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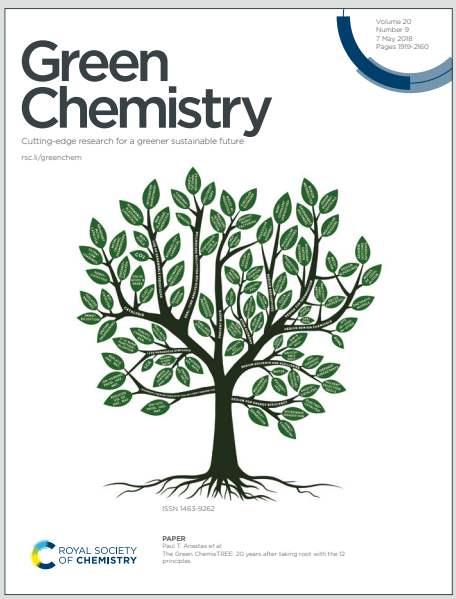

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COMMUNICATION

Sustainable Access to Sulfonic Acids from Halides and Thiourea Dioxide with Air

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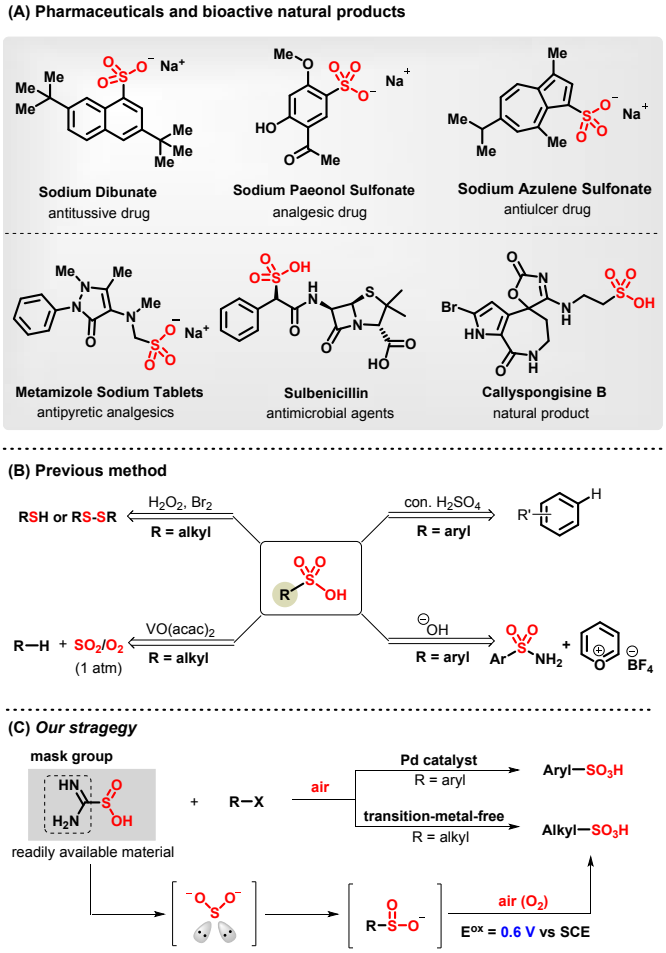
A sustainable and mild one-step strategy is explored for the synthesis of aryl and alkyl sulfonic acids with facile combination of halides and sulfur dioxide surrogates under air conditions. The cheap industrial material thiourea dioxide was employed as an eco-friendly and easy-handling sulfur dioxide surrogate, meanwhile air was used as a green oxidant. Both aryl and alkyl sulfonic acids were obtained under transition metal-catalyzed or transition metal-free conditions. Mechanistic studies demonstrated that sulfinate was involved as intermediates in this transformation. Notably, this protocol has been applied to the late-stage sulfonation of drugs naproxen, isoxepac and ibuprofen.

