

these two experiments do not completely rule out the possibility of an SET mechanism for either the initial step or the second step,^{17,18} they do suggest that both steps may be best viewed as direct substitution by S_N2 processes. Entries 8 and 9 further indicate that S_N2 processes are favored over S_N2' for both the initial as well as the second attack.

In summary, this work provides a facile route for the regioselective introduction of substituents in the 1,4-positions of 1,4-diphenyl-1,3-butadiene. While the addition

(16) For ring closure of 5-hexenyl radicals, see: (a) Lamb, R. C.; Ayers, P. W.; Toney, M. K. *J. Am. Chem. Soc.* **1963**, *85*, 3483. (b) Walling, C.; Pearson, M. S. *Ibid.* **1964**, *86*, 2262. (c) Garst, J. F.; Ayers, P. W.; Lamb, R. C. *Ibid.* **1966**, *88*, 4260. (d) Lamb, R. C.; Ayers, P. W.; Toney, M. K.; Garst, J. F. *Ibid.* **1966**, *88*, 4261. (f) Julia, M.; Manney, M. *Bull. Soc. Chim. Fr.* **1966**, 434; **1968**, 1603; **1969**, 2415; **1969**, 2427. (g) Garst, J. F.; Barton, F. D. *Tetrahedron Lett.* **1969**, 587. (h) Kochi, J. K.; Powers, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 137. (i) Walling, C.; Cioffari, A. *Ibid.* **1970**, *92*, 6609 and references therein.

(17) The SET mechanism is favored by the presence of small amounts of transition metals. This was evident by the dimerization of ketyls to give pinacols, during the addition of Grignard reagents to ketones. Ashby, E. C.; Buhler, J. D.; Lopp, I. G.; Wieseman, T. L.; Bowers, J. S.; Laemmle, J. T. *J. Am. Chem. Soc.* **1976**, *98*, 6561.

(18) About 10% of benzil was obtained in the reaction with benzoyl chloride (Table I, entry 13).

Ortho-Metalated Aryl *tert*-Butyl Sulfones. Comparison with Other Directing Groups and New Methodology for Polysubstituted Aromatics

Summary: The general utility of ortho-lithiated aryl *tert*-butyl sulfones for the synthesis of a variety of 2- and 2,6-carbon- and -heteroatom-substituted products in good to excellent yields is described (Schemes I, VI, VII).

Sir: During the recent emergence of the aromatic directed metalation strategy in organic synthesis,¹ a number of sulfur-based directed metalation groups have been studied: SO₂NR₂,^{2a} SO₂NHR,^{2b} SO₂R,^{2c} SO₂Li,^{2d} SR,^{2e} SLi.^{2f} The *tert*-butyl sulfone group, despite its early discovery³ and adequate recognition,^{1a} has not received methodological attention.^{4,5} We have pursued the early observations of

(1) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 305. (c) Snieckus, V. *Lectures in Heterocyclic Chemistry*; R. N. Castle, Ed., Heterocorp. *J. Heterocycl. Chem.* **1984**, *95*. (d) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67.

(2) See, inter alia (a) Watanabe, H.; Schwarz, R. A.; Hauser, C. R.; Lewis, J.; Slocum, D. W. *Can. J. Chem.* **1969**, *47*, 1543. (b) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843. (c) Bonfiglio, J. N. *Ibid.* **1986**, *51*, 2833. (d) Figuly, G. D.; Martin, J. C. *Ibid.* **1980**, *45*, 3728. (e) Narasimhan, N. S.; Chandrachud, P. S. *Synthesis* **1979**, 589. Babin, D.; Fourneron, J. D.; Harwood, L. M.; Julia, M. *Tetrahedron* **1981**, *37*, 325. Horner, L.; Lawson, A. J.; Simons, G. *Phosphorus Sulfur* **1983**, *12*, 779. (f) Smith, K.; Lindsay, C. M.; Pritchard, G. *J. Am. Chem. Soc.*, in press. Figuly, G. D.; Loop, C. K.; Martin, J. C. *Ibid.*, in press. Recently, the X-ray structure of *o*-lithiophenyl *tert*-butyl thioether has been determined: Bauer, W.; Klusener, P. A. A.; Harder, S.; Kanters, J. A.; Duisenberg, A. J. M.; Brandsma, L.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 552.

