A Remarkable Access to γ-Fluoroalkylated Propargylamine Derivatives or Fluoroalkylated Dihydroisoxazoles via the Reaction of Fluoroalkylated Acetylides with Various Nitrones

Tsutomu Konno,* Kazuki Moriyasu, Takashi Ishihara

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan
Fax +81(75)7247580; E-mail: konno@chem.kit.ac.jp

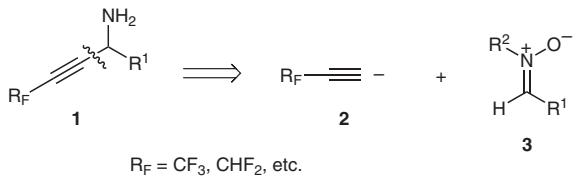
Received 4 November 2008; revised 10 December 2008

Abstract: The reactions of fluoroalkylated acetylides with various nitrones were investigated. When nitrones with an alkyl substituent were employed, hydroxylamines were obtained in high yields, and smooth dehydroxylation followed, to give the corresponding propargylamines. Nitrones with an aryl substituent underwent nucleophilic addition and subsequent intramolecular cyclization, affording the corresponding fluoroalkylated dihydroisoxazoles in moderate yields. These sequences were also extended to chiral versions.

Key words: fluorine-containing compounds, propargylamines, nitrones, amines, heterocycles

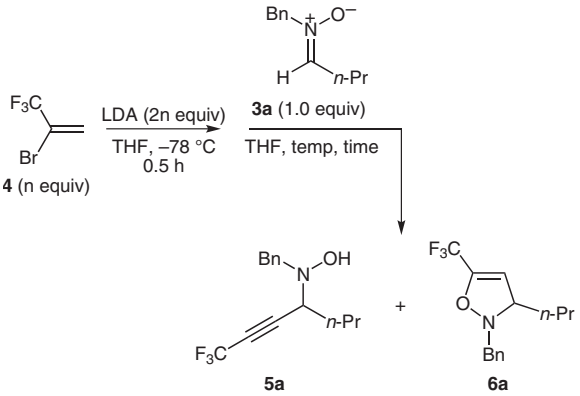
Propargylamines are considered to be one of the most important groups of synthetic intermediates in the synthesis of various organic molecules of pharmaceutical and biological interest, such as amino acids and amino sugars.[1] The introduction of fluorine atom(s) into lead molecules, on the other hand, has been used quite often as one of the most efficient tools for modification of the lead molecules in view of biological activity.[2] Therefore, it is not surprising that fluorine-containing propargylamines **1** have been paid much attention by many scientists (Scheme 1). Despite the potential utility of fluorine-containing propargylamines, their preparation has been studied to only a limited extent.[3] Herein is described a convenient and efficient approach to γ-fluoroalkylated propargylamine derivatives **1** via the reaction of fluoroalkylated acetylides **2** with various nitrones **3** (Scheme 1).[4] Additionally, we also describe a one-pot synthesis of dihydroisoxazoles[5] through the nucleophilic addition of acetylides to nitrones and subsequent intramolecular cyclization.

Our initial studies focused on the nucleophilic addition of trifluoromethylated acetylide, prepared from commercially available 2-bromo-3,3,3-trifluoropropene (**4**),[6] to nitrone **3a**[7] (Table 1). Thus, treatment of two equivalents of **4** with four equivalents of lithium diisopropylamide in tetrahydrofuran at –78 °C for half an hour, followed by the addition of one equivalent of nitrone **3a** and stirring of the reaction mixture for two hours, gave the corresponding hydroxylamine **5a** in 31% yield (Table 1, entry 1). As shown in entry 2, a longer reaction time led to an increase in the yield from 31% to 58%. The reaction at –20 °C for two hours proceeded very smoothly to afford **5a** in 82% yield (entry 3), whereas stirring of the reaction mixture for 15 hours did not provide a satisfactory result (entry 4). Additionally, higher temperatures caused a significant decrease of the yield as shown in entries 5 and 6. Interestingly, a small amount of cyclization product **6a** was obtained in these cases. The use of only one equivalent of **4** provided **5a** in only 38% yield (entry 7).



Scheme 1 Reaction under investigation

Table 1 Investigation of Reaction Conditions



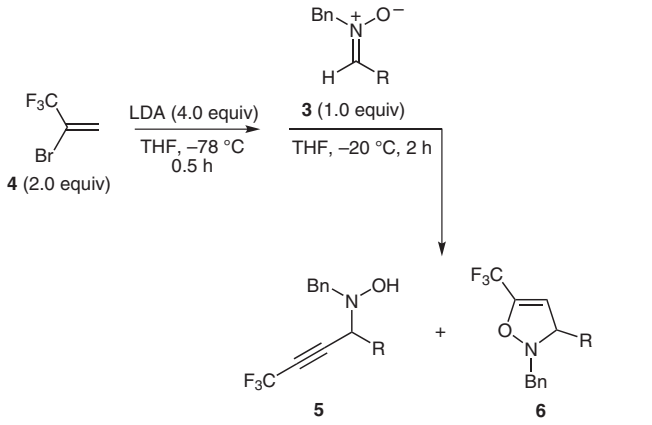
Entry	n (equiv)	Temp (°C)	Time (h)	Yield[a] (%) of **5a**	Yield[a] (%) of **6a**
1	2.0	–78	2	31	0
2	2.0	–78	15	58	0
3	2.0	–20	2	82 (73)	0
4	2.0	–20	15	40	3
5	2.0	0	2	38	7
6	2.0	r.t.	2	27	18
7	1.0	–20	2	38	0

[a] Determined by ^{19}F NMR spectroscopy. Isolated yields are given in parentheses.

SYNTHESIS 2009, No. 7, pp 1087–1094
Advanced online publication: 06.03.2009
DOI: 10.1055/s-0028-1087988; Art ID: F22808SS

We next examined the nucleophilic addition to various nitrones **3** (Table 2). Nitrones with an alkyl substituent, such as *n*-propyl, isopropyl, and cyclohexyl, gave the corresponding adducts **5** in high yields (entries 1–3). However, the nitrone carrying a bulky *tert*-butyl group did not participate in the reaction, giving only a trace of the desired adduct (entry 4). Additionally, the nitrone derived from cinnamaldehyde also led to an unsatisfactory result (entry 5). The use of the nitrone of benzaldehyde resulted in the formation of 17% of dihydroisoxazole **6d**, together with only 17% of hydroxylamine **5d** (entry 6).

