2.06–2.26 (m, 2 H), 5.76 (t, J = 7 Hz, 1 H), and 7.10–7.36 (m, 5 H); mass spectrum, m/e (M^+) 202.

5-Isopropyl-(*E*)-5-decene (3J): ^{1}H NMR ($CDCl_3$/TMS) δ 0.83–1.40 (m, 20 H), 1.80–2.50 (m, 5 H), and 5.06 (t, J = 6 Hz, 1 H); mass spectrum, m/e (M^+) 182.

The preparation of 5-(2-furanyl)-(*Z*)-5-decene (4A) is representative. In a dry 100-mL flask were placed (*Z*)-2-(1-butyl-1-hexenyl)-1,3,2-dioxaborinane (**2A**, 10 mmol, 2.44 mL) and diethyl ether (20 mL). The flask was cooled to −78 °C, and 2-lithiofuran (prepared by treating 10 mmol of furan with 10 mmol of *n*-butyllithium in diethyl ether (10 mL) at 0 °C for 0.5 h) was added dropwise. The reaction mixture was stirred at −78 °C for 0.5 h and at 0 °C for 1 h. The solvents were then pumped off, and methanol (10 mL) was added at 0 °C. Iodine (10 mmol, 2.54 g) in methanol (40 mL) was added slowly with vigorous stirring at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then brought to room temperature. Sodium hydroxide (10 mL of a 3 M solution) was added, and the reaction mixture was stirred for 15 min. It was then diluted with water (150 mL) and extracted with *n*-pentane (3 × 25 mL). The combined pentane extract was washed with an aqueous 1 M solution of sodium thiosulfate (25 mL) and water (2 × 25 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a crude product, which was purified by distillation to provide 5-(2-furanyl)-(*Z*)-5-decene (**4A**, 1.64 g, 80%): bp 54–56 °C/0.01 mm; n^{20}_D 1.4816; GC analysis showed >97% stereochemical purity; IR (neat) ν 1651, 1584, 800, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.80–1.60 (m, 14 H), 2.16–2.38 (m, 4 H), 5.40 (t, J = 6 Hz, 1 H), 6.13–6.36 (m, 2 H), and 7.30 (unresolved d, 1 H); mass spectrum, m/e (M^+) 206.

5-Phenyl-(*Z*)-5-decene (4B): IR (neat) ν 1598, 1568, 770, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.46 (m, 14 H), 1.83–2.36 (m, 4 H), 5.40 (t, J = 6.20 Hz, 1 H), and 7.00–7.23 (m, 5 H); mass spectrum, m/e (M^+) 216.

5-(2-Thiophene-yl)-(*Z*)-5-decene (4C): IR (neat) ν 1644, 1578, 847, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.50 (m, 14 H), 2.00–2.40 (m, 4 H), 5.46 (t, J = 7 Hz, 1 H), and 6.80–7.20 (m, 3 H); mass spectrum, m/e (M^+) 222.

5-Phenyl-(*Z*)-5-dodecene (4D): IR (neat) ν 1598, 770, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.46 (m, 18 H), 1.83–2.46 (m, 4 H), 5.43 (t, J = Hz, 1 H), and 7.06–7.36 (m, 5 H); mass spectrum, m/e (M^+) 244.

2-Phenyl-(*Z*)-2-nonene (4E): IR (neat) ν 1598, 763, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.80–1.53 (m, 11 H), 1.83–2.10 (m, 5 H), 5.46 (t, J = Hz, 1 H), and 7.10–7.36 (m, 5 H); mass spectrum, m/E (M^+) 202.

2-Methyl-3-phenyl-(*Z*)-3-octene (4F): IR (neat) ν 1598, 763, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.83 (distorted t, 3 H), 1.00 (d, J = 6 Hz, 6 H), 1.13–1.53 (m, 4 H), 1.70–2.80 (m, 3 H), 5.40 (t, J = 7 Hz, 1 H), and 6.93–7.36 (m, 5 H); mass spectrum, m/e (M^+) 202.

5-Isopropyl-(*Z*)-5-decene (4G): ^{1}H NMR ($CDCl_3$/TMS) δ 0.86–1.53 (m, 20 H), 1.90–2.56 (m, 5 H), and 5.03 (t, J = 6 Hz, 1 H); mass spectrum, m/e (M^+) 182.

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE 8706102) for support of this work.

Registry No. **1a**, 105763-12-0; **1g**, 117582-75-9; **1** (R^1 = *n*-C_4H_9, R^2 = CH_3), 117582-72-6; **1** (R^1 = *c*-C_6H_{11}, R^2 = CH_3), 105763-14-2; **1** (R^1 = $(CH_2)_3Cl$, R^2 = CH_3), 117582-73-7; **1** (R^1 = *n*-C_6H_{13}, R^2 = C_4H_9), 105763-13-1; **1** (R^1 = C_2H_5, R^2 = CH_3), 117582-74-8; **1** (R^1 = *n*-C_6H_{13}, R^2 = CH_3), 117582-90-8; **2a**, 105763-18-6; **2b**, 117582-76-0; **2c**, 117582-77-1; **2d**, 117605-92-2; **3a**, 66619-22-5; **3b**, 117582-78-2; **3c**, 117582-79-3; **3d**, 83021-58-3; **3e**, 117582-80-6; **3f**, 117582-81-7; **3g**, 117582-82-8; **3h**, 70303-28-5; **3i**, 62135-01-7; **3j**, 117582-83-9; **3k**, 117582-84-0; **4a**, 117582-85-1; **4b**, 110897-35-3; **4c**, 117582-86-2; **4d**, 117582-87-3; **4e**, 62135-02-8; **4f**, 117582-88-4; **4g**, 117582-89-5; PhLi, 591-51-5; $(CH_3)_2CHMgCl$, 1068-55-9; C_2H_5MgBr, 925-90-6; 2-lithiothiophene, 2786-07-4; 2-lithiofuran, 2786-02-9.

Addition of Organocuprates to Acetylenic Di- and Trifluoromethyl Ketones. Regiospecific Synthesis of β,β-Disubstituted Unsaturated Fluoro Ketones

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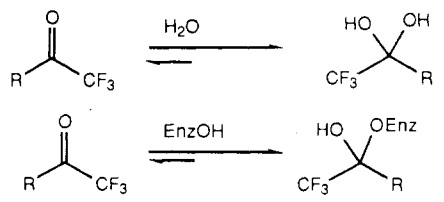
A regiospecific synthesis of β,β-disubstituted-α,β-unsaturated di- and trifluoromethyl ketones has been achieved by the conjugate addition of higher order cyano cuprate reagents to acetylenic di- and trifluoromethyl ketones. An efficient and reproducible synthesis of the acetylenic fluoro ketones required was devised by alkylation of lithio acetylides with ethyl di- or trifluoroacetate in the presence of boron trifluoride etherate. Several cuprate reagents were studied for regio- and stereoselectivity in addition reactions with the acetylenic fluoro ketones. Although complete regioselectivity was achieved, the stereochemistry of the reaction was quite variable. The *E* isomers predominated; however, the use of in situ trimethylsilyl chloride reversed the selectivity, producing the *Z* isomers as the major product. Nevertheless, stereochemically pure compounds were isolated by chromatographic separation. Reactions with organocuprate reagents derived from alkyl Grignard reagents were ineffective, producing a mixture of 1,4- and 1,2-addition products as well as the reduced fluoro ketones. Copper(I) iodide mediated Grignard additions provided only the reduction product in good yield.

Over the past several years, organofluorine compounds have gained considerable interest due to the potential to achieve enhanced biological activity for this class of molecules as compared to the nonfluorinated counterpart.[1] In particular, α-fluorocarbonyl compounds have recently been shown to function as transition state analogue inhibitors for a variety of hydrolytic enzymes due to the inherent stability of the hydrate or hemiacetal form.[2] For



(1) (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier: New York, 1982. (b) Filler, R. In *Organofluorine Chemicals and their Industrial Applications*; Banks, R. F., Horwood, E., Eds.; Halstead: New York, 1979. (c) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

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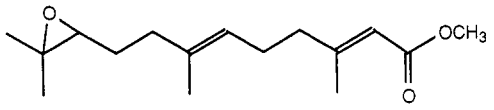
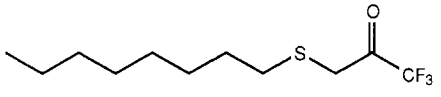
these reasons, there is considerable interest in the synthesis of functionalized α-fluorocarbonyl compounds not only as potential inhibitors themselves but also as starting materials for more complex fluorinated compounds. Methods for the selective fluorination of carbonyl compounds have recently been reviewed,[3] as well as synthetic methods for the synthesis of polyfluorinated molecules.[4]

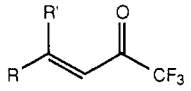
Fluorinated compounds have also been important in the agrochemical field, including the area of potential insect control agents. The synthesis of fluorinated analogues of insect juvenile hormones and pheromones has recently been reviewed.[5] Specific fluorinated inhibitors for insect juvenile hormone (JH) esterase, a key metabolic enzyme in the hormonal regulation of insect growth and development, have also been developed.[6] The initial studies in this area by Hammock and co-workers[6b] revealed that the incorporation of an α'-thio group in the fluoro ketone JH esterase inhibitor resulted in increased efficacy, presumably due to the thio moiety acting as a mimic for the unsaturation present in the natural substrate. We were interested in preparing trisubstituted α,β-unsaturated trifluoromethyl ketones to test this assumption and to possibly generate more specific, highly active inhibitors of JH esterase.



