Asymmetric Organocatalytic Synthesis of Fluorinated β-Hydroxy Diazenes

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Abstract: The nucleophilic addition of formaldehyde *tert*-butyl hydrazone to fluoromethyl ketones provides a valuable tool for the synthesis of highly functionalized β-hydroxy β-tri- and difluoromethyl diazenes. Excellent reactivities and moderate to good enantioselectivities (up to 90% ee) were achieved by *H*-bonding activation exerted by *tert*-Leucine derived *H*-bonding (squaramide or thiourea) organocatalysts. Subsequent derivatizations in one-pot fashion provide synthetically useful intermediates for target-oriented synthesis: tri- and di-fluoromethylated azoxy compounds, β-aminoalcohols, α-hydroxy aldoximes and derivatives thereof.

Introduction

Among other fluorinated compounds, derivatives bearing fluoroalkyl groups such as CF_3 and CF_2H have attracted much attention in drug development programs over the last years.[1] In addition to the improved metabolic stability, increased binding affinity and better bioavailability common to all fluorinated compounds,[2] difluoromethylated analogues of biologically active compounds are becoming desirable targets for pharmaceuticals, as it is known that the CF_2H group might be isosteric and isopolar to an OH and SH unit, and thereby act as a hydrogen donor in binding enzyme active sites.[3] Therefore, chiral tri- and di-fluoromethyl tertiary carbinols appear as relevant building blocks for target-oriented synthesis. Accordingly, a variety of protocols for accessing some of these fluoromethyl targets have been developed.[4] Asymmetric trifluoromethylation of ketones have been described employing metal catalysis and organocatalysis,[5] while stereoselective difluoromethylation of ketones are particularly scarce.[6] A complementary approach relies on the asymmetric addition of diverse nucleophiles to tri- and di-fluoromethyl ketones, still underexplored for the later substrate.[7]

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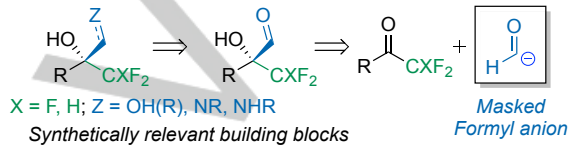
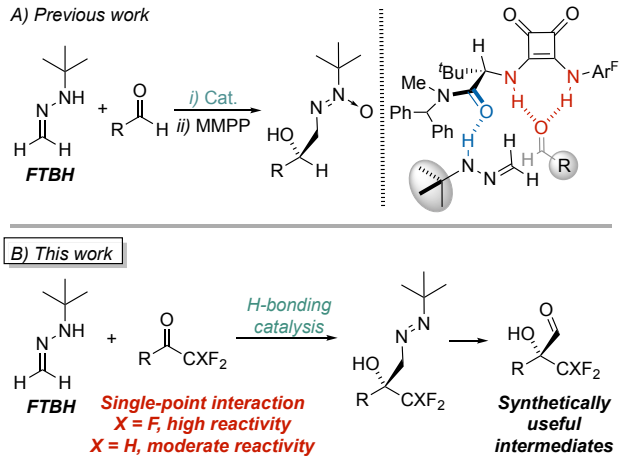
In this context, α-hydroxy aldehydes bearing quaternary α-CF_3 and α-CHF_2 stereogenic carbons might be conveniently built by employing fluoromethyl ketones as electrophiles for the attack of masked formyl anion reagents (Scheme 1).



Scheme 1. Approach to functionalized fluoromethyl carbinols.

This approach, however, has been scarcely investigated.[8] Over the years, our research team has exploited the nucleophilic reactivity of formaldehyde *N,N*-dialkyl hydrazones (masked formyl anion) for the stereoselective introduction of single-carbon functional groups into several electrophiles.[9] More recently, we have exploited the distinct properties of formaldehyde *tert*-butyl hydrazone (**FTBH**, **1a**) in combination with bifunctional *H*-bonding organocatalysis[10] for the asymmetric functionalization of activated carbonyl compounds (α-keto esters,[11] α-keto phosphonates[12] and isatins[13]) to afford highly functionalized β-hydroxy diazenes as precursors of azoxy alcohols, α-hydroxy aldehydes and derivatives thereof. Recently, the functionalization of simple aldehydes was accomplished using a dual activation of reagents by amino acid derived squaramides as the key to achieve good catalytic activities and stereocontrol (Scheme 2, A).[14]



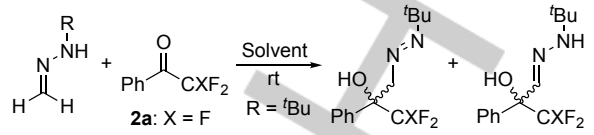
Scheme 2. Organocatalytic asymmetric 1,2-addition of **1a** to monocarbonyl compounds (A: Simple aldehydes, B: fluoromethyl ketones).

Moreover, an unprecedented formal diaza-carbonyl-ene reaction of **1a** and trifluoromethyl ketones under solvent free conditions was reported as key step of an efficient 2-step strategy for the nucleophilic formylation of trifluoromethyl ketones.[15] Aiming to expand the scope of this strategy, we now report on the asymmetric functionalization of fluorinated ketones for the synthesis of densely functionalized tri- and di-fluoromethyl alcohols, useful intermediates for target-oriented synthesis (Scheme 2, B). Fluorinated methyl ketones are a priori very challenging electrophilic substrates in asymmetric catalytic processes for three main reasons: 1) their low-lying LUMO energy (inductive effect by CF_3/CHF_2 group), which enhances the intrinsic reactivity of the carbonyl, facilitating the uncatalyzed background reaction; 2) the low basicity of the carbonyl group, making necessary a relatively strong Lewis/Brønsted acid for its activation and 3) a potentially poor stereodiscrimination in catalyst-substrate complexes due to steric similarity of the R and CF_3/CHF_2 groups. In this paper, the 1,2-addition of **1a** to tri- and di-fluoromethyl ketones has been explored as a synthetic tool to access highly functionalized fluoromethyl carbinols.

Results and Discussion

Preliminary reactivity experiments were performed employing formaldehyde *N*-mono(alkyl)/aryl hydrazones **1a**,**b** and 2,2,2-trifluoroacetophenone (**2a**) or 2,2-difluoro-1-phenylethan-1-one (**2b**) as model substrates (Table 1). Formaldehyde *N*-*tert*-butyl hydrazone (**1a**) smoothly added to **2a** in CH_3CN, affording β-hydroxy β-tri-fluoromethyl diazene **3a** in 90% yield (entry 1). Remarkably, the reaction carried out under neat conditions proceeded cleanly and at high rate to afford pure diazene **3a** in quantitative yield after removing the 0.5-fold excess of hydrazone **1a** (entry 3). Alternatively, the use of water as solvent provided full conversion in less than one hour, yielding **3a** in 90% yield after an operationally simple L-L extraction with Et_2O (entry 4). Hydrocarbons (*n*-hexane or toluene) slowed the reaction rates (31 h), affording tautomeric hydrazone **4a** (ca. 10%) and diazene **3a** in a lower 80% isolated yield (entries 5,6). Next, difluoromethyl ketone **2b** was analyzed. As expected, the lower intrinsic reactivity of this substrate made necessary longer reaction times (40-48 h) to reach high conversions [CH_3CN: >95% (entry 8); H_2O: >95% (entry 11)]. The positive effect that neat conditions had on the addition rate of **1a** to **2a** was not observed in this system, leading to lower conversion to **3b** (73%) along with hydrazone **4b** (ca. 20%, entry 10). In toluene the reaction was slightly slower (90% conv. after 48 h at room temperature, entry 12). Cooling to 0 °C, the uncatalyzed reaction of **1a** with **2a**,**b** could not be inhibited (entries 7 and 13), highlighting the difficulties to overcome the background in the enantioselective catalytic reactions. In line with previous investigations,[14],[15] *N*-anisyl derivative **1b** showed no reactivity (entries 2 and 9). In conclusion, the thermal reactivity between **1** and **2** appears to be highly dependent on the reaction media and the structure of the reagent, thereby opening opportunities for the development of both uncatalyzed (racemic) and asymmetric catalytic versions. Diazenes **3a**,**b** partially decompose during chromatographic purification, consequently complicating the measurement of enantioselectivities. Alternatively, more stable azoxy compounds

