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

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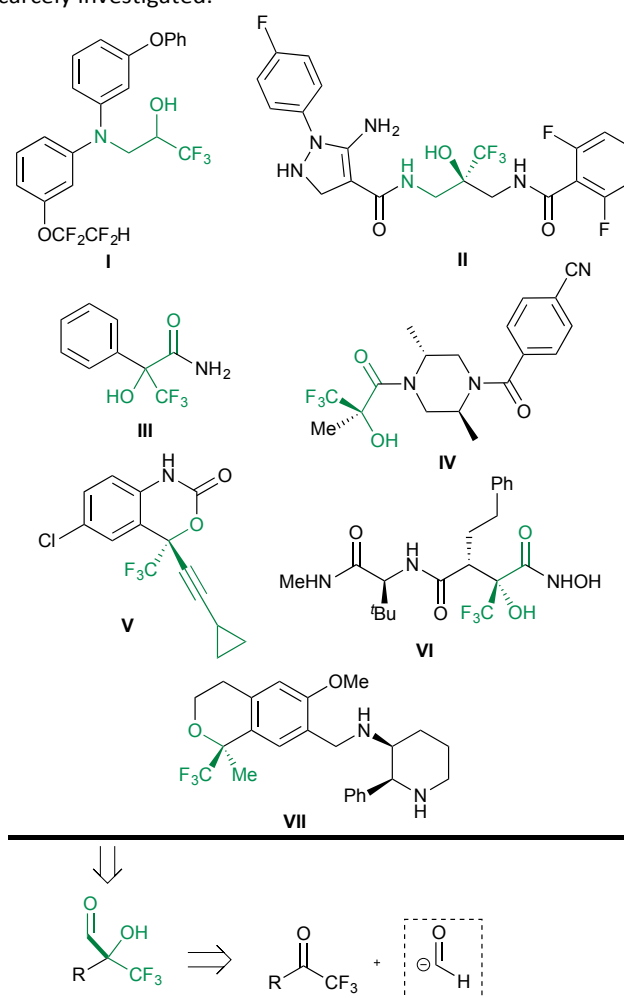
Esteban Matador,^a David Monge,^{*a} Rosario Fernández^{*a} and José M. Lassaletta^{*b}

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 trifluoromethylketones under solvent-free conditions. This reaction proved to be very fast, clean and high-yielding, affording densely functionalised α -hydroxy α -trifluoromethyl diazenes. Ensuing diazene-to-aldehyde transformation, avoiding protection/deprotection reactions and chromatographic purifications, and subsequent derivatizations in one-pot fashion provides a direct entry to a variety of useful trifluoromethylated building blocks.

Introduction

Organofluorine compounds have attracted the interest of academy and industry from the viewpoint of their fruitful applications in pharmaceutical (approximately 20% on the markets, including some of the most selling drugs)¹ and material sciences.² Therefore, the development of synthetic methods for accessing new fluorinated compounds is an increasing 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 a second strategy is based on the addition of carbon nucleophiles to trifluoromethyl ketones.¹² The retrosynthetic analysis for the selected targets suggests the use of α -hydroxy 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



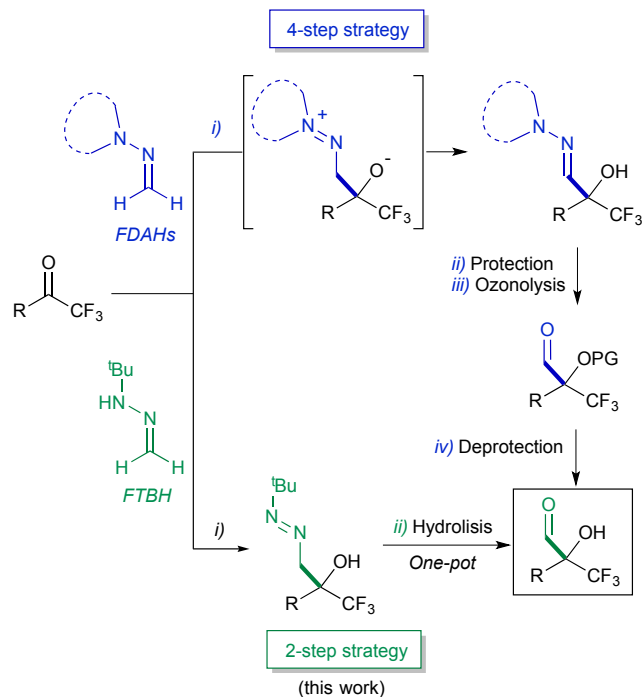
Scheme 1. Retrosynthetic analysis for biologically relevant functionalized trifluoromethyl carbinols and derivatives.

