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Authors: Ming Wang, Jiaoyan Zhao, and Xuefeng Jiang

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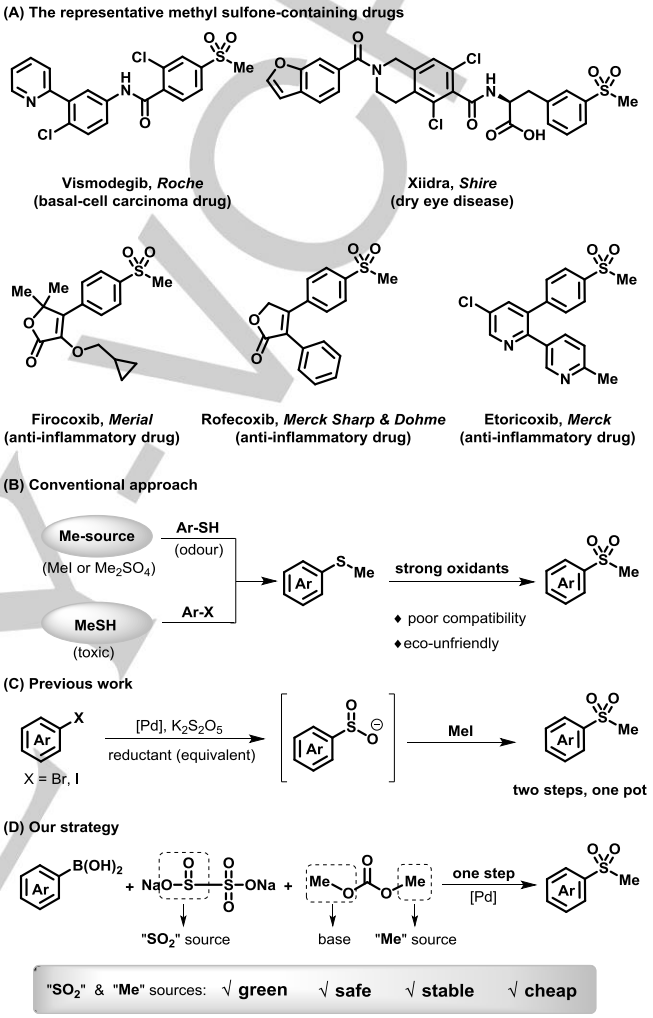
Aryl Methyl Sulfone Construction from Eco-Friendly Inorganic Sulfur Dioxide and Methyl Reagents

Ming Wang, Jiaoyan Zhao and Xuefeng Jiang*

Abstract: A three-component cross-coupling protocol of boronic acid, sodium metabisulfite and dimethyl carbonate is developed for the construction of significant functional methyl sulfones, in which introduction of sulfur dioxide at last stage was successfully achieved in one step. Inorganic sodium metabisulfite was served as an eco-friendly sulfur dioxide source. Green dimethyl carbonate was employed as methyl reagent in this transformation. The diversiform functional methyl sulfones were comprehensively achieved from various readily available boronic acids. Notably, the last stage modification of pharmaceuticals and the synthesis of Firocoxib were efficiently established through this strategy.

Methyl sulfone, consisting of a sulfonyl group and a methyl group, has attracted considerable interest due to its extensive applications in pharmaceuticals.[1] For example, Vismodegib has been found to be an exclusive basal-cell carcinoma drug, which was first explored by Roche.[2] Xiidra has been applied for dry eye disease.[3] Firocoxib, Rofecoxib and Etoricoib have been widely used as nonsteroidal anti-inflammatory pharmaceuticals for different inflammation types (Scheme 1A).[4-6] Since methyl sulfone is a common structural motif in pharmaceutical due to its excellent oxidation resistance and stability in vivo, continous contributions for its synthesis have been pursued. Conventionally, methyl sulfone were achieved through oxidation of the corresponding thioethers, which are prepared via odorous thiols, highly toxic Me_2SO_4 or expensive MeI (Scheme 1B).[7] Recently, the strategy of straightforward introduction of sulfur dioxide into organic frameworks has been paid great attention due to its atom economy, step economy, oxidation economy and recycling hazardous sulfur dioxide.[8] Shavnya, Willis, Wu and Toste have established the insertion of sulfur dioxide into C_{Ar}-palladium bond for generation of aryl sulfinate salts employing DABSO or potassium metabisulfite as a sulfur dioxide surrogate.[9] The resulting aryl sulfinate salts can be quenched with alkyl electrophiles in a one-pot, two-step process for the construction of aryl alkyl sulfones, which is the pioneer work for the synthesis of methyl sulfones.[9a-9b] Subsequently, the one-step processes were explored by Toste and Shavnya, in which benzyl bromide and alkyl halides were used as the electrophiles