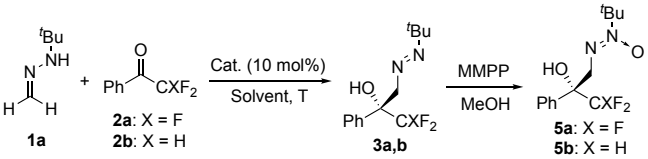
Table 1. Preliminary reactivity experiments.[a]



Entry	1	2	Solvent	*t* (h)	3, Yield (%)[b]
1	**1a**	**2a**	CH_3CN	6	**3a**, 90
2	**1b**	**2a**	CH_3CN	48	nr
3	**1a**	**2a**	--	0.4	**3a**, >99
4	**1a**	**2a**	H_2O	0.8	**3a**, 90
5	**1a**	**2a**	*n*-Hexane	31	**3a**, 80
6	**1a**	**2a**	Toluene	31	**3a**, 80
7[c]	**1a**	**2a**	Toluene	31	**3a**, 68
8	**1a**	**2b**	CH_3CN	40	**3b**, (>95)
9	**1b**	**2b**	CH_3CN	48	nr
10	**1a**	**2b**	--	48	**3b**, (73)
11	**1a**	**2b**	H_2O	40	**3b**, (>95)
12	**1a**	**2b**	Toluene	48	**3b**, (90)
13[c]	**1a**	**2b**	Toluene	48	**3b**, (35)

[a] Reactions were performed at 0.5 mmol scale (0.5M) using **2** (0.5 mmol) and **1** (0.75 mmol). [b] Isolated yield after flash chromatography (entries 1, 5-7), after removing the excess of hydrazone **1a** under reduced pressure (entry 3), after L-L extraction (entry 4). In parenthesis conversions determined by 1H-NMR (entries 8, 10-13). [c] Reaction performed at 0 °C.

5a,**b** could be easily obtained applying high-yielding and regioselective *N*-oxidation with magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) in MeOH (Scheme 3).



Scheme 3. Model reaction of **1a** with **2a,b**

Taking into account the higher intrinsic reactivity of **2a** with **1a**, difluoromethylketone **2b** was initially chosen as model substrate for the optimization of the enantioselective version (Table 2). The uncatalyzed reaction of **1a** with **2b** in toluene could be almost completely inhibited by cooling to −20 °C (17% conv. after 72 h, entry 1). Under these conditions, a preliminary screening of common bifunctional *H*-bonding catalysts (see ESI) served to identify amino acid derived squaramide **I** (Figure 1) and thiourea **II** as the best options, reaching yet moderate enantioselectivities

(entries 2,3). The influence of the *H*-bond donor group was analysed next. A diminished *H*-bond donor capability of the

Table 2. Optimization of the catalized reaction of **1a** with **2a,b**.[a]

Entry	2	Cat.	Solvent	T (°C)	Conv. (%)[b]	ee (%)[c]
1	**2b**	**-**	Toluene	–20	17	--
2	**2b**	**I**	Toluene	–20	69	50
3	**2b**	**II**	Toluene	–20	90	46
4	**2b**	**III**	Toluene	–20	53	48
5	**2b**	**IV**	Toluene	–20	38	42
6	**2b**	**V**	Toluene	–20	46	22
7	**2b**	**VI**	Toluene	–20	69	49
8	**2b**	**VII**	Toluene	–20	50	50
9	**2b**	**VIII**	Toluene	–20	80	66
10	**2b**	**I**	*n*-Hexane	–20	71	17
11	**2b**	**I**	**CF_3Ph**	**–20**	**88 (87)**	**68**
12	**2b**	**I**	CF_3Ph	–20	79	59
13	**2b**	**VIII**	*n*-Hexane	–20	81	47
14	**2b**	**VIII**	CF_3Ph	–20	77	61
15	**2b**	**VIII**	**Toluene**	**–30**	**72 (70)**	**74**
16[d]	**2a**	**I**	CF_3Ph	–20	(95)	46
17	**2a**	**VIII**	Toluene	–20	(99)	53

[a] Reactions were performed at 0.15 mmol scale (0.2M) using **2a,b** (0.15 mmol) and **1a** (0.225 mmol) with 10 mol% catalyst loading (reaction time of the addition step = 72 h). [b] Conversion was estimated by ^{1}H-NMR spectroscopy [in parenthesis isolated yield of (*R*)-**5a,b** after column chromatography]. [c] The enantiomeric excess (ee) was determined by HPLC. [d] Reaction time of the addition step = 48 h.

catalysts (estimated from the chemical shifts of the NH protons in ^{1}H NMR spectra)[14] in squaramides **III** (pentafluorophenyl derivative) and **IV** [bis(trifluoromethyl)benzyl derivative] correlates with a poorer catalytic activity and, hence, provided lower enantioselectivities (entries 4,5). The influence of the amino acid fragment was also evaluated: A significant decrease in enantioselectivity was observed when phenylalanine-derived analogue **V** was used (entry 6), highlighting the better conformational control exerted by the *tert*-butyl group in the chiral amide fragment [^{1}H NMR spectra in DMSO at 303 K for **I** and **V** show (Z)/(E)-amide rotamers in ratios of 6:1 and 4:1, respectively].[14]

On the other hand, the terminal dialkylamino group had no significant impact in the outcome of the reaction: squaramides **VI**, with relatively more flexible dibenzylamino group, and **VII**, bearing a bulkier bis(naphtalen-1-ylmethyl)amino group, afforded similar results (entries 7,8). Finally, Jacobsen-type amide-thiourea **VIII** (pKa ca. 18), substantially less acidic than **II** (pK_a ca. 13),[16] exhibited a good catalytic activity (80% conv.) and higher enantioselectivity (66% ee, entry 9). This surprising result

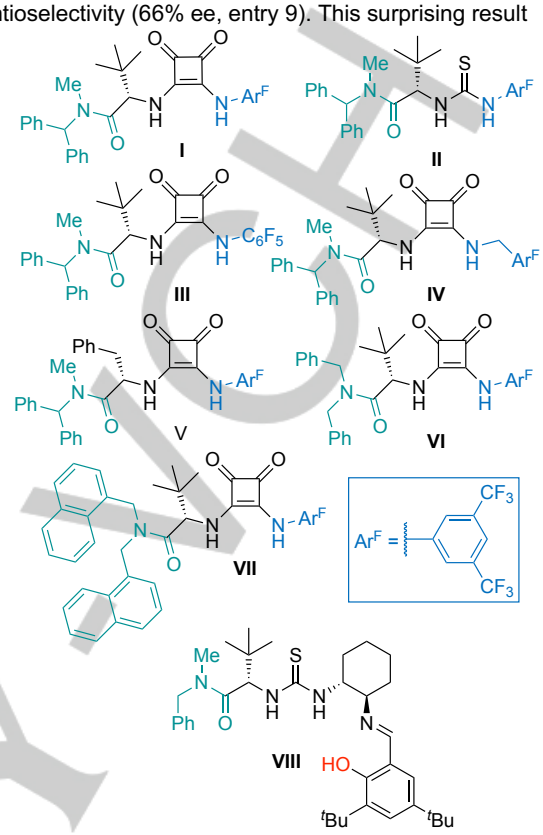
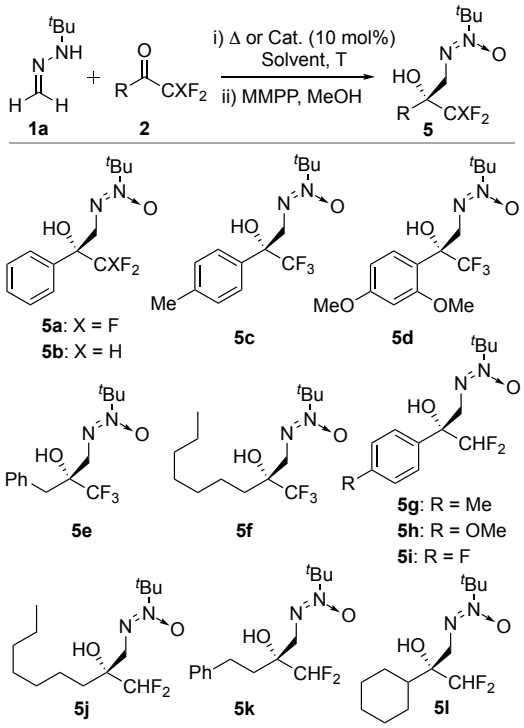


