Synthesis of Perfluoroalkyl-Substituted Aryl Bromides and Their Purification Over Fluorous Reverse Phase Silica

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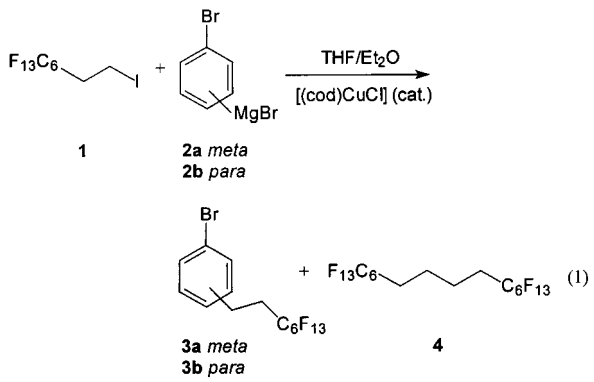
Abstract: (1*H*,1*H*,2*H*,2*H*-Perfluorooctyl)-substituted aryl bromides **3a,b** were synthesized via copper catalyzed cross-coupling of the iodide **1** with the corresponding arylmagnesium bromides **2a,b**. A new, efficient method for the purification of highly fluorinated compounds by column chromatography on fluorous reverse phase silica is also described.

Key words: perfluorinated compounds, copper-catalyzed C–C coupling, fluorous reverse phase silica, catalysis, ligands

Compounds containing highly fluorinated chains $-(CH_2)_z(CF_2)_yF$ are receiving great current interest as stoichiometric reagents and as catalysts for selective chemical transformations. The unique solubility properties of highly fluorinated compounds open possibilities to apply these materials to organic syntheses in innovative reaction media like "fluorous biphasic systems" (FBS)[1] or in supercritical carbon dioxide ($scCO_2$).[2] Likewise, highly fluorinated reagents, reactants and substrates are also useful for synthesis in traditional solvents, because they can readily be separated from non-fluorinated compounds.[3] These potential practical applications lead to a considerable and ever increasing demand for readily accessible and versatile building blocks containing perfluoroalkyl chains at the end of short alkylene (typically ethylene) spacers.

In this context, aryl bromides of type **3** are of special interest because they allow the introduction of (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-substituted aryl groups like $[Ar(CH_2)_2(CF_2)_6F]$ into a wide variety of target molecules via well-established transformations of the reactive aryl–bromide bond. The ethylene spacer effectively blocks the strong electron-withdrawing effect of the long perfluoroalkyl chain from the aromatic ring in **3a,b** and potential derivatives thereof. The variable substitution pattern of commercially available dibromobenzenes should result in a systematic variation of the steric properties of the substituted aryl group. As a first demonstration of this approach, we have recently synthesized *ortho*-, *meta*- and *para*-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-substituted aryl phosphines starting from compounds of type **3**;[2a] these phosphines were successfully applied as ligands in the rhodium-catalyzed hydroformylation of higher olefins in $scCO_2$.[2a,b] Related phosphines lacking the spacer have been synthesized for FBS applications by other groups.[4]



We now report details on the synthesis of two representative examples of (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-substituted aryl bromides, **3a,b**, via copper catalyzed cross-coupling of the iodide **1** with the corresponding arylmagnesium bromides **2a,b**. A new, efficient method for the purification of highly fluorinated compounds by column chromatography on fluorous reverse phase silica is also described. The preparative separation of fluorinated from non-fluorinated compounds by fluorous reverse phase silica gel has recently been introduced,[5] and this is the first application of separation of fluorinated compounds from each other based on the number of fluorines contained.

The mono-Grignard reagents **2a,b** are readily available by reaction of the corresponding dibromobenzenes with excess magnesium turnings in refluxing Et_2O in high yields.[6] Not surprisingly, direct treatment of 4-BrC_6H_4MgBr **(2b)** with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane (**1**, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl iodide) did not result in formation of the corresponding cross-coupled product **3b**. However, **3b** was obtained in fair to good yield when catalytic amounts of Cu(I) were introduced in form of [(cod)CuCl] (cod = 1,5-cyclooctadiene).[7]

The catalytic activity of Cu(I) compounds for cross-coupling reactions of Grignard reagents with alkyl halides is well-established [8] and has been independently applied by Shimizu et al. for similar reactions.[9] In the present case, addition of diethyl ether solutions of the Grignard reagents **2a,b** to a slurry of the Cu(I) complex in THF containing **1** at temperatures below 0°C and subsequent warming of the resulting mixtures to room temperature gave optimum results. The crude products obtained after aqueous workup contained the desired compounds **3a**,**b** together with small amounts of bromobenzene resulting from hydrolysis of unreacted **2** and the symmetrical homodimer 1,4-bis(perfluorohexyl)butane **(4)** as the major side products.

