JOC Article

Azo Group-Assisted Nucleophilic Aromatic Substitutions in Haloarene Derivatives: Preparation of Substituted 1-Iodo-2,6-bispropylthiobenzenes

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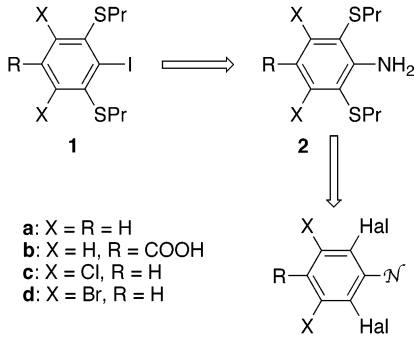
Aryldiazo substituents were used in nucleophilic aromatic substitution reactions of halogens. The Ph-N═N− group activates ortho fluorine atoms toward alkylthiolation under mild conditions. In contrast, the Me_2N-C_6H_4-N═N− group has virtually no activation effect in nucleophilic aromatic substitution, and serves as a "neutral" mask for the amino group. The Ph-N═N− group was efficiently introduced by diazo coupling of aryllithium with dry $PhN_2^+BF_4^-$ salt.

Further progress in the study of stable free heterocyclic radicals[1,2] required[3] 4-substituted 1-iodo-2,6-bis(propylthio)benzenes **1** as synthetic intermediates. Such iodides could be obtained from the corresponding amines **2** as was already demonstrated for **1a**.[4] Therefore, we focused on the preparation of **2** by propanethiolation of appropriate 1,3-dihalides bearing a nitrogen-containing substituent $\mathcal{N}$ in position 2.



Alkylthiolation by displacement of halogens in aryl halides is well-studied and documented.[5,6] The process is very facile for haloarenes activated by electron accepting groups such as nitro, but it requires polar aprotic conditions for nonactivated halides[5,7] and high temperatures and long reaction times for deactivated substrates such as chloroanilines.[6,8]

The use of a nitro group as an activating group for chloroarenes and as a precursor to the amino functionality is very attractive but it is also limited. The NO_2 has higher leaving group mobility than the Cl substituent[9] and can be replaced with nucleophiles in preference to Cl.[5,10] Thus, thiolation of 2,6-dichloro-1-nitrobenzene (**3**, R = H) gave the products of halogen displacement **4**, R = H, and nitro group substitution **5**, R = H, in about a 1:1 ratio.[4] However, in the case of 3,5-dichloro-4-nitrobenzoic acid (**3**, R = COOH) the undesired 3,5-dichloro-4-propylthiobenzoic acid (**5**, R = COOH) was formed exclusively (Scheme 1).

Searching for another functional group $\mathcal{N}$ that could (i) activate halogens in the ortho positions toward nucleophilic aromatic substitution (NAS), (ii) would not compete with the halogens in NAS, and (iii) can easily be converted to NH_2, we focused on the azo group.[11] It has been reported that the Ph-N═N− group has a relatively high substituent constant[12] σ_p^- of +0.65 (cf. $\sigma_p^-(NO_2) = +1.27$), and moderately activates halogens in the ortho and para positions toward nucleophilic displacement.[9,13,14] For instance, it accelerates the rate of substitution of chlorine in 4-substituted 1-chloro-2-