(3) Truce, W. E.; Amos, M. F. *J. Am. Chem. Soc.* **1951**, *73*, 3013. Gilman, H.; Esmay, D. L. *Ibid.* **1953**, *75*, 278. For recent studies, see: Krizan, T. D.; Martin, J. C. *Ibid.* **1983**, *105*, 6155. Vollhardt, J.; Gais, H. J.; Lukas, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 610. Hartman, G. D.; Halczenko, W. *Tetrahedron Lett.* **1987**, *28*, 3241. McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Ibid.* **1987**, *28*, 4123.

(4) *o,o*-Dilithioallyl phenyl sulfone has been generated and used in synthesis with ingenuity (Gais, H.-J.; Ball, W. A.; Bund, J. *Tetrahedron Lett.* **1988**, 781 and references therein) while *o,o*-dilithioisopropyl phenyl sulfone was extensively studied some time ago by Meyers and Parady (Parady, T. E. M.S. Thesis, Southern Illinois University, 1977). We are grateful to Professor Meyers for informing us of these results. For solid state structures of *o*-lithiated and dilithiated sulfones, see: Hollstein, W.; Harms, K.; Marsch, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1287. Gais, H.-J.; Vollhardt, J.; Hellmann, G.; Paulus, H.; Lindner, H. J. *Tetrahedron Lett.* **1988**, *29*, 1259.

of alkyl halides gives a mixture of two diastereomers, the reaction with acyl chlorides results predominantly in the formation of one isomer after isomerization of the double bond. Mixed alkylation, i.e. introduction of one substituent at one benzylic position followed by trapping the other anionic benzylic position with a different alkyl halide, has also been successful (entries 10 and 11). Minor amounts of disubstitution with the same electrophile, however, was also observed in both cases. The addition of a carbonyl compound (entry 16) gave only monosubstitution (compound 5g). Further work exploring the mechanistic aspects of these reactions as well as development of other synthetic applications are continuing in our laboratories.

Acknowledgment. We thank the National Science Foundation for support of this research (Grant CHE-8719728).

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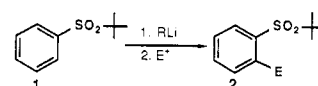
Department of Chemistry

University of Nebraska—Lincoln

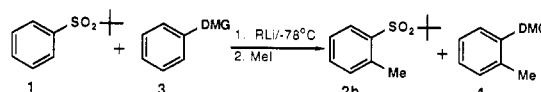
Lincoln, Nebraska 68588-0304

Received August 3, 1988

Scheme I

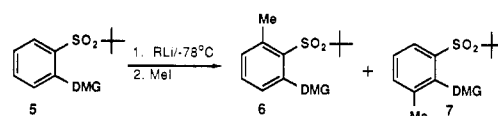


Scheme II



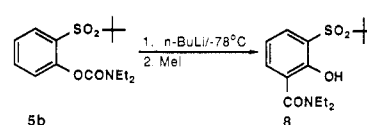
DMG (directed metalation group) = a, CON(i-Pr)₂; b, OCON(i-Pr)₂; c, OMOM; d, NHCO₂t-Bu

Scheme III



DMG = a, CONEt₂ (=2f); b, OCONEt₂; c, OMOM; d, NHCO₂t-Bu

Scheme IV



Stoyanovich and Fedorov⁶ and report that the *tert*-butyl sulfone group (a) is an excellent directed ortho metalation

(5) This state may be contrasted with the continuing high rate of synthetic activity in which the ArSO₂ is a carbanion stabilizing and disposable group, see, inter alia, e.g.: Trost, B. M.; Ghandiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260. Najera, C.; Yus, M. *Tetrahedron Lett.* **1987**, *28*, 6709. Fuchs, P. L.; Hutchinson, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 4755. Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031. Thomsen, M. W.; Handwerker, B. M.; Katz, S. A.; Belser, R. B. *Ibid.* **1988**, *53*, 906. For ArSO use, see: Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *Ibid.* **1988**, *53*, 507. Theobald, P. G.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6565. Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966. Bäckvall, J.-E.; Najera, C.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 1445.