Sulfonic acid is an indispensable motif in pharmaceuticals[1], natural products[2] and fine chemicals.[3] For example, diverse sulfonic acids served in antipyretic analgesics, antiulcer drug, antimicrobial agents, hemostatic and antiatherosclerotic drugs.[4-8] Sulfonic acid-containing natural product Callyspongisine B was isolated from an Australian marine sponge, *Callyspongia* sp.[2a] Furthermore, sulfonic acid is an important starting material for the preparation of sulfonyl chloride in organic synthesis.[9] Generally, alkylsulfonic acids are prepared by the oxidation of thiols with bromine in the presence of hydrogen peroxide combined with acetic acid.[10] Sulfonation of aromatic compounds is a frequently used synthetic method for the synthesis aryl sulfonic acids, in which concentrated sulfuric acid is employed and the regio-byproducts are inevitable.[11] In 2001, Ishii developed a novel approach for alkyl sulfonic acids by SO_2/O_2 under the assistance of $VO(acac)_2$.[12] Recently, Cornella *et al* explored the transformation of primary sulphonamides to aryl sulfonic acids via a sulfonyl chloride intermediate.[13] Although these elegant works have been achieved, it is still desiderating to develop green and mild methods for the construction of sulfonic acid.



Scheme 1. The significance and synthesis of sulfonic acid.

To the best of our knowledge, there is still no general method for both aryl and alkyl sulfonic acid construction with sensitive functional group under mild conditions. In the past years, the strategy of parallel-oxidative-state introduction of hypervalent sulfur has been well developed.[14] Thiourea dioxide, which is a bleaching and decolorizing agent used in printing and papermaking industry, enable to generate sulfur dioxide anion serving as a sulfur dioxide source under base conditions.[15,16c]

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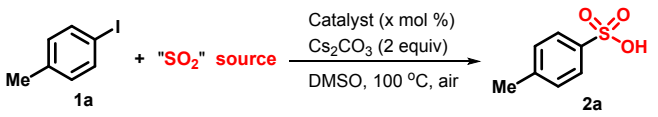
Table 1 Conditions optimization[a]



Entry	Catalyat (x mol %)	PTC	"SO_2" source	Yield[a]
1	$Fe(acac)_3$ (10 mol %)	TBAB	"SO_2"[b]	NR
2	$CuCl_2$ (10 mol %)	TBAB	"SO_2"[b]	NR
3	NiCl·DME (10 mol %)	TBAB	"SO_2"[b]	NR
4	$PdCl_2$(dppf) (10 mol %)	TBAB	$Na_2S_2O_5$	NR
5	$PdCl_2$(dppf) (10 mol %)	TBAB	$Na_2S_2O_4$	46%
6	$PdCl_2$(dppf) (10 mol %)	TBAB	$CH_4N_2O_2S$	>95%
7	$PdCl_2$(dppf) (10 mol %)	TBAB	$CH_4N_2O_2S$	67-88%[c]
8	$PdCl_2$(dppf) (2.5 mol %)	TBAB	$CH_4N_2O_2S$	>95%
9	-	TBAB	$CH_4N_2O_2S$	NR
10	***$PdCl_2$(dppf) (2.5 mol %)***	-	***$CH_4N_2O_2S$***	***87%***
11	$PdCl_2$(dppf) (2.5 mol %)	-	$CH_4N_2O_2S$	85%[d]
12	$PdCl_2$(dppf) (2.5 mol %)	-	$CH_4N_2O_2S$	86%[e]

[a] Standard conditions: **1a** (0.1 mmol), sulflur source (0.3 mmol), base (0.2 mmol), PTC (0.15 mmol), DMSO (1 mL), 14 h, yield is determined by LC-MS using 4-chlorobenzenesulfonic acid as an internal standard. [b] "SO_2" = $CH_4N_2O_2S$, $Na_2S_2O_5$ and $Na_2S_2O_4$. [c] DIPEA, DBU, $NaHCO_3$ or K_3PO_4 takes place of Cs_2CO_3. [d] H_2O (10 equiv) was added. [e] Under O_2 atmosphere. PTC = phase transfer catalyst.

