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# Highly regio- and stereo-selective carbometallation reaction of fluorine-containing internal acetylenes with organocopper reagents

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**Abstract**—The carbometallation reactions of fluoroalkylated internal alkynes with various organocopper reagents derived from organolithium, Grignard, and organozinc reagents were examined. All carbocupration reactions proceeded smoothly in a highly regio- and stereo-selective manner to give the corresponding vinylcopper intermediates. The intermediates reacted with $H^+$ smoothly, leading to the trisubstituted alkenes in high to excellent yields, whereas they reacted only with strictly limited carbon electrophiles such as allyl-, crotyl-, methallyl bromide, etc, probably due to the low reactivity exerted by an electron-withdrawing fluoroalkyl group. Treatment of vinylcopper with iodine resulted in a high yield of the corresponding vinyl iodide, which was employed successfully for Suzuki–Miyaura and Sonogashira cross-coupling reactions. In addition, two key reactions, the carbocupration and the Suzuki–Miyaura cross-coupling reaction realized the first highly stereoselective total synthesis of anti-estrogen drug, panomifene.


## 1. Introduction

Much interest has been focused on fluorine-containing materials due to their unique properties derived from modified electron density, acidity, and hydrogen-bonding patterns.[1] Fluoroalkyl groups increase lipophilicity allowing for easier drug transportation, cellular absorption, blood–brain barrier penetration, and improved binding within hydrophobic pockets of receptor. Consequently, the development of novel synthetic methods for the preparation of fluoroalkylated molecules has been becoming much more important in the fluorine chemistry.[2] Among a diversity of fluoroalkylated molecules, alkenes having a fluoroalkyl group (**1**) are well known as one of the most important synthetic targets because they are found in the framework of biologically active compounds such as panomifene (Fig. 1).[3] Though several synthetic methods for such molecules have been reported thus far,[4] carbocupration of fluoroalkylated alkynes is very attractive because the C–C and C–Cu bonds are simultaneously introduced across a triple bond in a highly stereoselective fashion to give the corresponding vinylcopper intermediates, which can react with electrophiles, variously substituted ethenes being provided with retention of configuration.[5] Despite of potentially great advantages, there have been quite limited studies on the carbocupration of fluorine-containing acetylene derivatives.[6] Herein we wish to describe the highly regio- and stereo-selective carbometallation of fluoroalkylated internal alkynes with organocopper reagents prepared from lithium,[7] magnesium,[8] and zinc reagents,[9] which serves a novel synthetic approach for the preparation of **1**.

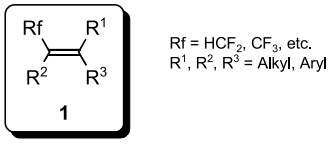


**Figure 1.**

## 2. Results and discussion

### 2.1. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from lithium reagents

Initially, the reaction of trifluoromethylated acetylene

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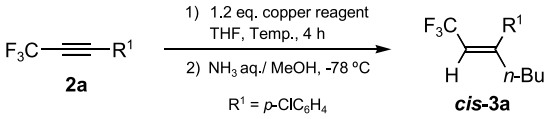
**Table 1**. Investigation of the reaction conditions for the carbocupration




| Entry | Copper reagent[a] | Temp./°C | Yield[b]/% of **3a** | Recovery[b]/% of **2a** |
|---|---|---|---|---|
| 1 | *n*-BuCu | −78 | 10 | 81 |
| 2 | *n*-BuCu | −45 | 73 | 26 |
| 3 | *n*-BuCu | −20 | 39 | 13 |
| 4 | *n*-$Bu_2CuLi$ | −78 | 53 | 15 |
| 5 | *n*-$Bu_2CuLi$ | −45 | 97 (81) | 0 |
| 6 | *n*-BuCu(CN)Li | −78 | 42 | 50 |
| 7 | *n*-BuCu(CN)Li | −45 | 75 | 25 |
| 8 | *n*-$Bu_2Cu(CN)Li_2$ | −78 | 77 | 13 |
| 9 | *n*-$Bu_2Cu(CN)Li_2$ | −45 | 96 (87) | 0 |
| 10[c] | *n*-$Bu_2Cu(CN)Li_2$ | −45 | 82 | 0 |
| 11[d] | *n*-$Bu_2Cu(CN)Li_2$ | −45 | 47 | 0 |

[a] Copper reagents were prepared from Grignard reagent and CuI or CuCN.
[b] Determined by $^{19}F$ NMR. Values in parentheses are of isolated yields.
[c] DME was employed instead of THF.
[d] $Et_2O$ was employed instead of THF.

derivative **2a**[10] ($R^1 = p\text{-}ClC_6H_4$) with various organocopper reagents, prepared from *n*-BuLi and copper salts, was examined as shown in Table 1. Thus, to a solution of 1.2 eq. of *n*-BuCu (prepared from 1.2 eq. each of *n*-BuLi and CuI at −78 °C) in THF was added a THF solution of **2a** at −78 °C and the mixture was stirred for 4 h at that temperature. After quenching the reaction with $NH_3$ aq./MeOH, only *cis*-addition product **3a** was obtained in 10% yield, together with 81% of the starting material (entry 1). Raising the reaction temperature from −78 to −45 °C caused a significant improvement of the yield, **3a** being produced in 73% yield with high regio- and stereo-selectivity, though 26% of **2a** still remained unreacted (entry 2). However, the reaction at −20 °C led to a partial decomposition of the intermediate, affording the desired compound in only 39% yield (entry 3). Switching the organocopper reagent from *n*-BuCu to *n*-$Bu_2CuLi$ brought about a dramatic change, the desired product being obtained quantitatively when the reaction was performed at −45 °C (entry 5). We next examined the reaction with cyanocuprates as shown in entries 6–9. The reaction with *n*-BuCu(CN)Li or *n*-$Bu_2Cu(CN)Li_2$ proceeded at −45 °C more smoothly than at −78 °C (entries 6 and 8 vs entries 7 and 9). In particular, the use of *n*-$Bu_2Cu(CN)Li_2$ at −45 °C resulted in complete consumption of the starting material, giving the corresponding alkene in 96% yield (entry 9). The investigation of the effect of the solvent, as shown in entries 10 and 11, revealed that THF was the solvent of choice. In all cases, the isomers such as *trans*-**3a**, *cis*-**4a**, and *trans*-**4a** were not detected at all (Fig. 2).

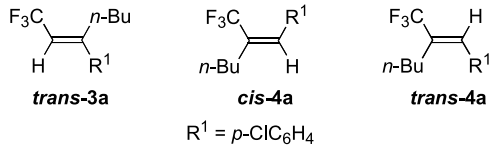
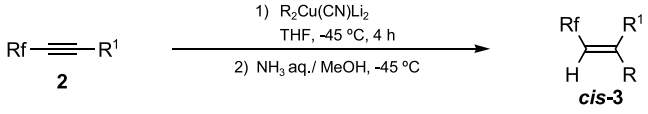



**Figure 2.**

With this optimised reaction conditions (Table 1, entry 9), the carbocupration reaction of various fluorine-containing acetylene derivatives was investigated in detail as listed in Table 2. As can be seen in entries 2 and 4, the use of 1.2 eq. of $Me_2Cu(CN)Li_2$ or $Ph_2Cu(CN)Li_2$ gave *cis*-**3** in only 38 or 42% yield, 57 or 56% of the starting alkyne being recovered, respectively. On the other hand, the use of 3.0 eq. of the cyanocuprate and the prolonged reaction time led to the complete consumption of the starting materials, affording the desired alkenes in high yields (entries 3 and 5). No influence of the substituents on the benzene ring in the alkynes was observed. Thus, the alkynes having either an electron-donating group (Me, MeO, entries 6 and 7) or an electron-withdrawing group ($EtO_2C$, entry 10) could participate nicely in the carbocupration reaction. It should be also noted that the position of the substituents on the benzene ring (*para*-; entry 7, *meta*-; entry 8, *ortho*-: entry 9) did not affect the yield. We also examined the effect of a fluoroalkyl group on the reaction as shown in entries 11–13. The alkynes bearing a difluoromethyl or hexafluoropropyl group caused a partial decomposition of the intermediate,

**Table 2**. The carbocupration reaction of fluoroalkylated alkynes with various organolithium reagents

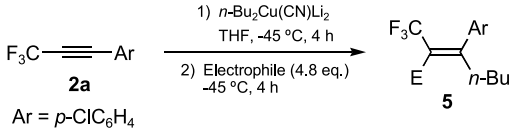


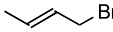
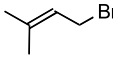

| Entry | Equiv of copper reagent | R | Rf | $R^1$ | Product | Yield[a]/% of *cis*-**3** | Recovery[a]/% of **2** |
|---|---|---|---|---|---|---|---|
| 1 | 1.2 | *n*-Bu | $CF_3$ | $p\text{-}ClC_6H_4$ | **3a** | 96 (87) | 0 |
| 2 | 1.2 | Me | $CF_3$ | $p\text{-}ClC_6H_4$ | **3b** | 38 | 57 |
| 3[b] | 3.0 | Me | $CF_3$ | $p\text{-}ClC_6H_4$ | **3b** | 79 (73) | 0 |
| 4 | 1.2 | Ph | $CF_3$ | $p\text{-}ClC_6H_4$ | **3c** | 42 | 56 |
| 5[b] | 3.0 | Ph | $CF_3$ | $p\text{-}ClC_6H_4$ | **3c** | 91 (88) | 0 |
| 6 | 1.2 | *n*-Bu | $CF_3$ | $p\text{-}MeC_6H_4$ | **3d** | 91 (83) | 0 |
| 7 | 2.4 | *n*-Bu | $CF_3$ | $p\text{-}MeOC_6H_4$ | **3e** | 96 (94) | 0 |
| 8 | 2.4 | *n*-Bu | $CF_3$ | $m\text{-}MeOC_6H_4$ | **3f** | 99 (89) | 0 |
| 9 | 2.4 | *n*-Bu | $CF_3$ | $o\text{-}MeOC_6H_4$ | **3g** | 94 (84) | 0 |
| 10 | 2.4 | *n*-Bu | $CF_3$ | $p\text{-}EtO_2CC_6H_4$ | **3h** | quant. (98) | 0 |
| 11 | 1.2 | *n*-Bu | $HCF_2$ | $p\text{-}ClC_6H_4$ | **3i** | 42 (27) | 0 |
| 12 | 1.2 | *n*-Bu | $HCF_2CF_2CF_2$ | $p\text{-}ClC_6H_4$ | **3j** | 16 | 34 |
| 13 | 2.4 | *n*-Bu | $HCF_2CF_2CF_2$ | $p\text{-}ClC_6H_4$ | **3j** | 33 (33) | 0 |

[a] Determined by $^{19}F$ NMR. Values in parentheses are of isolated yields.
[b] Stirred for 8 h.

the desired product being obtained in low yields. Next, we investigated the coupling reaction of the carbometallated adduct with a variety of electrophiles instead of $H_2O$. The results are collected in Table 3.

