α-Trifluoromethyl-Substituted *β*-Ethoxyvinyl Zinc Reagent: Preparation and Palladium-Catalyzed Cross-Coupling as a Novel Route to Functionalized CF_3-Containing Compounds

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For the past few decades, great efforts have been made in the search for practical and efficient methods for the synthesis of selectively fluorinated organic compounds.[1] Fluorinated organometallic reagents provide a useful method for the introduction of fluorine into organic molecules.[2] However, due to the lack of suitable precursors as well as the limited thermal stability of many of these fluorinated organometallic reagents, their chemistry is much less developed than that of their hydrocarbon analogs. A particular example is various α-trifluoromethyl-substituted organolithium and magnesium reagents. These reagents are known to be rather thermally unstable due to their proclivity toward *β*-elimination, thus making carbon−carbon bond formation at a CF_3-substituted carbanionic center a challenging problem.[3] Fortunately, the stability of fluorinated organometallic reagents is very much dependent on the nature of the metal employed. Thus, by changing from lithium or magnesium to a less electropositive metal such as zinc, two α-CF_3-substituted vinyl zinc reagents, namely $CF_3(ZnX)C{=}CH_2$ and $CF_3(ZnX)C{=}CF_2$, have been recently prepared.[4,5] The exceptional thermal stability of these two "internal" vinyl zinc reagents, in contrast to their lithium and magnesium counterparts, ensured several synthetic applications with these two carbanion equivalents. However, the general lack of functionality in the products derived from these reagents set a severe limit to their practical utility in the synthesis of functionalized CF_3-containing compounds.

We have recently established a very convenient method for the synthesis of (*Z*)-3,3,3-trifluoropropenyl ethers **2** from the readily available 2-bromo-3,3,3-trifluoropropene (**1**).[6] As a part of our effort to explore the synthetic utility of these CF_3-containing vinyl ethers, we have conceived the possibility to make the organometallic derivatives of these vinyl ethers (Scheme 1). While our attempt at the preparation of α-metalated vinyl ether **3** by direct metalation with a strong base turned out to be problematic,[7] we have been able to obtain the *β*-metalated reagent **4** via direct zinc insertion into the carbon−bromine bond of the corresponding vinyl bromide. Such a zinc reagent can be regarded as a synthetic equivalent of α-CF_3-substituted acetaldehyde enolate **5** and is valuable for the incorporation of a functionalized CF_3-substituted C_2-unit into organic molecules. In this paper, we report the preparation and synthetic application of the vinyl zinc reagent **4**.

Preparation of the Vinyl Bromide 7. The bromination of the trifluoromethylated vinyl ether **2** was simply achieved by a bromination−dehydrobromination sequence. Thus, when treated consecutively with 1 equiv of bromine and 2 equiv of triethylamine in CH_2Cl_2 at 0 °C, vinyl ether **2** was readily converted to vinyl bromide **7** as a 60:40 *Z*/*E* mixture in 80% yield (Scheme 2). The assignment of the *Z*/*E* configuration was based on the large difference of ^{19}F chemical shifts of the two isomers ($\Delta\delta$ = 3.5 ppm), the downfield signal being assigned to the one *E* isomer that has a CF_3 group experiencing a greater steric interaction with the vincinal substitutent[8] (OC_2H_5 *vs* H).

Since the stereochemistry of the vinyl bromide **7** was considered to be important for the subsequent preparation of the zinc reagent, efforts have been made to control the *Z*/*E* selectivity during the formation of **7**. At 0 °C, the addition of bromine to vinyl ether **2** was already found not to be stereoselective, affording *syn*/*anti* adducts **6** in a ratio of 3:2. When this step was conducted at −78 °C, the stereochemistry of the initial adduct and, consequently, the final *Z*/*E* ratio of the elimination product remained essentially unchanged. The use of a solvent other than CH_2Cl_2 could not significantly improve the *Z*/*E* ratio either. Finally, we accidentally found that the use of 2 equiv of bromine at the first addition step followed by the same treatment with triethylamine led to formation of vinyl bromide **7** exclusively as *Z*-form. This led us to assume that isomerization of **7** had occurred in the presence of excess bromine and triethylamine. Indeed, in a control experiment, addition of bromine (1.0 equiv) to a 60:40 *Z*/*E* mixture of **7** rapidly afforded the adduct **8** which, when treated with triethylamine, lost a molecule of bromine to give back compound **7** with a 98:2 *Z*/*E* ratio. In this reaction, triethylamine has acted as a nucleophile for halophilic debromination.[9] The high stereoselectivity of the latter step can be rationalized by assuming that the debromination had taken place in an *anti* manner and that conformation A is much more preferred than B due to minimization of the electrostatic repulsion between the CF_3 and ethoxy groups.[10] Thus, by controlling

(1) (a) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington DC, 1991. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (c) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (d) Hudlicky, M. *Chemistry of Organic Fluorine Compounds;* Ellis Horwood: Chichester, 1992.

(2) For recent reviews see (a) Burton, D. J.; Yang, Z.-Y.; Morken, D. A. *Tetrahedron* **1994**, *50*, 2993. (b) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189.

