CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201003657

VIP

Difunctionalisation of Arenes and Heteroarenes by Directed Metallation and Sulfoxide–Magnesium Exchange

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Dedicated to Professor Alfredo Ricci on the occasion of his 72th birthday

Abstract: The aryl sulfoxide moiety allows an expedient two-step difunctionalisation of readily available diaryl sulfoxides. Highly functionalised 1,2,4-trisubstituted arenes and difunctionalised heteroarenes (furans, thiophenes, benzofurans and pyridines) were prepared in a two-step sequence, triggered by an aryl sulfoxide group. In the first step, the sulfoxide moiety acts as a metallation-directing group, allowing smooth *ortho*-magnesiation with TMPMgCl·LiCl (TMP = tetramethylpiperidine). After a quenching reaction with an electrophile, the resulting sulfoxide is converted into a second magnesium reagent with *i*PrMgCl·LiCl (sulfoxide–magnesium exchange), which can be trapped with various electrophiles. Highly chemoselective TMPMgCl·LiCl and *i*PrMgCl·LiCl are compatible with a broad range of functional groups (e.g., F, Cl, CF_3, CN, CO_2tBu, alkynyl, ethers, thioethers). Large-scale reactions (25–40 mmol) and the preparation of fully functionalised furans and thiophenes are also reported.

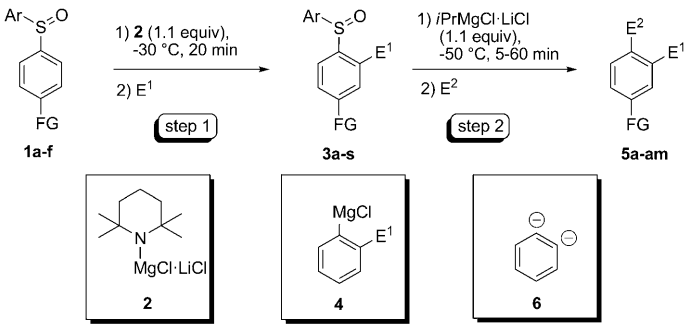
Keywords: arenes · heterocycles · magnesium · metalation · sulfoxide–magnesium exchange

Introduction

The functionalisation of arenes and heteroarenes via organometallic intermediates is of central importance for the preparation of polyfunctional aromatics.[1] Whereas organomagnesium compounds are readily prepared by a directed *ortho*-metallation,[2] a magnesium insertion[3] or a halogen–magnesium exchange,[4] the use of diaryl sulfoxides for the synthesis of functionalised aryl- or hetarylmagnesium derivatives by a sulfoxide–magnesium exchange have barely been reported.[5] This is surprising because the sulfoxide group also has an exceptional directing-metallation ability[6] and would therefore allow access to unusual substitution patterns of aromatic scaffolds. Furthermore, the sulfoxide moiety is a versatile functionality, which has found numerous applications in organic synthesis.[7] Recently, we have shown that the sulfoxide group undergoes smooth sulfoxide–magnesium exchange on a variety of aromatic and heteroaromatic substrates, providing that a *para*-methoxyphenyl or *para*-dimethylaminophenyl group was attached to the sulfur centre.[8] Herein, we report the full scope of these aromatic difunctionalisation reactions using the sulfoxide moiety in a two-step sequence.

Results and Discussion

We have envisaged that aromatic sulfoxides of type **1**, with various functional groups (FG = F, Cl, CN, CO_2tBu, CF_3, alkynyl) can be magnesiated in the *ortho*-position by using **2**,[9] leading, after quenching with an electrophile (E^1), to arenes of type **3** (Scheme 1). A subsequent sulfoxide–magnesium exchange with *i*PrMgCl·LiCl provides an intermediate magnesium reagent **4**. After reaction with a second electrophile (E^2), *meta*- and *para*-difunctionalised aromatics of type **5** can be obtained. This type of substitution pattern is difficult to achieve by standard methods.[10] Thus, the starting diaryl sulfoxides **1a–f** can be considered as synthetic equivalents of the *bis*-carbanionic synthon **6** (Scheme 1). To successfully perform this sequence, sulfoxides **1a–f** should



Scheme 1. Metallation of sulfoxides, followed by a sulfoxide–magnesium exchange reaction, leading to 1,2,4-trifunctionalised arenes.

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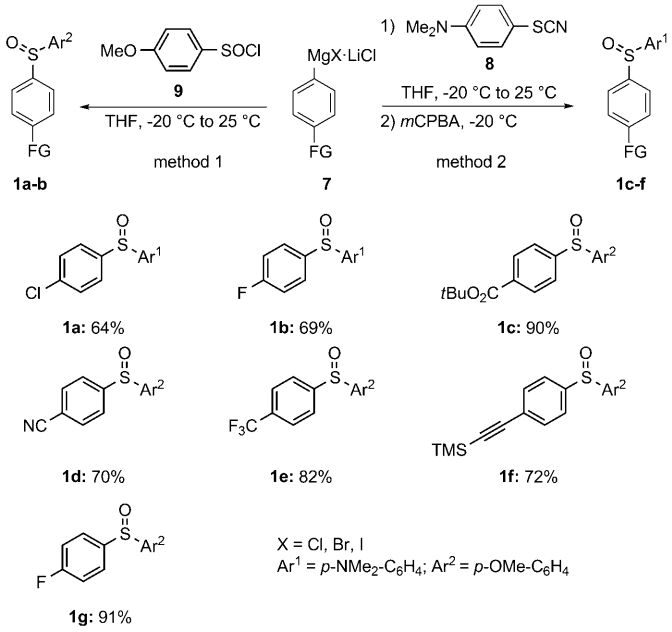
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003657.

undergo a regioselective deprotonation on the aromatic ring containing FG, as well as a regioselective sulfoxide–magnesium exchange reaction producing the organomagnesium reagent **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**.[11]

Two types of diaryl sulfoxides proved to be excellent starting materials: the 4-*N*,*N*-dimethylaminophenyl sulfoxide derivatives (**1a** and **1b**) and the 4-methoxyphenyl sulfoxide compounds (**1c–f**). These sulfoxides were obtained by two convergent and practical synthetic routes (Scheme 2). Thus,



Scheme 2. Preparation of sulfoxides **1a–g**. *m*CPBA = *meta*-chloroperbenzoic acid.

