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An efficient and straightforward route to terminal vinyl sulfones via palladium-catalyzed Suzuki reactions of α-bromo ethenylsulfones

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ABSTRACT

A general and simple protocol for the synthesis of α-substituted alkenylsulfones has been developed firstly via palladium-catalyzed Suzuki reactions between α-bromo ethenylsulfones and organoborons. Using a catalyst composed of $Pd(OAc)_2$ and SPhos, a variety of aryl, heteroaryl, and alkylboron reagents could efficiently couple with α-bromo ethenylsulfones under mild conditions. Moreover, it has been demonstrated for the first time that vinyl sulfones underwent smooth reduction by diimide generated from 2-nitrobenzenesulfonylhydrazide.

Vinyl sulfones are an important class of organosulfur compounds and ubiquitous in a variety of biologically active molecules and pharmaceuticals.[1] Moreover, they are valuable synthetic intermediates in organic transformations such as Michael addition,[2] desulfonylation,[3] and cycloaddition reactions.[4] Recently, vinyl sulfones have found interesting applications in visible light photoredox catalysis.[5] Owing to the importance of these scaffolds, a number of synthetic methods are well elaborated. Conventional methods[5,6] include olefination reactions, addition–elimination sequential reactions, hydrozirconation of 1-alkynyl sulfones, and the oxidation of vinyl sulfides. Recently, considerable efforts[7] have been devoted to the development of new methods with sulfonyl chloride, sulfinic acid, sodium sulfinate, or sulfonyl hydrazide as the sulfone unit in the presence of transition-metal catalyst or under metal-free conditions.

Compared to numerous procedures for the preparations of β-substituted vinyl sulfones,[7,8] protocols for the specific synthesis of α-substituted vinyl sulfones have been rarely reported.[9] Consequently, the synthetic applications of α-substituted vinyl sulfones were less explored. In this regard, Shi and co-workers have developed a general method for the synthesis of α-substituted vinyl sulfones from terminal alkynes and sulfinic acid in the presence of gold catalyst (Scheme 1).[10] However, the unusual and expensive catalyst ([BrettPhosAu(TA)]OTf) (TA = 1*H*-benzotriazole) and additive [$Ga(OTf)_3$] preclude the procedure for the practical applications. Considering the importance of the α-substituted vinyl sulfones, we had great desire to synthesize this kind of high-value added molecules based on cross-coupling reactions from easily prepared or commercially available coupling partners using a simple catalyst.[11] Motivated by our recent Letters on the synthesis of alkenylphosphonates,[12] we envisioned that an alternative pathway for the synthesis of α-substituted alkenylsulfones could be developed via Suzuki cross-coupling reactions.[13] Hereby, we are disclosing an efficient protocol for the synthesis of α-substituted vinyl sulfones via Suzuki reactions of α-bromo alkenylsulfones in the presence of $Pd(OAc)_2$/SPhos catalyst.

For the purpose of optimization of the experimental conditions, we chose a model reaction between α-bromo ethenylsulfone **1a** and 3,4-dimethoxyphenylboronic acid **2a**. A series of ancillary ligands were then evaluated for their efficacy in this C–C bond coupling reactions. As is apparent from Table 1, no product was observed in the absence of ligand (entry 1). After some experiments, we found that SPhos (entry 8) turned out to be the best ligand compared to other monophosphine ligands (PPh_3, *t*-$Bu_3P{\cdot}HBF_4$, and $Cy_3P{\cdot}HBF_4$) (entries 2–4) and Buchwald's ligands[14] (XPhos, BrettPhos, and RuPhos) (entries 5–7). The use of precatalyst $PdCl_2$dppf, a common catalyst for Suzuki reactions, afforded only trace products (entry 9). In the next step of the screening procedure, different bases were examined for their ability to promote the cross-coupling of the model substrates. The screened inorganic