JH III



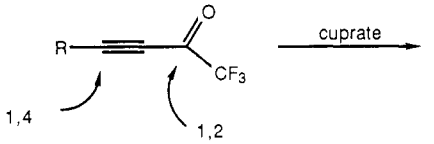
JH Esterase inhibitor



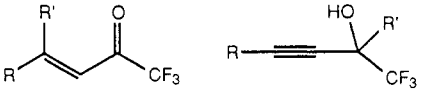
Unsaturated trifluoromethylketone

Unsaturated trifluoromethyl ketones, as functionalized trifluoromethyl ketones in general, are not readily accessible.[7] Procedures that are commonly employed in the synthesis of unsaturated ketones are not applicable to the preparation of the fluorinated counterpart. An aldol condensation–dehydration route has been described for trifluoroacetone and unsaturated aldehydes, yet this procedure was not general for other aldehydes.[8] Recently an approach to unsaturated monofluoromethyl ketones, which employed a sulfone stabilized anion, has been reported.[9] Trifluoromethyl ketones readily react as electrophiles with ylids or phosphonate-stabilized anionic reagents;[10] however, the preparation of a fluorocarbonyl functionalized stabilized ylide has not been reported. Vinyl anions have been added to trifluoroacetaldehyde,[11] and trifluoromethyl anionic reagents undergo condensation reactions with unsaturated aldehydes,[12] generating the α,β-unsaturated trifluorocarbinol; however, until recently, the oxidation of fluorocarbinols to the corresponding ketone has not been a general reaction.[13] β-Functionalized α,β-unsaturated trifluoromethyl ketones are available by the reaction of trifluoroacetic anhydride with electron-rich olefins, but this reaction is not applicable to nonactivated double bonds.[14]

Acetylenic esters and ketones are readily prepared and provide reactive electrophilic substrates for organocuprate additions.[15] This approach has been applied as a general route to substituted unsaturated carbonyl compounds;[16] however, the analogous addition reaction with acetylenic fluoro ketones has not been investigated. We anticipated that the regioselectivity (1,2 vs 1,4) of cuprate addition to



modes of addition



1,4 1,2

the acetylenic fluoro ketone compounds would be problematic due to the extreme electrophilic character of the trifluorocarbonyl moiety.[17] Therefore, we sought to study this regiocontrol question and to develop a general route to α,β-unsaturated trifluoromethyl ketones by the regiospecific addition of organocuprate reagents to acetylenic trifluoromethyl ketones.[18]

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(18) For a preliminary account of a portion of this work, see: Linderman, R. J.; Lonikar, M. S. *Tetrahedron Lett.* **1987**, *28*, 5271.

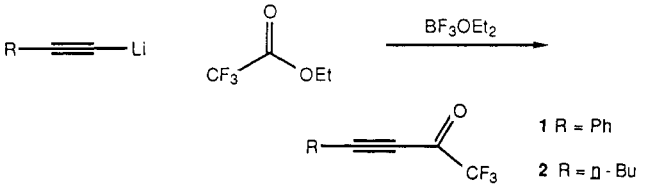
Table I. Di- and Trifluoromethyl Acetylenic Ketones

entry	R′C(O)C≡CR² R′	R²	compd no.	^{19}F NMR[a]	yield,[b] %
1	CF_3	C_6H_5	1	−78.0	81
2	CF_3	n-C_4H_9	2	−79.3	71
3	CF_3	n-C_6H_{13}	3	−79.7	69
4	CF_3	n-C_7H_{15}	4	−79.0	81
5	CF_3	n-C_8H_{17}	5	−79.3	83
6	CF_3	n-$C_{10}H_{21}$	6	−79.3	91
7	CF_3	n-$C_{12}H_{25}$	7	−79.0	42
8	CF_3	$(CH_2)_3CH_2OTHP$	8	−79.0	72
9	CF_3	$(CH_2)_2CH_2OSi(Me)_2$-(t-Bu)	9	−79.3	71
10	HCF_2	C_6H_5	10	−126.0	77
11	HCF_2	n-C_4H_9	11	−126.0	74
12	HCF_2	n-C_7H_{15}	12	−126.0	71
13	HCF_2	n-C_8H_{17}	13	−126.0	66
14	HCF_2	n-$C_{10}H_{21}$	14	−126.0	64

[a] Chemical shifts are reported in ppm from $CFCl_3$. Upfield shifts are designated as negative. [b] Isolated yields of product.

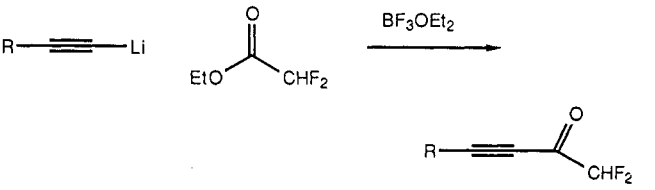
Results and Discussion

Alkyl or aryl trifluoromethyl ketones are traditionally prepared by the addition of an organolithium or Grignard reagent to trifluoroacetic acid itself or to one of several derivatives.[19] Margarethra et al. have prepared two acetylenic trifluoromethyl ketones by the addition of a magnesio acetylide anion to trifluoroacetic acid.[20] Kobayashi and co-workers employed a lithio acetylide and ethyl trifluoroacetate in the synthesis of a fluorinated vitamin D analogue,[21] and Kitazume and Sato have reported this method as a general procedure for the synthesis of acetylenic trifluoromethyl ketones.[22] Although we were able to prepare **1** from phenylacetylene by this procedure,[22] we were unable to prepare **2** from hexyne in yields comparable to those reported. Several methods for improving the

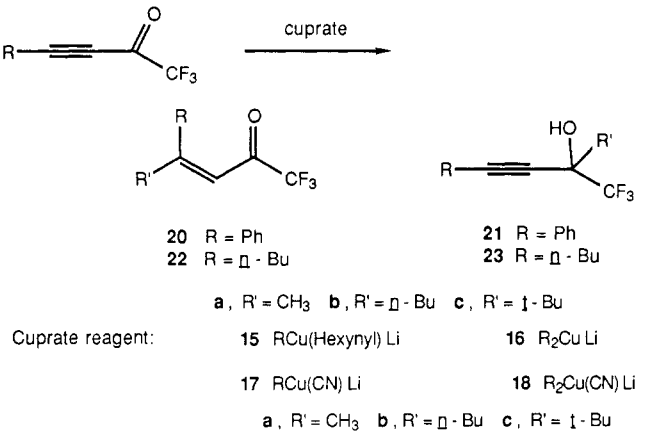


yield were then investigated. Ultimately, a modification of the procedure reported by Yamaguchi et al. for the synthesis of nonfluorinated acetylenic ketones[23] employing boron trifluoride etherate furnished a significant improvement in the yield of **2**. More importantly, the yield for the reaction was reproducible, and the synthesis could be readily carried out on a preparative scale. The procedure was equally effective with ethyl difluoroacetate in place of ethyl trifluoroacetate as the electrophile. The yields for the synthesis of several acetylenic di- and trifluoromethyl ketones are given in Table I.

The regioselectivity of organocuprate addition to ketones **1** and **2** was examined with the hexynyl **15**, homo **16**, cyano **17**, and higher order[24] cyano **18** cuprate reagents for the

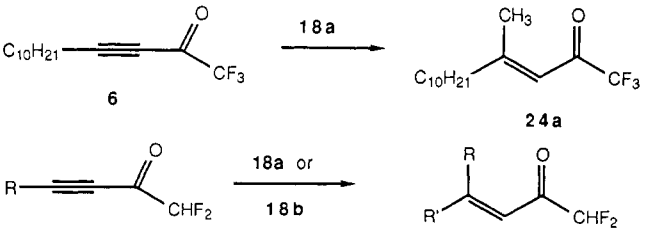


transfer of methyl (**a**), n-butyl (**b**), and $tert$-butyl (**c**) alkyl groups. The results of this survey are presented in Table



II. In each example, the transfer of an alkyl group from the hexynyl **15a–c** and homo **16a–c** cuprate reagents resulted in mixtures of 1,2- and 1,4-addition products. The cyano and higher order cyano cuprates underwent regiospecific reaction with ketone **1** for methyl (**17a** and **18a**) and $tert$-butyl (**17c** and **18c**) transfer (see Table II, entries 3, 4, 13, 14) but not for n-butyl transfer (**17b** and **18b**) (entries 9, 10).

Complete regioselectivity for n-butyl addition was achieved in the reactions of cuprates **17b** and **18b** with ketone **2** (entries 18, 19). In general, improved yields of the 1,4-addition products **20a–c** and **22a–c** were obtained with the higher order cyano cuprate with isolated yields ranging from 17 to 80%. The organolithium reagents **19a** and **19b** gave only the 1,2-addition product in reactions with either ketone **1** or **2**. Interestingly, the reaction of $tert$-butyllithium (**19c**) with ketone **1** resulted primarily in the 1,4-addition product **20c**, nearly a 4:1 ratio of 1,4:1,2-addition. The reaction of **19c** with ketone **2** led only to the expected 1,2-addition **23c** product in good yield. The higher order cyano cuprate reagents were also examined in reactions with ketones **6**, **13**, and **14**. As observed for reactions with ketones **1** and **2**, the addition reactions were completely regioselective, resulting in only the 1,4-addition products **24a**, **25a**, **26a**, and **26b** (see Table II, entries 21–24).



