Fluoro- or Trifluoromethyl-Substituted Benzyl and Phenethyl Alcohols: Substrates for Metal-Mediated Site-Selective Functionalization

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Keywords: Fluorinated substituents / Hydrogen-metal permutation / Regioselectivity / Organometallic reagents / Protecting groups

It was possible to functionalize the three fluorobenzyl alcohols and the three 2-(fluorophenyl)ethanols by metalation and subsequent carboxylation, the prototype electrophilic trapping reaction. Triisopropylsilyl (TIPS) outperformed methoxymethyl (MOM) as an *O*-protective group making seven new fluorobenzoic acids accessible in 63% average yield. Moreover, the TIPS group tolerates weakly basic and acidic media and, therefore, may facilitate further structural elaboration. The unprotected alcohols reacted more sluggishly and were unable to provide two of the targeted products (acids **1** and **2**). The yield averaged only 46% in the five other cases (acids **3**–**7**). The direct metalation of fluorinated benzyl and phenethyl alcohols remains nevertheless an attractive option because of its operational simplicity. All three (trifluoromethyl)benzyl alcohols and two of the three (trifluoromethyl)phenethyl alcohol isomers were successfully submitted to the metalation/functionalization sequence. These five starting materials gave rise to a total of nine new benzoic acids or lactones (compounds **8**–**14** and **17**–**18**). Despite the poor yields (31% on average), the organometallic methods employed are, in general, extremely selective, economical and easy to perform.
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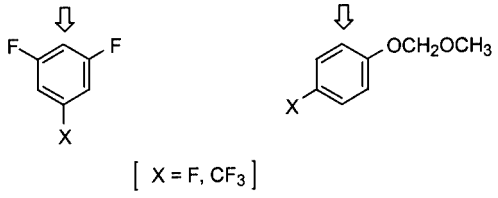
A fluorine atom exerts the strongest and a trifluoromethyl group the weakest *ortho*-metalation promoting effect among all halogenated substituents.[1] This, at first sight, is in conflict with the rule-of-thumb according to which a trifluoromethyl group has the same acidifying (or anion-stabilizing) potential as a single fluorine. As an example, one may quote the dissociation constants of fluoroacetic acid (pK_a 2.6) and 3,3,3-trifluoropropionic acid (pK_a 2.9).[2] However, metalation (hydrogen/metal permutation) reactions are usually irreversible or, in other words, kinetically controlled. As transition states are much more sensitive to steric hindrance than ground states, the bulkiness of the trifluoromethyl entity indeed impedes reactions in its vicinity.[3–6]

Besides in size, these two archetypal fluorine substituents differ characteristically as far as the distance dependence of their electronic effects is concerned. When moving the deprotonation site from the *ortho* through the *meta* to the *para* position, the activating effect of fluorine drops by roughly half with each step,[7] whereas the effect of a trifluoromethyl group is almost position-invariant.[8] This difference reveals itself unequivocally in competition experiments. When treated with *sec*-butyllithium, 3,5-difluorobenzotrifluoride [1,3-difluoro-5-(trifluoromethyl)benzene] undergoes deprotonation at the fluorine-flanked position 16 times faster than 1,3,5-trifluorobenzene does (after statistical correction), and 1-methoxymethoxy-4-(trifluoromethyl)benzene reacts with butyllithium 4.5 times faster than 1-fluoro-4-(methoxymethoxy)benzene at the oxygen-adjacent position.[9]



Finally, fluorine and trifluoromethyl exhibit divergent behavior in yet another practically important respect. When *ortho*-metalated, fluoroarenes do not suffer a 1,2-elimination of metal fluoride in general up to −50 °C, thus avoiding the generation of energy-rich dehydroarene ("aryne") species. Metalated benzotrifluorides are stable up to +25 °C and beyond, unless they carry alkyl groups at

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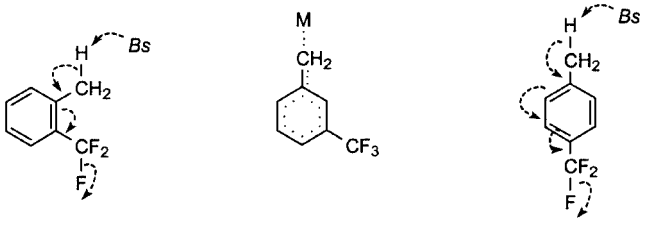
the *ortho*- or *para*-positions. In this case they undergo an instantaneous 1,4- or 1,6-dehydrofluorination (and subsequent nucleophilic addition[10]), respectively, even at the lowest temperatures, when exposed to organometallic reagents or metal amides.[11] Only *meta*-isomers such as 3-(trifluoromethyl)toluene can be deprotonated at the benzylic position[11] or, alternatively, at the 4-position,[12] depending on the base (*Bs*) employed.



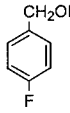
The purpose of the present investigation was to explore the possibility of preventing such 1,4- and 1,6-eliminations of hydrogen fluoride. In particular, we wanted to find out whether *O*-protected hydroxymethyl and β-hydroxyethyl groups would be less prone to benzylic deprotonation than simple alkyl groups are. Therefore, we have studied the metalation and subsequent carboxylation of 2-, 3- and 4-(trifluoromethyl)benzyl alcohols and of the 2-, 3- and 4-isomers of 2-[(trifluoromethyl)phenyl]ethanol and, for comparison, of the corresponding monofluoroaryl analogs.

Fluorobenzyl Alcohols, 2-(Fluorophenyl)ethanols and *O*-Protected Derivatives as Substrates

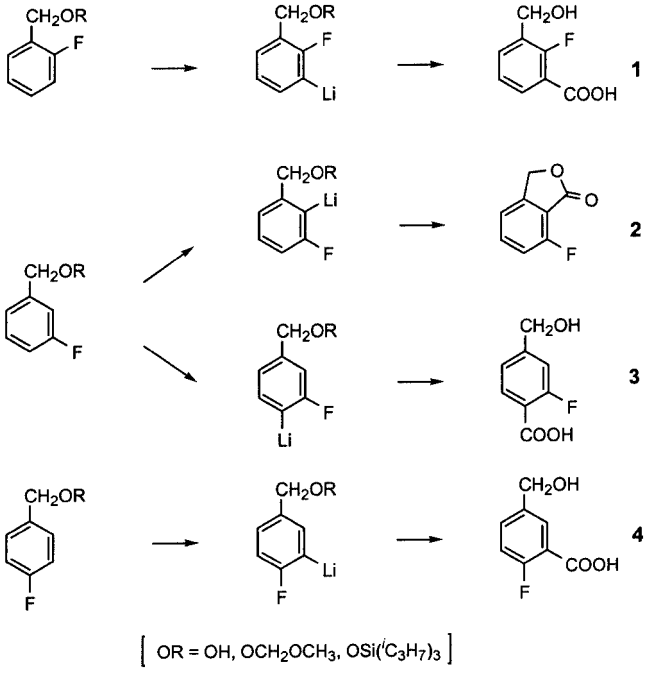
The *O*-lithiated hydroxymethyl group is only a weak *ortho*-directing substituent.[12–17] Thus, we expected metalation to occur next to the fluorine atom and remote from the oxygen functional group whenever there were two different sites available for deprotonation. This was found to be true not only for the competition between fluorine and the CH_2OLi entity, but also between fluorine and the methoxymethyl (MOM) or the triisopropylsilyl (TIPS) protected hydroxymethyl group.

The results are summarized below (see Table 1). The MOM- or TIPS-protected 2- and 4-fluorobenzyl alcohols afforded, after metalation, carboxylation and deprotection, the 2-fluoro-3-(hydroxymethyl)benzoic acid (**1**, 36% or 61%) and the 2-fluoro-5-(hydroxymethyl)benzoic acid (**4**, 56% or 84%), respectively. The unprotected 2-fluorobenzyl alcohol reacted sluggishly to produce an inseparable mixture, whereas the 4-isomer again gave the acid **4** (49%). A regiochemical alternative was encountered only with the 3-fluorobenzyl alcohol. When this alcohol was treated with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethylethylenetriamine (PMDTA) in tetrahydrofuran for 2 h at −75 °C, 2-fluoro-4-(hydroxymethyl)benzoic acid (**3**; 47%) was obtained exclusively. The same product resulted, although in lower yields (15% and 31%), when the MOM- and TIPS-protected derivatives were the starting materials. However, the lactone **2**, the spontaneously formed dehydration product of the 2-fluoro-6-(hydroxymethyl)benzoic acid, was isolated in 29% and 51% yield, respectively, when the MOM derivative was metalated with uncomplexed *sec*-butyllithium or the TIPS derivative with *sec*-butyllithium in the presence of both PMDTA and potassium *tert*-butoxide.

Table 1. Summary of the results obtained with 2-, 3- and 4-fluorobenzyl alcohols and their MOM- and TIPS-protected derivatives

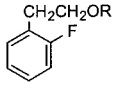
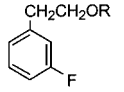
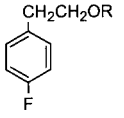
Substrate[a]	Product[b,c]	OR = OLi(OK)	OR = OMOM	OR = OTIPS
	**1** (*o*-F)	–	36%[d]	61%[d]
	**3** (*o*,*o*′) **3** (*o*-F)	– 47%[d]	29%[e] 15%[d]	51%[f] 31%[d]
	**4** (*o*-F)	49%[d]	56%[d]	84%[d]

[a] Protective groups: OMOM = OCH_2OCH_3; OTIPS = $OSi(^iC_3H_7)_3$. [b] Regiochemistry: "*o*-F" means metalation at a position adjacent to fluorine but remote from the CH_2OR group; "*o*,*o*′" means metalation at the position flanked by both substituents. [c] Reaction conditions: metalation in a 7:3 mixture of tetrahydrofuran (THF) and hydrocarbons at −75 °C for 2 h unless stated otherwise. Metalation reagents: [d] *sec*-Butyllithium (LIS) in the presence of *N*,*N*,*N*′,*N*′′*N*′′ pentamethyldiethylenetriamine (PMDTA). [e] LIS alone. [f] LIS in the presence of PMDTA and potassium *tert*-butoxide.