(3) For synthetic studies on α-CF_3-substituted organometallic reagents, see (a) Nemoto, H.; Satoh, A.; Fukumoto, K. *Synlett* **1995**, 199. (b) Yamazaki, T.; Hiraoka, S.; Kitazame, T. *J. Org. Chem.* **1994**, *59*, 5100. (c) Watanabe, H.; Yan, F.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758. (d) Watanabe, H.; Yamashita, F.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 1941. (e) Qian C.-P.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 7043. (f) Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1307. (g) Ishihara T.; Kuroboshi, M.; Yamaguchi, K. *Chem. Lett.* **1990**, 211. (h) Uneyama, K.; Momota, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3378. (i) Fujita, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3321. (j) Yokozawa, T.; Ishikawa, N.; Nakai, T. *Chem. Lett.* **1987**, 1971. (k) Hemer, I.; Posta, A.; Dedek, V. *J. Fluorine Chem.* **1984**, *61*, 3321. (l) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276 and references cited therein. (m) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481. (n) Arakesmith, F. G.; Steward, O. J.; Tarrant, P. *J. Org. Chem.* **1968**, *33*, 280.

(4) Jiang, B.; Xu, Y.-Y. *J. Org. Chem.* **1991**, *56*, 7336.

(5) (a) Morken, P. A.; Lu, H.-Y.; Nakamara, A.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 4271. (b) Morken, P. A.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 1167.

(6) Fong, H.; Hu, C.-M. *Chem. Commun.* **1996**, 57.

(7) After the reaction of vinyl ether **2** (R = OC_2H_5) with *n*-BuLi or *t*-BuLi at −78 °C was quenched with water, the reaction mixture was very complicated as revealed by ^{19}F NMR analysis.

(8) Gunther, H. *NMR Spectroscopy, An Introduction;* John Wiley & Sons: New York, 1980; p 342.

(9) A similar reaction has been recently studied. Cho, B.-R.; Lee, S.-H.; Kim, Y.-K. *J. Org. Chem.* **1995**, *60*, 2072.

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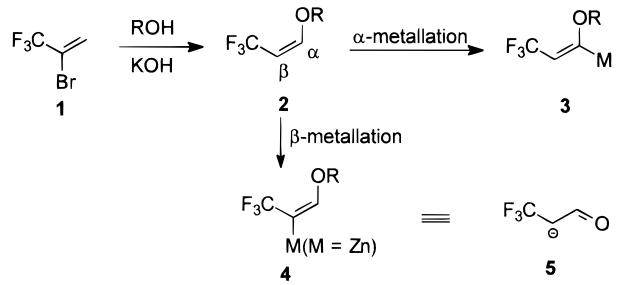
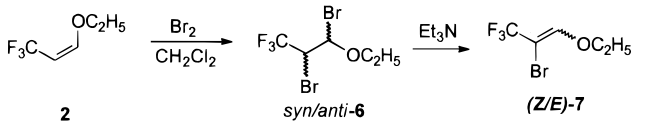
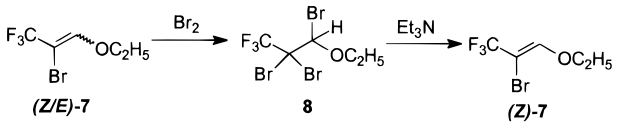
Scheme 1

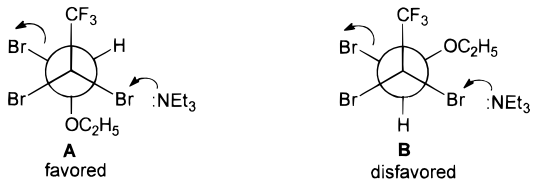


Scheme 2



equiv. of Br_2	(Z)-7 / (E)-7	yield(%)
1.0	60 : 40	80
2.0	> 98 : 2	77

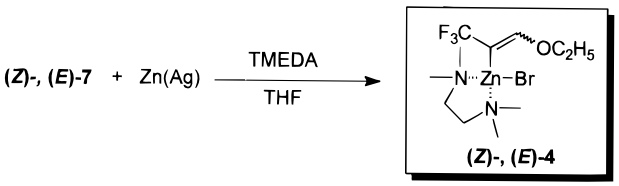




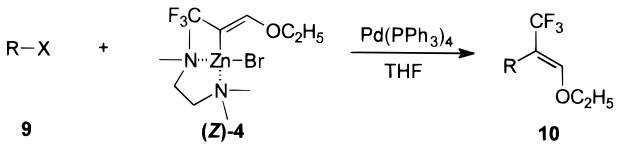
the experimental conditions, we were able to obtain vinyl bromide **7** with high *Z*-selectivity.

