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Meta- and *Para*-Difunctionalization of Arenes via a Sulfoxide−Magnesium Exchange Reaction

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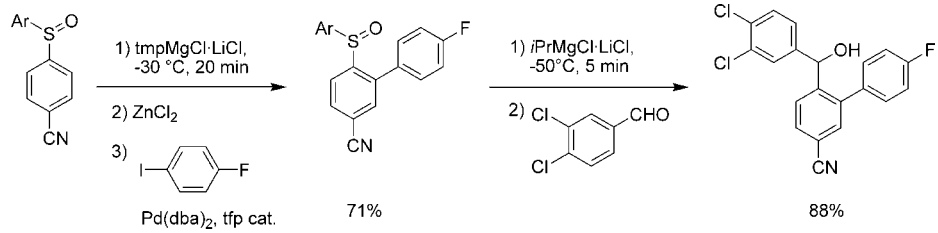
ABSTRACT



The aryl sulfoxide moiety (ArSO) allows an expedient two-step *meta*-, *para*-difunctionalization of readily available diaryl sulfoxides. In the first step, the sulfoxide plays the role of a directing metalation group. In the second step, triggered by *i*-PrMgCl·LiCl, it becomes a leaving group and undergoes a regioselective sulfoxide−magnesium exchange.

The functionalization of arenes via organometallic intermediates is of central importance for the preparation of polyfunctional aromatics.[1] Whereas arylmagnesium compounds are readily prepared via a directed *ortho*-metalation,[2] a magnesium insertion,[3]or a halogen−magnesium exchange,[4] the use of diaryl sulfoxides for the synthesis of functionalized arylmagnesium derivatives via a sulfoxide−magnesium exchange has barely been reported.[5] This is surprising since the sulfoxide group also has an exceptional directing metalation ability[6] and would therefore allow access to unusual substitution patterns of arenes. Furthermore, the sulfoxide group is a versatile functionality, which has found numerous applications in organic synthesis.[7]

We have envisaged that sulfoxides of type **1**, bearing various functional groups (FG = F, Cl, CN, CO_2-*t*-Bu, CF_3, alkynyl) can be magnesiated in the *ortho*-position using tmpMgCl·LiCl (**2**),[8] leading after quenching with an electrophile (E^1) to arenes of type **3**. A subsequent sulfoxide-magnesium exchange using *i*-PrMgCl·LiCl will provide an intermediate magnesium reagent **4**, which by reaction with a second electrophile (E^2) is giving *meta*- and *para*-difunctionalized aromatics of type **5**, a substitution pattern difficult to reach by standard methods.[9] Thus, the starting diaryl sulfoxides **1a**−**f** can be considered as being synthetic equivalents of the bis-carbanionic synthon **6** (Scheme 1). To perform successfully this sequence, the sulfoxides **1a**−**f**

(1) (a) Hartung, C. G.; SnieckusV. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; 330. (b) Schlosser, M. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 2002; 1. (c) Knochel, P. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.;Wiley-VCH: Weinheim, 2005. (d) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

(2) (a) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (b) Giuliano, C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681.

(3) (a) Rieke, R. D. *Science* **1989**, *246*, 1260. (b) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, 1925. (c) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

(4) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V.-V. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(5) (a) Ogawa, S.; Furukawa, N. *J. Org. Chem.* **1991**, *56*, 5723. (b) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933. (c) Yamamoto, T.; Ogawa, S.; Sugawara, M.; Kawai, Y.; Sato, R. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 460.

(6) Quesnelle, C.; Iihama, T.; Aubert, T.; Terrier, H.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2625.

