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General sulfone construction *via* sulfur dioxide surrogate control†

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A highly efficient one-step synthesis of alkyl–alkyl and aryl–alkyl sulfones with a facile combination of halides, sulfur dioxide surrogates and phosphate esters is described. When thiourea dioxide was employed as a reductive sulfur dioxide surrogate, alkyl–alkyl sulfones were obtained under transition metal free conditions. Aryl–alkyl sulfones were obtained with an extremely low catalytic loading (0.2 mol%) *via* altering the mask of sulfur dioxide surrogates to sodium dithionite. A phosphate ester was employed as a stable and readily available alkyl source. Notably, this protocol has been applied to the late-stage modification of natural products and bioactive molecules.

Sulfones[1] are an indispensable motif in pharmaceuticals,[2] agrochemicals,[3] natural products[4] and organic materials.[5] For example, apremilast, containing an alkyl–methyl sulfone structure, is a medication for the treatment of psoriasis and psoriatic arthritis.[6] The alkyl–ethyl sulfone molecule Tinidazole is a well-known anti-inflammatory drug. Vismodegib, possessing an aryl–methyl sulfone fragment, has been used for the treatment of basal-cell carcinoma.[7] The aryl–methyl sulfone-containing corn herbicide Topramezone is an inhibitor of the 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) enzyme.[3a] The heterocyclic-alkyl sulfone Fluensulfone is a new nematicide, which is effective against a number of plant parasitic nematodes in a range of agricultural and horticultural crops.[3d] The sulfone-containing natural product Craniformin, which was isolated from Calvatia craniformis, shows an activity against K562 leukemia cells[4a] (Scheme 1A).

Conventionally, strategies for obtaining sulfones rely on the oxidation of sulfides,[8] in which the application of strong oxidants resulting in low functional group compatibility was the predicament. DABSO [DABCO $(SO_2)_2$], an air-stable and easy-handling reagent first reported in 1988,[9] was pioneered by Willis and Wu, applying it as a sulfur dioxide surrogate.[10] Subsequently, the direct insertion strategy of SO_2 into two coupling partners has been intensively developed due to its step economy and oxidative economy for sulfone synthesis.[11] For example, two steps in one-pot processes were developed *via* the use of aryl halides for the synthesis of aryl–alkyl sulfones.[12] The one-step construction of sulfones from arylboronic acid,[13] aryllithium,[14] aryl magnesium bromide,[15] aryl triethoxysilanes,[16] and aryl halides[17] has been explored (Scheme 1B). Although the above coupling of aryl reagents with alkyl halides affords aryl–alkyl sulfones effectively and has been reported in considerable studies, the access to both alkyl–alkyl and aryl–alkyl sulfones under green conditions controllably is still unresolved.[18] We envisioned that modification of reducibility of sulfur dioxide surrogates *via* the masked effect will tune the coupling rate between alkyl and aryl halides (Scheme 1C). Based on the transformation from inorganic sulfur to organic sulfides by our group,[19] herein, we employed two different types of sulfur dioxide surrogates to adjust to diverse coupling partners for the divergent synthesis of sulfones under transition metal free or low catalytic loading (0.2 mol%) conditions. A phosphate ester was employed as a stable and readily available alkyl source in the current one-step strategy (Scheme 1D).

To explore the assumption, our initial investigations were performed *via* three component coupling of (2-bromoethyl) benzene **1a**, thiourea dioxide and phosphate esters (Table 1). First, the influence of a base was investigated (entries 1–9). No product was observed in the absence of a base even with the addition of KI and TBAB (entry 1). After screening of the different organic (entries 2–5) and inorganic bases (entries 6–9), caesium carbonate was found to be the best base providing the desired sulfone **2a** in 67% yield (entry 8). When

