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ARTICLE

Efficient Synthesis of Aliphatic Sulfones by Mg Mediated Coupling Reactions of Sulfonyl Chlorides and Aliphatic Halides

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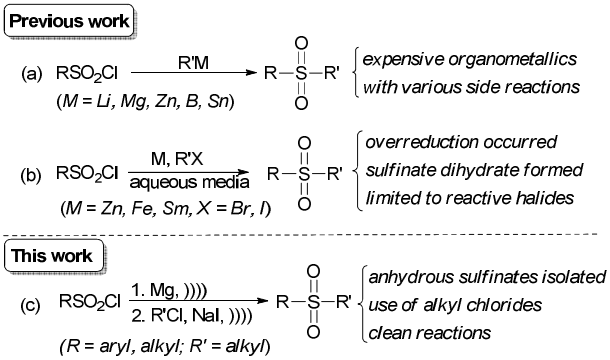
Sulfonyl chlorides were reduced to anhydrous sulfinate salts by magnesium under sonication. These sulfinates were alkylated to sulfones by alkyl chlorides in the presence of catalytic sodium iodide under sonication. A variety of aliphatic sulfones was efficiently prepared by this one-pot two-step procedure.

1. Introdction

Sulfonyl group presents as a key structural motif in various pharmaceutical,[1] agrochemical,[2] polymeric[3] compounds and many important synthetic intermediates.[4] As a consequence, the development of general and environmentally benign methods for sulfone synthesis has received significant attention.[5] Among them, protocols employing sulfonyl chloride as sulfonylating agent, which comprise the Friedel-Crafts sulfonylating of arenes,[6] transition metal catalyzed coupling of boronic acid[7] and sulfonylation of organometallics[8] etc. still occupy an important place in practical sulfone compounds synthesis (Scheme 1a). Undoubtedly, these protocols are efficient albeit most of them are only suitable to arylsulfone synthesis.

The reductive cross-coupling of sulfonyl chlorides and haloalkanes provides the most direct, atom economical and clean methods for aliphatic sulfone synthesis. Nevertheless, this concise methodology has not yet been fully developed that so far only Zn,[9] Fe-$AlCl_3$,[10] Sm-$NiCl_2$[11] and telluride ion[12] are employed to promote this type of cross-coupling in aqueous media and only primary alkyl iodides and some reactive bromides or chlorides are applicable substrates (Scheme 1b). Based on our recent interests on C-S bond formation employing sulfonyl chlorides as the sulfur source,[13] we herein report an efficient one-pot, two-step process to build a large variety of aliphatic sulfones through reductive coupling of sulfonyl chlorides and aliphatic halides (Scheme 1c). In sharp contrast to previous synthetic methods,[9-12] the prominent advantages of our method include employing cheap aliphatic chlorides as the alkylating agents and isolation of anhydrous sulfinate salt intermediates.



Scheme 1 Protocols for aliphatic sulfone synthesis employing sulfonyl chlorides as sulfur sources

2. Results and discussion

Previously, we reported a convenient synthesis of aromatic sulfones based on CuI catalyzed coupling of arylsulfonyl chlorides with organozinc reagents.[8a] On continuation of this work, we were interested to perform these reactions by one-pot protocol, with the expectation that organozinc would be *in situ* formed and react with sulfonyl chloride to form sulfones *via* a tandem one-pot fashion. Thus *p*-tosyl chloride **1a** and benzyl chloride **2a** were selected as the representative reactants to optimize the reaction conditions (Table 1). In the presence of zinc metal, stirring the reaction mixture in THF under argon at room temperature for 1h, sulfone **3a** was not formed whereas *p*-tosyl chloride **2a** was totally consumed by zinc metal within one hour, delivering a THF insoluble *p*-tolylsulfinate zinc salt in 82% yield (entry 1). This unexpected result implied that sulfonyl chlorides are much more reactive species toward zinc metal than benzyl chlorides that under this reaction condition, benzylzinc chloride was not formed at all. With this information in hand, we quickly determined that, under sonication, quantitative reduction of *p*-tosyl chloride **1a** can be achieved using magnesium turnings as a reductant in 1h in THF at room temperature (25 °C). The THF-insoluble magnesium *p*-tolylsulfinate salt could be isolated as white