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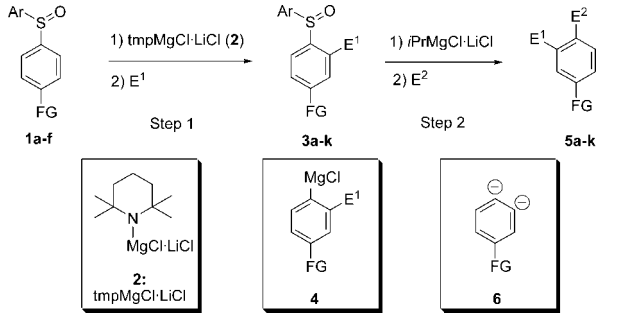
Scheme 1. Metalation of Sulfoxides, Followed by a Sulfoxide−Magnesium Exchange Reaction Leading to *Meta*- and *Para*-Difunctionalized Arenes (FG = F, Cl, CN, CO_2-*t*-Bu, CF_3, Alkynyl)

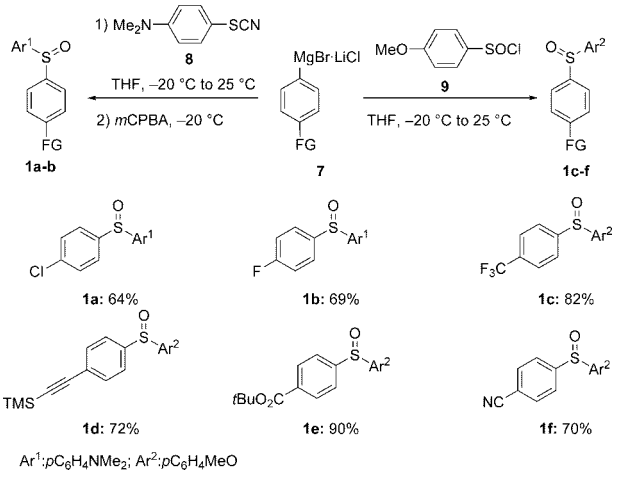


should undergo a regioselective deprotonation on the aromatic ring bearing the functional group FG, as well as a regioselective sulfoxide−magnesium exchange reaction producing an intermediate magnesium reagent of type **4** (and not the alternative exchange product: ArMgCl; Scheme 1). After extensive experimentation, we have solved both of these problems by introducing donor substituents at the *para*-position of the Ar group of **1**.[10] Thus, two types of diaryl sulfoxides proved to be excellent starting materials: the 4-*N*,*N*-dimethylaminophenyl sulfoxide derivatives **1a**,**b** and the 4-methoxyphenyl sulfoxide compounds **1c**−**f**. These sulfoxides were prepared by two convergent and practical synthetic routes (Scheme 2). Thus, the *N*,*N*-dimethylamino-substituted sulfoxides **1a**,**b** were prepared by the reaction of functionalized arylmagnesium reagents of type **7**[4] with 4-(dimethylamino)phenyl thiocyanate (**8**, $Me_2NC_6H_4SCN$)[11,12] followed by *m*-CPBA oxidation (CH_2Cl_2, −20 °C, 1.1 equiv), leading to sulfoxides **1a** (64%) and **1b**[13] (69%).

On the other hand, the reaction of functionalized arylmagnesium reagents of type **7**[4] with 4-methoxybenzenesulfinyl chloride (**9**, $MeOC_6H_4S(O)Cl$)[14] affords the desired 4-methoxy-substituted sulfoxides **1c**−**f** (FG: CF_3,[15] CN, CO_2-*t*-Bu, alkynyl[16]) in 70−90% yield. Having prepared the required diaryl sulfoxides **1a**−**f**, we have performed the directed metalation step (step 1 of Scheme 1). Thus, the sulfoxide **1a** was deprotonated with tmpMgCl·LiCl at −30 °C within 20 min. After transmetalation to the corresponding zinc reagent (using $ZnCl_2$ in THF), a Pd-catalyzed ($Pd(Ph_3)_4$, 2 mol %) cross-coupling[17] with 4-iodobenzonitrile or 4-iodobromobenzene gave the expected sulfoxides **3a**,**b** in 82−92% yield (entries 1 and 2, Table 1). Reaction of the magnesiated derivative of **1a** (FG = Cl) with tosyl cyanide led to the nitrile **3c** in 73% yield (entry 3). Similarly, the sulfoxide **1b** (FG = F) was metalated with tmpMgCl·LiCl at −30 °C within 20 min. Quenching of this magnesium species with iodine, followed by a Negishi cross-coupling with 2-phenylethynylzinc chloride, furnished the product **3d** in 95% yield (entry 4).[16]

