Trifluoromethyl nitrones: from fluoral to optically active hydroxylamines†

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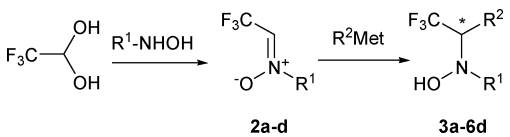
Trifluoromethyl nitrones were obtained in high yields by condensation of various hydroxylamines with trifluoroacetaldehyde hydrate. The nucleophilic diastereoselective additions of organometallic reagents to these nitrones afforded the corresponding optically active trifluoroethyl hydroxylamines in good yields.

Introduction

N-Hydroxylamine derivatives are attractive synthetic targets due to their potential applications as therapeutics in iron overload,[1] and protease inhibition.[2] On the other hand, optically active trifluoromethyl-substituted nitrogen compounds, such as trifluoroethyl amines, are versatile and interesting building blocks in organic and medicinal chemistry.[3] The corresponding trifluoroethyl hydroxylamines should also find applications, offering the specific properties of the trifluoromethyl group: electron withdrawing character, resulting in decreased pK_a of neighbouring functions and increased hydrogen bonding.[4] Surprisingly, only a few syntheses of trifluoroethyl hydroxylamines have been reported: (i) trifluoromethylation reactions of nitrones;[5] (ii) reduction of trifluoromethyl oximes;[6] (iii) addition of hydroxylamines to trifluorocrotonate derivatives.[7] However, none of these reactions are suitable for affording enantiopure hydroxylamines. Herein we document our research on the first general method for the synthesis of optically active trifluoroethyl *N*-hydroxylamines from fluoral (Scheme 1).



2a-d **3a-6d**

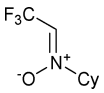
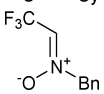
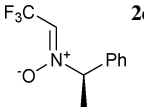
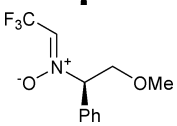
Scheme 1 Synthetic scheme for trifluoroethyl hydroxylamines.

Results and discussion

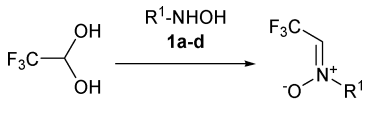
Our approach is based on the addition of organometallic reagents to trifluoromethyl nitrones. Although nitrones find large applications in the field of age-related diseases,[8] only two trifluoromethyl nitrones are reported in the literature: Janzen *et al.*[9] described the synthesis of a C-trifluoromethyl endocyclic nitrone for the purpose of spin trapping in free radical biology, and Tanaka *et al.*[10] reported the synthesis of one *N*-methyl-trifluoromethyl nitrone. However, due to its volatility, the *N*-methyl-trifluoromethyl nitrone was not isolated, and was hence used in 1,3-dipolar cycloadditions in a one-pot manner. Therefore, our attention was primarily focused on the synthesis and isolation of trifluoromethyl nitrones using commercially available trifluoroacetaldehyde hydrate.

Nitrones **2a**,**b** and **2d** were easily prepared by treating the corresponding hydroxylamines with fluoral hydrate in toluene for 2 h, using Dean–Stark apparatus (Scheme 2, Table 1). Evaporation of toluene yielded nitrones **2a**,**b** and **2d** in high purity. In the case of the nitrone **2c** better results were obtained using $MgSO_4$ in refluxing chloroform. Finally, the nitrones were recovered in high yields as stable solids and could be stored in a refrigerator for several months.

Table 1 Preparation of trifluoromethyl nitrones[a]

Entry	Hydroxylamine **1**	Nitrone **2**	Yield (%)
1	CyclohexylNHOH **1a**	 **2a**	80
2	BnNHOH **1b**	 **2b**	86
3	(*R*)-PhCH(Me)NHOH **1c**	 **2c**	89
4	(*R*)-PhCH(CH_2OMe)NHOH **1d**	 **2d**	93

[a] Reaction conditions: fluoral (1.1 mmol), hydroxylamine (1 mmol) in refluxing toluene with Dean–Stark apparatus (entries 1, 2 and 4) or chloroform in presence of $MgSO_4$ (entry 3).



2a-d

Scheme 2 Preparation of trifluoromethyl nitrones **2a–d**.

