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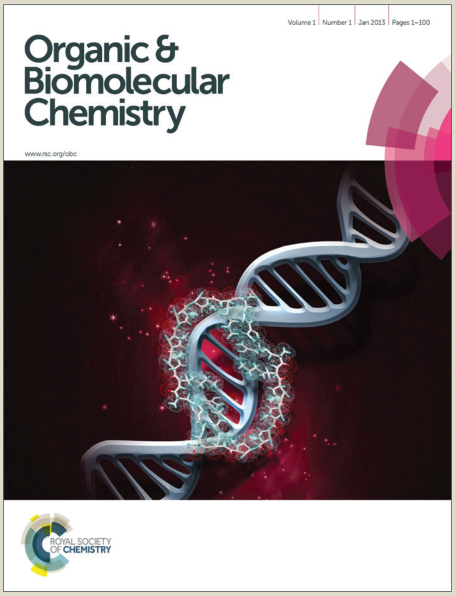

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ARTICLE TYPE

CuI Catalyzed Sulfonylation of Organozinc Reagents with Sulfonyl halides

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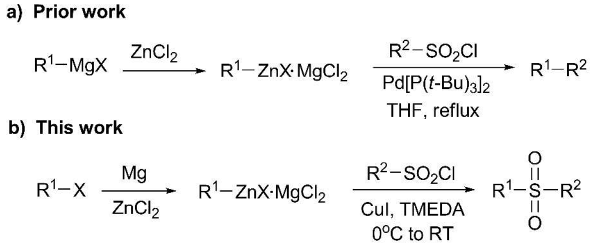
In this study, a facile CuI catalyzed synthesis of sulfones involving a nucleophilic addition of functionalized organozinc reagents to organic sulfonyl chlorides is realized. This reaction proceeds efficiently at room temperature, giving rise to variously functional substituted sulfones, generally in moderate to high yields. The method provides a novel, simple, and promising strategy for functionalized sulfone synthesis in the research field of sulfur chemistry.

Sulfones are ubiquitous bioactive molecules[1] and are widely applied as important intermediates in organic synthesis[2] and polymeric compounds.[3] The Friedel-Crafts (FC) sulfonylation of arenes by organic sulfonyl halides or sulfonic anhydrides,[4] and the nucleophilic substitution reaction of organic halides with thiols, followed by oxidation of the corresponding sulfides[5] are the two most commonly used synthetic approaches for the preparation of aryl and alkyl sulfones. However, these methods generally involve drawbacks as the FC sulfonylation is limited to arenes bearing electron-donating substituents and always leads to formation of isomeric mixtures of products. For sulfide oxidation, the use of odoriferous and hazardous thiols is a major concern. Thus alternative procedures, especially those using organic sulphinates as the sulfonylation precursor, the use of aryl halides,[6] arylboronic acids,[7] diaryliodonium salts,[8] heterocycles[9] or olefins[10] as substrates have been developed in recent years. However, drawbacks such as the use of expensive noble metal complexes, limited substrate availability, use of air- or moisture-sensitive reagents, incompatibility with various functional groups etc. are some disadvantages of these procedures. Therefore, it is imperative that a simple, convenient and generally applicable protocol for both aryl and alkyl sulfones synthesis is found.

The nucleophilic addition of Grignard reagents or organolithium reagents to sulfonyl halides[11] or esters[12] are straightforward, albeit limited to practical sulfone synthesis owing to the strong nucleophilicity of these organometallic reagents and the weak C-S bond of sulfonyl halides and sulfones. Various kinds of by-products are obtained with the sulfone products, and the mechanisms of these side reactions are still unconfirmed. Nevertheless, C-C formed products instead of C-S cross coupling sulfone products were frequently obtained using transition metal catalysis. [13]

Organozinc reagents are mild and functional group tolerant organometallic reagents that are widely used as surrogates for Grignard reagents or organolithium reagents.[14] Previously Vogel's group reported that the palladium catalysed reaction of organozinc reagents with sulfonyl chloride occurred via a desulfinylative Negishi-type cross-coupling reaction to give alkanes in low to moderate yield.[13b] However, From our experiences concerning the reactivity and applications of organometallic reagents[15] in organic synthesis, and a brief report on the synthesis of allyllic sulfones via a zinc Barbier type reaction of allylic bromides with sulfonyl chloride,[16] we were enticed to explore the possibility of C-S bond construction by the reaction of organozinc reagents with sulfonyl chlorides with mild reaction conditions (Scheme 1).