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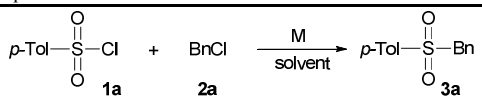
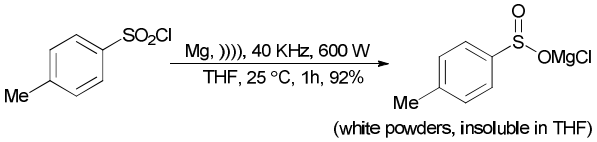
Table 1. Optimization of the reaction conditions [a, b]



Entry	Solvent	M	T/°C	3a/%
1	THF	Zn	RT	/
2	THF	Mg	RT to reflux	<10
3	DMF	Mg	RT to 60	53
4	DMSO	Mg	RT to 60	64
5	CH_3CN	Mg	RT to 60	62
6	THF/DMSO	Mg	RT to 60	81[c,d]

[a] Reaction conditions: M (1.2 mmol) was added into a solution of **1a** (1 mmol) and **2a** (1.2 mmol) in a designated solvent (3 ml). The suspension was then stirred at room temperature for 1h, afterwards, the reaction mixture was heated to 65 °C for 1h. [b] Isolated yields. [c] NaI (0.2 mmol) and DMSO (1 ml) were added after reduction of **1a**. [d] Reaction was carried out in a one-pot, two-step process under sonication.

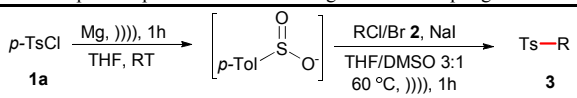


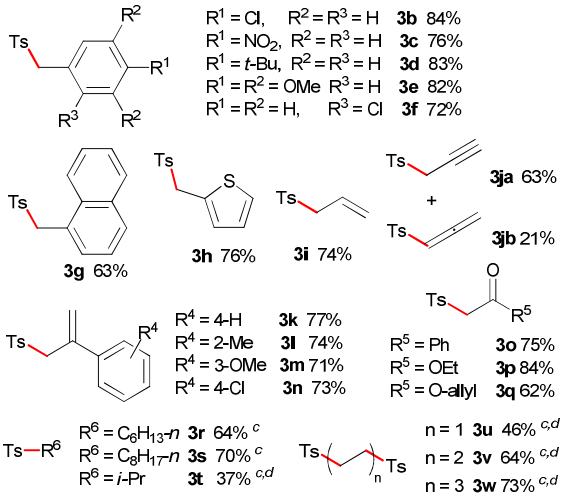
Scheme 2. Synthesis of anhydrous magnesium sulfinate chloride

powder in 92% yield (Scheme 2). To our best knowledge, this is the first report on quick and straightforward preparation of anhydrous sulfinate salts from sulfonyl chlorides.[14]

This encouraging result incited us to further convert the *in situ* formed sulfinate magnesium salt into sulfone via a one-pot process. However, the low solubility of magnesium sulfinate in THF completely inhibited this type of conversion even under refluxed condition (Table 1, entry 2). When a polar aprotic solvent, such as DMF, DMSO or acetonitrile was employed instead of THF as a solvent, a clear solution formed whereas the desired sulfone **3a** was not formed unless the reaction system was heated to 60 °C. Simultaneously, significant amount of unidentified byproducts were formed (entries 3-5). Further reaction condition optimization showed that side reactions could be largely suppressed by performing the reaction in a one-pot, two-step process under sonication, employing catalytic amount of NaI (0.2 equiv.) as an additive. First, under sonication, *p*-tolylsulfonyl chloride **1a** was converted into its sulfinate salt with Mg in THF at room temperature. Then, in the presence of a catalytic amount of NaI and with DMSO as cosolvent (THF/DMSO 3:1, v/v), one-pot benzylation of sulfinate salt was conducted under sonication at 60°C for one hour to give **3a** in 81% isolated yield (entry 6). With these optimized reaction conditions in hand, the scope of aliphatic halides were then explored using *p*-tosyl chloride **1a** as the sulfonylating agent. As summarized in Table 2, benzylic chlorides equipped with diverse functional groups (Cl, NO_2, *t*-Bu and OMe) were well applied under this optimized reaction condition, affording the corresponding benzylic sulfones in 72% to 84% yields (**3b-3f**). The substrate scope could be further extended to 1-(chloromethyl)naphthalene and 2-(chloromethyl)thiophene, producing the corresponding sulfones (**3g** & **3h**) in good yields. Allylic sufone **3i** was easily

