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Halogen–lithium exchange between substituted dihalobenzenes and butyllithium: application to the regioselective synthesis of functionalized bromobenzaldehydes

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Abstract—Halogen–lithium interconversion reactions between unsymmetrically substituted mono- and bifunctional dihalobenzenes $C_6H_3XHal_2$ and $C_6H_2XYHal_2$ (Hal = Br, I; X, Y = F, OR, CF_3, $CH(OMe)_2$) and butyllithium were investigated. The resultant organolithium intermediates were converted into the corresponding benzaldehydes in moderate to good yields. As a rule, bromine atoms in the position *ortho* to the functional group were replaced preferentially with lithium. Intramolecular competition experiments with bifunctional systems revealed that fluorine is capable of activating the neighboring bromine atom more strongly than methoxy and dimethoxymethyl groups. On the replacement of the non-activated bromine with iodine a complete reversal of this reactivity pattern can be accomplished due to the preferred iodine–lithium exchange.

1. Introduction

Halogen–lithium exchange (HLE) is one of the fundamental, and perhaps, most versatile methods used to generate organolithium compounds. Its important advantage is that it is extremely rapid even at very low temperatures providing a direct access to many unstable organolithium intermediates. Furthermore, this method offers a convenient route to compounds that are not readily prepared by directed metalation reactions.[1] Nevertheless, there are drawbacks to HLE including the availability of halogen-containing starting materials. The HLE reaction between polyhalobenzenes and BuLi has been investigated with special emphasis on regiospecifity in halolithiobenzene formation. It was found initially that the methoxy group increases the reactivity of neighboring bromine atoms in the HLE reaction.[2] This observation facilitated valuable synthetic applications.[3] More recently, similar effects with nitrogen functionalities such as amino and nitro groups have been described.[4] This study probes directing effects on HLE with other dibromo- and bromoiodobenzene derivatives containing functionalities based on oxygen and/or fluorine. Moreover, it is demonstrated that isomeric halogenated aryllithium intermediates may be selectively generated by the treatment of appropriate polyhalobenzenes with the most common alkyllithium reagent, i.e. BuLi, which cannot be overestimated from the viewpoint of any synthetic organic process.

2. Results and discussion

The regioselective *ortho*-directed bromine–lithium exchange between 2,4-dibromoanisole as well as 2,4,6-tribromoanisole and BuLi has been known since 1940.[1,5] Accordingly, this reaction is suitable for the synthesis of the corresponding benzaldehydes as shown in Table 1 (entries 1 and 2). Similarly, *ortho*-directed bromine–magnesium exchange for these and related systems has been developed.[6] It was interesting to determine how and to what extent the regioselectivity of the HLE is tuned by the steric effect of a bulky alkoxy group since it has been reported that the protection of chlorophenols with TBDMS groups prevents oxygen *ortho*-directed metalation.[7] For this purpose, TBDMS ethers of 2,5-dibromophenol and 2,4-dibromophenol were subjected to the HLE reactions (entries 3 and 4). We found that the steric hindrance provided by the TBDMS group was not reflected by any change of selectivity as the bromine atom in the position *ortho* to the oxygen atom was exclusively replaced with lithium. On the other hand, the conversion into corresponding benzaldehydes was not quantitative as substantial amounts

Keywords: Dihalobenzenes; Halogen–lithium exchange; Arylithium compounds; Benzaldehydes.
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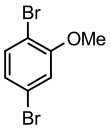
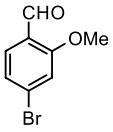
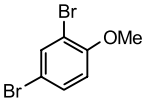
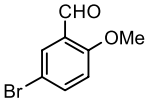
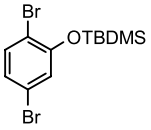
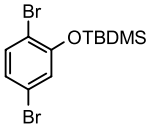
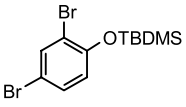
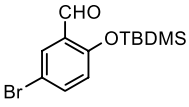
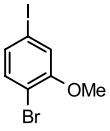
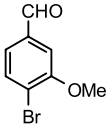
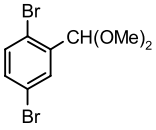
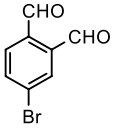
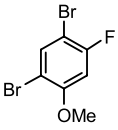
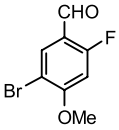
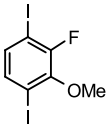
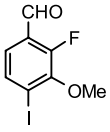
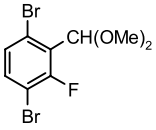
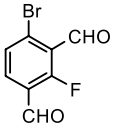
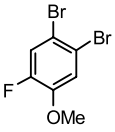
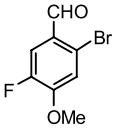
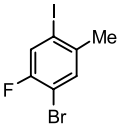
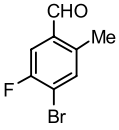
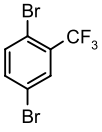
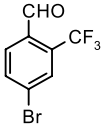
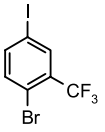
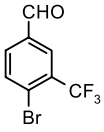
Table 1. Preparation of functionalized bromobenzaldehydes via halogen–lithium exchange and subsequent DMF quench

