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Trifluoromethide as a Strong Base: [CF_3^-] Mediates Dichloromethylation of Nitrones by Proton Abstraction from the Solvent

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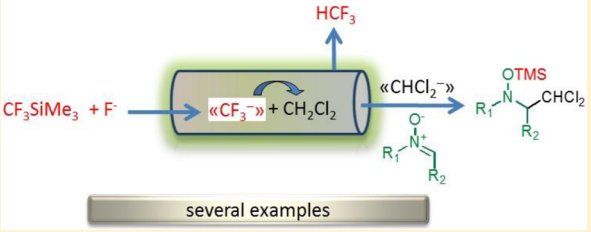
Supporting Information

ABSTRACT: An unprecedented reactivity of CF_3-TMS has been revealed, which exploits the basic character of the generated [CF_3^-] capable of delivering dichloromethide from dichloromethane with subsequent transfer to nitrones under smooth conditions. The proton-abstraction pathway was demonstrated through isotopic labeling experiments in CD_2Cl_2. The same reaction was achieved in acetonitrile with the introduction of a cyanomethyl group onto the nitrones.



INTRODUCTION

Fluoroform (HCF_3) is a very weak acid (pK_a 25−28 in water), the utility of which has been extremely scarce in organic synthesis, until recently.[1] In contrast to the other haloforms, deprotonation of trifluoromethane to generate the trifluoromethide [CF_3^-], a reactive form of HCF_3, is challenging due to the high instability of this electron-rich anion and its instantaneous collapse in solution, even at very low temperature.[2] The stabilization of [CF_3^-] has been achieved by coordination to a metal such as Ag, Cu, Sn, Hg, and Zn (mainly covalent organometallics) or to Si, giving rise to convenient trifluoromethyl transfer reagents.[3] (Trifluoromethyl)trimethylsilane (CF_3-TMS), often referred to as the Ruppert−Prakash reagent,[4] is the gold-standard source of trifluoromethide, the utility of which has been demonstrated during the two last decades for the trifluoromethylation of C=O-,[5] C=N-,[6] sulfur-,[7] or Si-containing[8] electrophiles. The generation of [CF_3^-] from CF_3-TMS is usually performed in THF and requires activation by a fluoride salt or, alternately, by other nucleophilic species such as amine *N*-oxides.[9] The high efficiency of (trifluoromethyl)trimethylsilane for transferring the CF_3 moiety, even at room temperature, was attributed to the tendency of silicon to increase its coordination sphere, accepting supplementary electron-rich substituents, which allows the transfer in a nearly intramolecular fashion, limiting decomposition. Other trifluoromethylating reagents have been developed recently, but the enhanced reactivity of CF_3-TMS make it indispensable in many cases.[10,11] In the absence of a suitable electrophile, two pathways prevail for the decomposition of the kinetically unstable [CF_3^-]: either α-elimination, which generates difluorocarbene and a fluoride anion, or proton abstraction from the solvent to afford HCF_3 (Figure 1). Whereas the production of difluorocarbene from the CF_3-TMS/F^- system has been recently highlighted by a first application toward the synthesis of *gem*-difluorocyclopropanes and *gem*-difluorocyclopropenes from alkenes and alkynes, respectively,[12] the development of the proton abstraction pathway is still pending. We present here a first synthetic application of CF_3-TMS/F^- as a strong base, capable of delivering [$CHCl_2^-$] in situ after proton abstraction from dichloromethane. In the presence of a nitrone the corresponding 2-(dichloromethyl) hydroxylamine is obtained in fairly good yield.

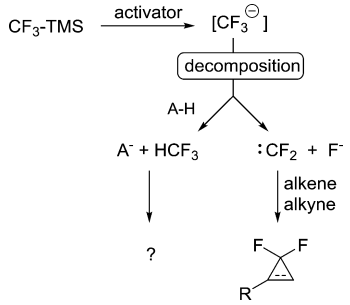


Figure 1. Two possible pathways for collapsing of [CF_3^-].

RESULTS AND DISCUSSION

Only a few reports have given observations on the basicity of [CF_3^-]. Experimental evidence of this character is scarce and results from unwanted and low-yielding side reactions. For instance, deprotonation of an aromatic ring to a benzyne intermediate by [CF_3^-] was postulated to account for the formation of several isomers (<14%) during aromatic nucleophilic substitution.[13] In another report, the use of CF_3-TMS/F^- in acetonitrile was found to generate [CH_2CN^-], which could in turn react with benzophenone to give the

