Directed lithiation of unprotected benzoic acids

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Benzoic acid gives the *ortho*-lithiated species **1** under standard conditions (Bu^{s}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. Complimentarity 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.

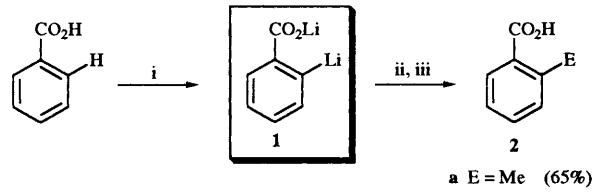
In recent years, aromatic directed metallation has developed into a broadly useful protocol for the regiospecific construction of polysubstituted aromatics.[1] This potentially valuable technique allows the preparation of *ortho*-disubstituted aromatic compounds completely free of the isomeric *meta* 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.[2] Of carboxylic acid-derived directing groups which include amides, esters, α-amino alkoxides, oxazolines, acetals, imidazolidines, imidazoles and cyclohexylimines, the tertiary amide and oxazolin-2-yl groups have evolved as powerful metallation directors for a variety of attempted syntheses.[1d,e,3]

More recently, substituents which undergo side-chain lithiation prior to ring *ortho*-lithiation have been studied.‡ We have reported[5] that lithiation *ortho* to an unprotected carboxylic acid group in benzenoid systems is a general and synthetically useful process. Herein, we record details of our investigations on the competitive intramolecular lithiations of substituted benzoic acids which establish that the carboxylic acid group is of intermediate capacity compared to other common functions in directing *ortho*-lithiation. We describe methodological aspects related to the preparation of simple *ortho*-substituted systems and convenient procedures for contiguously tri- and tetra-substituted benzoic acids.

Results and discussion

Reaction of lithium 2-lithiobenzoate 1 with electrophiles

The efficiency of *ortho*-lithiation is a function of the reaction solvent, organolithium and complexing agent employed, the reaction 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 BuLi–TMEDA,§ BuLi–Bu^{t}OK[6] and Bu^{s}Li in THF§ at −78 °C. Reaction with 2.2 equiv. of Bu^{s}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^{s}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).



a E = Me (65%)
b E = SMe (52%)
c E = Cl (48%)
d E = Br (55%)

Scheme 1 *Reagents and conditions:* i, Bu^{s}Li–TMEDA, −90 °C, THF; ii, EX, −78 °C; iii, H^+

Lithiation 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

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‡ Related dimetallations include those of arenesulfonic acids, benzyl alcohols, secondary amides, thioamides hydroxamates, sulfonamides, isonitriles, anilides, sulfonylhydrazones, phenols and thiophenols. For leading references, see ref. 4.

§ TMEDA = *N,N,N′,N′*-tetramethylethylene-1,2-diamine, THF = tetrahydrofuran, DMF = dimethylformamide.

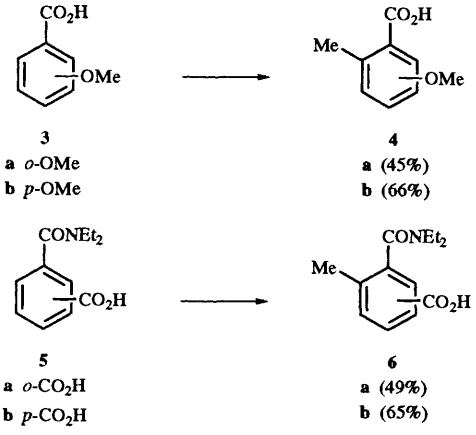
¶ α-Methylbutyrophenone results from nucleophilic addition of Bu^{s}Li to benzoic acid and was formed along with unidentified material. The ketone which was separated by column chromatography on silica, using CH_2Cl_2 as eluent, was identified by ^{1}H NMR spectral comparison.[7]

‖ Under the optimum conditions small amounts of ketones (*i.e.*, ≤10%) were observed.

and the solution is allowed to warm to room temperature. Standard work-up and subsequent recrystallization afford *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*-metallation 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 Bu^{s}Li–TMEDA. The strength of the carboxylic acid group is illustrated by the observation that 2- and 4-methoxybenzoic acids **3a**, **b** are metallated exclusively *ortho* to the carboxylic acid group [Bu^{s}Li–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



Scheme 2

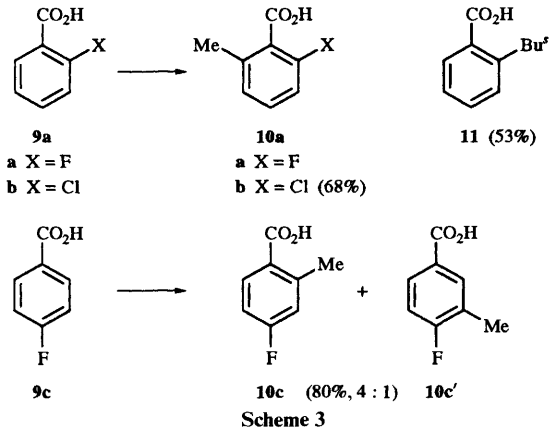
substituent was confirmed by ^{1}H NMR spectroscopy and mass spectroscopy while its location was established by ^{13}C NMR spectroscopy.[8]

An interesting reversal of regioselectivity can be achieved by lithiating *N*,*N*-diethylphthalamic acid **5a**[3b] and *N*,*N*-diethylterephthalamic 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 Bu^{s}Li–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 Bu^{s}Li–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 observed[10] and **11** was formed (53%) (Scheme 3). However, exposure of 2-chlorobenzoic acid **9b** to Bu^{s}Li–TMEDA and then quenching of the reaction with an excess of methyl iodide led to methylation 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