We envisioned that the nucleophilic property of sulfur dioxide radical anion accords with the general construction of both aryl and alkyl sulfinates respectively, followed by a compatible oxidation with matched oxidation potential (E = 0.6 V vs SCE) (Scheme 1C). Based on the transformation from inorganic sulfur to organic sulfides in our group,[16] herein, we employed the abundant industrial material thiourea dioxide as the hypervalent sulfur source to achieve the synthesis of organic sulfonic acids under air condition.

We commenced the sulfonation reaction with 4-methyliodobenzene **1a** and sulfur dioxide source in the existence of base under air condition. To increase the solubility of sulfur dioxide salts, a stoichiometric amount of phase transfer catalyst tetrabuylammonium bromide (TBAB) was added. Different iron, copper and nickel catalysts were tested employing different sulfur dioxide sources. However, the desired sulfonic acid **2a** was not detected (Table 1, entries 1-3). When sodium metabisulfite was used as the sulfur dioxide source, the desired product was not available under the assistant of $PdCl_2$(dppf) catalyst either (Table 1, entry 4). Delightfully, sulfonic acid **2a** was obtained in 46% yield when sodium dithionite was employed as sulfur dioxide source (Table 1, entry 5). Further evaluation of hypervanlent sulfur salts revealed that thiourea dioxide furnished the best yield of 95% (Table 1, entry 6). Various bases were further investigated for their assisted ability of releasing sulfur dioxide anion from thiourea dioxide, in which caesium carbonate was found to be the best results (Table 1, entry 7). When the equivalent of $PdCl_2$(dppf) catalyst was decreased from 10 mol% to 2.5 mol%, the yield of the desired sulfonic acid **2a** had no apparent decline (Table 1, entry 8). However, no sulfonic acid product was detected in the absence of $PdCl_2$(dppf) catalyst even with the addition of TBAB (Table 1, entry 9). The desired sulfonic acid product can be obtained in an excellent yield even in the absence of phase transfer catalyst TBAB (Table 1, entry 10). It was found that the addition of water can not affect the transformation in non-drying reaction system (Table 1, entry 11). The efficiency of the transformation was not further improved in the pure oxygen atmosphere (Table 1, entry 12).

With the optimal conditions in hand, the reaction scope was explored for this sulfonation reaction, which afforded a functionalized sulfonic acid library (Scheme 2). A broad range of aryl iodides with electron-neutral, -rich (**2a**-**2d**) groups were well tolerated in this transformation and provided the desired products with high efficiency. Gram-scale operation of 4-iodotoluene could afford the desired product **2a** in a moderate yield by recrystallization. It should be noted that thiomethyl was compatible in the current reaction, which was not found the corresponding oxidized sulfone (**2d**). Subsequently, various aryl iodides with electron-deficient (**2e**-**2i**) groups, including fluoro (**2f**) were well tolerated in this sulfonation reaction. Notably, the substrates containing sensitive but transformable functional groups, such as bromine (**2h**) and carboxyl (**2i**), generated the corresponding products in good yields. Substituents, including ester and cyano groups at the *meta* and even *ortho* positions of the aromatic ring of the aryl iodides were compatible. Aryl iodides with fused ring systems were converted to the desired sulfonic acids in good yields (**2m**-**2p**). The structure of **2m** was further confirmed via X-ray diffraction analysis.[17] This reaction was quite efficient for heteroaryliodide, namely, thiophene-derived substrate (**2q**). Compounds **2r** and **2s** were afforded in excellent yields when piperonyl and polysubstituted substrates were employed in the current transformation. Besides aryl iodide substrates, the bromostyrene was proven to be applicable in this transformation as well, affording the alkenyl sulfonic acid product **2t** in a moderate yield. The sulfonation of functionalized molecules worked smoothly under the standard conditions, and the desired product **2v** and **2w** were obtained in excellent yields. Furthermore, this sulfonation reaction can be successfully applied to nonsteroidal anti-inflammatory drug naproxen-derived aryl iodide (**2x**).