Figure 1. Selected amide-squaramide/thiourea organocatalysts tested.

suggests a cooperative assistance by the phenolic hydroxyl group, helping to fix the geometry of the catalysts/substrate complex while increasing the efficiency of the substrate activation. Further experiments (entries 10-15) served to identify two optimal catalytic systems: Squaramide **I** in α,α,α-trifluorotoluene (TFT provides more homogeneous reaction media)[14] at –20 °C and thiourea **VIII** in toluene at –30 °C. Reactions completed under such conditions, followed by in situ oxidation, yielded **5b** in high yields (70-87%) and enantioselectivities up to 68% and 74% ee, respectively (entries 11 and 15). As a result of the unavoidable, relatively faster background reaction, the catalysed addition of **1a** to trifluoromethyl ketone **2a** gave the desired azoxy alcohol **5a** in very high yields but lower enantioselectivity (46-53% ee, entries 16,17) under the optimized conditions.[17]

Azoxy-containing natural products constitute an interesting under-explored family of compounds with varied biological activities.[18] Therefore, the synthesis of trifluoromethylated and difluoromethylated azoxymethyl alcohols **5** was accomplished from a variety of aryl- and alkyl-substituted ketones in racemic and enantioselective versions (Scheme 4). Exploiting the high rates achieved under solvent-free conditions and the operational simplicity of the subsequent oxidation, an efficient one-pot protocol for the synthesis of trifluoromethylated alcohols was developed, affording **5a** and **5c-f** in good to excellent yields (Table 3, entries 1-5). Employing organocatalytic activation by thiourea **VIII**, a similar protocol was also applied for the asymmetric

synthesis of (*R*)-**5a** and (*R*)-**5c-f** in good yields, albeit in moderate enantioselectivities (entries 6-10).



Scheme 4. Synthesis of azoxymethyl alcohols **5**.

Table 3. Synthesis of trifluoromethylated azoxy alcohols **5**.[a]

Entry	**2**	Cat.	Solvent	T (°C)	*t* (h)[b]	**5**, Yield (%)[c]	ee (%)[d]
1	**2a**	--	neat	rt	0.4	(±)-**5a**, 99	--
2	**2c**	--	neat	rt	1.6	(±)-**5c**, 99	--
3	**2d**	--	neat	rt	5	(±)-**5d**, 90	--
4	**2e**	--	neat	rt	1	(±)-**5e**, 80	--
5	**2f**	--	neat	rt	1.5	(±)-**5f**, 86	--
6	**2a**	**VIII**	Toluene	–20	48	(*R*)-**5a**, 99	53
7	**2c**	**VIII**	Toluene	–20	60	(*R*)-**5c**, 99	54
8	**2d**	**VIII**	Toluene	–20	72	(*R*)-**5d**, 45	63
9	**2e**	**VIII**	Toluene	–20	48	(*R*)-**5e**, 90	49
10	**2f**	**VIII**	Toluene	–20	48	(*R*)-**5f**, 77	54

[a] Reactions were performed at 0.6 mmol scale. [b] Reaction time of the addition step. [c] Isolated yield after column chromatography. [d] The enantiomeric excess (ee) was determined by HPLC.

The scope of the asymmetric addition of **1a** to difluoromethylketones was explored using both squaramide **I** and thiourea **VIII** as the catalysts. The reaction of **2b** carried out at 0.6 mmol scale provided similar or slightly better yields than those at 0.15 mmol and essentially the same ee's (Table 4, entries 1,2).

The generality of the reaction was then explored with a range of aryl- and alkyl-substituted difluoromethyl ketones **2g-l**. The collected data summarized in Table 4 shows that thiourea **VIII** is a more selective catalyst for aryl-substituted substrates (entries 1-8).

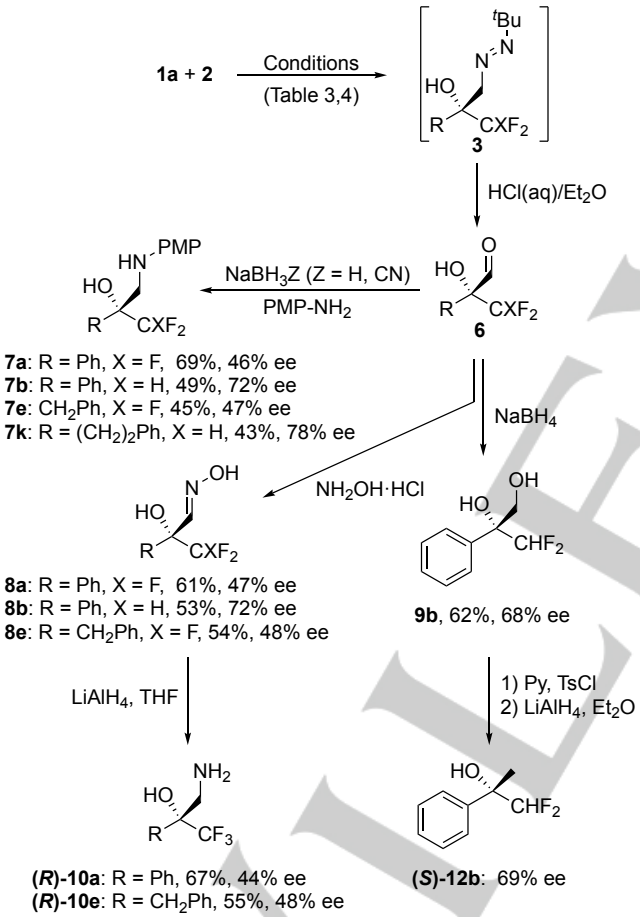
Table 4. Synthesis of difluoromethylated azoxy alcohols **5**.[a]

Entry	**2**	Cat.	Solvent	T (°C)	*t* (h)[b]	(*R*)-**5**, Yield (%)[c]	ee (%)[d]
1	**2b**	**I**	CF_3Ph	–20	72	**5b**, 88[e]	68
2	**2b**	**VIII**	Toluene	–30	72	**5b**, 80[e]	74
3	**2g**	**I**	CF_3Ph	–20	120	**5g**, 65	59
4	**2g**	**VIII**	Toluene	–30[f]	120	**5g**, 25	73
5	**2h**	**I**	CF_3Ph	–20	120	**5h**, 58	66
6	**2h**	**VIII**	Toluene	–30[f]	120	**5h**, <5	nd
7	**2i**	**I**	CF_3Ph	–20	72	**5i**, 81	61
8	**2i**	**VIII**	Toluene	–30	72	**5i**, 76	66
9	**2j**	**I**	CF_3Ph	–20	72	**5j**, 83	90
10	**2j**	**VIII**	Toluene	–30	120	**5j**, 54	80
11	**2k**	**I**	CF_3Ph	–20	72	**5k**, 81	86
12	**2k**	**VIII**	Toluene	–30	72	**5k**, 69	61
13	**2l**	**I**	CF_3Ph	–20	144	**5l**, 52	87
14	**2l**	**VIII**	Toluene	–30[f]	144	**5l**, <5	nd

[a] Reactions were performed at 0.6 mmol scale. [b] Reaction time of the addition step. [c] Isolated yield after column chromatography. [d] The enantiomeric excess (ee) was determined by HPLC. [e] This yield is slightly better than obtained at 0.15 mmol scale (Table 2, entry 15), [f] After 72 h the temperature was raised to –20 °C.