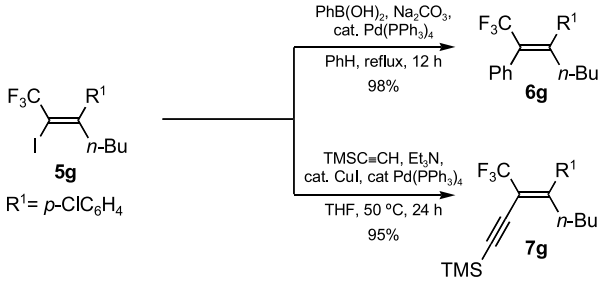
**Table 3**. The cross-coupling reaction of the carbocuprated adduct with various electrophiles




| Entry | Electrophile ($E^+$) | Product | Yield[a]/% of **5** |
|---|---|---|---|
| 1 |  | **5a** | 91 (86) |
| 2 |  | **5b** | 97 (88) |
| 3 |  | **5c** | 85 (81) |
| 4 |  | **5d** | 88 (84) |
| 5 |  | **5e** | quant. (76) |
| 6 |  | **5f** | 84 (63) |
| 7 | $I_2$ | **5g** | 90 (88) |

[a] Determined by $^{19}F$ NMR. Values in parentheses are of isolated yields.

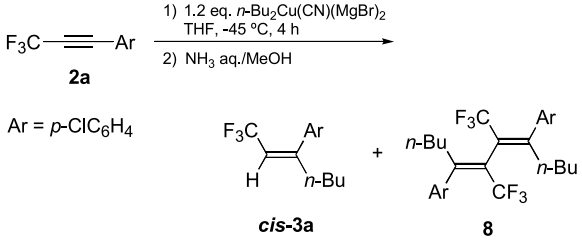
As can be seen in entries 1–5, variously-substituted allyl bromide such as allyl- methallyl-, crotyl-, prenyl-bromide, and β-(methoxycarbonyl)allyl bromide, could undergo the coupling reaction nicely to give the corresponding fluorine-containing tetrasubstituted alkenes **5a**–**e** in excellent yields. The propargyl bromide was also a good electrophile (entry 6), but other carbon electrophiles such as benzyl bromide, ethyl bromoacetate, iodomethane, and ethyl chloroformate were not subjected to the coupling reaction at all, the protonated *cis*-**3a** being obtained in moderate yield after quenching the reaction with $NH_3$ aq./MeOH. Additionally, trimethylsilyl chloride and tributylstannyl chloride were also found to be poor electrophiles, the desired tetra-substituted alkenes being obtained in low yields. On the other hand, the reaction with iodine took place smoothly to give the corresponding vinyl iodide **5g** in 90% yield (entry 7). Hereupon, we attempted the cross-coupling reaction of **5g** with organometallic reagents in the presence of a transition metal catalyst (Scheme 1). Thus, treatment of **5g** with phenylboronic acid and sodium carbonate in the presence of a catalytic amount of $Pd(PPh_3)_4$ in benzene at the reflux temperature for 12 h gave the corresponding coupling product **6g** almost quantitatively.[11] Furthermore, the reaction of **5g** with trimethylsilylacetylene and $Et_3N$ in the presence of a catalytic amount of CuI and $Pd(PPh_3)_4$ took place smoothly to give the fluorine-containing enyne compound **7g** in 95% yield.[12]




**Scheme 1.** Suzuki–Miyaura and Sonogashira cross-coupling reactions.

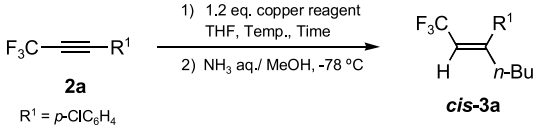
## 2.2. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from Grignard reagents

As an extension of the studies on the carbocupration reaction, our interest was next directed toward the reaction of fluoroalkylated alkynes with organocopper reagents derived from Grignard reagents in place of lithium reagents. Initially, the reaction was carried out under the optimised reaction conditions in the case of lithium reagents ($n$-$Bu_2Cu(CN)(MgBr)_2$, THF, −45 °C, 4 h), but the desired compound was given in only 43% yield together with 12% of the dimer **8** and 20% of **2a** recovered (Scheme 2). Therefore, we reexamined the feasibility of the carbometallation reaction with a series of organocopper reagents by using trifluoromethylated alkyne **2a** in order to determine the optimum linchpin (Table 4). Treatment of **2a** with $n$-BuCu at −45 °C for 4 h furnished *cis*-**3a** in only 5% yield, together with 48% of the starting material, after quenching the reaction with $NH_3$ aq./MeOH at −45 °C. The product was proved to be a *cis*-adduct as a single isomer. Using a lower ordered dibutylcuprate, generated from butylmagnesium bromide and CuBr, significantly improved the yield of *cis*-**3a** from 5 to 58% (entry 2). Furthermore, the reaction at −78 °C was found to give the desired product




**Scheme 2.** The carbocupration using cyanocuprate.

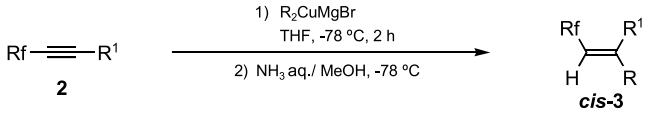
**Table 4**. Investigation of the reaction conditions for the carbocupration




| Entry | Copper reagent[a] | Temp./°C | Time/h | Yield[b]/% of **3a** | Recovery[b]/% of **2a** |
|---|---|---|---|---|---|
| 1 | $n$-BuCu | −45 | 4 | 5 | 48 |
| 2 | $n$-$Bu_2CuMgBr$ | −45 | 4 | 58 | 0 |
| 3 | $n$-$Bu_2CuMgBr$ | −78 | 2 | 94 (85) | 0 |
| 4[c] | $n$-$Bu_2CuMgBr$ | −78 | 2 | 31 | 68 |
| 5 | $n$-BuCu(CN)MgBr | −78 | 2 | 24 | 76 |
| 6 | $n$-$Bu_2Cu(CN)(MgBr)_2$ | −78 | 2 | 69 | 28 |

[a] Copper reagents were prepared from Grignard reagent and CuBr or CuCN, unless otherwise noted.
[b] Determined by $^{19}F$ NMR. Value in parentheses is of isolated yield.
[c] CuI was employed instead of CuBr.

**Table 5**. The carbocupration reaction of fluoroalkylated alkynes with various Grignard reagents

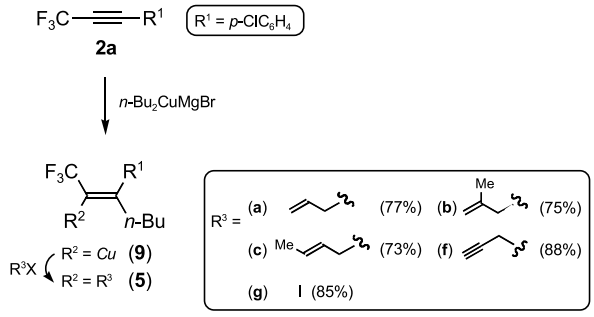



| Entry | Equiv of copper reagent | R | Rf | $R^1$ | Product | Yield[a]/% of *cis*-**3** |
|---|---|---|---|---|---|---|
| 1 | 1.2 | *n*-Bu | $CF_3$ | *p*-$ClC_6H_4$ | **3a** | 93 (83) |
| 2 | 2.4 | *s*-Bu | $CF_3$ | *p*-$ClC_6H_4$ | **3k** | 84 (69) |
| 3 | 1.2 | *c*-Hex | $CF_3$ | *p*-$ClC_6H_4$ | **3l** | 74 |
| 4[b] | 1.2 | Bn | $CF_3$ | *p*-$ClC_6H_4$ | **3m** | quant. (69) |
| 5[c] | 1.2 | Allyl | $CF_3$ | *p*-$ClC_6H_4$ | **3n** | 98 (86) |
| 6 | 2.4 | Vinyl | $CF_3$ | *p*-$ClC_6H_4$ | **3o** | 53 (41) |
| 7 | 2.4 | Ph | $CF_3$ | *p*-$ClC_6H_4$ | **3c** | 93 |
| 8 | 2.4 | *p*-$MeOC_6H_4$ | $CF_3$ | *p*-$ClC_6H_4$ | **3p** | 61[d] |
| 9 | 2.4 | *n*-Bu | $CF_3$ | *m*-$ClC_6H_4$ | **3q** | 90 (70) |
| 10 | 1.2 | *n*-Bu | $CF_3$ | *o*-$ClC_6H_4$ | **3r** | 89 (83) |
| 11 | 1.2 | *n*-Bu | $CF_3$ | *p*-$MeOC_6H_4$ | **3e** | 97 (93) |
| 12 | 1.2 | *n*-Bu | $CF_3$ | *p*-$MeC_6H_4$ | **3d** | 96 (90) |
| 13 | 1.2 | *n*-Bu | $CF_3$ | *p*-$EtO_2CC_6H_4$ | **3h** | 84 (80) |
| 14 | 1.2 | *n*-Bu | $CF_3$ | *p*-$(MeOC_6H_4)$-$CH_2$ | **3s** | quant. (99) |
| 15 | 1.2 | *n*-Bu | $HCF_2$ | *p*-$ClC_6H_4$ | **3i** | 65 (55) |

[a] Determined by $^{19}F$ NMR. Values in parentheses are of isolated yields.
[b] Benzylmagnesium chloride was used for the preparation of copper reagent.
[c] Allylmagnesium chloride was used for the preparation of copper reagent.
[d] CuCN was employed instead of CuBr because the copper reagents prepared from Grignard reagent and CuBr did not give a reproducible result.

*cis*-**3a** in 94% yield. Additional studies focused on a copper salt such as CuI and CuCN, both of which had proven to be good copper salts in the carbocupration reaction using organolithium reagents. Thus, changing a copper salt from CuBr to CuI appreciably affected the yield (entry 4). Higher ordered cyanocuprate realized the satisfactory reaction at −78 °C, resulting in the formation of *cis*-**3a** in 69% yield (entry 6), whereas lower ordered cyanocuprate did not lead to the good results (entry 5). In order to examine the scope and limitation of this carbocupration, the optimised reaction conditions were applied for various types of fluoroalkylated alkynes **2** as shown in Table 5. Primary and secondary Grignard reagents such as *n*-BuMgBr and *s*-BuMgBr (entries 1 and 2), cyclohexyl, benzyl, and allyl Grignard reagents (entries 3–5) could participate well in the carbocupration reaction to give the corresponding adducts *cis*-**3** in good to excellent yields (69–86% isolated yields). However, the yield was somewhat eroded with vinyl Grignard reagent employed (entry 6). Switching R in Grignard reagent from aliphatic to aromatic groups had no discernible effect on the yield, though 2.4 eq. of copper reagents or CuCN were required for the smooth reaction (entries 7 and 8). Changing the aromatic substituent ($R^1$) of the alkynes **2** from *p*-chlorophenyl to *m*-chloro- or *o*-chlorophenyl also did not significantly affect the yield (entries 1, 9 and 10). In addition, no influence of the yield on the substituents in $R^1$, such as the electron-donating (MeO, Me, entries 11 and 12) or the electron-withdrawing group ($EtO_2C$, entry 13), was observed. It is worthwhile to note that the internal alkynes having an alkyl side chain as $R^1$ (entry 14) or a difluoromethyl moiety as Rf (entry 15) could also undergo the smooth carbocupration reaction to afford the corresponding adducts in good to high yields.