Encouraged by the above results, this protocol was further applied in the preparation of alkyl sulfonic acids (Scheme 2). Excitingly, the sulfonation reaction of alkyl bromide substrates can be achieved under a transition-metal-free condition to provide the corresponding alkyl sulfonic acid products efficiently. KI was added to activate alkyl bromide via a bromine-iodide exchange process. Diverse chain length alkyl bromides were well tolerated in the sulfonation reaction under standard conditions, delivering the desired alkyl sulfonic acid products **3a**-**3b**. Anti-inflammatory drug isoxepac and ibuprofen-derived alkyl bromides were successfully compatible (**3c**-**3d**). Gram-scale operation of ibuprofen-derived alkyl bromide could afford the desired product **3d** in a moderate yield.

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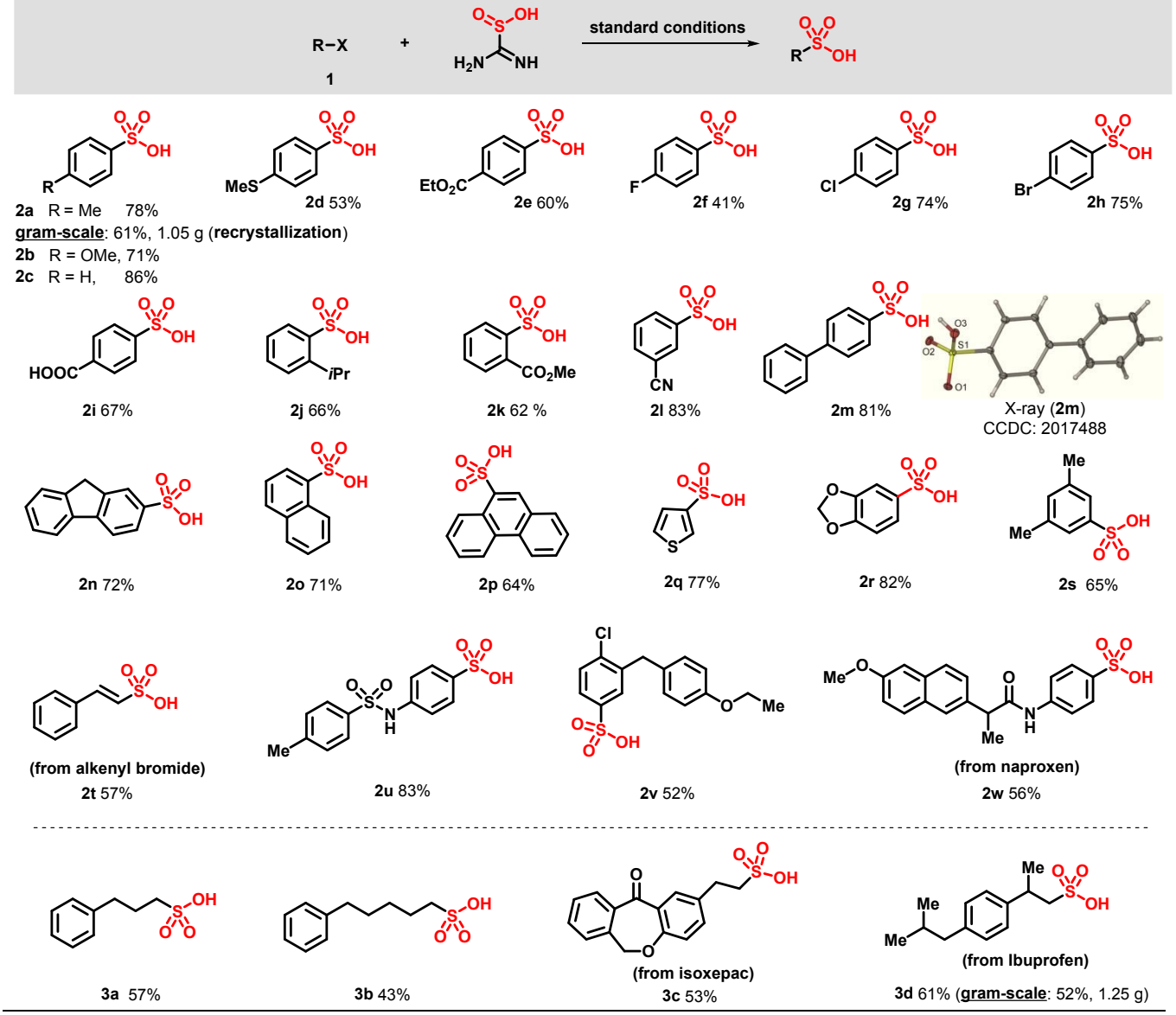
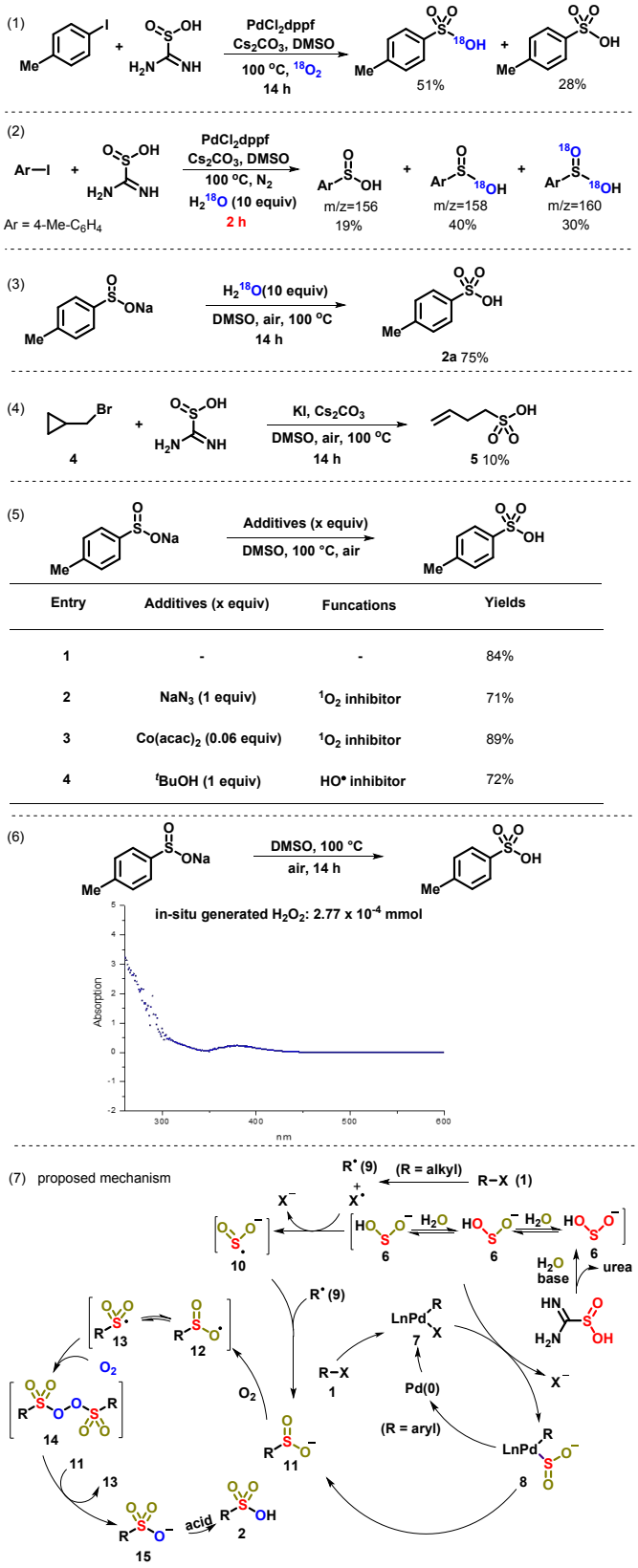


Scheme 2. General synthesis of sulfonic acids[a] [a] R = aryl iodides: **1** (0.5 mmol), $CH_4N_2O_2S$ (1.5 mmol), $PdCl_2(dppf)$ (0.0125 mmol), Cs_2CO_3 (1.0 mmol); R = alkyl bromides: **1** (0.5 mmol), $CH_4N_2O_2S$ (1.5 mmol), Cs_2CO_3 (1.0 mmol), KI (1.0 mmol). DMSO (5 mL), 100 °C, under air, 14 h, isolated yields.