Scheme 1. Significant functional Methyl Sulfones.

to construct sulfones efficiently.[9b,10] However, the direct construction of methyl sulfone without reductant via the insertion of sulfur dioxide strategy in one-step still remains a challenge to synthetic community.[11] Recently, we found that sodium metabisulfite ($Na_2S_2O_5$) was another special candidate as the sulfur dioxide source for the synthesis of sulfones especially in multicomponent tandem assembled process.[12] Meanwhile, dimethyl carbonate (DMC) have been proved to be an ideal methylating reagent due to their low toxicity and high biodegradability.[13] Since of the rapid decomposition property of DMC and CO_2 releasing from DMC with an alkoxide anion generation, we postulated that it will play not only as a methylating reagent, but also as a base to promote the transmetalation of boronic acids. Logically, a three-component system, comprising a boronic acid, an inorganic sulfur dioxide source and DMC, may lead to aryl methyl sulfone formation

[*] Dr. M. Wang,[+] J. Zhao,[+] Prof. Dr. X. Jiang
Shanghai Key Laboratory of Green Chemistry and Chemical Process, School of Chemistry and Molecular Engineering, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, P. R. China
E-mail: xfjiang@chem.ecnu.edu.cn
Prof. Dr. X. Jiang
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China
[+] These authors contributed equally to this work.

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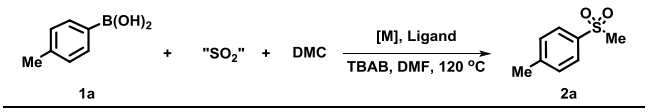
Table 1.Condition Optimization.[a]



Entry	Catalyst	Ligand	"SO_2"	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	$K_2S_2O_5$	9
2	$Pd(OAc)_2$	PPh_3	$Na_2S_2O_5$	33
3	$Pd(OAc)_2$	PPh_3	$NaHSO_3$	22
4	$Pd(OAc)_2$	$P^tBu_3{\cdot}HBF_4$	$Na_2S_2O_5$	48
5	$Pd(OAc)_2$	dppe	$Na_2S_2O_5$	56
6	$Pd(OAc)_2$	dppf	$Na_2S_2O_5$	71(66)
7	$Pd(OAc)_2$	SPhos	$Na_2S_2O_5$	68(64)
8	$Pd(OAc)_2$	XPhos	$Na_2S_2O_5$	65
9	$Pd(OAc)_2$	XantPhos	$Na_2S_2O_5$	73(71)
10	***$PdCl_2$***	***^{t}BuXPhos***	***$Na_2S_2O_5$***	***81(75)***
11	$Pd(TFA)_2$	^{t}BuXPhos	$Na_2S_2O_5$	60
12	$Pd(PPh_3)_2Cl_2$	^{t}BuXPhos	$Na_2S_2O_5$	59
13	$Pd_2(dba)_3$	^{t}BuXPhos	$Na_2S_2O_5$	52