However, the diminished catalytic activity observed for electron-rich ketones (entries 4 and 6) hampered a broader scope. Electron-rich ketones **2g**,**h** required activation by squaramide catalyst **I** for longer reaction times to afford, after in situ oxidation, the corresponding azoxy compounds (*R*)-**5g**,**h** in moderate-to-good yields and enantioselectivities (entries 3 and 5). Electron-poor ketone **2i** reacted similarly to **2b**, affording **5i** in good yields (76-81%) employing both catalysts (entries 7 and 8) and reaching up to 66% ee (thiourea **VIII**). Squaramide **I**, instead, was the best catalyst for the functionalization of alkyl-substituted difluoromethyl ketones **2j-l** in terms of catalytic activities and enantioselectivities (entries 9-14). For representative substrates bearing linear alkyl chains (**2j**,**k**), azoxymethyl alcohols **5j**,**k** were synthesized in high yields (>80%, 2-steps) and good enantioselectivities (86-90%) (entries 9 and 11). To illustrate the limit of reactivity, substrate **2l**, carrying a cyclic chain, kept unreactive in presence of **VIII** while a prolonged reaction time (144 h) was required when **I** was used, affording **5l** in 52% yield and 87% ee (entry 13). Functionalized fluorinated azomethyl alcohols **3** are precursors of the desired α-

hydroxy α-trifluoro(difluoro)methyl aldehydes **6** and derivatives thereof (Scheme 5). The one-pot diazene-to-aldehyde transformation from crude **3** was easily performed by applying acidic hydrolysis in a biphasic H_2O/Et_2O medium. Sensitive aldehydes **6** could not resist chromatographic purification, but were isolated with a high degree of purity (estimated by ^1H NMR) and directly used in subsequent reductive aminations or condensation with hydroxylamine to yield enantioenriched trifluoro(difluoro)methylated β-aminoalcohols **7** and α-hydroxy aldoximes **8** in satisfactory overall yields for the three-step transformations. The absolute configurations of trifluoromethylated aldoximes **8a**,**e** and difluoromethylated diol **9b** were assigned to be *R* by chemical correlation of their corresponding free β-aminoalcohols **10a**,**e** and alcohol **12b** (see ESI). The remaining configurations of **3**, **6** and **7** were assigned by analogy assuming a uniform reaction pathway.



Scheme 5. Diazene-to-aldehyde transformation and further functional groups derivatizations.

Conclusions

In summary, the formal diaza-ene reactivity of formaldehyde *tert*-butyl hydrazone (***FTBH***) with fluoromethyl ketones has been exploited in the synthesis of densely functionalized tertiary alcohols. *H*-Bonding organocatalysts enabled an asymmetric approach, affording good to excellent yields and moderate to good enantioselectivities (49-63% ee for α-CF_3, 59-90% ee for α-CHF_2). Ensuing operationally simple transformations in one-pot fashion provide a direct entry to a variety of useful enantioenriched fluoromethylated building blocks: azoxy compounds, β-aminoalcohols and α-hydroxy aldoximes.

Experimental Section

^1H NMR spectra were recorded at 300 MHz or 500 MHz (internal reference; $CDCl_3$ = 7.26). ^{13}C NMR spectra were recorded at 75.5 or 126 MHz (internal reference; $CDCl_3$ = 77.0); ^{19}F NMR spectra were recorded at 471 MHz. 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 $KMnO_4$, vainilline or phosphomolibdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Optical rotations were measured on a JASCO *P-2000* polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IA/IB/IC/IE/OD/OJ-H columns). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. Formaldehyde *tert*-butyl hydrazone **1a**[19] and not commercially available ketones **2f**,[15] **2g**,[20] **2h**,[20] **2i**,[20] **2k**[21] and squaramide organocatalysts[14] (**I**, **III**, **IV**, **V**, **VI**, **VII**) were synthesized according to literature procedures.

General procedure for the racemic synthesis of trifluoromethylated azoxy alcohols 5 (Table 3, entries 1-5)

Freshly distilled formaldehyde *tert*-butyl hydrazone **1a** (85 µL, 0.75 mmol) was added to the corresponding trifluoromethyl ketone **2** (0.5 mmol) at rt. The mixture was stirred until consumption of starting material (TLC monitoring). After this time, the excess of hydrazone was removed under reduced pressure and MeOH (2.50 mL) and $MMPP·6H_2O$ (1.50 g, 2.50 mmol) were subsequently added at 0 °C. The mixture was allowed to warm to rt and stirred until completion (3 hours, TLC monitoring). The mixture was then diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (pentane/CH_2Cl_2 1/1) to afford pure azoxy alcohols **5**. Characterization data matched those given bellow for the catalytic reactions.

General procedure for the enantioselective synthesis of fluoromethylated azoxy alcohols 5 (Table 3, entries 6-10; Table 4)

Freshly distilled formaldehyde *tert*-butyl hydrazone **1a** (102 µL, 0.9 mmol) was added to a solution of fluorinated ketones **2** (0.6 mmol) and the catalyst **I** or **VIII** (37 mg or 36 mg respectively, 0.06 mmol) in the solvent (0.2 M, 3 mL) and at the temperature specified for each substrate (see Table **3** and **4**). The mixture was stirred until consumption of the starting material (TLC or ^1H-NMR monitoring). After this time, MeOH (3 mL) and MMPP (950 mg, 3 mmol) were subsequently added and the reaction mixture was allowed to warm up to rt for completion (3 hours, TLC monitoring). The mixture was then diluted with H_2O (12 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (1 × 40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (CF_3 derivatives: pentane/CH_2Cl_2 1/1; CHF_2 derivatives:

cyclohexane/CH_2Cl_2/AcOEt 1/6/1) to afford pure azoxy alcohols **5**. Enantiomeric excess was determined by HPLC analysis.

(*R*)-1-(*tert*-Butyl)-2-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) diazene 1-oxide (5a). Following the general procedure, starting from **2a** (84 µL, 0.6 mmol) and thiourea **VIII** in toluene at −20 °C, azoxy compound **5a** was obtained as white solid (174 mg, 99%); mp = 63-65 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.62 – 7.54 (m, 2H), 7.44 – 7.33 (m, 3H), 4.23 (d, *J* = 17.7 Hz, 1H), 4.05 (s, 1H), 3.97 (dd, *J* = 0.8, 17.7 Hz, 1H), 1.50 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 137.0, 129.1, 128.7, 126.6 (d, $J_{C,F}$ = 1.1 Hz), 125.6 (q, $J_{C,F}$ = 286.1 Hz), 78.0, 76.1 (q, $J_{C,F}$ = 28.2 Hz), 56.7, 28.5. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −78.62 (s, 3F). **HRMS** (ESI): m/z calcd for $C_{13}H_{17}F_3N_2O_2Na$ [M$^+$+Na] 313.1134, found 313.1125. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 5.2 min, τ_{minor} = 8.2 min (53% ee); $[\alpha]_D^{20}$ = +24.6 (*c* 0.5, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-(3,3-difluoro-2-hydroxy-2-phenylpropyl) diazene 1-oxide (5b). Following the general procedure, starting from **2b** (76 µL, 0.6 mmol) and thiourea **VIII** in toluene at −30 °C, azoxy compound **5b** was obtained as off-white solid (146 mg, 80%); mp = 34-36 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 7.53 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.32 (m, 3H), 5.89 (t, *J* = 55.8 Hz, 1H), 4.07 (dd, *J* = 17.7, 0.8 Hz, 1H), 3.95 (dd, *J* = 17.7, 0.8 Hz, 1H), 3.57 (s, 1H), 1.50 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 138.1, 128.3, 128.3, 126.1, 116.2 (t, $J_{C,F}$ = 249.9 Hz), 77.3, 75.3 (t, $J_{C,F}$ = 21.4 Hz), 56.33 – 56.19 (m), 28.1. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −129.20 (dd, *J* = 280.2, 55.9 Hz, 1F), −131.45 (dd, *J* = 280.2, 55.9 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{13}H_{18}O_2N_2F_2Na$ [M$^+$+Na] 295.1229, found 295.1228. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 6.0 min, τ_{minor} = 9.5 min (74% ee); $[\alpha]_D^{20}$ = +11.8 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[3,3,3-trifluoro-2-hydroxy-2-(*p*-tolyl)propyl] diazene 1-oxide (5c). Following the general procedure, starting from **2c** (94 µL, 0.6 mmol) and thiourea **VIII** in toluene at −20 °C, azoxy compound **5c** was obtained as white solid (182 mg, 99%); mp = 66-68 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 0.6, 8.1 Hz, 2H), 4.21 (d, *J* = 17.7 Hz, 1H), 4.00 (s, 1H), 3.95 (dd, *J* = 0.8, 17.7 Hz, 1H), 2.36 (s, 3H), 1.50 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 138.6, 133.6, 129.0, 126.1 (d, $J_{C,F}$ = 1.1 Hz), 125.0 (q, $J_{C,F}$ = 286.1 Hz), 77.5, 75.6 (q, $J_{C,F}$ = 28.2 Hz), 56.3, 28.1, 21.1. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −78.69 (s, 3F). **HRMS** (ESI): m/z calcd for $C_{14}H_{19}F_3N_2O_2Na$ [M$^+$+Na] 327.1291, found 327.1286. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 5.0 min, τ_{minor} = 6.4 min (54% ee); $[\alpha]_D^{20}$ = +15.8 (*c* 0.5, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[2-(2,4-dimethoxyphenyl)-3,3,3-trifluoro-2-hydroxypropyl]diazene 1-oxide (5d). Following the general procedure, starting from **2d** (147 mg, 0.6 mmol) and thiourea **VIII** in toluene at −20 °C, azoxy compound **5d** was obtained as colorless oil (95 mg, 45%). **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, *J* = 8.4 Hz, 1H), 6.54 – 6.46 (m, 2H), 5.53 (s, 1H), 4.24 (d, *J* = 18.4 Hz, 1H), 4.06 (d, *J* = 18.4 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 1.48 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 161.1, 158.9, 130.4, 125.4 (q, $J_{C,F}$ = 287.7 Hz), 116.0, 104.9, 99.6, 77.2, 56.0, 55.5, 55.3, 28.1. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −78.57 (s, 3F). **HRMS** (ESI): m/z calcd for $C_{15}H_{21}F_3N_2O_4Na$ [M$^+$+Na] 373.1346, found 373.1338. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (99:1)]; flow rate 1 mL/min; τ_{major} = 15.0 min, τ_{minor} = 11.8 min (63% ee); $[\alpha]_D^{20}$ = +23.4 (*c* 0.5, $CHCl_3$).

