Preparation and Reactivity of some New Keto- and Styrene-Based Trifluoromethoxylated Synthons

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Abstract: We describe the preparation, by the means of an initial fluorodesulfurization reaction, of 2-trifluoromethoxy acetophenone as well as β-trifluoromethoxystyrenes derivatives. The synthesis and reactivity of these compounds are discussed in relation to the perturbation induced by the aliphatic trifluoromethoxy group.

Key words: ethers, fluorine, halogenation, Heck reaction, ketones

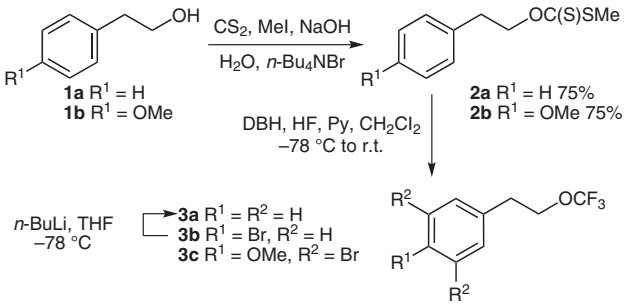
The preparation and study of trifluoromethyl ethers is currently the subject of intense research owing to the peculiar properties of this substituent, close to those of fluorine or chlorine, but with increased lipophilicity and a moderate steric bulk, accompanied by interesting conformational plasticity.[1,2] Moreover trifluoromethyl ethers are usually stable under strongly acidic or basic conditions.[3] However, these observations can only be strictly applied to the aromatic series as very little is known concerning the behavior of, and the properties induced by a trifluoromethoxy substituent in the aliphatic series. This is easily explained by the few available methods for the introduction of this group on aliphatic positions and explains therefore the poor number of compounds previously described in the literature.

The story of aliphatic trifluoromethyl ethers began during the sixties with Aldrich and Sheppard disclosure of the reaction of alkyl fluoroformates with SF_4.[4] Meanwhile, the addition reactions of CF_3OF or CF_3OCl to double bonds or diazoketones gave access to unique trifluoromethoxylated structures.[5] Much more recently, extension of the fluorodesulfurization reaction[6] to the specific case of xanthates enabled the introduction of a trifluoromethoxy group on an aliphatic substrate, under relatively mild conditions, accessible to the common chemist.[7,8] This gave a new impetus to the preparation of functionalized trifluoromethyl ethers as exemplified by a series of recent patents from a Merck group describing a novel generation of 'green' and highly efficient fluorinated surfactants,[9] and our own work concerning the preparation of 2-trifluoromethoxyethyl triflate and its derivatives,[10] as well as an easy entry to α-trifluoromethoxylated esters and their Knoevelagel-like adducts.[11] Very recently, some progress has been made for the direct introduction of the trifluoromethoxy entity on organic molecules including those which are functionalized, either via direct trifluoromethylation of alcohols with trifluoromethyloxonium salts,[12] stabilization and use of the formerly elusive CF_3OH,[13] and a new method for the generation of the trifluoromethoxide anion.[14]

Despite all these recent advances, no laboratory-scale convenient methods for the preparation of simple molecules such as α-trifluoromethoxyketones or β-trifluoromethoxystyrenes appear in the literature. We thought that the synthesis and the study of the reactivity of these molecules will bring some new knowledge about the very poorly known influence of a trifluoromethoxy group on aliphatic structures.

We selected the fluorodesulfurization reaction of a xanthate for the introduction of the trifluoromethoxy group.[7,15] Based on our earlier experience,[10] the possible participation of adjacent functionalities during the fluorodesulfurization process led us to believe that the presence of a carbonyl group should be avoided during this reaction. Moreover, the known propensity of ketones to furnish ketene dithioacetals under basic conditions used for the formation of xanthates reinforced this opinion.[16] The keto functionality should thus be preferably introduced after the fluorination step. We guessed that the presence of a phenyl group, providing a benzylic position susceptible to further oxidation, could constitute an entry point for the introduction of the requisite carbonyl group while not interfering with the fluorination reaction. Based on these considerations phenethyl alcohol (**1a**) was selected as the starting material for our study (Scheme 1).

