Synthesis of 2,2′,6-Trisubstituted and 2,2′,6,6′-Tetrasubstituted Diaryl Sulfides and Diaryl Sulfones by Copper-Promoted Coupling and/or Ortholithiation

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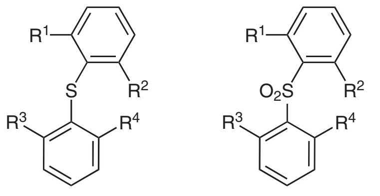
Abstract: Stoichiometric copper(I) iodide, in the presence of potassium carbonate and ethylene glycol, promotes the coupling of even highly sterically encumbered 2,6-disubstituted thiophenols and aryl iodides to form hindered diarylsulfides. Hindered diarylsulfones may be made in a complementary fashion by ortholithiation of the sulfone oxidation products of less hindered diarylsulfides.

Key words: copper, Ullmann, coupling, sulfide, sulfone, lithiation

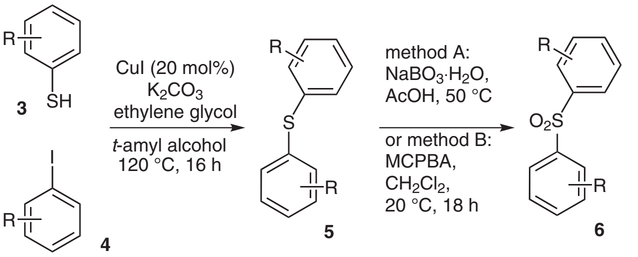
In connection with studies on the stereochemical properties[1] of potentially atropisomeric sulfur compounds,[2] we required a supply of various hindered (i.e. tri or tetra-*ortho*-substituted) diarylsulfides **1** and diarylsulfones **2** (Figure 1). A recently reported method[3] employs Cu(I) to catalyse the Ullmann-style coupling of thiophenols (and other thiols) with aryl halides.[4] However, this method was used only to make relatively unhindered sulfides bearing one or two groups *ortho* to the sulfur atom, and no examples were reported with either coupling partner being 2,6-disubstituted. In this paper we report an extension of Buchwald's method to the synthesis of more heavily substituted diarylsulfides and diarylsulfones either by increasing the quantity of metal used or by oxidation of the sulfide coupling products to sulfones and subsequent directed ortholithiation.[5] The only previous synthesis of a 2,2′,6,6′-tetraalkyl (in fact, tetramethyl) diaryl sulfide by direct coupling employed the sodium thiolate with CuI in the presence of toxic HMPA.[4n]



1 **2**

Figure 1 Hindered diarylsulfides **1** and diarylsulfones **2**

Precursors for lithiation in the form of less hindered 2,2′-disubstituted diarylsulfides **5** were made from thiols **3** and iodides **4** by the method of Buchwald et al.[3] and oxidised to the corresponding sulfones **6**. Sodium perborate in acetic acid at 50 °C[6] was found to be a reliable reagent for the transformation in all the but the most hindered systems, such as **5c**, for which MCPBA was required to ensure oxidation of the intermediate sulfoxide (Scheme 1).



5a R = Et 96%	**6a** R = Et 86% (method A)
5b R = *i*-Pr 91%	**6b** R = *i*-Pr 85%, 85% (method A, B)
5c R = *t*-Bu 88%	**6c** R = *t*-Bu 0%[b], 65% (method A, B)
5d R = 2,3-benzo[a] 90%	**6d** R = 2,3-benzo[a] 83% (method A)

Scheme 1 Synthesis of 2,2′disubstituted sulfones by coupling and oxidation. [a] 1-Naphthyl; [b] Method A gave the sulfoxide in 90% yield

The 2,2′-bis-*t*-butyl sulfone **6c** was successfully monolithiated and quenched with a range of electrophiles[6–8] to give 2,2′,6-tri-orthosubstituted sulfones **7a**–**d** as shown in Scheme 2. Yields were good in all cases.

Further attempted lithiations of **7** were unsuccessful, as was the attempted one-pot double lithiation of either **6c** or **6d**. Even the use of excess *sec*-BuLi with **6b** gave a singly quenched product **8** when acetone was used as the electrophile. However, after methylation to yield **9**, further lithiation was possible and, in the presence of cyclobutanone, the tetra-*ortho*-substituted sulfone **10** was obtained, which has the property of being atropisomeric.[2]

Martin showed[8] that substituted diarylsulfones may be made by lithiating the cyclic sulfone **12**, which is conveniently made from diphenylsulfone **11**. We used a related strategy for the synthesis of tetrasubstituted diaryl ethers.[9] Attempted double lithiation of **12**[8] returned a mixture of **13** and **14**, both of which were converted into alkenes **15** and **16** on attempted reduction with triethylsilane (Scheme 3). Hydrogenation of **15** gave the diisopropyl-substituted cyclic sulfone **17**.