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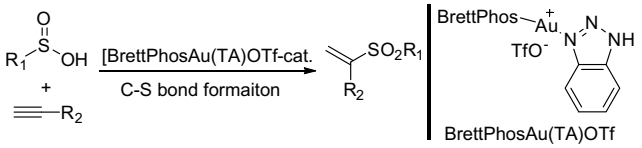
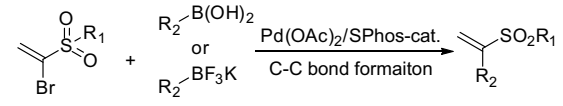
0040-4039/

(a) Shi's Method: Gold-Catalyzed C–S Bond Formation



(b) Our Strategy: Palladium-Catalyzed C–C Bond Formation



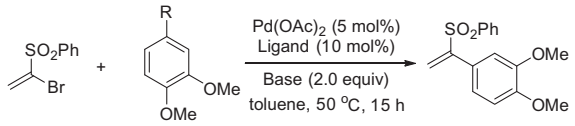
- easily available coupling partners
- broad substrate scope
- mild reaction conditions
- simple and efficient catalyst

Scheme 1. Transition-metal-catalyzed synthesis of α-substituted vinyl sulfones.

bases, such as Cs_2CO_3 (entry 8), K_2CO_3 (entry10), and K_3PO_4 (entry 11), displayed similar results, and high yields could be achieved. However, Na_2CO_3 and Et_3N were inferior (entries 12 and 13). Potassium 3,4-dimethoxyphenyltrifluoroborate **3a** also could be employed as an efficient coupling partner[15] and delivered the product **5a** in 92% yield in a 4:1 toluene and water mixture (entry 14). Additionally, 3,4-dimethoxyphenylboronic acid pinacol ester **4** was also a suitable coupling partner albeit with much lower yield (entry 15). Based on these results, the combination of 5 mol % of $Pd(OAc)_2$, 10 mol % SPhos, and 2.0 equiv of Cs_2CO_3 in toluene or 4:1 toluene and water mixture at 50 °C for 15 h emerged as the optimal conditions.

With the optimized reaction conditions in hand, we examined the scope of this transformation, and the results of this investigation are listed in Table 2. As shown, the present procedure of Pd-catalyzed synthesis of α-substituted ethenylsulfones manifests a broad substrate scope, and the reaction tolerated both electron-donating and electron-withdrawing groups on the aryl ring of arylboronic acids. α-Bromovinyl phenyl sulfone **1a**, α-bromovinyl methyl sulfone **1b**, and α-bromovinyl ethyl sulfone **1c** all could serve as the electrophilic coupling partners. *meta*- and *para*-methylphenylboronic acids reacted smoothly to afford the

Table 1
Optimization of α-bromo ethenylsulfone **1a** and 3,4-dimethoxyphenylboronic acid **2a**[a]