Table I. Reaction of Phenyl *tert*-Butyl Sulfone with Electrophiles

electrophile	2, E =	yield, ^a %	mp (bp), °C
MeOD	2a, D ^b	96	101–102 (Et ₂ O-petroleum ether)
MeI	2b, Me	92	99–100.5 (Et ₂ O-hexane)
CH ₂ =CHCH ₂ Br	2c, CH ₂ CH=CH ₂	78	(120–125) (0.2 mmHg)
DMF	2d, CHO	90	123–125 (CH ₂ Cl ₂ -hexane)
PhNCO	2e, CONHPh	83	217–218 (EtOH)
ClCONEt ₂	2f, CONEt ₂	55	69 (EtOAc-hexane)
<i>o</i> -pyridyl-CHO	<i>o</i> -pyridyl-CH(OH)	86	102–104 (Et ₂ O-petroleum ether)
<i>p</i> -CH ₃ O-C ₆ H ₄ -CHO	2h, <i>p</i> -CH ₃ O-C ₆ H ₄ -CH(OH)	>97	139–139.5 (Et ₂ O)
Me ₃ SiCl	2i, SiMe ₃	>97	100–101 (Et ₂ O-petroleum ether)
Me ₃ SnCl	2j, SnMe ₃	96	124.5–125.5 (hexane)
(1) B(OMe) ₃ ; (2) H ₂ O ₂ , HOAc	2k, OH	90	113–114 (Et ₂ O-petroleum ether)
(1) B(OMe) ₃ ; (2) H ⁺	2l, B(OH) ₂	c	c
(1) TsN ₃ ; (2) NaBH ₄	2m, NH ₂	35	112–113 (EtOAc-hexane)
I ₂	2n, I	81	74–75

^a Unless otherwise indicated, yields are of chromatographed materials. ^b >98% d₁ content by ¹H NMR analysis. ^c Yields not calculated. This material was used directly in cross-coupling reactions.

Table II. Intermolecular (1,3a–d) Metalation Competition^a

compound (DMG)	methylated product, (yield, %)	starting material (yield, %)
3a [CON(<i>i</i> -Pr) ₂]	2b (93)	4a (<1)
3b [OCON(<i>i</i> -Pr) ₂]	2b (91)	4b (<1)
3c [OMOM]	2b (89)	4c (<1)
3d [NHCO ₂ t-Bu] ^b	2b (42)	4d (<1)

^a Unless otherwise indicated, the following conditions were used: (1) *n*-BuLi (1 equiv)/THF/−78 °C/30 min; (2) MeI (2 equiv). ^b (1) *t*-BuLi (2 equiv)/THF/−20 °C/20 min; (2) MeI (2 equiv). ^c In addition, the *N*-methylated 3d (83%) was obtained.

group, more powerful than the tertiary carboxamide; (b) is of general utility for the synthesis of a variety of ortho carbon- and heteroatom-substituted aryl sulfones that are inaccessible by conventional means; (c) may serve as a latent directed ortho metalation group for the synthesis of meta-substituted aromatics; and (d) tolerates transition metal catalyzed cross-coupling conditions leading to biaryl *tert*-butyl sulfones. These results indicate that the *tert*-butyl sulfone deserves to occupy a prominent position in the repertoire of directed ortho metalation strategies.

Treatment of phenyl *tert*-butyl sulfone (1)⁷ with *n*-BuLi (THF/−78 °C/0.5 h) followed by electrophile quench leads to ortho-substituted products 2 in good to excellent yields (Scheme I, Table I). Of special interest is the ability to introduce *o*-halo, -OH, -NH₂, and -B(OH)₂ substituents leading to products that are difficult to prepare otherwise. The relative hierarchy of directed metalation potential was

(6) Stoyanovich, F. M.; Fedorov, B. P. *Angew. Chem.* 1966, 78, 116. Stoyanovich, F. M.; Karpenko, R. G.; Gorushkina, G. I.; Gol'dfarb, Y. L. *Tetrahedron* 1972, 28, 5017.

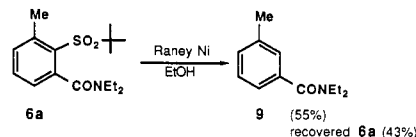
(7) Prepared in 88% yield by reaction of phenyllithium with (*t*-BuS)₂ (THF/−78 °C) followed by oxidation with H₂O₂/HOAc/100 °C/3 h, mp 97 °C [lit. mp 98–99 °C (Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* 1938, 60, 2731)].