Based on the above-described results on the regio- and stereo-selective carbometallation of the fluoroalkylated internal alkynes **2** with organocopper reagents, our interest was directed toward the cross-coupling reaction using the carbometallated adduct **9** (Scheme 3).




**Scheme 3.** The cross-coupling reaction.

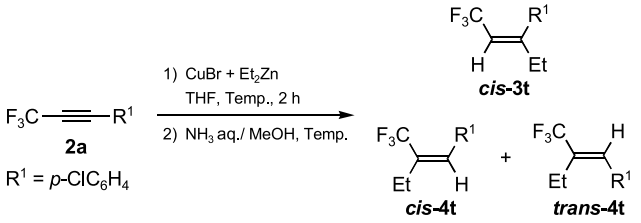
Treatment of **9** with 4.0 eq. of allyl-, methallyl-, crotyl-, propargyl bromide or iodine at −78 °C resulted in the smooth coupling reaction, affording the tetrasubstituted alkenes **5a–c,f,g** in high yields. Similar to the results on the lithium reagents, other electrophiles such as benzyl bromide, ethyl chloroformate, ethyl bromoacetate, etc. were all unreacted, leading to the formation of trisubstituted alkene *cis*-**3a** after quenching the reaction with $NH_3$ aq./MeOH. The coupling reaction of **9** with iodobenzene under the influence of palladium catalyst at 0 °C–rt did not give any desired product due to the decomposition of **9**.

### 2.3. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from organozinc reagents

Organozinc reagents are well known as useful intermediates, and their chemistry has been actively investigated in the recent years. They tolerate a broad range of functionalities and undergo various reactions such as Michael addition, $S_N2$ reaction, and so on, in the presence

of a copper salt like CuBr, CuCN, etc.[13] Therefore, we next attempted the carbometallation reaction of various fluorine-containing alkynes with copper reagents derived from organozinc reagents (Table 6). In initial experiments, **2a** was treated with 1.2 eq. of copper reagent (prepared from 1.2 eq. each of copper bromide and $Et_2Zn$) at −45 °C for 2 h to give a mixture of *cis*-**3t**, *cis*-**4t**, and *trans*-**4t** in 78% yield. The $^{19}F$ NMR analysis showed that the ratio of *cis*-**3t**:(*cis*-**4t**+*trans*-**4t**) was 94:6 (entry 1). Interestingly, the reaction at −78 °C led to a decrease in the regioselectivity (entry 2). The use of 2.4 eq. of $Et_2Zn$ caused a smooth carbocupration, *cis*-**3t** being produced with high regio- and stereo-selectivity (entry 3). It should be noted that the present reaction proceeded smoothly even in the presence of a catalytic amount of CuBr, 73% of the desired compounds being obtained, though the regioselectivity decreased slightly (entry 5). With the optimised reaction conditions (Table 6, entry 3), the scope of the carbocupration reaction with various organozinc reagents was examined. The results are summarized in Table 7. In the case of diorganozinc reagents, the reaction took place smoothly to afford *cis*-**3** with high regio- and stereoselectivity in high yields (entries 1–3). As can be seen in entries 5 and 6, an ester or a nitrile group in the organozinc reagents did not influence on the yield and the regioselectivity, whereas the zinc reagent derived from ethyl bromoacetate did not react with **2a** at all, the starting material being recovered quantitatively (entry 4). It is noteworthy that the carbometallation reaction with *n*-butylzinc iodide at −78 °C gave the desired molecule in a higher regioselective manner than the reaction at −45 °C (entry 7 vs 8). We also investigated the cross-coupling reaction of the carbometallated adduct **9** with various electrophiles (Scheme 4). Initially, treatment of the in situ generated carbometallated adduct with an excess amount of iodine at −78 °C did not give the corresponding vinyl iodide at all, the starting alkyne **2a** being recovered quantitatively. After several trials, we have found that the addition of DMF to the reaction mixture promoted the cross-coupling reaction significantly. Thus, to a solution of the in situ generated carbometallated adduct in THF was added the same volume of DMF as THF at −78 °C. After stirring of the reaction mixture for 10 min, then 4.8 eq. of iodine was added to the reaction mixture, and the whole was stirred for 1 h at room temperature before the reaction was quenched with $NH_3$ aq./MeOH. As a result, the vinyl iodide **5g** was obtained in high yield as a single isomer. The same reaction procedure could be applied for the reaction of the carbometallated adduct with allyl bromide, tetrasubstituted alkene **5a** being afforded in high yields with high regioselectivity. However, the reaction with methallyl- and crotylbromide gave the coupling products in moderate yields, 37 and 43% of **2a** being recovered, respectively.

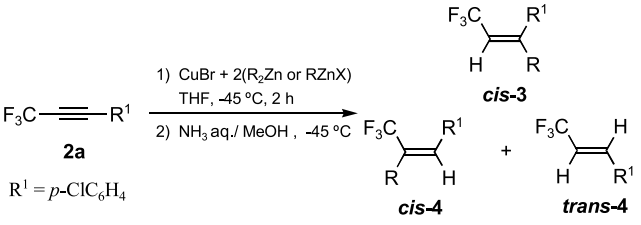
**Table 6**. Investigation of the reaction conditions




| Entry | Eq. of CuBr | Eq. of $Et_2Zn$ | Temp./°C | Yield[a]/% of **3**+**4** | Ratio[a,b] (**3**:**4**) | Recovery[a]/% of **2a** |
|---|---|---|---|---|---|---|
| 1 | 1.2 | 1.2 | −45 | 78 | 94:6 | 0 |
| 2 | 1.2 | 1.2 | −78 | 86 | 85:15 | 0 |
| 3 | 1.2 | 2.4 | −45 | 92 (84) | 98:2 | 0 |
| 4 | 1.2 | 2.4 | −78 | 92 | 96:4 | 0 |
| 5 | 0.2 | 2.4 | −45 | 73 | 89:11 | 20 |
| 6 | None | 2.4 | −45 | 0 | — | 99 |

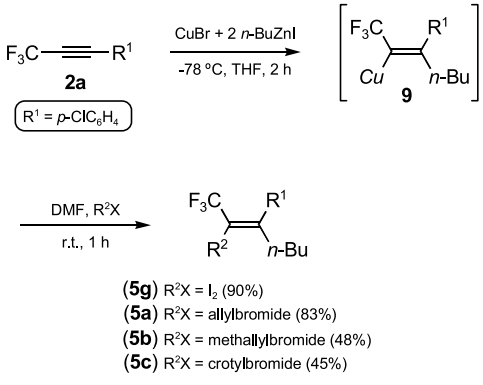
[a] Determined by $^{19}F$ NMR. Value in parentheses is of isolated yield.
[b] A ratio of *cis*-**4t**:*trans*-**4t** was not determined.

**Table 7**. The carbocupration reaction of fluoroalkylated alkynes with various organozinc reagents




| Entry | Zinc reagent | Product | Yield[a]/% of **3**+**4** | Ratio[a,b] (**3**:**4**) |
|---|---|---|---|---|
| 1 | $Et_2Zn$ | **3t** | 92(84) | 98:2 |
| 2 | *n*-$Bu_2Zn$ | **3a** | 80(80) | 100:0 |
| 3 | $Ph_2Zn$ | **3c** | 80 | 100:0 |
| 4 | $BrZnCH_2CO_2Et$ | — | 0 | — |
| 5 | $IZnCH_2CH_2CO_2Me$ | **3u** | 80(79) | 95:5 |
| 6 | $IZnCH_2CH_2CH_2CN$ | **3v** | 95(90) | 100:0 |
| 7 | *n*-BuZnI | **3a** | 80 | 78:22 |
| 8[c] | *n*-BuZnI | **3a** | 96(96) | 100:0 |

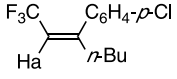
[a] Determined by $^{19}F$ NMR. Values in parentheses are of isolated yields.
[b] A ratio of *cis*-**4**:*trans*-**4** was not determined.
[c] Carried out at −78 °C.




**Scheme 4.** The cross-coupling reaction.

## 2.4. Determination of the stereochemistry of the carbocupration products

The stereochemistry in the carbocupration was determined as follows. Thus, the $^1H$ and $^{19}F$ NMR spectra of *cis*-**3a** showed a quartet signal due to the vinylic proton $H_a$ and a




$^1H$ NMR: q, $J$ = 8.2 Hz
$^{19}F$ NMR: d, $J$ = 8.2 Hz

**Figure 3.**

doublet signal due to the $CF_3$ group, respectively (Fig. 3). Additionally, the NOE between $H_b$ and $H_c$ in **5f** was observed in the NOESY, strongly indicating that the propargyl and the butyl groups were situated in the *cis* configuration (Fig. 4). These spectral data suggest that the present carbocupration reaction occurred in a highly *cis* addition manner, in which the copper metal was attached with a carbon bearing a fluoroalkyl group.

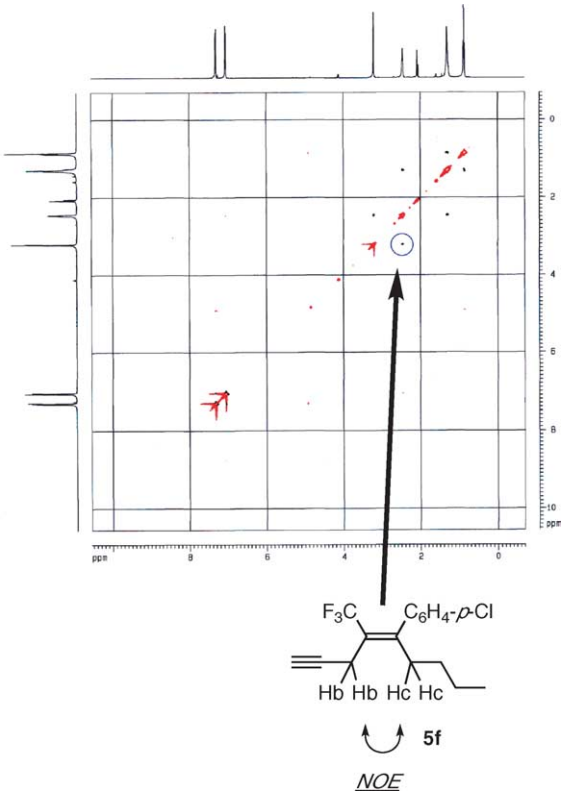
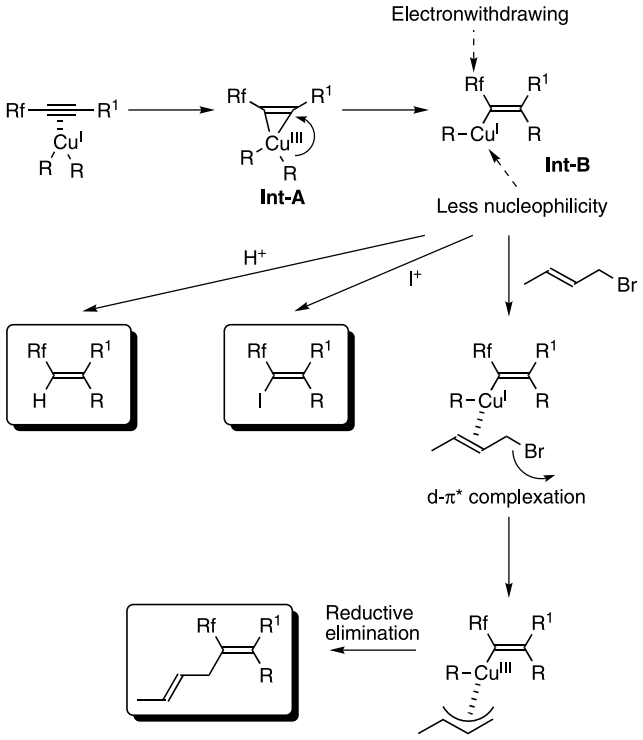



