α-(Trifluoromethyl)amine Derivatives via Nucleophilic Trifluoromethylation of Nitrones

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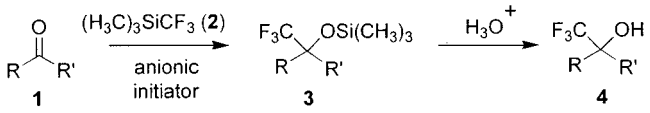
(Trifluoromethyl)trimethylsilane ($TMSCF_3$) reacts with nitrones to afford α-(trifluoromethyl)-hydroxylamines protected as *O*-trimethylsilyl ethers. Potassium *t*-butoxide initiates the nucleophilic trifluoromethylation. The reaction works best with α,*N*-diaryl nitrones, and the conditions are compatible with a range of substituents on the aryl groups. Acidic deprotection of the nitrone/$TMSCF_3$ adducts generates α-(trifluoromethyl)hydroxylamines. Catalytic hydrogenation of the adducts produces α-(trifluoromethyl)amines. Nitrone/$TMSCF_3$ adducts with strong electron-withdrawing groups on the α-aryl ring or heterocyclic α-aryl groups undergo an elimination/addition sequence to generate α,α-bis(trifluoromethyl)amines. Nitrones with alkyl groups bound directly to the 1,3-dipolar moiety fail to react with $TMSCF_3$, but trifluoromethylation of β,γ-unsaturated nitrones followed by reduction of the double bond can circumvent this limitation.

Introduction

Organic molecules containing small perfluoroalkyl groups often exhibit behavior distinct from their hydrocarbon counterparts. Moieties such as the trifluoromethyl group can dramatically influence the polarity, solubility, chemical reactivity, and intermolecular interactions of an entire molecule. Applications for partially fluorinated organic molecules include pharmaceuticals,[1] agrochemicals,[2] and polymers.[3] The utility of fluoroorganic molecules motivates the search for new synthetic methods for their preparation.

A variety of strategies may be used to incorporate perfluoroalkyl groups into organic molecules, including nucleophilic, electrophilic, and radical processes.[4] Recent developments in nucleophilic perfluoroalkylation methods have expanded the utility of this approach. The inherent instability of small perfluoroalkanide nucleophiles has been modified by the use of organometallic complexes.[5] The use of these reagents can accomplish efficient nucleophilic aromatic substitution, but is often not practical for trifluoromethylation of carbonyl groups and related π electrophiles.

Scheme 1



Procedures for in situ generation of trifluoromethanide equivalents exist, and these methods accomplish nucleophilic trifluoromethylation with varying degrees of success.[6] Perfluoroalkylsilane reagents such as (trifluoromethyl)trimethylsilane[7] ($TMSCF_3$, **2**) efficiently generate α-(trifluoromethyl)alcohols (**4**) from the corresponding carbonyl compounds (**1**) (Scheme 1).[8] The reactivity of **2** has been extended to include other perfluoroalkyl nucleophiles and a range of electrophiles,[9] but certain limitations remain. Imines react poorly with **2**, except in the reactions of azirines (**5**)[10] and azenes (**7**)[11] (Scheme

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(1) (a) *Organofluorine in Medicinal Chemistry and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds.; Elsevier: Amsterdam, 1993. (b) *Fluorine-Containing Amino Acids*: *Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, D.C., 1996. (d) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print No. 58; *Tetrahedron* **1996**, *52*, 1−330.

(2) (a) Yoshika, H.; Nakayama, C.; Matsuo, N *J. Synth. Org. Chem. Jpn*. **1984**, *42*, 809. (b) *The Agrochemicals Handbook*, 2nd ed.; Ellis Horwood: Chichester, U.K., 1979. (b) Bellus, D. *Chimia* **1991**, *45*, 154.

(3) (a) Schmiegel, W. W. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Press: Washington, 1995; p 1101−1118. (b) *Organofluorine Chemistry − Principals and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994.

(4) (a) *Topics in Current Chemistry − Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer: Berlin, 1997; Volume 192. (b) *Topics in Current Chemistry − Organofluorine Chemistry: Techniques and Synthons*; Chambers, R. D., Ed.; Springer: Berlin, 1997; Volume 193.

(5) (a) For brief reviews of the reactivity of specific reagents, see: Tamborski, C. *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Press: Washington, 1995; (a) copper, pp 699−708; (b) zinc, pp 674−691; (c) cadmium, pp 692−696. (b) Burton, D. J.; Yang, Y.-Z. *Tetrahedron* **1992**, *48*, 189.

(6) (a) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett*. **1981**, 1719. (b) Hartkopf, U.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 443. (c) Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 921. (d) Pawelke, G. *J. Fluorine Chem*. **1989**, *42*, 429. (e) Yokoyama, Y.; Mochida, K. *Synlett* **1996**, 1191. (f) Yokoyama, Y.; Mochida, K. *Tetrahedron Lett*. **1997**, *38*, 3443. (g) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771. (h) Mispelaere, C.; Roques, N. *Tetrahedron Lett*. **1999**, *40*, 6411.

(7) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett*. **1984**, *25*, 2195.

(8) (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc*. **1989**, *111*, 393. (b) For a related procedure, see: Stahly, G. P.; Bell, D. R. *J. Org. Chem*. **1989**, *54*, 2873.

(9) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev*. **1997**, *97*, 757. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.

(10) Félix, C. P.; Khatimi, N.; Laurent, A. J. *Tetrahedron Lett*. **1994**, *35*, 3303.

(11) Patel, N. R.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem*. **1993**, *32*, 4802.

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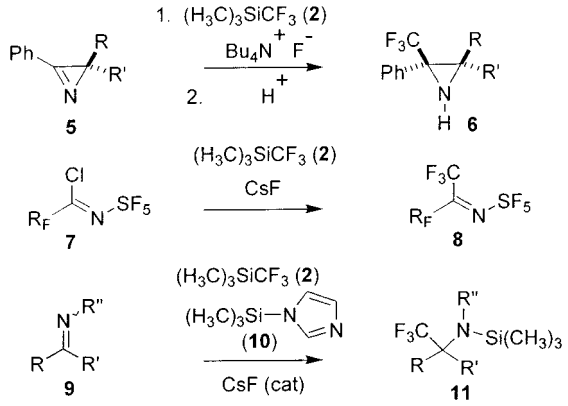
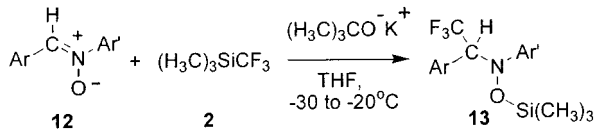
Scheme 2



2). The combination of **2** and trimethylsilylimidazole (**10**) accomplishes the trifluoromethylation of imines (**9**) of nonenolizable carbonyl compounds (Scheme 2).[12]

We recently reported a method for the preparation of α-(trifluoromethyl)hydroxylamine derivatives by nucleophilic trifluoromethylation of nitrone substrates (**12**) using **2** (eq 1).[13]



The nitrone reaction offers certain advantages to direct trifluoromethylation of imines.[6e,f,12] Nitrones are accessible by several different routes,[14−16] the reaction does not require additional silylating reagents, and inexpensive potassium *t*-butoxide initiates the addition. Formation of the silylated hydroxylamine derivatives creates opportunities for subsequent synthetic manipulation. The scope of the nitrone trifluoromethylation, and transformations of the adducts, are reported here.

Results

Process and Characterization. Preliminary work focused on optimization of reaction conditions that generated the nitrone/**2** adducts (**13**).[13] The anionic initiators frequently used with **2** (tetrabutylammonium fluoride (TBAF), cesium fluoride, and alkoxides) were evaluated. The influences of temperature, stoichiometry, solvent, and concentration were also studied. Of the anionic initiators tested, potassium *t*-butoxide provided the highest yields of the adducts. The optimized procedure for the formation of adducts (**13**) employed 2 equiv of **2**. Complete conversion of the nitrones required the addition of small aliquots of a *t*-butoxide slurry (∼0.1 M) in THF at regular intervals. The *t*-butoxide/**2** ratio required to complete the reactions depended on the specific nitrone and often varied between identical reactions. Generally, addition of the *t*-butoxide in small quantities at regular intervals was continued until the nitrone was consumed or until byproduct formation was observed.

Lower temperatures (typically from −30 to −20 °C) favored clean formation of the adducts. For highly soluble nitrones, reactions were run under homogeneous conditions at substrate concentrations of 0.2 M. Several nitrone substrates were only partially soluble at lower temperatures, however. For limitedly soluble substrates, the nitrone concentration was decreased to 0.05−0.1 M. The reactions could be performed under biphasic conditions, and unreacted solid nitrones gradually dissolved as the reaction progressed. The reactions were monitored by thin-layer chromatography. The nonpolar adducts and the polar nitrones decomposed quickly upon UV irradiation ($\lambda = 254$ nm). The products were easily purified by flash chromatography (silica gel/0−5% ethyl acetate in hexanes). The low-melting adducts were stable to the atmosphere at room temperature for several weeks.

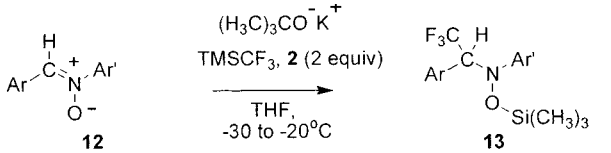
The incorporation of the trifluoromethyl group was confirmed by NMR analysis of the adducts (**13**). A characteristic quartet appeared at 4−5 ppm in the ^{1}H NMR spectrum caused by heteronuclear H−F coupling ($^3J_{H-F} \sim 8$ Hz). The equivalent protons of the trimethylsilyl group resonated at ∼0.1 ppm, but the integration for the TMS group ranged from 6 to 8H using delay (*d*1) values of 1−2 s. Distinctive heteronuclear C−F coupling was observed in the broadband decoupled ^{13}C NMR spectra of the adducts. The trifluoromethyl group produced a quartet at ∼125 ppm with a characteristically large $^1J_{C-F}$ coupling of ∼280 Hz. The C−F coupling diminished by an order of magnitude with each intervening carbon atom and was usually not observed beyond $^2J_{C-F}$.

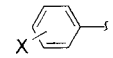
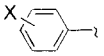
Reaction Scope. Process optimization employed α,*N*-diphenyl nitrone (**12*c***). The compatibility of the reaction with a variety of substrates was then investigated. Table 1 contains the isolated yields of a variety of α,*N*-diaryl nitrone/$TMSCF_3$ adducts (**13**). Few byproducts were formed from nitrones bearing extended aromatic systems or electron-donating substituents on the α-aryl ring. Nitrones bearing strong electron-withdrawing substituents on the α-aryl group (**12*e***) and those with heterocyclic α-aryl groups (**12*g*−*i***) afforded poor yields of the adducts but successfully produced a secondary product.