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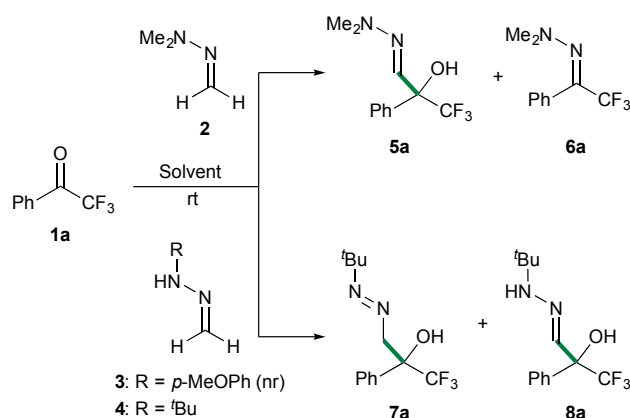
Our research team has intensively explored the nucleophilic reactivity of formaldehyde *N,N*-dialkylhydrazones (**FDAHs**),¹⁵ which behave as formyl anion equivalents (d^1 synthons) in their reactions with a variety of electrophiles, including carbonyl compounds.¹⁶ In particular, pyrrolidine derivatives spontaneously add to trifluoromethyl ketones affording α -hydroxy α -trifluoromethyl hydrazones (Scheme 2, up).^{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, down) based on the positive effect that solvent-free conditions have on the reaction rate of the first step, allowing subsequent transformations in one-pot fashion.



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

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** very slowly added to the carbonyl compound (employed in a 2-fold excess) to afford the corresponding α -hydroxy α -trifluoromethyl



Scheme 3. Preliminary reactivity experiments.

hydrazone **5a** in a modest 55% yield (after 20 days in CH_2Cl_2 at room temperature) along with small amounts of 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 CH_3CN and H_2O , respectively]. 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 used as 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).

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

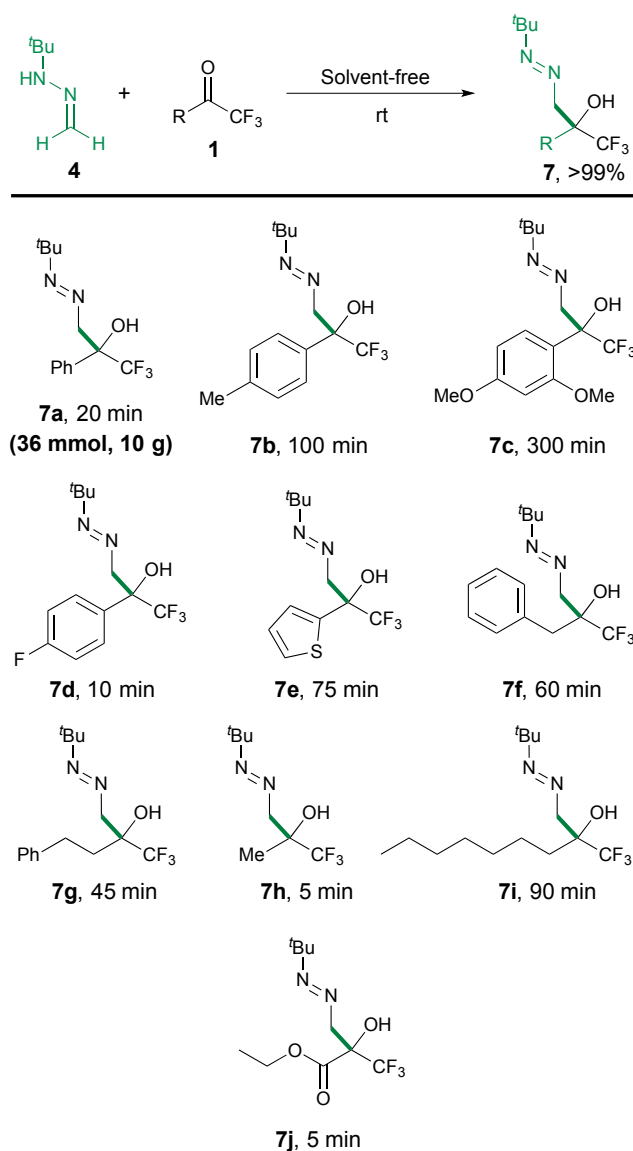
Entry	Solvent	<i>t</i>	7a : 8a ^b	Yield (%) ^c	<i>E</i> -factor (g/g) ^d
1	CH_2Cl_2	9 h	10:0	83	12.08
2	CHCl_3	7 h	8:2	70	16.31
3	<i>n</i> -hexane	31 h	10:0	80	6.49
4	toluene	31 h	10:0	81	8.27
5	Et_2O	31 h	10:0	74	7.63
6	CH_3CN	6 h	10:0	90	6.69
7	H_2O	45 min	10:0	90	1.31
8	--	20 min	10:0	>99	0.18
9 ^e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