13 R = n-C_8H_{17}

14 R = n-$C_{10}H_{21}$

25a R' = CH_3, R = n-C_8H_{17}

26a R' = CH_3, R = n-$C_{10}H_{21}$

26b R' = n-Bu, R = n-$C_{10}H_{21}$

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Table II. Organocuprate and Organolithium Addition to Acetylenic Fluoro Ketones

entry	cuprate	regioselectivity[a] 1,4:1,2	stereoselectivity[b] *E*:*Z*	isolated yield,[c] % 1,4*E*	1,4*Z*	1,2	total yield,[d] %
			A. Reactions with Ketone **1**				
1	**15a**	76:24	85:15	22	1	6	29
2	**16a**	88:12	76:24				*e*
3	**17a**	100:0	53:47	14	3	0	75[f]
4	**18a**	100:0	71:29	51	1	0	93[g]
5	**19a**	0:100		0	0	76	76
6	**15b**			0	0	0	67[h]
7	**16b**	61:39	52:48	15	5	16	36
8	**17b**	91:9	69:31	34	22	7	63
9	**18b**	81:19	59:41	37	14	16	67
10	**19b**	0:100		0	0	82	82
11	**15c**	84:16	52:48	33	23	21	77
12	**16c**	86:14	77:23	33	9	17	59
13	**17c**	100:0	69:31	45	20	0	65
14	**18c**	100:0	54:46	46	34	0	80
15	**19c**	79:21	51:49	39	29	24	92
			B. Reactions with Ketone **2**				
16	**15b**	80:20		31		19	50
17	**16b**	82:18		64		25	89
18	**17b**	100:0		44		0	44
19	**18b**	100:0		55		0	55
20	**19b**	0:100				64	64
			C. Reactions with Ketone **6**				
21	**18a**	100:0	55:45	21	23	0	44
			D. Reactions with Ketone **13**				
22	**18a**	100:0	45:55	15	14	0	29
			E. Reactions with Ketone **14**				
23	**18a**	100:0	50:50	11	12	0	23[i]
24	**18b**	100:0	53:47			0	44[i,j]

[a] Regioselectivity determined by capillary GC analysis of the crude reaction mixture. [b] Stereoselectivity determined by capillary GC analysis of the crude reaction mixture. *E* and *Z* isomer GC retention times were assigned after isolation, separation, and analysis of each isomer by ^{1}H NMR. [c] Yield of regio- and stereochemically pure material after chromatography of crude reaction products. [d] Yield of all reaction products isolated from the crude mixture. [e] Not isolated. [f] Cyanohydrins **27** and **28** comprised 58% of the isolated product mixture. [g] Cyanohydrins **27** and **28** comprised 41% of the isolated product mixture. [h] Only the hexynyl 1,2-addition product **29** was isolated. [i] Cyanohydrin **30** was observed in the crude reaction product but not isolated. [j] The yield reported is for the combined *E* and *Z* isomers, which were inseparable by chromatography.

The acetylenic and unsaturated trifluoromethyl ketones are somewhat unstable, and considerable loss of material can occur upon purification. Isomeric (regiochemical and stereochemical) mixtures given in Table II were determined by capillary gas chromatographic analysis of the crude reaction mixture. This analytical procedure affords the actual selectivity obtained in the organocuprate reaction and is not biased by any material loss encountered during purification.

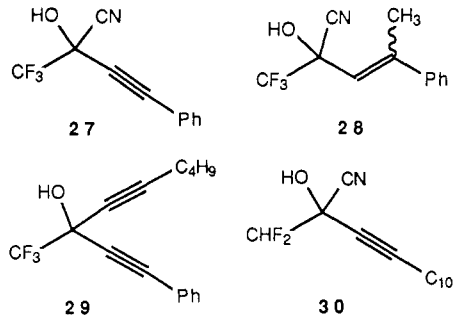
In contrast to the regioselectivity, the stereoselectivity of the reaction was not dependent on the type of cuprate reagent employed. Mixtures of *E* and *Z* isomers were obtained in each case with the ratio being quite variable, ranging from 50:50 (Table II, entry 23) to 85:15 (entry 1). In all cases, the *E* isomer predominated, indicating that, as in the addition reactions with acetylenic esters,[16] the initial organocuprate syn addition product undergoes isomerization through an allenoate intermediate to result in the thermodynamic *E* isomer as the major product. Attempts to improve the stereoselectivity of the reaction using a low-temperature quench[25] (methanol or glacial acetic acid) were not effective. It is important to note that the *E* and *Z* isomers could be readily separated by flash chromatography and that the yields given in Table II are for regio- and stereochemically pure β,β-disubstituted α,β-unsaturated trifluoromethyl ketones. Since either isomer was obtainable in pure form, further efforts in directing the stereoselectivity by variation of the reaction quench conditions were not undertaken.

The *E* and *Z* stereochemical assignments of the unsaturated fluoro ketone products were made by ^{1}H NMR. The olefinic proton for the *E* isomer appeared downfield relative to the chemical shift for the *Z* isomer for the β-phenyl-substituted compounds **20** derived from ketone **1**. The allylic protons of the β-alkyl-β-phenyl-substituted compounds (Me, **20a**; *n*-Bu, **20b**) also exhibited a downfield shift for the *E* isomer relative to that observed for the *Z* isomer due to the deshielding effect of the carbonyl moiety. Assignments for the β-methyl-β-alkyl- or β-*tert*-butyl-β-alkyl-substituted compounds (vida infra) were also made by comparing the chemical shift of the methyl or *tert*-butyl group for each isomer. The *E* isomer was assigned to the compound exhibiting the greatest downfield shift for the methyl group. Due to priority considerations, the *tert*-butyl-substituted compound **20c** was assigned as *Z* for the isomer exhibiting the most downfield signal for the *tert*-butyl group. The ^{19}F NMR chemical shifts could not be used to unambiguously assign *E* or *Z* isomers since no predictable pattern emerged in which one isomer always appeared upfield or downfield relative to the other. In the cases of β,β-dialkyl-substituted compounds, **26b** and **32b**, definitive stereochemical assignments could not be made by ^{1}H NMR analysis.

Two anomalous reactions were noted in this survey, the generation of a cyanohydrin derivative (**27** and **28**) and the transfer of a "nontransferable" ligand from an hexynyl

(25) For an example of the stereocontrolled low-temperature quench of a cuprate acetylenic ester addition intermediate, see: Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905.

cuprate reagent (**29**). Both of these side reactions are



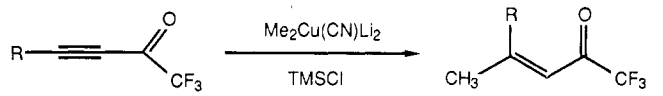
novel in organocuprate chemistry and must be attributed to the exceptional electrophilic character of the fluoro ketone.[17] The diyne product **29** was isolated from the reaction of cuprate **15b** and ketone **1** in 67% yield. The diyne was identified by ^{1}H NMR and GC/MS (CI) analysis and ultimately by independent synthesis with hexynyllithium. The 1,2-addition product was obtained reproducibly from several experiments with cuprate **15b** and ketone **1**; however, no trace of the corresponding diyne from the reaction of cuprate **15b** and ketone **2** was observed. The fact that the "normal" mode of cuprate reactivity was adhered to in the reaction of **15b** and **2** serves to discount the possibility that hexynyl addition occurred due to the lack of formation of the hexynyl hetero cuprate. We have no satisfactory explanation at this time for this unusual mode of reactivity.

The cyanohydrin **27** and **28** formation is, to our knowledge, unprecedented as a byproduct from a cyano or higher order cyano cuprate reaction.[24] Cyanohydrins of trifluoromethyl ketones have been prepared by other means.[26] The cyanohydrin of the starting material **1**, as well as that of the 1,4-addition product **20a**, could be readily prepared by the addition of 1 drop of methyllithium to an ethereal solution of the ketone containing an equimolar amount of copper(I) cyanide. The analogous in situ formation of the cyanohydrins **27** and **28** in the organocuprate reaction is not readily explained since presumably only trace amounts of "free" copper(I) cyanide would be present. The transfer of a cyano ligand from the cuprate species seems unlikely; however, the exact nature of the solution structure of higher order cyano cuprates is not known.[27] It is certainly possible that the cyanohydrins are produced during the acidic aqueous workup of the reaction. The acetylenic derivative **27** would arise from unreacted starting material, while **28** would be produced from the 1,4-addition product after protonation of the initial anionic intermediate. In many runs, 10–25% of the startir g acetylenic fluoro ketone could be recovered from the cuprate reaction. A definitive answer to the question of how the cyanohydrins arise unfortunately cannot be given at this point.

The cyanohydrins were difficult to hydrolyze to the ketone and could be purified by column chromatography but not by distillation. The compounds were thermally unstable and provided only the starting ketone **1** (from **27**) or 1,4-addition product **20a** (from **28**) upon GC analysis. For the reaction of **17a** and **1** (Table II, entry 3), the 58% yield of cyanohydrin analyzed as a 57:43 (*E*:*Z*) mixture of **20a**, and the ratio of 1,4-addition product **20** to starting material **1** was 48:52.

The complete regioselectivity exhibited by the higher order cyano cuprates in reactions with ketones **1** and **2** was also observed in the reaction of cuprate **18a** and **18b** with the difluoromethyl ketone **14** as noted previously. The stereoselectivity in this example (Table II entries 23, 24) was poor, virtually 50:50 in each case, and the combined (*E*, *Z* mixture) 1,4-addition yields were somewhat lower. The β-methyl-substituted product **26a** *E* and *Z* isomers were cleanly separated by column chromatography while the β-butyl derivative **26b** *E* and *Z* isomers were inseparable. In both of these reactions, a trace of the cyanohydrin derivative **30** was noted in the crude reaction mixture by IR examination. By these results, the regiospecificity question for organocuprate addition to acetylenic di- and trifluoromethyl ketones has been resolved by the application of higher order cyano organocuprate reagents.

