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THE tert-BUTYL SULFOXIDE DIRECTED ortho METALATION GROUP. NEW SYNTHETIC METHODOLOGY FOR SUBSTITUTED AROMATICS AND PYRIDINES AND COMPARISON WITH OTHER METALATION DIRECTORS

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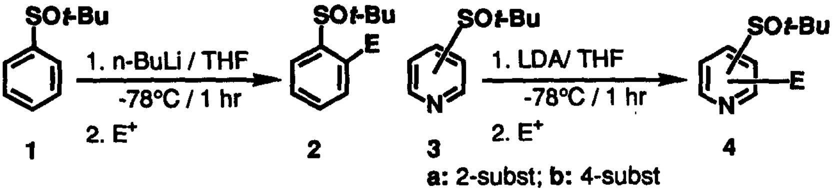
Abstract: Details of the directed ortho metalation of tert-butyl phenyl sulfoxide (**1**) *and 2- and 4-tert-butyl pyridyl sulfoxides* (**3a,b**) *are described along with comparisons with established metalation directors ($CONR_2$, $OCONR_2$, OMOM, SO_2t-Bu) via inter- and intramolecular competition experiments.*

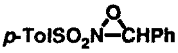
As a contribution to the evolving area of directed *ortho* metalation chemistry,[2] we have recently reported on the metalation of aryl *tert*-butyl sulfones.[3,4] As a sequal to this study, we have investigated the metalation of the corresponding sulfoxides.[5,6,7] In this Letter, we describe preliminary results of *ortho* metalation of phenyl (**1**) and 2- and 4-pyridyl *tert*-butyl sulfoxides (**3a,b**) (**Scheme 1**) as well as inter- and intra-molecular competition experiments of *t*-BuSO *vis à vis* other frequently used directed metalation groups. These results show that the *tert*-butyl sulfoxide is a powerful *ortho* metalation director, comparable to the corresponding sulfone,[3] and constitutes a valuable addition to the repertoire of groups which allow the continuing development of new metalation methodology for the preparation of substituted aromatic and pyridine derivatives.

Scheme 1



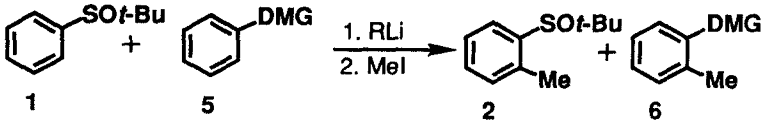
Metalation (*n*-BuLi/THF/-78°C/1h) of phenyl *tert*-butyl sulfoxide[8] followed by quenching with a variety of electrophiles led to *ortho*-substituted products in good to excellent yields (**Table 1**). Noteworthy are the introductions of *ortho*-(HO)CHPh, $-CONEt_2$, -OH, and $B(OH)_2$, groups. The relative hierarchy of *ortho* metalation potential was probed by inter- and intra-molecular competition experiments (**Tables 2, 3**). Phenyl sulfoxide and aryl-DMG substrates, **1** and **5**, were allowed to compete for 1.05 equiv of *n*-BuLi (THF/-78°C/1h) followed by excess MeI quench. Product mixtures, analyzed by NMR and chromatographic separation, indicate the dominant *ortho*-metalating capacity of the *t*-BuSO with respect to $CON(i\text{-}Pr)_2$, $OCON(i\text{-}Pr)_2$, and OMOM groups and its approximately similar metalation ability to the t-BuSO$_2$ DMG.[9] In intramolecular experiments, *n*-BuLi metalation of **7** led to products **8** or **9** thus further demonstrating the greater directing power of *t*-BuSO (**Table 3**).

