JOC*Note*

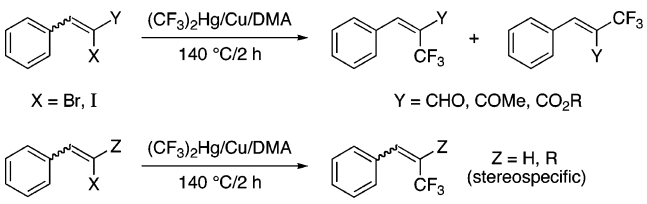
Trifluoromethylation of Alkenyl Bromides and Iodides (Including 5-Iodouracils) with $(CF_3)_2Hg$ and Cu ("Trifluoromethylcopper")[1]

Ireneusz Nowak and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

morris_robins@byu.edu

Received December 12, 2006



Bromo- and iodoalkenes undergo trifluoromethylation efficiently in DMA with "CF_3Cu" generated from $(CF_3)_2Hg$ and Cu. Variable stereochemical inversion is observed with substrates having a *gem*-carbonyl group. Substrates having *gem*-hydrogen, -alkyl, or -alkenyl groups give products with stereochemical retention.

An increasing number of agrochemicals, materials, and pharmaceutical agents that contain CF_3 groups have been developed. A notable recent example is "fludelone" an anticancer analogue of Epothilone B.[2] Therefore, development of methodology for the efficient and selective synthesis of compounds with trifluoromethyl substituents is a timely goal. Fluorinated organocopper reagents with reasonable thermal stabilities are known. "Trifluoromethylcopper" is more important and interesting than its homologues because of its applications and reactivity, but it is less thermally stable. Different approaches have been described for its preparation, but conditions often are not compatible with medicinal substrates and/or common laboratory equipment. The elusive nature of "CF_3Cu" represents an additional difficulty.

Burton reported the presence of three copper species in DMF solution,[3] which were suggested to include CF_3CuL (L = metal halide), $CdI^+[(CF_3)_2Cu]^-$, and $CdI^+[(CF_3)_4Cu]^-$ (a Cu^{3+} oxidation product).[4] The existence of a copper difluorocarbenoid ($F_2C{=}CuF$) was postulated more recently.[5] A low-temperature procedure[3] (and the method of Matsui et al., CF_3CO_2Na/CuI)[6a] gave small quantities of pentafluoroethyl analogues[6b] that presumably resulted from difluorocarbene insertion into C−Cu bonds. Electrochemical generation of CF_3Cu produced three species depending on the nature of the ligand.[7]

A method with a halogen-free environment that does not generate difluorocarbene is advantageous. Yagupolskii had reported high-temperature trifluoromethylations of aryl bromides and iodides with $(CF_3)_2Hg/Cu$,[8] but such reactions of CF_3Cu with vinyl halides have not been investigated carefully. Coupling of perfluoroalkylcopper reagents with (*E*)-1,2-diiodoethene gave products with retained configurations.[9] However, vicinal rather than gem-disubstituted alkenes had been obtained by analogous treatment of 1-bromo-1-perfluoroalkylethenes.[10] Coupling of other haloalkenes with CF_3Cu has been reported, but the cyclic and symmetrical alkenes or *E*/*Z* mixtures employed did not allow definitive stereochemical analysis.[11] Recently Qing and coworkers noted that couplings of α-bromo-α,β-unsaturated esters with $FSO_2CF_2CO_2Me/CuI$ occurred with high *E* diastereoselectivity.[12] Sterospecific couplings of α-iodo-α,β-unsaturated esters were claimed, but most were performed with *Z*-diastereomer-enriched mixtures.[13] We now report couplings of bromo- and iodoalkenes of defined stereochemistry with CF_3Cu generated by the halogen-free procedure of Yagupolskii.[8]