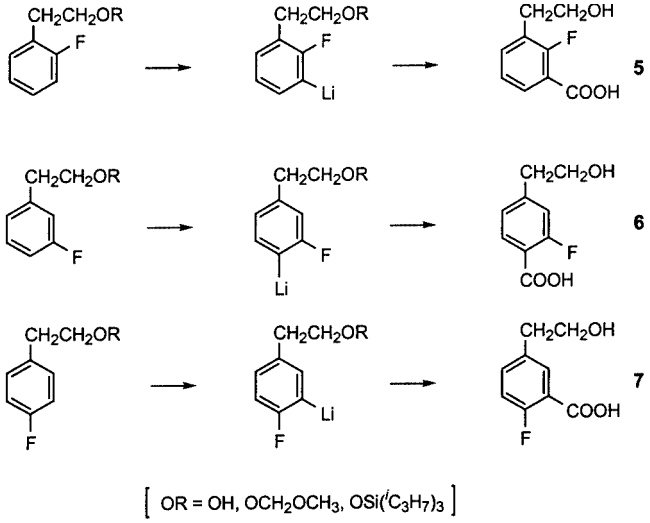


No such "optional site selectivity" [18–20] was achieved in the fluorophenethyl alcohol series (see Table 2). Deprotonation with lithium 2,2,6,6-tetramethylpiperidide of each of the three isomers, followed by carboxylation and neutralization, afforded 2-fluoro-3-(2-hydroxyethyl)benzoic acid (**5**; 31%), 2-fluoro-4-(2-hydroxyethyl)benzoic acid (**6**; 61%) and 2-fluoro-5-(hydroxyethyl)benzoic acid (**7**; 43%). Employing the MOM- and TIPS-protected starting materials and PMDTA-activated *sec*-butyllithium as the base gave, after deprotonation, the same acids in 35% and 39%, 70% and 67%, and 71% and 77% yield, respectively.

Table 2. Summary of the results obtained with 2-(2-, 3- and 4-fluorophenyl)ethanols and their MOM- and TIPS-protected derivatives

Substrate[a]	Product[b,c]	OR = OLi(OK)	OR = OMOM	OR = OTIPS
	**5** (*o*-F)	31%[d]	35%[e]	67%[e]
	**6** (*o*-F)	61%[d]	39%[e]	71%[e]
	**7** (*o*-F)	43%[d]	70%[e]	77%[e]

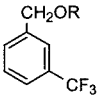
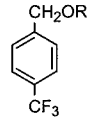
[a] Protective groups: OMOM = OCH_2OCH_3; OTIPS = $OSi(^iC_3H_7)_3$. [b] Regiochemistry: "*o*-F" means metalation at a position adjacent to fluorine but remote from the CH_2CH_2OR group. [c] Reaction conditions: metalation in a 7:3 mixture of tetrahydrofuran (THF) and hydrocarbons at −75 °C for 2 h unless stated otherwise. Metalation reagents: [d] Lithium 2,2,6,6-tetramethylpiperidide (LITMP). [e] *sec*-Butyllithium (LIS) in the presence of *N*,*N*,*N*′,*N*′′*N*′′-pentamethyldiethylenetriamine (PMDTA).



Trifluoromethyl-Substituted Benzyl Alcohols and 2-Phenylethanols as Substrates

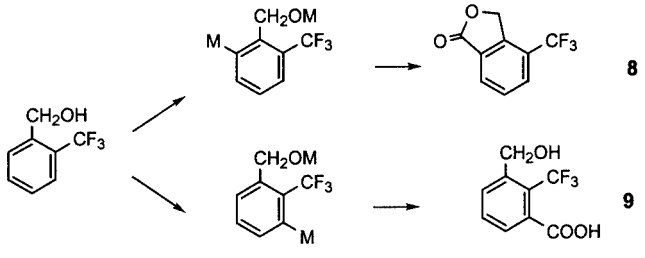
All three isomers of (trifluoromethyl)benzyl alcohol and of 2-[(trifluoromethyl)phenyl]ethanol were allowed to react with standard metalating reagents such as lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide with butyllithium, *sec*-butyllithium or *tert*-butyllithium either alone or in combination with potassium *tert*-butoxide and PMDTA. Only the best results are listed below (see Table 3 and text).

Table 3. Summary of the major results obtained with 2-, 3- and 4-(trifluoromethyl)benzyl alcohols

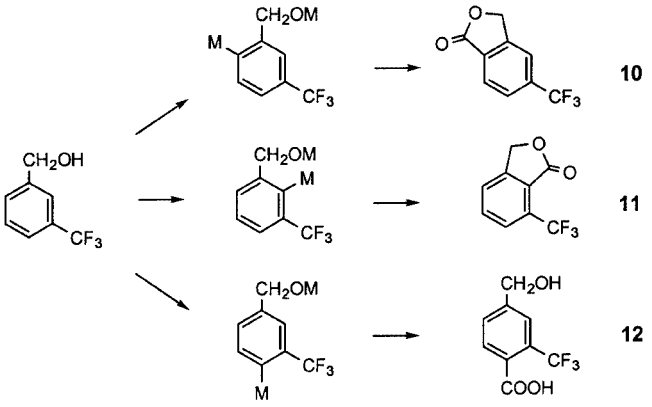
Substrate[a]	Product[b,c]	OR = OLi(OK)	OR = OMOM	OR = OTIPS
	**8** (*o*-CH_2OR)	24%[d]	[e]	[e]
	9 (*o*-CF_3)	33%[f]	[e]	[e]
	**10** (*o*-CH_2OR)	12%[g]	[e]	[e]
	11 (*o*,*o*′)	47%[h]	[e]	[e]
	2 (*o*-CF_3)	25%[i]	[e]	[e]
	**13** (*o*-CH_2OR)	29%[d]	[e]	[e]
	14 (*o*-CF_3)	36%[i]	[e]	[e]

[a] Protective groups: OMOM = OCH_2OCH_3; OTIPS = $OSi(^iC_3H_7)_3$. [b] Regiochemistry: "*o*-CH_2OR" means metalation at a position adjacent to the *O*-deprotonated hydroxymethyl, but remote from the trifluoromethyl group; "*o*-CF_3" means the opposite. [c] Reaction conditions: metalation in a 7:3 mixture of tetrahydrofuran (THF) and hydrocarbons at −75 °C for 2 h unless stated otherwise. Metalation reagents: [d] Butyllithium (LIC). [e] See text (last paragraph of the general part preceding the Exp. Sect.). [f] LIC in the presence of potassium *tert*-butoxide (KOR) and PMDTA. [g] *tert*-butyllithium (LIT). [h] LIC in the presence of KOR. [i] LIS in the presence of KOR and PMDTA.

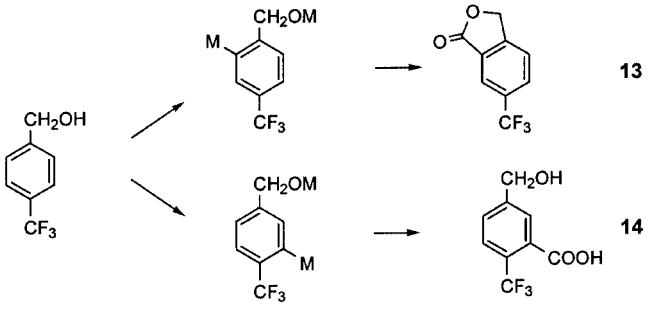
The steric congestion caused by the trifluoromethyl group offers a chance to the oxygen-functional substituent to direct the metalation in its vicinity. Thus, 2-(trifluoromethyl)benzyl alcohol was attacked by butyllithium at the 6-position as evidenced by the isolation of the lactone **8** (24%), spontaneously formed by dehydration of the 2-hydroxymethyl-3-(trifluoromethyl)benzoic acid. However, when the same organolithium reagent was applied in the presence of potassium *tert*-butoxide and PMDTA, deprotonation occurred at the CF_3-adjacent site and ultimately produced 3-hydroxymethyl-2-(trifluoromethyl)benzoic acid (**9**; 33%).



3-(Trifluoromethyl)benzyl alcohol offered the rare possibility of threefold optional site selectivity. Whereas a proton was abstracted by *tert*-butyllithium from the CF_3-remote 6-position, and by *sec*-butyllithium, if simultaneously coordinated to potassium *tert*-butoxide and PMDTA, from the CH_2OM-remote 4-position, metalation was accomplished with butyllithium in the presence of potassium *tert*-butoxide at the 2-position surrounded by the two substituents. After carboxylation and neutralization the lactones **10** (12%) and **11** (47%) and 4-hydroxymethyl-2-(trifluoromethyl)benzoic acid (**12**; 25%) were isolated as pure compounds.

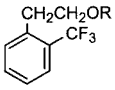
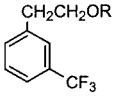
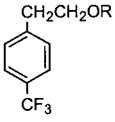


4-(Trifluoromethyl)benzyl alcohol was found to obey the same rules as its 2-isomer. When butyllithium was used as the metalating reagent, the lactone **13** (29%) was formed, whereas 5-hydroxymethyl-2-(trifluoromethyl)benzoic acid (**14**; 36%) was obtained instead with *sec*-butyllithium simultaneously activated by potassium *tert*-butoxide and PMDTA.

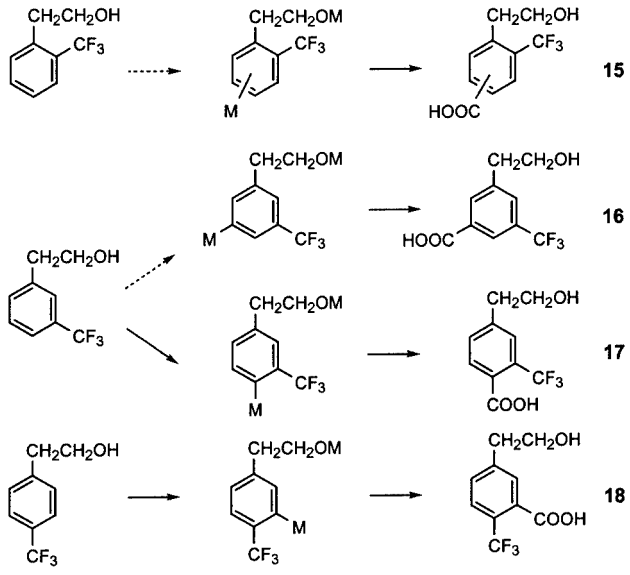


All attempts to convert 2-[(2-trifluoromethyl)phenyl]-ethanol into a well-defined derivative failed. Several isomers **15** were produced simultaneously and in minor quantities. The reaction between 2-[(3-trifluoromethyl)phenyl]ethanol and *sec*-butyllithium in the presence of potassium *tert*-butoxide and PMDTA lacked the usually perfect regioselectivity. Along with the main product [4-(2-hydroxyethyl)-2-(trifluoromethyl)benzoic acid (**17**; 64%)] small amounts of the isomeric 3-(2-hydroxyethyl)-5-(trifluoromethyl)benzoic acid (**16**; 5%) were identified (see Table 4). The structure of the latter compound was assigned on the basis of gas chromatographic comparison with an authentic sample made by a multi-step sequence starting with 3-bromobenzotrifluoride (for details, see Exp. Sect.). Finally, 2-[(4-trifluoromethyl)-phenyl]ethanol gave 5-(2-hydroxyethyl)-2-(trifluoromethyl)-benzoic acid (**18**; 13%) when treated consecutively with the butyllithium/potassium *tert*-butoxide/PMDTA complex and dry ice (see Table 4).