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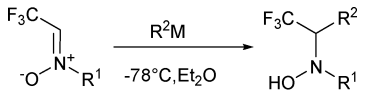
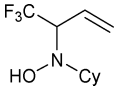
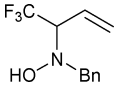
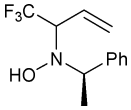
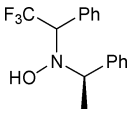
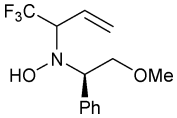
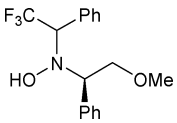
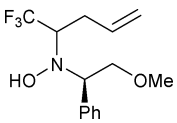
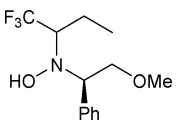
† Electronic supplementary information (ESI) available: Characterization data (^{1}H, ^{13}C and ^{19}F NMR spectra and elemental analysis) of the products **2–8** and X-ray structure of **2d**. CCDC reference number 722468. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c001791d

Table 2 Preparation of trifluoroethyl *N*-hydroxylamines



Entry	Nitrone **2**	R^2Met	Hydroxylamines	Product	Yield (%)	dr
1	**2a**	vinylMgBr		**3a**	94	—
2	**2b**	vinylMgBr		**3b**	87	—
3	**2c**	vinylMgBr		**3c**	94	75 : 25
4	**2c**	PhMgBr		**4c**	72	65 : 35
5	**2c**	PhLi		**4c**	63	67 : 33
6	**2d**	vinylMgBr		**3d**	88	76 : 24
7	**2d**	PhLi		**4d**	99	85 : 15
8	**2d**	PhMgBr		**4d**	81	78 : 22
9	**2d**	AllylMgBr		**5d**	91	75 : 25
10	**2d**	EtMgBr		**6d**	87	70 : 30

Homo- and hetero-nOe experiments indicated that nitrone **2b** adopted the *Z* configuration. X-ray analysis‡ of the nitrone **2d** confirmed this result and hence, all nitrones were assumed to adopt the same *Z* configuration.

Nucleophilic addition to nitrones has been extensively studied;[11] however, the addition of organometallics to their trifluoromethyl analogues has never been described. This reaction was thus investigated with nitrones **2a–d**, using Grignard and organolithium reagents, as a synthetic route to trifluoroethyl hydroxylamines. Typically, reactions of nitrones with organometallic reagents were carried out in diethyl ether at −78 °C and had progressed to completion after 30 min. When treated with vinylMgBr, the achiral nitrones **2a** and **2b** afforded the corresponding hydroxylamines **3a** and **3b** in high yields and high purities (Table 2, entries 1 and 2). The reaction of chiral nitrones **2c** and **2d** with vinylMgBr furnished pairs of diastereoisomeric trifluoroethyl hydroxylamine adducts, **3c** and **3d** in good yields and modest diastereoselectivities (Table 2, entries 3 and 5).

The isomeric ratios of the hydroxylamine adducts were determined by ^{19}F NMR spectra analysis of the crude products. Diastereoselectivities and yields were shown to not fluctuate in different solvents (THF, toluene or dichloromethane). Surprisingly the change of the chiral auxiliary carried by the nitrogen atom of the nitrone (**2c** *vs.* **2d**) did not significantly modify the

‡ See the ORTEP view in supporting information.

diastereoselectivity. This can perhaps be explained by the reaction rate. Indeed, there was no starting material after only 15 min, indicating that the reaction is very fast. The scope of the reaction was then extended to various other organometallic reagents. The addition of phenylMgBr, allylMgBr and ethylMgBr reagents to the nitrone **2d** afforded the corresponding trifluoroethyl hydroxylamines in good yields, with comparable diastereoselectivities (Table 2, entries 7–9). Nevertheless, the reaction of phenyl lithium with the same nitrone **2d** provided hydroxylamine adducts **4d** with a slightly better diastereoselectivity (dr 85 : 15) (Table 2, entry 7).

In accordance with our previous work on vinylation reactions of trifluoromethyl aldimines,[12] the resulting chiral centre in the major isomer of **4d** was assumed to have (*R*) configuration. This view is supported by the findings of Chang *et al.* on organometallic additions to chiral nitrones (Fig. 1).[11] Nevertheless, the modest diastereoselectivity observed could be explained by a competition between the previous model and another involving an metal-fluorine type interaction, which has already been reported in the literature.[13]

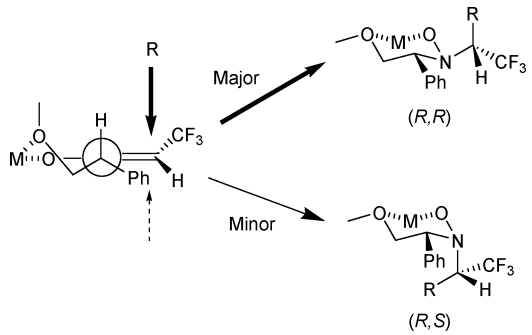
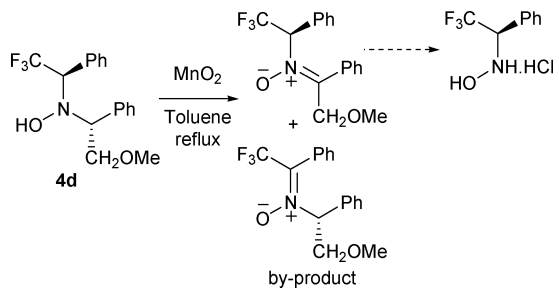


Fig. 1 Chelated transition state model.