(*R*)-2-(2-Benzyl-3,3,3-trifluoro-2-hydroxypropyl)-1-(*tert*-butyl) diazene 1-oxide (5e). Following the general procedure, starting from **2e** (96 µL, 0.6 mmol) and thiourea **VIII** in toluene at −20 °C, azoxy compound **5e** was obtained as white solid (164 mg, 90%); mp. = 56-58 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.36 – 7.23 (m, 5H), 3.71 (d, *J* = 18.3 Hz, 1H), 3.53 – 3.41 (m, 2H), 3.23 (d, *J* = 14.1 Hz, 1H), 2.96 (d, *J* = 14.1 Hz, 1H), 1.47 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 133.9, 131.0, 128.3, 127.2, 125.8 (q, $J_{C,F}$ = 286.9 Hz), 77.3, 74.5 (q, $J_{C,F}$ = 27.0 Hz), 53.6, 38.7 (d, $J_{C,F}$ = 1.3 Hz), 28.0. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −80.09 (s, 3F). **HRMS** (ESI): m/z calcd for $C_{14}H_{19}F_3N_2O_2Na$ [M$^+$+Na] 327.1291, found 327.1280. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 18.4 min, τ_{minor} = 22.4 min (49% ee); $[\alpha]_D^{20}$ = +40.4 (*c* 0.5, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[2-hydroxy-2-(trifluoromethyl)nonyl]diazene 1-oxide (5f). Following the general procedure, starting from **2f** (114 µL, 0.6 mmol) and thiourea **VIII** in toluene at −20 °C, azoxy compound **5f** was obtained as colorless oil (144 mg, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 3.76 (d, *J* = 18.4 Hz, 1H), 3.57 (d, *J* = 18.4 Hz, 1H), 3.29 (s, 1H), 1.89 – 1.65 (m, 2H), 1.56 (s, 9H), 1.51 – 1.18 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 126.0 (q, $J_{C,F}$ = 287.3 Hz), 77.3, 74.3 (q, $J_{C,F}$ = 27.3 Hz), 54.1, 33.3, 31.7, 29.9, 29.0, 28.1, 22.6, 22.4, 14.0. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −80.01 (s, 3F). **HRMS** (ESI): m/z calcd for $C_{14}H_{27}F_3N_2O_2Na$ [M$^+$+Na] 335.1917, found 335.1912. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (99.5:0.5)]; flow rate 0.8 mL/min; τ_{major} = 23.4 min, τ_{minor} = 20.5 min (54% ee); $[\alpha]_D^{20}$ = +21.8 (*c* 0.5, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[3,3-difluoro-2-hydroxy-2-(*p*-tolyl)propyl] diazene 1-oxide (5g). Following the general procedure, starting from **2g** (102 mg, 0.6 mmol) and squaramide **I** in α,α,α-trifluorotoluene at −20 °C, azoxy compound **5g** was obtained as colorless oil (111 mg, 65%). **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 7.41 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.87 (t, *J* = 55.9 Hz, 1H), 4.06 (dd, *J* = 17.7, 1.2 Hz, 1H), 3.92 (dd, *J* = 17.7, 1.2 Hz, 1H), 3.49 (s, 1H), 2.35 (s, 3H), 1.51 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 138.1, 135.1, 129.0, 126.0, 116.3 (t, $J_{C,F}$ = 250.2 Hz), 77.3, 75.2 (t, $J_{C,F}$ = 21.5 Hz), 56.3 (t, $J_{C,F}$ = 2.6 Hz), 28.1, 21.0. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −129.20 (dd, *J* = 279.8, 56.0 Hz, 1F), −131.53 (dd, *J* = 279.8, 56.0 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{14}H_{20}O_2N_2F_2Na$ [M$^+$+Na] 309.1385, found 309.1384. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 5.7 min, τ_{minor} = 7.4 min (59% ee); $[\alpha]_D^{20}$ = +22.8 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[2-(4-methoxyphenyl)-3,3-difluoro-2-hydroxypropyl]diazene 1-oxide (5h). Following the general procedure, starting from **2h** (112 mg, 0.6 mmol) and squaramide **I** in α,α,α-trifluorotoluene at −20 °C, azoxy compound **5h** was obtained as pale yellow oil (105 mg, 58%). **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 7.44 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.85 (t, *J* = 56.0 Hz, 1H), 4.04 (dd, *J* = 17.7, 1.2 Hz, 1H), 3.93 (dd, *J* = 17.7, 1.2 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 1H), 1.50 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 159.5, 130.1, 127.4, 116.3 (t, $J_{C,F}$ = 249.8 Hz), 113.7, 77.3, 75.0 (t, $J_{C,F}$ = 21.5 Hz), 56.2, 55.2, 28.1. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −129.12 (dd, *J* = 279.6, 55.5 Hz, 1F), −131.54 (dd, *J* = 279.6, 55.5 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{14}H_{20}O_3N_2F_2Na$ [M$^+$+Na] 325.1334, found 325.1333. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (85:15)]; flow rate 1 mL/min; τ_{major} = 4.8 min, τ_{minor} = 9.4 min (66% ee); $[\alpha]_D^{20}$ = +11.5 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[3,3-difluoro-2-(4-fluorophenyl)-2-hydroxypropyl]diazene 1-oxide (5i). Following the general procedure, starting from **2i** (105 mg, 0.6 mmol) and thiourea **VIII** in toluene at −30 °C, azoxy compound **5i** was obtained as off-white solid (133 mg, 76%); mp = 41-43 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 7.55 – 7.48 (m, 2H), 7.10 – 7.03 (m, 2H), 5.85 (t, *J* = 55.8 Hz, 1H), 4.05 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.93 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.60 (s, 1H), 1.50 (s, 9H). **^{13}C NMR** (126