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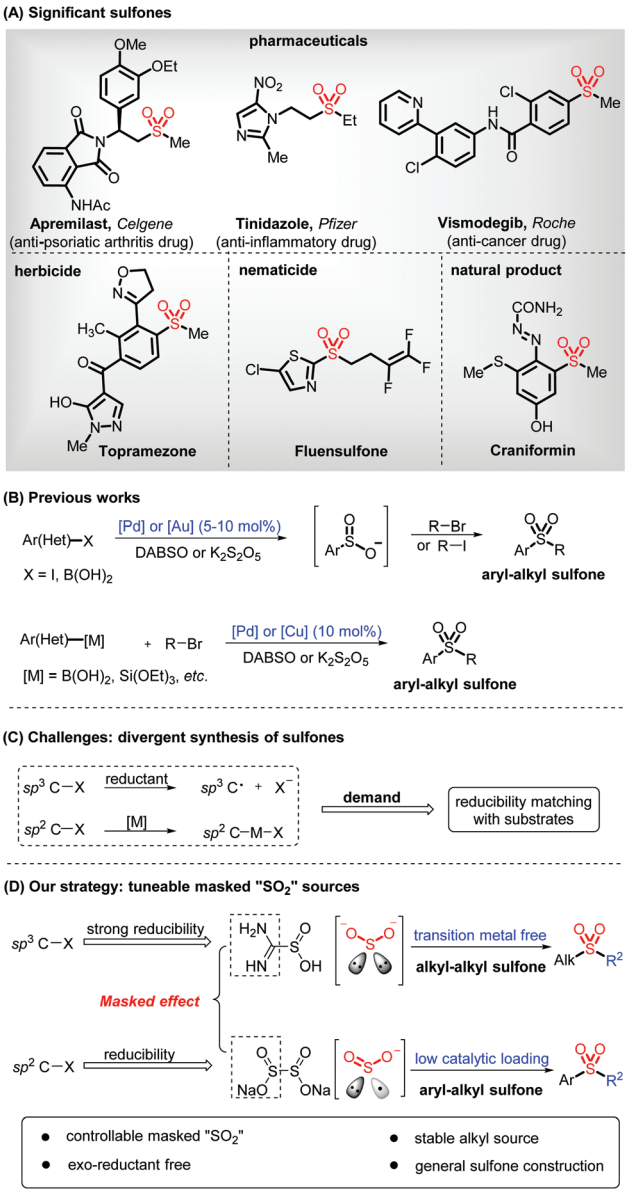


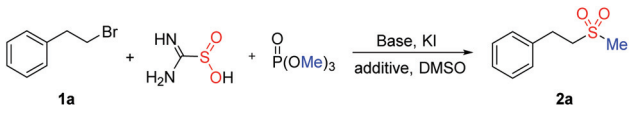
Scheme 1 The synthesis and application of sulfones.

stronger base KO^{t}Bu was used, the desired product was not detected (entry 9). Further examination of phase transfer catalysts of different species (entries 10 and 11) indicated that TBAI was the best choice. The efficiency of the reaction was lower without TBAI (entry 12), and only a half equivalent of TBAI was enough to keep the reaction working efficiently (entry 14). It was found that the yield of the reaction was dramatically lower in the absence of KI since it was necessary to activate alkyl bromides *via* a bromine–iodide exchange process (entry 16). However, no apparent decline was observed when KI was decreased to 1.5 equivalents (entry 17).

With the optimal conditions in hand, the reaction scope was then explored for this catalyst-free reaction, which afforded a divergent functionalized sulfone library. A broad range of alkyl bromides with electron-neutral (**2a–2c**), -deficient (**2d–2h**), and -rich (**2i–2k**) groups, including heterocycles (**2i**, **2l**, **2m**, and **2p**), were well tolerated in this sulfonylated reaction. The structure of **2i** was further confirmed *via* X-ray diffraction analysis.[20] Notably, the substrates containing sensitive but transformable functional groups, such as bromine (**2f**), alkyne (**2n**) and olefin (**2o**), generated the corresponding products in acceptable yields. The cyclobutyl bromide with a tension ring worked well under standard conditions, and the desired product **2q** was obtained in 76% yield. Compound **2r** was afforded in 63% yield when cyclopentane bromide was employed in this transformation. Besides cyclic substrates, secondary bromide with an open chain could also be converted into the desired sulfone smoothly (**2s**). The triethyl phosphate was proved to be applicable in this transformation as well, affording the ethyl sulfone **2t** in a moderate yield.