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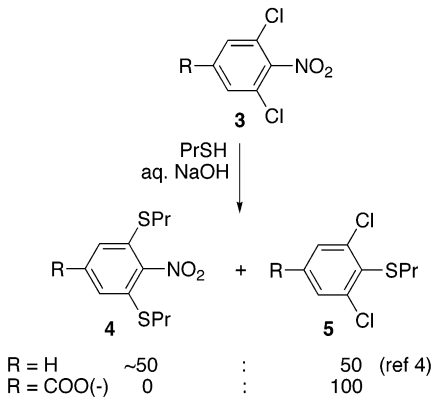
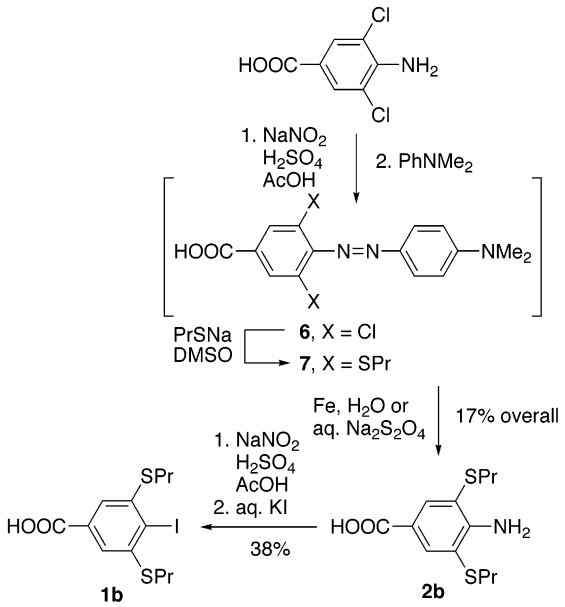
SCHEME 1



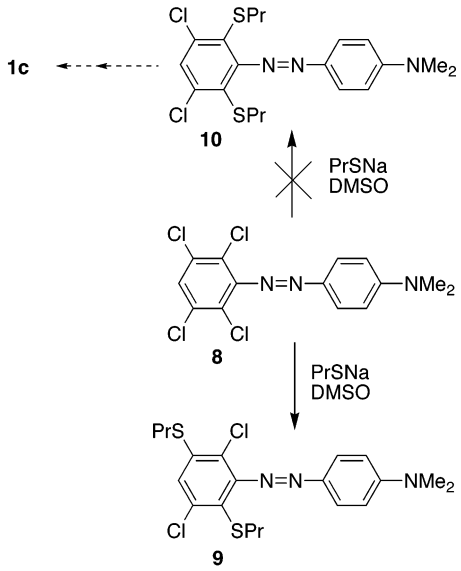
SCHEME 2



nitrobenzenes by a factor of about 500 relative to H, which compares to about 10^3 for an ester and 10^5 for the NO_2 group.[9] In addition, the azo group cannot be displaced by the thiolate anion, and can easily be reduced to the requisite amino group. Therefore, we focused on the aryldiazo group to activate halogens as a key step in the preparation of **2**.

The phenyldiazo group could not be introduced easily into 3,5-dichlorobenzoic acid, and therefore the 4-dimethylaminophenyldiazo group was used instead. Thus, azo acid **6**, prepared from 4-amino-3,5-dichlorobenzoic acid by diazo coupling, was converted to its sodium salt and reacted with propanethiolate anion under polar aprotic conditions to give the expected bispropylthio derivative **7** (Scheme 2). The optimum temperature for the reaction was between 90 and 100 °C. At lower temperatures the reaction was slow, and above 100 °C, the reduction of the azo functionality by the thiolate was observed. Both of the azo compounds **6** and **7** were difficult to purify and were used in their crude forms. Reduction of **7** with iron or sodium dithionate gave the amino acid **2b** in about 17% overall yield based on the starting amino acid. Diazotization of **2b** followed by reaction with iodide gave the desired 4-iodo-3,5-bis(propylthio)benzoic acid (**1b**) in 38% unoptimized yield.

SCHEME 3



Extension of this method to the preparation **2c** was unsuccessful. The thiolation of **8** with sodium 1-propanethiolate in DMSO gave a mixture of compounds among which the dithiolated product was identified by ^{1}H NMR to be the 2,5-bis(propylthio) derivative **9** instead of the desired 2,6-bis(propylthio) isomer **10** (Scheme 3).