Table 2. Scope of aliphatic halides in the Mg-mediated coupling reactions [a, b]





[a] Reaction conditions: A suspension of Mg (1.2 mmol) and **1a** (1 mmol) in THF (3 ml) was sonicated at room temperature for 1h. Afterwards, RCl **2** (1.2 mmol), NaI (0.2 mmol) and DMSO (1 ml) were added and the reaction mixture was further sonicated at 60°C for 1h. [b] Isolated yields. [c] NaI (1 mmol) was added, afterwards, sonication was conducted at 60 °C for 4h. [d] Alkyl bromides were employed.

prepared from allyl chloride in 74% yield whereas propargyl chloride, under same reaction condition, gave an inseparable mixture of propargyl sulfone **3ja** and 1,2-Propadienyl sulfone **3jb** in 84% yield (**3ja:3jb** = 3:1, based on ^{1}H NMR analysis). 2-Chloromethylstyrenes, bearing either electron-withdrawing or electron-donating groups at the ortho or para position, worked quite well under the optimized reaction conditions, affording the corresponding sulfones (**3k-3n**) in 71% to 77% yields. 2-Chloroacetophenone and 2-chloroacetates are reactive electrophiles and furnished the corresponding sulfones (**3o-3q**) in high yields. Gratifyingly, primary alkyl chlorides were well applied in this reaction system and gave aliphatic sulfones (**3r** & **3s**) in moderate isolated yields. Secondary alkyl bromide, as represented by 2-bromopropane, proceeded this transformation sluggishly and only 37% yield of sulfone **3t** was obtained. Undoubtedly, bis-tosylation of α, ω-dibromoalkanes were achieved without any difficulties (**3u-w**).

Encouraged by these successful results on aliphatic halides, we subsequently set out to expand the scope of sulfonyl chlorides. As shown in Table 3, a variety of aromatic sulfonyl chlorides having halogen (**4c**, **4f**, **4p-4r**), OMe (**4e** & **4h**), nitro (**4g** & **4l**) and amido (**4i** & **4j**) groups could be employed in these reaction systems, delivering aliphatic sulfones in good to high yields. Again, allyl chloride reacted readily with aryl sulfonyl chlorides to give β, γ-unsaturated sulfones (**4d-4g**) in high yields. The reaction conditions were mild and no isomerisation[15] was induced. The hindrance effect of aromatic sulfonyl chlorides was not obvious as the highly sterically hindered 2,4,6-trimethylbenzenesulfonyl chloride could be employed and reacted with ethyl 2-chloroacetate to produce

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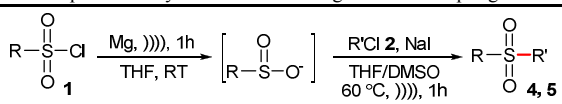
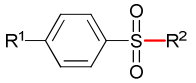
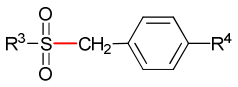
Table 3. Scope of sulfonyl chlorides in the Mg-mediated coupling reactions[a,b]

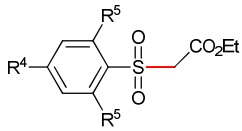




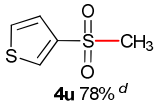
R^1 = H	R^2 = Me	**4a** 74% [d]	
R^1 = H	R^2 = *n*-octyl	**4b** 70% [c]	
R^1 = F	R^2 = *n*-Hexyl	**4c** 84% [c]	
R^1 = H	R^2 = Allyl	**4d** 79%	
R^1 = OMe	R^2 = Allyl	**4e** 76%	
R^1 = Br	R^2 = Allyl	**4f** 78% [f]	
R^1 = NO_2	R^2 = Allyl	**4g** 59% [f]	
R^1 = OMe	R^2 = Propargyl	**4h** 53%	
R^1 = NHAc	R^2 = *n*-octyl	**4i** 74% [c]	
R^1 = NHAc	R^2 = *i*-Pr	**4j** 37% [c,e]	



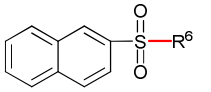
R^3 = Ph	R^4 = H	**4k** 84%
R^3 = 4-NO_2Ph	R^4 = ^{t}Bu	**4l** 52% [f]
R_3 = 2-thienyl	R^4 = H	**4m** 87%
R_3 = 3-pyridyl	R^4 = H	**4n** 74%



