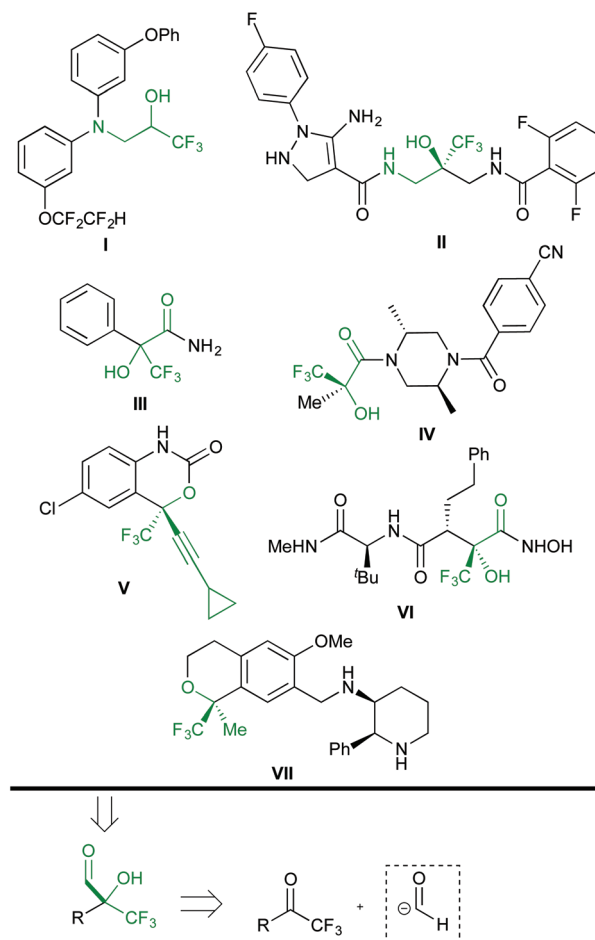
Esteban Matador,^a David Monge,^{*a} Rosario Fernández^{*a} and José M. Lassaletta^{*b}

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



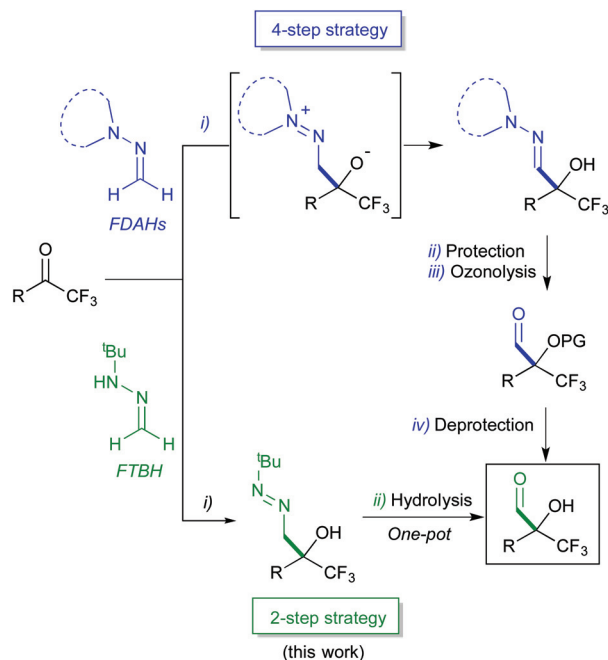
Scheme 1 Retrosynthetic analysis of biologically relevant functionalized trifluoromethyl carbinols and derivatives.

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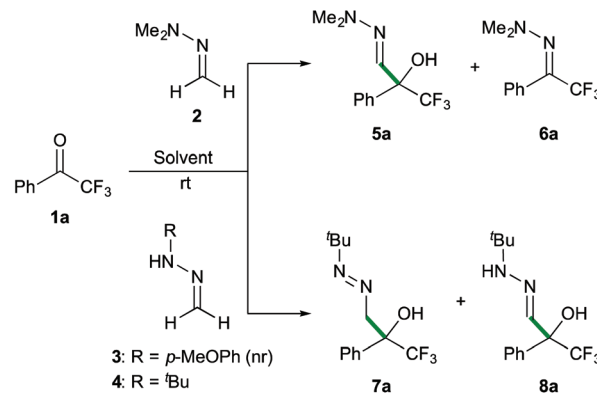
Scheme 2 Nucleophilic formylations of trifluoromethyl ketones employing formaldehyde hydrazones as d^1 reagents.

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 d^1 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 (d^1 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 isatins¹⁸ 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-



Scheme 3 Preliminary reactivity experiments.