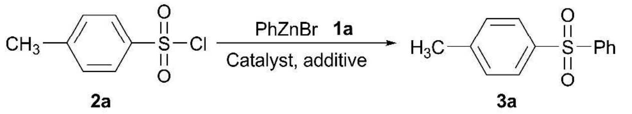


Scheme 1 Comparison of this work and a previous report reaction of organozinc reagents with sulfonyl chlorides. (a) Pd[P(t-Bu)$_3$]$_2$ catalyzed dusulfitative C-C cross-coupling coupling reaction selective towards biphenyls. (b) CuI-catalyzed C-S cross-coupling reactions selective towards sulfones (this work).

Initially we prepared phenylzinc bromide (**1a**), by stirring PhBr with magnesium turnings in the presence of one equiv of ZnCl$_2$, as the nucleophile (Table 1).[17] Examination of the products of the reaction of (**1a**) with *p*-toluenesulfonyl chloride (**2a**) at room temperature for 24 h, detected only a trace amount of sulfone (**3a**) with nearly all of **2a** being recovered (entry 1). Lewis acids are known to be powerful additives in promoting nucleophilic addition reaction of organometallic reagents towards carbonyl or imine compounds. However, in this reaction system, no appreciable effect was observed after the addition of one equivalent of LiCl (entry 2).[18] Other Lewis acids such as TMSCl, BF$_3$·Et$_2$O, ZnCl$_2$ all failed in promoting this reaction. The phenomenon that Lewis acids did not enhance the electrophilicity of sulfonyl chlorides implies that the electron density of the sulfonyl oxygens is too low to effectively complex with Lewis acids.

On the other hand, Lewis bases showed some efficiency in this reaction system. As shown in Table 1, after the addition of 2 equiv of Et_3N, **3a** was obtained in 23% yield. A slightly higher yield of **3a** (36%) was obtained when 2 equiv of TMEDA was added (entry 4). Transition metal complexes also showed some efficacy in these reactions. As illustrated in Table 1, the addition of 5% equivalent of $Ni(acac)_2$ slightly enhanced the reaction rate after 12 hours, sulfone **3a** was obtained in 42% isolated yield (entry 5). $Ni(PPh_3)_2Cl_2$ and $Ni(OAc)_2$ showed similar beneficial effects on this reaction and sulfone **3a** was obtained in similar yields (entries 6 and 7). Cuprous salts are attractive catalysts in promoting the nucleophilicity of organozinc reagents.[19] Gratifyingly, these catalysts showed great efficiency on the nucleophilic addition of the organozinc reagent **1a** towards sulfonyl chloride **2a**. Of the cuprous salts studied, CuI (1 mmol) was shown to be the most efficient, as after half an hour all of the sulfonyl chloride **2a** was consumed (entry 11).

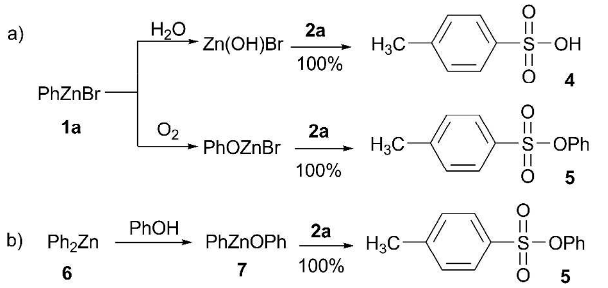
Table 1. Optimization of the reaction conditions[a]



Entry	Additive	Catalyst	Time (h)	Yield [%][b]
1	-	-	24	trace
2	LiCl	-	24	trace
3	Et_3N	-	24	23
4	TMEDA	-	24	36
5	TMEDA	$Ni(acac)_2$[c]	12	42
6	TMEDA	$Ni(PPh_3)_2Cl_2$[c]	12	46
7	TMEDA	$Ni(OAc)_2$[c]	12	40
8	TMEDA	CuCl[d]	2	63
9	TMEDA	CuBr[d]	2	65
10	TMEDA	CuCN[d]	1	62
11	TMEDA	CuI[d]	0.5	65
12	TMEDA	CuI[d]	0.5	91[e]

[a] Reaction conditions: *p*-toluenesufonyl chloride **2a** (5 mmol) was treated with phenylzinc reagent **1a** (10 mmol) in THF (15 mL) under nitrogen. [b] Isolated yields. [c] 0.5 mmol of catalyst was added. [d] 1.0 mmol of catalyst was added. [e] Reaction carried out under extremely strict moisture and air free condition.

