The synthesis of novel highly substituted benzene derivatives for use in palladium-catalysed cross-coupling reactions

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A combination of conventional electrophilic aromatic substitution reactions and low-temperature *ortho*-directed lithiations has been used in the efficient synthesis of some novel highly substituted benzene derivatives containing alkoxy, alkyl, bromo, cyano, fluoro and iodo functions. The use of such compounds is exemplified by selective palladium-catalysed cross-coupling reactions to generate a series of liquid crystalline terphenyls with a lateral fluoro substituent *ortho* to a lateral cyano group.

Introduction

Palladium-catalysed cross-coupling reactions[1–6] have revolutionised the synthetic routes to aryl systems in many areas such as liquid crystals,[7–11] pharmaceuticals,[12–15] natural products[16] and polymers.[17–20] The modern synthetic methodology often requires apparently simple substituted benzene units in a convergent synthetic strategy and yet, surprisingly, such units have frequently not been reported. The difficulty in the synthesis of highly substituted benzene units, arises because the substituent(s) initially present may direct an electrophile to an undesired position, or prevent a reaction through deactivation and/or by steric hindrance. The methods and intermediates reported here are useful generally in providing units suitable for inclusion in pharmaceuticals, liquid crystals and oligomeric and polymeric light-emitting systems. In addition to sites for selective coupling, the benzene unit requires the presence of other substituents to give the properties required of the final material. In the work reported here, bromo and iodo leaving groups and the boronic acid unit have been employed for the coupling reactions, and alkoxy, alkyl, cyano and fluoro substituents provide the desired properties in a selection of liquid crystals. A discussion of the liquid crystal properties of the lateral cyanofluoroterphenyls will be published later as part of a larger programme of work.

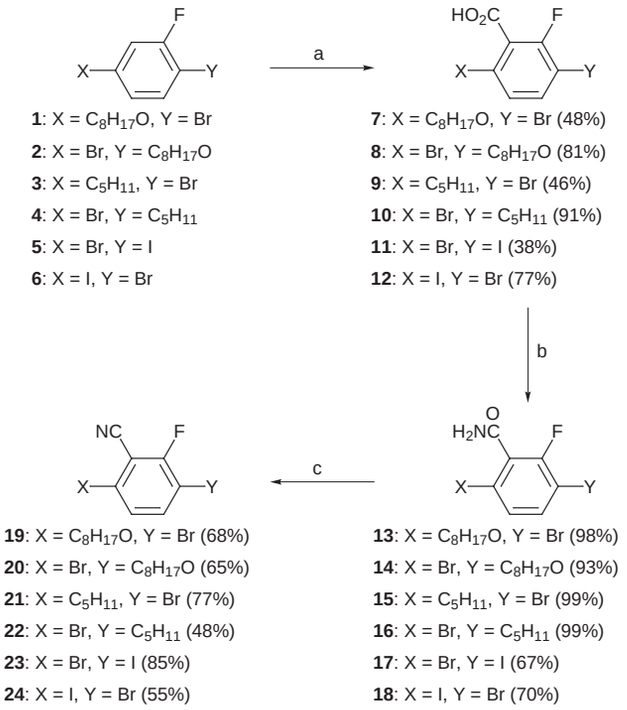
One useful method for introducing functional units into an aromatic ring, which complements electrophilic substitution and may circumvent any limitations, is through hydrogen–metal exchange reactions.[7,21–29] Such metallation techniques are, of course, only feasible where a proton is sufficiently acidic to be removed by a convenient base such as butyllithium or lithium diisopropylamide (LDA). Iodo and bromo substituents are employed as the sites for palladium-catalysed cross-coupling reactions and further substituents provide the required properties of the final materials. For example, a fluoro substituent is often present to generate the required mesomorphic and dielectric properties of liquid crystals for commercial display devices,[7,30–33] or to provide enhanced biological activity and reduced side effects in pharmaceuticals,[22,34–36] and alkyl and alkoxy chains are essential features of viable liquid crystals,[7] and they give greater processability to light-emitting polymers.[17–20] All of the halogeno units mentioned above are of great significance because they can render the neighbouring protons acidic, and hence enable the introduction of a wide range of moieties either directly (*e.g.* aldehyde, carboxylic acid, halogens, boronic acid) or through subsequent functional group interconversions (*e.g.* amide, amine, nitrile, phenol, aryl, alkyl).[7,21–29]