The conditions to effect the thiolation of **6** and **8** suggest that the 4-Me_2N-C_6H_4-N=N− substituent has a "neutral" character in NAS and the halides are nonactivated. This is consistent with the formation of the 2,5-regioisomer **9** instead of the 2,6-derivative **10** in thiolation of **8**, which parallels the formation of 1,4-bis(alkylthio)-2,5-dichlorobenzene as the sole product of thiolation of 1,2,4,5-tetrachlorobenzene under PTC conditions.[15] Also, the observation of small amounts of the mono- and trithiolated derivatives, as identified by ^{1}H NMR, suggests that the thiolation of **8**, and presumably **6**, is qualitatively not different from the reaction of the parent chloroarene. Thus, the weak activating effect of the parent Ph-N=N− group appears to be compensated by the strong positive resonance effect of the Me_2N substituent, and the role of the 4-Me_2N-C_6H_4-N=N− group in NAS can be described best as a neutral mask for the amino functionality.

To increase the regioselectivity of the thiolation, we focused on partially fluorinated arenes, since it has been reported that thiolate anions exclusively replace fluorine on benzene rings when both bromine and fluorine atoms are present.[16,17] It was also expected that use of Ph-N=N− instead of 4-Me_2N-C_6H_4-N=N− group should have a significant effect on activation of ortho halogens. Therefore, the strategy of making the azo compounds was changed and it took advantage of the regioselective ortholithiation reported[17,18] for **11d** and diazo coupling with aromatic carbanions.[19−22]

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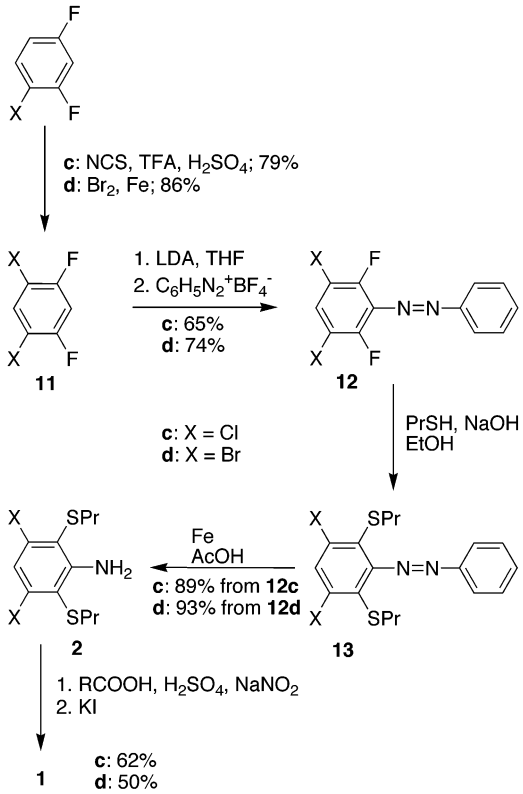
SCHEME 4



The starting difluoroarenes **11** were prepared by halogenation of the appropriate 1-halo-2,4-difluorobenzenes (Scheme 4). Chlorination of 1-chloro-2,4-difluorobenzene to form **11c** was accomplished with NCS by using conditions for the bromination of deactivated compounds with NBS.[23] The quality of the NCS was found to be crucial for efficient and complete chlorination, and only freshly purchased reagent gave high yields of **11c**. The original procedure[24] for the preparation of **11d** was modified to make it more efficient for large-scale synthesis.

The lithiation of **11** with LDA at −78 °C gave the corresponding phenyl anion.[17] Its subsequent reaction with dry benzenediazonium salt gave the azo derivatives **12c** and **12d** in 65% and 74% optimized yield, respectively, as a mixture of cis and trans isomers in ratios as high as 2:3 (**12d**).[25] The temperature of the lithiation and the reaction with the diazonium salt proved to be important for yield and purity of the azo product. If the temperature was allowed to increase from −78 °C due to fast addition of reagents, especially the dry diazonium salt, the formation of other compounds was observed by TLC and the purification of the product **12** was more difficult.