**Figure 4.** NOESY spectrum of **5f**.

## 2.5. Mechanism

Based on the results of the stereochemical assignment, the proposed mechanism for the present carbocupration reaction is outlined in Scheme 5. Thus, when copper reagent coordinates on the triple bond, oxidative addition of the alkyne to $Cu^{(I)}$ takes place to form the intermediate **Int-A**. Due to the strong electron-withdrawing effect exerted by a fluoroalkyl group (Rf), (Rf)C–$Cu^{(III)}$ bond may be stronger than ($R^1$)C–$Cu^{(III)}$. Accordingly, R on $Cu^{(III)}$ may transfer to the olefinic carbon distal to a fluoroalkyl group, vinylcopper intermediate **Int-B** being produced preferentially. Low nucleophilicity exerted by a fluoroalkyl group results in the coupling reaction of **Int-A** with only active electrophiles such as $H^+$, $I^+$, and variously-substituted allyl bromide. In the reaction of **Int-B** with variously-substituted allyl bromide, d-π* complexation between $Cu^{(I)}$ and the double bond may promote the generation of π-allylcopper intermediate, leading to the formation of tetrasubstituted alkenes via reductive elimination at the less hindered carbon.[14]




**Scheme 5.** Mechanism.

## 2.6. The synthetic application of the carbocupration reaction of fluorine-containing alkynes—total synthesis of anti-estrogenic drug, panomifene

As a synthetic application of the carbocupration reaction of fluorine-containing internal acetylenes, the total synthesis of panomifene **10**[3] (EGIS-5656, GYKI-13504), which is a follow-up molecule of tamoxifen **11**[15] (Nolvadex), the well-known triarylethylene type anti-estrogenic drug in the therapy of breast cancer and for the treatment of menstrual disorders (Fig. 5), was executed as follows (Scheme 6). Thus, alkyne **2x**[10] was exposed to the carbocupration reaction with $(4\text{-}MeOC_6H_4)_2Cu(CN)(MgBr)_2$ (1.2 eq.) at −45 °C for 2 h, followed by addition of 2.4 eq. of iodine at −78 °C, to afford vinyl iodide **5x** in 51% yield. The $^1H$, $^{13}C$, $^{19}F$ NMR, and GLC analyses were indicative of no other stereoisomers being formed. The stereochemically pure **5x** was treated with 4.0 eq. of phenylboronic acid under the Suzuki–Miyaura cross-coupling reaction conditions, producing the triarylethylene derivative **12x** almost quantitatively with complete retention of the stereochemistry. Surprisingly, treatment of **12x** with $BBr_3$ gave **13x** in low yield.[16] All attempts for improving this demethylation were unsuccessful. On the other hand, the demethylation of **5x** with $BBr_3$ proceeded readily to give the corresponding phenol derivative. The following nucleophilic substitution

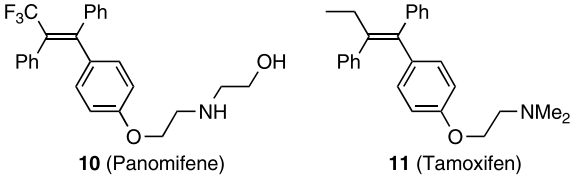
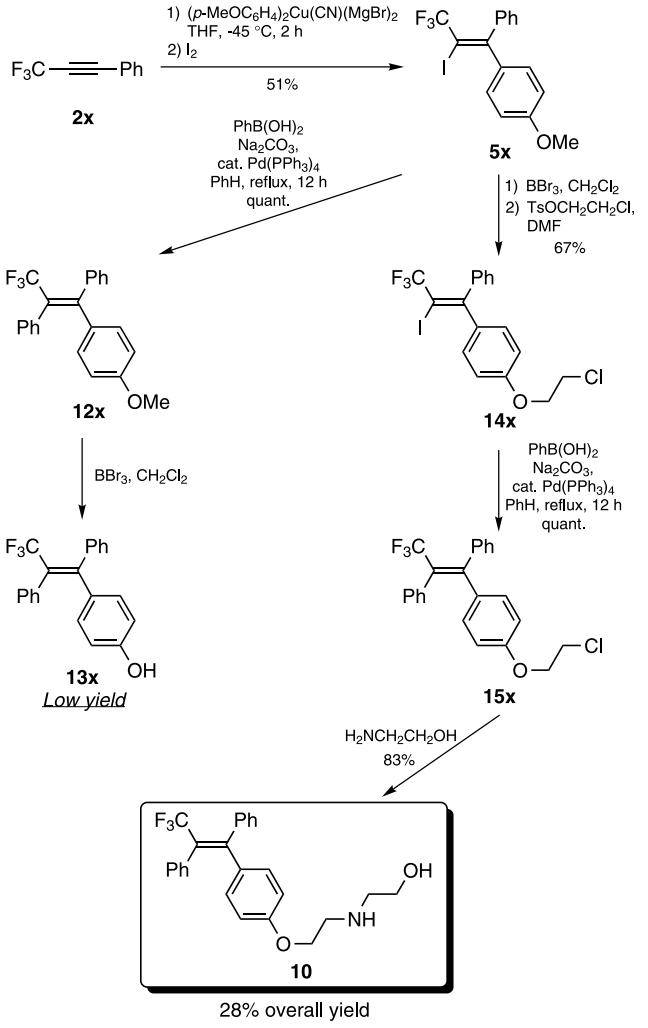



**Figure 5.** Panomifene and tamoxifen.




**Scheme 6.** A short total synthesis of panomifene.

reaction between phenoxide and 2-chloroethyl tosylate in DMF at the reflux temperature gave rise to the desired ether **14x** in 67% yield. The Suzuki–Miyaura cross-coupling reaction of **14x** with phenylboronic acid afforded the corresponding alkene **15x** quantitatively. Finally, on treating **15x** with ethanolamine in 2-methoxyethyleneglycol, the desired panomifene **10** was obtained in 83% yield (28% overall yield from **2x**).

## 3. Conclusion

In summary, we have investigated the carbocupration reaction of fluoroalkylated internal acetylene derivatives with various copper reagents derived from organolithium, Grignard, and organozinc reagents. The carbocupration reaction of fluoroalkylated internal alkynes proceeded in a highly regio- and stereo-selective manner to give the corresponding trisubstituted alkenes in high yields. Zinc reagents possessing a functional group such as an ester or a nitrile moiety were also applied for the reaction of the alkynes in a similar manner. The vinylcopper intermediate reacted only with a few carbon electrophiles such as allyl-, methally-, crotyl-bromide, etc, probably due to low reactivity exerted by an electron-withdrawing fluoroalkyl group. Treatment of vinylcopper with iodine resulted in the high yield of the corresponding vinyl iodide, which was employed successfully for the Suzuki–Miyaura and Sonogashira cross-coupling reactions. Two key reactions, the carbocupration and the Suzuki–Miyaura cross-coupling reaction realized the first highly stereoselective total synthesis of anti-estrogenic drug, panomifene **10** (total yield for five steps: 28%).[17]

## 4. Experimental

### 4.1. General

$^{1}$H NMR spectra were measured with a Bruker DRX (500.13 MHz) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane ($Me_4Si$) as an internal reference. $^{13}$C NMR spectra were recorded on a Bruker DRX (125.77 MHz). A JEOL JNM-EX90F (54.21 MHz, FT) spectrometer was used for determining $^{19}$F NMR yield with internal $C_6F_6$. It was used for determining regioselectivity and stereoselectivity and was used for taking $^{19}$F NMR spectra in a $CDCl_3$ solution with internal $CFCl_3$. $CFCl_3$ was used ($\delta_F=0$) as an internal standard for $^{19}$F NMR. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-700.

### 4.2. Materials

All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with Merck silica gel 60 $F_{254}$ plates. Preparative thin layer chromatography (TLC) was done with Merck silica gel 60 $F_{254}$, 1 mm.

### 4.3. Typical procedure for the reaction of fluoroalkylated acetylene derivatives with cuprate derived from lithium reagents

To a solution of copper cyanide (53 mg, 0.6 mmol) in THF (2.0 mL) was added 0.76 mL (1.2 mmol) of *n*-BuLi (1.6 M hexane solution) at −78 °C and the whole was stirred for 10 min, then allowed to warm to −20 °C and stirred for 30 min. To this solution was added dropwise 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (102 mg, 0.5 mmol). The reaction was stirred for 4 h at −78 °C, and was then quenched with $NH_3$ aq./MeOH (1 mL/5 mL), extracted with $Et_2O$ three times. The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane only) to afford (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-heptene (0.114 g, 0.44 mmol, 87% yield).

**4.3.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3a).** $^{1}$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J=7.0$ Hz), 1.31–1.34 (4H, m), 2.35–2.40 (2H, m), 5.67 (1H, q, $J=8.2$ Hz), 7.08 (2H, d, $J=8.3$ Hz), 7.33 (2H, d, $J=8.3$ Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.70 (3F, d, $J=8.2$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.7, 22.1, 29.2, 39.7, 115.7 (q, $J=33.4$ Hz), 122.7 (q, $J=271.0$ Hz), 128.3, 128.6, 133.9, 136.8, 153.2 (q, $J=5.9$ Hz); IR (neat) $\nu$ 2962, 2873, 1666, 1492, 1280 cm$^{-1}$; HRMS

(FAB) calcd for $C_{13}H_{14}{}^{35}ClF_3$ ($M^+$) 262.0736, found 262.0751. Anal. Calcd: C, 59.44; H, 5.37. Found: C, 59.03; H, 5.15.

**4.3.2. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-butene (3b).** $^1H$ NMR ($CDCl_3$) $\delta$ 2.13 (3H, q, $J$=2.0 Hz), 5.71 (1H, qq, $J$=1.5, 8.2 Hz), 7.16 (2H, d, $J$=8.5 Hz), 7.33 (2H, d, $J$=8.5 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −59.94 (3F, d, $J$=8.2 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 26.7, 116.2 (q, $J$=33.6 Hz), 122.4 (q, $J$=271.3 Hz), 128.2, 128.4, 134.1, 137.5, 148.9 (q, $J$=5.9 Hz); IR (neat) $\nu$ 1670, 1492 $cm^{-1}$; HRMS (FAB) calcd for $C_{10}H_8{}^{35}ClF_3$ ($M^+$) 220.0267, found 220.0260.