One aspect of our research on the synthesis of liquid crystals requires compounds (*e.g.* **27**–**30**, **35** and **36**) with a nitrile group located next to a fluoro substituent to achieve a large lateral dipole; such materials are expected to confer a high dielectric biaxiality to ferroelectric mixtures.[37,38] The preparation of these liquid crystals required the synthesis of benzene intermediates with four different substituents (compounds **19**–**24**). Starting materials **1**–**6** have been reported previously[31,39] and have two or three aromatic protons that are acidic. In each case the presence of bromo and iodo substituents precludes the use of butyllithium, which could undergo halogen–metal exchange instead of hydrogen–metal exchange, whereas lithium diisopropylamide circumvents such problems and only gives hydrogen–metal exchange.[21] This paper explores the selectivity of lithium diisopropylamide metallation in such compounds.

Results and discussion

All three aromatic protons of compound **1** are acidic, but the proton between the reinforcing influences of the fluoro substituent and the alkoxy chain proved, as expected, to be the most acidic. Treatment of compound **1** with LDA (prepared *in situ* from diisopropylamine and *n*-butyllithium)[28,40] produced an aryllithium salt which was quenched with carbon dioxide to give carboxylic acid **7** on acidification (Scheme 1). In compound **2**, the reinforcing effects of the fluoro and bromo substituents make the proton between the two units most acidic and allowed the efficient preparation of the desired carboxylic acid **8**. There are similar acidity-reinforcing effects of two substituents in compounds **4**–**6**, which allowed the generation of compounds **10**–**12** in good yields. The issue for compound **3** is less clear-cut because there is not a proton between two acidity-promoting units and the pentyl chain could reduce the tendency for proton abstraction next to the fluoro substituent by its inductive effect and by steric hindrance. In fact, treatment of compound **3** with LDA and subsequent quenching of the lithium salt with solid carbon dioxide gave compound **9** as the sole product, proving that the proton next to the fluoro substituent is the more acidic position. In all cases shown in Scheme 1, the lithiations with LDA were necessarily carried out at low temperature (−78 °C) in order to prevent the formation of a benzyne derivative through the elimination of lithium halide.

The structures of the carboxylic acids **7**–**12** were easily and convincingly assigned through ^{1}H NMR spectroscopy on the basis of the expected frequency and coupling constants of the aromatic protons. The proton *meta* to the fluoro substituent gave a double doublet due to a $^3J_{HH}$ coupling constant of 8 Hz



Scheme 1 *Reagents*: a (i), LDA, THF; (ii), CO_2, THF; (iii), HCl, H_2O; b (i), oxalyl chloride, DMF; (ii), 35% NH_3, diglyme; c thionyl chloride, DMF.

and a $^4J_{HF}$ coupling constant of 7 Hz. The proton *para* to the fluoro substituent also gave a double doublet due to a $^3J_{HH}$ coupling constant of 8 Hz and a $^5J_{HF}$ coupling constant of 1 Hz. If an alternative proton had been abstracted and hence the carboxy group located differently, then the fluoro substituent in the product would have been *ortho* to a proton and the ^{1}H NMR spectrum would clearly have revealed a signal with a large coupling constant ($^3J_{HF}$ = 12 Hz).

Standard functional group interconversions on acids **7**–**12** gave the desired cyano-substituted compounds (**19**–**24**) through the intermediate amides (**13**–**18**); these nitriles represent final materials before coupling reactions and so the structures were further characterised by elemental combustion analyses.

Palladium-catalysed cross-coupling reactions with arylboronic acids were used to construct liquid crystalline materials **27**–**30**, **35** and **36**. In the case of nitriles **19**–**22**, the bromo substituent is the only viable coupling site, and reaction in each case with an appropriate biphenylboronic acid (**25** or **26**) gave good yields of four isomeric liquid crystalline terphenyls with a fluoro substituent and a cyano group inherently fixed on the same side of the molecule to provide a high lateral dipole (Scheme 2).

