Highly Stereoselective Addition−Elimination Reaction of Nucleophiles with Ethyl 3,3-Difluoro-2-[(trimethylsilyl)methyl]propenoate

Xian-hai Huang,† Pi-yan He,† and Guo-qiang Shi*,†,‡

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, 200032 Shanghai, People's Republic of China, and Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065-0900

Received September 14, 1999

Introduction of fluorine into organic molecules has become an important subject in modern organic synthesis because of the profound and favorable influence of fluorine on biological activity.[1] Preparation of fluorine-containing building blocks and their further synthetic transformation represent an important approach to selectively fluorinated compounds.[2] Recently we introduced a novel 1,3-bifunctional CF_2-containing building block, namely, compound **2** (Scheme 1), which was prepared from the reduction of the corresponding propenoate **1** with diisobutylaluminum hydride (Scheme 1).[3] In a related transformation, we found that the reduction of the same ester with $LiAlH_4$ led exclusively to the formation of the *Z*-configurated monofluorinated allylic alcohol, isolated as its acetate **3**. This was in sharp contrast with the result from the $LiAlH_4$ reduction of a simple 2-alkyl- rather than 2-[(trimethylsilyl)methyl]-substituted 3,3-difluoropropenoate, which led to monofluoroallylic alcohols with little stereoselectivity.[4] Encouraged by this interesting observation, we became interested in exploring the reactions of **1** with nucleophiles other than hydrides to see if they could proceed in the same fashion to afford synthetically useful monofluorinated products. Herein we report the result of our investigation.

Several representative carbon and heteroatom nucleophiles have been chosen to react with the difluoroacrylate **1**. As summarized in Table 1, all nucleophiles were able to react with **1**, affording products formed from the expected addition−elimination. Unlike similar reactions with simple β,β-difluoro-α,β-unsaturated carbonyl compounds,[5] which led to products with no selectivity or with exhaustive substitution of two fluorine atoms, all reactions with **1** virtually stopped at the stage of one fluorine substitution owing to the presence of the electron-donating silyl group at the allylic position. More importantly, all products are formed with high stereoselectivity in favor of the stereoisomer with fluorine and silicon cis to each other ((*Z*)-**4**) (Scheme 2),[6] except for those using an oxygen nucleophile and organocuprates.

Scheme 1

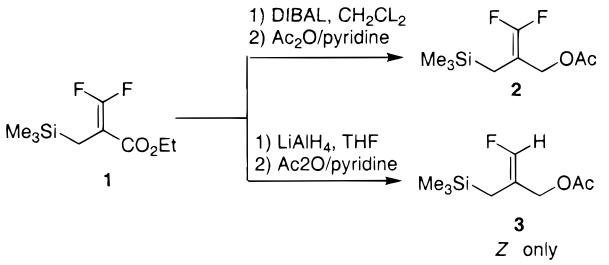
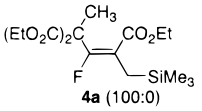
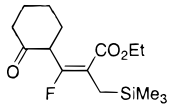
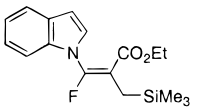
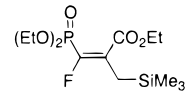
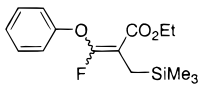
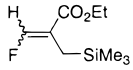
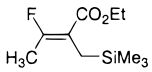
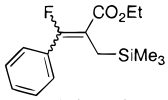