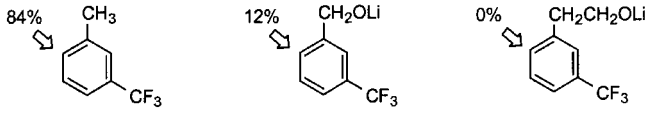
Table 4. Summary of the major results obtained with 2-[2-, 3- and 4-(trifluoromethyl)phenyl]ethyl alcohols

Substrate[a]	Product[b,c]	OR = OLi(OK)	OR = OMOM	OR = OTIPS
	**15**	[d]	[d]	[d]
	**16** (*m,m'*) **17** (*o*-CF_3)	5%[e,f] 64%[e,f]	[d] [d]	[d]
	**18** (*o*-CF_3)	13%[g]	[d]	[d]

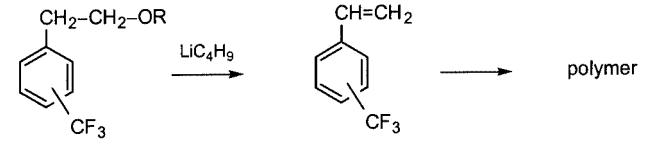
[a] Protective groups: OMOM = OCH_2OCH_3; OTIPS = $OSi(^iC_3H_7)_3$. [b] Regiochemistry: "*m,m'*" means metalation at a position remote from both substituents; "*o*-CF_3" means metalation at a position adjacent to the trifluoromethyl but remote from the *O*-deprotonated hydroxyethyl group. [c] Reaction conditions: metalation in a 7:3 mixture of tetrahydrofuran (THF) and hydrocarbons at −75 °C for 2 h unless stated otherwise. [d] See text (last paragraph of the general part preceding the Exp. Sect.). [e] The isomers **16** and **17** were formed together in a 7:93 ratio. [f] LIS + KOR + PMDTA. [g] LIC + KOR + PMDTA.



No evidence was gained suggesting extensive 1,4- or 1,6-elimination of hydrogen fluoride (as proposed in the introduction). The poor yields obtained with 2- and 4-trifluoromethyl-substituted benzyl and phenethyl alcohols are probably due to aggregate and mixed aggregate formation. Alkyllithiums are known to combine with alkoxides to form association complexes.[21−25] The latter may be too stable to sustain an intramicellar hydrogen/metal transfer. In agreement with this assumption, the metalating reagents were found to be unconsumed to a large extent and most of the starting material that did not show up as a new product was recovered unchanged. Moreover, lithium alkoxides tend to aggregate with themselves to form oligomeric or polymeric clusters.[26−28] The oxygen-functionalized side chain is thus converted into a huge and voluminous substituent that sterically shields the neighboring *ortho* positions. A comparison of the deprotonation efficiencies at the 6-position of 3-(trifluoromethyl)toluene,[12] lithium 3-(trifluoromethylbenzyl alkoxide and lithium 2-[(3-trifluoromethyl)phenyl]ethoxide (see above) is quite revealing in this respect.



Of course we had hoped to improve on the yields in the CF_3-substituted series by switching from the lithium alkoxides to *O*-protected benzyl and phenethyl alcohols. However, regardless of whether MOM- or TIPS-masked derivatives were employed, the results were worse than those reported above with the unprotected precursors. Presumably, the benzyl ethers are too prone to α-deprotonation and subsequent Wittig rearrangement, whereas the phenethyl ethers appear to undergo a 1,2-elimination of H and OR, thus releasing a styrene which polymerizes immediately.



Experimental Section

Generalities: For laboratory routine and abbreviations, see previous articles from this laboratory.[29−30] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, samples being dissolved in deuteriochloroform unless stated otherwise. All mass spectra were produced by chemical ionization ("c.i.") in an ammonia atmosphere at a potential of 96 eV and a source temperature of 100 °C.

1. Starting Materials

All benzyl alcohols and 2-phenylethanols carrying a fluoro atom or a trifluoromethyl group as a ring substituent are commercial, though expensive. They can be readily prepared from the suitable bromofluorobenzene or bromobenzotrifluoride isomer by bromine/lithium permutation and subsequent reaction with paraformaldehyde or oxirane. The following working procedure is representative.

2-(3-Fluorophenyl)ethanol: At −75 °C, 1-bromo-3-fluorobenzene (11 mL, 18 g, 0.10 mol) and oxirane (4.8 mL, 4.2 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (85 mL) and hexanes (65 mL). The mixture was allowed to reach +25 °C and the volatiles were then stripped off. The residue was treated with an excess (0.20 mol) of 5.0 M ethereal hydrochloric acid (40 mL). A colorless liquid was collected upon distillation; b.p. 70−71 °C/2 Torr (ref.:[32] b.p. 90 °C/3 Torr); n_D^{20} = 1.5026; yield: 10.8 g (77%).

All MOM-protected benzyl and phenethyl alcohols were prepared in the same way. Chloromethyl methyl ether[33] (4.6 m, 4.8 g, 60 mmol) was added dropwise, over 15 min, to a solution of the alcohol (50 mmol) and *N*-ethyldiisopropylamine ("Hünig's base"; 17 mL, 13 g, 0.10 mol) in dichloromethane (40 mL), kept at 0 °C. After standing for 2 h at 25 °C, the mixture was poured into a 3.0 M aqueous solution (0.10 L) of sodium hydroxide and extracted with diethyl ether (3 × 25 mL). A colorless liquid was collected upon distillation.

1-Fluoro-2-[(methoxymethoxy)methyl]benzene: From 2-fluorobenzyl alcohol (5.3 mL, 6.3 g, 50 mmol); b.p. 42−43 °C/0.8 Torr; n_D^{20} = 1.4871; d_4^{20} = 1.178; yield: 6.1 g (72%). ^{1}H NMR: δ = 7.40 (t, *J* = 7.4 Hz, 1 H), 7.3 (m, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 8.4 Hz, 1 H), 4.69 (s, 2 H), 4.64 (s, 2 H), 3.39 (s, 3 H) ppm. ^{13}C NMR: δ = 160.8 (d, *J* = 247 Hz), 130.2 (d, *J* = 4 Hz), 129.5 (d, *J* = 8 Hz), 125.0 (d, *J* = 1 4 Hz), 124.0 (d, *J* = 4 Hz), 115.2 (d, *J* = 20 Hz), 95.3 (s), 62.9 (d, *J* = 4 Hz), 55.2 (s) ppm. MS (c.i.): *m/z* (%) = 188 (49) [$M^+ + NH_4$], 170 (8) [M^+], 130 (78), 109 (100). $C_9H_{11}FO_2$ (170.19): calcd. C 63.52, H 6.52; found C 63.52, H 6.47.

1-Fluoro-3-[(methoxymethoxy)methyl]benzene: From 3-fluorobenzyl alcohol (5.4 mL, 6.3 g, 50 mmol); b.p. 44−45 °C/1 Torr; n_D^{20} = 1.4768; d_4^{20} = 1.159; yield: 6.0 g (71%). ^{1}H NMR: δ = 7.30 (m, 1 H), 7.10 (m, 2 H), 6.96 (td, *J* = 8.3, 2.7 Hz, 1 H), 4.70 (s, 2 H), 4.57 (s, 2 H), 3.39 (s, 3 H) ppm. ^{13}C NMR: δ = 163.0 (d, *J* = 246 Hz), 140.7 (d, *J* = 7 Hz), 129.9 (d, *J* = 8 Hz), 123.1 (d, *J* = 2 Hz), 114.5 (d, *J* = 21 Hz), 95.8 (s), 68.4 (s), 55.4 (s) ppm. MS (c.i.): *m/z* (%) = 188 (16) [$M^+ + NH_4$], 170 (21) [M^+], 109 (100). $C_9H_{11}FO_2$ (170.19): calcd. C 63.52, H 6.52; found C 63.78, H 6.56.

1-Fluoro-4-[(methoxymethoxy)methyl]benzene: From 4-fluorobenzyl alcohol (5.4 mL, 6.3 g, 50 mmol); b.p. 76−77 °C/9 Torr (ref.[34] b.p. 55 °C/0.4 Torr); n_D^{20} = 1.4789; d_4^{20} = 1.183; yield: 5.8 g (68%). ^{1}H NMR: δ = 7.32 (dd, *J* = 8.2, 5.3 Hz, 2 H), 7.04 (t, *J* = 8.2 Hz, 2 H), 4.71 (s, 2 H), 4.55 (s, 2 H), 3.41 (s, 3 H) ppm. ^{13}C NMR: δ = 162.4 (d, *J* = 245 Hz), 133.7 (d, *J* = 3 Hz), 129.7 (d, *J* = 9 Hz, 2 C), 115.3 (d, *J* = 21 Hz, 2 C), 95.7 (s), 68.5 (s), 55.4 (s) ppm. MS (c.i.): *m/z* (%) = 188 (21) [$M^+ + NH_4$], 138 (29), 109 (100).