The reaction of the α-(*p*-nitrophenyl)-*N*-phenyl nitrone (**12*e***) with **2** illustrates the source of the secondary product (Scheme 3). Addition of **2** to nitrone **12*e*** afforded the formal adduct **13*e*** in modest yield, even though the starting nitrone was entirely consumed. During the reaction, the initial adduct **13*e*** was converted to a second product (**15*e***) that accounted for the majority of the mass balance. The structure of bis(trifluoromethyl)amine **15*e*** was difficult to deduce because the ^{1}H NMR spectrum lacked the distinctive ^{1}H−^{19}F splitting observed in the nitrone/$TMSCF_3$ adducts, and the trimethylsilyl group was absent. The ^{13}C NMR spectra of **15*e*** exhibited resonances characteristic of both the trifluoromethyl group ($\delta \sim 125$ ppm, q, $^1J_{C-F} \sim 280$ Hz) and a quaternary carbon bearing two equivalent trifluoromethyl groups ($\delta \sim 70$ ppm, sept, $^2J_{C-F} \sim 28$ Hz). The intensity of the latter signal was very low, and it was easily overlooked if the signal-to-noise ratio was poor. The IR spectrum of the secondary product contained a typical secondary amine N−H stretch at ∼3400 cm^{-1}. The spectroscopic data from

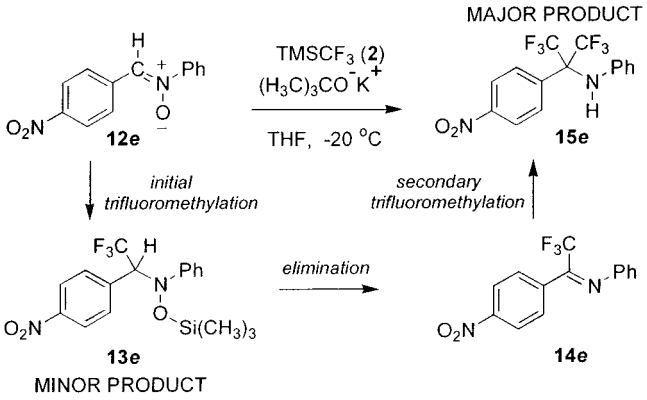
(12) Blazejewski, J.-C.; Anselmi, E.; Wilmshurst, M. P. *Tetrahedron Lett.* **1999**, *40*, 5475.
(13) Nelson, D. W.; Easley, R. A.; Pintea, B. N. V. *Tetrahedron Lett.* **1999**, *40*, 25.
(14) Brüning, I.; Grashey, R.; Hauck, H.; Huisgen, R.; Seidl, H. *Organic Syntheses*; Wiley and Sons: New York, 1973; Vol. V, p 1124.
(15) Lobo, A. M.; Prabhakar, S.; Rzepa, H. S.; Skapski, A. C.; Tavares, M. R.; Widdowson, D. A. *Tetrahedron* **1983**, *39*, 3833.
(16) (a) Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth.* **1991**, *70*, 265. (b) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.

Table 1. Compatibility of Substituted Diaryl Nitrones with Trifluoromethylation Conditions



entry	Ar (Ar' = Ph)	% isolated yield	entry	Ar' (Ar = Ph)	% isolated yield
					
a	4-OCH_3	77-90			
b	2-OCH_3	59-74			
c	H	85-93	*j*	4-OCH_3	62-79
d	4-Cl	71-90			
e	4-NO_2	10-22			
f		83-90	*k*	4-CH_3	71-84
g		18-43	*l*	4-Cl	52-59
h		< 5	*m*	3-CF_3	60-72
i		< 5			

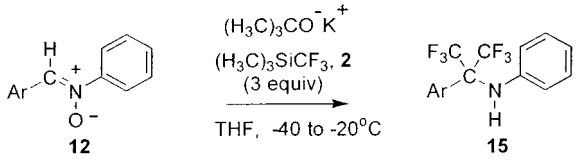
Scheme 3

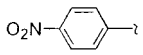


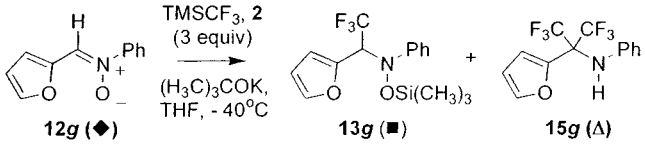
compounds **15*e*, *g*−*i*** are consistent with those from related compounds reported in the literature.[12]

The proposed elimination−addition sequence requires formation of an intermediate α-(trifluoromethyl)imine (**14*e***, Scheme 3). Such imines have been isolated from nitrone/**2** reactions,[13] and precedence for addition of **2** to electron-deficient C−N double bonds exists.[11] In the nitrone/**2** reactions, longer reaction times and the use of excess base and excess **2** favored formation of the α,α-bis(CF_3)amines. Modified reaction conditions, using 3.0 equiv of **2**, provided the highest yields of **15**, and isolated yields from the optimized procedure are listed in Table 2. As with the procedure for formation of the initial adducts, the precise quantity of potassium *t*-butoxide necessary to produce only the bistrifluoromethylated amines varied for different substrates, as well as for different reactions using identical conditions. Aliquots of the initiator solution were added at regular intervals until the starting nitrone *and* the initial adduct were no longer observed.

Table 2. Formation of Bis(trifluoromethyl)amines from Selected Nitrones



entry	Ar	% isolated yield
e		64-77
g		78-82
h		72-75
i		51-76



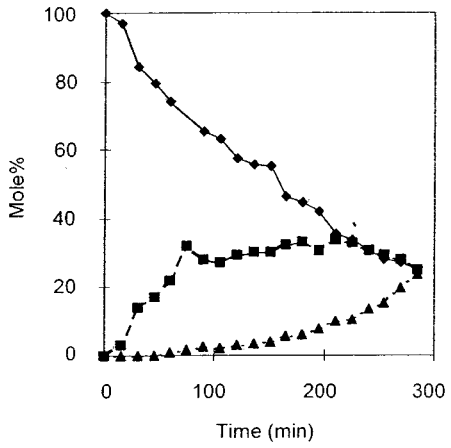
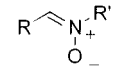


Figure 1. Plot of product distribution vs time.

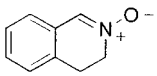
To gain insight into the competition between the initial and secondary trifluoromethylation processes, the reaction of the α-(2-furyl)-*N*-phenyl nitrone (**12*g***) with excess **2** at −40 °C was analyzed by gas chromatography. Figure 1 illustrates the composition of the reaction mixture during the reaction. The data reveal that high yield (>40−50%) of adduct **13*g*** was not possible. The concentration of **13*g*** reached a plateau at ∼40% and then decreased. The reaction depicted in Figure 1 was monitored until approximately 75% of the starting nitrone was consumed. At this level of nitrone conversion, the yield of the bis(CF_3) adduct **15*g*** was relatively low. Continued addition of the *t*-butoxide initiator eventually led to complete conversion of the starting material and the initial adduct to afford amine **15*g*** as the major product in 82% yield.

The addition of **2** to α,*N*-diaryl nitrones was successful for a variety of aryl groups. Nitrones with alkyl substituents worked poorly in the trifluoromethylation protocol.

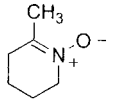
Chart 1



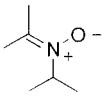
16	R	R'
a	Ph	CH_3
b	Ph	CH_2Ph
c	Ph	C_6H_{11}
d	Ph	$C(CH_3)_3$
e	$H_3C(CH_2)_4$	Ph
f	$(H_3C)_3C$	Ph



17

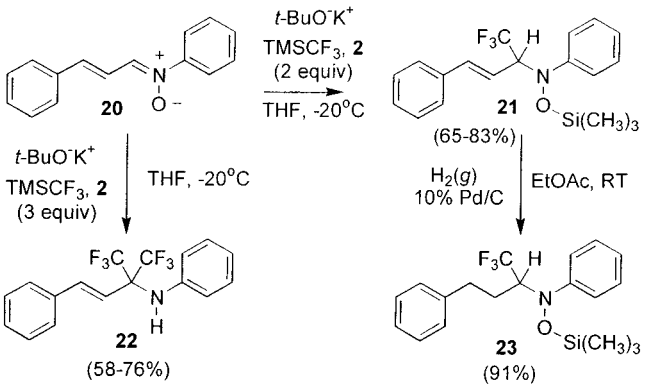


18



19

Scheme 4



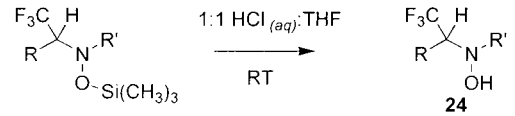
Several such nitrones (**16**−**19**, Chart 1) were treated with **2** and alkoxide and fluoride initiators, but at best trace amounts (<5%) of impure adducts were obtained. The reaction conditions (temperature, concentration, stoichiometry, order of addition, etc.) were varied, but adduct formation occurred in very low yields.

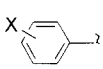
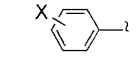
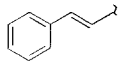
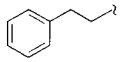
The failure of the trifluoromethylation protocol with alkyl-substituted nitrones can be circumvented through the use of β,γ-unsaturated nitrones. Addition of **2** to nitrone **20** using the conditions outlined in Table 1 afforded adduct **21** in good yield (Scheme 4). Excess of both *t*-butoxide and **2** in conjunction with long reaction times provided good yields of the bis(trifluoromethyl)-amine **22**. Products obtained from conjugate addition to nitrone **20** were not isolated in the reactions.

Saturation of the double bond in adduct **21** afforded the α-(trifluoromethyl)hydroxylamine derivative. Catalytic hydrogenation of **21**, over 10% palladium on carbon at room temperature, quickly reduced the double bond to form **23**. Reductive cleavage of the N−O bond also occurred in the hydrogenation reaction, but formation of the free amine was slow compared to alkene saturation. The silylated hydroxylamine **23** was a stable oil at room temperature.

Synthetic Manipulation of Nitrone/$TMSCF_3$ Adducts. The silylated hydroxylamine derivatives accessible by the nitrone/**2** reactions were readily transformed into the corresponding hydroxylamines or the free amine compounds. Treatment of the adducts (**13**, **21**, and **23**) with a 1:1 mixture of 1 N HCl:THF cleaved the oxygen−silicon bond cleanly to produce the hydroxylamines (**24**). Table 3 lists the isolated yields for this acid-catalyzed deprotection. The products were purified by flash chromatography (silica gel/5% ethyl acetate in hexanes), and analytical samples were obtained by recrystallization from hexane. The solid α-(trifluoromethyl)hydroxylamines were stable to air at room temperature for weeks. In solution, particularly using halogenated solvents such as dichloromethane and chloroform, decomposition occurred. Hydroxylamines **24*b***, ***g***, and ***h*** exhibited poor stabilities that prevented their isolation and/or complete characterization. For the stable hydroxylamines, the ^1H and ^{13}C NMR spectra indicated the presence of the trifluoromethyl group. The resonances of the hydroxyl protons appeared as sharp singlets at ~5.3−5.5 ppm in the ^1H NMR spectra. The chemical shift and width of these signals did not change appreciably with changes in concentration.

Table 3. Hydroxylamine Formation by Acidic Deprotection



adduct	R (R' = Ph)	% isolated yield (**24**)	*adduct*	R' (R = Ph)	% isolated yield (**24**)
13			**13**		
a	4-OCH_3	***a*** 86-93	***j***	4-OCH_3	***j*** - [a]
b	2-OCH_3	***b*** 61-70[a]	***k***	4-CH_3	***k*** 77-80
c	H	***c*** 89-95	***l***	4-Cl	***l*** 81-88
d	4-Cl	***d*** 87-89	***m***	3-CF_3	***m*** 72-79
f		***f*** 90-94	**21**		***n*** 75-82
			23		***o*** - [a]

[a] The hydroxylamine decomposed before isolation and characterization were completed.