Table 1. Reaction of Nucleophiles with Compound 1

Entry	Nucleophile (reaction conditions)	Product (*Z*/*E*)[a]	Yield (%)[b]
1	$(EtO_2C)_2CHCH_3$ / NaH (1.0 eq., 0 ° C, THF)	 **4a** (100:0)	89
2	cyclohexanone / LDA (1.0 eq., -78- 0 ° C, THF)	 **4b** (100:0)	55
3	indole / n-BuLi (1.0 eq., -78 °C, THF)	 **4c** (100:0)	94
4	$(EtO)_2P(O)H$ / NaH (1.5 eq., -78 °C, THF)	 **4d** (0:100)	88
5	PhOH / NaH (1.0 eq., 0 °C, THF)	 **4e** (20:80)	90
6	$NaBH_4$ (1.0 eq., 0 °C, EtOH)	 **4f** (88:12)	97
7	$(CH_3)_2CuLi$ (1.0eq., -78 °C, THF)	 **4g** (0:100)	86
8	Ph_2CuLi (1.0eq., -78 °C, THF)	 **4h** (60:40)	65

[a] The *Z*/*E* ratio was determined by ^{19}F NMR intergration. [b] Yield of isolated product.

A mechanism involving an addition−elimination process may be proposed as depicted in Scheme 3. The

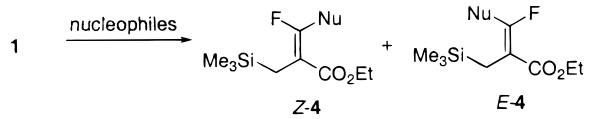
† Chinese Academy of Sciences.
‡ Merck Research Laboratories.

(1) Welch, J. T.; Eswaraktishnan S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990.
(2) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131.
(3) Shi, G.-q.; Huang, X.-h. *Tetrahedron Lett.* **1996**, *37*, 5401.
(4) Watanabe, S.; Sugahara, K.; Fujita, T.; Sakamoto, M.; Kitazume, T. *J. Fluorine Chem.* **1993**, *62*, 201.
(5) (a) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *50*, 11637. (b) Shi, G.; Cao, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 1969. (c) Ichikawa, J.; Yokota, N.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186.

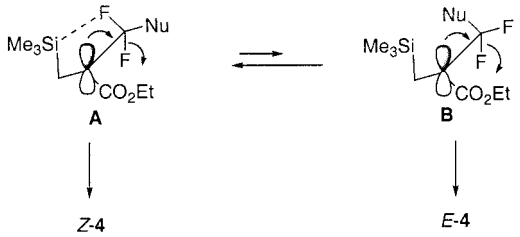
(6) The configurations of (*Z*,*E*)-**4f** were assigned by NOE correlations as well as the coupling constant between fluorine and C*H*$_2$TMS ($^4J_{H,F}$ = 3.6 Hz for the cis isomer and 1.0 Hz for the trans isomer). All other compounds were subsequently assigned on the basis of the $^4J_{H,F}$ couplings to C*H*$_2$TMS.

10.1021/jo991450g CCC: $19.00
Published on Web 12/21/1999

Scheme 2



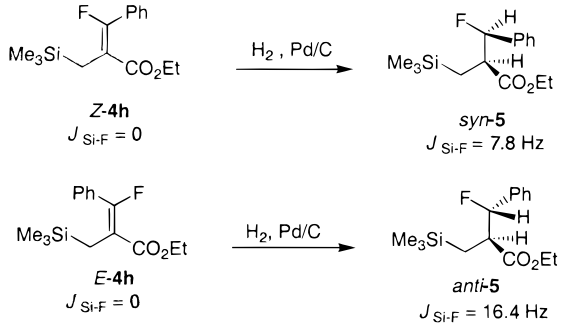
Scheme 3



configuration of the product is controlled by the transition-state conformation of the initial adduct, which must assume a parallel relationship between the breaking C−F bond and the p orbital on the α carbon. Several factors may contribute to the predominant conformation, leading to the observed high stereoselectivity. With simple nucleophiles other than organocuprate, we have proposed a control of the transition-state conformation by an intramolecular C−F···Si coordinative interaction (Scheme 3). Due to such interaction, conformation A is favored over conformation B so that formation of product (*Z*)-**4** is preferred. The reaction of phenoxide with **1** (Table 1, entry 5) might have suggested that C−F···Si coordination is less effective than the known interaction between silicon and an ether oxygen,[7] which appears to control the stereoselectivity in this example. Our proposed mechanism cannot explain the results of organocuprate reaction (Table 1, entries 7 and 8). This could be because the mechanism of organocuprate 1,4-addition reactions is far from being a simple addition process.[8]

