JOC Article

Synthesis of Polyfunctionalized Biphenyls as Intermediates for a New Class of Liquid Crystals

Jason T. Manka,[§] Fengli Guo, Jianping Huang, Huiyong Yin, John M. Farrar,[⊥] Monika Sienkowska, Vladimir Benin,[‡] and Piotr Kaszynski*

Organic Materials Research Group, Chemistry Department, Vanderbilt University, Nashville, Tennessee 37235

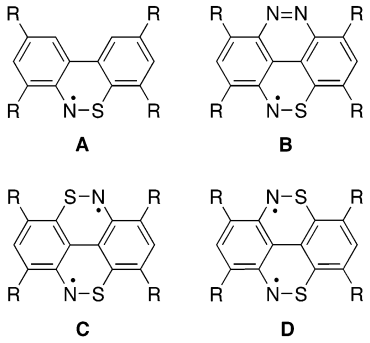
piotr@ctrvax.vanderbilt.edu

Received July 7, 2003

A series of hexa- and octasubstituted biphenyls containing halogen, amino, nitro, and propylthio substituents were prepared by metal-mediated convergent synthesis from halobenzene precursors. The Pd-assisted C−C coupling methods were ineffective in the formation of the Ar−Ar bond except for the synthesis of **1b**. All tetra-ortho-substituted biphenyls were prepared via Ullmann coupling reactions. The halogens were introduced after formation of the biphenyl by utilizing the directing properties of the amino group(s). In the case of **3b**, a polyhalogenated benzene substrate was used for biphenyl formation via Ullmann coupling.

Introduction

Several years ago we proposed that certain cyclic thioaminyl radicals could be used as structural elements of liquid crystals.[1,2] In this context, we envisioned three- and four-ring heteroaromatic radicals and biradicals **A**−**D**, which upon substitutions with four alkoxyphenyl groups (R = Ar) may form columnar mesophases.



Recently, we described the synthesis of the parent radicals **A** and **B** (R = H) and demonstrated their significant chemical stability.[3] Our calculations indicate that the disjoint biradical **C** (R = H) has degenerate singlet and triplet states and is more stable than the closed-shell structure by 6.3 kcal/mol. In contrast, the parent biradical **D** is predicted to be a triplet species with the triplet−singlet gap E_{TS} of 4.2 kcal/mol.[2,4] Generally, all four heterocyclic radicals appear to be suitable for use in the design of discotic mesogens.[5] However, preparation of such materials requires appropriate substrates that allow the introduction of aryl substituents R. Here we describe the syntheses of several specifically designed hexa- and octasubstituted biphenyls as key intermediates to discotic liquid crystal radicals.

Molecular Design and Synthetic Strategy

Retrosynthetic analysis indicates that the precursors to the mesogens **A**−**D** could be functionalized biphenyls of the general structure shown in Figure 1. The four halogen atoms (X and X′) facilitate the introduction of aryl groups. The nitrogen-based substituent (*N*) and the alkylthio group are the precursors to the thioaminyl group (− N•−S−), and the groups G and G′ will form the azo bridge in **B** or an additional thioaminyl group in **C** and **D**. In **A**, the groups G and G′ are hydrogen atoms.

The preparation of the discotic radicals involves two critical steps: (i) the generation of the N−S bond and (ii) introduction of the aryl substituents. A convenient method for the formation of the sulfenamido group −NH−S−, a precursor to the thioaminyl group −N•−S−, was described by Hori and relies on oxidative cyclization of an amine sulfide followed by electrocyclic elimination of an olefin.[6] Therefore, we chose an alkylthioether

* Author to whom correspondence should be sent. Vanderbilt University, Box 1822, Station B. Phone: (615) 322-3458. Fax: (615) 343-1234.

§ Present address: Roche Palo Alto LLC, Palo Alto, CA 94304.

⊥ Present address: Chemistry Department, Indiana University Purdue University, Fort Wayne, IN 46805.

‡ Present address: Chemistry Department, University of Dayton, Dayton, OH 45469.

(1) Patel, M. K.; Huang, J.; Kaszynski, P. *Mol. Cryst. Liq. Cryst.* **1995**, *272*, 87−97.

(2) Kaszynski, P. In *Magnetic Properties of Organic Materials*; Lahti, P. M., Ed.; Marcel Dekker: New York, 1999; pp 305−324.

(3) Benin, V.; Kaszynski, P. *J. Org. Chem.* **2000**, *65*, 8086−8088.

(4) Benin, V.; Sienkowska, M.; Kaszynski, P. Unpublished results.

(5) Chandrasekhar, S. In *Handbook of Liquid Crystals*; Demus, D., Goodby, J. W., Gray, G. W., Spiess, H.-W., Vill, V., Eds.; Wiley-VCH: New York, 1998; Vol. 2B.; pp 749−780.

(6) (a) Shimizu, H.; Matsuo, K.; Kataoka, T.; Hori, M. *Chem. Pharm. Bull.* **1984**, *32*, 4360−4371. (b) Shimizu, H.; Ikedo, K.; Hamada, K.; Ozawa, M.; Matsumoto, H.; Kamata, K.; Nakamura, H.; Ji, M.; Kataoka, T.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1733−1747.

10.1021/jo030212p CCC: $25.00
Published on Web 11/12/2003

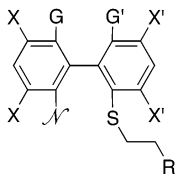


FIGURE 1. General design of precursors to radicals **A**−**D**: X and X′ are halogens, $\mathcal{N}$ is a nitrogen-based group, G and G′ are H, $\mathcal{N}$, or SCH_2CH_2R.

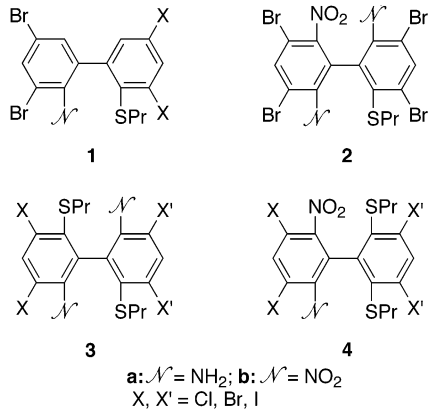
containing at least two carbon atoms, and $\mathcal{N}$ that is an amino group or can be converted to one in the biphenyl precursor. For convenience, we chose the propyl substituent on the sulfur (R = Me in Figure 1). The sensitive nature of the −N−S− bond[7] requires its formation at the last stage of the synthetic sequence after the introduction of aryl substituents.

For the introduction of aryl substituents to the biphenyl moiety,[8,9] the method of choice is the Suzuki coupling reaction[10,11] that appears to be efficient and versatile, and tolerates many functional groups. The reaction works well with aromatic halides containing electron-withdrawing substituents such as the nitro group, but gives less satisfactory results when electron-rich halides, such as haloanilines, are used.[11,12] In the latter case, the effectiveness of the coupling reaction can be improved by converting the amino group to *N*-acylamino[13] or by using Ni(0) catalyst instead of Pd(0).[12]

The introduction of halogens and the formation of the biphenyl central bond are the two intertwined key issues in the synthesis of the biphenyl precursors and we considered four general routes shown in Figure 2. The use of an amino group, either as $\mathcal{N}$ in Methods A−C or as a substituent $\mathcal{A}$ in Method D (Figure 2), facilitates regioselective halogenation of the biphenyl, but becomes problematic at the arylation stage. Therefore, after halogenation, the amino group should be either converted to another $\mathcal{N}$ substituent that activates the halogens toward arylation reactions, or removed (Method D). The introduction of the halogens prior to the biphenyl formation process faces the problem of chemo- and regioselectivity of the C−C bond formation. The convenient C−C coupling methods[8] based on Pd-catalysis[14] (Suzuki,[11,15] Stille,[16] and Negishi[17]) are generally highly sensitive to the steric hindrance of the organometallic reactants. The Stille,[18] Suzuki,[19] and also some organocopper[20] methods give 2,2′,6,6′-tetrasubstituted biphenyls and sterically hindered binaphthalenes[21] in low yields at best. However, several recent examples demonstrate that both the Negishi[22] and Suzuki reaction[23] can be optimized to give sterically hindered biaryls in practical yields. Both of these methods require the intermediacy of an organolithium or magnesium compound to prepare the necessary organozinc or organoboron reagents. Symmetrical 2,2′,6,6′-tetrasubstituted biphenyls can be prepared in a Ni(0)-catalyzed homocoupling reaction of aryl halides,[24] but the requisite presence of Zn dust may not be compatible with the nitro group. Therefore, the classical Ullmann coupling method still remains an attractive alternative for synthesis of tetra-ortho-substituted biphenyls due to its simplicity and generality.[25] In contrast to the Pd- or Ni-catalyzed reactions, the yields and selectivity of the Ullmann reactions involving heterocoupling and polyhalogenated substrates are generally more difficult to control.

Considering the electronic effects of the $\mathcal{N}$ group and the reactivity of the halogens, the biphenyls could be obtained according to several methods as shown in Figure 2. In all methods except for Method C, the introduction of halogens to the biphenyl is accomplished by using the directing properties of the amino group. In the simplest case, the biphenyls could be prepared by sequential building-in of the functionalities starting from 2,2′-dinitrobiphenyl (Method A2). The partially halogenated biphenyl in Method A1 could also be obtained in a C−C coupling reaction of appropriately substituted benzenes.

Here we describe the preparation of four classes of tetrahalobiphenyls **1**−**4** as potential precursors to radicals **A**−**D**, respectively. Biphenyl **1** was prepared by using Methods A2 and C. Method B was used to prepare biphenyls **2** and **3**. The latter was also prepared according to Method C, and biphenyl **4** was prepared by using Method A1. We also describe unsuccessful attempts at the preparation of biphenyls **2** and **3** using Method D.



Results

Preparation of Hexasubstituted Biphenyls 1. The original strategy for the preparation of **1a** and **1b** followed Method A2 and took advantage of the directing

(7) Schubart, R. In *Organische Schwefel-Verbindungen*; Methoden der Organischen Chemie Vol. E11; Klamann, D., Ed.; Georg Thieme: New York, 1985; pp 107−127 and references therein.
(8) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303.
(9) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, pp 481−520.
(10) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213−222.
(11) Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press: Stamford, CT, 1998; Vol. 6, pp 187−243.
(12) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030.
(13) Yang, Y.; Hörnfeldt, A.-B.; Gronowitz, S. *Chem. Scr.* **1988**, *28*, 275−279.
(14) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley & Sons: New York, 2002; Vol. 1.
(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(16) Farina, V.; Krishnamurthy, V. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley & Sons: New York, 1997; Vol. 50, pp 1−652.
(17) Negishi, E.-i. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999; Vol. 15, pp 214−231.
(18) Saá, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963−1966.
(19) Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001−7002.
(20) Cornforth, Sir. J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans.* 1 **1982**, 2299−2315.

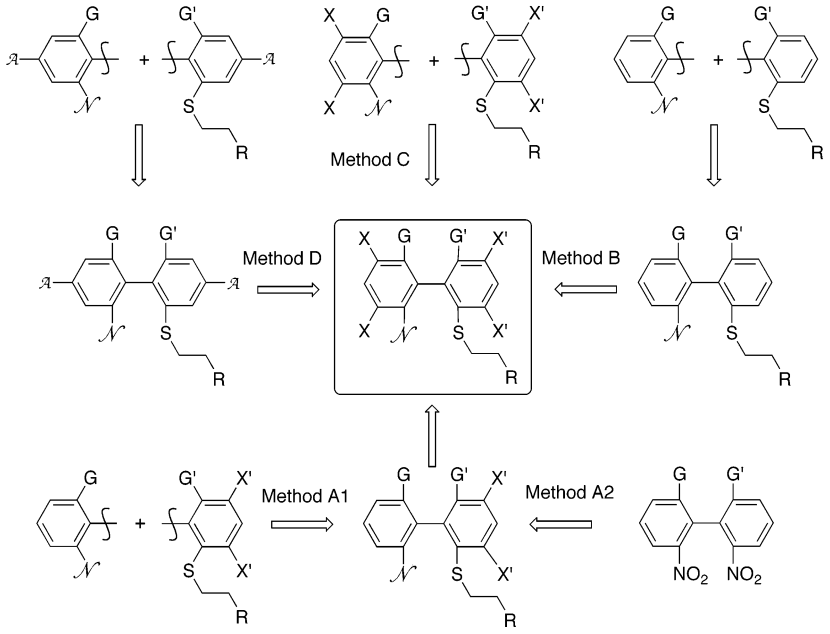
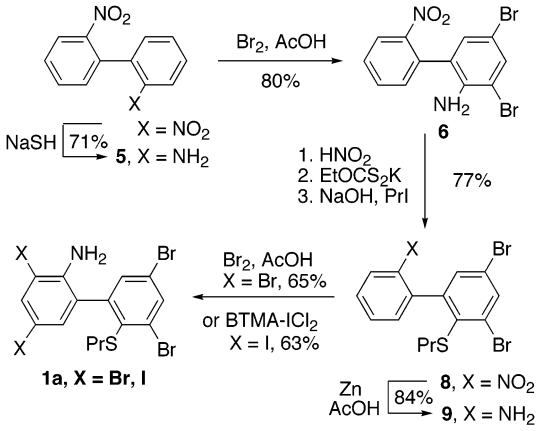


FIGURE 2. Synthetic strategy for preparation of functionalized biphenyls **1**−**4**. The $\mathcal{N}$ group is not necessarily the same in each stage of synthesis.