The anticancer/antiviral drug "trifluorothymidine" [2′-deoxy-5-(trifluoromethyl)uridine] has been used topically for decades.[14] Treatment of acetylated 5-iodouracil nucleosides with a large excess of CF_3I/Cu in HMPA had given 5-(trifluoromethyl)uracil derivatives (38−54%), and solutions obtained by filtration of $CF_3I/Cu/HMPA$ in a glove box under nitrogen gave higher yields.[15] One review quotes a 78% yield using CF_3Br/Cu.[16]

We generated a CF_3Cu reagent[8] in situ by heating $(CF_3)_2Hg$[17] and "active" copper powder[18] at 140 °C for 2 h in *N*,*N*-dimethylacetamide (DMA) (Hg that separates forms an amalgam with excess Cu). Solutions of nucleoside derivatives **1** (Scheme 1) in DMA were then added, and heating was continued at 140 °C for 2 h. The first reaction (compound **1a**,

(1) Nucleic Acid Related Compounds. 142. Paper 141: Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2007**, *72*, 532−537.

(2) (a) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T.-C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913−10922. (b) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329−8351.

(3) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *108*, 832−834.

(4) Willert-Porada, M.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1633−1634.

(5) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **2000**, *102*, 89−103.

(6) (a) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, 1719−1720. (b) Wrobel, J.; Dietrich, A.; Gorham, B. J.; Sestanj, K. *J. Org. Chem.* **1990**, *55*, 2694−2702.

(7) Paratian, J. M.; Labbé, E.; Sibille, S.; Périchon, J. *J. Organomet. Chem.* **1995**, *489*, 137−143.

(8) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932−933.

(9) Coe, P. L.; Milner, N. E.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 654−656.

(10) Santini, G.; Le Blanc, M.; Riess, J. G. *Tetrahedron* **1973**, *29*, 2411−2414.

(11) Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *42*, 4071−4072.

(12) (a) Zhang, X.; Qing, F.-L.; Yu, Y. *J. Org. Chem.* **2000**, *65*, 7075−7082. (b) Qing, F.-L.; Zhang, X. *Tetrahedron Lett.* **2001**, *42*, 5929−5931.

(13) Zhang, X.; Quing, F.-L.; Peng, Y. *J. Fluorine Chem.* **2001**, *108*, 79−82.

(14) Heidelberger, C.; King, D. H. *Pharmacol. Ther.* **1979**, *6*, 427−442.

(15) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755−2761.

(16) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.

(17) Knunyants, I. L; Komissarov, Y. F.; Dyatkin, B. L.; Lansteva, L. T. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1973**, *4*, 943−944.

(18) Brewster, R. Q.; Groening, T. *Organic Syntheses*; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. II, p 446.

10.1021/jo062544a CCC: $37.00
Published on Web 03/03/2007

SCHEME 1. Trifluoromethylation of 5-Iodouracil Nucleosides 1

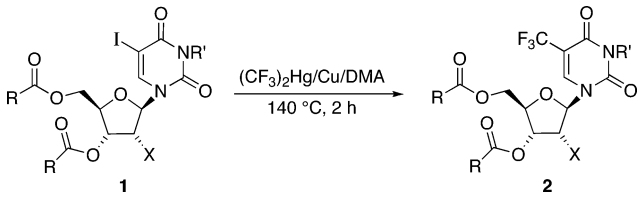
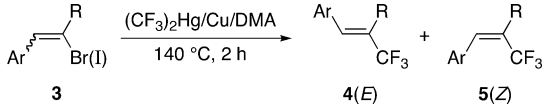


TABLE 1. Yields of Trifluoromethylation Reactions of 1[a]

entry[b]	R	R′	X	yield[c]
1 (**1a**)	Ph	H	$PhCO_2$	94[d]
2 (**1b**)	Ph	Me	$PhCO_2$	94
3 (**1c**)	Ph	Bz	$PhCO_2$	49[e]
4 (**1d**)	MePh	PMB	H	90[f]

[a] See Supporting Information for the general procedure. [b] Starting material in parentheses. [c] Percent of **2** isolated relative to starting unprotected nucleoside. [d] 2′,3′,5′-Tri-*O*-benzoyluridine (product of C−I reduction). [e] Product **2c′** had R′ = H (Bz group underwent hydrolysis). [f] Reaction temperature 110 °C.