MHz, $CDCl_3$, 25 °C): δ = 162.9 (d, $J_{C,F}$ = 247.3 Hz), 133.8, 128.1 (d, $J_{C,F}$ = 8.2 Hz), 116.0 (t, $J_{C,F}$ = 249.9 Hz), 115.2 (d, $J_{C,F}$ = 21.4 Hz), 77.5, 75.1 (t, $J_{C,F}$ = 21.7 Hz), 56.2, 28.1. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −113.99 – −114.12 (m, 1F), −129.01 (dd, *J* = 280.8, 56.0 Hz, 1F), −131.52 (dd, *J* = 280.8, 56.0 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{13}H_{17}O_2N_2F_3Na$ [M^++Na] 313.1134, found 313.1134. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 6.0 min, τ_{minor} = 7.6 min (66% ee); $[\alpha]_D^{20}$ = +8.7 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[2-hydroxy-2-(difluoromethyl)nonyl]diazene 1-oxide (5j). Following the general procedure, starting from **2j** (107 mg, 0.6 mmol) and squaramide **I** in α,α,α-trifluorotoluene at −20 °C, azoxy compound **5j** was obtained as pale yellow oil (147 mg, 83%). **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 5.75 (t, *J* = 56.0 Hz, 1H), 3.66 (dd, *J* = 18.3, 1.0 Hz, 1H), 3.50 (dd, *J* = 18.3, 1.0 Hz, 1H), 2.70 (s, 1H), 1.76 – 1.60 (m, 2H), 1.56 (s, 9H), 1.51 – 1.16 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 116.8 (t, $J_{C,F}$ = 248.0 Hz), 77.1, 73.5 (t, $J_{C,F}$ = 20.7 Hz), 54.7 (t, $J_{C,F}$ = 2.3 Hz), 33.2 (t, $J_{C,F}$ = 2.1 Hz), 31.7, 30.0, 29.1, 28.2, 22.6, 22.2, 14.0. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −132.67 (dd, *J* = 282.2, 55.8 Hz, 1F), −134.01 (dd, *J* = 282.2, 55.8 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{14}H_{28}O_2N_2F_2Na$ [M^++Na] 317.2011, found 317.2009. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_{major} = 5.0 min, τ_{minor} = 5.4 min (90% ee); $[\alpha]_D^{20}$ = +14.6 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-[2-(difluoromethyl)-2-hydroxy-4-phenylbutyl] diazene 1-oxide (5k). Following the general procedure, starting from **2k** (110 mg, 0.6 mmol) and squaramide **I** in α,α,α-trifluorotoluene at −20 °C, azoxy compound **5k** was obtained as off-white solid (147 mg, 81%); mp. = 50-52 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): δ = 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.17 (m, 3H), 5.79 (t, *J* = 55.9 Hz, 1H), 3.74 (dd, *J* = 18.2, 1.5 Hz, 1H), 3.60 (dd, *J* = 18.2, 1.5 Hz, 1H), 2.82 (s, 1H), 2.81 – 2.69 (m, 2H), 2.11 – 1.93 (m, 2H), 1.58 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 141.6, 128.5, 128.3, 126.1, 116.7 (t, $J_{C,F}$ = 248.3 Hz), 77.2, 73.5 (t, $J_{C,F}$ = 20.8 Hz), 54.6, 35.1, 28.8, 28.2. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −132.68 (dd, *J* = 282.9, 56.0 Hz, 1F), −133.64 (dd, *J* = 282.9, 56.0 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{15}H_{22}O_2N_2F_2Na$ [M^++Na] 323.1542, found 323.1537. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (99:1)]; flow rate 1 mL/min; τ_{major} = 18.6 min, τ_{minor} = 20.3 min (86% ee); $[\alpha]_D^{20}$ = −3.9 (*c* 1.0, $CHCl_3$).

(*R*)-1-(*tert*-Butyl)-2-(2-cyclohexyl-3,3-difluoro-2-hydroxypropyl) diazene 1-oxide (5l). Following the general procedure, starting from **2l** (97 mg, 0.6 mmol) and squaramide **I** in α,α,α-trifluorotoluene at −20 °C, azoxy compound **5l** was obtained as colorless oil (86 mg, 52%). **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 5.83 (t, *J* = 55.5 Hz, 1H), 3.73 (d, *J* = 17.5 Hz, 1H), 3.52 (d, *J* = 17.5 Hz, 1H), 2.93 (s, 1H), 1.91 – 1.62 (m, 6H), 1.56 (s, 9H), 1.32 – 1.09 (m, 5H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 117.0 (t, $J_{C,F}$ = 248.6 Hz), 74.7 (t, $J_{C,F}$ = 19.6 Hz), 52.9 (t, $J_{C,F}$ = 2.6 Hz), 50.2, 42.8, 28.2, 28.2, 26.7, 26.6, 26.5, 26.3. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −131.56 (d, *J* = 55.5 Hz, 2F). **HRMS** (ESI): m/z calcd for $C_{13}H_{24}F_2N_2O_2Na$ [M^++Na] 301.1698, found 301.1699. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (93:7)]; flow rate 1 mL/min; τ_{major} = 6.8 min, τ_{minor} = 13.6 min (87% ee); $[\alpha]_D^{20}$ = +21.8 (*c* 1.0, $CHCl_3$).

General procedure for the synthesis of fluorinated α-hydroxy aldehydes 6

Freshly distilled formaldehyde *tert*-butyl hydrazone **1a** (102 µL, 0.9 mmol) was added to a solution of fluorinated ketones **2** (0.6 mmol) and the catalyst **I** or **VIII** (37 mg or 36 mg respectively, 0.06 mmol) in the solvent and at the temperature specified for each substrate (see Tables **3** and **4**). The mixture was stirred until consumption of the starting material (TLC or ^{1}H-NMR monitoring). After this time, the organic solvent was removed under reduced pressure at 0 °C. Et_2O (5.4 mL) and HCl aq. (3 mL, 6M) were subsequently added at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 5 hours. The organic phase was separated and the water phase was extracted with Et_2O (3 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure (35 mmHg, 5 °C) to afford crude aldehyde **6**.

General procedure for the synthesis of fluorinated β-aminoalcohols 7

Procedure A (trifluoromethylated aminoalcohols): *p*-Methoxyphenylaniline (73 mg, 0.6 mmol) was added to a solution of crude aldehyde **6** (0.6 mmol) in TFE (1.5 mL). The mixture was stirred at 30 °C for 20 minutes. After this time, $NaBH_4$ powder (28 mg, 0.72 mmol) was added and the reaction was stirred vigorously until the end of gas evolution (30 minutes approximately, TLC monitoring). After completion of the reaction, the mixture was filtered on celite, and the residue was washed with TFE (1 mL). The solvent was removed under reduced pressure and the product was purified by flash chromatography (Pentane/CH_2Cl_2: 2/1) to afford the pure β-aminoalcohols **7**. Enantiomeric excess was determined by HPLC analysis. **Procedure B (difluoromethylated aminoalcohols):** *p*-Methoxyphenylaniline (112 mg, 0.9 mmol) and $NaCNBH_3$ (92 mg, 1.35 mmol) were subsequently added to a solution of crude aldehyde **6** (0.6 mmol) in CH_2Cl_2 (3 mL). The suspension was stirred overnight at room temperature. After completion of the reaction (TLC monitoring), the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Hexane/EtOAc: 4/1) to afford the pure β-aminoalcohols **7**. Enantiomeric excess was determined by HPLC analysis.

(*R*)-1,1,1-Trifluoro-3-[(4-methoxyphenyl)amino]-2-phenylpropan-2-ol (7a). Following the general procedure A, β-aminoalcohol **7a** was obtained as brown solid (129 mg, 69%). Spectroscopic data is in accordance with literature report (E. Matador, D. Monge, R. Fernández, J. M. Lassaletta, *Green Chem*. **2016**, *18*, 4042-4050). **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): 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, *J* = 13.8 Hz, 1H), 3.75 (s, 3H), 3.61 (dd, *J* = 0.4, 13.8 Hz, 1H), 3.10 (s, 1H). The enantiomeric excess was determined by HPLC using a Chiralpak IC column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 7.3 min, τ_{minor} = 6.1 min (46% ee); $[\alpha]_D^{20}$ = +6.3 (*c* 0.5, $CHCl_3$).