Formation of the xanthate **2a** from phenethyl alcohol readily occurred (75% yield) under phase-transfer conditions.[17] Further fluorodesulfurization of xanthate **2a** af-



Scheme 1 Fluorodesulfurization reaction

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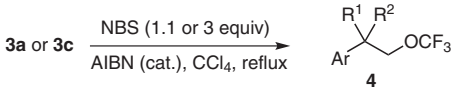
forded a mixture of trifluoromethyl ether **3a**[12] and its *para*-brominated derivative **3b**[8] in various relative amounts (1:1 to 3:1) depending on the exact reaction conditions (time and temperature). These two compounds could be partially separated either by column chromatography or by tedious distillation. Nevertheless, more conveniently, the debromination can occur cleanly by direct treatment of the mixture with butyllithium. The overall yield for **3a** from **2a** was 58% in the latter case.[18]

As explained above, we thought that the benzylic position in **3a** could be easily amenable to keto functionality. However, all attempts to oxidize this position with powerful reagents (PCC, CrO_3/H_2SO_4, $KMnO_4$, $RuO_2/NaIO_4$, Mn_2O_7)[19,20] failed, showing the strong deactivating effect of the trifluoromethoxy group. Contrary to the aromatic series where the inductive deactivating power of OCF_3 may be counter balanced by its resonance electron-donating effect, no such compensation seems possible in the aliphatic series.[21,22]

In an effort to enhance the reactivity of the benzylic position towards oxidation, we also investigated the fluorodesulfurization of *para*-methoxyphenethyl alcohol (**1b**, Scheme 1). Using the same reaction sequence as before: formation of a xanthate **2b** (75%), followed by fluorodesulfurization, the dibromo compound **3c** was obtained in 84% yield. Unfortunately, this compound could not be debrominated cleanly with BuLi.

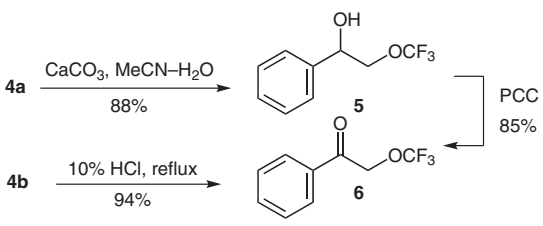
However, we were pleased to find that the benzylic positions in **3a** or **3c** while deactivated for oxidation were still susceptible to radical reactions (Scheme 2).



4a Ar = Ph, R^1 = H, R^2 = Br 96%
4b Ar = Ph, R^1 = R^2 = Br 99%
4c Ar = 3,5-Br_2-4-$MeOC_6H_2$, R^1 = H, R^2 = Br 91%
4d Ar = 3,5-Br_2-4-$MeOC_6H_2$, R^1 = R^2 = Br 80%

Scheme 2 Benzylic bromination

Ethers **3a** or **3c** could thus selectively be mono (96% and 91% yield, respectively) or dibrominated (99% and 80% yield), by radical bromination with one or three equivalents of NBS ensuring a potential entry point to the wanted ketone.[23,24] Effective access to the trifluoromethoxylated acetophenone **6**[25] was further secured either from monobrominated ether **4a**[26] or the dibrominated derivative **4b** (Scheme 3).



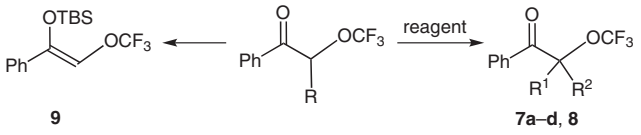
Scheme 3 Preparation of α-trifluoromethoxy acetophenone

Transformation of monobrominated ether **4a** to the corresponding alcohol **5** (not isolated) was readily accomplished with calcium carbonate in a mixed solvent system in 88% crude yield.[27] Ensuing oxidation of the crude benzylic alcohol **5** to ketone **6** occurred uneventfully using classical PCC conditions (85% yield).[19]

In a more straightforward way, dibrominated ether **4b** could be directly converted to acetophenone derivative **6** (94% yield) upon hydrolysis in an acidic medium.[28,29]

The α-functionalization of the carbonyl group of acetophenone **6** and its derivatives was further studied (Table 1).