SCHEME 2. Trifluoromethylation of Haloolefins 3



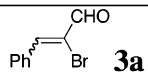
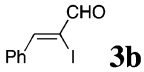
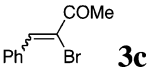
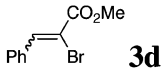
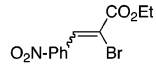
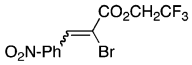
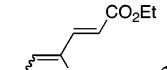
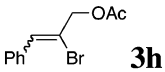
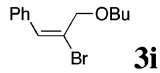
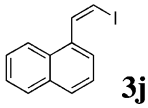
entry 1, Table 1) resulted in reduction of the C−I bond to give 2′,3′,5′-tri-*O*-benzoyluridine (94%). In contrast, the 3-methyl derivative **1b** underwent trifluoromethylation at C5 to give **2b** (94%) (entry 2). The 3-benzoyl derivative **1c** underwent loss of the *N*-benzoyl protection and gave 49% of the trifluoromethylated product **2c′** (entry 3). Protection of 2′-deoxy-5-iodo-3′,5′-di-*O*-(4-methylbenzoyl)uridine at N3 with 4-methoxybenzyl chloride gave PMB-derivative **1d**, which underwent trifluoromethylation at 110 °C to give **2d** (90%, entry 4). The lower temperature caused less thermal cleavage of the 2′-deoxyglycosyl linkage. Copper-assisted nucleophilic aromatic substitution has been the favored mechanism for couplings of $[CF_3CuI]^-$ with haloaromatics,[19] but CF_3Cu generated in a halogen-free process might react differently.

We also subjected a number of linear haloalkenes to our standard $(CF_3)_2Hg$/Cu/DMA conditions. Aldehydes **3a** and **3b** and ketone **3c** provided the *E* diastereomers **4** as major products (Scheme 2) (Table 2, entries 1−6). This is in marked contrast with the stereospecific process reported (without definitive characterization of products)[7] for the reaction of electrochemically generated CF_3Cu and **3a**. The *E*/*Z* selectivity with our trifluoromethylation reactions of α-bromoesters **3d**−**3f** varied with the nature of the aromatic ring and the ester group (entries 5−12). Other vinyl halides we examined (i.e., without a carbonyl group geminal to the halide) underwent stereospecific coupling with retention.

A critical observation was that the neat *E* isomers of **3a** and **3c** were completely converted into their *Z* diastereomers at 140 °C within 2 h. Isomer **3a**(*E*) was stereochemically labile even in the dark at ambient temperature and was purified at low temperature and used immediately or stored in solution. Incorrect assignments of *E* stereochemistry to **3a**(*Z*) and **3c**(*Z*)

(19) Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 921−926.

TABLE 2. Trifluoromethylation of 3 to Give 4 and/or 5[a]

entry	3		4[b]	5[b]	yield[c]
1	 **3a**	*Z*	75	25	90
2		*E*	77	23	75
3	 **3b**	*Z*	77	23	87
4		*Z*	84	16	93[d]
5	 **3c**	*Z*	75	25	87
6		*E*	74	26	90
7	 **3d**	*Z*	5	95	92
8		*E*	98	2	88
9		*Z*	23	77	93
10	**3e**	*E*	95	5	86
11		*Z*	81	19	92
12	**3f**	*e*	82	18	89
13		*Z*	0	100	85
14	**3g**	*E*[f]	99	1	92
15	 **3h**	*Z*	0	100	93
16		*E*	100	0	91
17	 **3i**	*E*	100	0	95
18	 **3j**	*Z*	0	100	93