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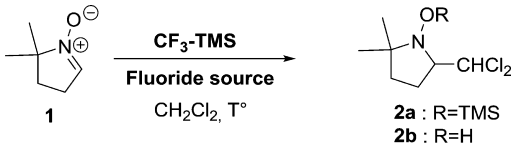
corresponding adduct in 12% yield.[14] However, the F^- anion itself was previously known to give $[CH_2CN^-]$,[15] so that the exact reactive base in this reaction remains elusive. At the same time, the formation of $[CHCl_2^-]$ and its addition to electrophiles is a very difficult task. The generation of the dichloromethide ion was described by reaction of methylene chloride with butyllithium or (tetramethylpiperidine)lithium at very low temperature (−100 °C).[16] In this work, we explored the tendency for the trifluoromethyl anion, generated from CF_3-TMS/F^-, to abstract proton from dichloromethane with concomitant transfer of the so-formed dichloromethide to a nitrone. We chose a nitrone as the electrophilic partner to limit the competitive nucleophilic addition of $[CF_3^-]$, the trifluoromethylation of nitrones being usually not as efficient as that of aldehydes or ketones, for instance.

In a first assay (Table 1, entry 1), 5,5-dimethylpyrroline *N*-oxide **1** was dissolved in dichloromethane and stirred at −50 °C with an excess of (trifluoromethyl)trimethylsilane (3 equiv) and tetramethylammonium fluoride (TMAF) as the promoter (2 equiv). TLC monitoring revealed a rapid disappearance of the starting nitrone within a few minutes accompanied by cessation of gas release and darkening of the reaction mixture.

Table 1. Optimization of the Reaction Conditions for the Dichloromethylation of Nitrone 1



1 **2a** : R=TMS **2b** : R=H

entry	F source (amt (equiv))	amt of CF_3-TMS (equiv)	T (°C)	conversion (%)[a]	product; yield (%)[b,c]
1	TMAF (2 equiv)	3	−50	100	**2a**; 67
2		3	−50	0	
3	TMAF (1 equiv)		−50	0	
4	TMAF (1 equiv)	3	−50	100	**2a**; 69
5	TMAF (0.3 equiv)	3	−50	30	
6	TMAF (1 equiv)	2.5	−50	100	**2a**; 71
7	TMAF (1 equiv)	2	−50	100	**2a**; 44
8	TMAF (1 equiv)	1	−50	70	
9	TMAF (1 equiv) then TBAF (1 equiv)	2.5	−50	100	**2b**; 58
10	TBAF (2 equiv)	3	−50	41	
11	TBAT (2 equiv)	3	−50	36	
12	TBAT (1 equiv)	6	−50	49	
13	TBAT (0.3 equiv)	6	−50	35	
14	TBAT (0.3 equiv) + TBAF (1 equiv)	6	−50	96	**2b**; 63
15	TMAF (1 equiv)	2.5	−20	95	**2a**; 48
16	TMAF (1 equiv)	2.5	0	94	**2a**; 38
17	TMAF (1 equiv)	2.5	room temp	66	
18	TBAT (0.3 equiv) + TBAF (1 equiv)	6	0	90	**2b**; 41
19	TBAT (0.3 equiv) + TBAF (1 equiv)	6	room temp	90	**2b**; 32

[a]Based on recovered nitrone **1**. [b]After purification by silica gel chromatography (when conversion >90%). [c]Desilylation of **2a** slightly occurred on silica gel.

To our delight, after a standard workup (addition of water, extraction with Et_2O), purification of the crude product afforded the expected dichloromethyl hydroxylamine as the *O*-trimethylsilyl derivative **2a** in 67% yield. No product resulting from the nucleophilic addition of $[CF_3^-]$ to the nitrone was detected. Modification of the reaction conditions was attempted to determine the requirements of the transformation in terms of equivalents of reagents, temperature, and fluoride sources. Thus, control experiments in the absence of either CF_3-TMS or TMAF (Table 1, entries 2 and 3) showed no transformation of the starting nitrone, precluding a possible participation of fluoride to the initial acid−base reaction as was observed with CH_3CN.[15,17] An autocatalytic process, the nitrone itself playing eventually the role of the promoter in the same manner as for amine *N*-oxides, also had to be ruled out.

Reducing the amount of TMAF to 1 or 0.3 equiv while keeping an excess of (trifluoromethyl)trimethylsilane (3 equiv) showed that subequimolar quantities of fluoride are insufficient for complete conversion, whereas 1 equiv afforded **2a** in 69% yield (Table 1, entries 4 and 5). This is surprising, since TMAF is sparsely soluble in CH_2Cl_2 and the reaction is clearly heterogeneous.[18] However, with larger amounts of activator the availability of fluoride ion might increase by a significant increase in the surface area, which could explain the higher activity. At the same time, experiments with various amounts of CF_3-TMS (entries 6−8) showed that 2 equiv was required to consume all the nitrone, only 70% conversion occurring with equimolar quantities. Although the reactions were carried out under strictly anhydrous conditions, partial consumption of reactant by residual water could explain this observation. Finally, the optimal conditions combined 1 equiv of TMAF and 2.5 equiv of CF_3-TMS, affording **2a** in 71% yield. Interestingly, *O*-desilylation could be performed in situ at −50 °C by addition of equimolar TBAF, which resulted in deprotected dichloromethylhydroxylamine (**2b**) in 58% yield after purification (entry 9).