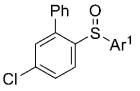
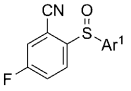
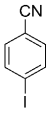
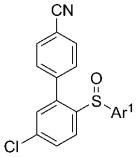
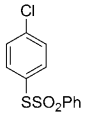
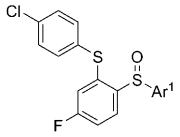
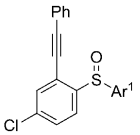
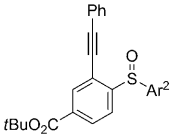
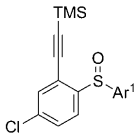
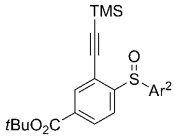
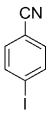
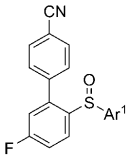
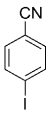
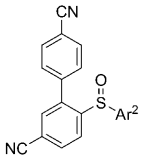
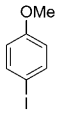
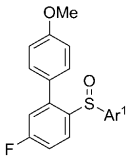
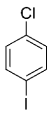
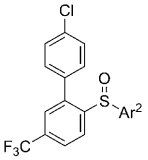
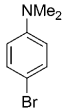
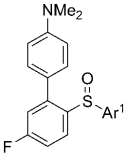
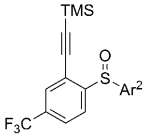
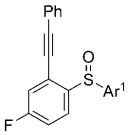
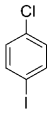
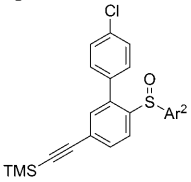
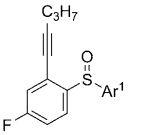
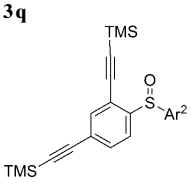
the *N*,*N*-dimethylamino-substituted sulfoxides **1a** and **1b** were prepared in 64–69% yield by the reaction of functionalised organomagnesium reagents (**7**)[4] with 4-(dimethylamino)phenyl thiocyanate (**8**),[12] followed by *m*CPBA oxidation (1.1 equiv, CH_2Cl_2, −20 °C).[13] On the other hand, the reaction of functionalised arylmagnesium reagents of type **7**[4] with 4-methoxybenzenesulfinyl chloride (**9**)[14] afforded the desired 4-methoxy-substituted sulfoxides **1c–f** in 70–91% yield.[15] Having prepared the required diaryl sulfoxides **1a–f**, we performed the directed-metallation step (step 1 of Scheme 1).

Preparation of functionalised sulfoxides 3a–s by direct metallation using 2: Thus, sulfoxide **1a** (FG = Cl) was deprotonated with **2** (1.1 equiv) in THF at −30 °C within 20 min. After transmetallation to the corresponding zinc reagent (using $ZnCl_2$ in THF), a Pd-catalysed (2% $[Pd(PPh_3)_4]$) cross-coupling[16] with iodobenzene or 4-iodobenzonitrile gave the expected sulfoxides **3a** and **3b** in 97 and 92% yield, respectively (Table 1, entries 1 and 2). Quenching the magnesiated derivative of **1a** with iodine, followed by a Negishi cross-coupling with 2-phenylethynylzinc chloride or 2-(trimethylsilyl)ethynylzinc chloride, gave products **3c** and **3d** in 91 and 88% yield, respectively (Table 1, entries 3 and 4).[16] Similarly, sulfoxide **1b** (FG = F) was metallated with **2** in THF at −30 °C within 20 min. After transmetallating to the organozinc species, a palladium-catalysed cross-coupling with 4-iodobenzonitrile, 4-iodoanisole or 4-bromo-*N*,*N*-dimethylaniline led to the corresponding sulfoxides **3e–g** in 84-95% yield (Table 1, entries 5–7). The organomagnesium species of **1b** could also be quenched with iodine and cross-coupled with 2-phenylethynylzinc chloride or 1-pentynylzinc chloride to give sulfoxides **3h** and **3i** in 94 and 74% yield, respectively (Table 1, entries 8 and 9). Likewise, tosyl (Tos) cyanide or (*S*)-(4-chlorophenyl)benzene thiosulfonate[17] were used to quench the magnesiated derivative of **1b** to give nitrile **3j** and thioether **3k** in 79 and 82% yield, respectively (Table 1, entries 10 and 11). Using similar procedures, we were able to functionalise the diaryl sulfoxides **1c** (FG = CO_2tBu), **1d** (FG = CN), **1e** (FG = CF_3) and **1f** (FG = trimethylsilyl (TMS)-acetylene) in 61–91% yield (Table 1, entries 12–18).

Preparation of 1,2,4-trisubstituted arenes (5a–l) by a sulfoxide–magnesium exchange using *i*PrMgCl·LiCl: The second step of the synthetic sequence (Scheme 1), that is, the sulfoxide–magnesium exchange, was >95% regioselective and provided only the desired magnesium reagent **4** (and not the alternative cleavage product ArMgCl). Thus, the reaction of **3a** with *i*PrMgCl·LiCl (1.1 equiv) in 2-methyltetrahydrofuran (2-Me-THF)[18] at −50 °C was complete within 1 h, and after transmetallation with $ZnCl_2$ was followed by a cross-coupling with 4-iodobenzonitrile to give terphenyl **5a** in 93% yield (Table 2, entry 1). Similarly, the arylmagnesium reagent obtained from the reaction of **3a** with *i*PrMgCl·LiCl could be cross-coupled with ethyl 4-iodobenzoate to give compound **5b** in 89% yield (Table 2, entry 2). The sulfoxide–magnesium exchange was also performed on sulfoxide **3b** (−50 °C, 1 h, 2-Me-THF) and quenching the intermediate arylmagnesium derivative with DMF led to benzaldehyde **5c** in 74% yield (Table 2, entry 3). A copper-catalysed allylation reaction with ethyl 2-(bromomethyl)acrylate[19] gave biphenyl **5d** in 48% yield, whereas a Pd-catalysed cross-coupling with **5e** in 90% yield (Table 2, entries 4 and 5, respectively). In the case of alkynyl-substituted sulfoxide **3c**, the sulfoxide–magnesium exchange took place in only 5 min (−50 °C, 2-Me-THF) and the functionalised benzaldehyde **5f** could be obtained in 93% yield after trapping with DMF (Table 2, entry 6). A range of polyfunctional compounds **5g–l** were prepared in 59–89% yield by applying the same procedure to sulfoxides **3c** and **3d** (Table 2, entries 7–12).

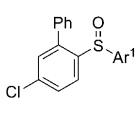
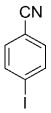
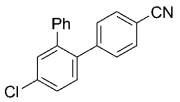
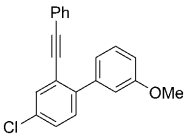
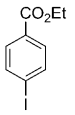
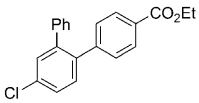
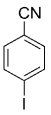
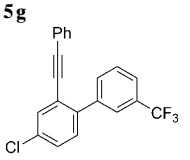
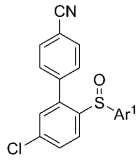
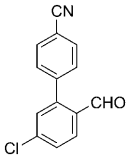
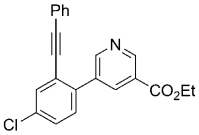
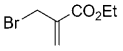
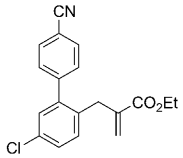
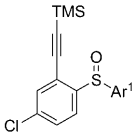
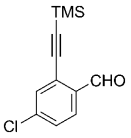
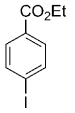
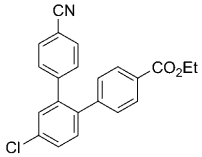
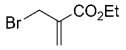
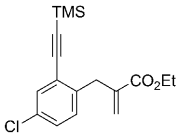
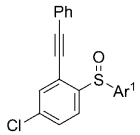
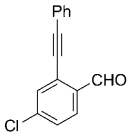
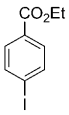
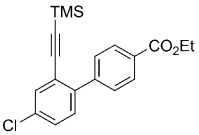
Preparation of 1,2,4-trisubstituted arenes (5m–z) by a sulfoxide–magnesium exchange using *i*PrMgCl·LiCl: The 2,4-disubstitued arylsulfoxide derivatives of **1b** (FG = F) reacted equally well in the sulfoxide–magnesium exchange reaction

Table 1. *ortho*-Magnesiation of functionalised sulfoxides **1a–f** followed by reaction with an electrophile.

