ortho-Substituted Unsymmetrical Biaryls from Aryl *tert*-Butyl Sulfones

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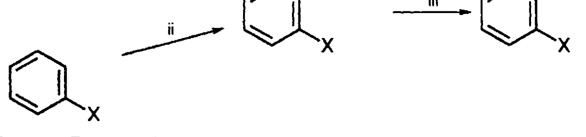
Nickel-catalysed coupling of arylmagnesium halides with aryl *tert*-butyl sulfones, and in particular with those bearing *ortho*-substituents introduced by ortholithiation, gives *ortho*-substituted unsymmetrical biaryls.

The *tert*-butylsulfonyl group has been shown to be an excellent director of ortholithiation, making *ortho*-substituted aryl *tert*-butyl sulfones very readily available.[1] The use of such molecules to the synthetic chemist would be enhanced if the sulfonyl group could subsequently be transformed into another substituent. In this communication, we describe the substitution of the aryl *tert*-butylsulfonyl group by arylmagnesium halides under nickel catalysis to give *ortho*-substituted unsymmetrical biaryls. Scheme 1 illustrates the strategy.

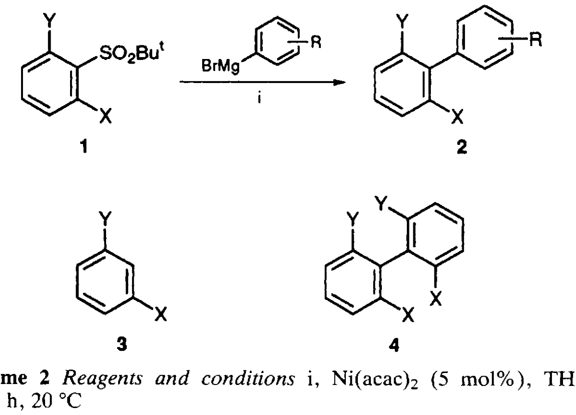
A variety of methods exist for the synthesis of biaryls,[2] many involving coupling of aryl subunits catalysed by nickel,[3] copper[4,5] or palladium.[5–7] In the field of sulfur chemistry, Wenkert[8] has shown that nickel(0) can insert into the sp^{2}C–S bond of an aryl alkyl sulfide to give a nickel(II) complex. He found that ligand exchange with arylmagnesium halides, followed by reductive elimination of nickel(0), leads to biaryls in an overall nucleophilic aromatic substitution of the alkylthio group.[9] Work in our laboratories directed towards the stereocontrolled synthesis of trisubstituted double bonds has shown that nickel can also catalyse the substitution of sulfonyl groups attached to aryl or vinyl sp^2 centres.[10]

We treated phenyl *tert*-butyl sulfone **1a** with *p*-tolylmagnesium bromide (2 equiv.) in the presence of 5 mol% nickel(II) acetylacetonate [Ni(acac)$_2$] at 20 °C in tetrahydrofuran (THF) (Scheme 2). After 20 h, GC showed an 80% yield of 4-methylbiphenyl **2a** (R = *p*-Me), together with a 15% yield of biphenyl **4a** arising from coupling of the sulfone with itself. 4,4′-Dimethylbiphenyl, from oxidative coupling of the Grignard reagent, was also observed. Using *o*-tolylmagnesium bromide as the second reagent produced 2-methylbiphenyl **2a** (R = *o*-Me) in 82% yield with only 4% biphenyl **4a** (Table 1, entries 1 and 2).



Scheme 1 *Reagents* i, 1 BuLi, 2 X$^+$; ii, 1 BuLi, 2 Bu$^t_2$S$_2$, 3 oxidase; iii, ArMgX, Ni

Combining this new substitution reaction with the ability of the *tert* butylsulfonyl group to direct ortholithiation[1] enabled us to make a number of *ortho*-substituted biphenyls. Aryl *tert*-butyl sulfones **1b–d** were synthesised by electrophilic capture of 2-lithiophenyl *tert*-butyl sulfone. Further *ortho*-substituted sulfones **1e** and **1f** were made by oxidation of aryl *tert*-butyl sulfides obtained by quenching ortholithiated species with di-*tert*-butyl disulfide. 1,6-Substituted aryl sulfones **1g** and **1h** were made by lithiation and methylation of **1e** and **1f**.†



