Articles

Synthesis of and Analysis of Thiol Additions to β-Alkyl-α,β-unsaturated Trifluoromethyl Ketones

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A series of β-alkyl-α,β-unsaturated trifluoromethyl ketones have been prepared from the corresponding α-acetylenic trifluoromethyl ketones. The addition of sulfur nucleophiles was shown by chemical and ^{19}F NMR studies to proceed exclusively by 1,4-addition with no indication of any 1,2-addition products. The unsaturated trifluoromethyl ketones have been shown to be effective inhibitors of rat cytosolic glutathione-S-transferase.

Fluoro ketones are highly reactive species toward nucleophilic addition reactions.[1] The inherent reactivity of fluoro ketones has been exploited in the design and synthesis of a number of fluoro ketone inhibitors of hydrolytic enzymes.[2] The 1,2-addition of the putative nucleophilic residue within the enzyme active site produces a tetrahedral intermediate which serves to mimic the transition state of the normal hydrolytic reaction. The applications of unsaturated fluoro ketones in the study of enzyme inhibition have not received as much attention.

Previous studies of nucleophilic addition to acetylenic trifluoromethyl ketones by this group[3] have shown that soft nucleophiles tend to undergo 1,4-addition reactions rather than 1,2-addition to the highly electrophilic carbonyl. This reactivity pattern can be fine-tuned such that regioselectivity of the addition of ambident nucleophiles such as hydroxylamine can be controlled by the choice of reaction conditions. In our studies of the application of fluoro ketones as enzyme inhibitors,[4] we were intrigued with the possibility that unsaturated trifluoromethyl ketones might be reactive as Michael acceptors rather than undergo direct 1,2-addition. We chose to examine β-alkyl-α,β-unsaturated trifluoromethyl ketones as potential inhibitors of glutathione-S-transferase (GST), a key enzyme in the detoxication of xenobiotics,[5] as part of our study on the mechanism and specificity of GST. GST catalyzes the conjugation of glutathione to a variety of electrophilic species, including unsaturated carbonyl compounds.[6] We chose simple β-alkyl substituted unsaturated trifluoromethyl ketones for study due to the known preference of GST for hydrophobic substrates.[5,6] We report here a convenient method for the synthesis of β-alkyl substituted α,β-unsaturated trifluoromethyl ketones from the corresponding acetylenic ketone and the analysis of the chemical reaction of these species with thiophenol and glutathione.

The synthesis of unsaturated trifluoromethyl ketones has not been trivial.[7] Typical methods for the synthesis of unsaturated ketones and esters are not generally applicable to trifluoromethyl substituted unsaturated carbonyl compounds. Hojo and co-workers[8] have prepared a variety of β-functionalized α,β-unsaturated fluoro ketones by reaction of trifluoroacetic anhydride with electron-rich alkenes. Vinyl organometallic reagents may be added to trifluoroacetaldehyde,[9] or trifluoromethyl organometallic reagents may be added to unsaturated aldehydes[10] followed by oxidation of the resulting allylic trifluoromethyl carbinol with the Dess-Martin periodinane;[11] however, fluorinated organometallic reagents are not convenient for larger scale synthesis and handling trifluoroacetaldehyde poses several safety hazards. The aldol condensation of trifluoroacetone fails to work with aliphatic aldehydes and provides only modest yields of unsaturated trifluoromethyl ketones with aryl or unsaturated aldehydes.[12] Since the synthesis of α-acetylenic trifluoromethyl ketones[13,14] is a versatile reaction which

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(7) For a recent review on the synthesis of trifluoromethyl ketones, see: Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207-3258.

(8) (a) Hojo, M.; Masuda, R.; Okada, E.; Yamamoto, H.; Morimoto, K.; Okada, K. *Synthesis* **1990**, 195-198 (b) Hojo, M.; Masuda, R.; Okada, E.; Sakaguchi, S.; Narumiga, H.; Morimoto, K. *Tetrahedron Lett.* **1989** *30*, 6173-6176. (c) Okada, E.; Masuda, R.; Hojo, M.; Inoue, R. *Synthesis* **1992**, 533-535, and references therein. For a recent study of β-enamino-α,β-unsaturated trifluoromethyl ketones, see: Vdovenko, S. I.: Gerus, I. I.; Gorbunova, M. G. *J. Chem. Soc., Perkin Trans. 2*, **1993**, 559-562.

(9) Kitazume, T.; Lin, J. T.; Yamazaki, T.; Takeda, M. *J. Fluor. Chem.* **1989**, *43*, 177-187.

(10) Tordeux, M.; Francese, C.; Wakselman, C. *J. Chem. Soc. Perkin Trans.* **1990**, 1951-1957. (b) O'Reilly, N. J.; Maruta, M.; Ishikawa, N. *Chem. Lett.* **1984**, 517-520. (c) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.

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Scheme 1

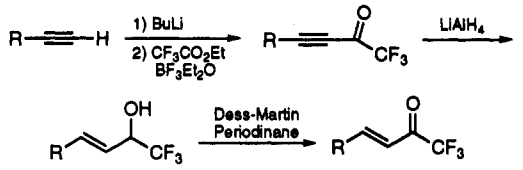
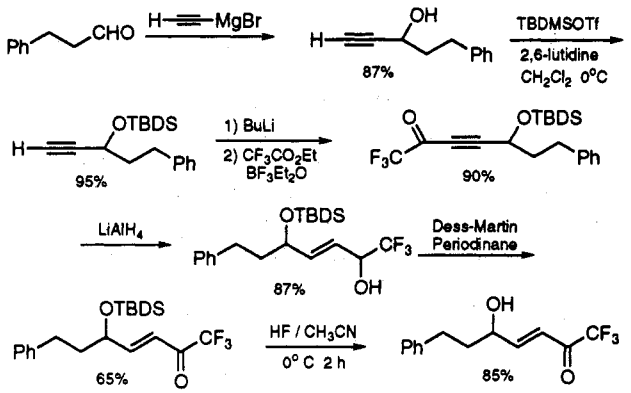


Table 1. Synthesis of β-Alkyl-α,β-unsaturated Trifluoromethyl Ketones

		yield, %	
entry	R	$RC(OH)HCF_3$	$RCOCF_3$
1	n-$C_4H_9CH{=}CH$	88	35
2	n-$C_6H_{13}CH{=}CH$	85	46
3	n-$C_8H_{17}CH{=}CH$	71	45
4	n-$C_{10}H_{21}CH{=}CH$	87	73
5	n-$C_{12}H_{25}CH{=}CH$	97	65
6	n-$C_{14}H_{29}CH{=}CH$	91	79
7	n-$C_{16}H_{33}CH{=}CH$	95	69