As shown in Scheme 3, selective couplings are particularly useful in the construction of unsymmetrical multi-aryl liquid crystals. Nitriles **23** and **24** each possess bromo and iodo leaving groups, and the first coupling reaction with the alkoxy-substituted arylboronic acid **31** occurs preferentially at the iodo site in each case to generate biphenyls **32** and **33** respectively in reasonably good yields. The subsequent exploitation of the less reactive bromo substituent of biphenyls **32** and **33** in a second coupling reaction, this time with the alkyl-substituted arylboronic acid **34**, generated unsymmetrical liquid crystalline terphenyls **35** and **36** respectively.

Summary

Selective *ortho*-directed metallation has enabled the efficient synthesis of some novel, highly substituted benzenes with iodo, bromo, fluoro, cyano, alkoxy and alkyl substituents (compounds **7**–**24**). Importantly, the intermediate carbanions generated through selective metallation permit the introduction of a wide range of functional units, as mentioned previously and exemplified here by the introduction of the carboxy group as a precursor to a nitrile function. The utility of the intermediate compounds in selective palladium-catalysed cross-coupling reactions at the bromo and iodo sites has been demonstrated by the efficient synthesis of a series of liquid crystalline terphenyls.

Experimental

Confirmation of the structures of intermediates and products was obtained by ^{1}H NMR spectroscopy (JEOL JNM-GX270 spectrometer), infrared spectroscopy (Perkin-Elmer 457 grating spectrophotometer) and mass spectrometry (Finnigan-MAT 1020 GC-MS spectrometer). Elemental analysis (Fisions EA1108 CHN) data were obtained for each of the following compounds, **19**–**24**, **27**–**30**, **32**, **33**, **35** and **36**. All the aromatic $^3J_{HH}$ coupling constants are approximately 8 Hz in each case, and they are not reported unless coupling with a fluoro substituent also occurs. The progress of reactions was frequently monitored using a Chrompack 9001 capillary gas chromatograph fitted with a CP-SIL 5 CB 10 m × 0.25 mm, 0.12 μm column (Cat. No. 7700). Melting points and transition temperatures were measured using a Mettler FP5 hot-stage and control unit in conjunction with an Olympus BH2 polarising microscope and these were confirmed using differential scanning calorimetry (Perkin-Elmer DSC-7 and IBM data station). The purities of compounds **19**–**24**, **27**–**30**, **32**, **33**, **35** and **36** were checked by GLC analysis (see above) and HPLC analysis (Merck-Hitachi with Merck RP 18 column, Cat. No. 16 051) and were found to be >99.9% pure in each case. The preparation of compounds **1**–**6** has been described previously,[39] and tetrakis(triphenylphosphine)palladium(0) was prepared as described in the literature.[41]

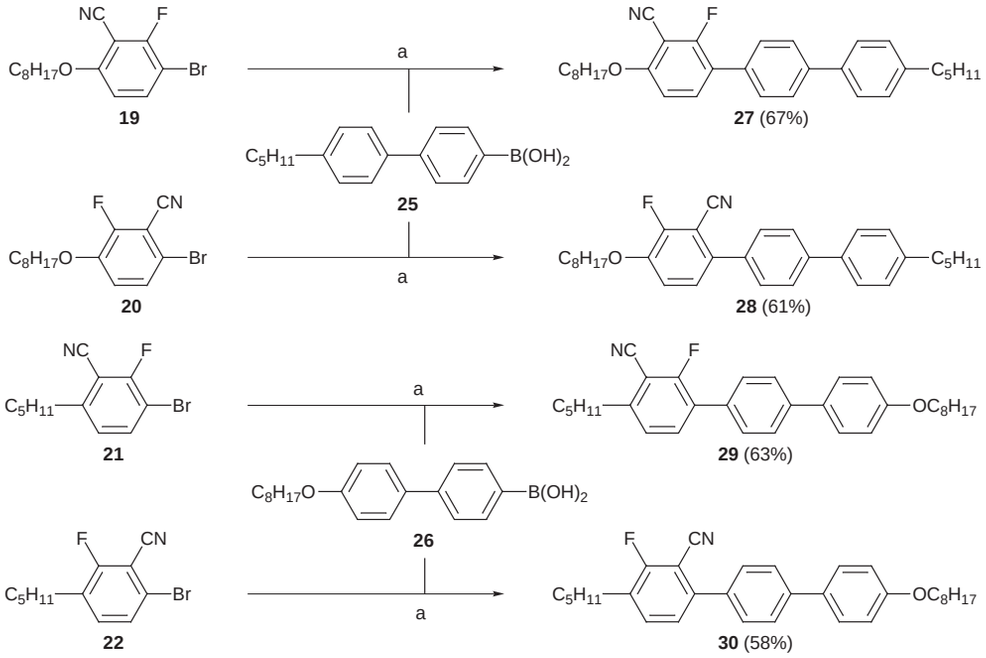
3-Bromo-2-fluoro-6-octyloxybenzoic acid 7