**4.3.3. (1*Z*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1-phenylprop-1-ene (3c).** $^1H$ NMR ($CDCl_3$) $\delta$ 6.14 (1H, q, $J$=8.2 Hz), 7.18 (2H, d, $J$=7.8 Hz), 7.23 (2H, d, $J$=7.8 Hz) 7.32–7.40 (5H, m); $^{19}F$ NMR ($CDCl_3$) $\delta$ −56.36 (3F, d, $J$=8.2 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 115.9 (q, $J$=34.0 Hz), 122.7 (q, $J$=264.8 Hz), 127.9, 128.4, 128.6, 129.6, 130.5, 134.7, 135.7, 139.7, 151.3 (q, $J$=5.8 Hz); IR (neat) $\nu$ 1643, 1492, 1361 $cm^{-1}$; HRMS (FAB) calcd for $C_{15}H_{10}{}^{35}ClF_3$ ($M^+$) 282.0423, found 282.0446.

**4.3.4. (*Z*)-1,1,1-Trifluoro-3-(4-methylphenyl)-2-heptene (3d).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$=7.0 Hz), 1.30–1.37 (4H, m), 2.37 (3H, s), 2.38–2.42 (2H, m), 5.66 (1H, q, $J$=8.3 Hz), 7.07 (2H, d, $J$=8.0 Hz), 7.16 (2H, d, $J$=8.0 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −57.99 (3F, d, $J$=8.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.8, 21.2, 22.1, 29.3, 39.9, 114.8 (q, $J$=33.1 Hz), 123.0 (q, $J$=270.3 Hz), 127.1, 128.7, 135.5, 137.6, 154.5 (q, $J$=5.6 Hz); IR (neat) $\nu$ 2931, 2873, 1662 $cm^{-1}$. HRMS (CI) calcd for $C_{14}H_{18}F_3$ (M+H) 243.1361, found 243.1362. Anal. Calcd: C, 69.40; H, 7.07. Found: C, 69.13; H, 7.15.

**4.3.5. (*Z*)-1,1,1-Trifluoro-3-(4-methoxyphenyl)-2-heptene (3e).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$=7.0 Hz), 1.28–1.36 (4H, m), 2.36–2.42 (2H, m), 3.82 (3H, s), 5.62 (1H, q, $J$=8.3 Hz), 6.88 (2H, d, $J$=8.8 Hz), 7.12 (2H, d, $J$=8.8 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −56.62 (3F, d, $J$=8.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.8, 22.1, 29.4, 39.8, 55.2, 113.4, 114.7 (q, $J$=33.1 Hz), 124.3 (q, $J$=270.6 Hz), 128.5, 130.6, 154.1 (q, $J$=5.6 Hz), 159.3; IR (neat) $\nu$ 2935, 2873, 1662, 1612 $cm^{-1}$. HRMS (FAB) calcd for $C_{14}H_{17}F_3O$ ($M^+$) 258.1231, found 258.1220. Anal. Calcd: C, 65.10; H, 6.63. Found: C, 65.20; H, 6.78.

**4.3.6. (*Z*)-1,1,1-Trifluoro-3-(3-methoxyphenyl)-2-heptene (3f).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.81 (3H, t, $J$=7.0 Hz), 1.22–1.31 (4H, m), 2.29–2.34 (2H, m), 3.74 (3H, s), 5.56 (1H, q, $J$=8.0 Hz), 6.64 (1H, s), 6.68 (1H, d, $J$=7.3 Hz), 6.78 (1H, dd, $J$=2.3, 8.4 Hz), 7.19 (1H, dd, $J$=7.3, 8.4 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −60.95 (3F, d, $J$=8.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.8, 22.1, 29.3, 39.7, 55.20, 113.1, 113.1, 115.0 (q, $J$=33.4 Hz), 119.6, 122.8 (q, $J$=270.4 Hz), 129.0, 139.8, 154.2 (q, $J$=5.6 Hz), 159.1; IR (neat) $\nu$ 2935, 2873, 1666, 1581 $cm^{-1}$; HRMS (FAB) calcd for $C_{14}H_{17}F_3$ ($M^+$) 258.1231, found 258.1220.

**4.3.7. (*Z*)-1,1,1-Trifluoro-3-(2-methoxyphenyl)-2-heptene (3g).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$=7.0 Hz), 1.30–1.39 (4H, m), 2.37–2.41 (2H, m), 33.80 (3H, s), 5.69 (1H, q, $J$=8.0 Hz), 6.90 (1H, d, $J$=7.9 Hz), 6.93 (1H, t, $J$=7.4 Hz), 7.01 (1H, dd, $J$=1.3, 7.4 Hz), 7.29 (1H, td, $J$=7.9, 1.8 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −62.78 (3F, d, $J$=8.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.8, 22.2, 29.3, 38.3, 55.4, 110.7, 115.6 (q, $J$=32.9 Hz), 120.0, 122.9 (q, $J$=270.6 Hz), 127.5, 129.0, 129.1, 152.1 (q, $J$=5.6 Hz), 155.79; IR (neat) $\nu$ 2935, 2873, 1672, 1492 $cm^{-1}$; HRMS (FAB) calcd for $C_{14}H_{17}F_3$ ($M^+$) 258.1231, found 258.1237.

**4.3.8. (*Z*)-Ethyl 4-(1-butyl-3,3,3-trifluoro-1-propenyl) benzoate (3h).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.80 (3H, t, $J$=7.0 Hz), 1.23–1.28 (4H, m), 1.32 (3H, t, $J$=7.0 Hz), 2.31–2.35 (2H, m), 4.31 (2H, q, $J$=7.0 Hz), 5.63 (1H, q, $J$=8.3 Hz), 7.16 (2H, d, $J$=8.3 Hz), 7.96 (2H, d, $J$=8.3 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −57.97 (3F, d, $J$=8.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.7, 14.3, 22.1, 29.1, 39.6, 61.0, 115.8 (q, $J$=33.6 Hz), 122.6 (q, $J$=271.4 Hz), 127.2, 129.3, 130.0, 143.1, 153.4 (q, $J$=5.3 Hz), 166.2; IR (neat) $\nu$ 2935, 2873, 1720, 1666 $cm^{-1}$; HRMS (FAB) calcd for $C_{16}H_{20}F_3O_2$ (M+H) 301.1416, found 301.1409. Anal. Calcd: C, 63.99; H, 6.38. Found: C, 64.01; H, 6.78.

**4.3.9. (*Z*)-3-(4-Chlorophenyl)-1,1-difluoro-2-heptene (3i).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.87 (3H, t, $J$=7.0 Hz), 1.28–1.36 (4H, m), 2.38–3.42 (2H, m), 5.69 (1H, q, $J$=7.7 Hz), 5.86 (1H, td, $J$=55.5, 7.7 Hz), 7.12 (2H, d, $J$=8.5 Hz), 7.35 (2H, d, $J$=8.5 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −109.23 to −109.55 (1F, m), −109.93 to −101.18 (1F, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.8, 22.1, 29.4, 38.4, 113.5 (t, $J$=229.6 Hz), 120.3 (t, $J$=26.4 Hz), 128.7, 129.3, 134.2, 136.6, 151.1 (t, $J$=1.3 Hz); IR (neat) $\nu$ 2958, 2862, 1662, 1492 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{15}{}^{35}ClF_2$ ($M^+$) 244.0830, found 244.0831.

**4.3.10. (*Z*)-5-(4-Chlorophenyl)-1,1,2,2,3,3-hexafluoro-4-nonene (3j).** $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$=7.0 Hz), 1.28–1.37 (4H, m), 2.44–2.48 (2H, m), 5.92 (1H, m), 6.02–6.29 (1H, m), 7.11 (2H, d, $J$=8.5 Hz), 7.33 (2H, d, $J$=8.5 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −127.10 to −127.50 (6F, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.7, 22.1, 29.7, 39.6, 105–109 (3C, m), 110.5 (dt, $J$=15.9, 7.8 Hz), 128.6, 128.7, 134.1, 137.5, 152.8 (d, $J$=8.3 Hz); IR (neat) $\nu$ 2958, 2873, 1631, 1492 $cm^{-1}$; *m/z* (EI) 306 (93) 271 (100) 215 (86) 177 (90) 164 (60) 137 (30).

### 4.4. Typical procedure for the synthesis of tetrasubstituted alkenes

To a solution of copper cyanide (53 mg, 0.6 mmol) in THF (2 mL) was added 0.76 mL (1.2 mmol) of *n*-BuLi (1.6 M hexane solution) at −45 °C, and the whole was stirred for 10 min, then allowed to warm to −20 °C and stirred for 30 min. To this solution was added dropwise 1-(4-chlorophenyl)-3,3-3-trifluoropropyne (102 mg, 0.5 mmol). The reaction was stirred for 4 h at −45 °C, and then was added dropwise allyl bromide (290 mg, 2.4 mmol). The reaction was stirred for 4 h at −45 °C, and then was quenched with $NH_4Cl$ aq. (3 mL), extracted with $Et_2O$ three times. The combined layers were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane only) to afford (*Z*)-5-(4-chlorophenyl)-4-trifluoromethyl-1,4-nonadiene (129 mg, 0.43 mmol, 86% yield).

**4.4.1. (*Z*)-5-(4-Chlorophenyl)-4-trifluoromethyl-1,4-nonadiene (5a).** $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (3H, t, $J$=7.0 Hz), 1.20–1.30 (4H, m), 2.33–2.37 (2H, m), 3.09 (2H, d, $J$=6.0 Hz), 5.11–5.20 (2H, m), 5.83–5.92 (1H, m), 7.04 (2H, d, $J$=8.3 Hz), 7.30 (2H, d, $J$=8.3 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −59.33 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.6, 29.2, 32.0, 35.7, 116.1, 124.2 (q, $J$=276.0 Hz), 124.3 (q, $J$=26.7 Hz), 128.0, 128.9, 133.1, 134.5, 139.1, 148.5 (q, $J$=3.6 Hz); IR (neat) $\nu$ 2962, 2866, 1651 cm$^{-1}$; HRMS (FAB) calcd for $C_{16}H_{18}{}^{35}ClF_3$ ($M^+$) 302.1049, found 302.1050.

**4.4.2. (*Z*)-5-(4-Chlorophenyl)-2-methyl-4-trifluoromethyl-1,4-nonadiene (5b).** $^1$H NMR ($CDCl_3$) $\delta$ 0.83 (3H, t, $J$=7.0 Hz), 1.17–1.28 (4H, m), 1.83 (3H, s), 2.28–2.32 (2H, m), 3.00 (2H, s), 4.79 (1H, s), 4.89 (1H, s), 7.06 (2H, d, $J$=8.5 Hz), 7.31 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −59.13 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.6, 23.0, 29.1, 35.5 (d, $J$=2.0 Hz), 35.9, 111.0, 124.1 (q, $J$=274.9 Hz), 124.4 (q, $J$=28.1 Hz), 128.0, 129.0, 133.1, 139.0, 141.8, 149.2 (q, $J$=3.4 Hz); IR (neat) $\nu$ 2962, 2862, 1651, 1488 cm$^{-1}$; HRMS (FAB) calcd for $C_{17}H_{20}{}^{35}ClF_3$ ($M^+$) 316.1206, found 316.1202. Anal. Calcd: C, 64.45; H, 6.36. Found: C, 64.65; H, 6.48.