The proposed C−F···Si interaction deserves further comments. Although recent studies have shown that C−F···M noncovalent interactions are possible when M is an acidic hydrogen (hydrogen bond)[9] or a "fluorophilic" metal such as zirconium[10] and aluminum,[11] no evidence has been reported in support of a noncovalent C−F···Si interaction despite the abundance of pentacoordinated fluorosilicates.[12] Thus, our current observation may represent the first evidence for this kind of interaction. To further support this, the ^{29}Si NMR of *syn*-**5** and *anti*-**5** (Scheme 4), which are structurally analogous to the

Scheme 4



intermediates **A** and **B** proposed in Scheme 3, was measured. Coupling constants of 16.4 and 7.8 Hz were observed, respectively, for the *syn*- and *anti*-**5**, whereas no couplings were observed for (*Z*)- and (*E*)-**4h** owing to the lone pairs of fluorine being tied up in conjugation with the electron-deficient π system and so not readily available for coordination. This has amply suggested the presence of a through-space C−F···Si interaction due to their spatial proximity.

In conclusion, the reaction of the difluoroacrylate **1** with a variety of nucleophiles has provided a variety of addition−elimination products with high stereoselectivity. A possible C−F···Si-type coordinative interaction has been proposed for the first time to explain the observed stereochemical outcome. The described reaction has not only provided an efficient method for the stereoselective preparation of monofluorinated olefins, useful as intermediates for the synthesis of biologically interesting fluorinated compounds, but also afforded a possibility to control the stereochemistry in other types of reactions.[13]

Experimental Section

^{1}H, ^{19}F, and ^{29}Si NMR were measured on a 300 MHz machine. Tetramethylsilane was used as an internal standard for ^{1}H and ^{29}Si nuclei. For fluorine chemical shifts, trifluoroacetic acid was used as an external standard, downfield shifts being designated negative.

Preparation of Ethyl 3,3-Difluoro-2-[(trimethylsilyl)-methyl]propenoate (1). The synthetic scheme for the preparation of this compound can be found in our previous communication.[3] The experimental details are described in the following: Ethyl *tert*-butyl 2-[(trimethylsilyl)methyl]malonate (3.16 g, 11.5 mmol), prepared from the sodium salt of ethyl *tert*-butyl malonate and (trimethylsilyl)methyl chloride in THF−HMPA, was added to a suspension of NaH (0.55 g, 13.8 mmol, 60% in paraffin) in THF (30 mL) at 25 °C under argon. The reaction mixture was stirred for 4 h, and then precooled CF_2Br_2 (1.5 mL, 11.5 mmol) was added all at once. The reaction flask was closed with a rubber stopper, and stirring at 25 °C was continued for 24 h. Aqueous workup and distillation under vacuum provided ethyl *tert*-butyl 2-(bromodifluoromethyl)-2-[(trimethylsilyl)methyl]malonate: ^{1}H NMR ($CDCl_3$) δ 4.28 (q, J = 7.1 Hz, 2 H), 1.50 (s, 9 H), 1.48 (s, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 0.05 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ −31 (s); MS (EI, *m*/*z*) 347 (2), 331 (47), 57 (100). Anal. Calcd for $C_{14}H_{25}BrF_2O_4Si$: C, 41.69; H, 6.25. Found: C, 42.19; H, 6.33. The product thus obtained (4.58 g, 11.4 mmol) was dissolved in CF_3CO_2H (20 mL), and the solution was heated at 60 °C for 10 h. Excess trifluoroacetic acid was removed under reduced pressure, and the residue was taken up in THF (14 mL) and neutralized with 2 N NaOH. After the gas evolution ceased, the reaction mixture was worked up as usual. Distillation under vacuum gave **1** as a colorless oil (2.0 g, 80%, 44−46 °C, 4.5 mmHg): ^{1}H NMR ($CDCl_3$) δ 4.17 (q, J = 7.1 Hz, 2 H), 1.52 (t, J = 2.6 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), −0.02 (s, 9 H); ^{19}F

(7) Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds;* John Wiley & Sons: New York, 1989; Chapter 20.