Other commercial sources of fluoride were then tested. Surprisingly, TBAF (THF solution) and TBAT, which both are soluble in dichloromethane, gave less favorable outcomes with only 41% and 36% conversions, respectively. When the reaction was repeated with variable amounts of TBAF/TBAT (entries 10−14), almost complete transformation of the nitrone was observed only with 1.3 equiv of fluoride as a mixture of TBAT and TBAF and a large excess of CF_3-TMS (6 equiv) yielding 63% of deprotected **2b**. We also studied the possibility of performing the reaction at higher temperature, using the best conditions stated above to access either **2a** or **2b**. A significant reduction in yield was observed at −20, 0, and 20 °C mainly due to the formation of side products, as characterized by the dark brown reaction mixtures. Nevertheless, the targeted dichloromethyl *N*-hydroxylamine was obtained in 32−48% yield, even at temperatures assumed to be incompatible with the presence of either $[CF_3^-]$ or $[CHCl_2^-]$. The rapidity of the reaction cascade could explain this surprising result.

To gain further insight into the reaction mechanism, the dichloromethylation of nitrone **1** was performed in CD_2Cl_2 and was followed by ^1H and ^{19}F NMR. Remarkably, monitoring showed complete disappearance of the nitrone **1** over 5 min with concomitant formation of deuterium-labeled adduct **3a** and DCF_3 as the only reaction products (Scheme 1). Formation of DCF_3 was easily evidenced by ^{19}F NMR (δ −79 ppm, t, J_{FD} = 12.1 Hz; see the Supporting Information).

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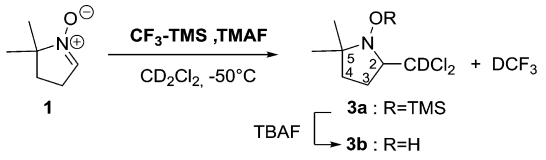
Scheme 1. Labelling Experiments in CD_2Cl_2



Desilylation with TBAF afforded deuterated hydroxylamine **3b**. The presence of the ^2H atom in the final structure of **3b** was apparent from the respective NMR spectra of **2b**/**3b** with a net disappearance of the signal of C*H*Cl_2 in **3b** and a simplification of the splitting pattern of the neighboring 2-H (Figure 2). In

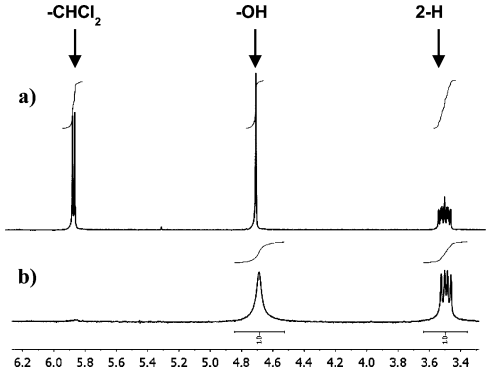


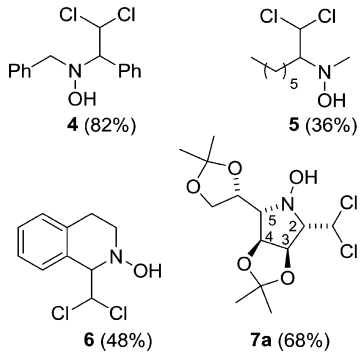
Figure 2. Partial ^1H NMR spectra (250 MHz, $CDCl_3$, 298 K) of compounds **2b** (a) and **3b** (b) isolated after reaction in CH_2Cl_2 and CD_2Cl_2, respectively.

the same way, mass spectroscopy analysis proved unambiguously the labeling with deuterium, resulting in a mass increase of 1 Da (*m*/*z* 198.0443 and 199.0511 for **2b** and **3b**, respectively). Since CD_2Cl_2 is the only source of deuterium in the system, this observation evidenced the role of trifluoromethide as a strong base responsible for proton abstraction from the solvent and subsequent transfer of a dichloromethyl group to the nitrone. The competing collapse of trifluoromethide into the corresponding carbene could explain also the low conversion observed when equimolar amounts of CF_3-TMS were used (Table 1, entry 8). Nevertheless, when the reaction was performed in the presence of phenylacetylene, no difluorocarbene addition product was formed, suggesting that this intermediate is present only in low amounts.[12] At this stage, the true nature of $[CF_3^-]$ as either a free base in solution or a complex with hypervalent silicon species is not clear cut.

