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Pd-Catalyzed Annulation of β–Iodovinyl Sulfones with 2-Halophenols: A General Route for the Synthesis of 3-Sulfonyl Benzofuran Derivatives

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Abstract. The palladium-catalyzed annulation between β-iodovinyl sulfones and 2-halophenols or 1-bromo-2-naphthol or 2-bromo-3-pyridinol is presented. The annulation process involving oxa-Michael addition-elimination and intramolecular Heck reaction leading to form 2,3-disubstituted benzofurans (aryl benzofuryl sulfones) in good to high yields. The regioselective tandem construction of C-O and C-C bonds has been achieved with a variety of substitution patterns. Moreover, the tandem process is reliable at gram-scale reactions and a plausible mechanism is also proposed.

Keywords: Benzofurans; Heck Reaction; β-Iodovinyl sulfones; Naphthofurans; oxa-Michael addition

Among the various natural and synthetic benzofuran derivatives,[1] the 2,3-disubstituted benzofurans are widely distributed in numerous natural products[2] and pharmaceutical chemistry.[3] To mention a few representative examples, benzbromarone (uricosuric agent),[4] amiodarone (antiarrhythmic agent),[5] obovaten (antitumor activity),[6] saprisartan (treatment of hypertension)[7] and anigopreissin A (antimicrobial activity)[8] as presented in Figure 1. Due to the aforementioned biological significance, several effective strategies have been devoted for assembly of 2,3-disubstituted benzofurans in recent years.[9-12] In this context, the most promising strategy involving base-mediated nucleophilic conjugate addition followed by Heck-type cyclization of 2-halophenols with activated alkynes.[12] However, these approaches are suffering from poor regioselectivity, require to use strong oxidants, expensive ligands and limitation of a variety substitutions. Therefore, the development of a rapid and convergent method that allows for diverse functional groups on benzofuran scaffold is highly desirable.

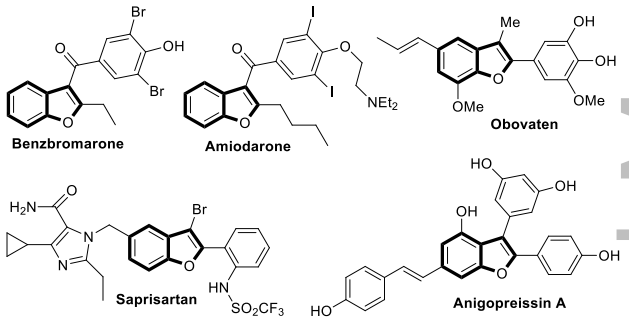

Figure 1. Biologically important 2,3-disubstituted benzofuran derivatives.

The sulfones are yet another class of prevalent scaffolds, which are extremely useful in organic synthesis as well as in medicinal chemistry.[13] Therefore, incorporation of the sulfone functionality into benzofuran frameworks may nurture their biological properties extensively. Indeed, our attention drawn to design a new synthetic route toward sulfonyl derived benzofuran variants. During our work being in progress, Banwell *et al*. reported the tandem construction of benzofuran derivatives *via* Pd/Cu-catalyzed Ullmann-Goldberg coupling and cyclopalladation of 3-haloenones with 2-halophenols (Scheme 1a).[14] To the best of our knowledge, there is no general method for the synthesis of aryl benzofuryl sulfones.[15] Nevertheless, a general and straight-forward method for the preparation of 3-sulfonyl benzofuran derivatives is high demand. Thus, we envisioned that the multifunctional β-iodovinyl sulfones could be the right starting material

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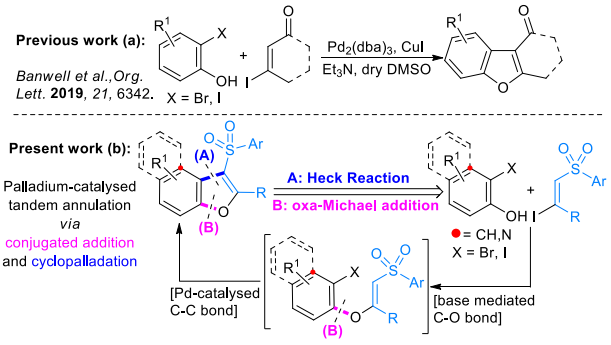
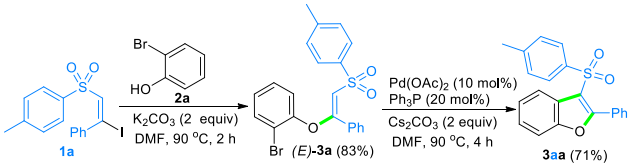
for the synthesis of benzofuran derivatives. Accordingly, we sought to investigate the possibility of annulation between β-iodovinyl sulfones and 2-halophenols to form 2,3-disubstituted benzofurans (Scheme 1b). As we assumed the reactions may proceed through the tandem process involving oxa-Michael addition and intramolecular Heck coupling, which is an interesting and challenging endeavour in organic synthesis. As part of our ongoing research programme on organosulfur chemistry,[16] we, herein, report an efficient and unique palladium-catalysed annulation of β-iodovinyl sulfones with 2-halophenols to produce 3-sulfonyl benzofuran derivatives through the tandem construction of C-O and C-C bonds in a single synthetic operation. Thus, the required β-iodovinyl sulfones are easily accessible from broadly available alkynes,[17] but their synthetic utility has not been much explored.[16b,17f,g]



Scheme 1. Strategy for tandem construction of benzofuran derivatives.