There have been several reports concerning the beneficial aspects of in situ trimethylsilyl chloride (TMSCl) in organocuprate conjugate addition reactions to unsaturated carbonyl compounds.[28] There have been no reports to date of TMSCl-mediated cuprate reactions with acetylenic carbonyl compounds. We, therefore, decided to investigate the effects of in situ TMSCl on the regio- and stereoselectivity of the addition of higher order cyano cuprates to acetylenic trifluoromethyl ketones. The results of this study are presented in Table III. In the reactions of ketone **1** and cuprates **18a–c** (Table III, entries 1–6), it is interesting to note that the stereoselectivity of the addition reaction was reversed when in situ TMSCl was present relative to the stereochemical outcome without TMSCl (Table II). In these examples, the *Z* isomer rather than the *E* was isolated as the major product. Interestingly, this stereochemical effect was only observed in TMSCl-mediated cuprate additions to the β-phenyl-substituted ketone **1** and not for reactions with β-alkyl-substituted ketones **3** and **5**. Although the stereoselectivity of the



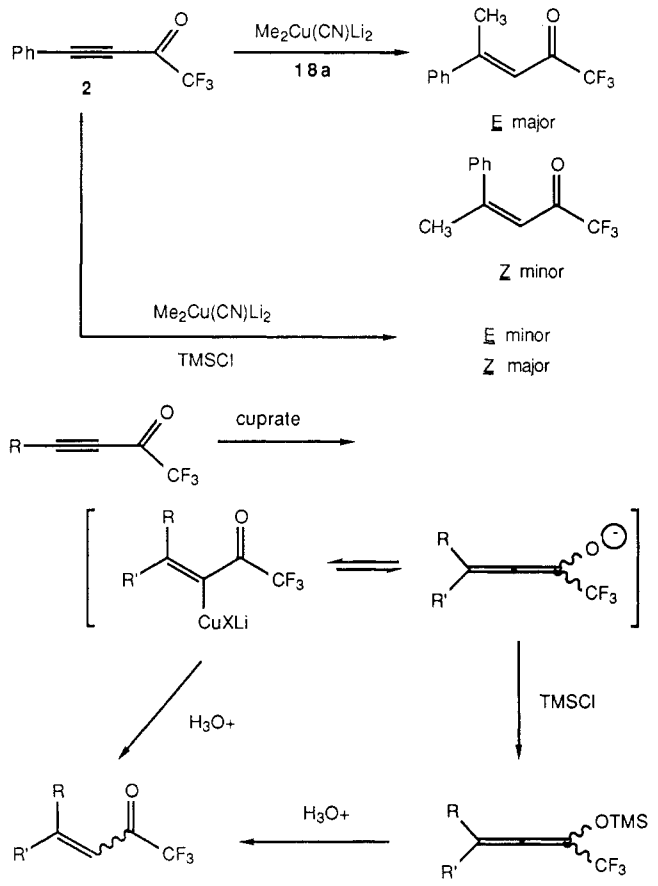
3 R = n-C_6H_{13} **31a** R = n-C_6H_{13}

5 R = n-C_8H_{17} **32a** R = n-C_8H_{17}

cuprate reactions with **3** and **5** were unaffected (Table III, entries 7–10), the yields of 1,4-addition products were improved somewhat with the TMSCl procedure. No 1,2-addition products were observed in any of the TMSCl-mediated reactions, indicating that the regioselectivity of the reaction is unaltered. These observations support the assumption[28] that the in situ TMSCl does not function solely as a Lewis acid activator of the carbonyl substrate. In that case, the electrophilic character of the fluoro ketone would be expected to increase, potentially leading to an increase in the formation of a greater percentage of 1,2-addition products.

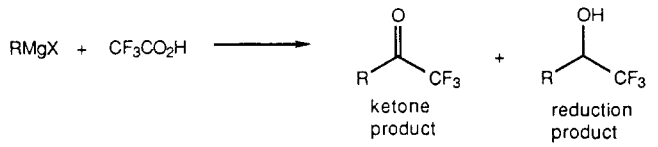
It would seem unlikely that the intermediate trifluoromethyl-substituted allenoate had been trapped as the trimethylsilyl allenol ether derivative[16] and subsequently been hydrolyzed during the aqueous acid workup without equilibration or isomerization to the *E* isomer. Recent

(26) Cantacuzene, J.; Atlanti, M. *Tetrahedron* **1970**, *26*, 2447.
(27) Lipshutz[27a] has shown that lithium dimethyl cuprate exists as an equilibrium mixture of cuprate species and methyllithium; however, recent studies by Bertz[27b] indicate that higher order cyano cuprates apparently exist as nonequilibrating dimeric species. (a) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197; (b) Bertz, S. H.; Gibson, C. P. *J. Am. Chem. Soc.* **1986**, *108*, 8286.
(28) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (d) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (e) Lindstedt, E.; Nilsson, M.; Olsson, T. *J. Organomet. Chem.* **1987**, *334*, 255.



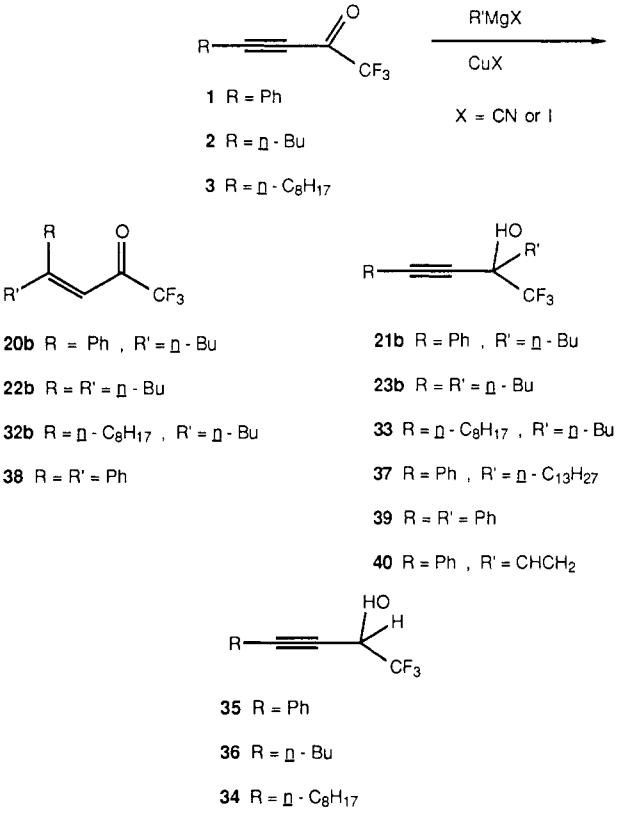
studies of TMSCl-mediated cuprate reactions[28e] indicate that the cuprate reagent might actually be structurally altered, thereby affecting reactivity. This possibility has not been pursued in this study, and further experiments are necessary to comment on this aspect of the reaction. These results demonstrate that the unique properties imparted by in situ TMSCl on cuprate additions to enones are also evident for acetylenic carbonyl substrates.

Simple trifluoromethyl ketones are traditionally prepared by the addition of Grignard reagents to trifluoroacetic acid.[29] In these reactions, the reduced ketone is also frequently obtained as a byproduct. We have found that in this classic approach, as an alkyl Grignard reagent increases in chain length, the reduction product, rather than the ketone, becomes the major product.[30] Interestingly,



Moreau[31] has recently described a similar phenomenon when alkyl Grignard species are added to perfluoroalkyl ketones. The extent of reduction for a given alkyl Grignard reagent increased as the perfluoroalkyl chain length increased. We sought to determine if an analogous problem would arise in the reactions of organocuprate species derived from Grignard reagents with acetylenic trifluoromethyl ketones. We anticipated a third possible mode of reaction, the reduction of the ketone, as well as 1,2- and 1,4-addition. The results of this portion of the study are presented in Table IV.

The homocuprate formed from 2 equiv of *n*-butylmagnesium bromide and copper(I) iodide in ether reacted with ketone 1 to provide a 62% yield of the reduction product **35** and none of the 1,2- or 1,4-addition products (Table IV, entry 6). The same reaction carried out with



copper(I) cyanide led to a mixture of all three possible products (entry 5). The addition of in situ TMSCl did not alter the outcome of either the copper(I) iodide or cyanide mediated reactions. Analogous results were obtained with β-alkyl-substituted ketones **2** and **3** providing the reduction products (**36** and **34**, respectively) while the copper(I) cyanide derived reagent gave 1,2- and 1,4-addition as well as reduction products (**22b**, **23b**, **36** and **32b**, **33**, **34**, respectively). Interestingly, as in the synthesis of simple long chain alkyl trifluoromethyl ketones discussed earlier, the longest chain alkyl Grignard derived cuprate species gave the greatest yield of reduction product (entry 8). The chain length of the β-alkyl substituent of the fluoro ketone had little effect (compare entries 2, 4, 6, and 8). The dependence of the extent of the reduction on the type of copper(I) salt used may reflect the purity of the copper salt, yet each source of copper employed presumably contained small amounts of copper(II) species. A single electron transfer mechanism may be operating; however, the reduction product presumably arises by a β-hydride elimination mechanism.[31] Indeed, in reactions using 1-tridecylmagnesium bromide and ketone 1 (entries 7 and 8), tridecene was isolated as a byproduct. A GC–MS analysis and comparison to an authentic sample indicated that only the terminal olefin was obtained. Grignard species derived from aryl or vinyl halides should be less susceptible to β-hydride elimination and should not yield the reduced product. Addition of the cuprates derived from phenyl- or vinylmagnesium bromide (entries 9–12)

(29) (a) McBee, E. T.; Pierce, O. R.; Meyer, D. D. *J. Am. Chem. Soc.* **1955**, *77*, 917. (b) Dishart, K. T.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 2268. See also ref 1, 7, and 18.