Table 1 Further Functionalization of Acetophenone Derivatives



9 **7a–d**, **8**

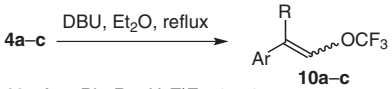
Entry	R	Reagent	Product	Yield (%)[a]
1	**6** H	TBSCl[b]	**9**	99
2	**6** H	MeI[c]	**8** R^1 = Me, R^2 = H	78
3	**6** H	NCS[d]	**7a** R^1 = Cl, R^2 = H	76
4	**6** H	NBS[d]	**7b** R^1 = Br, R^2 = H	95
5	**7a** Cl	NCS[e]	**7c** R^1 = R^2 = Cl	81
6	**7b** Br	NBS[e]	**7d** R^1 = R^2 = Br	37

[a] Isolated yield.
[b] Conditions: KHMDS, THF, –78 °C.
[c] Conditions: LiHMDS, THF, 0 °C.
[d] Conditions: PTSA (1 equiv), CCl_4, reflux.
[e] Conditions: LiHMDS, HMPA, –78 °C.

Attempted direct conversion of **6** to its silyl enol ether derivative **9** using Et_3N failed,[30] showing the poor acidity of the α-protons in the presence of a trifluoromethoxy group. However, the potassium enolate derived from ketone **6** was converted in high yield (99%) to **9** as the single *Z*-isomer (entry 1).[31] This stereochemistry was based on a positive NOE observed between the vinylic hydrogen nucleus and the *ortho* protons of the aromatic ring. The reactivity of this compound was relatively poor under classical silyl enol ether activations (Lewis acid treatment or fluorodesilylation). We did not succeed in alkylation or halogenation reactions with good and/or reproducible yields by this method.

By contrast, alkylation of **6** with iodomethane to propiophenone **8** proceeded with a good yield in a basic medium (entry 2). Under acidic conditions, halogenation of acetophenone **6** stopped cleanly at the monosubstitution stage even with an excess of halogenating agent (entries 3 and 4).[32] Further dichlorination to **7c** from **6** or dibromination to **7d** from **7b** could be effected under basic conditions (entries 5 and 6).

The benzylic brominated derivatives **4a–c**, readily made available by this work, led us also to consider a facile access to the series of trifluoromethoxystyrenes (Scheme 4).



10a Ar = Ph, R = H *Z*/*E* = 2.5:1

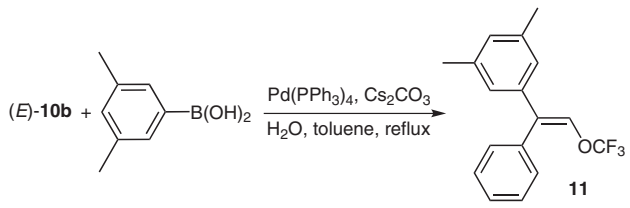
10b Ar = Ph, R = Br *Z*/*E* = 1:9

10c Ar = 3,5-Br_2-4-$MeOC_6H_2$, R = H *Z*/*E* = 10:1

Scheme 4 Access to trifluoromethoxylated styrenes

Under the action of the non-nucleophilic base DBU, in refluxing diethyl ether, we observed a clean dehydrobromination reaction of **4a–c** leading to the corresponding β-trifluoromethoxystyrene derivatives **10a–c** in good yield (73–92%) as isomeric mixtures.[33] Like in the case of silyl enol ether **9**, the stereochemistry of these compounds was ascertained by ^{1}H NMR NOE experiments. These molecules proved to be quite stable and did not polymerize when kept at room temperature in the laboratory. This stability was reflected upon our failure to obtain any adducts during attempted Diels–Alder reactions with common dienes like dimethyl-2-butene or cyclopentadiene. This behavior is in line with our recent observation that the trifluoromethoxy group acts as a fluorine twin in Diels–Alder reactions,[34] and the known very poor reactivity of fluorinated styrenes under such conditions.[35]

The β-brominated styrene **10b** seemed an attractive substrate for further functionalization of the double bond by coupling reactions. We were thus pleased to find that Suzuki coupling[36] of the *E*-isomer of **10b** with 3,5-dimethylbenzene boronic acid, as an example, occurred readily to give the styrene **11** (85% yield), opening the way to more elaborate trifluoromethoxy-bearing substrates (Scheme 5).[37]



Scheme 5 Suzuki coupling

In conclusion, on aliphatic chains the long range inductive deactivating power of the trifluoromethoxy group seems to be the main factor influencing the reactivity of neighboring positions. This is in contrast to the case of aromatic substrates where this effect may be compensated by the resonance electron-donating effect. Nevertheless, the use of radical reactions, which are still operative, enabled us to prepare a representative example of α-trifluoromethoxyketones and study its reactivity. Some intermediates were also easily transformed to new β-trifluoromethoxystyrenes with promising potential for further functionalization by coupling reactions.