Another mechanistic possibility could be the transient formation of TMS-$CHCl_2$, this intermediate being the true source of $[CHCl_2^-]$. Nevertheless, when commercial TMS-$CHCl_2$ was reacted with TMAF in CD_2Cl_2 at −50 °C, no reaction occurred, suggesting that such a mechanistic pathway is unlikely. Finally, the formation of the dichloromethyl hydroxylamine could also result from the addition of a chlorocarbene (formed in situ by reaction of methylene chloride with the base and concomitant release of Cl^-) to the nitrone, affording an aziridinium ion, which would subsequently react with the released chloride.[19]

The general applicability of this new reaction was challenged using other nitrone substrates. Following the optimized protocol, several aliphatic and aromatic nitrones were successfully transformed into the corresponding α-dichloromethyl hydroxylamines **4**−**6** and **7a** after *O*-desilylation with TBAF (Chart 1), in 36−82% overall yields.

Chart 1. Structures of the Prepared α-Dichloromethyl Hydroxylamines



Interestingly, the addition proved highly stereoselective with a chiral carbohydrate-derived nitrone, affording the 2*S* diastereoisomer **7a** in 68% yield after purification. The configuration at C-2 in **7a** was unambiguously assigned after NOE experiments, revealing interactions between −C*H*Cl_2 and *H*-3 and between H-2 and H-5, assessing a relative cis position of each set of protons. The same selectivity was previously observed for nucleophilic addition of other reagents to the same nitrone.[20] This reaction seems particularly interesting, allowing access to an unprecedented series of imino sugars featuring a reactive function at the pseudoanomeric position, which might react with the nucleophilic residues of the catalytic site of glycosidases and glycosyltransferases. It is worth noting that the reaction of nitrone **8**, the precursor of **7**, under analogous experimental conditions but using THF in place of CH_2Cl_2 gave the desired trifluoromethyl adduct.[20a] To compare the efficiency of $[CF_3^-]$ to act as either a nucleophile or a base in our system, **8** was treated with CF_3-TMS/TBAT in THF in the presence of only 6 mol equiv of dichloromethane. Surprisingly, only the dichloromethylhydroxylamine was formed during the reaction, strengthening the prevalence of the kinetically favored acid−base pathway over nucleophilic addition of $[CF_3^-]$.

The replacement of CF_3-TMS by other alkyltrimethylsilanes R-TMS (where R is allyl, benzyl, ethynyl, or ethyl acetate) as putative generators of a strong base failed. Indeed, when the mannose-derived nitrone **8** was reacted with these silyl reagents, no formation of the targeted dichloromethyl hydroxylamine **7a** was observed (Scheme 2). When the reaction was carried out at −50 °C, the starting nitrone was recovered unaffected. However, except for allyltrimethylsilane, new compounds **7b**−**d** were obtained in 20−41% yield when the reaction was conducted at 0 °C, which resulted from direct nucleophilic addition of the R group to the nitrone. As for **7a**, a single stereoisomer was obtained after addition of the R substituent exclusively from the less hindered side.

Next, we wished to explore the capability of the CF_3-TMS/F^- system to abstract protons from other solvents to generate *alternative* nucleophiles. We used nitrone **9** as the electrophilic trap for this series of experiments, since **9** gave the best results among the tested nitrones during dichloromethylation. The procedure stated above (Table 1, entry 6) was applied successively to CH_2Br_2, CH_2I_2, $CHCl_3$, phenylacetylene, butyronitrile, and acetonitrile, adapting the temperature of the

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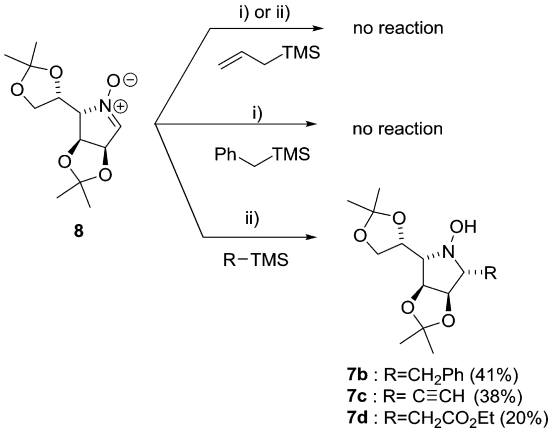
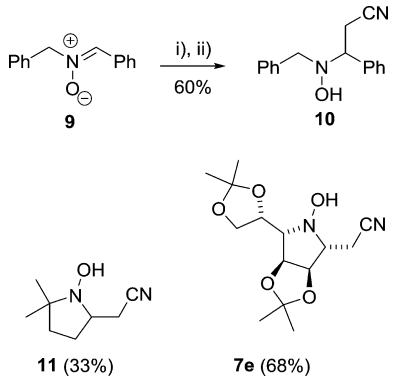
Scheme 2. [a]



[a]Conditions: (i) TMAF (1 equiv), TMS-R (3 equiv), CH_2Cl_2, −50 °C; (ii) TBAT (0.3 equiv), TMS-R (6 equiv), CH_2Cl_2, 0 °C, then TBAF (1 equiv).

reaction to the melting point of each solvent, to avoid freezing (Scheme 3). Only the reaction in acetonitrile afforded the

Scheme 3. [a]



[a]Conditions: (i) TMAF (1 equiv), TMS-CF_3 (2.5 equiv), CH_3CN, −40 °C to room temperature; (ii) TBAF (1 equiv).

expected addition product **10**, the starting nitrone **9** being recovered unreacted in all other attempts. Compounds **11** and **7e** were obtained in the same manner, illustrating the generality of the reaction with acetonitrile also.