A solution of compound **1** (11.00 g, 0.036 mol) in dry THF (40 ml) was added dropwise to a stirred, cooled (−78 °C) solution of lithium diisopropylamide [prepared in the usual way from dry diisopropylamine (4.15 g, 0.041 mol) and *n*-butyllithium (15.2 ml, 2.5 M, 0.038 mol)][28,40] in dry THF (80 ml) under dry nitrogen. The mixture was stirred at −78 °C for 1 h and poured onto a slurry of solid carbon dioxide in dry THF. The mixture was allowed to warm to room temperature, the solvent was removed *in vacuo* and 10% aqueous potassium hydroxide was added. The solution was washed with ether and the aqueous layer was acidified with 36% hydrochloric acid (congo red). The product was extracted into ether (twice) and the combined ethereal extracts were washed with water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel–dichloromethane) to yield a colourless crystalline solid.

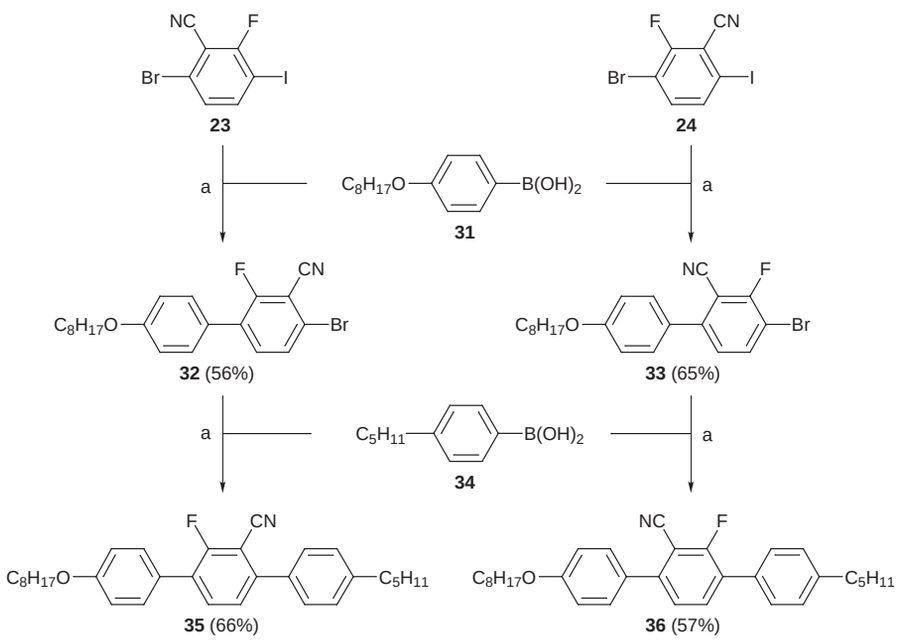
Yield 6.02 g (48%); mp 50–51 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.10 (2H, t), 6.69 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.58 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 10.10 (1H, s); ν_{max}(KBr)/cm^{-1} 3100–2850, 1710, 1480, 1300, 1270, 1080; MS *m*/*z* 248 (M^+), 246 (M^+).