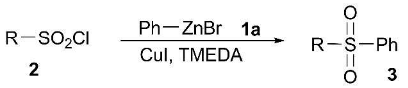
Initially, we are concerned that Vogel's C-C cross-coupling products would be predominant, since these have been extensively studied in the cross-coupling reactions with various organometallic reagents[13] including boronic acids,[20] organostannane[21] and alkenes.[22] However, our GC-MS product analysis confirmed their absence. In fact the main challenge we encountered in our Lewis base and cuprous salt catalyzed sulfonylation of organozinc reagents was not the low nucleophilicity of organozinc reagents **1a**, nor the low electrophilicity of sulfonyl chlorides **2a** or the desulfonylation of organic sulfonyl chlorides, but the high sensitivity of the sulfonyl chlorides and organozinc reqagents towards oxygen and moisture in the reaction environment when THF was dried without nitrogen protection, the dried THF is air saturated; after drying glassware in an oven, trace amounts of moisture and air are absorbed on the silica surface; sulfonyl chlorides can quickly absorb moisture from the environment. All the trace amounts of moisture and air accumulated in the reaction flask resulted in nearly one-third of the sulfonyl chloride forming byproducts as denoted in Scheme 2. The phenomenon that large amounts of sulfonyl chloride is consumed by zinc phenoxide and zinc hydroxide species is in sharp contrast to the reactions of organometallic reagents with carbonyl compounds (aldehydes and ketones) as in which trace amounts of moisture and oxygen do did react with organometallic reagents immediately, however, the resulting alkoxide and hydroxide do not irreversibly attack carbonyl compounds. In order to compare the nucleophlicities of phenyl and phenoxide in organozinc reagents, diphenylzinc (**6**) derived from phenyl magnesium bromide and half an equivalent of $ZnBr_2$ was converted to phenylzinc phenoxide (**7**) and was then added to a solution of *p*-toluenesulfonyl chloride (**2a**) with the same reaction conditions. After half an hour's stirring, phenyl 4-methylbenzenesulfonate (**5**) was obtained in quantitative yield whereas the desired sulfone (**3a**) was undetected. With the exclusion of moisture/air, the modified reaction conditions increased the yield of sulfone (**3a**) to 91% (Table 1, entry 12).



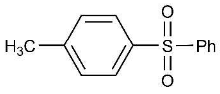
Scheme 2 Influence of oxygen and moisture in the reactions of sulfonyl halides with organozinc reagents: (a) sulfonyl chlorides are highly oxygen and moisture sensitive reagents. (b) the phenoxide nucleophilic substitution reaction with sulfonyl chloride.

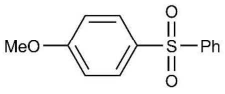
With the optimized reaction conditions in hand, the scope and limitation of various functionalized sulfonyl chlorides were then examined using phenylzinc bromide **1a** as the nucleophile. As summarized in Table 2, aryl sulfonyl chlorides substituted with electron-donating or electron-withdrawing groups were successfully converted into the corresponding diaryl sulfones (**3a-h**) in good to excellent yields. Generally, aryl sulfonyl chlorides bearing electron-donating groups in the benzene rings reacted slightly slower than those sulfonyl chlorides bearing electron-withdrawing substituents, albeit the yields are generally higher. Notably, alkyl sulfonyl chlorides can also be used in this reaction system, as shown in Table 2, reaction of phenylzinc bromide **1a** with methyl sulfonyl chloride gave the phenyl methyl sulfone **3j** in 68% yield. However, highly sterically hindered aromatic sulfonyl chlorides, such as 2-fluoro-6-(trifluoromethyl)benzene-1-sulfonyl chloride and 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)benzene-1-sulfonyl chloride are especially unstable in these reaction systems and decomposed immediately after **1a** was added, even when the reaction was cooled to -78 ^oC (**3k** and **3l**). A prominent advantage of this methodology is the compatibility of functional groups including amide, halogenes (Cl, Br and F) and nitro (**3c**, **3e**, **3f~h**).

