Directed lithiation of unprotected benzoic acids

Bernard Benettaut,* Jacques Mortier,*† Joël Moyroud§ and Jean-Luc Guesnet†

* Laboratoire de chimie organique et organométallique, URA CNRS n° 35, Université Bordeaux I, 351 cours de la Libération, 33405 TALENCE, France.
† Rhône-Poulenc Secteur Agro, Centre de recherches de la Dargoire, BP 9163, 69263 LYON Cedex 09, France.

Benzoic acid gives the ortho-lithiated species 1 under standard conditions (Bu'Li-TMEDA-THF, -90 °C). Reaction of 1 at -78 °C with either methyl iodide, dimethyl disulfide, hexachloroethane, or 1,2-dibromotetrachloroethane gives the ortho-substituted product. Intramolecular competition between the carboxylic acid and methoxy, chloro, fluoro, or diethylamido functions in ortho- and para-substituted benzoic acids establishes the carboxylic acid group to be of intermediate capacity in directing metallation. Complementarity of directing effects is observed with the chloro and fluoro groups in the meta-substituted benzoic acids but not with the methoxy and trifluoromethyl groups. Electrophile introduction into meta- and para-lithiated benzoates occurs with equal efficacy and comparable scope. The 2,4-dihalogenobenzoic acids undergo hydrogen/metal exchange at the position flanked by both halogen substituents. 2,2-Difluoro-1,3-benzodioxole-4-carboxylic acid undergoes lithiation adjacent to the oxygen atom. By use of such methods, routes to benzoic acids contiguously tri- and tetra-substituted with a variety of functionalities have been developed.

In recent years, aromatic directed metallation has developed into a broadly useful protocol for the regiospecific construction of polysubstituted aromatics. This potentially valuable technique allows the preparation of ortho-disubstituted aromatic compounds completely free of the isomeric meta and para isomers. To date, there has been no report of a direct and general synthesis of ortho-substituted benzoic acids from readily available starting materials and contiguously tri- and tetra-substituted benzoic acids are accessible only by multistep sequences if traditional approaches are used. Of carboxylic acid-derived directing groups which include amides, esters, α-aminoketones, isonitriles, anilides, sulfonylhydrazones, phenols and thiophenols. For condensation reactions temperature and order of addition of reagents. General conditions were chosen on the basis of preliminary experiments with methyl iodide: benzoic acid was not dimetallated at all by reaction with 2.2 equiv. of Bu'Li-TMEDA;§ Bu'Li-Bu'OK § and Bu'Li in THF§ at -78 °C. Reaction with 2.2 equiv. of Bu'Li-TMEDA at -78 °C, followed by quenching with methyl iodide, afforded a mixture of o-toluic acids (52%) and α-methylbutyrophenone (22%).§ Optimum conditions which have been found for metallation of benzoic acid are slow addition of the acid in THF to a slight excess (2.2 equiv.) of a 1:1 Bu'Li-TMEDA complex in THF at -90 °C. After quenching with methyl iodide, 2a in 65% yield and the undesired ketone in only 8% yield were obtained [see Scheme 1].

Results and discussion

Reaction of lithium 2-lithiobenzoate 1 with electrophiles

The efficiency of ortho-lithiaction is a function of the reaction solvent, organolithium and complexing agent employed. The reaction appears to be complete after 30 min, but lithium 2-lithiobenzoate 1 and its congeners are stable for up to 2 h at -78 °C. Normally, the solution of the metallated species is quenched with the appropriate electrophile in excess at -78 °C.

§ TMEDA = N,N,N',N'-tetramethylethylene-1,2-diamine; THF = tetrahydrofuran; DMF = dimethylformamide.
† α-Methylbutyrophenone results from nucleophilic addition of Bu'Li to benzonic acid and was formed along with unidentified material. The ketone which was separated by column chromatography on silica, using CH₂Cl₂ as eluent, was identified by 1H NMR spectral comparison.
‡ Under the optimum conditions small amounts of ketones (i.e., ≤10%) were observed.

Scheme 1 Reagents and conditions: i, Bu'Li-TMEDA, -90 °C, THF; ii, EX, -78 °C; iii, H⁺
and the solution is allowed to warm to room temperature. Standard work-up and subsequent recrystallization afforded ortho-substituted benzoic acids 2a-d in 48-65% isolated yields.