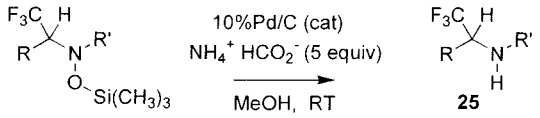
Selective cleavage of the nitrogen−oxygen bond in the nitrone/**2** adducts proved more complex. Catalytic hydrogenation over palladium catalyst cleaved the N−O bond, but complete conversion often required more than 72 h. Reductive cleavage using zinc meta1[17] afforded the free amine, but the reaction was also sluggish. The most efficient protocol for zinc reduction used 1:1 acetic acid: THF as the solvent, excess zinc, and reflux conditions. Complete reductive cleavage of the N−O bond under these conditions required 48−72 h. Transfer hydrogenation[18] efficiently accomplished the reductive deprotection. Treatment of a 0.2 M methanolic solution of the α-(trifluoromethyl)hydroxylamine *O*-trimethylsilyl ethers with 10% Pd/C and 5 equiv of ammonium formate cleaved the silyloxy group in 3−5 h at room temperature. The isolated yields for the α-(trifluoromethyl)amines (**25**) produced by this method are listed in Table 4.

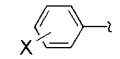
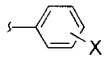
Complications arose in the transfer hydrogenation reactions using certain nitrone/**2** adducts. Reductive dechlorination occurred concomitantly with N−O cleavage in the reduction of adducts **13*d*** and ***l***. Rapid dehalogenation of haloaromatics under transfer hydrogenation conditions has been reported, particularly using

(17) (a) Howell, A. R.; Pattenden, G. *J. Chem. Soc., Chem. Comm.* **1990**, 103. (b) Moody, C. J.; Gallagher, P. T.; Lightfoot, A. P.; Slawin, A. M. Z. *J. Org. Chem.* **1999**, *64*, 4419.

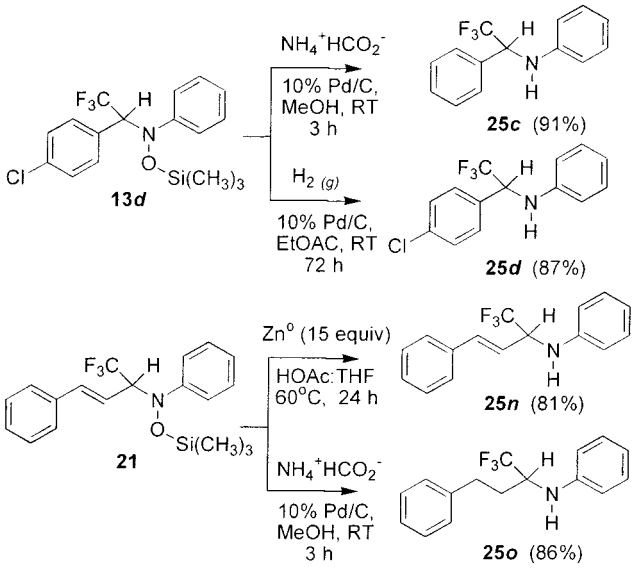
(18) For reviews on catalytic hydrogen transfer reductions, see: (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. (b) Johnstone, R. A. W.; Wilby, A. H.; Entwhistle, T. D. *Chem. Rev.* **1985**, *85*, 129.

Table 4. Amine Formation by Transfer Hydrogenation Deprotection



adduct	R (R' = Ph)	% isolated yield (**25**)	adduct	R' (R = Ph)	% isolated yield (**25**)
13			**13**		
a	X = 4-OCH_3	***a*** 87-90			
b	2-OCH_3	***b*** 78-83	***j***	X = 4-OCH_3	***j*** 79-85
c	H	***c*** 91-95	***k***	4-CH_3	***k*** 88-90
f		***f*** 90-94	***m***	3-CF_3	***m*** 86-92

Scheme 5

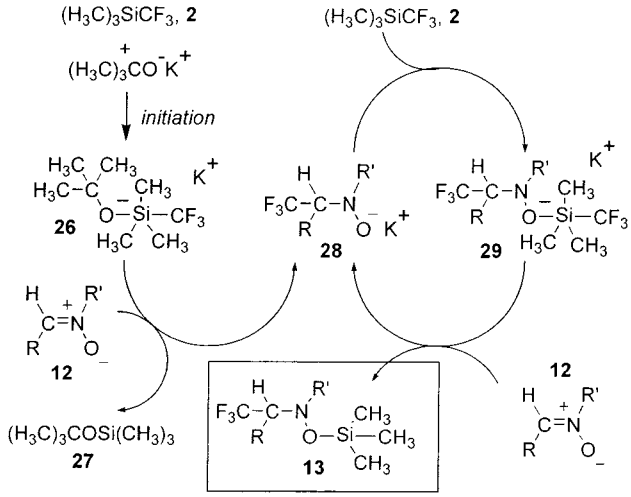


ammonium formate as the hydrogen source.[19] Standard catalytic hydrogenation afforded the secondary amine from adduct **13*d*** with the chlorophenyl moiety intact (Scheme 5). Transfer hydrogenation also reduced the trans double bond in adduct **21** at approximately the same rate as N−O cleavage occurred. Zinc metal reduction of **21** cleanly produced the α-(trifluoromethyl)allylic amine **25*n***, but the reaction required 24 h at reflux (Scheme 5). The α-(trifluoromethyl)amines exhibited absorbances of moderate intensity at ~3400 cm^{-1} in their IR spectra. The ^1H and ^{13}C NMR spectra were consistent with the designated structures.

Discussion

Mechanistic Proposal. The nucleophilic trifluoromethylation procedure described herein demonstrates the suitability of nitrones as electrophiles for silane trifluoromethylation reagents. The choice of nitrone substrates was based on the mechanistic hypothesis that 1,3-addition of **2** should avoid formation of a weak and labile N−Si bond.[12] Scheme 6 proposes a catalytic cycle that

Scheme 6



can explain the formation of the initial nitrone/**2** adducts (**13**). The proposed pathway for the adduct formation closely parallels the pathway suggested for trifluoromethylation of carbonyl compounds using **2**.[9] In both systems, a negatively charged pentavalent silane intermediate transfers the trifluoromethanide group to the electrophilic carbon. The trifluoromethyl and trimethylsilyl groups in the formal adducts originate from *different* molecules of **2**. Finally, both carbonyl and nitrone trifluoromethylation require anionic initiation.

On first inspection of Scheme 6, addition of an external anionic initiator may seem unnecessary. The negative charge of the oxide group in the nitrone could function as a nucleophile and attack **2**, resulting in the spontaneous initiation of a catalytic mechanism. Nitrone nucleophiles react with a variety of electrophiles,[20] and extremely hindered nucleophiles, including *t*-butoxide, react with **2**. In the present study, spontaneous reaction between **2** and a nitrone in the absence of an anionic initiator was never observed.

Propagation of the catalytic cycle via a deprotonated α-(trifluoromethyl)hydroxylamine (**28**) and subsequently formed pentavalent silane intermediate (**29**) can rationalize adduct formation. The nucleophilicity of **28** was demonstrated in an experiment where hydroxylamine **24*c*** was deprotonated by potassium hydride, and the resulting intermediate **28*c*** was used to initiate the addition of **2** to nitrone **12*f*** (Scheme 7). Formation of adduct **13*c*** (32% isolated yield) and hydroxylamine **24*f*** (4% isolated yield) supports a catalytic mechanism with a limited amount of turnover. The structure of putative pentavalent silanes **26** and **29** has not been determined, and the mechanism of trifluoromethanide transfer is not known. For related species invoked as intermediates in the trifluoromethylation of carbonyl compounds, different geometries at silicon have been proposed.[9,21]

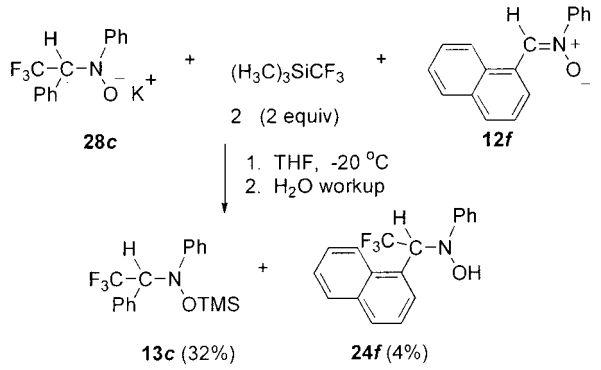
Formation of the bis(trifluoromethyl)amines (**15**) is more complex than initial adduct formation (Scheme 8).

(19) Rajagopal, S.; Spatola, A. F. *J. Org. Chem.* **1995**, *60*, 1347.

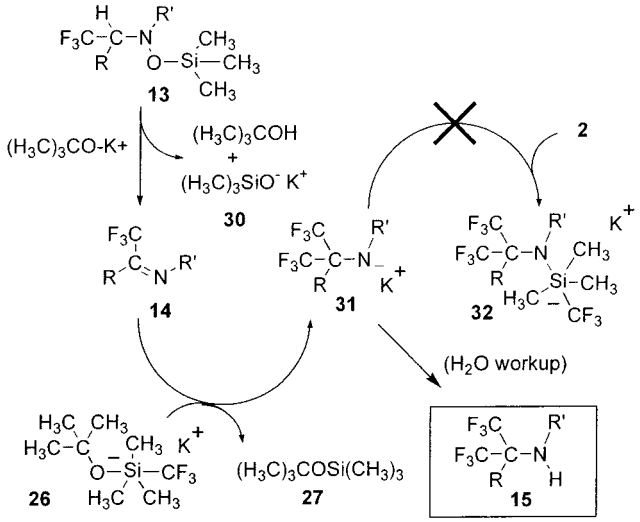
(20) Nitrones function as nucleophiles with the following common electrophiles. (a) Acetic anhydride: Tamagaki, S.; Kozuka, S.; Oae, S. *Tetrahedron* **1970**, *26*, 1795. (b) Acetyl chloride: Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070. (c) Tosyl chloride: Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764.

(21) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179.

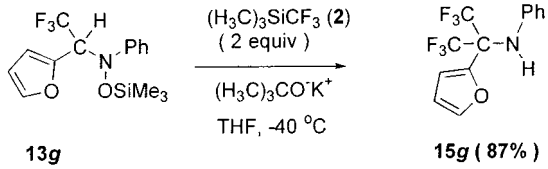
Scheme 7



Scheme 8



Scheme 9



Elimination of the silyloxy group (**30**) from adduct **13** explains the formation of α-(trifluoromethyl)imine **14**. Related elimination of silyloxy groups has been observed in the chemistry of the silyl nitronates used in 1,3-dipolar cycloadditions.[22] The α-(trifluoromethyl)imines (**14**) can be isolated from nitrone/**2** reactions, although yields vary and higher temperatures are required.[13] Resubmission of adduct **13*g*** to the trifluoromethylation conditions (Scheme 9) cleanly produced bis(trifluoromethyl)amine **15*g*** as the single major product, providing evidence for the sequential formation of the mono- and bis(CF_3) products.