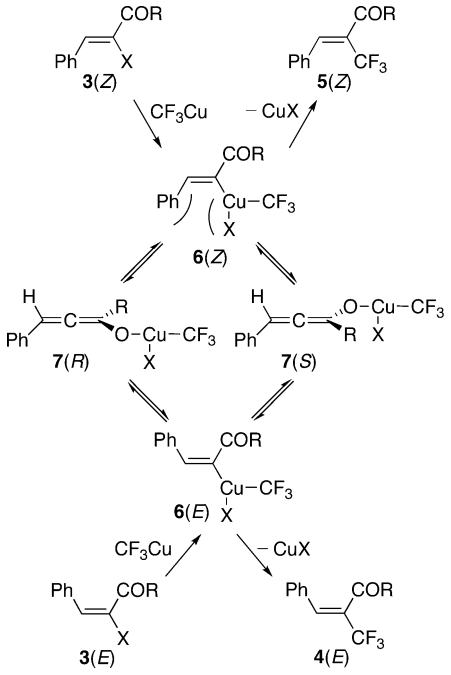
[a] See Supporting Information for the general procedure. [b] *E*/*Z* ratios were determined by ^{19}F NMR. [c] Isolated yields. [d] Temperature was 100 °C. [e] A mixture of *E*/*Z* (2:1) isomers was used. [f] Trace contamination with **3g**(*Z*) occurred during the Wittig reaction.

add to the confusion,[20] and the *E* configuration assigned to **3b** also is erroneous. The only isomer that appears to have been isolated is **3b**(*Z*).[21] Only **3f**(*E*) of the other carbonyl-containing starting materials **3** was converted into its *Z* isomer at 140 °C (∼30 h, neat or in DMA). Starting material stereochemistry was

(20) (a) Marsura, A.; Luu-Duc, C.; Gellon, G. *Synthesis* **1985**, 537−541. (b) Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* **1988**, 236−238. (c) Berteina, S.; De Mesmaeker, A.; Wendeborn, S. *Synlett* **1999**, 1121−1123. (d) Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Martin, C. G.; Kennedy, A. L.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2395−2408. (e) Bour, C.; Suffert, J. *Eur. J. Org. Chem.* **2006**, 1390−1395.

(21) Coulomb, F.; Roumenstat, M.-L.; Gore, J. *Bull. Soc. Chim. Fr.* **1973**, 3352−3359.

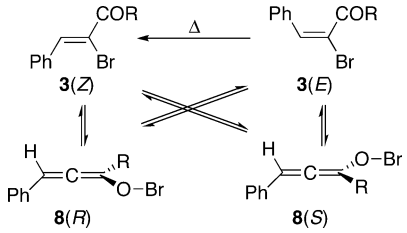
SCHEME 3. Possible Pathways for Trifluoromethylation of Vinyl Halides 3 Containing a *gem*-Carbonyl Group



assigned from vinyl proton chemical shifts (**3c**−**3g**).[13] Aromatic proton signals for the *Z* isomers also have more complex patterns,[22] and an X-ray crystal structure of **3g**(2*E*,4*Z*) was determined (Supporting Information). Configurations of the products were assigned from ^{19}F NMR chemical shifts (CF_3, 65 ± 2 ppm for the *E* isomers **4**[23] and 58 ± 2 ppm for the *Z* isomers **5**).

Because most starting materials were thermally stable under our conditions, different intermediates must be involved with formation of products **4** and **5** (Scheme 3). CF_3Cu might undergo insertion into the C−Br(I) bond to give intermediates such as **6**. Substrates **3h**−**3j** without a *gem*-carbonyl group might undergo direct ligand coupling to give trifluoromethyl products with retention of configuration. Aldehydes **3a**(*Z*) and **3b**(*Z*), ketone **3c**(*Z*), and esters **3d**−**3f** might undergo initial insertion followed by dissociation/combination equilibria involving copper allenoates **7**(*R*/*S*). Relief of steric strain between the arene and ligated copper in **6**(*Z*) would favor equilibration to **6**(*E*) and ultimately the thermodynamically stable *E* isomer **4**. It is noteworthy that a higher *E*-isomer product selectivity (more inversion) was observed at a lower temperature (100 °C, entry 3) for the more reactive iodide **3b**. The larger steric bulk of the iodine ligand might also favor formation of **6**(*E*). Structures analogous to **6** and **7** were recently proposed as intermediates in a mechanism for copper-catalyzed hydrostannation of activated alkynes, which gave exclusive *syn*-stannation of esters but inversion of stereochemistry for ketones.[24] Marino had previously suggested that (α-carbethoxyvinyl)cuprates[25] react