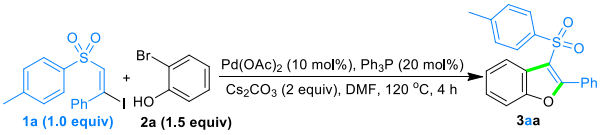
To test our hypothesis depicted in Scheme 1, our investigations commenced with (*E*)-1-[(2-iodo-2-phenylvinyl)sulfonyl]-4-methylbenzene **1a** and 2-bromophenol **2a** as model substrates (Scheme 2). Initial experiments were conducted in a step-wise manner. The oxa-Michael addition of **1a** with **2a** in the presence of K_2CO_3 gave the anticipated aryloxy vinylsulfone ether (**3a**) in 83% yield with *E*-major isomer (see the Supporting Information).[18] Subsequently, the cyclopalladation of **3a** to furnish the desired 2-phenyl-3-sulfonyl-benzofuran **3aa** in 71% yield under unoptimized conditions.



Scheme 2. Step-wise synthesis of 2-phenyl-3-tosyl-benzofuran (**3aa**).

Encouraged by this result, we questioned whether it could be possible to conduct the two steps in a one-pot operation. Accordingly, several experiments were performed to identify the best reaction conditions and the results were summarised in Table 1 (also see Table S1 in the Supporting Information for an extensive survey of reaction conditions). We were pleased to found that the best reaction conditions: **1a** (1.0 equiv) with **2a** (1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%) and Cs_2CO_3 (2 equiv) in DMF at 120 °C for 4 h, affording the desired 2-phenyl-3-tosylbenzofuran (**3aa**) in 89% yield (entry 1). The use of K_2CO_3 instead of Cs_2CO_3, the product yield slightly decreased (entry 2). Reducing the catalyst loading, lowering the Cs_2CO_3 (1.5 equiv) and **2a** (1.2 equiv) affected the outcome (entries 3-5). Further screening of solvents (DMA, chlorobenzene and toluene) offered the product **3aa** in diminished yields (entries 6-8). Likewise, changing the catalysts, $PdCl_2(Ph_3P)_2$ and $Pd(Ph_3P)_4$ delivered **3aa** in 64% and 76% yields, respectively (entries 9 and 10). The use of CuI (10 mol%); absence of triphenylphosphine and role of concentration were unsuccessful in improving the product yield (entries 11-13). The reaction at 90 °C and the reverse equimolar quantities of **1a** (1.5 equiv) and **2a** (1.0 equiv) led to lower yields (entries 14 and 15).

Table 1. Optimization for the synthesis of 2-phenyl-3-tosyl-benzofuran (**3aa**).[a]



Entry	Deviation from the standard conditions	Yield **3aa**[b]
1	***standard conditions***	***89%***
2	K_2CO_3 instead of Cs_2CO_3	81%
3	5 mol% $Pd(OAc)_2$; 10 mol% Ph_3P	78%
4	with 1.5 equiv of Cs_2CO_3	76%
5	with 1.2 equiv of **2a**	59%
6	DMA instead of DMF	66%
7	Chlorobenzene instead of DMF	47%
8	Toluene instead of DMF	53%
9[c]	$PdCl_2(Ph_3P)_2$ instead of $Pd(OAc)_2$	64%
10[c]	$Pd(Ph_3P)_4$ instead of $Pd(OAc)_2$	76%
11	CuI (10 mol%) instead of Ph_3P	74%
12	without Ph_3P	77%
13	2 mL of DMF used instead of 1 mL	83%
14	at 90 °C for 6 h	59%
15	use of **1a** (1.5 equiv) and **2a** (1.0 equiv)	61%

[a] Unless otherwise specified, all reactions were performed on a 0.2 mmol scale **1a** (1.0 equiv), **2a** (1.5 equiv) in solvent (1.0 mL) under N_2 at 120 °C for 4 h.
[b] Isolated yield. DMA = *N*,*N*-Dimethylacetamide.
[c] Without Ph_3P.