Table 2 Reaction of Trifluoromethylated Acetylide with Various Nitrones



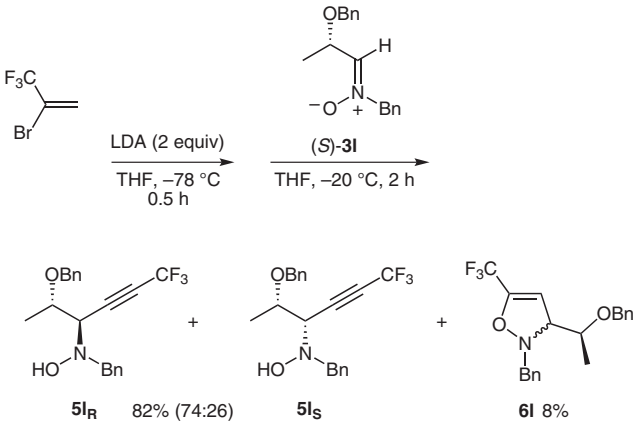
Entry	R	5	Yield[a] (%)	6	Yield[a] (%)
1	*n*-Pr	**5a**	82 (73)	**6a**	0
2	*i*-Pr	**5b**	86 (85)	**6b**	3
3	Cy	**5c**	96 (95)	**6c**	4
4	*t*-Bu	–	trace	–	trace
5	(*E*)-CH=CHPh	–	trace	–	trace
6	Ph	**5d**	17	**6d**	17

[a] Determined by ^{19}F NMR spectroscopy. Isolated yields are given in parentheses.

We next investigated the reaction with nitrones with aryl substituents (Table 3). A higher reaction temperature (0 °C instead of –20 °C) led to a significant increase in the yield of **6d** from 17% to 38% (entry 2). When three equivalents of **4** and six equivalents of lithium diisopropylamide were employed, the yield increased to 45%, and only dihydroisoxazole **6d** was obtained, with no hydroxylamine **5d** detected at all (entry 3). Conducting the reaction at room temperature or using longer reaction times did not influence the yield significantly (entries 4–6). The use of aryl substituents other than phenyl, namely 4-chlorophenyl, 4-methoxyphenyl, and 1-naphthyl, did not affect the reaction significantly, with the corresponding products **6e**, **6f**, and **6g** obtained in moderate to good yields (entries 7, 8, and 10). The 4-nitrophenyl-substituted nitrone did not give significant amounts of adduct **6** (entry 9).

To expand the synthetic applications of the procedure, we also examined the reactions of nitrones **3** with various fluoroalkylated acetylides, prepared from fluorinated iodides **7** and *n*-butyllithium[8] (Table 4). The (trifluoromethyl)-substituted acetylide (generated from **7**, $R_F = CF_3$) was found to be as reactive as the one generated from 2-bromo-3,3,3-trifluoropropene and lithium diisopropylamide, giving the corresponding hydroxylamine **5a** in 91% yield (entry 1). Changing the fluoroalkyl group from CF_3 to CF_2H or $(CF_2)_2CF_2H$ had no significant influence on the reaction, with products **5h** and **5i** obtained in 86 and 88% yield, respectively (entries 2 and 3). Reactions with nitrones with aryl substituents gave, in addition to hydroxylamine **5**, the corresponding dihydroisoxazoles **6** in moderate yields (entries 4, 7, 8, and 10). Changing the fluoroalkyl group from CF_3 to CF_2H or $(CF_2)_2CF_2H$ caused a significant decrease in yield (entries 4–6). Additionally, the 4-nitrophenyl-substituted nitrone gave only a trace of adduct (entry 9).

Next, the reaction was extended to the chiral version, as shown in Scheme 2. Thus, the reaction with the chiral nitrone (*S*)-**3l**, derived from (*S*)-methyl lactate, in tetrahydrofuran at –20 °C for two hours gave the corresponding hydroxylamines $\mathbf{5l_R}$ and $\mathbf{5l_S}$ as a separable diastereomeric mixture (74:26) in 82% yield, along with 8% of the cyclization product **6l**.

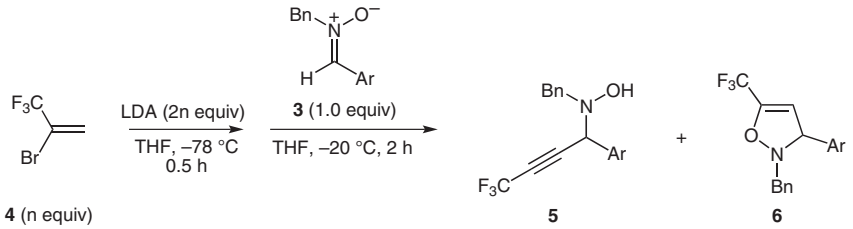


Scheme 2 Reaction of trifluoromethylated acetylide with the chiral nitrone derived from (*S*)-methyl lactate

The thus-obtained hydroxylamines **5a**, **5c**, and $\mathbf{5l_R}$ were easily converted into the corresponding propargylamines **8a**, **8c**, and $\mathbf{8l_R}$ in 59–85% yield in the presence of 1.5 equivalents of phosphorus trichloride in benzene at room temperature for seven hours (Scheme 3).