Intramolecular competition by different directing groups
The hierarchy of different functions in directing ortho-
methylation clearly is important for the development of synthetic methodologies. Since the ability of the carboxylic acid group to direct and activate ortho-lithiation has been recognized, its ranking with respect to the other directing groups needs to be established. We have carried out intramolecular competition between the carboxylic acid group and previously known directing groups by investigation of the position of lithiation of substituted benzoic acids with BuLi-
TMEDA. The strength of the carboxylic acid group is illustrated by the observation that 2- and 4-methoxybenzoic acids 3a, b are metalled exclusively ortho to the carboxylic acid group [BuLi-TMEDA (2.2 equiv.), THF, -90 °C] to give 4a, b in 45 and 66% yields, respectively, after quenching with methyl iodide (Scheme 2). The incorporation of the methyl substituent was confirmed by 1H NMR spectroscopy and mass spectroscopy while its location was established by 13C NMR spectroscopy.6

An interesting reversal of regioselectivity can be achieved by lithiating N,N-diethylphthalamic acid 5a and N,N-diethyl-
terephthalamic acid 5b.9 In this case the products 6a, b are derived from lithiation ortho to the amide function.

In a test of a system containing no ortho hydrogens, 2,6-dichlorobenzoic acid 7 underwent lithiation with BuLi-
TMEDA to give 2,6-dichloro-3-methylbenzoic acid 8 (92%) after quenching with methyl iodide.

It was desirable to ascertain whether treatment of ortho-halogenobenzoic acids 9a, b with BuLi-TMEDA would proceed with lithiation ortho to the carboxylic acid or the halogen group. In the case of 2-fluorobenzoic acid 9a, fluorine displacement was observed10 and 11 was formed (53%) (Scheme 3). However, exposure of 2-chlorobenzoic acid 9b to BuLi-TMEDA and then quenching of the reaction with an excess of methyl iodide led to metallyation exclusively adjacent to the carboxylic acid functionality (68%). Metallation of 4-fluorobenzoic acid 9c occurs both in the 2- and 3-positions, as reflected by the isolation of 10c and 10c' (4:1; 80%).

An important feature of directed ortho-metallation is the cooperative effect of 1,3-interrelated ortho-directors in promoting metallation at a common site. Starting with commercially available meta-substituted benzoic acids, lithiation–electrophile quench sequences were carried out to give the corresponding products 12a-p. The results with a variety of electrophiles are summarized in Table 1 (entries 1–16). The lithium carboxylate moiety in a meta relationship with Cl and F shows exclusive metallaion at C-2, the ortho site which they have in common, while the 1,3-CO2Li,0Me system shows an astonishingly low regioselectivity (entry 12, C-2: C-4 80:20).10 In contrast, we found that 3(trifluoromethyl)-
benzoic acid failed to react (entry 13). Methylation, ethylation, and propylation of 3-chlorobenzoic acid gave 12a-e in low to acceptable yields (entries 1–3). Attempted reactions with isopropyl iodide were unsuccessful. Whereas alkylation of tertiary benzamides can only be achieved by prior transformation to the corresponding solfer ortho Grignard reagents,12 3-chlorobenzoic acid does not require this transmetallation tactic (entry 4).

The regioselectivity was ascertained by reaction with DMF: the α-formyl product 12h undergoes cyclization to hydroxy-
phthalide upon work-up (entry 8). A variety of chlorine and bromine derivatives was conveniently obtained from reactions of meta-substituted benzoic acids with hexachloroethane and 1,2-dibromotetrachloroethane (entries 5, 10, 11, 14, 15). Notable among the halogen electrophiles introduced is the absence of ortho-fluorination although new F+ reagents have recently been used successfully in directed ortho-metallation (DOM) chemistry13 and 3- and 4-fluorobenzoic acids have themselves been metallated (entries 9-n, 14-16). When located meta to the deprotonation site an F substituent shows a strong acidifying effect that parallels that observed for the corre-
sponding ortho series (entries 14-16).14 The Me3Si group was introduced with ease (entry 7) and finds further utility in regimens associated with protection of a reactive metallation site15 and ipso desilylation.16

The method was extended to ortho-para and ortho-meta substituted benzoic acids (entries 17-20 and 21-23) providing an interesting and useful route to continuously tetrasubstituted benzoic acids. There are few literature reports on the metallation of halogenated benzoic acids and those available appear at first sight to be inconsistent. To our knowledge the sole example, reported in 1966,17 described the reaction between BuLi (2 equiv.) and 2,3,5,6-tetrafluorobenzoic acid in THF, a reaction which, on carbonation, gave tetrafluoro-
terephthalic acid (94%).