^aReactions performed on a 0.5 mmol scale (0.5M) using **1a** (0.5 mmol) and **4** (0.75 mmol). ^bDetermined by ^1H NMR. ^cIsolated yield after column chromatography (entries 1-6), after L-L extraction (entry 7), after removing 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. ^eReactions performed on a 6 mmol scale. ^f1:1 **1a**/**4** Molar ratio.

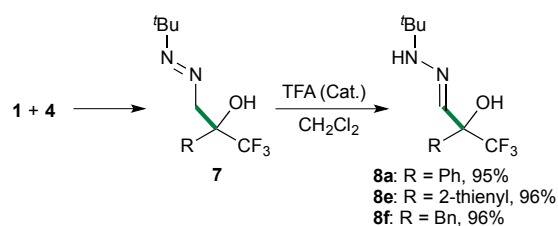
Next, we decided to explore the possibility of performing the reaction “on water”, exploiting the rate acceleration previously observed for **FDAHs** in reactions with α -keto esters.^{16e} When pure water was used as the reaction medium, full conversion was observed in only 45 minutes, giving **7a** in 90% isolated yield after simple L-L extraction with Et₂O, with a *E-factor* of 1.31⁵ (entry 7). Finally, we were delighted that the reaction carried out in absence of solvent^{11,21,22} 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 excess of hydrazone **4** under reduced pressure and without need of chromatographic purification (*E-factor* = 0.18, entry 8). Finally, scaling-up from 0.5 to 6 mmol made the reaction to 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 need of chromatographic purification. The reaction rates correlate with stereoelectronic properties of the substituents, with the more reactive **1d** (R = 4-F-C₆H₄), **1h** (R = Me), and **1j** (R = CO₂Et) reaching completion in less than 10 minutes. Solid ketone **1c**, bearing an electron-rich aryl group, appeared as the most challenging substrate but, although requiring an extra time for complete solubilisation, afforded also 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 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 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, subsequent one-pot diazene-to-aldehyde transformation from **7** 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^f afforded the desired α -hydroxy α -trifluoromethyl aldehydes **9** in good yields with a high degree of purity (>95% estimated by ¹H NMR, see ESI).