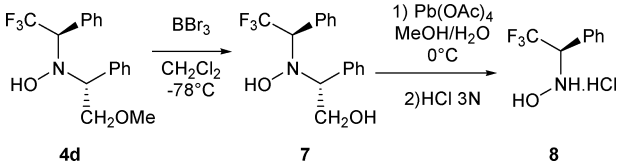
The major isomer of the 85 : 15 mixture of hydroxylamine **4d** was isolated by column chromatography, as a pure compound.[14] Subsequently, we then investigated the removal of the (*R*)-phenylglycinol chiral auxiliary, with the main challenge being to retain the hydroxyl group on the nitrogen whilst avoiding racemisation. The direct deprotection protocol involves an oxidation of **4d** to a nitrone followed by hydrolysis, to obtain the free hydroxylamine.

Unfortunately treatment of **4d** with MnO_2 in refluxing toluene[15] afforded a mixture of inseparable structural isomers of nitrones in the ratio 60 : 40 as indicated by ^{19}F NMR spectrum (Scheme 3).



Scheme 3 Removal of the (*R*)-phenylglycinol chiral auxiliary.

This obstacle was circumvented using milder conditions, involving initial demethylation of the enantiopure **4d** with BBr_3 at –78 °C, followed by oxidative cleavage with $Pb(OAc)_4$ at 0 °C and subsequent acid hydrolysis (Scheme 4). The optically active trifluoroethyl *N*-hydroxylamine **8** could then be isolated in good yield (52% over two steps).[16]



Scheme 4 Removal of the (*R*)-phenylglycinol methyl ether.

Conclusions

In summary, we report a novel, general and practical method for the preparation of trifluoromethyl nitrones and their diastereoselective conversion into optically active trifluoroethyl *N*-hydroxylamines. The trifluoromethyl group may dramatically influence the physico-chemical properties of such compounds, which are of increasing importance in medicinal chemistry. Furthermore, due to their stable nature, the novel trifluoromethyl nitrones may serve as a versatile platform for further synthetic transformations.

Experimental

Material and methods

Commercial reagents were purchased from ALDRICH or ACROS and used as received. Trifluoroacetaldehyde-hydrate was generously offered by Central Glass Company. All organometallic addition reactions were performed under argon atmosphere with oven-dried glassware fitted with rubber septa. Ether and THF were distilled under nitrogen from sodium/benzophenone prior to use. Flash chromatography was performed on 254F Geduran SiO_2 60 (40–63 μm or 63–200 mm.) silica gel. Thin layer chromatography was performed on precoated aluminium sheets (Merck Silica gel $60G_{254}$). NMR spectra were recorded with a Bruker AC 200 or 300 spectrometer (^1H: 200 or 300 MHz; ^{19}F: 188 MHz; ^{13}C: 75 MHz). Chemical shifts (δ) are reported in ppm relative to Me_4Si and $CFCl_3$ [for ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C)] as internal standards. For the ^{13}C NMR data, reported signal multiplicities were measured relative to C–F coupling. Infrared (IR) spectra were performed on a Bruker Vector 22. Specific rotations were determined on an automatic polarimeter polAAr32 from Optical Activity Limited. Melting points were measured on a Stuart SMP10 apparatus.

General procedure for the synthesis of trifluoromethyl nitrones 2a,b and 2d

Trifluoroacetaldehyde hydrate (1.1 eq) is added to a solution of the hydroxylamine in toluene stirring in a hot oil bath. The reaction mixture is then stirred at reflux with Dean–Stark apparatus. The reaction is followed by ^{19}F NMR till completion. The solvent is then removed to afford the nitrone.

N-Cyclohexyl-*N*-[(*Z*)-2,2,2-trifluoroethylidene]amine oxide (2a)

Obtained from *N*-cyclohexyl hydroxylamine (0.3 g, 2.61 mmol) following the general procedure for the synthesis of nitrones, as a

pale orange solid (0.51 g, 99%); mp 109–111 °C; ν_{max}/cm^{-1} 1586, 1265, 1206, 1142, 943, 735; δ_H (300 MHz; $CDCl_3$) 1.11–2.13 (10H, m), 3.81–3.98 (1H, m), 7.10 (1H, q, $J = 5.5$ Hz); δ_C (75 MHz; $CDCl_3$) 24.7, 24.7, 30.9, 76.3, 119.6 (q, $J = 270$ Hz), 121.7 (q, $J = 38$ Hz); δ_F (188 MHz; $CDCl_3$) –66.3 (d, $J = 5.5$ Hz). Found C, 49.33; H, 6.03; N, 7.27. calc. for $C_8H_{12}F_3NO$: C, 49.23; H, 6.20; N, 7.18%.