Scheme 3

electrophiles are summarized in Table 1 (entries 1–16). The lithium carboxylate moiety in a *meta* relationship with Cl and F shows exclusive metallation at C-2, the *ortho* site which they have in common, while the 1,3-CO_2Li,OMe system shows an astonishingly low regioselectivity (entry 12, C-2:C-4 80:20).**[,11] In contrast, we found that 3-(trifluoromethyl)-benzoic acid failed to react (entry 13). Methylation, ethylation, and propylation of 3-chlorobenzoic acid gave **12a–c** in low to acceptable yields (entries 1–3). Attempted reactions with isopropyl iodide were unsuccessful. Whereas allylation of tertiary benzamides can only be achieved by prior transformation to the corresponding softer *ortho* Grignard reagents,[12] 3-chlorobenzoic acid does not require this transmetallation tactic (entry 4).

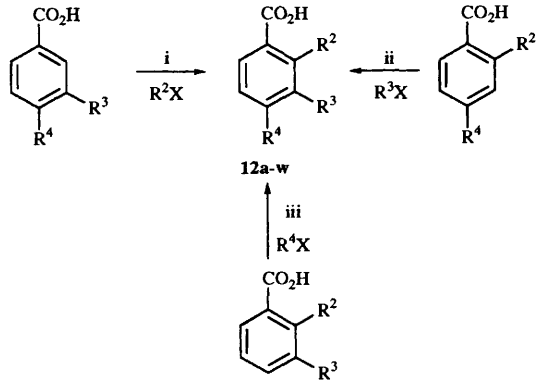
The regioselectivity was ascertained by reaction with DMF: the *o*-formyl product **12h** undergoes cyclization to hydroxyphthalide upon work-up (entry 8). A variety of chlorine and bromine derivatives was conveniently obtained from reactions of *meta*-substituted benzoic acids with hexachloroethane 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) chemistry[13] 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 corresponding *ortho* series (entries 14–16).[11d,14] The Me_3Si group was introduced with ease (entry 7) and finds further utility in regimens associated with protection of a reactive metallation site[15] 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 contiguously 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,[11b] described the reaction between BuLi (2 equiv.) and 2,3,5,6-tetrafluorobenzoic acid in THF, a reaction which, on carbonation, gave tetrafluoroterephthalic 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 metallation. See ref. 1 for comprehensive references.

Table 1 Directed *ortho*-lithiation of unprotected benzoic acids[a]



Entry	Route	R^2	R^3	R^4	$R^{2-4}X/R^{2-4}$	Product	Yield[b] (%)
1	i	Me	Cl	H	MeI/Me	**12a**	62
2	i	Et	Cl	H	EtI/Et	**12b**	41
3	i	Pr	Cl	H	PrI/Pr	**12c**	19
4	i	Allyl	Cl	H	AllylBr/Allyl	**12d**	46
5	i	Br	Cl	H	$(CCl_2Br)_2$/Br	**12e**	61
6	i	SMe	Cl	H	$(MeS)_2$/MeS	**12f**	65
7	i	TMS	Cl	H	TMSCl/TMS	**12g**	53
8	i	CHO	Cl	H	DMF/CHO	**12h**	66[c]
9	i	Me	F	H	MeI/Me	**12i**	74
10	i	Cl	F	H	C_2Cl_6/Cl	**12j**	71
11	i	Br	F	H	$(CCl_2Br)_2$	**12k**	71
12	i	Me	OMe	H	MeI/Me	**12l**	36[d]
13	i	Me	CF_3	H	MeI/Me	**12m**	0
14	i	Cl	Cl	F	C_2Cl_6/Cl	**12n**	79
15	i	Cl	F	F	C_2Cl_6/Cl	**12o**	85
16	i	SMe	F	F	$(MeS)_2$/MeS	**12p**	83
17	ii	CF_3	SMe	F	$(MeS)_2$/MeS	**12q**	0[e]
18	ii	Cl	SMe	F	$(MeS)_2$/MeS	**12r**	57
19	ii	F	SMe	F	$(MeS)_2$/MeS	**12s**	51
20	ii	F	Cl	F	C_2Cl_6/Cl	**12t**	60
21	iii	OCF_2O	—	SMe	$(MeS)_2$/MeS	**12u**	50
22	iii	OCF_2O	—	Me	MeI/Me	**12v**	55
23	iii	OCF_2O	—	Cl	C_2Cl_6/Cl	**12w**	61

[a] All reactions were carried out under Bu^s–TMEDA–THF (−90 to −78 °C) conditions. [b] Yields are based on purified (recrystallized) material. [c] Not isolated but converted directly into the hydroxyphthalide by acid treatment upon work-up (see Experimental section). [d] Accompanied by the 4-methyl derivatives **12l′** (9%). [e] 5-Methylsulfanyl and 6-methylsulfanyl derivatives (**12q′** and **12q″**) formed (40%, ratio 72:18 ^{1}H NMR determination).

fluoro atom in **12s, t** stands in contrast to the replacement of the *ortho*-fluoro group of 2-fluorobenzoic acid **9a** by Bu^sLi (*vide supra*).[17] 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[2b] underwent lithiation adjacent to the oxygen atom with Bu^sLi–TMEDA in THF (entries 21–23).

