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Deaminative metal-free reaction of alkenylboronic acids, sodium metabisulfite and Katritzky salts

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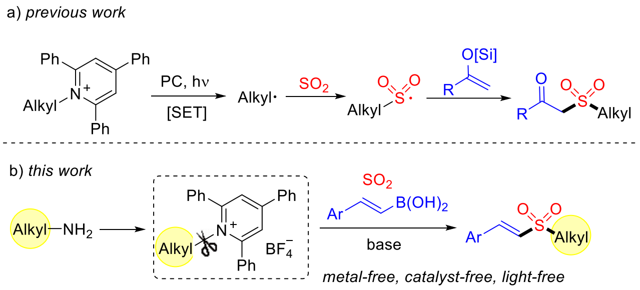
A convenient and efficient approach to (*E*)-alkylsulfonyl olefins *via* a metal/light-free three-component reaction of alkenylboronic acids, sodium metabisulfite and Katritzky salts is described. This alkylsulfonylation proceeds smoothly with a broad substrate scope, leading to diverse (*E*)-alkylsulfonyl olefins in moderate to good yields. During the process, excellent functional group tolerance is observed and sodium metabisulfite is used as the source of sulfur dioxide. Mechanistic studies show that alkyl radical generated *in situ* from Katritzky salt via a single electron transfer with alkenylboronic acid or DIPEA is the key step providing alkyl radical intermediate, which undergoes further alkylsulfonylation with sulfur dioxide.

Since amines are one of the most ubiquitous molecules in natural products and pharmaceuticals, conversion of amino-group for the synthesis of new functional molecules *via* the cleavage of C(sp^3)-N bond has been of great significance and has attracted growing interest in synthetic community.[1] Recently, rapid progress has been witnessed for the chemistry of Katritzky salts from alkylamines through the activation of C(sp^3)-N bond.[2] So far, Katritzky salts have been utilized broadly as alkyl radical precursors in organic transformations. Usually, alkyl radicals are generated under transition metal catalysis or visible-light induced conditions *via* a single electron transfer process.[3,4] In 2018, Shi and co-workers described a metal-free deaminative borylation of Katritzky salts in absence of visible-light irradiation.[5a] Subsequently, Loh and co-workers reported the synthesis of *trans*-1,2-disubstituted olefins under catalyst-free conditions through a deaminative alkenylation of Katritzky salts with alkenyl boronic acids.[5b] *N*-Heterocyclic carbene-catalyzed deaminative carbonylation of Katritzky salts with aldehydes was demonstrated as well by Hong's group.[5c] Later, a transition-metal-free deaminative carbonylation of Katritzky salts with styrenes in the presence of carbon monoxide was disclosed by Wu and co-workers.[5d] The above results showed that this metal-free deaminative reaction of Katritzky salts was promising, since it would provide innovative routes for the construction of complex functional molecules under mild conditions.



Scheme 1. Synthesis of (*E*)-alkylsulfonyl olefins *via* the deaminative insertion of sulfur dioxide.

In the past decade, sulfonylation from sulfur dioxide for the construction of sulfonyl compounds has developed rapidly by using DABCO$\cdot$(SO$_2$)$_2$ and sodium/potassium metabisulfite as the sulfur dioxide surrogates.[6] As part of our interests in sulfones, we focused on the exploration in the method development for the synthesis of vinyl sulfones through the insertion of sulfur dioxide[7], due to their versatile reactivities in organic synthesis[8] and importance in pharmaceuticals.[9] For instance, vinyl sulfones have been reported as a novel class of neuroprotective agents toward Parkinson's disease therapy.[10] Prompted by the recent advance in the metal-free deaminative transformations of Katritzky salts, we envisioned that vinyl alkylsulfones would be produced from Katritzky salts with the insertion of sulfur dioxide. Our previous result showed that in the presence of visible light irradiation, photocatalytic deaminative insertion of sulfur dioxide using Katritzky salts as alkyl radical precursors would give rise to β-keto sulfones (Scheme 1a).[11] Encouraged by this achievement and the result from Katritzky salts and boronic acids, we hypothesized that the generation of (*E*)-alkylsulfonyl olefins might be accessed under metal- and light-free conditions (Scheme 1b). Herein, we described a convenient and efficient approach to (*E*)-alkylsulfonyl olefins *via* a metal/light-free three-component reaction of alkenylboronic acids, sodium metabisulfite and Katritzky salts. This

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† Electronic Supplementary Information (ESI) available: Experimental details and spectral data, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra. See DOI: 10.1039/x0xx00000x