From entries 17-23, it can be seen that electrophilic attack of meta- and para-lithiated benzoates occurs with equal efficacy and comparable scope to that observed for ortho-lithiated species. The ortho-para substituted benzoic acids underwent hydrogen/metal exchange at the position flanked by both halogen substituents (entries 18-20). Retention of the ortho-

** It is well known that OMe group in aromatic systems activates the ortho-hydrogen for metallaion. See ref. 1 for comprehensive references.
fluoro atom in 12s, t stands in contrast to the replacement of the ortho-fluoro group of 2-fluorobenzoic acid 9a by Bu'Li (vide supra). Addition of dimethyl disulfide to the lithiated 4-fluoro-2-trifluoromethylbenzoic acid gave 12q' and 12q" substituted in the 5- and 6-positions (72:18; 40% yield, entry 17). 2,2-Difluoro-1,3-benzodioxole-4-carboxylic acid gave 12q' and 12q" formed (40%, ratio 72:18) 1H NMR determination.

Clearly there are limitations in the present study in providing information about the factors which influence ortho-lithiation. Thus, it is well-known that the site of lithiation can be affected by solvent and complexing agents and the present work was carried out systematically only with Bu'Li-TMEDA in THF. Although it is unclear as to whether the present results involve kinetic or thermodynamic control, the effect of complexation provides an explanation for them. Thus, since the carboxylate group is a strong binder of lithium it is likely that it undergoes pre-equilibrium association with the organolithium base. If this is the case, kinetic control would result from intramolecular association of the lithium with the ortho-directing group(s) in the metallated compound. Clearly more work is needed to define the nature of the reactive species in these and related reactions.††

**Table 1** Directed ortho-lithiation of unprotected benzoic acids

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* All reactions were carried out under Bu'Li-TMEDA-THF (-90 to -78 °C) conditions. ¹ Yields are based on purified (recrystallized) material. ² Not isolated but converted directly into the hydroxyphthalide by acid treatment upon work-up (see Experimental section). ³ Accompanied by the 4-methyl derivatives 12q'. ⁴ 5-Methylsulfanyl and 6-methylsulfanyl derivatives (12q' and 12q'') formed (40%, ratio 72:18). ¹¹ Interest in

**Conclusion**

The present work provides the first examples of the carboxylate group functioning as a metallation ortho-director in lithiations of benzenoid systems. The carboxylic acid function is shown to be of intermediate capacity compared to other common functions in directing ortho-lithiation in intramolecular competition under the prescribed conditions. Since many electrophiles are available for the introduction of a large range of functional groups, the present procedure provides a general route to contiguously tri- and tetra-substituted benzoic acids. This new method of ortho-lithiation is both attractive and useful since it allows further modification and transformation of the functional groups, the present procedure provides a general method of ortho-lithiation in intramolecular competition under the prescribed conditions. Since many electrophiles are available for the introduction of a large range of functional groups, the present procedure provides a general route to contiguously tri- and tetra-substituted benzoic acids. This new method of ortho-lithiation is both attractive and useful since it allows further modification and transformation of the carboxylic acid group into, for example, (i) ketones via sequential treatment with alkylithium base and chlorotrimethylsilane and (ii) aldehydes by reduction. Interest in
manipulation of the carboxylic functional group is on-going in our laboratories and further results will be reported in due course.

**Experimental**

**General**

Elemental analyses were performed by CNRS in Lyon. Melting points were taken on a Büchi 510 apparatus and are uncorrected. NMR spectra were recorded on a 250-MHz spectrometer operating in the Fourier transform mode. 13C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in CDCl3, chemical shifts are referenced to 13CHCl3. For spectra recorded in CD2COCD2, used as solvents, chemical shifts are given relative to the solvent signals.

Mass spectra were obtained with a VG 70 spectrometer operating in the Fourier transform mode. NMR spectra were recorded on a 250-MHz instrument using 1H NMR, 13C NMR, and IR spectroscopy. For spectra recorded in DMSO, chemical shifts are given relative to the solvent signals. For spectra recorded in CDCl3, chemical shifts are given relative to internal TMS (tetramethylsilane) as reference signal.

**Results**

2-Methylsulfanylbenzoic acid 2a.

To a mixture of benzoic acid (6.11 g, 50 mmol), Bu′Li (1.4 mol dm−3 solution; 78.6 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) in THF (50 cm3), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (20 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 2a (4.42 g, 65%).

