# Synthesis of 3-Trifluoroethylfurans by Palladium-Catalyzed Cyclization−Isomerization of (*Z*)-2-Alkynyl-3-trifluoromethyl Allylic Alcohols

Feng-Ling Qing,* Wen-Zhong Gao, and Jiewen Ying

*Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China*

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Hydroiodonation of trifluoromethyl propargylic alcohols **1** regio- and stereoselectively produce (*Z*)-2-iodo-3-trifluoromethyl allylic alcohols **2**. (*Z*)-2-Alkynyl-3-trifluoromethyl allylic alcohols **5**, available through $Pd(PPh_3)_4$-mediated coupling of **2** and terminal alkynes **4**, cyclize and subsequently isomerize to 3-trifluoroethylfurans **6** upon catalysis under $PdCl_2(CH_3CN)_2$ in THF at 5−10 °C.

## Introduction

There has been considerable interest in organofluorine compounds as pharmaceutical and agrochemical agents.[1] It is believed that the fluorine atom alters the physiochemical properties of organic compounds, thereby modifying biological activity. This has been particularly true for fluoroheterocycles.[2] Furan and polysubstituted furans, as one of the representative five-membered heterocycles, play an important role in organic chemistry not only because of their presence as structural units in many natural products and in important pharmaceuticals but also because they can also be employed in synthetic chemistry as building blocks.[3] Therefore, new methods for the synthesis of fluorofurans have received considerable attention. Although monofluorofurans[4] and trifluoromethylfurans[5] are well documented, trifluoroethylfurans are much less known.[6] This is ascribed to the absence of practical and convenient methods for the introduction of the trifluoroethyl group ($CF_3CH_2$) to organic compounds. It is well-known that 2,2,2-trifluoroethyl halides cannot be used as trifluoroethylation agents by nucleophilic substitution because the trifluoromethyl group strongly deactivates the neighboring carbon.[7] Thus, alternative approaches using 2,2,2-trifluoroethyl phenyl iodonium triflate[8] and a free-radical addition of 2,2,2-trifluoroethyl iodide to electron-rich terminal alkenes[9] have been developed for introducing the trifluoroethyl group into organic molecules. However, these methods are limited because of low yields, the use of expensive reagents, or unsuitability for the synthesis of trifluoroethylfuran. Here, a novel synthesis of 3-trifluoroethylfurans based on palladium-catalyzed cyclization−isomerization of (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols is described.

## Results and Discussion

**Preparation of (Z)-2-Iodo-3-trifluoromethyl Allylic Alcohols.** Trifluoromethyl propargylic alcohols (**1**) that were easily prepared from 2-bromo-3,3,3-trifluoropropene and aldehydes in the presence of 2 equiv of LDA have been used as building blocks for the synthesis of trifluoromethyl-containing compounds.[10] Following our previous work describing the stereoselective synthesis of ethyl (*Z*)-4,4,4-trifluoro-3-iodobutenoate by hydroiodonation of ethyl 4,4,4-trifluoro-2-butynoate,[11] we now extend this methodology to the synthesis of iodo-3-trifluoromethyl allylic alcohols from trifluoromethyl propargylic alcohols **1**. A mixture of 4,4,4-trifluoro-1-phenyl-2-butyn-1-ol **1a** (1.0 equiv) and sodium iodide (1.5 equiv) in acetic acid was stirred at 70 °C for 8 h. $^{19}F$ NMR monitoring of the reaction mixture revealed that compound **1a** had disappeared, and the $^{19}F$ NMR spectrum displayed a new double peak at −18.0 ppm ($J$ = 7.0 Hz)[12] corresponding

* To whom correspondence should be addressed. Fax: 86-21-641661128. E-mail: flq@pub.sioc.ac.cn.

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(12) $^{19}F$ NMR spectra (56.4 Hz) were recorded on a Varian EM-360L instrument using $CF_3CO_2H$ as an external standard, upfield positive.