(*R*)-1,1-Difluoro-3-[(4-methoxyphenyl)amino]-2-phenylpropan-2-ol (7b). Following the general procedure B, β-aminoalcohol **7b** was obtained as yellow solid (86 mg, 49%); mp: 66-68 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.58 (d, *J* = 7.4 Hz, 2H), 7.48 – 7.33 (m, 3H), 6.82 – 6.74 (m, 2H), 6.73 – 6.63 (m, 2H), 5.84 (t, *J* = 56.0 Hz, 1H), 3.83 (d, *J* = 13.1 Hz, 1H), 3.75 (s, 3H), 3.54 (d, *J* = 13.1 Hz, 1H), 1.64 (s, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 153.7, 141.4, 138.0 (d, $J_{C,F}$ = 2.0 Hz), 128.6, 128.5, 126.2, 118.8, 116.9, 116.3, 114.9, 74.8 (t, $J_{C,F}$ = 21.2 Hz), 55.7, 50.5. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −128.82 (dd, *J* = 280.4, 56.2 Hz, 1F), −130.20 (dd, *J* = 280.4, 56.2 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_{16}H_{18}F_2NO_2Na$ [M^++Na]$^+$ 294.1300, found 294.1299. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (96:4)]; flow rate 1 mL/min; τ_{major} = 22.0 min, τ_{minor} = 23.5 min (72% ee); $[\alpha]_D^{20}$ = +11.2 (*c* 1.0, $CHCl_3$).

(*R*)-2-Benzyl-1,1,1-trifluoro-3-[(4-methoxyphenyl)amino]propan-2-ol (7e). Following the general procedure A, β-aminoalcohol **7e** was obtained as brown oil (87 mg, 45%). Spectroscopic data is in accordance with

literature report (E. Matador, D. Monge, R. Fernández, J. M. Lassaletta, *Green Chem*. **2016**, *18*, 4042-4050). **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): 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, *J* = 14.1 Hz, 1H), 3.27 (d, *J* = 13.9 Hz, 1H), 3.18 (dd, *J* = 0.6, 13.9 Hz, 1H), 2.87 (d, *J* = 13.9 Hz, 1H). The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 9.1 min, τ_{minor} = 14.6 min (47% ee); $[\alpha]_D^{20}$ = +9.4 (*c* 0.5, $CHCl_3$).

(*R*)-1,1-Difluoro-2-{[(4-methoxyphenyl)amino]methyl}-4-phenylbutan-2-ol (7k). Following the general procedure B, β-aminoalcohol **7k** was obtained as yellow solid (82 mg, 43%); mp: 45-47 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 – 7.26 (m, 2H), 7.26 – 7.17 (m, 3H), 6.84 – 6.76 (m, 2H), 6.73 – 6.65 (m, 2H), 5.80 (t, *J* = 56.2 Hz, 1H), 3.76 (s, 3H), 3.45 (d, *J* = 13.5 Hz, 1H), 3.27 – 3.08 (m, 2H), 2.88 – 2.77 (m, 2H), 2.10 – 1.83 (m, 2H), 1.60 (s, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$, 25 °C): δ = 153.3, 142.1, 141.5, 128.6, 128.3, 126.2, 117.6 (t, $J_{C,F}$ = 248.2 Hz), 115.8, 114.9, 72.8 (t, $J_{C,F}$ = 20.9 Hz), 55.7, 48.7, 35.1, 28.9. **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −132.01 (d, *J* = 56.2 Hz, 2F). **HRMS** (ESI): m/z calcd for $C_{18}H_{22}F_2NO_2$ $[M^+{+}H]^+$ 322.1613, found 322.1615. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_{major} = 16.6 min, τ_{minor} = 14.2 min (78% ee); $[\alpha]_D^{20}$ = −5.9 (*c* 1.0, $CHCl_3$).

General procedure for the synthesis of trifluoromethylated α-hydroxy aldoxymes 8.

Hydroxylamine hydrochloride (50 mg, 0.72 mmol) and sodium hydroxide pellets (29 mg, 0.72 mmol) were subsequently added to a solution of crude aldehyde 6 (0.6 mmol) in MeOH (4.5 mL). The mixture was stirred at room temperature overnight. After completion of the reaction, the mixture was diluted with water (1.5 mL) and the organic phase was extracted with CH_2Cl_2 (2 x 3 mL) and Et_2O (2 x 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The product was purified by flash chromatography (CyH/AcOEt: 3/1) to afford the pure α-hydroxy aldoxymes **8**. Enantiomeric excess was determined by HPLC analysis.

(*R*)-3,3,3-Trifluoro-2-hydroxy-2-phenylpropanal oxime (8a). Following the general procedure, α-hydroxy aldoxyme **8a** was obtained as a white solid (80 mg, 61%). Spectroscopic data is in accordance with literature report (E. Matador, D. Monge, R. Fernández, J. M. Lassaletta, *Green Chem*. **2016**, *18*, 4042-4050). **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): 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). The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 34.9 min, τ_{minor} = 30.8 min (47% ee); $[\alpha]_D^{20}$ = +8.9 (*c* 0.5, $CHCl_3$).

(*R*)-2-Benzyl-3,3,3-trifluoro-2-hydroxypropanal oxime (8e). Following the general procedure, α-hydroxy aldoxyme **8e** was obtained as a colorless oil (76 mg, 54%). Spectroscopic data is in accordance with literature report (E. Matador, D. Monge, R. Fernández, J. M. Lassaletta, *Green Chem*. **2016**, *18*, 4042-4050). **^{1}H NMR** (500 MHz, $CDCl_3$, 25 °C): 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, *J* = 14.0 Hz, 1H), 3.09 (d, *J* = 14.0 Hz, 1H). The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 9.8 min, τ_{minor} = 13.1 min (48% ee); $[\alpha]_D^{20}$ = +28.2 (*c* 0.5, $CHCl_3$).

Synthesis of (*R*)-3,3-difluoro-2-hydroxy-2-phenylpropanal oxime (8b). Hydroxylamine hydrochloride (42 mg, 0.6 mmol) was added to a solution crude aldehyde **6b** (0.6 mmol) in THF (1.2 mL). The mixture was stirred at room temperature overnight. After completion of the reaction, the solvent was removed under reduced pressure. The crude mixture was diluted with water (10 mL) and extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography (CyH/AcOEt: 3/1) to afford α-hydroxy aldoxyme **8b** as off-white solid (65 mg, 53%); mp: 65-67 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.88 (s, 1H), 7.59 – 7.52 (m, 2H), 7.47 – 7.37 (m, 3H), 5.88 (t, *J* = 56.2 Hz, 1H), 1.62 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 149.0 – 148.9 (m), 136.2, 128.9, 128.7, 126.2, 115.6 (t, $J_{C,F}$ = 250.7 Hz), 75.2 (t, $J_{C,F}$ = 22.1 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −128.06 (dd, *J* = 279.8, 55.2 Hz, 1F), −128.94 (dd, *J* = 279.8, 55.2 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_9H_{10}F_3NO_2$ $[M+H]^+$ 202.0674, found 202.0675. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (95:5)]; flow rate 1 mL/min; τ_{major} = 14.4 min, τ_{minor} = 12.4 min (72% ee); $[\alpha]_D^{20}$ = +20.8 (*c* 1.0, $CHCl_3$).

Synthesis of (*R*)-3,3-difluoro-2-phenylpropane-1,2-diol (9b).

$NaBH_4$ (29 mg, 0.72 mmol) was added to a solution of crude aldehyde 6b (0.6 mmol) in TFE (1.5 mL) at room temperature. The mixture was stirred at this temperature overnight. After completion of the reaction (TLC monitoring), the mixture was filtered on celite, and the residue was washed with TFE (1 mL). The solvent was removed under reduced pressure and the product was purified by flash chromatography (CyH/AcOEt: 3/2) to afford diol **9b** as a white solid (71 mg, 62%); mp: 46-48 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 25 °C): δ = 7.57 – 7.48 (m, 2H), 7.46 – 7.33 (m, 3H), 5.92 (t, *J* = 55.8 Hz, 1H), 4.19 (d, *J* = 11.7 Hz, 1H), 3.86 (d, *J* = 11.7 Hz, 1H), 3.36 (s, 1H), 2.02 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, 25 °C): δ = 136.8 – 136.6 (m), 128.6, 126.0, 116.4 (t, $J_{C,F}$ = 249.1 Hz), 75.9 (t, $J_{C,F}$ = 21.2 Hz), 65.3 – 65.1 (m). **^{19}F NMR** (471 MHz, $CDCl_3$, 25 °C): δ = −128.30 (dd, *J* = 283.6, 55.8 Hz, 1F), −132.34 (ddd, *J* = 57.4, 55.8, 1.7 Hz, 1F). **HRMS** (ESI): m/z calcd for $C_9H_{10}F_2O_2Na$ $[M+Na]^+$ 211.0541, found 211.0541. The enantiomeric excess was determined by HPLC using a Chiralpak IE column [hexane/i-PrOH (93:7)]; flow rate 1 mL/min; τ_{major} = 9.4 min, τ_{minor} = 10.1 min (68% ee); $[\alpha]_D^{20}$ = −19.7 (*c* 1.0, $CHCl_3$).