As shown in Scheme 8, an α,α-bis(trifluoromethyl)-amide anion **31** should be formed when **2** reacts with imine **14**. Comparable rates of initial adduct formation and elimination result in a "steady-state" concentration of **13** (Figure 1). An attempt to use amide anion **31*e*** to initiate trifluoromethylation via **2** failed, and this provided evidence against propagation by pentavalent silane (**32**). In addition, formation of anion **31*e*** with chlorotrimethylsilane at −20 °C did not produce detectable (GC) levels of the silylated amine. Anion **31** may be protonated directly by the aqueous workup or by another proton source.

Conclusion

The addition of **2** to nitrones in the presence of an alkoxide initiator provides a direct route to the formation of new trifluoromethylated amine derivatives. α-(Trifluoromethyl)hydroxylamines, protected as *O*-trimethylsilyl, can be formed in good yields from a variety of α,*N*-diaryl nitrones, but α-alkyl and *N*-alkyl nitrones fail to react. The use of an *β*,*γ*-unsaturated nitrone in the trifluoromethylation procedure works satisfactorily, and catalytic hydrogenation of the double bond affords a **2**/adduct with an alkyl group bound to the α-carbon of the protected hydroxylamine. Certain diaryl nitrones, specifically those with strong electron-withdrawing groups on the α-aryl group or heterocyclic α-aryl groups, generate α,α-bis(trifluoromethyl)amines directly. A complex series of catalytic cycles has been proposed to rationalize the formation of both of the observed products.

Simple and efficient procedures for selective deprotection of the protected α-(trifluoromethyl)hydroxylamines have been developed. Trifluoromethylated hydroxylamines or free amines can be obtained in high yield. The methods described here offer practical alternatives to direct trifluoromethylation of imines[6e,f,12] because the yields for trifluoromethylation of nitrones are high and expensive or esoteric reagents are not required. In addition, the silylated hydroxylamine products are relatively stable and can serve as intermediates in a variety of subsequent synthetic transformations. The nitrone/**2** reactions presented here should complement other methods[4,23,24] for the preparation of α-CF_3 amines.

Experimental Section

Anhydrous tetrahydrofuran was distilled from sodium/benzophenone under inert atmosphere (N_2 or Ar). The (trifluoromethyl)trimethylsilane ($TMSCF_3$, **2**) was prepared using previously reported methods.[25] Potassium *t*-butoxide was dried under vacuum (<1 mmHg) for 1 h before use. Preparative chromatography employed 230−400 mesh silica gel, and the TLC plates were visualized using UV light ($\lambda = 254$ nm). NMR spectra were obtained in chloroform-*d*. ^{1}H NMR spectra were recorded at 400 MHz with chemical shifts referenced to residual chloroform (δ 7.26 ppm) or tetramethylsilane (δ 0.00 ppm). ^{13}C NMR spectra were recorded at 100 MHz with chemical shifts referenced to the solvent triplet (δ 77.0 ppm). Multiplicities for ^{13}C resonances were determined by DEPT135 experiments. Melting points are uncorrected.

Representative Procedure for the Addition of $TMSCF_3$ (2) to Nitrones—Preparation of 13*c*. An oven-dried, 100-mL, round-bottomed flask containing a magnetic stir bar was sealed with a septum, and dry nitrogen atmosphere was introduced. The vacuum-dried nitrone **12*c*** (1.79 g, 10.0 mmol) was added as a solid followed by addition of anhydrous

(22) (a) Torssell, K. B. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (b) Dehaen, W.; Hassner, A. *Tetrahedron Lett.* **1990**, *31*, 743. (c) Kim, B. H.; Lee, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1359. (c) Stack, J. A.; Heffner, T. A.; Geib, S. J.; Curran, D. P. *Tetrahedron* **1993**, *49*, 995.

(23) Soloshonok, V. A.; Ono, T. *J. Org. Chem*. **1997**, *62*, 3030.

(24) Amouri, H.; Begue, J.-P.; Chennoufi, A.; Bonnet-Delphon, D.; Gruselle, M.; Malezieux, B. *Org. Lett*. **2000**, *2*, 807.

(25) (a)Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S. *Org. Synth*. **1995**, *72*, 232. (b) Nelson, D. W.; O'Reilly, N. J.; Speier, J.; Gassman, P. G. *J. Org. Chem*. **1994**, *59*, 8157. Due to difficulties in obtaining bromotrifluoromethane, iodotrifluoromethane was used.

tetrahydrofuran (50 mL) via cannula. Silane **2** (2.84 g, 2.95 mL, 20.0 mmol) was added via syringe. A balloon containing anhydrous N_2(g) was attached, and the flask was cooled to −20 °C for 15 min in a cryogenic bath. A slurry of anhydrous potassium *t*-butoxide in THF (∼0.1 M) was prepared, and aliquots (∼50−100 μL) of the slurry were added to the reaction mixture at ∼15 min intervals. The reaction mixture turned yellow upon addition of the initiator. The reaction was monitored by TLC (silica gel/CH_2Cl_2: nitrone $R_f = 0.2$; product $R_f = 0.9$), and alkoxide addition was continued until the nitrone was consumed (∼48 h). The brown reaction mixture was poured into a separatory funnel containing distilled water and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a yellow oil. The product was purified by flash chromatography (silica gel/2% EtOAc in hexanes: product $R_f = 0.3$) to give a clear, colorless oil that crystallized upon standing in the refrigerator.

***O*-Trimethylsilyl Phenyl[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (13*c*):** mp 32−33 °C; ^{1}H NMR δ 7.33−7.29 (m, 1H), 7.25−7.15 (m, 6H), 7.03−6.97 (m, 3H), 4.56 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 0.06 (s, 9H); ^{13}C NMR δ 151.9 (s), 131.1 (d), 129.4 (s), 128.8 (d), 128.3 (d), 127.7 (d), 124.8 (q, $^1J_{C-F} =$ 280 Hz), 124.6 (d), 120.9 (d), 75.3 (dq, $^2J_{C-F} = 29$ Hz), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3066, 3035, 2962, 1597, 1489, 1257, 1164. Anal. Calcd for $C_{17}H_{20}F_3NOSi$: C, 60.15; H, 5.94; N, 4.13. Found: C, 60.03; H, 5.95; N, 4.12.

***O*-Trimethylsilyl Phenyl[2-(2-[4-methoxyphenyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*a*):** chromatography, silica gel/8% EtOAc in hexanes (product $R_f = 0.4$); mp 42−44 °C; ^{1}H NMR δ 7.19−7.15 (m, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.04−6.98 (m, 3H), 6.75 (d, $J = 8.7$ Hz, 2H), 4.50 (q, $^3J_{H-F} = 8.3$ Hz, 1H), 3.77 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 159.9 (s), 152.0 (s), 132.3(d), 128.3 (d), 124.9 (q, $^1J_{C-F} = 280$ Hz), 124.6 (d), 121.5 (s), 120.9 (d), 113.0 (d), 74.8 (dq, $^2J_{C-F} = 29$ Hz), 55.0 (q), −0.5 (q); IR (melt, NaCl plate, cm^{-1}) 3006, 2960, 1612, 1514, 1252, 1182, 1036. Anal. Calcd for $C_{18}H_{22}F_3NO_2Si$: C, 58.52; H, 6.00; N, 3.79. Found: C, 58.22; H, 6.07; N, 4.02.

***O*-Trimethylsilyl Phenyl[2-(2-[2-methoxyphenyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*b*):** chromatography, silica gel/4% EtOAc in hexanes (product $R_f = 0.3$); liquid at room temperature; ^{1}H NMR δ 7.85 (d, $J = 7.6$ Hz, 1H), 7.32 (ddd, $J = 8.1$, 7.5, and 2.0 Hz, 1H), 7.22−7.18 (m, 2H), 7.10−7.08 (m, 2H), 7.04−7.00 (m, 2H), 6.73 (dd, $J = 8.0$ and 0.8 Hz, 1H), 5.56 (q, $^3J_{H-F} = 8.8$ Hz, 1H), 3.34 (s, 3H), 0.12 (s, 9H); ^{13}C NMR δ 157.7 (s), 152.4 (s), 132.0 (d), 129.9 (d), 127.8 (d), 125.2 (q, $^1J_{C-F} = 281$ Hz), 124.1(d), 120.6 (d), 119.8 (d), 118.4 (s), 110.5 (d), 65.0 (dq, $^2J_{C-F} = 29$ Hz), 55.4 (q), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3062, 2962, 1601, 1489, 1250, 1161. Anal. Calcd for $C_{18}H_{22}F_3NO_2Si$: C, 58.52; H, 6.00; N, 3.79. Found: C, 58.16; H, 6.02; N, 3.91.

***O*-Trimethylsilyl Phenyl[2-(2-[4-chlorophenyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*d*):** chromatography, silica gel/4% EtOAc in hexanes (product $R_f = 0.4$); liquid at room temperature; ^{1}H NMR δ 7.23−7.16 (m, 2H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.05−7.01 (m, 1H), 6.98−6.94 (m, 2H), 4.53 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 0.07 (s, 9H); ^{13}C NMR δ 151.6 (s), 135.0 (s), 132.3 (d), 128.4 (d), 127.9 (d), 127.6 (s), 124.8 (d), 124.5 (q, $^1J_{C-F} = 280$ Hz), 120.8 (d), 74.7 (dq, $^2J_{C-F} = 29$ Hz), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3066, 2962, 1597, 1489, 1257, 1169. Anal. Calcd for $C_{17}H_{19}ClF_3NOSi$: C, 54.61; H, 5.12; N, 3.75. Found: C, 54.41; H, 5.10; N, 3.66.

***O*-Trimethylsilyl Phenyl[2-(2-[4-nitrophenyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*e*):** liquid at room temperature; chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.2$); ^{1}H NMR δ 8.09 (d, $J = 8.8$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.22−7.17 (m, 2H), 7.07−7.03 (m, 1H), 6.97−6.95 (m, 2H), 4.67 (q, $^3J_{H-F} = 8.0$ Hz, 1H), 0.08 (s, 9H); ^{13}C NMR δ 151.2 (s), 148.2 (s), 136.0 (s), 132.0 (d), 128.6 (d), 125.2 (d), 124.1 (q, $^1J_{C-F} = 280$ Hz), 122.7 (d), 120.5 (d), 74.6 (dq, $^2J_{C-F} = 29$ Hz), −0.6 (q).

***O*-Trimethylsilyl Phenyl[2-(2-[1-naphthyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*f*):** chromatography, silica gel/2% EtOAc in hexanes (product $R_f = 0.3$); liquid at room temperature; ^{1}H NMR δ 7.96 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.51−7.47 (m, 2H), 7.38−7.34 (m, 1H), 7.30−7.26 (m, 1H), 7.09−7.03 (m, 4H), 6.95−6.90 (m, 1H), 5.61 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 0.03 (s, 9H); ^{13}C NMR δ 151.9 (s), 133.4 (s), 132.6 (s), 129.5 (d), 128.8 (d), 128.3 (d), 127.9 (d), 127.1 (s), 126.2 (d), 125.2 (q, $^1J_{C-F} = 282$ Hz) 125.2 (d), 124.9 (d), 124.6 (d), 122.4 (d), 121.3 (d), 68.4 (dq, $^2J_{C-F} = 28$ Hz), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3059, 2958, 1597, 1489, 1253, 1161, 1126. Anal. Calcd for $C_{21}H_{22}F_3NOSi$: C, 64.76; H, 5.69; N, 3.60. Found: C, 64.17; H, 5.66; N, 3.67.