Acknowledgment

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References and Notes

(1) Olah, G. A.; Yamato, T.; Hashimoto, T.; Shih, J. G.; Trivedi, N.; Singh, B. P.; Piteau, M.; Olah, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 3708.

(2) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827.

(3) However, see: Iijima, A.; Amii, H. *Tetrahedron Lett.* **2008**, *49*, 6013.

(4) (a) Aldrich, P. E.; Sheppard, W. A. *J. Org. Chem.* **1964**, *29*, 11. (b) Yagupol'skii, L. M.; Alekseenko, A. N.; Il'chenko, A. Y. *Sov. Prog. Chem. (Engl. Transl.)* **1978**, *44*, 52.

(5) (a) Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 101. (b) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2604. (c) Kamil, W. A.; Haspel-Hentrich, F.; Shreeve, J. M. *Inorg. Chem.* **1986**, *25*, 376; and references cited therein. (d) Leroy, J.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1224.

(6) (a) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1976**, *41*, 3107. (b) Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.

(7) (a) Kuroboshi, M.; Kanie, K.; Hiyama, T. *Adv. Synth. Catal.* **2001**, *343*, 235. (b) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214.

(8) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 471.

(9) (a) Kirsch, P.; Franz, K.-D.; Ruhl, A. WO 2006072401, **2006**. (b) Kirsch, P.; Franz, K.-D.; Ruhl, A. US 2008149878, **2008**. (c) Wolfgang, H.; Ignatyev, N. M.; Seidel, M.; Montenegro, E.; Kirsch, P.; Bathe, A. WO 2008003444, **2008**. (d) Wolfgang, H.; Ignatyev, N. M.; Seidel, M.; Montenegro, E.; Kirsch, P.; Bathe, A. WO 2008003446, **2008**. (e) We thank one of the referees for bringing these works to our attention.

(10) Blazejewski, J.-C.; Anselmi, E.; Wakselman, C. *J. Org. Chem.* **2001**, *66*, 1061.

(11) Blazejewski, J.-C.; Anselmi, E.; Wernicke, A.; Wakselman, C. *J. Fluorine Chem.* **2002**, *117*, 161.

(12) Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem.* **2007**, *72*, 6905.

(13) Christe, K. O.; Hegge, J.; Hoge, B.; Haiges, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 6155.

(14) Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* **2008**, *49*, 449.

(15) The preparation of some α-trifluoromethoxylated esters was recently described using the direct nucleophilic substitution of α-triflyl esters with the trifluoromethoxide anion, see ref. 14. However, the possibility to extend this reaction to the case of α-keto triflates remains to be established.

(16) Anselmi, E.; Blazejewski, J.-C.; Wakselman, C. *Tetrahedron Lett.* **1998**, *39*, 9651.

(17) Lee, A. W. M.; Chan, W. H.; Wong, H. C.; Wong, M. S. *Synth. Commun.* **1989**, *19*, 547.

(18) **Preparation of Phenethyl Trifluoromethyl Ether (3a)** HF–pyridine complex (50 mL) was added dropwise to a

cooled (–78 °C) suspension of 1,3-dibromo-5,5-dimethylhydantoin (DBH, 55 g, 1.92 mol) in CH_2Cl_2 (250 mL), followed by a solution of the xanthate (15 g, 70.7 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at –78 °C for 1 h, then for 2 h at r.t., and poured in cold H_2O (200 mL). The organic layer was separated. The aqueous phase was sat. with NaCl and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with a 37% $NaHSO_3$ solution, brine (2 × 250 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, pentane) to give 9.5 g of a mixture of brominated and nonbrominated products. This mixture was dissolved in dry THF (56 mL), cooled at –78 °C under argon, and a solution of *n*-BuLi in hexanes (2.5 M, 11.3 mL) was added dropwise. The solution was stirred for an additional 30 min, H_2O (10 mL) was added, and the mixture was warmed to r.t. A sat. soln of NH_4Cl (50 mL) and Et_2O (50 mL) were added and the two phases separated. The aqueous layer was extracted twice with Et_2O (50 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated under vacuum to give 7.6 g (58%) of pure **3a** as a colorless oil. The spectroscopic data were in full accord with previous publication.[12] ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.01 (t, *J* = 7.3 Hz, 2 H, CH_2), 4.16 (t, *J* = 7.3 Hz, 2 H, CH_2), 7.18–7.41 (m, 5 H, $5CH_{Ar}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.3 (CH_2), 67.8 (q, J_{CF} = 3 Hz, CH_2), 121.4 (q, J_{CF} = 254 Hz, C), 127.0 (CH_{Ar}), 128.7 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 136.6 (C_{Ar}). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –61.2 (OCF_3). MS: *m/z* (%) = 191 [M + H$^+$], 105 (100) [$C_8H_9^+$].