1-Fluoro-2-[2-(methoxymethoxy)ethyl]benzene: From 2-(2-fluorophenyl)ethanol (6.7 mL, 7.0 g, 50 mmol); b.p. 54−55 °C/0.7 Torr; n_D^{20} = 1.4755; d_4^{20} = 1.151; yield: 4.5 g (67%). ^{1}H NMR: δ = 7.27 (t, *J* = 8.4 Hz, 1 H), 7.19 (symm. m, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 7.04 (t, *J* = 9.2 Hz, 1 H), 4.51 (s, 2 H), 3.79 (t, *J* = 7.1 Hz, 2 H), 3.31 (s, 3 H), 2.97 (t, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR: δ = 161.3 (d, *J* = 245 Hz), 131.2 (d, *J* = 5 Hz), 128.0 (d, *J* = 8 Hz), 125.8 (d, *J* = 16 Hz), 123.9 (d, *J* = 3 Hz), 115.2 (d, *J* = 22 Hz), 96.3 (s), 57.0 (s), 55.1 (s), 29.6 (s) ppm. MS (c.i.): *m/z* = 202 (0) [$M^+ + NH_4$], 184 (4) [M^+], 154 (35), 122 (100), 109 (68). $C_{10}H_{13}FO_2$ (184.21): calcd. C 65.20, H 7.11; found C 65.20, H 6.94.

1-Fluoro-3-[2-(methoxymethoxy)ethyl]benzene: From 2-(3-fluorophenyl)ethanol (6.3 mL, 7.0 g, 50 mmol); b.p. 50−52 °C/10 Torr; n_D^{20} = 1.4758; d_4^{20} = 1.160; yield: 4.3 g (69%). ^{1}H NMR: δ = 7.24 (ddd, *J* = 9.8, 8.1, 1.9 Hz, 1 H), 7.01 (d, *J* =7.7 Hz, 1 H), 6.96 (td, *J* = 9.8, 2.1 Hz, 1 H), 6.89 (td, *J* = 8.6, 2.5 Hz, 1 H), 4.61 (s, 2 H), 3.75 (t, *J* = 6.6 Hz, 2 H), 3.28 (s, 3 H), 2.89 (t, *J* = 6.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 162.9 (d, *J* = 245 Hz), 141.6 (d, *J* = 7 Hz), 129.7 (d, *J* = 8 Hz), 124.5 (s), 115.8 (d, *J* = 21 Hz), 113.1 (d, *J* = 21 Hz), 96.4 (s), 67.8 (s), 55.2 (s), 36.0 (s) ppm. MS (c.i.): *m*/*z* (%) = 202 (72) [M^+ + NH_4], 130 (100), 122 (74), 109 (33). $C_{10}H_{13}FO_2$ (184.21): calcd. C 65.20, H 7.11; found C 65.04, H 6.97.

1-Fluoro-4-[2-(methoxymethoxy)ethyl]benzene: From 2-(4-fluorophenyl)ethanol (6.3 mL, 7.0 g, 50 mmol); b.p. 54−55 °C/0.6 Torr; n_D^{20} = 1.4769; d_4^{20} = 1.085; yield: 6.7 g (73%). ^{1}H NMR: δ = 7.19 (ddd, *J* = 7.6, 5.5, 1.8 Hz, 2 H), 6.98 (td, *J* = 8.8, 1.8 Hz, 2 H), 4.61 (s, 2 H), 3.74 (t, *J* = 6.7 Hz, 2 H), 3.29 (s, 3 H), 2.86 (t, *J* = 6.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 161.5 (d, *J* = 244 Hz), 134.7 (s), 130.3 (d, *J* = 8 Hz, 2 C), 115.1 (d, *J* = 21 Hz, 2 C), 96.4 (s), 68.3 (s), 55.1 (s), 35.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 202 (0) [M^+ + NH_4], 122 (100), 109 (76). $C_{10}H_{13}FO_2$ (184.21): calcd. C 65.20, H 7.11; found C 65.24, H 7.10.

The TIPS-protected benzyl and phenethyl alcohols were also prepared according to a general protocol. The alcohol (50 mmol), chlorotriisopropylsilane (13 mL, 12 g, 60 mmol) and imidazole (8.8 g, 0.13 mol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water and extracted with dichloromethane (3 × 20 mL). Distillation under reduced pressure gave a colorless liquid.

(2-Fluorobenzyloxy)triisopropylsilane: From 2-fluorobenzyl alcohol (5.3 mL, 6.3 g, 50 mmol); b.p. 113−115 °C/41 Torr; n_D^{20} = 1.4857; yield: 7.2 g (51%). ^{1}H NMR: δ = 7.57 (t, *J* = 7.8 Hz, 1 H), 7.2 (m, 1 H), 7.14 (t, *J* = 8 Hz, 1 H), 6.98 (t, *J* = 9.8 Hz, 1 H), 4.90 (s, 2 H), 1.2 (m, 3 H), 1.08 (d, *J* = 7.2 Hz, 18 H) ppm. ^{13}C NMR: δ = 159.6 (d, *J* = 239 Hz), 128.8 (d, *J* = 14 Hz), 128.1 (d, *J* = 8 Hz), 127.8 (d, *J* = 4 Hz), 124.0 (d, *J* = 3 Hz), 114.5 (d, *J* = 22 Hz), 59.1 (d, *J* = 5 Hz), 18.1 (s), 12.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 300 (0) [M^+ + NH_4], 283 (4) [M^+ + 1], 282 (2) [M^+], 256 (33), 239 (87), 91 (100). $C_{16}H_{27}FOSi$ (282.47): calcd. C 68.03, H 9.63; found C 68.13, H 9.54.

(3-Fluorobenzyloxy)triisopropylsilane: From 3-fluorobenzyl alcohol (5.4 mL, 6.3 g, 50 mmol); b.p. 139−141 °C/25 Torr; n_D^{20} = 1.4845; yield: 11.7 g (83%). ^{1}H NMR: δ = 7.28 (td, *J* = 7.7, 5.2 Hz, 1 H), 7.1 (m, 2 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 4.83 (s, 2 H), 1.2 (m, 3 H), 1.09 (d, *J* = 6.5 Hz, 18 H) ppm. ^{13}C NMR: δ = 163.1 (d, *J* = 245 Hz), 144.5 (d, *J* = 7 Hz), 129.5 (d, *J* = 8 Hz), 121.0 (s), 113.4 (d, *J* = 22 Hz), 112.5 (d, *J* = 22 Hz), 64.4 (s), 17.9 (s), 12.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 300 (0) [M^+ + NH_4], 283 (5) [M^+ + 1], 282 (2) [M^+], 256 (69), 239 (100). $C_{16}H_{27}FOSi$ (282.47): calcd. C 68.03, H 9.63; found C 67.97, H 9.63.

(4-Fluorobenzyloxy)triisopropylsilane: From 4-fluorobenzyl alcohol (5.4 mL, 6.3 g, 50 mmol); b.p. 134−135 °C/53 Torr; n_D^{20} = 1.4853; yield: 13.1 g (93%). ^{1}H NMR: δ = 7.31 (dd, *J* = 8.5, 5.7 Hz, 2 H), 7.01 (7, *J* = 8.6 Hz, 2 H), 4.79 (s, 2 H), 1.2 (m, 3 H), 1.08 (d, *J* = 6.6 Hz, 18 H) ppm. ^{13}C NMR: δ = 161.9 (d, *J* = 244 Hz), 137.3 (s), 127.2 (d, *J* = 8 Hz), 114.9 (d, *J* = 22 Hz), 64.4 (s), 18.0 (s), 12.0 (s) ppm. MS (c.i.): *m*/*z* (%) = 300 (49) [M^+ + NH_4], 283 (48) [M^+ + 1], 282 (10) [M^+], 256 (72), 190 (100). $C_{16}H_{27}FOSi$ (282.47): calcd. C 68.03, H 9.63; found C 67.96, H 9.47.

[2-(2-Fluorophenyl)ethoxy]triisopropylsilane: From 2-(2-fluorophenyl)ethanol (6.7 mL, 7.0 g, 50 mmol); b.p. 105−106 °C/0.6 Torr; n_D^{20} = 1.4798; yield: 12.8 g (86%). ^{1}H NMR: δ = 7.24 (td, *J* = 6.8, 1.8 Hz, 1 H), 7.16 (tdd, *J* = 7.7, 5.5, 1.9 Hz, 1 H), 7.04 (td, *J* = 7.0, 1.3 Hz, 1 H), 6.99 (ddd, *J* = 10.5, 8.1, 1.1 Hz, 1 H), 3.88 (t, *J* = 6.6 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H), 1.1 (m, 3 H), 1.01 (d, *J* = 5.1 Hz, 18 H) ppm. ^{13}C NMR: δ = 161.4 (d, *J* = 245 Hz), 131.7 (d, *J* = 5 Hz), 127.8 (d, *J* = 8 Hz), 126.0 (d, *J* = 16 Hz), 123.7 (d, *J* = 4 Hz), 115.1 (d, *J* = 22 Hz), 63.2 (s), 32.9 (s), 17.8 (s), 11.8 (s) ppm. MS (c.i.): *m*/*z* (%) = 315 (12) [M^+ + NH_4], 298 (77) [M^+ + 1], 297 (100) [M^+], 253 (100). $C_{17}H_{29}FOSi$ (296.50): calcd. C 68.87, H 9.86; found C 68.66, H 9.81.

[2-(3-Fluorophenyl)ethoxy]triisopropylsilane: From 2-(3-fluorophenyl)ethanol (6.3 mL, 7.0 g, 50 mmol); b.p. 106−107 °C/0.71 Torr; n_D^{20} = 1.4795; yield: 12.6 g (85%). ^{1}H NMR: δ = 7.21 (dd, *J* = 14.1, 7.6 Hz, 1 H), 6.98 (d, *J* = 7.2 Hz, 1 H), 6.94 (d, *J* = 10.1 Hz, 1 H), 6.88 (td, *J* = 8.8, 2.4 Hz, 1 H), 3.88 (t, *J* = 6.6 Hz, 2 H), 2.84 (t, *J* = 6.8 Hz, 2 H), 1.1 (m, 3 H), 1.03 (d, *J* = 5.3 Hz, 18 H) ppm. ^{13}C NMR: δ = 162.4 (d, *J* = 244 Hz), 141.9 (d, *J* = 7 Hz), 129.4 (d, *J* = 8 Hz), 124.8 (s), 116.1 (d, *J* = 21 Hz), 112.9 (d, *J* = 21 Hz), 64.3 (s), 39.4 (s), 17.9 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 315 (2) [M^+ + NH_4], 298 (33) [M^+ + 1], 297 (100) [M^+], 270 (47), 253 (44). $C_{17}H_{29}FOSi$ (296.50): calcd. C 68.87, H 9.86; found C 68.62, H 9.80.