CONCLUSION

In summary, we have reported a new reactivity of the Ruppert−Prakash reagent. In the presence of TMAF and CH_2Cl_2 or CH_3CN as the solvent, CF_3-TMS generates the strong base [CF_3^-], which abstracts proton from the solvent. The new nucleophilic species thus formed can be trapped by nitrones to yield 2-(dichloromethyl) or 2-(cyanomethyl) hydroxylamines under smooth conditions. The course of the reaction was analyzed through isotopic labeling experiments with CD_2Cl_2. Different reaction parameters were studied, such as the temperature, the source of fluoride, the nature of the solvent, and the use of other commercial trimethylsilanes. The reaction was observed exclusively with CF_3-TMS, and better results were obtained at low temperature using TMAF as the promoter. To the best of our knowledge, this is the first application of [CF_3^-] as a base in synthetic chemistry.

EXPERIMENTAL SECTION

General Information. Nitrone **1** was purchased from commercial sources. The other nitrones were prepared according to previously reported procedures.[21] Dichloromethane was purified by simple distillation before use. All reactions were performed under argon. Silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid, followed by heating. Flash column chromatography was performed over silica gel M 9385 (40−63 μm) Kieselgel 60. NMR spectra were recorded at 250 MHz for ^1H, 62.5 MHz for ^{13}C or 500 MHz for ^1H, 125 MHz for ^{13}C. Chemical shifts are expressed in parts per million (ppm) and were calibrated to the residual solvent peak. Coupling constants are in Hz, and splitting pattern abbreviations are as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Optical rotations were determined at 20 °C in the specified solvents. High resolution mass spectra (HRMS) were performed on a Q-TOF instrument (ESI).

General Procedure for Dichloromethylation of Nitrones. To a solution of the nitrone (0.1 mmol) in CH_2Cl_2 (0.5 mL) at −50 °C were added successively TMAF (9.3 mg, 0.1 mmol) and CF_3-TMS (38 μL, 0.25 mmol). The heterogeneous mixture was left to react for 30 min at −50 °C. At this stage, variations of the protocol permitted isolation of either the *N*-OTMS protected hydroxylamine or the *N*-OH analogue. To obtain the protected form, after addition of water (0.5 mL), the reaction was warmed to room temperature and extracted with supplementary CH_2Cl_2/water. The organic phase was dried for a short 5 min period with $MgSO_4$ and purified using a 3−5 cm height column chromatograph (Et_2O/petroleum ether, 5/95, v/v). To isolate the deprotected *N*-OH product, TBAF (100 μL of a 1 M solution, 0.1 mmol) was added at −50 °C and the reaction mixture was stirred for a supplementary 30 min period. Water was then added, and the mixture was warmed to room temperature and extracted with supplementary CH_2Cl_2/water. The organic phase was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (Et_2O/petroleum ether, 2/8, v/v).

2-(Dichloromethyl)-5,5-dimethyl-1-((trimethylsilyl)oxy)pyrrolidine ***(2a)****:* colorless oil, 18 mg (71%); R_f = 0.72 (Et_2O/petroleum ether, 1/9, v/v); ^1H NMR ($CDCl_3$) 0.20 (9H, s), 1.09 (3H, s), 1.12 (3H, s), 1.58−1.60 (2H, m), 1.83−2.05 (2H, m), 3.49 (1H, ddd, *J* = 2.3, 6.5, 9.2 Hz), 5.80 (1H, d, *J* = 2.3 Hz); ^{13}C NMR ($CDCl_3$) 0.8, 18.4, 19.7, 29.6, 34.4, 65.5, 72.5, 74.9; HRMS (ESI) calcd for $C_{10}H_{22}NOCl_2Si$ [M + H] 270.0848, found 270.0859.