Table 1 Optimization of the reaction of **1a** and **4**^a

Entry	Solvent	<i>T</i>	7a : 8a ^b	Yield ^c (%)	<i>E</i> -factor ^d (g g ⁻¹)
1	CH ₂ Cl ₂	9 h	10 : 0	83	12.08
2	CHCl ₃	7 h	8 : 2	70	16.31
3	<i>n</i> -Hexane	31 h	10 : 0	80	6.49
4	Toluene	31 h	10 : 0	81	8.27
5	Et ₂ O	31 h	10 : 0	74	7.63
6	CH ₃ CN	6 h	10 : 0	90	6.69
7	H ₂ O	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.

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 -trifluoromethyl-hydrazone **5a** in a modest 55% yield (after 20 days in CH₂Cl₂ at room temperature) along with small amounts of the hydrazone 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[‡] ²⁰ was

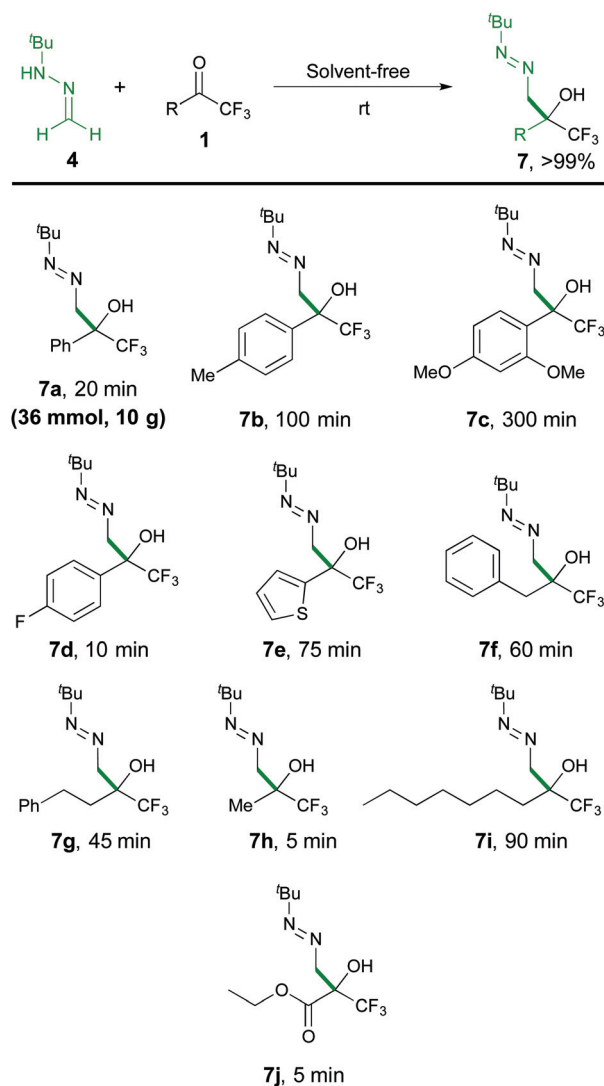
[‡] The *E*-factor is defined as the mass ratio of the waste to the desired product. For *E*-factors including solvents after chromatographic purifications or L–L extractions see the ESI.[†]



used as a descriptor of the environmental impact. Using CHCl_3 instead of CH_2Cl_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_3CN 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_2O , 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).

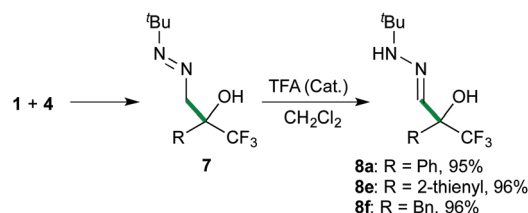
The scope of the reaction was then explored with a range of trifluoromethyl ketones **1**, including aromatic (**1a–1d**), hetero-aromatic (**1e**), aliphatic derivatives (**1f–1i**) and the densely functionalized ethyl 3,3,3-trifluoropyruvate (**1j**), as outlined in Scheme 4. The collected data indicate 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** ($\text{R} = 4\text{-F-C}_6\text{H}_4$), **1h** ($\text{R} = \text{Me}$), and **1j** ($\text{R} = \text{CO}_2\text{Et}$) 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**