SCHEME 1



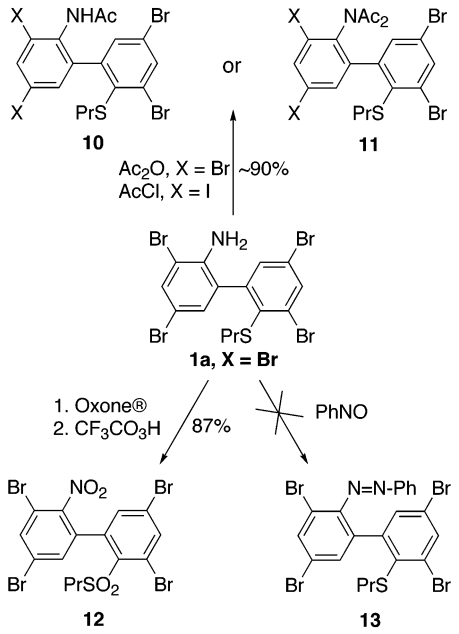
ability of the amino groups in electrophilic aromatic halogenation. Thus, synthesis of **1a** (Scheme 1) begins with partial reduction of 2,2′-dinitrobiphenyl to 2-amino-2′-nitrobiphenyl (**5**), using sodium hydrosulfide hydrate. The original procedure[26] was modified by using a mixture of methanol and toluene[27] instead of pure methanol for reduction, and acid extraction for isolation of **5**. Careful monitoring of the extraction process yielded amine **5** in yields of about 70% and sufficient purity for the next step. Bromination of amine **5** in acetic acid gave the known 2-amino-3,5-dibromo-2′-nitrobiphenyl[28] (**6**). The yield and quality of dibromobiphenyl **6** proved to be sensitive to the purity of amine **5**; a black tar was produced presumably by impurities in **5** formed during the reduction process.[26,28,29]

The introduction of the propylthio fragment was accomplished through diazotization of the amine **6** followed by reaction with potassium ethyl xanthate according to a general procedure.[30] The resulting crude xanthate **7** was hydrolyzed with NaOH in the presence of 1-iodopropane to yield 3,5-dibromo-2′-nitro-2-propylthiobiphenyl (**8**). The yield of **8** was dependent on the efficiency of the formation of the hydrochloride salt of amine **6**. Best yields of **8** were obtained when a very fine powder of **6** and concentrated HCl were vigorously stirred until a uniform pale paste of the hydrochloride was formed prior to diazotization. With this procedure little unreacted **6** remained in the crude product, and it was unnecessary to purify **8** since most of the minor impurities were removed in the next step.

After reduction of the nitro group with Zn in acetic acid, the resulting amine **9** was further brominated to form the tetrabromo derivative **1a**, X = Br. Alternatively, two iodine atoms were placed on the aniline ring in **1a**, X = I using benzyltrimethylammonium dichloroiodate[31] (BTMA-ICl_2) in methanol to enhance the reactivity of the halogens in Pd-catalyzed coupling reactions and also to differentiate the two benzene rings. Yields of **1a**, X = I were improved by using anhydrous methanol and by protecting the reaction from light. The diiodo product **1a**, X = I proved to be susceptible to deiodination if an excess of sodium bisulfite was used in the workup. To increase reactivity of the halogens in the Suzuki arylation reaction, the conversion of the amino substituent to other

(21) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1993**, *34*, 2225−2228. For the general method see: Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161−8162.
(22) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.
(23) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163.
(24) Hong, R.; Hoen, R.; Zhang, J.; Lin, G.-q. *Synlett* **2001**, 1527−1530.
(25) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139−196; *Chem. Rev.* **1964**, *64*, 613−632; *Synthesis* **1974**, 9−21.
(26) Badger, G. M.; Sasse, W. F. H. *J. Chem. Soc.* **1957**, 4−8.
(27) Idoux, J. P. *J. Chem. Soc., Part C* **1970**, 435−437.
(28) Corbett, J. F.; Holt, P. F. *J. Chem. Soc.* **1961**, 5029−5037.
(29) Ross, S. D.; Kuntz, I. *J. Am. Chem. Soc.* **1952**, *74*, 1297−1302.
(30) Tarbell, D. S.; Fukushima, D. K.; Allen, C. F. H.; Byers, J. R., Jr. In *Organic Syntheses*; Horning, E. C., Ed.; Wiley & Sons: New York, 1955; Collect. Vol. III, pp 809−811.
(31) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600−602.

SCHEME 2



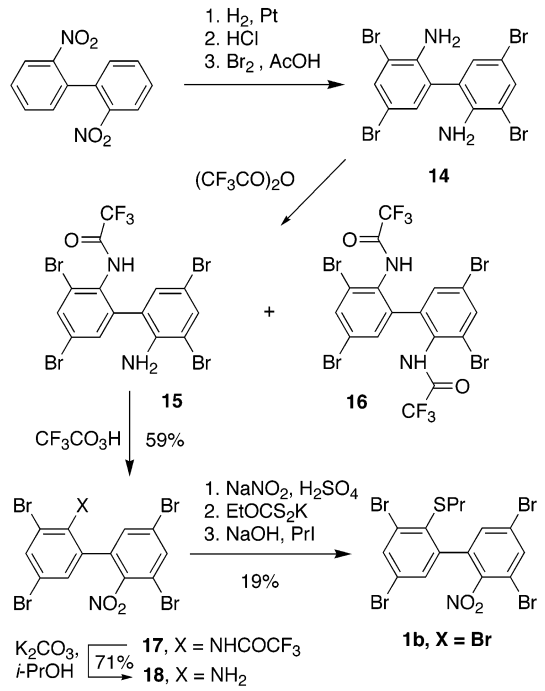
groups $\mathcal{N}$ with larger σ values[32] was briefly studied (Scheme 2). The groups of choice were *N*-acetyl ($\sigma_p = 0.0$), *N*,*N*-diacetyl ($\sigma_p = 0.33$), phenylazo ($\sigma_p = 0.39$), and nitro ($\sigma_p = 0.78$).

Acetylation of **1a** gave either the *N*-monoacetyl or *N*,*N*-diacetyl derivatives **10** and **11**, depending on the reaction conditions. Tetrabromoamine **1a**, X = Br was efficiently monoacetylated by using acetic anhydride in benzene to give **10**, X = Br. With use of excess acetic anhydride and catalytic amounts of H_2SO_4, the formation of the diacetylated derivative **11**, X = Br was observed. Diiodoamine **1a**, X = I proved to be sensitive to acid and decomposed under conditions used for the preparation of **11**, X = Br. The acetylation of **1a**, X = I and formation of **10**, X = I or **11**, X = I was accomplished by using acetyl chloride in the presence of pyridine.

The oxidation of the amine to the nitro group could not be accomplished chemoselectively in the presence of the sulfide group, and only sulfone nitro biphenyl **12** was obtained in good yield from a two-step sequence. Initially, the sulfide functionality in **1a**, X = Br was oxidized to the corresponding sulfone by using potassium peroxymonosulfate (Oxone) in a buffer solution under phase transfer catalysis conditions.[33] Without purification, the crude sulfone containing some of the intermediate sulfoxide was used directly for oxidation of the amino group with trifluoroperacetic acid[34] to form **12** in 87% overall yield.

The formation of azo compound **13** by condensation of amine **1a**, X = Br and nitrosobenzene under general conditions[35] was unsuccessful and only the starting material was recovered. In another attempt either to form an azo compound or to convert the amino to a nitro group through a diazonium salt derived from amine **1a**, X = Br no desired product was obtained, presumably due to the intramolecular reaction involving the nucleophilic S center.

SCHEME 3



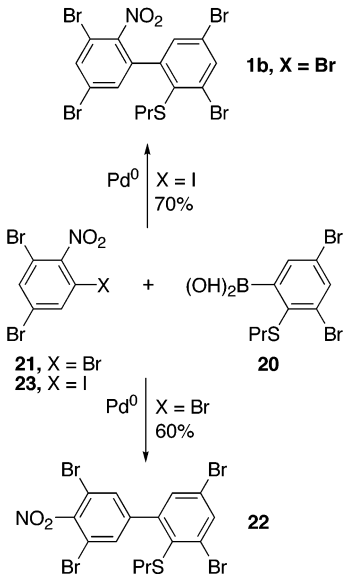
Among the derivatives **10**−**12** only the nitro sulfone **12** gave a satisfactory yield of the tetraarylated product under Suzuki conditions, but the reduction of the sulfonyl group to the required sulfide proved to be difficult.[36] The unquestionable benefit of the nitro group to the arylation reaction prompted us to develop a synthetic route to nitro sulfide **1b**, X = Br shown in Scheme 3. Analysis showed that the nitro group could be obtained from an amino group and the known 2,2′-diamino-3,3′,5,5′-tetrabromobiphenyl[37] (**14**) was chosen as the precursor.

The differentiation of the amine functions in diamine **14** was accomplished by reacting it with 1 equiv of trifluoroacetic anhydride. The resulting statistical reaction mixture of starting diamine **14**, *N*-trifluoroacetylated, and *N*,*N*′-bistrifluoroacetylated derivatives **15** and **16** was separated chromatographically yielding about 50% of the desired monoacylated **15**. Additional amounts of the monoamide were obtained by partial hydrolysis of the crude diamide **16** followed by chromatographic separation. Overall, the desired amide **15** was obtained in yields up to 70% based on the recovered starting material.

Similar polarity of the mono- and diacylated compounds made the chromatographic separation difficult on larger scales. In one experiment, only starting diamine was separated and a mixture of the **15** and **16** was oxidized with trifluoroperacetic acid giving a mixture of **17** and **16** that was easily separated. The trifluoroacetyl group was found to be superior to other amino protecting groups such as *t*-BOC, acetyl chloride, or 2-trimethylsilylethyl chloride.[38]

(32) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(33) Evans, T. L.; Grade, M. M. *Synth. Commun.* **1986**, *16*, 1207−1216.
(34) Emmons, W. D. *J. Am. Chem. Soc.* **1954**, *76*, 3470−3472.
(35) Lang-Fugmann, S. In *Organische Stickstoff*, Verbindung IV; Klamann, D., Ed.; Methoden der Organischen Chemie, Vol. E16d; Georg Thieme: New York, 1992; pp 56−59 and references therein.
(36) Huang, J. M.S. Thesis, Vanderbilt University, Nashville, TN, 1995.
(37) Corbett, J. F.; Holt, P. F. *J. Chem. Soc.* **1961**, 3695−3699.

SCHEME 4



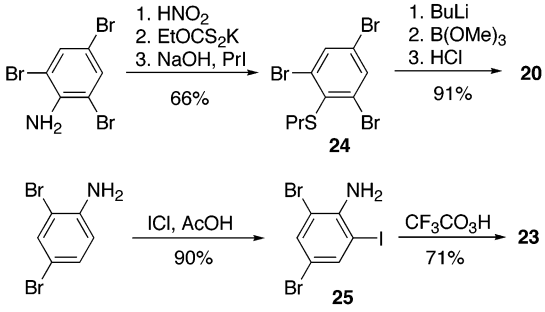
The protective trifluoroacetyl group in the nitro derivative **17** was removed with K_2CO_3 in *i*-PrOH to yield 2-amino-3,3′,5,5′-tetrabromo-2′-nitrobiphenyl (**18**). The same reaction in MeOH gave mostly products of nucleophilic displacement of bromine by the solvent. The propylthio group was introduced through the xanthate **19** in a way analogous to the synthesis of **8**. Diazotization of the nitro amine **18** was accomplished by using nitrosyl sulfuric acid in acetic acid,[39,40] and after pH adjustment, the diazonium salt was reacted with potassium ethyl xanthate. Treatment of the resulting xanthate **19** with 1-iodopropane in the presence of NaOH gave the desired 3,3′,5,5′-tetrabromo-2-nitro-2′-propylthiobiphenyl (**1b**, X = Br) in 19% yield based on **18**.

The low yield in the linear synthesis of **1b**, X = Br imposed a serious limitation on its use as a precursor for liquid crystals. Therefore, a more efficient convergent synthesis of **1b**, X = Br was developed according to Method C in Figure 2 and shown in Scheme 4.

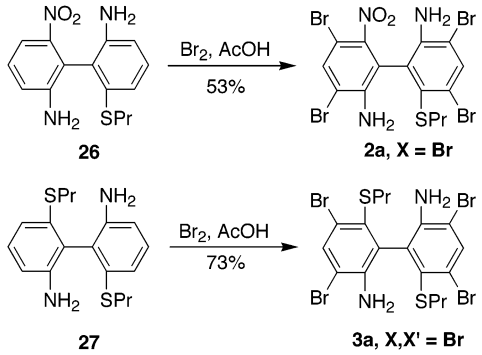
Initial attempts to prepare **1b**, X = Br with boronic acid **20** and 2,4,6-tribromonitrobenzene (**21**) under standard Suzuki coupling conditions[41] gave mainly the 4-nitro-2′-thiopropyl-3,3′,5,5′-tetrabromobiphenyl (**22**) with the desired isomer **1b**, X = Br isolated only in amounts less than 10%. Subsequent differentiation of the halogens by replacing one of the ortho bromine atoms with iodine in 2,4-dibromo-6-iodonitrobenzene (**23**) changed the regiochemistry of the coupling, and the desired isomer, the biphenyl **1b**, X = Br was obtained in good yield as the sole product.

The required 3,5-dibromo-6-propylthiophenylboronic acid (**20**) was prepared in 59% overall yield from 2,4,6-tribromoaniline through 2,4,6-tribromo-1-propylthiobenzene (**24**) as shown in Scheme 5. Sulfide **24** was obtained

SCHEME 5



SCHEME 6



according to a modified general procedure.[42] Thus, the diazonium salt derived from 2,4,6-tribromoaniline was reacted with potassium ethyl xanthate followed by *S*-propylation with 1-iodopropane under hydrolytic conditions. The resulting sulfide **24** was converted to the boronic acid **20** by treatment with *n*-butyllithium followed by trimethyl borate and acidic hydrolysis.

2,4-Dibromo-6-halonitrobenzenes **21** and **23** were obtained by oxidation of the corresponding anilines with trifluoroperacetic acid according to a general procedure.[34] 2,4-Dibromo-6-iodoaniline (**25**) was conveniently prepared by iodination of 2,4-dibromoaniline, instead of 2-amino-3,5-dibromobenzenesulfonic acid,[43] with iodine monochloride in acetic acid.

Preparation of Octasubstituted Biphenyls 2 and 3. The synthesis of compounds **2a** and **3a** was accomplished by bromination of the corresponding diamines **26**[44] and **27** (Scheme 6). The yield of the tetrabromobiphenyl **3a**, X = X′ = Br was 73%, while **2a**, X = Br was obtained only in 53% yield. The main side product in the latter bromination was isolated in about 10% yield and identified by ^{1}H NMR and MS as ylide **28**.

The formation of ylide **28** can be rationalized by the competition between the sulfur and ring carbon atoms for the electrophilic bromine. In the case of electron-rich substrate **27** the C-bromination is fast and chemoselectivity of the reaction is high. In contrast, the nitroaniline ring in **26** is deactivated and the introduction of the last two bromine atoms is slow. This allows the sulfur center either in an intermediate or in product **2a** to compete for the electrophile and presumably the transient bro-

(38) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley & Sons: New York, 1991; pp 309−405.

(39) Gunstone, F. D.; Tucker, S. H.; Cope, A. C.; Marshall, D. J.; Pike, R. M. In *Organic Syntheses*; Rabjohn, N., Ed.; Wiley & Sons: New York, 1963; Collect. Vol IV, pp 160−161.

(40) Conditions used for diazotization of **6** were ineffective in this case.