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**Scheme 1**

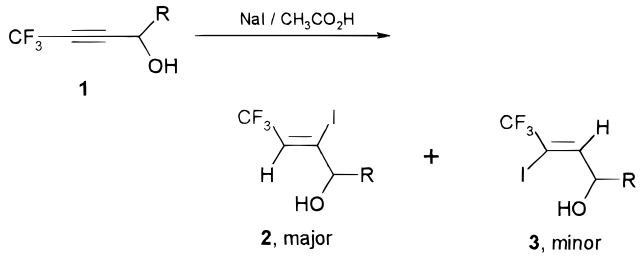


**Table 1. Preparation of (Z)-2-Iodo-3-trifluoromethyl Allylic Alcohols 2**

| entry | **1**, R | product | isolated yield of **2**[a] (%) | **2**:**3**[b] |
|---|---|---|---|---|
| 1 | **1a**, Ph | **2a** | 82 | 91:9 |
| 2 | **1b**, *n*-$C_3H_7$ | **2b** | 75 | 97:3 |
| 3 | **1c**, *p*-$CH_3OPh$ | **2c** | 70 | 91:9 |
| 4 | **1d**, H | **2d** | 37 | 97:3 |

[a] Based on compound **1**. [b] Ratio of **2**:**3** determined by $^{19}F$ NMR of reaction mixture.

to compound **2a** and a single peak at −13.0 ppm corresponding to compound **3a** in a ratio of 91:9. Usual workup and purification by column chromatography gave pure **2a** and **3a**. On the basis of the chemical shift and coupling constant in $^{19}F$ NMR and $^{1}H$ NMR spectra, the structure of compound **2a** was assigned to (*Z*)-2-iodo-3-trifluoromethyl allylic alcohol. The olefinic configuration of **2a** was determined by the strong correlation NOE between the vinylic proton and the allylic proton in the NOESY spectrum of **2a**. The structure of **3a** was determined by comparison with $^{1}H$ NMR and $^{19}F$ NMR spectroscopic data of the authentic sample prepared by treatment of **1a** with $LiAlH_4$ and followed with $I_2$.[13] Under the same reaction conditions, hydroiodonation of 1-substituted trifluoromethyl propargylic alcohols **1** smoothly afforded (*Z*)-2-iodo-3-trifluoromethyl allylic alcohols (**2**) as the major product (Scheme 1 and Table 1). The ratio of **2**:**3** is relatively lower with aryl aldehydes. This method provides a novel process for synthesizing a useful trifluoromethylated building blocks.

**Palladium-catalyzed reaction of 2 with terminal alkynes. 2** is a valuable building block in the synthesis of compounds containing the trifluoromethyl group because three functional groups are present: the C−I bond, the C═C bond, and the hydroxyl group. To demonstrate the synthetic utilities of **2**, the palladium-catalyzed reaction of **2** with terminal alkynes was investigated.[14,15] Reaction of **2** with terminal alkyne **4** in the presence of $Pd(PPh_3)_4$ and CuI in triethylamine at 50 °C for 8 h afforded conjugated (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols **5** in moderate to high yield (Scheme 2). The results are summarized in Table 2. The configuration of double bonds remained intact. $PdCl_2(PPh_3)_2$, which is a better catalyst in the Sonogashira reaction, gave only a 20−30% isolated yield of **5**.

**Scheme 2**

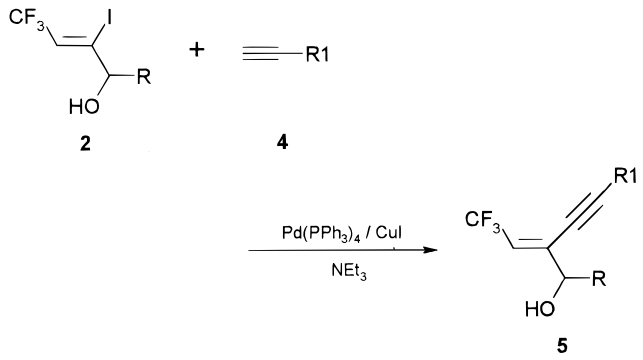


**Table 2. Palladium-Catalyzed Reaction of 2 with Terminal Alkynes[a]**

| entry | **2** | R1 | product | isolated yield[b] (%) |
|---|---|---|---|---|
| 1 | **2a** | Ph | **5a** | 83 |
| 2 | **2a** | *n*-$C_6H_{13}$ | **5b** | 73 |
| 3 | **2a** | $(CH_3)_3Si$ | **5c** | 69 |
| 4 | **2a** | *p*-$CH_3OPh$ | **5d** | 78 |
| 5 | **2b** | Ph | **5e** | 91 |
| 6 | **2b** | *n*-$C_6H_{13}$ | **5f** | 66 |
| 7 | **2b** | $(CH_3)_3Si$ | **5g** | 88 |
| 8 | **2d** | Ph | **5h** | 53 |
| 9 | **2d** | *n*-$C_6H_{13}$ | **5i** | 64 |