Table 1. Synthesis of *ortho*-Substituted Phenyl Sulfoxides (**2**) and Substituted Pyridyl Sulfoxides (**4**)

E^+	**2**, E	Yield, %[a]	**3**, Subst	E^+	**4**, E	Yield, %[a]
MeOD	D	88	2-	MeOD	D	75[f]
MeI	Me	96		MeI	Me	82
EtI	Et	87		PhCHO	(HO)CHPh	74
		41[b]		$ClCONEt_2$	$CONEt_2$	20
PhCHO	(HO)CHPh	82[c]		OH^{+}[g]	OH	70
DMF	CHO	0		I_2	I	35
$ClCONEt_2$	$CONEt_2$	54[d]		TMSCl	TMS	70
	OH	48		Bu_3SnCl	Bu_3Sn	90
$(TMSO)_2$	OH	44	4-	MeOD	D	72[h]
	Br	85		MeI	Me	74
$B(OMe)_3$/HCl	$B(OH)_2$	69[e]		TMSCl	TMS	66
TMSCl	TMS	89		Bu_3SnCl	Bu_3Sn	74
Me_3SnCl	Me_3Sn	85				

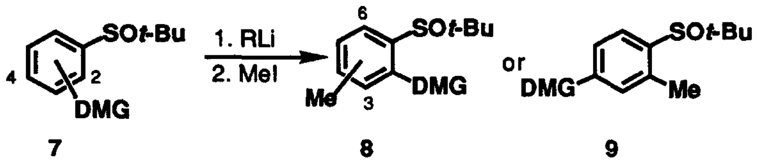
[a] Yields are of chromatographed materials; [b] Based on recovered SM; [c] 55:45 diastereomeric mixture based on ^1H NMR analysis of *t*-Bu signals; [d] 1.2 equiv TMEDA added; [e] Yield based on the isolated diethanolamine adduct; [f] 68% d_1 by MS; [g] 1. $B(OMe)_3$; 2. H_2O_2 HOAc; [h] 71% d_1 by MS.

Table 2. Intermolecular Metalation Competition



DMG	Methylated Product, Yield, %		Starting Material, Yield, %	
	2	**6**	**1**	**5**
CON(*i*-Pr)$_2$	78	<1	9	95
OCON(*i*-Pr)$_2$	85	<1	4	86
OMOM	86	<1	3	85
SO$_2$*t*-Bu	41	44	50	36

Table 3. Intramolecular Metalation Competition



DMG = **a**: 2-OMOM; **b**: 4-OMOM; **c**: 4-CONEt$_2$; **d**: 4-NH*t*-Boc

Compound	Products (Yield, %)^a	
7a	**8a**, 6-Me (57.5)	**8a**, 3-Me (2.4)
7b	**9b** (84)	
7c	**9c** (88)^b	
7d	**9d** (72)^b	

^{a} Yield of chromatographed material; ^{b} Yield based on HPLC of an inseparable mixture of SM and product. Product **9c** was compared to an independently prepared sample.

The results of 2- and 4-pyridyl *tert*-butyl sulfoxide metalation are also summarized in **Table 1**. Deprotonation of **3a** and **3b** under conditions similar to those used by Furukawa (LDA/-78°C/THF/ 0.5 h)[6b] followed by quenching with selected electrophiles led to substituted pyridyl sulfoxides **4** invariably in good yields.[10]

Ortho functionalization of phenyl and pyridyl *tert*-butyl sulfoxides further expands the scope of the directed *ortho* metalation reaction for the preparation of substituted aryl and pyridyl derivatives. Demonstration of the diverse potential of this strategy in organic synthesis continues to be a goal in our laboratories.[11,12]