The following compounds were prepared using the experimental procedure described for the preparation of compound **7**.

6-Bromo-2-fluoro-3-octyloxybenzoic acid 8. Quantities: compound **2** (8.70 g, 0.029 mol). Yield 8.20 g (81%); mp 54–56 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.00 (2H, t), 6.92 (1H, dd, $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.31 (H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 11.30 (1H, s); ν_{max}(KBr)/cm^{-1} 3100–2850, 1710, 1480, 1300, 1270, 1080; MS *m*/*z* 348 (M^+), 346 (M^+).



Scheme 2 *Reagents*: a $Pd(PPh_3)_4$, DME, Na_2CO_3, H_2O.



Scheme 3 *Reagents*: a $Pd(PPh_3)_4$, DME, Na_2CO_3, H_2O.

3-Bromo-2-fluoro-6-phenylbenzoic acid 9. Quantities: compound **3** (7.00 g, 0.029 mol). Yield 3.85 g (46%); oil; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (4H, m), 1.65 (2H, quintet), 2.70 (2H, t), 6.96 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.56 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 3200–2860, 1710, 1300; MS *m*/*z* 290 (M^+), 288 (M^+).

6-Bromo-2-fluoro-3-pentylbenzoic acid 10. Quantities: compound **4** (7.90 g, 0.032 mol). Yield 8.37 g (91%); mp 70–71 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (4H, m), 1.60 (2H, quintet), 2.65 (2H, t), 7.16 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.34 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 10.30 (1H, s); ν_{max}(KBr)/cm^{-1} 3200–2860, 1700, 1450, 1390, 1280; MS *m*/*z* 290 (M^+), 288 (M^+).

6-Bromo-2-fluoro-3-iodobenzoic acid 11. Quantities: compound **5** (9.63 g, 0.032 mol). Yield 4.20 g (38%); mp 179–181 °C; δ_H(270 MHz; $CDCl_3$) 7.16 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.63 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 9.10 (1H, s); ν_{max}(KBr)/cm^{-1} 3100–2700, 1700, 1450, 1395, 1300; MS *m*/*z* 346 (M^+), 344 (M^+).

3-Bromo-2-fluoro-6-iodobenzoic acid 12. Quantities: compound **6** (9.63 g, 0.032 mol). Yield 7.77 g (77%); mp 166–168 °C; δ_H(270 MHz; $CDCl_3$) 7.36 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.58 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 9.30 (1H, s); ν_{max}(KBr)/cm^{-1} 3100–2700, 1700, 1450, 1395, 1300; MS *m*/*z* 346 (M^+), 344 (M^+).

3-Bromo-2-fluoro-6-octyloxybenzamide 13

A solution of oxalyl chloride (3.30 g, 0.026 mol) in dry benzene (5 ml) was added dropwise to a stirred solution of compound **7** (4.50 g, 0.013 mol) and dry DMF (5 drops) in dry benzene (30 ml) at room temperature under dry nitrogen. The solution was stirred at room temperature overnight and the benzene and excess of oxalyl chloride were removed *in vacuo*. A solution of the residue in dry diglyme (10 ml) was added to stirred 35% aqueous ammonia (100 ml) at room temperature. The resulting

precipitate was filtered off, washed with water and dried (P_2O_5) *in vacuo* to give a colourless solid.

Yield 4.40 g (98%); mp 120–122 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.00 (2H, t), 6.00 (1H, s), 6.10 (1H, s), 6.64 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.49 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 3390, 3180, 2920, 1650, 1450, 1290, 800; MS *m*/*z* 347 (M^+), 345 (M^+).

The following compounds were prepared using the experimental procedure described for the preparation of compound **13**.

6-Bromo-2-fluoro-3-octyloxybenzamide 14. Quantities: compound **8** (8.20 g, 0.024 mol). Yield 7.70 g (93%); mp 82–84 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.00 (2H, t), 5.56 (1H, s), 6.05 (1H, s), 6.87 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.28 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 3390, 3180, 2920, 1650, 1460, 1260, 870; MS *m*/*z* 347 (M^+), 345 (M^+).