2-(Dichloromethyl)-5,5-dimethyl-1-hydroxypyrrolidine ***(2b)****:* white solid, 11.5 mg (58%); R_f = 0.25 (Et_2O/petroleum ether, 1/9, v/v); ^1H NMR ($CDCl_3$) 1.10 (3H, s), 1.23 (3H, s), 1.53−1.70 (2H, m), 1.75−1.82 (1H, m), 1.89−2.11 (1H, m), 3.49 (1H, ddd, *J* = 3.5, 5.6, 9.6 Hz), 4.72 (1H, br s), 5.81 (1H, d, *J* = 3.5 Hz); ^{13}C NMR ($CDCl_3$) 18.2, 20.7, 26.9, 34.4, 65.0, 71.1, 75.3; HRMS (ESI) calcd for $C_7H_{14}NOCl_2$ [M + H] 198.0452, found 198.0443.

d-2-(Dichloromethyl)-5,5-dimethyl-1-((trimethylsilyl)oxy)-pyrrolidine ***(3a)****:* colorless oil, 15 mg (56%); R_f = 0.72 (Et_2O/petroleum ether, 1/9, v/v); ^1H NMR ($CDCl_3$) 0.20 (9H, s), 1.09 (3H, s), 1.12 (3H, s), 1.61 (2H, dd, *J* = 6.3, 9.2 Hz), 1.83−2.05 (2H, m), 3.49 (1H, dd, *J* = 6.7, 9.3 Hz); ^{13}C NMR ($CDCl_3$) 0.9, 18.5, 19.8, 29.7, 34.5, 65.7, 72.6; HRMS (ESI) calcd for $C_{10}H_{21}{}^2HNOCl_2Si$ [M + H] 271.0911, found 271.0916.

d-2-(Dichloromethyl)-5,5-dimethyl-1-hydroxypyrrolidine ***(3b)****:* white solid, 9 mg (47%); R_f = 0.25 (Et_2O/petroleum ether, 1/9, v/v); ^1H NMR ($CDCl_3$) 1.10 (3H, s), 1.23 (3H, s), 1.53−1.70 (2H, m), 1.75−1.82 (1H, m), 1.89−2.11 (1H, m), 3.49 (1H, dd, *J* = 5.6, 9.7 Hz), 4.60 (1H, br s); ^{13}C NMR ($CDCl_3$) 18.3, 20.9, 26.8, 34.5, 65.2, 71.1; HRMS (ESI) calcd for $C_7H_{13}{}^2HNOCl_2$ [M + H] 199.0515, found 199.0511.

N-Benzyl-α-(dichloromethylbenzyl)hydroxylamine ***(4)****:* colorless oil, 24 mg (82%); R_f = 0.24 (Et_2O/petroleum ether, 1/9, v/v); ^1H NMR ($CDCl_3$) 3.20 (1H, d, *J* = 13.6 Hz), 3.79 (1H, d, *J* = 13.6 Hz), 4.13 (1H, d, *J* = 5.4 Hz), 5.03 (1H, br s), 6.46 (1H, d, *J* = 5.4 Hz), 7.27−7.50 (10H, m); ^{13}C NMR ($CDCl_3$) 62.0, 73.1, 77.0, 127.5, 128.1, 128.4, 129.0, 129.2, 130.5, 133.8, 137.1; HRMS (ESI) calcd for $C_{15}H_{15}NOCl_2Na$ [M + Na] 318.0428, found 318.0428.

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*N-Methyl-(1′-dichloromethyl)heptylhydroxylamine (**5**):* yellow oil, 8 mg (36%); R_f = 0.62 (Et_2O:petroleum ether, 35:65, v/v); ^1H NMR ($CDCl_3$) 0.78−0.87 (3H, t), 1.25−1.60 (9H, m), 1.75−1.83 (1H, m), 2.75 (3H, s), 2.95 (1H, m), 6.12 (1H, br s), 6.25 (1H, d, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) 14.1, 22.6, 26.5, 28.1, 29.4, 31.6, 44.8, 73.8, 74.5; HRMS (ESI) calcd for $C_9H_{20}NOCl_2$ [M + H] 228.0922, found 228.0918.

*1-(Dichloromethyl)-N-hydroxy-1,2,3,4-tetrahydroisoquinoline (**6**):* white solid, 11 mg (48%); R_f = 0.24 (Et_2O/petroleum ether, 2/8, v/v); ^1H NMR ($CDCl_3$) 2.70−2.81 (1H, m), 2.90−3.16 (2H, m), 3.42−3.55 (1H, m), 4.60 (1H, d, J = 1.9 Hz), 5.24 (1H, br s), 6.20 (1H, d, J = 1.9 Hz), 7.04−7.22 (3H, m), 7.45−7.50 (1H, m); ^{13}C NMR ($CDCl_3$) 28.1, 53.8, 74.6, 75.0, 126.3, 127.3, 127.8, 128.3, 131.6, 135.8; HRMS (ESI) calcd for $C_{10}H_{12}NOCl_2$ [M + H] 232.0296, found 232.0292.