The stereochemical assignment of $\mathbf{5l_R}$ and $\mathbf{5l_S}$ was made as follows (Scheme 4). Treatment of (2*S*,R_S)-sulfinimine **9**[9] with the (trifluoromethyl)acetylide prepared from 2-bromo-3,3,3-trifluoropropene and lithium diisopropylamide, in tetrahydrofuran at –78 °C for two hours and then at –40 °C for five hours, gave the corresponding propargylamines (1*R*,2*S*,R_S)-$\mathbf{10_R}$ and (1*S*,2*S*,R_S)-$\mathbf{10_S}$ in a ratio of 81:19 in 94% combined yield, as described in the literature.[3] The thus-obtained diastereomeric mixture was

Table 3 Reaction of Trifluoromethylated Acetylide with Various Nitrones with Aryl Substituents

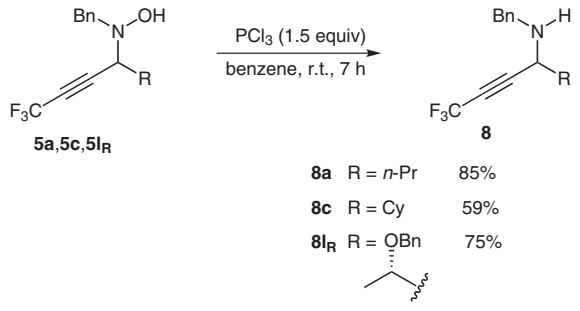


Entry	Ar	n (equiv)	Temp (°C)	Time (h)	5	Yield[a] (%)	6	Yield[a] (%)
1	Ph	2.0	–20	2	**5d**	17	**6d**	17
2	Ph	2.0	0	2	**5d**	trace	**6d**	38
3	Ph	3.0	0	2	**5d**	trace	**6d**	45 (42)
4	Ph	2.0	r.t.	2	**5d**	trace	**6d**	31
5	Ph	2.0	r.t.	15	**5d**	0	**6d**	29
6	Ph	3.0	r.t.	15	**5d**	0	**6d**	46
7	4-ClC_6H_4	3.0	0	2	**5e**	trace	**6e**	36
8	4-$MeOC_6H_4$	3.0	0	2	**5f**	trace	**6f**	58 (55)
9	4-$O_2NC_6H_4$	3.0	0	2	–	trace	–	trace
10	1-naphthyl	3.0	0	2	**5g**	trace	**6g**	68 (65)

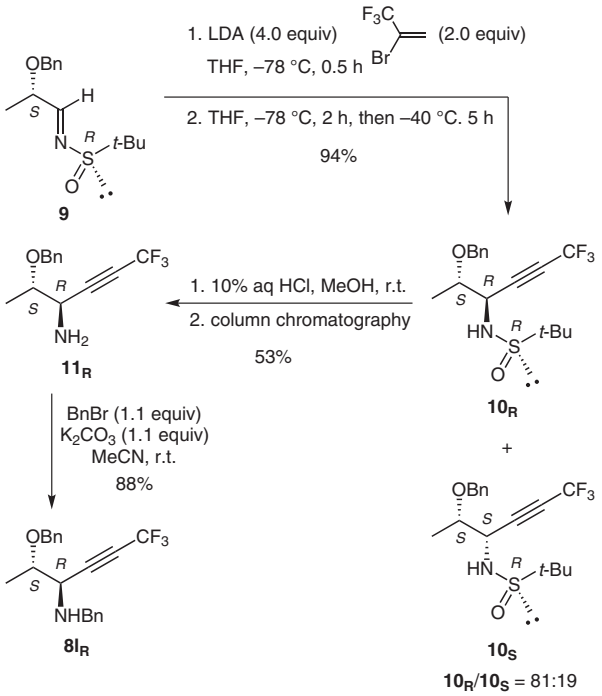
[a] Determined by ^{19}F NMR spectroscopy. Isolated yields are given in parentheses.

then treated with 10% aqueous hydrogen chloride in methanol at room temperature, followed by column chromatography over silica gel; this gave the corresponding (1*R*,2*S*)-propargylamine $\mathbf{11_R}$ in 53% yield. Then, monobenzylation[10] of $\mathbf{11_R}$ afforded *N*-benzylpropargylamine $\mathbf{8l_R}$ in 88% yield. It was found from ^1H NMR analysis that the *N*-benzylpropargylamine $\mathbf{8l_R}$ obtained from $\mathbf{11_R}$ was completely identical with that derived from the product of (trifluoromethyl)acetylide and the chiral nitrone (*S*)-**3l** (Schemes 2 and 3), thus indicating that the major isomer $\mathbf{5l_R}$ and the minor isomer $\mathbf{5l_S}$ have (1*R*,2*S*)- and (1*S*,2*S*)-configurations, respectively.

Therefore, the proposed mechanism for the reaction with the chiral nitrones is as follows (Scheme 5). On the basis of a Felkin–Ahn model,[11] intermediate **A**, in which a benzyloxy group occupies a position perpendicular to the C=N group, is more stable than intermediate **B**, because



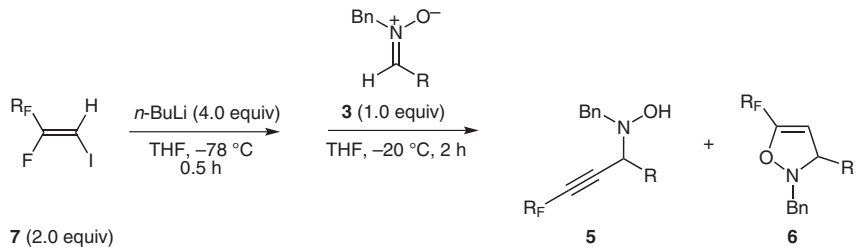
Scheme 3 Conversion of hydroxylamines **5** into propargylamines **8**



Scheme 4 Determination of stereochemistry

the low-lying σ^*_{C-O} orbital is aligned parallel with the π and π* orbitals of the C=N group, allowing delocalization of electron density by hyperconjugation from the reaction center toward the benzyloxy. Then (trifluoromethyl)acetylide preferably attacks the *re* face of intermediate

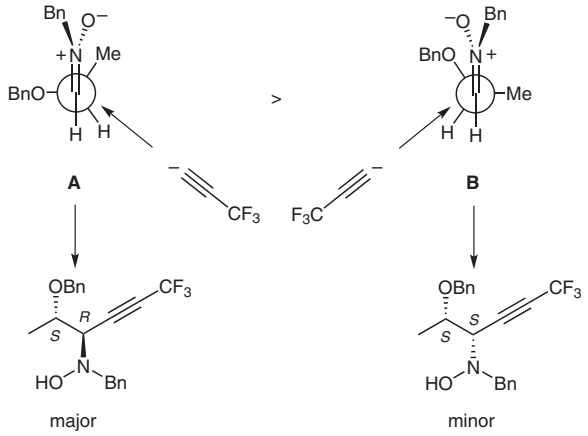
Table 4 Reactions of Various Fluoroalkylated Acetylides with Various Nitrones