(19) Hudlicky, M. *Oxidations in Organic Chemistry*, ACS Monograph 186; American Chemical Society: Washington DC, **1990**.

(20) Trömel, M.; Russ, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1007.

(21) Leroux, F. R.; Manteau, B.; Vors, J.-P.; Pazenok, S. *Beilstein J. Org. Chem.* **2008**, *4*, doi:10.3762/bjoc.4.13.

(22) Agouridas, V.; Laïos, I.; Cleeren, A.; Kizilian, E.; Magnier, E.; Blazejewski, J.-C.; Leclercq, G. *Bioorg. Med. Chem.* **2006**, *14*, 7531.

(23) March, J. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley and Sons: New York, **1992**, 694–697.

(24) **Preparation of (2,2-Dibromo-2-phenyl)ethyl Trifluoromethyl Ether (4b)**
A solution of trifluoromethyl ether **3a** (5 g, 26.3 mmol), NBS (14.04 g, 78.9 mmol), and AIBN (0.21 g, 1.3 mmol) in CCl_4 (100 mL) was refluxed until completion (TLC). The mixture was concentrated, and the residue was filtered through a short silica gel column, rinsed with pentane. After concentration of the filtrate, the resulting oil was purified by flash chromatography (SiO_2, pentane) to give 9 g (99%) of **4b** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.70 (s, 2 H, CH_2), 7.31 (3 H, CH_{Ar}), 7.69 (m, 2 H, CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 61.9 (C), 75.3 (q, J_{CF} = 3 Hz, CH_2), 121.1 (q, J_{CF} = 257 Hz, C), 127.3 (2 CH_{Ar}), 128.6 (2 CH_{Ar}), 129.9 (CH_{Ar}), 140.5 (C). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –60.8 (OCF_3). Anal. Calcd (%) for $C_9H_7Br_2F_3O$: C, 31.07; H, 2.02. Found: C, 31.12; H, 1.76.

(25) Farnham, W. B.; Middleton, W. J. EP 164124 A2 19851211, **1985**; *Chem. Abstr.* **1985**, *105*, 114600.

(26) This compound was also obtained albeit in poor yield (10%) upon oxidation with $NaBrO_3$/$NaHSO_3$ system. See: Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023.

(27) Smith, J. G.; Dribble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762.

(28) Gelling, J. O.; Feringa, B. L. *J. Am. Chem. Soc.* **1990**, *12*, 7599.

(29) **2-Trifluoromethoxy Acetophenone (6)**
Compound **4b** (9.1 g) was refluxed for 8 h in a solution of 10% HCl (150 mL) and MeCN (60 mL). After extraction with Et_2O (4 × 50 mL), the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane–Et_2O, 9:1) afforded 4.48 g (84%) of **6** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.17 (s, 2 H, CH_2), 7.48 (m, 2 H, CH_{Ar}), 7.62 (m, 1 H, CH_{Ar}), 7.88 (m, 2 H, CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 68.3 (q, J_{CF} = 2.7 Hz, CH_2), 121.7 (q, J_{CF} = 254 Hz, CF_3), 126.8 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 133.7 (C_{Ar}), 134.3 (CH_{Ar}), 190.2 (C). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –61.5. Anal. Calcd (%) for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 52.71; H, 3.29. MS: *m/z* (%) = 205 (100) [M + H$^+$].

(30) Poirier, J.-M.; Hennequin, L.; Fomani, M. *Bull. Soc. Chim. Fr.* **1986**, 436.