*(2S,3R,4S,5S)-3,4-Dihydroxy-5-((1′R)-1′,2′-dihydroxyethyl)-3,4:1′,2′-di-O-isopropylidene-2-(dichloromethyl)pyrrolidine (**7a**):* white solid, 10 mg (starting from 11 mg of nitrone **8**, 68%); R_f = 0.34 (EtOAc/petroleum ether, 2/8, v/v); $[\alpha]_D^{20}$ = −69.0° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.26 (3H, s), 1.27 (3H, s), 1.48 (3H, s), 1.50 (3H, s), 3.05 (1H, t, J = 6.1 Hz), 3.54 (1H, dd, J = 2.7, 3.9 Hz), 3.93 (1H, dd, J = 4.8, 8.8 Hz), 4.03 (1H, dd, J = 6.3, 8.8 Hz), 4.18−4.26 (2H, m), 4.62 (1H, dd, J = 3.9, 6.9 Hz), 5.51 (1H, br s), 5.87 (1H, d, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$) 25.3, 25.4, 26.5, 27.4, 66.2, 71.1, 74.4, 76.6, 76.8, 77.3, 78.3, 110.3, 114.2; HRMS (ESI) calcd for $C_{13}H_{21}NO_5Cl_2Na$ [M + Na] 364.0694, found 364.0693.

Reaction of Nitrone 8 with Other Alkyltrimethylsilanes. To a solution of nitrone **8** (13 mg, 0.05 mmol) in CH_2Cl_2 at 0 °C was added successively TBAT (7 mg, 0.013 mmol) and 6 equiv of $RSi(CH_3)_3$ (R = allyl, benzyl, ethynyl, CH_2CO_2Et). The reaction mixture was stirred at 0 °C for 30 min, and TBAF (100 μL of a 1 M solution in THF) was added. After 30 min, water was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography using Et_2O/petroleum ether (5/5, v/v) as the eluent.

*(2R,3R,4S,5S)-3,4-Dihydroxy-5-((1′R)-1′,2′-dihydroxyethyl)-3,4:1′,2′-di-O-isopropylidene-2-benzylpyrrolidine (**7b**):* white solid, 7 mg (starting from 13 mg of nitrone **8**, 41%); R_f = 0.38 (Et_2O/petroleum ether, 5/5, v/v); ^1H NMR ($CDCl_3$) 1.16 (3H, s), 1.29 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 2.97 (1H, dd, J = 6.7 14.2 Hz), 3.02−3.07 (2H, m), 3.29 (1H, dt, J = 5.4, 6.5 Hz), 3.91 (1H, dd, J = 5.4, 8.7 Hz), 4.06 (1H, dd, J = 5.4, 7.1 Hz), 4.14 (1H, dd, J = 5.4, 7.1 Hz), 4.18 (1H, dd, J = 5.6, 7.1 Hz), 4.28 (1H, dt,, J = 5.5, 6.5 Hz), 5.20 (1H, br s), 7.17−7.31 (5H, m); ^{13}C NMR ($CDCl_3$) 25.4, 25.5, 26.6, 27.1, 37.4, 66.4, 73.3, 74.4, 77.1, 77.6, 79.9, 110.0, 113.8, 126.3, 128.4, 129.7, 138.3; HRMS (ESI) calcd for $C_{19}H_{28}NO_5$ [M + H] 350.1967, found 350.1976.

*(2R,3R,4S,5S)-3,4-Dihydroxy-5-((1′R)-1′,2′-dihydroxyethyl)-3,4:1′,2′-di-O-isopropylidene-2-ethynylpyrrolidine (**7c**):* yellow oil, 8 mg (starting from 20 mg of nitrone **8**, 38%); R_f = 0.25 (Et_2O/petroleum ether, 5/5, v/v); ^1H NMR ($CDCl_3$) 1.30 (3H, s), 1.37 (3H, s), 1.49 (3H, s), 1.54 (3H, s), 2.41 (1H, d, J = 2.0 Hz), 3.11 (1H, dd, J = 5.3, 5.9 Hz), 3.73 (1H, dd, J = 2.0, 6.4 Hz), 3.93 (1H, dd, J = 5.2, 8.7 Hz), 4.09 (1H, dd, J = 6.6, 8.7 Hz), 4.33 (1H, dd, J = 5.9, 7.0 Hz), 4.37 (1H, m), 4.51 (1H, dd, J = 6.4, 7.0 Hz), 5.49 (1H, br s); ^{13}C NMR ($CDCl_3$) 25.3, 25.3, 26.6, 27.3, 64.9, 66.3, 73.2, 74.1, 76.1, 77.8, 81.1, 81.2, 110.2, 114.6; HRMS (ESI) calcd for $C_{14}H_{21}NO_5Na$ [M + Na] 306.1317, found 306.1308.