Palladium-catalyzed cross-coupling with 4-iodoanisole gave the sulfoxide **3e** in 93% yield (entry 5). Using similar procedures, we were able to functionalize the diaryl sulfoxides **1c** (FG = CF_3), **1d** (FG = TMS-acetylene), **1e** (FG = CO_2-*t*-Bu), and **1f** (FG = CN) in 68−79% yield (entries 6−9). The second step of the synthetic sequence (Scheme 1), i.e., the sulfoxide−magnesium exchange, was >95% regioselective, providing only the desired magnesium re-

Scheme 2. Preparation of Sulfoxides of Type **1**



(7) (a) Oae, S.; Kawai, T.; Furukawa, N. *Tetrahedron Lett.* **1984**, *25*, 69. (b) Kawai, T.; Furukawa, N. *Tetrahedron Lett.* **1984**, *25*, 2549. (c) Oae, S.; Takeda, T.; Wakabayashi, S. *Heterocycles* **1989**, *28*, 99. (d) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1989**, *30*, 7091. (e) Furukawa, N.; Ogawa, S.; Matsumura, K.; Shibutani, T.; Fujihara, H. *Chem. Lett.* **1990**, *20*, 979. (f) Shibutani, T.; Fujihara, H.; Furukawa, N. *Tetrahedron Lett.* **1991**, *32*, 2943. (g) Uenishi, J.; Yamamoto, A.; Takeda, T.; Wakabayashi, S.; Oae, S. *Heteroat. Chem.* **1992**, *3*, 73. (h) Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502. (i) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072. (j) Satoh, T.; Taguchi, D.; Suzuki, C.; Fujisawa, S. *Tetrahedron* **2001**, *57*, 493. (k) Satoh, T.; Akita, K. *Chem. Pharm. Bull.* **2003**, *51*, 181. (l) Kagan, H. B.; LuukasT. O. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; 479. (m) Capozzi, M.; Cardellicchio, C.; Naso, F. *Eur. J. Org. Chem.* **2004**, *9*, 1845. (n) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Tetrahedron* **2005**, *61*, 6386. (o) Cardellicchio, C.; Naso, F.; Capozzi, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1161. (p) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773. (q) Manchena, O. G.; Bolm, C. *Org. Lett.* **2006**, *11*, 2349. (r) Sugiyama, S.; Shimizu, H.; Satoh, T. *Tetrahedron Lett.* **2006**, *47*, 8771. (s) Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 1561. (t) Ferber, B.; Kagan, H. B. *Adv. Synth. Catal.* **2007**, *349*, 493. (u) Brebion, F.; Goddard, J.-P.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2008**, *10*, 1917.

(8) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(9) Rohbogner, C. J.; Giuliano, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503.

(10) Key for the regioselectivity of the sulfoxide−magnesium exchange is an electronic differentiation of the two aromatic rings attached to the sulfoxide moiety. Thus, the most stable organometallic species is always formed (the one bearing the most electron-withdrawing substituent).

(11) Brewster, R. Q.; Schroeder, W. *Org. Synth.* **1943**, *19*, 79.

(12) Jendralla, H.; Chen, L. *Synthesis* **1990**, 827.

(13) Lang, S. A.; Fields, T. L.; Wilkinson, R. G.; Kang, S. M.; Lin, Y. J. *Eur. Pat. Appl.* **1984**, 38.