Isolation of analytically pure (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)aryl bromides from the crude materials obtained by the

above procedure proved to be a key problem limiting the use of **3a,b** as synthetic building blocks. Attempts to separate **3** and **4** by flash chromatography on silica gel or by crystallization from various solvents failed owing to the similar polarity and solubility behavior of these compounds. Distillation under reduced pressure gave main fractions (50–60% of the crude product) containing **3a,b** with GC purities ~90%. Further purification to yield analytically pure samples of **3a,b** was possible by preparative GC, if desired. NMR spectroscopic data and elemental analyses suggested that the actual content of **3a,b** in the main fractions of distillation was somewhat higher than indicated by GC[10] and the material proved sufficiently pure for most preparative purposes.[2a] Nevertheless, the wasteful and time-consuming distillation procedure is not fully satisfactory from a practical and analytical point of view. In our search for further improvement, we found that chromatography with fluorous reverse phase silica gel offers significant advantages over conventional techniques. This methodology allows rapid and quantitative purification of crude **3a,b** with potential for applications on a synthetically useful scale.

We have recently introduced the new technique of fluorous solid phase extraction for the separation of fluorous (highly fluorinated) compounds from organic compounds.[5] Fluorous reverse phase (FRP) silica gel is prepared by silylation of standard silica gel with $ClSi(Me_2)CH_2CH_2C_6F_{13}$. This FRP silica has a low affinity for organic compounds compared to fluorous compounds. As an extension of this approach, it seems probable that differentially fluorinated compounds will be retained differently on FRP silica: highly fluorinated compounds will be more strongly retained while molecules with fewer fluorines will be more weakly retained.[11]

Dimer **4** contains two 1*H*,1*H*,2*H*,2*H*-perfluorooctyl chains while **3a** and **3b** contain only one chain with a substantive organic part. Thus, we hypothesized that the retention of **3a** and **3b** on FRP silica would be weaker than that of dimer **4**. To test this notion, a mixture of **3b** (~75%) and **4** (~25%) obtained by fractional distillation was charged onto a short column packed with FRP silica. Elution with acetonitrile and evaporation provided pure **3b**. Washing the column with diethyl ether in turn gave pure **4**. Thus, both compounds can be recovered quantitatively in a process that resembles a solid phase extraction more than a chromatography, and expensive fluorocarbon solvents are not needed. In small trial experiments, we found that using about ten times weight of FRP silica compared to the weight of the mixture of **3b** and **4** was satisfactory; reducing the amount of silica by half overloaded the column. Assorted distillation fractions containing 50–90% **3b** were separated by this method to give individual, pure products. Similarly, a mixture of **3a** and **4** was also separated with FRP silica. After use, the fluorous FRP silica was washed and dried prior to repeated reuse.

In summary, (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-substituted aryl bromides **3a** and **3b** were synthesized via Cu(I) catalyzed Grignard reaction. The desired products **3a** and **3b** were very difficult to separate from the homocoupling product **4** by flash chromatography or distillation, but were readily separated by filtration over fluorous reverse phase silica. The aryl bromides **3a** and **3b** are generally useful fluorinated components for making ligands, reagents and catalysts, and separations over fluorous reverse phase silica may frequently prove to be the methods of choice in preparing other highly fluorinated compounds.

All reactions involving air- or moisture-sensitive materials were performed under argon using standard Schlenk techniques in dried and oxygen-free solvents. 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane (**1**, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl iodide) as well as *m*- and *p*-dibromobenzene were commercial products (Clariant, Aldrich) and used as received. FC-72 is a trademark of the 3M corporation and is mostly perfluorohexanes.