***O*-Trimethylsilyl Phenyl[2-(2-[2-furyl]-1,1,1-trifluoroethyl)]hydroxylamine (13*g*):** chromatography, silica gel/3% EtOAc in hexanes (product $R_f = 0.4$); liquid at room temperature; ^{1}H NMR δ 7.29 (dd, $J = 1.6$ and 0.8 Hz, 1H), 7.24−7.20 (m, 2H), 7.09−7.03 (m, 3H), 6.50 (d, $J = 3.6$ Hz, 1H), 6.34 (dd, $J = 3.6$ and 2.0 Hz, 1H), 4.79 (q, $^3J_{H-F} = 8.0$ Hz, 1H), 0.05 (s, 9H); ^{13}C NMR δ 151.7 (s), 143.9 (s), 142.7 (d), 128.4 (d), 124.8 (d), 123.7 (q, $^1J_{C-F} = 280$ Hz), 120.4 (d), 112.6 (d), 110.4 (d), 69.2 (dq, $^2J_{C-F} = 29$ Hz), −0.6 (q); IR (neat, NaCl plate, cm^{-1}) 3066, 3032, 2962, 1597, 1493, 1257, 1169. Anal. Calcd for $C_{15}H_{18}F_3NO_2Si$: C, 54.70; H, 5.51; N, 4.25. Found: C, 54.59; H, 5.50; N, 4.20.

***O*-Trimethylsilyl (4-Methoxyphenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (13*j*):** chromatography, silica gel/4% EtOAc in hexanes (product $R_f = 0.3$); liquid at room temperature; ^{1}H NMR δ 7.33−7.29 (m, 1H), 7.26−7.18 (m, 4H), 6.90 (d, $J = 9.2$ Hz, 2H), 6.67 (d, $J = 9.2$ Hz, 2H), 4.44 (q, $^3J_{H-F} = 8.0$ Hz, 1H), 3.74 (s, 3H), 0.04 (s, 9H); ^{13}C NMR δ 157.0 (s), 144.7 (s), 131.1 (d), 129.8 (s), 128.7 (d), 127.6 (d), 124.7 (q, $^1J_{C-F} = 280$ Hz), 123.2 (d), 113.3 (d), 75.4 (dq, $^2J_{C-F} = 28$ Hz), 55.2 (q), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3035, 2959, 1504, 1250, 1165. Anal. Calcd for $C_{18}H_{22}F_3NO_2Si$: C, 58.52; H, 6.00; N, 3.79. Found: C, 57.89; H, 5.89; N, 3.61.

***O*-Trimethylsilyl (4-Methylphenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (13*k*):** chromatography, silica gel/2% EtOAc in hexanes (product $R_f = 0.3$); liquid at room temperature; ^{1}H NMR δ 7.34−7.30 (m, 1H), 7.26−7.18 (m, 4H), 6.96 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.0$ Hz, 2H), 4.52 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 2.26 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 149.4 (s), 134.2 (s), 131.1 (d), 129.6 (s), 128.9 (d), 128.8 (d), 127.6 (d), 124.8 (q, $^1J_{C-F} = 280$ Hz), 121.1 (d), 75.4 (dq, $^2J_{C-F} = 28$ Hz), 20.8 (q), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3032, 2962, 1506, 1257, 1161, 1122. Anal. Calcd for $C_{18}H_{22}F_3NOSi$: C, 61.17; H, 6.27; N, 3.96. Found: C, 61.21; H, 6.34; N, 3.95.

***O*-Trimethylsilyl (4-Chlorophenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (13*l*):** chromatography, silica gel/4%EtOAc in hexanes (product $R_f = 0.4$); mp 51−52 °C; ^{1}H NMR δ 7.35−7.31 (m, 1H), 7.27−7.23 (m, 2H), 7.18 (d, $J = 7.6$ Hz, 2H), 7.13 (d, $J = 9.0$ Hz, 2H), 6.92 (d, $J = 9.0$ Hz, 2H), 4.50 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 0.06 (s, 9H); ^{13}C NMR δ 150.5 (s), 131.0 (d), 129.9 (s), 129.0 (d), 128.4 (d), 127.8 (d), 124.6 (q, $^1J_{C-F} = 281$ Hz), 122.4 (d), 75.2 (dq, $^2J_{C-F} = 28.6$ Hz), −0.5 (q);[26] IR (neat, NaCl plate, cm^{-1}) 3035, 2962, 1485, 1369, 1254, 1169, 1126. Anal. Calcd for $C_{17}H_{19}ClF_3NOSi$: C, 54.61; H, 5.12; N, 3.75. Found: C, 54.48; H, 5.11; N, 3.52.

***O*-Trimethylsilyl [3-(Trifluoromethyl)phenyl][2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (13*m*):** chromatography, silica gel/2% EtOAc in hexanes (product $R_f = 0.3$); mp 28−30 °C; ^{1}H NMR δ 7.36−7.16 (m, 9H), 4.58 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 0.07 (s, 9H); ^{13}C NMR δ 152.5 (s), 130.9 (d), 130.9 (q, $^2J_{C-F} = 32$ Hz), 129.2 (d), 128.9 (d), 127.9 (d), 124.6 (q, $^1J_{C-F} = 280$ Hz), 124.1 (d), 123.8 (q, $^1J_{C-F} = 271$ Hz), 121.3 (dq, $^3J_{C-F} = 4$ Hz), 117.5 (dq, $^3J_{C-F} = 4$ Hz), 75.2 (dq, $^2J_{C-F} = 29$ Hz), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3035, 2962, 1331, 1169, 1126. Anal. Calcd for $C_{18}H_{19}F_6NOSi$: C, 53.06; H, 4.70; N, 3.44. Found: C, 53.38; H, 4.81; N, 3.43.

***O*-Trimethylsilyl Phenyl[3-(*trans*-1-phenyl-4,4,4-trifluorobut-1-enyl)]hydroxylamine (21):** chromatography, silica gel/4% EtOAc in hexanes (product $R_f = 0.4$); mp 36−37 °C; ^{1}H NMR δ 7.33−7.23 (m, 7H), 7.18−7.16 (m, 2H), 7.07−

(26) Accidental equivalence was observed for at least one resonance in the ^{13}C NMR spectrum. The spectra are included in the Supporting Information.

7.03 (m, 1H), 6.45 (dd, J = 16.2 and 9.0 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 4.08 (dq, $^3J_{H-F}$ = 8.2 and 8.0 Hz, 1H), 0.08 (s, 9H); ^{13}C NMR δ 152.1 (s), 138.3 (d), 136.0 (s), 128.5 (d), 128.4 (d), 128.3 (d), 126.8 (d), 124.5 (q, $^1J_{C-F}$ = 280 Hz), 124.4 (d), 120.5 (d), 116.9 (d), 74.0 (dq, $^2J_{C-F}$ = 29 Hz), −0.5 (q); IR (neat, NaCl plate, cm^{-1}) 3062, 3032, 2962, 1597, 1489, 1254. Anal. Calcd for $C_{19}H_{22}F_3NOSi$: C, 62.44; H, 6.07; N, 3.83. Found: C, 62.21; H, 6.14; N, 3.81.

Catalytic Hydrogenation of Adduct 21—Preparation of 23. To a 25-mL, round-bottomed flask, containing magnetic stir bar, were added nitrone **21** (365 mg, 1.00 mmol) and ethyl acetate (8 mL). The solution was sparged with nitrogen gas for 10 min. The palladium catalyst (35 mg, 10% Pd/C) was added, followed by the addition of ethyl acetate (2 mL). A balloon filled with hydrogen gas was attached, and the reaction mixture was stirred at room temperature. The reaction was monitored by ^{1}H NMR. After 4 h, the starting material was consumed. The catalyst was removed by filtration through a small plug of silica gel. The solvent was removed by rotary evaporation, and the product was purified by flash chromatography (silica gel/4% EtOAc in hexanes; product R_f = 0.4) to give 330 mg (91%) of a clear, colorless oil.

***O*-Trimethylsilyl Phenyl[2-(4-phenyl-1,1,1-trifluorobutyl)]hydroxylamine (23):** ^{1}H NMR δ 7.28−7.15 (m, 5H), 7.10−7.07 (m, 2H), 7.04−6.99 (m, 1H), 6.94 (d, J = 6.8 Hz, 2H), 3.67−3.57 (m, 1H), 2.71−2.63 (m, 1H), 2.60−2.51 (m, 1H), 2.54−2.36 (m, 1H), 2.05−1.96 (m, 1H), 0.12 (s, 9H); ^{13}C NMR δ 152.9 (s), 140.6 (s), 128.6 (d), 128.4 (d), 128.3 (d), 126.0 (d), 125.7 (q, $^1J_{C-F}$ = 281 Hz), 123.1 (d), 118.1 (d), 69.7 (dq, $^2J_{C-F}$ = 27 Hz), 32.4 (t), 25.2 (t), −0.3 (q); IR (neat, NaCl plate, cm^{-1}) 3028, 2962, 1597, 1489, 1257, 1122. Anal. Calcd for $C_{19}H_{24}F_3NOSi$: C, 62.10; H, 6.58; N, 3.81. Found: C, 62.16; H, 6.82; N, 3.76.

Representative Procedure for the Addition of TMSCF$_3$ (2) to Nitrones to form Bis(trifluoromethyl)amines—Preparation 15*g*. To a 100-mL, round-bottomed flask, containing a magnetic stir bar, was added nitrone **12*g*** (0.936 g, 5.00 mmol). The flask was sealed with a septum, and the atmosphere was displaced with dry N_2(g). Anhydrous THF (50 mL) was added via cannula. Silane **2** (2.21 mL, 2.13 g, 15.0 mmol) was added via syringe. A balloon containing dry N_2(g) was attached, and the reaction mixture was cooled to −25 to −30 °C in a low-temperature bath for 15 min. A slurry of potassium *t*-butoxide in anhydrous THF (∼0.1 M) was prepared, and small aliquots (50−100 μL) of the slurry were added to the reaction mixture at ∼15 min intervals. A brown color formed upon addition of the base. The reaction was monitored by TLC (silica gel/3% ethyl acetate in hexanes: nitrone R_f = 0, initial nitrone adduct R_f = 0.4, bis(trifluoromethyl)amine R_f = 0.3), and alkoxide addition was continued until both the nitrone and the initial adduct were completely converted. The reaction mixture was poured into a separatory funnel containing distilled water. The cloudy mixture was extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a yellow oil. The product was purified by flash chromatography (silica gel/3% ethyl acetate in hexanes) to give 1.22 g (82%) of a pale, yellow oil.

Product Distribution Study. The analysis of the competition between formation of the mono- and bistrifluoromethylated products (Figure 1) was performed as described above, but all quantities were scaled for use with 2.00 mmol of the nitrone. An internal standard (tetrahydronaphthalene, 2.00 mmol) was added, and the progress of the reaction was monitored by gas chromatography (HP-1 capillary column, 30 m, isothermal analysis at 100 °C). Aliquots (50 μL) of the *t*-butoxide slurry (5.00 mmol in 10 mL of anhydrous THF) were added at 5 min intervals over 5 h. Aliquots of the reaction mixture were removed via syringe at 15 min intervals. Each aliquot was quenched by addition to a mixture of 1:1 dichloromethane:water. The aqueous layer was separated before injection. Calibration curves for each of nitrone, the initial adduct, and the bis(trifluoromethyl)amine were prepared using samples obtained from preparative reactions.