Table III. Intramolecular (5a–d) Metalation Competition^a

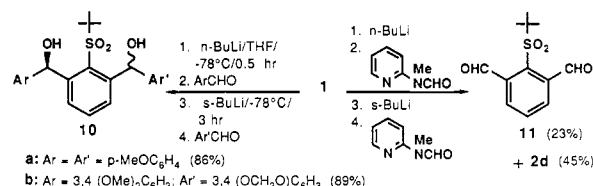
compound (DMG)	products (%)	
5a (=2f) (CONEt ₂)	6a (76)	7a (<1)
5b (OCONEt ₂)	6b (<1)	8 (81) ^b
5c (OMOM)	6c (55)	7c (31)
5d (NHCO ₂ t-Bu)	6d (62)	7d (<1) ^c

^a Unless otherwise indicated, the following conditions were used: (1) *n*-BuLi (1 equiv)/THF/−78 °C/30 min; (2) MeI (2 equiv). ^b *t*-BuLi (1.1 equiv)/THF/−78 °C → room temperature. ^c 5d (26%) was recovered.

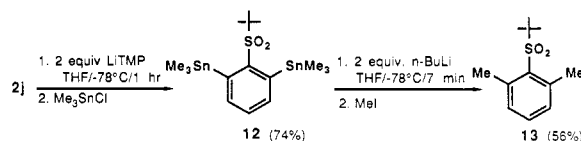
Scheme V



Scheme VI



Scheme VII



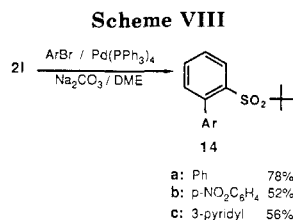
probed by inter- and intramolecular competition experiments.⁸ Aryl sulfone and amide substrates, 1 and 3a, were allowed to compete for 1 equiv of *n*-BuLi (THF/−78 °C) followed by excess MeI quench. Product analysis by NMR and chromatographic separation indicated exclusive formation of *o*-methyl sulfone 2b and no detection of the *o*-methyl benzamide 4a (Scheme II). Parallel competition experiments with sulfone 1 and other metalation directors (3b–d, Table II) demonstrate, with the exception of NHCO₂t-Bu, the dominance of the *tert*-butyl sulfone group.⁹ In intramolecular competition trials, similar treatment of compound 5a led to the formation of 6a without detection of the alternate potential regioisomer 7a (Scheme III, Table III). In spite of MeI quench at −78 °C, the carbamate sulfone 5b undergoes exclusive and rapid ortho-Fries rearrangement¹⁰ to give 8 (Scheme IV) while the corresponding OMOM derivative 5c shows a 1.8:1 metalation ratio favoring the sulfone 6c. The behavior of the NHCO₂t-Bu system 5d paralleled the corresponding amide 5a, producing 6d, albeit in somewhat lower yield. Interpretation of the intramolecular results is precluded by uncertain electronic and ortho steric effects, but the intermolecular results demonstrate the power of the *t*-BuSO₂ group over other metalation directors.^{9,11}

(8) For studies of inter- and intramolecular competition of a series of directed metalation groups, see: Beak, P.; Brown, R. A. *J. Org. Chem.* 1979, 44, 4463. Meyers, A. I.; Lutowski, K. *Ibid.* 1979, 44, 4464.

(9) Relative yields of products 2b:4 and 6:7 do not necessarily reflect the relative amounts of the respective lithiated precursors since transmetalation may occur.

(10) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* 1983, 48, 1935.

(11) To compare with a sulfur directing group for which competition experiments are available, the SO₂NMe₂ gives anomalous results in metalation efficacy with respect to CONEt₂ and 2-oxazolino directors.⁸



That the *tert*-butyl sulfone may act as a latent directed metalation group for the provision of meta-substituted aromatics is indicated by hydrogenolysis (Raney Ni/EtOH/reflux/15 h) of **6a** into the corresponding desulfonated product **9** (Scheme V).

Access to 2,6-disubstituted phenyl *tert*-butyl sulfones was accomplished by sequential metalation-electrophile quench procedures (Scheme VI). Thus treatment of **1** under the conditions shown involving the same or two different aromatic aldehyde electrophiles provided 2,6-dicarbonyl products **10a** and **10b** as mixtures of two diastereomers in high yields.¹² Under similar conditions, but using a 2-(methylamino)pyridine formyl transfer reagent, a low yield of the 2,6-diformylated phenyl sulfone **11** was obtained together with a greater amount of monoformylated product **2d**. Since the preparation of 2,6-dimethylphenyl *tert*-butyl sulfone **13** (Scheme VII) under these conditions is precluded by proton exchange in the monomethylated intermediate, an alternate transmetalation procedure was tested in order to obtain this

(12) **10a**: 69:31, **10b**: 64:36 ratios, the less polar compound by TLC being indicated first. Their relative configurations have not been established.

