The lithiation of fluorinated benzenes and its dependence on solvent and temperature

Paul Leslie Coe,* Anthony John Waring * and Thomas David Yarwood
School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

The formation of lithio derivatives from fluorinated benzenes and fluorinated bromobenzenes has been studied. The bases used were lithium diisopropylamide (LDA) in THF–hexane, butyllithium in diethyl ether–hexane and butyllithium in THF–hexane. The lithiated intermediates have been trapped using acetone, to form fluorinated 2-arylpropan-2-ols, or have been warmed to produce benzynes which have been trapped by furan in Diels–Alder additions. The use of LDA allows clean removal of the most acidic proton in the aromatic ring: butyllithium in ether–hexane brings about clean bromine–lithium exchange. In contrast, the use of butyllithium in THF–hexane at −78 °C results in autometallation and the formation of more complex product mixtures. For the formation of the benzynes involved in the Diels–Alder reactions it is necessary to warm the reaction mixtures. When ether–hexane is used as solvent the reactions remain fairly clean, but when THF is added the increasing autometallation again results in more complex reaction mixtures.

Introduction

In connection with other work we were interested in the metallation of fluorobenzenes which contain other halogen groups, and in some synthetic uses of the intermediates so formed. A number of major, and often competing, reactions has previously been identified when substituted fluorobenzenes are treated with lithium bases. First, deprotonation may occur with metallation to form a phenyllithium derivative. If the benzene ring carries another halogen group this may undergo halogen–metal exchange with a lithium alkyl or lithium aryl, to form a fluorophenyllithium species. A number of further reactions can then occur, which will be introduced later in this paper. Tetrahydrofuran (THF) is believed to be the solvent of choice for generating reactive organolithium compounds in a state of low aggregation.[1] Diethyl ether (ether) also encourages low aggregation, whereas hydrocarbon solvents give more highly aggregated and less reactive organolithium species. It has also been observed[1] that lithium dialkylamides—of which lithium diisopropylamide (LDA) is the most common example—are generally more effective lithiating agents than are the thermodynamically more basic lithium alkyls. This reflects the fact that the lithium dialkylamides have higher kinetic basicities and are more hindered nucleophiles. A cyclic mechanism has been proposed for their lithiation reactions which avoids the formation of a free carbanion.[2]

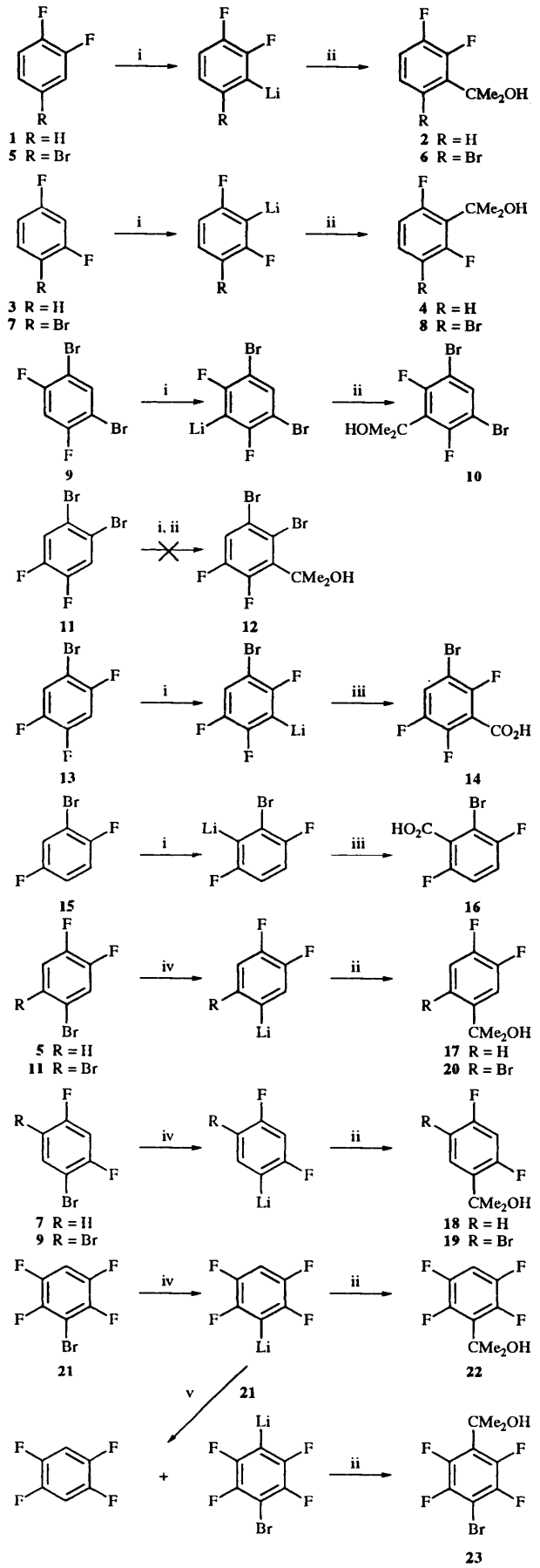
When we started the present study little was known about the lithiation behaviour of fluorobenzenes which bear other halogens; for example, about the sites of lithiation, or the importance of halogen–lithium exchange relative to hydrogen–lithium exchange, or about the importance of autometallation reactions (see later), or the variation of the various processes with temperature and solvent. We decided to investigate these matters using LDA in THF, and butyllithium in ether or THF as our lithiating agents, and either to trap the lithiated products with acetone, or allow them to decompose to produce benzyne intermediates which would then be intercepted by added furan to produce Diels–Alder adducts. The products formed by trapping with acetone were fluorine-containing 2-arylpropan-2-ols, from which the corresponding 2-(fluorophenyl)prop-2-enes (*i.e.* fluorinated α-methylstyrenes) were prepared.[3] When much of this work was complete a careful study was published in which some related lithiated species were formed and carboxylated to form the corresponding halogenobenzoic acids.[4] This work agreed with our own conclusions about the pattern of metallation and, in particular, confirmed the dramatic solvent effect that we had found in the lithiations by butyllithium in THF compared to those in ether. We have also shown that if direct halogen–lithium exchange is needed for preparative purposes it is best to treat the bromine-containing aromatic compounds with butyllithium in ether, in order to reduce the problem of autometallation.

Results and discussion

The simplest results were obtained by using LDA in THF as the metallating agent. This was produced in the usual way by adding butyllithium in hexane to a solution of diisopropylamine in THF at −10 °C. The final solution contained THF and hexane in a 2:1 ratio (v/v). This was cooled to −78 °C and an equimolar amount of the aromatic substrate was added neat, or occasionally in THF solution. Acetone was then added and the mixture allowed to warm to room temperature prior to work-up.

Reaction of 1,2-difluorobenzene **1** with LDA clearly formed the 3-lithio derivative, which was trapped with acetone to give a product identified as the ring-fluorinated 2-phenylpropan-2-ol **2** (75%), isolated by distillation. The ^1H and ^{19}F NMR spectra (given in Tables 1 and 2) and the mass spectra are discussed in the Experimental section where necessary. Column chromatography removed the small amount of impurities, believed to result from aldol reaction of the acetone; the same impurities were formed in all our similar reactions using acetone. The removal of 3-H in **1** is consistent with other studies, including Wittig's[5] and Gilman's[6] early work on fluorobenzene, in which 2-fluorophenyllithium could be hydrolysed or trapped with CO_2. Reaction of 1,3-difluorobenzene **3** with LDA led to lithiation at C-2 and the subsequent formation of 2-(2,6-difluorophenyl)propan-2-ol **4** (58% of theory). This is in full accord with our other results, which will be discussed later.