3-Bromo-2-fluoro-6-pentylbenzamide 15. Quantities: compound **9** (3.10 g, 0.011 mol). Yield 3.13 g (99%); mp 88–90 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (4H, m), 1.65 (2H, quintet), 2.70 (2H, t), 5.85 (1H, s), 6.15 (1H, s), 6.94 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.48 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 3400, 3200, 2980, 2880, 1660, 1400; MS *m*/*z* 289 (M^+), 287 (M^+).

6-Bromo-2-fluoro-3-pentylbenzamide 16. Quantities: compound **10** (8.25 g, 0.029 mol). Yield 8.30 g (99%); mp 118–120 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.30 (4H, m), 1.70 (2H, quintet), 2.60 (2H, t), 5.85 (1H, s), 6.10 (1H, s), 7.10 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.30 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 3390, 3200, 2920, 1650, 1460, 1380, 870; MS *m*/*z* 289 (M^+), 287 (M^+).

6-Bromo-2-fluoro-3-iodobenzamide 17. Quantities: compound **11** (4.00 g, 0.012 mol). Yield 2.66 g (67%); mp 219–221 °C; δ_H(270 MHz; $CDCl_3$) 7.30 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.77 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.85 (1H, s), 8.10 (1H, s); ν_{max}(KBr)/cm^{-1} 3390, 3200, 2920, 1650, 1460, 1380, 870; MS *m*/*z* 345 (M^+), 343 (M^+).

3-Bromo-2-fluoro-6-iodobenzamide 18. Quantities: compound **12** (7.50 g, 0.022 mol). Yield 5.30 g (70%); mp 188–190 °C; δ_H(270 MHz; $CDCl_3$) 7.23 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.32 (1H, s), 7.46 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.80 (1H, s); ν_{max}(KBr)/cm^{-1} 3390, 3200, 2920, 1650, 1460, 1380, 870; MS *m*/*z* 345 (M^+), 343 (M^+).

3-Bromo-2-fluoro-6-octyloxybenzonitrile 19

A solution of thionyl chloride (7.70 g, 0.065 mol) in dry DMF (10 ml) was added dropwise to a stirred solution of compound **13** (4.20 g, 0.013 mol) in dry DMF (25 ml) at room temperature. The stirred mixture was heated at 120 °C for 3 h and poured into ice–water. The product was extracted into ether (twice) and the combined ethereal extracts were washed with water, saturated sodium hydrogen carbonate solution, water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by column chromatography [silica gel–light petroleum (bp 40–60 °C) with the gradual introduction of dichloromethane] to yield a colourless solid.

Yield 2.88 g (68%); mp 51–53 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.10 (2H, t), 6.67 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.65 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2960, 2920, 2240, 1460, 1300, 1220, 1080, 820; MS *m*/*z* 329 (M^+), 327 (M^+); Found: C, 54.83; H, 5.77; N, 4.26; $C_{15}H_{19}BrFNO$ requires C, 54.89; H, 5.83; N, 4.27%.

The following compounds were prepared using the experimental procedure described for the preparation of compound **19**.

6-Bromo-2-fluoro-3-octyloxybenzonitrile 20. Quantities: compound **14** (7.70 g, 0.022 mol). Yield 4.66 g (65%); mp 50–52 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.05 (2H, t), 7.06 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.35 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 2960, 2920, 2240, 1460, 1300, 1230, 1100, 820; MS *m*/*z* 329 (M^+), 327 (M^+); Found: C, 54.85; H, 5.81; N, 4.27; $C_{15}H_{19}BrFNO$ requires C, 54.89; H, 5.83; N, 4.27%.

3-Bromo-2-fluoro-6-pentylbenzonitrile 21. Quantities: compound **15** (3.00 g, 0.010 mol). Yield 2.08 g (77%); mp 25–27 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (4H, m), 1.65 (2H, quintet), 2.80 (2H, t), 7.02 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.68 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1450, 850; MS *m*/*z* 271 (M^+), 269 (M^+); Found: C, 53.50; H, 4.81; N, 5.15; $C_{12}H_{13}BrFN$ requires C, 53.35; H, 4.85; N, 5.18%.