Entry	Sulfoxide	Electrophile	Product	Yield [%][a]	Entry	Sulfoxide	Electrophile	Product	Yield [%][a]
1	**1a**	PhI	 **3a**	97[b]	10	**1b**	TosCN	 **3j**	79
2	**1a**		 **3b**	92[b]	11	**1b**		 **3k**	82
3	**1a**	1) I_2 2) Ph—≡—ZnCl	 **3c**	91	12	**1c**	1) I_2 2) Ph—≡—ZnCl	 **3l**	61
4	**1a**	1) I_2 2) TMS—≡—ZnCl	 **3d**	88	13	**1c**	1) I_2 2) TMS—≡—ZnCl	 **3m**	68
5	**1b**		 **3e**	94[b]	14	**1d**		 **3n**	88[b]
6	**1b**		 **3f**	93[b]	15	**1e**		 **3o**	91[b]
7	**1b**		 **3g**	84[b]	16	**1e**	1) I_2 2) TMS—≡—ZnCl	 **3p**	79
8	**1b**	1) I_2 2) Ph—≡—ZnCl	 **3h**	94	17	**1f**		 **3q**	73[b]
9	**1b**	1) I_2 2) C_3H_7—≡—ZnCl	 **3i**	74	18	**1f**	1) I_2 2) TMS—≡—ZnCl	 **3r**	72

[a] Yield of isolated, analytically pure product. [b] After transmetallation to zinc using 1 M zinc chloride in THF. [c] $Ar^1 = p\text{-}NMe_2\text{-}C_6H_4$; $Ar^2 = p\text{-}OMe\text{-}C_6H_4$.

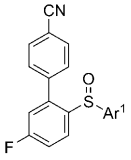
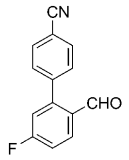
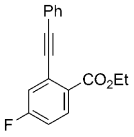
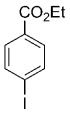
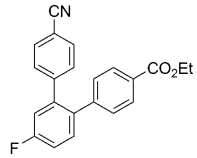
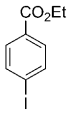
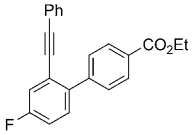
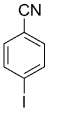
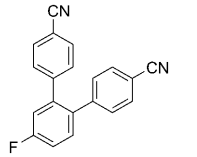
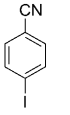
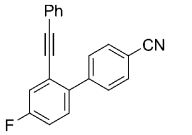
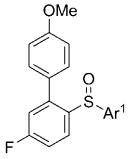
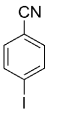
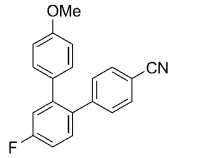
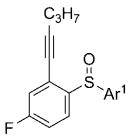
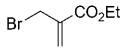
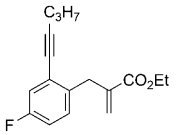
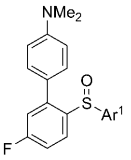
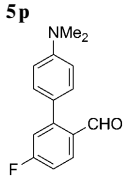
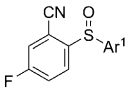
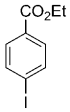
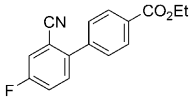
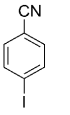
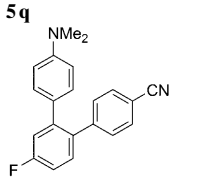
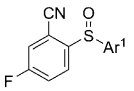
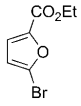
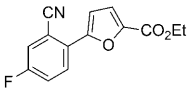
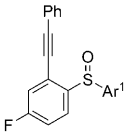
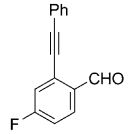
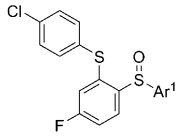
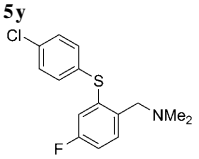
Table 2. Sulfoxide–magnesium exchange of functionalised sulfoxides **3a–d** followed by reaction with an electrophile.

Entry	Sulfoxide	Electrophile	Product	Yield [%][a]	Entry	Sulfoxide	Electrophile	Product	Yield [%][a]
1	 **3a**		 **5a**	93[b]	7	**3c**		 **5g**	73[b]
2	**3a**		 **5b**	89[b]	8	**3c**		 **5h**	72[b]
3	 **3b**	DMF	 **5c**	74	9	**3c**		 **5i**	59[b]
4	**3b**		 **5d**	48	10	 **3d**	DMF	 **5j**	89
5	**3b**		 **5e**	90[b]	11	**3d**		 **5k**	87
6	 **3c**	DMF	 **5f**	93	12	**3d**		 **5l**	84[b]

[a] Yield of isolated, analytically pure product with respect to 0.8 equiv of electrophile. [b] After transmetallation to zinc using 1 M zinc chloride in THF. [c] $Ar^1 = p\text{-}NMe_2\text{-}C_6H_4$.

for the second step of the two-step sequence (Scheme 1). Thus, sulfoxide **3e** could be exchanged with *i*PrMgCl·LiCl (−50 °C, 1 h, 2-Me-THF) and quenching of the intermediate Grignard reagent with DMF gave the functionalised benzaldehyde **5m** in 76 % yield (Table 3, entry 1). Alternatively, the magnesium species resulting from the exchange reaction could be transmetallated into an organozinc reagent and used in a Negishi-type cross-coupling reaction with 4-iodobenzonitrile or ethyl 4-iodobenzoate, leading to terphenyls **5n** and **5o** in 76 and 75 % yield, respectively (Table 3, entries 2 and 3). The sulfoxide–magnesium exchange was also performed on electron-rich substituted sulfoxides **3f** and **3g** (0 °C, 1 h, 2-Me-THF) and by performing cross-coupling reactions or directly reacting the magnesiumorganyl compound with DMF, we obtained trisubstituted arenes **5p–r** in 72–86 % yield (Table 3, entries 4–6). With the 2-alkynyl-substituted *bis*-aryl sulfoxides **3h** and **3i**, the *i*PrMgCl·LiCl-triggered exchange step took place within 5 min (−50 °C, 2-Me-THF). Trapping with DMF or ethyl chloroformate and by performing a cross-coupling reaction (after transmetallation with $ZnCl_2$ in THF) with aryl iodides or an allylation reaction led to the polyfunctionalised arylacetylenes **5s–w** in 67–94 % yield (Table 3, entries 7–11). Sulfoxide **3j**, with a nitrile *ortho* to the sulfoxide, was treated with *i*PrMgCl·LiCl (−50 °C, 5 min, 2-Me-THF), transmetallated and used in cross-coupling reactions with ethyl 4-iodobenzoate or ethyl 5-bromofuran-2-carboxylate. The resulting disubstituted benzonitrile derivatives **5x** and **5y** were obtained in 78 and 72 % yield, respectively (Table 3, entries 12 and 13). In the same manner, sulfoxide **3k** underwent the exchange reaction (−50 °C, 3 h, 2-Me-THF) and was submitted to an aminoalkylation. The biologically active sulfide **5z**, which is a

Table 3. Sulfoxide–magnesium exchange of functionalised sulfoxides **3e–k** followed by reaction with an electrophile.