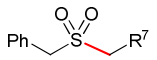
R^4 = R^5 = H	**4o** 82%	
R^4 = F R^5 = H	**4p** 84%	
R^4 = Cl R^5 = H	**4q** 88%	
R^4 = Br R^5 = H	**4r** 92% [f]	
R^4 = Ph R^5 = H	**4s** 75%	
R^4 = R^5 = Me	**4t** 66%	



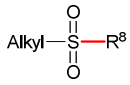
4u 78% [d]



R^6 = Allyl	**4v** 90%	
R^6 = *n*-Hex	**4w** 77% [c]	
R^6 = CH_2CO_2Et	**4x** 83%	



R^7 = H	**5a** 52% [d]
R^7 = CO_2Et	**5b** 63%



Alkyl = CH_3	R^8 = $CH_2C_6H_4$-Cl-*p*	**5c** 61%
Alkyl = CH_3	R^8 = CH_2COPh	**5d** 60%
Alkyl = *n*-butyl	R^8 = CH_2CO_2Et	**5e** 72%
Alkyl = *n*-octyl	R^8 = Allyl	**5f** 71%
Alkyl = *n*-octyl	R^8 = *n*-octyl	**5g** 74% [c]
Alkyl = *n*-octyl	R^8 = CH_2CO_2Et	**5h** 78%

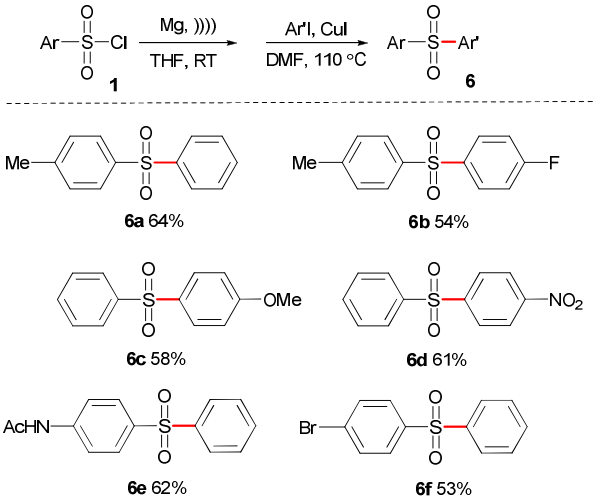
[a] Reaction conditions: A suspension of Mg (1.2 mmol) and **1** (1 mmol) in THF (3 ml) was sonicated at room temperature for 1h. **2** (1.2 mmol), NaI (0.2 mmol) and DMSO (1 ml) were then added and the reaction mixture was further sonicated at 60°C for 1h. [b] Isolated yields. [c] NaI (1 mmol) was added and sonication was conducted at 60 °C for 4 h. [d] MeI (2 equiv.) was used.[e] Alkyl bromides were employed. [f] An equimolar combination of Mg (1.2 mmol) and $ZnCl_2$ (1.2 mmol) were used.

sulfone **4t** in 66% yield. Different types of aryl and heteroaryl sulfonyl chlorides containing 2-naphthyl (**4v-4x**), biphenyl (**4s**), thiophenyl (**4m** & **4u**) and pyridinyl (**4n**) were successfully employed and reacted with various aliphtic halides to produce the corresponding aliphatic sulfones in good to excellent yields. In case when a magnesium metal sensitive group, e.g., Br (**4f** & **4r**) and nitro (**4g** & **4l**), were presented on the ring of aryl sulfonyl chloride, reduction of sulfonyl chlorides were better conducted by employing an equimolar combination of magnesium metal and zinc chloride.

Aliphatic sulfonyl chlorides could also participate in this type of reactions. Benzyl sulfones have significant functions in organic synthesis[16] and biochemistry.[17] These compounds are normally synthesized from the corresponding benzyl chloride via sulfinate salts[18] or oxidation of sulfide in multiple steps. In our protocol, benzylic sulfones could be readily prepared from benzylsulfonyl chlorides too. Thus, treatment of *in situ* formed benzylsulfinate salts with MeI or ethyl 2-chloroacetate produced the desired benzyl sulfones (**5a** & **5b**) in moderate yields.

