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Activation of chlorine and fluorine by a phenylazo group towards nucleophilic aromatic substitution. Regioselective preparation of polysubstituted anilines

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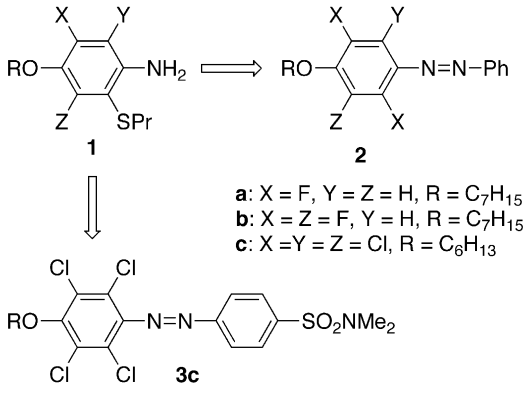
Abstract—A phenylazo group was used for selective activation of *ortho* fluorine and chlorine atoms towards nucleophilic aromatic substitution with the propanethiolate anion. This enabled a regioselective synthesis of three substituted 4-alkoxyanilines. The regioselectivity of substitution was confirmed by comparison of experimental NMR chemical shifts with empirically predicted values. The observed reactivity of the substrates is discussed in the context of the substituent effect.

1. Introduction

Recently, we demonstrated[1] that a phenylazo group moderately activates *ortho* fluorine atoms towards nucleophilic aromatic substitution (NAS)[2] and therefore is an effective and attractive alternative to the nitro group in the preparation of substituted anilines. Using this methodology, we prepared[1] a series of anilines required for the synthesis of polyfunctionalized biphenyls.[3] We also developed synthetic access to benzo[1,2,4]thiadiazines using 2-alkylthioanilines as the staring materials.[4] The preparation of partially halogenated 7-alkoxybenzo[1,2,4]-thiadiazines,[5] requires *p*-alkoxyanilines **1a–c**, which, in principle, can be derived from the corresponding polyhalogenated azo derivatives **2a–c** (Scheme 1).

Here we describe the application of the phenylazo group as an activator of *ortho* F and Cl atoms towards NAS with a thiolate anion, and also as a mask for an amino group in regioselective preparation of anilines **1**. We also briefly investigate the activating ability of the arylazo group substituted in the *para* position by the strongly electron-withdrawing sulfonyl group in **3c**.



Scheme 1.

2. Results

The key step in the synthesis of anilines **1** is the regioselective introduction of the propylthio substituent. Following an earlier established protocol,[1] the fluoro derivatives **2a** and **2b** were reacted with 1.1 equiv of the propanethiolate in boiling ethanol. Substrate **2b** was completely consumed after 4 h and the corresponding product **4b** was isolated in 75% yield (Scheme 2). In contrast, only about half of fluoride **2a** reacted after 8 h under the same conditions to give **4a** in 41% isolated yield. In both reactions, the formation of about 15% of ethoxy derivatives **5a** and **5b** was observed. Approximately the same amounts of **5** were observed when excess PrSH (1.6 equiv) was used with the same amount of base

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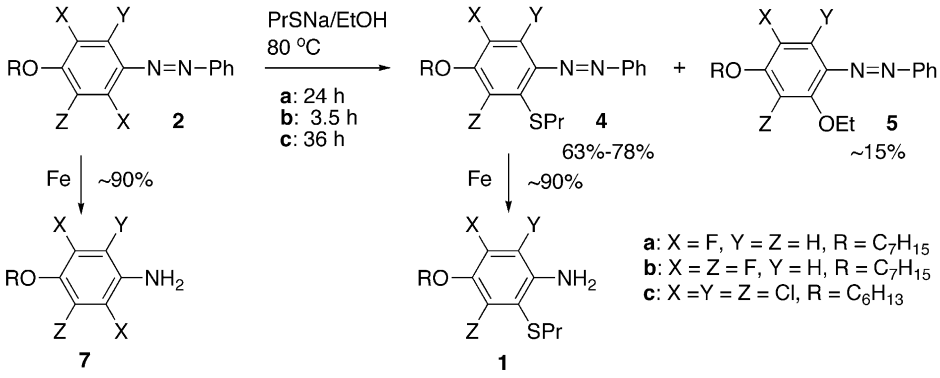


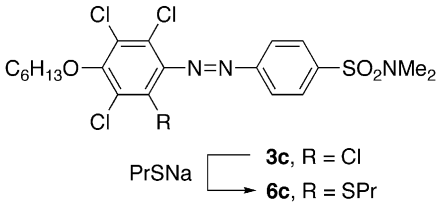
Scheme 2.

(1.1 equiv). This suggests that low concentration of the nucleophile and equilibrium with the solvent (EtOH) are responsible for the appearance of the side product **5**, rather than partial loss of the thiolate due to air oxidation. The formation of **5b** was almost completely suppressed and the reaction time was shortened when 2.2 equiv of the thiolate and 1 equiv of PrSH were used, and the desired product **4b** was isolated in 75% yield. Thus, higher concentrations of the nucleophile are needed for selective substitution.

A similar thiolation reaction of the tetrachloro derivative **2c** with 1.6 equiv of PrSNa in ethanol gave about 80% yield of an 8:1 mixture of monosubstituted product **4c** and presumably the ethoxy side product **5c**. No 2,6-bispropane-thiolated product was found despite a 60% excess of the nucleophile. Complete conversion of the starting **2c** was observed after 36 h, which compares to 3.5 h for **2b** and 24 h for **2a** under similar conditions. No reaction of 2,3,5,6-tetrachloroanisole (lacking the azo group) with PrSNa was detected by GC–MS after 48 h under similar conditions.

In order to increase the rate of replacement of the Cl atom in **2c** by stabilization of the negative charge on the nitrogen atoms, a strongly electron-withdrawing sulfonamido group was introduced in substrate **3c**. A small-scale reaction demonstrated that after 18 h about half of **3c** was consumed, but NMR analysis of the crude and complex reaction mixture showed only traces of the desired product **6c** (Scheme 3). This poor selectivity for **6c** presumably resulted from removing the electron density from the azo group in **3c** and activating it towards reduction by the thiolate anion.