Entry	Aryl halide	Solvent, temperature	Product	Yield (%)
1		Et_2O, −78 °C		84
2		Et_2O, −78 °C		90
3		Et_2O, −78 °C		32
4		Et_2O, −78 °C		36
5		Et_2O, −78 °C		69
6		Et_2O, −78 °C		52
7		THF/Et_2O (1:1), −78 °C		82
8		THF/Et_2O (1:1), −78 °C		72
9		THF/Et_2O (1:1), −78 °C		48
10		THF/Et_2O (4:1), −100 °C		13[a]
11		Et_2O, −100 °C		46
12		Et_2O, −78 °C		70
13		Et_2O, −78 °C		73

[a] The major product isolated from the mixture with the regioisomeric by-product 2-bromo-4-fluoro-3-methoxybenzaldehyde and 2,3-dibromo-5-fluoro-6-methoxybenzaldehyde.

of unreacted TBDMS ethers were recovered (ca. 30% of and 40% for entries 3 and 4, respectively) which indicates that the lithiation proceeds quite sluggishly in Et_2O at about −70 °C. Interestingly, 3-bromobenzaldehyde is derived from 1,3-dibromobenzene by the HLE rapidly under these conditions. We also investigated the competitive metalations with 2-bromo-5-iodoanisole and in this case a selective replacement of iodine was observed. Thus, bromine kinetically activated by adjacent methoxy group is less reactive than iodine. Furthermore, the HLE product, i.e. 4-bromo-3-methoxyphenyllithium does not undergo rearrangement to the thermodynamically more stable 2-methoxyphenyllithium system at low temperature in ether solution. Hence, it can be converted cleanly into the corresponding 4-bromo-3-methoxybenzaldehyde[8] (entry 5) which is not available by the direct bromination of 3-methoxybenzaldehyde. It should be noted that a more recent attempt to prepare this compound was reported[9] but comparison of the NMR spectroscopic data suggests clearly that the spectra were interpreted erroneously.[10]

The reaction of 2,5-dibromo-1-(dimethoxymethyl)benzene with BuLi followed by DMF quench and aqueous workup with deprotection of the dimethoxymethyl group afforded 4-bromophtalaldehyde[11] (entry 6). The *ortho*-directing ability of the methoxy group can be explained in terms of the inductive effect but for the dimethoxymethyl group this is not so obvious as its electronegative character is weak. Hence, it can be assumed that in the case of 2,5-dibromo-1-(dimethoxymethyl)benzene the initial precoordination of lithium by the acetal oxygen atoms may be important. To support this view, it should be noted, that the lithiation of 3-(dimethoxymethyl)thiophene proceeds selectively in the 2-position[12,13] which suggests a significant *ortho*-directing ability by the dimethoxymethyl group.