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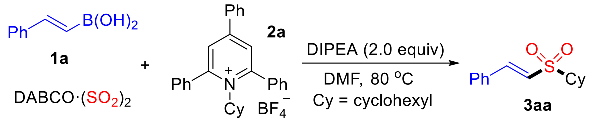
alkylsulfonylation proceeds smoothly with a broad substrate scope, leading to diverse (*E*)-alkylsulfonyl olefins in moderate to good yields. During the process, excellent functional group tolerance is observed and sodium metabisulfite is used as the source of sulfur dioxide. Mechanistic studies show that alkyl radical generated *in situ* from Katritzky salt via a single electron transfer with alkenylboronic acid or DIPEA is the key step providing alkyl radical intermediate, which undergoes further alkylsulfonylation with sulfur dioxide.

Table 1. Effects of variation of reaction parameters [a]

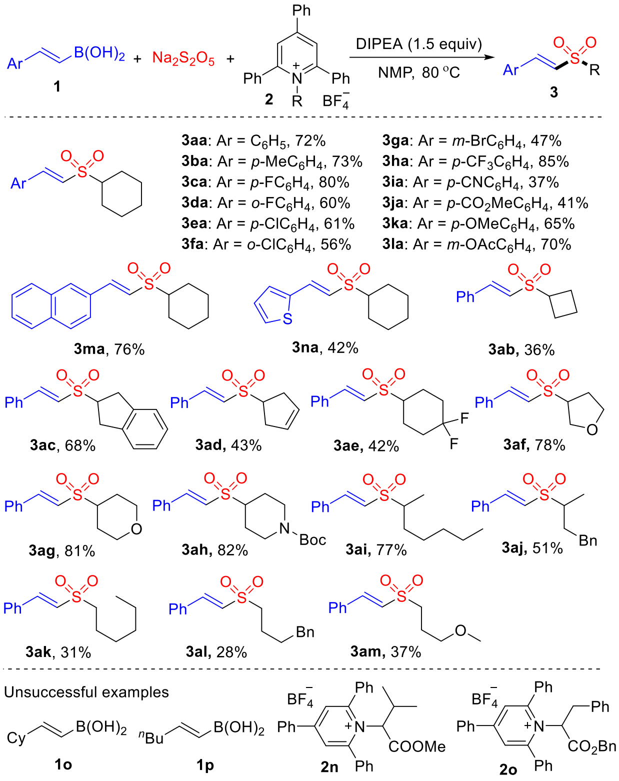


Entry	Variation of conditions	Yield (%)[b]
1	none	32
2	other bases instead of DIPEA	trace to 24
3	NMP instead of DMF	38
4	other solvents instead of DMF	trace to 27
5[c]	$Na_2S_2O_5$ instead of DABCO·$(SO_2)_2$	65
6[c]	$K_2S_2O_5$ instead of DABCO·$(SO_2)_2$	49
7[c]	3.0 equiv. of DIPEA	59
8[c]	1.5 equiv. of DIPEA	71
9[c]	1.0 equiv. of DIPEA	39
10[c,d]	50 °C	trace
11[c,d]	110 °C	36
12[c,d]	1.2 equiv. of **2a**	77(72)

[a] Reaction condition: alkenylboronic acid **1a** (0.2 mmol, 1.0 equiv), DABCO·$(SO_2)_2$ (0.3 mmol, 1.5 equiv), 1-cyclohexyl-2,4,6-triphenyl-pyridin-1-ium tetrafluoroborate **2a** (0.3 mmol, 1.5 equiv), DIPEA (0.4 mmol, 2.0 equiv), DMF (1.0 mL), N_2, 80 °C, 12 h. [b] ^1H NMR yield using 1,3,5-trimethoxybenzene as internal standard (Isolated yield in parentheses). [c] NMP was employed as the solvent. [d] In the presence of DIPEA (0.3 mmol, 1.5 equiv).