[a] Reaction conditions: 1 mmol of **2**, 1.5 mmol of **4**, 0.1 mmol of CuI, 0.02 mmol of $Pd(PPh_3)_4$, and 6 mL of $Et_3N$. [b] Based on compound **2**.

**Palladium-Catalyzed Cyclization−Isomerization of (*Z*)-2-Alkynyl-3-trifluoromethyl Allylic Alcohols.** Recently, a novel methodology for the synthesis of 2,3-disubstituted furans using 3-alkynyl allylic alcohols as ring cyclization precursors under basic conditions[16] or catalyzed by Ru[17] and Pd[18] was described. This methodology stimulated us to prepare 3-trifluoroethylfurans from (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols **5**. Initial attempts to synthesize 3-trifluoroethylfurans **6a** by treatment of **5a** with KO-*t*-Bu in *t*-BuOH−THF [16a] failed, because (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohol was sensitive to base. We next examined the possibility of the preparation of **6a** by palladium-catalyzed cyclization−isomerization of **5a**. A variety of palladium complexes were tested, and we found that $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ exhibited similar activities leading to the complete conversion of **5a** to **6a** with 4 h in THF at 10 °C, while $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $PdCl_2(PPh_3)_2$ were inactive under similar reaction conditions. The reaction temperature was an important factor. When **5a** was reacted at over 15 °C in the presence of $PdCl_2(CH_3CN)_2$, a complex mixture was formed. The reaction to form the 3-trifluoroethylfuran **6a** was found to be highly solvent dependent. For example, use of acetonitrile as solvent did not provide as high a conversion as THF, and there was no observable reaction in triethylamine. The other (*Z*)-

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**Scheme 3**

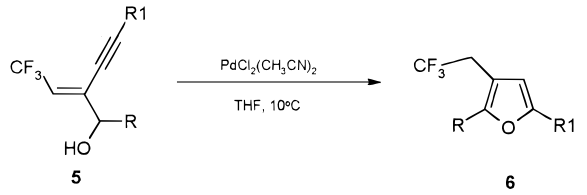
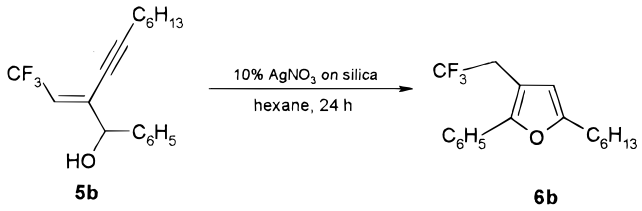



**Table 3. Palladium-Catalyzed Preparation of Furans 6 from 5[a]**

| entry | 5 | product | isolated yield[b] (%) |
|---|---|---|---|
| 1 | **5a** | **6a** | 74 |
| 2 | **5b** | **6b** | 71 |
| 3 | **5d** | **6d** | 75 |
| 4 | **5e** | **6e** | 77 |
| 5 | **5f** | **6f** | 64 |
| 6 | **5i** | **6i** | 72 |

[a] Reaction conditions: 1 mmol of **5**, 0.05 mmol of $PdCl_2(CH_3CN)_2$, and 10 mL of THF. [b] Based on compound **5**.

**Scheme 4**




2-alkynyl-3-trifluoromethyl allylic alcohols were smoothly converted to the corresponding 3-trifluoroethylfurans **6** (Scheme 3 and Table 3). Thus, this methodology offers a novel process for synthesizing a 3-trifluoroethylfuran. The ease of availability of (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols makes such methods particularly convenient. However, the (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols **5c** and **5g** bearing a trimethylsilyl group did not convert to 3-trifluoroethylfuran and were totally recovered even at elevated temperatures.