The thiolation of a cis and trans mixture of isomers **12** with sodium 1-propanethiolate occurred smoothly in warm ethanol yielding a single isomer of bispropylthio derivative **13**. This is in sharp contrast with the results for **6** and **8**. Considering that **11d**, in which the azo group is absent, is completely inert toward the thiolate in hot ethanol during 48 h, the Ph-N=N− substituent activates the ortho fluorine atoms for NAS. The observed significantly higher reactivity of **12c** as compared to **8** is related to a combination of two effects:[9] (a) higher mobility of F than Cl by a factor of 10^2-10^3 and (b) higher ability of the Ph-N=N− group to accommodate the negative charge as compared to the 4-Me_2N-C_6H_4-N=N− substituent.

Reduction of the crude azo **13** with iron in acetic acid gave amine **2** in about 90% overall yield based on azo **12** (Scheme 4). The amine **2** was converted to the iodide **1** via the corresponding diazonium salt prepared in acetic acid. Substitution of propionic acid for acetic acid improved the procedure and the yield (**1c**) by decreasing the viscosity of the reaction mixture at low temperatures and more efficient stirring. Both iodides **1c** and **1d** are nonpolar oils and their purification proved to be quite difficult, especially the dichloro derivative **1c**. Repeated column chromatography allowed both iodides to be isolated in >95% purity, which was sufficient for further transformations.

This study demonstrates that the phenyldiazo group is a useful alternative to a nitro group in the activation of fluorine atoms toward nucleophilic aromatic substitution (NAS) with an alkanethiolate nucleophile. The azo group can be conveniently introduced by diazo coupling to an aryl anion generated by ortho lithiathion with LDA. This sequence and another involving azo condensation[26]−NAS−reduction can, in principle, be extended to other fluoro(chloro)benzenes and haloanilines.

Experimental Section

4-Iodo-3,5-bis(propylthio)benzoic Acid (1b). Solid $NaNO_2$ (120 mg, 1.8 mmol) was added to concentrated H_2SO_4 (1.8 mL). The mixture was stirred and heated to 70 °C until full dissolution of the solid. The resultant nitrosylsulfuric acid was cooled to 0 °C, and amino acid **2b** (150 mg, 0.53 mmol) dissolved in AcOH (1.1 mL) was added dropwise at 0 °C. After 45 min of stirring, a solution of KI (340 mg, 2.2 mmol) in water (3.8 mL) was added. The reaction was stirred at 70 °C for 0.5 h and then poured into water (50 mL). The organics were extracted with CH_2Cl_2, and the crude product was purified on a silica gel column (benzene/EtOAc, 3:1) to give acid **1b** (80 mg, 38% yield) as a white solid. An analytical sample of **1b** was obtained by recrystallizing from AcOH: mp 136−137 °C; ^{1}H NMR δ 1.11 (t, J = 7.2 Hz, 6H), 1.80 (sextet, J = 7.4 Hz, 4H), 2.97 (t, J = 7.3 Hz, 4H), 7.57 (s, 2H); ^{13}C NMR δ 13.7, 21.5, 36.2, 108.4, 122.3, 129.3, 145.4, 171.5; IR (KBr) 1689 (C=O), 1290 (C−O) cm^{-1}. Anal. Calcd for $C_{13}H_{17}IO_2S_2$: C, 39.40; H, 4.32. Found: C, 39.52; H, 4.37.

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1,5-Dibromo-3-iodo-2,4-bis(propylthio)benzene (1d). A solution of amine **2d** (595 mg, 1.5 mmol) in AcOH (5 mL) was added dropwise with stirring to nitrosylsulfuric acid (1.9 mmol of $NaNO_2$; see **1b**) at 5 °C. After 0.5 h, a solution of KI (840 mg, 5.1 mmol) in water (10 mL) was added at once, and the resultant mixture was stirred for 20 min at 70 °C. This mixture was then poured into 5% $Na_2S_2O_5$ solution (100 mL) and extracted (CH_2Cl_2). The extracts were dried (Na_2SO_4) and passed through a short silica gel column (CH_2Cl_2). The crude product was dissolved in pentane and placed in a freezer overnight to separate a white fluffy byproduct. Pentane was removed, and the oily residue was purified on a silica gel column (CH_2Cl_2/hexanes, 1:7) to give iodide **1d** (380 mg, 50% yield) as a pale yellow oil: ^{1}H NMR δ 1.04 (t, J = 7.4 Hz, 6H), 1.65 (sextet, J = 7.3 Hz, 4H), 2.90 (t, J = 7.4 Hz, 4H), 8.01 (s, 1H); ^{13}C NMR δ 13.7, 22.7, 39.2, 127.5, 129.6, 136.8, 142.2; EI-MS *m*/*z* 512, 510, 508 (M, 34:58:26), 218 (100). Anal. Calcd for $C_{12}H_{15}Br_2IS_2$: C, 28.26; H, 2.96. Found: C, 28.40; H, 2.98.