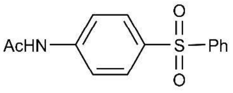
Table 2. Reaction Results of phenylzinc bromide with sulphonyl chlorides[a,b]

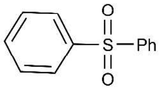


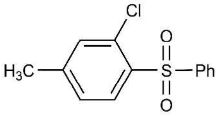
2a: R = 4-tolyl **2b**: R = 4-CH$_3$OC$_6$H$_4$ **2c**: R = CH$_3$CONHC$_6$H$_4$
2d: R = Ph **2e**: R = 2-Cl-4-CH$_3$C$_6$H$_3$ **2f**: R = 4-BrC$_6$H$_4$
2g: R = 4-FC$_6$H$_4$ **2h**: R = 4-NO$_2$C$_6$H$_4$ **2i**: R = 3-thienyl
2j: R = methyl **2k**: R = 2-F-6-CF$_3$C$_6$H$_3$ **2l**: R = 2-CF$_3$-6-(OCH$_2$CHF$_2$)C$_6$H$_3$

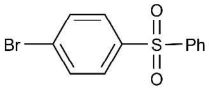

3a: 90%

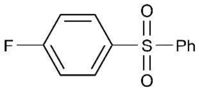

3b: 87%

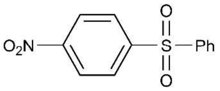

3c: 92%

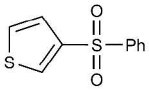

3d: 87%

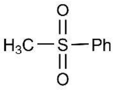

3e: 82%

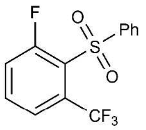

3f: 86%

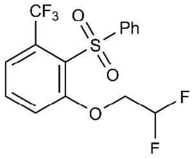

3g: 77%


3h: 72%


3i:66%


3j: 68%

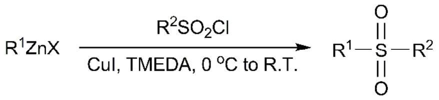

3k: trace

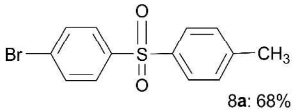

3l: 0%

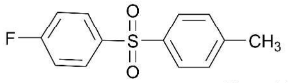
[a] Reaction conditions: *p*-toluenesulfonyl chloride **2a** (5 mmol) was treated with phenylzinc reagent **1a** (10 mmol) in THF (15 mL) under nitrogen. [b] Isolated yields.

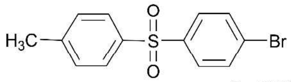
Encouraged by these successful results on sulfonyl chlorides, we subsequently set out to explore the scope of organozinc reagents. As demonstrated in Table 3, functionalized organozinc reagents having chloro- (**8g, 9d** and **9e**), bromo- (**8a** ~ **8d**), fluoro-(**8e, 8f** and **8h**) trifluoromethyl-(**8g** and **8h**), and cyano groups (**9f**) could be employed in these reaction systems obtaining good to high yields of sulfones. Different type of aryl and heteroarylzinc reagents, such as α- and β-naphthylzinc bromide, 4-biphenylzinc bromide and 3-thienylzinc bromide all reacted with aromatic sulfonyl chlorides to give the diaryl sulfones in good to excellent yields. Sterically hindered aromatic zinc reagents, such as 2-chloro-6-(trifluoromethyl)phenylzinc(II) chloride, prepared by in situ transformation of corresponding lithium reagent with one equivalent of ZnCl$_2$, did not react with sulfonyl chloride **2a**. (**8e**).