(8) (a) Kingsburg, L.; Smith, R. A. *J. Org. Chem.* **1997**, *62*, 4629 and references cited therein. (b) Nilsson, K.; Ullenius, C.; Krause, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194.

(9) (a) Thalladi, V. R.; Weiss, H. C.; Blaser, D.; Boese, R.; Nangia, A.; Deiraju, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 8702. (b) Pham, M.; Gdaniec, M.; Polonski, T. *J. Org. Chem.* **1998**, *63*, 3731. (c) Hughes, R. P.; Lindner, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 11544.

(10) (a) Pindado, S.; Lancaster, J.; Thornton-Pett, M.; Bochmann, M. *J. Am. Chem. Soc.* **1998**, *120*, 6816. (b) Karl, J.; Erker, G.; Frohlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 11165. (c) Karl, J.; Dahlmann, M.; Erker, G.; Berganler, K. *J. Am. Chem. Soc.* **1998**, *120*, 5643.

(11) (a) Ooi, T; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105. (b) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754.

(12) (a) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds;* John Wiley & Sons: New York, 1989; Chapter 20. (c) Prakasha, T. K.; Srinivasan, S.; Chandrasekaran, A.; Day, R. D.; Holmes, R. R. *J. Am. Chem. Soc.* **1995**, *117*, 10003. (d) Brescia, M. R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156.

(13) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

NMR ($CDCl_3$) δ −1.8 (1 F), −5.6 (1 F); MS (EI, *m*/*z*) 222 (M^+, 5), 207 (45), 73 (100). Anal. Calcd for $C_9H_{16}F_2O_2Si$: C, 48.65; H, 7.21. Found: C, 48.73; H, 7.06.

(*Z*)-3-Fluoro-2-[(trimethylsilyl)methyl]-2-propenyl Acetate (3). A solution of compound **1** (0.5 g, 2.3 mmol) in diethyl ether (5.0 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (0.072 g, 1.9 mmol) in Et_2O (10 mL). The resulting reaction mixture was stirred for 2 h at 25 °C before it was quenched with 0.1 N hydrochloric acid. After the usual workup, the residue was stirred with acetic anhydride (0.70 g, 6.9 mmol) in pyridine (5 mL) for 3 h. The reaction mixture was then poured into water and extracted with ether. The organic phase was washed with 0.5 N aqueous HCl and brine, dried, and concentrated. The residue was distilled to give product **3** as a colorless oil (0.28 g, 60%, 53−55 °C, 4.0 mmHg): ^{1}H NMR ($CDCl_3$) δ 6.65 (br d, J = 82.0 Hz, 1 H), 4.38 (d, J = 3.8 Hz, 2 H), 2.03 (s, 3 H), 1.56 (t, J = 2.6 Hz, 2 H), 0.02 (s, 9 H); ^{19}F NMR (CCl_4) δ +54.5 (d, J = 82 Hz, 1 F); MS (EI, *m*/*z*) 204 (M^+, 2), 161 (2), 43 (100); HRMS calcd for $C_9H_{17}FO_2Si$ 204.0947, found 204.0990.

General Procedure for the Reaction of Nucleophiles with Compound 1. A solution of the nucleophile anion (1.5 mmol) in THF (10 mL), generated by mixing an equal molar amount of the nucleophile with an appropriate base as specified in Table 1, was added to compound **1** (1.0 mmol) in THF (5 mL) under the conditions indicated in Table 1. After 30 min the reaction was warmed to room temperature and quenched with water (20 mL). After the usual extractive workup, the crude product was directly used for ^{19}F NMR determination of the isomeric ratio. Pure products were obtained by column chromatography on silica gel.