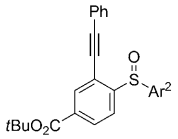
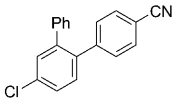
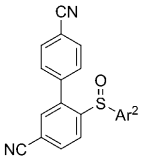
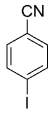
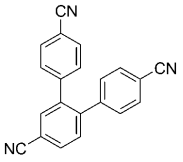
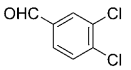
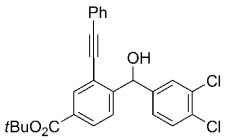
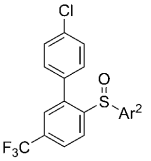
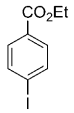
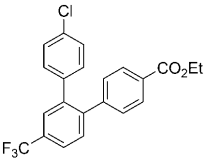
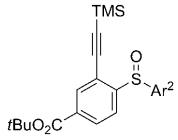
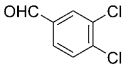
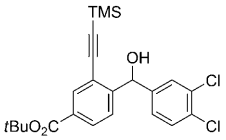
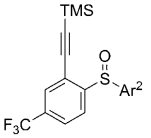
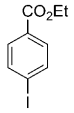
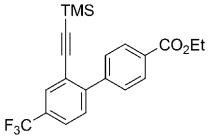
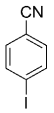
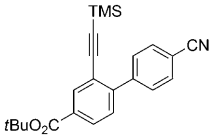
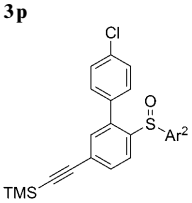
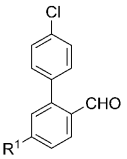
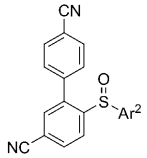
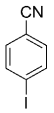
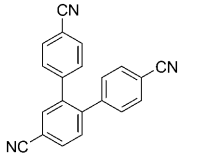
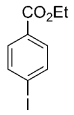
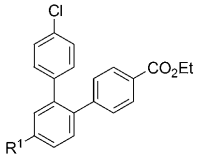
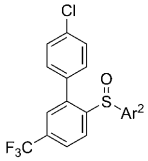
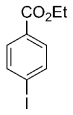
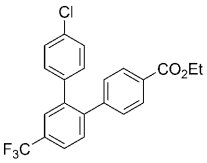
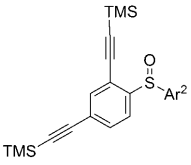
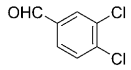
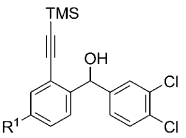
Entry	Sulfoxide	Electrophile	Product	Yield [%][a]	Entry	Sulfoxide	Electrophile	Product	Yield [%][a]
1	 **3e**	DMF	 **5m**	76	8	**3h**	$ClCO_2Et$	 **5t**	67[b]
2	**3e**		 **5n**	76[b]	9	**3h**		 **5u**	84[b]
3	**3e**		 **5o**	75[b]	10	**3h**		 **5v**	83[b]
4	 **3f**		 **5p**	86[b]	11	 **3i**		 **5w**	71
5	 **3g**	DMF	 **5q**	79	12	 **3j**		 **5x**	78
6	**3g**		 **5r**	72[b]	13	 **3j**		 **5y**	72
7	 **3h**	DMF	 **5s**	94	14	 **3k**	$H_2C{=}NMe_2^+$ $CF_3CO_2^-$	 **5z**	82

[a] Yield of isolated, analytically pure product with respect to 0.8 equiv of electrophile. [b] After transmetallation to zinc using 1 M zinc chloride in THF. [c] $Ar^1 = p\text{-}NMe_2\text{-}C_6H_4$.

serotonin reuptake inhibitor,[20] was obtained in 82% yield (Table 3, entry 14).

Preparation of 1,2,4-trisubstituted arenes (5aa–aj) by a sulfoxide–magnesium exchange using *i*PrMgCl·LiCl: The sulfoxide–magnesium exchange protocol is compatible with a variety of other functional groups, such as an ester, a trifluoromethyl or a nitrile. Thus, *bis*-aryl sulfoxide **3l** (FG = CO_2tBu) underwent a smooth exchange reaction with *i*PrMgCl·LiCl (−50 °C, 5 min, 2-Me-THF), and quenching with DMF gave aldehyde **5aa** in 71% yield (Table 4, entry 1). The intermediate arylmagnesium compound derived from **3l** could also be trapped with 3,4-dichlorobenzaldehyde, leading to the secondary alcohol **5ab** in 84% yield (Table 4, entry 2). Similarly, sulfoxide **3m** underwent the exchange reaction (−50 °C, 5 min, 2-Me-THF) and could be functionalised by using 3,4-dichlorobenzaldehyde or 4-iodobenzonitrile, which led to the trisubstituted arenes **5ac** and

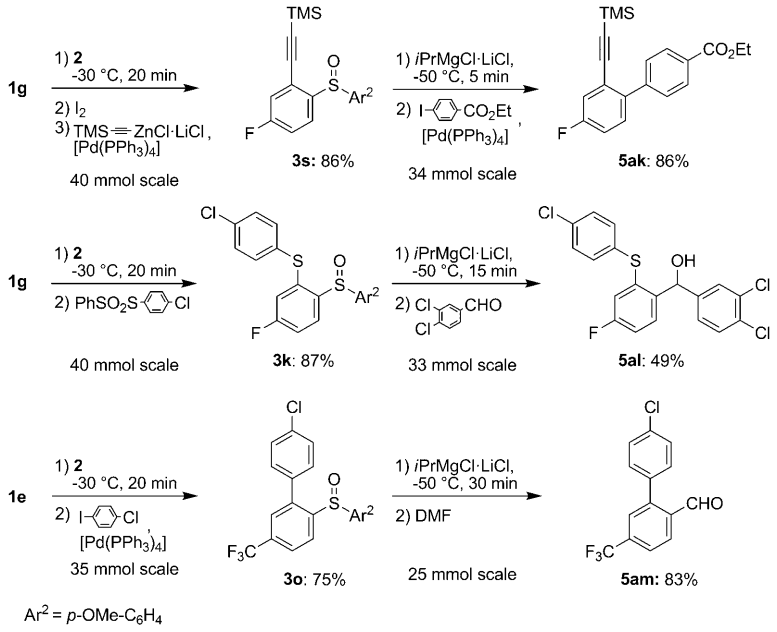
Table 4. Sulfoxide–magnesium exchange of functionalised sulfoxides **3l–r** followed by the reaction with an electrophile.