Scheme 2

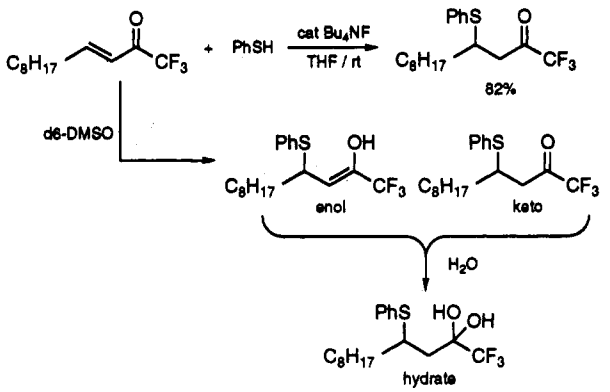


is amenable to scaleup, we chose to pursue the three-step sequence shown in Scheme 1 as a general synthesis of β-alkyl-α,β-unsaturated trifluoromethyl ketones.

Direct synthesis of the acetylenic ketone from the corresponding acetylene using boron trifluoride etherate was straightforward.[13] Complete reduction of the ketone and the alkyne was then realized using 2.1 equiv of lithium aluminum hydride (LAH) at reflux in THF. The reduction of the α-acetylenic trifluoromethyl ketone provided only the trans isomer of the allylic trifluoromethyl carbinol. Oxidation of the allylic alcohol to the ketone was then accomplished using 3.7 equiv of the Dess–Martin reagent.[11] As in our previous study of the oxidation of fluorocarbinols, no other oxidant proved as effective as the Dess–Martin reagent. The yields for a series of trifluoromethyl ketones produced by this three-step protocol are given in Table 1. The overall sequence can be readily modified to produce difluoro ketones by substituting ethyl difluoroacetate for ethyl trifluoroacetate in the initial condensation reaction of the acetylide.[13]

γ -Functionalized trifluoromethyl ketones are also prepared by this procedure as illustrated in Scheme 2. Addition of acetylene as the magnesium salt to dihydrocinnamaldehyde provided the propargylic alcohol in 87% yield. Protection of the alcohol as the *tert*-butyldimethylsilyl ether followed by generation of the lithium acetylide and condensation with ethyl trifluoroacetate

Scheme 3



generated the acetylenic ketone in 86% overall yield. Reduction by LAH[15] and oxidation of the allylic alcohol to the ketone was then accomplished in good overall yield (57%). Attempted desilylation of the ether using tetrabutylammonium fluoride was surprisingly unsuccessful; however, clean conversion to the alcohol was achieved using HF in acetonitrile.[16]

The reaction of α,β-unsaturated trifluoromethyl ketones with thiol nucleophiles was then examined to determine the extent of 1,2- vs 1,4- regioselectivity. As anticipated, only the product of 1,4-addition was observed upon the fluoride-catalyzed[17] reaction of *trans*-1,1,1-trifluoro-3-dodecen-2-one with thiophenol in anhydrous THF, Scheme 3. The isolated thiophenol adduct (82% yield) exhibited an ^{19}F NMR resonance at −79.8 ppm, indicative of the keto form rather than the thio hemiacetal, and an absorption in the IR at 1765 cm^{-1}. Clearly the thiol nucleophile undergoes base-catalyzed 1,4-addition in THF rather than 1,2-addition to the unsaturated trifluoromethyl ketone. Reaction progress of thiophenol addition monitored by ^1H NMR in d_6-DMSO revealed that the vinyl proton signals of the starting trifluoromethyl ketone (δ 6.40, 7.32) rapidly disappeared. Initial 1,2-addition of thiophenol would have been noted by the observation of new olefinic signals in the ^1H NMR. No signals were observed in the olefinic region (δ 4 to 6) of the ^1H NMR spectrum. ^{19}F NMR analysis in d_6-DMSO showed that the starting material exhibited a resonance at −78.8 ppm for the keto form of the trifluoromethyl ketone. The thiophenol 1,4-adduct exhibited two signals in the ^{19}F NMR at −77.7 and −70.5 ppm. The subsequent addition of water to the NMR sample led to the formation of a single product which exhibited an ^{19}F NMR signal at −83.5 ppm, indicative of a trifluoromethyl ketone hydrate.[18] The ^1H and ^{19}F NMR data also indicate that no 1,2-addition of the thiol to the unsaturated trifluoromethyl carbonyl was observed in DMSO. The ^{19}F NMR signal at −70.5 ppm was attributed to the formation of the enol form of the adduct. The assignment of the enol isomer was verified by comparison of these data with ^{19}F NMR spectra of 3-phenyl-1,1,1-trifluoropropan-2-one. The enol form was observed in the ^{19}F NMR at −69.3 ppm and in the ^{13}C

(14) For other synthetic routes to trifluoroacetyl acetylenes, see: (a) Margaretha, P.; Schroder, C.; Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1983**, *48*, 1925–1926. (b) Hanzawa, Y.; Yamada, A.; Kobayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 2881–2884. See also ref 12b,c.

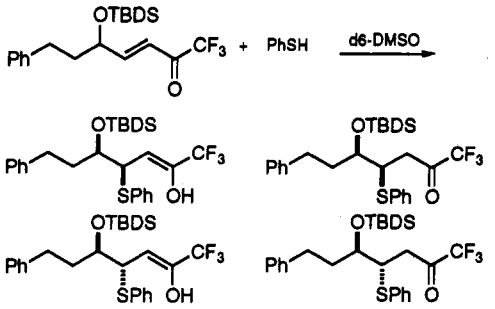
(15) Reduction of trifluoroacetyl acetylenes using $NaBH_4$ or Red-Al also leads to the allylic alcohol, see ref 12c.

(16) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981–3984.