2-Chlorobenzoic acid 2c.

To a mixture of benzoic acid (6.11 g, 50 mmol), Bu′Li (1.4 mol dm−3 solution; 78.6 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) in THF (50 cm3), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of N,N-diethylphthalamic acid (2.50 g, 11.3 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm3) at −100 °C. Work-up followed by recrystallization (heptane-EtOAc) afforded 2c (4.42 g, 65%).

2-Bromobenzoic acid 2d.

To a mixture of 2-chloro-6-methylbenzoic acid (2.40 g, 10.9 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm3) at −100 °C. Work-up followed by recrystallization (heptane-EtOAc) afforded 2d (5.53 g, 55%).

2,6-Dichloro-3-methylbenzoic acid 2e.

To a mixture of 2-bromo-6-methylbenzoic acid (7.64 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of potassium iodide (28.4 g, 200 mmol) in THF (50 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 2e (5.53 g, 55%).

2-Methoxy-6-methylbenzoic acid 4a.

To a mixture of 2-methoxybenzoic acid (7.61 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 4a (5.53 g, 55%).

4-Methoxy-2-methylbenzoic acid 4b.

To a mixture of 4-methoxybenzoic acid (7.61 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 4b (5.53 g, 55%).

2-Methoxy-6-methylbenzoic acid 4a.

To a mixture of 2-methoxybenzoic acid (7.61 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 85 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm3) at −100 °C. Work-up followed by recrystallization (heptane-EtOAc) afforded 4a (5.53 g, 55%).

2-Chloro-6-methylbenzoic acid 6a.

To a mixture of N,N-diethylphthalamic acid (2.50 g, 11.3 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm3) at −100 °C. Work-up followed by recrystallization (heptane-EtOAc) afforded 6a (5.53 g, 55%).

2,6-Dichloro-3-methylbenzoic acid 6b.

To a mixture of N,N-diethylphthalamic acid (2.50 g, 11.3 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol), Bu′Li (1.3 mol dm−3 solution; 19.2 cm3, 24.9 mmol) and TMEDA (3.76 cm3, 110 mmol) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm3) at −100 °C. Work-up followed by recrystallization (heptane-EtOAc) afforded 6b (5.53 g, 55%).

2-Chloro-6-methylbenzoic acid 6c.

To a mixture of 2,6-dichloro-3-methylbenzoic acid (9.55 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 55 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol), Bu′Li (1.3 mol dm−3 solution; 55 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 6c (5.53 g, 55%).

2-Chloro-6-methylbenzoic acid 7a.

To a mixture of 2,6-dichloro-3-methylbenzoic acid (9.55 g, 50 mmol), Bu′Li (1.3 mol dm−3 solution; 55 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm3). Work-up followed by recrystallization (heptane-EtOAc) afforded 7a (5.53 g, 55%).
as a colourless solid (5.80 g, 68%), mp 100–102 °C; δH(250 MHz; CDCl3) 10.7 (1 H, br), 7.28 (2 H, m), 7.18 (1 H, m) and 2.47 (3 H, s).

4-Fluoro-2-methylbenzoic acid 10c and 4-fluoro-3-methylbenzoic acid 10d. To a mixture of 4-fluorobenzoic acid (14.0 g, 100 mmol), Bu'Li (1.4 mol dm−3 solution; 157 cm3, 220 mmol) and TMEDA (33.2 cm3, 220 mmol) was added a solution of methyl iodide (56.8 g, 400 mmol) in THF (50 cm3). Work-up followed by fractional recrystallization (heptane–Et2O) afforded 10c (3.3 g, 88%), mp 155–157 °C (Found: C, 56.90; H, 4.05; F, 19.15. C6H4ClO2 requires C, 57.00; H, 4.00; F, 19.00%). δH(250 MHz; CDCl3) 11.50 (1 H, s) 7.92 (1 H, dd, J 13.6 and 7.6), 7.51 (1 H, dt, J 13 and 7.6), 7.41 (1 H, dd, J 1.3 and 7.6), 7.28 (1 H, t, J 7.9); 2.47 (3 H, s).