Preparation of the Zinc Reagent 4. With the vinyl bromide **7** in hand, we attempted to prepare the vinyl zinc reagent **4** by way of oxidative addition of zinc to **7**. Although the presence of a CF_3 group α to the carbon−halogen bond in vinyl halide was known to facilitate the metal insertion into the carbon−halogen bond,[4,5] the feasibility to perform such a reaction with compound **7** was not obvious because of the presence of the synthetically desirable ethoxy group *β* to the reaction center. The electron-donating effect of this ethoxy group may have increased the electron density on the brominated carbon, thereby making the metal insertion into the carbon−halogen bond difficult. Furthermore, vinyl zinc compounds bearing an alkoxy group *β* to the anionic center might be prone to undergo demetalloalkoxylation. In fact, simple (*β*-alkoxyvinyl)lithium was found to be stable only at a temperature below −70 °C,[11] and no corresponding zinc derivative has been prepared before. Fortunately, when vinyl bromide (*Z*)-**7** was treated with silver-activated zinc in THF in the presence of 1 equiv of TMEDA, an exothermic reaction occurred. ^{19}F NMR analysis of the reaction mixture revealed that the starting material disappeared and a single new peak at −25.4 ppm appeared which corresponded to the zinc reagent ***Z*-4** (Scheme 3). On the other hand, use of a 60:40 *Z*/*E* mixture of **7** for the same reaction gave rise to two new peak at −25.4 and −28.8 ppm, respectively, with a 60:40 intensity ratio, indicating that the corresponding *E*-isomer of **7** was also able to undergo metal insertion reaction with the retention of the stereochemistry of the double bond. The geometry of the double bond in **7** has thus appeared to be not crucial to the reactivity of the carbon−bromine bond toward insertion reaction. Since TMEDA was found to be indispensable to the formation of the zinc reagent, the latter was assumed to have a chelate structure with TMEDA as a bidentate ligand (Scheme 3). Remarkably, both isomers of the zinc reagent **4** have been found to be stable indefinitely at room temperature or for a prolonged time in refluxing THF.

Scheme 3



Scheme 4

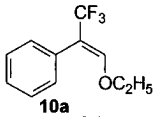
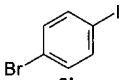
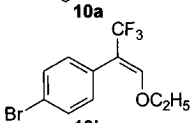
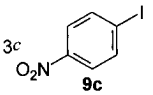
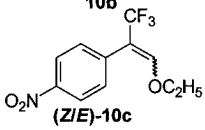
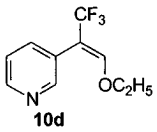
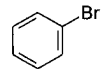
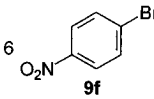
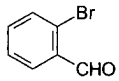
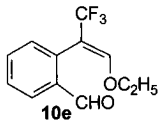
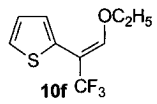
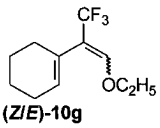
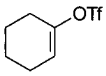
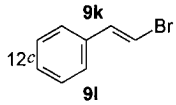
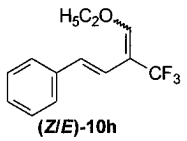


Cross-Coupling Reactions of the Zinc Reagent 4. With a convenient route to the CF_3-containing vinyl zinc reagent **4**, we decided to establish the feasibility of using **4** in cross-coupling reactions. In the case of nonfluorinated materials, the transition metal-catalyzed coupling reaction of organic zinc reagents has already been established as an efficient method for the construction of a new carbon-carbon bond.[12] The palladium-catalyzed coupling reactions of some perfluorinated alkenyl zinc reagents have also found their use in organofluorine synthesis.[2] When the zinc reagent ***Z*-4** was reacted with a variety of aryl and alkenyl substrates in THF using 2 mol% of $Pd(PPh_3)_4$ as the catalyst, the expected cross-coupling reaction occurred smoothly affording the the expected coupling product **10** as a single stereoisomer in high yield (Scheme 4). The results were summarized in Table 1.

As shown in the table, both bromides and iodides can be effectively used for the coupling reaction. With the bromides, however, the reaction required a higher temperature (70 °C) in order to have a reaction rate comparable to that observed with the iodides at 50 °C. This difference of reactivity has made the chemoselective coupling possible with *p*-bromoiodobenzene (entry 2, Table 1). It is worth noting that the zinc reagent was inert toward an aldehyde group so that the coupling reaction with *o*-bromobenzaldehyde was able to proceed normally (entry 7, table 1). Also noteworthy is the coupling reaction with vinyl halides and triflates (entry 9−12), which opened a convenient route to 2-trifluoromethylated 1-alkoxy-1,3-dienes. These dienes should be valuable for the synthesis of CF_3-containing cyclic compounds by virtue of their ability to undergo cycloaddition reactions.

(10) CHARMm 22 force field calculation indicated that conformation **A** is 3.88 kcal/mol lower in energy compared to conformation **B**.
(11) Kreisler, S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.
(12) For recent reviews, see (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

Table 1. Palladium-Catalyzed Cross-Coupling Reactions of the Zinc Reagent (*Z*)-4 with Organic Halides and Triflates[a]

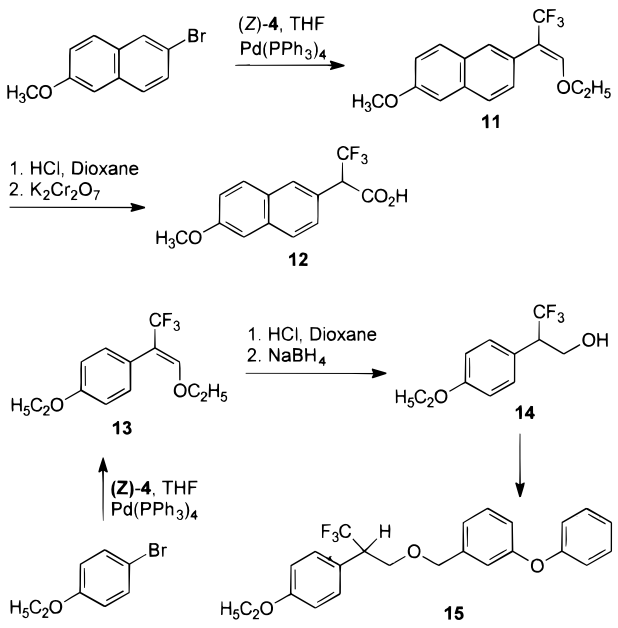
entry	substrate	temp.(°C)/time(h)	product	yield (%)[b]
1	 **9a**	50 / 6	 **10a**	95
2	 **9b**	50 / 7	 **10b**	94
3[c]	 **9c**	50 / 7	 **(*Z*/*E*)-10c**	94[d]
4	 **9d**	50 / 6	 **10d**	91
5	 **9e**	70 / 8	**10a**	90
6	 **9f**	70 / 8	**(*E*)-10c**	92
7	 **9g**	70 / 12	 **10e**	72
8	 **9h**	70 / 6	 **10f**	85
9[c]	 **9i**	50 / 6	 **(*Z*/*E*)-10g**	93[d]
10	 **9j**	70 / 7	**(*E*)-10g**	90
11	 **9k**	50 / 6	**(*E*)-10g**	86
12[c]	 **9l**	70 / 7	 **(*Z*/*E*)-10h**	91[d]