Entry	Sulfoxide	Electrophile	Product	Yield [%][a]	Entry	Sulfoxide	Electrophile	Product	Yield [%][a]
1	 **3l**	DMF	 **5aa**	71	5	 **3n**		 **5ae**	64[b]
2	**3l**		 **5ab**	84	6	 **3o**		 **5af**	79[b]
3	 **3m**		 **5ac**	82	7	 **3p**		 **5ag**	87[b]
4	**3m**		 **5ad**	77[b]	8	 **3q**	DMF	 **5ah**	68
5	 **3n**		 **5ae**	64[b]	9	**3q**		 **5ai**	68[b]
6	 **3o**		 **5af**	79[b]	10	 **3r**		 **5aj**	72

[a] Yield of isolated, analytically pure product with respect to 0.8 equiv of electrophile. [b] After transmetallation to zinc using 1 M zinc chloride in THF. [c] $Ar^2 = p$-OMe-C_6H_4; R^1 = TMS-acetylene.

5ad in 82 and 77% yield, respectively (Table 4, entries 3 and 4). Sulfoxide **3n**, with two nitrile groups, could readily be exchanged with *i*PrMgCl·LiCl (−50 °C, 5 min, 2-Me-THF), transmetallated with $ZnCl_2$ and cross-coupled with 4-iodobenzonitrile, yielding the tricyanoterphenyl **5ae** in 64% yield (Table 4, entry 5). Diaryl sulfoxides **3o–r** (FG = CF_3, TMS-acetylene) could be metallated and functionalised in the same fashion to give 1,2,4-trisubstituted arenes **5af–aj** in 68–87% yield (Table 4, entries 6–10).

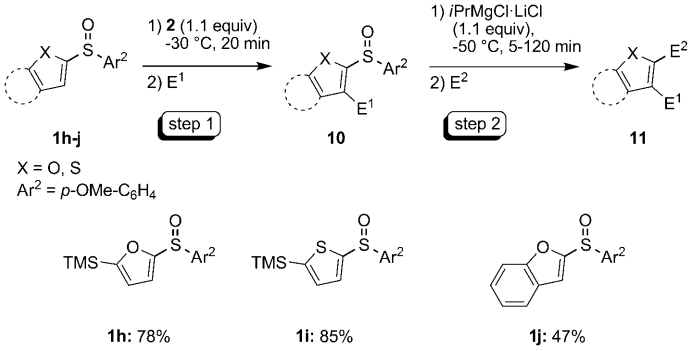
Large-scale preparation of 1,2,4-trisubstituted arenes (5ak–am) using the two-step protocol: The two-step protocol (step 1 being the metallation using **2** directed by the sulfoxide group, and step 2 being the sulfoxide–magnesium exchange using *i*PrMgCl·LiCl) could also be applied to large-scale reactions. Thus, sulfoxide **1g** (FG = F) was magnesiated with **2** (−30 °C, 20 min, 40 mmol scale, THF) and trapped with iodine. The resulting aryliodide then underwent a smooth Negishi cross-coupling reaction with TMS-acetylene-zinc chloride using a Pd catalyst to give sulfoxide **3s** in 86% yield (Scheme 3). Treating **3s** with *i*PrMgCl·LiCl (−50 °C, 5 min, 34 mmol scale, 2-Me-THF) and subsequent transmetallation ($ZnCl_2$ in THF) and cross-coupling with ethyl 4-iodobenzoate gave trisubstituted benzene **5ak** in 86% yield. Alternatively, sulfoxide **1g** could be deprotonated by using the same conditions as those described above and the magnesiated species was trapped with (*S*)-(4-chlorophenyl)benzene thiosulfonate to give diaryl thioether **3k** in 87% yield



Scheme 3. Large-scale preparation of 1,2,4-trisubstituted arenes (**5ak–am**).

(Scheme 3). By treating **3k** with the exchange reagent *i*PrMgCl·LiCl (−50 °C, 15 min, 33 mmol scale, 2-Me-THF) and quenching with 3,4-dichlorobenzaldehyde, we isolated benzylic alcohol **5al** in 49 % yield. Sulfoxide **1e** underwent smooth magnesiation (**2**, −30 °C, 20 min, 35 mmol scale, THF) and gave biphenyl **3o** in 75 % yield after a Pd-catalysed cross-coupling reaction with 4-iodochlorobenzene (Scheme 3). Finally, by treating **3o** with *i*PrMgCl·LiCl (−50 °C, 30 min, 2-Me-THF) on a 25 mmol scale and trapping the intermediate with DMF, the trisubstituted benzaldehyde **5am** was provided in 83 % yield.

Preparation of 1,2-disubstituted heteroarenes (11) by using the two-step protocol: The two-step difunctionalisation synthesis was used for five-membered heterocyclic sulfoxides in a similar manner (Scheme 4). The required sulfoxides **1h–j** were prepared according to method 1 in Scheme 2 starting from the corresponding 2-heteroaryl organolithiums.

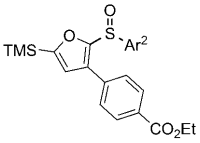
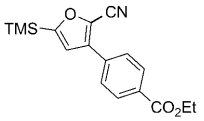
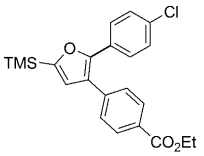
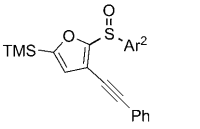
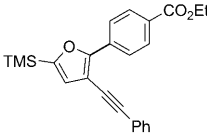
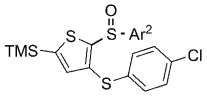
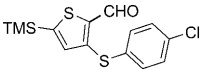
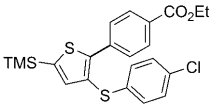
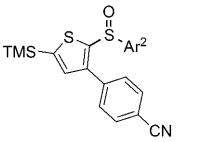
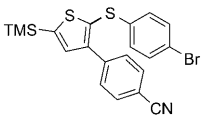
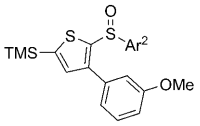
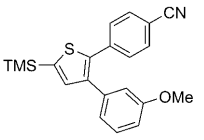
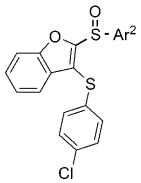
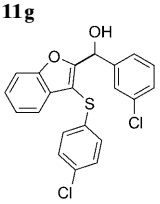
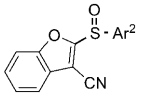
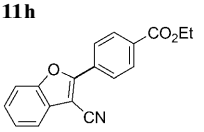


Scheme 4. Metallation of 2-heteroaryl sulfoxides (**1h–j**), followed by a sulfoxide–magnesium exchange reaction, leading to 1,2-difunctionalised 5-membered heterocycles.