From 1-bromo-3,4-difluorobenzene **5** we obtained the usual minor aliphatic side products and the substituted 2-phenylpropan-2-ol **6**. This clearly results from the lithiation of the aromatic substrate at C-2 which must be, as expected, the most acidic centre. The ^1H NMR spectrum of **6** shows some interesting features which are found in all the 2-(2- or 6-fluorophenyl)propan-2-ols or the 2-(2,6-difluorophenyl)-propan-2-ols. There is a small but clear long-range coupling



Scheme 1 *Reagents and conditions:* i, LDA/THF, −78 °C; ii, MeCOMe, −78 °C; iii, CO_2; iv, BuLi/Et_2O/hexane, −78 °C; v, BuLi/THF/hexane, −78 °C

(J 1–4 Hz) between the *ortho* fluorine atoms and the methyl groups of the alcohol. This is evident in both the ^1H and ^{19}F NMR spectra (Tables 1 and 2), and is valuable in determining the disposition of these groups.

The reaction of 1-bromo-2,4-difluorobenzene **7** with LDA again led to removal of the most acidic proton, with lithiation at C-3. Trapping with acetone formed 2-(3-bromo-2,6-difluorophenyl)propan-2-ol **8** (69% crude, 50% pure material). A similar result was obtained by Bridges *et al.*[4] who were able to isolate 76% of the crude 3-bromo-2,6-difluorobenzoic acid after carboxylation of the lithio derivative.

We then investigated two more heavily substituted compounds. Reaction of 1,5-dibromo-2,4-difluorobenzene **9** with LDA, and distillation under reduced pressure, produced a crude product containing about 30% of unchanged starting material and 41% of the alcohol **10**, isolated pure as a white solid. This had a triplet aromatic resonance in the ^1H spectrum and a methyl triplet integrating for two methyl groups. The couplings indicate that the aromatic proton is *meta* to the two fluorines and that the alcoholic side chain is between them. The product again results from the removal of the most acidic aromatic proton, that between the two fluorine atoms.

In contrast, reaction of 1,2-dibromo-4,5-difluorobenzene **11** with LDA led to none of the corresponding 2-arylpropan-2-ol **12**. Only half of the starting aromatic compound was recovered and there was considerable colouration. We did not establish whether the compound has too low a thermodynamic or kinetic acidity, or whether the lithiated species was formed but was too hindered to react with acetone. Bridges *et al.*[4] were able to lithiate 1-bromo-2,4,5-trifluorobenzene **13** and to carboxylate this at the expected site, C-3, to give **14**, but this site will be more acidic and less subject to steric hindrance with buttressing than C-3 or C-6 in **11**, which are both flanked by a fluorine and a bromine atom. However, it is possible to lithiate a position flanked by a fluorine and a bromine atom, as shown by the lithiation at C-3 of 2-bromo-1,4-difluorobenzene **15** which was then carboxylated to give 70% of the crude acid **16**.[4]

The preparation of halogenated phenyllithiums, using butyllithium in ether

Our preliminary studies suggested that the lithiation of bromine-containing aromatics with butyllithium is best carried out in ether if one wishes to avoid the complication of autometallation. (This will be discussed in more detail later.) There are reports of the lithiation of 1,2-[7] and 1,3-difluorobenzene[7,8] in THF–hexane or THF–heptane and subsequent carboxylation to form the difluorobenzoic acids. We were interested in studying the formation of the lithiated intermediates in ether and THF, the effects of solvent on them, and their use in synthesis. When we started this work there were very few preparations of difluorophenyllithiums by halogen–metal exchange in ether.[9]

The butyllithium (in hexane) was added *via* a syringe, in small portions at −78 °C, to an ether solution of the bromodifluorobenzene, over about 1 h. An excess of acetone was then added in small portions at −78 °C. The mixture was allowed to warm to room temperature, worked up, and distilled to remove traces of diacetone alcohol and mesityl oxide: these impurities were best removed by column chromatography. Reaction of 1-bromo-3,4-difluorobenzene **5** under similar conditions gave the product of bromine–lithium exchange, 3,4-difluorophenyllithium, and thence 2-(3,4-difluorophenyl)propan-2-ol **17** (51% of pure material). Similarly, 1-bromo-2,4-difluorobenzene **7** afforded 62% of pure 2-(2,4-difluorophenyl)propan-2-ol **18**. The ^{19}F NMR spectra of both products showed two signals of equal intensity. The ^1H NMR spectrum of **18** included a sharp doublet ($J_{Me,F}$ *ca.* 1.2) for the two methyl groups of the side chain coupling with the one *ortho* fluorine on the aromatic ring.

Table 1 ^{1}H NMR data for fluorinated 2-phenylpropan-2-ols (δ values in $CDCl_3$); R = H unless otherwise indicated

Compd.	2-R	3-R	4-R	5-R	6-R	Me	OH
2	F	F	6.86–7.48[a]	6.86–7.48[a]	6.86–7.48[a]	1.63[b]	2.7
4	F	6.6–7.3[a]	6.6–7.3[a]	6.6–7.3[a]	F	1.69[c]	3.1
6	F	F	6.92[d]	7.33[e]	Br	1.74[f]	3.25
8	F	Br	7.44[g]	6.72[h]	F	1.70[c]	3.0
10	F	Br	7.70[i]	Br	F	1.72[j]	2.85
17	7.1[a]	F	F	7.3[a]	7.1[a]	1.53	2.57
18	F	6.65–6.95[a]	F	6.65–6.95[a]	7.54[k]	1.61[l]	2.29
19	F	6.86[m]	F	Br	7.81[n]	1.61[l]	2.27
20	Br	7.61[o]	F	F	7.40[p]	1.73	2.51
22	F	F	7.00[q]	F	F	1.76[r]	2.95
23	F	F	Br	F	F	1.74[s]	2.72

[a] Complex coupling, not analysed. [b] d, *J* 1.3 (Me coupling to 2-F). [c] t, *J* 1.9 (Me coupling to 2-F and 6-F). [d] dd, *J* 16.0 and 7.3 (*ortho* coupling of 4-H to 3-F; *ortho* coupling of 4-H to 5-H). [e] td, *J* 7.3 and 2.0 (t: *ortho* coupling of 4-H to 5-H and *meta* coupling of 5-H to 3-F; d: *J* 2.0 *para* coupling of 5-H to 2-F). [f] d, *J* 4.2 (Me coupling to 2-F). [g] dt, *J* 8.0 and 6.0 (d: *ortho* coupling of 4-H to 5-H; t: *meta* coupling of 4-H to 2-F and 6-F). [h] ddd, *J* 12.0, 8.0 and 2.0 (*ortho* coupling of 5-H to 6-F; *ortho* coupling of 5-H to 4-H; *para* coupling of 5-H to 2-F). [i] t, *J* 7.15 (*meta* coupling of 4-H to 2-F and 6-F). [j] t, *J* 2.2 (Me coupling to 2-F and 6-F). [k] tdm, *J* 9.0, 6.6 and *ca.* 1.2 (t: *meta* coupling of 6-H to 2-F and 4-F; d: *ortho* coupling of 6-H to 5-H; m: 6-H coupling to Me). [l] d, *J* 1.1–1.2 (Me coupling to 2-F or 6-F). [m] dd, *J* 11.2 and 8.2 (*ortho* coupling of 3-H to 2-F; *ortho* coupling of 3-H to 4-F). [n] t, *J* 8.2 (*meta* coupling of 6-H to 2-F and 4-F). [o] dd, *J* 12.5 and 8.7 (*ortho* coupling of 3-H to 4-F; *meta* coupling of 3-H to 5-F). [p] dd, *J* 9.7 and 7.5 (*ortho* coupling of 6-H to 5-F; *meta* coupling of 6-H to 4-F). [q] tt, *J* 9.2 and 7.5 (*ortho* coupling of 4-H to 3-F; *meta* coupling of 4-H to 2-F and 6-F). [r] t, *J* 1.6 (Me coupling to 2-F and 6-F). [s] t, *J* 2.1 (Me coupling to 2-F and 6-F).