It is well-documented that fluorine possesses a strong *ortho*-directing ability in the metalation reaction[14] and this property should also be reflected in the HLE between *ortho*-bromofluoro- or *ortho*-iodofluorobenzenes and BuLi. Indeed, the high-yield preparation of 2-fluoro-4-bromobenzaldehyde starting with 1,4-dibromo-2-fluorobenzene and $Li[MgBu_3]$ ate complex as the metalating agent was reported recently.[15] We were interested to compare the relative directing potential of fluorine with respect to oxygen-based functionalities such as methoxy and dimethoxymethyl groups. The results are shown in Table 1 (entries 7–9). THF was used as a solvent as it is more suitable for the stabilization of *ortho*-halogenated aryllithium species.[16] Based on these internal directing group competition experiments, it is clear that fluorine is a more powerful *ortho*-directing group than methoxy (entries 7 and 8),[17] or dimethoxymethyl group (entry 9). It should be noted that BuLi/THF slowly deprotonates *ortho* to the methoxy group, whereas the selective metalation (deprotonation) of 2- and 4-fluoroanisole in the position *ortho* to fluorine requires superbasic mixture of BuLi with PMDTA or $KOBu^t$.[18] The competition of long-range inductive interactions of fluorine and methoxy groups was probed by the reaction of 4,5-dibromo-2-fluoroanisole with BuLi. The reaction was not as selective as found in previous examples and a mixture of products was formed. However, the distinct influence of fluorine was observed again as 2-bromo-5-fluoro-4-methoxybenzaldehyde (entry 10) was formed as a major product (according to GC/MS analysis, ca. 70% in the crude reaction mixture containing ca. 20% of 2-bromo-4-fluoro-5-methoxybenzaldehyde and 10% of 2,3-dibromo-6-fluoro-5-methoxybenzaldehyde) resulting from the preferred exchange of the bromine atom in the position meta to fluorine.

In addition to these efforts, we studied the competition between iodine and *ortho*-activated bromine in 5-bromo-4-fluoro-2-iodotoluene. It was plausible that the strong activating effect of fluorine (which should be stronger than that of the methoxy group in 2-bromo-5-iodoanisole) together with some deactivating effect of methyl group[19] may significantly change the reaction course. However, iodine-lithium exchange was preferred again, and the corresponding lithiated compound was relatively stable as demonstrated by the isolation of 4-bromo-5-fluoro-2-methylbenzaldehyde (entry 11) in moderate yield.

The trifluoromethyl group is known as a strong electron-withdrawing substituent,[20] and has also been found as effective *ortho*-director for HLE. 1,4-Dibromo-2-(trifluoromethyl)benzene was converted into 4-bromo-2-trifluoromethylbenzaldehyde (entry 12). On the other hand, 1-bromo-4-iodo-2-(trifluoromethyl)benzene produces 4-bromo-3-(trifluoromethyl)phenyllithium by the treatment with BuLi via the selective iodine–lithium exchange and the corresponding benzaldehyde[21] in subsequent steps (entry 13). This last example confirms the general reactivity pattern observed for bromoiodobenzenes with activating substituent adjacent to bromine. The thermal stability of 4-bromo-3-(trifluoromethyl)phenyllithium in Et_2O was investigated. A solution of this compound was warmed up to 0 °C prior to DMF quench and aqueous workup. GC/MS analysis of the isolated material revealed that 4-bromo-2-trifluoromethylbenzaldehyde (27%) and 4-iodo-2-trifluoromethylbenzaldehyde (45%) together with some amount of the starting material (18%) and 1,4-diiodo-2-trifluoromethylbenzene (8%) were formed. Hence, the isomerization of the primary aryllithium species leading to the formation of more stable 2-CF_3 substituted phenyllithium derivatives was accompanied by extensive halogen redistribution processes.

In conclusion, the halogen–lithium exchange of substituted dibromobenzenes and BuLi is strongly controlled by the electronegative substituent adjacent to bromine. Fluorine competes effectively with methoxy and dimethoxymethyl groups to provide high regioselectivity. On the other hand, the replacement of the non-activated bromine with iodine gives access to thermodynamically less stable but still relatively inert organolithium species that under appropriate conditions do not rearrange spontaneously to their more stable isomers via halogren migration ('halogen dance') processes.[22] Hence, the synthesis of multiple isomeric halogenated benzaldehydes can be readily accomplished by means of this modification. Obviously, the synthetic potential of all described HLE experiments is not limited to benzaldehydes and promises broad applicability.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents were stored over sodium wire before use. Butyllithium (10 M solution in hexanes) and anhydrous *N*,*N*-dimethylformamide (Aldrich) were used as received. 2,4-Dibromoanisole, 2,5-dibromoanisole and 1,4-dibromo-2-(trifluoromethyl)benzene were received from Aldrich, whereas 1-bromo-4-iodo-2-(trifluoromethyl)benzene was prepared according to the published procedure from 3-bromo-4-(trifluoromethyl)aniline (Aldrich).[23] Remaining functionalized dihalobenzenes are novel compounds. 2-(*tert*-Butyldimethylsilyloxy)-1,4-dibromobenzene and 1-(*tert*-butyldimethylsilyloxy)-2,4-dibromobenzene were obtained by treatment of corresponding sodium dibromophenolates with *tert*-butyldimethylsilyl chloride. 2,4-Dibromo-5-fluoroanisole and 4,5-dibromo-2-fluoroanisole were prepared by multistep procedures involving regioselective bromination of appropriate bromofluorophenols as a key step.[24] The synthesis of 3,6-diiodo-2-fluoroanisole and 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene involved regioselective metalation of 2-fluoro-6-iodoanisole[25] and 1,4-dibromo-2-fluorobenzene,[26] respectively. Detailed procedures for these novel dihalobenzenes are provided in the Supplementary Material.