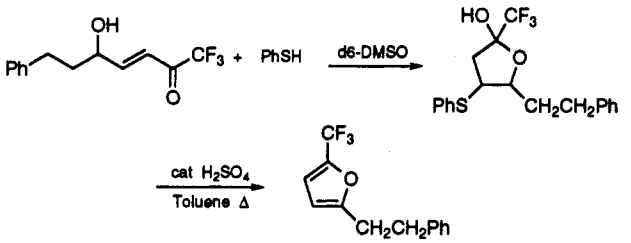
(17) Tetrabutylammonium fluoride catalyzed addition of thiophenol to unsaturated esters has been reported (Kuwajima, I; Mirofushi, T.; Nakamura, E. *Synthesis* **1976**, 602–604. The conditions reported by Nakamura and co-workers were employed without change).

(18) Linderman, R. J.; Jamois, E. A.; Roe, R. M. *Rev. Pestic. Toxicol.* **1991**, *1*, 261–270.

Scheme 4



Scheme 5

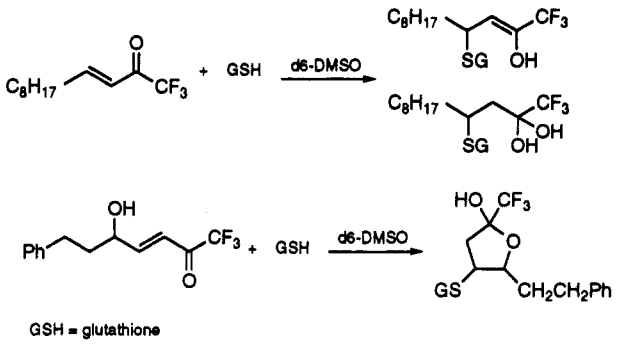


NMR at 106.70 and 139.29 ppm (q, J^2_{C-F} = 31 Hz). Addition of water to the 3-phenyl-1,1,1-trifluoropropan-2-one NMR sample resulted in complete conversion to a single hydrate species with an ^{19}F NMR signal at −81.9 ppm and a ^{13}C NMR signal at 93.06 ppm (q, J^2_{C-F} = 29 Hz).

Similar results were obtained in thiophenol addition to the γ-silyloxy trifluoromethyl ketone, Scheme 4. The starting ketone exhibited an ^{19}F NMR resonance at −76.3 ppm (d_6-DMSO). The 1,4-adduct was produced as a mixture of enol (^{19}F NMR, −70.4 and −70.5 ppm) and keto (^{19}F NMR, −77.6 and −77.7 ppm) diastereomers, each in a 1:1 ratio. It is significant to note that although the CF_3 group is remote from the chiral centers produced, the diastereomers were completely resolved in the ^{19}F NMR spectrum (the relative stereochemistry shown in Scheme 4 has been arbitrarily assigned). The addition of thiophenol to the γ-hydroxy unsaturated trifluoromethyl ketone (in d_6-DMSO) was more complex. As shown in Scheme 5, the ketone undergoes 1,4-addition of the thiol and is subsequently trapped by intramolecular hemiacetal formation. The hemiacetal is readily identified by ^{19}F NMR. Signals for four diastereomers were observed at −81.90, −82.57, −82.64, and −82.86 ppm with relative intensities of 1.0:0.2:0.2:0.3, respectively. This result is in accord with our previous analysis of the reactivity of oxygen and nitrogen nucleophiles to acetylenic trifluoromethyl ketones.[3] The tetrahydrofuran intermediate was easily converted to the furan (46% overall unoptimized yield from the unsaturated ketone) upon treatment with concentrated sulfuric acid in benzene.[19] Attempted dehydration and aromatization using *p*-toluenesulfonic acid and azeotropic removal of water was not successful. Therefore, the regioselective synthesis of 2-(trifluoromethyl)-5-alkylfurans is also possible via this methodology.

The addition of glutathione was also examined, Scheme 6. The 1,4-glutathione adduct obtained from *trans*-1,1,1-trifluoro-3-dodecene-2-one was produced as a diastereomeric mixture of enols (^{19}F NMR, −70.2 and −70.3 ppm) and hydrates (^{19}F NMR, −83.6 and −83.8 ppm). None of

Scheme 6



GSH = glutathione

the free keto form was observed by ^{19}F NMR in the reaction mixture. The hydrate is presumably formed from water introduced with glutathione. As in the thiophenol studies shown in Scheme 3, the addition of more water to the NMR sample completely converted the enol isomer to the hydrate. In addition, the disappearance of the starting material olefinic signals could be monitored by ^1H NMR. Glutathione addition to the γ-hydroxy unsaturated trifluoromethyl ketone also resulted in formation of the cyclic hemiacetal as the only product as evidenced by a complex signal pattern from −82.0 to −82.9 ppm in the ^{19}F NMR. The cyclic hemiacetal structure was assigned based on the complexity of the ^{19}F NMR pattern and on the results obtained when glutathione was reacted with the γ-silyloxy unsaturated trifluoromethyl ketone (analogous to the reaction with thiophenol shown in Scheme 6). In the latter case, both enol (^{19}F NMR, complex signals from −70.2 to −70.4 ppm) and hydrate (^{19}F NMR, complex signals from −83.6 to −83.9 ppm) products were observed. The hemiacetal and the hydrate of very similar compounds are therefore clearly distinguished in the ^{19}F NMR.

In summary, we have described a general route for the synthesis of β-alkyl- α,β-unsaturated trifluoromethyl ketones. As anticipated, these ketones undergo regioselective addition of sulfur nucleophiles and may serve as versatile synthetic intermediates for the synthesis of other trifluoromethylated heterocyclic compounds. We have also determined that simple α,β-unsaturated trifluoromethyl ketones act as effective inhibitors of rat liver cytosolic GST. Inhibition constants in the range of 10^{-6} to 10^{-9} M have been observed for rat liver GST isozyme 4-4.[20] The inhibition of GST by γ-hydroxy-α,β-unsaturated aldehydes has been reported.[21] The efficacy of the hydroxy aldehydes as inhibitors is presumed to arise from the formation of an intramolecular hemiacetal upon addition of glutathione. The data presented herein implies that structurally analogous γ-hydroxy-α,β-unsaturated fluoro ketones will be even more effective inhibitors. Full details of the application of the unsaturated fluoro ketones in the study of GST inhibition will be reported elsewhere.

Experimental Section

General. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. All anionic reactions were carried out in flame-dried glassware under an atmosphere of argon. All reagents were purchased from Aldrich Chemical Co. except glutathione which was obtained from Sigma. Butyllithium

(19) For a recent example of a 2-(trifluoromethyl)pyrrole synthesis via a trifluoromethyl dihydrofuran intermediate, see: Hoffmann, M. G.; Wenkert, E. *Tetrahedron* **1993**, 1057-1062.