[2-(4-Fluorophenyl)ethoxy]triisopropylsilane: From 2-(4-fluorophenyl)ethanol (6.3 mL, 7.0 g, 50 mmol); b.p. 103−104 °C/0.8 Torr; n_D^{20} = 1.4830; yield: 10.8 g (73%). ^{1}H NMR: δ = 7.16 (dd, *J* = 8.6, 5.5 Hz, 2 H), 6.94 (t, *J* = 8.9 Hz, 2 H), 3.84 (t, *J* = 7.1 Hz, 2 H), 2.81 (t, *J* = 7.2 Hz, 2 H), 1.1 (m, 3 H), 1.04 (d, *J* = 5.4 Hz, 18 H) ppm. ^{13}C NMR: δ = 161.5 (d, *J* = 244 Hz), 135.1 (d, *J* = 3 Hz), 130.5 (d, *J* = 8 Hz), 114.8 (d, *J* = 21 Hz), 64.7 (s), 38.9 (s), 18.1 (s), 12.0 (s) ppm. MS (c.i.): *m*/*z* (%) = 315 (17) [M^+ + NH_4], 298 (87) [M^+ + 1], 297 (100) [M^+], 270 (45), 253 (52). $C_{17}H_{29}FOSi$ (296.50): calcd. C 68.87, H 9.86; found C 68.79, H 9.84.

2. Reactions of Benzyl Alcohols and Derivatives Thereof

Methoxymethoxy (MOM)-Protected Benzyl Alcohols: The acetal (25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA; 5.2 mL, 4.3 g, 25 mmol) in tetrahydrofuran (35 mL) and cyclohexane (15 mL) kept in a dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water and washed with dichloromethane (2 × 25 mL). The aqueous phase was acidified to pH 1 with hydrochloric acid (1.0 M) and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried and the solvents evaporated. The product was purified by crystallization.

2-Fluoro-3-(hydroxymethyl)benzoic Acid (1): From 1-fluoro-2-[(methoxymethoxy)methyl]benzene (3.6 mL, 4.3 g, 25 mmol); colorless needles; m.p. 135−136 °C (from toluene); yield: 1.5 g (36%). ^{1}H NMR (CD_3COCD_3): δ = 7.85 (td, *J* = 7.6, 1.9 Hz, 1 H), 7.78 (tm, *J* = 7.3 Hz, 1 H), 7.29 (t, *J* = 7.7 Hz, 1 H), 4.79 (s, 1 H) ppm. ^{13}C NMR (CD_3COCD_3): δ = 165.6 (d, *J* = 2 Hz), 160.0 (d, *J* = 259 Hz), 134.1 (d, *J* = 6 Hz), 131.7 (d, *J* = 15 Hz), 131.5 (s), 124.6 (d, *J* = 4 Hz), 119.6 (d, *J* = 10 Hz), 58.2 (d, *J* = 6 Hz) ppm. MS (c.i.): *m*/*z* (%) = 188 (100) [M^+ + NH_4], 170 (6) [M^+], 123 (20). $C_8H_7FO_3$ (170.14): calcd. C 56.48, H 4.15; found C 56.46, H 4.29.

2-Fluoro-4-(hydroxymethyl)benzoic Acid (3): From 1-fluoro-3-[(methoxymethoxy)methyl]benzene (3.7 mL, 4.2 g, 25 mmol); colorless needles (from toluene); m.p. 173.5−175 °C; yield: 0.6 g (15%). ^{1}H NMR (CD_3COCD_3): δ = 7.93 (t, *J* = 7.7 Hz, 1 H), 7.28 (d, *J* = 7.3 Hz, 1 H), 7.26 (d, *J* = 12.7 Hz, 1 H), 4.74 (s, 2 H) ppm.

^{13}C NMR (CD_3COCD_3): δ = 165.3 (d, *J* = 4 Hz), 163.0 (d, *J* = 258 Hz), 151.7 (d, *J* = 8.0 Hz), 133.0 (s), 124.4 (d, *J* = 3 Hz), 117.9 (d, *J* = 11 Hz), 115.0 (d, *J* = 23 Hz), 63.4 (s) ppm. MS (c.i.): *m*/*z* (%) = 188 (100) [$M^+ + NH_4$], 170 (19) [M^+], 123 (17). $C_8H_7FO_3$ (170.14): calcd. C 56.48, H 4.15; found C 56.41, H 4.09.

2-Fluoro-5-(hydroxymethyl)benzoic Acid (4): From 1-fluoro-4-[(methoxymethoxy)methyl]benzene (3.6 mL, 4.2 g, 25 mmol); colorless needles (from hexanes); m.p. 136.5−138 °C; yield: 2.4 g (56%). ^{1}H NMR (CD_3COCD_3): δ = 7.96 (dd, *J* = 7.1, 2.4 Hz, 1 H), 7.6 (m, 1 H), 7.21 (dd, *J* = 10.8, 8.5 Hz, 1 H), 4.68 (s, 2 H) ppm. ^{13}C NMR (CD_3COCD_3): δ = 165.6 (d, *J* = 2 Hz), 161.7 (d, *J* = 257 Hz), 139.4 (d, *J* = 3 Hz), 133.6 (d, *J* = 9 Hz), 131.0 (s), 119.4 (d, *J* = 10 Hz), 117.4 (d, *J* = 22 Hz), 63.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 188 (100) [$M^+ + NH_4$], 170 (7), [M^+], 123 (20). $C_8H_7FO_3$ (170.14): calcd. C 56.48, H 4.15; found C 56.25, H 4.58.

7-Fluoroisobenzofuran-1(3*H*)-one (2): The reaction was performed with 1-fluoro-3-[(methoxymethoxy)methyl]benzene (3.7 mL, 4.2 g, 25 mmol) and *sec*-butyllithium (25 mmol) in the absence of any additive and worked up as described above; colorless cubes (from toluene); m.p. 164−166 °C (ref.[35] m.p. 166−167 °C); yield: 1.1 g (29%). ^{1}H NMR: δ = 7.69 (td, *J* = 8.0, 4.5 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 5.33 (s, 2 H) ppm. ^{13}C NMR: δ = 159.8 (d, *J* = 264 Hz), 149.2 (s), 136.7 (d, *J* = 8 Hz), 118.1 (d, *J* = 4 Hz), 116.1 (d, *J* = 19 Hz), 95.3 (s), 69.3 (s) ppm. MS (c.i.): *m*/*z* (%) = 170 (100) [$M^+ + NH_4$], 153 (27), [$M^+ + 1$], 123 (51).

Triisopropylsilyl (TIPS)-Protected Benzyl Alcohols: The reactions were carried out as described above (see the preparation of acid **1**) unless stated otherwise. After evaporation of the volatiles, the alkaline phase was treated with a 10% aqueous solution (20 mL) of acetic acid and extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried and the solvents evaporated. Crystallization from a mixture of ethyl acetate and hexanes or neat hexanes afforded the fluoro(triisopropylsilyloxymethyl)benzoic acids as colorless needles. Quantitative deprotection was achieved by dissolving the product (15 mmol) in dichloromethane (15 mL) and adding boron trifluoride diethyl etherate (2.1 g, 1.9 mL, 15 mmol). After 1 h at 25 °C, methanol (1 mL) was added and the solvents were evaporated to dryness. The resulting benzoic acid or lactone was crystallized as specified above.

2-Fluoro-3-[(triisopropylsilyloxy)methyl]benzoic Acid (*O*-TIPS protected acid 1): From (2-fluorobenzyloxy)triisopropylsilane (7.1 g, 25 mmol); colorless needles; m.p. 81−83 °C; yield: 5.0 g (61%). ^{1}H NMR: δ = 7.91 (t, *J* = 7.3 Hz, 1 H), 7.85 (t, *J* = 7.1 Hz, 1 H), 7.2 (m, 1 H), 4.93 (s, 2 H), 1.2 (m, 3 H), 1.10 (d, *J* = 7 Hz, 18 H) ppm. ^{13}C NMR: δ = 169.1 (s), 159.2 (d, *J* = 261 Hz), 133.4 (d, *J* = 6 Hz), 130.9 (s), 130.6 (d, *J* = 14 Hz), 123.9 (d, *J* = 4 Hz), 116.7 (d, *J* = 10 Hz), 58.8 (d, *J* = 7 Hz), 18.0 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 344 (1) [$M^+ + NH_4$], 327 (12) [$M^+ + 1$], 326 (5) [M^+], 283 (100), 133 (76).

2-Fluoro-6-[(triisopropylsilyloxy)methylbenzoic Acid (*O*-TIPS-protected hydrolysis product of lactone 2): At −75 °C, (3-fluorobenzyloxy)triisopropylsilane (7.1 g, 25 mmol) was treated for 2 h with *sec*-butyllithium (25 mmol) and PMDTA (5.2 mL, 4.3 g, 25 mmol) in the presence of potassium *tert*-butoxide (2.8 g, 25 mmol). According to gas chromatography (30 m, DB-1701, 180 °C; 2 m, 5% SE-30 200 °C; internal standard: methyl benzoate) the raw material (yield: 85%) isolated after the usual workup (see preparation of acid **1**) contained small amounts of the TIPS-protected acid **3**. This isomeric contamination was lost completely upon crystallization; m.p. 65−67 °C; yield: 4.2 g (51%). ^{1}H NMR: δ = 7.3 (m, 2 H), 6.9 (m, 1 H), 4.80 (s, 2 H), 1.54 (hept, *J* = 7.2 Hz, 3 H), 1.13 (d, *J* = 7.3 Hz, 18 H) ppm. ^{13}C NMR: δ = 179.6 (s), 167.8 (d, *J* = 240 Hz), 149.3 (d, *J* = 5 Hz), 131.1 (d, *J* = 10 Hz), 123.8 (s), 114.4 (d, *J* = 30 Hz), 110.4 (d, *J* = 24 Hz), 65.2 (s), 19.1 (s), 13.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 344 (11) [$M^+ + NH_4$], 327 (14) [$M^+ + 1$], 301 (62), 300 (100).