6-Bromo-2-fluoro-3-pentylbenzonitrile 22. Quantities: compound **16** (7.10 g, 0.025 mol). Yield 3.25 g (48%); mp 32–34 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (4H, m), 1.65 (2H, quintet), 2.65 (2H, t), 7.31 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.40 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 2950, 2240, 1600, 1450, 1220, 870, 820; MS *m*/*z* 271 (M^+), 269 (M^+); Found: C, 53.34; H, 4.84; N, 5.18; $C_{12}H_{13}BrFN$ requires C, 53.35; H, 4.85; N, 5.18%.

6-Bromo-2-fluoro-3-iodobenzonitrile 23. Quantities: compound **17** (2.60 g, 7.56 mmol). Yield 2.10 g (85%); mp 112–114 °C; δ_H(270 MHz; $CDCl_3$) 7.27 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.84 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2240, 1620, 1500, 1420, 1150, 890, 820; MS *m*/*z* 327 (M^+), 325 (M^+); Found: C, 25.76; H, 0.60; N, 4.25; C_7H_2BrFIN requires C, 25.80; H, 0.62; N, 4.30%.

3-Bromo-2-fluoro-6-iodobenzonitrile 24. Quantities: compound **18** (5.00 g, 0.015 mol). Yield 2.71 g (55%); mp 108–110 °C; δ_H(270 MHz; $CDCl_3$) 7.50 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.60 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 2240, 1600, 1500, 1420, 1150, 900, 820; MS *m*/*z* 327 (M^+), 325 (M^+); Found: C, 25.78; H, 0.60; N, 4.27; C_7H_2BrFIN requires C, 25.80; H, 0.62; N, 4.30%.

3-Cyano-2-fluoro-4-octyloxy-4″-pentyl-1,1′:4′,1″-terphenyl 27

Compound **25** (1.00 g, 3.73 mmol) was added to a stirred mixture of compound **19** (1.00 g, 3.05 mmol), tetrakis-(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) and sodium carbonate (3.50 g) in DME (35 ml) and water (35 ml) at room temperature under nitrogen. The stirred mixture was heated under reflux for 4 h (GLC analysis revealed a complete reaction) and the cooled mixture was added to water (100 ml). The product was extracted into ether (twice) and the combined ethereal extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography [silica gel–light petroleum (bp 40–60 °C) with the gradual introduction of dichloromethane] to give a colourless solid which was recrystallised from ethanol to yield fine colourless crystals.

Yield 0.96 g (67%); transitions (°C) C 100.0 S_A 163.5 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.65 (2H, quintet), 1.85 (2H, quintet), 2.65 (2H, t), 4.10 (2H, t), 6.83 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.27 (2H, d), 7.53 (2H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.55 (2H, d), 7.62 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.67 (2H, d); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.48; H, 8.10; N, 2.95; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

The following compounds were prepared using the experimental procedure described for the preparation of compound **27**.

2-Cyano-3-fluoro-4-octyloxy-4″-pentyl-1,1′:4′,1″-terphenyl 28. Quantities: compound **20** (1.50 g, 4.57 mmol), compound **25** (1.50 g, 5.60 mmol). Yield 1.32 g (61%); transitions (°C) C 116.5 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.65 (2H, quintet), 1.85 (2H, quintet), 2.65 (2H, t), 4.10 (2H, t), 7.25 (4H, m), 7.54 (2H, d), 7.58 (2H, d), 7.68 (2H, d); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.45; H, 8.11; N, 2.95; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

3-Cyano-2-fluoro-4″-octyloxy-4-pentyl-1,1′:4′,1″-terphenyl 29. Quantities: compound **21** (1.20 g, 4.44 mmol), compound **26** (1.75 g, 5.37 mmol). Yield 1.32 g (63%); transitions (°C) C 61.5 S_C 84.5 S_A 160.5 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.75 (2H, quintet), 1.85 (2H, quintet), 2.85 (2H, t), 4.05 (2H, t), 6.99 (2H, d), 7.18 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.57 (4H, d), 7.62 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.66 (2H, d); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.46; H, 8.09; N, 2.92; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