Entry	R_F	R	5	Yield[a] (%)	6	Yield[a] (%)
1	CF_3	*n*-Pr	**5a**	91 (90)	**6a**	trace
2	CHF_2	*n*-Pr	**5h**	86 (83)	**6h**	14
3	$(CF_2)_2CF_2H$	*n*-Pr	**5i**	88 (76)	**6i**	n.d.[b]
4	CF_3	Ph	**5d**	30 (29)	**6d**	33 (30)
5	CHF_2	Ph	**5j**	30 (28)	**6j**	5
6	$(CF_2)_2CF_2H$	Ph	**5k**	14	**6k**	17
7	CF_3	4-ClC_6H_4	**5e**	26	**6e**	40
8	CF_3	4-$MeOC_6H_4$	**5f**	21 (16)	**6f**	21 (15)
9	CF_3	4-$O_2NC_6H_4$	–	trace	–	trace
10	CF_3	1-naphthyl	**5g**	8	**6g**	58

[a] Determined by ^{19}F NMR spectroscopy. Isolated yields are given in parentheses.
[b] n.d. = not determined.

A, giving the corresponding (1*R*,2*S*)-adduct as the major isomer.



Scheme 5 Felkin–Ahn model

In summary, we have investigated the reactions of fluoroalkylated acetylides with various nitrones in detail. The reactions with nitrones with alkyl substituents took place smoothly to give the corresponding hydroxylamines in good to high yields. In the reactions with the nitrones with aryl substituents, on the other hand, the nucleophilic addition was followed by intramolecular cyclization, affording the corresponding dihydroisoxazoles in moderate yields. The thus-obtained hydroxylamines were easily converted into the desired propargylamines in high yields in the presence of phosphorus trichloride. Additionally, this system could be extended to the chiral version, the chiral propargylamines being obtained in high yields.

IR spectra were recorded on a JASCO FT/IR-4100 type A spectrometer; samples were prepared as films on NaCl plates. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 NMR spectrometer and a JEOL JNM-AL 400 NMR spectrometer; samples were prepared as $CDCl_3$ solns with TMS as internal reference. A JEOL JNM-EX90A (84.21 MHz) FT-NMR spectrometer and a JEOL JNM-AL 400-NMR spectrometer were used for determining the yields of the products with the aid of C_6F_6. ^{19}F NMR (376.05 MHz) spectra were recorded on a JEOL JNM-AL 400 NMR spectrometer; samples were prepared as $CDCl_3$ solns with $CFCl_3$ as internal standard. HRMS was carried out on a Hitachi M-80B mass spectrometer by EI, CI, and FAB methods. All chemicals were of reagent grade and, when necessary, were purified in the usual manner prior to use. TLC was performed on aluminum sheets coated with Merck silica gel 60 F_{254} plates, and column chromatography was carried out on Wakogel C-200.

N-Benzyl-*N*-(4,4,4-trifluoro-1-propylbut-2-ynyl)hydroxylamine (5a); Typical Procedure

A 1.6 M soln of *n*-BuLi (1.25 mL, 2.0 mmol) was added to a soln of *i*-Pr_2NH (0.28 mL, 2.0 mmol) in THF (3.0 mL) at –78 °C and the mixture was stirred for 0.5 h. Then 2-bromo-3,3,3-trifluoropropene (**4**; 0.11 mL, 1.0 mmol) was added dropwise, followed by (*Z*)-*N*-butylidenebenzylamine *N*-oxide (**3a**; 0.089 g, 0.50 mmol) in THF (1.0 mL). After the reaction mixture had stirred at –20 °C for 2 h, it was quenched with aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10

mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (silica gel, hexane–EtOAc, 3:1); this afforded **5a**.

Yield: 99 mg (73%); yellow solid; mp 62–64 °C.

IR (KBr): 3255, 2972, 2263, 1727, 1458, 1276, 1162, 747, 700, 588, 504, 467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 2.6 Hz, 3 H), 1.46–1.53 (m, 2 H), 1.76–1.85 (m, 2 H), 3.65 (m, 1 H), 3.83 (d, *J* = 4.5 Hz, 1 H), 4.07 (d, *J* = 4.3 Hz, 1 H), 4.85 (s, 1 H), 7.28–7.36 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.3, 34.2, 58.0, 61.1–61.5 (m), 73.8 (q, *J* = 52.0 Hz), 85.5 (q, *J* = 6.5 Hz), 114.0 (q, *J* = 257.1 Hz), 127.9, 128.5, 129.8, 136.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.0 (s, 3 F).

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{14}H_{18}F_3NO$: 272.1262; found: 272.1280.

N-Benzyl-N-(4,4,4-trifluoro-1-isopropylbut-2-ynyl)hydroxylamine (5b)
Yellow solid; mp 71–73 °C.

IR (KBr): 3267, 2973, 2909, 2251, 1456, 1282, 1136, 1068, 1024, 916, 829, 746, 692, 550, 506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 6.8 Hz, 6 H), 2.04–2.17 (m, 1 H), 3.24–3.26 (m, 1 H), 3.82 (d, *J* = 13.2 Hz, 1 H), 4.11 (d, *J* = 13.2 Hz, 1 H), 4.65 (s, 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (d, *J* = 4.1 Hz), 30.4, 61.8, 65.0, 74.4 (q, *J* = 52.0 Hz), 85.1 (q, *J* = 256.2 Hz), 127.7, 128.47, 129.4, 136.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.0 (s, 3 F).

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{14}H_{18}F_3NO$: 272.1262; found: 272.1271.

N-Benzyl-N-(1-cyclohexyl-4,4,4-trifluorobut-2-ynyl)hydroxylamine (5c)
Yellow solid; mp 124–127 °C.