Therefore, 2-furyl sulfoxide (**1h**) was selectively metallated with **2** (20 min, −30 °C, THF) in position 3. The resulting heterocyclic magnesium reagent was transmetallated (using $ZnCl_2$ in THF) and cross-coupled with ethyl 4-iodobenzoate using Pd catalysis, leading to furan derivative **10a** in 77 % yield (Table 5, entry 1). By using *i*PrMgCl·LiCl, the sulfoxide moiety was exchanged (−50 °C, 2 h, 2-Me-THF) and the organometallic species was quenched with TosCN to give the 1,2-disubstituted furanyl derivate **11a** in 63 % yield. Alternatively, after exchanging the sulfoxide group of **10a** and transmetallation to the zinc species, a Negishi cross-coupling with 4-iodo chlorobenzene was performed to yield heterocycle **11b** in 68 % yield (Table 5, entry 2). By deprotonating **1h** with **2** and trapping with iodine, the 3-iodo-furanyl derivative was obtained. This underwent a straightforward cross-coupling with 2-phenylethynylzinc chloride to give compound **10b** in 69 % yield (Table 5, entry 3). After exchanging the sulfoxide group of **10b** (*i*PrMgCl·LiCl, −78 °C, 15 min, 2-Me-THF) a second cross-coupling was performed to afford the disubstituted furanyl derivate **11c** in 68 % yield. 2-Thiophenyl and 2-benzofuryl sulfoxides were also suitable for our reaction conditions, and therefore, we prepared the 1,2-difunctionalised 5-membered heterocycles **11d–i** in 77–97 % yield (Table 5, entries 4–9).

Preparation of fully functionalised five-membered heteroarenes: These 2,3-difunctionalised heterocycles were readily converted into tetra-substituted heterocycles in a straightforward manner. Thus, the 2-silylated furan **11b** was converted to the corresponding 2-iodofuran (ICl, 1.5 equiv, 0 °C, 1 h, 79 %).[21] A subsequent I–Mg exchange with *i*PrMgCl·LiCl[4b] (1.1 equiv, −40 °C, 20 min) gave the expected organomagnesium intermediate, which was treated with ethyl cyanoformate, leading to the furan **12** in 86 % yield (Scheme 5). Further metallation at position 4 of this furan with $TMP_2Mg{\cdot}2\,LiCl$[2b] (TMP = tetramethylpiperidine; 1.35 equiv, −40 °C, 25 min) and consecutive copper(I)-mediated acylation with 3,3-dimethylbutyryl chloride led to the tetra-substituted furan **13** in 93 % yield. This full functionalisation of the furan ring was realised in 5 steps and 42 % overall yield (Scheme 5). The thiophene scaffold could be tetra-functionalised in a similar manner. First, the trimethylsilyl group of **11g** was converted with ICl (1.5 equiv, 0 °C, 1 h) to the corresponding 2-iodothiophene, which was used in the next step without further purification. Then, cross-coupling with trimethylsilylethynylzinc chloride (2 % $[Pd(PPh_3)_4]$, 25 °C,

Table 5. Directed *ortho*-metallation and sulfoxide–magnesium exchange of functionalised sulfoxides **1h–j** followed by reaction with an electrophile.

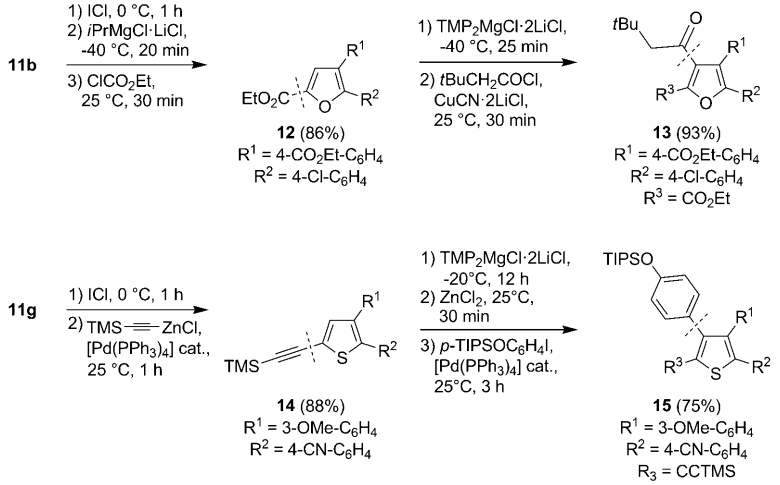
Entry	E^1	Sulfoxide **10**	Yield [%][a]	E^2	Product **11**	Yield [%][b]
1	4-$IC_6H_4CO_2Et$	 **10a**	77[c]	TosCN	 **11a**	63
2		**10a**		4-IC_6H_4Cl	 **11b**	68[c]
3	a) I_2, b) Ph—≡—ZnCl	 **10b**	69	4-$IC_6H_4CO_2Et$	 **11c**	68[c]
4	$PhSO_2SC_6H_4Cl$	 **10c**	78	DMF	 **11d**	97
5		**10c**		4-$IC_6H_4CO_2Et$	 **11e**	88[c]
6	4-IC_6H_4CN	 **10d**	89[c]	$PhSO_2SC_6H_4Br$	 **11f**	94
7	3-IC_6H_4OMe	 **10e**	87[c]	4-IC_6H_4CN	 **11g**	85[c]
8	$PhSO_2SC_6H_4Cl$	 **10f**	88	3-ClC_6H_4CHO	 **11h**	77
9	TosCN	 **10g**	43	4-$IC_6H_4CO_2Et$	 **11i**	87[c]

[a] Yield of isolated, analytically pure product. [b] Yield of isolated, analytically pure product with respect to 0.8 equiv of electrophile. [c] After transmetallation to zinc using 1 M zinc chloride in THF. [d] $Ar^2 = p$-OMe-C_6H_4.

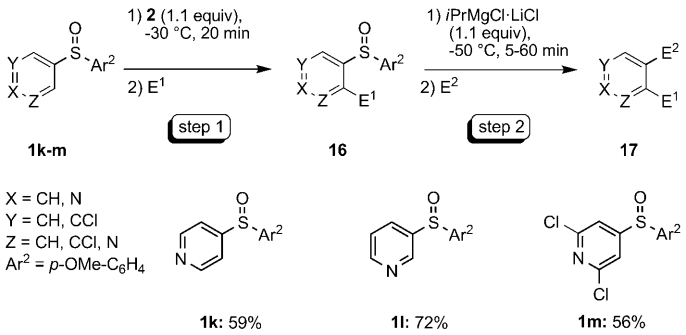
1 h) led to the tri-substituted product **14** in 88% yield. Finally, thiophene **14** was treated with $TMP_2Mg{\cdot}2LiCl$ (1.5 equiv, −20 °C, 12 h) and submitted to a Negishi cross-coupling (2% $[Pd(PPh_3)_4]$, 25 °C, 3 h) with (4-iodophenoxy)triisopropylsilane[22] to give the fully functionalised thiophene **15** in 75% yield. The tetra-substitution of the thiophene was therefore carried out in 4 steps and 49% overall yield (Scheme 5).