SCHEME 4. Possible Isomerization Pathways for Vinyl Halides 3 Containing a *gem*-Carbonyl Group



with electrophiles via mechanisms involving copper allenoates.[26]

Esters **3d** gave products with ≤5% inversion (entries 7 and 8). The electron-withdrawing CF_3 ligand on copper and/or the elevated temperature might contribute to a small loss of stereochemical retention. Increased electron demand by the aryl group influenced the stereoselectivity with **3e**(*Z*) (entry 9) but had no effect with **3e**(*E*) (entry 10). Our X-ray crystal structure of **3g**(2*E*/4*Z*) shows a 39° twist between the planes of the phenyl ring and the C═C double bond (presumably resulting from steric interactions between bromine and an ortho-hydrogen on the benzene ring). Larger deviations from coplanarity might result from steric effects in *E* diastereomers of **3d** and **3e** with proximal ester and phenyl groups on the double bond. Such distortions of the π-system might limit transmission of electronic effects from the *p*-nitro group to the reaction center in **3e**(*E*). Increased electron demand by a proximal trifluoroethoxy group in **3f**(*Z*) resulted in predominant inversion, and the same *E*/*Z* ratio (entry 11) was obtained with a **3f**(*E*)-rich mixture of isomers (entry 12). In contrast, no inversion was observed with **3g**, the vinylogous analogue of **3d**, with the carbonyl group farther separated from the reaction center (entries 13 and 14).

Interactions of CF_3Cu species with ortho-substituent groups (NO_2, CHO, COR, CO_2R) had been invoked to rationalize unexpectedly high substitution yields with some chloroaromatic compounds.[27] Treatment of (*Z*)-(2-bromo-2-nitrovinyl)benzene by our procedure gave (*E*)-(2-nitrovinyl)benzene as the major product. Ligand coupling of a transient organometallic intermediate might have failed, and its protonolysis during aqueous workup would generate the debrominated compound.

Stereospecific cross-coupling reactions of **3a**(*Z*) and other α-bromo-α,β-unsaturated carbonyl compounds (catalyzed by metals including copper) have been reported to occur with retention of configuration, even at elevated temperatures.[28] Inversion observed in some of our examples might result from equilibration with copper allenoates, with formation promoted by the electron-withdrawing CF_3 ligand. Related equilibration via allenyl intermediates **8** might explain the noted isomerization of some vinyl bromides **3** that contain a *gem*-carbonyl group (Scheme 4). Such "halotautomerization" of bromide between

(22) Agoff, J. M.; Cabaleiro, M. C.; Podesta, J. C. *Chem. Ind.* **1974**, 305−306 and references therein.

(23) Furuta, S.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 805−819.

(24) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249−5252.

(25) Marino, J. P.; Floyd, D. M. *J. Am. Chem. Soc*. **1974**, *96*, 7138−7140; These authors reported generation of (α-carbethoxyvinyl)cuprates from α-bromoacrylate and organocopper reagents.

(26) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621−4628.

(27) (a) Clark, J. H.; McClinton, M. A.; Blade, R. J. *J. Chem. Soc. Chem. Commun.* **1988**, 638−639. (b) Clark, J. H.; Denness, J. E.; McClinton, M. A.; Wynd, A. J. *J. Fluorine Chem.* **1990**, *50*, 411−426.