Table 2 ^{19}F NMR data for fluorinated 2-phenylpropan-2-ols in $CDCl_3$, δ upfield of $CFCl_3$: R = F unless otherwise stated

Compd.	2-R	3-R	4-R	5-R	6-R
2	139.0–140.9[a]	139.0–140.9[a]	H	H	H
4	110.5[a]	H	H	H	110.5[a]
6	129.4 or 137.1[a]	129.4 or 137.1[a]	H	H	Br
8	101.5[a]	Br	H	H	101.5[a]
10	102.1[b]	Br	H	Br	102.1[b]
17	H	138.5 or 141.9[a]	138.5 or 141.9[a]	H	H
18	109.7 or 113.5[a]	H	109.7 or 113.5[a]	H	H
19	106.4 or 110.8[a]	H	106.4 or 110.8[a]	Br	H
20	Br	H	123.7–124.2[a]	123.7–124.2[a]	H
22	141.65[c]	139.64[d]	H	139.64[d]	141.65[c]
23	139.6[e] or 134.1[f]	139.6[e] or 134.1[f]	Br	139.6[e] or 134.1[f]	139.6[e] or 134.1[f]

[a] Complex multiplets: not analysed or assigned more specifically. Couplings derived from the ^{1}H spectra are given in Table 1. [b] m, *J ca.* 7.1 and 2.2 (*meta* coupling of 2-F and 6-F to 4-H; 2-F and 6-F coupled to Me). [c] ddd, *J* 10.6, 7.5 and 4.6 (*ortho* coupling of 2-F to 3-F and 5-F to 6-F; *meta* coupling of 2-F and 6-F to 4-H; *para* coupling of 2-F to 5-F and 6-F to 3-F). [d] ddd, *J* 10.6, 9.2 and 4.6 (*ortho* coupling of 3-F to 2-F; *ortho* coupling of 3-F to 4-H; *para* coupling of 3-F to 6-F and 5-F to 2-F). [e] Not assigned with certainty: d, *J* 15 (*ortho* coupling of 2-F to 3-F and 6-F to 5-F). [f] Not assigned with certainty: d, *J* 8.9 (*para* coupling of 3-F to 6-F and 2-F to 5-F).

Table 3 ^{1}H and ^{19}F NMR data for adducts of furan with fluorobenzynes: δ in $CDCl_3$

Compd.	5-R	6-R	7-R	8-R	1-H	4-H	2-H	3-H
28	F	F	H	H				
	144.3[a]	142.5[b]	6.7–7.1[c]	6.7–7.1[c]	5.65[d]	5.92[e]	7.0–7.1[e]	7.0–7.1[e]
32	H	F	H	H				
	7.0–7.1[e]	118.2[f]	6.62[g]	7.13[h]	5.62[i]	5.62[i]	7.0–7.1[e]	7.0–7.1[e]
33	H	F	F	H				
	7.05[j]	138.2[e]	138.2[e]	7.05[j]	5.66[e]	5.66[e]	7.0[k]	7.0[k]
34	H	Br	F	H				
	7.35[l]		111.0[m]	7.03[n]	5.69	5.69	7.0[k]	7.0[k]
35	Br	H	Br	F				
		7.27[o]		118.0[m]	6.01	5.77[p]	7.09[q]	7.09[q]
37	F	Br	H	H				
	115.8[m]		7.16[r]	6.89[s]	5.69[t]	5.95[e]	7.03[e]	7.03[e]

[a] dd, *J* 22 and 5 (*ortho* coupling to 6-F; *meta* coupling to 7-H). [b] dd, *J* 22 and 8–9 (*ortho* coupling to 5-F; *ortho* coupling to 7-H). [c] Complex m, with 2-H, 3-H superimposed. [d] dm, *J* 1.5. [e] br s. [f] dd, *J* 11.0 and 8.8 (*ortho* coupling to 5-H; *ortho* coupling to 7-H). [g] ddd, *J* 11.0, 8.0 and 2.5 (*ortho* coupling to 6-F; *ortho* coupling to 8-H; *meta* coupling to 5-H). [h] dd, *J* 8.0 and 4.6 (*ortho* coupling to 7-H; *meta* coupling to 6-F). [i] m, $\Delta < 2.5$ Hz. [j] dd, *J* 8.0 and 5.3 (*ortho* coupling to 6-F or 7-F; *meta* coupling to 7-F or 6-F), superimposed on 2-H and 3-H. [k] br s, superimposed on 5-H and 8-H. [l] d, *J ca.* 6.0 (*meta* coupling to 7-F). [m] br m. [n] d, *J* not determined, (*ortho* coupling to 7-F). [o] d, *J* 5.1 (*meta* coupling to 8-F). [p] d, *J* 1.6 (coupling to 8-F). [q] m, *J ca.* 1.1. [r] dd, *J ca.* 7.6 and 5.7 (*ortho* coupling to 8-H; *meta* coupling to 5-F). [s] d, *J* 7.6 (*ortho* coupling to 7-H). [t] m, coupled to 5-F.

HRMS and elemental analysis confirmed that the products had resulted from the exchange process shown. A similar result has been reported by Bridges *et al.*[4] who found carboxylation of the lithio derivative from **7** gave about 83% of crude 2,4-difluorobenzoic acid.

1,5-Dibromo-2,4-difluorobenzene **9** and 1,2-dibromo-4,5-

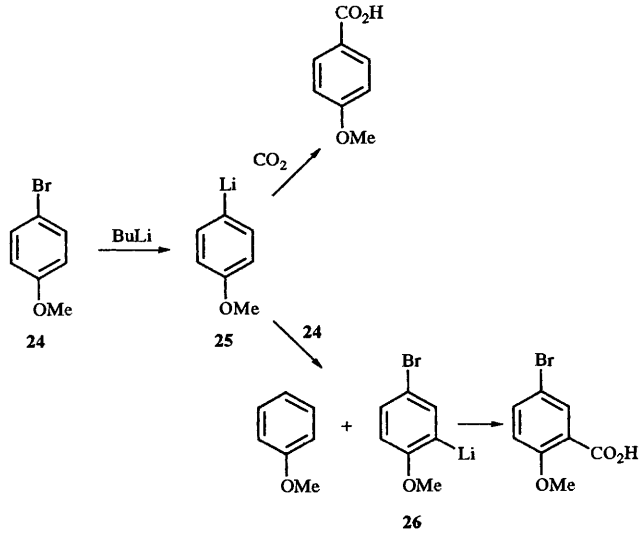
difluorobenzene **11** were treated as above with butyllithium in ether and the resulting phenyllithiums trapped with acetone. The procedure was improved by adding the butyllithium and the acetone in ether solution at −78 °C, and by allowing a longer time for the metallation. Some diacetone alcohol was still produced, but good yields were obtained of 2-(5-bromo-2,4-difluorophenyl)propan-2-ol **19** and 2-(2-bromo-4,5-difluorophenyl)propan-2-ol **20** respectively (74 and 66% of pure compounds), showing that clean bromine–lithium exchange had occurred.