(20) Unpublished results, Linderman, R. J.; Jamois, E. J.; Tennyson, S. D.; Dauterman, W.

(21) (a) Danielson, U. H.; Esterbauer, H.; Mannervik, B. *Biochem. J.* **1987**, *247*, 707-713. (b) Ishikawa, T.; Esterbauer, H.; Sies, H. *J. Biol. Chem.* **1986**, *261*, 1576-1581.

was titrated prior to use using 1,10-phenanthroline.[22] The Dess-Martin periodinane reagent was prepared by literature procedure.[23] NOTE: The Dess-Martin reagent has been reported to explode upon heating under confinement.[24] Due precautions should be exercised when using this oxidant. ^{1}H and ^{13}C NMR spectra were obtained at 300 MHz. ^{19}F NMR spectra were obtained at 90 or 500 MHz using freon as an internal standard. Elemental analyses were carried out by Atlantic Microlab Inc., Norcross, GA.

General Synthesis of TFM α-Acetylenic Ketones. The acetylenic trifluoromethyl ketones were prepared as described.[13] Acetylenic precursors for entries 1-5 in Table 1 have previously been reported.[13]

1,1,1-Trifluorooctadec-3-yn-2-one: 36% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.4 Hz), 1.20-1.45 (m, 22H), 1.63 (quin, 2H, J = 7.2 Hz), 2.47 (t, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.00, 19.33, 22.69, 27.11, 28.73, 28.89, 29.38, 29.54, 29.67, 31.93, 76.03, 105.08, 114.64 (q, J^1_{C-F} = 286 Hz), 167.09 (q, J^2_{C-F} = 41 Hz); ^{19}F NMR ($CDCl_3$/$CFCl_3$) -79.5 (s) ppm; IR (neat) (cm^{-1}) 2930, 2860, 2210, 1710, 1460, 1215, 1155, 920, 745. Anal. Calcd for $C_{18}H_{29}F_3O$: C, 67.89; H, 9.18. Found: C, 68.01; H, 9.23

1,1,1-Trifluoroeicos-3-yn-2-one: 24% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.20-1.45 (m, 26H), 1.62 (quin, 2H, J = 7.1 Hz), 2.47 (t, 2H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 19.36, 22.72, 27.18, 28.76, 28.96, 29.41, 29.57, 29.73, 31.96, 76.06, 105.08, 114.70 (q, J^1_{C-F} = 286 Hz), 167.11 (q, J^2_{C-F} = 43 Hz); ^{19}F NMR ($CDCl_3$/$CFCl_3$) (s) -79.4 ppm; IR (neat)(cm^{-1}) 2930, 2855, 2295, 2210, 1710, 1460, 1215, 1155, 920, 745. Anal. Calcd for $C_{20}H_{33}F_3O$: C, 69.33; H, 9.60. Found: C, 69.40; H, 9.61.

General Synthesis of Allylic TFM Alcohols. A suspension of lithium aluminum hydride (21.5 mmol, 2.1 equiv) was prepared by introducing the solid in small portions to 20 mL of THF. The suspension was cooled to 0 °C (ice bath) and the acetylenic trifluoromethyl ketone (1 equiv) was then added dropwise as a solution in 5 mL THF. After stirring for 30 min, the reaction mixture was gradually warmed to ambient temperature and then gently refluxed for 8 h. The reaction mixture was cooled to 0 °C followed by the sequential addition of water (820 μL), 20% aqueous sodium hydroxide (820 μL), and water (2.5 mL) with vigorous stirring. The reaction mixture was then allowed to warm to ambient temperature and stirred for 30 min. The precipitated salts were removed by filtration, and the filtrate was washed with ether (2 × 30 mL). The combined ether phases and organic reaction phase were sequentially washed with saturated aqueous ammonium chloride (50 mL), water (50 mL), and saturated aqueous sodium chloride (50 mL). The organic phase was dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The crude product was carried on to the next step without further purification.

***trans*-1,1,1-Trifluorooct-3-en-2-ol:** 88% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.35 (m, 4H), 2.09 (q, 2H, J = 6.8 Hz), 4.37 (quin, 1H, J^3_{H-F} = 6.6 Hz, J^3_{H-H} = 6.6 Hz), 5.49 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} =7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.77, 22.04, 30.64, 31.90, 71.57 (q, J^2_{C-F} = 32.2 Hz), 121.88, 124.33 (q, J^1_{C-F} = 281 Hz), 139.07; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -80.4 (d, J^3_{F-H} = 6.6 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2960, 2930, 2860, 1670, 1265, 1170, 1120, 1035, 970, 855, 690.

***trans*-1,1,1-Trifluorodec-3-en-2-ol:** 85% yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.5 Hz), 1.20-1.45 (m, 8H), 2.10 (q, 2H, J = 7.2 Hz), 2.32 (br s, 1H), 4.39 (m, 1H), 5.50 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.50, 28.50, 28.67, 31.57, 32.22, 71.46 (q, J^2_{C-F} = 31.5 Hz), 122.01, 124.39 (q, J^1_{C-F} = 281 Hz), 138.87; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -80.6 (d, J^3_{F-H} = 6.6 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2930, 2860, 1670, 1270, 1170, 1120, 965, 855, 690.

***trans*-1,1,1-Trifluorododec-3-en-2-ol:** 71% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m, 12H), 2.08 (q, 2H, J = 7.0 Hz), 2.17 (br d, 1H, J = 6.0 Hz), 4.37 (br m, 1H), 5.49 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.62, 28.54, 29.02, 29.18, 29.34, 31.80, 32.22, 71.56 (q, J^2_{C-F} = 31.5 Hz), 121.88, 124.35 (q, J^1_{C-F} = 279 Hz), 139.10; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -80.8 (d, J^3_{F-H} = 6.5 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2930, 2860, 1670, 1460, 1265, 1170, 1120, 1040, 965, 860, 690.

***trans*-1,1,1-Trifluorotetradec-3-en-2-ol:** 87% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.5 Hz), 1.20-1.45 (m, 16H), 2.10 (q, 2H, J = 7.6 Hz), 4.40 (sextet, 1H, J^3_{H-F} = 6.6 Hz, J^3_{H-H} = 6.6 Hz), 5.51 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.97 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.62, 28.54, 29.02, 29.28, 29.38, 29.54, 31.86, 32.22, 71.59 (q, J^2_{C-F} = 31.5 Hz), 121.88, 124.33 (q, J^1_{C-F} = 281 Hz), 139.13; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -80.7 (d, J^3_{F-H} = 6.6 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2930, 2860, 1670, 1460, 1265, 1170, 1120, 1040, 965, 860, 690.