3.1.1. 4-Bromo-2-methoxybenzaldehyde (entry 1). The method described here is representative for the preparation of other benzaldehydes (modifications may concern the choice of solvent and temperature as shown in Table 1): A solution of 2,5-dibromoanisole (5.32 g, 20 mmol) in Et_2O (10 mL) was added to the solution of BuLi (10 M solution in hexanes, 2.0 mL, 20 mmol) in Et_2O (20 mL) at −78 °C. After 15 min DMF (1.61 g, 22 mmol) was added slowly. The mixture was stirred for 15 min and hydrolyzed with aq. H_2SO_4 (1 M, 20 mL). The organic layer was separated and solvents were removed in vacuo. The residue was washed with water (20 mL) and recrystallized from hexane (10 mL) to give the title compound (3.6 g, 84%) as colorless crystals, mp 68–70 °C (Ref. 27 mp 66–68 °C); (Found: C, 44.60; H, 3.47. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 10.39 (1H, d, J=1.0 Hz, CHO), 7.68 (1H, d, J=8.0 Hz, Ph), 7.17 (1H, ddd, J=8.0, 1.5, 1.0 Hz, Ph), 7.15 (1H, d, J=1.5 Hz, Ph), 3.93 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$): 188.9, 162.1, 130.7, 129.8, 124.3, 123.8, 115.5, 56.2.

3.1.2. 5-Bromo-2-methoxybenzaldehyde (entry 2). The title compound was prepared from 2,4-dibromoanisole (5.32 g, 20 mmol) as colorless crystals (3.9 g, 90%), mp 115–118 °C (from hexane, Ref. 28 mp 116–119 °C); (Found: C, 44.29; H, 3.48. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 10.37 (1H, s, CHO), 7.90 (1H, d, J=2.5 Hz, Ph), 7.62 (1H, dd, J=9.0, 2.5 Hz, Ph), 6.89 (1H, d, J=9.0 Hz, Ph), 3.92 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$) 188.5, 160.9, 138.4, 131.1, 125.2, 113.9, 113.6, 56.1.

3.1.3. 4-Bromo-2-(*tert*-butyldimethylsilyloxy)benzaldehyde (entry 3). The title compound was prepared from 2-(*tert*-butyldimethylsilyloxy)-1,4-dibromobenzene (7.32 g, 20 mmol) as colorless crystals (2.3 g, 36%), mp 34–36 °C (from methanol); (Found: C, 49.43; H, 6.31. $C_{13}H_{19}BrO_2Si$ requires C, 49.52; H, 6.07%); ν_{max}(KBr) 2938, 2855, 1684, 1588, 1470, 1265 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.39 (1H, d, J=1.0 Hz, CHO), 7.67 (1H d, J=8.0 Hz, Ph), 7.19 (1H, ddd, J=8.0, 1.5, 1.0 Hz, Ph), 7.06 (1H, d, J=1.0 Hz, Ph), 1.02 (9H, s, Bu^tMe_2Si), 0.30 (6H, s, Bu^tMe_2Si); δ_C (100.6 MHz, $CDCl_3$) 189.3, 159.3, 130.1, 129.7, 126.4, 125.3, 123.7, 25.8, 18.5, −4.2. *m*/*z* (EI, 70 kV) molecular ion not found, 259 (100), 257 (100, M−$(CH_3)_3C$), 241(36), 239 (35%).