Resubmission Experiment. To a 25-mL round-bottomed flask, containing a magnetic stir bar, was added adduct **13*g*** (329 mg, 1.00 mmol). The flask was sealed, and dry N_2(g) atmosphere was introduced. Anhydrous THF (10 mL) was added via cannula followed by addition of **2** (284 mg, 295 μL, 2.00 mmol) via syringe. A balloon containing N_2(g) was attached, and the flask was cooled to −40 °C for 15 min. A slurry of potassium *t*-butoxide (∼1 M in THF) was added to the reaction mixture at 15 min intervals, and the reaction was monitored by TLC. When the adduct was entirely consumed, the reaction mixture was quenched with water and extracted with dichloromethane. The combined extracts were dried (MgSO4), filtered, and concentrated by rotary evaporation. Amine **15*g*** was purified by flash chromatography (87% yield).

Phenyl[2-(2-[2-furyl]-1,1,1,3,3,3-hexafluoropropyl)]-amine (15*g*): liquid at room temperature; ^{1}H NMR δ 7.54 (dd, J = 1.8 and 0.6 Hz, 1H), 7.11−7.07 (m, 2H), 6.88 (m, 1H), 6.73 (dd, J = 3.4 and 0.6 Hz, 1H), 6.50 (dd, J = 3.2 and 1.6 Hz, 1H), 6.44−6.42 (m, 2H), 4.32 (br s, 1H); ^{13}C NMR δ 144.3 (d), 142.0 (s), 140.9 (s), 128.8 (d), 122.9 (q, $^1J_{C-F}$ = 290 Hz), 121.8 (d), 118.6 (d), 114.4 (d), 111.1 (d), 67.0 (sept, $^2J_{C-F}$ = 28 Hz); IR (neat, NaCl plate, cm^{-1}) 3421, 3062, 3032, 1604, 1500, 1250, 1203, 1157. Anal. Calcd for $C_{13}H_9F_6NO$: C, 50.50; H, 2.93; N, 4.53. Found: C, 50.34; H, 3.17; N, 5.04.

Phenyl[2-(2-[4-nitrophenyl]-1,1,1,3,3,3-hexafluoropropyl)]amine (15*f*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.3); yellow, crystalline solid; mp 180−182 °C; ^{1}H NMR δ 8.31 (d, J = 9.6 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.10−7.06 (m, 2H), 6.88−6.84 (m, 1H), 6.40 (d, J = 8.0 Hz, 2H), 4.54 (br s, 1H); ^{13}C NMR δ 148.9 (s), 141.1 (s), 134.9 (s), 130.5 (d), 128.9 (d), 123.7 (d), 123.1 (q, $^1J_{C-F}$ = 291 Hz), 121.2 (d), 117.3 (d), 70.0 (sept, $^2J_{C-F}$ = 27 Hz); IR (thin film, NaCl plate, cm^{-1}) 3406, 3055, 1523, 1350, 1242, 1180. Anal. Calcd for $C_{15}H_{10}F_6N_2O_2$: C, 49.46; H, 2.77; N, 7.69. Found: C, 49.38; H, 2.82; N, 7.66.

Phenyl[2-(2-[4-pyridyl]-1,1,1,3,3,3-hexafluoropropyl)]-amine (15*h*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.2); mp 144−146 °C; ^{1}H NMR δ 8.76−8.74 (m, 2H), 7.65 (d, J = 5.2 Hz, 2H), 7.09−7.05 (m, 2H), 6.87−6.85 (m, 1H), 6.42 (d, J = 8.0 Hz, 2H), 4.49 (br s, 1H); ^{13}C NMR δ 150.5 (d), 141.3 (s), 137.4 (s), 128.9 (d), 123.6 (d), 123.0 (q, $^1J_{C-F}$ = 288 Hz), 121.1 (d), 117.3 (d), 69.7 (sept, $^2J_{C-F}$ = 27 Hz); IR (thin film, NaCl plate, cm^{-1}) 3305, 3062, 2924, 1601, 1234, 1180. Anal. Calcd for $C_{14}H_{10}F_6N_2$: C, 52.51; H, 3.15; N, 8.75. Found: C, 52.73; H, 3.20; N, 8.75.

Phenyl[2-(2-[2-pyridyl]-1,1,1,3,3,3-hexafluoropropyl)]-amine (15*i*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.4); liquid at room temperature; ^{1}H NMR δ 8.78 (m, 1H), 7.78−7.77 (m, 2H), 7.46−7.40 (m, 1H), 7.14−7.09 (m, 2H), 6.90−6.86 (1H), 6.64 (d, J = 8.0 Hz, 2H), 5.33 (br s, 1H); ^{13}C NMR δ 148.8 (d), 148.6 (s), 142.1 (s), 136.9 (d), 128.7 (d), 125.0 (d), 124.7 (d), 123.3 (q, $^1J_{C-F}$ = 290 Hz), 121.4 (d), 119.1 (d), 70.3 (sept, $^2J_{C-F}$ = 28 Hz); IR (neat, NaCl plate, cm^{-1}) 3410, 3267, 3062, 1604, 1500, 1254. Anal. Calcd for $C_{14}H_{10}F_6N_2$: C, 52.51; H, 3.15%, N, 8.75. Found: C, 52.43; H, 3.19; N, 8.69.

Phenyl[2-(*trans*-3-[trifluoromethyl]-1-phenyl-4,4,4-trifluorobut-1-enyl)]amine (22): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.4); liquid at room temperature; ^{1}H NMR δ 7.42−7.34 (m, 5H), 7.20−7.16 (m, 2H), 7.06 (d, J = 16.8 Hz, 1H), 6.95−6.91 (m, 3H), 6.19 (d, J = 16.4 Hz, 1H), 4.22 (br s, 1H); ^{13}C NMR δ 141.9 (s), 139.2 (d), 135.1 (s), 129.3 (d), 128.9 (d), 128.8 (d), 127.1 (d), 123.6 (q, $^1J_{C-F}$ = 288 Hz), 121.8 (d), 119.8 (d), 115.6 (d), 67.5 (sept, $^2J_{C-F}$ = 27 Hz); IR (neat, NaCl plate, cm^{-1}) 3417, 3062, 3032, 2927, 1601, 1500, 1254, 1165. Anal. Calcd for $C_{17}H_{13}F_6N$: C, 59.13; H, 3.79; N, 4.06. Found: C, 59.44; H, 3.98; N, 3.94.

Representative Procedure for Acidic Deprotection of α-CF$_3$ *O*-Trimethylsilyl Hydroxylamine Derivatives—Preparation of 24*c*. To a 50-mL, round-bottomed flask containing a magnetic stir bar were added adduct **13*c*** (339 mg, 1.00 mmol), reagent grade tetrahydrofuran (10 mL), and 1 N HCl (10 mL). The flask was stoppered, and the biphasic reaction was stirred vigorously at room temperature for 24 h. A light yellow color formed in the reaction mixture. The

reaction was monitored by TLC (silica gel/5% ethyl acetate in hexanes; product $R_f = 0.3$). The reaction mixture was poured into a separatory funnel containing a saturated sodium bicarbonate solution. When gas evolution ceased, 2 N KOH-(aq) was added to adjust the pH to ~10. The aqueous mixture was extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a yellow oil. The product was purified by flash chromatography (TLC conditions) to give 249 mg (93%) of a white powdery solid. Recrystallization from hexanes afforded an analytically pure sample.

Phenyl[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (24*c*): mp 80−81 °C; ^{1}H NMR δ 7.36−7.23 (m, 7H), 7.08−6.99 (m, 3H), 5.25 (s, 1H), 4.89 (q, $^3J_{H-F} = 9.2$ Hz, 1H); ^{13}C NMR δ 150.4 (s), 130.2 (d), 129.3(s), 129.0 (d), 128.8 (d), 128.1 (d), 125.0 (q, $^1J_{C-F} = 281$ Hz), 123.5 (d), 117.9 (d), 72.7 (dq, $^2J_{C-F} = 29$ Hz); IR (KBr pellet, cm^{-1}) 3356, 3062, 3032, 1597, 1489, 1369, 1281, 1180. Anal. Calcd for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53; N, 5.24. Found: C, 62.83; H, 4.55%, N, 5.12.

Phenyl[2-(2-[4-methoxyphenyl]-1,1,1-trifluoroethyl)]hydroxylamine (24*a*): chromatography, silica gel/5%EtOAc in hexanes (product $R_f = 0.2$); liquid at room temperature; ^{1}H NMR δ 7.28−7.23 (m, 2H), 7.22 (d, $J = 9.2$ Hz, 2H), 7.06−6.99 (m, 3H), 6.81 (d, $J = 8.8$ Hz, 2H), 5.26 (s, 1H), 4.83 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 3.78 (s, 3H); ^{13}C NMR δ 159.9 (s), 150.5 (s), 131.5 (d), 128.7 (d), 125.1 (q, $^1J_{C-F} = 281$ Hz), 123.4 (d), 121.3 (s), 117.9 (d), 113.5 (d), 72.2 (dq, $^2J_{C-F} = 29$ Hz), 55.1 (q); IR (KBr pellet, cm^{-1}) 3421, 3035, 2939, 2843, 1612, 1516, 1250, 1165, 1126. Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 60.60; H, 4.75; N, 4.71. Found: C, 60.38; H, 4.87; N, 4.60.

Phenyl[2-(2-[2-methoxyphenyl]-1,1,1-trifluoroethyl)]hydroxylamine (24*b*): chromatography, silica gel/5%EtOAc in hexanes (product $R_f = 0.2$); recrystallized from hexanes; mp 91−93 °C; ^{1}H NMR δ 7.78 (d, $J = 7.6$ Hz, 1H), 7.32−7.20 (m, 3H), 7.09−7.07 (m, 2H), 7.00−6.93 (m, 2H), 6.77 (d, $J = 8.4$ Hz, 1H), 5.71 (q, $^3J_{H-F} = 8.8$ Hz, 1H), 5.25 (s, 1H), 3.45 (s, 3H); ^{13}C NMR δ 157.6 (s), 150.8 (s), 131.3 (d), 130.2 (d), 128.3 (d), 125.4 (q, $^1J_{C-F} = 281$ Hz), 122.9 (d), 120.3 (d), 118.5 (s), 117.4 (d), 110.7 (d), 63.2 (dq, $^2J_{C-F} = 29$ Hz), 55.4 (q); IR (thin film, NaCl plate, cm^{-1}) 3309, 3028, 2976, 1601, 1493, 1250, 1126. Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 60.60; H, 4.75; N, 4.71. Found: C, 60.59; H, 4.67; N, 4.59.

Phenyl[2-(2-[4-chlorophenyl]-1,1,1-trifluoroethyl)]hydroxylamine (24*d*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.2$); recrystallized from hexanes; mp 90 °C; ^{1}H NMR δ 7.28−7.20 (m, 6H), 7.05−7.00 (m, 3H), 5.28 (s, 1H), 4.83 (q, $^3J_{H-F} = 8.0$ Hz, 1H); ^{13}C NMR δ 150.2 (s), 135.3 (s), 131.6 (d), 128.9 (d), 128.4 (d), 127.7 (s), 124.8 (q, $^1J_{C-F} = 281$ Hz), 123.8 (d), 118.0 (d), 72.3 (dq, $^2J_{C-F} = 29$ Hz); IR (NaCl, thin film, cm^{-1}) 3344, 3035, 1593, 1493, 1284, 1122. Anal. Calcd for $C_{14}H_{11}ClF_3NO$: C, 55.74; H, 3.68; N, 4.64. Found: C, 55.70; H, 3.76; N, 4.58.