IR (KBr): 3449, 2940, 2855, 2251, 1638, 1450, 1282, 1135, 934, 826, 749, 692, 602, 505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.04 (m, 2 H), 1.14–1.31 (m, 3 H), 1.67–1.82 (m, 4 H), 2.03 (dd, *J* = 12.8, 38.8 Hz, 2 H), 3.32–3.35 (m, 1 H), 3.82 (d, *J* = 12.8 Hz, 1 H), 4.10 (d, *J* = 13.2 Hz, 1 H), 4.63 (s, 1 H), 7.34–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.6, 25.8, 26.3, 30.1, 30.3, 39.3, 61.5, 63.9, 114.1 (q, *J* = 256.2 Hz), 74.6 (q, *J* = 52.0 Hz), 85.0 (q, *J* = 6.6 Hz), 127.7, 128.4, 129.4, 136.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –49.8 (s, 3 F).

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{17}H_{21}F_3NO$: 312.1575; found: 312.1583.

2-Benzyl-3-phenyl-5-(trifluoromethyl)-2,3-dihydroisoxazole (6d); Typical Procedure
A 1.6 M soln of *n*-BuLi (1.88 mL, 3.0 mmol) was added to a soln of *i*-Pr_2NH (0.42 mL, 3.0 mmol) in THF (4.5 mL) at –78 °C, and the mixture was stirred for 0.5 h. 2-Bromo-3,3,3-trifluoropropene (**4**; 0.17 mL, 1.5 mmol) was added dropwise, followed by (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (0.114 g, 0.50 mmol) in THF (1.0 mL). After the reaction mixture had stirred for 2 h at 0 °C, it was quenched with aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (silica gel, hexane–EtOAc, 5:1) of the residue afforded **6d**.

Yield: 0.064 g (42%); yellow solid; mp 37–39 °C.

IR (KBr): 3089, 3065, 3033, 2926, 2855, 1685, 1602, 1496, 1455, 1357, 1247, 1183, 1144, 1087, 1029, 734, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.09 (d, *J* = 12.8 Hz, 1 H), 4.40 (d, *J* = 13.2 Hz, 1 H), 5.06 (t, *J* = 2.4 Hz, 1 H), 7.19–7.39 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.3, 72.7, 103.9 (q, *J* = 2.4 Hz), 118.4 (q, *J* = 270.3 Hz), 126.9, 127.9, 128.2, 128.5, 128.7, 129.6, 139.6 (d, *J* = 1.7 Hz), 143.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –58.7 (s, 3 F).

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{17}H_{14}F_3NO$: 305.1027; found: 305.1010.

2-Benzyl-3-(4-methoxyphenyl)-5-(trifluoromethyl)-2,3-dihydroisoxazole (6f)
Dark brown solid; mp 39–42 °C.

IR (KBr): 2932, 1726, 1685, 1612, 1513, 1456, 1354, 1252, 1177, 1144, 1079, 1034, 834, 739, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 4.07 (d, *J* = 13.2 Hz, 1 H), 4.37 (d, *J* = 13.2 Hz, 1 H), 5.01 (s, 1 H), 5.52–5.54 (m, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 7.30–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 63.1, 72.3, 104.1 (q, *J* = 2.5 Hz), 114.1, 118.5 (q, *J* = 270.2 Hz), 127.9, 128.2, 128.4, 129.5, 131.6, 135.2, 143.4 (q, *J* = 39.7 Hz), 159.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6 (s, 3 F).

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{18}H_{17}F_3NO_2$: 336.1211; found: 336.1211.

2-Benzyl-3-(1-naphthyl)-5-(trifluoromethyl)-2,3-dihydroisoxazole (6g)
Yellow oil.

IR (neat): 3040, 2960, 2858, 2371, 1736, 1683, 1597, 1510, 1455, 1356, 1248, 1173, 1135, 1081, 1044, 934, 786, 740, 698, 518, 448 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (d, *J* = 13.2 Hz, 1 H), 4.45 (d, *J* = 12.4 Hz, 1 H), 5.76 (s, 1 H), 7.28–7.89 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.2–63.3 (m), 69.5, 104.2–104.3 (m), 118.5 (q, *J* = 267.9 Hz), 122.2, 124.8, 125.7, 125.8, 126.4, 127.9, 128.5, 128.6, 129.0, 129.5, 130.1, 133.8, 134.7–134.8 (m), 135.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6 (s, 3 F).

HRMS–FAB: *m/z* [M]$^+$ calcd for $C_{21}H_{16}F_3NO$: 355.1184; found: 355.1176.

N-Benzyl-N-(4,4,4-trifluoro-1-phenylbut-2-ynyl)hydroxylamine (5d) and 2-Benzyl-3-phenyl-5-(trifluoromethyl)-2,3-dihydroisoxazole (6d) (Table 4, entry 4); Typical Procedure
A 1.6 M soln of *n*-BuLi in hexane (1.25 mL, 2.0 mmol) was added dropwise to a soln of 2,3,3,3-tetrafluoro-1-iodoprop-1-ene (0.24 g, 1.0 mmol) in THF (2 mL) at –78 °C. The reaction mixture was stirred at that temperature for 0.5 h, before the addition of (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (0.114 g, 0.50 mmol) in THF (2.0 mL). After the reaction mixture had stirred for 2 h at –20 °C, it was quenched with aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (silica gel, hexane–EtOAc, 5:1) of the residue afforded **5d** and **6d**.

Yield (**5d**): 0.044 g (29%); yield (**6d**): 0.046 g (30%).

N-Benzyl-N-(4,4-difluoro-1-propylbut-2-ynyl)hydroxylamine (5h)
Yellow oil.

IR (neat): 3231, 2959, 2932, 2873, 2371, 2244, 1720, 1459, 1375, 1262, 1157, 1138, 1037, 861, 801, 737, 699, 499, 460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 1.43–1.53 (m, 2 H), 1.71–1.87 (m, 2 H), 3.65 (br s, 1 H), 3.84 (d, *J* = 13.2 Hz, 1 H), 4.08 (d, *J* = 12.4 Hz, 1 H), 4.72–4.78 (m, 1 H), 6.30 (t, *J* = 55.2 Hz, 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.4, 34.5 (t, *J* = 1.6 Hz), 58.1–58.3 (m), 61.2–61.4 (m), 77.9 (t, *J* = 33.9 Hz), 86.7 (t, *J* = 7.4 Hz), 127.7, 128.5, 129.7, 136.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.3 (dd, *J* = 1.3, 12.1 Hz).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}F_2NO$: 254.1356; found: 254.1351.