[a] All reactions were performed in THF on a 2.0 mmol scale for 1.5 equiv of the zinc reagent using 2 mol % of $Pd(PPh_3)_4$ as the catalyst. [b] Yield of isolated product. [c] For these entries, a 60:40 mixture of the zinc reagent (*Z*)-**4** and (*E*)-**4** was used instead of pure (*Z*)-**4**. [d] Total yield of two separable isomers.

In order to find out whether the other isomer (*E*)-**4** could also be used for the coupling reaction, a 60:40 *Z*/*E* mixture of **4** was used to react with halide substrate **9c, 9i,** and **9l** under the same reaction conditions. The results showed that both isomers exhibited comparable reactivity in the coupling reaction affording easily separable *Z*/*E* isomers of the coupling product **10c**, **10g**, and **10h**, each in approximately 50:50 *Z*/*E* ratio (entry 3, 9, 12; Table 1).

The reaction described above has allowed us to have a simple route to two important CF_3-containing compounds

Scheme 5



with proved biological activities,[13,14] i.e. the fluoro analog of Naproxen **12** and the fluorinated pyrethroid **15** (Scheme 5). Thus, simple acid hydrolysis of the coupling product **11** followed by oxidation of the resulting aldehyde directly afforded **12** in 85% overall yield. On the other hand, reduction of the aldehyde obtained from the hydrolysis of the coupling product **13** with $NaBH_4$ gave the alcohol **14,** which was used as the key intermediate for the novel synthetic pyrethroid **15**. The previous methods for the preparation of such CF_3-substituted compounds appeared to be much less efficient.[13,14]

In conclusion, we have developed a convenient preparation of a novel α-trifluoromethyl-substituted *β*-ethoxyvinyl zinc reagent **4** and used it successfully in the palladium-catalyzed cross-coupling reactions with a variety of aryl and vinyl halides or triflates. The ease of preparation, the presence of a latent carbonyl group and the feasibility of palladium-catalyzed cross-coupling reaction should make the zinc reagent **4** find further synthetic utilities as a valuable CF_3-containing synthon in the construction of various trifluoromethylated target molecules.

Experimental Section

^1H NMR spectra were recorded on 300 or 400 MHz spectrometers with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a 60 MHz spectrometer using trifluoroacetic acid as an external standard, downfield shifts being designated as negative. 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. THF was distilled from sodium benzophenone ketyl, and TMEDA was freshly distilled from calcium hydride. Silver-activated zinc powder was prepared by a published method using commercial zinc dust.[15]

(*Z*)-1-Ethoxy-3,3,3-trifluoropropene (2, R = C_2H_5).[6] A reaction flask equipped with a dry-ice condenser and an addition funnel was charged with a solution of potassium hydroxide (33.3

(13) Middleton, W. J.; Binghan, E. M. *J. Fluorine Chem.* **1983**, *22*, 561.

(14) (a) Bushell, M. J. In *Recent Advances in the Chemistry of Insect Control II*; Crombie, L., Ed.; The Royal Society of Chemistry: Cambridge, 1990; p 125. (b) Matsuo, N.; Tsushima, K.; Takagaki, T.; Hirano, M.; Ohno, N. *Recent Advances in the Chemistry of Insect Control III*; The Royal Society of Chemistry: Cambridge, 1994; p 208.

(15) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649.

g, 0.59 mol) in ethanol. 2-Bromo-3,3,3-trifluoropropene (34.9 g, 0.20 mol) was added over 5 min, during which the reaction mixture started to reflux. After being stirred for 60 min, the reaction mixture was poured into water (150 mL). The organic layer was separated, dried over Na_2SO_4, and distilled to afford 27.4 g (96%) of **2**; bp 102−104 °C (lit.[16] 102−103 °C). ^{1}H NMR ($CDCl_3$) δ 6.32 (d, J = 6.8 Hz, 1 H), 4.56−4.74 (m, 1 H), 4.0 (q, J = 7.0 Hz, 2 H), 1.32 (t, J = 7.0 Hz, 3 H); ^{19}F NMR ($CDCl_3$) δ −20.0 (d, 6.7 Hz).