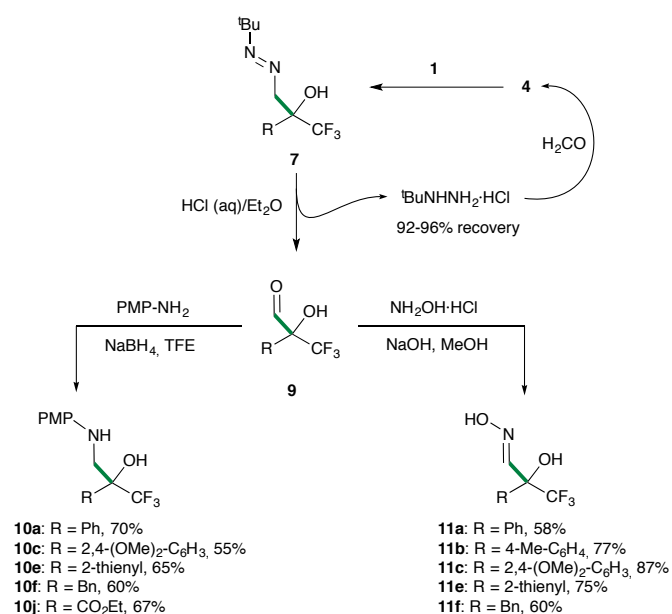
Scheme 4. Scope^a



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

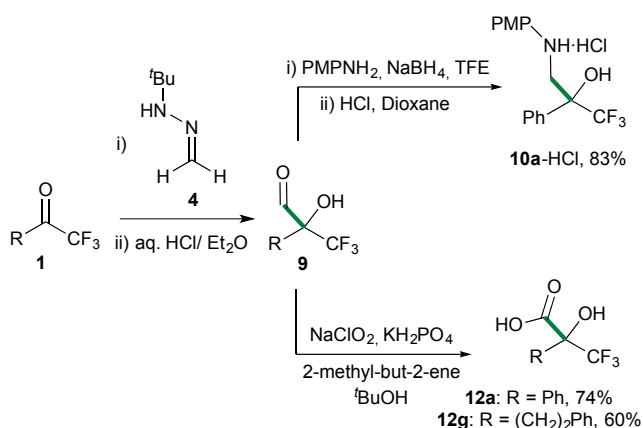
Remarkably, the *tert*-butyl hydrazone was recovered (92-96%) as its hydrochloride salt and reused for the synthesis of **4**, thus minimizing waste production in the formylation procedure.^{20c} Sensitive aldehydes **9** were directly used in subsequent reductive aminations or condensations with hydroxylamine to yield valuable trifluoromethylated β -aminoalcohols **10** and α -hydroxy aldoximes **11** in satisfactory overall yields for the three-step transformations. To demonstrate again the preparative utility of this methodology,

the synthesis of **10a** and **11a** was performed on a 18 mmol scale without compromising the chemical yield.

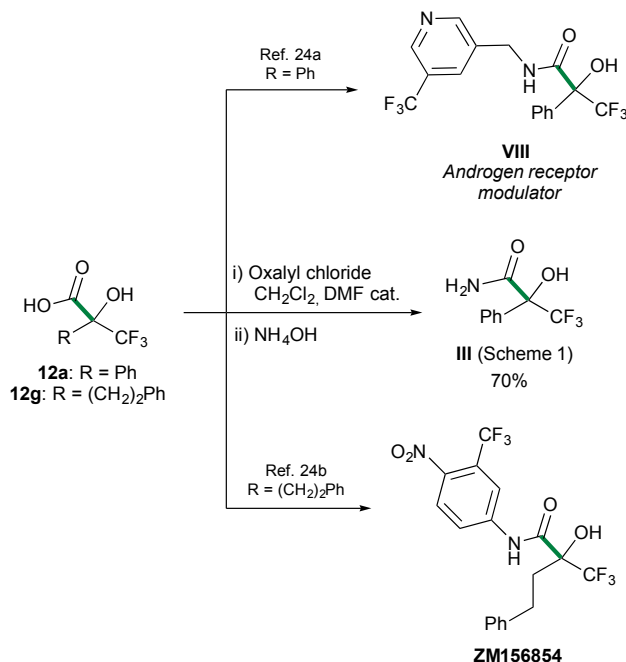


Scheme 6. Synthesis of β -aminoalcohols **10** and α -hydroxy aldoximes **11**. Overall yield for the three-step sequence.

Finally, the efficiency and simplicity of the present methodology is 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 need of further chromatographic purifications for these products.



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 formal synthesis of *rac*-**VIII** and **ZM156854**.