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[1a] and the present work was carried out systematically only with Bu^sLi–TMEDA in THF. Although it is unclear as to whether the present results involve kinetic and/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 delivery of the organolithium base to the acidic proton, whilst thermodynamic control would arise 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.††

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 carboxylic acid group into, for example, (*i*) ketones *via* sequential treatment with alkyllithium base and chlorotrimethylsilane[19] and (*ii*) aldehydes by reduction.[20] Interest in

†† The mechanism of this novel lithiation reaction could illustrate a complex-induced proximity effect in which kinetic domination over the more well-known resonance and inductive effects is operative.

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. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, chemical shifts are recorded relative to the internal TMS (tetramethylsilane) reference signal. For [$^2H_6$]DMSO and CD_3COCD_3 used as solvents, chemical shifts are given relative to the solvent signals. Mass spectra were obtained with a VG 70 E mass spectrometer.

Reactions were performed in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was distilled from deep blue solutions of sodium–benzophenone ketyl prior to use. Bu^{s}Li, 1.3 and 1.4 mol dm^{-3} in cyclohexane, purchased from Janssen Chimica and Aldrich Chemical Company, Inc., was titrated periodically against 2,5-dimethoxybenzyl alcohol. *N,N,N′,N′*-Tetramethylethylene-1,2-diamine (TMEDA) was distilled from CaH_2 before use.

General procedure

To a vigorously stirred solution of a Bu^{s}Li–TMEDA (1:1) complex in anhydrous THF (75 cm^3) at −90 °C was added dropwise under argon, over a period of 30 min, the recrystallized benzoic acid dissolved in dry THF (50 cm^3).‡‡ After a further 30 min at −90 °C, the mixture was allowed to warm to −78 °C and then treated with an excess of the appropriate electrophile. The resulting solution was allowed to warm to ambient temperature, after which water was added to it. The aqueous layer was washed with diethyl ether, shaken and then acidified with 4 mol dm^{-3} HCl. After the mixture had been diluted with diethyl ether, the organic layer was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude benzoic acids. These were purified by recrystallization prior to characterization.

2-Toluic acid 2a. To a mixture of benzoic acid (6.11 g, 50 mmol), Bu^{s}Li (1.4 mol dm^{-3} solution; 78.6 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (20 cm^3). Work-up followed by recrystallization (heptane) afforded **2a** (4.42 g, 65%).§§

2-Methylsulfanylbenzoic acid 2b. To a mixture of benzoic acid (6.11 g, 50 mmol), Bu^{s}Li (1.4 mol dm^{-3} solution; 78.6 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of dimethyl disulfide (18.8 g, 200 mmol) in THF (30 cm^3). Work-up followed by recrystallization (water) afforded **2b** (4.37 g, 52%).§§[21]

2-Chlorobenzoic acid 2c. To a mixture of benzoic acid (6.11 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of hexachloroethane (47.3 g, 200 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane–Et_2O), afforded **2c** (3.76 g, 48%).§§

2-Bromobenzoic acid 2d. To a mixture of benzoic acid (6.11 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of 1,2-dibromotetrachloroethane (65.1 g, 200 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane–EtOAc) afforded **2d** (5.53 g, 55%).§§

2-Methoxy-6-methylbenzoic acid 4a. To a mixture of 2-methoxybenzoic acid (7.61 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (20 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **4a** as a colourless solid (3.74 g, 45%), mp 137–138 °C (lit.,[22] 139–140 °C) (Found: C, 64.9; H, 6.05. $C_9H_{10}O_3$ requires C, 65.05; H, 6.1%); δ_H(250 MHz; $CDCl_3$) 7.31 (1 H, t, *J* 8.2), 6.89 (1 H, d, *J* 8.2), 6.84 (1 H, d, *J* 8.2), 3.93 (s, 3 H) and 2.50 (s, 3 H); δ_C(62.9 MHz; $CDCl_3$) 170.4, 157.2, 139.4, 131.4, 123.7, 121.1, 108.8, 56.2 and 20.6.

4-Methoxy-2-methylbenzoic acid 4b. To a mixture of 4-methoxybenzoic acid (7.61 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (10 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **4b** as a colourless solid (5.48 g, 66%), mp 172–174 °C (lit.,[23] 176–177 °C) (Found: C, 65.1; H, 6.1. $C_9H_{10}O_3$ requires C, 65.05; H, 6.1%); δ_H(250 MHz; [$^2H_6$]-DMSO) 12.40 (1 H, s), 7.87 (1 H, d, *J* 8.2), 6.85 (1 H, s), 6.83 (1 H, d, *J* 8.2), 3.80 (3 H, s) and 2.53 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 172.2, 169.9, 144.1, 134.0, 117.1, 110.9, 55.2 and 22.5.

***N,N*-Diethyl-6-methylphthalamic acid 6a**. To a mixture of *N,N*-diethylphthalamic acid (2.50 g, 11.3 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 19.2 cm^3, 24.9 mmol) and TMEDA (3.76 cm^3, 24.9 mmol) in THF (20 cm^3) was added a solution of methyl iodide (6.42 g, 45.2 mmol) in THF (10 cm^3) at −100 °C. Work-up followed by recrystallization (heptane–Et_2O) afforded **6a** as a colourless solid (1.30 g, 49%), mp 127–128 °C (Found: C, 66.1; H, 7.4; N, 5.7. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.00 (1 H, br), 7.79 (1 H, d, *J* 7.9), 7.49 (1 H, d, *J* 7.9), 7.39 (1 H, t, *J* 7.9), 3.49 (2 H, m), 3.00 (2 H, m), 2.23 (3 H, s), 1.19 (3 H, t, *J* 7.6) and 0.97 (3 H, t, *J* 7.6); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 168.5, 167.1, 138.6, 134.5, 134.4, 128.1, 128.0, 127.9, 42.1, 37.8, 18.6, 13.2 and 12.2; *m/z* 235 (1%), 200 (34) and 163 (100).