Alternatively, the thiolation of the tetrachloro derivatives **2c** and **3c** was conducted under PTC conditions, as reported for non-activated polychlorinated substrates.[6] Each substrate was consumed within 3 h, which is comparable to the reaction times reported for some non-activated chloroarenes under analogous conditions.[6] Compound **2c** produced pure



Scheme 3.

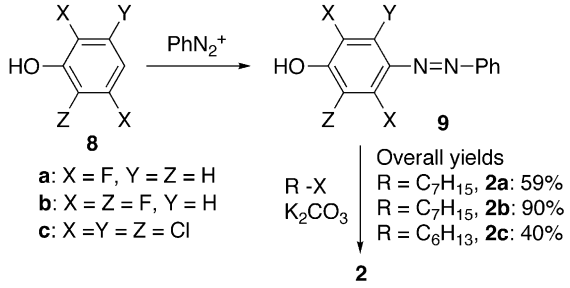
4c in a 78% isolated yield. In contrast, **3c** formed a complex mixture of products, from which **6c** was obtained in about 60% yield or $<10\%$ of analytically pure sample.

The resulting substituted azo compounds **4** were reduced to the desired amines **1** using iron powder. For comparison, the starting azo compounds **2a** and **2b** were also converted to amines **7a** and **7b**, respectively, and both series of amines were generally obtained in about 90% isolated yields (Scheme 2).

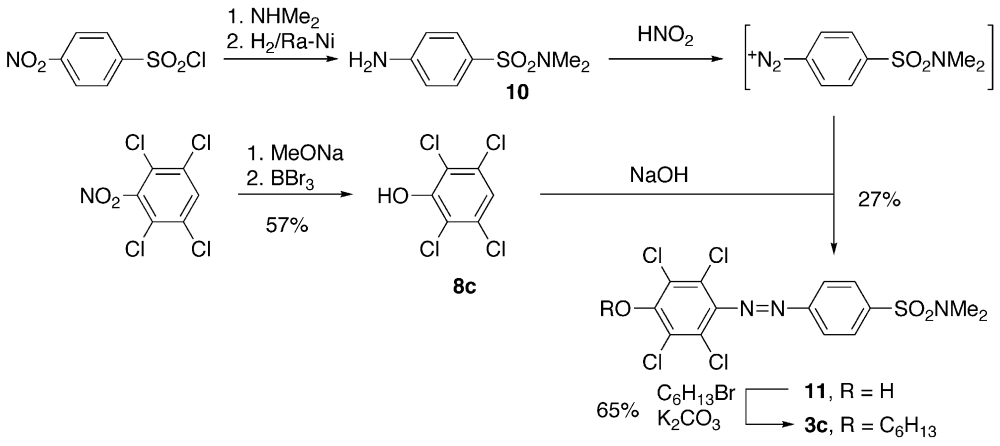
The required azo compounds **2** were prepared by a diazo coupling reaction of the appropriate phenols **8** and benzenediazonium chloride followed by alkylation of the resulting crude azophenols **9** with either *n*-heptyl iodide (**9a** and **9b**) or *n*-hexyl bromide (**9c**, Scheme 4). The yields of azophenols **9a** and **9b** were above 70%. In contrast, **9c** was isolated in only 44% yield, which is consistent with the results for the tetrafluoro analog.[7] Generally, the crude phenols were pure enough for subsequent O-alkylation under PTC conditions. This was demonstrated on 2,3,6-trifluorophenol (**8b**), which gave a 90% overall yield of **2b** in two steps.

The sulfonamide **3c** was prepared in a similar manner in about 20% overall yield by diazo coupling of 2,3,5,6-tetrachlorophenol (**8c**) with a diazonium salt derived from amine **10** followed by alkylation of the resulting phenol **11** (Scheme 5).

Azo compounds that are exposed to sunlight partially isomerize to form *cis*/*trans* mixtures, as evident from the NMR spectra. For instance, spectra of **2b** and **4b** show significantly shielded aromatic hydrogen atoms in the *cis* isomer up to 1 ppm relative to those in the *trans* isomers. At



Scheme 4.



Scheme 5.

a photochemical equilibrium, the ratio of the *trans* and *cis* isomers of **2b** was 3:1 in a chloroform solution. Pure *trans* isomers were obtained by heating samples above 80 °C for 1 h.

2,3,5,6-Tetrachlorophenol (**8c**) was obtained in two steps in 57% overall yield by nucleophilic displacement of the nitro group in 2,3,5,6-tetrachloronitrobenzene with the methoxy group,[8] followed by demethylation of the resulting 2,3,5,6-tetrachloroanisole with BBr_3 (Scheme 5). The original methoxylation procedure[8] was modified by using THF to increase solubility of the starting nitro compound. *p*-Aminobenzenesulfonamide **10** was prepared from 4-nitrobenzenesulfonyl chloride with aqueous $NHMe_2$ followed by catalytic reduction of the resulting nitro amide (Scheme 5).[9]

3. Discussion and conclusions

Results show that the phenylazo group effectively activates both fluorine and chlorine towards nucleophilic substitution and tolerates the reaction conditions. Considering the ready accessibility of the azo precursors through diazo coupling either to phenols or metalloarenes,[1] the method is synthetically useful for the preparation of *ortho*-substituted anilines. If general, the method may be particularly valuable for substitution of chlorine in NAS reactions, since the most common activating group NO_2 is replaced preferentially or exclusively by nucleophiles in many polychlorinated nitroarenes.[1,10] An alternative approach to substitution of halogen in chloroaniline derivatives requires high temperatures and long reaction times.[11] In contrast, NAS in chloroazobenzenes, such as **2c**, can be accomplished selectively under mild conditions and short reaction times (PTC).

The phenylazo group appears to be an optimum substituent for NAS reactions due to its activating ability and synthetic simplicity. The previously investigated 4-Me_2N substituent appears to completely compensate the moderate activating effect of the PhN_2 group,[1] presumably due to the strong donating character of the amino group. In the current study, the 4-sulfonyl group in **3c** activates other undesired reaction pathways, which result in complex reaction mixtures.