N-Benzyl-N-(4,4,5,5,6,6-hexafluoro-1-propylhex-2-ynyl)hydroxylamine (5i)

Brown solid; mp 43–45 °C.

IR (KBr): 3272, 3033, 2965, 2936, 2876, 2253, 1497, 1456, 1402, 1358, 1274, 1223, 1162, 1135, 998, 806, 745, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.6 Hz, 3 H), 1.45–1.54 (m, 2 H), 1.73–1.89 (m, 2 H), 3.67 (m, 1 H), 3.83 (d, *J* = 13.2 Hz, 1 H), 4.07 (d, *J* = 13.2 Hz, 1 H), 4.78 (d, *J* = 6.0 Hz, 1 H), 6.14 (tt, *J* = 5.2, 52.0 Hz, 1 H), 7.28–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 19.3, 34.2, 58.2, 61.2–61.7 (m), 73.2 (t, *J* = 36.3 Hz), 91.6 (t, *J* = 6.6 Hz), 105.1–110.8 (m, 3 H), 127.9, 128.5, 129.7, 136.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –137.2 (d quin, *J* = 7.1, 51.5 Hz, 2 F), –131.5 (t, *J* = 4.9 Hz, 2 F), –99.7 (sext, *J* = 4.9 Hz, 2 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}F_6NO$: 354.1293; found: 354.1301.

N-Benzyl-N-(4,4,4-trifluoro-1-phenylbut-2-ynyl)hydroxylamine (5d)

Dark brown solid; mp 88–91 °C.

IR (KBr): 3423, 2926, 2370, 2251, 1638, 1498, 1457, 1268, 1135, 819, 755, 699, 555, 499 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (d, *J* = 12.8 Hz, 1 H), 4.05 (d, *J* = 12.8 Hz, 1 H), 4.76 (s, 1 H), 4.90–4.93 (m, 1 H), 7.27–7.53 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.3–60.7 (m), 61.8–61.9 (m), 75.3 (q, *J* = 52.1 Hz), 83.8 (q, *J* = 6.6 Hz), 114.1 (q, *J* = 257.0 Hz), 127.9, 128.55, 128.69, 128.70, 128.78, 129.5, 134.9, 136.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.2 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}F_3NO$: 305.1027; found: 305.1030.

N-Benzyl-N-(4,4-difluoro-1-phenylbut-2-ynyl)hydroxylamine (5j)

Yellow solid; mp 101–104 °C.

IR (KBr): 3231, 2918, 2370, 2251, 1726, 1453, 1373, 1265, 1147, 1044, 758, 739, 701, 523, 473 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (d, *J* = 13.2 Hz, 1 H), 4.05 (d, *J* = 13.2 Hz, 1 H), 4.78 (s, 1 H), 4.91 (br s, 1 H), 6.39 (t, *J* = 54.8 Hz, 1 H), 7.28–7.56 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.1–60.5 (m), 61.9–62.0 (m), 79.5 (t, *J* = 33.8 Hz), 84.9 (t, *J* = 6.6 Hz), 103.6 (t, *J* = 232.2 Hz), 127.0, 127.8, 128.5, 128.6, 128.8, 129.6, 135.5–135.6 (m), 136.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.7 (dd, *J* = 4.9, 52.6 Hz).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}F_2NO$: 288.1200; found: 288.1192.

N-Benzyl-N-(4,4,5,5,6,6-hexafluoro-1-phenylhex-2-ynyl)hydroxylamine (5k)

Dark brown solid; mp 100–103 °C.

IR (KBr): 3240, 2927, 2371, 2258, 1720, 1497, 1455, 1262, 1224, 1089, 1026, 818, 697, 539, 494 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (d, *J* = 13.2 Hz, 1 H), 4.03 (d, *J* = 13.2 Hz, 1 H), 4.89 (s, 1 H), 4.91 (s, 1 H), 6.16 (tt, *J* = 5.2, 52.0 Hz, 1 H), 7.27–7.52 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.5–60.9 (m), 62.1, 74.8 (t, *J* = 36.3 Hz), 89.6 (t, *J* = 6.6 Hz), 104.7–110.7 (m, 3 C), 127.8, 128.5, 128.69, 128.74, 129.4, 130.9, 135.0, 136.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –137.1 (d quin, *J* = 7.5, 53.4 Hz, 2 F), –131.1 (m, 2 F), –99.9 (m, 2 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}F_6NO$: 388.1136; found: 388.1154.

2-Benzyl-5-(1,1,2,2,3,3-hexafluoropropyl)-3-phenyl-2,3-dihydroisoxazole (6k)

Brown oil.

IR (neat): 3065, 3033, 2927, 2856, 1725, 1676, 1676, 1496, 1455, 1403, 1277, 1219, 1150, 1029, 980, 863, 802, 735, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.09 (d, *J* = 12.8 Hz, 1 H), 4.40 (d, *J* = 13.2 Hz, 1 H), 5.07 (m, 1 H), 5.63–5.64 (m, 1 H), 6.02 (tt, *J* = 5.2, 52.0 Hz, 1 H), 7.17–7.38 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.3, 72.8, 105.8 (t, *J* = 16.4 Hz), 107.4–110.8 (m, 3 C), 127.0, 128.0, 128.2, 128.5, 128.8, 129.5, 135.0, 139.6, 143.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –137.5 to –137.2 (m, 2 F), –131.4 to –130.8 (m, 2 F), –116.2 to –112.4 (m, 2 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}F_6NO$: 388.1136; found: 388.1143.

N-Benzyl-N-[1-(4-chlorophenyl)-4,4,4-trifluorobut-2-ynyl]hydroxylamine (5e)

Compounds **5e** and **6e** could not be purified by column chromatography (silica gel). A small amount of a mixture of **5e** and **6e** was obtained, and this was used to identify the two compounds.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (d, *J* = 13.2 Hz, 1 H), 4.42 (d, *J* = 12.4 Hz, 1 H), 4.87–4.91 (m, 1 H), 5.53 (q, *J* = 1.2 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.26–7.36 (m, 7 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –64.87 (s, 3 F).