**4.4.3. (2*E*,5*Z*)-6-(4-Chlorophenyl)-5-trifluoromethyl-2,5-decadiene (5c).** $^1$H NMR ($CDCl_3$) $\delta$ 0.84 (3H, t, $J$=7.0 Hz), 1.19–1.30 (4H, m), 1.70 (3H, dd, $J$=1.3, 6.8 Hz), 2.31–2.36 (2H, m), 3.00 (2H, d, $J$=6.3 Hz), 5.43–5.49 (1H, m), 5.52–5.60 (1H, m), 7.03 (2H, d, $J$=8.3 Hz), 7.29 (2H, d, $J$=8.3 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.00 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 17.9, 22.6, 29.2, 31.0, 35.6, 124.3 (q, $J$=276.0 Hz), 125.1 (q, $J$=22.5 Hz), 126.8, 127.1, 128.9, 133.0, 139.3, 147.7 (q, $J$=3.8 Hz); IR (neat) $\nu$ 2962, 2873, 1630 cm$^{-1}$; HRMS (EI) calcd for $C_{17}H_{20}{}^{35}ClF_3$ ($M^+$) 316.1256, found 316.1187. Anal. Calcd: C, 64.45; H, 6.36. Found: C, 64.35; H, 6.11.

**4.4.4. (*Z*)-6-(4-Chlorophenyl)-2-methyl-5-trifluoromethyl-2,5-decadiene (5d).** $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (3H, t, $J$=6.8 Hz), 1.21–1.29 (4H, m), 1.70 (3H, s), 1.74 (3H, s), 2.31–2.35 (2H, m), 3.01 (2H, d, $J$=6.8 Hz), 5.10 (1H, t, $J$=6.8 Hz), 7.03 (2H, d, $J$=8.5 Hz), 7.29 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −62.10 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 17.8, 22.7, 25.7, 27.1, 29.3, 35.8, 121.1, 124.9 (q, $J$=276.0 Hz), 126.0 (q, $J$=27.3 Hz), 128.0, 128.9 (d, $J$=2.0 Hz), 132.8, 133.0, 139.40, 147.0 (q, $J$=3.6 Hz); IR (neat) $\nu$ 2962, 2862, 1651, 1488 cm$^{-1}$; HRMS (FAB) calcd for $C_{18}H_{22}{}^{35}ClF_3$ ($M^+$) 329.1283, found 329.1285.

**4.4.5. (*Z*)-Methyl 5-(4-chlorophenyl)-2-methylene-4-trifluoromethyl-4-nonenate (5e).** $^1$H NMR ($CDCl_3$) $\delta$ 0.81 (3H, t, $J$=7.0 Hz), 1.17–1.27 (4H, m), 2.24–2.29 (2H, m), 3.35 (2H, s), 3.81 (3H, s), 5.62 (1H, s), 6.33 (1H, s), 7.06 (2H, d, $J$=8.5 Hz), 7.32 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −61.83 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.5, 29.1, 29.6, 36.0, 52.1, 123.9 (q, $J$=275.8 Hz), 123.0 (q, $J$=28.0 Hz), 125.1, 128.1, 128.9, 133.3, 136.8, 138.5, 150.5 (q, $J$=3.1 Hz); IR (neat) $\nu$ 2958, 2837, 1724, 1635, 1488 cm$^{-1}$; HRMS (FAB) calcd for $C_{18}H_{21}{}^{35}ClF_3O_2$ ($M^+$) 361.1183, found 361.1180.

**4.4.6. (*Z*)-5-(4-Chlorophenyl)-4-trifluoromethyl-4-nonen-1-yne (5f).** $^1$H NMR ($CDCl_3$) $\delta$ 0.86 (3H, t, $J$=6.8 Hz), 1.24–1.35 (4H, m), 2.08 (1H, t, $J$=2.5 Hz), 2.44–2.48 (2H, m), 3.21 (2H, d, $J$=2.5 Hz), 7.05 (2H, d, $J$=8.3 Hz), 7.31 (2H, d, $J$=8.3 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −59.53 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 17.6, 22.6, 28.9, 36.1, 68.9, 80.1, 121.4 (q, $J$=275.1 Hz), 121.9 (q, $J$=28.1 Hz), 128.1, 128.7, 133.4, 138.3, 149.4 (q, $J$=3.4 Hz); IR (neat) $\nu$ 3309, 2962, 2873, 1654 cm$^{-1}$; HRMS (FAB) calcd for $C_{16}H_{16}{}^{35}ClF_3$ ($M^+$) 300.0893, found 300.0896.

**4.4.7. (*E*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (5g).** $^1$H NMR ($CDCl_3$) $\delta$ 0.89 (3H, t, $J$=7.0 Hz), 1.30–1.36 (4H, m), 2.62–2.67 (2H, m), 7.02 (2H, d, $J$=8.5 Hz), 7.32 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −55.23 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.4, 28.2, 46.3, 86.6 (q, $J$=34.2 Hz), 120.8 (q, $J$=273.7 Hz), 128.3, 128.4, 134.0, 137.3, 157.2 (q, $J$=2.9 Hz); IR (neat) $\nu$ 2958, 2862, 1593 cm$^{-1}$; HRMS (FAB) calcd for $C_{13}H_{13}{}^{35}ClF_3I$ ($M^+$) 387.9703, found 387.9694. Anal. Calcd: C, 40.18; H, 3.37. Found: C, 40.55; H, 3.23.

### 4.5. The Suzuki–Miyaura cross-coupling of 5g with phenyl iodide in the presence of palladium catalyst

To a solution of (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (109 mg, 0.273 mmol), $Pd(PPh_3)_4$ (34 mg, 0.024 mmol), in benzene (6 mL) was added $Na_2CO_3$ (72 mg, 0.68 mmol), $PhB(OH)_2$ (133 mg, 1.092 mmol), $H_2O$ (0.35 mL), and EtOH (0.3 mL). The reaction mixture was refluxed for 12 h, then quenched with saturated $NH_4Cl$ aq. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over $Na_2SO_4$, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-phenyl-2-heptene (91 mg, 0.269 mmol, 98% yield).

**4.5.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-phenyl-2-heptene (6g).** $^1$H NMR ($CDCl_3$) $\delta$ 0.66 (3H, t, $J$=7.1 Hz), 1.03–1.13 (4H, m), 2.13 (2H, d, $J$=7.2 Hz), 7.18 (2H, d, $J$=8.3 Hz), 7.29 (2H, d, $J$=8.3 Hz), 7.35–7.46 (5H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.43 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.6, 22.2, 29.3, 36.7, 123.2 (q, $J$=274.9 Hz), 125.3, 127.2, 127.2, 128.2, 128.4, 128.8, 129.8, 133.4, 134.6, 138.2, 149.3 (q, $J$=2.4 Hz); IR (neat) $\nu$ 2929, 2862, 1643 cm$^{-1}$; HRMS (FAB) calcd for $C_{19}H_{18}{}^{35}ClF_3$ ($M^+$) 338.1049, found 338.1051.

### 4.6. The Sonogashira cross-coupling reaction of 8b with trimethylsilyl acetylene

To a solution of 3-(4-chlorophenyl)-2-iodo-1,1,1-trifluoro-2-heptene (100 mg, 0.260 mmol), trimethylsilylacetylene (50 mg, 0.52 mmol) and copper (I) iodide (5 mg, 0.026 mmol) in THF (2.0 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.02 mmol), $Et_3N$ (1.5 mL) and the whole was stirred for 24 h at 50 °C. The reaction mixture was quenched with $NH_4Cl$ aq. and extracted with $Et_2O$ three times. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel to afford (*Z*)-4-(4-chlorophenyl)-3-trifluoromethyl-1-trimethylsilyl-3-heptene-1-yne (90 mg, 0.247 mmol, 95% yield).

**4.6.1. (*Z*)-4-(4-Chlorophenyl)-3-trifluoromethy-1-trimethylsilyl-3-hepten-1-yne (7g).** $^1$H NMR ($CDCl_3$) $\delta$ 0.25 (9H, s), 0.89 (3H, t, $J$=7.0 Hz), 1.33 (4H, m), 2.70 (2H, t, $J$=6.7 Hz), 7.05 (2H, d, $J$=8.5 Hz), 7.32 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −57.42 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.3, 13.8, 22.4, 29.0, 38.8, 97.3, 102.8, 112.9 (q, $J$=33.2 Hz), 121.5 (q, $J$=274.7 Hz), 128.3, 128.4, 134.1, 137.0, 158.7 (q, $J$=2.6 Hz); IR (neat) $\nu$ 2862, 2152, 1488 cm$^{-1}$; HRMS (EI) calcd for $C_{18}H_{22}{}^{35}ClF_3Si$ ($M^+$) 358.1131, found 358.1137. Anal. Calcd: C, 60.24; H, 6.18. Found: C, 60.06; H, 6.18.

### 4.7. Typical procedure for the carbocupration of fluorine-containing acetylene derivatives with Grignard reagents

To a solution of CuBr (47 mg, 0.328 mmol) in THF (2 mL) was added a THF solution of *n*-butylmagnesium bromide (0.66 mmol, prepared by magnesium and 1-bromobutane) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (49 mg, 0.240 mmol) in THF (2 mL). After stirring at that temperature for 2 h, the reaction was quenched with $NH_3$ aq./MeOH, and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-heptene (52 mg, 0.198 mmol, 83% yield).

**4.7.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-4-methyl-2-hexene (3k).** $^1$H NMR ($CDCl_3$) $\delta$ 0.92 (3H, t, $J$=7.5 Hz), 1.05 (3H, d, $J$=6.5 Hz), 1.26 (1H, dq, $J$=7.5, 21.0 Hz), 1.46 (1H, m), 2.34 (1H, q, $J$=6.5 Hz), 5.65 (1H, q, $J$=7.8 Hz), 7.05 (2H, d, $J$=8.5 Hz), 7.32 (2H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.25 (3F, d, $J$=7.8 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.5, 18.4, 27.1, 44.1, 115.7 (q, $J$=33.3 Hz), 122.9 (q, $J$=271.2 Hz), 128.0, 129.0, 133.7, 136.1, 157.3 (q, $J$=5.2 Hz); IR (neat) $\nu$ 2966, 2935, 2877, 1662 cm$^{-1}$; HRMS (FAB) calcd for $C_{13}H_{14}{}^{35}ClF_3$ ($M^+$) 262.0736, found 262.0735.

**4.7.2. (*Z*)-1-(4-Chlorophenyl)-1-cyclohexyl-3,3,3-trifluoropropene (3l).** $^1$H NMR ($CDCl_3$) $\delta$ 1.08–1.40 (5H, m), 1.66–1.98 (5H, m), 2.16 (1H, t, $J$=11.7 Hz), 5.62 (1H, q, $J$=8.0 Hz), 7.04 (2H, d, $J$=8.4 Hz), 7.31 (2H, d, $J$=8.4 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.17 (3F, d, $J$=8.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 25.9, 26.3, 31.3, 46.8, 114.7 (q, $J$=33.3 Hz), 123.1 (q, $J$=271.2 Hz), 128.0, 128.9, 133.6, 136.6, 158.0 (q, $J$=5.4 Hz); IR (neat) $\nu$ 2931, 2856, 1664, 1595 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{16}{}^{35}ClF_3$ ($M^+$) 288.0893, found 288.0897.