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Keywords: Hydrazones • Fluorinated ketones • *H*-bonding organocatalysis • Azoxy compounds • Aminoalcohols • Oximes

[1] a) T. Hiyama, in *Organofluorine Compounds: Chemistry Applications*, (Eds.: H. Yamamoto), 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) V. A. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Wiley, Hoboken, New Jersey, **2009**; e) C. Isanbor, D. O´Hagan, *J. Fluorine Chem.* **2006**, *127*, 303-319; f) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; g) M. Hird, *Chem. Soc. Rev.* **2007**, *36*, 2070-2095. h) D. O´Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308-319; i) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

[2] a) T. Yamazaki, T. Taguchi, I. Ojima, in *Fluorine in Medicinal Chemistry and Chemical Biology*, (Eds.: I. Ojima), Wiley-Blackwell, Chichester, **2009**; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359-4369; c) D.

O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071-1081; d) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3-11.

[3] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529-2591; b) F. Narjes, K. F. Koehler, U. Koch, B. Gerlach, S. Colarusso, C. Steinkühler, M. Brunetti, S. Altamura, R. De Francesco, V. G. A. Matassa, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701-704; c) M. A. Chowdhury, K. R. Abdellatif, Y. Dong, D. Das, M. R. Suresh, E. E. Knaus, *J. Med. Chem.* **2009**, *52*, 1525-1529.

[4] a) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1 and references cited therein; b) G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018-2037; c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470-477.

[5] Selected examples: a) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707-3710; b) H. Kawai, K. Tachi, E. Tokunaga, M. Shiro, N. Shibata, *Org. Lett.* **2010**, *12*, 5104-5107.

[6] For a review, see: J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465-7478.

[7] Selected examples: a) F. Tur, J. M. Saá, *Org. Lett.* **2007**, *9*, 5079-5082; b) M. Bandini, R. Sinisi, A. Umani-Ronchi, *Chem. Commun.* **2008**, 4360-4362; c) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727-1739; d) J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng, J.-A. Ma, *Chem. Commun.* **2009**, 2356-2358; e) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun.* **2010**, *46*, 6282-6284; f) C. Palacio, S. J. Connon, *Org. Lett.* **2011**, *13*, 1298-1301; g) K. Aikawa, S. Yoshida, D. Kondo, Y. Asai, K. Mikami, *Org. Lett.* **2015**, *17*, 5108-5111; h) P. Wang, H.-F. Li, J.-Z. Zhao, Z.-H. Du, C.-S. Da, *Org. Lett.* **2017**, *19*, 2634-2637.

[8] Some examples: a) P. Bravo, M. Frigerio, G. Resnati, *J. Org. Chem.* **1990**, *55*, 4216-4218; b) A. Dondoni, A. Boscarato, P. Formaglio, J.-P. Bégué, F. Benayoud, *Synthesis* **1995**, 654-658.

[9] a) R. Fernández, J. M. Lassaletta, *Synlett* **2000**, 1228-1240; b) R. Brehme, D. Enders, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem.* **2007**, 5629-5660.

[10] Hydrazones in asymmetric organocatalysis. a) Review: M. G. Retamosa, E. Matador, D. Monge, J. M. Lassaletta, R. Fernández, *Chem. Eur. J.* **2016**, *22,* 13430-13445. Selected examples: b) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Köckritz, A. Pews-Davtyan, N. Nemati, M. Beller, *Org. Lett.* **2007**, *9*, 1065-1068; c) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem* **2007**, *72*, 3565-3568; d) T. Hashimoto, M. Hirose, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 7556-7557; d) T. Hashimoto, H. Kimura, K. Maruoka, *Angew. Chem. Int. Ed.* **2010**, *49*, 6844-6847; e) M. Fernández, J. L. Vicario, E. Reyes, L. Carrillo, D. Badía, *Chem. Commun.* **2012**, *48*, 2092-2094; f) M. Fernández, U. Uria, J. L. Vicario, E. Reyes, L. Carrillo, *J. Am. Chem. Soc.* **2012**, *134*, 11872-11875; g) L. Lykke, B. D. Carlsen, R. S. Rambo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 11296-11299; h) C. M. R. Volla, A. Das, I. Atodiresei, M. Rueping, *Chem. Commun.* **2014**, *50*, 7889-7892; i) W, Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu, J. Ye, *Org. Lett.* **2013**, *15*, 4524-4527.

[11] a) A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2012**, *134*, 12912-12915; b) J. A. Carmona, G. de Gonzalo, I. Serrano, A. M. Crespo-Peña, M. Šimek, D. Monge, R. Fernández, J. M. Lassaletta, *Org. Biomol. Chem.* **2017**, 15, 2993-3005.

[12] I. Serrano, D. Monge, E. Álvarez, R. Fernández, J. M. Lassaletta, *Chem. Commun.* **2015**, *51*, 4077-4080.

[13] D. Monge, A. Crespo-Peña, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2013**, *19,* 8421-8425.

[14] E. Matador, M. G. Retamosa, D. Monge, J. Iglesias-Sigüenza, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2018**, *24*, 6854-6860.

[15] E. Matador, D. Monge, R. Fernández, J. M. Lassaletta, *Green Chem.* **2016**, *18*, 4042-4050.

[16] For discussions on hydrogen-bond donating ability, see: a) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407-414; b) S. J. Connon, *Synlett* **2009**, 354-376; c) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724-1727.

[17] Modification of these reaction conditions in order to improve the enantioselectivity were unsuccessfully explored (see ESI).

[18] a) The antimicrobial and cytotoxic elaiomycins: L. Ding, B. L. T. Ndejouong, A. Maier, H. H. Fiebig, C. Hertweck, *J. Nat. Prod.* **2012**, *75*, 1729-1734; b) the antibiotic valanimycin: R. P. Garg, X. L. L. Qian, L. B. Alemany, S. Moran, R. J. Parry, *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 6543-6547; c) and the antifungal agents maniwamycin A: M. Nakayama, Y. Takahashi, H. Itoh, K. Kamiya, M. Shiratsuchi, G. Otani, *J. Antibiot.* **1989**, *42*, 1535-1540.

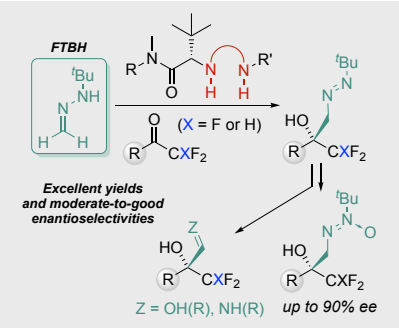
[19] J.-S. M. Lehn, S. Javed, D. M. Hoffman, *Inorg. Chem.* **2007**, *46*, 993-1000.

[20] M. Bos, W.-S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *56*, 13319-13323.

[21] C. B. Kelly, M. A. Mercadante, E. R. Carnaghan, M. J. Doherty, D. C. Fager, J. J. Hauck, A. E. MacInnis, L. J. Tilley, N. E. Leadbeater, *Eur. J. Org. Chem.* **2015**, 4071-4076.

FULL PAPER

A formylation strategy: *tert*-Leucine derived organocatalysts promote the enantioselective 1,2-addition of **FTBH** to fluorinated ketones to afford quaternary β-hydroxy β-fluoromethyl diazenes in excellent yields and moderate-to-good enantioselectivities. Subsequent high-yielding and racemization-free transformations provide an expedient entry to enantioenriched azoxy compounds, aldehydes and derivatives thereof.



Fluorinated alcohols*

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Asymmetric Organocatalytic Synthesis of Fluorinated β-Hydroxy Diazenes