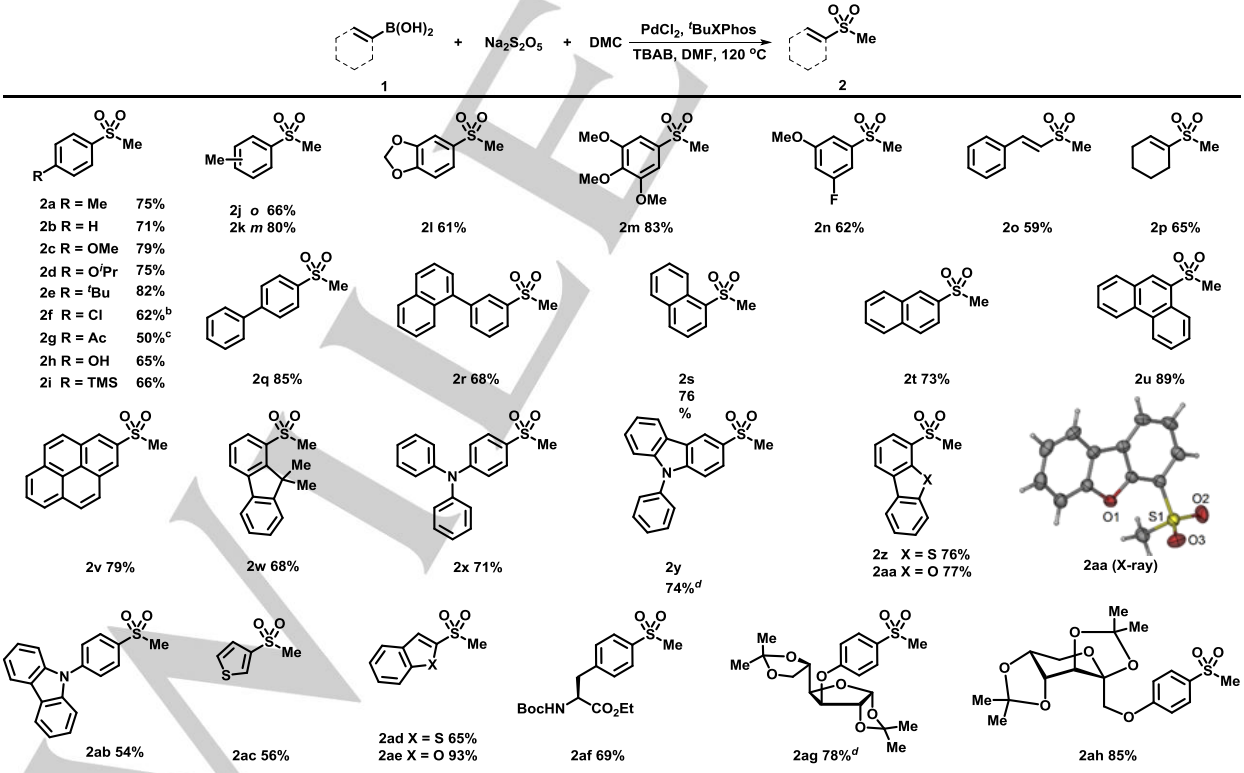
[a] Reaction conditions: **1a** (0.25 mmol), $Na_2S_2O_5$ (0.75 mmol), DMC (1.25 mmol) [M] (0.025 mmol), ligand (0.050 mmol), TBAB (0.75 mmol), DMF (1 mL), 120 °C, N_2, 12 h. [b] Isolated yields of **2a**.

under the assistant of a catalyst. We have been studying on transformation from a series of inorganic sulfur salts to multiple functional organic sulfides.[14] Further to our understanding, we disclose a palladium-catalyzed direct three-component reaction of boronic acid, sodium metabisulfite and dimethyl carbonate for the synthesis of methyl sulfone (Scheme 1D).

To explore this assumption, we commenced with the coupling of 4-tolylboronic acid **1a**, $Na_2S_2O_5$, and DMC as the model reaction. Tetrabutylammonium bromide (TBAB) was added to increase the solubility of inorganic sulfur salt in the transformation. Initial testing results of various inorganic sulfur dioxide source found that $K_2S_2O_5$ provided the desired sulfone product in a poor yield (9%) (Table 1, entry 1).[7-8] Pleasantly, $Na_2S_2O_5$ delivered a 33% yield of aryl methyl sulfone **2a** as a better result (Table 1, entries 1-3). Further studies on the structurally diverse ligand effects revealed that that electron-rich, sterically encumbered ligand ^{t}BuXPhos consistently supported the efficiency of the catalysis for this transformation (Table 1, entries 4-9). The reaction under $PdCl_2$ as a catalyst afforded a relatively superior yield compared to $Pd(OAc)_2$ as the catyalyst. Ultimately, the optimized conditions were achieved to afford **2a** in 81% yield (Table 1, entry 10).