3.1.4. 5-Bromo-2-(*tert*-butyldimethylsilyloxy)benzaldehyde (entry 4). The title compound was prepared from 1-(*tert*-butyldimethylsilyloxy)-2,4-dibromobenzene (7.32 g, 20 mmol) as colorless crystals (2.0 g, 32%), mp 60–62 °C (from methanol); (Found: C, 49.36; H, 6.09. $C_{13}H_{19}BrO_2Si$ requires C, 49.52; H, 6.07%); ν_{max}(KBr) 2936, 2858, 1685, 1590, 1478, 1271, 916 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, s, CHO), 7.91 (1H, d, J=2.5 Hz, Ph), 7.53 (1H, dd, J=9.0, 2.5 Hz, Ph), 6.80 (1H, d, J=9.0 Hz, Ph), 1.02 (9H, s, Bu^tMe_2Si), 0.29 (6H, s, Bu^tMe_2Si); δ_C (100.6 MHz, $CDCl_3$) 188.8, 158.0, 138.4, 131.1, 128.6, 122.3, 114.3, 25.8, 18.5, −4.2. *m*/*z* (EI, 70 kV) molecular ion not found, 259 (100), 257 (100, M−$(CH_3)_3C$), 241(24), 239 (24%).

3.1.5. 4-Bromo-3-methoxybenzaldehyde (entry 5). The title compound was prepared from 2-bromo-5-iodoanisole (4.0 g, 13 mmol) as colorless crystals (1.9 g, 69%), mp 74–76 °C (from hexane, Ref. 7 mp 74 °C); (Found: C, 44.65; H, 3.16. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 9.95 (1H, s, CHO), 7.74 (1H, d, J=8.0 Hz, Ph), 7.39 (1H, d, J=2.0 Hz, Ph), 7.33 (1H, dd, J=8.0, 2.0 Hz, Ph); δ_C (100.6 MHz, $CDCl_3$) 191.3, 156.8, 136.9, 134.1, 124.8, 119.8, 110.0, 56.6.

3.1.6. 4-Bromophtalaldehyde (entry 6). The title compound was prepared from 1,4-dibromo-2-(dimethoxymethyl)benzene (6.20 g, 20 mmol). The heating of the crude product with boiling 1 M aq. HCl (20 mL) was necessary to complete the cleavage of the acetal moiety and deprotect the second formyl group. Colorless crystals (2.2 g, 52%), mp 98–100 °C (from hexane/toluene 3:1, Ref. 10 mp 99–100 °C); (Found: C, 44.91; H, 2.36. $C_8H_5BrO_2$ requires C, 45.11; H, 2.37%); δ_H (400 MHz, $CDCl_3$) 10.52 (1H, s, CHO), 10.45 (1H, s, CHO), 8.10 (1H, d, J=2.0 Hz, Ph), 7.92 (1H, dd, J=8.5, 2.0 Hz, Ph), 7.85 (1H, d, J=8.5 Hz, Ph); δ_C (100.6 MHz, $CDCl_3$) 191.4, 190.9, 137.6, 136.9, 135.0, 133.8, 133.0, 129.3.

3.1.7. 5-Bromo-2-fluoro-4-methoxybenzaldehyde (entry 7). The title compound was prepared from 2,4-dibromo-5-fluoroanisole (5.68 g, 20 mmol) as colorless crystals (3.8 g, 82%), mp 98–100 °C (from hexane); (Found: C, 41.02; H, 2.65. $C_8H_6BrFO_2$ requires C, 41.23; H, 2.60%); ν_{max}(KBr) 3082, 2869, 1672, 1608, 1274, 1137, 1043, 852, 660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.16 (1H, s, CHO), 8.05 (1H, d, J=7.5 Hz, Ph), 6.69 (1H, d, J=12.0 Hz, Ph), 3.98 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$) 184.9 (d, $^3J_{CF}$=6.0 Hz), 165.5 (d, $^1J_{CF}$=260.0 Hz), 162.0 (d, $^3J_{CF}$=11.0 Hz), 132.7 (d, $^3J_{CF}$=3.5 Hz), 118.4 (d, $^2J_{CF}$=9.5 Hz), 107.9 (d, $^4J_{CF}$=3.0 Hz), 100.3 (d, $^2J_{CF}$=26.0 Hz), 57.2; *m*/*z* (EI, 70 kV) 234 (74, M+2), 233 (100), 232 (74, M^+), 231 (95), 163 (14), 161 (14), 81 (25%).