4-Amino-3,5-bis(propylthio)benzoic Acid (2b). A suspension of 4-amino-3,5-dichlorobenzoic acid (5.00 g, 24.3 mmol) in AcOH (60 mL) was added dropwise to nitrosylsulfuric acid (36.2 mmol of $NaNO_2$; see **1b**) at 0−5 °C. After the mixture was stirred for 1.5 h, ice (300 g) was added, and the reaction mixture was added to a stirring solution of *N*,*N*-dimethylaniline (4.00 g, 33.1 mmol) in AcOH (70 mL) at 0 °C. The mixture was stirred overnight at room temperature. The resultant dark-red mixture was neutralized to pH 6−7 with aqueous NaOH and refrigerated for several hours. The precipitate that formed upon neutralization was filtered off and washed with brine. On the basis of NMR, the crude product (4.36 g) contained about 75% 4-(4-(*N*,*N*-dimethylamino)phenyldiazo)-3,5-dichlorobenzoic acid (**6**), and it was used in the subsequent step without further purification: ^{1}H NMR (major peaks) δ 3.14 (s, 6H), 6.78 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 9.9 Hz, 2H), 8.09 (s, 2H).

NaH (60% dispersion in mineral oil, 2.80 g, 70 mmol) was carefully added to a solution of crude azo acid **6** (7.35 g, 21.73 mmol) in dry DMSO (80 mL) at room temperature. 1-Propanethiol (3.33 g, 43.5 mmol) was slowly added to the flask via syringe and the solution was stirred at 100 °C overnight. The mixture was slowly poured into 1 M HCl (350 mL) and the precipitate that formed was either filtered or extracted with CH_2Cl_2. On the basis of NMR, the resulting crude 4-(4-(*N*,*N*-dimethylamino)phenyldiazo)-3,5-bis(propylthio)benzoic acid (**7**) product (5.34 g) was about 75−80% pure, and it was used in the subsequent step without further purification: ^{1}H NMR (major peaks) δ 1.06 (t, J = 7.4 Hz, 6H), 1.72 (sextet, J = 7.3 Hz, 4H), 2.93 (t, J = 7.3 Hz, 4H), 3.12 (s, 6H), 6.77 (d, J = 9.2 Hz, 2H), 7.96 (d, J = 9.2 Hz, 2H), 8.08 (s, 2H).

A mixture of water (20 mL), reduced iron powder (250 mg), and the crude azo acid **7** (2.19 g) was gently refluxed overnight. Alternatively, crude acid **7** (5.5 g, 13.2 mmol) was reduced with an alkaline solution (50 mL of 10% NaOH) of $Na_2S_2O_4$ (6.07 g, 34.9 mmol). The mixture was stirred and heated until full dissolution. After acidification the precipitate was filtered off. The resulting crude acid was dissolved in a small amount of CH_2Cl_2 and passed through a silica gel plug (CH_2Cl_2/acetone, 20:1). The solvent was removed and the crude product was recrystallized twice (isooctane) to give pure acid **2b** in about 40% yield based on **7** or 17% overall yield based on the starting amino acid: mp 112−114 °C; ^{1}H NMR δ 1.00 (t, J = 7.3 Hz, 6H), 1.60 (sextet, J = 7.3 Hz, 4H), 2.76 (t, J = 7.2 Hz, 4H), 5.65 (br s, 2H), 8.09 (s, 2H); ^{13}C NMR δ 13.3, 22.9, 37.0, 117.6, 117.9, 137.8, 154.0, 171.4; IR (KBr) 3462 and 3352 (N−H), 1669 (C=O), 1270 (C−O) cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.71; H, 6.71; N, 4.91; S, 22.47. Found: C, 54.81; H, 6.72: N, 4.91; S, 22.35.