Based on the observed reaction times, the reactivity of the haloarenes follows the order **2b** > **2a** > **2c**. The significantly higher mobility of fluorine in **2b** than in **2a** (c.f. 3.5 h vs 24 h reaction time) results from the activating effect of the *ortho* fluorine atom in the former, which is absent in **2a**. According to a comparative study of penta- and hexafluorobenzenes,[12] *ortho* substitution with fluorine, as in **2b**, may increase the NAS rate by a factor of about 30, while fluorine in the *para* position, as in **2a**, is expected to be modestly deactivating. Thus, fluorine atoms in **2b** and those studied before[1] are additionally activated by *ortho* halogens and show significantly enhanced reactivity (shorter reaction times).

The lowest reactivity in the series is exhibited by the chloroarene **2c** (36 h reaction time), which reflects the generally observed[13] 2–3 order-of-magnitude lower mobility of Cl than F in NAS reactions. However, the mobility of chlorine in **2c** is increased by the presence of three other Cl atoms exerting strong *ortho*, and moderate *meta* and *para* activating effects.[12,14] Therefore, it is conceivable that a precursor lacking the additional Cl atoms, e.g. the hypothetical chloro analog of **2a**, would exhibit low reactivity and a synthetically useful NAS reaction would have to be performed under the PTC conditions.[6] Support for this expectation is provided by the high selectivity for monosubstituted product **4c**, which results from lower activation of the mobile chlorine atom (*ortho* to the azo group) by the SPr group in **4c** than by the Cl in the same position in **2c**. According to the results for substituted 2- and 4-chloroquinolines,[14] the change of Cl to a SMe group retards the NAS rate by a factor >20, which is consistent with the trends in the σ_m values (0.37 and 0.15, respectively).[15] Interestingly, these studies found the SMe substituent to be even less effective than H in activation of the *meta* chlorine towards NAS.[14]

Nucleophilic substitution in **2** occurs regioselectively, which is expected based on the small *ortho* deactivating effect of the alkoxy group[16] and the moderately *ortho* activating ability of the azo group. Proton NMR analysis of the azo compounds **4** and the amines **1**, combined with the results for unsubstituted derivatives **2** and **7**, shows a good correlation between the predicted and experimental chemical shifts (Fig. 1). The plot reflects stronger solvent-solute

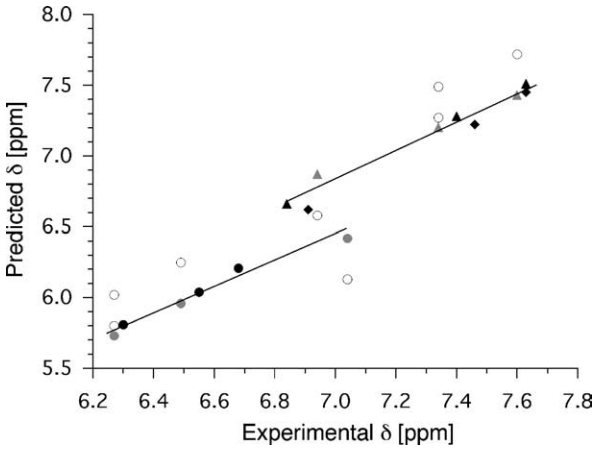


Figure 1. Correlation between experimental and predicted (ChemDraw 8.0 Ultra) chemical shifts for fluorinated anilines **1** (black dots) and **7** (gray dots), azo compounds **2** (black triangles) and **4** (gray triangles) and phenols **9** (black diamonds). Best fit lines: $y=0.92x$ ($R^2=0.97$) for **1** and **7**, and $y=0.98x$ ($R^2=0.96$) for **4** and **9**. Open circles represent the calculated chemical shift for other regioisomers of **1** and **4**.

interactions for anilines **1** and **7**, which are deshielded relative to the predicted values (slope 0.92), than observed for azo compounds **2** and **4** (slope 0.98). In contrast, chemical shifts predicted for other regioisomers of **4** and **1** lie outside the correlation. The magnitude of the ^1H–^{19}F coupling constants (J_{HF}) in the NMR spectra is also consistent with the assigned structures. For instance, in **1a** the more shielded proton adjacent to the amino group is more strongly coupled to the ^{19}F nucleus ($J_{HF}=12.6$ Hz) than the downfield hydrogen atom ($J_{HF}=9.0$ Hz).

Although the main focus of this work was the introduction of an alkylthio substituent through the NAS process, the isolation of the ethoxy derivatives **5** as side products suggests a more general application of the PhN_2 group as an activating mask for the NH_2 group in other NAS reactions.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, and referenced to the solvent, unless specified otherwise. ^{19}F NMR spectra were recorded at 282.4 MHz and referenced to CF_3COOH (external standard). IR spectra were recorded by deposition of a thin film from solution on sodium chloride plates or as KBr pellets.

4.1.1. 5-Fluoro-4-heptyloxy-2-propylthioaniline (1a). Azo compound **4a** (89 mg, 0.23 mmol) was added in one portion to a vigorously stirred suspension of iron dust (130 mg, 2.32 mmol) in water (3 mL) and acetic acid (0.1 mL) at 100 °C and stirred for 1 h. The reaction mixture was cooled down, poured into satd $NaHCO_3$ and extracted with diethyl ether. Combined organic layers were dried ($MgSO_4$) and concentrated to give an oily residue which was short-path distilled (bp 185 °C/0.15 Torr) to give 63 mg (90% yield) of amine **1a** as a transparent oil: ^1H NMR δ 0.89 (t, $J=6.6$ Hz, 3H), 0.99 (t, $J=7.2$ Hz, 3H), 1.25–1.49 (m, 8H), 1.53 (sextet, $J=7.3$ Hz, 2H), 1.75 (quintet, $J=6.6$ Hz, 2H), 2.66 (t, $J=7.2$ Hz, 2H), 3.93 (t, $J=6.6$ Hz, 2H), 4.2 (brs, 2H), 6.49 (d, $J=12.6$ Hz, 1H), 7.04 (d, $J=9.0$ Hz, 1H); ^{13}C NMR δ 13.2, 14.0, 22.6, 22.9, 25.8, 29.0, 29.4, 31.7, 37.3, 71.0, 103.2 (d, $J=22.2$ Hz), 112.5 (d, $J=3.4$ Hz), 124.4 (d, $J=3.6$ Hz), 139.9 (d, $J=11.8$ Hz), 143.3 (d, $J=9.9$ Hz); 154.3 (d, $J=246.8$ Hz); ^{19}F NMR δ −132.34 (s, 1F); IR (neat) ν_{max} 3460 and 3360 (NH_2), 1497 cm^{-1}; MS, *m/e* (relative intensity) 299 (M^+, 45), 159 (100). HR-FABMS, calcd for $C_{16}H_{26}FNOS$ ($[M]^+$): *m/e* 299.1719; found: *m/e* 299.1704. Anal. Calcd for $C_{16}H_{26}FNOS$: C, 64.18; H, 8.75; N, 4.68. Found: C, 64.80; H, 8.84; N, 4.92.