Scheme 2 *Reagents and conditions* i, Ni(acac)$_2$ (5 mol%), THF, 2–20 h, 20 °C

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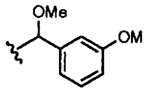
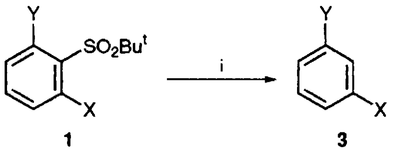
† Reagents and yields for the synthesis of sulfones **1b–d** from phenyl *tert*-butyl sulfone: **1b**: 1. BuLi, 2. MeI (83%); **1c**: 1. BuLi, 2. Me$_3$SiCl (90%); **1d**: 1. BuLi, 2. *m*-anisaldehyde (88%), 3. NaH, 4. MeI (99%). Sulfone **1e** was synthesised from *N*,*N*-diisopropylbenzamide: 1. BuLi, 2. Bu$^t_2$S$_2$ (68%), 3 NaBO$_3$–AcOH (96%) and sulfone **1f** from anisole: 1. BuLi, 2. Bu$^t_2$S$_2$ (20%), 3. NaBO$_3$–AcOH (94%). Methylation of sulfone **1e** gave sulfone **1g**: 1. BuLi, 2. MeI (66%), and methylation of sulfone **1f** gave sulfone **1g**: 1. BuLi, 2. MeI (95%).

Table 1 Nickel-catalysed reactions of aryl *tert*-butyl sulfones with arylmagnesium bromides

Entry	Starting material **1**	X	Y	R	Equiv.	**2**[a]	**3**[a]	**4**[a]	**1**[a]	Product isolated yield (%)
1	**a**	H	H	*p*-Me	2	80	—	15	0	
2	**a**	H	H	*o*-Me	2	82	—	4	0	
3	**b**	Me	H	H	4	66	12	12	0	
4	**c**	$SiMe_3$	H	*p*-Me	4	67	27	0	0	
5	**d**		H	*p*-Me	4	36	25	0	20	
6	**e**	$CONPr^i_2$	H	H	4	95	2	0	0	**2e** (R = H), 81
7	**e**	$CONPr^i_2$	H	*p*-Me	4	92	2	0	0	**2e** (R = *p*-Me), 86
8	**e**	$CONPr^i_2$	H	*o*-Me	4	58	41	0	0	**2e** (R = *o*-Me), 42
9	**f**	OMe	H	H	4	38	16	24	5	
10	**f**	OMe	H	*p*-Me	4	33	3	15	17	
11	**g**	$CONPr^i_2$	Me	*p*-Me	6	48	5	0	41	**2g** (R = *p*-Me), 47
12	**h**	OMe	Me	*p*-Me	4	20	53	0	16	

[a] Yield (%) measured by GC of crude product mixture.



Scheme 3 *Reagents and conditions* i, Pr^iMgCl (4 equiv.), $Ni(acac)_2$ (5 mol%), THF, 20 h, 20 °C

Table 1 shows the results of the reactions of these eight sulfones with phenyl-, *o*-tolyl-, and *p*-tolyl-magnesium bromide in the presence of 5 mol% nickel acetylacetonate (Scheme 3).‡ In each case, the starting sulfone **1** gave rise to three products in varying proportions: the desired substitution product **2**, a reduction product **3** and the self-coupled product **4**. Symmetrical biaryls formed by oxidative coupling of the excess of Grignard reagent were always present as by-products. In most cases, 4 equiv. of Grignard reagent were used to ensure completion of the reaction.

The *ortho*-substituted sulfones **1b**, **1c** and **1e** all gave good to excellent yields of unsymmetrical biaryls with phenyl- or *p*-tolyl-magnesium bromide (Table 1, entries 3, 4, 6 and 7). With more hindered reactants the reactions were slower, sometimes failing to reach completion, and generally giving increased yields of the reduced by-product **3** (entries 8, 11 and 12). Sulfones **1d** and **1f**, which both contain methoxy groups, also seemed particularly reluctant to form the desired substitution products (entries 5, 9 and 10).