***N,N*-Diethyl-2-methylterephthalamic acid 6b**. To a mixture of *N,N*-diethylterephthalamic acid (2.40 g, 10.9 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 18.4 cm^3, 23.9 mmol), and TMEDA (3.60 cm^3, 23.9 mmol) in THF (20 cm^3) was added a solution of methyl iodide (6.17 g, 43.6 mmol) in THF (10 cm^3). Work-up followed by chromatography (heptane–EtOAc) afforded **6b** as a colourless solid (1.63 g, 65%), mp 113 °C (Found: C, 66.45; H, 7.4; N, 5.7. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 5.95%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.05 (1 H, br), 7.84 (1 H, s), 7.80 (1 H, d, *J* 7.6), 7.27 (1 H, d, *J* 7.6), 3.80–2.80 (4 H, br), 2.24 (3 H, s), 1.15 (3 H, t, *J* 7.6) and 0.95 (3 H, t, *J* 7.6); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 168.6, 166.9, 141.3, 133.8, 130.9, 130.6, 126.8, 125.5, 42.0, 38.2, 18.1, 13.7 and 12.6; *m/z* 235 (30%), 234 (62), 220 (42) and 163 (100).

2,6-Dichloro-3-methylbenzoic acid 8. To a mixture of 2,6-dichlorobenzoic acid (9.55 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **8** as a colourless solid (9.43 g, 92%), mp 126–127 °C (Found: C, 46.6; H, 2.85; Cl, 34.6. $C_8H_6Cl_2O_2$ requires C, 46.9; H, 2.95; Cl, 34.6%); δ_H(250 MHz; $CDCl_3$) 11.2 (s, 1 H), 7.29–7.26 (2 H, m) and 2.40 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 170.5, 135.6, 132.5, 132.2, 131.6, 128.5, 127.8 and 19.6.

2-Chloro-6-methylbenzoic acid 10b. To a mixture of 2-chlorobenzoic acid (7.84 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3}; 85 cm^3, 110 mmol), and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane) afforded **10b**[24]

‡‡ If the Bu^{s}Li/TMEDA solution is cooled in a −107 °C bath and the benzoic acid in THF is added slowly to this solution (over a period of 30 min), the internal temperature remains below −90 °C.

§§ Products were characterized on the basis of ^1H NMR, ^{13}C and IR spectroscopic results and by matching their melting points with those of authentic samples.

as a colourless solid (5.80 g, 68%), mp 100–102 °C; δ_H(250 MHz; $CDCl_3$), 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 10c'. To a mixture of 4-fluorobenzoic acid (14.0 g, 100 mmol), Bu^{s}Li (1.4 mol dm^{-3} solution; 157 cm^3, 220 mmol) and TMEDA (33.2 cm^3, 220 mmol) was added a solution of methyl iodide (56.8 g, 400 mmol) in THF (50 cm^3). Work-up followed by fractional recrystallization (heptane–Et_2O) afforded **10c**[25] (9.87 g, 64%), mp 170 °C and **10c**[26] (1.23 g, 16%), mp 168–169 °C (Found: C, 62.1; H, 4.5; F, 12.2. $C_8H_7FO_2$ requires C, 62.3; H, 4.6; F, 12.35%) as colourless solids; **10c** δ_H(250 MHz; [$^2H_6$]-DMSO), 12.85 (1 H, s), 7.90 (1 H, dd, *J* 5.9 and 7.6), 7.19 (1 H, m), 7.10 (1 H, m) and 2.55 (3 H, s); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 167.6, 163.6, 143.0, 133.1, 126.9, 118.0, 112.7 and 21.3; **10c'** δ_H(250 MHz; [$^2H_6$]-DMSO), 12.85 (1 H, s), 7.81 (2 H, m), 7.21 (1 H, m) and 2.52 (3 H, s).

2-*sec*-Butylbenzoic acid 11. To a mixture of 2-fluorobenzoic acid (7.0 g, 50 mmol), Bu^{s}Li (1.4 mol dm^{-3} solution; 78.6 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of methyl iodide (28.4 g, 200 mmol) in THF (10 cm^3). Work-up afforded **11** as a colourless oil (4.72 g, 53%); δ_H(250 MHz; $CDCl_3$),11.50 (1 H, s), 7.92 (1 H, dd, *J* 1.3 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, dt, *J* 1.3 and 7.6), 3.72 (1 H, m), 1.68 (2 H, m), 1.29 (3 H, d, *J* 7.3) and 0.89 (3 H, t, *J* 7.3); δ_C(62.9 MHz; $CDCl_3$) 174.2, 149.8, 132.6, 130.1, 126.8, 125.4, 36.1, 31.1, 21.8 and 12.1.