Diethyl (*Z*)-2-(Ethoxycarbonyl)-3-fluoro-2-methyl-4-[(trimethylsilyl)methyl]pent-3-enedioate (4a): oil; ^{1}H NMR ($CDCl_3$) δ 4.18 (m, 4 H), 4.09 (q, J = 7.2 Hz, 2 H), 1.79 (d, J = 5.1 Hz, 2 H), 1.76 (d, J = 1.3 Hz, 3 H), 1.23 (m, 9 H), 0.00 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +13.2 (s); MS (EI, *m*/*z*) 376 (M^+, 1), 331 (18) 303 (47), 157 (100). Anal. Calcd for $C_{17}H_{29}FO_6Si$: C, 54.23; H, 7.76. Found: C, 54.19; H, 7.79.

Ethyl 3-Fluoro-3-(2-oxocyclohexyl)-2-[(trimethylsilyl)methyl]-(*Z*)-propenoate (4b): oil; ^{1}H NMR ($CDCl_3$) δ 4.18 (q, J = 7.2 Hz, 2 H), 1.69−2.55 (m, 9 H), 1.82 (d, J = 4.6 Hz, 2 H), 1.31 (t, J = 7.2 Hz, 3 H), 0.04 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +12.2 (d, J = 24.0 Hz); MS (EI, *m*/*z*) 300 (M^+ + 1, 5), 280 (14), 239 (49), 73 (100); HRMS calcd for $C_{15}H_{25}FO_3Si$ 300.1585, found 300.1571.

Ethyl (*Z*)-3-(1-Indolyl)-3-fluoro-2-[(trimethylsilyl)methyl]propenoate (4c): oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.6 Hz, 1 H), 7.28 (m, 3 H), 7.08 (d, J = 3.3 Hz, 1 H), 6.60 (d, J = 3.3 Hz, 1 H), 3.81 (q, J = 7.2 Hz, 2 H), 2.00 (d, J = 4.0 Hz, 2 H), 0.75 (t, J = 7.2 Hz, 3 H), 0.13 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ −3.8 (s); MS (EI, *m*/*z*) 319 (M^+, 70), 203 (40), 73 (100). Anal. Calcd for $C_{17}H_{22}FNO_2Si$: C, 63.92; H, 6.94; N, 4.38. Found: C, 63.64; H, 7.08; N, 4.57.

Ethyl (*E*)-3-(Diethylphosphoryl)-3-fluoro-2-[(trimethylsilyl)methyl]propenoate (4d): oil; ^{1}H NMR ($CDCl_3$) δ 4.23 (q, J = 7.1 Hz, 2 H), 4.17 (m, 4 H), 1.90 (dd, J = 3.7, 0.8 Hz, 2 H), 1.32 (m, 9 H), 0.07 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +49.0 (d, J = 100, Hz); MS (EI, *m*/*z*) 341 (M^+ + 1, 100), 295 (98). Anal. Calcd for $C_{13}H_{26}FO_5PSi$: C, 45.87; H, 7.70. Found: C, 46.14; H, 7.58.

Ethyl (*Z*)-3-Fluoro-3-phenoxy-2-[(trimethylsilyl)methyl]-propenoate ((*Z*)-4e): oil; ^{1}H NMR ($CDCl_3$) δ 7.09−7.39 (m, 5 H), 4.13 (q, J = 7.1 Hz, 2 H), 1.78 (d, J = 3.5 Hz, 2 H), 1.16 (t, J = 7.1 Hz, 3 H), 0.09 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ −3.0 (s); MS (EI, *m*/*z*) 295 (M^+, 12), 281 (29), 73 (100); HRMS calcd for $C_{15}H_{21}FO_3Si$ 296.1113, found 296.1159.