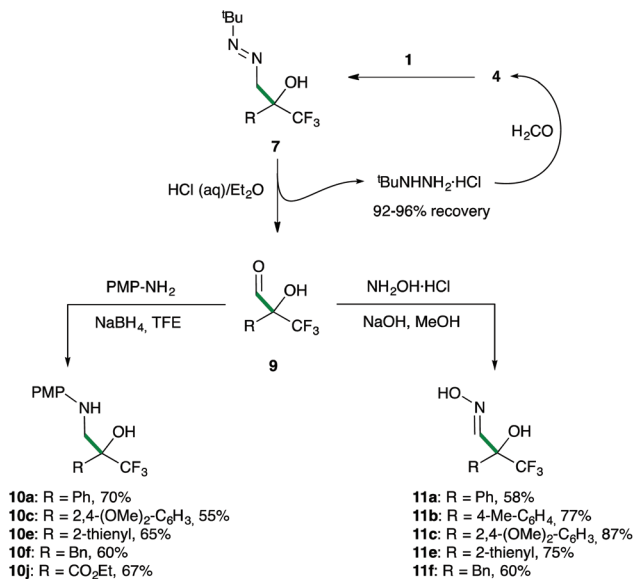


Scheme 5 Synthesis of α -hydroxy α -trifluoromethyl hydrazones.

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

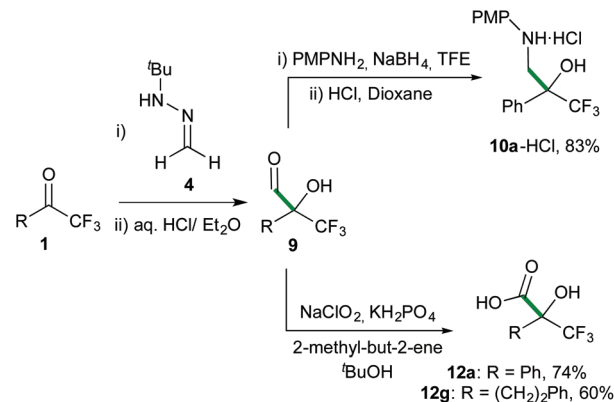
was easily performed (Scheme 6). Thus, upon completion of the addition step, a simple treatment with HCl in a biphasic H₂O/Et₂O or H₂O/MTBE medium^{||} afforded the desired α -hydroxy α -trifluoromethyl aldehydes **9** in good yields with a high degree of purity (>95% estimated by ¹H NMR, see the ESI†).

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.

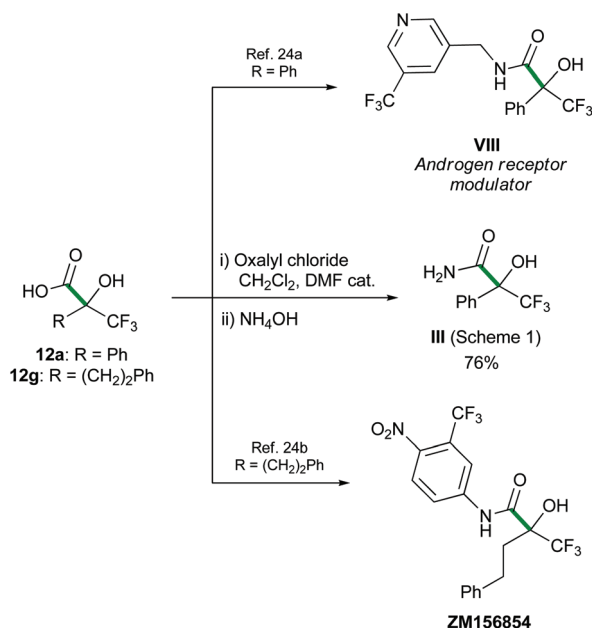
Finally, the efficiency and simplicity of the present methodology are highlighted with 3-step protocols outlined in Scheme 7 for the synthesis of representative trifluoromethylated β -aminoalcohol hydrochloride **10a**-HCl and α -hydroxy acids **12a** and **12g** in good overall yields, without the need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

^{||} For products **9** of relatively low volatility, Et₂O can be replaced by less hazardous MTBE, as illustrated for **9c** (see crude ¹H-NMR in the ESI†).