(30) Unpublished results, J. Leazer, M. Lonikar of this laboratory.

(31) Moreau, P.; Naji, M.; Commeyras, A. *J. Fluorine Chem.* **1987**, *34*, 421.

(32) Watson, S. C.; Eastham, J. E. *J. Organomet. Chem.* **1967**, *9*, 165.

Table III. Effects of in Situ Trimethylsilyl Chloride on the Reaction of Higher Order Cyanocuprates and Acetylenic Trifluoromethyl Ketones

entry	$CF_3C(O)C{\equiv}CR$, R	compd no.	cuprate	equivalents[a] of TMSCl	stereoselectivity[b] E:Z	isolated yield,[c] % E	isolated yield,[c] % Z
1	Ph	1	**18a**	0	71:29	51	1
2	Ph	1	**18a**	5	23:77	8	44
3	Ph	1	**18b**	0	70:30	34	22
4	Ph	1	**18b**	5	18:82	10	35
5	Ph	1	**18c**	0	54:46	46	34
6	Ph	1	**18c**	5	22:78	9	61
7	n-C_6H_{13}	**3**	**18a**	0	48:52	6	13
8	n-C_6H_{13}	**3**	**18a**	5	44:56	14	14
9	n-C_8H_{17}	**5**	**18a**	0	50:50	10	17
10	n-C_8H_{17}	**5**	**18a**	5	45:55	23	33

[a] Equivalents of trimethylsilyl chloride (TMSCl) combined with the acetylenic fluoro ketone prior to addition to the cuprate reagent. [b] Stereoselectivity determined by capillary GC analysis of the crude reaction mixture. [c] Yield of regio- and stereochemically pure material after chromatography of the crude protein products.

Table IV. Addition of Organocuprate Reagents Derived from Grignard Reagents to Acetylenic Trifluoromethyl Ketones

entry	$CF_3C(O)C{\equiv}CR$, R	compd no.	R′MgBr, R′	CuX, X	product ratios[a] 1,4:1,2:redn	isolated yields,[b] % 1,4	1,2	redn
1	n-C_4H_9	**2**	n-C_4H_9	CN	78:15:7	40	8	4
2	n-C_4H_9	**2**	n-C_4H_9	I	0:0:100	0	0	7
3	n-C_8H_{17}	**5**	n-C_4H_9	CN	54:15:31	38	21	40
4	n-C_8H_{17}	**5**	n-C_4H_9	I	0:0:100	0	0	65
5	Ph	1	n-C_4H_9	CN	29:54:17	30	28	21
6	Ph	1	n-C_4H_9	I	0:0:100	0	0	62
7	Ph	1	n-$CH_3(CH_2)_{12}$	CN		9	38	28
8	Ph	1	n-$CH_3(CH_2)_{12}$	I		0	0	85[c]
9	Ph	1	Ph	CN	14:86:0	9	75	0
10	Ph	1	Ph	I	4:96:0	1	74	0
11	Ph	1	$CHCH_2$	CN	8:92:0	1	63	0
12	Ph	1	$CHCH_2$	I	0:100:0	0	21	0

[a] Ratios determined by capillary GC analysis of the crude reaction. E/Z mixtures of the 1,4-addition products were obtained. Redn is the reduction product (see text). [b] The yield of 1,4-addition product represents the combined yield of E and Z isomers. [c] Tridecane was also isolated from the reaction mixture.

to ketone **1** did not provide any reduced product **35** but did afford the 1,2-addition products (**39** and **40**, respectively) with only trace amounts of the 1,4-addition products.

Summary

In summary, we have achieved a regiospecific synthesis of β,β-disubstituted α,β-unsaturated di- and trifluoromethyl ketones by the addition of higher order cyano cuprate reagents to acetylenic di- and trifluoromethyl ketones. Unique organocuprate chemistry, the transfer of a nontransferable ligand from a hexynyl heterocuprate and the formation of cyanohydrin derivatives, was observed and attributed to the electrophilic character of the α-fluorinated carbonyl compounds. Although the reactions were not highly stereoselective, stereochemically pure E or Z isomers were obtained by chromatography. The use of in situ TMSCl favored the Z isomer, while "normal" reaction conditions favored the E isomer of the 1,4-addition product. Organocuprates generated from Grignard species were ineffective and complicated the procedure by reduction of the starting acetylenic fluoroketone. The use of a Grignard reagent and copper(I) iodide resulted in clean reduction of the ketone without competing 1,2- or 1,4-addition. Nevertheless, a general route for the synthesis of unsaturated fluoro ketones has been devised, providing useful starting materials for the synthesis of fluorinated compounds of interest for biomedical and industrial applications. Biological assay data of these compounds as inhibitors of insect juvenile hormone esterase will be reported elsewhere.

Experimental Section

General Procedures. Infrared spectra were obtained on either a Beckman Acculab I or a Perkin-Elmer 1430 ratio recording spectrophotometer. ^1H NMR spectra were obtained on either a Varian EM360A or a EM390 spectrometer with tetramethylsilane as an internal standard. ^{19}F NMR were obtained on either a Varian EM390 or an IBM 100 spectrometer with freon as an internal standard. Capillary gas chromatographic analyses were carried out using a Hewlett-Packard 5890 gas chromatograph equipped with a FID detector. All analyses were carried out on a SE-30, 25m fused silica column using a temperature ramp program. Ether and tetrahydrofuran were freshly distilled from lithium aluminum hydride or sodium benzophenone. All reactions were carried out in flame-dried glassware under an inert atmosphere. Grignard reagents were prepared from freshly distilled alkyl or aryl halide precursors. Alkyne reagents were purchased from Aldrich or Farchan and distilled before use. Ethyl di- and trifluoroacetate were purchased from PCR and used without further purification. Alkyllithium reagents were purchased from Aldrich and titrated[31] prior to use. Flash chromatography was performed on silica gel 60, 230–400 mesh ASTM, obtained from American Scientific Products. All chromatography solvents were distilled prior to use. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA. Exact-mass mass spectroscopic analyses were carried out on a JEOL HMX-110 mass spectrometer. GC/MS analyses were carried out on a Hewlett-Packard 5895B GC/MS system.

Synthesis of Acetylenic Di- and Trifluoromethyl Ketones. A hexane solution of n-butyllithium (15 mmol) was added to a solution of the acetylene (15 mmol) in 22 mL of dry tetrahydrofuran at −78 °C (CO_2/acetone). The solution was stirred for 30 min at −78 °C, and ethyl trifluoroacetate (15 mmol, 2.13 g) as a solution in tetrahydrofuran (30 mL) and boron trifluoride etherate (2.25 mL) were then added successively. The reaction

mixture was stirred an additional 90 min at −78 °C, saturated aqueous ammonium chloride (8 mL) was then added, and the slurry was allowed to warm to ambient temperature. The tetrahydrofuran was removed under reduced pressure, and the residue was taken up in ether, washed with saturated aqueous sodium chloride (2 × 25 mL), and dried over anhydrous magnesium sulfate. The crude acetylenic trifluoromethyl ketone was then purified by distillation under reduced pressure or by column chromatography with either hexane/ethyl acetate or hexane/methylene chloride as eluant. For difluoro ketones the same procedure was followed, substituting ethyl difluoroacetate in place of ethyl trifluoroacetate as the electrophile.

4-Phenyl-1,1,1-trifluorobut-3-yn-2-one (1) (81%): bp 93–95 °C (25 mmHg); ^{1}H NMR (CCl_4) δ 7.26–7.8 (m, 5 H); ^{19}F NMR (CCl_4) δ −78.0 (s); IR (neat) (cm^{-1}) 2180, 1685. Anal. Calcd for $C_{10}H_5F_3O$: C, 64.10; H, 8.07. Found: C, 64.18; H, 8.10.

1,1,1-Trifluorooct-3-yn-2-one (2) (71%): bp 70 °C (65 mmHg); ^{1}H NMR (CCl_4) δ 0.96 (t, 3 H), 1.26–1.93 (m, 4 H), 2.50 (br d, 2 H); ^{19}F NMR (CCl_4) δ −79.33 (s); IR (neat) (cm^{-1}) 2160, 1690. Anal. Calcd for $C_8H_9F_3O$: C, 66.17; H, 8.67. Found: C, 66.28; H, 8.72.

1,1,1-Trifluorodec-3-yn-2-one (3) (69%): bp 70 °C (40 mmHg); ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.10–1.20 (m, 8 H), 2.50 (br d, 2 H); ^{19}F NMR (CCl_4) δ −79.67 (s); IR (neat) (cm^{-1}) 2180, 1690. Anal. Calcd for $C_{10}H_{13}F_3O$: C, 58.24; H, 6.35. Found: C, 58.37; H, 6.40.

1,1,1-Trifluoroundec-3-yn-2-one (4) (81%): ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.07–1.86 (m, 10 H), 2.50 (t, 2 H); ^{19}F NMR (CCl_4) δ −79.0 (s); IR (neat) (cm^{-1}) 2215, 1700. Anal. Calcd for $C_{11}H_{15}F_3O$: C, 59.98; H, 6.86. Found: C, 60.03; H, 6.92.