Initial investigation was carried out for the reaction of (*E*)-styrylboronic acid **1a**, DABCO·$(SO_2)_2$ and 1-cyclohexyl-2,4,6-triphenyl-pyridin-1-ium tetrafluoroborate **2a** in DMF at 80 °C using *N,N*-diisopropylethylamine (DIPEA) as a base. To our delight, the desired product **3aa** was produced in 32% yield (Table 1, entry 1). Further exploration of other bases revealed that DIPEA was the best choice (Table 1, entry 2, for details see ESI). Evaluation of solvents showed that product **3aa** could be generated in 38% yield by using 1-methyl-2-pyrrolidinone (NMP) instead of *N,N*-dimethylformamide (DMF) as the solvent (Table 1, entry 3). However, the results were inferior when other solvents were used as a replacement of DMF (Table 1, entry 4, for details see ESI). Fortunately, the yield of compound **3aa** was dramatically improved when sodium metabisulfite was employed as the sulfur dioxide surrogate, and the result from potassium metabisulfite was not better (Table 1, entry 5 *vs* entry 6). Further optimization revealed that increasing the amount of DIPEA could not improve the final outcome (Table 1, entry 7). Interestingly, a higher yield was obtained when the amount of DIPEA was decreased to 1.5 equiv (71%, Table 1, entry 8). Subsequently, the effect of reaction temperature was evaluated. It was found that the reaction worked efficiently at 80 °C (Table 1, entries 8 and 9). Additionally, after optimization of the substrate ratio, the corresponding product **3aa** was afforded in 77% isolated yield (Table 1, entry 12).

Table 2. Scope exploration for the metal/light-free three-component reaction of alkenylboronic acids **1**, Katritzky salts **2** and sodium metabisulfite [a,b]



[a] Reaction condition: alkenylboronic acid **1** (0.3 mmol, 1.0 equiv), sodium metabisulfite (0.45 mmol, 1.5 equiv), Katritzky salt **2** (0.36 mmol, 1.2 equiv), DIPEA (0.45 mmol, 1.5 equiv), NMP (1.5 mL), N_2, 80 °C, 12 h. [b] Isolated yield based on alkenylboronic acid **1**.

Having identified effective conditions, we next evaluated the synthesis of (*E*)-alkylsulfonyl olefins *via* a metal/light-free three-component reaction of alkenylboronic acids **1**, sodium metabisulfite and Katritzky salts **2**. The results are summarized in Table 2. At the outset, we explored the substrate scope of alkenylboronic acids **1**. Generally, various alkenylboronic acids **1** bearing either electron-withdrawing or electron-donating groups were applicable in this transformation, giving rise to the corresponding (*E*)-alkylsulfonyl olefins **3aa-3la** in 37-85% yields. A variety of functional groups including halo (F, Cl, Br), CF_3, CN, CO_2Me, OMe and OAc were all compatible under the standard conditions. Additionally, reaction of (2-(naphthalen-2-yl)vinyl)boronic acid **1m** worked efficiently, leading to the target product **3ma** in 76% yield. The substrate with thiophene substituent was suitable as well, providing the expected product **3na** in 42% yield. Subsequently, the scope of Katrizky salts **2** prepared from alkyl amines was evaluated. The results showed that both cyclic and chain alkyl amine derivatives were workable in the transformation, giving rise to the desired products in moderate to good yields. Unfortunately, alkyl-substituted alkenylboronic acids **1o** and **1p** were not suitable in

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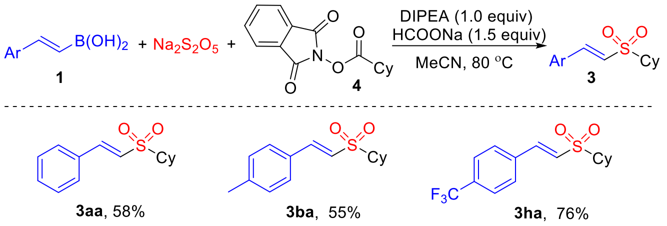
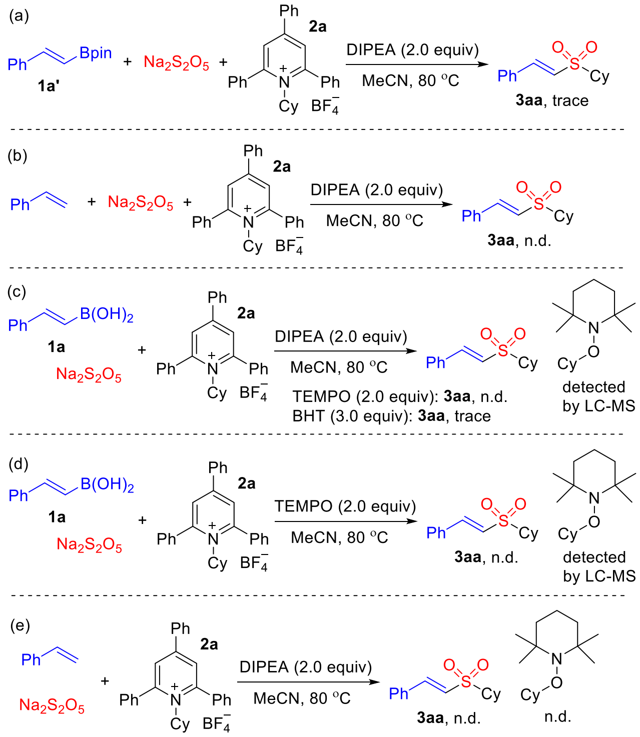
this transformation. Moreover, the reaction failed to provide the desired product when Katritzky salt **2n** or **2o** from amino acids was employed in the reaction of (*E*)-styrylboronic acid **1a** and sodium metabisulfite.