The three-component cross-coupling, exhibiting a powerful synthesis of functionalized sulfones, is shown in Table 2. A broad range of boronic acids with electron-neutral (**2a**-**2b**), - rich (**2c**-**2e**), and -deficient (**2f**-**2g**) groups at *para*-position were

Table 2. Sulfonemethylation with Various Arylboronic Acids.[a]



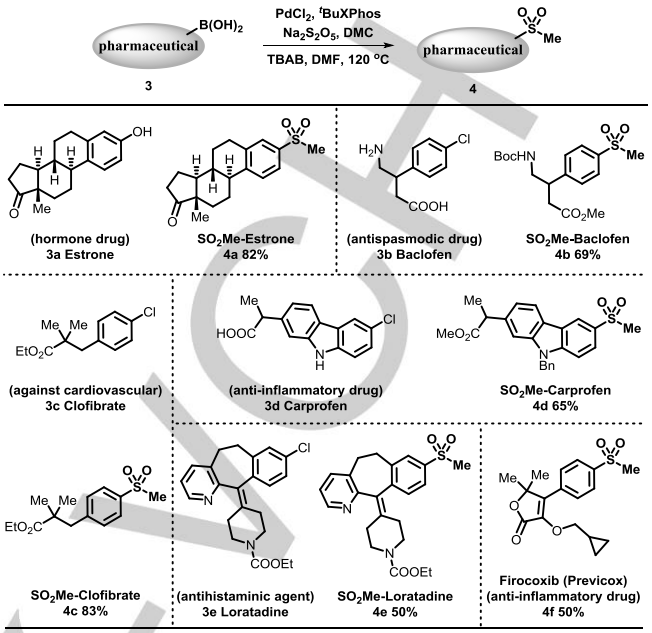
[a] Reaction conditions: **1** (0.25 mmol), $Na_2S_2O_5$ (0.75 mmol), DMC (1.25 mmol), $PdCl_2$ (0.025 mmol), ^{t}BuXPhos (0.05 mmol), TBAB (0.75 mmol), DMF (1 mL), 120 °C, N_2, 12 h, Isolated yields. [b] Tris(3-methoxyphenyl)phosphane (0.05 mmol). [c] ^{t}BuXPhos (0.10 mmol). [d] 24 h.

all readily achieved. Remarkably, substrates containing active hydrogen (**2h**) and sensitive functional group TMS (**2i**), could be well tolerated. The substituents on *meta*- and even *ortho*-positions (**2j** and **2k**) gave seldom impeding with efficiency. The corresponding aryl methyl sulfones, bearing naturally occurring piperonyl or 2,3,4- trimethoxyl, were readily achieved in good yields (**2l-2m**). Arylboronic acid with two different substituents was also effective candidate (**2n**). Gratifyingly, the one-step three-component cross-coupling reaction can be successfully extended to cinnamenyl and cyclohexenyl affording the desired aryl methyl sulfone products **2o**-**2p**. Fused rings, such as diphenyl, naphthyl, phenanthryl and pyrenyl, were proved to be entirely compatible affording the corresponding conjugated sulfones **2q**-**2v**. Gem-dimethyl fluorenyl, triphenylamine, carbazolyl, dibenzothiophenyl and dibenzofuranyl, which are significant contributor for charge transporting amorphous molecular materials, were successfully accommodated affording the corresponding products (**2w**-**2ab**). The representative structure **2aa** was further confirmed via X-ray diffraction analysis.[15] Thiophene (**2ac**), benzothiophene (**2ad**) and benzofuran (**2ae**) can be present for aryl methyl sulfone products. Notably, amino acid and saccharides were proved to be entirely compatible in the current transformation (**2af**-**2ah**).