(28) (a) Zapata, A. J.; Ruíz, J. *J. Organomet. Chem.* **1994**, *479*, C6−C8. (b) Urdaneta, N.; Ruíz, J.; Zapata, A. J. *J. Organomet. Chem.* **1994**, *464*, C33−C34. (c) Dai, W.-M.; Wu, A.; Hamaguchi, W. *Tetrahedron Lett.* **2001**, *42*, 4211−4214. (d) Lautens, M.; Maddess, M. L.; Sauer, E. L.; Ouellet, S. G. *Org. Lett.* **2002**, *4*, 83−86. (e) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497−2500. (f) Sahli, S.; Stump, B.; Welti, T.; Schweizer, W. B.; Diederich, F.; Blum-Kaelin, D.; Aebi, J. D.; Böhm, H.-J. *Helv. Chim. Acta* **2005**, *88*, 707−730. (g) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950−3956.

the α-vinyl carbon and carbonyl oxygen would produce enantiomers **8** of equal energy. It is noteworthy that the iodo analogue **3b**(*E*) could not be isolated by the same procedure used for **3a**(*E*), and carbon−iodine/oxygen−iodine bonds are more polarizable than those with bromine.

In conclusion, we have employed $(CF_3)_2Hg$/Cu/DMA for trifluoromethylation of bromo- and iodoalkenes (including protected 5-iodouracil nucleosides). Higher temperatures are required than for some methods that use CF_3Cu generated from CuX (X = Br, I), but a variety of vinyl halides give high yields in DMA at 140 °C. Reactions with *E* and *Z* isomers of several haloalkenes **3** showed that *gem*-carbonyl groups can alter cross-coupling stereochemistry in some cases. Insertion of copper species into carbon−halogen bonds followed by equilibration involving copper allenoates **7** might rationalize formation of products with inverted configurations. Our $(CF_3)_2Hg$/Cu/DMA methodology does not require stainless steel reactors, glove box techniques, syringe-pump reagent additions, or lengthy reaction times, and no CF_2 insertion byproducts have been observed. NOTE: **caution** must be exercised when handling volatile and toxic organomercury compounds.

Experimental Section[29]

General Procedure for Trifluoromethylation of Alkenyl Bromides and Iodides. Freshly generated copper powder[18] (341 mg, 5.33 mmol) was dried at 140 °C for 1 h under vacuum in a 30-mL flask equipped with a Teflon valve. After cooling to ambient temperature, $(CF_3)_2Hg$[8,17] (452 mg, 1.33 mmol) and dried *N*,*N*-dimethylacetamide (DMA; 2.0 mL) were added under a nitrogen atmosphere, and the mixture was stirred at 140 °C for 2 h. [**CAUTION**: bis(trifluoromethyl)mercury is volatile and toxic and should be used only by experienced researchers with appropriate safety precautions.] A solution of the vinyl iodide or bromide (1.33 mmol) in DMA was then added to the dark-green suspension, and stirring was continued for 2 h at 140 °C. The cooled supernatant was transferred into a vigorously stirred solution of brine (50 mL), and the mixture was extracted (EtOAc; 3 × 20 mL). Volatiles were evaporated from the organic layer, and the residue was chromatographed to give the purified product.

2′-Deoxy-3-(4-methoxybenzyl)-3′,5′-di-*O*-(4-methylbenzoyl)-5-(trifluoromethyl)uridine (2d). ^{1}H NMR δ 2.23 (ddd, *J* = 6.8, 7.8, 14.2 Hz, 1H), 2.39 (s, 3H), 2.44 (s, 3H), 2.87 (ddd, *J* = 1.0, 5.4, 14.2 Hz, 1H), 3.78 (s, 3H), 4.59−4.61 (m, 1H), 4.67−4.75 (m, 2H), 5.00 (d, *J* = 13.7 Hz, 1H), 5.06 (d, *J* = 13.7 Hz, 1H), 5.59 (d, *J* = 6.3 Hz, 1H), 6.33 (dd, *J* = 5.4, 8.3 Hz, 1H), 6.82−7.94 (m, 12H), 8.05 (s, 1H); ^{19}F NMR δ 64.3 (s, 3F); ^{13}C NMR δ 21.3, 21.4, 38.8, 43.7, 54.8, 63.7, 68.7, 74.7, 83.0, 87.0, 104.4 (q, *J* = 32.8 Hz), 113.5, 121.7 (q, *J* = 270.2 Hz), 126.0, 127.8, 129.0−130.8 (ovlp), 137.8 (q, *J* = 5.0 Hz), 144.2, 144.3, 149.5, 157.6, 159.1, 165.6, 165.7; FAB-MS *m*/*z* 675 ([M + Na^+] 100%); HRMS ($C_{34}H_{31}F_3N_2O_8Na$) calcd 675.1924, found 675.1923.