More recently, Marshall et al.[19] described a mild, fast, and efficient procedure of isomerization of $\beta$-alkynyl allylic alcohols to furans catalyzed by silver nitrate on silica gel. It was therefore of interest to compare the palladium with the silver nitrate on silica gel on (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols. We subjected **5b** to 10% $AgNO_3$ on silica gel in hexane. A clean, but relatively slow (24 h) reaction ensued, leading to 3-trifluoroethylfuran **6b** in 75% yield (Scheme 4).

Trost and co-workers once reported the addition of terminal alkynes to $\gamma$-hydroxyalkynoates catalyzed by palladium produced furans.[20] Because the trifluoromethyl group possesses powerful electron-withdrawing ability, we reasoned that 1-substituted trifluoromethyl propargylic alcohols **1** can be used as a acceptor alkyne in Trost reaction for the preparation of 3-trifluoroethylfurans in one step. However, treatment of **1b** with phenylacetylene under Trost reaction conditions (in the presence of $Pd(OAc)_2$ and tris(2,6-dimethoxyphenyl)phosphine) did not produce the expected 3-trifluoroerthylfuran **6e**, and compound **7** was isolated in 25% yield (Scheme 4), although compound **1b** was totally converted in 3 h at

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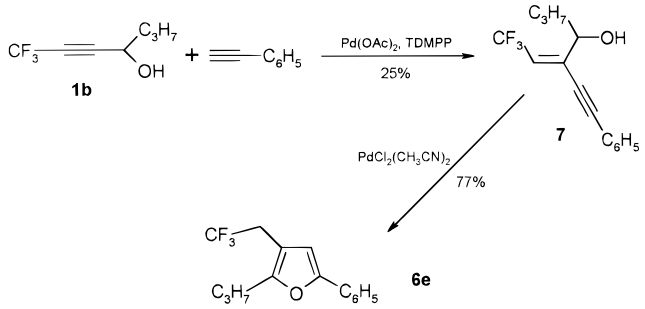
**Scheme 5**




room temperature as shown by monitoring of the reaction mixture by $^{19}F$ NMR. The $PdCl_2(CH_3CN)_2$-catalyzed cyclization−isomerization of **7**, a isomer of **5e**, gave **6e** in 77% yield (Scheme 5). These results indicated that the palladium-catalyzed cyclization−isomerization for formation of 3-trifluoroethylfurans was independent to the configuration of double bond in 2-alkynyl-3-trifluoromethyl allylic alcohols.

In conclusion, with the readily available (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols, the palladium-catalyzed cyclization−isomerization presented herein provides a novel route to the 3-trifluoroethylfurans.

## Experimental Section

$^1H$ NMR spectra were recorded on a 300 MHz spectrometer with $Me_4Si$ as internal standard. $^{19}F$ NMR spectra were obtained on a 56.4 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. IR spectra were recorded on a Shimadzu IR-440 spectrometer. Mass spectra were obtained using EI ionization at 70 eV. All reactions were routinely monitored with the aid of TLC or $^{19}F$ NMR spectroscopy. 2-Bromo-3,3,3-trifluoropropene[21] was prepared according to published procedures.

**General Procedure for Preparation of Trifluoromethyl Propargylic Alcohols 1. 4,4,4-Trifluoro-1-phenyl-2-butyn-1-ol 1a.**[10a] *n*-BuLi (20 mL, 40 mmol, 2.0 M in hexanes) was added dropwise to a solution of diisopropylamine (4.3 g, 43 mmol) in THF (20 mL) at −78 °C. Then the reaction mixture was warmed to room temperature and was stirred for 10 min before being recooled to −78 °C, and a solution of 2-bromo-3,3,3-trifluoropropene (3.5 g, 20 mmol) in THF (20 mL) was added. After the mixture was stirred for 10 min, PhCHO (2.6 g, 24 mmol) was added, and the whole was stirred for 1 h at −78 °C. The reaction mixture was quenched with 2 N HCl and extracted with ether. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. The residue was distilled under reduced pressure to afford **1a** (3.6 g, 90% yield) as a colorless liquid: bp 75−76 °C/2 mmHg; $^{19}F$ NMR ($CDCl_3$) $\delta$ −26.5 (s); $^1H$ NMR ($CDCl_3$) $\delta$ 2.86 (br, 1H), 5.53 (q, $J$ = 2.9 Hz, 1H), 7.35−7.52 (m, 5H); MS *m/z* 200 ($M^+$, 100); IR (neat) 3329, 2277 $cm^{-1}$.