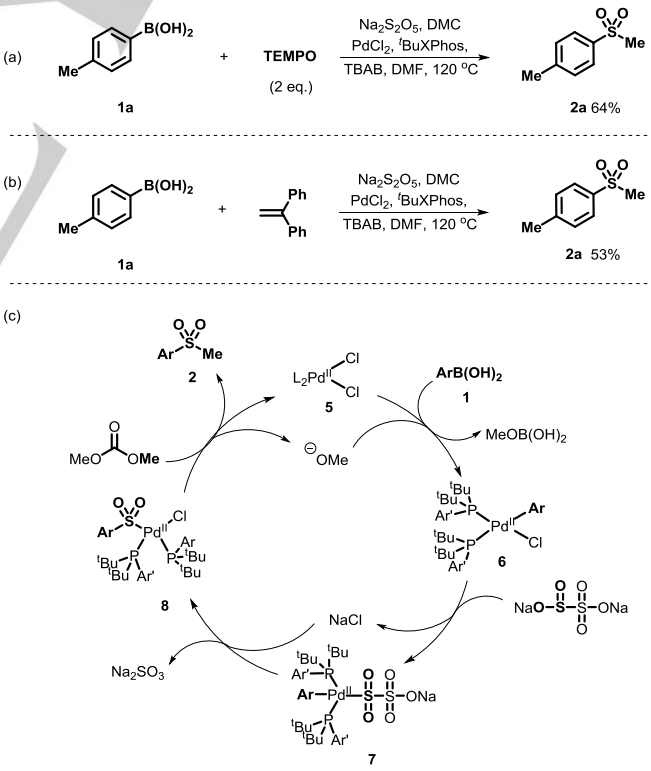
To further reveal the practicability of the three-component cross-coupling protocol, the late-stage modification and synthesis of pharmaceutical molecules were further conducted (Scheme 2). A series of pharmaceuticals substituted with multiple heteroatoms and active hydrogen functional groups allowed the incorporation of $-SO_2Me$ motify, such as hormone drug (Estrone, **3a**), anti-spasmodic (Baclofen, **3b**), against cardiovascular (Clofibrate, **3c**), anti-inflammatory (Carprofen, **3d**) and anti-histaminic (Loratadine, **3e**) drugs. The non-steroidal anti-inflammatory drug Firocoxib (**4f**), as the first COX-2 inhibitor approved by FDA for horses, was afforded from the corresponding arylboronic acid through the current strategy, which provided a novel synthetic route for Firocoxib.

Radical trapping experiments were conducted in order to confirm the possibility of radical pathway in this transformation. The reaction wasn't inhibited and no radical intermediate was trapped when TEMPO or 1,1-diphenylethylene was added under the standard conditions. These experiments indicated that the current reaction was not possible to undergo a radical pathway. A postulated reaction pathway is depicted in Scheme 3c. Palladium species **5** was formed through the coordination of Pd(II) catalyst with the ligand in situ. Alkoxide anion, generating from DMC with methyl group emitting,[16] promotes the transmetalation of aryl boronic acid **1** to produce intermediate **6**. Ligand exchange between intermediate **6** and $Na_2S_2O_5$ led to intermediate **7** through a nucleophilic process. Subsequently, SO_2 insertion into the Pd-C bond to afford intermediate **8** under the assistant of electron-rich ligand, alkylation with DMC affords the methyl sulfone product **2**, as well as regenerating the palladium species **5**.

In summary, a novel synthetic pathway to access aryl methyl sulfones was established through a three-component cross-coupling protocol of boronic acid, sodium metabisulfite and dimethyl carbonate. This efficient transformation employs sodium metabisulfite as the sulfur dioxide source to realize the



Scheme 2. Late-stage Modification and Synthesis of Pharmaceuticals.



Scheme 3. Possible Mechanism.

assembly modification strategy. DMC was served not only as a methylating reagent, but also as a base to promote the transmetalation of boronic acids. Divergent functionalized sulfones libraries were efficiently established through the present transformation. Late-stage modifications of pharmaceuticals were achieved efficiently via this protocol. Further explorations of sulfone-containing molecules employing the multicomponent cross-coupling strategy for drug discovery are in progress in our laboratory.

Acknowledgements

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Keywords: Sulfonemethylation • dimethyl carbonate • sodium metabisulfite • pharmaceutical • late-stage modification

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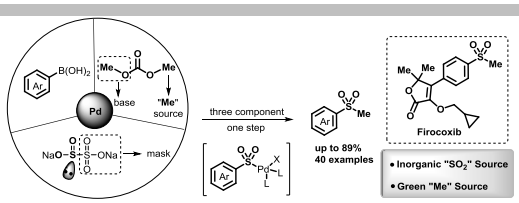
A three-component cross-coupling reaction of boronic acid, sodium metabisulfite and dimethyl carbonate was efficiently established for the construction of aryl methyl sulfone library. Pharmaceutical synthesis and late-stage diversification were afforded through this protocol.



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