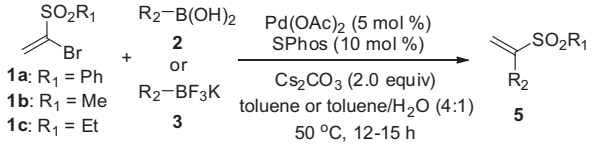


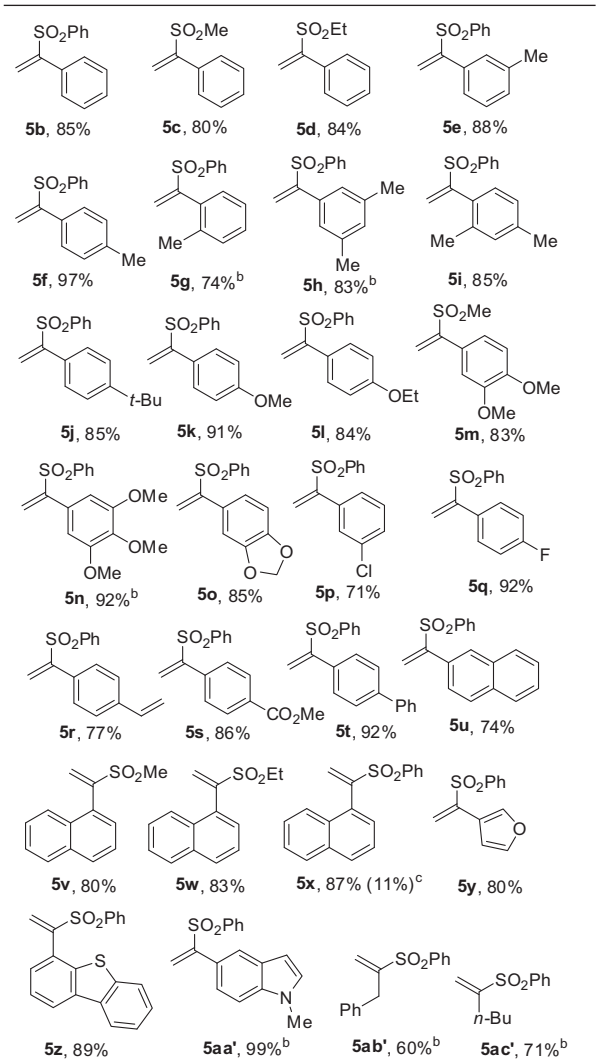
1a **2a**: R = $B(OH)_2$ **3a**: R = BF_3K **4**: R = BPin **5a**

Entry	Ligand	Base	Yield of **5a** (%)
1	—	Cs_2CO_3	0
2	PPh_3	Cs_2CO_3	10
3	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	Trace
4	t-$Bu_3P{\cdot}HBF_4$	Cs_2CO_3	77
5	XPhos	Cs_2CO_3	17
6	BrettPhos	Cs_2CO_3	29
7	RuPhos	Cs_2CO_3	67
8	SPhos	Cs_2CO_3	87
9	$PdCl_2dppf$	Cs_2CO_3	Trace
10	SPhos	K_2CO_3	84
11	SPhos	K_3PO_4	87
12	SPhos	Na_2CO_3	29
13	SPhos	Et_3N	22
14	SPhos	Cs_2CO_3	92[b,c]
15	SPhos	Cs_2CO_3	35[d]

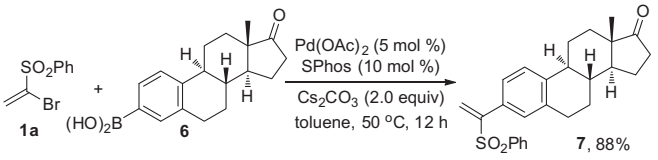
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), base (0.6 mmol), $Pd(OAc)_2$ (5 mol %), phosphine ligand (10 mol %), toluene (2 mL), 50 °C, 15 h, isolated yield.
[b] **3a** (0.45 mmol) was used in place of **2a**.
[c] Toluene/H_2O (4:1, 0.15 M) were used as the solvent.
[d] **4** (0.45 mmol) was employed as the coupling partner. XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. BrettPhos: 2-dicyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropylbiphenyl. RuPhos: 2-dicyclohexylphosphino-2′,6′-diisopropoxy biphenyl. SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Table 2
Pd-catalyzed cross-coupling of **1** with various organoboron reagents[a]



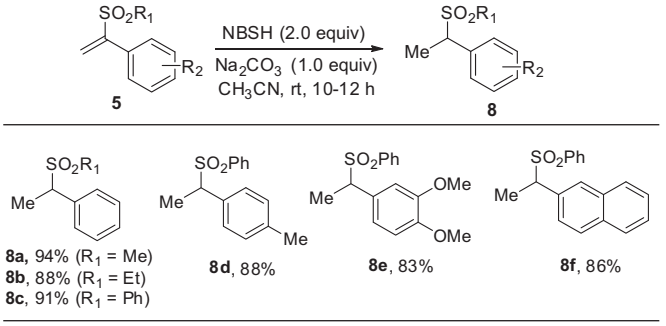


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), base (0.6 mmol), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), toluene (2.0 mL), 50 °C, 12–15 h, isolated yield.
[b] **3** (0.45 mmol) was used in place of **2** with toluene/H_2O (4:1, 0.15 M) as the solvent.
[c] Number in bracket is the yield of side product (*E*)-1-[2-(phenylsulfonyl) vinyl]naphthalene.