**1,1,1-Trifluoro-2-heptyn-4-ol 1b:** bp 63−65 °C/10 mmHg; $^{19}F$ NMR ($CDCl_3$) $\delta$ −26.8 (s); $^1H$ NMR ($CDCl_3$) $\delta$ 0.98(t, $J$ = 7.35 Hz, 3H), 1.44−1.56 (m, 2H), 1.72−1.81 (m, 2H), 2.08 (br, 1H), 4.47−4.53 (m, 1H); MS *m/z* 165 ($M^+$, 0.6), 43 (100); IR (neat) 3329, 2262 $cm^{-1}$. Anal. Calcd for $C_7H_9F_3O$: C, 50.61; H, 5.46. Found: C, 50.78; H, 5.85.

**4,4,4-Trifluoro-1-(4-methoxyphenyl)-2-butyn-1-ol 1c:** $^{19}F$ NMR ($CDCl_3$) $\delta$ −27.6 (s); $^1H$ NMR ($CDCl_3$) $\delta$ 2.59 (br, 1H), 3.82 (s, 1H), 5.47 (q, $J$ = 2.63 Hz, 1H), 6.90−6.95 (m, 2H), 7.39−7.44 (m, 2H); MS *m/z* 230 ($M^+$, 14), 229 (100); IR (neat) 3381, 2276 $cm^{-1}$. Anal. Calcd for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found: C, 57.59; H, 4.00.

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**4,4,4-Trifluoro-2-butyn-1-ol 1d:**[22] bp 68−73 °C/80 mmHg; $^{19}$F NMR ($CDCl_3$) $\delta$ −27.0 (t, $J$ = 3.1 Hz).

**General Procedure for Preparation of (*Z*)-2-Iodo-3-trifluoromethyl Allylic Alcohols 2. (*Z*)-2-Iodo-4,4,4-trifluoro-1-phenyl-2-buten-1-ol 2a.** A mixture of **1a** (1.32 g, 6.6 mmol), NaI (1.5 g, 10 mmol), and HOAc (10 mL) was placed in a tube. The reaction was carried out with magnetic stirring under nitrogen at 70 °C for 8 h. Then, water (50 mL) was added, and the mixture was cautiously neutralized with solid sodium carbonate, added in portions. Then the aqueous solution was extracted with ether, and the organic layer was dried over anhydrous $Na_2SO_4$, concentrated, and flash chromatographed on silica gel (hexanes/ether = 20:1) to yield **2a** (1.79 g, 82%) and **3a** (0.15 g): $^{19}$F NMR ($CDCl_3$) $\delta$ −17.5 (d, $J$ = 7.1 Hz); $^1$H NMR ($CDCl_3$) $\delta$ 2.18 (br, 1H), 5.27 (t, $J$ = 1.66 Hz, 1H), 7.04 (dq, $J$ = 1.47, 7.22 Hz, 1H), 7.35−7.45 (m, 5 H); MS $m/z$ 327 ($M^+ - 1$, 41), 107 (100); IR (neat) 3362, 1651 cm$^{-1}$. Anal. Calcd for $C_{10}H_8F_3IO$: C, 36.61; H, 2.46. Found: C, 36.62; H, 2.31.

***(Z)*-3-Iodo-4,4,4-trifluoro-1-phenyl-2-buten-1-ol 3a:** $^{19}$F NMR ($CDCl_3$) $\delta$ −12.4 (s); $^1$H NMR ($CDCl_3$) $\delta$ 2.40 (br, 1H), 5.47 (d, $J$ = 7.81 Hz, 1H), 6.86 (dd, $J$ = 0.90, 7.73 Hz, 1H), 7.34−7.48 (m, 5H); MS $m/z$ 327 ($M^+ - 1$, 2), 107 (100); IR (neat) 3341, 1643 cm$^{-1}$. Anal. Calcd for $C_{10}H_8F_3IO$: C, 36.61; H, 2.46. Found: C, 36.88; H, 2.61.