(*E*)-4-Phenyl-3-(trifluoromethyl)but-3-en-2-one (4c). ^{1}H NMR δ 2.21 (s, 3H), 7.30−7.44 (m, 6H); ^{19}F NMR δ 63.9 (s, 3F); ^{13}C NMR δ 30.7, 122.1 (q, *J* = 274.2 Hz), 128.7, 129.0, 130.3, 131.3 (q, *J* = 29.1 Hz), 132.1, 137.0 (q, *J* = 6.1 Hz), 198.8; EI-MS *m*/*z* 214 ([M $^+$] 65%), 213 (100%); HRMS ($C_{11}H_9F_3O$) calcd 214.0605, found 214.0607.

(*Z*)-4-Phenyl-3-(trifluoromethyl)but-3-en-2-one (5c). ^{1}H NMR δ 2.48 (s, 3H), 7.41 (m, 5H), 7.88 (s, 1H); ^{19}F NMR δ 57.4 (s, 3F); ^{13}C NMR δ 27.8, 122.1 (q, *J* = 274.2 Hz), 128.3, 129.4, 130.1 (q, *J* = 28.9 Hz), 130.2, 132.4, 146.8 (q, *J* = 3.2 Hz), 194.7; EI-MS *m*/*z* 214 ([M $^+$] 40%), 213 (100%); HRMS ($C_{11}H_9F_3O$) calcd 214.0605, found 214.0589.

Methyl (*E*)-3-Phenyl-2-(trifluoromethyl)prop-2-enoate[12a] (4d). ^{1}H NMR δ 3.90 (s, 3H), 7.35−7.42 (m, 6H); ^{19}F NMR δ 64.3 (s, 3F); ^{13}C NMR δ 52.5, 122.1 (q, *J* = 273.1 Hz), 123.1 (q, *J* = 31.5 Hz), 128.6, 129.1, 130.4, 132.1, 140.4 (q, *J* = 5.6 Hz), 163.8; EI-MS *m*/*z* 230 ([M $^+$] 100%); HRMS ($C_{11}H_9F_3O_2$) calcd 230.0554, found 230.0562.

Methyl (*Z*)-3-Phenyl-2-(trifluoromethyl)prop-2-enoate[12a] (5d). ^{1}H NMR δ 3.77 (s, 3H), 7.37−7.43 (m, 5H), 8.11 (s, 1H); ^{19}F NMR δ 58.5 (s, 3F); ^{13}C NMR δ 52.4, 121.8 (q, *J* = 274.1 Hz), 122.1 (q, *J* = 32.0 Hz), 128.1, 129.1, 129.9, 132.3, 148.3, 163.5; EI-MS *m*/*z* 230 ([M $^+$] 100%); HRMS ($C_{11}H_9F_3O_2$) calcd 230.0554, found 230.0554.