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**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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.01 (s, CF₃). HRMS (ESI): m/z calcd for C₁₃H₁₈F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.07 (s, CF₃). HRMS (ESI): m/z calcd for C₁₄H₂₀F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –79.29 (s, CF₃). HRMS (ESI): m/z calcd for C₁₅H₂₁F₃N₂O₃Na [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.32 (s, CF₃), [–113.35]–[–113.44] (m, 1F). HRMS (ESI): m/z calcd for C₁₃H₁₇F₄N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –79.25 (s, CF₃). HRMS (ESI): m/z calcd for C₁₁H₁₆F₃N₂OS [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.64 (s, CF₃). HRMS (ESI): m/z calcd for C₁₄H₂₀F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): δ 141.2, 128.7, 128.3, 126.2, 126.0 (q, $J_{C,F}$ = 286.8), 77.2, 75.1 (q, $J_{C,F}$ = 27.8 Hz), 68.7, 35.3, 28.9, 26.6. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.95 (s, CF₃). HRMS (ESI): m/z calcd for C₁₅H₂₂F₃N₂O [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%). ¹H NMR (300 MHz, CD₂Cl₂): 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). ¹³C NMR (125 MHz, CD₂Cl₂): 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). ¹⁹F NMR (470.6 MHz, CDCl₃): δ –81.14 (s, CF₃). HRMS (ESI): m/z calcd for C₈H₁₅F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ –78.98 (s, CF₃). HRMS (ESI): m/z calcd for C₁₄H₂₈F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR



(470.6 MHz, CDCl₃): δ -77.49 (s, CF₃). HRMS (ESI): m/z calcd for C₁₀H₁₇F₃N₂O₃Na [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 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 \times 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: 72–75 °C. ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.18 (s, CF₃). HRMS (CI): m/z calcd for C₁₃H₁₇F₃N₂O [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -79.30 (s, CF₃). HRMS (ESI): m/z calcd for C₁₁H₁₆F₃N₂OS [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. ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.95 (s, CF₃). HRMS (ESI): m/z calcd for C₁₄H₂₀F₃N₂O [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 Et₂O (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 Et₂O (2 \times 30 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure (35 mmHg, 5 °C) to afford α -hydroxy aldehyde **9** (purity > 95% estimated by ¹H-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. 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-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. ¹H NMR (300 MHz, CDCl₃): δ 7.69–7.59 (m, 2H), 7.50–7.39 (m, 3H), 6.83–6.74 (m, 2H), 6.72–6.64 (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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.28 (s, CF₃). HRMS (ESI): m/z calcd for C₁₆H₁₇F₃NO₂ [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%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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). ¹⁹F NMR (470.6 MHz, CDCl₃): δ -79.84 (s, CF₃). HRMS (ESI): m/z calcd for C₁₈H₂₁F₃NO₄ [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 -aminoalcohol **10e** was obtained as a brown solid (1.24 g, 65%); mp: 41–43 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃):



δ -79.39 (s, CF₃). HRMS (ESI): m/z calcd for C₁₄H₁₅F₃NO₂S [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%). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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). ¹⁹F NMR (470.6 MHz, CDCl₃): δ -80.21 (s, CF₃). HRMS (ESI): m/z calcd for C₁₅H₂₀F₃NO₂ [M + H]⁺ 326.1338, found 326.1350.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-[(4-methoxyphenyl)amino]-methylpropanoate (10j). Following the general procedure, β -aminoalcohol **10j** was obtained as a brown oil (1.23 g, 67%). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -77.26 (s, CF₃). HRMS (ESI): m/z calcd for C₁₃H₁₇F₃NO₄ [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 CH₂Cl₂ (2 \times 30 mL) and Et₂O (2 \times 30 mL). The combined organic layer was dried (MgSO₄), 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. ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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). ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.24 (s, CF₃). HRMS (ESI): m/z calcd for C₉H₈F₃NO₂Na [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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -79.27 (s, CF₃). HRMS (ESI): m/z calcd for C₁₀H₁₀F₃NO₂Na [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. ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.59 (s, CF₃). HRMS (ESI): m/z calcd for C₁₁H₁₃F₃NO₄ [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%). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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). ¹⁹F NMR (470.6 MHz, CDCl₃): δ -78.30 (s, CF₃). HRMS (ESI): m/z calcd for C₇H₆F₃NO₂Na [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%). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -79.85 (s, CF₃). HRMS (ESI): m/z calcd for C₁₀H₁₀F₃NO₂Na [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, 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-*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). ¹³C NMR (75.5 MHz, CDCl₃): 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. ¹⁹F NMR (470.6 MHz, CDCl₃): δ -77.07 (s, CF₃). HRMS (ESI): m/z calcd for C₁₆H₁₇F₃NO₂⁺ [M⁺] 312.1206, found 312.1198.



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 ^tBuOH (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 acidified 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-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. ¹H NMR (500 MHz, acetone-d₆): 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). ¹³C NMR (125 MHz, acetone-d₆): 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. ¹⁹F NMR (470.6 MHz, acetone-d₆): δ -78.80 (s, CF₃). HRMS (ESI): *m/z* calcd for C₁₁H₁₁F₃O₃ [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 NH₃ (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 MgSO₄, 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 diazo-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.

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