3-Chloro-2-methylbenzoic acid 12a. To a mixture of 3-chlorobenzoic acid (15.7 g, 100 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 170 cm^3) and TMEDA (33.2 cm^3, 220 mmol) was added a solution of methyl iodide (56.8 g, 400 mmol) in THF (40 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12a** as a colourless solid (10.6 g, 62%), mp 153–155 °C (Found: C, 56.45; H, 4.05; Cl, 20.6. $C_8H_7ClO_2$ requires C, 56.35; H, 4.15; Cl, 20.8%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.1 (1 H, br), 7.69 (1 H, dd, *J* 1.2 and 7.9), 7.60 (1 H, dd, *J* 1.2 and 7.9), 7.30 (1 H, t, *J* 7.9) and 2.51 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 168.4, 135.4, 134.8, 133.9, 131.9, 128.4 and 127.1.

3-Chloro-2-ethylbenzoic acid 12b. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of ethyl iodide (31.2 g, 200 mmol) in THF (40 cm^3). Work-up followed by recrystallization (heptane) afforded **12b**[27] as a colourless solid (3.78 g, 41%), mp 87–89 °C (Found: C, 58.55; H, 4.8; Cl, 19.15. $C_9H_9ClO_2$ requires C, 58.55; H, 4.9; Cl, 19.2%); δ_H(250 MHz; $CDCl_3$) 11.7 (1 H, br), 7.91 (1 H, d, *J* 7.9), 7.58 (1 H, d, *J* 7.9), 7.23 (1 H, t, *J* 7.9), 3.20 (2 H, q, *J* 7.3) and 1.29 (3 H, t, *J* 7.3); *m*/*z* 184 (94%), 169 (100) and 166 (76).

3-Chloro-2-propylbenzoic acid 12c. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 85 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added a solution of propyl iodide (34.0 g, 200 mmol) in THF (60 cm^3). Work-up afforded **12c** as a viscous oil (1.89 g, 19%) (Found: C, 60.75; H, 5.4; Cl, 17.85. $C_{10}H_{11}ClO_2$ requires C, 60.45; H, 5.6; Cl, 17.85%); δ_H(250 MHz; $CDCl_3$) 9.4 (1 H, br), 7.89 (1 H, dd, *J* 1.2 and 7.9). 7.57 (1 H, dd, *J* 1.2 and 7.9), 7.22 (1 H, t, *J* 7.9, 1 H), 3.13 (2 H, m), 1.67 (2 H, m) and 1.04 (3 H, t, *J* 7.3).

2-Allyl-3-chlorobenzoic acid 12d. To a mixture of 3-chlorobenzoic acid (40 g, 255 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 432 cm^3, 562 mmol) and TMEDA (84.8 cm^3, 562 mmol) in THF (300 cm^3) was added a solution of allyl bromide (88.4 cm^3, 1.02 mol) in THF (100 cm^3). Work-up followed by recrystallization (heptane) afforded **12d** as a colourless solid (23.1, 46%), mp 65–66 °C (Found: C, 61.05; H, 4.5; Cl, 17.75. $C_{10}H_9ClO_2$ requires C, 61.1; H, 4.6; Cl, 18.05); δ_H(250 MHz; [$^2H_6$]-DMSO), 13.2 (1 H, br), 7.72 (1 H, dd, *J* 1.2 and 7.9), 7.62 (1 H, dd, *J* 1.2 and 7.9), 7.34 (1 H, t, *J* 7.9), 5.88 (1 H, ddd, *J* 6.1, 10.4 and 17.1), 5.00 (1 H, dd, *J* 1.8 and 10.4), 4.90 (1 H, dd, *J* 1.8 and 17.1) and 3.82 (2 H, dt, *J* 6.1 and 1.8); δ_C(62.9 MHz; [$^2H_6$]-DMSO), 168.2, 136.9, 135.3, 134.9, 134.0, 133.8, 128.8, 127.6, 115.8 and 33.7; *m*/*z* 196 (41%), 181 (100) and 115 (94).

2-Bromo-3-chlorobenzoic acid 12e. To a mixture of 3-chlorobenzoic acid (40 g, 255 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 432 cm^3, 562 mmol) and TMEDA (84.8 cm^3, 562 mmol) in THF (300 cm^3) was added a solution of 1,2-dibromotetrachloroethane (332.7 g, 1.02 mol) in THF (100 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12e** as a colourless solid (36.6 g, 61%), mp 146–147 °C (Found: C, 35.55; H, 1.75; Br, 33.65; Cl, 15.0. $C_7H_4BrClO_2$ requires C, 35.7; H, 1.7; Br, 33.95; Cl, 15.05%); δ_H(250 MHz; $CDCl_3$) 9.50 (1 H, br), 7.80 (1 H, dd, *J* 1.5 and 7.9), 7.66 (1 H, dd, *J* 1.5 and 7.9) and 7.36 (1 H, t, *J* 7.9; δ_C(62.9 MHz; [$^2H_6$]-DMSO) 167.3, 137.6, 134.8, 130.5, 129.0, 128.0 and 119.4; *m*/*z* 234 (100%), 217 (94) and 189 (25).

3-Chloro-2-methylsulfonylbenzoic acid 12f. To a mixture of 3-chlorobenzoic acid (30 g, 192 mmol), Bu^{s}Li (1.3 mol dm^{-3}; 325 cm^3, 422 mmol) and TMEDA (64 cm^3, 422 mmol) in THF (300 cm^3) was added a solution of dimethyl disulfide (69.1 cm^3, 768 mmol) in THF (60 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12f** as a colourless solid (25.2 g, 65%), mp 126–128 °C (Found: C, 47.6; H, 3.45; Cl, 17.4. $C_8H_7ClO_2S$ requires C, 47.4; H, 3.5; Cl, 17.5%); δ_H(250 MHz; CD_3COCD_3) 9.60 (1 H, br), 7.64 (1 H, dd, *J* 1.2 and 7.9), 7.52 (1 H, dd, *J* 1.2 and 7.9), 7.48 (1 H, t, *J* 7.9) and 2.46 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 168.6, 141.9; 138.9, 131.5, 131.1, 129.9, 126.2 and 18.7; *m*/*z* 202 (100%), 187 (34), 155 (44) and 45 (47).