NMR spectra were recorded in 5 mm tubes on a Bruker AC 200 and AM 200 spectrometer operating at 200.1 and 50.3 for ^1H and ^{13}C and on a Bruker AMX 300 spectrometer operating at 282.4 MHz for ^{19}F. Chemical shifts are reported in ppm relative to external TMS for ^1H and ^{13}C and $CFCl_3$ for ^{19}F, using the solvent resonance as a secondary standard if possible. Coupling constants *J* are given in Hz. The assignments of ambiguous signals in the aromatic region are based on the increment method.[12] Multiplets marked with a star (e.g. d*) are part of higher order spin systems which were not fully analyzed.

MS were measured on a Finnigan MAT 8200 with EI technique. GC-MS-coupling was performed on a Finnigan MAT SSQ with EI technique. GC analyses were carried out on a Carlo Erba 4100 EIS chromatograph (column: 30 m, 100% methylpolysiloxan, inner diameter: 0.25 mm, coat thickness: 0.25 μm, detector: FID, temp: 6 °C/min injector: 220 °C, oven: 60–330 °C, 6/min, 10 min isotherm, detector: 320 °C, gas: 0.6 bar H_2). The given GC-purities are taken from the integrated peak areas without corrections.[10] Purification by preparative GC was carried out on a Perkin–Elmer F21 chromatograph (column: 4.5 m, 8 mm, 20% SE-54 on volaspher A4, 100–120 mesh, column temp: 160 °C, flow: 120 mL/min N_2). Elemental analyses were carried out in the microanalytical laboratory Dornis & Kolbe, Mülheim a. d. Ruhr.

1-Bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)benzene (3a):

A solution of *m*-dibromobenzene (38.1 g, 0.16 mol) in Et_2O (50 mL) was added dropwise under stirring to Mg turnings (4.31 g, 0.18 mol) in Et_2O (20 mL). The rate of addition was adjusted to maintain the solution under gentle reflux. The resulting mixture was stirred for 3 d at r.t. and then filtrated to give a greenish ethereal solution of **2a** (1.9 M, 87%).[13] Part of this solution (55.1 mL, 104.7 mmol **2a**) was added to a suspension of **1** (45.1 g, 95.0 mmol) and [(cod)CuCl] (ca. 300 mg) in THF (40 mL) at –3 °C. The mixture was allowed to warm to r.t. under stirring overnight. Hydrolysis and extraction with Et_2O gave 44.8 g of a red oil which was distilled over a Vigreux column (19 cm, 16 mm) to give 24.3 g of a colorless oil at a boiling point of 95–100 °C (10^{-2} Torr). This material contained 89% **3a** according to GC analysis (21.6 g, 45%). An analytically pure sample of **3a** was obtained by preparative GC.

^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 7.10–7.66 (m, 4H; *H*C2, *H*C4, *H*C5, *H*C6), 2.94 (m, 2H; H_2C1), 2.41 (m, 2H; H_2C2).

$^{13}C\{^1H\}$ NMR (50.3 MHz, $CDCl_3$, 27 °C): δ = 141.5 (s; *C*3), 122.8 (s; *C*1), 131.5 (s; H*C*2), 130.3 (s; HC5), 130.0 (s; H*C*6), 127.0 (s; H*C*4), 26.2 (t, $^3J_{FC}$ = 4.4 Hz; H_2C1), 32.8 (t, $^2J_{FC}$ = 22.7 Hz; H_2C2), 105.0–125.0 (6 signals, m; F_2C3–F_3C8).

$^{19}F\{^1H\}$ NMR (282.4 MHz, $CDCl_3$, 29 °C): δ = –81.9 (t, 3F, $^3J_{FF}$ = 4 Hz; F_3C8), –127.0 (br, 2F; F_2C7), –124.3 (br, 2F; F_2C6), –123.7 (br, 2F; F_2C5), –122.7 (br, 2F; F_2C4), –115.4 (t, 2F, $^3J_{FF}$ = 4 Hz; F_2C3).

MS (70 eV, EI): *m/z* (%) = 502 (100) [M^+], 423 (25) [$M^+ - (^{79}Br)$], 169 (85) [$M^+ - CH_2C_6F_{13}$].
Anal. $C_{14}H_8BrF_{13}$ (503.10) calcd C, 33.42; H, 1.60; Br, 15.88; F, 49.09. Found C, 33.59; H, 1.71; Br, 15.68; F, 49.17.