(31) **1-*tert*-Butyldimethylsilyloxy-2-trifluoromethoxystyrene (9)**
To a solution of ketone **6** (0.31 g, 1.52 mmol) in THF (10 mL) was added, at –78 °C under argon, KHMDS (3.8 mL, 2.43 mmol, 1.0 M solution in toluene) and HMPA (0.3 mL, 1.52 mmol). After 5 min, a solution of TBSCl (340 mg, 2.28 mmol) in THF (2 mL) was added dropwise and stirring was continued at the same temperature for 8 h. The reaction mixture was allowed to reach r.t. and a sat. soln of NH_4Cl was added. The organic layer was collected, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (SiO_2, pentane–Et_2O, 9:1) to give 0.53 g (99%) of **9** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 (s, 6 H, 2 CH_3), 0.98 (s, 9 H, 3 CH_3), 6.48 (s, 1 H, CH), 7.35–7.45 (m, 3 H, $3CH_{Ar}$), 7.46–7.52 (m, 2 H, 2 CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.34 (s, 2 CH_3), 18.57 (C), 25.79 (3 CH_3), 119.40 (q, J_{C-F} = 13.0 Hz, CH), 120.9 (q, J_{C-F} = 257 Hz, CF_3), 125.6 (2 CH_{Ar}), 128.5 (2 CH_{Ar}), 128.8 (CH_{Ar}), 135.2 (C_{Ar}), 142.5 (C). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –60.9. Anal. Calcd (%) for $C_{15}H_{21}F_3O_2Si$: C, 56.58; H, 6.65. Found: C, 56.65; H, 6.96.

(32) Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* **2008**, *64*, 5191.

(33) **α-Bromo-β-trifluoromethoxystyrene (10b)**
DBU (1.66 mL, 11.1 mmol) was added to a solution of dibromide **4b** (2.95 g, 8.52 mmol) in dry Et_2O (60 mL). The mixture was refluxed for 8 h. After evaporation of the solvent, the crude product was purified by flash chromatography (SiO_2, pentane) giving 2.1 g (92%) of a mixture of *Z*/*E* isomers of **10b** as a colorless oil. Anal. Calcd (%) for $C_9H_6BrF_3O$: C, 40.48; H, 2.26. Found: C, 40.49; H, 2.41. Further purification allowed the separation of the two isomers.
E-Isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.10 (s, 1 H, CH), 7.35 (m, 3 H, CH_{Ar}), 7.46 (m, 2 H, CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 112.9 (C), 121.1 (q, J_{CF} = 258 Hz, CF_3), 127.9 (2 CHar), 128.8 (2 CH_{Ar}), 129.6 (CH_{Ar}), 132.9 (q, J_{CF} = 3 Hz, CH), 134.9 (C_{Ar}). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –60.4 (OCF_3).
Z-Isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.95 (s, 1 H, CH), 7.37 (m, 3 H, CH_{Ar}), 7.55 (m, 2 H, CH_{Ar}). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –60.9 (OCF_3).

(34) Magnier, E.; Diter, P.; Blazejewski, J.-C. *Tetrahedron Lett.* **2008**, *49*, 4575.

(35) (a) Ernet, T.; Haufe, G. *Tetrahedron Lett.* **1996**, *37*, 7251. (b) Bogachev, A. A.; Kobrina, L. S.; Meyer, O. G. J.; Haufe, G. *J. Fluorine Chem.* **1999**, *97*, 135.

(36) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(37) **Preparation of α-(3,5-Dimethylphenyl)-β-trifluoromethoxystyrene (11)**

A mixture of bromostyrene **10b** (212 mg, 0.8 mmol), $Pd(PPh_3)_4$ (44 mg, 0.5 mol%), 3,5-dimethylbenzene boronic acid (144 mg, 0.96 mmol), Cs_2CO_3 (520 mg, 1.6 mmol), distilled H_2O (0.32 mL), and toluene (8 mL) was stirred for 2 h at reflux. The solution was extracted with Et_2O (4 × 10 mL). Drying of the organic layers ($MgSO_4$), followed by concentration and flash chromatography (SiO_2, pentane) gave 199 mg (85%) of pure **11** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.20 (s, 6 H, 2 CH_3), 6.66 (s, 1 H, CH), 6.82 (s, 2 H, 2 CHar), 6.87 (s, 1 H, CH_{Ar}), 7.15 (m, 2 H, CH_{Ar}), 7.21 (m, 3 H, CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (2 CH_3), 121.6 (q, J_{CF} = 256 Hz, C), 127.7 (2 CHar), 128.1 (CH_{Ar}), 128.3 (2 CH_{Ar}), 128.6 (2 CH_{Ar}), 129.8 (CH_{Ar}), 130.7 (C), 130.8 (q, J_{CF} = 3.8 Hz, CH), 135.3 (C), 137.8 (C), 138.3 (C). ^{19}F NMR (188 MHz, $CFCl_3$): δ = –60.63. Anal. Calcd (%) for $C_{17}H_{15}F_3O$: C, 69.85; H, 5.17. Found: C, 70.09; H, 5.27.