3-Chloro-2-trimethylsilylbenzoic acid 12g. To a mixture of 3-chlorobenzoic acid (30 g, 192 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 325 cm^3, 422 mmol) and TMEDA (64 cm^3, 422 mmol) in THF (300 cm^3) was added a solution of chlorotrimethylsilane (98 cm^3, 768 mmol) in THF (100 cm^3). Work-up followed by recrystallization (heptane) afforded **12g** as a colourless solid (23.3 g, 53%), mp 72–73 °C (Found: C, 52.55; H, 5.65; Cl, 15.4. $C_{10}H_{13}ClO_2Si$ requires C, 52.5; H, 5.75; Cl, 15.5%); δ_H(250 MHz; [$^2H_6$]-DMSO) 7.60–7.35 (3 H, m) and 0.37 (9 H, s); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 170.6, 143.1, 140.9, 136.1, 131.1, 130.6, 126.0 and 1.4.

4-Chloro-3-hydroxy-3*H*-isobenzofuran-1-one 12h. To a mixture of 3-chlorobenzoic acid (7.83 g, 50 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 84.6 cm^3, 110 mmol) and TMEDA (16.6 cm^3, 110 mmol) was added dimethylformamide (15.5 cm^3, 200 mmol) in THF (10 cm^3). Work-up followed by recrystallization (heptane–EtOAc) afforded **12h** as a colourless solid (6.09 g, 66%), mp 124–126 °C (Found: C, 54.65; H, 3.6; Cl, 17.55. $C_9H_7ClO_3$ requires C, 54.45; H, 3.55; Cl, 17.85%); δ_H(250 MHz; $CDCl_3$) 7.97 (1 H, br), 7.75 (1 H, d, *J* 7.6), 7.65 (1 H, d, *J* 7.6) and 7.55 (1 H, t, *J* 7.6); δ_C(62.9 MHz; $CDCl_3$) 167.7, 143.9, 134.6, 131.9, 130.0, 129.3, 123.3 and 97.3.

3-Fluoro-2-methylbenzoic acid 12i. To a mixture of 3-fluorobenzoic acid (26.9 g, 192 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 325 cm^3, 422 mmol) and TMEDA (64 cm^3, 422 mmol) in THF (300 cm^3) was added a solution of methyl iodide (47.8 cm^3, 768 mmol) in THF (200 cm^3). Work-up followed by recrystallization (heptane–EtOAc) afforded **12i** as a colourless solid (21.9 g, 74%), mp 161–162 °C[28] (Found: C, 62.05; H, 4.55; F, 12.25. $C_8H_7FO_2$ requires C, 62.35; H, 4.6; F, 12.35%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.1 (1 H, br), 7.62 (1 H, m), 7.33 (1 H, m), 7.30 (1 H, m) and 2.40 (3 H, d, *J* 2.4); δ_F(235.4 MHz; [$^2H_6$]-DMSO, TMS) −115.5; δ_C(62.9 MHz; [$^2H_6$]-DMSO) 167.8, 160.8, 133.1, 126.8, 125.8, 125.4 and 118.1; *m*/*z* 154 (100%), 136 (90) and 108 (75).

2-Chloro-3-fluorobenzoic acid 12j. To a mixture of 3-fluorobenzoic acid (26.9 g, 192 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 325 cm^3, 422 mmol) and TMEDA (64 cm^3, 422 mmol) in THF (300 cm^3) was added a solution of hexachloroethane (182 g, 768 mmol) in THF (300 cm^3). Work-up followed by

recrystallization (heptane–Et_2O) afforded **12j** as a colourless solid (23.8 g, 71%), mp 169–171 °C (Found: C, 48.4: H, 2.35; Cl, 20.5; F, 10.7. $C_7H_4ClFO_2$ requires C, 48.2; H, 2.3; Cl, 20.3; F, 10.9%); δ_H(250 MHz; [$^2H_6$]-DMSO) 12.8 (1 H, br), 8.02 (1 H, m), 7.30 (1 H, m) and 7.25 (1 H, m); δ_F(235.4 MHz; [$^2H_6$]-DMSO) −113.3; δ_C(62.9 MHz; [$^2H_6$]-DMSO) 165.7, 157.7, 133.5, 128.6, 126.3, 119.2 and 118.9; *m/z* 174 (95%), 157 (100) and 129 (49).

2-Bromo-3-fluorobenzoic acid 12k. To a mixture of 3-fluorobenzoic acid (26.9 g, 192 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 325 cm^3, 422 mmol) and TMEDA (64 cm^3, 422 mmol) in THF (300 cm^3) was added a solution of 1,2-dibromotetrachloroethane (250 g, 768 mmol) in THF (300 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12k** as a colourless solid (29.9 g, 71%), mp 165–168 °C (Found: C, 38.7; H, 1.8; Br, 36.4; F, 8.7. $C_7H_4BrFO_2$ requires C, 38.4; H, 1.85; Br, 36.5; F, 8.7%); δ_H(250 MHz; CD_3COCD_3) 11.75 (1 H, br), 7.67 (1 H, dd, *J* 7.6 and 1.0) and 7.50 (2 H, m); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 160.5, 158.6, 136.0, 129.4, 126.1, 118.7 and 107.3; *m/z* 218 (100%) and 201 (92).