N-Benzyl-*N*-[(*Z*)-2,2,2-trifluoroethylidene]amine oxide (2b)

Obtained from the *N*-benzyl-hydroxylamine[17] (4.21 g, 34.1 mmol) following the general procedure for the synthesis of nitrones, as a white solid after recrystallisation from hexane (5.95 g, 86%); mp 66–67 °C. ν_{max}/cm^{-1} 3082, 1598, 1497, 1456, 951, 877; δ_H (300 MHz; $CDCl_3$) 5.05 (2H, s), 6.89 (1H, q, $J = 5.5$ Hz), 7.32–7.57 (5H, m); δ_C (75 MHz; $CDCl_3$) 71.5, 119.5 (q, $J = 270$ Hz), 123.6 (q, $J = 39$ Hz), 129.4, 129.8, 129.9, 130.8; δ_F (188 MHz; $CDCl_3$) –66.29 (d, $J = 5.5$ Hz); Found C, 53.10; H, 4.11; N, 6.88; calc. for $C_9H_8F_3NO$: C, 53.21; H, 3.97; N, 6.89%.

N-[(*S*)-1-Phenylethyl]-*N*-[(*Z*)-2,2,2-trifluoroethylidene]amine oxide (2c)

(*S*)-*N*-(1-Phenylethyl)-hydroxylamine[18] (1.32 g, 9.63 mmol) in chloroform (60 mL) was treated with trifluoroacetaldehyde hydrate (1.1 eq, 10.6 mmol, 1.24 g) in the presence of $MgSO_4$. The reaction mixture was heated at reflux for 18 h before being filtered and concentrated to yield a white solid. Purification by flash chromatography (30% ethyl acetate in cyclohexane) afforded a white powder (1.85 g, 89%). mp 115–116 °C; $[\alpha]^{20}_{589}$ –11 ($c = 1$, $CHCl_3$); ν_{max}/cm^{-1} 3097, 1589, 1456, 1317, 1247, 1149, 999, 921; δ_H (300 MHz; $CDCl_3$) 1.90 (3H, d, $J = 6.9$ Hz), 5.10 (1H, q, $J = 6.9$ Hz), 7.04 (1H, q, $J = 5.5$ Hz), 7.39–7.58 (5H, m); δ_C (75 MHz; $CDCl_3$) 18.9, 76.3, 119.3 (q, $J = 270$ Hz), 122.3 (q, $J = 37$ Hz), 127.4, 129.1, 129.6, 136.7. δ_F (188 MHz; $CDCl_3$) –66.28 (d, $J = 5.5$ Hz). Found C, 55.87; H, 4.69; N, 6.20. calc. for $C_{10}H_{10}F_3NO$: C, 55.30; H, 4.64; N, 6.45%.

N-[(*R*)-2-Methoxy-1-phenylethyl]-*N*-[(*Z*)-2,2,2-trifluoroethylidene]amine oxide (2d)

Obtained from *N*-(2-methoxy-1-phenylethyl)-hydroxylamine[19] (2.20 g, 13.14 mmol) following the general procedure for the synthesis of nitrones, as a pale yellow solid (3.24 g, 93%). mp 94.5 °C. $[\alpha]^{20}_{589}$ –27 ($c = 1$, $CHCl_3$); ν_{max}/cm^{-1} 3402, 3103, 1596, 1455, 1326, 1256, 1197, 1126, 1030, 972, 885, 772, 747; δ_H (300 MHz; $CDCl_3$) 3.48 (3H, s), 3.74 (1H, dd, $J = 3.2$ Hz, $J = 10.4$ Hz), 4.37 (1H, t, $J = 10.4$ Hz), 5.19 (1H, dd, $J = 3.2$ Hz, $J = 10.4$ Hz), 7.19 (1H, q, $J = 5.5$ Hz), 7.39–7.61 (5H, m); δ_C (75 MHz; $CDCl_3$) 59.4, 71.5, 80.1, 119.5 (q, $J = 270$ Hz), 123.9 (q, $J = 38$ Hz), 127.9, 129.0, 129.8, 132.9; δ_F (188 MHz; $CDCl_3$) –66.3 (d, $J = 5.5$ Hz). Found C, 54.65; H, 5.00; N, 5.89. calc. for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67%.