Phenyl[2-(2-[1-naphthyl]-1,1,1-trifluoroethyl)]hydroxylamine (24*f*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.2$); recrystallized from hexanes; mp 124−126 °C; ^{1}H NMR δ 8.01 (d, $J = 7.2$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.49 (dd, $J = 7.8$ and 7.8 Hz, 1H), 7.39 (ddd, $J = 7.9$, 7.4, and 1.2 Hz, 1H), 7.31 (ddd, $J = 8.0$, 7.8, and 1.6 Hz, 1H), 7.18−7.14 (m, 2H), 7.09 (dd, $J = 8.8$ and 1.2 Hz, 2H), 6.96−6.92 (m, 1H), 5.82 (q, $^3J_{H-F} = 8.1$ Hz, 1H), 5.41 (s, 1H); ^{13}C NMR δ 150.4 (s), 133.6 (s), 132.2 (s) 129.8 (d), 129.0 (d), 128.9 (d), 128.8 (d), 126.6 (d), 125.9 (s), 125.5 (d), 125.4 (q, $^1J_{C-F} = 282$ Hz), 124.9 (d), 123.7 (d), 122.4 (d), 118.1 (d), 66.7 (dq, $^2J_{C-F} = 28$ Hz); IR (thin film, NaCl plate, cm^{-1}) 3317, 3062, 1597, 1485, 1277, 1153, 1126. Anal. Calcd for $C_{18}H_{14}F_3NO$: C, 68.13; H, 4.45; N, 4.41. Found: C, 67.74; H, 4.38; N, 4.27.

(4-Methylphenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (24*k*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.3$); recrystallized from hexanes; mp 59−60 °C; ^{1}H NMR δ 7.36−7.25 (m, 5H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 5.28 (s, 1H), 4.80 (q, $^3J_{H-F} = 8.4$ Hz, 1H), 2.27 (s, 3H); ^{13}C NMR δ 148.0 (s), 133.2 (s), 130.3 (d), 129.4 (s), 129.2 (d), 128.9 (d), 128.0 (d), 125.0 (q, $^1J_{C-F} = 281$ Hz), 118.4 (d), 73.0 (dq, $^2J_{C-F} = 29$ Hz), 20.6 (q); IR (thin film, NaCl plate, cm^{-1}) 3313, 3032, 2923, 1508, 1273, 1160, 1122. Anal. Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 64.02; H, 5.03; N, 4.90.

(4-Chlorophenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (24*l*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.2$); recrystallized from hexanes; mp 80−81 °C; ^{1}H NMR δ 7.37−7.27 (m, 5H), 7.20 (d, $J = 9.2$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 5.34 (s, 1H), 4.81 (q, $^3J_{H-F} = 8.3$ Hz, 1H); ^{13}C NMR δ 149.0 (s), 130.2 (d), 129.2 (d), 129.0 (s), 128.8 (d), 128.2 (d), 124.8 ($^1J_{C-F} = 280$ Hz), 119.4 (d), 72.9 (dq, $^2J_{C-F} = 29$ Hz);[26] IR (thin film, NaCl plate, cm^{-1}) 3305, 3066, 2924, 1485, 1277, 1172, 1122. Anal. Calcd for $C_{14}H_{11}ClF_3NO$: C, 55.74; H, 3.68; N, 4.64. Found: C, 55.67; H, 3.67; N, 4.61.

[3-(Trifluoromethyl)phenyl][2-(2-phenyl-1,1,1-trifluoroethyl)]hydroxylamine (24*m*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.3$); recrystallized from hexanes; mp 38 °C; ^{1}H NMR δ 7.39−7.21 (m, 9H), 5.43 (s, 1H), 4.92 (q, $^3J_{H-F} = 8.0$ Hz, 1H); ^{13}C NMR δ 150.8 (s), 131.4 (q, $^2J_{C-F} = 32$ Hz), 130.2 (d), 129.4 (d), 128.9 (s), 128.3 (d), 124.8 (q, $^1J_{C-F} = 281$ Hz), 123.9 (q, $^1J_{C-F} = 271$ Hz), 120.8 (d), 120.7 (d), 120.1 (dq, $^3J_{C-F} = 4$ Hz), 114.6 (dq, $^3J_{C-F} = 4$ Hz), 72.5 (dq, $^2J_{C-F} = 29$ Hz); IR (melt, NaCl plate, cm^{-1}) 3506, 3070, 3035, 2979, 1454, 1331, 1277, 1126. Anal. Calcd for $C_{15}H_{11}F_6NO$: C, 53.74; H, 3.31%, N, 4.18. Found: C, 53.49; H, 3.21%, N, 4.00.

Phenyl[3-(*trans*-1-phenyl-4,4,4-trifluorobut-1-enyl)]hydroxylamine (24*n*): chromatography, silica gel/5% EtOAc in hexanes (product $R_f = 0.2$); recrystallized from hexanes; mp 80−82 °C; ^{1}H NMR δ 7.35−7.26 (m, 7H), 7.17−7.14 (m, 2H), 7.05−7.01 (m, 1H), 6.50−6.40 (m, 2H), 5.25 (s, 1H), 4.37 (dq, $J = 8.0$, $^3J_{H-F} = 8.0$ Hz, 1H); ^{13}C NMR δ 150.5 (s), 138.5 (d), 135.6 (s), 128.8 (d), 128.5 (d), 128.4 (d), 126.8 (d), 124.9 (q, $^1J_{C-F} = 284$ Hz), 123.5 (d), 117.8 (d), 116.1 (d), 71.7 (dq, $^2J_{C-F} = 29$ Hz); IR (thin film, NaCl plate, cm^{-1}) 3471, 3082, 3055, 3028, 2962, 1593, 1485, 1269. Anal. Calcd for $C_{16}H_{14}F_3NO$: C, 65.52; H, 4.81; N, 4.78. Found: C, 65.84; H, 4.98; N, 4.68.

Representative Procedure for Formation of the α-CF_3 Amines by Transfer Hydrogenation−Preparation of 25*c*. To a 25-mL, round-bottomed flask, containing a magnetic stir bar, was added adduct **13*c*** (679 mg, 2.00 mmol). Reagent grade methanol was added to the reaction mixture, followed by addition of 10% Pd/C (50 mg). Ammonium formate (630 mg, 10.0 mmol) was added to the reaction mixture. The flask was stoppered, and the reaction mixture was stirred vigorously at room temperature. The reaction was monitored by TLC (silica gel/5% ethyl acetate in hexanes: adduct $R_f = 0.4$, amine $R_f = 0.3$). After 4 h, the starting material was consumed. The catalyst was removed by filtration through a plug of cotton wool, and the solvent was removed by rotary evaporation. The crude product, which contained unreacted ammonium formate, was purified by flash chromatography (TLC conditions) to give 234 mg (93%) of a clear colorless oil.

Phenyl[2-(2-phenyl-1,1,1-trifluoroethyl)] Amine (25*c*): liquid at room temperature; ^{1}H NMR δ 7.46−7.44 (m, 2H), 7.41−7.35 (m, 3H), 7.18−7.13 (m, 2H), 6.79−6.74 (m, 1H), 6.65−6.62 (m, 2H), 4.91 (dq, $^3J_{H-F} = 7.2$ and 7.2 Hz, 1H), 4.32 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR δ 145.5 (s), 134.1 (s), 129.3 (d), 129.1 (d), 128.9 (d), 127.9 (d), 125.1 (q, $^1J_{C-F} = 281$ Hz), 119.2 (d), 113.9 (d), 60.6 (dq, $^2J_{C-F} = 30$ Hz); IR (neat, NaCl plate, cm^{-1}) 3417, 3059, 1604, 1504, 1250, 1172, 1122. Anal. Calcd for $C_{14}H_{12}F_3N$: C, 66.93; H, 4.81; N, 5.57. Found: C, 66.84; H, 4.77; N, 5.39.

Phenyl[2-(2-[4-methoxyphenyl]-1,1,1-trifluoroethyl)] Amine (25*a*): chromatography, silica gel/5% ethyl acetate in hexanes (product $R_f = 0.2$); liquid at room temperature; ^{1}H NMR δ 7.36 (d, $J = 8.4$ Hz, 2H), 7.17−7.13 (m, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.78−6.74 (m, 1H), 6.64−6.62 (m, 2H), 4.86 (q, $^3J_{H-F} = 7.3$ Hz, 1H), 4.27 (br s, 1H), 3.79 (s, 3H); ^{13}C NMR δ 160.1 (s), 145.6 (s), 129.3 (d), 129.1 (d), 126.0 (s), 125.1 (q, $^1J_{C-F} = 280$ Hz), 119.1 (d), 114.3 (d), 113.9 (d), 60.0 (dq, $^2J_{C-F} = 30$ Hz), 55.3 (q); IR (neat, NaCl plate, cm^{-1}) 3410, 3008, 2939, 1608, 1511, 1307, 1254, 1172. Anal. Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 63.66; H, 5.00; N, 4.85.

Phenyl[2-(2-[2-methoxyphenyl]-1,1,1-trifluoroethyl)] Amine (25*b*): chromatography, silica gel/5% ethyl acetate in

hexanes (product R_f = 0.3); liquid at room temperature; ^{1}H NMR δ 7.38 (d, J = 7.2 Hz, 1H), 7.31 (ddd, J = 8.3, 7.4, and 1.8 Hz, 1H), 7.17−7.13 (m, 2H), 6.98−6.94 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.76−6.72 (m, 1H), 6.67−6.65 (m, 2H), 5.55 (br s, 1H), 4.48 (br s, 1H), 3.89 (s, 3H); ^{13}C NMR δ 157.5 (s), 145.8 (s), 130.1 (d), 129.3 (d), 128.1 (d), 125.4 (q, $^1J_{C-F}$ = 281 Hz), 122.6 (s), 121.0 (d), 118.9 (d), 113.7 (d), 111.1 (d), 55.8 (q), 53.6 (dq, $^2J_{C-F}$ = 30 Hz); IR (neat, NaCl plate, cm^{-1}) 3410, 3008, 2939, 1608, 1509, 1307. Anal. Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 63.72; H, 5.07; N, 4.80.

Phenyl[2-(2-[1-naphthyl]-1,1,1-trifluoroethyl)] Amine (25*f*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.3); liquid at room temperature; ^{1}H NMR δ 8.11 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.2 Hz, 1H), 7.63−7.48 (m, 3H), 7.16−7.12 (m, 2H), 6.78−6.74 (m, 1H), 6.65−6.62 (m, 2H), 5.84 (q, $^3J_{H-F}$ = 6.8 Hz, 1H), 4.49 (br s, 1H); ^{13}C NMR δ 145.5 (s), 133.9 (s), 131.6 (s), 129.9 (s), 129.7 (d), 129.4 (d), 129.2 (d), 127.0 (d), 125.9 (d), 125.6 (q, $^1J_{C-F}$ = 281 Hz), 125.3 (d), 125.2 (d), 122.2 (d), 119.2 (d), 113.6 (d), 55.6 (dq, $^2J_{C-F}$ = 30 Hz); IR (neat, NaCl plate, cm^{-1}) 3413, 3055, 1604, 1508, 1250, 1169, 1122. Anal. Calcd for $C_{18}H_{14}F_3N$: C, 71.75; H, 4.68; N, 4.65. Found: C, 71.47; H, 4.78; N, 4.55.