*(2R,3R,4S,5S)-3,4-Dihydroxy-5-((1′R)-1′,2′-dihydroxyethyl)-3,4:1′,2′-di-O-isopropylidene-2-(carboxyethyl)methylpyrrolidine (**7d**):* colorless oil, 3 mg (starting from 11 mg of nitrone **8**, 20%); R_f = 0.56 (Et_2O/petroleum ether, 7/3, v/v); ^1H NMR ($CDCl_3$) 1.26 (3H, t, J = 7.1 Hz), 1.36 (3H, s), 1.29 (3H, s), 1.48 (3H, s), 1.53 (3H, s), 2.58 (1H, dd, J = 2.9, 14.7 Hz), 2.62 (1H, dd, J = 3.4, 14.7 Hz), 3.08 (1H, t, J = 5.6 Hz), 3.37 (1H, q, J = 5.9 Hz), 3.93 (1H, dd, J = 5.3, 8.7 Hz), 4.08 (1H, dd, J = 6.6, 8.7 Hz), 4.12−4.20 (2H, m), 4.25 (1H, dd, J = 5.4, 7.0 Hz), 4.28−4.33 (1H, m), 4.35 (1H, dd, J = 6.0, 7.0 Hz), 5.30 (1H, br s); ^{13}C NMR ($CDCl_3$) 14.3, 25.4, 25.4, 26.6, 27.4, 36.8, 60.7, 66.4, 69.7, 74.3, 76.7, 77.6, 80.1, 110.1, 114.0, 171.6; HRMS (ESI) calcd for $C_{16}H_{27}NO_7Na$ [M + Na] 368.1685, found 368.1682.

General Procedure for Cyanomethylation of Nitrones. To a solution of the nitrone (0.1 mmol) in CH_3CN (0.5 mL) at −40 °C were added successively TMAF (9.3 mg, 0.1 mmol) and CF_3-TMS (38 μL, 0.25 mmol). In some cases, additional CF_3-TMS (38 μL) was added to improve the conversion. The mixture was left to react for 30 min at −40 °C and then warmed to room temperature. After 30 min at room temperature, TBAF (100 μL of a 1 M solution in THF) was added and the mixture was stirred for an additional hour at room temperature. Water was added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography.

*N-Benzyl-α-((cyanomethyl)benzyl)hydroxylamine (**10**):* yellow oil, 15 mg (60%); R_f = 0.28 (Et_2O/petroleum ether, 35/65, v/v); ^1H NMR ($CDCl_3$) 2.95 (1H, dd, J = 7.0, 16.5 Hz), 3.05 (1H, dd, J = 5.4, 16.5 Hz), 3.53 (1H, d, J = 13.4 Hz), 3.78 (1H, d, J = 13.4 Hz), 4.01 (1H, dd, J = 5.4, 7.0 Hz), 5.24 (1H, br s), 7.25−7.50 (10H, m); ^{13}C NMR ($CDCl_3$) 23.8, 61.8, 67.5, 122.4, 127.5−129.2 (Ar-C); HRMS (ESI) calcd for $C_{16}H_{17}N_2O$ [M + H] 253.1341, found 253.1347.

*2-(Cyanomethyl)-1-hydroxy-5,5-dimethylpyrrolidine (**11**):* colorless oil, 5 mg (33%); R_f = 0.40 (Et_2O/petroleum ether, 6/4, v/v); ^1H NMR ($CDCl_3$) 1.03 (3H, s), 1.21 (3H, s), 1.38−1.71 (3H, m), 1.90−2.05 (1H, m), 2.59 (2H, d, J = 5.4 Hz), 3.25 (1H, m), 4.70 (1H, br s); ^{13}C NMR ($CDCl_3$) 18.4, 22.9, 23.7, 27.1, 34.0, 59.8, 63.6, 118.5; HRMS (ESI) calcd for $C_8H_{15}N_2O$ [M + H] 155.1184, found 155.1191.

*(2R,3R,4S,5S)-3,4-Dihydroxy-5-((1′R)-1′,2′-dihydroxyethyl)-3,4:1′,2′-di-O-isopropylidene-2-cyanomethylpyrrolidine (**7e**):* white solid, 15 mg (starting from 19 mg of nitrone **8**, 68%); R_f = 0.45 (Et_2O/petroleum ether, 7/3, v/v); $[\alpha]_D^{20}$ = −30.4° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.29 (3H, s), 1.36 (3H, s), 1.50 (3H, s), 1.51 (3H, s), 2.70 (1H, dd, J = 4.2, 17.0 Hz), 2.81 (1H, dd, J = 4.8, 17.0 Hz), 3.05−3.17 (2H, m), 3.96 (1H, dd, J = 4.8, 9.0 Hz), 4.10 (1H, dd, J = 6.7, 9.0 Hz), 4.23−4.39 (3H, m), 5.72 (1H, br s); ^{13}C NMR ($CDCl_3$) 19.5, 25.2, 25.3, 26.6, 27.2, 66.3, 68.2, 74.4, 76.5, 77.3, 78.5, 110.3, 114.5, 117.3; HRMS (ESI) calcd for $C_{14}H_{22}N_2O_5Na$ [M + Na] 321.1426, found 321.1436.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra of compounds **2**−**7a**−**e**, **10**, and **11** and NMR monitoring of the reaction in CD_2Cl_2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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