2-Benzyl-3-(4-chlorophenyl)-5-(trifluoromethyl)-2,3-dihydroisoxazole (6e)

^1H NMR (400 MHz, $CDCl_3$): δ = 4.07 (d, *J* = 13.2 Hz, 1 H), 4.41 (d, *J* = 12.4 Hz, 1 H), 5.02 (m, 1 H), 5.53 (q, *J* = 1.2 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.26–7.36 (m, 7 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.63 (s, 3 F).

N-Benzyl-N-[4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-ynyl]hydroxylamine (5f)

Yellow oil.

IR (neat): 2500, 2962, 2370, 2245, 1736, 1610, 1516, 1459, 1264, 1139, 1035, 797, 701, 460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.88 (d, *J* = 12.4 Hz, 1 H), 3.98 (d, *J* = 12.4 Hz, 1 H), 4.83 (s, 1 H), 4.90 (s, 1 H), 6.91 (s, 1 H), 6.93 (s, 1 H), 7.28–7.43 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 59.8–60.4 (m), 61.3–61.4 (m), 75.0 (q, *J* = 52.0 Hz), 84.2 (q, *J* = 6.6 Hz), 114.0, 114.1 (q, *J* = 257.0 Hz), 126.8–126.9 (m), 127.8, 128.5, 129.6, 130.0, 136.4, 159.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.2 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}F_3NO_2$: 336.1211; found: 336.1211.

(1*R*,2*S*)-*N*-Benzyl-*N*-[2-(benzyloxy)-1-(3,3,3-trifluoroprop-1-ynyl)propyl]hydroxylamine (5l$_R$)
Low-polarity, major isomer; yellow solid; mp 49–50 °C; $[\alpha]_D^{26}$ +19.3 (*c* 0.98, $CHCl_3$).

IR (KBr): 3389, 3033, 2981, 2934, 2251, 1604, 1496, 1455, 1378, 1278, 1214, 1143, 1028, 910, 818, 739, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.4 Hz, 3 H), 3.69 (sext, *J* = 3.2 Hz, 1 H), 3.84 (d, *J* = 12.8 Hz, 1 H), 3.90 (quin, *J* = 6.4 Hz, 1 H), 4.14 (d, *J* = 12.8 Hz, 1 H), 4.59 (d, *J* = 12.4 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.69 (s, 1 H), 7.28–7.38 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 62.1 (d, *J* = 10.7 Hz), 63.1 (d, *J* = 1.7 Hz), 71.3, 74.1, 74.8 (q, *J* = 52.1 Hz), 83.5 (q, *J* = 6.6 Hz), 113.9 (q, *J* = 257.0 Hz), 127.7, 127.85, 127.89, 128.4, 128.5, 129.4, 136.5, 138.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.2 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}F_3NO_2$: 364.1524; found: 364.1516.

(1*R*,2*R*)-*N*-Benzyl-*N*-[2-(benzyloxy)-1-(3,3,3-trifluoroprop-1-ynyl)propyl]hydroxylamine (5l$_S$)
High-polarity, minor isomer; yellow solid; mp 58–61 °C; $[\alpha]_D^{27}$ –22.0 (*c* 1.17, $CHCl_3$).

IR (KBr): 3408, 3033, 2931, 2254, 1604, 1496, 1455, 1376, 1278, 1141, 910, 741, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.0 Hz, 3 H), 3.56 (m, 1 H), 3.86–3.94 (m, 2 H), 4.15 (d, *J* = 12.8 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.67 (d, *J* = 11.2 Hz, 1 H), 4.97 (m, 1 H), 7.30–7.39 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 62.4, 63.1, 71.7 (q, *J* = 45.9 Hz), 71.9, 73.4, 73.9, 74.1, 74.4, 75.4, 84.2 (q, *J* = 6.6 Hz), 114.0 (q, *J* = 257.0 Hz), 127.9 (d, *J* = 5.8 Hz), 128.5 (d, *J* = 12.3 Hz), 129.3, 136.1, 137.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.0 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}F_3NO_2$: 364.1524; found: 364.1528.

***N*-Benzyl-*N*-(4,4,4-trifluoro-1-propylbut-2-ynyl)amine (8a); Typical Procedure**
Hydroxylamine **5a** (0.041 g, 0.15 mmol) was dissolved in benzene (0.75 mL). To this soln was added PCl_3 (0.020 mL, 0.23 mmol) at r.t., and the mixture was stirred for 6 h. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic fraction was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (silica gel, hexane–EtOAc, 5:1) of the residue afforded **8a**.

Yield: 0.033 g (85%); yellow oil.

IR (neat): 3319, 3065, 3031, 2962, 2875, 2262, 1728, 1604, 1496, 1456, 1276, 1141, 1029, 869, 803, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3 H), 1.44–1.54 (m, 3 H), 1.64–1.73 (m, 2 H), 3.45–3.49 (m, 1 H), 3.80 (d, *J* = 12.8 Hz, 1 H), 4.01 (d, *J* = 12.8 Hz, 1 H), 7.28–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.65, 19.02, 36.94, 48.61–48.62 (m), 51.27, 89.46 (q, *J* = 6.6 Hz), 114.18 (q, *J* = 256.2 Hz), 127.31, 128.31, 128.50, 139.01.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.0 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}F_3N$: 256.1313; found: 256.1305.

***N*-Benzyl-*N*-(1-cyclohexyl-4,4,4-trifluorobut-2-ynyl)amine (8c)**
Yellow oil.

IR (neat): 3335, 3065, 3031, 2929, 2855, 2264, 1728, 1604, 1496, 1452, 1274, 1212, 1140, 1074, 1029, 894, 804, 735, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–1.88 (m, 12 H), 3.26 (sext, *J* = 2.8 Hz, 1 H), 3.78 (d, *J* = 13.2 Hz, 1 H), 4.02 (d, *J* = 13.2 Hz, 1 H), 7.25–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.83, 25.94, 26.21, 28.70, 29.77, 41.88, 51.48, 54.32–54.34 (m), 72.10 (q, *J* = 51.3 Hz), 88.95 (q, *J* = 5.8 Hz), 114.21 (q, *J* = 257.0 Hz), 127.24, 128.28, 128.44, 139.24.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –49.8 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}F_3N$: 296.1616; found: 296.1625.