***trans*-1,1,1-Trifluorohexadec-3-en-2-ol:** 97% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m, 20H), 2.08 (q, 2H, J = 7.2 Hz), 4.37 (quin, 1H, J^3_{H-F} = 6.6 Hz, J^3_{H-H} = 6.6 Hz), 5.49 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.69, 28.60, 29.05, 29.41, 29.57, 29.64, 31.93, 32.25, 71.56 (q, J^2_{C-F} = 31.5 Hz), 121.94, 124.38 (q, J^1_{C-F} = 279 Hz), 139.07; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -80.4 (d, J^3_{F-H} = 6.6 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2930, 2855, 1670, 1465, 1265, 1170, 1125, 1040, 965, 855, 690.

***trans*-1,1,1-Trifluorooctadec-3-en-2-ol:** 91% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m, 24H), 2.08 (q, 2H, J = 6.7 Hz), 2.18 (d, 1H, J = 6.6 Hz), 4.37 (sextet, 1H, J^3_{H-F} = 6.6 Hz, J^3_{H-H} = 6.6 Hz), 5.48 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.66, 28.57, 29.05, 29.34, 29.41, 29.54, 29.67, 31.90, 32.25, 71.52 (q, J^2_{C-F} = 31.5 Hz), 121.94, 124.36 (q, J^1_{C-F} = 281Hz), 138.97; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -79.95 (d, J^3_{F-H} = 6.6 Hz) ppm; IR (neat) (cm^{-1}) 3370 , 2930, 2855, 1670, 1460, 1270, 1175, 1125, 1050, 970, 860, 695.

***trans*-1,1,1-Trifluoroeicos-3-en-2-ol:** 95% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m, 28H), 2.08 (q, 2H, J = 7.0 Hz), 2.19 (d, 1H, J = 6.6 Hz), 4.37 (sextet, 1H, J^3_{H-F} = 6.6 Hz, J^3_{H-H} = 6.6 Hz), 5.48 (dd, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 6.6 Hz), 5.96 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.66, 28.57, 29.05, 29.34, 29.41, 29.54, 29.57, 29.67, 31.90, 32.25, 71.49 (q, J^2_{C-F} = 31.5 Hz), 122.01, 124.38 (q, J^1_{C-F} = 279Hz), 138.87; ^{19}F NMR ($CDCl_3$/$CFCl_3$) -79.94 (d, J^3_{F-H} = 5.5 Hz) ppm; IR (neat) (cm^{-1}) 3380, 2930, 2855, 1670, 1460, 1270, 1175, 1125, 1050, 970, 860.

General Synthesis of β-Substituted-α,β-unsaturated TFM Ketones. To a solution of the Dess-Martin periodinane (1.56 g, 3.7 mmol) in dry CH_2Cl_2 (35 mL) was added dropwise a sample of the trifluoromethyl allylic alcohol (1 mmol) as a solution in CH_2Cl_2 (2.5 mL) over a period of 10 min. The reaction mixture was stirred at ambient temperature for 2.5 h. Ether (25 mL) and 5% aqueous sodium hydroxide (50 mL) were then added to the reaction flask and the mixture was stirred for 45 min. The layers were separated, and the organic phase was washed with 5% aqueous sodium hydroxide (40 mL). The aqueous reaction phase was extracted with ether (3 × 25 mL), and the combined organic fractions were then sequentially washed with saturated aqueous ammonium chloride (50 mL), water (50 mL), and saturated aqueous sodium chloride (50 mL). The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude reaction product was purified by flash chromatography (SiO_2) using hexanes as eluent.

***trans*-1,1,1-Trifluorooct-3-en-2-one:** 30% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.36 (m, 2H), 1.48 (m, 2H), 2.32 (qd, 2H, J^3_{H-H} = 7.3 Hz, J^4_{H-H} = 1.5Hz), 6.38 (d, 1H, J^3_{trans} = 15.4 Hz), 7.31 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.71, 22.20, 29.64, 32.93, 116.20 (q, J^1_{C-F} = 289 Hz), 121.30, 156.93, 179.77 (q, J^2_{C-F} = 34 Hz); ^{19}F NMR ($CDCl_3$/$CFCl_3$) -78.5 (s) ppm; IR (neat) (cm^{-1}) 2960, 2930, 2870, 1735, 1715, 1635, 1215, 1160, 725. Anal. Calcd for $C_8H_{11}F_3O$: C, 53.33; H, 6.16. Found: C, 53.32; H, 6.19.

***trans*-1,1,1-Trifluorodec-3-en-2-one:** 46% yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m, 6H), 1.47-1.55 (m, 2H), 2.34 (qd, 2H, J^3_{H-H} = 7.2 Hz, J^4_{H-H} = 1.5 Hz), 6.41 (d,

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(24) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68*, 3. We have not experienced any problems with the preparation or use of the Dess-Martin periodinane; however, as a precaution, reactions are never carried out on more than a 1-2-g scale.

1H, J^3_{trans} = 15.4 Hz), 7.34 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.43, 27.50, 28.76, 31.44, 33.22, 116.19 (q, J^1_{C-F} = 291 Hz), 121.26, 156.93, 179.74 (q, J^2_{C-F} = 34 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.7 (s) ppm; IR (neat) (cm^{-1}) 2930, 2860, 1725, 1705, 1200, 1145, 1070, 715. Anal. Calcd for $C_{10}H_{15}F_3O$: C, 57.68; H, 7.26. Found: C, 57.61; H, 7.29.

***trans*-1,1,1-Trifluorododec-3-en-2-one:** 45% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.5 Hz), 1.20–1.40 (br s, 10H), 1.47–1.55 (m, 2H), 2.33 (qd, 2H, J^3_{H-H} = 7.0 Hz, J^4_{H-H} = 1.5Hz), 6.40 (d, 1H, J^3_{trans} = 15.4 Hz), 7.32 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.00, 22.59, 27.60, 29.12, 29.25, 31.77, 33.25, 116.24 (q, J^1_{C-F} = 288 Hz), 121.33, 156.93, 179.76 (q, J^2_{C-F} = 36 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.8 (s) ppm; IR (neat) (cm^{-1}) 2930, 2860, 1735, 1715, 1630, 1470, 12.05, 1150, 715. Anal. Calcd for $C_{12}H_{19}F_3O$: C, 61.00; H, 8.11. Found: C, 61.22; H, 8.06.