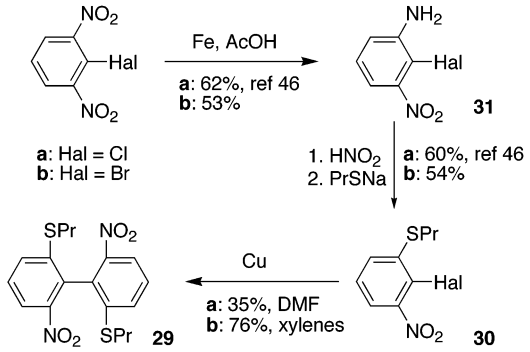
(41) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519.

(42) Hunter, W. H.; Kohlhase, A. H. *J. Am. Chem. Soc.* **1932**, *54*, 2425−2432.

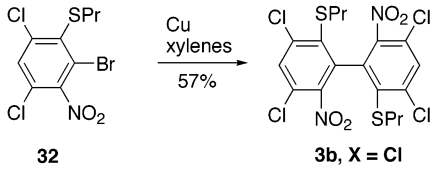
(43) Sudborough, J. J.; Lakhumalani, J. V. *J. Chem. Soc.* **1917**, *111*, 41−49.

(44) Benin, V.; Kaszynski, P.; Pink, M.; Young, V. G., Jr. *J. Org. Chem.* **2000**, *65*, 6388−6397.

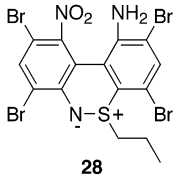
SCHEME 7



SCHEME 8



mosulfonium ion[45] is trapped intramolecularly by the amino group to form the N−S bond.



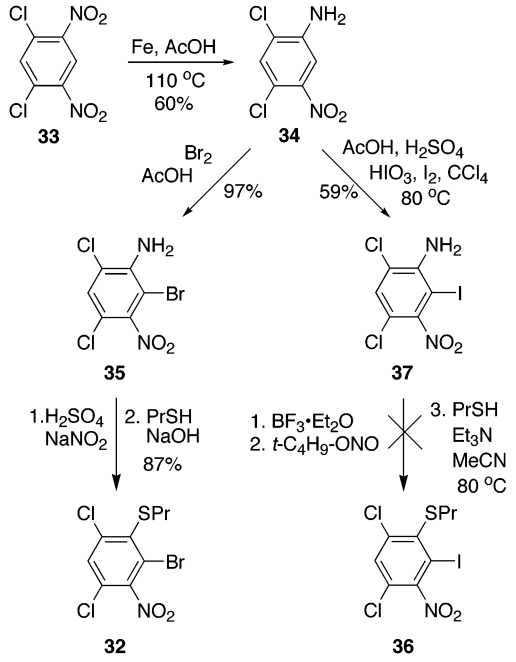
The diaminobiphenyl **27** was prepared by reduction of the corresponding dinitrobiphenyl **29** with a slightly substoichiometric amount of $SnCl_2$. Using excess reducing reagent resulted in partial loss of the propylthio group and significant complications in the isolation of the pure diamine **27**. The dinitrobiphenyl **29** was previously obtained as a byproduct in the Ullmann heterocoupling reaction.[44] Initial efforts to prepare **29** by homocoupling of 1-chloro-2-nitro-6-propylthiobenzene[46] (**30a**) were moderately successful and only 35% of **29** was isolated from a reaction in DMF with use of freshly prepared copper (Scheme 7). Substitution of 1-bromo-2-nitro-6-propylthiobenzene (**30b**) for the chloride **30a** facilitated the reaction and the dinitrobiphenyl **29** was readily isolated in over 70% yield.

Bromide **30b** was obtained from 2-bromo-3-nitroaniline[47] (**31b**) according to the procedure for the chloro analogue **30a**[46] as shown in Scheme 7.

The preparation of biphenyl **3b**, X = Cl was accomplished in 57% yield by Ullmann coupling of **32** in dry xylenes in the presence of freshly prepared copper as shown in Scheme 8 (Method C in Figure 2).

In an attempt to obtain **3b**, X = Cl halide **32** was reacted for 6 h with 0.5 equiv of Sn_2Me_6 in HMPTA at 110 °C in the presence of $Pd(PPh_3)_4$ according to a general literature procedure for modified Stille coupling.[48] After workup with aqueous KF, about 50% of starting bromide **32** was recovered along with about 40% of 1,3-dichloro-4-nitro-6-propylthiobenzene, product of debromination of **32**, identified by NMR and MS.[49] No reaction was observed when toluene was used as the solvent.[50]

SCHEME 9

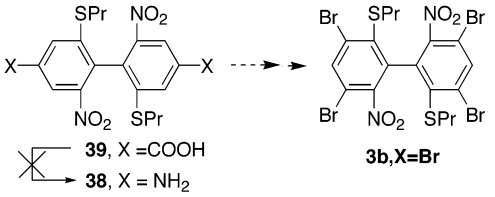


Bromide **32** was obtained from 1,3-dichloro-4,6-dinitrobenzene (**33**) in 50% overall yield as shown in Scheme 9. Partial reduction of **33** with iron according to a general literature procedure[46] gave the amine **34**, which was brominated to yield 2-bromo-4,6-dichloro-3-nitroaniline (**35**). Conversion of the amino group to propylthio in **32** was accomplished by reacting the diazonium salt derived from aniline **35** with sodium propylthiolate followed by thermolysis according to a general procedure.[46,51]

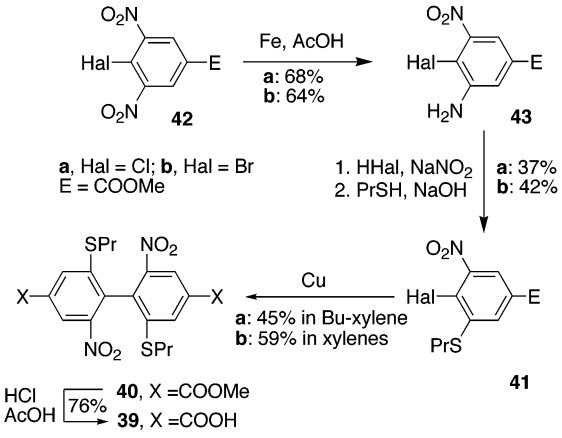
2-Iodo-4,6-dichloro-3-nitro-1-propylthiobenzene (**36**), the iodo analogue of **32** with the expected greater reactivity in the coupling reactions, could not be prepared. The attempted preparation of **36** began with iodination of aniline **34**, which proved to be difficult. Molecular iodine I_2 and ICl were ineffective, and only a mixture of iodic acid and I_2 under acidic conditions[52] gave the desired iodide **37** in 59% yield (Scheme 9). The subsequent transformation of the amino group to propylthio in **36**, in a similar way to the preparation of **32**, gave a complex mixture of products based on GC-MS and ^{1}H NMR analysis of the crude reaction mixture. This presumably resulted from activation of the iodine by the formation of a transient C-radical site ortho to iodine during the decomposition of the azosulfide.[51]

(45) Oae, S.; Ohnishi, Y.; Kozuka, S.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 364−366.
(46) Sienkowska, M.; Benin, V.; Kaszynski, P. *Tetrahedron* **2000**, *56*, 165−173.
(47) Liedholm, B. *Acta Chem. Scand.* **1971**, *25*, 106−112.
(48) Gulevich, Y. V.; Beletskaya, I. P. *Metalloorg. Khim.* **1988**, *1*, 704−707.
(49) 1,5-Dichloro-2-nitro-4-propylthiobenzene: ^{1}H NMR δ 1.07 (t, J = 7.3 Hz, 3H), 1.77 (sextet, J = 7.3 Hz, 2H), 2.96 (t, J = 7.3 Hz, 2H), 7.53 (s, 1H), 7.69 (s, 1H); EI-MS m/z 269, 267, 265 (M, 8:55:76), 223 (100).
(50) Kosugi, M.; Shimizu, K.; Ohtani, A.; Migita, T. *Chem. Lett.* **1981**, 829−830.
(51) Brokken-Zijp, J.; Bogaert, H. v. d. *Tetrahedron* **1973**, *29*, 4169−4174.
(52) Wirth, H. O.; Königstein, O.; Kern, W. *Liebigs Ann. Chem.* **1960**, *634*, 84−104.

SCHEME 10



SCHEME 11



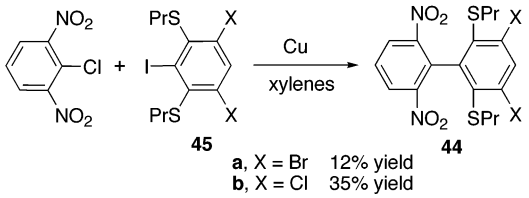
A route to biphenyl **3b**, X = Br containing a nitro group followed Method D (Figure 2), and was envisioned to involve bromination and subsequent deamination of diamine **38** (Scheme 10). Unfortunately, efforts to convert the carboxyl groups in diacid **39** to the corresponding amine functionalities following a report for a related compound[53] were unsuccessful. Schmidt[54] degradation and Curtius[55] rearrangement conditions decomposed the starting diacid without formation of **38**.

The diacid **39** was obtained by acidic hydrolysis of diester **40** whose preparation is shown in Scheme 11. The initially chosen substrate for the Ullmann coupling reaction, methyl 4-chloro-3-nitro-5-propylthiobenzoate (**41a**), was prepared by partial reduction of the dinitro derivative **42a**[53,56] with iron, followed by diazotization of the resulting amine **43a** and reaction with alkaline propanethiol. The resulting azosulfide intermediate was thermally decomposed to give the desired sulfide **41a**. The yield of the product depended upon the reaction conditions.[51] It was found that the optimal temperature for the decomposition of the transient azosulfide was 85−95 °C, and the ester **41a** was obtained in 37% yield based on the amine **43a**.

Surprisingly, ester **41a** showed significant resistance to Ullmann conditions. No reaction of **41a** was observed in boiling xylene or DMF (130 °C) in the presence of either activated or freshly prepared copper powder. Only under solvent-free conditions at temperatures above 200 °C, or in a high boiling solvent such as 5-*tert*-butyl-*m*-xylene (bp 205−206 °C), was efficient formation of biphenyl **40** observed.

To increase the reactivity of halide **41** in the Ullmann coupling reaction, the chlorine atom was replaced with bromine. The initial attempt to prepare the bromo ester **41b** utilized the same reaction conditions as the analogous chloro ester **41a**. However, the excess of HCl and heating led to halo-dehalogenation and bromine was substituted with chlorine to give **41a**. This problem was resolved by replacing HCl with HBr, and the ester **41b** was prepared from methyl 4-bromo-3,5-dinitrobenzoate[57] (**42b**) in 27% overall yield. Increased yields and easier purification of **41b** was observed when a diazonium salt solution prepared from amine **43b** was quickly filtered before reaction with the mercaptan.

SCHEME 12



As expected, Ullmann coupling reactions of the bromo derivative **41b** in xylene were more efficient than the chloro analogue **41a** and the desired biphenyl **40** was isolated in 59% yield.

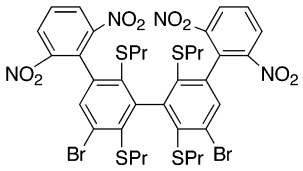
Preparation of Octasubstituted Biphenyl 4. Preparation of **4** was the most challenging of all biphenyls since it required either the halogenated bis(propylthio)benzene precursor (Method A1 and C) or using an auxiliary amino group to introduce the halogen atoms in the biphenyl (Method D). Both of these routes were investigated.

The preparation of **4a** was envisioned by bromination of the nitroaniline ring, in an analogous way to the preparation of **2a** (Scheme 6). Initial attempts to prepare **44a** by Ullmann coupling of 1,3-dibromo-5-iodo-4,6-bis(propylthio)benzene[58] (**45a**) and 1-chloro-2,6-dinitrobenzene gave a complex mixture of products. The desired biphenyl **44a** was isolated only in about 12% yield (Scheme 12). The major byproduct was also isolated in about 12% yield and identified as quaterphenyl derivative **46**. The use of 1,3-dichloro-5-iodo-4,6-bis(propylthio)-benzene[58] (**45b**) showed a greatly improved chemoselectivity in the coupling reaction, and the desired biphenyl **44b** was free of regioisomers.

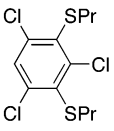
The yield of **44b**, however, depended on the solvent. When DMF was used for the Ullmann reaction, most of the starting iodide **45b** was converted to the inert trichloro derivative **47** by a halogen exchange reaction mediated by CuCl formed in situ, which is particularly effective in DMF.[59] In fact, the authentic sample of **47** for comparison was conveniently prepared by reacting bromide **45a** with CuCl under these conditions. This undesired reaction was largely suppressed in xylene, and **44b** was isolated in 35% yield.

Subsequent partial reduction of **44b** was accomplished by using sodium sulfide according to a general procedure.[29] The dibromination of the resulting amine **48** gave the desired tetrahalobiphenyl **4a**, X = Br, X′ = Cl in 90%

(53) Nielsen, A. T.; Norris, W. P.; Atkins, R. L.; Vuono, W. R. *J. Org. Chem.* **1983**, *48*, 1056−1059.
(54) Koldobskii, G. I.; Ostrovskii, V. A.; Gidaspov, B. V. *Russ. Chem. Rev.* **1978**, *47*, 1084−1094.
(55) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38−40.
(56) Ullmann, F. *Liebigs Ann. Chem.* **1909**, 79−118.
(57) Blanksma, J. J.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1934**, *53*, 988−1000.
(58) Manka, J. T.; McKenzie, V. C.; Kaszynski, P. Submitted for publication.
(59) Sasson, Y. In *Supplement D2: The chemistry of halides, pseudo-halides and azides*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, 1995; pp 548−549 and references therein.



46



47

yield (Scheme 13). The high yield of **4a** compared to the analogous preparation of **2a** suggests that the sulfur centers in **48** are much less competitive for bromine.

Several attempts were made to prepare **4b** with both nitro groups preserved in the biphenyl product (Scheme 14). In the first series of reactions, organozinc and organoboron[60] reagents, **49a** and **49b**, respectively, were generated in situ from tribromide **50** and reacted with 1-bromo-3,5-dichloro-2,6-dinitrobenzene (**51**) under general Negishi[61] or modified Suzuki[62] conditions (Scheme 14). In both cases no desired biphenyl **4b** was observed, and only the debrominated product **52** and largely unreacted **51** were isolated.

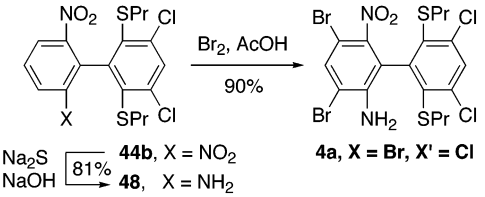
None of the expected biphenyl **44b** was observed in the cross-coupling reaction of iodide **45b** with 1-bromo-2,6-dinitrobenzene under modified Negishi conditions[22] with $Pd(t\text{-}Bu_3P)_2$ catalyst (Scheme 14). A simultaneously run control reaction with 1-iodo-4-nitrobenzene gave the oily cross-coupling product **53** in about 30% of unoptimized yield identified by ^1H NMR and MS.