Encouraged by the above results, this protocol was further applied in the preparation of (hetero)aryl alkyl sulfones. We commenced the study with the coupling of aryl iodides, sodium dithionite and phosphate esters. Excitingly, the reactions provide the corresponding products efficiently with an extremely low catalytic loading (0.2 mol% $PdCl_2$dppf). A wide range of aryl iodides with electron-withdrawing or electron-donating groups at the *para*-position were well tolerated under standard conditions, delivering the desired products **3a–3i** with fluoro, chloro, trifluoromethyl, cyano, amide and methylthio groups. Substitutions from the *para* position to either *meta*-(**3j–3m**) or even *ortho*-(**3n–3p**) showed that steric and electronic effects were successfully compatible. It is worth men-

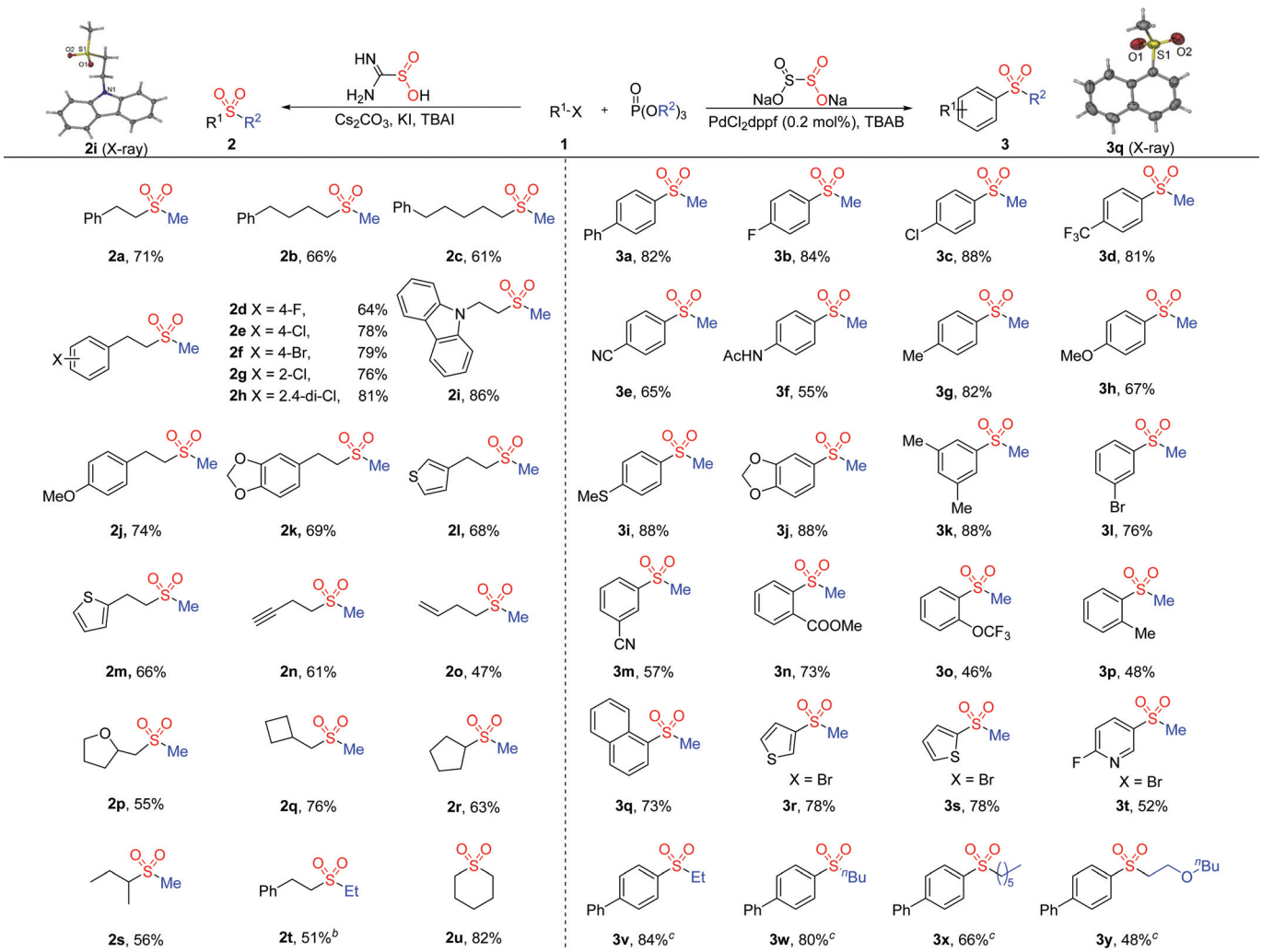
Table 1 Condition optimization[a]