1,1,1-Trifluorododec-3-yn-2-one (5) (83%): bp 110 °C (40 mmHg); ^{1}H NMR (CCl_4) δ 0.93 (t, 3 H), 1.13–2.00 (m, 12 H), 2.53 (br t, 2 H); ^{19}F NMR (CCl_4) δ −79.33 (s); IR (neat) (cm^{-1}) 2180, 1690. Anal. Calcd for $C_{12}H_{17}F_3O$: C, 61.52; H, 7.31. Found: C, 61.42; H, 7.33.

1,1,1-Trifluorotetradec-3-yn-2-one (6) (91%): ^{1}H NMR (CCl_4) δ 0.86 (t, 3 H), 1.07–1.96 (m, 16 H), 2.46 (t, 2 H); ^{19}F NMR (CCl_4) δ −79.30 (s); IR (neat) (cm^{-1}) 2180, 1690. Anal. Calcd for $C_{14}H_{21}F_3O$: C, 64.10; H, 8.07. Found: C, 64.18; H, 8.10.

1,1,1-Trifluorohexadec-3-yn-2-one (7) (42%): ^{1}H NMR (CCl_4) δ 0.86 (t, 3 H), 1.07–1.90 (m, 20 H), 2.46 (t, 2 H); ^{19}F NMR (CCl_4) δ −79.00 (s); IR (neat) (cm^{-1}) 2100, 1700. Anal. Calcd for $C_{16}H_{25}F_3O$: C, 66.17; H, 8.67. Found: C, 66.28; H, 8.72.

8-(Tetrahydropyranyloxy)-1,1,1-trifluorooct-3-yn-2-one (8) (72%): ^{1}H NMR (CCl_4) δ 1.07–2.13 (m, 10 H), 2.60 (t, 2 H), 3.16–4.07 (m, 4 H), 4.53 (s, 1 H); ^{19}F NMR (CCl_4) δ −79.00 (s); IR (neat) (cm^{-1}) 2200, 1710; exact mass calcd for $C_{13}H_{17}F_3O_3$ 278.1130, found 278.1105.

7-[[Dimethyl(2-methylprop-2-yl)silyl]oxy]-1,1,1-trifluorohept-3-yn-2-one (9) (71%): ^{1}H NMR (CCl_4) δ 0.03 (s, 6 H), 0.86 (s, 9 H), 1.60–2.10 (m, 2 H), 2.60 (t, 2 H), 3.70 (t, 2 H); ^{19}F NMR (CCl_4) δ −79.33 (s); IR (neat) (cm^{-1}) 2218, 1710. Anal. Calcd for $C_{13}H_{21}F_3O_2Si$: C, 53.03; H, 7.19. Found: C, 53.30; H, 7.29.

1,1-Difluoro-4-phenylbut-3-yn-2-one (10) (77%): ^{1}H NMR (CCl_4) δ 5.76 (t, J = 54 Hz, 1 H), 6.90–7.96 (m, 5 H); ^{19}F NMR (CCl_4) δ −126.00 (d); IR (neat) (cm^{-1}) 2210, 1690. Anal. Calcd for $C_{10}H_6F_2O$: C, 66.47; H, 3.33. Found: C, 66.66; H, 3.35.

1,1-Difluorooct-3-yn-2-one (11) (74%): bp 85 °C (60 mmHg); ^{1}H NMR (CCl_4) δ 0.97 (t, 3 H), 1.13–1.83 (m, 4 H), 2.50 (t, 2 H), 5.67 (t, J = 54 Hz, 1 H); ^{19}F NMR (CCl_4) δ −126.0 (d); IR (neat) (cm^{-1}) 2205, 1690. Anal. Calcd for $C_8H_{10}F_2O$: C, 59.99; H, 6.29. Found: C, 59.88; H, 6.29.

1,1-Difluoroundec-3-yn-2-one (12) (71%): ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.10–1.90 (m, 10 H), 2.46 (t, 2 H), 5.63 (t, J = 57 Hz, 1 H); ^{19}F NMR (CCl_4) δ −126.0 (d); IR (neat) (cm^{-1}) 2217, 1695. Anal. Calcd for $C_{11}H_{16}F_2O$: C, 65.32; H, 7.97. Found: C, 65.45; H, 8.01.

1,1-Difluorododec-3-yn-2-one (13) (66%): ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.03–1.83 (m, 12 H), 2.46 (t, 2 H), 2.53 (t, J = 54 Hz, 1 H); ^{19}F NMR (CCl_4) δ −126.0 (d); IR (neat) (cm^{-1}) 2210, 1695. Anal. Calcd for $C_{12}H_{18}F_2O$: C, 66.64; H, 8.38. Found: C, 66.72; H, 8.44.

1,1-Difluorotetradec-3-yn-2-one (14) (64%): ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.06–1.93 (m, 16 H), 2.46 (t, 2 H), 5.63 (t, J = 54 Hz, 1 H); ^{19}F NMR (CCl_4) δ −126.00 (d); IR (neat) (cm^{-1}) 2210, 1695. Anal. Calcd for $C_{14}H_{22}F_2O$: C, 68.95; H, 9.12. Found: C, 68.82; H, 9.07.

Cuprate Additions to Ketones 1, 2, 6, 13, and 14. Experimental procedures for the reaction of cuprates **15a–18a** and ketone **1** are given in detail. Reactions of the fluoroketones listed in Table II with cuprate reagents followed the same procedure, substituting the correct alkyllithium and ketone where appropriate in the experimental procedure given.

Hexynyl Cuprate 15a Addition. A 0.48-mL (4.2-mmol) sample of hexyne was added to 20 mL of dry ether, and the solution was cooled to 0 °C. A 2.25-mL (4-mmol) sample of a 1.77 M ether solution of methyllithium (Aldrich, low halide) was added, and the mixture was stirred for 30 min. The resulting white slurry of hexynyllithium was then cannulated into a second flask, which contained 0.78 g (4.1 mmol) of ultrapure copper(I) iodide (Alfa) suspended in 20 mL of dry ether at −20 °C. The bright yellow slurry was stirred for 1 h at 0 °C (bath temperature, ice/H_2O), and then cooled to −78 °C (CO_2/acetone), and stirred for an additional hour. A 2.25-mL (4-mmol) sample of a 1.77 M ether solution of methyllithium was added, and the mixture was stirred for 1 h at −78 °C. A 0.864-g (4-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one (**1**) was added to the rapidly stirred cuprate mixture, producing a bright yellow heterogeneous mixture. The reaction mixture was stirred for 2 h at −78 °C and then quenched (at −78 °C) by the addition of 5 mL of a 10% aqueous hydrogen chloride solution and allowed to warm to room temperature. The mixture was filtered through a pad of Celite, and the organic phase was separated and then washed with saturated aqueous sodium chloride (25 mL). The ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude product was chromatographed (silica gel) with a gradient elution of 100% hexane, 95:5 hexane/methylene chloride, and finally 80:20 hexane/methylene chloride.

Homocuprate 16a Addition. A 0.78-g (4.1-mmol) sample of ultrapure copper(I) iodide was suspended in 45 mL of dry ether and cooled to −45 °C (bath temperature). A 4.77-mL (8-mmol) sample of a 1.77 M ether solution of methyllithium was then added dropwise. The clear, slightly yellow solution was then cooled to −78 °C and stirred for 1 h. A 0.864-g (4-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one (**1**) was then added, producing a bright orange heterogeneous mixture. After being stirred for 2 h at −78 °C, the reaction was quenched by the addition of 5 mL of a 10% aqueous hydrogen chloride solution and allowed to warm to room temperature. The material was isolated and purified as described for the hexynyl cuprate reaction. For the *n*-butyl **16b** and *tert*-butyl **16c** cuprate preparation, the alkyllithium reagent was added to the suspension of copper(I) iodide at −78 °C.

Cyano Cuprate 17a Addition. A 0.73-g (8.2-mmol) sample of copper(I) cyanide (Aldrich, tan colored) was suspended in 40 mL of dry ether and cooled to −45 °C. A 4.77-mL (8-mmol) sample of a 1.77 M ether solution of methyllithium was added. The light yellow solution was stirred at −40 to −45 °C for 30 min, and then cooled to −78 °C and stirred for an additional hour. A 1.72-g (8-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one was then added, producing a yellow/orange slurry. The reaction mixture was stirred for 2 h at −78 °C and then quenched (at −78 °C) by the addition of 5 mL of 10% aqueous hydrogen chloride. **CAUTION**: The acidic quench should only be carried out in a well-ventilated hood due to the liberation of hydrogen cyanide. The reaction mixture was allowed to warm to room temperature and then worked up as described above. For the *n*-butyl **17b** and *tert*-butyl **17c** cuprate preparation, the alkyllithium reagent was added to the suspension of copper(I) cyanide at −78 °C.

Higher Order Cyanocuprate 18a Addition. The higher order cyano cuprate reagent was prepared exactly as the cyano cuprate reagent with 2 equiv of alkyllithium, typically 8 mmol, to 1 equiv of copper(I) cyanide, 4.1 mmol, in 40–45 mL of dry ether. Ketone addition and workup procedures were identical with those of the cyano cuprate reaction.

Organolithium 19a Addition. A 0.864-g (4-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one (**1**) was dissolved in 40 mL of dry ether and cooled to −78 °C. A 4.77-mL (8-mmol) sample of a 1.77 M ether solution of methyllithium was then added, and the mixture was stirred at −78 °C for 1 h. The reaction was then quenched by the addition of 5 mL of 10% aqueous hydrogen chloride solution and allowed to warm to room temperature. The

1,2-addition product was isolated and purified as described above. Identical procedures were followed for *n*-butyllithium **19b** and *tert*-butyllithium **19c** additions.