***trans*-1,1,1-Trifluorotetradec-3-en-2-one:** 73% yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.0 Hz), 1.20–1.40 (br s, 14H), 1.47–1.55 (m, 2H), 2.34 (qd, 2H, J^3_{H-H} = 7.1 Hz, J^4_{H-H} = 1.5Hz), 6.42 (d, 1H, J^3_{trans} = 15.4 Hz), 7.35 (dt, 1H, J^3_{trans} = 15.4 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.66, 27.60, 29.15, 29.28, 29.44, 29.54, 31.86, 33.25, 116.22 (q, J^1_{C-F} = 288 Hz), 121.30, 156.93, 179.72 (q, J^2_{C-F} = 37 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.5 (s) ppm; IR (neat) (cm^{-1}) 2930, 2850, 1725, 1705, 1625, 1460, 1200, 1145, 715. Anal. Calcd for $C_{14}H_{23}F_3O$: C, 63.61; H, 8.77. Found: C, 63.73; H, 8.80.

***trans*-1,1,1-Trifluorohexadec-3-en-2-one:** 65% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.5 Hz), 1.20–1.40 (br s, 18H), 1.45–1.53 (m, 2H), 2.31 (qd, 2H, J^3_{H-H} = 7.3 Hz, J^4_{H-H} = 1.5Hz), 6.38 (d, 1H, J^3_{trans} = 16.9 Hz), 7.31 (dt, 1H, J^3_{trans} = 16.1 Hz, J^3_{H-H} = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.66, 27.60, 29.15, 29.34, 29.44, 29.64, 31.90, 33.22, 116.22 (q, J^1_{C-F} = 291 Hz), 121.30, 156.87, 179.69 (q, J^2_{C-F} = 37 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.8 (s) ppm; IR (neat) (cm^{-1}) 2930, 2850, 1725, 1705, 1625, 1460, 1200, 1145, 715. Anal. Calcd for $C_{16}H_{27}F_3O$: C, 65.72; H, 9.31. Found: C, 65.77; H, 9.30.

***trans*-1,1,1-Trifluorooctadec-3-en-2-one:** 79% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.0 Hz), 1.20–1.40 (br s, 22H), 1.45–1.55 (m, 2H), 2.31 (qd, 2H, J^3_{H-H} = 7.3 Hz, J^4_{H-H} = 1.5 Hz), 6.38 (d, 1H, J^3_{trans} = 15.4 Hz), 7.31 (dt, 1H, J^3_{trans} = 16.1 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.66, 27.57, 29.12, 29.28, 29.34, 29.44, 29.64, 31.90, 33.22, 116.20 (q, J^1_{C-F} = 289 Hz), 121.26, 156.87, 179.69 (q, J^2_{C-F} = 36 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.07 (s) ppm; IR (neat) (cm^{-1}) 2930, 2855, 1725, 1705, 1620, 1460, 1205, 1150, 715. Anal. Calcd for $C_{18}H_{31}F_3O$: C, 67.47; H, 9.75. Found: C, 67.57; H, 9.71.

***trans*-1,1,1-Trifluoroeicos-3-en-2-one:** 69% yield; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.0 Hz), 1.20–1.40 (br s, 26H), 1.47–1.55 (m, 2H), 2.31 (qd, 2H, J^3_{H-H} = 7.3 Hz, J^4_{H-H} = 1.5 Hz), 6.38 (d, 1H, J^3_{trans} = 15.4 Hz), 7.31 (dt, 1H, J^3_{trans} = 16.1 Hz, J^3_{H-H} = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.69, 27.60, 29.15, 29.31, 29.38, 29.47, 29.60, 29.67, 31.93, 33.25, 116.24 (q, J^1_{C-F} = 288 Hz), 121.30 156.87, 179.69 (q, J^2_{C-F} = 36 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.10 (s) ppm; IR (neat) (cm^{-1}) 2930, 2855, 1725, 1705, 1625, 1460, 1205, 1150, 715. Anal. Calcd for $C_{20}H_{35}F_3O$: C, 68.93; H, 10.12. Found: C, 69.04; H, 10.16.

Synthesis of *trans*-7-Phenyl-5-hydroxy-1,1,1-trifluoro-3-penten-2-one. 5-Phenylpent-1-yn-3-ol: 87% yield. The alcohol was prepared by the addition of ethynylmagnesium bromide to dihydrocinnamaldehyde according to the procedure of Brandsma.[25] ^{1}H NMR ($CDCl_3$) δ 1.60–1.90 (br s, 1H, OH), 2.00–2.12 (m, 2H), 2.52 (d,1H, J^4_{H-H} = 2.1 Hz), 2.82 (t, 2H, J = 7.7 Hz), 4.38 (td,1 H, J^3_{H-H} = 6.6 Hz, J^4_{H-H} = 2.1 Hz), 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.19, 39.00, 61.49, 73.32, 84.56, 126.01, 128.44, 141.04; IR (neat)(cm^{-1}) 3370, 3300, 3035, 2950, 2930, 2865, 1600, 1495, 1450, 1040, 1010, 745, 700, 630.

5-Phenyl-3-(*tert*-butyldimethylsiloxy)pentyne: 95% yield. A solution of 5-phenylpent-3-ol (1.00 g, 6.24 mmol) and 2,6 lutidine (1.60 mL,13.7 mmol) in 6.0 mL of dry methylene chloride was cooled to 0 °C. A sample of *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.15 mL, 9.36 mmol) was added dropwise as a solution in dry methylene chloride (6.0 mL) over a 30-min period while keeping the temperature at 0 °C. The mixture was then stirred at 0 °C for10 min and then allowed to warm to ambient temperature. The reaction mixture was stirred for an additional 15 min with reaction progress monitored by GC analysis. Upon disappearance of the starting material, the reaction mixture was diluted with pentanes (50 mL). The reaction flask was rinsed with pentanes (20 mL) to ensure complete transfer of the material. The organic phase was then sequentially washed with 0.05 M HCl (4 × 25 mL), saturated aqueous sodium bicarbonate (25 mL), and water (2 × 25 mL). The organic phase was then dried over anhydrous magnesium sulfate. The solvents were then removed under reduced pressure to yield 2.12 g of a colorless oil. The product was purified by bulb-to-bulb distillation, yielding 1.68 g (95%). The product was of sufficient purity (>95% by GC) to be used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.97–2.04 (m, 2H), 2.43 (d,1H, J^4_{H-H} = 2.1 Hz), 2.77 (td, 2H, J^3_{H-H} = 8.3 Hz, J^4_{H-H} = 34 Hz), 4.38 (td, 1H, J^3_{H-H} = 8.3 Hz, J^4_{H-H} = 2.1 Hz), 7.18–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 5.10, 4.58, 18.16, 25.73, 31.28, 40.14, 62.04, 72.35, 85.24, 125.82, 128.34, 128.40, 141.55, IR (neat)(cm^{-1}) 3310, 2960, 2940, 2860, 1490, 1460, 1250, 1090, 835, 775, 695.