Although lithiation of the sulfones provided some usefully hindered sulfones,[2] it was not general enough for our purposes, so we returned to the synthesis of 2,2,6,6′-tetrasubstituted diarylsulfides by Cu-promoted coupling of 2,6-disubstituted thiophenols and 2,6-disubstituted aryl halides. Buchwald's original publication[3] did not detail

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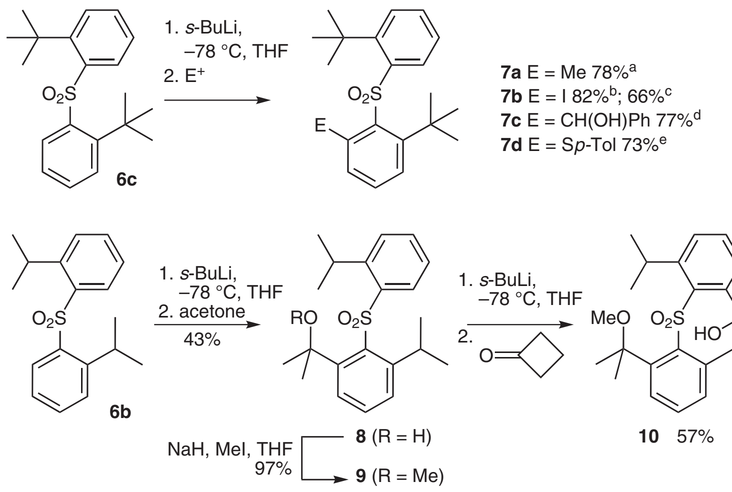
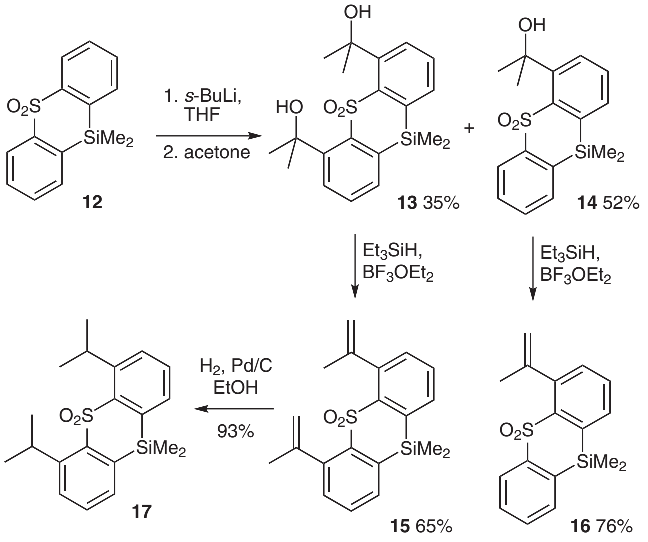
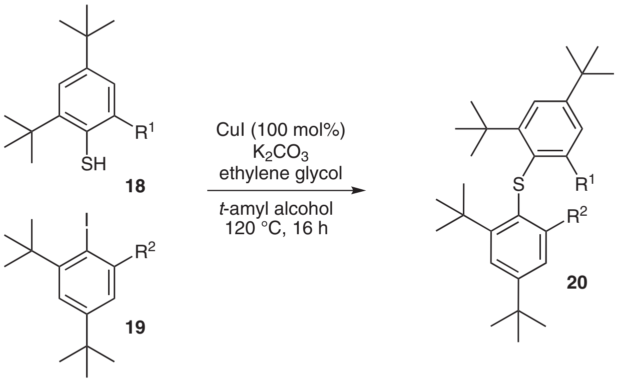


Scheme 2 Functionalisation of diarylsulfones by lithiation. [a] $E^+ = MeI$; [b] $E^+ = I_2$; [c] $E^+ = (CH_2I)_2$; [d] $E^+ = PhCHO$; [e] $E^+ = p\text{-}Tol_2S_2$



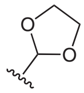
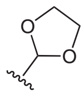
Scheme 3 Functionalisation of a thiasilaanthracene-*S*,*S*-dioxide **12**

the direct synthesis of such tetrasubstituted diarylsulfides by coupling, but we found that 2,6-disubstituted thiophenols **18** and the related aryl iodides **19** nonetheless made suitable coupling partners (Scheme 4). Both of the starting materials were made from readily made aryl bromides by the methods shown in Scheme 5. Thus, bromide **21b** (made by bromination of available 3,5-di-*tert*-butyltoluene **21a**) was converted into the corresponding aryllithium by bromine-lithium exchange. Trapping with iodine gave the iodide **19a** in 87% yield; trapping with dimethyldisulfide yielded methylsulfide **21f** (93%), which was demethylated using sodium 2-propanethiolate[10] to yield thiophenol **18a** in 93% yield. Bromination and oxidation[11] of **21b** yielded aldehyde **21d**, which was protected and converted into the iodide **19b** similarly. Both the 2-bromo-substituted iodide **19c** and thiophenol **18b** were made by iodination (I_2, Selectfluor[12]) of **21g**, followed by (iodide-selective[13]) copper-catalysed coupling[3] with 4-methoxybenzylthiol (to give **21h**) and acid-catalysed deprotection.