Ethyl (*E*)-3-(4-Nitrophenyl)-2-(trifluoromethyl)prop-2-enoate[12a] (4e). ^{1}H NMR δ 1.21 (t, *J* = 7.3 Hz, 3H), 4.23 (q, *J* = 7.3 Hz, 2H), 7.51 (s, 1H), 7.55 and 8.26 (2 × d, *J* = 8.3 Hz, 2 × 2H); ^{19}F NMR δ 64.8 (s, 3F); ^{13}C NMR δ 13.4, 62.2, 121.5 (q, *J* = 273.7 Hz), 123.4, 126.6 (q, *J* = 31.6 Hz), 129.6, 138.4 (q, *J* = 5.6 Hz), 138.8, 148.2, 162.0; EI-MS *m*/*z* 289 ([M $^+$] 90%), 244 (100%); HRMS ($C_{12}H_{10}F_3NO_4$) calcd 289.0562, found 289.0569.

Ethyl (*Z*)-3-(4-Nitrophenyl)-2-(trifluoromethyl)prop-2-enoate[12a] (5e). ^{1}H NMR δ 1.40 (t, *J* = 7.3 Hz, 3H), 4.39 (q, *J* = 7.3 Hz, 2H), 7.53 and 8.27 (2 × d, *J* = 8.3 Hz, 2 × 2H), 8.11 (s, 1H); ^{19}F NMR δ 58.4 (s, 3F); ^{13}C NMR δ 13.8, 62.3, 121.3 (q, *J* = 274.7 Hz), 123.3, 125.6 (q, *J* = 32.0 Hz), 129.4, 139.1, 145.1 (q, *J* = 2.3 Hz), 148.1, 162.2; EI-MS *m*/*z* 289 ([M $^+$] 90%), 244 (100%); HRMS ($C_{12}H_{10}F_3NO_4$) calcd 289.0562, found 289.0574.

2,2,2-Trifluoroethyl (*E*)-3-(4-Nitrophenyl)-2-(trifluoromethyl)prop-2-enoate (4f). ^{1}H NMR δ 4.55 (q, *J* = 8.1 Hz, 2H), 7.35−7.55 (m, 2H), 7.73 (s, 1H), 8.26−8.28 (m, 2H); ^{19}F NMR δ 64.7 (s, 3F), 74.0 (t, *J* = 8.5 Hz, 3F); ^{13}C NMR δ 60.9 (q, *J* = 37.4 Hz), 121.3 (q, *J* = 273.9 Hz), 122.3 (q, *J* = 276.9 Hz), 123.6, 124.7 (q, *J* = 32.3 Hz), 129.5, 138.4, 142.0 (q, *J* = 6.1 Hz), 148.5, 160.4; EI-MS *m*/*z* 343 ([M + Na^+] 100%); HRMS ($C_{12}H_7F_6NO_4$) calcd 343.0279, found 343.0293.

2,2,2-Trifluoroethyl (*Z*)-3-(4-Nitrophenyl)-2-(trifluoromethyl)prop-2-enoate (5f). ^{1}H NMR δ 4.70 (q, *J* = 8.1 Hz, 2H), 7.55−7.57 (m, 2H), 8.21 (s, 1H), 8.29−8.31 (m, 2H); ^{19}F NMR δ 58.6 (s, 3F), 74.2 (t, *J* = 8.5 Hz, 3F); EI-MS *m*/*z* 343 ([M + Na^+] 100%); ^{13}C NMR δ 61.5 (q, *J* = 32.8 Hz), 120.9 (q, *J* = 275.2 Hz), 121.7 (q, *J* = 277.2 Hz), 123.6, 124.2 (q, *J* = 32.3 Hz), 129.7, 138.3, 147.4, 148.5, 160.8; HRMS ($C_{12}H_7F_6NO_4$) calcd 343.0279, found 343.0280.

Acknowledgment. We gratefully acknowledge NIH grant GM029332, pharmaceutical company unrestricted gift funds (M.J.R.), and Brigham Young University for support of this research and Professor Steven R. Herron for determining the X-ray crystal structure of **3g**(2*E*,4*Z*).

Supporting Information Available: Experimental procedures, data, X-ray crystal structure of **3g**(2*E*,4*Z*) in CIF format, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062544A

(29) See Supporting Information for general experimental details, preparation of starting materials, and other trifluoromethyl compounds, data, and spectra.