The dinitro derivative **51** was obtained by CF_3CO_3H oxidation of nitroaniline **35**. The 1,3,5-tribromo-2,6-bis-(propylthio)benzene (**50**) was prepared by bromination of *m*-phenylenediamine to 2,4,6-tribromophenylene-1,3-diamine[63] (**54**), and subsequent conversion of both amino groups to the propylthio substituents (Scheme 15). The diamine was converted to dry monodiazonium salt **55** by using the Doyle's procedure[64] and subsequently reacted with propylthiolate anion under general conditions.[46] The resulting azosulfide **56** was decomposed to amine **57** by refluxing in acetonitrile. The procedure was repeated to give **50** in 51% yield or 17% overall yield based on **54**. A similar overall yield was obtained for a recently discovered three-step preparation of **50** from 3,5-difluoroaniline.[65]

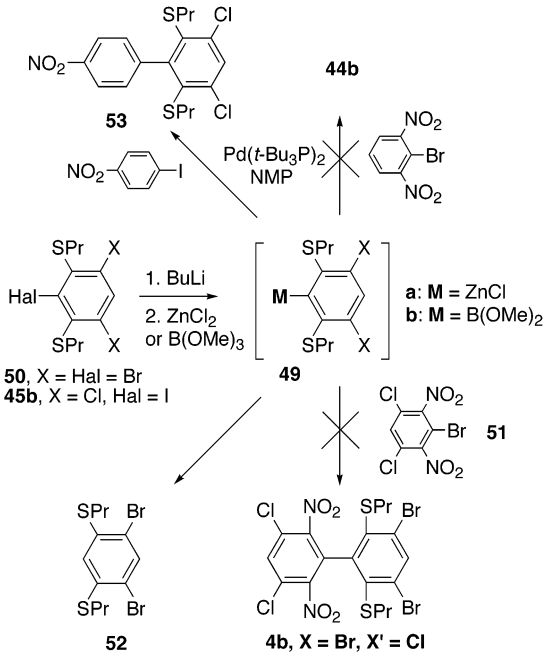
In another attempt at the preparation of biphenyl **4b**, X = X′ = Br we investigated an Ullmann heterocoupling reaction between esters **41** and **42** (Method D in Figure 2). No heterocoupling Ullmann product **58** was observed in the reaction of the chloro derivatives **41a** and **42a** and only homocoupling product **40** and de-chlorinated starting materials were isolated (Scheme 16).

In the reaction between the bromo derivative **41b** and the chloro ester **42a** in 5-*tert*-butyl-*m*-xylene, the expected heterocoupling product **58** was formed as a major component of a mixture of three possible biphenyls. ^1H NMR analysis of the mixture showed that the ratio of **58** and

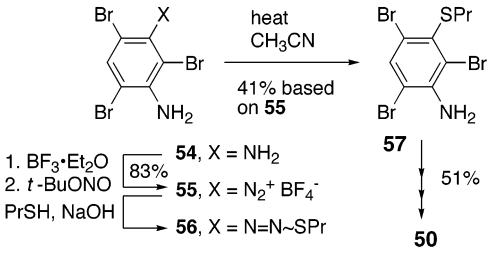
SCHEME 13



SCHEME 14



SCHEME 15



the two homocoupling products **59** and **40** is 4:3:1. Unfortunately, the close structural similarity of the three biphenyls led to separation problems and an analytically pure sample of the heterocoupling product **58** was not obtained.

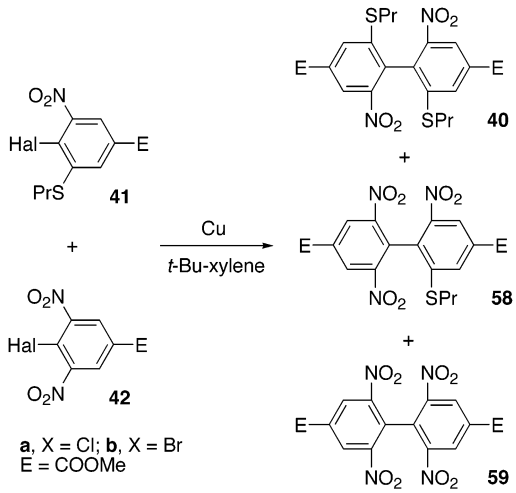
Discussion and Conclusions

All four biphenyls **1**−**4** were prepared in metal-mediated convergent syntheses from halobenzene precursors. In most cases, the introduction of four (e.g. **2a** and **3a**) or two halogens (e.g. **4a**) followed the biphenyl bond formation. The exceptions are **1b**, X = Br, and **3b**, X = Cl, which were prepared directly in Suzuki and Ullmann coupling reactions, respectively, from appropriately substituted halobenzenes. The preparation of **1** clearly demonstrates the advantage of the convergent over linear synthesis.

The preparation of unsymmetrical biphenyls **2** and **4** in Ullmann reactions required halogens of matching reactivity to maximize yields of the desired heterocou-

(60) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556−9559.
(61) Negishi, E.-I.; Takahashi, T.; King, A. O.; Kawai, K.; Noyori, R. In *Organic Syntheses*; Freeman, J. P., Ed.; Wiley & Sons: New York, 1993; Collect. Vol. VIII, pp 430−434.
(62) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210.
(63) Jackson, C. L.; Calvert, S. *Am. Chem. J.* **1896**, *18*, 465−489.
(64) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574.
(65) Manka, J. T.; Kaszynski, P. J. *Fluorine Chem.* **2003**, *124*, 39−43.

SCHEME 16



pling products. In both reactions a combination of chlorine on the electron-deficient nitrobenzene ring and iodine on the electron-rich propylthiobenzene ring was used to maximize the yield of the cross-coupling product. The choice of halogens is in accordance with previous findings[25] and our observations.[44]

Among the 9 prepared biphenyls of the general formula shown in Figure 1, only **1b**, X = Br was prepared in a Pd-catalyzed process. Unlike the other biphenyls, **1b** has only two ortho substituents whose steric bulk does not inhibit the catalytic process. Preparation of the remaining biphenyls **2**−**4** could, in principle, benefit from the new Pd-based methods specifically developed for this type of molecular systems with four ortho substituents.[22−24,66] Unfortunately, the scope of substituents tested in these new reactions is insufficient to judge the extent of usefulness of these methods to the present synthetic problem. To our knowledge there are no examples of highly substituted biphenyls with bulky *o*-alkylthio groups, and only one with the *o*-nitro group. The preparation of **2b** or **3b** with the Negishi and Suzuki coupling methods requires organometallic species that would have to be generated from *o*-nitrohalobenzene such as **32**. Although metalation of nitrobenzenes is a known process,[67,68] it introduces an additional synthetic step and the overall advantage of the Pd-catalyzed over the Cu-mediated method for biphenyl formation becomes questionable. The only transformation that could significantly benefit from the two methods is the synthesis of **4b** and **44** in Scheme 14 in which the organometallic species could be conveniently generated from halides **50** and **45**, respectively. Unfortunately, none of the classical Suzuki or Negishi reactions gave the expected products, and even the modified Negishi cross-coupling recommended for sterically crowded biaryls[22] failed in our hands to produce detectable amounts of the desired biphenyl **44**, a precursor to **4a**. This demonstrates continued need for development of efficient Pd-based catalysts and viability of the alternative Cu-based Ullmann-type coupling methods for the preparation of highly substituted and sterically congested biaryls.

An important issue in the metal-mediated formation of the biphenyl bond is the chemo- and regioselectivity when the benzene substrates contain more than one halogen. Generally, the order of reactivity follows I > Br > Cl.[25] When two halogens are the same, the ortho halogen is usually more reactive especially when the substituent is an electronegative group[25,69,70] such as nitro. In the synthesis of **1b**, however, the para bromine atom was replaced preferentially to the ortho halogens despite the more favorable statistics and the activating role of the nitro group. Using iodine in place of one of the ortho bromine atoms in **23** dramatically improved the regioselectivity of the Suzuki coupling, and biphenyl **1b** was obtained as the sole product.

The use of polyhalogenated substrates in the Ullmann coupling reactions often leads to dehalogenation and multiple couplings largely due to high temperature and excess copper used in the reaction. A literature search revealed that there are relatively few Ullmann reactions performed in the presence of other reactive halogens.[25,71] Our attempt at coupling the iodide **45a** containing iodide and two bromine atoms demonstrated a competitive attack on the C−Br and the formation of undesired byproducts such as **46**. Biphenyl **44a** was isolated only in 12% yield with **45a**, but the yield was improved to 35% when bromine atoms were replaced with the less reactive chlorine atoms in **45b**.

Our studies found that the quality of copper powder affects the yields of Ullmann coupling. Copper powder freshly prepared by reduction of $CuSO_4$ with Zn powder appears to be more reactive than commercial copper activated with iodine. This is consistent with a literature report.[72]

In a broader context, it should be noted that there are relatively few polyfunctionalized biphenyls, and only a handful of them have halogens in the 3,3′,5,5′ positions. Most of the biphenyls have been prepared by electrophilic halogenation or nitration of substituted 2,2′-biphenols, which in turn are prepared by oxidative dimerization of the corresponding phenols.[73] Other biphenyls are generally prepared in Ullmann coupling reactions. To our knowledge, polysubstituted biphenyls **1**−**4** represent first examples containing a combination of alkylthio, nitro, and halogen substituents. There are only a handful of unsymmetrically polysubstituted biphenyls obtained either by dissymmetrization of biphenyls or by Ullmann heterocoupling.

Derivatives **1**−**4** of the general structure shown in Figure 1 offer two functionalization spheres. The internal sphere of functionalities that includes the 2,2′,6,6′ positions provides a means to control the π electronic structure of the biphenyl core by closing heterocyclic rings or generation of chelation sites. The second, external sphere of functionalities offers the possibility to expand the biphenyl core structure and build it into a supramolecular assembly (covalent or noncovalent). This general

(66) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1993**, *34*, 2225−2228.
(67) Köbrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412−1419.
(68) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610−1611.
(69) Newman, M. S.; Logue, M. W. *J. Org. Chem.* **1971**, *36*, 1398−1401.
(70) Farrar, J. M.; Sienkowska, M.; Kaszynski, P. *Synth. Commun.* **2000**, *30*, 4039−4045.
(71) Forrest, J. J. *Chem. Soc.* **1960**, 566−601.
(72) Gore, P. H.; Hughes, G. K. *J. Chem. Soc.* **1959**, 1615−1616.
(73) Musso, H. In *Oxidative Coupling of Phenols*; Taylor, W. I., Battersby, A. R., Eds.; Marcel Dekker: New York, 1967; pp 1−94.

strategy is adapted in our research of disklike liquid crystalline materials.[2] It has also been utilized in new designs of catalysts[74] and biphenyl networks,[75,76] and it may be used in the construction of sensors.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 300 or 400 MHz, and ^{13}C NMR were measured at 75 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where noted otherwise. IR spectra were recorded for neat samples (liquid or microcrystalline) on AgCl plates, unless otherwise noted. Mass spectrometry data were acquired by using a GC-MS system in EI mode with the maximum *m*/*z* range of 600.

All reagents were used as received except as noted. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl. *N*,*N*-Dimethylformamide (DMF) was purchased anhydrous and subsequently dried over activated 4 Å molecular sieves. K_3PO_4 was dried in a vacuum (100 °C/0.5 Torr). Commercial copper powder from Aldrich (cat. no. 29,258-3) for Ullmann coupling reactions was activated according to a literature procedure.[77] Alternatively, active copper powder was obtained by reduction of copper sulfate with zinc powder according to a literature procedure.[77]

2-Amino-3,3′,5,5′-tetrabromo-2′-propylthiobiphenyl (1a, X = Br). Br_2 (1.92 g, 12.0 mmol) was added dropwise to a solution of amine **9** (2.42 g, 6.04 mmol) in AcOH (50 mL), and the solution was stirred at room temperature. After 2 h, water was added and precipitate was filtered off and dried. The crude product was purified by column chromatography (CH_2Cl_2) to give **1a**, X = Br (2.21 g, 65% yield) as a yellow viscous liquid: ^{1}H NMR δ 0.83 (t, J = 7.3 Hz, 3H), 1.35−1.43 (m, 2H), 2.56−2.65 (m, 2H), 3.97 (br s, 2H), 7.07 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H); ^{13}C NMR δ 13.1, 22.7, 38.2, 108.8, 109.8, 123.0, 128.1, 131.5, 132.8, 133.0, 134.2, 135.2, 136.0, 140.7, 145.4; IR 3483 and 3387 (N−H), 1610 and 1456 (C=C) cm^{-1}; EI-MS *m*/*z* 563, 561, 559, 557, 555 (M, 5:20:41:21:5), 483 (100). Anal. Calcd for $C_{15}H_{13}Br_4NS$: C, 32.23; H, 2.34; Br, 57.18; N, 2.51; S, 5.74. Found: C, 32.26; H, 2.34; Br, 57.12; N, 2.46; S, 5.70.

2-Amino-3′,5′-dibromo-3,5-diiodo-2′-propylthiobiphenyl (1a, X = I). Amine **9** (0.37 g, 0.92 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and MeOH (7 mL) was added followed by $CaCO_3$ (0.70 g). To the stirred yellow suspension was added 0.74 g of benzyltrimethylammonium dichloroiodate[31] (BTMA-ICl_2). The flask was wrapped in aluminum foil to protect it from light and the mixture was stirred overnight. Additional BTMA-ICl_2 (0.69 g) was added and the reaction was stirred 2 h. After solids were filtered off, the solvent was removed and 5% $NaHSO_3$ was added to the black residue (warning: excess $NaHSO_3$ deiodinates the product). The organics were extracted with ether, the combined extracts dried ($MgSO_4$), and solvents evaporated to give a dark-brown solid (0.45 g) that was purified by column chromatography (toluene:hexane, 1:1) to give **1a**, X = I (0.379 g, 63% yield) as a tan solid. An analytical sample was obtained by recrystallizing twice from hexanes, then EtOH to leave an off-white solid: mp 98.5−99.0 °C; ^{1}H NMR δ 0.84 (t, J = 7.3 Hz, 3H), 1.33−1.46 (m, 2H), 2.53−2.69 (m, 2H), 4.00 (br s, 2H), 7.23 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ 13.2, 22.7, 38.2, 78.3, 85.2, 123.0, 127.7, 132.7, 133.0, 135.1, 136.0, 138.0, 143.7, 145.6, 145.8; IR (KBr) 3465 and 3369 (N−H), 1603 and 1446 (C=C) cm^{-1}; EI-MS *m*/*z* 575−580 (M − SPr, max at 577, 84), 196 (100). Anal. Calcd for $C_{15}H_{13}Br_2I_2NS$: C, 27.59; H, 2.01; N, 2.15; Br, 24.47; I, 38.87. Found: C, 27.47; H, 1.97; N, 2.11; Br, 24.56; I, 39.00.