We next studied the reaction of 3-bromo-1,2,4,5-tetrafluorobenzene **21** with butyllithium in ether at −78 °C to find whether the very high degree of halogenation in this compound affects the reactions. The single proton in the molecule is likely to be more acidic than those in less-substituted benzenes. However, the sole product was 2-(2,3,5,6-tetrafluorophenyl)propan-2-ol **22**, indicating that only bromine–metal exchange was occurring in ether. The yield, 63% of oily product, 50% of pure white crystalline solid, suggests that steric interactions are not significantly worse in this case than for the compounds discussed above. We shall show later that the path of this reaction is dramatically different in THF from that in ether.

Our results demonstrate that butyllithium in ether at −78 °C gives clean bromine–lithium exchange, and thus parallel those of Bridges *et al.*,[4] who used a largely different group of bromofluorobenzenes.

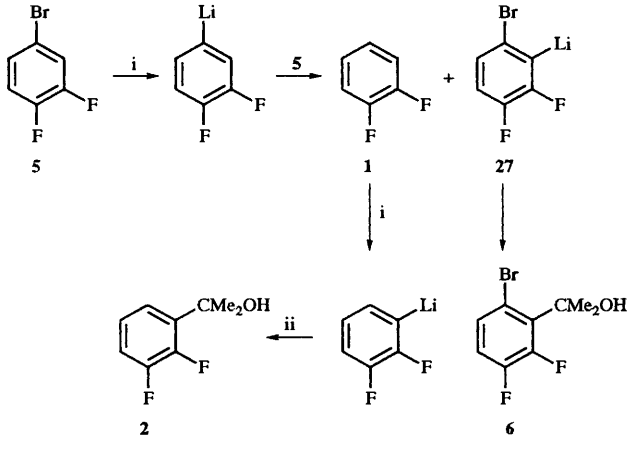
The reaction of polyhalogenobenzenes with butyllithium in THF

Before discussing the results obtained from our reactions using butyllithium in THF we shall give some background on the autometallation process. This was studied particularly by Gilman and co-workers.[10–12] As an example[10,11] (see Scheme 2), 1-bromo-4-methoxybenzene **24** was treated with butyllithium in ether, at room temperature or above, to give butyl bromide and the normal product of bromine–lithium exchange, 4-methoxyphenyllithium **25**, which could be trapped with CO_2 to give 4-methoxybenzoic acid. However, the lithium compound **25** is now a stronger base than is butyllithium and can lithiate the strongest acid present, *i.e.* further 1-bromo-4-methoxybenzene, to form equivalent amounts of 5-bromo-2-methoxyphenyllithium **26** and methoxybenzene. The former was then trapped in the reaction with CO_2. As Gilman pointed out,[12] if reaction were only to occur *via* autometallation (his so-called 'two-stage reaction') the yields of methoxybenzene or 5-bromo-2-methoxyphenyllithium, based on 1-bromo-4-methoxybenzene, could not be greater than 50%. It is, of course, possible for part of the reactions to involve this process and part to proceed by direct lithiation, the competition depending on the reagents, the solvent, the temperature, and the nature of the halogen, so that mixtures of products can be obtained.[12] Further clearly defined examples are given by Bridges *et al.*[4]



Scheme 2

We initially investigated the formation and trapping of the phenyllithiums in THF at −78 °C. They were allowed to decompose to benzynes, which were then trapped by Diels–Alder addition with furan; this work will be described later in the paper, for the sake of clarity. However, it became clear that autometallation reactions were taking place when the phenyllithiums were warmed to 25 °C. Therefore, for the present study we prepared and treated the phenyllithiums with acetone in THF at −78 °C, where we believed trapping would be rapid and the results from the metallation would be clearer. The butyllithium in hexane was added in small portions to the aromatic substrate in THF at −78 °C so that the final composition of the solvent was 3:1 THF–hexane (v/v). The mixture was stirred at −78 °C for 2 h to allow adequate time for metallation and any autometallation to occur. Acetone was then added to the mixture at −78 °C, in a procedure otherwise identical with that used with ether as solvent. Reaction of 1-bromo-3,4-difluorobenzene **5** (Scheme 3) gave two products



Scheme 3 *Reagents and conditions:* i, BuLi/THF/hexane, −78 °C; ii, MeCOMe, −78 °C

(as indicated by TLC). They were separated by column chromatography and identified as 2-(2,3-difluorophenyl)-propan-2-ol **2** and 2-(6-bromo-2,3-difluorophenyl)propan-2-ol **6**, in a molar ratio of about 1:5. The former, bromine-free product **2**, was clearly different from **17**, the product from the direct bromine–lithium exchange reaction which occurs in ether. It is identical with our samples of **2**, the sole product isolated from the metallation of 1,2-difluorobenzene by LDA in THF. The second product, **6**, could have been formed either by direct metallation by butyllithium of the starting material, with hydrogen–lithium exchange at C-2, or by the autometallation process illustrated in Scheme 3. However, the production of 2-(2,3-difluorophenyl)propan-2-ol **2** would seem to provide strong evidence that autometallation is occurring. This result also explains some of the products which are generated in the Diels–Alder reaction (see later). It is significant that no 2-(3,4-difluorophenyl)propan-2-ol **17** was isolated from this reaction, even though it is the sole product from the reaction in ether. This suggests that with THF as the solvent the autometallation between 3,4-difluorophenyllithium and its bromobenzene precursor **5** was complete, even at −78 °C.

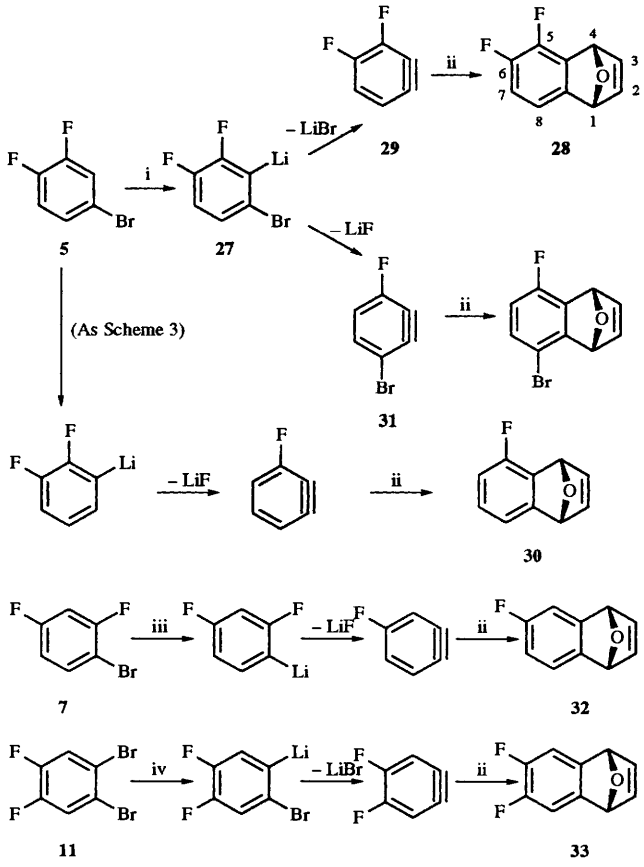
The autometallation generates 1,2-difluorobenzene **1** and 2-bromo-5,6-difluorophenyllithium **27** (see Scheme 3). It should be noted that when 0.5 equiv. of butyllithium has been added, and if the autometallation occurs at a rate comparable with that of the initial bromine–lithium exchange, the process shown will be complete and all the starting bromide will have been consumed. Any additional butyllithium can then metallate the 1,2-difluorobenzene formed in the reaction. This would be completely converted into 2,3-difluorophenyllithium if 1 equiv. of butyllithium were used. The driving force for autometallation is presumably the achievement of greater stability of the products, and 2-bromo-5,6-difluorophenyllithium **27** will be the most stable of the possible organometallic species. Although the 2-bromo-5,6-difluorophenyllithium, and thus 2-(6-bromo-2,3-difluorophenyl)propan-2-ol **6**, might be formed by direct hydrogen–lithium exchange of **5** by butyllithium, we believe that the most likely reason for its high yield compared to 2,3-difluorophenyllithium, and thus to 2-(2,3-difluorophenyl)-propan-2-ol **2**, is that less than 1 equiv. of butyllithium was inadvertently used, and the remaining (volatile) unlithiated 1,2-difluorobenzene was lost in the work-up. This result would be compatible with some of the results of Bridges *et al.*[4]