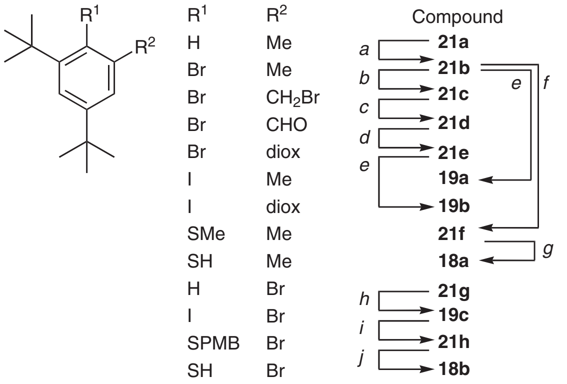


Scheme 4 Tetra-*ortho*-substituted diarylsulfides by Cu-promoted coupling

Table 1 Synthesis of 2,2′,6,6′-Tetrasubstituted Diarylsulfides by the Coupling Method of Scheme 4

Entry	Thiol **18** (R^1)	Iodide **19** (R^2)	Product **20**, Yield (%)
1	**18a** (Me)	**19a** (Me)	**20a** (79)
2	**18a** (Me)	**19c** (Br)	**20b** (76)
3	**18b** (Br)	**19c** (Br)	**20c** (30)
4	**18a** (Me)	 **19b**	**20d** (55)
5	**18b** (Br)	 **19b**	**20e** (40)

Optimal yields for the hindered couplings shown in Scheme 4 were obtained by using equimolar amounts of each of the coupling partners **18** and **19**, along with one equivalent of copper(I) iodide and two equivalents of ethylene glycol. Heating this mixture with base (potassium carbonate) in *tert*-amyl alcohol at 120 °C for 16 hours



Scheme 5 Preparation of the starting materials for the hindered coupling. *Reaction conditions*: (a) Br_2, Fe, $CHCl_3$; (b) NBS, $(PhCO_2)_2$, CCl_4, 16 h, Δ (94%); (c) 2-nitropropane, NaOEt, EtOH, 4 h (61%); (d) ethylene glycol, *p*-TsOH, toluene, 18 h, Δ (97%); (e) 1. *t*-BuLi, THF, –78 °C; 2. I_2 (88% **19a**; 87% **19b**); (f) 1. *t*-BuLi, THF, –78 °C; 2. Me_2S_2 (93%); (*g*) *t*-BuSNa, DMF, Δ, 18 h (93%); (h) Selectfluor, I_2, MeCN, Δ, 5 h (44%); (i) CuI, K_2CO_3, ethylene glycol, *t*-amyl alcohol, 120 °C, 18 h (73%); (j) CF_3CO_2H, PhOMe (82%).

generally returned moderate to high yields of the coupled sulfides **20** (Scheme 4 and Table 1).[14] Notably, the selectivity for insertion of Cu into even a hindered C–I bond allowed sulfides containing bromo-substituents to be made – substituents which, in principle, allow further functionalisation to more elaborate derivatives.

In summary, highly hindered sulfides may be formed by copper-promoted coupling of thiols with aryl iodides;[14] comparably hindered sulfones may be formed either by oxidation of these sulfides or by lithiation/electrophilic quenching of simpler sulfones.

Acknowledgment

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References and Notes

(1) For examples of atropisomerism and discussions on the conformational properties of non-biaryl systems, see: (a) Clayden, J.; Turner, H.; Helliwell, M.; Moir, E. *J. Org. Chem.* **2008**, *73*, 4415. (b) Adler, T.; Bonjoch, J.; Clayden, J.; Font-Bardía, M.; Pickworth, M.; Solans, X.; Solé, D.; Vallverdú, L. *Org. Biomol. Chem.* **2005**, *3*, 3173. (c) Clayden, J.; Worrall, C. P.; Moran, W.; Helliwell, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3234. (d) Betson, M. S.; Clayden, J.; Worrall, C. P.; Peace, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 5803. (e) Clayden, J.; Fletcher, S. P.; McDouall, J. J. W.; Rowbottom, S. J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5331. (f) For an overview of this area, see: Clayden, J. *Chem. Commun.* **2004**, 127.