3,3′5,5′-Tetrabromo-2′-nitro-2-propylthiobiphenyl (1b, X = Br). Method A. Concentrated H_2SO_4 (2 mL) and solid $NaNO_2$ (0.179 g, 2.59 mmol) were stirred at 0 °C. After the solid dissolved, amine **18** (1.21 g, 2.32 mmol) in AcOH (4 mL) was added and stirring continued for 1 h. Water (4 mL) was added followed by NaOAc to adjust the pH to 4−5. A few crystals of $NiCl_2$ were added to the orange mixture followed by EtOCSSK (0.536 g, 3.35 mmol) in water (5 mL) at 0−5 °C. The resulting suspension was slowly warmed to room temperature and stirred for 30 min. The brown crude xanthate **19** was dissolved in CH_2Cl_2, separated, dried (Na_2SO_4), and flashed through a silica gel plug. After the solvent was removed, a solution of NaOH (0.346 g, 8.6 mmol) in MeOH (20 mL) was added to the residue. 1-Iodopropane (0.4 mL, 4.1 mmol) was added dropwise, and the reaction mixture was gently refluxed for 15 min. Water was added, and the organics were extracted (CH_2Cl_2). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was separated by column chromatography (hexane), giving **1b**, X = Br (0.264 g, 19% yield) as a viscous oil.

Method B. A mixture of boronic acid **20** (1.95 g, 5.5 mmol), iodide **23** (2.03 g, 5 mmol), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), 2 M Na_2CO_3 (15 mL, 30 mmol), and toluene (40 mL) was refluxed under N_2 for 24 h. An additional amount of boronic acid **20**, catalyst, and 2 M Na_2CO_3 may be necessary, if iodide **23** is still present. The product was extracted (ether) and the combined extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by column chromatography (hexanes:CH_2Cl_2, 4:1) to give **1b**, X = Br (2.27 g, 70% yield) as a brown oil: ^{1}H NMR δ 0.89 (t, J = 7.3 Hz, 3H), 1.49 (sextet, J = 7.4 Hz, 2H), 2.63 (dt, J_1 = 12.0 Hz, J_2 = 7.4 Hz, 1H), 2.77 (dt, J_1 = 12.0 Hz, J_2 = 7.4 Hz, 1H), 7.34 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ 13.3, 22.6, 38.3, 114.1, 122.5, 123.9, 131.7, 133.1, 133.5, 135.1, 135.76, 135.83, 137.1, 141.9, 149.1; IR 1538 and 1365 (NO_2) cm^{-1}; EI-MS, *m*/*z* 589 (M, 1), 504, 502, 500, 498, 496 (19:70:100:67:18). Anal. Calcd for $C_{15}H_{11}Br_4NO_2S$: C, 30.59, H, 1.88, N, 2.38. Found: C, 30.77, H, 1.96, N, 2.40.

2,2′-Diamino-3,5,3′,5′-tetrabromo-6-nitro-6′-propylthiobiphenyl (2a, X = Br). A 1 M solution of Br_2 in AcOH (5.6 mL, 5.6 mmol) was added dropwise at room temperature to a stirred solution of diamine **26**[44] (429 mg, 1.4 mmol) in AcOH (9 mL). After 1 h, additional Br_2 solution (1.4 mL) was added and the stirring was continued for 3 h. Water and CH_2Cl_2 were added and the mixture was successively treated with aqueous solutions of $NaHCO_3$ and Na_2SO_3. The organic layer was dried (Na_2SO_4) and the solvent removed. The residue was separated on a silica gel column (hexanes:CH_2Cl_2, 1:1, followed by 1:2 ratio, and finally pure CH_2Cl_2) to give **2a**, X = Br (487 mg, 53% yield) as a reddish solid. An analytical sample was obtained by recrystallization from a benzene/hexanes mixture: mp 157−158 °C; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 1.54 (sextet, J = 7.3 Hz, 2H), 2.76 (dt, J_1 = 11.2 Hz, J_2 = 7.4 Hz, 2H), 2.88 (dt, J_1 = 11.2 Hz, J_2 = 7.4 Hz, 2H), 4.14 (br s, 2H), 4.22 (br s, 2H), 7.80 (s, 2H); ^{13}C NMR δ 13.3, 22.6, 38.4, 99.2, 110.5, 110.8, 116.9, 118.9, 122.1, 136.3, 137.2, 137.5, 142.7, 142.9, 150.2; IR 3478 and 3379 (N−H), 1607 (C=C) cm^{-1}. Anal. Calcd for $C_{15}H_{13}Br_4N_3O_2S$: C, 29.10; H, 2.12; N, 6.79. Found: C, 29.37; H, 2.10; N, 6.76.

2,2′-Diamino-3,5,3′,5′-tetrabromo-6,6′-bis(propylthio)-biphenyl (3a, X = Br). A 1 M solution of Br_2 in AcOH (1.4 mL, 1.4 mmol) was added dropwise to diamine **27** (0.105 g, 0.316 mmol) in AcOH (4 mL). After 3 h the reaction mixture was poured into water and the product was extracted into CH_2Cl_2 and washed with 15% $NaHCO_3$. The organics were dried (Na_2SO_4), the solvent was removed, and the residue was purified on a silica gel column (hexanes:CH_2Cl_2, 4:1) to give

(74) Hultzsch, K. C.; Jernelius, J. A.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 589−593.
(75) Gómez-Lor, B.; Echavarren, A. M.; Santos, A. *Tetrahedron Lett.* **1997**, *38*, 5347−5350.
(76) Xu, M.-H.; Lin, Z.-M.; Pu, L. *Tetrahedron Lett.* **2001**, *42*, 6235−6238.
(77) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: New York, 1989; p 426.

3a, X = Br (0.15 g, 73% yield) as a colorless oil: ^{1}H NMR δ 0.86 (t, J = 7.3 Hz, 6H), 1.48 (sextet, J = 7.3 Hz, 4H), 2.78−2.73 (m, 4H), 3.96 (br s, 4H), 7.79 (s, 2H); ^{13}C NMR δ 13.3, 22.8, 38.2, 109.8, 118.6, 129.3, 135.8, 136.3, 141.5; IR 3477 and 3378 (N−H), 1602 (C=C) cm^{-1}. Anal. Calcd for $C_{18}H_{20}Br_4N_2S_2$: C, 33.36; H, 3.11; N, 4.32. Found: C; 33.70; H, 3.15; N, 4.33.

3,3′,5,5′-Tetrachloro-2,2′-dinitro-6,6′-bis(propylthio)biphenyl (3b, X = Cl). A mixture of halide **32** (96 mg, 0.3 mmol), freshly prepared Cu powder (60 mg, 0.9 mmol), and dry xylenes (4 mL) was stirred overnight at 130 °C under N_2. The reaction was cooled and flushed through a silica gel plug (CH_2Cl_2:hexanes, 1:1). The solvent was removed and the residue was separated on a silica gel column (CH_2Cl_2:hexanes, 1:3) to give **3b**, X = Cl (42 mg, 57% yield) as a white solid: mp 130−131 °C; ^{1}H NMR δ 0.93 (t, J = 7.4 Hz, 6H), 1.58 (sextet, J = 7.4 Hz, 4H), 2.84 (dt, J_1 = 11.2 Hz, J_2 = 7.4 Hz, 2H), 2.96 (dt, J_1 = 11.2 Hz, J_2 = 7.4 Hz, 2H), 7.73 (s, 2H); ^{13}C NMR δ 13.3, 22.6, 38.1, 126.4, 132.5, 135.2, 137.2, 143.1, 146.3; IR 1537 and 1355 (NO_2) cm^{-1}; EI-MS m/z 482 (M − NO_2, 73), 369 (100), 367 (98); HRMS (FAB+) calcd for $C_{18}H_{17}Cl_4N_2O_4S_2$ 528.9384, found 528.9380. Anal. Calcd for $C_{18}H_{16}Cl_4N_2O_4S_2$: C, 40.77; H 3.04; N, 5.28. Found: C, 40.97; H, 3.05; N, 5.32.

2-Amino-3,5-dibromo-3′,5′-dichloro-6-nitro-2′,6′-bis(propylthio)biphenyl (4a, X = Br, X′ = Cl). A 0.5 M solution of Br_2 in AcOH (4.4 mL, 2.2 mmol) was added dropwise to aminobiphenyl **48** (431 mg, 1.0 mmol) dissolved in AcOH (5 mL). After 3 h, the mixture was worked up as described for **3a**, and the crude product was purified by column chromatography (CH_2Cl_2:hexanes, 3:2) to give **4a**, X = Br, X′ = Cl (528 mg, 90% yield) as a yellow solid: mp 158−159 °C; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 6H), 1.53 (sextet, J = 7.3 Hz, 4H), 2.78 (dt, J_1 = 11.4 Hz, J_2 = 7.3 Hz, 2H), 2.88 (dt, J_1 = 11.4 Hz, J_2 = 7.3 Hz, 2H), 4.06 (br s, 2H), 7.67 (s, 1H), 7.78 (s, 1H); ^{13}C NMR δ 13.3, 22.7, 37.9, 99.6, 110.6, 121.5, 132.4, 135.6, 141.3, 141.8, 143.5, 148.7; IR 3474 and 3373 (N−H), 1612 and 1442 (C=C), 1532 and 1369 (NO_2) cm^{-1}. Anal. Calcd for $C_{18}H_{18}Br_2Cl_2N_2O_2S_2$: C, 36.69; H, 3.08; N, 4.75. Found: C, 36.83; H, 3.06; N, 4.74.

3,5-Dibromo-2-nitro-2′-propylthiobiphenyl (8). Powdered amine **6** (15.35 g, 41.49 mmol) was slowly added with stirring to concentrated HCl (100 mL). After 30 min, water (50 mL) was added, and the resulting suspension was cooled in an ice bath. A solution of $NaNO_2$ (3.06 g, 44.3 mmol) in water (20 mL) was added dropwise at a temperature below 5 °C. The resulting green solution was stirred in the ice bath for 45 min, and then a cold 40% solution of NaOAc was added to adjust the pH of the solution to 4−5. A few crystals of $NiCl_2$ were added, followed by a solution of EtOCSSK (6.8 g, 42.5 mmol) in water (20 mL). A yellow precipitate immediately formed, which turned brown as the suspension was slowly warmed to room temperature. The resulting brown viscous organic product was dissolved in CH_2Cl_2. The organic phase was separated, dried, and flushed through a silica gel plug (CH_2Cl_2). The filtrate was evaporated to dryness, and the resulting crude xanthate **7** was used without further purification for the alkylation step.

A solution of NaOH (2.00 g, 50 mmol) in MeOH (100 mL) was added to the crude xanthate **7**, and after 30 min, 1-iodopropane (9.0 mL, 92.3 mmol) was added. The reaction mixture was stirred for 25 h at 70 °C until no xanthate remained by GC/MS. Water was added, the organic products extracted (CH_2Cl_2), and the extracts dried (Na_2SO_4), passed through a silica gel plug (CH_2Cl_2), and partially decolorized with charcoal. The solvent was removed leaving **8** (13.78 g, 77% yield based on amine **6**) as a brown oil: ^{1}H NMR δ 0.76 (t, J = 7.3 Hz, 3H), 1.26−1.41 (m, 2H), 2.46 (dt, J_1 = 12.1 Hz, J_2 = 7.2 Hz, 1H), 2.65 (dt, J_1 = 12.1 Hz, J_2 = 7.1 Hz, 1H), 7.29 (dd, J_1 = 7.4 Hz, J_2 = 1.1 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.54−7.59 (m, 1H), 7.64−7.69 (m, 1H), 7.84 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 13.1, 22.5, 37.9, 122.4, 124.4, 129.1, 129.7, 131.0, 132.1, 132.5, 132.9, 133.9, 135.4, 146.9, 147.8; IR 1529 and 1350 (NO_2) cm^{-1}; EI-MS m/z 433, 431, 429 (M, 0.5:1:0.5), 264 and 262 (100:100). Anal. Calcd for $C_{15}H_{13}Br_2NO_2S$: C, 41.79; H, 3.04; Br, 37.07; N, 3.25; S, 7.44. Found: C, 41.88; H, 3.07; Br, 36.95; N, 3.17; S, 7.52.

2-Amino-3,5-dibromo-2′-propylthiobiphenyl (9). A mixture of nitrobiphenyl **8** (3.11 g, 7.20 mmol), Zn powder (2.35 g, 36.0 mmol), and AcOH (30 mL) was stirred overnight at room temperature. The reaction mixture was filtered to remove solids, and the solids were washed with CH_2Cl_2. Water was added to the filtrate, and CH_2Cl_2 was used to extract the organic products. Dilute HCl was added at this stage to dissolve the emulsion. The extract was washed with $NaHCO_3$ solution and dried (Na_2SO_4), and the solvent was removed. The yellow oil was purified by column chromatography (CH_2Cl_2:hexanes, 2:1) to give amine **9** (2.42 g, 84% yield) as a light yellow liquid: ^{1}H NMR δ 0.79 (t, J = 7.3 Hz, 3H), 1.35 (sextet, J = 7.3 Hz, 2H), 2.46−2.58 (m, 2H), 3.54 (br s, 2H), 6.74−6.83 (m, 2H), 6.98 (d, J = 7.6 Hz, 1H), 7.14−7.22 (m, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H); ^{13}C NMR δ 13.1, 22.6, 37.8, 115.5, 118.0, 122.5, 126.2, 129.2, 129.8, 130.7, 132.3, 133.2, 135.0, 143.3, 147.3; IR 3471 and 3382 (N−H), 1617 (C=C) cm^{-1}; EI-MS, m/z 405, 403, 401 (M, 19:39:20), 326 (100). Anal. Calcd for $C_{15}H_{15}Br_2NS$: C, 44.91; H, 3.77; Br, 39.84; N, 3.49; S, 7.99. Found: C, 45.00; H, 3.80; Br, 39.75; N, 3.49; S, 7.96.