Synthesis of trifluoromethyl hydroxylamines: general procedure

The organometallic reagent (1.5 eq) is added to a solution of the nitrone stirring in anhydrous Et_2O under argon at –78 °C. After 30 min the reaction mixture is diluted in Et_2O and washed with saturated aqueous NaCl. The organic phase is dried ($MgSO_4$) and concentrated to yield the hydroxylamine.

N-Cyclohexyl-*N*-(1-trifluoromethyl-allyl)-hydroxylamine (3a)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2a** (0.20 g, 1.03 mmol) with vinyl magnesium bromide afforded the racemic mixture as a yellow oil (0.21 g, 94%). ν_{max}/cm^{-1} 3540, 3065, 1586, 1704, 1223, 920; δ_H (300 MHz; $CDCl_3$) 0.95–2.17 (10H, m), 2.53–2.20 (1H, m), 3.77 (1H, p, $J = 8.2$ Hz), 5.10 (1H, s), 5.33 (1H, d, $J = 17.5$ Hz), 5.45 (1H, d, $J = 10.4$ Hz), 6.02 (1H, ddd, $J = 10.4$, $J = 8.0$ Hz, $J = 17.5$ Hz). δ_C (75 MHz; $CDCl_3$) 23.6, 23.7, 24.9, 27.6, 29.2, 61.2, 65.7 (q, $J = 28$ Hz), 122.7, 124.1 (q, $J = 281$ Hz), 126.0. δ_F (188 MHz; $CDCl_3$) –71.6 (d, $J = 8.0$ Hz). Found C, 55.10; H, 7.27; N, 6.48. calc. for $C_{10}H_{16}F_3NO$: C, 53.80; H, 7.22; N, 6.27%.

N-Benzyl-*N*-(1-trifluoromethyl-allyl)-hydroxylamine (3b)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2b** (0.10 g, 0.49 mmol) with vinyl magnesium bromide afforded the racemic mixture as a pale yellow oil (0.10 g, 87%). ν_{max}/cm^{-1} 3402, 3083, 3032, 2978, 2924, 1813, 1695, 1235, 1083, 918, 732; δ_H (300 MHz; $CDCl_3$) 3.52 (1H, qd, $J = 7.8$, $J = 8.1$ Hz), 3.72 (1H, d, $J = 12.8$ Hz), 3.93 (1H, d, $J = 12.8$ Hz), 5.32 (1H, dd, $J = 1.3$ Hz, $J = 17.4$ Hz), 5.56 (1H, dd, $J = 1.3$ Hz, $J = 10.4$ Hz), 5.65 (1H, sbr), 6.04 (1H, ddd, $J = 8.1$ Hz, $J = 10.4$ Hz, $J = 17.4$ Hz), 7012–7.40 (5H, m); δ_C (75 MHz; $CDCl_3$) 61.5, 69.2 (q, $J = 28$ Hz), 124.7 (q, $J = 281$ Hz), 125.3, 126.0, 127.9, 128.6, 129.5, 136.3; δ_F (188 MHz; $CDCl_3$) –71.6 (d, $J = 7.8$ Hz); Found C, 57.54; H, 5.14; N, 5.95. calc. for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06%.

N-[(*S*)-1-Phenylethyl]-*N*-(1-trifluoromethyl-allyl)-hydroxylamine (3c)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2c** (0.10 g, 0.46 mmol) with vinyl magnesium bromide afforded the mixture of diastereoisomers (75 : 25, d.e. 50%) as a pale yellow oil (0.1 g, 94%). ν_{max}/cm^{-1} 3482, 3268, 3042, 1680, 1210, 924, 728; Found C, 59.07; H, 5.39; N, 5.40. calc. for $C_{12}H_{14}F_3NO$: C, 58.77; H, 5.75; N, 5.71%. Major diastereoisomer: δ_H (300 MHz; $CDCl_3$) 1.39 (3H, d, $J = 6.4$ Hz), 3.40 (1H, q, $J = 8.1$ Hz), 3.83 (1H, q, $J = 6.4$ Hz), 5.00 (1H, s, H^d), 5.05 (1H, dd, $J = 17.4$ Hz, $J = 1.2$ Hz), 5.47 (1H, dd, $J = 10.3$ Hz, $J = 1.2$ Hz), 5.98–6.14 (1H, m), 7.14–7.40 (5H, m); δ_C (75 MHz; $CDCl_3$) 22.0, 64.4, 66.3 (q, $J = 28$ Hz), 124.9, 125.0 (q, $J = 281$ Hz), 125.9, 127.5, 129.0, 142.3; δ_F (188 MHz; $CDCl_3$) –72.1 (d, $J = 8.1$ Hz).