4.1.2. 3,5-Difluoro-4-heptyloxy-2-propylthioaniline (1b). The amine **1b** was obtained in 94% yield according to the procedure described for **1a** and purified by chromatography (CH_2Cl_2–hexane, 3:1) to give a transparent quickly darkening in air oil: ^1H NMR δ 0.89 (t, $J=6.9$ Hz, 3H), 0.98 (t, $J=7.4$ Hz, 3H), 1.26–1.49 (m, 8H), 1.55 (sextet, $J=7.4$ Hz, 2H), 1.72 (quintet, $J=7.2$ Hz, 2H), 2.65 (t, $J=7.2$ Hz, 2H), 3.96 (t, $J=6.6$ Hz, 2H), 4.45 (brs, 2H), 6.27 (dd, $J_1=12.3$ Hz, $J_2=2.0$ Hz, 1H); ^{19}F NMR δ −127.32 (d, $J=10.4$ Hz, 1F), −120.18 (d, $J=10.4$ Hz, 1F); IR (neat) ν_{max} 3470 and 3371 (NH_2), 1493 cm^{-1}; MS, *m/e* (relative intensity) 317 (M^+, 25), 177 (100). HR-FABMS, calcd for $C_{16}H_{25}F_2NOS$ ($[M]^+$): *m/e* 317.1625; found: *m/e* 317.1599.

4.1.3. 3,5,6-Trichloro-4-hexyloxy-2-propylthioaniline (1c). The amine **1c** was obtained in 65% yield as a transparent oil according to the procedure described for **1a** and purified by column chromatography (CH_2Cl_2–hexanes, 1:1): ^1H NMR δ 0.91 (t, $J=7.1$ Hz, 3H), 0.99 (t, $J=7.4$ Hz, 3H), 1.32–1.38 (m, 4H), 1.46–1.53 (m, 2H), 1.57 (sextet, $J=7.3$ Hz, 2H), 1.82 (quintet, $J=7.1$ Hz, 2H), 2.75 (t, $J=7.4$ Hz, 2H), 3.92 (t, $J=6.6$ Hz, 2H), 5.0 (brs, 2H); ^{13}C NMR δ 13.4, 14.0, 22.6, 23.2, 25.5, 29.9, 31.6, 36.7, 73.7, 115.8, 116.1, 129.6, 134.2, 143.7, 144.2; IR (neat) ν_{max} 3480 and 3368 (NH_2), 1586, 1431 cm^{-1}. Anal. Calcd for $C_{15}H_{22}Cl_3NOS$: C, 48.59; H, 5.98; N, 3.78. Found: C, 48.74; H, 5.98; N, 3.76.

4.1.4. 2,5-Difluoro-4-(heptyloxy)azobenzene (2a). A mixture of 2,5-difluoro-4-phenylazophenol (**9a**, 4.70 g, 20.1 mmol), anhydrous K_2CO_3 (3.60 g, 26 mmol), *n*-heptyl iodide (4.70 g, 20.8 mmol), Aliquat®336 (0.2 mL) and acetone (30 mL) was stirred and refluxed overnight. Hexane (30 mL) was added and the mixture was filtered through a silica gel plug and washed with CH_2Cl_2. The filtrate was concentrated, the residue dissolved in hexanes and filtered again through a silica gel plug with warm hexanes as the eluent. The orange filtrate was evaporated to give a solid, which was recrystallized from pentane to yield 5.25 g (79% yield) of **2a** as orange crystals: mp 80–81 °C; bp 220 °C/0.2 Torr (short path); ^1H NMR δ 0.90 (t, $J=6.6$ Hz, 3H), 1.31–1.51 (m, 8H), 1.88 (quintet, $J=7.0$ Hz, 2H), 4.08 (t, $J=6.6$ Hz, 2H), 6.84 (dd, $J_1=11.7$ Hz, $J_2=7.2$ Hz, 1H), 7.45–7.54 (m, 3H), 7.63 (dd, $J_1=11.7$ Hz, $J_2=7.2$ Hz, 1H), 7.88–7.94 (m, 2H); ^{19}F NMR δ −139.32 (d, $J=13.6$ Hz, 1F), −126.85 (d, $J=13.6$ Hz, 1F); IR (KBr) ν_{max} 1623, 1503, 1282 cm^{-1}; MS, *m/e* (relative intensity) 332 (M^+, 30), 77 (100). Anal. Calcd for $C_{19}H_{22}F_2N_2O$: C, 68.66; H, 6.67; N, 8.43. Found: C, 68.69; H, 6.67; N, 8.44.