1-Bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)benzene (3b):
A solution of *p*-dibromobenzene (236 g, 0.97 mol) in Et_2O (ca. 450 mL) was added dropwise under stirring to Mg turnings (25.5 g, 1.05 mol) in Et_2O (60 mL). The rate of addition was adjusted to maintain the solution under gentle reflux. The resulting mixture was stirred overnight at r.t. and then filtrated to give a brownish ethereal solution of **2b** (1.92 M, 100%).[13] Part of this solution (520 mL, 0.97 mol **2b**) was added to a suspension of **1** (477 g, 0.97 mmol) and [(cod)CuCl] (ca. 1.6 g) in THF (640 mL) at –20 °C. The mixture was warmed to r.t. under stirring over a period of 4 h. Hydrolysis and extraction with Et_2O yielded 478 g of a brown oil which was distilled over a Vigreux column (19 cm, 16 mm) to give two colorless main fractions: the first fraction (119 g) was collected between 78–80 °C/10^{-2} Torr and contained 90% **3b** according to GC analysis. The second fraction (116 g) collected at temperatures of 80–93 °C/10^{-2} Torr was analytically pure. The total isolated yield of preparatively useful **3b** was 223 g (46%).
^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 7.33 (d*, 2H, *J* = 8.4 Hz; *H*C2, *H*C6), 6.97 (d*, 2H, *J* = 8.4 Hz; *H*C3, *H*C5), 2.77 (m, 2H; H_2C1), 2.24 (m, 2H; H_2C_2).
^{13}C{^{1}H} NMR (50.3 MHz, $CDCl_3$, 27 °C): δ = 138.2 (s; *C*4), 120.7 (s; *C*1), 130.0 (s; H*C*3, H*C*5), 132.0 (s; H*C*2, H*C*6), 26.0 (t, $^3J_{FC}$ = 4.4 Hz; H_2C1), 32.8 (t, $^2J_{FC}$ = 22.2 Hz; H_2C2), 105.0 – 128.0 (6 signals, m; $F_2C3 - F_3C8$).
^{19}F{^{1}H} NMR (282.4 MHz, $CDCl_3$, 29 °C): δ = –81.9 (t, 3F, $^3J_{FF}$ = 8.5 Hz; F_3C8), –127.1 (br, 2F; F_2C7), –124.3 (br, 2F; F_2C6), –123.7 (br, 2F; F_2C5), –122.7 (br, 2F; F_2C4), –115.4 (br, 2F; F_2C3).
GC-MS-coupling (70 eV, EI): *m/z* (%): = 502 (55) [M^+], 423 (15) [$M^+ - (^{79}Br)$], 169 (100) [$M^+ - CH_2C_6F_{13}$].
Anal. $C_{14}H_8BrF_{13}$ (503.10) calcd C, 33.42; H, 1.60; Br, 15.88; F, 49.09. Found C, 33.55; H, 1.70; Br, 15.97; F, 48.69.

Preparation of Fluorous Reverse Phase Silica:[5]
Flash chromatography grade silica (ICN silicaTech 32-63 D 60 A) was dried at 120 °C under high vacuum overnight. The dried silica gel (30.0 g) was heated at 100 °C in dry toluene (80 mL) containing imidazole (9.5 g) and $ClSi(Me)_2CH_2CH_2C_6F_{13}$ (50.0 g) for 3 d without stirring. The resulting silica gel was washed sequentially with toluene, MeOH, MeOH/H_2O, THF, Et_2O, and MeCN before drying under high vacuum to yield fluorous reverse phase silica gel (47.8 g).

Purification of 3a and 3b Over Fluorous Reverse Phase Silica:
A short column packed with FRP silica (3.66 g) was wetted with Et_2O before washing with MeCN. To this column, a 3:1 mixture (NMR integration) of **3b** and **4** (350 mg) was loaded. The column was first eluted with MeCN (8 mL) to give pure **3b** (244 mg). Pure **4** (97 mg) was washed out with Et_2O (16 mL): total recovery, 97%. Resonances for **3b** could not be detected in the ^{1}H NMR spectrum of the Et_2O fraction while resonances for **4** could not be detected in the spectrum of the MeCN fraction. Similarly, a 1:1 mixture (NMR integration) of **3a** and **4** (33 mg) was separated with FRP silica (330 mg) by eluting with MeCN (2 mL) and FC-72 (1 mL) successively to give pure **3a** (13 mg) and pure **4** (18 mg): total recovery, 94%. The FRP silica was recovered after washing with acetone, MeCN, Et_2O, hexanes and FC-72.

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