In order to investigate the source of oxygen in sulfonic acid, ^{18}O-labeling experiment was conducted. When the reaction was conducted under ^{18}O atmosphere, the single ^{18}O-labeling sulfonic acid product was afforded, which indicated that sulfinate was oxidized to sulfonic acid by oxygen (Scheme 5-1). Interestingly, the entire ^{18}O-labeling sulfinic acid product was also furnished when $H_2{}^{18}O$ was added and the reaction was conducted under O_2 atmosphere (Scheme 5-2). However, no ^{18}O-labeling sulfonic acid product was obtained when sodium benzenesulfinate was conducted under the conditions of $H_2{}^{18}O$ and air (Scheme 5-3). These results indicated that water was involved in the exchange with thiourea dioxide to release sulfur dioxide source. Ring-opened product **5** was obtained in 10% yield, which provided strong evidences for an alkyl radical intermediate being involved in the alkyl sulfonic acid formation (Scheme 5-4). Control experiments with active oxygen species inhibitors, such as singlet oxygen ($^1O_2$) inhibitors (NaN_3 and $Co(acac)_3$), and hydroxyl radical (•OH) inhibitors, indicated that neither singlet oxygen ($^1O_2$) nor hydroxyl radicals (•OH) were crucial species (Scheme 5-5). UV-Vis absorption of I^{3-} demonstrated that hydrogen peroxide was not generated in the system (Scheme 5-6). Thus, a postulated reaction pathway is displayed in Scheme 5-7. Initially, the sulfur dioxide anion **6** was formed from thiourea dioxide in the presence of caesium carbonate and water (non-drying reaction system). An oxygen exchange happened between **6** and water, which was proved in the control experiments. Oxidation addition of Pd^0 catalyst with aryl iodide generated palladium species **7**. The ligand exchange between intermediates **7** and **6** afforded



Scheme 5. Mechanistic study.

intermediate **8**, which underwent a reductive elimination formed sulfinate intermediate **11**. On the other hand, when alkyl bromides were used as the substrates, alkyl radical halogen radical was generated first. Sulfur dioxide anion **6** underwent a single electron oxidation by halogen radical to form sulfur dioxide radical anion **10**. Meanwhile, alkyl radical was trapped with sulfur dioxide radical anion providing sulfinate intermediate **11**. Then, sulfinate intermediate **11** was oxidized to radical intermediate **12**,[18] which is equilibrium with intermediate **13**. Intermediate **13** was trapped by oxygen to generate bis(sulfonyl) peroxide intermediate **14**,[19] which was reduced by sulfinate to furnished intermediate **15**. Finally, the desired product was formed by acidification.

Conclusions

In summary, a protocol to access both aryl and alkyl sulfonic acids was established via the coupling of halides and thiourea dioxide under air conditions. The abundant industrial material thiourea dioxide was used as the hypervalent sulfur source, and air was employed as the green and mild oxidant. Aryl sulfonic acids were furnished in low catalyst loading conditions, and alkyl sulfonic acids could be achieved in a transition-metal-free condition. Furthermore, the late-stage direct sulfonation of pharmaceuticals naproxen, isoxepac and ibuprofen were achieved efficiently through the current transformation. Mechanistic studies further demonstrated that two kinds of sulfur dioxide intermediates were involved in the current reaction to achieve the construction of aryl and alkyl sulfonic acids respectively. Further hypervalent sulfur molecules syntheses and corresponding drug discovery are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text 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.

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