3-Methoxy-2-methylbenzoic acid 12l and 3-methoxy-4-methylbenzoic 12l′. To a mixture of 3-methoxybenzoic acid (30.0 g, 197 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 333 cm^3, 434 mmol) and TMEDA (65.5 cm^3, 434 mmol) in THF (300 cm^3) was added methyl iodide (49.1 cm^3, 788 mmol) in THF (100 cm^3). Work-up followed by fractional recrystallization (heptane–EtOAc) afforded **12l** (18.3 g, 36%) and **12l′** [29] (6.5 g, 9%) (Found: C, 65.2; H, 5.95. $C_9H_{10}O_3$ requires C, 65.05; H, 6.05%) as colourless solids; **12l** δ_H(250 MHz; [$^2H_6$]-DMSO) 12.8 (1 H, s), 7.32 (1 H, d, *J* 7.6), 7.24 (1 H, t, *J* 7.6), 7.10 (1 H, d, *J* 7.6), 3.80 (3 H, s) and 2.36 (3 H, s); **12l′** δ_H(250 MHz; [$^2H_6$]-DMSO), 12.8 (1 H, s), 7.50 (1 H, d, *J* 7.6), 7.48 (1 H, s), 7.23 (1 H, d, *J* 7.6), 3.88 (3 H, s) and 2.20 (3 H, s).

2,3-Dichloro-4-fluorobenzoic acid 12n. To a mixture of 3-chloro-4-fluorobenzoic acid (20.0 g, 115 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 194 cm^3, 252 mmol) and TMEDA (38 cm^3, 252 mmol) in THF (200 cm^3) was added hexachloroethane (108.5 g, 458 mmol) in THF (200 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12n** as a colourless solid (18.9 g, 79%), mp 189–191 °C (Found: C, 40.3; H, 1.3; Cl, 33.65; F, 8.95. $C_7H_3Cl_2FO_2$: C, 40.25; H, 1.45; Cl, 33.9; F, 9.1%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.7 (1 H, br), 7.83 (1 H, dd, *J* 5.8 and 8.5), 7.51 (1 H, dd, *J* 8.8 and 8.5); δ_F(235.4 MHz; [$^2H_6$]-DMSO) −104.9.

2-Chloro-3,4-difluorobenzoic acid 12o. To a mixture of 3,4-difluorobenzoic acid (5.0 g, 32 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 53.5 cm^3, 69.6 mmol) and TMEDA (10.5 cm^3, 69.6 mmol) in THF (100 cm^3) was added hexachloroethane (30.0 g, 127 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12o** as a colourless solid (5.18 g, 85%), mp 159–160 °C (Found: C, 43.3; H, 1.5; Cl, 18.4; F, 19.65. $C_7H_3ClF_2O_2$ requires C, 43.7; H, 1.55; Cl, 18.4; F, 19.75%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.1 (1 H, br), 7.74 (1 H, m) and 7.54 (1 H, m); δ_F(235.4 MHz; [$^2H_6$]-DMSO) −129.6 and −135.9; δ_C(62.9 MHz; [$^2H_6$]-DMSO) 164.8, 151.7, 146.6, 128.3, 126.8, 121.6 and 116.0.

3,4-Difluoro-2-methylsulfanylbenzoic acid 12p. To a mixture of 3,4-difluorobenzoic acid (5.5 g, 35 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 58.9 cm^3, 76.5 mmol) and TMEDA (11.5 cm^3, 76.5 mmol) in THF (100 cm^3) was added dimethyl disulfide (12.5 g, 139 mmol) in THF (20 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12p** as a colourless solid (5.90 g, 83%), mp 149–150 °C (Found: C, 47.1; H, 2.9; F, 18.4. $C_8H_6F_2O_2S$ requires C, 47.05; H, 2.95; F, 18.6%); δ_H(250 MHz; $CDCl_3$) 13.4 (1 H, br), 7.55 (1 H, m), 7.40 (1 H, m) and 2.47 (1 H, d, *J* 2.3); δ_F(235.4 MHz; [$^2H_6$]-DMSO) −130.6 and −132.3; δ_C(62.9 MHz; $CDCl_3$) 166.7, 151.3, 149.8, 132.4, 126.9, 125.2, 115.6 and 17.8.

4-Fluoro-5-methylsulfanyl-2-trifluoromethylbenzoic acid 12q′ and 4-fluoro-6-methylsulfanyl-2-trifluoromethylbenzoic acid 12q″. To a mixture of 4-fluoro-2-trifluoromethylbenzoic acid (7.28 g, 35 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 59.2 cm^3, 77 mmol) and TMEDA (11.6 cm^3, 77 mmol) was added dimethyl disulfide (12.6 g, 140 mmol) in THF (10 cm^3). Work-up followed by fractional recrystallization (heptane) afforded **12q′** (2.58 g, 29%) and **12q″** (1.07 g, 12%), mp 136–137 °C (Found: C, 42.4; H, 2.2; F, 29.85. $C_9H_6F_4O_2S$ requires C, 42.5; H, 2.4; F, 29.9%) as colourless solids; **12q′** δ_H(250 MHz; [$^2H_6$]-DMSO + $CDCl_3$) 11.70 (1 H, s), 7.75 (1 H, d, *J* 5.3), 7.39 (1 H, d, *J* 7.3) and 2.55 (1 H, s); **12q″** δ_H(250 MHz; $CDCl_3$) 14.0 (1 H, br), 7.60 (1 H, dd, *J* 9.2 and 2.1), 7.50 (1 H, dd, *J* 9.2 and 2.1) and 2.56 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 164.4, 161.5, 128.5, 127.0, 122.2, 117.1, 110.0 and 15.3.