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

Experimental

Spectra were recorded at [¹H NMR (300 or 500 MHz); ¹³C NMR (75.5 or 125 MHz); ¹⁹F NMR (470.6 MHz)] 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 phosphomolibdic 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 hydrazones **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 (Table 2, 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, 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, $J_{\text{C,F}} = 285.6$ Hz), 76.6 (q, $J_{\text{C,F}} = 28.7$ 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 $\text{C}_{13}\text{H}_{18}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 285.6$ Hz), 76.5 (q, $J_{\text{C,F}} = 28.8$ 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 $\text{C}_{14}\text{H}_{20}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 287.3$), 115.8, 104.8, 99.4, 77.5 (q, $J_{\text{C,F}} = 28.3$ 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 $\text{C}_{15}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 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, 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, $J_{\text{C,F}} = 247.7$ Hz), 132.1 (d, $J_{\text{C,F}} = 3.1$ Hz), 128.5 (dd, $J_{\text{C,F}} = 8.2, 1.1$ Hz), 124.6 (q, $J_{\text{C,F}} = 286.0$ Hz), 115.2 (d, $J = 21.5$ Hz), 76.3 (q, $J_{\text{C,F}} = 28.6$ 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 $\text{C}_{13}\text{H}_{17}\text{F}_4\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 285.8$ Hz), 70.0 (q, $J_{\text{C,F}} = 28.5$ 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 $\text{C}_{11}\text{H}_{16}\text{F}_3\text{N}_2\text{OS}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 297.2$ Hz), 75.4 (q, $J_{\text{C,F}} = 27.0$ 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 $\text{C}_{14}\text{H}_{20}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 286.8$), 77.2, 75.1 (q, $J_{\text{C,F}} = 27.8$ 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 $\text{C}_{15}\text{H}_{22}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, CD_2Cl_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_2Cl_2): δ 125.9 (q, $J_{\text{C,F}} = 284.3$ Hz), 73.4 (q, $J_{\text{C,F}} = 28.5$ Hz), 70.7, 68.3, 26.3, 20.0 (d, $J_{\text{C,F}} = 1.0$ Hz). ^{19}F NMR (470.6 MHz, CDCl_3): δ -81.14 (s, CF_3). HRMS (ESI): m/z calcd for $\text{C}_8\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 286.7$ Hz), 75.3 (q, $J_{\text{C,F}} = 27.7$ 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 $\text{C}_{14}\text{H}_{28}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, 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, $J_{\text{C,F}} = 286.2$ Hz), 76.7 (q, $J_{\text{C,F}} = 29.2$ 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 $\text{C}_{10}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 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 (Table 2, tlc monitoring) to afford pure diazene **7**. Subsequently, a solution of TFA (0.1 mmol) in CH_2Cl_2 (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 × 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 (Table 2, TLC monitoring) to afford pure diazene **7**. Subsequently, HCl aq. (30 mL, 6M) 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 × 30 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent 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)propano-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]-methyl]propanoate (**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 × 30 mL) and Et₂O (2 × 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), washing with a mixture pentane/CH₂Cl₂ (2/1, 10 mL). Solvents were removed under reduced pressure and the product was dissolved in dry Et₂O (15 mL). HCl (1M 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 NaOH 2M and extracted with Et₂O. The aqueous layer was acidified to pH 1 (HCl 2M) and extracted with

EtOAc. The combined organic layer was dried (MgSO_4), filtered and the solvent 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 (300 MHz, CDCl_3): δ (500 MHz, Acetone- d_6): 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, $J_{\text{C,F}}$ = 286.7 Hz), 77.3 (c, $J_{\text{C,F}}$ = 28.2 Hz), 34.2. ^{19}F NMR (470.6 MHz, CDCl_3): δ -78.80 (s, CF_3). HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{11}\text{F}_3\text{O}_3$ [$\text{M}+\text{Na}$] $^+$ 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 \times 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 (200 mg, 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 transformation 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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Notes and references

‡ The *E*-factor is defined as the mass ratio of waste to desired product. For *E*-factors including solvents after chromatographic purifications or L-L extractions see the *Electronic Supplementary Information*.

§ 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 leads to milder conditions, very high volumetric productivity, increased safety and cost reduction (ref 22).

‡ 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).

- 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. O'Hagan, *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. O'Hagan, *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, 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, 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* (6th ed.), Wiley-Interscience: New York, 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, 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. Vázquez, M. Alcarazo, E. Álvarez, R. Fernández and J. M. Lassaletta, *Org. Lett.* 2007, **9**, 2867, (g) R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández 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. Lassaletta, *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) *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 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 2009/0275515 A1. (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 catacterization 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 catacterization 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.