2-Fluoro-4-[(triisopropylsilyloxy)methyl]benzoic Acid (*O*-TIPS-protected acid 3): From (3-fluorobenzyloxy)triisopropylsilane (7.1 g, 25 mmol); colorless needles; m.p. 135−136 °C; yield: 2.5 g (31%; raw material, according to gas chromatography: 51% and 29% of *O*-TIPS protected acid **3** and hydrolysate of lactone **2**, respectively). ^{1}H NMR: δ = 8.02 (t, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 12.6 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 4.88 (s, 2 H), 1.2 (m, 3 H), 1.09 (d, *J* = 6.6 Hz, 18 H) ppm. ^{13}C NMR: δ = 169.0 (s), 162.9 (d, *J* = 262 Hz), 151.1 (d, *J* = 8 Hz), 132.6 (s), 120.8 (d, *J* = 3 Hz), 115.6 (d, *J* = 10 Hz), 114.0 (d, *J* = 23 Hz), 64.1 (s), 18.0 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 344 (100) [$M^+ + NH_4$], 327(28) [$M^+ + 1$], 300 (52).

2-Fluoro-5-[(triisopropylsilyloxy)methyl]benzoic Acid (*O*-TIPS-protected acid 4): From (4-fluorobenzyloxy)triisopropylsilane (7.1 g, 25 mmol); colorless prisms; m.p. 72−74 °C; yield: 6.9 g (84%). ^{1}H NMR: δ = 8.00 (dd, *J* = 7.1, 2.6 Hz, 1 H), 7.6 (m, 1 H), 7.15 (dd, *J* = 10.3, 8.2 Hz, 1 H), 4.89 (s, 2 H), 1.2 (m, 3 H), 1.09 (d, *J* = 6.1 Hz, 18 H) ppm. ^{13}C NMR: δ = 170.0 (s), 161.6 (d, *J* = 261 Hz), 137.6 (d, *J* = 3 Hz), 132.9 (d. *J* = 8 Hz), 129.8 (s), 117.1 (s), 116.9 (s), 63.9 (s), 17.9 (s), 12.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 344 (100) [$M^+ + NH_4$], 327(13) [$M^+ + 1$], 326 (6) [M^+].

Unprotected Benzyl Alcohols: The reactions were carried out as described for the preparation of acid **1** although with different metalating reagents. The workup procedure was always the same (as indicated above). The 2-fluorobenzyl alcohol failed to give any useful result.

2-Fluoro-4-(hydroxymethyl)benzoic Acid (3): From 3-fluorobenzyl alcohol (2.7 mL, 3.1 g, 25 mmol) with *sec*-butyllithium (50 mmol), PMDTA (11 mL, 8.7 g, 50 mmol) and potassium *tert*-butoxide (5.6 g, 50 mmol). According to gas chromatography (30 m, DB-1701, 150 °C; 2 m, 5% SE-30 180 °C; internal standard: methyl benzoate) the raw material isolated contained 12% of lactone **2** along with 71% of acid **3**. The by-product was removed upon crystallization from chloroform; yield: 2.0 g (47%).

2-Fluoro-5-(hydroxymethyl)benzoic Acid (4): From 4-fluorobenzyl alcohol (2.7 mL, 3.1 g, 25 mmol) with butyllithium (75 mmol), PMDTA (15.7 mL, 13.0 g, 75 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol); yield: 2.1 g (49%).

4-(Trifluoromethyl)isobenzofuran-1(3*H*)-one (8): From 2-(trifluoromethyl)benzyl alcohol (3.3 mL, 4.4 g, 25 mmol) in tetrahydrofuran (50 mL) and butyllithium (75 mmol) in hexanes (50 mL); for 2 h at +25 °C; colorless prisms; m.p. 79−81 °C (after sublimation); yield: 1.2 g (24%). ^{1}H NMR: δ = 8.29 (d, *J* = 7.8 Hz, 1 H), 8.09 (d, *J* = 7.8 Hz, 1 H), 7.87 (t, *J* = 7.8 Hz, 1 H), 5.58 (s, 2 H) ppm. ^{13}C NMR: δ = 169.4 (s), 143.7 (s), 130.9 (q, *J* = 4 Hz), 129.9 (s), 129.4 (s), 127.4 (s), 125.6 (q, *J* = 34 Hz), 123.3 (q, *J* = 272 Hz), 69.6 (s) ppm. MS (c.i.): *m*/*z* (%) = 220 (100) [$M^+ + NH_4$], 203 (5) [$M^+ + 1$], 202 (1) [M^+], 173 (40), 145 (63). $C_9H_5F_3O_2$ (202.13): calcd. C 53.48, H 2.49; found C 53.69, H 2.27.

3-(Hydroxymethyl)-2-(trifluoromethyl)benzoic Acid (9): From 2-(trifluoromethyl)benzyl alcohol (3.3 mL, 4.4 g, 25 mmol) with butyllithium (75 mmol) PMDTA (15.7 mL, 13.0 g, 75 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol); colorless needles; m.p.

190−192 °C (from chloroform); yield: 1.8 g (33%). ^{1}H NMR (D_3CCOCD_3): δ = 8.01 (d, *J* = 7.9 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 4.89 (s, 2 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 168.7 (s), 142.3 (s), 133.8 (m), 131.9 (s), 129.4 (s), 126.6 (s), 124.3 (q, *J* = 275 Hz), 60.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 238 (100) [$M^+ + NH_4$], 220 (8) [M^+], 134 (16). $C_9H_9F_3O_3$ (220.15): calcd. C 49.10, H 3.20; found C 49.07, H 3.00.

5-(Trifluoromethyl)isobenzofuran-1(3*H*)-one (10): From 3-(trifluoromethyl)benzyl alcohol (3.4 mL, 4.4 g, 25 mmol) in tetrahydrofuran (60 mL) with *tert*-butyllithium (75 mmol) in pentanes (65 mL). As revealed by gas chromatography (2 m, C-20M 180 °C; 2 m, 5% SE-30, 150 °C; internal standard: methyl benzoate). The amount of 5-(trifluoromethyl)-2-benzofuran-1(3*H*)-one **(10)** and of 7-(trifluoromethyl)-2-benzofuran-1(3*H*)-one (**11**) formed was determined by comparison of their peak areas with that of the internal standard. The yields found were 26% and 21% for **10** and **11**, respectively. The rest of the solution after evaporation of the solvents, three crystallizations of the crude material from hexanes, and sublimation, gave colorless platelets; m.p. 65−67 °C (ref.[36] no physical constants or analysis reported); yield: 0.6 g (12%). ^{1}H NMR: δ = 8.21 (d, *J* = 8.2 Hz, 1 H), 7.97 (d, *J* = 10.4 Hz, 1 H), 7.96 (s, 1 H), 5.51 (s, 2 H) ppm. ^{13}C NMR: δ = 169.6 (s), 146.8 (s), 136.1 (q, *J* = 33 Hz), 129.0 (s), 126.6 (s), 126.5 (q, *J* = 3 Hz), 123.4 (q, *J* = 273 Hz), 119.7 (q, *J* = 3 Hz), 69.6 (s) ppm. MS (c.i.): *m*/*z* (%) = 220 (0) [$M^+ + NH_4$], 203 (28) [$M^+ + 1$], 202 (6) [M^+], 173 (100), 145 (27), 125 (6). $C_9H_5F_3O_2$ (202.13): calcd. C 53.48, H 2.49; found C 53.61, H 2.49.

7-(Trifluoromethyl)-2-benzofuran-1(3*H*)-one (11): From 3-(trifluoromethyl)benzyl alcohol (3.4 mL, 4.4 g, 25 mmol) with potassium *tert*-butoxide (5.6 g, 50 mmol) and butyllithium (from which the commercial solvent was stripped off, 50 mmol) in tetrahydrofuran (50 mL) at 0 °C for 2 h. Colorless needles, m.p. 112−114 °C (from hexanes); yield: 2.4 g (47%). ^{1}H NMR: δ = 7.99 (d, *J* = 7.3 Hz, 1 H), 7.96 (t, *J* = 7.3 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 5.47 (s, 2 H) ppm. ^{13}C NMR: δ = 166.9 (s), 148.9 (s), 134.0 (s), 128.8 (q, *J* = 36 Hz), 126.7 (q, *J* = 5 Hz), 125.9 (s), 122.2 (q, *J* = 273 Hz), 123.1 (s), 68.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 220 (100) [$M^+ + NH_4$], 203 (31) [$M^+ + 1$], 202 (10) [M^+], 173 (54). $C_9H_5F_3O_2$ (202.13): calcd. C 53.48, H 2.49; found C 53.62; H 2.57.

4-(Hydroxymethyl)-2-(trifluoromethyl)benzoic Acid (12): From 3-(trifluoromethyl)benzyl alcohol (3.4 mL, 4.4 g, 25 mmol) with *sec*-butyllithium (75 mmol), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (15.7 mL, 13.0 g, 75 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol) in tetrahydrofuran (70 mL) and cyclohexane (55 mL) colorless needles were obtained; m.p. 129−131 °C; yield: 1.4 g (25%). ^{1}H NMR (CD_3COCD_3): δ 7.91 (d, *J* = 7.9 Hz, 1 H), 7.86 (s, 1 H), 7.74 (dd, *J* = 8.1, 0.7 Hz, 1 H), 4.91 (s, 2 H) ppm. ^{13}C NMR (CD_3COCD_3): δ = 166.8 (s), 146.6 (s), 130.4 (s), 130.0 (s), 129.6 (s), 127.9 (q, *J* = 32 Hz), 124.2 (q, *J* = 5 Hz), 123.7 (q, *J* = 273 Hz), 62.6 (s) ppm. MS (c.i.): *m*/*z* (%) = 238 (100) [$M^+ + NH_4$], 220 (11) [M^+], 151 (45), 127 (43). $C_9H_9F_3O_3$ (220.15): calcd. C 49.10, H 3.20; found C 48.81, H 3.13.