The reaction of 1-bromo-2,4-difluorobenzene **7** with butyllithium in THF was carried out in the same manner as for the 3,4-difluorophenyl isomer **5**. Column chromatography recovered the sole product visible on TLC, which was identified as 2-(3-bromo-2,6-difluorophenyl)propan-2-ol **8**. We again believe that this is formed by the autometallation process. We found no trace of 2-(2,4-difluorophenyl)propan-2-ol **18** which had been formed by bromine–lithium exchange using butyllithium in ether. However, we also found no 2-(2,6-difluorophenyl)propan-2-ol **4** which would have been formed by metallation of any 1,3-difluorobenzene produced in the autometallation process. Bridges *et al.*[4] found that this process can occur, to give about 20% of their products, but that it became much less important when there was a deficiency of butyllithium. Although it is possible that the only process occurring was direct metallation of the 1-bromo-2,4-difluorobenzene, with hydrogen–lithium exchange at C-3, it is generally believed that bromine–lithium exchange is faster than acidic hydrogen–lithium exchange,[13] and our other reactions and those of Bridges *et al.*[4] support this view. Certainly, both our results show that butyllithium in ether gives bromine–lithium exchange, and Bridges *et al.*[4] were able to show that the subsequent addition of THF allows autometallation to proceed, with the formation of the same product as would be expected from direct hydrogen–lithium exchange.

The reaction of 3-bromo-1,2,4,5-tetrafluorobenzene **21** with butyllithium in THF was studied to see whether there would be autometallation in this highly substituted compound. Chromatography separated two materials. The major one was a white solid, identified as 2-(4-bromo-2,3,5,6-tetrafluorophenyl)-propan-2-ol **23**. The other fraction appeared to be a mixture of unchanged starting material and an unidentified hydrocarbon material, believed to result from attack of butyl anion on an organolithium or a benzyne intermediate (see later). There was also evident from the ^{19}F spectrum a small amount of 1,2,4,5-tetrafluorobenzene. It is significant that the major product retains its bromine atom, consistent with bromine–lithium exchange of some of the bromotetrafluorobenzene followed by autometallation. This is in marked contrast to the behaviour with butyllithium in ether (see earlier). The yields in the reaction were rather low, possibly as a result of steric effects.

Diels–Alder reactions of benzynes formed from fluorinated phenyllithiums (Scheme 4)

In the next stage of our work we studied whether lithium fluoride or lithium bromide would be preferentially eliminated from *ortho* lithiated bromofluorobenzenes. The Diels–Alder reaction with furan was used to intercept any benzynes formed. Unfortunately, the results were not always clear, for reasons which will be explained.



Scheme 4 *Reagents and conditions:* i, BuLi/THF/hexane, −78–20 °C; ii, furan; iii, BuLi/Et_2O/hexane, −78; iv, BuLi/Et_2O/hexane, −78–20 °C

We first discuss the reaction of 1-bromo-3,4-difluorobenzene **5** with butyllithium in THF. The butyllithium in hexane was added in small portions to the aromatic substrate in THF at −78 °C, the final composition of the solvent being 3:1 THF–hexane (v/v). An excess of furan was then added to it, and the mixture warmed to 20 °C overnight to trap any benzyne intermediates. The product contained three main components, comprising about 14, 63 and 20% of the mixture. Column chromatography allowed the isolation of two main fractions. The first, believed to be a mixture, gave a ^1H NMR spectrum dominated by alkyl signals in a ratio of about 2:1 over the aromatic signals and a ^{19}F spectrum containing three signals (see later). The second fraction gave ^1H signals close to those expected for structure **28**, and two signals of equal intensity in the ^{19}F spectrum, as expected for an unsymmetrical furan adduct. The latter would be formed from 3,4-difluorobenzyne **29**, produced by loss of lithium bromide and not lithium fluoride from **27** formed as earlier (Scheme 3). Other possibilities include attack by further butyllithium on 1,2-difluorobenzene formed during autometallation, which could form 3-fluorobenzyne and then the adduct **30** and account for one signal in the ^{19}F NMR spectrum of the first fraction. The benzyne **29** or 3-bromo-6-fluorobenzyne **31**, which would be formed by loss of lithium fluoride from **27**, may also be attacked by butyllithium to form the butylated product(s) believed to be in the first fraction. Analysis of the NMR data was aided by the work of Gribble and co-workers, who showed that the characteristic long-range coupling (*J ca.* 2) of a bridgehead proton (1-H) is to a

remote fluorine atom at C-5, and not to a proximal one at C-8.[14]

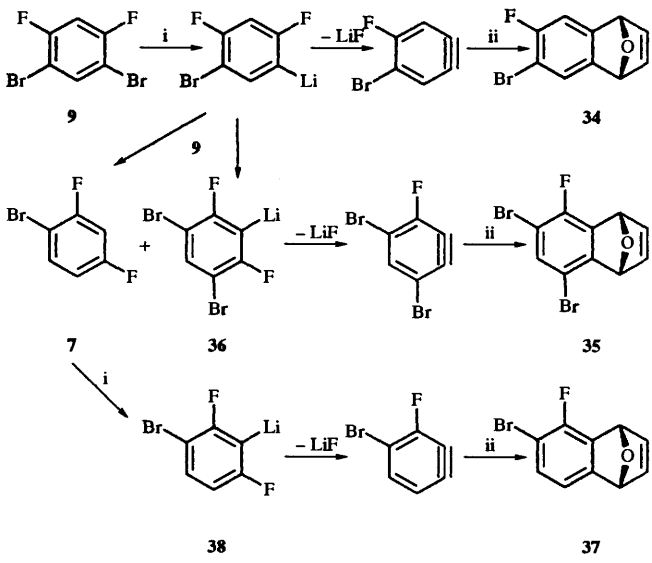
The reaction of 1-bromo-2,4-difluorobenzene **7** with butyllithium in ether–hexane followed by furan was studied next. The product showed only one signal in its ^{19}F NMR spectrum, and its ^{1}H NMR spectrum was consistent with the structure **32**. The direct bromine–lithium exchange found in our earlier experiments in ether could only be followed by loss of lithium fluoride to form 4-fluorobenzyne.

The reaction of 1-bromo-2,4-difluorobenzene **7** with butyllithium in THF followed by furan gave much more complicated results. The experimental procedure was the same as for 1-bromo-3,4-difluorobenzene. Although we have evidence of the formation of a furan adduct which would be expected to follow direct bromine–lithium exchange and aryne formation, the NMR of the crude product indicated that there had also been nucleophilic attack by butyl anion. However, the products could not be separated properly.

Although the foregoing experiments did not allow full separation or characterization of the Diels–Alder adducts they do confirm the strong solvent effect on the formation and reactions of the halogenated phenyllithiums. Reactions in a solvent mixture rich in ether allow clean preparation of the benzyne adduct and appear to prevent autometallation. In contrast, the use of a solvent rich in THF makes autometallation reactions rapid and important. This can produce a greater variety of lithiated products and subsequent benzynes, and then of the Diels–Alder adducts. The reaction also seems to be complicated by trapping of the benzyne intermediates by butyl anion instead of furan.