(*Z*/*E*)-2-Bromo-1-ethoxy-3,3,3-trifluoropropene (7). To a solution of (*Z*)-1-ethoxy-3,3,3-trifluoropropene (5.6 g, 40 mmol) in CH_2Cl_2 (40 mL) cooled to −20 °C was added dropwise a solution of bromine (6.4 g, 40 mmol) in CH_2Cl_2 (10 mL). After the reaction mixture was kept at 0 °C for 30 min and then recooled to −20 °C, triethylamine (8.1 g, 80 mmol) was added over 10 min. The reaction mixture was stirred at room temperature for 1 h and then poured into water (100 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with 2 N HCl to pH neutral and dried over $MgSO_4$. Distillation under reduced pressure gave 7.0 g (80%) of **7** as a 60:40 *Z*/*E* mixture; bp 60−62 °C/37 mmHg. (*Z*)-**7**: ^{1}H NMR ($CDCl_3$) δ 7.23 (q, J = 1.6 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 3 H); ^{19}F NMR ($CDCl_3$) δ −13.5 (d, J = 1.6 Hz); MS (EI, *m*/*z*) 220 (M^+ + 1, 6), 218 (M^+ − 1, 6), 149 (78), 140 (34), 69 (100). Anal. Calcd for $C_5H_6BrF_3O$: C, 27.42; H, 2.76. Found: C, 27.44; H, 2.75. (*E*)-**7**: ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 1 H); 4.05 (q, J = 7.1 Hz, 2 H); 1.32 (t, J = 7.1 Hz, 3 H); ^{19}F NMR($CDCl_3$) δ −17.0 (s). When the above reaction was performed with 2 equiv of bromine (12.8 g, 80 mmol), compound **7** was obtained in 77% yield with a *Z*/*E* ratio of ≥98:2.

1,2-Dibromo-1-ethoxy-3,3,3-trifluoropropane (6). When the above reaction was worked up before addition of triethylamine, a 3:2 *syn*/*anti* mixture of **6** was obtained quantitatively. The assignment of the relative stereochemistry was based on the coupling constant between 1-H and 2-H (J_{H-H} 2.1 Hz for the *syn* vs 4.1 Hz for the *anti* isomer). ^{1}H NMR ($CDCl_3$) δ 6.18 (d, J = 2.1 Hz, 1 × 0.6 H), 6.05 (d, J = 4.1 Hz, 1 × 0.4 H), 4.60 (dq, J = 4.1, 6.5 Hz, 1 × 0.4 H), 4.53 (dq, J = 2.1, 6.5 Hz, 1 × 0.6 H), 3.07 (m, 2 × 0.4 H), 3.63 (m, 2 × 0.6 H), 1.32 (t, J = 7.2 Hz, 3 H); ^{19}F NMR ($CDCl_3$) δ -32.0 (d, J = 6.5 Hz, 3 × 0.4 F), −30.0 (d, J = 6.5, 3 × 0.6 F).

Preparation of the Zinc Reagent 4. A small quantity of trimethylchlorosilane (ca. 0.5 mL) was added to a stirred suspension of silver-activated zinc powder (4.0 g, 60 mmol) in dry THF (30 mL). After 10 min, TMEDA (5.8 mL, 40 mmol) and vinyl bromide (*Z*)-**7** (8.8 g, 40 mmol) were successively added in one portion. The reaction commenced in less than 1 min when the solution became warm and turned deep-brown. After the heat evolution ceased, ^{19}F NMR analysis of the reaction mixture indicated the appearance of a new peak at −25.4 ppm corresponding to the zinc reagent (*Z*)-**4** and a small peak at −18 ppm attributable to (*E*)-1-ethoxy-3,3,3-trifluoropropene formed from the protonation of the zinc reagent. The yield of the zinc reagent determined by ^{19}F NMR integration *vs* internal $PhCF_3$ standard ranged 80−85%.

When the same reaction was performed using a 60:40 *Z*/*E* mixture of the vinyl bromide **7**, a 60/40 mixture of zinc reagent (*Z*)-**4** and (*E*)-**4** was formed as revealed by two new ^{19}F NMR peaks at −25.4 and −28.8 ppm.

General Procedure for the Cross-Coupling Reactions Exemplified by the Reaction of the Zinc Reagent (*Z*)-4 with Iodobenzene. To a solution of iodobenzene (0.41 g, 2.0 mmol) and $Pd(PPh_3)_4$ (0.046 g, 0.040 mmol) in THF (10 mL) was added a solution of the zinc reagent (*Z*)-**4** in THF (5.0 mL, ca. 3.0 mmol). The reaction mixture was heated at 50 °C and monitored by TLC for the disappearance of the starting iodobenzene. Diethyl ether (20 mL) was added, and the organic phase was washed with water (10 mL). Evaporation of the solvents gave a residue which was subjected to chromatography eluting with a 9:1 mixture of petroleum ether and ethyl acetate to afford 0.41 g (95%) of the coupling product **(*E*)-1-ethoxy-3,3,3-trifluoro-2-phenylpropene (10a)** as an oil: ^{1}H NMR (CD_3COCD_3) δ 7.40 (m, 5 H), 7.25 (q, J = 1.7 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −16.8 (d, J = 1.7 Hz); MS (EI, *m*/*z*) 217 (M^+ + 1, 19), 216 (M^+, 100), 188 (5), 168 (14), 140 (33), 109 (12). Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 60.65; H, 5.30.