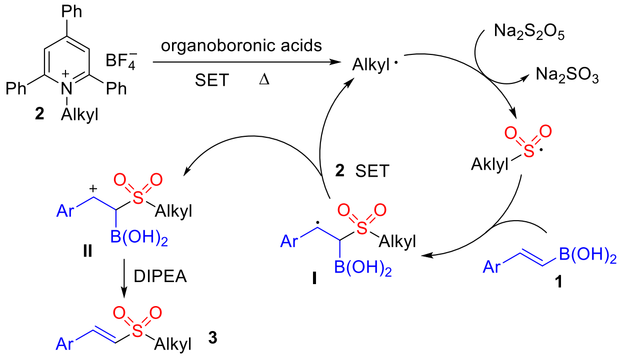
Scheme 2. Synthesis of *(E)*-alkylsulfonyl olefins *via* the decarboxylative insertion of sulfur dioxide.

Moreover, further exploration revealed that not only Katritzky salts but also *N*-hydroxyphthalimide (NHP) esters[12] could be applied as the alkyl radical precursors in the synthesis of (*E*)-alkylsulfonyl olefins *via* a deaminative insertion of sulfur dioxide. Several examples are presented in Scheme 2.



Scheme 3. Control experiments.

Additionally, to gain more insights for the reaction pathway, several control experiments were performed. It was found that only a trace amount of product **3aa** was detected when 4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane **1a'** was used instead of styrylboronic acid **1a** (Scheme 3, eqn a). No reaction occurred when styrene was employed as a replacement under the standard conditions (Scheme 3, eqn b). These results demonstrated the crucial role of organoboronic acids in the transformation. Moreover, the model reaction was completely hampered in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 3, eqn c). These results revealed that this conversion might undergo a radical process. In order to verify the formation of alkyl radical, the model reaction was carried out in the absence of DIPEA. It was found that cyclohexyl radical could be trapped by TEMPO (Scheme 3, eqn d). However, the cyclohexyl radical was not detected when styrene was employed in the presence of DIPEA (Scheme 3, eqn e), which indicated that the formation of alkyl radical might go through a single electron transfer (SET) between alkenylboronic acid and Katritzky salt.



Scheme 4. Proposed mechanism.

Prompted by the above results and related reports,[5] we proposed a plausible mechanism as shown in Scheme **4**. We reasoned that assisted by organoboronic acid under thermal conditions, alkyl radical would be formed from Katrizky salt **2** *via* a single electron transfer process. This alkyl radical would be trapped by sulfur dioxide from sodium metabisulfite,[13] giving rise to alkylsulfonyl radical. Subsequently, addition of alkylsulfonyl radical to alkenylboronic acid **1** would occur, generating a more stable radical intermediate **I**. Another SET process between radical intermediate **I** and Katritzky salt **2** would take place, leading to alkyl radical and cation intermediate **II**. In the presence of base, this cation intermediate **II** would undergo deboronization to provide the desired product **3**.

In conclusion, we have developed a convenient and efficient approach to (*E*)-alkylsulfonyl olefins *via* a metal/light-free three-component reaction of alkenylboronic acids, sodium metabisulfite and Katritzky salts. This alkylsulfonylation proceeds smoothly with a broad substrate scope, leading to diverse (*E*)-alkylsulfonyl olefins in moderate to good yields. During the process, excellent functional group tolerance is observed and sodium metabisulfite is used as the source of sulfur dioxide. Mechanistic studies show that alkyl radical generated *in situ* from Katritzky salt via a single electron transfer with alkenylboronic acid or DIPEA is the key step providing alkyl radical intermediate, which undergoes further alkylsulfonylation with sulfur dioxide.

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Conflicts of interest

There are no conflicts to declare.

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