The conclusions reached above are supported by reactions in which 1,2-dibromo-4,5-difluorobenzene **11** was treated with butyllithium in ether–hexane, followed by the addition of furan (Scheme 4). We showed earlier that the phenyllithiums can be prepared smoothly, with bromine–lithium exchange, from 1,5-dibromo-2,4-difluorobenzene **9** and the 1,2-dibromo-4,5-difluoro isomer **11** when ether was used as solvent at −78 °C. However, when we allowed the intermediate from **11** to warm to room temperature overnight in the presence of excess furan at least three products were formed. The first fraction from column chromatography was shown by NMR spectroscopy to contain an alkyl group, probably from trapping of a benzyne intermediate by butyl anion, although the ^{1}H NMR spectrum was not fully consistent with this material being pure 1-butyl-3,4-difluorobenzene. The main product had NMR spectra which confirm its symmetry and, with the mass spectrum, are consistent with the structure **33**. A further fraction appeared to be an aryne–furan adduct, but there was too little material to allow further purification. A little 1-bromo-3,4-difluorobenzene was present, probably from an autometallation reaction.

The reaction of 1,5-dibromo-2,4-difluorobenzene **9** with butyllithium in ether–hexane was studied next, with trapping of the benzynes by furan. The experimental procedure was identical with the previous one, but some striking results were obtained. TLC indicated the presence of at least five compounds (see Scheme 5). There was some unchanged starting material containing 1-bromo-2,4-difluorobenzene **7**, probably formed in the autometallation process (see earlier). The other three materials, separated by chromatography, all showed single signals in their ^{19}F NMR spectra and were identified as furan adducts. The largest (third) fraction is assigned the structure 6-bromo-7-fluoro-1,4-epoxy-1,4-dihydronaphthalene **34**. This would arise by formation of 5-bromo-2,4-difluorophenyllithium (see Scheme 5), loss of lithium fluoride to give 4-bromo-5-fluorobenzyne, and Diels–Alder trapping with furan. The first fraction was identified as 6,8-dibromo-5-fluoro-1,4-epoxy-1,4-dihydronaphthalene **35**. This could form by autometallation of further **9** by the previous organolithium to give **36** and **7**, loss of lithium fluoride to give 4,6-dibromo-3-fluorobenzyne, and trapping. The second, small fraction had spectra consistent with it being 6-bromo-5-fluoro-1,4-epoxy-1,4-dihydronaphthalene **37**. This could arise by the 1-bromo-2,4-difluorobenzene **7**, above, reacting to form 3-bromo-2,6-difluorophenyllithium **38** which could give two possible elimination products. Loss of 6-F would give 3-fluoro-4-bromobenzyne and then **37**. However, the required lithio compound is not that given from 1-bromo-2,4-difluorobenzene by direct reaction with phenyllithium. The alternative loss of 2-F would lead to a furan adduct having bromine and fluorine atoms in a *para* relationship: the ^{1}H NMR spectrum shows that this is not the case, thereby excluding the isomeric structure, 5-bromo-8-fluoro-1,4-epoxy-1,4-dihydronaphthalene. It is notable that evidence of autometallation *is* found in the reactions of 1,5-dibromo-2,4-difluorobenzene **9** in the present experiments. It results in the loss of lithium fluoride from the (symmetrical) intermediate **36**, and the formation of the adduct **35** which retains both bromine atoms of the starting material. It contrasts with the results of trapping with acetone at −78 °C of the lithiated species formed in ether–hexane, which gave **19**. The clear and essential difference is that the lithiated intermediate has to be warmed to allow decomposition to the benzyne for the Diels–Alder additions, and this also allows autometallation to occur.



Scheme 5 *Reagents and conditions:* i, BuLi/Et_2O/hexane, −78–20 °C; ii, furan

Experimental

All solvents were purified and dried according to Vogel.[15] Butyllithium was used as purchased, as a 1.6 mol dm^{-3} solution in hexane, unless otherwise stated. All reactions using strong bases were conducted under an atmosphere of purified nitrogen. Analytical GLC was run on Pye–Unicam Series 304 or Shimadzu GC-R1A machines using silicone gum SE 30 columns on Celite. Column chromatography used silica, with CH_2Cl_2 as solvent unless otherwise stated. Mps were taken on a Gallenkamp apparatus, and are uncorrected. IR spectra were run on a Perkin-Elmer series 1600 FT IR machine. NMR spectra were run on a Perkin-Elmer R-12B machine at 60 MHz (^{1}H) and at 56.4 MHz (^{19}F), on a JEOL FX-90Q machine at 90 MHz (^{1}H) or 84.26 MHz (^{19}F), or on a JEOL GX-270 machine at 270 MHz (^{1}H only). The references used were TMS (^{1}H) and $CFCl_3$ (^{19}F, chemical shift as ppm upfield). Mass spectra were recorded on a Kratos MS80 instrument. Ether refers to diethyl ether.

General procedure for LDA reactions in THF, and trapping with acetone

Butyllithium in hexane (32.5 cm^3, 0.052 mol) was added in portions to dry diisopropylamine (7.3 cm^3) in dry THF at 0 °C under nitrogen. The mixture was stirred at 0 °C for 15 min then cooled to −78 °C. The aromatic substrate was added in portions to the mixture. After being stirred for 30 min acetone (4 × 5 cm^3) was added at −78 °C and the mixture allowed to warm to room temperature. The products were poured into 1 mol dm^{-3} hydrochloric acid (200 cm^3) and extracted with ether (100 cm^3), the ether solution washed with water (200 cm^3) and dried ($MgSO_4$). The solvents were removed by rotary evaporation to give an oil, in each case.

Reaction of 1,2-difluorobenzene 1 with LDA and trapping with acetone: preparation of 2-(2,3-difluorophenyl)propan-2-ol 2. 1,2-Difluorobenzene **1** (5.3 cm^3, 0.052 mol) was treated with LDA as above. Distillation under reduced pressure of the yellow product (7.9 g) gave a colourless oil (6.9 g), bp 80–82 °C at 5.0 mmHg. Column chromatography gave 2-(2,3-difluorophenyl)propan-2-ol **2** (74%) (Found: C, 63.0; H, 5.9. $C_9H_{10}F_2O$ requires C, 62.8; H, 5.8%); *m/z* 172 $(M)^+$ and 157 $(M - CH_3)^+$. The ^{19}F NMR spectrum of this product shows a single signal. Mass spectrometry indicates the presence of two fluorines, so the two ^{19}F NMR signals must accidentally coincide. The product must result from the removal of 3-H from the 1,2-difluorobenzene, as in its reaction with butyllithium. In contrast, the product from reaction of 1-bromo-3,4-difluorobenzene with butyllithium in ether showed two ^{19}F NMR signals.

Reaction of 1,3-difluorobenzene 3 with LDA and trapping with acetone: preparation of 2-(2,6-difluorophenyl)propan-2-ol 4. The procedure was identical with that preceding. Distillation of the crude product (6.9 g) gave 2-(2,6-difluorophenyl)propan-2-ol **4** (5.2 g, 56%), bp 70–72 °C at 6.0 mmHg; traces of impurity were removed by column chromatography (Found: C, 62.3; H, 5.8. $C_9H_{10}F_2O$ requires C, 62.8; H, 5.8%); *m/z* 172 $(M)^+$, 171 $(M - H)^+$ and 157 $(M - CH_3)^+$. The product shows a single ^{19}F NMR signal and the ^1H NMR spectrum shows the methyl resonance as a fine triplet, indicating coupling to two equivalent *ortho* fluorines.