4.1.5. 2,3,5-Trifluoro-4-(heptyloxy)azobenzene (2b). The compound **2b** was synthesized in 90% overall yield based on **8b** according to the procedure described for **2a** as an orange oily mixture of *trans–cis* isomers in a 5:1 ratio that solidified upon standing: bp 210 °C/0.2 Torr (short path); mp 36–37 °C; ^{1}H NMR (major isomer) δ 0.90 (t, J=6.6 Hz, 3H), 1.31–1.55 (m, 8H), 1.81 (quintet, J=7.0 Hz, 2H), 4.29 (t, J=6.6 Hz, 2H), 7.40 (ddd, J_1=11.7 Hz, J_2=3.0 Hz, J=0.9 Hz, 1H), 7.50–7.55 (m, 3H), 7.91–7.96 (m, 2H); (minor isomer, selected signals) δ 1.73 (quintet, J=7.0 Hz, 2H), 4.13 (t, J=6.6 Hz, 2H), 6.48 (ddd, J_1=10.2 Hz, J_2=6.0 Hz, J_3=2.4 Hz, 1H), 6.88–6.92 (m, 2H), 7.29–7.34 (m, 2H); ^{19}F NMR (major isomer) δ −151.83 (d, J=7.6 Hz, 2F), −133.46 (t, J=7.7 Hz, 1F); (minor isomer) δ −149.91 (dd, J_1=21.7 Hz, J_2=5.0 Hz, 1F), −147.86 (dd, J_1=21.7 Hz, J_2=11.9 Hz, 1F), −132.40 (dd, J_1=11.9 Hz, J_2=5.1 Hz, 1F); IR (KBr) ν_{max} 1493, 1347 cm^{-1}; MS, *m/e* (relative intensity) 350 (M^+, 15), 77 (100). Anal. Calcd for $C_{19}H_{21}F_3N_2O$: C, 65.13; H, 6.04; N, 8.00. Found: C, 65.21; H, 6.08; N, 8.11.

4.1.6. 2,3,5,6-Tetrachloro-4-(hexyloxy)azobenzene (2c). The compound **2c** was synthesized in 91% yield according to the procedure described for **2a** using *n*-hexyl bromide and acetonitrile as a solvent: mp 64–65 °C; ^{1}H NMR δ 0.93 (t, J=7.0 Hz, 3H), 1.34–1.42 (m, 4H), 1.50–1.60 (m, 2H), 1.89 (quintet, J=7.0 Hz, 2H), 4.06 (t, J=6.5 Hz, 2H), 7.53–7.60 (m, 3H), 7.94–7.99 (m, 2H); ^{13}C NMR δ 14.0, 22.6, 25.4, 29.9, 31.5, 74.2, 119.5, 123.2, 124.1, 128.5, 129.3, 132.9, 146.5, 152.0; IR (KBr) ν_{max} 1371 cm^{-1}. Anal. Calcd for $C_{18}H_{18}Cl_4N_2O$: C, 51.46; H, 4.32; N, 6.67. Found: C, 51.36; H, 4.32; N, 6.65.

4.1.7. *N,N*-Dimethyl-4-[2,3,5,6-tetrachloro-4-hexyloxyphenyl(azo)]benzene-sulfonamide (3c). Compound **3c** was synthesized in 65% yield as a 6:1 mixture of *trans–cis* isomers according to the procedure described for **2a** using *n*-hexyl bromide and acetonitrile as a solvent and recrystallized from *i*-octane: mp 100–101 °C; ^{1}H NMR δ (major isomer) 0.92 (t, J=7.2 Hz, 3H), 1.32–1.41 (m, 4H), 1.50–1.60 (m, 2H), 1.90 (quintet, J=6.9 Hz, 2H), 2.79 (s, 6H), 4.08 (t, J=6.5 Hz, 2H), 7.98 (d, J=8.4 Hz, 2H), 8.08 (d, J=8.4 Hz, 2H); (minor isomer, selected signals) δ 2.70 (s, 6H), 4.00 (t, J=6.6 Hz, 2H), 7.13 (d, J=8.7 Hz, 2H), 7.73 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 14.1, 22.6, 25.4, 30.0, 31.6, 37.9, 74.4, 123.6, 124.3, 128.5, 128.9, 139.1, 145.9, 152.7, 153.8; IR (KBr) ν_{max} 1351, 1167 cm^{-1}. HR-FABMS, calcd for $C_{20}H_{24}Cl_4N_3O_3S$ ($[M+H]^+$): *m/e* 526.0292; found: *m/e* 526.0278. Anal. Calcd for $C_{20}H_{23}Cl_4N_3O_3S$; C, 45.56; H, 4.40; N, 7.97. Found: C, 45.93; H, 4.49; N, 7.85.

4.1.8. 5-Fluoro-4-heptyloxy-2-(propylthio)azobenzene (4a). Compound **2a** (112 mg, 0.34 mmol) was suspended in ethanol (3 mL, 95%), then a solution of NaOH (15 mg, 0.375 mmol in 1.5 mL EtOH) was added, followed by propanethiol (50 μL, 0.552 mmol) at rt under N_2. The mixture was stirred at 90 °C for 10 h, more propanethiol (50 μL, 0.552 mmol) was added and the stirring was continued overnight. When the TLC analysis showed absence of the starting **2a** (about 24 h) the reaction mixture was evaporated to dryness. The product was purified by flash chromatography (CH_2Cl_2–hexanes, 1:5) followed by recrystallization from EtOH to give 82 mg (63% yield) of **4a** as orange needles: mp 66–67 °C; ^{1}H NMR δ 0.91 (t, J=6.6 Hz, 3H), 1.09 (t, J=7.3 Hz, 3H), 1.28–1.54 (m, 8H), 1.78 (sextet, J=7.4 Hz, 2H), 1.87 (quintet, J=7.2 Hz, 2H), 2.97 (t, J=7.2 Hz, 2H), 4.11 (t, J=6.6 Hz, 2H), 6.94 (d, J=7.8 Hz, 1H), 7.41–7.51 (m, 3H), 7.60 (d, J=12.0 Hz, 1H), 7.90–7.95 (m, 2H); ^{13}C NMR δ 13.7, 14.1, 22.2, 22.6, 25.9, 29.0, 29.1, 31.7, 35.1, 69.6, 104.4 (d, J_{CF}=20.1 Hz), 112.6 (br), 123.1 129.1, 130.8, 136.7 (d, J_{CF}=2.6 Hz), 143.3 (d, J_{CF}=4.1 Hz), 150.0 (d, J_{CF}=12.2 Hz), 151.3 (d, J_{CF}=248.2 Hz), 152.7. ^{19}F NMR δ −138.1 (s, 1F); IR (KBr) ν_{max} 1600, 1503, 1267 cm^{-1}. Anal. Calcd for $C_{22}H_{29}FN_2OS$: C, 68.01; H, 7.52; N, 7.21. Found: C, 67.87; H, 7.54; N, 7.15.