N-[(*S*)-1-Phenylethyl]-*N*-(1-trifluoromethyl-phenyl)-hydroxylamine (4c)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2c** (0.10 g, 0.46 mmol) with phenyl lithium afforded the mixture of diastereoisomers (67 : 33, d.e. 34%) as a pale yellow oil (0.85 g, 63%); ν_{max}/cm^{-1} 3502, 3018, 2987, 1483, 1218, 756; Found C, 64.95; H, 5.22; N, 5.03. calc. for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74%. Major diastereoisomer: δ_H (300 MHz; $CDCl_3$) 1.33 (3H, d, $J = 6.4$ Hz), 3.59 (1H, q,

J = 6.4 Hz), 4.04 (1H, q, J = 8.4 Hz), 4.87 (1H, s), 7.13–7.51 (10H, m); δ_C (75 MHz; $CDCl_3$) 22.1, 64.1, 67.3 (q, J = 28 Hz, C^3), 124.2 (q, J = 281 Hz), 127.8, 127.9, 128.2, 128.5, 128.7, 128.9, 131.3, 142.1; δ_F (188 MHz; $CDCl_3$) –69.4 (d, J = 8.4 Hz, CF_3).

N-[(*R*)-2-Methoxy-1-phenylethyl]-*N*-(1-trifluoromethyl-allyl)-hydroxylamine (3d)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2d** (0.20 g, 0.81 mmol) with vinyl magnesium bromide afforded the mixture of diastereoisomers (76 : 24, d.e. 52%) as a pale yellow oil (0.19 g, 88%). Purification by flash chromatography (5% ethyl acetate in cyclohexane) yielded the major diastereoisomer and the minor diastereoisomer separately. Major diastereoisomer: pale yellow oil (0.14 g); $[\alpha]^{20}_{589}$ +44°(c = 1, $CHCl_3$); ν_{max}/cm^{-1} 3484, 3118, 3034, 1583, 1207, 1183, 924, 736; Found C, 57.08; H, 5.80; N, 5.04. calc. for $C_{13}H_{16}F_3NO_2$: C, 56.72; H, 5.86; N, 5.09%. δ_H (300 MHz; $CDCl_3$) 3.23 (3H, s), 3.39 (1H, p, J = 8.4 Hz), 3.69 (1H, dd, J = 9.7 Hz, J = 5.5 Hz), 3.77 (1H, dd, J = 9.7 Hz, J = 4.8 Hz), 3.94 (1H, t, J = 5.1 Hz), 5.04 (1H, dd, J = 17.4 Hz, J = 1.0 Hz), 5.47 (1H, dd, J = 10.4 Hz, J = 1.4 Hz), 5.68 (1H, s), 6.05 (1H, ddd, J = 17.4 Hz, J = 10.3 Hz, J = 8.4 Hz), 7.20–7.32 (5H, m); δ_C (75 MHz; $CDCl_3$) 59.2, 66.7 (q, J = 29 Hz), 67.4, 75.6, 124.9 (q, J = 281 Hz), 125.1, 125.8, 128.3, 128.7, 128.8, 138.0; δ_F (188 MHz; $CDCl_3$) –71.8 (d, J = 8.0 Hz, CF_3). Minor diastereoisomer pale yellow oil (0.04 g); Found C, 57.40; H, 5.66; N, 5.17. calc. for $C_{13}H_{16}F_3NO_2$: C, 56.72; H, 5.86; N, 5.09%; $[\alpha]^{20}_{589}$ –124°(c = 1, $CHCl_3$) δ_H (300 MHz; $CDCl_3$) 3.24 (3H, s), 3.37 (1H, dd, J = 11.0 Hz, J = 2.7 Hz), 3.64 (1H, dd, J = 11.0 Hz, J = 8.1 Hz), 4.12 (1H, dd, J = 8.1 Hz, J = 2.6 Hz), 4.30 (1H, p, J = 8.3 Hz), 4.70 (1H, s), 5.42 (1H, dd, J = 17.4 Hz, J = 1.5 Hz), 5.51 (1H, dd, J = 10.4 Hz, J = 1.7 Hz), 6.03 (1H, ddd, J = 17.4 Hz, J = 10.5 Hz, J = 8.6 Hz), 7.17–7.34 (5H, m); δ_C (75 MHz; $CDCl_3$) 58.8, 67.1 (q, J = 28 Hz), 68.4, 75.7, 124.7, 125.2 (q, J = 281 Hz), 126.6, 127.8, 127.8, 128.7, 139.7; δ_F (188 MHz; $CDCl_3$) –71.8 (d, J = 8.2 Hz).