3,5-Dibromo-2,6-bis(propylthio)aniline (2d). Crude azo compound (**13d**, 6.5 g, 13.3 mmol) was dissolved in AcOH (80 mL), electrolytic grade iron (1 g) was added, and the reaction was stirred at 90 °C overnight. The reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2. The combined extracts were passed through a silica gel plug (CH_2Cl_2). The solvent was removed and the crude product was purified on a silica gel column (CH_2Cl_2/hexanes, 1:4) to give amine **2d** (3.61 g, 93% yield from **12d**) as an off-white solid: mp 45−46 °C; ^{1}H NMR δ 0.99 (t, J = 7.4 Hz, 6H), 1.58 (sextet, J = 7.4 Hz, 4H), 2.74 (t, J = 7.3, 4H), 5.79 (br s, 2H), 7.29 (s, 1H); ^{13}C NMR δ 13.5, 23.1, 36.8, 117.1, 124.5, 133.3, 154.1; IR (KBr) 3450 and 3341 (N−H) cm^{-1}; EI-MS *m*/*z* 401, 399, 397 (M, 56:100:46). Anal. Calcd for $C_{12}H_{17}Br_2NS_2$: C, 36.11; H, 4.29; N, 3.51. Found: C, 36.37; H, 4.30; N, 3.53.

3,5-Dichloro-4-propylthiobenzoic Acid (5, R = COOH). A mixture of crude acid **3** (R = COOH; 7.4 g, 31.4 mmol), 1-propanethiol (8.6 mL, 100 mmol), NaOH (6.4 g, 160 mmol), and water (125 mL) was stirred at 90 °C for 5 h. A spoonful of charcoal was added, the reaction mixture was filtered, and the crude product was precipitated by adding concentrated HCl. The product was filtered and, after drying, recrystallized twice (hexanes) to give acid **5** (R = COOH, 5.8 g, 70% yield) as a white solid: mp 124−125 °C; ^{1}H NMR δ 1.01 (t, J = 7.3 Hz, 3H), 1.58 (sextet, J = 7.3 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 8.06 (s, 2H); ^{13}C NMR δ 13.3, 23.2, 37.5, 129.5, 130.1, 140.4, 141.3, 170.1. Anal. Calcd for $C_{10}H_{10}Cl_2S$: C, 45.30; H, 3.80. Found: C, 45.37; H, 3.84.

1,3-Dibromo-4,6-difluoro-5-phenyldiazobenzene (12d). A 2.4 M solution of *n*-BuLi (24 mL, 57.6 mmol) was slowly added to diisopropylamine (6.3 g, 62.3 mmol) in dry THF (30 mL) under N_2 at −5 °C. After 0.5 h, the solution of LDA was transferred via cannula to a jacketed addition funnel (−78 °C), and added dropwise to halobenzene **11d** (13.6 g, 50 mmol) in THF (110 mL) at −78 °C. After the mixture was stirred for 45 min, dry benzenediazonium tetrafluoroborate[27] (11.5 g, 60.0 mmol) was added in small portions from an attached flask via a flexible transfer tube over a 0.5-h period. The temperature during addition was maintained at −78 °C. The mixture was stirred at −78 °C for an additional 3 h, and was allowed to warm to room temperature. A 6 M solution of HCl (30 mL) was added. The volume of THF was reduced, and the mixture was poured into water and extracted (CH_2Cl_2/hexanes, 1:7). The combined extracts were dried (Na_2SO_4) and passed through a short silica gel column (CH_2Cl_2/hexanes, 1:7). The solvent was removed to give 18.2 g of crude material that solidified upon standing. The material was dissolved in refluxing MeOH and then allowed to cool to room temperature. This produced 6.2 g of pure orange crystals that were filtered and washed with cold MeOH. The mother liquor and washings were concentrated and refluxed to redissolve the product and placed in the freezer overnight to give an additional 3.2 g of pure crystals. MeOH was removed from the filtrate and the residue passed through a silica gel column to give an additional 4.6 g of the product. This gave the combined yield of 14.0 g or 74% of an isomeric mixture of **12d**: EI-MS *m*/*z* 378, 376, 374 (M^+, 8, 16, 8), 77 (100). Anal. Calcd for $C_{12}H_6Br_2F_2N_2$: C, 38.33; H, 1.61; N, 7.45. Found: C, 38.54; H, 1.57; N, 7.47.