4.1.9. 3,5-Difluoro-4-heptyloxy-2-(propylthio)azobenzene (4b). Compound **4b** was prepared in 69% yield according to the procedure described for **4a** and without using additional PrSH. Full conversion of **2b** was achieved after 3.5 h. When double the amount of NaOH and PrSH was used, the reaction was completed after 2 h and compound **4b** was isolated in 75% yield. The product was purified by PTLC (hexanes) to give a red oil of **4b** as a 6:1 mixture of *trans–cis* isomers: ^{1}H NMR (major isomer) δ 0.90 (t, J=6.6 Hz, 3H), 0.98 (t, J=7.3 Hz, 3H), 1.25–1.50 (m, 8H), 1.59 (sextet, J=7.3 Hz, 2H), 1.80 (quintet, J=7.1 Hz, 2H), 2.94 (t, J=7.2 Hz, 2H), 4.22 (t, J=6.6 Hz, 2H), 7.34 (dd, J_1=11.7 Hz, J_2=2.1 Hz, 1H), 7.49–7.57 (m, 3H), 7.93–7.98 (m, 2H); (minor isomer, selected signals) δ 2.88 (t, J=7.2 Hz, 2H), 4.07 (t, J=6.6 Hz, 2H), 5.96 (dd, J_1=10.2 Hz, J_2=1.8 Hz, 1H), 6.86–6.90 (m, 2H); ^{19}F NMR (major isomer) δ −127.65 (d, J=9.4 Hz, 1F), −121.17 (d, J=9.5 Hz, 1F); (minor isomer) δ −126.16 (d, J=10.5 Hz, 1F), −121.25 (d, J=10.6 Hz, 1F); IR (neat) ν_{max} 1481 cm^{-1}; FAB, *m/e* (relative intensity) 407 (MH^+, 52) 363 (M^+-C_3H_7, 100). HR-FABMS, calcd for $C_{22}H_{29}F_2N_2OS$ ($[M+H]^+$): *m/e* 407.1969; found: *m/e* 407.1975.

4.1.10. 2,3,5-Trichloro-4-hexyloxy-6-(propylthio)azobenzene (4c). *Method A*. Compound **2c** was reacted with sodium propanethiolate in EtOH as described for **4a**. When TLC analysis showed full conversion of the substrate after 36 h, the reaction mixture was worked up and product **4c** contaminated with small amounts of the presumably ethoxy derivative **5c** was isolated in 78% yield.

Method B. Compound **2c** (1800 mg, 4.29 mmol), powdered KOH (317 mg, 0.76 mmol), and hexadecyltributylphosphonium bromide (109 mg, 0.215 mmol) were stirred in toluene (8 mL) under nitrogen. Propanethiol (343 mg, 4.51 mmol) was added via syringe, and the syringe was washed with toluene (3 mL). The reaction was monitored by TLC. Upon total conversion of the starting material (~3 h), the reaction mixture was passed through a silica gel plug using first pure hexanes and proceeding up to CH_2Cl_2–hexanes in 1:1 ratio, to afford 1.54 g (78% yield) of **4c** as a dark red oil: ^{1}H NMR δ 0.87 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.0 Hz, 3H), 1.36–1.41 (m, 4H), 1.46 (sextet, J=7.3 Hz, 2H), 1.51–1.59 (m, 2H), 1.89 (quintet, J=6.9 Hz, 2H), 2.70 (t, J=7.2 Hz, 2H), 4.05 (t, J=6.6 Hz, 2H), 7.56–7.59 (m, 3H), 7.94–7.97 (m, 2H); ^{13}C NMR δ 13.2, 14.0, 22.6, 22.8, 25.5, 30.0, 31.6, 38.2, 73.9, 123.1, 123.2, 126.4, 129.3, 130.0, 132.4, 134.2, 151.5, 152.0, 152.3; IR (KBr) ν_{max}

1363 cm^{-1}. Anal. Calcd for $C_{21}H_{25}Cl_4N_2OS$: C, 54.85; H, 5.48; N, 6.09. Found: C, 55.22; H, 5.62; N, 5.77.

4.1.11. 2-Ethoxy-5-fluoro-4-(heptyloxy)azobenzene (5a). The ethoxy derivative **5a** was isolated in about 10% yield and ~95% purity as a second fraction in chromatographic purification of **4a** (CH_2Cl_2–hexanes, 1:1) in the form of a red oil: ^{1}H NMR δ 0.90 (t, J=6.6 Hz, 3H), 1.25–1.50 (m, 8H), 1.52 (t, J=7.1 Hz, 3H), 1.87 (quintet, J=7.0 Hz, 2H), 4.09 (t, J=6.6 Hz, 2H), 4.28 (q, J=7.0 Hz, 2H), 6.67 (d, J=7.2 Hz, 1H), 7.41–7.54 (m, 3H), 7.62 (d, J=12.3 Hz, 1H), 7.85–7.92 (m, 2H); ^{19}F NMR δ −143.53 (s, 1F); FAB, *m/e* (relative intensity) 359 (MH+, 100). HR-FABMS, calcd for $C_{21}H_{28}FN_2O_2$ ($[M+H]^+$): *m/e* 359.2135; found: *m/e* 359.2146.

4.1.12. 2-Ethoxy-3,5-difluoro-4-(heptyloxy)azobenzene (5b). The ethoxy derivative **5b** was isolated in about 10% yield and ~90% purity as a second fraction in chromatographic purification of **4b** (CH_2Cl_2–hexanes, 1:1) in the form of a red oil: ^{1}H NMR δ 0.89 (t, J=6.6 Hz, 3H), 1.23–1.40 (m, 8H), 1.46 (t, J=7.0 Hz, 3H), 1.80 (quintet, J=7.2 Hz, 2H), 4.25 (t, J=6.6 Hz, 2H), 4.36 (q, J=7.0 Hz, 2H), 7.36 (dd, J_1=12.0 Hz, J_2=2.1 Hz, 1H), 7.47–7.56 (m, 3H), 7.88–7.95 (m, 2H); ^{19}F NMR δ −145.32 (d, J=4.5 Hz, 1F); −134.27 (d, J=4.5 Hz, 1F); FAB, *m/e* (relative intensity) 377 (MH+, 100). HR-FABMS, calcd for $C_{21}H_{27}F_2N_2O_2$ ($[M+H]^+$): *m/e* 377.2041; found: *m/e* 377.2017.