4-Phenyl-1,1,1-trifluoropent-3-en-2-one (20a): ^{1}H NMR (CCl_4) δ, *E* isomer, 2.70 (d, 3 H), 6.73 (s, 1 H), 7.43 (m, 5 H); *Z* isomer, 2.33 (d, 3 H), 6.47 (s, 1 H), 7.26 (m, 5 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −79.67 (s); Z isomer, −80.00 (s); IR (neat) (cm^{-1}) 3300 (hydrate), 1650, 1580, 1140. Anal. Calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.23. Found: C, 61.74; H, 4.29.

4-Phenyl-1,1,1-trifluorooct-3-en-2-one (20b): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.93 (t, 3 H), 1.33 (m, 4 H), 3.13 (t, 2 H), 6.60 (s, 1 H), 7.36 (m, 5 H); *Z* isomer, 0.9 (t, 3 H), 1.33 (m, 4 H), 2.53 (t, 2 H), 6.33 (s, 1 H), 7.16 (m, 5 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −80.00 (s); *Z* isomer, −83.00 (s); IR (neat) (cm^{-1}) 3390 (hydrate), 1715, 1590, 1140. Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.61; H, 5.90. Found: C, 65.69; H, 5.96.

5,5-Dimethyl-4-phenyl-1,1,1-trifluorohex-3-en-2-one (20c): ^{1}H NMR (CCl_4) δ, *Z* isomer, 1.26 (s, 9 H), 6.23 (s, 1 H), 7.23 (m, 5 H); *E* isomer, 1.16 (s, 9 H), 6.53 (s, 1 H), 7.06 (m, 5 H); ^{19}F NMR (CCl_4) δ, *Z* isomer, −79.50 (s); *E* isomer, −80.00 (s); IR (neat) (cm^{-1}) 1710, 1570, 1150. Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.61; H, 5.90. Found: C, 65.64; H, 5.93.

2-Methyl-4-phenyl-1,1,1-trifluorobut-3-yn-2-ol (21a): ^{1}H NMR (CCl_4) δ 1.66 (s, 3 H), 2.90 (br s, OH), 7.30 (m, 5 H); ^{19}F NMR (CCl_4) δ −83.66 (s); IR (neat) (cm^{-1}) 3350, 2200, 1120. Anal. Calcd for $C_{11}H_9F_3O$: C, 61.68; H, 4.23. Found: C, 61.55; H, 4.25.

1-Phenyl-3-(trifluoromethyl)hept-1-yn-3-ol (21b): ^{1}H NMR (CCl_4) δ 0.96 (t, 3 H), 1.55 (m, 6 H), 2.83 (br s, OH), 7.40 (m, 5 H); ^{19}F NMR (CCl_4) δ −82.66 (s); IR (neat) (cm^{-1}) 3360, 2210, 1150. Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.61; H, 5.90. Found: C, 65.71; H, 5.92.

4,4-Dimethyl-1-phenyl-3-(trifluoromethyl)pent-1-yn-3-ol (21c): ^{1}H NMR (CCl_4) δ 1.23 (s, 9 H), 2.70 (br s, OH), 7.30 (m, 5 H); ^{19}F NMR (CCl_4) δ −73.33 (s); IR (neat) (cm^{-1}) 3300, 2100, 1150. Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.61; H, 5.90. Found: C 65.72; H, 5.94.

4-Butyl-1,1,1-trifluorooct-3-en-2-one (22b): ^{1}H NMR (CCl_4) δ 0.96 (t, 6 H), 1.36 (m, 8 H), 2.30 (t, 2 H), 2.66 (t, 2 H), 6.23 (s, 1 H); ^{19}F NMR (CCl_4) δ −79.67 (s); IR (neat) (cm^{-1}) 3390, 1690, 1580, 1135. Anal. Calcd for $C_{12}H_{19}F_3O$: C, 60.99; H, 8.10. Found: C, 61.44; H, 8.20.

5-(Trifluoromethyl)undec-6-yn-5-ol (23b): ^{1}H NMR (CCl_4) δ 0.96 (t, 6 H), 1.46 (m, 10 H), 2.26 (t, 2 H), 2.5 (br s, OH); ^{19}F NMR (CCl_4) δ −83.00 (s); IR (neat) (cm^{-1}) 3360, 2190, 1160. Anal. Calcd for $C_{12}H_{19}F_3O$: C, 60.99; H, 8.10. Found: C, 61.15; H, 8.14.

4-Methyl-1,1,1-trifluorotetradec-3-en-2-one (24a): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.89 (t, 3 H), 1.03–1.67 (m, 16 H), 2.26 (d, 3 H), 2.26 (t, 2 H), 6.30 (s, 1 H); *Z* isomer, 0.87 (t, 3 H), 1.06–1.57 (m, 16 H), 2.04 (d, 3 H), 2.67 (t, 2 H), 6.30 (s, 1 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −80.0 (s); *Z* isomer, −79.0 (s); IR (neat) (cm^{-1}) 1718, 1610. Anal. Calcd for $C_{15}H_{25}F_3O$: C, 64.72; H, 9.05. Found: C, 64.90; H, 9.01.

1,1-Difluoro-4-methyldodec-3-en-2-one (25a): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.86 (t, 3 H), 1.0–1.66 (m, 12 H), 2.20 (d, 3 H), 2.20 (t, 2 H), 5.56 (t, J = 57 Hz, 1 H), 6.30 (s, 1 H); *Z* isomer, 0.87 (t, 3 H), 1.0–1.66 (m, 12 H), 2.0 (d, 3 H), 2.63 (t, 2 H), 5.56 (t, J = 57 Hz, 1 H), 6.30 (s, 1 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −125.0 (d); *Z* isomer, −126.0 (d); IR (neat) (cm^{-1}) 1700, 1610. Anal. Calcd for $C_{13}H_{22}F_2O$: C, 67.21; H, 9.54. Found: C, 67.11; H, 9.59.

1,1-Difluoro-4-methyltetradec-3-en-2-one (26a): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.87 (t, 3 H), 1.07–1.70 (m, 16 H), 2.20 (t, 2 H), 2.21 (d, 3 H), 5.56 (t, J = 54 Hz, 1 H), 6.33 (s, 1 H); *Z* isomer, 0.90 (t, 3 H), 1.10–1.66 (m, 16 H), 2.03 (d, 3 H), 2.63 (t, 2 H), 5.57 (t, J = 54 Hz, 1 H), 6.33 (s, 1 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −127.0 (d); *Z* isomer, −126.08 (d); IR (neat) (cm^{-1}) 1700, 1610, 1108. Anal. Calcd for $C_{15}H_{26}F_2O$: C, 69.19; H, 10.06. Found: C, 69.04; H, 10.10.

1,1-Difluoro-4-butyltetradec-3-en-2-one (26b): ^{1}H NMR (CCl_4) δ (mixture of *E* and *Z* isomers) 0.90 (t, 3 H), 0.96 (t, 3 H), 1.13–2.0 (m, 20 H), 2.26 (t, 2 H), 2.60 (t, 2 H), 5.56 (t, J = 54 Hz, 1 H), 6.20 (s, 1 H); ^{19}F NMR (CCl_4) δ −126.66 (d); IR (neat) (cm^{-1}) 1700, 1615, 1110. Anal. Calcd for $C_{18}H_{32}F_2O$: C, 71.48; H, 10.66. Found: C, 71.58; H, 10.68.

Cyanohydrin 27, 28 Preparation. A 0.086-g (0.4-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one (1) was added to a suspension of 0.036 g (0.41 mmol) of copper(I) cyanide in 15 mL of dry ether at 0 °C. Immediate formation of the cyanohydrin **27** was observed (by TLC analysis) upon the addition of 1 drop of methyllithium. The same observation was made if trifluoropent-3-en-2-one (**20a**) was employed in place of ketone **1**, producing cyanohydrin **28**.

2-Cyano-4-phenyl-1,1,1-trifluorobut-3-yn-2-ol (27): ^{1}H NMR (CCl_4) δ 7.3–7.6 (m, 5 H); ^{19}F NMR (CCl_4) δ −79.0; IR (neat) (cm^{-1}) 3450, 2120, 2110, 1710, 1490, 1160.

2-Cyano-4-phenyl-1,1,1-trifluoropent-3-en-2-ol (28): (mixture of *E* and *Z* isomers) ^{1}H NMR (CCl_4) δ 2.43 (s, 3 H), 3.33 (br s, 1 H), 7.26 (m, 5 H), 7.25 (m, 1 H); ^{19}F NMR (CCl_4) δ −76.66 (s), −80.00 (s); IR (neat) (cm^{-1}) 3460, 2220, 1610, 1160.

Hexyne Addition Product. Hexynyllithium was prepared as described for the hexynyl cuprate reagent generation. A sample (0.8 equiv) of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one (1) was added to the lithio anion at −78 °C. After being stirred for 1 h at −78 °C, the reaction was quenched by the addition of 5 mL of aqueous hydrogen chloride. The crude product was isolated and purified as described for the cuprate reactions.

1-Phenyl-3-(trifluoromethyl)nona-1,4-diyn-3-ol (29): ^{1}H NMR (CCl_4) δ 0.90 (t, 3 H), 1.50 (m, 4 H), 2.23 (t, 3 H), 3.13 (br s, OH), 7.40 (m, 5 H); ^{19}F NMR (CCl_4) δ −83.00 (s); IR (neat) (cm^{-1}) 3260, 2200, 1180; MS (CI/isobutane), m/e 280 (M^+), 281 (M + 1), 263 (M + 1 − H_2O)(base).