**General Procedure for Preparation of (*E*)-2-Alkynyl-3-trifluoromethyl Allylic Alcohols 5.** To a three-necked, round-bottomed flask were added **2** (1 mmol), terminal alkyne **4** (1.5 mmol), CuI (0.1 mmol), $Pd(PPh_3)_4$ (0.02 mmol), and triethylamine (6 mL) under nitrogen. The reaction mixture was stirred at 40−50 °C for 8 h. The mixture was filtered. The filtrate was concentrated and flash chromatographed on silica gel (hexanes/ether = 15:1) to yield **5**.

***(Z)*-1,4-Diphenyl-2-(1,1,1-trifluoroethylene)-3-butyn-1-ol 5a:** $^{19}$ F NMR ($CDCl_3$) $\delta$ −17.9 (d, $J$ = 7.5 Hz); $^1$H NMR ($CDCl_3$) $\delta$ 2.10 (br, 1H), 5.35 (s, 1H), 6.49 (dq, $J$ = 1.21, 7.54 Hz), 7.27−7.52 (m, 10H); MS $m/z$ 301($M^+ - 1$, 21), 285 (100); IR (neat) 3368, 2210, 1645 cm$^{-1}$. Anal. Calcd for $C_{18}H_{13}F_3O$: C, 71.52; H, 4.33. Found: C, 71.87; H, 4.33.

**General Procedure for Preparation of 3-Trifluoroethylfuran 6.** A mixture of **5** (1 mmol), $PdCl_2(CH_3CN)_2$ (0.05 mmol), and THF (10 mL) was stirred at 5−10 °C for 4 h. Then the mixture was concentrated under pressure and flash chromatographed on silica gel (hexanes/ether = 50:1) to yield **6**.

**1,5-Diphenyl-3-(1,1,1-trifluoroethyl)furan 6a:** $^{19}$F NMR ($CDCl_3$) $\delta$ −12.6 (t, $J$ = 10.7 Hz); $^1$H NMR ($CDCl_3$) $\delta$ 3.47 (q, $J$ = 10.53 Hz, 2H), 6.76 (s, 1H), 7.28−7.49 (m, 6H), 7.63−7.74 (m, 4H); MS $m/z$ 302 ($M^+$, 100); IR (neat) 1596, 1494, 1247, 1130 cm$^{-1}$. Anal. Calcd for $C_{18}H_{13}F_3O$: C, 71.52; H, 4.33. Found: C, 71.10; H, 4.23.

**Cyclization−Isomerization of 5b to 6b Catalyzed by Silver Nitrate on Silica Gel.** To a stirred solution of **5b** (0.31 g, 1 mmol) in hexane (10 mL) was added 0.17 g (0.1 mmol) of 10% $AgNO_3$ on silica gel. The mixture was allowed to stir protected from light for 24 h at room temperature. The mixture was then diluted with ether, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel afforded **6b** (0.23 g, 75%).

***(E)*-1-Phenyl-3-(1,1,1-trifluoroethylene)-1-heptyn-4-ol 7.** A mixture of **1b** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), TDMPP (0.02 mmol), and phenylacetylene (1.5 mmol) in THF (6 mL) was stirred at 25−30 °C for 3 h. Then the mixture was concentrated under pressure and flash chromatographed (hexanes/ether = 15:1) to yield **7** (67 mg, 25% yield): $^{19}$F NMR ($CDCl_3$) $\delta$ −21.9 (d, $J$ = 9.0 Hz); $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (t, $J$ = 7.32 Hz, 3H), 1.39−1.50 (m, 2H), 1.66−1.83 (m, 2H), 1.93 (br, 1H), 4.71 (t, $J$ = 6.62 Hz, 1H), 6.03 (q, $J$ = 8.84 Hz, 1H), 7.32−7.43 (m, 3H), 7.46−7.53 (m, 2H); MS $m/z$ 268 ($M^+$, 5), 226 (100); IR (neat) 3391, 2209, 1633 cm$^{-1}$.

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**Supporting Information Available:** Characterization data for all new compounds. This material ia available free of charge via the Internet at http://pubs.acs.org.

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