A sample of the mixture was separated by column chromatography to give the trans isomer as the first fraction and cis isomer as the second.

Trans isomer **12d** was obtained as orange crystals (MeOH): mp 77−78 °C; ^{1}H NMR δ 7.46−7.51 (m, 3H), 7.72 (t, J = 6.8 Hz, 1H), 7.85−7.89 (m, 2H); ^{13}C NMR δ 105.4−105.8 (m), 123.3, 129.3, 132.6 (t, $^2J_{CF}$ = 13 Hz), 132.8, 134.9, 151.3 (dd, $^1J_{CF}$ = 260 Hz, $^3J_{CF}$ = 4 Hz), 152.8; ^{19}F NMR δ −114.4.

Cis isomer **12d** was obtained as yellow-orange microcrystals (MeOH): mp 68−69 °C; ^{1}H NMR δ 6.85 (d, J = 7.1 Hz, 2H), 7.19−7.30 (m, 3H), 7.50 (t, J = 6.8 Hz, 1H); ^{13}C NMR δ 104.8−105.1 (m), 118.5, 129.0, 129.2, 132.3 (t, $^2J_{CF}$ = 22 Hz), 133.5, 146.4 (dd, $^1J_{CF}$ = 251 Hz, $^3J_{CF}$ = 5 Hz), 154.6; ^{19}F NMR δ −112.2.

1,3-Dibromo-5-phenyldiazo-4,6-bis(propylthio)benzene (13d). An isomeric mixture of azo derivative **12d** (5.0 g,

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13.4 mmol) was dissolved in 95% EtOH (50 mL) with stirring at 70 °C. A solution of NaOH (1.4 g, 35 mmol) and 1-propanethiol (2.56 g, 34 mmol) in 95% EtOH (15 mL) was added, and the reaction was stirred overnight at 80 °C. Most of the EtOH was removed and 6 M HCl (40 mL) was added. The mixture was poured into water (300 mL) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and passed through a silica gel plug (CH_2Cl_2/hexane, 1:2). The solvent was then removed to give **13d** (6.5 g) as a red-orange oil that was used without purification for the next step. An analytical sample of **13d** was obtained by column chromatography (CH_2Cl_2/hexanes, 1:3): ^{1}H NMR δ 0.79 (t, J = 7.3 Hz, 6H), 1.38 (sextet, J = 7.3 Hz, 4H), 2.58 (t, J = 7.1 Hz, 4H), 7.46−7.51 (m, 3H), 7.85−7.89 (m, 3H); ^{13}C NMR δ 13.3, 22.7, 38.4, 123.1, 126.9, 129.2, 132.1, 132.3, 134.7, 151.9, 163.1. Anal. Calcd for $C_{18}H_{20}Br_2N_2S_2$: C, 44.28; H, 4.13; N, 5.74. Found: C, 44.48; H, 4.22; N, 5.76.

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Supporting Information Available: General experimental procedures, full experimental details, and characterization for known compounds (**3** (R = COOH),[28] **11c**,[29] and **11d**[24,30]), analogous compounds (**1c**, **2c**, **12c**, and **13c**), and **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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