(*E*)-2-(4-Bromophenyl)-1-ethoxy-3,3,3-trifluoropropene (10b). Organozinc reagent (*Z*)-**4** (3.0 mmol) and *p*-bromoiodobenzene (0.57 g, 2.0 mmol) for 7 h at 50 °C yielded 0.55 g (94%) of **10b** as an oil after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent: ^{1}H NMR (CD_3COCD_3) δ 7.60 (d, J = 8.7 Hz, 2 H), 7.40 (d, J = 8.7 Hz, 2 H), 7.30 (q, J = 1.7 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −16.7 (d, J = 1.7 Hz); MS (EI, *m*/*z*) 296 (M^+ + 1, 45), 295 (M^+, 7), 294 (M^+ − 1, 47), 262 (100), 157 (13), 139 (44). Anal. Calcd for $C_{11}H_{10}BrF_3O$: C, 44.77; H, 3.42. Found: C, 44.56; H, 3.26.

(*Z*/*E*)-1-Ethoxy-3,3,3-trifluoro2-(4-nitrophenyl)propene (10c). A 60:40 mixture of the zinc reagent (*Z*)- and (*E*)-**4** (3.0 mmol) and *p*-nitroiodobenzene (0.50 g, 2.0 mmol) for 7 h at 50 °C yielded first 0.24 g (46%) of (*E*)-**10c** and then 0.25 g (48%) of (*Z*)-**10c** after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent. (*E*)-**10c**: ^{1}H NMR (CD_3COCD_3) δ 8.26 (d, J = 7.0 Hz, 2 H), 7.79 (d, J = 7.0 Hz, 2 H), 7.47 (q, J = 1.8 Hz, 1 H), 4.29 (q, J = 7.1 Hz, 2 H), 1.35 (t. J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −17.0 (d, J = 1.8 Hz); MS (EI, *m*/*z*) 261 (M^+, 22), 249 (100), 203 (30), 233 (23), 139 (6). Anal. Calcd for $C_{11}H_{10}F_3NO_3$: C, 50.58; H, 3.86; N, 5.36. Found: C, 50.52; H, 3.94; N, 5.28. (*Z*)-**10c**: ^{1}H NMR (CD_3COCD_3) δ 8.25 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 8.2 Hz, 2 H), 7.21 (s, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 1.35 (t. J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −20.0 (s); MS (EI, *m*/*z*) 262 (M^+ + 1, 74), 261 (M^+, 100), 245 (24), 233 (23), 139 (17).

Use of organozinc reagent (*Z*)-**4** (3.0 mmol) and 1-bromo-4-nitrobenzene (**9f**, 0.40 g, 2.0 mmol) for 8 h at 70 °C yielded only the *E* isomer of **10c** in 92% yield.

(*E*)-1-Ethoxy-3,3,3-trifluoro-2-(3-pyridyl)propene (10d). Organozinc reagent (*Z*)-**4** (3.0 mmol) and 3-iodopyridine (0.41 g, 2.0 mmol) for 6 h at 50 °C yielded 0.39 g (91%) of **10d** as an oil after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent: ^{1}H NMR (CD_3COCD_3) δ 8.68 (s, 1 H), 8.53 (dd, J = 4.8, 1.5 Hz, 1 H), 7.82 (d, J = 8.1 Hz, 1 H), 7.40 (m, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −16.7 (d, J = 1.8 Hz); MS (EI, *m*/*z*): 218 (M^+ + 1, 85), 217 (M^+, 100), 189 (17), 169 (25), 141 (28), 63 (10). Anal. Calcd for $C_{10}H_{10}F_3NO$: C, 55.30; H, 4.64; N, 6.45. Found: C, 54.91; H, 4.84; N, 6.31.

2-[(*E*)-2-Ethoxy-1-(trifluoromethyl)ethenyl]benzaldehyde (10e). Organozinc reagent (*Z*)-**4** (3.0 mmol) and 2-bromobenzaldehyde (0.38 g, 2.0 mmol) for 12 h at 70 °C yielded 0.35 g (72%) of **10e** as an oil after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent: ^{1}H NMR (CD_3COCD_3) δ 10.08 (s, 1 H), 7.95 (d, J = 7.0 Hz, 1 H), 7.75 (t, J = 7.0 Hz, 1 H), 7.60 (t, J = 7.0 Hz, 1 H), 7.47 (q, J = 1.8 Hz, 1 H), 7.45 (d, J = 7.0 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −15.3 (d, J = 1.8 Hz); MS (EI, *m*/*z*) 245 (M^+ + 1, 7), 244 (M^+, 2), 217 (19), 200 (100), 167 (28), 131 (51), 89 (9). Anal. Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 58.86; H, 4.80.

(*E*)-1-Ethoxy-3,3,3-trifluoro-2-(2-thiophene-yl)propene (10f). Organozinc reagent (*Z*)-**4** (3.0 mmol) and 2-bromothiophene (0.33 g, 2.0 mmol) for 6 h at 70 °C yielded 0.38 g (85%) of **10f** as an oil after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent: ^{1}H NMR (CD_3COCD_3) δ 7.30 (d, J = 5.4 Hz, 1 H), 7.11 (q, J = 1.5 Hz, 1 H), 7.03 (m, 1 H), 6.91 (dd, J = 5.3, 3.8 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −15.4 (d, J = 1.5 Hz); MS (EI, *m*/*z*) 223 (M^+ + 1, 18), 222 (M^+, 100), 174 (23), 165 (23), 146 (21), 115 (21). Anal. Calcd for $C_9H_9F_3OS$: C, 48.64; H, 4.08. Found: C, 48.55; H, 4.14.