7-Phenyl-5-(*tert*-butyldimethylsiloxy)-1,1,1-trifluoro-3-heptyn-2-one: 90% yield. The ketone was prepared by trifluoroacetylation of the alkyne as described above: ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 2.05–2.15 (m, 2H), 2.79 (td, 2H, J^3_{H-H} = 8.1 Hz, J^4_{H-H} = 3 Hz), 4.58 (t, 1H, J = 6 Hz), 7.18–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.26, −4.87, 18.04, 25.53, 31.02, 39.00, 62.07, 78.36, 102.81, 114.61 (q, J^1_{C-F} = 285 Hz), 126.24, 128.37, 128.53, 140.45, 166.75 (q, J^2_{C-F} = 40 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −79.07 (s) ppm; IR (neat)(cm^{-1}) 3400, 2960, 2930, 2860, 2200, 1720, 1490, 1460, 1255, 1215, 1160, 1125, 1100, 835, 775, 745, 695. Anal. Calcd for $C_{19}H_{25}F_3O_2Si$: C, 61.59; H, 6.80. Found: C, 61.64; H, 6.84.

(*trans*)-7-Phenyl-5-(tert-butyldimethylsiloxy)-1,1,1-trifluoro-3-hepten-2-ol: 87% yield. The trifluoromethyl alcohol was prepared by LAH reduction of the ketone as described above: ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 0.04, 0.06 (s, 3H), 0.09, 0.10 (s, 3H), 0.92, 0.95 (s, 9H), 1.87 (q, 2H, J = 7.0 Hz), 2.31 (m,1 H), 2.68 (q, 2H, J = 7.0 Hz), 4.28 (br m,1H), 4.46 (br m, 1H), 5.72, 5.75 (d, 1H, J = 6.0 Hz), 6.00-6.05 (br m,1H), 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.93, −4.58, 18.17, 25.79, 31.15, 39.36, 39.42, 71.01 (q, J^2_{C-F} =31.5 Hz), 70.85 (q, J^2_{C-F} =31.5 Hz), 71.54, 71.64, 121.52, 124.25 (q, J^1_{C-F} = 280 Hz), 125.79, 128.37, 140.04, 140.58, 142.04; ^{19}F NMR ($CDCl_3/CFCl_3$) −80.30 (d, J^3_F H = 6.8 Hz), −80.36 (d, J^3_F H = 6.8 Hz) ppm; IR (neat)(cm^{-1}) 3430, 2980, 2960, 2880, 1500, 1470, 1370, 1270, 1180, 1135, 980, 845, 785, 705. Anal. Calcd for $C_{19}H_{29}F_3O_2Si$: C, 60.93; H, 7.80. Found: C, 60.98; H, 7.85.

(*trans*)-7-Phenyl-5-(tert-butyldimethylsiloxy)-1,1,1-trifluoro-3-hepten-2-one: 65% yield. The ketone was prepared by oxidation of the trifluoromethyl alcohol as described above: ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.95 (s, 9H), 1.92 (m, 2H), 2.66 (m, 2H), 4.50 (m, 1H), 6.65 (d, 1H, J^3_{trans} = 16 Hz), 7.15–7.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −4.97, −4.84, 18.13, 25.66, 30.93, 38.39, 71.12, 116.11 (q, J^1_{C-F} = 288 Hz), 119.42, 126.04, 128.27, 128.47, 141.26, 157.35, 179.90 (q, J^2_{C-F} = 43 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −78.70 (s) ppm; IR (neat)(cm^{-1}) 2960, 2930, 2860, 1785, 1725, 1630, 1490, 1460, 1360, 1245, 1205, 1145, 975, 835, 775, 695. Anal. Calcd for $C_{19}H_{27}F_3O_2Si$: C, 61.26; H, 7.31. Found: C, 61.45; H, 7.35.

(*trans*)-7-Phenyl-5-hydroxy-1,1,1-trifluoro-3-hepten-2-one: 85% yield. Two milliliters of 48% hydrofluoric acid was added to acetonitrile (6.0 mL) and the solution was cooled to 0 °C (ice bath). A sample of (*trans*)-7-phenyl-5-(*tert*-butyldimethylsiloxy)-1,1,1-trifluoro-3-hepten-2-one (150 mg, 0.40 mmol) was then added as a solution in acetonitrile (1.5 mL) and the mixture stirred at 0 °C for 2 h. Chloroform (25 mL) and water (15 mL) were then added to the reaction mixture and the layers separated. The organic layer was washed successively with water (10 mL), saturated aqueous sodium bicarbonate (15 mL), and saturated aqueous sodium chloride (10 mL) and then dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure, and the crude product was purified by chromatography to afford 88 mg (85%) of the alcohol: ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2H), 2.42 (br s, 1H), 2.81 (m, 2H), 4.45 (m, 1H), 6.73 (d, 1H, J^3_{trans} = 18 Hz), 7.22-7.36 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 31.32, 37.42, 70.21, 116.01 (q, J^1_{C-F} = 288 Hz), 119.16,

(25) Brandsma, L. *Preparative Acetylenic Chemistry*: Elsevier: New York, 1971; p 71.

126.21, 128.34, 128.53, 140.65, 156.77, 179.98 (q, J^2_{C-F} = 37 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −79.00 (s) ppm; IR (neat)(cm^{-1}): 3480, 3030, 2930, 2860, 1730, 1640, 1495, 1450, 1250, 1200, 1145, 1060, 975, 740, 700. Anal. Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.52; H, 5.08.