**4.7.3. (*Z*)-2-(4-Chlorophenyl)-4,4,4-trifluoro-1-phenyl-2-butene (3m).** $^1$H NMR ($CDCl_3$) $\delta$ 3.65 (2H, s), 5.59 (1H, q, $J$=8.0 Hz), 7.01 (2H, d, $J$=8.0 Hz), 7.08 (2H, d, $J$=8.0 Hz), 7.22–7.30 (5H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.72 (3F, d, $J$=8.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 46.2, 117.4 (q, $J$=33.6 Hz), 121.6 (q, $J$=271.3 Hz), 127.1, 128.3, 128.7, 129.3, 134.0, 136.1, 136.4, 152.3 (q, $J$=5.5 Hz); IR (neat) $\nu$ 3062, 3031, 1666, 1596 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{12}{}^{35}ClF_3$ ($M^+$) 296.0580, found 296.0579. Anal. Calcd: C, 64.77; H, 4.08. Found: C, 65.20; H, 4.03.

**4.7.4. (4*Z*)-4-(4-Chlorophenyl)-6,6,6-trifluoro-1,4-hexadiene (3n).** $^1$H NMR ($CDCl_3$) $\delta$ 3.11 (2H, d, $J$=5.5 Hz), 5.11 (1H, d, $J$=17.0 Hz), 5.16 (1H, d, $J$=10.0 Hz), 5.72 (2H, m), 7.13 (2H, d, $J$=8.0 Hz), 7.33 (2H, d, $J$=8.0 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.68 (3F, d, $J$=8.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 43.8, 116.6 (q, $J$=34.0 Hz), 119.0, 124.8 (q, $J$=270.4 Hz), 128.4, 128.6, 132.9, 134.1, 136.7, 151.2 (q, $J$=5.0 Hz); IR (neat) $\nu$ 3082, 1670, 1639, 1596 cm$^{-1}$; HRMS (FAB) calcd for $C_{12}H_{10}{}^{35}ClF_3$ ($M^+$) 246.0423, found 246.0420. Anal. Calcd: C, 58.43; H, 4.08. Found: C, 58.15; H, 3.98.

**4.7.5. (3*Z*)-3-(4-Chlorophenyl)-5,5,5-trifluoro-1,3-pentadiene (3o).** $^1$H NMR ($CDCl_3$) $\delta$ 5.01 (1H, d, $J$=17.2 Hz), 5.43 (1H, d, $J$=10.4 Hz), 5.82 (1H, q, $J$=8.1 Hz), 6.56 (2H, dd, $J$=10.4, 17.2 Hz), 7.11 (2H, d, $J$=8.4 Hz), 7.37 (2H, d, $J$=8.4 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.56 (3F, d, $J$=8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 118.8 (q, $J$=33.6 Hz), 122.8 (q, $J$=270.5 Hz), 123.4, 128.3, 128.6, 130.0, 132.8, 134.2, 149.1 (q, $J$=5.5 Hz); IR (neat) $\nu$ 2360, 1643, 1610, 1596 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_8{}^{35}ClF_3$ ($M^+$) 262.0736, found 262.0735.

**4.7.6. (*Z*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1-(4-methoxyphenyl)-propene (3p).** $^1$H NMR ($CDCl_3$) $\delta$ 3.81 (3H, s), 6.06 (1H, q, $J$=8.3 Hz), 6.85 (2H, d, $J$=8.9 Hz), 7.1$\delta$ 6 (2H, d, $J$=8.3 Hz), 7.17 (2H, d, $J$=8.9 Hz), 7.37 (2H, d, $J$=8.3 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −57.23 (3F, d, $J$=8.3 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.4, 113.9 (q, $J$=34.1 Hz), 113.9, 123.1 (q, $J$=270.5 Hz), 128.3, 129.3, 131.9, 134.5, 135.9, 150.6 (q, $J$=5.8 Hz), 160.8; IR (neat) $\nu$ 1604, 1512, 1490 cm$^{-1}$; HRMS (FAB) calcd for $C_{16}H_{12}{}^{35}ClF_3O$ ($M^+$) 312.0529, found 312.0526.

**4.7.7. (*Z*)-3-(3-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3q).** $^1$H NMR ($CDCl_3$) $\delta$ 0.89 (3H, t, $J$=7.0 Hz), 1.33 (4H, m), 2.37 (2H, m), 5.67 (1H, q, $J$=8.0 Hz), 7.05 (1H, d, $J$=7.0 Hz), 7.16 (1H, s), 7.24–7.32 (2H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.62 (3F, d, $J$=8.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.1, 29.1, 39.6, 115.8 (q, $J$=33.4 Hz), 122.6 (q, $J$=271.2 Hz), 125.5, 127.1, 128.0, 129.3, 133.9, 140.2, 152.8 (q, $J$=5.7 Hz); IR (neat) $\nu$ 2963, 2936, 2874, 2500, 1666, 1600 cm$^{-1}$; HRMS (CI) calcd for $C_{13}H_{14}{}^{35}ClF_3$ ($M^+$) 262.0736, found 262.0739. Anal. Calcd: C, 59.44; H, 5.17. Found: C, 59.67; H, 5.17.

**4.7.8. (*Z*)-3-(2-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3r).** $^1$H NMR ($CDCl_3$) $\delta$ 0.83 (3H, t, $J$=6.5 Hz), 1.25–1.37 (4H, m), 2.32 (2H, t, $J$=7.0 Hz), 5.69 (1H, q, $J$=7.5 Hz), 7.01 (1H, d, $J$=9.0 Hz), 7.16–7.21 (2H, m), 7.32 (1H, d, $J$=9.0 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −58.72 (3F, d, $J$=7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.2, 29.0, 38.0, 116.5 (q, $J$=33.8 Hz), 122.6 (q, $J$=271.1 Hz), 126.2, 129.0, 129.3, 129.3, 129.4, 131.4, 151.7 (q, $J$=5.8 Hz); IR (neat) $\nu$ 3066, 2960, 2933, 2864, 1672, 1593 cm$^{-1}$; HRMS (CI) calcd for $C_{13}H_{14}{}^{35}ClF_3$ ($M^+$) 262.0736, found 262.0744. Anal. Calcd: C, 59.44; H, 5.17. Found: C, 59.79; H, 5.01.

**4.7.9. (*Z*)-1,1,1-Trifluoro-3-[(4-methoxyphenyl)methyl]-2-heptene (3s).** $^1$H NMR ($CDCl_3$) $\delta$ 0.86 (3H, t, $J$=7.4 Hz), 1.24 (2H, tq, $J$=7.4, 7.5 Hz), 1.38 (2H, tt, $J$=7.5, 7.6 Hz), 3.54 (2H, s), 3.79 (3H, s), 5.54 (1H, q, $J$=8.5 Hz), 6.83 (2H, d, $J$=8.4 Hz), 7.09 (2H, d, $J$=8.4 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.01 (3F, d, $J$=8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.8, 22.2, 29.4, 35.2, 36.4, 55.2, 113.9, 114.8 (q, $J$=32.9 Hz), 123.5 (q, $J$=274.9 Hz), 129.7, 129.8, 129.9, 154.2 (q, $J$=5.2 Hz), 158.3; IR (neat) $\nu$ 2933, 2861, 2837, 1668, 1612 cm$^{-1}$; HRMS (FAB) calcd for $C_{15}H_{19}{}^{35}ClF_3$ ($M^+$) 272.1388, found 272.1387.

**4.7.10. (5*Z*,7*Z*)-5,8-Bis(4-chlorophenyl)-6,7-bis(trifluoromethyl)-5,7-dodecadiene (8).** $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (6H, t, $J$=7.3 Hz), 1.15–1.25 (4H, m), 1.26–1.33 (4H, m), 2.34–2.42 (2H, m), 2.48–2.60 (2H, m), 7.12 (4H, d, $J$=8.5 Hz), 7.37 (4H, d, $J$=8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −55.58 (6F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.7, 22.8, 28.6, 37.2, 122.1 (q, $J$=31.8 Hz), 122.5 (q, $J$=275.9 Hz), 128.3, 128.7, 133.9, 136.7, 154.4; IR (neat) $\nu$ 2962, 2873, 1631, 1488 cm$^{-1}$; HRMS (FAB) calcd for $C_{26}H_{26}{}^{35}Cl_2F_6$ ($M^+$) 522.1316, found 522.1309.

### 4.8. Typical procedure for the carbocupration of the fluorine-containing acetylene derivatives and the following coupling reaction of various carbon electrophiles

To a solution of CuBr (96 mg, 0.669 mmol) in THF (4 mL) was added a THF solution of *n*-butylmagnesium chloride (1.34 mmol, purchased from Aldrich) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (114 mg, 0.56 mmol) in THF (2 mL). After stirring at that temperature for 2 h, allyl bromide (324 mg, 2.68 mmol) was added slowly to the reaction mixture. After stirring of the solution for 1 h, the reaction was quenched with $NH_3$ aq./MeOH, and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (4*Z*)-5-(4-chlorophenyl)-4,4,4-trifluoro-1,3-nonadiene (110 mg, 0.364 mmol, 77% yield).

### 4.9. Preparation of fluorine-containing vinyl iodide

To a solution of CuBr (91 mg, 0.634 mmol) in THF (4 mL) was added a THF solution of *n*-butylmagnesium chloride (1.260 mmol, purchased from Aldrich) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (94 mg, 0.459 mmol) in THF (2 mL). After stirring at that temperature for 2 h, iodine (644 mg, 2.54 mmol) in THF (2 mL) was added to the reaction mixture slowly. After 1 h, the reaction was quenched with $NH_3$ aq./MeOH, and a few drops of $Na_2SO_3$ were added until the color of the reaction mixture changed. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (152 mg, 0.392 mmol, 85% yield).

### 4.10. Typical procedure for the carbocupration of fluorine-containing acetylene derivatives with organozinc reagents

To a suspension of CuBr (50 mg, 0.349 mmol) in THF (4 mL) was added a THF solution of *n*-BuZnI (0.73 M, 0.95 mL, 0.697 mmol) at −78 °C for 20 min. To this solution was added dropwise a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (57 mg, 0.279 mmol) in THF (2 mL). After stirring at that temperature for 2 h, DMF (6 mL) was added as a co-solvent. The whole was allowed to warm to room temperature, and then to this solution was added a solution of iodine (355 mg, 1.40 mmol) in THF (2 mL). After stirring of the reaction mixture for 1 h, the reaction was quenched with $NH_3$ aq./MeOH, and a few drops of $Na_2SO_3$ were added until the color of the reaction mixture changed. The whole was extracted with $Et_2O$ three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (98 mg, 0.252 mmol, 90% yield).