(2) For studies of conformational interconversions in diarylsulfides and sulfones, see: (a) Kessler, H.; Rieker, A.; Rundel, W. *Chem. Commun.* **1968**, 475. (b) Lam, W. Y.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 4458. (c) Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2001**, 4444. (d) Lunazzi, L.; Mazzanti, A.; Minzoni, M. *Tetrahedron* **2005**, *61*, 6782. (e) Clayden J., Senior J., Helliwell M.; *Angew. Chem. Int. Ed.*; in press

(3) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.

(4) Other recent methods for C–S bond formation in less hindered systems have been described, see: (a) Fernandez-Rodrıguez, M.-A.; Shen, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (b) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880. (c) Zhang, H.; Cao, W.; Ma, D. *Synth. Commun.* **2007**, *37*, 25. (d) Xu, H. J.; Zhao, X. Y.; Deng, J.; Fu, Y.; Feng, Y.-S. *Tetrahedron Lett.* **2009**, *50*, 434. (e) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (f) For a review, see: Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. For further representative examples, see: (g) Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283. (h) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. (i) McWilliams, J. C.; Fleitz, F. J.; Zheng, N.; Armstrong, J. D. *Org. Synth.* **2002**, *79*, 43. (j) Li, G. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513. (k) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (l) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069. (m) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (n) Only one previous report, a coupling method employing HMPA as solvent, addresses a 2,2′,6,6′-tetraalkyl diarylsulfide, see: Fujihara, H.; Chiu, J.; Furukawa, N. *J. Am. Chem. Soc.* **1988**, *110*, 1280.

(5) For recent reviews of directed lithiation, see: (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, **2002**. (b) Clayden, J. *Directed Metallation of Aromatic Compounds. In Chemistry of Organolithium Compounds*, Vol. 1; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester, **2004**, 495. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

(6) Clayden, J.; Cooney, J. J. A.; Julia, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 7.

(7) Iwao, M.; Iihama, T.; Mahalanabis, K. K.; Perrier, H.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 24.

(8) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(9) Betson, M. S.; Clayden, J. *Synlett* **2006**, 745.

(10) Pinchart, A.; Dallaire, C.; Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1999**, 5479.

(11) Kimura, S.; Bill, E.; Bothe, E.; Weyhermller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **2001**, *123*, 6025.

(12) Stavber, S.; Kralj, P.; Zupan, M. *Synthesis* **2002**, 1513.

(13) For examples of selectivity of I over Br in related reactions, see: Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254.

(14) Copper-Promoted Coupling; Typical Procedure for (2,4-Di-*tert*-butyl-6-bromophenyl)-(2,4-di-*tert*-butyl-6-methylphenyl) sulfane (**20b**)
Thiophenol **18a** (574 mg), copper(I) iodide (462 mg) and potassium carbonate (560 mg) were charged to a flask fitted with a reflux condenser, which was evacuated/back-filled with nitrogen (×3). A solution of iodide **19c** (800 mg) and ethylene glycol (0.23 mL) in *tert*-amyl alcohol (6 mL) was added via syringe and the reaction mixture was heated to reflux for 24 h. The reaction mixture was allowed to cool to r.t., diluted with ethyl acetate (40 mL) and filtered through a glass sinter. The filtrate was washed with water (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether) to yield the title compound as a white solid that was recrystallised from acetone (1.27 g, 76%); mp 125–129 °C(acetone); R_f = 0.69 (petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 2 Hz, 1 H, ArH), 7.36 (d, *J* = 2 Hz, 1 H, ArH),

7.33 (d, *J* = 2 Hz, 1 H, ArH), 6.93 (d, *J* = 2 Hz, 1 H, ArH), 1.75 (s, 3 H, ArC*H*$_3$), 1.65 (s, 9 H, CMe$_3$), 1.64 (s, 9 H, CMe$_3$), 1.30 (s, 9 H, CMe$_3$), 1.28 (s, 9 H, CMe$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 150.8, 150.2, 149.0, 148.5, 139.0, 133.1, 131.8, 129.7, 127.0, 126.1, 123.6, 122.5, 38.3, 37.5, 34.7, 34.5, 31.3, 31.3, 31.1, 30.9, 23.0; MS (CI): *m*/*z* (%) = 502 (40) [^{79}Br M]$^+$, 504 (40) [^{81}Br M]$^+$, 503 (50) [^{79}BrM + H]$^+$, 505 (50) [^{81}BrM + H]$^+$; HRMS: *m*/*z* calcd for $C_{29}H_{43}BrS$: 502.2263; found: 502.2264.