Entry	Base	Additive	Equivalent of additive	Yield (%)
1	—	TBAB	2	ND
2	DABCO	TBAB	2	ND
3	DIPEA	TBAB	2	25
4	Et_3N	TBAB	2	42
5	DBU	TBAB	2	60
6	$KHCO_3$	TBAB	2	ND
7	KOAc	TBAB	2	52
8	Cs_2CO_3	TBAB	2	67
9	KO^{t}Bu	TBAB	2	ND
10	Cs_2CO_3	TBAC	2	66
11	Cs_2CO_3	TBAI	2	79
12	Cs_2CO_3	—	—	71
13	Cs_2CO_3	TBAI	0.2	70
14	Cs_2CO_3	TBAI	0.5	77
15	Cs_2CO_3	TBAI	1.5	79
16[b]	Cs_2CO_3	TBAI	0.5	66
17[c]	**Cs_2CO_3**	**TBAI**	**0.5**	**76(71)**[d]

[a] Reaction conditions: **1a** (0.2 mmol), thiourea dioxide (0.6 mmol, 3 equiv.), $PO(OMe)_3$ (0.6 mmol, 3 equiv.), base (0.4 mmol, 2 equiv.), KI (0.4 mmol, 2 equiv.), additive (0.1 mmol, 0.5 equiv.), DMSO (2.0 mL), 80 °C, N_2, 15 h. NMR yields. [b] KI was absent. [c] KI (0.3 mmol, 1.5 equiv.). [d] Isolated yields.

Table 2 General synthesis of alkyl–alkyl and aryl–alkyl sulfones.[a]

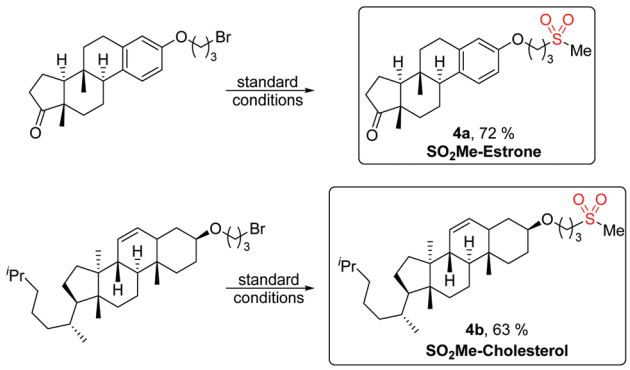


[a] Reaction conditions: **1** (0.5 mmol), $PO(OR^2)_3$ (1.5 mmol, 3 equiv.), isolated yields. R^1 = alkyl: thiourea dioxide (1.5 mmol, 3 equiv.), Cs_2CO_3 (1.0 mmol, 2 equiv.), KI (0.75 mmol, 1.5 equiv.), TBAI (0.25 mmol, 0.5 equiv.), DMSO (2 mL), 80 °C, 15 h; R^1 = aryl: $PdCl_2(dppf)_2$ (0.001 mmol, 0.2 mol%), $Na_2S_2O_4$ (1.5 mmol, 3 equiv.), TBAB (0.75 mmol, 1.5 equiv.), DMSO (5 mL), 120 °C, 15 h. [b] *T* = 120 °C. [c] **1** (0.2 mmol), $PO(OR^2)_3$ (0.6 mmol, 3 equiv.), $Na_2S_2O_5$ (0.4 mmol, 2 equiv.), $PdCl_2(dppf)_2$ (0.01 mmol, 5 mol%), Mn (0.6 mmol, 3 equiv.), TBAB (0.3 mmol, 1.5 equiv.), DMSO (2 mL).