2-sec-Butylbenzoic acid 11a. To a mixture of 2-fluorobenzoic acid (7.0 g, 50 mmol), Bu'Li (1.4 mol dm−3 solution; 78.6 cm3, 110 mmol) and TMEDA (16.6 cm3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (10 cm3). Work-up afforded 11a as a colourless oil (4.72 g, 53%); δH(250 MHz; CDCl3) 12.10 (1 H, s) 7.90 (1 H, dd, J 13.6 and 7.6), 7.30 (1 H, m), 1.68 (2 H, m), 1.29 (3 H, d, J 7.3) and 1.18 (3 H, t, J 7.3); δS(100 MHz; CDCl3) 154.2, 149.8, 132.6, 130.1, 128.5, 126.4, 36.1, 31.1, 21.8 and 12.1.

3-Chloro-2-methylbenzoic acid 12a. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu'Li (1.3 mol dm−3 solution; 170 cm3) and TMEDA (33.2 cm3, 220 mmol) was added a solution of hexachloroethane (182 g, 562 mmol) in THF (10 cm3). Work-up followed by recrystallization (heptane–Et2O) afforded 12a as a colourless solid (10.6 g, 62%), mp 135–136 °C (Found: C, 56.45; H, 4.05; Cl, 19.15. C6H5ClO2 requires C, 56.50; H, 4.00; Cl, 19.00%). δH(250 MHz; CDCl3) 11.50 (1 H, s) 7.92 (1 H, dd, J 13.6 and 7.6), 7.51 (1 H, dt, J 13.6 and 7.6), 7.28 (1 H, t, J 7.9); 2.47 (3 H, s).

3-Chloro-2-ethylbenzoic acid 12b. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu'Li (1.3 mol dm−3 solution; 170 cm3) and TMEDA (33.2 cm3, 220 mmol) was added a solution of 1,2-dibromotetrachloroethane (250 cm3) was added a solution of TMEDA (84.8 cm3, 562 mmol) in THF (300 cm3) and a solution of dimethyl disulfide (69.1 g, 768 mmol) in THF (60 cm3). Work-up followed by recrystallization (heptane–Et2O) afforded 12b as a colourless solid (23.3 g, 53%), mp 126–128 °C (Found: C, 54.55; H, 4.8; Cl, 20.5%. C6H5Cl2O2 requires C, 54.60; H, 4.8; Cl, 20.50%). δH(250 MHz; CDCl3) 13.1 (1 H, br, broad) 7.60 (1 H, d, J 7.9); 7.60 (1 H, d, J 7.9); 7.30 (1 H, t, J 7.9) and 2.51 (3 H, s); δS(100 MHz; CDCl3) 168.4, 135.4, 134.8, 133.9, 131.9, 128.4 and 127.1.

3-Chloro-2-ethylbenzoic acid 12d. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu'Li (1.3 mol dm−3 solution; 170 cm3) and TMEDA (33.2 cm3, 220 mmol) was added a solution of acetonitrile (31.2 g, 200 mmol) in THF (40 cm3). Work-up followed by recrystallization (heptane–Et2O) afforded 12d as a colourless solid (3.50 g, 41%), mp 87–89 °C (Found: C, 56.55; H, 4.8; Cl, 19.15. C6H5ClO2 requires C, 56.50; H, 4.8; Cl, 19.05%). δH(250 MHz; CDCl3) 11.50 (1 H, s) 7.92 (1 H, dd, J 13.6 and 7.6), 7.51 (1 H, dt, J 13.6 and 7.6), 7.28 (1 H, t, J 7.9); 2.47 (3 H, s).
recrystallization (heptane-EtO) afforded 12 as a colourless solid (23.8 g, 71%), mp 169-171 °C (Found: C, 43.3; H, 2.7; Cl, 18.3; F, 15.9; requires C, 43.55; H, 1.6; Cl, 18.4; F, 15.3%).

2-Chloro-4-fluoro-3-methylsulfanylbenzoic acid 12q
To a mixture of 2-chloro-4-fluoro-benzoic acid (5 g, 28.6 mmol), BuLi (1.3 mol dm⁻³ solution; 48.5 cm³, 63 mmol) and TMEDA (95.1 cm³, 63 mmol) was added dimethyl disulfide (10.32 cm³, 63 mmol) in THF (200 cm³). Work-up followed by recrystallization (heptane-EtO) afforded 12q as a colourless solid (35.9 g, 57%), mp 162-163 °C (Found: C, 43.3; H, 2.7; Cl, 15.8; F, 8.7; C₄H₆F₂CO₂S requires C, 43.55; H, 2.75; Cl, 16.05; F, 8.6%); δ₁ (250 MHz; CDCl₃) 13.5 (1 H, br), 7.75 (1 H, dd, J 9.1 and 2.1), 7.50 (1 H, dd, J 9.2 and 2.1) and 2.56 (3 H, s); δ₂ (62.9 MHz; CDCl₃) 166.2, 163.0, 135.5, 130.7, 129.7, 114.7 and 17.4.