2-Acetylamino-3,3′,5,5′-tetrabromo-2′-propylthiobiphenyl (10, X = Br). A mixture of biphenyl **1a**, X = Br (30 mg, 0.05 mmol) and Ac_2O (1 mL) in benzene (5 mL) was refluxed overnight. Benzene was removed and the residue was purified by column chromatography (CH_2Cl_2) to give **10**, X = Br (24 mg, 74% yield) as a brown oil: ^{1}H NMR δ 0.79 (t, J = 7.3 Hz, 3H), 1.24−1.38 (m, 2H), 1.92 (s, 3H), 2.44−2.62 (m, 2H), 6.92 (s, 1H), 7.34 (d, J = 1.9 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.83−7.84 (m, 2H); IR 3239 (N−H), 1666 (C=O) cm^{-1}; EI-MS m/z 601 (M, 4), 43 (100).

2-Acetylamino-3′,5′-dibromo-3,5-diiodo-2′-propylthiobiphenyl (10, X = I). Amine **1a**, X = I (1.00 g, 1.53 mmol) was dissolved in pyridine (20 mL). Acetyl chloride (1.20 mL, 17 mmol) was added dropwise, immediately forming a precipitate. After being stirred overnight, the reaction mixture was passed through a silica gel plug (CH_2Cl_2), eluent washed with 1 M HCl, dried, and evaporated to give 2.33 g of a tan sticky solid. The crude product was purified by column chromatography (CH_2Cl_2:hexanes, 2:1) to give **10**, X = I (0.97 g, 91% yield) as a white powdery solid: mp 174−175 °C; ^{1}H NMR δ 0.79 (t, J = 7.3 Hz, 3H), 1.24−1.40 (m, 2H), 1.91 (s, 3H), 2.43−2.61 (m, 2H), 6.89 (s, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 1.6 Hz, 1H); ^{13}C NMR δ 13.1, 22.5, 23.2, 38.1, 92.8, 101.6, 122.7, 131.8, 132.7, 132.9, 135.8, 137.0, 138.9, 141.7, 146.0, 146.8, 167.9; IR (KBr) 3219 (N−H), 1664 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{15}Br_2I_2NOS$: C, 29.38; H, 2.18; N, 2.02. Found: C, 28.85; H, 2.08; N, 1.93.

2-Diacetylamino-3,3′,5,5′-tetrabromo-2′-propylthiobiphenyl (11, X = Br). 11, X = Br was obtained quantitaively as described for for **10**, X = Br, using catalytic amounts of concentrated H_2SO_4. An analytically pure sample of **11**, X = Br was obtained by column chromatography (CH_2Cl_2:hexanes, 2:1): ^{1}H NMR δ 0.98 (t, J = 7.2 Hz, 3H), 1.61 (sextet, J = 7.3 Hz, 2H), 2.03 (s, 3H), 2.43 (s, 3H), 2.81−2.93 (m, 2H), 7.27 (s, 1H), 7.44 (s, 1H), 7.85 (s, 1H), 7.90 (s, 1H); ^{13}C NMR δ 13.4, 22.4, 25.4, 26.5, 39.0, 122.2, 122.4, 125.6, 129.7, 131.4, 133.0, 133.8, 135.6, 135.7, 136.5, 142.2, 143.9, 171.0, 173.0; IR 1723 (C=O) cm^{-1}.

2-Diacetylamino-3′,5′-dibromo-3,5-diiodo-2′-propylthiobiphenyl (11, X = I). Amine **1a**, X = I (2.24 g, 3.6 mmol) was dissolved in dry benzene (100 mL). Pyridine (0.60 mL) was added followed by acetyl chloride (1.8 mL), and the reaction was stirred overnight at 50 °C. Volatiles were removed under vacuum. The residue was redissolved in CH_2Cl_2 and passed through a silica gel plug. The solvent was evaporated to yield 2.47 g of a brown oil that was purified by column

chromatography (CH_2Cl_2:hexanes, 2:1) to give **11**, X = I (2.09 g, 88% yield) as a light tan solid. Double recrystallization (hexanes:toluene) gave **11**, X = I as a white solid: mp 129−130 °C; ^{1}H NMR δ 1.00 (t, J = 7.3 Hz, 3H), 1.63 (sextet, J = 7.3 Hz, 2H), 2.02 (s, 3H), 2.45 (s, 3H), 2.82 (dt, J_1 = 11.4 Hz, J_2 = 7.3 Hz, 1H), 2.93 (dt, J_1 = 11.4 Hz, J_2 = 7.3 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 13.6, 22.6, 26.0, 27.1, 39.2, 94.1, 103.0, 122.5, 131.4, 133.2, 133.9, 136.6, 139.6, 140.8, 141.8, 144.2, 147.5, 171.1, 173.2; IR (KBr) 1722 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{17}Br_2I_2NO_2S$: C, 30.96; H, 2.32; N, 1.90; Br, 21.68; I, 34.44. Found: C, 31.14; H, 2.38; N, 1.82; Br, 21.77; I, 34.57.

3,3′,5,5′-Tetrabromo-2-nitro-2′-propylsulfonylbiphenyl (12). Amine **1a**, X = Br (789 mg, 1.41 mmol), $Bu_4N(HSO_4)$ (31 mg), Oxone (3.52 g, 5.63 mmol), CH_2Cl_2 (20 mL), and acetone (20 mL) were stirred at room temperature. Two products, sulfone and intermediate sulfoxide, were detected by GC/MS: EI-MS *m*/*z* for sulfoxide 579, 577, 575 (M, 55:42:10), and for sulfone 597, 595, 593, 591 (M, 20:13:4:1), 405 (100). The resulting mixture of products, H_2O_2 (50%, 1.0 mL), $(CF_3CO)_2O$ (6 mL), and CH_2Cl_2 (16 mL), was stirred for 6 h. The crude product was purified by column chromatography (CH_2Cl_2) to give product **12** (0.756 g, 87% yield based on amine **1a**, X = Br) as light yellow crystals: mp 49−50 °C; ^{1}H NMR δ 1.08 (t, J = 7.5 Hz, 3H), 1.82−1.95 (m, 2H), 3.28−3.38 (m, 1H), 3.58−3.68 (m, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 1.9 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H); ^{13}C NMR δ 13.0, 14.8, 56.3, 113.8, 123.7, 124.0, 127.2, 132.6, 134.0, 134.7, 135.8, 136.9, 137.7, 139.6, 147.5; IR 1538 and 1366 (NO_2) cm^{-1}; EI-MS *m*/*z* 579, 577, 575, 573, 571 (M − NO_2, 10:40:50:40:10), 533 (100). Anal. Calcd for $C_{15}H_{11}Br_4NO_4S$: C, 29.02; H, 1.79; Br, 51.46; N, 2.26; S, 5.16. Found: C, 28.93; H, 1.80; Br, 51.41; N, 2.20; S, 5.21.

2-Amino-3,3′,5,5′-tetrabromo-2′-trifluoroacetylaminobiphenyl (15). A mixture of $(CF_3CO)_2O$ (7.42 mL, 52.6 mmol) and anhydrous THF (5 mL) were added dropwise to a solution of diamine **14**[37,78] (21.92 g, 43.8 mmol) in a mixture of anhydrous pyridine (4.25 mL, 52.6 mmol) and THF (45 mL) at 0 °C, under N_2. The mixture was allowed to warm to room temperature and stirred for 4 h, then the dark red solution was evaporated to dryness. The black residue was dissolved in CH_2Cl_2, washed with water, and dried (Na_2SO_4) and the solvent was evaporated to give 28.20 g of a mixture of starting diamine **14**, monoamide **15**, and diamide **16**. The mixture was separated on a silica gel column (CH_2Cl_2:hexanes, 1:2) to give pure **14** (1.90 g) and a mixture of mono- and diprotected compounds, which was separated on alumina (EtOAc:hexanes, 1:7). The combined yield of **15** was 13.02 g (50%): mp 148−149 °C; ^{1}H NMR δ 4.08 (br s, 2H), 7.11 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 8.38 (br s, 1H); ^{13}C NMR δ 110.8, 111.3, 115.4 (q, J_{CF} = 288 Hz), 123.1, 124.1, 125.1, 130.4, 131.8, 133.1, 135.2, 136.1, 138.1, 140.0, 155.2 (q, J_{CF} = 38 Hz); IR (KBr) 3456, 3413, 3367, and 3327 (N−H), 1716 (C=O), 1615 and 1451 (C=C) cm^{-1}; EI-MS *m*/*z* 594, 596, 598 (M, 32:41:28), 483 (100). Anal. Calcd for $C_{14}H_7Br_4F_3N_2O$: C, 28.22, H, 1.18, N, 4.70. Found: C, 28.47; H, 1.21; N, 4.62.

3,3′,5,5′-Tetrabromo-2,2′-bis(trifluoroacetylamino)biphenyl (16). The compound was isolated as a byproduct in the synthesis of **15**: ^{1}H NMR δ 7.29 (d, J = 2.2 Hz, 2H), 7.89 (d, J = 2.1 Hz, 2H), 8.31 (br s, 2H); ^{13}C NMR δ 115.3 (q, J_{CF} = 288 Hz), 122.9 123.7, 129.9, 131.6, 136.8, 138.0, 156.4 (q, J_{CF} = 38 Hz); IR (KBr) 3294 (N−H), 1715 (C=O) cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_7Br_4F_6N_2O_2$ 688.7145, found 688.7155.

3,3′,5,5′-Tetrabromo-2′-trifluoroacetylamino-2-nitrobiphenyl (17). A solution of $(CF_3CO)_2O$ (5 mL, 35.4 mmol) in CH_2Cl_2 (10 mL) was slowly added to cooled H_2O_2 (47%, 2.5 g, 31.1 mmol). The mixture was stirred at 0 °C for 1.5 h and amine **15** (2.01 g, 3.38 mmol) in CH_2Cl_2 (10 mL) was added dropwise. When the starting material was no longer detected by TLC, water was added, and organics were extracted (CH_2Cl_2). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified on a silica gel column (EtOAc:hexanes, 1:10) to give **17** (3.13 g, 59% yield) as an off-white solid: mp 174−174.5 °C; ^{1}H NMR δ 7.43 (d, J = 2.1 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.87 (br s, 1H), 7.92−7.94 (m, 2H); ^{13}C NMR δ 114.0, 115.3 (q, J_{CF} = 288 Hz), 123.4, 124.3, 124.9, 130.2, 131.7, 132.4, 132.8, 135.9, 136.8, 137.2, 148.8, 155.6 (q, J_{CF} = 39 Hz); IR (KBr) 3273 (N−H) 1740 and 1721 (C=O), 1543 and 1368 (NO_2) cm^{-1}; EI-MS *m*/*z* 578, 580, 582 (M −NO_2, 82:100:78). Anal. Calcd for $C_{14}H_5Br_4F_3N_2O_3$: C, 26.87, H, 0.81, N, 4.48, Br, 51.07. Found: C, 27.17; H, 0.90; N, 4.31; Br, 50.87.

2-Amino-3,3′,5,5′-tetrabromo-2′-nitrobiphenyl (18). A mixture of amide **17** (1.4 g, 2.24 mmol), *i*-PrOH (30 mL), K_2CO_3 (2 g), and water (6 mL) was stirred and refluxed until no starting material remained by TLC. Water was added, and organics were extracted with EtOAc. After drying (Na_2SO_4) the solvent was removed. The residue was separated on a column (EtOAc:hexanes, 1:10) giving **18** (1.2 g, 88% yield): mp 189−190 °C; ^{1}H NMR δ 4.08 (br s, 2H), 7.06 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.92 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ 109.3, 110.5, 114.7, 120.8, 124.9, 131.3, 132.8, 133.5, 135.9, 136.3, 141.2, 150.2; IR 3484 and 3393 (N−H), 1614 and 1460 (C=C), 1540 and 1370 (NO_2) cm^{-1}; EI MS *m*/*z* 534, 532, 530, 528, 526 (M, 18:78:100:83:19). Anal. Calcd for $C_{12}H_6Br_4N_2O_2$: C, 27.20, H, 1.14, N, 5.29, Br, 60.33. Found; C, 27.47; H, 1.18; N, 5.31; Br, 60.31.

3,5-Dibromo-6-propylthiophenylboronic Acid (20). A 2.5 M solution of *n*-BuLi in hexane (8.6 mL, 3.4 mmol) was added dropwise to a stirred solution of tribromide **24** (7.96 g, 20.5 mmol) in dry ether (130 mL) under N_2 at −78 °C. After 2 h, a cooled (−78 °C) solution of $B(OMe)_3$ (3.5 mL, 30.8 mmol) in dry ether (30 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. HCl (10%, 60 mL) was added and the mixture was stirred for 1.5 h. The product was extracted with ether and the extracts were dried (Na_2SO_4). The solvent was removed and the product was purified on a silica gel plug, eluted first with hexane to remove nonpolar impurities, followed by EtOAc to give acid **20** (6.60 g, 91% yield) as a yellowish solid. An analytical sample of acid **20** was prepared by recrystallization from hexane: mp 97−98 °C; ^{1}H NMR δ 0.99 (t, J = 7.3 Hz, 3H), 1.62 (sextet, J = 7.3 Hz, 2H), 2.85 (t, J = 7.5 Hz, 2H), 7.16 (br s, 2H), 7.91 (d, J = 2.1 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 13.5, 22.8, 39.4, 123.9, 133.0, 138.2, 138.3, 138.8 (the ^{13}C−B signal was not located); IR 3389 and 3248 (O−H), 1321 (B−O) cm^{-1}. Anal. Calcd for $C_9H_{11}BBr_2O_2S$: C, 30.55, H, 3.13. Found; C, 31.43; H, 3.26.

2,4-Dibromo-6-iodonitrobenzene (23). A solution of aniline **25** (9.42 g, 25 mmol) in CH_2Cl_2 (50 mL) was added dropwise to CF_3CO_3H (0.25 mol) in CH_2Cl_2 (100 mL) prepared as described for **17**. The reaction mixture was gently refluxed overnight, cooled, poured into water, and extracted with CH_2Cl_2. The combined extracts were washed with a solution of 5% $NaHCO_3$ and dried (Na_2SO_4). The solvent was evaporated and the residue was purified on a silica gel plug (hexanes:CH_2Cl_2, 2:1) to give **23** (7.22 g, 71% yield) as brown crystals. The product was used without further purification. An analytical sample of **23** was obtained by purification on a short silica gel column (hexanes) to yield white crystals: mp 141−142 °C; ^{1}H NMR δ 7.81 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 86.2, 113.4, 124.7, 136.0, 141.2, 154.3; IR (KBr) 1537 and 1367 (NO_2) cm^{-1}; EI-MS *m*/*z* 409, 407, 405 (M, 52:100:54). Anal. Calcd for $C_6H_2Br_2INO_2$: C, 17.72; H, 0.50; N, 3.44. Found: C, 17.96; H, 0.62, N, 3.40.