3.1.8. 2-Fluoro-4-iodo-3-methoxybenzaldehyde (entry 8). The title compound was prepared from 2-fluoro-3,6-diiodoanisole (7.56 g, 20 mmol) in a mixed solvent (Et_2O–THF 1:1) at −90 °C. In this case, lithiation was carried out by the addition of the solution of BuLi (10 M, 2 mL, 20 mmol) in hexane (10 mL) to the solution of 2-fluoro-3,6-diiodoanisole. Pale yellow crystals (4.0 g, 72%), mp 97–99 °C (from hexane); (Found: C, 33.42; H, 2.35. $C_8H_6FIO_2$ requires C, 34.31; H, 2.16%); ν_{max}(KBr) 3080, 2866, 1682, 1423, 1262, 1031, 772 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, d, J=0.5 Hz, CHO), 7.68 (1H, ddd, J=8.5, 1.5, 0.5 Hz, Ph), 7.30 (1H, dd, J=8.5, 6.5 Hz, Ph), 4.00 (3H, d, OMe); δ_C (100.6 MHz, $CDCl_3$) 186.4 (d, $^3J_{CF}$=7.5 Hz), 156.4 (d, $^1J_{CF}$=264.0 Hz), 148.5 (d, $^2J_{CF}$=10.5 Hz), 134.7 (d, $^3J_{CF}$=4.0 Hz), 126.0 (d, $^2J_{CF}$=7.0 Hz), 123.9 (d, $^4J_{CF}$=2.0 Hz), 101.0, 61.7 (d, $^4J_{CF}$=5.5 Hz); *m/z* (EI, 70 kV) 280 (100, M^+), 279 (42), 265 (12), 137 (14, 30%).

3.1.9. 4-Bromo-1,3-diformyl-2-fluorobenzene (entry 9). The title compound was prepared from 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene (6.56 g, 20 mmol). The heating of the crude product with boiling dil. aq. HCl was necessary to complete the cleavage of the acetal moiety and deprotect the second formyl group. Colorless crystals (2.2 g, 48%), mp 120–122 °C (from hexane/toluene 3:1); (Found: C, 41.37; H, 1.82. $C_8H_4BrFO_2$ requires: C, 41.59; H, 1.75%); ν_{max}(KBr) 3086, 2896, 1693, 1688, 1591, 1392, 1222, 955 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, d, J=1.0 Hz, CHO), 10.37 (1H, s, CHO), 7.94 (1H, dd, J=8.0, 7.0 Hz, Ph), 7.66 (1H, d, J=8.0 Hz, Ph);. δ_C (100.6 MHz, $CDCl_3$) 187.5 (d, $^3J_{CF}$=2.5 Hz), 185.3 (d, $^3J_{CF}$=7.5 Hz), 164.6 (d, $^1J_{CF}$=276.0 Hz), 133.3 (d, $^4J_{CF}$=4.0 Hz), 132.4 (d, $^3J_{CF}$=4.0 Hz), 130.9 (d, $^3J_{CF}$=4.5 Hz), 124.4 (d, $^2J_{CF}$=8.5 Hz), 123.7 (d, $^2J_{CF}$=10.0 Hz); *m/z* (EI, 70 kV) 232 (79, M+2), 231 (100), 230 (81, M^+), 229 (93), 203 (15), 201 (15), 175 (21), 173 (22), 121 (25), 94 (40%).

3.1.10. 2-Bromo-5-fluoro-4-methoxybenzaldehyde (entry 10). The title compound was identified as the main product of the reaction of 4,5-dibromo-2-fluoroanisole (5.68 g, 20 mmol) with BuLi and DMF at −100 °C in THF–Et_2O (4:1) and isolated by two-fold fractional recrystallization of the crude product from hexane/toluene (1:1, 10 mL). Pale yellow crystals (0.60 g, 13%), mp 99–102 °C; (Found: C, 41.00; H, 2.58. $C_8H_6BrFO_2$ requires C, 41.23; H, 2.60%); ν_{max}(KBr) 3079, 2881, 1678, 1608, 1495, 1278, 1138, 1021, 804 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.14 (1H, d, J=3.5 Hz, CHO), 7.62 (1H, d, J=11.0 Hz, Ph), 7.17 (1H, d, J=7.0 Hz, Ph), 3.98 (3H, d, J=1.0 Hz, OMe); δ_C (100.6 MHz, $CDCl_3$) 189.9, 153.2 (d, $^2J_{CF}$=12.0 Hz), 151.8 (d, $^1J_{CF}$=250.0 Hz), 126.8 ($^3J_{CF}$=4.5 Hz), 122.9 ($^3J_{CF}$=3.0 Hz), 117.6, 116.3 ($^2J_{CF}$=20.0 Hz), 56.8; *m/z* (EI, 70 kV) 234 (62, M+2), 233 (100), 232 (62, M^+), 231 (96), 163 (10), 161 (10), 81 (30%).