N-[(*R*)-2-Methoxy-1-phenylethyl]-*N*-(2,2,2-trifluoro-1-phenyl-ethyl)-hydroxylamine (4d)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2d** (0.50 g, 2.02 mmol) with phenyl lithium afforded a mixture of diastereoisomers (85 : 15, d.e. 70%) as a pale yellow oil (0.65 g, 99%). Purification by flash chromatography (5% ethyl acetate in cyclohexane) yielded the major and minor isomer separately. Major diastereoisomer as a pale yellow oil (0.54 g); ν_{max}/cm^{-1} 3487, 3031, 2925, 1530, 1031, 904. Found C, 62.21; H, 5.41; N, 4.32. calc. for $C_{17}H_{18}F_3NO_2$: C, 62.76; H, 5.58; N, 4.31%. $[\alpha]^{20}_{589}$ –63 (c = 1, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 3.18 (3H, s), 3.59 (1H, dd, J = 9.4 Hz, J = 5.2 Hz), 3.69 (1H, t, J = 5.3 Hz), 3.78 (1H, dd, J = 9.4 Hz, J = 5.5 Hz), 4.03 (1H, q, J = 8.2 Hz), 5.51 (1H, s), 7.17–7.40 (10H, m); δ_C (75 MHz; $CDCl_3$) 59.1, 67.4, 67.9 (q, J = 28 Hz), 75.1, 125.2 (q, J = 281 Hz), 128.3, 128.4, 128.7, 129.1, 129.2, 130.0, 131.1, 137.4; δ_F (188 MHz $CDCl_3$) –68.9 (d, J = 8.2 Hz).

Minor diastereoisomer as a pale yellow oil (0.08 g); Found C, 62.02; H, 5.10; N, 4.53. calc. for $C_{17}H_{18}F_3NO_2$: C, 62.76; H, 5.58; N, 4.31%. $[\alpha]^{20}_{589}$ –16 (c = 1, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 3.26 (3H, s), 3.44 (1H, dd, J = 10.5 Hz, J = 3.0 Hz), 3.31–3.41 (1H, m), 4.00 (1H, dd, J = 8.1 Hz, J = 2.9 Hz), 4.83–4.95 (2H, m), 7.02–7.41 (10H, m); δ_C (75 MHz; $CDCl_3$) 58.9, 67.1, 68.4 (q, J = 27 Hz), 74.6, 119.9–131.8 (m), 126.5, 127.2, 127.8, 127.9, 128.2, 128.6, 128.9, 131.2, 131.4, 139.5; δ_F (188 MHz; $CDCl_3$) –68.6 (d, J = 8.3 Hz).

N-[(*R*)-2-Methoxy-1-phenylethyl]-*N*-(1-trifluoromethyl-but-3-enyl)-hydroxylamine (5d)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone **2d** (0.20 g, 0.81 mmol) with allyl magnesium bromide afforded the crude mixture of diastereoisomers as a pale yellow oil. Purification by flash chromatography (5% ethyl acetate in cyclohexane) yielded the pure mixture of inseparable diastereoisomers (75 : 25, d.e. 50%) as a pale yellow oil (0.21 g, 91%). ν_{max}/cm^{-1} 3518, 3436, 1576, 1218, 946, 937, 703. Found C, 58.17; H, 6.21; N, 4.83. calc. for $C_{14}H_{18}F_3NO_2$: C, 58.12; H, 6.27; N, 4.84%.

Major diastereoisomer: δ_H (300 MHz; $CDCl_3$) 2.37 (1H, m), 2.71 (1H, m), 3.15 (1H, s, J = 8 Hz), 3.22 (3H, s), 3.64 (1H, dd, J = 9.8 Hz, J = 5.3 Hz), 3.76 (1H, dd, J = 9.8 Hz, J = 5.3 Hz), 4.18 (1H, t, J = 5.3 Hz), 4.98 (2H, m), 5. 51 (1H, s) 5.68 (1H, m), 7.18–7.35 (5H, m); δ_C (75 MHz; $CDCl_3$) 27.0, 59.0, 62.5 (q, J = 26 Hz), 68.7, 75.7, 117.4, 125.8 (q, J = 283 Hz), 128.0, 128.1, 128.2, 134.8, 138.4; δ_F (188 MHz; $CDCl_3$) –72.04 (d, J = 8.1 Hz).

Minor diastereoisomer: δ_H (300 MHz; $CDCl_3$) 2.37 (1H, m), 2.58 (1H, m), 3.25 (3H, s), 3.45 (1H, dd, J = 9.8 Hz, J = 5.4 Hz), 3.51 (1H, s, J = 8.5 Hz), 3.64 (1H, m), 4.27 (1H, dd, J = 5.4 Hz), 4.98 (2H, m), 5.05 (2H, m), 5.15 (1H, s), 5.68 (1H, m), 7.18–7.35 (5H, m); δ_C (75 MHz; $CDCl_3$) 28.8, 58.6, 63.1 (q, J = 28 Hz), 68.8, 75.9, 117.0, 125.8 (q, J = 282 Hz), 127.8, 128.3, 128.7, 134.7, 139.1; δ_F (188 MHz; $CDCl_3$) –70.0 (d, J = 8.3 Hz).