2-Cyano-3-fluoro-4″-octyloxy-4-pentyl-1,1′:4′,1″-terphenyl 30. Quantities: compound **22** (1.20 g, 4.44 mmol), compound **26** (1.80 g, 5.52 mmol). Yield 1.52 g (58%); transitions (°C) C 89.0 N 100.0 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.65 (2H, quintet), 1.85 (2H, quintet), 2.70 (2H, t), 4.00 (2H, t), 6.99 (2H, d), 7.27 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.47 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.56 (2H, d), 7.60 (2H, d), 7.68 (2H, d); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.48; H, 8.12; N, 2.96; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

4-Bromo-3-cyano-2-fluoro-4′-octyloxybiphenyl 32. Quantities: compound **23** (1.84 g, 5.64 mmol), compound **31** (1.63 g, 6.48 mmol). Yield 1.28 g (56%); mp 59–61 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.10 (2H, t), 6.99 (2H, d), 7.35 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz), 7.42 (2H, d), 7.52 (2H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.67 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz); ν_{max}(KBr)/cm^{-1} 2920, 2240, 1610, 1500, 1250, 1120, 820; MS *m*/*z* 405 (M^+), 403 (M^+); Found: C, 62.36; H, 5.73; N, 3.43; $C_{21}H_{23}BrFNO$ requires C, 62.38; H, 5.73; N, 3.46%.

4-Bromo-2-cyano-3-fluoro-4′-octyloxybiphenyl 33. Quantities: compound **24** (2.50 g, 7.67 mmol), compound **31** (2.21 g, 8.882 mmol). Yield 2.02 g (65%); mp 43–45 °C; δ_H(270 MHz; $CDCl_3$) 0.90 (3H, t), 1.35 (8H, m), 1.45 (2H, quintet), 1.85 (2H, quintet), 4.10 (2H, t), 7.00 (2H, d), 7.17 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.47 (2H, d), 7.77 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2920, 2240, 1610, 1470, 1250, 1180, 820; MS *m*/*z* 405 (M^+), 403 (M^+); Found: C, 62.35; H, 5.71; N, 3.42; $C_{21}H_{23}BrFNO$ requires C, 62.38; H, 5.73; N, 3.46%.

2′-Cyano-3′-fluoro-4″-octyloxy-4-pentyl-1,1′:4′,1″-terphenyl 35. Quantities: compound **32** (1.20 g, 2.97 mmol), compound **34** (0.68 g, 3.54 mmol). Yield 0.92 g (66%); transitions (°C) C 90.0 S_A 99.0 N 101.0 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.65 (2H, quintet), 1.85 (2H, quintet), 2.65 (2H, t), 4.00 (2H, t), 7.01 (2H, d), 7.31 (2H, d), 7.34 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.49 (2H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.52 (2H, d), 7.67 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.45; H, 8.10; N, 2.97; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

2′-Cyano-3′-fluoro-4-octyloxy-4″-pentyl-1,1′:4′,1″-terphenyl 36. Quantities: compound **33** (1.00 g, 2.50 mmol), compound **34** (0.60 g, 3.13 mmol). Yield 0.67 g (57%); transitions (°C) C 96.5 N 90.0 I; δ_H(270 MHz; $CDCl_3$) 0.90 (6H, 2 × t), 1.35 (12H, m), 1.45 (2H, quintet), 1.65 (2H, quintet), 1.85 (2H, quintet), 2.65 (2H, t), 4.10 (2H, t), 7.02 (2H, d), 7.25 (2H, d), 7.30 (1H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.41 (2H, d), 7.50 (2H, dd; $^3J_{HH}$ = 8 Hz, $^5J_{HF}$ = 1 Hz), 7.68 (1H, dd; $^3J_{HH}$ = 8 Hz, $^4J_{HF}$ = 7 Hz); ν_{max}(KBr)/cm^{-1} 2980, 2960, 2860, 2240, 1610, 1490, 1250, 810; MS *m*/*z* 471 (M^+); Found: C, 81.45; H, 8.10; N, 2.97; $C_{32}H_{38}FNO$ requires C, 81.49; H, 8.12; N, 2.97%.

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