2-Chloro-4-fluoro-3-methylsulfanylbenzoic acid 12r. To a mixture of 2-chloro-4-fluorobenzoic acid (5 g, 28.6 mmol), BuLi (1.3 mol dm^{-3} solution; 48.5 cm^3, 63 mmol) and TMEDA (9.51 cm^3, 63 mmol) was added dimethyl disulfide (10.32 cm^3, 115 mmol) in THF (20 cm^3). Work-up followed by recrystallization (heptane) afforded **12r** as a colourless solid (3.59 g, 57%), mp 162–163 °C (Found: C, 43.3; H, 2.7; Cl, 15.85; F, 8.7. $C_8H_6ClFO_2S$ requires C, 43.55; H, 2.75; Cl, 16.05; F, 8.6%); δ_H(250 MHz; $CDCl_3$) 13.5 (1 H, br), 7.75 (1 H, dd, *J* 6.2 and 9), 7.35 (1 H, t, *J* 9) and 1.46 (3 H, d, *J* 1.5); δ_F(235.4 MHz; $CDCl_3$) −97.5; δ_C(62.9 MHz; $CDCl_3$) 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), Bu^{s}Li (1.3 mol dm^{-3} solution; 113 cm^3, 147 mmol) and TMEDA (22.2 cm^3, 147 mmol) in THF (200 cm^3) was added dimethyl disulfide (24.06 cm^3, 267 mmol) in THF (50 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12s** as a colourless solid (6.96 g, 51%), mp 182–184 °C; δ_H(250 MHz; $CDCl_3$) 13.4 (1 H, br), 7.85 (1 H, dt, *J* 8.5 and 8), 7.25 (1 H, dt, *J* 1.8 and 8.5) and 2.55 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 164.5, 163.9, 161.3, 132.3, 116.3, 113.5, 111.7 and 17.1 (Found: C, 47.05; H, 2.85; F, 18.7. $C_8H_6F_2O_2S$ requires C, 47.05; H, 2.95; F, 18.6%).

3-Chloro-2,4-difluorobenzoic acid 12t. To a mixture of 2,4-difluorobenzoic acid (20 g, 126 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 214 cm^3, 278 mmol) and TMEDA (41.9 cm^3, 278 mmol) in THF (200 cm^3) was added hexachloroethane (119.8 g, 506 mmol) in THF (100 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12t** as a colourless solid (14.6 g, 60%), mp 169–171 °C (Found: C, 43.55; H, 1.6; Cl, 18.35; F, 19.5. $C_7H_3ClF_2O_2$ requires C, 43.7; H, 1.6; Cl, 18.4; F, 19.75%); δ_H(250 MHz; $CDCl_3$) 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 [2b] (20.2 g, 100 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 169 cm^3, 220 mmol) and TMEDA (33.2 cm^3, 220 mmol) in THF (150 cm^3) was added dimethyl disulfide (36 cm^3, 400 mmol) in THF (10 cm^3). Work-up followed by recrystallization (heptane–Et_2O) afforded **12u** as a colourless solid, 12.4 g, 50%), mp 227–229 °C (Found: C, 43.3; H, 2.4; F, 15.15. $C_9H_6F_2O_4S$ requires C, 43.55; H, 2.45; F, 15.3%); δ_H(250 MHz; CD_3COCD_3) 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-7-methyl-1,3-benzodioxole-4-carboxylic acid 12v. To a mixture of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid [2b] (10 g, 49.5 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 83.8 cm^3, 109 mmol) and TMEDA (16.4 cm^3, 109 mmol) was added methyl iodide (12.33 cm^3, 198 mmol) in THF (20 cm^3). Work-up afforded **12v** as a colourless solid (5.89 g, 55%), mp 200 °C; δ_H(250 MHz; [$^2H_6$]-DMSO) 13.5 (1 H, br), 7.54 (1 H, d, *J* 8.2), 7.15 (1 H, d, *J* 8.2) and 2.33 (3 H, s); δ_C(62.9 MHz; $CDCl_3$) 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[2b] (7.50 g, 37.1 mmol), Bu^{s}Li (1.3 mol dm^{-3} solution; 62.8 cm^3, 81.7 mmol) and TMEDA (12.3 cm^3, 81.7 mmol) was added hexachloroethane (35.2 g, 149 mmol) in THF (40 cm^3). Work-up afforded **12w** as a colourless solid (5.36 g, 61%), mp 185 °C (Found: C, 40.5; H, 1.2; Cl, 14.95; F, 16.0. $C_8H_3ClF_2O_4$ requires C, 40.6; H, 1.3; Cl, 15.0; F, 16.05%); δ_H(250 MHz; [$^2H_6$]-DMSO) 13.6 (1 H, br), 7.62 (1 H, d, *J* 8.8) and 7.41 (1 H, d, *J* 8.8); δ_C(62.9 MHz; $CDCl_3$) 162.9, 143.1, 140.4, 131.1, 126.2, 124.6, 117.9 and 114.9.

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