6-(Trifluoromethyl)isobenzofuran-1(3*H*)-one (13): From 4-(trifluoromethyl)benzyl alcohol (3.4 mL, 4.4 g, 25 mmol) in tetrahydrofuran (50 mL) and butyllithium (75 mmol) in hexanes; for 2 h at +25 °C; white powder; m.p. 88−90 °C (after sublimation); yield: 1.5 g (29%). ^{1}H NMR: δ = 8.36 (s, 1 H), 8.10 (dd, *J* = 8.1, 1 Hz, 1 H), 7.82 (d, *J* = 8.3 Hz, 1 H), 5.51 (s, 2 H) ppm. ^{13}C NMR: δ = 169.5 (s), 149.7 (s), 132.2 (q, *J* = 33 Hz), 130.9 (q, *J* = 2 Hz), 126.7 (s), 123.2 (q, *J* = 3 Hz), 123.1 (q, *J* = 3 Hz), 123.4 (q, *J* = 272 Hz), 69.6 (s) ppm. MS (c.i.): *m*/*z* (%) = 220 (37) [$M^+ + NH_4$], 203 (37) [$M^+ + 1$], 202 (8) [M^+], 173 (100), 145 (28). $C_9H_5F_3O_2$ (202.13): calcd. C 53.48, H 2.49, found C 53.42, H 2.44.

5-(Hydroxymethyl)-2-(trifluoromethyl)benzoic Acid (14): From 4-(trifluoromethyl)benzyl alcohol (3.4 mL, 4.4 g, 25 mmol) as described above for compound **12**; colorless needles; m.p. 143−145 °C (from chloroform); yield: 2.0 g (36%). ^{1}H NMR (CD_3COCD_3): δ = 7.89 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.71 (dm, *J* = 8.4 Hz, 1 H), 4.81 (s, 2 H) ppm. ^{13}C NMR (CD_3COCD_3): δ = 167.0 (s), 147.4 (s), 131.7 (s), 128.6 (s), 127.7 (s), 126.6 (s), 126.5 (q, *J* = 5 Hz, 2 C), 123.8 (q, *J* = 272 Hz), 62.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 238 (100) [$M^+ + NH_4$], 220 (40) [M^+], 151 (16). $C_9H_9F_3O_3$ (220.15): calcd. C 49.10, H 3.20; found C 49.04, H 3.08.

3. Reactions of Phenethyl Alcohols and Derivatives Thereof

Methoxymethoxy (MOM)-Protected 2-(Fluorophenyl)ethanols: The acetal (25 mmol) was again treated with *sec*-butyllithium (25 mmol) and PMDTA (5.4 mL, 4.3 g, 25 mmol) in tetrahydrofuran (35 mL) and cyclohexane (16 mL) at −75 °C, but for 6 h. The quenching with dry ice and the workup followed exactly the procedure established for MOM-protected alcohols (see the first paragraph of Section 2). The product was purified by recrystallization from hexanes and sublimation.

2-Fluoro-3-(2-hydroxyethyl)benzoic Acid (5): From 1-fluoro-2-[2-(methoxymethoxy)ethyl]benzene (4.0 mL, 4.6 g, 25 mmol); white needles; m.p. 116−117 °C; yield: 1.6 g (35%). ^{1}H NMR: δ = 7.94 (t, *J* = 6.4 Hz, 1 H), 7.58 (t, *J* = 6.4 Hz, 1 H), 7.25 (t, *J* = 7.9 Hz, 1 H), 3.89 (t, *J* = 6.7 Hz, 2 H), 2.99 (t, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 166.4 (s), 160.4 (d, *J* = 258 Hz), 135.7 (d, *J* = 6 Hz), 130.4 (s), 127.4 (d, *J* = 17 Hz), 123.4 (d, *J* = 4 Hz), 119.2 (d, *J* = 10 Hz), 61.6 (s), 32.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 202 (100) [$M^+ + NH_4$], 185 (6) [$M^+ + 1$], 164 (85), 109 (50). $C_9H_9FO_3$ (184.17): calcd. C 58.70, H 4.93; found C 58.78, H 4.77.

2-Fluoro-4-(2-hydroxyethyl)benzoic Acid (6): From 1-fluoro-3-2-[(methoxymethoxy)ethyl]benzene (4.0 mL, 4.6 g, 25 mmol); colorless platelets; m.p. 122−123 °C; yield: 1.6 g (39%). ^{1}H NMR: δ = 7.78 (t, *J* = 7.9 Hz, 1 H), 7.2 (m, 2 H), 3.64 (t, *J* = 6.7 Hz, 2 H), 2.79 (t, *J* = 6.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 165.4 (d, *J* = 3 Hz), 161.5 (d, *J* = 256 Hz), 148.3 (d, *J* = 8 Hz), 132.0 (s), 125.4 (d, *J* = 3 Hz), 117.5 (d, *J* = 22 Hz), 117.1 (d, *J* = 10 Hz), 61.6 (s), 39.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 202 (1) [$M^+ + NH_4$], 185 (15), [$M^+ + 1$], 184 (48), [M^+], 154 (79), [$M^+ - COOH$], 109 (100). $C_9H_9FO_3$ (184.17): calcd. C 58.70, H 4.93; found C 58.67, H 4.76.

2-Fluoro-5-(2-hydroxyethyl)benzoic Acid (7): From 1-fluoro-4-[2-(methoxymethoxy)ethyl]benzene (4.2 mL, 4.6 g, 25 mmol); colorless needles; m.p. 133−134.5 °C; yield: 3.2 g (70%). ^{1}H NMR: δ = 7.83 (dd, *J* = 7.1, 2.2 Hz, 1 H), 7.39 (ddd, *J* = 7.1, 4.6, 2.2 Hz, 1 H), 7.06 (td, *J* = 10.3, 8.2 Hz, 1 H), 3.83 (t, *J* = 6.6 Hz, 2 H), 2.86 (t, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 166.2 (s), 160.7 (d, *J* = 257 Hz), 135.1 (d, *J* = 4 Hz), 134.8 (d, *J* = 8 Hz), 132.5 (s), 118.9 (d, *J* = 10 Hz), 116.6 (d, *J* = 22 Hz), 62.8 (s), 38.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 202 (0) [$M^+ + NH_4$], 184 (11) [M^+], 154 (100) [$M^+ - COOH$], 133 (31), 109 (73). $C_9H_9FO_3$ (184.17): calcd. C 58.70, H 4.93; found C 58.75, H 5.13.

Triisopropylsilyl(TIPS)-Protected 2-(Fluorophenyl)ethanols: The reaction, workup and deprotection conditions were identical to those specified above for TIPS-protected benzyl alcohols as the substrates (PMDTA-activated *sec*-butyllithium in a 2:1 mixture of tetrahydrofuran and cyclohexane for 2 h at −75 °C, carboxylation, extraction, treatment with boron trifluoride and recrystallisation from ethyl acetate and hexanes).

2-Fluoro-3-[(triisopropylsilyloxy)ethyl]benzoic Acid (*O*-TIPS protected acid 5): From [2-(2-fluorophenyl)ethoxy]triisopropylsilane (7.4 g, 25 mmol); colorless prisms; m.p. 75−76 °C; yield: 5.7 g (67%). ^{1}H NMR: δ = 7.88 (td, *J* = 7.8, 1.9 Hz, 1 H), 7.52 (td, *J* = 7.7, 2.1 Hz, 1 H), 7.15 (t, *J* = 7 Hz, 1 H), 3.91 (t, *J* = 6.5 Hz, 2 H), 2.94 (td, *J* = 7.1, 1.3 Hz, 2 H), 1.1 (m, 3 H), 1.00 (d, *J* = 5.6 Hz, 18 H) ppm. ^{13}C NMR: δ = 169.9 (s), 160.9 (d, *J* = 261 Hz), 137.6 (d, *J* = 6 Hz), 130.7 (s), 128.0 (d, *J* = 17 Hz), 123.4 (d, *J* = 4 Hz), 117.3 (d, *J* = 11 Hz), 62.8 (s), 32.7 (s), 17.9 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 358 (89) [$M^+ + NH_4$], 342 (55) [$M^+ + 1$], 341 (100) [M^+].

2-Fluoro-4-[(triisopropylsilyloxy)ethyl]benzoic Acid (*O*-TIPS protected acid 6): From [2-(3-fluorophenyl)ethoxy]triisopropylsilane (7.4 g, 25 mmol); colorless platelets; m.p. 102−103 °C; yield: 6.0 g (71%). ^{1}H NMR: δ = 7.94 (t, *J* = 7.8 Hz, 1 H), 7.11 (dd, *J* = 9.4, 1.6 Hz, 1 H), 7.07 (d, *J* = 12.1 Hz, 1 H), 3.92 (t, *J* = 6.1 Hz, 2 H), 2.88 (t, *J* = 6.5 Hz, 2 H), 1.1 (m, 3 H), 1.01 (d, *J* = 5.8 Hz, 18 H) ppm. ^{13}C NMR: δ = 169.1 (s), 162.6 (d, *J* = 262 Hz), 149.0 (d, *J* = 9 Hz), 132.4 (s), 125.1 (d, *J* = 3 Hz), 117.6 (d, *J* = 22 Hz), 115.1 (d, *J* = 10 Hz), 63.6 (s), 39.4 (s), 17.9 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 358 (39) [$M^+ + NH_4$], 341 (36) [M^+], 297 (100).

2-Fluoro-5-[(triisopropylsilyloxy)ethyl]benzoic Acid (*O*-TIPS protected acid 7): From From [2-(4-fluorophenyl)ethoxy]triisopropylsilane (7.4 g, 25 mmol); colorless needles; m.p. 57−59 °C; yield: 6.6 g (77%). ^{1}H NMR: δ = 7.89 (dd, *J* = 7.3, 2.4 Hz, 1 H), 7.45 (ddd, *J* = 7.1, 4.7, 2.3 Hz, 1 H), 7.07 (dd, *J* = 10.5, 8.1 Hz, 1 H), 3.89 (t, *J* = 6.6 Hz, 2 H), 2.85 (t, *J* = 6.4 Hz, 2 H), 1.0 (m, 3 H), 1.01 (d, *J* = 5.1 Hz, 18 H) ppm. ^{13}C NMR: δ = 169.5 (s), 161.3 (d, *J* = 261 Hz), 136.5 (d, *J* = 9 Hz), 135.6 (d, *J* = 5 Hz), 133.1 (s), 116.9 (d, *J* = 10 Hz), 116.7 (d, *J* = 22 Hz), 64.1 (s), 38.6 (s), 17.9 (s), 11.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 358 (100) [$M^+ + NH_4$], 341 (46) [M^+], 314 (24).