4.1.13. *N*,*N*-Dimethyl-4-[4-hexyloxy-2,3,5-trichloro-6-propylthiophenyl(azo)]benzenesulfonamide (6c). Following Method B described for **4c**, compound **6c** was obtained from **3c** in 63% yield and about 75% purity after chromatography (CH_2Cl_2). An analytical sample was obtained by recrystallization from Et_2O–heptane mixture: mp 100–101 °C; ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 0.93 (t, J=6.9 Hz, 3H), 1.33–1.44 (m, 6H), 1.47 (sextet, J=7.0 Hz, 2H), 1.90 (quintet, J=7.0 Hz, 2H), 2.74 (t, J=7.2 Hz, 2H), 2.80 (s, 6H), 4.07 (t, J=6.6 Hz, 2H), AA′MM′ 7.98 and 8.07 (d, J=8.7 Hz, 4H); IR (KBr) ν_{max} 1352, 1169 cm^{-1}. HR-FABMS, calcd for $C_{23}H_{31}Cl_3N_3O_3S_2$ ($[M+H]^+$): *m/e* 566.0872; found: *m/e* 566.0858.

4.1.14. 2,5-Difluoro-4-heptyloxyaniline (7a). The amine **7a** was synthesized in 91% yield according to the procedure described for **1a** using 4.5 g of **2a**, 5.0 g of iron 60 mL of water and 8 mL acetic acid: bp 150 °C/0.1 Torr (short path); mp 45–46 °C; ^{1}H NMR δ 0.89 (t, J=6.8 Hz, 3H), 1.29–1.45 (m, 8H), 1.76 (quintet, J=7.0 Hz, 2H), 3.5 (bs, 2H), 3.91 (t, J=6.6 Hz, 2H), 6.55 (dd, J_1=12.0 Hz, J_2=8.4 Hz, 1H), 6.68 (dd, J_1=11.7 Hz, J_2=7.5 Hz, 1H); ^{13}C NMR δ 14.1, 22.6, 25.8 29.0, 29.3, 31.8, 70.9, 104.6 (dd, J_1=23.9 Hz, J_1=2.8 Hz), 105.2 (dd, J_1=23.9 Hz, J_1=4.4 Hz), 127.7 (dd, J_1=15.2 Hz, J_1=9.6 Hz), 138.8 (dd, J_1=12.6 Hz, J_1=9.1 Hz), 147.0 (d, J=232.1 Hz), 149.4 (d, J=239.6 Hz); ^{19}F NMR δ −139.69 (d, J=13.8 Hz, 1F), −139.26 (d, J=13.8 Hz, 1F); IR (KBr) ν_{max} 3411, 3307 and 3207 (NH_2), 1537 cm^{-1}; MS, *m/e* (relative intensity) 243 (M^+, 5), 145 (100). Anal. Calcd for $C_{13}H_{19}F_2N_2O$: C, 64.18; H, 7.87; N, 5.76. Found: C, 64.37; H, 7.89; N, 5.79.

4.1.15. 2,3,5-Trifluoro-4-heptyloxyaniline (7b). The amine **7b** was synthesized in 94% yield according to the procedure described for **1a** and purified by distillation (150–151 °C/0.1 Torr) to give a light yellow oil: ^{1}H NMR δ 0.88 (t, J=6.6 Hz, 3H), 1.25–1.48 (m, 8H), 1.72 (quintet, J=7.0 Hz, 2H), 3.7 (brs, 2H), 4.00 (t, J=6.6 Hz, 2H), 6.30 (ddd, J_1=10.3 Hz, J_2=7.8 Hz, J_3=2.5 Hz, 1H); ^{19}F NMR δ −163.80 (dd, J_1=19.5 Hz, J_2=10.2 Hz, 1F), −152.86 (d, J=19.5 Hz, 1F), −135.17 (d, J=10.2 Hz, 1F); IR (KBr) ν_{max} 3485 and 3390 (NH_2), 1522, 1490 cm^{-1}; MS *m/e* (relative intensity) 261 (M^+, 5), 163 (100). Anal. Calcd for $C_{13}H_{18}F_3N_2O$: C, 59.76; H, 6.94; N, 5.36. Found: C, 60.17; H, 7.09; N, 5.37.

4.1.16. 2,3,5,6-Tetrachlorophenol.[17](8c) A solution sodium metal (2.72 g, 120 mmol) in methanol (100 mL) was added to 2,3,5,6-tetrachloronitrobenzene (26.18 g, 100 mmol) in dry THF (75 mL) at rt. The reaction mixture was stirred for 4 h at 60 °C, filtered and solvents evaporated. The residue was treated with water and extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and evaporated. The residue was recrystallized from EtOH to give 17.34 g (71% yield) of pure 2,3,5,6-tetrachloroanisole: mp 88–89 °C (lit.[8] mp 89–90 °C); ^{1}H NMR δ 3.92 (s, 3H), 7.41 (s, 1H).

A 1.0 M solution of BBr_3 in CH_2Cl_2 (10 mL) was added to the anisole solution (2.46 g, 10 mmol) in CH_2Cl_2 (100 mL) under inert atmosphere at 0 °C. The reaction mixture was allowed to warm up to rt, stirred overnight, poured into water and extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was recrystallized from *i*-octane to give 1.86 g (80% yield or 57% overall) of phenol **8c** as pale yellow crystals: mp 115–116 °C (lit.[18] mp 115 °C); ^{1}H NMR δ 6.10 (s, 1H), 7.23 (s, 1H). Anal. Calcd for $C_6H_2Cl_4O$: C, 31.08; H, 0.87. Found: C, 30.97; H, 0.89.