N-[(*R*)-2-Methoxy-1-phenylethyl]-*N*-(1-trifluoromethyl-propyl)-hydroxylamine (6d)

According to the general procedure for synthesis of trifluoromethyl hydroxylamines, reaction of nitrone (0.10 g, 0.4 mmol) with ethyl magnesium bromide afforded the crude mixture of diastereoisomers. Purification by flash chromatography (5% ethyl acetate in cyclohexane) yielded the pure mixture of diastereoisomers (70 : 30, d.e. 40%) as a pale yellow oil (0.09 g, 87%). ν_{max}/cm^{-1} 3532, 3321, 3046, 3031, 2927, 1486, 1228, 1018, 976, 782. Found C, 56.03; H, 6.09; N, 4.91. calc. for $C_{13}H_{18}F_3NO_2$: C, 56.31; H, 6.54; N, 5.05%.

Major diastereoisomer: δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, J = 7.4 Hz), 1.62 (2H, m), 2.90 (1H, m), 3.22 (3H, s), 3.60 (1H, dd, J = 9.6 Hz, J = 5.1 Hz), 3.76 (1H, dd, J = 9.8 Hz, J = 5.1 Hz), 4.14 (1H, t, J = 5.1 Hz), 5.24 (1H, sbr), 7.20–7.41 (5H, m); δ_C (75 MHz; $CDCl_3$) 12.0,16.0, 58.9, 64.1 (q, J = 26 Hz), 68.9, 75.9, 125.9 (q, J = 284 Hz), 128.3, 128.5, 128.8, 138.8; δ_F (188 MHz; $CDCl_3$) –71.49 (d, J = 8.2 Hz, CF_3).

Minor diastereoisomer: δ_H (300 MHz; $CDCl_3$) 0.91 (3H, t, J = 7.4 Hz), 1.85 (2H, m), 3.15 (1H, m), 3.24 (3H, s), 3.51 (1H, dd, J = 3.6 Hz, J = 10.4 Hz), 3.62 (1H, m), 4.32 (1H, dd, J = 7.4 Hz, J = 3.6 Hz), 5.12 (1H, sbr), 7.20–7.41 (5H, m); δ_C (75 MHz; $CDCl_3$) 11.2, 18.0, 58.6, 64.1 (q, J = 26 Hz), 68.9, 76.2, 126.2 (q, J = 284 Hz), 128.1, 128.5, 128.7, 139.1; δ_F (188 MHz; $CDCl_3$) –69.47 (d, J = 8.1 Hz).

N-(2,2,2-Trifluoro-1-phenylethyl)-hydroxylamine, HCl (8)

Enantiopure *N*-[(*R*)-2-methoxy-1-phenylethyl]-*N*-(2,2,2-trifluoro-1-phenylethyl)-hydroxylamine, **4d** (0.53 g, 1.62 mmol) in anhydrous CH_2Cl_2 (7 mL) was treated with BBr_3 (2.5 eq, 1 M, 4.05 mL) at −78 °C then back to −10 °C under argon. After 30 min the solution was basified with a saturated aqueous solution of $NaHCO_3$ and the product extracted into CH_2Cl_2. The organic phase was washed with a saturated solution of NaCl, dried ($MgSO_4$) and concentrated to yield a yellow waxy solid, which was treated with $Pb(OAc)_4$ (1.2 eq, 1.94 mmol, 0.86 g) in a 2 : 1 mixture of MeOH–CH_2Cl_2 (10 mL) at 0 °C. After 30 min the solution was filtered through Celite and the filtrate concentrated to yield an orange waxy solid, which was treated with HCl/H_2O (6 N, 10 mL) at ambient temperature. After 24 h the solution was washed with Et_2O and the aqueous phase basified with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated to yield a yellow oil. Purification by flash chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded the pure product as a pale yellow oil (136 mg, 52% over 2 steps). $[\alpha]^{20}_{589}$ −10 ($c = 1$, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 4.42 (1H, q, $J = 7.2$ Hz), 5.53 (1H, s), 7.20–7.53 (5H, m); δ_C (75 MHz; $CDCl_3$) 68.2 (q, $J = 28$ Hz), 124.4 (q, $J = 281$ Hz), 128.7, 128.9, 129.6, 131.7; δ_F (188 MHz $CDCl_3$) −72.5 (d, $J = 7.2$ Hz); ν_{max}/cm^{-1} 3486, 3031, 2986, 1213, 1180, 942, 770, 736.

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