Preparation of 3,4-disubstituted pyridines (17) by using the two-step protocol: The developed method was also suitable for pyridinyl sulfoxides, which could be prepared similarly to method 1 in Scheme 2 with 3- or 4-pyridinyl Grignard reagents (Scheme 6).

Therefore, 4-[(4-methoxyphenyl)sulfinyl]pyridine (**1k**) underwent a smooth magnesiation reaction with **2** (−30 °C, 30 min, THF) in the first step of the reaction sequence and was trapped with iodine. This pyridinyliodide was used for a Negishi-type cross-coupling reaction with trimethylsilylethynylzinc chloride and sulfoxide **16a** was obtained in 69% yield (Table 6, entry 1). Compound **16a** reacted with *i*PrMgCl·LiCl (−50 °C, 5 min, 2-Me-THF) in the sulfoxide–magnesium exchange (the second step of the synthesis) and after trapping with DMF the 3,4-disubstituted pyridine **17a** was isolated in 58% yield (Table 6, entry 1). In another reaction sequence, the exchange of the sulfoxide moiety was performed on sulfoxide **16a**, the organomagnesium reagent was transmetallated to zinc and used in a cross-coupling with ethyl 4-iodobenzoate to give **17b** in 63% yield (Table 6, entry 2). Similarly, sulfoxide **11** was used in the reaction protocol and led to difunctionalised pyridines **17c** and **17d** in 50 and 67% yield, respectively (Table 6, entries 3 and 4). Finally, sulfoxide **1m** was also a suitable starting material for the difunctionalisation method. Hence, tetra-sub-



Scheme 5. Synthesis of fully functionalised furan **13** and thiophene **15**. TIPS = triisopropylsilyl.

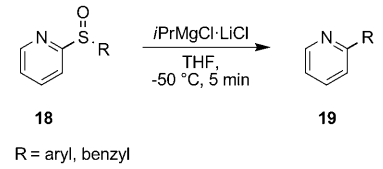


Scheme 6. Metallation of 3- and 4-pyridinyl sulfoxides **1k**–**m**, followed by a sulfoxide–magnesium exchange reaction, leading to 3,4-difunctionalised pyridines **17**.

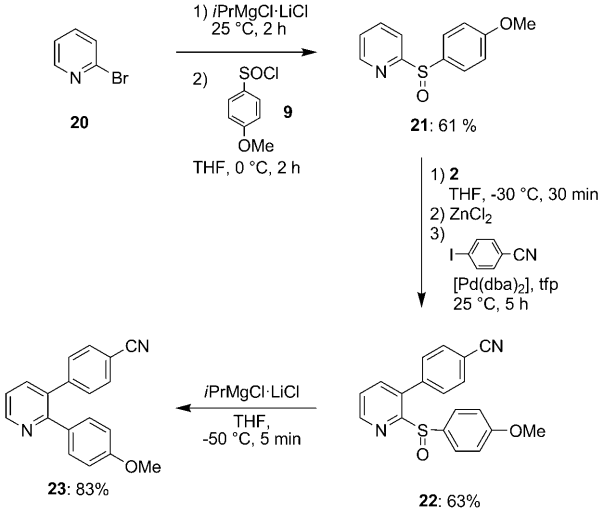
stituted pyridines **17e** and **17f** were obtained after directed *ortho*-metallation and sulfoxide–magnesium exchange in 61 and 82% yield, respectively (Table 6, entries 5 and 6).

Preparation of a cyclooxygenase-2 inhibitor by directed metallation with 2 and ligand exchange with *i*PrMgCl·LiCl: A remarkable characteristic of 2-pyridinyl sulfoxides **18** was reported by Oae et al.[23] When treated with a Grignard reagent, instead of sulfoxide–magnesium exchange creating a new organomagnesium reagent, these compounds undergo a so-called ligand-exchange reaction by directly connecting the two aromatic groups attached to the sulfoxide moiety to generate 2-substituted pyridines **19** (Scheme 7).

We have used this interesting behaviour by applying this very clean and fast reaction to a short total synthesis. Hence, we performed a bromine–magnesium exchange on 2-bromopyridine (**20**) using *i*PrMgCl·LiCl (0°C, 2 h, THF) and trapped the 2-pyridinylmagnesium chloride with 4-methoxybenzenesulfinyl chloride (**9**). The expected 2-[(4-methoxyphenyl)sulfinyl]pyridine (**21**) was isolated in 61% yield (Scheme 8). This sulfoxide was treated with **2** (−30°C, 30 min, THF) according to the methodology described above, transmetallated ($ZnCl_2$ in THF) and submitted to a Negishi cross-coupling with 4-iodobenzonitrile to give pyridine **22** in 63% yield. To accomplish the final step of the synthesis, the ligand-exchange reaction, we treated sulfoxide **22** with *i*PrMgCl·LiCl (−50°C, 5 min, THF) and obtained the cyclooxygenase-2 inhibitor[24] **23** in 83% yield. The total synthesis was therefore carried out in 3 steps and 32% overall yield (Scheme 8).



Scheme 7. Ligand-exchange reaction of 2-pyridinyl sulfoxides.

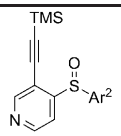
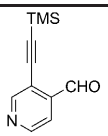
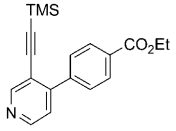
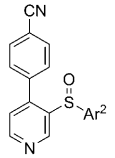
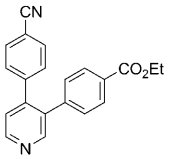
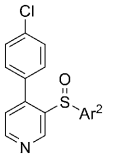
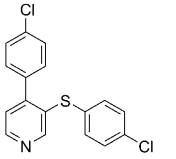
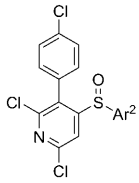
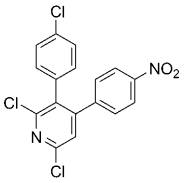
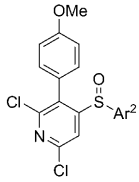
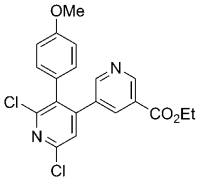


Scheme 8. Synthesis of the cyclooxygenase-2 inhibitor **23**. DBA = dibenzylideneacetone, TFP = tris-2-furylphosphine.

Conclusion

We have developed an efficient two-step sequence that allows *meta*-, *para*-difunctionalisation of substituted aromatics using the chameleon chemical behaviour of the sulfoxide moiety. This versatile functional group acts as a metallation-directing group in the presence of **2** and as a leaving group in the presence of *i*PrMgCl·LiCl, generating a new Grignard reagent. The protocol is suitable for multi-gram synthesis.

Table 6. Directed *ortho*-metallation and sulfoxide–magnesium exchange of functionalised sulfoxides **1k–m** followed by reaction with an electrophile.