Reaction of 1-bromo-3,4-difluorobenzene 5 with LDA and trapping with acetone: preparation of 2-(6-bromo-2,3-difluorophenyl)propan-2-ol 6. 1-Bromo-3,4-difluorobenzene **5** (10.0 g, 0.052 mol) was treated as above. Distillation of the crude product (10.0 g) under reduced pressure gave material, bp 82–85 °C at 0.5 mmHg. Column chromatography gave 2-(6-bromo-2,3-difluorophenyl)propan-2-ol **6**, a pale brown waxy solid (3.7 g, 28%) (Found: C, 42.9; H, 3.6. $C_9H_9F_2BrO$ requires C, 43.0; H, 3.6%) *m/z* 252, 250 (M^+) and 237, 235 $(M - CH_3)^+$ with ^{81}Br and ^{79}Br. The ^1H NMR spectrum showed a methyl doublet, indicating coupling to a single *ortho* fluorine. This product was identical with that formed from reaction of the same aromatic substrate with butyllithium.

Reaction of 1-bromo-2,4-difluorobenzene 7 with LDA and trapping with acetone: preparation of 2-(3-bromo-2,6-difluorophenyl)propan-2-ol 8. 1-Bromo-2,4-difluorobenzene **7** reacted with LDA in a procedure identical with that above. Distillation under reduced pressure of the crude product (10.5 g) gave a pale green oil (9.3 g), bp 82–85 °C at 0.75 mmHg. The two main components were separated by column chromatography: the second (0.3 g) did not contain fluorine (NMR). The first fraction was 2-(3-bromo-2,6-difluorophenyl)propan-2-ol **8** (6.5 g, 50%) (Found: C, 43.0; H, 3.6. $C_9H_9F_2BrO$ requires C, 43.0; H, 3.6%); *m/z* 252, 250 and 237, 235 for M^+ and $(M - CH_3)^+$ with ^{81}Br and ^{79}Br. This product contained two fluorine and one bromine atom (^{19}F NMR and mass spectrometry). The ^1H NMR signal for the methyl protons was split into a fine triplet by the two *ortho* fluorines. The same product was produced using butyllithium in THF as the base.

Reaction of 1,5-dibromo-2,4-difluorobenzene 9 with LDA and trapping with acetone: preparation of 2-(3,5-dibromo-2,6-difluorophenyl)propan-2-ol 10. 1,5-Dibromo-2,4-difluorobenzene **9** (10.0 g, 0.037 mol) in THF (25 cm^3) was added in 2 cm^3 portions to 1.0 equiv. of LDA at −78 °C. Distillation at reduced pressure of the crude yellow oil (8.5 g) gave two fractions. The first (0.2 g) was starting material contaminated with 1-bromo-3,4-difluorobenzene, mesityl oxide and diacetone alcohol. The second fraction (2.7 g) was also unchanged starting material (NMR). Purification of the residue (5.0 g) by column chromatography gave 2-(3,5-dibromo-2,6-difluorophenyl)propan-2-ol **10**, a white amorphous solid (3.2 g, 26%), mp 62.8–64.0 °C; *m/z* 332, 330, 328 for M^+ of the dibromo compound, and 317, 315 and 313 for $(M - CH_3)^+$.

Reaction of 1,2-dibromo-4,5-difluorobenzene 11 with LDA and trapping with acetone: attempted preparation of 2-(2,3-dibromo-5,6-difluorophenyl)propan-2-ol 12. 1,2-Dibromo-4,5-difluorobenzene **11** (10.0 g) in THF (25 cm^3) was treated as above. Distillation under reduced pressure of the dark green mixture gave unchanged starting material (4.6 g) and a colourless oil (0.75 g), bp 62–66 °C at 10.0 mmHg, which contained 1-bromo-3,4-difluorobenzene, a minor impurity in the starting material, unchanged 1,2-dibromo-4,5-difluorobenzene **11**, and mesityl oxide from attack by LDA on acetone. None of the desired product had formed in this reaction.

General procedure for the preparation of difluorophenyllithiums in ether, using butyllithium in ether, and their reactions with acetone

Butyllithium (portions of 1–2 cm^3) was added over about 1 h to a solution of the bromodifluorobenzene (10.0 g) in ether (50 cm^3) at −78 °C. The excess of acetone (portions of about 1 cm^3) was added to the solution, maintained at −78 °C. The mixture was allowed to warm to room temperature, poured into dilute acid and extracted with ether. Evaporation of the solvent gave yellow oils which were distilled to remove most of the diacetone alcohol and mesityl oxide, then further purified by column chromatography. In both cases the ^{19}F NMR spectrum showed two signals of equal intensity. Mass spectrometry and elemental analysis confirmed that the products resulted from the bromine–lithium exchange process shown in Scheme 1.

Reaction of 1-bromo-3,4-difluorobenzene 5 with butyllithium in ether followed by trapping with acetone: preparation of 2-(3,4-difluorophenyl)propan-2-ol 17. 3,4-Difluorophenyllithium (0.052 mol) prepared from **5** as above, reacted with acetone to give a pale yellow oil (6.5 g, 73%). Distillation under reduced pressure (twice) gave 2-(3,4-difluorophenyl)propan-2-ol **17** (4.5 g, 51%), bp 87–88 °C at 6.0 mmHg (Found: C, 62.8; H, 5.8. $C_9H_{10}F_2O$ requires C, 62.8; H, 5.8%); *m/z* 172 $(M)^+$ and 157 $(M - CH_3)^+$.

Reaction of 1-bromo-2,4-difluorobenzene 7 with butyllithium in ether followed by trapping with acetone: preparation of 2-(2,4-difluorophenyl)propan-2-ol 18. In a procedure identical with that preceding, 1-bromo-2,4-difluorobenzene **7** gave 2-(2,4-difluorophenyl)propan-2-ol **18** (5.5 g, 62%), bp 74–76 °C at 6.0 mmHg (Found: C, 62.5; H, 6.0. $C_9H_{10}F_2O$ requires C, 62.8; H, 5.8%); *m/z* 172 $(M)^+$ and 157 $(M - CH_3)^+$.

Reaction of 1,5-dibromo-2,4-difluorobenzene 9 with butyllithium in ether followed by trapping with acetone: preparation of 2-(5-bromo-2,4-difluorophenyl)propan-2-ol 19. In an otherwise identical preparation, 1,5-dibromo-2,4-difluorobenzene **9** gave a yellow oil (8.08 g, 87%). Chromatography gave the product **19** as a white solid (6.86 g, 74%), mp 62.0–62.6 °C (Found: C, 43.0; H, 3.40. $C_9H_9F_2BrO$ requires C, 43.0; H, 3.4%).

Reaction of 1,2-dibromo-4,5-difluorobenzene 11 with butyllithium in ether followed by trapping with acetone: preparation of 2-(2-bromo-4,5-difluorophenyl)propan-2-ol 20. Butyllithium (in hexanes; 23.0 cm^3, 0.037 mol) reacted with 1,2-dibromo-4,5-

difluorobenzene **11** (10.0 g, 0.027 mol) at −78 °C in ether, then with acetone to give a pale green oil (7.42 g, 80%). Chromatography gave 2-(2-bromo-4,5-difluorophenyl)propan-2-ol **20** (6.17 g, 66%), a colourless oil (Found: C, 42.7; H, 3.7. $C_9H_9F_2BrO$ requires C, 43.0; H, 3.6%).