**4.10.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-pentene (3t).** $^1$H NMR ($CDCl_3$) $\delta$ 1.03 (3H, t, $J$=7.4 Hz), 2.40 (2H, q, $J$=7.4 Hz), 5.66 (1H, q, $J$=8.0 Hz), 7.11 (2H, d, $J$=8.4 Hz), 7.33 (2H, d, $J$=8.4 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.50 (3F, d, $J$=8.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.8, 32.9, 114.9 (q, $J$=33.6 Hz), 122.8 (q, $J$=270.9 Hz), 128.3, 128.5, 133.9, 136.9, 154.4 (q, $J$=5.5 Hz); IR (neat) $\nu$ 2976, 2943, 1492, 1465 cm$^{-1}$; HRMS (FAB) calcd for $C_{11}H_{10}{}^{35}ClF_3$ ($M^+$) 234.0423, found 234.0421.

**4.10.2. Methyl (*Z*)-4-(4-chlorophenyl)-6,6,6-trifluoro-4-hexenoate (3u).** $^1$H NMR ($CDCl_3$) $\delta$ 2.36 (2H, t, $J$=7.5 Hz), 2.71 (2H, t, $J$=7.5 Hz), 3.65 (3H, s), 5.72 (1H, q, $J$=7.9 Hz), 7.11 (2H, d, $J$=8.4 Hz), 7.33 (2H, d, $J$=8.4 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.87 (3F, d, $J$=7.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 31.6, 34.8, 51.8, 116.8 (q, $J$=33.7 Hz), 122.4 (q, $J$=271.1 Hz), 128.5, 128.7, 134.3, 135.6, 151.0 (q, $J$=5.5 Hz), 172.3; IR (neat) $\nu$ 2955, 1740, 1668 cm$^{-1}$; HRMS (FAB) calcd for $C_{13}H_{13}{}^{35}ClF_3O_2$ ($M^+$) 293.0556, found 293.0563.

**4.10.3. (*Z*)-4-(4-Chlorophenyl)-6,6,6-trifluoro-4-hexenenitrile (3v).** $^1$H NMR ($CDCl_3$) $\delta$ 1.70 (2H, tt, $J$=7.0, 7.6 Hz), 2.34 (2H, t, $J$=7.0 Hz), 2.57 (2H, t, $J$=7.6 Hz), 5.76 (1H, q, $J$=7.9 Hz), 7.11 (2H, d, $J$=8.3 Hz), 7.36 (2H, d, $J$=8.3 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −56.82 (3F, d, $J$=7.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.4, 22.8, 38.3, 117.4 (q, $J$=34.0 Hz), 118.7, 122.2 (q, $J$=271.3 Hz), 128.5, 128.7, 134.6, 135.3, 150.5 (q, $J$=5.4 Hz); IR (neat) $\nu$ 2943, 2248, 1668 cm$^{-1}$; HRMS (FAB) calcd for $C_{13}H_{11}{}^{35}ClF_3N$ ($M^+$) 273.0532, found 273.0528.

### 4.11. Typical procedure for the carbocupration of the fluorine-containing acetylene derivatives with organozinc reagents and the following coupling reaction of various electrophiles

To a suspension of CuBr (50 mg, 0.349 mmol) in THF (4 mL) was added $Et_2Zn$ (0.70 ml, 0.700 mmol) at −45 °C for 20 min. To this solution was added dropwise a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (63 mg, 0.308 mmol) in THF (2 mL). After stirring at that temperature for 2 h, DMF (6 mL) was added as additive. The whole was stirred for 10 min, then to this solution was added a solution of iodine (355 mg, 1.40 mmol) in THF (2 mL). After 1 h later, the reaction was quenched with $NH_3$ aq./MeOH, and a few drops of $Na_2SO_3$ were added until color of the reaction mixture was changed. And the whole was extracted with $Et_2O$ three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-pentene (81 mg, 0.225 mmol, 73%).

### 4.12. Total synthesis of panomifene

To a solution of CuCN (56 mg, 0.625 mmol) and 3,3,3-trifluoro-1-phenylpropyne (81 mg, 0.476 mmol) in THF (4 mL) was added *p*-methoxyphenylmagnesium bromide (1.25 mmol, purchased from Aldrich) at −45 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −5 °C, then stirred for 30 min. The reaction mixture was again cooled to −45 °C. After stirring at that temperature for 2 h, iodine (635 mg, 2.50 mmol) in THF (2 mL) was added slowly. After 1 h, the reaction was quenched with $NH_3$ aq./MeOH, and a few drops of $Na_2SO_4$ were added until the color of the reaction mixture changed. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous $Na_2SO_4$, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3,3,3-trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (99 mg, 0.245 mmol, 51% yield).

**4.12.1. (*Z*)-3,3,3-Trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (5x).** $^1$H NMR ($CDCl_3$) $\delta$ 3.81 (3H, s), 6.87 (2H, d, $J$=8.2 Hz), 7.13–7.17 (4H, m), 7.30–7.31 (3H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −54.21 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.2, 85.2 (q, $J$=34.2 Hz), 113.7, 121.4 (q, $J$=270.5 Hz), 128.1, 128.1, 129.8, 137.7, 139.7, 158.6 (q, $J$=3.2 Hz), 160.8; IR (neat) $\nu$ 1604, 1508, 1461 cm$^{-1}$; HRMS (FAB) calcd for $C_{16}H_{12}F_3IO$ ($M^+$) 403.9885, found 403.9889. Anal. Calcd: C, 47.55; H, 2.99. Found: C, 47.54; H, 2.71.

To a solution of (*Z*)-3,3,3-trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (100 mg, 0.247 mmol) in $CH_2Cl_2$ (5 mL) was added a $CH_2Cl_2$ solution of boron tribromide (0.5 mmol, purchased from Aldrich) at room temperature. After stirring at that temperature for 1 h, the reaction was quenched with saturated $NH_4Cl$ aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over $Na_2SO_4$, and then concentrated in vacuo. Without purification, the reaction mixture was used for next reaction.

To a solution of NaH (12 mg, 0.494 mmol) in DMF (4 mL) was added a solution of the above-obtained crude product in DMF (2 mL) at 0 °C, and the resulting mixture was stirred at this temperature for 30 min. Then 2-chloroethyl tosylate (116 mg, 0.494 mmol) was added to this mixture. The reaction mixture was allowed to 80 °C. After 2 h, the reaction was quenched with saturated $NH_4Cl$ aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over $Na_2SO_4$, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-2-iodo-1-phenylpropene (74 mg, 0.163 mmol, 67% yield).

**4.12.2. (*Z*)-3,3,3-Trifluoro-2-iodo-1-[4-(2-chloroethoxy)phenyl]-1-phenylpropene (14x).** $^1$H NMR ($CDCl_3$) $\delta$ 3.82 (2H, t, $J$=5.8 Hz), 4.23 (2H, t, $J$=5.8 Hz), 6.89 (2H, d, $J$=8.7 Hz), 7.15–7.32 (7H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −54.26 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 44.7, 67.9, 85.8 (q, $J$=34.3 Hz), 114.3, 121.3 (q, $J$=274.0 Hz), 128.1, 128.4, 129.9, 138.4, 139.5, 158.3 (q, $J$=6.4 Hz); IR (KBr) $\nu$ 1606, 1510, 1454, 1296, 1249 cm$^{-1}$; HRMS (FAB) calcd for $C_{17}H_{13}{}^{35}ClF_3IO$ ($M^+$) 451.9652, found 451.9656. Anal. Calcd: C, 45.11; H, 2.89. Found: C, 45.18; H, 2.80.

A solution of (*Z*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-2-iodo-1-phenylpropene (59 mg, 0.130 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.013 mmol) in benzene (5 mL) was added $Na_2CO_3$ (34 mg, 0.325 mmol), $PhB(OH)_2$ (63 mg, 0.517 mmol), $H_2O$ (0.15 mL) and EtOH (0.15 mL). The whole was refluxed for 12 h, then the reaction was quenched with saturated $NH_4Cl$ aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over $Na_2SO_4$, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-1,2-diphenylpropene (52 mg, 0.130 mmol, 100% yield).

**4.12.3. (*E*)-3,3,3-Trifluoro-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylpropene (15x).** Mp 108–109 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.63 (3H, t, $J$=5.8 Hz), 3.99 (3H, t, $J$=5.8 Hz), 6.48 (2H, d, $J$=8.8 Hz), 6.48 (2H, d, $J$=8.8 Hz), 6.74 (2H, d, $J$=8.8 Hz), 7.14–7.31 (10H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −57.05 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 41.7, 67.7, 113.7, 123.7 (q, $J$=275.5 Hz), 127.8, 127.8, 127.9, 128.0, 128.6, 128.6 (q, $J$=28.8 Hz), 131.4, 131.5, 134.0, 135.3, 140.2, 149.6 (q, $J$=3.4 Hz), 157.3; IR (KBr) $\nu$ 1606, 1510, 1326 cm$^{-1}$; HRMS (FAB) calcd for $C_{23}H_{18}{}^{35}ClF_3O$ ($M^+$) 402.0998, found 402.0995. Anal. Calcd: C, 68.58; H, 4.50. Found: C, 68.23; H, 4.18.

A mixture of (*E*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-1,2-diphenylpropene (84 mg, 0.201 mmol) and 2-methoxyethanol (3 mL) was refluxed for 10 h. It was diluted with dichloromethane and washed with 4% aqueous NaOH solution and water, dried ($Na_2SO_4$) and evaporated. The residue was purified by silica gel column

chromatography to give the target compound, panomifene (71 mg, 0.167 mmol, 83% yield).

**4.12.4. (*E*)-3,3,3-Trifluoro-1-{4-[2-(2-hydroxyethylamino)ethoxy]phenyl}-1,2-diphenylpropene (Panomifene, 10).** Mp 96–98 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.02 (2H, br s), 2.73 (2H, t, $J$=5.1 Hz), 2.86 (2H, t, $J$=5.1 Hz), 3.55 (2H, t, $J$=5.1 Hz), 3.85 (2H, t, $J$=5.1 Hz), 6.48 (2H, d, $J$=8.7 Hz), 6.74 (2H, d, $J$=8.7 Hz), 7.14–7.31 (10H, m); $^{19}$F NMR ($CDCl_3$) $\delta$ −55.94 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 48.1, 50.7, 60.8, 67.1, 113.5, 123.7 (q, $J$=274.9 Hz), 127.7, 129.8, 127.9, 128.0, 128.3 (q, $J$=28.4 Hz), 128.6, 131.40, 131.50, 133.50, 135.34, 140.79, 149.70 (q, $J$=2.8 Hz), 157.87; IR (KBr) $\nu$ 3348, 3032, 2925, 1735, 1606, 1573, 1510, 1445, 1415, 1363, 1249, 1074, 981, 952, 918, 821, 762, 707, 630, 588 cm$^{-1}$; HRMS (FAB) calcd for $C_{25}H_{25}F_3NO_2$ (M+H) 428.1837, found 428.1839. Anal. Calcd: for $C_{25}H_{25}F_3NO_2$: C, 70.24; H, 5.66; N, 3.28. Found: C, 69.44; H, 5.84; N, 3.18.

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