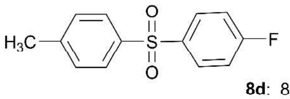
Table 3. Reaction results of functionalied organozinc reagents with sulphonyl chlorides[a]

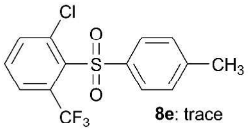


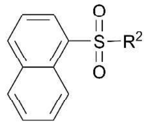

8a: 68%

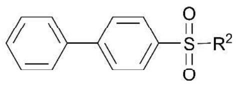

8b: 63%

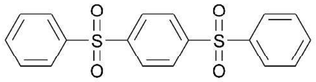

8c: 87%

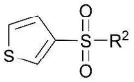

8d: 82%

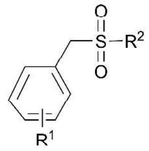

8e: trace


R^2 = Ph, **8f**: 74%
R^2 = 4-MeC$_6$H$_4$, **8g**: 79%
R^2 = Me, **8h**: 62%


R^2 = Ph **8i**: 76%
R^2 = 4-MeC$_6$H$_4$ **8j**: 78%
R^2 = Me **8k**: 64%


8l: 62%

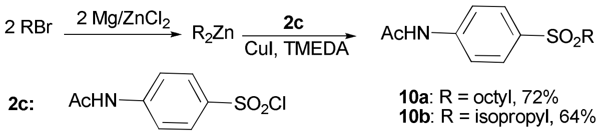

R^2 = Ph **8m**: 72%
R^2 = 4-MeC$_6$H$_4$ **8n**: 75%
R^2 = Me **8o**: 76%


R^1 = H; R^2 = Ph, **9a**: 71%
R^1 = H; R^2 = 4-MeC$_6$H$_4$, **9b**: 76%
R^1 = H; R^2 = CH$_3$ **9c**: 63%
R^1 = 4-Cl; R^2 = Ph, **9d**: 78%
R^1 = 4-Cl; R^2 = 4-MeC$_6$H$_4$ **9e**: 81%
R^1 = 4-Cl; R^2 = CH$_3$ **9f**: 72%
R^1 = 4-CN; R^2 = 4-MeC$_6$H$_4$ **9g**: 58%
R^1 = 4-Bu^t; R^2 = 4-NO$_2$C$_6$H$_4$ **9h**: 63%

[a] Reaction conditions: organic sulfonyl chloride (5 mmol) was treated with organozinc reagent (10 mmol) in THF (15 mL) under nitrogen. [b] Isolated yields.

Benzyl sulfones have significant functions in organic synthesis[23] and biochemistry.[24] These compounds are normally synthesized from corresponding benzyl chloride via sulfinate[25] or sulfide in multiple steps. In our protocol, benzylic zinc reagents, easily prepared from benzylic halides with zinc metal, reacted smoothly with sulfonyl chlorides to give the corresponding sulfones in moderate to high yields (**9a** ~ **9h**).

Attempts to introduce aliphatic zinc halide reagents into this protocol failed, presumably owing to the weak nucleophilicity and strong alkalinity of these organozinc reagents. Neither aromatic nor aliphatic sulfonyl chlorides gave the corresponding sulfones in acceptable yields. Gratifyingly, diorganozinc reagents showed good efficiency in these reaction systems. As shown in Scheme 3, primary and secondary dialkyl zinc reagents (dioctylZn and diisopropylZn), readily prepared via the *in situ* reaction of *n*-octyl and isopropyl bromide, magnesium turnings and 0.5 equivalent of ZnCl$_2$, reacted readily to give the corresponding sulfones in good yields.



Scheme 3 Reaction of dialkyl zinc reagents with sulfonic chloride

Conclusions

In summary, we have developed a new efficient and general approach for a CuI catalyzed synthesis of alkyl, aryl and heteroaryl sulfones bearing various kinds functional groups. The sluggish reactivity of organozinc reagents towards sulfonyl chlorides can be efficiently improved by the addition of CuI and bidentate chelate ligand, TMEDA. This practical procedure considerably extends the reactivity scope of organozinc reagents. In particular, the direct reaction with sulfonyl chlorides allows the expeditious preparation of various sulfones in high yields.

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Notes and references

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[b] *Health Innovations Research Institute & School of Applied Sciences, RMIT University, Melbourne, VIC 3001 Australia.*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 For recent reviews, see: (a) N. Isoherranen, J. D. Lutz, S. P. Chung, H. Hachad, R. H. Levy and I. Ragueneau-Majlessi, *Chem. Res. Toxicol.*, 2012, **25**, 2285; (b) S. S.Bharate and S. B. Bharate, *ACS Chem. Neurosci.* 2012, **3**, 248.

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