2,4-Difluoro-3-methylsulfanylbenzoic acid 12s
To a mixture of 2,4-difluorobenzoic acid (10.56 g, 66.8 mmol), BuLi (1.3 mol dm⁻³ solution; 113 cm³, 147 mmol) and TMEDA (22.2 cm³, 147 mmol) in THF (200 cm³) was added dimethyl disulfide (24.06 cm³, 147 mmol) in THF (50 cm³). Work-up followed by recrystallization (heptane-EtO) afforded 12s as colourless solid (66.96 g, 51%), mp 182-184 °C; δ₁ (250 MHz; CDCl₃) 13.4 (1 H, br), 7.85 (1 H, dt, J 8.5 and 8.5); 7.25 (1 H, dt, J 8.5 and 8.5); 2.56 (3 H, s); δ₂ (62.9 MHz; CDCl₃) 166.2, 163.0, 129.7, 114.7 and 17.4.

2-Chloro-4,4-difluorobenzoic acid 12t
To a mixture of 2,4-difluorobenzoic acid (20.2 g, 100 mmol), BuLi (1.3 mol dm⁻³ solution; 214 cm³, 278 mmol) and TMEDA (41.9 cm³, 278 mmol) in THF (200 cm³) was added dimethyl disulfide (246.06 cm³, 109 mmol) in THF (50 cm³). Work-up followed by recrystallization (heptane-EtO) afforded 12t as a colourless solid (136.9 g, 506 mmol) in THF (100 cm³). Work-up followed by recrystallization (heptane-ETo) afforded 12t as a colourless solid (146.4 g, 60%), mp 169-171 °C (Found: C, 43.55; H, 2.45; Cl, 15.8; F, 16.3%; δ₁ (250 MHz; CDCl₃) 13.2 (1 H, br), 7.99 (1 H, m) and 7.09 (1 H, m).

2,2-Difluoro-7-methylsulfanyl-1,3-benzodioxole-4-carboxylic acid 12u
To a mixture of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid 28 (20.2 g, 100 mmol), BuLi (1.3 mol dm⁻³ solution; 169 cm³, 220 mmol) and TMEDA (33.2 cm³, 220 mmol) in THF (150 cm³) was added dimethyl disulfide (36 cm³, 400 mmol) in THF (10 cm³). Work-up followed by recrystallization (heptane-ETo) afforded 12u as a colourless solid (12.4 g, 50%), mp 127-129 °C (Found: C, 43.3; H, 2.4; Cl, 15.8; F, 16.3%; δ₁ (250 MHz; CDCl₃) 13.5 (1 H, br), 7.69 (1 H, d, J 8.5); 7.23 (1 H, d, J 8.5) and 2.67 (3 H, s).

2,2-Difluoro-1,3-benzodioxole-4-carboxylic acid 12v
To a mixture of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid 28 (10 g, 49.5 mmol), BuLi (1.3 mol dm⁻³ solution; 83.8 cm³, 109 mmol) and TMEDA (16.4 cm³, 109 mmol) was added methyl iodide (12.7 cm³, 198 mmol) in THF (20 cm³). Work-up followed by recrystallization (heptane-ETo) afforded 12v as a colourless solid (5.89 g, 55%), mp 127-129 °C; δ₁ (250 MHz; CDCl₃) 13.5 (1 H, br), 7.54 (1 H, d, J 8.2) and 7.15 (1 H, d, J 8.2) and 2.33 (3 H, s); δ₂ (62.9 MHz; CDCl₃) 163.6, 142.1, 131.3, 125.7, 125.0, 112.6 and 14.3.
7-Chloro-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid 12w.
To a mixture of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (12.5 g, 75 mmol), BuLi (1.3 mol dm⁻³ solution; 62.8 cm³, 81.7 mmol) and TMEDA (12.3 cm³, 81.7 mmol) was added hexachloroethane (35.2 g, 149 mmol) in THF (40 cm³). Work-up afforded 12w as a colourless solid (5.36 g, 61.5%), mp 185 °C. [Found: C, 40.5; H, 1.2; Cl, 14.9; F, 16.0. C₁₇H₁₁ClF₂O₂ requires C, 40.4; H, 1.2; Cl, 14.9; F, 15.6%].

References