The reductive desulfonylation reaction, which can lead to *meta*-substituted compounds **3**, could be encouraged by using isopropylmagnesium chloride in the place of the aryl Grignard reagent (Scheme 3). The yields of reduced products **3**, shown in Table 2, were good to excellent. Raney nickel has been used[1] to accomplish a similar transformation, but in rather lower yield.

The strategy we have begun to develop here makes use of the *tert*-butylsulfonyl group as a versatile latent aryl or hydrogen substituent which can both direct and be introduced by ortholithiation. The easy access, by a variety of synthetic routes, to the starting sulfones, along with their stability and crystallinity, shold enable this new method to complement the well-developed existing strategies[7] for the synthesis of polyaromatic systems.

Table 2 Nickel-catalysed reductive desulfonations of aryl *tert*-butyl sulfones using isopropylmagnesium chloride

Entry	Starting material **1**	X	Y	**3**[a]	Product, isolated yield (%)
1	**e**	$CONPr^i_2$	H	89	**3e**, 81
2	**g**	$CONPr^i_2$	Me	60	
3	**h**	OMe	Me	96	**3h**, 92

[a] Yield (%) measured by GC of crude product mixture.

We are grateful to the Royal Society for a Western European Research Fellowship (to J. C.).

Received, 3rd August 1993; Com. 3/04630C

References

1 M. Iwao, T. Iihama, K. K. Mahalanabis, H. Perrier and V. Snieckus, *J. Org. Chem.*, 1989, **54**, 24.

2 (*a*) M. Sainsbury, *Tetrahedron*, 1980, **36**, 3327; (*b*) A. I. Meyers and R. J. Himmelsbach, *J. Am. Chem. Soc.*, 1985, **107**, 682.

3 (*a*) K. Tomao, K. Sumitani, M. Zembayashi, A. Funoka, S. Kodama, I. Nakajima, A. Minato and M. Kumada, *Bull. Chem. Soc. Jap.*, 1976, **49**, 1958; (*b*) M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. Speltz Ryono, J. Gorzynski Smith and R. D. Stauffer, *J. Am. Chem. Soc.*, 1981, **103**, 6460.

4 F. E. Ziegler, I. Chliver, K. W. Fowler, J. J. Karfer, S. J. Kuo and N. D. Senha, *J. Am. Chem. Soc.*, 1980, **102**, 790.

5 (*a*) W. J. Thompson and J. Gaudino, *J. Org. Chem.*, 1984, **49**, 5237; (*b*) N. Shimizu, T. Kitamura, K. Watanabe, T. Yamaguchi, H. Shigyo and T. Ohta, *Tetrahedron Lett.*, 1993, **34**, 3421.

6 N. Miyaura. T. Yanagi and A. Suzuki, *Syn. Comm.*, 1981, **11**, 513.

7 (*a*) M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, 1985, **26**, 5997; (*b*) M. J. Sharp, W. Cheng and V. Snieckus, *Tetrahedron Lett.*, 1987, **28**, 5093; (*c*) W. Cheng and V. Snieckus, *Tetrahedron Lett.*, 1987, **28**, 5097; (*d*) M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1988, **29**, 5463; (*e*) B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui and V. Snieckus, *J. Org. Chem.*, 1991, **56**, 3763.

8 E. Wenkert, M. E. Shepard and A. T. McPhail, *J. Chem. Soc., Chem. Commun.*, 1986, 1390.

9 E. Wenkert, T. W. Ferreira and E. L. Michelotti, *J. Chem. Soc., Chem. Commun.*, 1979, 637.

10 (*a*) J.-L. Fabre, M. Julia and J.-N. Verpeaux, *Tetrahedron Lett.*, 1982, **23**, 2469; (*b*) J.-L. Fabre, M. Julia and J.-N. Verpeaux, *Bull. Soc. Chim. Fr.*, 1985, 762.

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‡ After reaction of **1e** with 4 equiv. of phenylmagnesium bromide in the absence of the nickel catalyst, no substitution product was detectable by GC in the crude product mixture.