2,4,6-Tribromopropylthiobenzene (24). 2,4,6-Tribromoaniline (19.79 g, 60 mmol) was suspended in concentrated HCl (120 mL) and heated at 70 °C for 0.5 h. The suspension was cooled to room temperature and poured into ice−water (300

(78) Berthon, J.-L.; Dias, M.; Mornet, R.; Camadro, J.-M. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 515−522.

mL). The anilinium salt was diazotized then converted to the corresponding xanthate[42] and subsequently to the product by using the procedure described for **8**. The product was purified by vacuum distillation (130 °C/0.01 Torr) to give **24** (15.45 g, 66% yield) as a pale yellow oil: ^{1}H NMR δ 1.02 (t, J = 7.3 Hz, 3H), 1.60 (sextet, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 7.77 (s, 2H); ^{13}C NMR δ 13.5, 22.9, 38.2, 122.9, 132.4, 135.0, 136.3; EI-MS m/z 392, 390, 388, 386 (M, 13:47:46:13), 346 (100). Anal. Calcd for $C_9H_9Br_3S$: C, 27.79, H, 2.33. Found: C, 27.60, H, 2.35.

2,4-Dibromo-6-iodoaniline[43] **(25).** A solution of ICl (2.03 g, 125 mmol) in AcOH (40 mL) was added to 2,4-dibromoaniline (2.03 g, 10 mmol) in AcOH (100 mL) at 60 °C under N_2. The dark brown solution was stirred at 60 °C for 5 min followed by the rapid addition of water (300 mL) to form a precipitate. The temperature of the well-stirred reaction mixture was gradually raised to 90 °C and maintained for 50 min. The mixture was allowed to cool to room temperature. The product was filtered off, washed with water, and dried in air. The crude product was purified on a silica gel plug (CH_2Cl_2:hexanes, 1:1) to give aniline **25** (2.74 g, 90% yield) as dark brown crystals which were used without further purification. An analytical sample of **25** was obtained by purification on a short silica gel column (hexanes) to yield white crystals: mp 121−122 °C (lit.[43] mp 124−125 °C); ^{1}H NMR δ 4.60 (br s, 2H), 7.53 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H); EI-MS m/z 379, 377, 375 (M, 48:100:50).

2,2′-Diamino-6,6′-bis(propylthio)biphenyl (27). Biphenyl **29** (1.21 g, 3.0 mmol) was dissolved in dry EtOH with heating. Concentrated HCl (10 mL) was added to the solution followed by portionwise addition of fresh $SnCl_2 \cdot 2H_2O$ (3.96 g, 17.6 mmol). Stirring was continued for 2 h at reflux. The mixture was cooled and alkalized by the addition of a sufficient amount of aq NaOH. The organic components were extracted with ether and the combined extracts were dried (Na_2SO_4). The solvent was removed and the residue separated on a silica gel column (CH_2Cl_2:hexanes in 1:1, followed by CH_2Cl_2: hexanes, 2:1, followed by CH_2Cl_2) to give diamine **27** (0.75 g, 77% yield) as a light yellow oil, which gradually solidified upon standing: mp 77−78 °C; ^{1}H NMR δ 0.96 (t, J = 7.4 Hz, 6H), 1.63 (sextet, J = 7.4 Hz, 4H), 2.79 (t, J = 7.4 Hz, 4H), 3.53 (br s, 4H), 6.58 (dd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 2H), 6.74 (dd, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 2H), 7.15 (t, J = 7.9 Hz, 2H); ^{13}C NMR δ 13.6, 22.1, 33.8, 112.1, 115.6, 119.6, 129.4, 139.1, 144.9; IR 3459 and 3361 (N−H), 1608 and 1452 (C═C) cm^{-1}; EI-MS, m/z 332 (M, 24), 214 (100). Anal. Calcd for $C_{18}H_{24}N_2S_2$: C, 65.02; H, 7.27; N, 8.42. Found: C, 65.18; H, 7.22; N, 8.49.

1-Bromo-2-nitro-6-propylthiobenzene (30b). Aniline **31b** (3.4 g, 15.7 mmol) was converted to the sulfide **30b** as described for the prepration of **41a** with use of concentrated HBr instead of HCl and stirring at 75 °C for 20 h. The crude product was separated on a silica gel plug (hexanes:CH_2Cl_2, 4:1) to give **30b** (2.35 g, 54% yield) as a pale yellow oil that solidified upon standing: mp 45−46 °C; ^{1}H NMR δ 1.10 (t, J = 7.4 Hz, 3H), 1.78 (sextet, J = 7.3 Hz, 2H), 2.96 (t, J = 7.3 Hz, 2H), 7.33 (dd, J_1 = 7.6 Hz, J_2 = 2.2 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.43 (dd, J_1 = 7.7 Hz, J_2 = 2.2 Hz, 1H); ^{13}C NMR δ 13.6, 21.5, 35.0, 113.2, 120.3, 127.9, 128.6, 143.4, 151.5; IR 1533 and 1362 (NO_2) cm^{-1}; EI-MS, m/z 277, 275 (M, 80, 78), 235, 233 (100). Anal. Calcd for $C_9H_{10}BrNO_2S$: C, 39.15; H, 3.65; N, 5.07. Found: C, 39.28; H, 3.61; N, 5.22.

1-Bromo-3,5-dichloro-6-propylthio-2-nitrobenzene (32). Solid $NaNO_2$ (0.74 g, 10.8 mmol) was added in small portions over a period of 15 min to a well-stirred mixture of concentrated H_2SO_4 (20 mL) and water (10 mL) at −5 °C. Subsequently, a solution of amine **35** (1.14 g, 4.0 mmol) in AcOH (40 mL) was added over 1.5 h at −10 °C. The resulting mixture was stirred for 2 h, during which the temperature was allowed to rise to 5 °C. The mixture was treated with a solution of NaOH (1.5 g, 37.5 mmol), water (10 mL), and 1-propanethiol (2.0 mL, 22 mmol). The stirred reaction mixture was allowed to warm to room temperature. MeCN (40 mL) was added and the solution was refluxed overnight until the intermediate 1-bromo-3,5-dichloro-6-propylthioazo-2-nitrobenzene (^{1}H NMR δ 1.08 (t, J = 7.3 Hz, 3H), 1.96 (sextet, J = 7.2 Hz, 2H), 3.75 (t, J = 7.1 Hz, 2H), 7.63 (s, 1H)) was no longer detected. Upon cooling the organics were extracted with CH_2Cl_2, the extracts washed with 5% NaOH and then with water and dried (Na_2SO_4), and the solvent evaporated. The residue was purified by column chromatography (hexanes) to give **32** (1.20 g, 87% yield) as a light-yellow oil: ^{1}H NMR δ 1.02 (t, J = 7.3 Hz, 3H), 1.60 (sextet, J = 7.3 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR δ 13.4, 23.1, 38.1, 123.8, 126.0, 130.2, 137.3, 142.6, 149.5; IR 1548 and 1359 (NO_2) cm^{-1}; EI-MS m/z 349, 347, 345, 343 (M, 4:33:67:40), 303 (100). Anal. Calcd for $C_9H_8BrCl_2NO_2S$: C, 31.33; H, 2.34; N, 4.06. Found: C, 31.54; H, 2.30; N, 4.02.

2,4-Dichloro-5-nitroaniline[79] **(34).** Iron powder (8.96 g, 0.16 mol) was added in portions to a solution of 1,3-dichloro-4,6-dinitrobenzene (**33**, 19.96 g, 0.084 mol) in AcOH (250 mL) at 110 °C. The reaction mixture was refluxed for 2.5 h and poured into cold water (300 mL), and the precipitate was collected and washed with cold water. The crude product was dried and then recrystallized from a mixture of benzene and hexanes to give 10.4 g (60% yield) of a yellow solid: mp 101−102 °C (lit.[79] mp 104−105 °C); ^{1}H NMR δ 4.38 (br s, 2H), 7.30 (s, 1H), 7.42 (s, 1H); EI-MS m/z 210, 208, 206 (M, 10:63:98), 160 (100).

2-Bromo-4,6-dichloro-3-nitroaniline (35). Amine **34** (0.91 g, 4.4 mmol) was treated with Br_2 (5.8 mmol) in AcOH (15 mL) as described for **1a**, X = Br. The crude product was recrystallized (EtOH) to give aniline **35** (1.22 g, 97% yield) as yellow crystals: mp 106−107 °C; ^{1}H NMR δ 4.83 (br s, 2H), 7.41 (s, 1H); ^{13}C NMR δ 99.7, 112.9, 120.1, 129.3, 141.5; IR (KBr) 3482 and 3384 (N−H), 1618 and 1465 (C═C), 1535 and 1359 (NO_2) cm^{-1}; EI-MS m/z 290, 288, 286, 284 (M, 6:45:100:63), 240 (100). Anal. Calcd for $C_6H_3Cl_2N_2O_2$: C, 25.21; H, 1.06; N, 9.80. Found: C, 25.29; H, 1.18; N, 9.63.

4,6-Dichloro-2-iodo-3-nitroaniline (37). A mixture of aniline **34** (3.0 g, 8.2 mmol), AcOH (10 mL), H_2SO_4 (0.5 mL), HIO_3 (0.620 g, 3.5 mmol), I_2 (1.58 g, 6.2 mmol), and CCl_4 (1.25 mL) was stirred overnight at 80 °C. The resulting reaction mixture was treated with a 10% solution of $Na_2S_2O_5$, cooled, filtered, and washed with water. The crude material was passed through a silica gel plug (CH_2Cl_2). The solvent was removed to give aniline **37** (2.8 g, 59% yield) as yellow-brown crystals: mp 97−98 °C; ^{1}H NMR δ 4.91 (br s, 2H), 7.42, (s, 1H); ^{13}C NMR δ 74.3, 112.4, 118.5, 130.2, 137.5, 144.1; IR (KBr) 3483 and 3382 (N−H), 1531 and 1367 (NO_2), 1606 and 1450 (C═C) cm^{-1}; EI-MS m/z 332, 334, 336 (M,100:65:14). Anal. Calcd for $C_6H_3Cl_2IN_2$: C, 21.65; H, 0.91; N, 8.41. Found: C, 22.38; H, 0.86; N, 8.53.

2,2′-Dinitro-6,6′-bis(propylthio)biphenyl-4,4′-dicarboxylic Acid (39). A solution of diester **40** (300 mg, 0.59 mmol) in AcOH (8 mL) and concentrated HCl (8 mL) was refluxed overnight and poured into water. The precipitate was filtered, washed with water, and dried under vacuum to give diacid **39** (216 mg, 76% yield) as a yellow powder: mp 244−245 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.4 Hz, 6H), 1.53 (sextet, J = 7.2 Hz, 4H), 3.04 (t, J = 6.9 Hz, 4H), 8.23 (d, J = 1.4 Hz, 2H), 8.45 (d, J = 1.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 13.0, 21.1, 33.5, 121.4, 131.1, 132.0, 132.9, 141.1, 147.7, 165.0; IR 1699 (C═O), 1526 and 1343 (NO_2) cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_8S_2$: C, 49.99; H, 4.20; N, 5.83. Found: C, 49.73; H, 4.12; N, 5.84.

Dimethyl 2,2′-Dinitro-6,6′-bis(propylthio)biphenyl-4,4′-dicarboxylate (40). A mixture of freshly activated Cu powder (1.2 g), ester **41a** (1.22 g, 4.22 mmol), and 5-*tert*-butyl-*m*-xylene (10 mL) was refluxed overnight under N_2. Copper was filtered off and the solvent removed under reduced pressure. The product was then purified on a silica gel column (CH_2Cl_2:

(79) Theodoridis, G.; Manfredi, M. C.; Krebs, J. D. *Tetrahedron Lett.* **1990**, *31*, 6141−6144.

hexanes, 2:1) to give 480 mg (45% yield) of a yellow-brown oil. Analogous reaction of the bromo ester **41b** in xylenes gave diester **40** in 59% yield: ^{1}H NMR δ 0.93 (t, J = 7.4 Hz, 6H), 1.58 (sextet, J = 7.2 Hz, 4H), 2.89 (t, J = 7.2 Hz, 4H), 3.99 (s, 6H), 8.20 (d, J = 1.2 Hz, 2H), 8.62 (d, J = 1.3 Hz, 2H); ^{13}C NMR δ 13.4, 21.6, 34.9, 52.9, 122.2, 131.5, 131.6, 133.6, 141.6, 147.6, 164.6; EI-MS m/z 508 (M, 23), 287 (100); IR 1729 (C=O), 1532 and 1347 (NO_2) 1272 (C−O) cm^{-1}; HRMS (FAB+) m/z calcd for $C_{22}H_{25}N_2O_8S_2$ $[M + H]^+$ 509.1052, found 509.1064. Anal. Calcd for $C_{22}H_{24}N_2O_8S_2$: C, 51.96; H, 4.76; N, 5.51. Found: C, 51.68; H, 4.73; N, 5.36.

Methyl 4-Chloro-3-nitro-5-propylthiobenzoate (41a). A mixture of concentrated HCl (28 mL) and amino ester **43a** (3.35 g, 13.9 mmol) was heated for 30 min at 75 °C. The mixture was cooled in an ice bath and a solution of $NaNO_2$ (1.25 g, 18.5 mmol) in water (5 mL) was added dropwise. At this point all solid dissolved and the solution was stirred for and additional 0.5 h. The mixture was then vacuum filtered and the filtrate was rapidly added to a stirred solution of NaOH (0.9 g, 22.5 mmol) and 1-propanethiol (1.20 g, 15.9 mmol) in water (20 mL) containing $Ni(OAc)_2$ (0.10 g). The resulting mixture was stirred overnight at about 90 °C and poured into water, and the organics were extracted (CH_2Cl_2). The extracts were dried ($MgSO_4$), solvents were removed, and the product was purified on a silica gel column (CH_2Cl_2:hexanes 3:1) and recrystallized from MeOH to give **41a** (1.55 g, 37% yield) as a yellow solid: mp 45−46 °C; ^{1}H NMR δ 1.12 (t, J = 7.3 Hz, 3H), 1.80 (sextet, J = 7.3 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 3.98 (s, 3H), 8.00 (d, J = 1.8 Hz, 1H), 8.12 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ 13.5, 21.5, 34.4, 53.0, 121.2, 128.0, 129.0, 129.3, 142.6, 149.0, 164.3; EI-MS m/z 289, 291 (M, 80:23), 247 (100); IR 1731 (C=O), 1540 and 1356 (NO_2) cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.17; N, 4.83. Found: C, 45.60; H, 4.15; N, 4.87.