4.1.17. 2,5-Difluoro-4-phenylazophenol (9a). A solution of benzenediazonium chloride prepared from aniline (4.80 g, 51.6 mmol), 3 M HCl (65 mL) and a solution of $NaNO_2$ (4.80 g, 69.5 mmol, in 60 mL of water) and treated with urea (0.4 g) was added dropwise to a stirred solution of 2,5-difluorophenol (**8a**, 5.00 g, 38.5 mmol) and NaOH (5.40 g, 135 mmol) in water (90 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm up to rt and was stirred for another 1 h. Diluted HCl was added and the resulting precipitation was filtered and recrystallized from aqueous acetic acid to give 6.70 g (74% yield) of phenol **9a** as brown crystals: mp 126–128 °C; ^{1}H NMR δ 6.91 (dd, J_1=10.2 Hz, J_2=7.5 Hz, 1H), 7.45–7.55 (m, 3H), 7.63 (dd, J_1=11.1 Hz, J_2=6.6 Hz, 1H), 7.88–7.94 (m, 2H); ^{19}F NMR δ −144.74 (d, J=14.0 Hz, 1F), −126.89 (d, J=14.0 Hz, 1F); IR (KBr) ν_{max} 3504, 1623, 1506, 1303 cm^{-1}. HR-FABMS, calcd for $C_{12}H_9F_2N_2O$ ($[M+H]^+$): *m/e* 235.0683; found: *m/e* 235.0692.

4.1.18. 2,3,6-Trifluoro-4-phenylazophenol (9b). The compound **9b** was obtained as a crude brown powder according to the procedure described for **9a** and was used without further purification: mp 117–119 °C; ^{1}H NMR δ 2.7 (br s, 1H), 7.46 (ddd, J_1=11.1 Hz, J_2=6.3 Hz, J_3=2.4 Hz, 1H), 7.50–7.57 (m, 3H), 7.89–7.96 (m, 2H); ^{19}F NMR δ −157.86 (dd, J_1=19.5 Hz, J_2=6.0 Hz, 1F), −151.70 (dd,

$J_1=19.5$ Hz, $J_2=11.1$ Hz, 1F), −140.74 (dd, $J_1=11.1$ Hz, $J_2=6.2$ Hz, 1F); IR (KBr) ν_{max} 3535, 1518, 1333 cm^{-1}. HR-FABMS, calcd for $C_{12}H_8F_3N_2O$ ($[M+H]^+$): *m/e* 253.0589; found: *m/e* 253.0596.

4.1.19. 2,3,5,6-Tetrachloro-4-phenylazophenol (9c). Phenol **9c** was obtained according to procedure described for **9a** in 44% yield after recrystallization from aqueous acetic acid as orange microcrystals: mp 144–148 °C; ^1H NMR δ 6.15 (s, 1H), 7.54–7.59 (m, 3H), 7.94–7.97 (m, 2H); ^{13}C NMR δ 119.9, 123.2, 124.6, 129.3, 132.7, 143.2, 148.3, 152.0; IR (KBr) ν_{max} 3100 (br, OH), 1385 cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_4N_2O$: C, 42.90; H, 1.80; N, 8.34. Found: C, 42.65; H, 1.69; N, 8.09.

4.1.20. *N,N*-Dimethyl-4-[2,3,5,6-tetrachloro-4-hydroxyphenyl(azo)]benzene-sulfonamide (11). Compound **11** was obtained as orange microcrystals according to the procedure described for **9a** in 27% yield after recrystallization from aqueous acetic acid: mp 235–236 °C; ^1H NMR (acetone-d_6) δ 2.73 (s, 6H), 7.66 (s, 1H), AA′MM′ 7.94 and 8.05 (d, $J=8.4$ Hz, 4H); IR (KBr) ν_{max} 3308, 1379, 1331, 1159, 1147 cm^{-1}. Anal. Calcd for $C_{14}H_{11}Cl_4N_3O_3S$: C, 37.95; H, 2.50; N, 9.48. Found: C, 37.95; H, 2.52; N, 9.14.

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References and notes

1. Manka, J.; McKenzie, V.; Kaszynski, P. *J. Org. Chem.* **2004**, *69*, 1967–1971.
2. Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.
3. Manka, J. T.; Guo, F.; Huang, J.; Yin, H.; Farrar, J. M.; Sienkowska, M.; Benin, V.; Kaszynski, P. *J. Org. Chem.* **2003**, *68*, 9574–9588.
4. Zienkiewicz, J.; Kaszynski, P.; Young, V. G., Jr. *J. Org. Chem.* **2004**, *69*, 2551–2561.
5. Fryszkowska, A.; Zienkiewicz, J.; Sienkowska, M.; Guo, F.; Kaszynski, P.; Jones, D. Submitted for publication.
6. Brunelle, D. J. *J. Org. Chem.* **1984**, *49*, 1309–1311.
7. Sander, W.; Hübert, R.; Kraka, E.; Gräfenstein, J.; Cremer, D. *Chem. Eur. J.* **2000**, *6*, 4567–4578.
8. Berckmans, V. S. F.; Holleman, A. F. *Recl. Trav. Chim. Pays-Bas* **1925**, *44*, 851–860.
9. Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619–1633.
10. Paradisi, C. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 4, pp 441–444.
11. Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem.* **1991**, *56*, 862–865.
12. Bolton, R.; Sandall, J. P. B. *J. Chem. Soc. Perkin Trans. 2* **1976**, 1541–1545.
13. Bressan, G. B.; Giardi, I.; Illuminati, G.; Linda, P.; Sleiter, G. *J. Chem. Soc. Part B* **1971**, 225–230. Also Ref. 2, pp 139–174 and references therein.
14. Belli, M. L.; Illuminati, G.; Marino, G. *Tetrahedron* **1963**, *19*, 345–355.
15. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
16. Ref. 2 Table 21, p 109, and references therein.
17. Holleman, A. F. *Recl. Trav. Chim. Pays-Bas* **1920**, *39*, 736–750.
18. Holleman, A. F. *Recl. Trav. Chim. Pays-Bas* **1921**, *40*, 318–319.