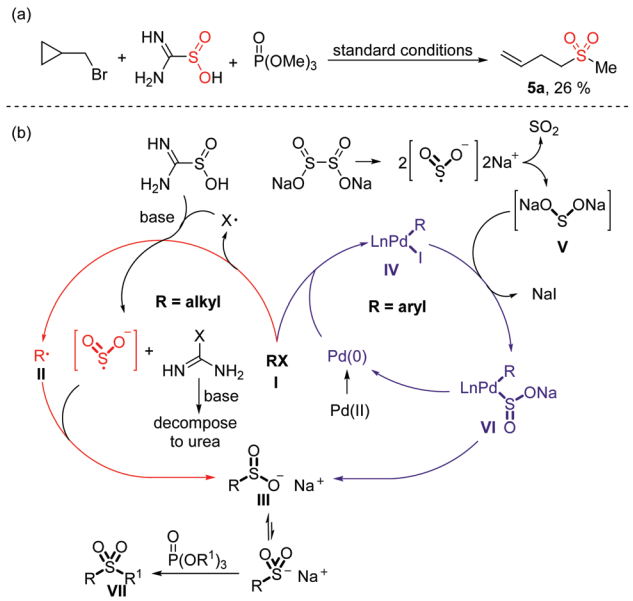
tioning that the heterocycles were also tolerated in this transformation affording the desired products (**3r–3t**) in good yields. Furthermore, a range of different types of phosphate esters, such as triethyl, tributyl, trihexyl and tris(2-butoxyethyl) phosphates, provided the desired products in satisfactory yields (**3v–3y**) (Table 2).

To reveal the versatility and applicability of the three-component coupling protocol, late-stage modification of estrone and cholesterol was further conducted (Scheme 2). The introduction of the $-SO_2R$ motif into hormone drug Estrone was achieved to provide the product **4a** in a good yield. The late-stage modification of steroid compound cholesterol was also tolerant *via* the present approach to afford the sulfone product **4b**.

In order to gain more insight into the reaction mechanism, the control experiment was performed. Compound **5a** was afforded in 26% yield when cyclopropyl bromide was employed in the current transformation, which provided the evidence of an alkyl radical intermediate involved in this transformation (Scheme 3a). A postulated reaction pathway is displayed in Scheme 3b; the sulfur dioxide radical anion was formed from thiourea dioxide in the presence of caesium carbonate.[12c] The alkyl radical was initiated to generate alkyl radical **II**, which was trapped by the sulfur dioxide radical anion providing alkyl sulfinate salt **III**. Then, alkylation of the intermediate **III** afforded the alkyl–alkyl sulfone product. On the other hand, oxidation addition of the Pd^0 catalyst to aryl iodides generated palladium species **IV**. A sulfur dioxide radical anion was generated from sodium dithionite with sulfur dioxide release, followed by intermediate **V** formation. Ligand exchange between intermediates **V** and **IV** gave intermediate **VI**. The reductive elimination and alkylation of intermediate **VI** formed the desired products, as well as regenerated the Pd(II) catalyst.



Scheme 2 Late-stage modification of estrone and cholesterol.



Scheme 3 Possible mechanism.

Conclusions

In summary, a novel pathway to access both alkyl–alkyl and aryl–alkyl sulfones was established *via* a three-component cross-coupling protocol of halides, masked sulfur dioxides and phosphate esters. Through exploring different masked sulfur dioxide surrogates, alkyl–alkyl sulfones were constructed under one-pot, transition metal free conditions *via* thiourea dioxide as the SO_2 surrogate. Aryl–alkyl sulfones were achieved under low catalyst loading conditions through employing sodium dithionite as both the SO_2 surrogate and reductant. A phosphate ester was employed as a stable and readily available alkyl source. Furthermore, late-stage modification of pharmaceuticals and bioactive molecules was achieved efficiently through the current transformation. Further sulfone-containing molecule syntheses and corresponding drug discovery are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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