Alkylsulfonyl chlorides represented as MsCl, *n*-$BuSO_2Cl$ and *n*-$OctSO_2Cl$ participated these conversions as well which, after reduction by magnesium metal, reacted with various aliphatic chlorides smoothly and gave dialkyl sulfones (**5c-5h**) in 60%-78% yields. Generally, with reactive aliphatic halides, e.g., MeI (**4a, 4u & 5a**), allyl chlorides (**4d-4g**, **4v**, **5f**), propargyl chlorides (**4h**), benzylic chlorides (**4k-4n**) and 2-chloroesters (**4o-4t**, **4x**, **5h**), alkylation of magnesium sulfinate salts could be finished in one hour. For primary and secondary alkyl chorides/bromides, better results were obtained after sonication the reaction mixtures at 60 °C for 4h.

It should be emphasized here that this cross-coupling methodology was more suitable to but not limited in aliphatic sulfone synthesis. These in situ formed anhydrous magnesium sulfinate salts were successfully applied in sulfonylating of iodoarenes too (Scheme 3). Under CuI catalysis, *p*-tosyl chloride **2a**, after conversion into its magnesium sulfinate salt, reacted readily with PhI [19] and 1-fluoro-4-iodobenzene to furnish the desired diaryl sulfones (**4a** & **4b**) in moderate isolated yields. Similarly, benzenesulfonyl chloride and functionalized aromatic sulfonyl chlorides selected, bearing amido and bromo groups, participated this transformation smoothly and produced the corresponding diaryl sulfones (**6c-6f**) in acceptable yields.



Scheme 3. Sulfonylating of iodoarenes

Aryl methyl sulfone moiety was found as an key structural motif in many drugs, e.g., in the antibacterial Laropiprant.[20] In order to examine the efficiency of our protocol in practical methyl sulfone synthesis, a 50 mmol scale synthesis of 4-fluorophenyl methyl sulfone **7** was carried out (Scheme 5). Thus 4-fluorobenzenesufonyl chloride **2c** (9.73g, 50 mmol) was first reduced by Mg (1.44g, 60 mmol) into corresponding magnesium sulfinate salt and was then submitted to react with MeI (10.64g, 75 mmol) to afford 4-fluorophenyl methyl sulfone **7** in 82% isolated yield (Scheme 4).

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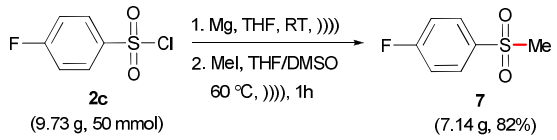

2c (9.73 g, 50 mmol) **7** (7.14 g, 82%)

Scheme 4. Large scale synthesis of 4-fluorophenyl methyl sulfone.

3. Conclusions

In summary, we have developed an easy and practical magnesium metal mediated cross-coupling reaction of sulfonyl chlorides with organic halides whereby different types of sulfones could be produced in moderate to excellent yields. By this method, anhydrous sulfinate salt could be readily prepared from corresponding sulfonyl chlorides in excellent yield. With catalytic amount of NaI, alkyl chlorides can be employed as alkylating agents to furnish the aliphatic sulfones in high yields. This protocol provides a direct and operationally simple synthetic method for a wide range of aliphatic sulfones in good to excellent yields.

4. Experimental

General experimental information. All the reactions were carried out under argon or nitrogen atmosphere. Sonochemical reactions were carried out in a commercially available ultrasound cleaning bath (40 kHz, 600 W) equipped with an automatic constant temperature heating-cooling circulatory system. ^{1}H NMR (400 and 600 MHz), and ^{13}C NMR (100 and 150 MHz) were recorded on Bruker AV400 or 600 NMR spectrometer with $CDCl_3$ as solvent. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) with TMS as an internal standard. Column chromatography was performed on silica gel 300-400 mesh. Analytical thin layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm).

Preparation of anhydrous *p*-tolylsulfinate magnesium salt

A dry and argon-flushed Schlenk flask containing *p*-tosyl chloride (1.90g, 10 mmol), magnesium turnings (0.24 g, 12 mmol) and 30 mL of THF was immersed in an ultrasound cleaning bath at room temperature for 1 h. Dry ether (50 mL) was added and the magnesium sulfinate salt suspensions but the small magnesium residues precipitated at the bottom of the flask was carefully transferred into a filter and the filter cake was washed with ether (20 mL) for 3 times. The cake was then transferred into a round-bottled flask and was evacuated under reduced pressure at room temperature for 3 h to remove any remaining solvent. The sulfinate salt powder thus prepared was determined to be magnesium *p*-tolylsulfinate chloride. 1.79g, 92% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.45 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 2.48 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 146.1, 138.1, 128.5, 126.0, 21.2. IR (KBr) ν (cm^{-1}): 1653, 1398, 1190, 1029. FTMS + pESI *m/z*: calcd for $C_7H_8ClMgO_2S$ $[M+H]^+$ 214.9784; found 214.9815.