Thiol Addition Reactions. 4-Thiophenoxy-1,1,1-trifluorododecan-2-one: 82% yield. Tetrabutylammonium fluoride (10 μL of a 1.0 M solution in tetrahydrofuran), (*trans*)-1,1,1-trifluorododec-3-en-2-one (50 mg, 0.21 mmol), and thiophenol (23 mg, 0.21 mmol) were dissolved in 1 mL of THF and stirred at ambient temperature for 4 h. The reaction mixture was then diluted with ether (15 mL), and water (10 mL) was added. The layers were then separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic phases were washed sequentially with water (3 × 10 mL) and saturated aqueous sodium chloride (10 mL) and then dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure, and the crude product was purified by chromatography (ether/petroleum ether, 1, 1.5 and 2% v/v gradient eluent) to afford 60 mg (82%) of the adduct: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz), 1.20–1.40 (m, 10H), 1.40–1.60 (m, 4H), 2.93 (qd, 2H, J^2_{H-H} = 19 Hz, J^3_{H-H} = 6.6 Hz), 3.56 (quin, 1H, J = 6.6 Hz), 7.24–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.62, 26.76, 29.15, 29.34, 31.80, 34.38, 42.27, 42.78, 115.29 (q, J^1_{C-F} = 292 Hz), 127.79, 129.11, 133.02, 133.31, 189.6; (q, J^2_{C-F} = 34.7 Hz); ^{19}F NMR ($CDCl_3/CFCl_3$) −79.88 (s) ppm; IR (neat)(cm^{-1}) 2930, 2855, 1765, 1465, 1435, 1210, 1145, 745, 690. Anal. Calcd for $C_{18}H_{25}F_3OS$: C, 62.40; H, 7.27. Found: C, 62.44; H, 7.30.

4-Thiophenoxy-2-hydroxy-2-(trifluoromethyl)-5-phenethyltetrahydrofuran. Thiophenol (43 mg, 0.387 mmol) and potassium hydroxide (33 mg, 0.58 mmol) were dissolved in acetonitrile (6 mL). A solution of *trans*-7-phenyl-5-hydroxy-1,1,1-trifluoro-3-hepten-2-one (100 mg, 0.387 mmol) in acetonitrile (1.0 mL) was then added dropwise and the reaction mixture stirred for 2 h at ambient temperature. The reaction mixture was diluted with pentanes (30 mL) and water (10 mL) was then added. The aqueous layer was extracted with pentanes (2 × 20 mL), and the combined organic layers were washed sequentially with saturated aqueous ammonium chloride (40 mL), water (40 mL), and saturated aqueous sodium chloride (40 mL). The organic phase was dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure to yield 100 mg of unstable crude product. The hemiacetal was used directly in the synthesis of 2-(trifluoromethyl)-5-phenethylfuran: ^{1}H NMR ($CDCl_3$) δ 1.70–2.25 (m, 3H), 2.45–2.80 (m, 3H), 2.82 (s, 0.5H), 3.12 (s, 0.5H), 3.45–3.60 (m,1 H), 3.96 (td, 0.5H, J = 9.3 Hz, J = 3 Hz), 4.18 (td, 0.5H, J = 8.1 Hz, J = 4 Hz), 7.1–7.4 (m, 10H); ^{13}C NMR, APT-($CDCl_3$) δ 31.54 (CH_2), 31.70 (CH_2), 34.97 (CH_2), 35.74 (CH_2), 40.39 (CH_2), 40.52 (CH_2), 48.02 (CH), 49.15 (CH), 84.56 (CH), 86.18 (CH), 100.60 (C, q, J^2_{C-F} = 35 Hz), 101.49 (C, q, J^2_{C-F} = 35 Hz), 122.30 (CF_3, q, J^1_{C-F} = 285 Hz), 122.58 (CF_3, q, J^1_{C-F} = 285 Hz), 125.95 (CH), 128.08 (CH), 128.37 (CH), 129.15 (CH), 129.24 (CH), 132.31 (C), 132.82 (CH), 133.18 (CH), 141.10 (C); ^{19}F NMR ($CDCl_3/CFCl_3$) −85.35 (s) ppm, IR (neat)(cm^{-1}) 3420, 3065, 3030, 2930, 1600, 1580, 1475, 1445, 1435, 1300, 1180, 905, 730, 695; GC-MS (*m/e*) 368 (M+), 350, 258, 234, 199, 129.

2-(Trifluoromethyl)-5-phenethylfuran. A sample of 4-thiophenoxy-2-hydroxy-2-(trifluoromethyl)-5-phenethyltetrahydrofuran (50 mg, 0.136 mmol) was dissolved in benzene (15 mL), and concentrated sulfuric acid (2 drops) was added with a catalytic amount of *p*-toluenesulfonic acid. The flask was fitted with a Dean–Stark trap and the reaction mixture refluxed for 1 h. Hexanes (15 mL) and water (10 mL) were then added and the layers separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate (15 mL) and saturated aqueous sodium chloride (15 mL) and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure, and the crude product was purified by chromatography to yield 15 mg (46% overall yield from *trans*-7-phenyl-5-hydroxy-1,1,1-trifluoro-3-hepten-2-one) of the furan: ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 4H), 6.00 (d, 1H, J = 3.7 Hz), 6.63 (d, 1H, J = 3.7 Hz), 7.10–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.76, 33.83, 106.43, 112.28, 119.30 (q, J^1_{C-F} = 266 Hz), 126.27, 128.27, 128.44, 140.42, 158.26; ^{19}F NMR ($CDCl_3/CFCl_3$) −65.2 (s) ppm; IR (neat)(cm^{-1}) 1610, 1555, 1490, 1380, 1150. Anal. Calcd for $C_{13}H_{11}F_3O$: C, 64.99; H, 4.62. Found: C, 64.82; H, 4.70.

^{19}F NMR Analysis of Conjugation Reactions. A sample of thiophenol (1.1 mg) or glutathione (3.0 mg) was dissolved in 0.5 mL of d_6-dimethyl sulfoxide and the solution transferred to a vial containing a sample of the appropriate trifluoromethyl ketone (1.0 equiv). The mixture was swirled for a 3 min at ambient temperature and the sample was then transferred to a 5-mm NMR tube and the ^{1}H and ^{19}F NMR spectra obtained. The NMR data are given in the text. The conjugate addition products from these experiments were not isolated.

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