3.1.11. 4-Bromo-5-fluoro-2-methylbenzaldehyde (entry 11). The title compound was prepared from 3-bromo-4-fluoro-2-iodotoluene (4.1 g, 13 mmol). Pale yellow crystals (1.3 g, 46%), mp 68–70 °C (from hexane); (Found: C, 44.26; H, 2.77. C_8H_6BrFO requires: C, 44.27; H, 2.79); ν_{max}(KBr) 3039, 2888, 1683, 1597, 1387, 1259, 732 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.20 (1H, J=1.5 Hz, CHO), 7.53 (1H, d, J=8.5 Hz, Ph), 7.51–7.48 (1H, m, Ph), 2.63 (3H, m, Me); δ_C (100.6 MHz, $CDCl_3$) 190.3 (d, $^4J_{CF}$=1.5 Hz), 157.9 (d, $^1J_{CF}$=247 Hz), 137.5 (d, $^4J_{CF}$=4.0 Hz), 136.8, 134.6 (d, $^3J_{CF}$=5.5 Hz), 117.8 (d, $^2J_{CF}$=23.0 Hz), 115.8 (d, $^2J_{CF}$=20.5 Hz), 18.3. *m/z* (EI, 70 kV) 218 (85, M+2), 217 (100), 216 (87, M^+), 215 (95), 189 (38), 187 (38), 108 (45), 107 (52%).

3.1.12. 4-Bromo-2-(trifluoromethyl)benzaldehyde (entry 12). The title compound was prepared from 1,4-dibromo-2-trifluoromethyl)benzene (6.08 g, 20 mmol). Pale yellow crystals (3.5 g, 69%), mp 48–50 °C (from hexane); (Found: C, 37.51; H, 1.45. $C_8H_4BrF_3O$ requires C, 37.98; H, 1.59); ν_{max}(KBr) 1703, 1591, 1304, 1172, 1134, 840 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.31 (1H, qd, J=2.0, 1.0 Hz, CHO), 7.98 (1H, d, J=8.5 Hz, Ph), 7.92 (1H, d, J=2.0 Hz, Ph), 7.86–7.83 (1H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 187.9 (q, $^4J_{CF}$=3.5 Hz), 135.8, 132.50 (q, $^2J_{CF}$=32.5 Hz), 132.49, 130.8, 129.6 (q, $^3J_{CF}$=6.0 Hz), 129.0, 122.9 (q, $^1J_{CF}$=275 Hz). *m/z* (EI, 70 kV) 254 (66, M+2), 253 (100), 252 (66, M^+), 251 (98), 225 (32), 223 (32), 145 (39), 144 (37), 125 (36%).

3.1.13. 4-Bromo-3-(trifluoromethyl)benzaldehyde (entry 13). The title compound was prepared from 1-bromo-4-iodo-2-(trifluoromethyl)benzene (7.02 g, 20 mmol). Colorless crystals 3.7 g (73%), mp 51–54 °C (from hexane, Ref. 22 mp 52.5–53.5 °C); (Found: C, 37.35; H, 1.62. $C_8H_4BrF_3O$: C, 37.98; H, 1.59); δ_H (400 MHz, $CDCl_3$) 10.04 (1H, s, CHO), 8.20–8.18 (1H, m, Ph), 7.94–7.89 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 189.9, 136.3, 135.3, 133.2, 131.6 (q, $^2J_{CF}$=33 Hz), 129.0 (q, $^3J_{CF}$=5.5 Hz), 127.3, 122.1 (q, $^1J_{CF}$=272 Hz).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.04.051

Synthetic procedures and analytical data for all new compounds prepared in the course of this work including copies of the ^{13}C NMR spectra of all new compounds and all isolated benzaldehydes.

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