(1*R*,2*S*)-*N*-Benzyl-*N*-[2-(benzyloxy)-1-(3,3,3-trifluoroprop-1-ynyl)propyl]amine (8l$_R$)
Yellow oil; $[\alpha]_D^{28}$ +48.1 (*c* 0.62, $CHCl_3$).

IR (neat): 3335, 3065, 3032, 2977, 2932, 2872, 2269, 1952, 1726, 1604, 1496, 1454, 1376, 1276, 1212, 1139, 1028, 911, 804, 738, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.0 Hz, 3 H), 1.89 (br s, 1 H), 3.49–3.51 (m, 1 H), 3.71–3.80 (m, 1 H), 4.03 (d, *J* = 13.2 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 7.27–7.34 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 51.2, 53.9 (d, *J* = 1.7 Hz), 71.3, 72.0 (q, *J* = 52.1 Hz), 75.7 (d, *J* = 1.6 Hz), 87.7 (q, *J* = 6.5 Hz), 114.1 (q, *J* = 257.0 Hz), 127.2, 127.7, 127.8, 128.2, 128.39, 128.43, 137.9, 139.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –50.2 (s, 3 F).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}F_3NO$: 348.1575; found: 348.1584

Stereochemical Determination
A 1.6 M soln of *n*-BuLi in hexane (1.88 mL, 3.00 mmol) was added to a soln of *i*-Pr_2NH (0.42 mL, 3.00 mmol) in THF (6 mL) at –78 °C. After the mixture had stirred for 0.5 h, (2*S*,*R*$_S$)-sulfinimine **9** (0.13 g, 0.50 mmol) was added and the mixture was stirred at –78 °C for 2 h and at –40 °C for 5 h. The reaction was quenched with sat. aq NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel) gave the corresponding adducts as a diastereomeric mixture (81:19); yield: 0.18 g (97%).

The thus-obtained diastereomeric mixture was dissolved in a mixture of 10% HCl (3.5 mL) and MeOH (2.5 mL). The soln was stirred at r.t. for several hours and was then poured into sat. aq $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried (Na_2SO_4), filtered, and concentrated. Column chromatography (silica gel) of the residue afforded pure **11$_R$**; yield: 0.066 g (53%).

Propargylamine **11$_R$** was dissolved in MeCN (2 mL). BnBr (0.050 g, 0.29 mmol) and K_2CO_3 (0.040 g, 0.29 mmol) were added, in this order, to the soln. Then the mixture was stirred at r.t. for several hours, after which it was poured into sat. aq NH_4Cl (10 mL), and subsequently extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel) gave *N*-benzylpropargylamine **8l$_R$**; yield: 0.078 g (88%); physical data as described above.

References

(1) (a) Murga, J.; Portolés, R.; Falomir, E.; Carda, N.; Marco, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1807. (b) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261. (c) Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716. (d) Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D. *J. Med. Chem.* **2000**, *43*, 3408. (e) Meffre, P.; Goffic, F. L. *Amino Acids* **1996**, *11*, 313.

(2) For reviews, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, 308. (b) Berkowitz, D. B.; Karukurichi, K. R.; de la Dalud-Bea, R.; Nelson, D. L.; McCune, C. D. *J. Fluorine Chem.* **2008**, *129*, 731. (c) Liu, P.; Sharon, A.; Chu, C. K. *J. Fluorine Chem.* **2008**, *129*, 743. (d) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (e) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (f) Pesenti, C.; Viani, F. *ChemBioChem* **2004**, *5*, 590. (g) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 673.

(3) Very recently, the synthesis of chiral propargylamines was reported. See: (a) Chen, X.-Y.; Qiu, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 2301. (b) Chen, Q.; Qiu, X.-L.; Qing, F.-L. *J. Fluorine Chem.* **2007**, *128*, 1182. (c) Jeon, S. L.; Kim, J. K.; Son, J. B.; Kim, B. T.; Jeong, I. H. *Tetrahedron Lett.* **2006**, *47*, 9107.

(4) For the reaction of nitrones with various nucleophiles, see: (a) Patel, S. K.; Py, S.; Pandya, S. U.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 525. (b) Pinet, S.; Pandya, U.; Chavant, P. Y.; Ayling, A.; Vallée, Y. *Org. Lett.* **2002**, *4*, 1463. (c) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3054. (d) Pandya, S. U.; Garcon, C.; Chavant, P. Y.; Py, S.; Vallée, Y. *Chem. Commun.* **2001**, 1806. (e) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (f) Merino, P.; Franco, S.; Gascon, J. M.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1867. (g) Merino, P.; Franco, S. *J. Org. Chem.* **1998**, *63*, 5627.

(5) For the synthesis or the synthetic applications of dihydroisoxazoles, see: (a) González-Cruz, D.; Tejedor, D.; de Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2007**, *13*, 4823. (b) Adamo, M. F.; Pergoli, R. *Org. Lett.* **2007**, *9*, 4443. (c) Coskun, N.; Öztürk, A. *Tetrahedron* **2006**, *62*, 12057. (d) González-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; García-Tellado, F. *Chem. Commun.* **2006**, 2798. For fluoroalkylated isoxazoles, see: (e) Murray, W. V.; Francois, D.; Maden, A.; Turchi, I. *J. Org. Chem.* **2007**, *72*, 3097.

(6) (a) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046. (b) Mizutani, K.; Yamazaki, T.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1995**, 51.

(7) For the synthesis of various nitrones, see: (a) Tokuyama, H.; Kuboyama, T.; Fukuyama, T. *Org. Synth.* **2003**, *80*, 207. (b) Dondoni, A.; Franxo, S.; Junquera, F.; Merchán, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *18*, 2537.

(8) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571.

(9) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(10) Ma, S.; Wu, B.; Jiang, X. *J. Org. Chem.* **2005**, *70*, 2588.

(11) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.