Cuprate Reactions with in Situ Trimethylsilyl Chloride. The procedure was the same as that described previously for each cuprate reagent except that the ketone was premixed with 5 equiv of trimethylsilyl chloride (distilled from calcium hydride) in 10 mL of ether, cooled to −78 °C, and cannulated into the flask containing the cuprate.

4-Methyl-1,1,1-trifluorodec-3-en-2-one (31a): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.93 (t, 3 H), 1.1–1.6 (m, 8 H), 2.26 (d, 3 H), 2.26 (t, 2 H), 6.26 (s, 1 H); *Z* isomer, 0.9 (t, 3 H), 1.1–1.8 (m, 8 H), 2.0 (d, 3 H), 2.64 (t, 2 H), 6.2 (s, 1 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −80.00 (s); *Z* isomer, −80.0 (s); IR (neat) (cm^{-1}) 3300 (hydrate), 1700, 1585, 1130. Anal. Calcd for $C_{11}H_{17}F_3O$: C, 59.44; H, 7.71. Found: C, 59.56; H, 7.73.

4-Methyl-1,1,1-trifluorododec-3-en-2-one (32a): ^{1}H NMR (CCl_4) δ, *E* isomer, 0.9 (t, 3 H), 1.13–1.83 (m, 12 H), 2.26 (d, 3 H), 2.26 (t, 2 H), 6.30 (s, 1 H); *Z* isomer, 0.9 (t, 3 H), 1.06–1.66 (m, 12 H), 2.06 (d, 3 H), 2.7 (t, 2 H), 6.26 (s, 1 H); ^{19}F NMR (CCl_4) δ, *E* isomer, −80.0 (s); *Z* isomer, −80.0 (s); IR (neat) (cm^{-1}) 3440 (hydrate), 1710, 1610, 1170. Anal. Calcd for $C_{13}H_{21}F_3O$: C, 62.37; H, 8.45. Found: C, 62.43; H, 8.47.

Grignard-Derived Cuprate Additions. A detailed procedure is given for the reaction of ketone **1** and higher order cyano cuprate **18b** derived from butylmagnesium bromide. Reactions using copper(I) iodide and other Grignard species were carried out by the same procedure.

A solution of butylmagnesium bromide (4.0 mmol in 20 mL of ether) was added to a suspension of 0.183 g (2.05 mmol) of copper(I) cyanide in 30 mL of dry ether at −78 °C. The slightly yellow heterogeneous mixture was stirred at −78 °C for 2 h. A 0.432-g (2.0-mmol) sample of 4-phenyl-1,1,1-trifluorobut-3-yn-2-one was then added, and the mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched (at −78 °C) by the addition of 5 mL of 10% aqueous hydrogen chloride and allowed to warm to room temperature. The mixture was filtered through Celite, and the layers were separated. The ether layer was washed with saturated sodium chloride (25 mL) and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude products were purified by column chromatography (silica gel) by use of a hexane/methylene chloride gradient elution system (95:5, 90:10, and then 75:25).

4-Butyl-1,1,1-trifluorododec-3-en-2-one (32b): ^{1}H NMR (CCl_4) δ (*E* and *Z* mixture) 0.93 (t, 6 H), 1.33 (m, 16 H), 2.30 (t, 2 H), 2.63 (t, 2 H), 6.23 (s, 1 H); ^{19}F NMR (CCl_4) δ −80.0 (s); IR (neat) (cm^{-1}) 3440 (hydrate), 1715, 1610, 1140. Anal. Calcd for $C_{16}H_{27}F_3O$: C, 65.72; H, 9.30. Found: C, 65.62; H, 9.32.

5-(Trifluoromethyl)pentadec-6-yn-5-ol (33): ^{1}H NMR (CCl_4) δ 0.96 (t, 6 H), 1.57 (m, 18 H), 2.6 (t, 2 H), 2.53 (br s, OH); ^{19}F NMR (CCl_4) δ −82.66 (s); IR (neat) (cm^{-1}) 3440, 2210, 1180. Anal. Calcd for $C_{16}H_{27}F_3O$: C, 65.72; H, 9.30. Found: C, 65.60; H, 9.34.

1,1,1-Trifluorododec-3-yn-2-ol (34): ^{1}H NMR (CCl_4) δ 0.86 (t, 3 H), 1.53 (m, 12 H), 2.26 (t, 2 H), 3.76 (br s, OH), 4.60 (q, 1 H); ^{19}F NMR (CCl_4) δ −80.06 (d); IR (neat) (cm^{-1}) 3400, 2242, 1180.

Anal. Calcd for $C_{12}H_{19}F_3O$: C, 60.90; H, 8.09. Found: C, 61.10; H, 8.20.

4-Phenyl-1,1,1-trifluorobut-3-yn-2-ol (35): ^1H NMR (CCl_4) δ 3.60 (s, OH), 4.86 (q, 1 H), 7.36 (m, 5 H); ^{19}F NMR (CCl_4) δ -80.0 (d); IR (neat) (cm^{-1}) 3300, 2200, 1130. Anal. Calcd for $C_{10}H_7F_3O$: C, 60.00; H, 3.53. Found: C, 59.95; H, 3.51.

1,1,1-Trifluorooct-3-yn-2-ol (36): ^1H NMR (CCl_4) δ 0.93 (t, 3 H), 1.53 (m, 4 H), 2.26 (t, 2 H), 3.76 (br s, OH), 4.6 (q, 1 H); ^{19}F NMR (CCl_4) δ -81.66 (d); IR (neat) (cm^{-1}) 3300, 2200, 1150. Anal. Calcd for $C_8H_{11}F_3O$: C, 53.32; H, 6.17. Found: C, 53.41; H, 6.14.

1-Phenyl-3-(trifluoromethyl)hexadec-1-yn-3-ol (37): ^1H NMR (CCl_4) δ 0.96 (t, 3 H), 1.26 (m, 22 H), 1.80 (t, 2 H), 2.50 (s, OH), 7.30 (m, 5 H); ^{19}F NMR (CCl_4) δ -86.30 (s); IR (CCl_4) (cm^{-1}) 3440, 2230, 1150. Correct combustion analysis not obtained.

4,4-Diphenyl-1,1,1-trifluorobut-3-en-2-one (38): ^1H NMR (CCl_4) δ 6.80 (s, 1 H), 6.98-7.53 (m, 10 H); ^{19}F NMR (CCl_4) δ -79.67 (s); IR (neat) (cm^{-1}) 1700, 1560, 1130. Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.35; H, 4.12.

2,4-Diphenyl-1,1,1-trifluorobut-3-yn-2-ol (39): ^1H NMR (CCl_4) δ 2.93 (br s, OH), 6.67-7.93 (m, 10 H); ^{19}F NMR (CCl_4) δ -82.10 (s); IR (neat) (cm^{-1}) 3500, 2240, 1170. Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.41; H, 4.05.

1-Phenyl-3-(trifluoromethyl)pent-4-en-1-yn-3-ol (40): ^1H NMR (CCl_4) δ 3.20 (s, OH), 5.27-5.67 (m, 2 H), 5.86-6.16 (m, 1 H), 7.07-7.67 (m, 5 H); ^{19}F NMR (CCl_4) δ -81.07 (s); IR (neat) (cm^{-1}) 3420, 2240, 1140. Anal. Calcd for $C_{12}H_9F_3O$: C, 63.71; H, 4.01. Found: C, 63.62; H, 4.05.

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α-Acylamino Radical Cyclizations: Application to the Synthesis of (-)-Swainsonine

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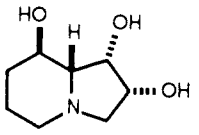
Free-radical precursor **21** was prepared in six steps from D-tartaric acid. Treatment of **21** with tri-*n*-butyltin hydride and AIBN gave a mixture of **23** and **24** in 81% yield. Ozonolysis of these isomeric olefins followed by the reduction of the resulting ketone gave indolizidinone **5**, which was converted to (-)-swainsonine (**1**) via a nine-step sequence that featured a sterically demanding alcohol inversion.

Swainsonine (**1**) is a polyhydroxylated indolizidine alkaloid first isolated from the fungus *Rhizoctonia leguminicola*[1] and later found in the legume *Swainsona canescens*[2] and the spotted locoweed *Astragalus lentiginosus*.[3] This simple base is believed to be responsible for locoism, a disease frequently contracted by range animals upon ingestion of the aforementioned plants.[3] Several years ago it was suggested that the physiological effects of swainsonine may in part be due to its ability to inhibit various mannosidases, enzymes involved in the processing of certain carbohydrates and glycoproteins. More recently it has been reported that swainsonine exhibits interesting immunoregulatory activity.[4] Although the structurally related glucosidase inhibitor castanospermine (**2**)[5] has received more attention as an immunoregulatory substance, the synthesis and biological evaluation of swainsonine and analogues thereof have been the focus of a number of research programs. A total of seven enantioselective syntheses of swainsonine have been reported. Given the structural relationship of swainsonine to mannose and glucose, it is not surprising that five of the syntheses use these carbohydrates as starting materials.[6-10] One of the remaining syntheses uses glutamic acid as a point of departure,[11] and the other synthesis relies on a series of enantioselective epoxidations to control asymmetry.[12]



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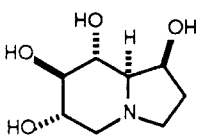

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As part of a program designed to explore the use of α-acylamino radical cyclizations in alkaloid synthesis, we

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