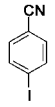
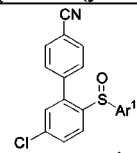
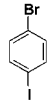
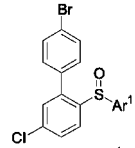
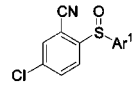
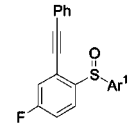
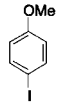
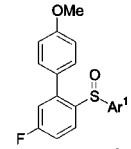
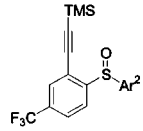
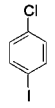
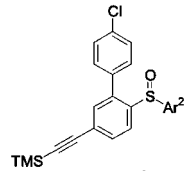
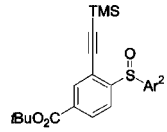
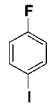
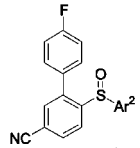
(14) Peyronneau, M.; Roques, N.; Mazieres, S.; Le Roux, C. *Synlett* **2003**, 631.

(15) Yano, T.; Sakaguchi, I.; Katsura, G.; Yoshikawa, N. *PCT Int. Appl.* **2002**, 51.

(16) For more details, see the Supporting Information.

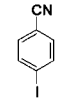
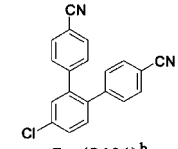
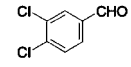
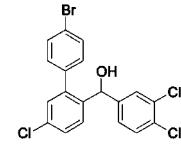
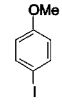
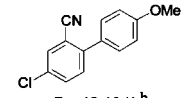
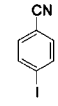
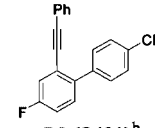
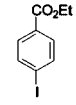
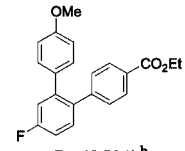
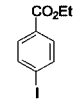
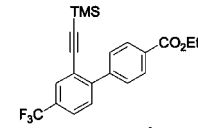
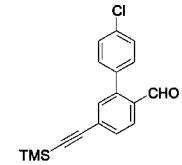
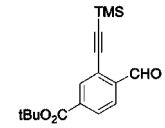
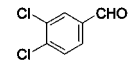
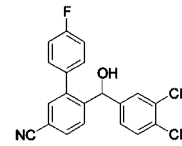
(17) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Zeng, X.; Quian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259.

Table 1. *ortho*-Magnesiation of Functionalized Sulfoxides Followed by Electrophilic Reaction

entry	sulfoxide	E^1	product (yield)[a]
1	**1a**		 **3a** (92%)[b]
2	**1a**		 **3b** (82%)[b]
3	**1a**	TsCN	 **3c** (73%)
4	**1b**	i) I_2 ii) Ph—≡—ZnCl	 **3d** (95%)
5	**1b**		 **3e** (93%)[b]
6	**1c**	i) I_2 ii) TMS—≡—ZnCl	 **3f** (79%)
7	**1d**		 **3g** (73%)[b]
8	**1e**	i) I_2 ii) TMS—≡—ZnCl	 **3h** (68%)
9	**1f**		 **3i** (71%)[b]

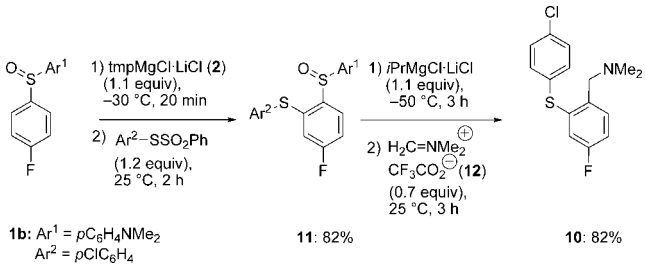
[a] Isolated yield of analytically pure product. [b] After transmetalation to zinc using zinc chloride 1 M in THF; $Ar^1 = pC_6H_4NMe_2$; $Ar^2 = pC_6H_4$-OMe.