(*Z*/*E*)-2-(1-Cyclohexenyl)-1-ethoxy-3,3,3-trifluoropropene (10g). A 60:40 mixture of the zinc reagent (*Z*)- and (*E*)-**4** and (3.0 mmol) and 1-iodocyclohexene (0.42 g, 2.0 mmol) for 6 h at 50 °C yielded first 0.21 g (47%) of (*E*)-**10g** and then 0.22 g (49%) of (*Z*)-**10g** after chromatography using a 9:1 mixture of petroleum ether and ethyl acetate as the eluent. (*E*)-**10g**: ^{1}H NMR (CD_3COCD_3) δ 6.90 (q, J = 2.0 Hz, 1 H), 5.75 (m, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 2.12 (m, 4 H), 1.65 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −15.7 (d, J = 2.0 Hz); MS (EI, *m*/*z*) 221 (M^+ + 1, 12), 220 (M^+, 100), 191 (70), 163 (52), 123 (41). Anal. Calcd for $C_{11}H_{15}F_3O$: C, 59.99; H, 6.86.

(16) Henne, A. L.; Nager, M. *J. Am. Chem. Soc.* **1952**, *74*, 650.

Found: C, 59.78; H, 7.06. (*Z*)-**10g**: ^{1}H NMR (CD_3COCD_3) δ 6.60 (s, 1 H), 5.69 (m, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 2.10 (m, 4 H), 1.63 (m, 4 H), 1.30 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −19.8 (s); MS (EI, m/z) 221 ($M^+ + 1$, 12) 220 (M^+, 100) 191 (59), 163 (38), 123 (27).

Use of organozinc reagent (*Z*)-**4** (3.0 mmol) and 1-bromocyclohexene (0.32 g, 2.0 mmol) for 7 h at 70 °C or cyclohexenyl triflate for 6 h at 50 °C yielded only the (*E*)-**10g** in 90% and 86% yield, respectively.

(1*Z*,2*E*)- and (1*E*, 2*E*)-1-Ethoxy-2-(trifluoromethyl)-4-phenyl-1,3-butadiene (10h). A 60:40 mixture of the zinc reagent (*Z*)- and (*E*)-**4** and (3.0 mmol) and (*E*)-1-bromo-2-phenylethene (0.37 g, 2.0 mmol) for 7 h at 70 °C yielded first 0.21g (44%) of (*E*)-**10h** and then 0.23g (47%) of (*Z*)-**10h** after chromatography using a 20:1 mixture of petroleum ether and ethyl acetate as the eluent. (*E*)-**10h**: ^{1}H NMR (CD_3COCD_3) δ 7.50 (m, 2 H), 7.39 (m, 2 H), 7.28 (m, 1H), 7.15 (s, 1 H), 6.95 (d, J = 17.0 Hz, 1 H), 6.82 (d, J = 17.0 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 1.38 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −15.0 (s); MS (EI, m/z) 243 ($M^+ + 1$, 17), 242 (M^+, 100), 165 (34), 145 (47), 115 (30). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.46; H, 5.41. Found: C, 64.58; H, 5.42. (*Z*)-**10h**: ^{1}H NMR (CD_3COCD_3) δ 7.45 (m, 2 H), 7.31 (m, 2 H), 7.23 (m, 1 H), 7.12 (s, 1 H), 6.69 (d, J = 16.5 Hz, 1 H), 6.61 (d, J = 16.5 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H);^{19}F NMR (CD_3COCD_3) δ −18.0 (s); MS (EI, m/z) 243 ($M^+ + 1$, 15), 242 (M^+, 100), 196 (34), 165 (43), 145 (58), 115 (37)

(*E*)-1-Ethoxy-3,3,3-trifluoro-2-(6-methoxy-2-naphthyl)-propene (11). Organozinc reagent (*Z*)-**4** (3.0 mmol) and 2-bromo-6-methoxynaphthalene (0.47 g, 2.0 mmol) for 8 h at 70 °C yielded 0.53 g (90%) of **11** as a white solid after chromatography using a 20:1 mixture of petroleum ether and ethyl acetate as the eluent: mp 90−92 °C; ^{1}H NMR (CD_3COCD_3) δ 7.70 (m, 3H), 7.37 (d, J = 8.7 Hz, 1 H), 7.20 (s, 1 H), 7.13 (q, J = 1.9 Hz, 1 H), 7.01 (dd, J = 8.7, 2.6 Hz, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 3.78(s, 3 H), 1.17(t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −16.5 (d, 1.9 Hz); MS (EI, m/z) 297 ($M^+ + 1$, 21), 296 (M^+, 100), 267 (42), 252 (46), 155 (6), 139 (7). Anal. Calcd for $C_{16}H_{15}F_3O_2$: C, 64.86; H, 5.10. Found: C, 64.55; H, 4.98.