General procedure for preparation of sulfones via Mg mediated coupling reaction of sulfonyl chlorides and alkyl halides

To a dry and argon-flushed Schlenk tube, sulfonyl chlorides (1 mmol), magnesium turnings (29 mg, 1.2 mmol), and 3 mL of THF were charged. The tube was then immersed in an ultrasound cleaning bath and was ultrasonicated at room temperature for one hour. NaI (30 mg, 0.2 mmol), alkyl halides (1.2 mmol) and DMSO (1 mL) was then added and the reaction mixture was sonicated for one hour at 60 °C (for alkyl chlorides, 4 hours). After usual work-up, the sulfone products were obtained by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent.

***n*-Hexyl *p*-tolyl sulfone 3r.**[21] Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.78 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 2.45 (s, 3H), 1.72-1.66 (m, 2H), 1.36-1.32 (m, 2H), 1.28-1.22 (m, 4H), 0.85 (t, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 144.5, 136.3, 129.8, 128.0, 56.4, 31.1, 27.9, 22.7, 22.3, 21.6, 13.9.

Allyl 4-nitrophenyl sulfone 4f.[22] White solid, mp 140-141 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.40 (d, J = 9.0 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 5.85-5.77 (m, 1H), 5.38 (d, J = 10.2 Hz, 1H), 5.16 (dd, J = 16.8, 0.6 Hz, 1H), 3.87 (d, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 137.2, 132.4, 130.1, 129.1, 125.1, 124.4, 60.8.

Benzyl methyl sulfone 5a.[23] White solid, mp 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (s, 5H), 4.26 (s, 2H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 130.5, 129.1, 128.3, 61.3, 39.0.

Allyl *n*-octyl sulfone 5f.[24] Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.97-5.92 (m, 2H), 5.48 (dd, J = 10.2, 0.6 Hz, 1H), 5.44 (dd, J = 16.8, 0.6 Hz, 1H), 3.69 (d, J = 7.8 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 1.85-1.79 (m, 2H), 1.44-1.41 (m, 2H), 1.33-1.25 (m, 10H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 125.3, 124.4, 57.6, 51.3, 31.7, 29.0, 28.9, 28.4, 22.6, 21.8, 14.0.

General procedure for the synthesis of diarylsulfones via Mg mediated coupling of arylsulfonyl chlorides with aryl halides (6a-6f)

A dry and argon-flushed Schlenk tube equipped with a magnetic stirrer and a septum was charged with sulfonyl chlorides (1 mmol), magnesium turnings (29 mg, 1.2 mmol) and 3 mL of THF. After sonication of the reaction mixture at room temperature for one hour, THF was removed under reduced pressure. CuI (0.29g, 1.5 mmol), aryl iodides (1 mmol) and DMF (3 mL) was added. The reaction mixture was heated to 110 °C and stirred for 12 hour under argon. After cooling, 10 mL of aqueous NH_4Cl and 10 mL of ethyl acetate was added and the organic phase was separated, washed with 10 mL of water and then with 10 mL of brine. The water phase was

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extracted with ethyl acetate (2×10 mL). The organic phase was combined, dried (Na_2SO_4) and concentrated under reduced pressure. The diarylsulfone products were obtained by column chromatography on silica gel using petroleum/ethyl acetate as an eluent.

Phenyl *p*-tolyl sulfone 6a.[25] White solid, mp 121-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.55 (tdd, *J* = 7.2, 2.4, 1.2 Hz, 1H), 7.49 (tdd, *J* = 7.2, 2.4, 0.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.2, 141.9, 138.6, 133.0, 129.9, 129.2, 127.7, 127.5, 21.6.

4-Bromodiphenyl sulfone 6f. [Error! Bookmark not defined.] White solid, mp 102-104 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.52 (tt, *J* = 7.6, 1.2 Hz, 2H), 7.59 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.65 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.80 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.91-7.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 127.6, 128.4, 129.2, 129.4, 132.6, 133.4, 140.6, 141.1.

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