Ethyl (*E*)-3-Fluoro-3-phenoxy-2-[(trimethylsilyl)methyl]-propenoate ((*E*)-4e): oil; ^{1}H NMR ($CDCl_3$) δ 7.09−7.39 (m, 5 H), 4.25 (q, J = 7.1 Hz, 2 H), 1.69 (d, J = 1.7 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H), 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ −0.3 (s).

Ethyl (*Z*)-3-Fluoro-2-[(trimethylsilyl)methyl]propenoate (*Z*)-4f): oil; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 82.4 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 0.173 (d, J = 3.6 Hz, 2 H), 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +42.0 (d, J = 87.5 Hz); MS (EI, *m*/*z*) 205 (M^+ + 1, 4), 185 (16), 73 (100). Anal. Calcd for $C_9H_{17}FO_2Si$: C, 52.91; H, 8.39. Found: C, 52.66; H, 8.62.

Ethyl (*E*)-3-Fluoro-2-[(trimethylsilyl)methyl]propenoate (*E*)-4f): oil; ^{1}H NMR ($CDCl_3$) δ 6.62 (d, J = 82.4 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.52 (dd, J = 3.7, 0.96 Hz, 2 H), 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +37.3 (d, J = 87.5 Hz).

Ethyl (*E*)-3-Fluoro-2-[(trimethylsilyl)methyl]-2-butenoate (4g): oil; ^{1}H NMR ($CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2 H), 2.32 (d, J = 20.0 Hz, 3 H), 1.80 (s, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ −4.1 (q, J = 20.0 Hz); MS (EI, *m*/*z*) 218 (M^+, 10), 203 (100); HRMS calcd for $C_{10}H_{19}FO_2Si$ 218.1108, found 218.1123.

Ethyl (*E*)-3-Fluoro-3-phenyl-2-[(trimethylsilyl)methyl]-propenoate ((*E*)-4h): oil; ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 5 H), 4.00 (q, J = 7.2 Hz, 2 H), 1.99 (d, J = 4.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H), 0.08 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +10.0 (s); MS (EI, *m*/*z*) 280 (M^+, 20), 265 (30), 73 (100); HRMS calcd for $C_{15}H_{21}FO_2Si$ 280.1247, found 280.1271; ^{29}Si NMR ($CDCl_3$/TMS) δ 3.10 (s).

Ethyl (*Z*)-3-Fluoro-3-phenyl-2-[(trimethylsilyl)methyl]-propenoate ((*Z*)-4h): oil; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.32 (q, J = 7.1 Hz, 2 H), 1.85 (d, J = 1.3 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 3 H), 0.00 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +12.6 (s); MS (EI, *m*/*z*) 280 (M^+, 20), 265 (30).

Ethyl 3-Fluoro-3-phenyl-2-[(trimethylsilyl)methyl]propanoate (5). A *Z*/*E* mixture of compound **4h** (0.056 g, 0.2 mmol) and palladium on carbon (10 mg) in anhydrous methanol (10 mL) was stirred under hydrogen (1 atm) for 30 min. The reaction mixture was filtered through silica gel to furnish pure **5** as a mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 5.47 (dd, J = 46.8, 8.1 Hz, 1 H), 3.97 (q, J = 7.1 Hz, 2 H), 2.73 (m, 1 H), 1.12 (d, J = 6.6 Hz, 2 H), 1.03 (t, J = 7.1 Hz, 3 H), 0.05 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ +103.5 (dd, J = 46.8, 16.0 Hz); MS (EI, *m*/*z*) 267 ($M^+ - CH_3$, 25), 249 (23), 173 (100); HRMS calcd for $C_{15}H_{23}FO_2Si$ 282.1420, found 282.1423; ^{29}Si NMR ($CDCl_3$/TMS) δ (syn) 1.13; (anti) 1.53 ((syn J = 7.8 Hz; (anti) J = 16.4 Hz).

JO991450G