Scheme 2. Suzuki reaction between **1a** with estrone derived arylboronic acid **6**.

Table 3
Diimide reduction of vinyl sulfones



corresponding α-tolylvinyl sulfones **5e–f** in 88% and 97% yields, respectively. However, potassium 2-methylphenyltrifluoroborate is recommended for the preparation of **5g**. Gratifyingly, arylboronic acids and potassium trifluoroarylborates having electron-donating groups on the phenyl ring (Me, *t*-Bu, OMe, and OEt) participated well in the reaction to deliver products **5h–o** in good to high yields. Moreover, halogen groups (**5p–q**), which enable further derivatizations via transition-metal-catalyzed cross-coupling reactions, are also compatible. This procedure also tolerates the presence of an alkene (**5r**) and ester (**5s**) on the phenyl ring at the nucleophilic coupling partners. As far as the size of aryl group is concerned, 4-biphenylboronic acid and naphthaleneboronic acids could be coupled with α-bromo ethenylsulfones **1a–c** efficiently to afford the desired products **5t–w**. Due to the steric effect arising from the phenyl and α-naphthyl groups, the coupling reaction of **1a** and α-naphthaleneboronic acid yielded a mixture comprising the expected product **5x** (87%) and (*E*)-1-[2-(phenylsulfonyl)vinyl]-naphthalene isomer (11%).[16] To challenge the applicability of our method further, we examined the cross-coupling of **1a** with some heteroarylboronic acids including furan, indole, and thiophene. Fortunately, the above heteroaromatic boronic acids were also successfully coupled to afford the expected products **5y–aa′** in high yields. Interestingly, the present C–C cross-coupling is not restricted to aryl and heteroarylboronic acids. Further investigation showed that alkyltrifluoroborates were also suitable coupling partners to yield the products **5ab′–ac′** in good yields.

To gauge the prospect for application to the complex synthesis, estronylboronic acid **6** was selected as a representative coupling partner. Under the standard reaction conditions, the estrone derivative **7** was successfully prepared in 88% yield (Scheme 2), which highlights the good functional group tolerance and potential application of this method.

The sulfone is an important organic structural motif in organic synthesis and biologically active compounds.[17] However, general and robust methods for the preparation of α-aryl ethylsulfones are still limited.[18] We envisioned that hydrogenation of α-substituted alkenylsulfones could provide an attractive and straightforward approach for the synthesis of α-aryl ethylsulfones. Fortunately, with 1.0 equiv of Na_2CO_3 as the additive, mixing 2.0 equiv of NBSH (2-nitrobenzenesulfonylhydrazide)[19] and **5** in acetonitrile at room temperature led to the desired products **8** in high yields after 10–12 h (Table 3). The present reduction protocol features broad substrates compatibility, operational simplicity, and metal-free conditions. To the best of our knowledge, this is the first example of metal-free diimide reduction of vinyl sulfones.[20]

In conclusion, we have developed an efficient and straightforward method for the preparation of α-substituted alkenylsulfones via Suzuki reactions of α-bromo ethenylsulfones with organoboron reagents. Investigation of the substrate scope showed that aryl, heteroaryl, and alkylboron reagents are suitable nucleophilic coupling partners. The present new protocol features the easy availability of coupling partners, mild reaction conditions, and great functional group tolerance. Moreover, we also have demonstrated that the first metal-free diimide reduction of α-substituted alkenylsulfones was feasible for the preparation of sulfones. The further elaboration of α-substituted vinyl sulfones is currently under investigation in our research group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.065.

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