(13) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* 1981, 11, 513. For recent work, which considerably advances this methodology, see: Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* 1987, 109, 4756. Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* 1988, 61, 3008.

(14) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* 1985, 26, 5997. Sharp, M. J.; Cheng, W.; Snieckus, V. *Ibid.* 1987, 28, 5093. Cheng, W.; Snieckus, V. *Ibid.* 1987, 28, 5097.

(15) Satisfactory analytical data, MS, and ¹H NMR spectra were obtained for all new compounds.

(16) **Note Added in Proof:** Parallel studies have shown that aryl *tert*-butyl sulfoxides are similarly powerful ortho-metalation directors: Iihama, T.; Quesnelle, C.; Perrier, H.; Snieckus, V., manuscript in preparation.

compound. LiTMP metalation-stannylation of **2j** yielded **12**, which upon treatment with 2 equiv of *n*-BuLi for short reaction times followed by methylation led to a good yield of the expected product **13**.

The ready availability of the boronic acid **21** provided opportunity to test the Suzuki transition metal catalyzed cross coupling procedure,¹³ whose value for the preparation of unsymmetrical biaryls and polyaryls has been recently demonstrated.¹⁴ Clean cross coupling reactions were realized with selected aryl bromides to give biphenyls **14a-c** (Scheme VIII).

The above results demonstrate that the *tert*-butyl sulfone is a powerful directed metalation group which should prove to be of general value for the regioselective construction of polysubstituted aromatics. Its use in conjunction with other directing groups opens new and diverse methodological possibilities. Further structure-reactivity relationships vis-à-vis other directed metalation groups and applications in synthesis are currently under investigation.^{15,16}

Acknowledgment. K.K.M. thanks NRC Canada for a CIDA/NSERC Fellowship and Jadavpur University, Calcutta, for a leave of absence. T.I. is a Visiting Scientist from Nippon Soda Co., Kanagawa, Japan. We are grateful to Dr. B. I. Alo for an initial cross coupling experiment and to NSERC Canada, Merck Frosst, Nippon Soda (V.S.), and the Ministry of Education, Science and Culture of Japan (M.I.) for financial support of our synthetic programs.

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Synthesis of Oogoniol

Summary: Oogoniol [(24*R*)-3β,11α,15β,29-tetrahydroxystigmast-5-en-7-one], a female-activating hormone of *Achlya*, has been synthesized from 4-androstene-3,11,17-trione. A novel step involved 1,4-addition of the magnesium cyanocuprate derivative of (*S*)-3-(1-methylethyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentyl bromide to 3β-hydroxy-15β,16β-epoxy-11-oxo-(17(20)*E*)-pregna-5,17-(20)-diene 3-*tert*-butyldimethylsilyl ether. Selective hydrogenation of the resulting Δ¹⁶ double bond gave only the stigmastene product with the correct stereochemistry at C₁₅, C₁₇, and C₂₀.

Sir: We reported some time ago the synthesis of dehydrooogoniol **15**, a female-activating hormone of the aquatic fungus *Achlya*.¹ We now describe the synthesis of a related steroid, oogoniol (**14**) [(24*R*)-3β,11α,15β,29-tetra-

hydroxystigmast-5-en-7-one] also isolated from *Achlya heterosexalis* but possessing lower biological activity than **15**.² The starting material was commercially available 4-androstene-3,11,17-trione (**1**) (adrenosterone). Construction of the side chain involved the novel reaction of the magnesium cyanocuprate **10** of (*S*)-3-(1-methylethyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentyl bromide with the steroidal intermediate 3β-hydroxy-15β,16β-epoxy-11-oxo-(17(20)*E*)-pregna-5,17(20)-diene 3-*tert*-butyldimethylsilyl ether (**9**).^{3,4} Although the synthesis required many steps, these were all high yielding so that the overall yield was 7%.

Adrenosterone (**1**) was first converted to the dienol acetate **2**, which was reduced with Ca(BH₄)₂ in absolute ethanol at -15 °C to 3β,11β,17β-trihydroxy-5-androstene

(2) Preus, M. W.; McMorris, T. C. *J. Am. Chem. Soc.* 1979, 101, 3066.

(3) Liu, D.; Stuhmiller, L. M.; McMorris, T. C. *J. Chem. Soc., Perkin Trans. 1* 1988, 2161.

(4) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* 1981, 103, 2907.

(1) McMorris, T. C.; Le, P. H.; Preus, M. W.; Schow, S. R.; Weihe, G. *R. J. Org. Chem.* 1983, 48, 3370.