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1. a) NSERC Canada Graduate Fellowship awardee 1989 - present; b) Visiting scientist from Nippon Soda Co., Kanagawa, Japan, 1988-89; c) Government of Canada Award (Canada-France Exchange Fellow), 1988-89.
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5. a) Taken in part from Perrier, H. M.Sc. Thesis, University of Waterloo, 1989. b) Presented in part at: 72nd CIC, Victoria, B.C., June, 1989, Abstr OR-4A^{P}-436; 31st National Organic Symposium, Ithaca, N.Y., June, 1989, Abstr B-30; 73rd CIC, Halifax, NS., July, 1990, Abstr 860 OR-C16; 74th CIC, Hamilton, Ont., June, 1991, Abstr 696P.
6. a) To the best of our knowledge, only isolated cases of ortho metalation of aryl sulfoxides had been previously described: Gilman, H.; Esmay, D.L. *J. Am. Chem. Soc.* **1952**, *74*, 266; Furukawa, N.; Kimura, T.; Horie, Y.; Ogawa, S. *Heterocycles* **1991**, *32*, 675. b) In the course of our work, reports concerning the metalation of isomeric pyridyl phenyl sulfoxides and sulfoxide displacement reactions with Grignard reagents leading to biaryls and heterobiaryls appeared: Shibutani, T.; Fujihara, H.; Furukawa, N. *Tetrahedron Lett.* **1991**, *32*, 2943; Shibutani, T.; Fujihara, H.; Furukawa, N. *Tetrahedron Lett.* **1991**, *32*, 2947 and references cited therein. See also Oae, S.; Furukawa, N. *Advan. Heterocyclic Chem.* **1990**, *48*, 1.
7. To date, aryl sulfoxides have served soley as carbanion stabilizing and (oftimes) disposable functionalities in synthesis, see, *inter alia*, α-metalation: Hua, D.H.; Miao, S.W.; Bravo, A.A.; Takemoto, D.J. *Synthesis* **1991**, 970; Solladie, G.; Ruiz, P.; Colobert, F.; Carreño, M.C.; Garcia-Ruano, J.L. *Synthesis* **1991**, 1011; Solladie, G. *Asymmetric Synthesis* J.D. Morison, Ed.; Academic, New York, **1983**, Vol. 2, p. 157; Drabowicz, J.; Mikolajczyk, M. *Org. Prep. Proc.* **1982**, *14*, 45; Columbo, L.; Gennari, C.; Scolastico, C. *J. Chem Soc. Chem. Comm.* **1979**, 591; α-vinyl metalation: Marino, J.P.; Laborde, E.; Paley, R.S. *J. Am. Chem. Soc.* **1988**, *110*, 966; Eisch, J.S.; Galle, J.E. *J. Org. Chem.* **1979**, *44*, 3279; Michael addition: Pyne, S.G.; Bloem, P.; Chapman, S.L.; Dixon, C.E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086; Takaki, K.; Maeda, T.; Ishikawa, M. *J, Org. Chem.* **1989**, *54*, 58; Hsiao, C.-N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688; Posner, G.; Hamill, T.G. *J. Org. Chem.* **1988**, *53*, 6031; Kahn, S.D.; Dobbs, K.D.; Hehre, W.J. *J. Am. Chem. Soc.* **1988**, *110*, 4602; and asymmetric synthesis: Davis, F.A.; Towson, J.C.; Weismiller, M.C.; Lal, S.; Carroll, P.J. *J. Am. Chem. Soc.* **1988**, *110*, 8477; Davis, R.; Kern, J.R.; Kurz, L.J.; Pfister, J.R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.
8. Prepared from the corresponding sulfide by $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (OXONE®) treatment, see Trost, B.; Curran, D.P. *Tetrahedron Lett.* **1981**, *22*, 1287.
9. Relative yields of products are considered to reflect amounts of respective *ortho* metalated species since metalation for shorter times (80 sec) led to product yields within experimental error of those observed in the 1 h metalation experiments.
10. For comparison with the corresponding sulfones, the synthesis of a variety of 3-substituted 2-pyridyl *tert*-butyl sulfones has been achieved from the 2-pyridyl sulfone under similar metalation conditions whereas the 4-pyridyl sulfone gives uncharacterizable mixtures of products under LDA and other standard alkyllithium conditions.[5a] Sulfone displacement in 2- and 4-pyridyl *tert*-butyl sulfones by *n*-BuLi treatment has been reported: Stoyanovich F.M.; Gol'dfarb, Y.L.; Marakatkina, M.A.; Karpenko, R.G. *Izv. Akad. Nauk. SSSR, Ser. Khim* **1978**, 2767; *Chem. Abstr.* **1979**, 90, 137632k.
11. All new compounds show spectral (IR, NMR, MS) and analytical data consistent with the assigned structures.
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