Unprotected 2-(Fluorophenyl)ethanols: 2,2,6,6-Tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol) and the alcohol (25 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (40 mL) and hexanes (30 mL) cooled in a dry ice/methanol bath and kept at −75 °C for 6 h. The carboxylation, isolation and purification of the final products were accomplished as described at the beginning of Section 2.

2-Fluoro-3-(2-hydroxyethyl)benzoic Acid (5): From 2-(2-fluorophenyl)ethanol (3.4 mL, 3.5 g, 25 mmol); yield: 1.6 g (31%).

2-Fluoro-4-(2-hydroxyethyl)benzoic Acid (6): From 2-(3-fluorophenyl)ethanol (3.1 mL, 3.5 g, 25 mmol); yield: 2.8 g (61%).

2-Fluoro-5-(2-hydroxyethyl)benzoic Acid (7): From 2-(4-fluorophenyl)ethanol (3.1 mL, 3.5 g, 25 mmol); yield 2.0 (43%).

Unprotected 2-[Tri(fluoromethyl)phenyl]ethanols: The metalation was brought about by butyllithium or *sec*-butyllithium simultaneously activated by PMDTA and potassium *tert*-butoxide in tetrahydrofuran (90 mL) and cyclohexane (35 mL) or hexanes (35 mL) at −75 °C for 2 h. Carboxylation and isolation followed the standard procedure (see at the beginning of Section 2). The *ortho* isomer gave a mixture of three unidentified products formed in roughly equal amounts and in a total yield of 46% (by gas chromatography).

4-(2-Hydroxyethyl)-2-(trifluoromethyl)benzoic Acid (17): From 2-[3-(trifluoromethyl)phenyl]ethanol (3.8 mL, 4.7 g, 25 mmol); with *sec*-butyllithium (50 mmol), PMDTA (10.4 mL, 8.7 g, 50 mmol) and potassium *tert*-butoxide (5.6 g, 50 mmol). According to gas chromatography (30 m, DB-1701, 150 °C isotherm; 2 m, 5% SE-30, 200 °C; internal standard: methyl benzoate) of the methyl esters (after exhaustive reaction with diazomethane), the principal product **17** (64%) was accompanied by small amounts of the isomer **16** (5%) which was identified by comparison of its retention times with those of an authentic sample (see below). Colorless stars; m.p. 116−118 °C (from ethyl acetate and hexanes); yield: 2.1 g (36%). ^{1}H NMR (D_3CCOCD_3): δ = 7.83 (d, *J* = 8.1 Hz, 1 H), 7.75 (s, 1 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 3.84 (t, *J* = 6.3 Hz, 2 H), 2.96 (t, *J* = 6.3 Hz, 2 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 166.9 (s), 144.2 (s), 132.7 (s), 130.3 (s), 129.3 (s), 126.6 (s), 127.8 (q, *J* = 32 Hz), 127.3 (q, *J* = 5 Hz), 123.7 (q, *J* = 273 Hz), 62.0 (s), 38.6 (s) ppm. MS (c.i.): *m*/*z* (%) = 253 (100), 252 (90) [$M^+ + NH_4$], 234 (3) [M^+], 186 (23). $C_9H_9F_3O_3$ (234.17): calcd. C 53.48, H 2.49; found C 53.69, H 2.27.

5-(2-Hydroxyethyl)-2-(trifluoromethyl)benzoic Acid (18): From 2-[4-(trifluoromethyl)phenyl]ethanol (3.9 mL, 4.7 g, 25 mmol) with butyllithium (75 mmol), PMDTA (15.7 mL, 13.0 g, 75 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol). Colorless needles; m.p. 99−101 °C (from chloroform); yield: 0.78 g (13%). ^{1}H NMR (D_3CCOCD_3): δ = 7.80 (s, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 3.85 (t, *J* = 5.9 Hz, 2 H), 2.96 (t, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 167.2 (s), 144.9 (s), 131.8 (s, 2 C), 130.8 (s), 126.4 (q, *J* = 6 Hz), 125.6 (q, *J* = 32 Hz), 121.2 (q, *J* = 272 Hz), 61.9 (s), 38.4 (s) ppm. MS (c.i.): *m*/*z* (%) = 252 (33) [$M^+ + NH_4$], 217 (19), 186 (44), 164 (100). $C_9H_9F_3O_3$ (234.17): calcd. C 53.48, H 2.49; found C 53.69, H 2.27.

3-(2-Hydroxyethyl)-5-(trifluoromethyl)benzoic Acid (16): 2,2,6,6-Tetramethylpiperidine (25 mL, 21 g, 0.15 mol) and 3-bromobenzotrifluoride (21 mL, 34 g, 0.15 mol) were added consecutively to a solution of butyllithium in tetrahydrofuran (0.20 L) and hexanes (90 mL) cooled to −100 °C. After 2 h at −100 °C, the mixture was treated with iodine (38 g, 0.15 mol) in tetrahydrofuran (50 mL). Distillation afforded 2-bromo-1-iodo-4-(trifluoromethyl)benzene, which eventually crystallized as colorless needles; m.p. 31−33 °C; b.p. 80−82 °C/10 Torr; yield: 43.1 g (82%). ^{1}H NMR: δ = 8.00 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 1.4 Hz, 1 H), 7.24 (dd, *J* = 8.2, 1.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 140.8 (s), 144.9 (s), 132.0 (q, *J* = 33 Hz), 130.5 (s), 129.4 (q, *J* = 4 Hz), 129.4 (q, *J* = 4 Hz), 124.9 (q, *J* = 3 Hz), 123.0 (q, *J* = 273 Hz), 106.0 (s) ppm. MS (c.i.): *m*/*z* (%) = 370 (0) [$M^+ + NH_4$], 368 (0) [$M^+ + NH_4$], 353 (14) [$M^+ + 1$], 352 (93) [M^+], 351 (12) [$M^+ + 1$], 350 (100) [M^+], 144 (36). $C_7H_3BrF_3I$ (350.91): calcd. C 23.96, H 0.86; found C 24.11, H 1.11. Diisopropylamine (14 mL, 10 g, 0.10 mol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (35 g, 0.10 mol) were added consecutively to a solution of butyllithium in tetrahydrofuran (0.14 L) and hexanes (60 mL) cooled to −100 °C and kept at that temperature for 2 h. After neutralization and distillation, 1-bromo-3-iodo-5-(trifluoromethyl)benzene was collected as a colorless liquid; m.p. −20 to −15 °C; b.p. 64−66 °C/2 Torr; n_D^{20} = 1.5584; yield: 23.2 g (66%). ^{1}H NMR: δ = 8.04 (s, 1 H), 7.88 (s, 1 H), 7.33 (s, 1 H) ppm. ^{13}C NMR: δ = 143.2 (s), 133.6 (q, *J* = 34 Hz), 133.0 (q, *J* = 4 Hz), 128.0 (q, *J* = 4 Hz), 123.3 (s), 122.0 (q, *J* = 274 Hz), 94.3 (s) ppm. MS (c.i.): *m*/*z* (%) = 370 (5) [$M^+ + NH_4$], 368 (30) [$M^+ + NH_4$], 352 (69) [M^+], 350 (69) [M^+], 288 (57), 287 (52). $C_7H_3BrF_3I$ (350.91): calcd. C 23.96, H 0.86; found C 23.83, H 0.96. At −75 °C, 1-bromo-3-iodo-5-(trifluoromethyl)benzene (18 g, 50 mmol) in precooled tetrahydrofuran (70 mL) was added to butyllithium (50 mmol) in hexanes (30 mL). Immediately afterwards, the mixture was poured onto an excess of freshly crushed dry ice. Extraction into the alkaline phase, acidification, extraction with diethyl ether and crystallization afforded 3-bromo-5-(trifluoromethyl)benzoic acid as colorless platelets; m.p. 133−135 °C (from hex-

anes); yield: 10.9 g (81%). ^{1}H NMR: δ = 8.43 (s, 1 H), 8.30 (s, 1 H), 8.01 (s, 1 H) ppm. ^{13}C NMR: δ = 169.6 (s), 136.4 (s), 133.6 (q, *J* = 4 Hz), 132.6 (q, *J* = 34 Hz), 131.8 (s), 125.8 (q, *J* = 4 Hz), 123.2 (s), 122.6 (q, *J* = 273 Hz) ppm. MS (c.i.): *m/z* (%) = 288 (16) [$M^+ + NH_4$], 286 (17) [$M^+ + NH_4$], 270 (42) [M^+], 268 (43) [M^+], 253 (91), 251 (100). $C_8H_4BrF_3O_2$ (269.17): calcd. C 35.72, H 1.50; found C 35.44, H 1.60. 3-Bromo-5-(trifluoromethyl)benzoic acid (6.7 g, 25 mmol) was introduced slowly, in the course of 45 min, and with vigorous stirring into a solution of butyllithium (50 mmol) in tetrahydrofuran (20 mL) and hexanes (30 mL). After the addition of oxirane (1.2 mL, 1.1 g, 25 mmol), the temperature was allowed to rise slowly to +25 °C. The mixture was then treated with 2.0 M ethereal hydrogen chloride before being evaporated to dryness. Crystallization from chloroform gave the acid **16** as colorless needles; m.p. 163−164 °C; yield: 0.61 g (9%). ^{1}H NMR (D_3CCOCD_3): δ = 8.21 (s, 1 H), 8.18 (s, 1 H), 7.88 (s, 1 H), 3.85 (t, *J* = 6.2 Hz, 2 H), 3.05 (t, *J* = 6.2 Hz, 2 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 166.5 (s), 143.4 (s), 134.9 (s), 132.4 (s), 130.9 (q, *J* = 4 Hz), 131.1 (q, *J* = 32 Hz), 124.6 (q, *J* = 4 Hz), 125.0 (q, *J* = 272 Hz), 63.0 (s), 39.4 (s) ppm. MS (c.i.): *m/z* (%) = 252 (100) [$M^+ + NH_4$], 234 (13) [M^+], 204 (26), 159 (23). $C_{10}H_9F_3O_3$ (269.17): calcd. C 51.15, H 3.77; found C 51.29, H 3.87.

Acknowledgments

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant 20-55′303-98) and the Bundesamt für Bildung und Wissenschaft, Bern (grant 97.0083 linked to the TMR project FMRXCT-970129).

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Received February 6, 2002
[O02081]