Table 2. Sulfoxide−Magnesium Exchange of Functionalized Sulfoxides Followed by Electrophilic Reaction

entry	sulfoxide	E^2	product (yield)[a]
1	**3a**		 **5a** (81%)[b]
2	**3b**		 **5b** (63%)
3	**3c**		 **5c** (84%)[b]
4	**3d**		 **5d** (84%)[b]
5	**3e**		 **5e** (85%)[b]
6	**3f**		 **5f** (87%)[b]
7	**3g**	DMF	 **5g** (68%)
8	**3h**	DMF	 **5h** (78%)
9	**3i**		 **5i** (88%)

[a] Isolated yield of analytically pure product referring to 0.8 equiv of electrophile. [b] After transmetalation to zinc using zinc chloride 1 M in THF.

Scheme 3. Two-Step Preparation of the Serotonin Reuptake Inhibitor **10**



agents **4** (and not the alternative cleavage product ArMgCl). Thus, the reaction of **3a** with *i*-PrMgCl•LiCl at −50 °C within 1 h, followed by cross-coupling with 4-iodobenzonitrile, furnished the terphenyl **5a** in 81% yield (entry 1, Table 2).[18] A range of polyfunctional compounds (**5c**−**f**) was obtained in 83−87% yield, applying the same procedure to the sulfoxides **3c**−**f** (entries 6−9). Interestingly, the bromine-substituted sulfoxide **3b** undergoes a selective sulfoxide−magnesium exchange within 5 h at −50 °C and gives with 3,4-dichlorobenzaldehyde the alcohol **5b** in 63% yield (entry 2), showing that this sulfoxide/magnesium exchange is faster than the corresponding Br/Mg exchange. Diaryl sulfoxides **3g**−**i** bearing sensitve functional groups (CO_2-*t*-Bu, CN) reacted smoothly with *i*-PrMgCl•LiCl and were trapped successfully with electrophiles, producing the compounds **5g**−**i** in 68−88% yield (entry 7−9). We have applied this sequence to the preparation of the biological active sulfide **10**, which is a serotonin reuptake inhibitor.[19] Thus, the sulfoxide **1b** (FG = F) was metalated with tmpMgCl•LiCl at −30 °C within 20 min. Quenching of the resulting magnesium species with (*S*)-(4-chlorophenyl)benzene thiosulfonate[20] led to the expected sulfide **11** in 82% yield. This sulfoxide was treated with *i*-PrMgCl•LiCl at −50 °C furnishing the corresponding magnesium intermediate within 3 h, which reacted cleanly with the iminium salt **12**[21] to give the serotonin reuptake inhibitor **10**[18] in 82% yield (Scheme 3).

In summary, we have developed an efficient two-step sequence allowing a *meta*-, *para*-difunctionalization of aromatics using the chameleon chemical behavior of the sulfoxide moiety (ArSO). This versatile functional group acts as a metalation directing group in the presence of tmpMgCl•LiCl (**2**) and as a leaving group in the presence of *i*-PrMgCl•LiCl, generating a new Grignard reagent. Further extensions of the use of the sulfoxide group for generating polyfunctional Grignard reagents are currently being studied in our laboratories.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Performing the sulfoxide−magnesium exchange reaction in THF led to 10−35% of protonated Grignard reagent **4**. In spite of numerous deuteration experiments, the proton source could not be identified. However, by using 2-methyltetrahydrofuran, this protonation could be reduced to 10−20%.

(19) Polivka, Z.; Dobrovsk, K.; Silhankova, A.; Sindelar, K.; Mickova, R.; Valenta, V.; Krejci, I. *PCT Int. Appl. WO 9717325*, 1997.

(20) Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.

(21) (a) Millot, N.; Piazza, C.; Avolio, S.; Knochel, P. *Synthesis* **2000**, 941. (b) Gommermann, N.; Koradin, C.; Knochel, P. *Synthesis* **2002**, 2143.