Reaction of 3-bromo-1,2,4,5-tetrafluorobenzene 21 with butyllithium in ether followed by trapping with acetone: preparation of 2-(2,3,5,6-tetrafluorophenyl)propan-2-ol 22. 3-Bromo-1,2,4,5-tetrafluorobenzene (10.0 g, 0.044 mol) was treated as above to give a yellow oil (5.77 g). Chromatography (silica, $CHCl_3$) afforded only 2-(2,3,5,6-tetrafluorophenyl)-propan-2-ol **22**, as a white crystalline solid (4.62 g, 50%) (Found: C, 51.8; H, 3.8. $C_9H_7F_4O$ requires C, 51.9; H, 3.8%); *m/z* 208 $(M)^+$ and 193 $(M - CH_3)^+$.

Preparation of difluorophenyllithiums in THF, using butyllithium in hexane–THF, and their reactions with acetone

Reaction of 1-bromo-3,4-difluorobenzene 5 with butyllithium in THF followed by trapping with acetone. To a solution of 1-bromo-3,4-difluorobenzene **5** (10.0 g, 0.052 mol) in THF (60 cm^3) at −78 °C was added butyllithium in hexanes (32.5 cm^3, 0.052 mol) mixed with THF (50 cm^3), at −78 °C, during 50 min. The mixture was stirred at −78 °C for 2 h, then acetone (20 cm^3) in THF (60 cm^3) was added to it *via* a syringe at −78 °C in portions (5 cm^3) over 80 min. After warming to room temperature overnight and work-up a yellow oil (7.65 g) was obtained. Chromatography afforded 2-(2,3-difluorophenyl)-propan-2-ol **2** (1.00 g) and 2-(6-bromo-2,3-difluorophenyl)-propan-2-ol **6** (5.45 g, 42%).

Reaction of 1-bromo-2,4-difluorobenzene 7 with butyllithium in THF followed by trapping with acetone. The procedure was identical with the previous preparation. Column chromatography of the green–yellow oil (5.20 g) gave the sole detectable product, 2-(3-bromo-2,6-difluorophenyl)propan-2-ol **8** (4.78 g, 37%).

Reaction of 3-bromo-1,2,4,5-tetrafluorobenzene 21 with butyllithium in THF followed by trapping with acetone. 3-Bromo-1,2,4,5-tetrafluorobenzene (10.0 g, 0.044 mol) was cooled to −78 °C in THF (50 cm^3). Butyllithium (1.6 mol dm^{-3} in hexanes; 28.0 cm^3, 0.045 mol) mixed with THF (50 cm^3) was added dropwise to the mixture with vigorous stirring at −78 °C then allowed to warm to room temperature. Work-up gave a pale yellow oil (5.8 g). Column chromatography ($CHCl_3$ on silica) separated the two components into a mixture (0.90 g) of starting material and an unknown hydrocarbon substance, and 2-(4-bromo-2,3,5,6-tetrafluorophenyl)propan-2-ol **23** (3.31 g, 27%), mp 60.6–61.3 °C (Found: C, 37.6; H, 2.5. $C_9H_7F_4BrO$ requires C, 37.6; H, 2.4%); *m/z* 288 $(M\ [^{81}Br])^+$, 286 $(M\ [^{79}Br])^+$, 273 $(M\ [^{81}Br] - CH_3)^+$ and 271 $(M\ [^{79}Br] - CH_3)^+$.

Preparation of difluorophenyllithiums in THF, using butyllithium in hexane–THF, and their reactions with furan

Reaction of 1-bromo-3,4-difluorobenzene 5 with butyllithium in THF followed by trapping with furan. Butyllithium (0.053 mol) was added as above to 1-bromo-3,4-difluorobenzene **5** (10.0 g, 0.052 mol) in dry THF (100 cm^3) at −78 °C, during 2 h. The mixture was stirred for a further 1 h at −78 °C, then furan (7.1 g, 0.11 mol) was added to it in portions of 1 cm^3, and the mixture allowed to warm to room temperature overnight. Work-up, and distillation of the orange oil (5.4 g) gave a colourless oil (2.0 g), bp 60–62 °C at 0.5 mmHg, and a resinous residue (2.2 g). Temperature-programmed GLC showed the presence of three components, representing 14, 63 and 20% of the mixture, in order of increasing retention time. Column chromatography gave two materials. The first was a colourless oil of uncertain composition (0.5 g), whose NMR spectra showed alkyl peaks, believed to arise from butyl groups, aromatic signals, and three ^{19}F signals of about equal intensity. The second, a pale green oil (2.5 g), is thought to be 5,6-difluoro-1,4-epoxy-1,4-dihydronaphthalene **28**, based on the ^1H NMR spectra and the ^{19}F spectrum (two signals of equal intensity, as expected for an unsymmetrical furan adduct). This would be formed from the benzyne **29**, produced by loss of lithium bromide from **27**.

Reaction of 1-bromo-2,4-difluorobenzene 7 with butyllithium in ether, followed by trapping with furan. Butyllithium, (32.5 cm^3, 0.052 mol) was added in portions of 1 cm^3 over 3 h, to a stirred solution of 1-bromo-2,4-difluorobenzene **7** (10.0 g, 0.052 mol) in dry ether (50 cm^3) at −78 °C. Furan (7.1 g, 0.110 mol) was added in portions over 10 min at −78 °C, then the mixture was allowed to warm to room temperature overnight. Work-up and purification by vacuum distillation gave 6-fluoro-1,4-epoxy-1,4-dihydronaphthalene **32** (5.2 g, 62%).

In a procedure identical with the one described above, but using THF as solvent instead of ether, an orange oil (5.14 g) was obtained, which was shown by TLC analysis to contain at least four components, one of which was probably 6-fluoro-1,4-epoxy-1,4-dihydronaphthalene **32** (^1H NMR), but the products could not be properly separated or characterized.

Reaction of 1,2-dibromo-4,5-difluorobenzene 11 with butyllithium in ether, followed by trapping with furan. To 1,2-dibromo-4,5-difluorobenzene **11** (10.0 g, 0.037 mol) in ether (50 cm^3) was added dropwise butyllithium (in hexanes; 23.0 cm^3, 0.037 mol) mixed with ether (50 cm^3), over 45 min at −78 °C. The mixture was stirred for a further 1 h at −78 °C, then furan (10.0 g, 0.147 mol) in ether (50 cm^3) was added to it *via* a syringe in 5 cm^3 portions over 30 min. The mixture was stirred and warmed to 20 °C overnight. Work-up with column chromatography (silica, $CHCl_3$) gave: (i), a pale unidentified yellow oil; (ii), an unidentified crystalline solid and (iii), a brown resin (4.22 g, 64%). This last fraction was recrystallized from methanol–water to give 6,7-difluoro-1,4-epoxy-1,4-dihydronaphthalene **33** (2.19 g, 33%) as a tan-coloured solid.

Reaction of 1,5-dibromo-2,4-difluorobenzene 9 with butyllithium in ether, followed by trapping with furan. An identical reaction using 1,5-dibromo-2,4-difluorobenzene **9** gave a brown oil (7.35 g) which crystallized on cooling. Five components were separated by column chromatography (1 : 1 CH_2Cl_2 : $CHCl_3$ on silica): (i), an unidentified pale yellow oil (0.56 g); (ii), 5,7-dibromo-8-fluoro-1,4-epoxy-1,4-dihydronaphthalene **35** (2.57 g), *m/z* 322, 320, 318 and 296, 294 and 292 $(M - C_2H_2)$; (iii), 6-bromo-5-fluoro-1,4-epoxy-1,4-dihydronaphthalene **37** (0.34 g), *m/z* 242 and 240 for fragments containing ^{81}Br and ^{79}Br, respectively, and 216 and 214 $(M - C_2H_2)$, and (iv), 6-bromo-7-fluoro-1,4-epoxy-1,4-dihydronaphthalene **34** (2.30 g), *m/z* 242 and 240, and 216 and 214 $(M - C_2H_2)$. A dark resinous residue (0.40 g) was not characterized.

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