Entry	E^1	Sulfoxide **16**	Yield [%][a]	E^2	Product **17**	Yield [%][b]
1	a) I_2, b) TMS–≡–ZnCl	 **16a**	69	DMF	 **17a**	58
2		**16a**		4-$IC_6H_4CO_2Et$	 **17b**	63[c]
3	4-IC_6H_4CN	 **16b**	38[c]	4-$IC_6H_4CO_2Et$	 **17c**	50[c]
4	4-IC_6H_4Cl	 **16c**	53[c]	$PhSO_2SC_6H_4Cl$	 **17d**	67
5	4-IC_6H_4Cl	 **16d**	74[c]	4-$IC_6H_4NO_2$	 **17e**	61[c]
6	4-IC_6H_4OMe	 **16e**	68[c]	$PhSO_2SC_6H_4Cl$	 **17f**	82[c]

[a] Yield of isolated, analytically pure product. [b] Yield of isolated, analytically pure product with respect to 0.8 equiv of electrophile. [c] After transmetallation to zinc using 1 M zinc chloride in THF. [d] Ar^2 = *p*-OMe-C_6H_4.

Furthermore, we used this method to prepare 1,2-disubstituted furans, thiophenes and benzofurans. A further use of *i*PrMgCl·LiCl and TMP_2Mg·2 LiCl allows the full functionalisation of the two remaining positions of these heterocycles. Moreover, the preparation of 3,4-disubstituted pyridines and the total synthesis of a cyclooxygenase-2 inhibitor, furthermore exploiting the properties of the sulfoxide group, have been shown. Further extensions of the use of the sulfoxide group for generating polyfunctional Grignard reagents are currently being studied in our laboratories.

Experimental Section

For experimental procedures, analytical data, and NMR spectra, see the Supporting Information.

Typical procedure for the directed metallation reaction and subsequent cross-coupling with an electrophile (step 1)

Representative preparation of ***16e***: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with **1m** (5.0 mmol, 1.51 g) in THF (10 mL). The reaction mixture was cooled to −30 °C and **2** (5.5 mmol, 4.58 mL, 1.20 M in THF) was added dropwise. After 20 min of stirring at −30 °C, zinc chloride (5.5 mmol, 5.5 mL, 1.0 M in THF) was added and the solution was stirred for 30 min at −30 °C. Then 4-iodoanisole (6.0 mmol, 1.40 g) and [Pd(PPh_3)$_4$] (0.01 mmol, 110 mg) were added and the solution was stirred at 50 °C for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (25 mL) and extracted three times with ethyl acetate (50 mL). The combined organic layers were dried ($MgSO_4$) and, after filtration, the solvent was removed under reduced pressure. Flash chromatographic purification (pentane/diethyl ether 1:1, silica gel) gave **16e** as a colourless solid (1.38 g, 68 %). M.p. 113–114 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.12 (s, 1H), 7.22 (dd, J = 8.58, 1.91 Hz, 1H), 7.01 (dd, J = 8.58, 2.86 Hz, 1H), 6.89–6.87 (m, 2H), 6.74–6.71 (m, 3H), 6.43 ppm (dd, J = 8.58, 1.91 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 162.6, 160.8, 160.3, 150.2, 132.8, 131.9 (CH), 131.5, 131.4, 130.6 (CH), 128.4 (CH), 123.9, 117.6 (CH), 114.7 (CH), 114.6 (CH), 113.5 (CH), 55.5 (CH_3), 55.3 ppm (CH_3); IR (ATR): $\tilde{\nu}$ = 3000 (vw), 2838 (w), 1610 (w), 1592 (m), 1576 (m), 1558 (m), 1510 (m), 1496 (m), 1404 (m), 1306 (m), 1258 (s), 1246 (vs), 1178 (s), 1152 (m), 1096 (m), 1084 (m), 1050 (s), 1034 (s), 1028 (s), 994 (m), 880 (w), 828 (s), 812 (m), 792 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 409 (28), 408 (9), 407 (41) [M^+], 391 (9), 261 (20), 156 (13), 155 (100), 139 (9), 124 (15), 43 (10); HRMS (EI): *m*/*z* calcd for $C_{19}H_{15}{}^{35}L_2NO_3{}^{32}S$: 407.0150; found: 407.0142.

Typical procedure for the sulfoxide–magnesium exchange reaction and subsequent cross-coupling with an electrophile (step 2)

Representative preparation of ***17f***: A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of **16e** (1.0 mmol, 402 mg) in 2-Me-THF (2 mL). The reaction mixture was cooled to −50 °C and *i*PrMgCl·LiCl (1.1 mmol, 0.92 mL, 1.20 M in THF) was added dropwise. After stirring at −50 °C for 5 min, zinc chloride (1.1 mmol, 1.1 mL, 1.0 M in THF) was added and the solution was stirred for 30 min at −50 °C. Then ethyl 5-bromonicotinate (0.8 mmol, 184 mg) and [Pd(PPh_3)$_4$] (0.02 mmol, 22 mg) were added and the solution was stirred at 50 °C for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and ex-

tracted three times with ethyl acetate (10 mL). The combined organic layers were dried ($MgSO_4$) and, after filtration, the solvent was removed under reduced pressure. Flash chromatographic purification (pentane/diethyl ether 7:3, silica gel) gave **17f** as a colourless solid (265 mg, 82%). M.p. 120–121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.07 (d, J = 1.73 Hz, 1H), 8.41 (d, J = 2.23 Hz, 1H), 8.02 (dd, J = 2.23, 1.73 Hz, 1H), 7.36 (s, 1H), 7.02–6.97 (m, 2H), 6.83–6.78 (m, 2H), 4.37 (q, J = 7.18 Hz, 2H), 3.76 (s, 3H), 1.37 ppm (t, J = 7.18 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.4, 159.6, 152.7 (CH), 151.2, 150.3 (CH), 149.6, 149.1, 137.1 (CH), 134.2, 133.1, 131.5 (CH), 126.0, 125.8, 123.6 (CH), 114.1 (CH), 61.7 (CH_2), 55.2 (CH_3), 14.2 ppm (CH_3); IR (ATR): $\tilde{\nu}$ = 2936 (vw), 1716 (s), 1608 (w), 1564 (m), 1528 (m), 1430 (m), 1370 (w), 1336 (m), 1306 (m), 1292 (s), 1272 (s), 1254 (vs), 1226 (m), 1178 (m), 1162 (m), 1136 (m), 1114 (m), 1088 (m), 1028 (m), 1016 (m), 882 (w), 858 (w), 840 (s), 820 (m), 794 (m), 764 (m), 706 (m), 698 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 406 (14), 405 (18), 404 (73), 403 (48), 402 (100) [M^+], 401 (34), 375 (21), 373 (30), 357 (11), 44 (55); HRMS (EI): m/z calcd for $C_{20}H_{16}Cl_2N_2O_3$: 402.0538; found: 402.0533.

Acknowledgements

We thank the European Research Council (ERC) for financial support. We also thank Chemetall GmbH (Frankfurt) and BASF SE (Ludwigshafen) for the generous gift of chemicals.

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Received: December 19, 2010
Published online: April 1, 2011