3,3,3-Trifluoro-2-(6-methoxy-2-naphthyl)propanoic acid (12). A mixture containing compound **11** (0.30 g, 1.0 mmol), dioxane (2.5 mL), and concentrated hydrochloric acid (1.0 mL) was heated at 60 °C for 1 h. After usual workup, the crude aldehyde was dissolved in acetone (2.5 mL) and treated with a solution of $K_2Cr_2O_7$ (0.44 g, 1.5 mmol) in 2 N sulfuric acid (2.0 mL). After 30 min, the reaction was quenched with 2-propanol (1.0 mL) and the mixture extracted with diethyl ether (3 × 10 mL). The ethereal phase was extracted with 2 M aqueous NaOH (2 × 10 mL). The combined aqueous layers were acidified with 2 N sulfuric acid and extracted with diethyl ether (3 × 10 mL). The organic phase was dried and concentrated. The solid was crystallized from hexane−diethyl ether to give 0.24 g (85% based on **11**) of **12**; mp 141−142 °C (lit.[13] 140−142 °C). ^{1}H NMR (CD_3COCD_3) δ 8.01 (s, 1 H), 7.90 (d, J = 3.0 Hz, 1 H), 7.87 (d, J = 3.0 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 7.38 (d, J = 2.5 Hz, 1 H), 7.22 (dd, J = 8.7, 2.5 Hz, 1 H), 4.82 (q, J = 9.0 Hz, 1 H), 3.95 (s, 3 H); ^{19}F NMR (CD_3COCD_3) δ −9.0 (d, J = 9.0 Hz).

(*E*)-1-Ethoxy-2-(4-ethoxyphenyl)-3,3,3-trifluoropropene (13). Organozinc reagent (*Z*)-**4** (3.0 mmol) and 1-bromo-4-ethoxybenzene (0.42 g, 2.0 mmol) for 8 h at 70 °C yielded 0.47 g (90%) of **13** as an oil after chromatography using a 20: 1 mixture of petroleum ether and ethyl acetate as the eluent: ^{1}H NMR (CD_3COCD_3) δ 7.33 (d, J = 8.6 Hz, 2 H), 7.17 (q, J = 1.5 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 2 H), 4.13 (q, J = 7.1 Hz, 2 H), 4.05 (q, J = 7.0 Hz, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{19}F NMR (CD_3COCD_3) δ −16.5 (d, 1.5 Hz); MS (EI, m/z) 261 ($M^+ + 1$, 18), 260 (M^+, 100), 203 (50), 184 (43), 175 (30), 156 (16), 94 (91) Anal. Calcd for $C_{13}H_{15}F_3O_2$: C, 60.00; H, 5.81. Found: C, 59.77; H, 5.75.

2-(4-Ethoxyphenyl)-3,3,3-trifluoro-1-propanol (14). A mixture containing compound **13** (0.52 g, 2.0 mmol), dioxane (5.0 mL), and concentrated hydrochloric acid (2.0 mL) was heated at 60 °C for 1 h. After usual workup, the crude aldehyde was dissolved in diethyl ether (5.0 mL), and $NaBH_4$ (0. 19 g, 5.0 mmol) was added. After being stirred at 25 °C, the reaction mixture was poured into water and extracted with diethyl ether (3 × 5 mL). The organic phase was concentrated, and the crude product was purified by column chromatography on silica gel eluting with a 2:1 mixture of petroleum ether and ethyl acetate to give 0.43 g (92%) of **14** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 6.7 Hz, 2 H), 6.85 (d, J = 6.7 Hz, 2 H), 4.10 (dd, J = 11.4, 5.7 Hz, 1 H), 3.98 (q, J = 7.0 Hz, 2H), 3.94 (dd, J = 11.4, 8.0 Hz, 1 H), 3.43 (m, 1H), 3.14 (broad s, 1 H), 1.38 (t, J = 7.0 Hz, 3 H); ^{19}F NMR ($CDCl_3$) δ −9.5 (d, J = 8.5 Hz); MS (EI, m/z) 234 (M^+, 34), 203 (57), 175 (90), 125 (37), 73 (100). Anal. Calcd for $C_{11}H_{13}F_3O_2$: C, 56.41; H, 5.59. Found: C, 56.78; H, 6.01.

2-(4-Ethoxyphenyl)-3,3,3-trifluoro-1-(3-phenoxybenzyl)-oxypropane (15). A mixture of compound **14** (0.23 g, 1.0 mmol), *m*-phenoxybenzyl bromide (0.53 g, 2.0 mmol) and tetrabutylamonium bromide (0.064 g, 0.20 mmol), in 10 M aqueous NaOH (2.0 mL) was stirred at 25 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The organic phase was washed with brine, dried, and concentrated. The residue was subjected to chromatography on silica gel eluting with a 20:1 mixture of petroleum ether and ethyl acetate to afford 0.39 g (94%) of **15**. ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 7 H), 6.90 (m, 6 H), 4.50 (AB system, J = 12.4 Hz, 2 H), 4.02 (q, J = 7.0 Hz, 2 H), 3.97 (dd, J = 9.9, 5.8 Hz, 1 H), 3.80 (dd, J = 9.9, 7.3 Hz, 1 H), 3.57 (m, 1 H), 1.43 (t, J = 7.0 Hz, 3 H); ^{19}F NMR ($CDCl_3$) δ −10.0 (d, J = 10.0 Hz); MS (EI, m/z) 417 ($M^+ + 1$, 7), 416 (M^+, 25), 386 (14), 203 (100), 183 (67), 125 (15). Anal. Calcd for $C_{24}H_{23}F_3O_3$: C, 69.22; H, 5.57. Found: C, 69.38; H, 5.47.

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