(4-Methoxyphenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)] Amine (25*j*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.2); liquid at room temperature; ^{1}H NMR δ 7.45−7.36 (m, 5H), 6.74 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 4.80 (q, $^3J_{H-F}$ = 7.2 Hz, 1H), 4.07 (br s, 1H), 3.71 (s, 3H); ^{13}C NMR δ 153.3 (s), 139.4 (s), 134.3 (s), 129.0 (d), 128.8 (d), 127.9 (d), 125.1 (q, $^1J_{C-F}$ = 281 Hz), 115.7 (d), 114.8 (d), 61.7 (dq, $^2J_{C-F}$ = 29 Hz), 55.6 (q); IR (neat, NaCl plate, cm^{-1}) 3390, 3035, 2939, 1515, 1246, 1176, 1126. Anal. Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 63.59; H, 5.15; N, 4.90.

(4-Methylphenyl)[2-(2-phenyl-1,1,1-trifluoroethyl)]Amine (25*k*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.3); liquid room temperature; ^{1}H NMR δ 7.47−7.45 (m, 2H), 7.42−7.36 (m, 3H), 6.99−6.95 (m, 2H), 6.56 (d, J = 8.4 Hz, 2H), 4.88 (q, $^3J_{H-F}$ = 7.3 Hz, 1H), 4.20 (br s, 1H), 2.22 (s, 3H); ^{13}C NMR δ 143.2 (s), 134.2 (s), 129.8 (d), 129.0 (d), 128.9 (d), 128.5 (s), 127.8 (d), 125.2 (q, $^1J_{C-F}$ = 281 Hz), 114.2 (d), 60.9 (dq, $^2J_{C-F}$ = 30 Hz), 20.3 (q); IR (neat, NaCl plates, cm^{-1}) 3417, 3032, 2924, 1620, 1520, 1249, 1172, 1122. Anal. Calcd for $C_{15}H_{14}F_3N$: C, 67.91; H, 5.32; N, 5.28. Found: C, 68.11; H, 5.44; N, 5.22.

[3-(Trifluoromethyl)phenyl][2-(2-phenyl-1,1,1-trifluoroethyl)] Amine (25*m*): chromatography, silica gel/5% ethyl acetate in hexanes (product R_f = 0.4); liquid at room temperature; ^{1}H NMR δ 7.47−7.39 (m, 5H), 7.27−7.23 (m, 1H), 7.02−7.00 (m, 1H), 6.88 (br s, 1H), 6.79−6.75 (m, 1H), 4.93 (dq, $^3J_{H-F}$ = 7.2 and 7.2 Hz, 1H), 4.52 (d, J = 6.0 Hz, 1H); ^{13}C NMR δ 145.8 (s), 133.4 (s), 131.8 (q, $^2J_{C-F}$ = 31 Hz), 129.9 (d), 129.4 (d), 129.1 (d), 127.8 (d), 124.9 (q, $^1J_{C-F}$ = 280 Hz), 124.1 (q, $^1J_{C-F}$ = 271 Hz), 116.2 (d), 115.7 (dq, $^3J_{C-F}$ = 4 Hz), 110.5 (dq, $^3J_{C-F}$ = 4 Hz), 60.4 (dq, $^2J_{C-F}$ = 30 Hz); IR (neat, NaCl plate, cm^{-1}) 3437, 3039, 2923, 1616, 1496, 1342, 1169. Anal. Calcd for $C_{15}H_{11}F_6N$: C, 56.43; H, 3.47; N, 4.39. Found: C, 56.62; H, 3.61; N, 4.37.

Catalytic Hydrogenation of Adduct 13*d*—Preparation of 25*d*. To a 10-mL, round-bottomed flask, containing a magnetic stir bar, were added reagent grade ethyl acetate (5 mL) and 10% Pd/C (100 mg). Adduct **13*d*** (374 mg, 1.00 mmol) was added. The solution was sparged with N_2(g) for 5 min, and a balloon of H_2(g) was attached. The reaction mixture was stirred at room temperature for 72 h. The reaction was monitored by TLC (silica gel/4% ethyl acetate in hexanes; adduct R_f = 0.4, product R_f = 0.3). The catalyst was removed by filtration through a small plug of silica gel. The solvent was removed by rotary evaporation to give a clear, colorless oil. The product was purified by flash chromatography (TLC conditions) to give 249 mg (87%) of **25*d***.

Phenyl[2-(2-[4-chlorophenyl)-1,1,1-trifluoroethyl)]Amine (25*d*): liquid at room temperature; ^{1}H NMR δ 7.42−7.36 (m, 4H), 7.18−7.14 (m, 2H), 6.81−6.77 (m, 1H), 6.62−6.59 (m, 2H), 4.90 (br s, 1H), 4.31 (br s, 1H); ^{13}C NMR δ 145.1 (s), 135.1 (s), 132.5 (s), 129.4 (d), 129.2 (d), 129.1 (d), 124.8 (q, $^1J_{C-F}$ = 280 Hz), 119.5 (d), 114.0 (d), 60.0 (dq, $^2J_{C-F}$ = 30 Hz); IR (neat, NaCl plates, cm^{-1}) 3417, 3059, 2931, 1604, 1493, 1254, 1176. Anal. Calcd for $C_{14}H_{11}ClF_3N$: C, 58.86; H, 3.88; N, 4.90. Found: C, 58.88; H, 3.75; N, 4.80.

Zinc Metal Reduction of Adduct 21—Preparation of 25*n*. To a 25-mL, round-bottomed flask, containing a magnetic stir bar, were added adduct **21** (365 mg, 1.00 mmol), glacial acetic acid (5 mL), and anhydrous THF (5 mL). Fine mesh zinc powder (981 mg, 15.0 mmol) was then added to the reaction mixture. A reflux condenser with an N_2(g) inlet was attached to the flask. The reaction mixture was stirred vigorously to prevent the zinc from settling and heated to ∼60 °C for 24 h. The gray slurry gradually turned lighter in color. The reaction was monitored by TLC (silica gel/4% EtOAc in hexanes; adduct R_f = 0.4, amine R_f = 0.3). The zinc/zinc oxide solids were removed by filtration through a glass frit. The acid was neutralized by dropwise addition of a saturated sodium bicarbonate solution, and a few drops of 2 N KOH solution was added to adjust the pH to ∼10. The reaction mixture was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a yellow oil. Purification by flash chromatography (TLC conditions) afforded a clear, colorless oil (225 mg, 81%).

Phenyl[3-(*trans*-1-phenyl-4,4,4-trifluorobut-1-enyl)] Amine (25*n*): ^{1}H NMR δ 7.41−7.21 (m, 7H), 6.84−6.80 (m, 1H), 6.81 (d, J = 16.4 Hz, 1H), 6.76−6.72 (m, 2H), 6.21 (dd, J = 15.8 and 6.0 Hz, 1H), 4.63 (dq, J = 7.2 and 6.0 Hz, 1H), 3.70 (br s, 1H); ^{13}C NMR δ 145.6 (s), 135.5 (d), 129.4 (d), 128.7 (d), 128.5 (d), 126.7 (d), 125.2 (q, $^1J_{C-F}$ = 281 Hz), 120.8 (d), 119.3 (d), 113.8 (d), 58.2 (dq, $^2J_{C-F}$ = 30 Hz); IR (neat, NaCl plate, cm^{-1}) 3413, 3059, 3028, 1604, 1500, 1250, 1180. Anal. Calcd for $C_{16}H_{14}F_3N$: C, 69.30; H, 5.09; N, 5.05. Found: C, 68.92; H, 5.00; N, 5.03.

Catalytic Hydrogenation of Adduct 21—Preparation 25*o*. To a 25-mL, round-bottomed flask, containing a magnetic stir bar, were added silylated hydroxylamine **21** (365 mg, 1.00 mmol) and ethyl acetate (8 mL). The solution was sparged with N_2(g) gas for 10 min. The palladium catalyst (100 mg of 10% Pd/C) was washed into the flask with additional ethyl acetate (2 mL). A balloon of H_2(g) was attached, and the reaction was stirred vigorously. The reaction was monitored by TLC (silica gel/6% ethyl acetate in hexanes; adduct R_f = 0.6, amine R_f = 0.4). After 24 h, no starting material remained. The reaction mixture was filtered through a small plug of silica gel. The product was purified by flash chromatography (TLC conditions) to give 260 mg (93%) of a clear, colorless oil.

Reductive deprotection of **21** by transfer hydrogenation afforded **25*o*** in 86% yield in 4 h.

Phenyl[2-(4-phenyl-1,1,1-trifluorobutyl)] Amine (25*o*): ^{1}H NMR δ 7.31−7.26 (m, 2H), 7.24−7.18 (m, 3H), 7.13−7.11 (m, 2H), 6.81−6.77 (m, 1H), 6.63−6.60 (m, 2H), 3.85−3.83 (m, 1H), 3.58−3.56 (m, 1H), 2.92−2.86 (m, 1H), 2.73 (ddd, J = 14.0, 8.4, and 8.2 Hz, 1H), 2.22 (dddd, J = 14.2, 8.4, 8.2, and 0.8 Hz, 1H), 1.94−1.85 (m, 1H); ^{13}C NMR δ 146.4 (s), 140.1 (s), 129.3 (d), 128.6 (d), 128.5 (d), 126.3 (d), 126.2 (q, $^1J_{C-F}$ = 282 Hz), 118.7 (d), 113.4 (d), 54.6 (dq, $^2J_{C-F}$ = 29 Hz), 31.3 (t), 31.1 (t); IR (neat, NaCl plate, cm^{-1}) 3410, 3028, 2931, 1604, 1512, 1254, 1165, 1122. Anal. Calcd for $C_{16}H_{16}F_3N$: C, 68.80; H, 5.77; N, 5.01. Found: C, 68.60; H, 5.99; N, 5.09.

Turnover Experiment. To a 25-mL, round-bottomed flask was added a mineral oil slurry of potassium hydride. The flask was sealed and a nitrogen atmosphere was introduced. The mineral oil was removed by successive washings with pentane to give a white powdery solid (32 mg, 0.80 mmol). Anhydrous THF (3 mL) was added to the solid via syringe. A solution of hydroxylamine **24*c*** (214 mg, 0.800 mmol) in dry THF (2 mL) was added to the KH slurry at 0 °C. When gas evolution ceased, the mixture containing the deprotonated hydroxylamine was added dropwise to a 25-mL round-bottomed flask containing a solution of nitrone **12*f*** (198 mg, 0.800 mmol) and **2** (228 mg, 237 μL, 1.60 mmol) in THF (5 mL) at −20 °C. The reaction was stirred at −20 °C for 12 h, and then the reaction was quenched with water. The biphasic mixture was extracted with dichloromethane. The combined extracts were dried

($MgSO_4$), filtered, and concentrated by rotary evaporation. The product mixture was separated by flash chromatography (silica gel, 5% ethyl acetate in hexanes) to give adduct **13*c*** (32%), hydroxylamine **24*c*** (26%), and hydroxylamine **24*f*** (4%).

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Supporting Information Available: Procedures for the preparation of nitrone starting materials, including characterization data; ^1H NMR and ^{13}C NMR spectra for selected compounds; selected chromatograms used for Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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