Methyl 4-Bromo-3-nitro-5-propylthiobenzoate (41b). The ester was obtained in an analogous procedure for the preparation of **41a** by starting from **43b** (369 mg, 1.3 mmol) and substituting HBr for HCl. The crude product was purified on a silica gel column (hexanes:CH_2Cl_2, 3:2) to give ester **41b** (189 mg, 42% yield) as a pale yellow solid: mp 84−85 °C; ^{1}H NMR δ 1.10 (t, J = 7.3 Hz, 3H), 1.78 (sextet, J = 7.3 Hz, 2H), 3.00 (t, J = 7.3 Hz, 2H), 3.94 (s, 3H), 7.91 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ 13.6, 21.4, 35.0, 52.3, 117.8, 120.8, 128.4, 130.1, 144.7, 151.4, 164.5; IR 1729 (C=O), 1541 and 1362 (NO_2) cm^{-1}; EI-MS m/z 335, 333 (M, 66:67), 293, 291 (100:100). Anal. Calcd for $C_{11}H_{12}BrNO_4S$: C, 39.53; H, 3.62; N, 4.19. Found: C, 39.60; H, 3.63; N, 4.07.

Methyl 3-Amino-4-chloro-5-nitrobenzoate (43a). Reduction of **42a** with Fe powder as described for the preparation of **34** gave amine **43a** in 68% yield as feathery yellow crystals: mp 154−155 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 6.42 (br s, 2H), 7.54 (d, J = 1.3 Hz, 1H), 7.64 (d, J = 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 52.6, 111.0, 111.2, 118.0, 129.1, 147.2, 149.0, 164.4; EI-MS m/z 230, 232 (M, 100:35); IR 3495 and 3389 (N−H), 1719 (C=O), 1532 and 1358 (NO_2) cm^{-1}. Anal. Calcd for $C_8H_7ClN_2O_4$: C, 41.74; H, 3.07; N 12.18. Found: C, 41.55; H, 3.03; N, 12.15.

Methyl 3-Amino-4-bromo-5-nitrobenzoate (43b). Reduction of **42b** with Fe powder as described for the preparation of **34** gave amine **43b** in 64% yield: mp 148−149 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 6.34 (br s, 3H), 7.45 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 52.9, 101.5, 111.1, 117.7, 130.1, 148.7, 151.7, 164.8; EI-MS m/z 274, 276 (M, 100:95); IR 3487 and 3385 (N−H), 1721 (C=O), 1530 and 1337 (NO_2) cm^{-1}. Anal. Calcd for $C_8H_7BrN_2O_4$: C, 35.04; H, 2.58; N, 10.22. Found: C, 35.20; H, 2.53; N, 10.05.

3,5-Dibromo-2′,6′-dinitro-2,6-bis(propylthio)biphenyl (44a). A mixture of 1,3-dibromo-5-iodo-4,6-bispropylthiobenzene[58] (**45a**, 98 mg, 0.2 mmol), 1-chloro-2,6-dinitrobenzene (39 mg, 0.2 mmol), freshly activated Cu powder (12 mg, 0.2 mmol), and dry xylenes (5 mL) was stirred overnight under N_2 at 100 °C. The reaction mixture was poured into 6 M HCl (50 mL) and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and the solvent removed. The crude product was purified on a silica gel column (CH_2Cl_2:hexanes, 1:1) to give **44a** (13 mg, 12% yield) as a viscous yellow oil: ^{1}H NMR δ 0.80 (t, J = 7.3 Hz, 6H), 1.41 (sextet, J = 7.3 Hz, 4H), 2.65 (t, J = 7.3 Hz, 4H), 7.74 (t, J = 8.2 Hz, 1H), 8.03 (s, 1H), 8.33 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 13.3, 22.5, 38.2, 128.7, 129.4, 131.9, 132.3, 135.1, 137.7, 145.8, 149.0; IR 1535 and 1344 (NO_2) cm^{-1}; EI-MS m/z 548 (M, 13), 212 (100). Anal. Calcd for $C_{18}H_{18}Br_2N_2O_4S_2$: C, 39.29; H, 3.30; N, 5.09. Found: C, 39.52; H, 3.50; N, 4.91.

3,5-Dichloro-2′,6′-dinitro-2,6-bis(propylthio)biphenyl (44b). A mixture of 1,3-dichloro-5-iodo-4,6-bispropylthiobenzene[58] (**45b**, 1.10 g, 2.6 mmol), 1-chloro-2,6-dinitrobenzene (635 mg, 3.1 mmol), freshly activated Cu powder (650 mg, 10.2 mmol), and dry xylenes (5 mL) was refluxed for 3 h under N_2. The cooled mixture was passed through a silica gel plug (CH_2Cl_2:hexanes, 1:1). The solvent was removed and the product was purified on a silica gel column (CH_2Cl_2:hexanes, 1:1) to give **44b** (420 mg, 35% yield) as a yellow oil: ^{1}H NMR δ 0.80 (t, J = 7.3 Hz, 6H), 1.41 (sextet, J = 7.3 Hz, 4H), 2.65 (t, J = 7.3 Hz, 4H), 7.65 (s, 1H), 7.74 (t, J = 8.2 Hz, 1H), 8.32 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 13.3, 22.5, 37.8, 128.7, 129.5, 131.4, 132.7, 141.0, 145.5, 149.1; IR 1535 and 1346 (NO_2) cm^{-1}; EI-MS m/z 464, 462, 460 (M, 5:14:24), 300 (100). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_4S_2$: C, 46.86; H, 3.93; N, 6.07. Found: C, 46.69; H, 3.87; N, 5.82.

2′-Amino-3,5-dichloro-6′-nitro-2,6-bis(propylthio)biphenyl (48). A solution of fresh $Na_2S{\cdot}9H_2O$ (584 mg, 2.4 mmol) in 2 M NaOH (5 mL) was added in one portion to a solution of biphenyl **44b** (460 mg, 1.0 mmol) in EtOH (10 mL), and the mixture was stirred at 90 °C for 2 h. The reaction mixture was poured into water (200 mL) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and the solvent was removed. The crude material was purified by column chromatography (CH_2Cl_2:hexanes, 3:2) to give amine **48** (350 mg, 81% yield) as a bright yellow solid: mp 97−98 °C; ^{1}H NMR δ 0.82 (t, J = 7.3 Hz, 6H), 1.43 (sextet, J = 7.3 Hz, 4H), 2.60 (dt, J_1 = 11.8 Hz, J_2 = 7.3 Hz, 2H), 2.72 (dt, J_1 = 11.8 Hz, J_2 = 7.3 Hz, 2H), 3.61 (br s, 2H), 7.00 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.58 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 1H), 7.67 (s, 1H); ^{13}C NMR δ 13.2, 22.6, 37.6, 114.0, 120.1, 121.4, 128.9, 130.7, 133.5, 141.4, 145.4, 148.0; EI-MS m/z 430 (M, 1), 267 (100). Anal. Calcd for $C_{18}H_{20}Cl_2N_2O_2S_2$: C, 50.11; H, 4.67; N, 6.49. Found: C, 50.24; H, 4.68; N, 6.56.

1,3,5-Tribromo-2,6-bis(propylthio)benzene (50). A solution of diamine **54** (6.9 g, 20 mmol) in THF (100 mL) was slowly added to $BF_3{\cdot}Et_2O$ (8.52 g, 60 mmol) at −15 °C. Subsequently, a solution of *t*-BuONO (4.94 g, 0.048 mol) in THF (10 mL) was added dropwise to the rapidly stirred reaction mixture over 10 min. The temperature of the reaction mixture was maintained at −15 °C for 10 min and then allowed to warm to 5 °C in an ice−water bath over a 30-min period during which a precipitate formed. Hexane was added and the precipitate filtered, washed with cold ether, and air-dried to give the diazonium salt **55** (7.35 g, 83% yield) as a red solid: ^{1}H NMR (DMSO-d_6) δ 6.96 (br s, 2H), 8.51 (s, 1H). To a solution of salt **55** (5.6 g, 12.6 mmol) in MeCN (100 mL) was added a mixture of NaOH (0.6 g, 15 mmol), water (5 mL), and 1-propanethiol (1.14 g, 15 mmol) at 0 °C with reflux overnight. The reaction was cooled, CH_2Cl_2 was added, and the organics were washed with water and dried (Na_2SO_4). Solvent was removed and the residue was purified by column chromatography (hexanes) to give aniline **57** (2.1 g, 41% yield) as a viscous oil: ^{1}H NMR δ 1.01 (t, J = 7.3 Hz, 3H), 1.59 (sextet, J = 7.4 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 4.7 (br s, 2H), 7.70 (s, 1H).

The above procedure was repeated with amine **57** (2.1 g, 5.2 mmol). Decomposition of the intermediate 1,3,5-tribromo-2-propylthio-6-propylthioazobenzene was monitored by NMR (^{1}H NMR δ 0.99 (t, J = 7.3 Hz, 3H), 1.07 (t, J = 7.3 Hz, 3H),

1.61 (sextet, $J = 7.4$ Hz, 2H), 1.83 (sextet, $J = 7.3$ Hz, 2H), 2.89 (t, $J = 7.2$ Hz, 2H), 3.40 (t, $J = 7.1$ Hz, 2H), 7.90 (s, 1H)). The resulting product was purified by column chromatography (hexanes) to give **50** (1.22 g, 51% yield) as an oil: ^{1}H NMR δ 1.00 (t, $J = 7.3$ Hz, 6H), 1.58 (sextet, $J = 7.3$ Hz, 4H), 2.88 (t, $J = 7.3$ Hz, 4H), 7.95 (s, 1H); ^{13}C NMR δ 13.6, 22.9, 38.4, 132.0, 135.9, 138.1, 141.8; EI-MS *m*/*z* 466, 464, 462, 460 (M, 33:100: 98:30), 380 and 378 (100:98). Anal. Calcd for $C_{12}H_{15}Br_3S_2$: C, 31.12; H, 3.26. Found: C, 31.42; H, 3.31.

1-Bromo-3,5-dichloro-2,6-dinitrobenzene (51). Aniline **35** was oxidized in a manner similar to the preparation of **17**. The product was recrystallized from EtOH to give **51** in 95% yield as white needles: mp 164−165 °C; ^{1}H NMR δ 7.73 (s); ^{13}C NMR δ 108.3, 128.5, 131.4 (C−NO_2 not observed); IR (KBr) 1544 and 1350 (NO_2) cm^{-1}; EI-MS *m*/*z* 320, 318, 316, 314 (M, 6:46:100:64). Anal. Calcd for $C_6HBrCl_2N_2O_4$: C, 22.81; H, 0.32; N, 8.87. Found: C, 22.90; H, 0.43, N, 8.74.

3,5-Dichloro-4′-nitro-2,6-(bispropylthio)biphenyl (53). Under argon, *n*-BuLi (2.5 M, 0.1 mL, 0.25 mmol) was added to iodide **45b** (105 mg, 0.25 mmol) in dry THF (0.5 mL) at −78 °C and the solution was stirred for 0.5 h. Then, $ZnCl_2$ (0.5 M in THF, 0.6 mL, 0.30 mmol) was added and the mixture was allowed to warm to room temperature over a 0.5-h period and stirred for an additional 0.5 h. Commercial dry *N*-methyl-2-pyrrolidinone (NMP, 0.5 mL) was added, followed after 5 min by 1-iodo-4-nitrobenzene (62 mg, 0.25 mmol) and Pd(*t*-$Bu_3P)_2$ (20 mg, 0.04 mmol) in a minimal amount of NMP. The reaction was stirred overnight at 100 °C. The mixture was allowed to cool to room temperature and HCl (3 M, 2 mL) was added, and the organics were extracted (CH_2Cl_2) and dried (Na_2SO_4). The crude product was passed through a silica gel plug (CH_2Cl_2) and separated on Chromatotron (CH_2Cl_2:hexanes, 1:4). The main fraction (50 mg) contained approximately 75% of **53**: ^{1}H NMR (main signals) δ 0.80 (t, $J = 7.3$ Hz, 6H), 1.33 (sextet, $J = 7.3$ Hz, 4H), 2.58 (t, $J = 7.3$ Hz, 4H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.69 (s, 1H), 8.30 (d, $J = 8.8$ Hz, 2H); EI-MS *m*/*z* 419, 417, 415 (M, 12, 59, 69), 284 (90), 248 (100); HRMS (FAB+) calcd for $C_{18}H_{19}Cl_2NO_2S_2$ 415.0234, found 415.0209.

Dimethyl 2,2′,6′-Trinitro-6-propylthiobiphenyl-4,4′-dicarboxylate (58). A mixture of activated Cu powder (350 mg, 5.5 mmol), bromo ester **41b** (175 mg, 0.5 mmol), chloro ester **42a** (200 mg, 7.7 mmol), and 5-*tert*-butyl-*m*-xylene was stirred at 200 °C for 3 h. The solvent was removed under reduced pressure and the residue was passed through a silica gel plug (CH_2Cl_2:hexanes, 1:1) to give 131 mg of a mixture of three coupling products. On the basis of matching intensities, comparison with authentic sample, and literature data, the aromatic protons in the ^{1}H NMR spectrum were assigned to diester **58** [^{1}H NMR δ 4.00 (s, 3H), 4.05 (s, 3H), 8.18 (d, $J = 1.4$ Hz, 2H), 9.02 (s, 2H)], dimethyl 2,2′,6,6′-tetranitrobiphenyl-4,4′-dicarboxylate (**59**) [^{1}H NMR δ 4.07 (s, 6H), 9.09 (s, 4H) (lit.[80] ^{1}H NMR (60 MHz) δ 4.2 (s, 6H) and 9.35 (s, 4H))], and diester **40** [^{1}H NMR δ 3.99 (s, 6H), 8.20 (d, $J = 1.4$ Hz, 2H), 8.61 (d, $J = 1.4$ Hz, 2H)]. The propyl group protons are located at δ 0.89−0.96, 1.50−1.63, and 2.85−2.92 ppm. The molar ratio of the three components is 4:3:1. HRMS (FAB+) *m*/*z* calcd for $C_{19}H_{17}N_3O_{10}S$ 479.0635, found 479.0618.

Acknowledgment. This project has been supported in part by the NSF grants (CHE-9703002 and CHE-0096827). J.M.F. was the recipient of a GAANN fellowship. We thank Mr. Kristopher B. McNeil for his technical assistance with the preparation of compound **41a**.

Supporting Information Available: General experimental procedures, full experimental details, and characterization for known compounds (**5**, **6**, **21**, **29**, **31b**, **42a**, **42b**, and **54**) and isolated byproducts (**22**, **28 46**, **47**, and **52**), and attempted preparation of **4b** (X = Cl, X′ = Br) and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030212P

(80) Castle, R. N.; Guither, W. D.; Hilbert, P.; Kempter, F. E.; Patel, N. R. *J. Heterocycl. Chem.* **1969**, *6*, 533−538.