With the optimized reaction conditions in hand, we next proceeded to explore the generality of the tandem process (Scheme 3). The reaction works well for an array of β-iodovinyl sulfones with 2-bromophenol (**2a**) and accessed the corresponding benzofuran derivatives in 45-87% yields. A variety of substitutions on aromatic sulfonyl derived

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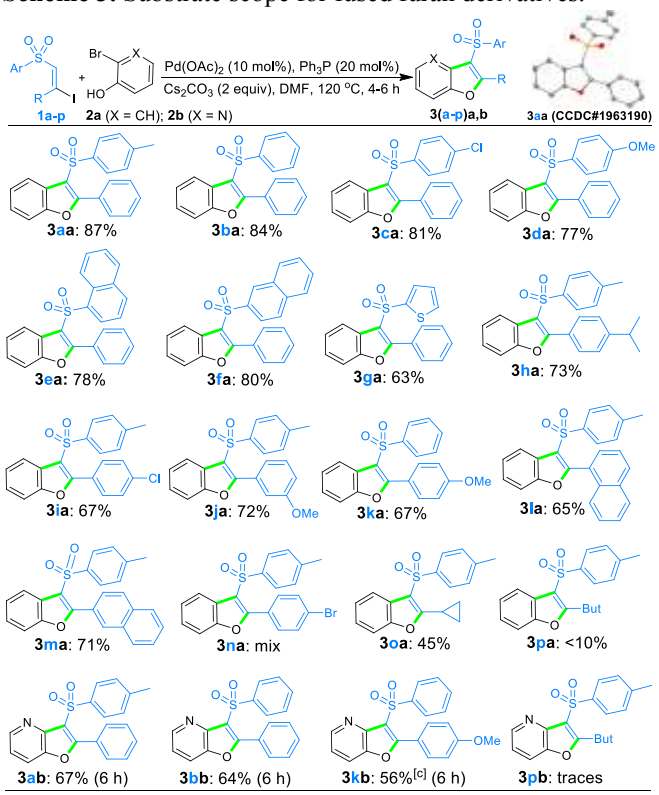
benzofurans **3(a-d)a** were obtained in high yields. The structure of **3aa** was unambiguously confirmed by single-crystal X-ray data analysis (see the Supporting Information).[19] The naphthalene-sulfonyl derived benzofurans **3ea** and **3fa** were produced in 78% and 80% yields, respectively. The 2-thiophenyl substituted vinylsulfone **1g** was also compatible substrate, gave the desired product **3ga** in 63% yield. Additionally, different aromatic substitutions (4-^{i}Pr, 4-Cl, 3- and 4-OMe) at C2-position of benzofuran derivatives **3(h-k)a** were obtained in relatively low yields. The C2-naphthyl benzofuran products **3la** and **3ma** were obtained with a little effect on the outcome. The 4-bromoaryl vinylsulfone **1n** led to form mixture under the same reaction conditions. The cyclopropyl derived vinylsulfone **1o** gave the expected product **3oa** in 45% yield. Further, we established additional versatility by using 2-bromo-3-pyridinol **2b** under the same reaction conditions. The anticipated pyridine fused furan derivatives (**3a,b,k**)**b** were accessed smoothly in 56-67% yields. In contrast, the butyl substituted vinylsulfone (**1p**) was not a suitable substrate for this tandem transformation.

Scheme 3. Substrate scope for fused furan derivatives.[a,b]



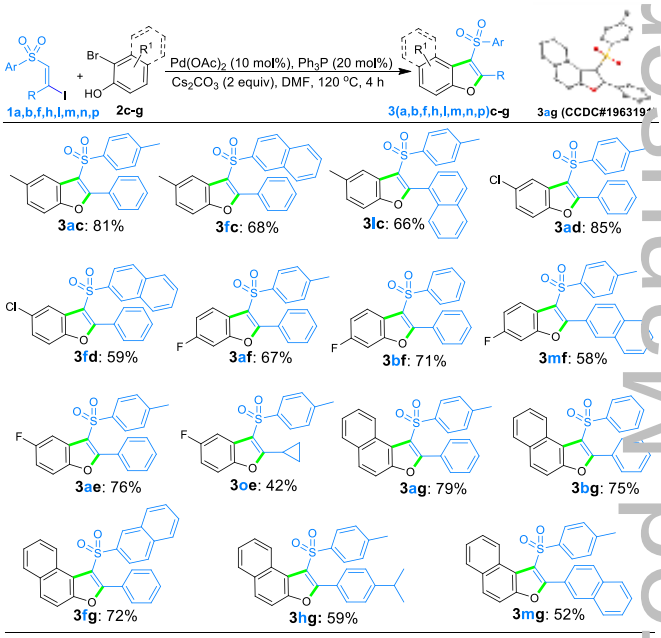
[a] Reactions were performed on a 0.5 mmol scale of **1a-p** (1.0 equiv), **2a/b** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), Cs_2CO_3 (2.0 equiv) in DMF (2.5 mL) under N_2 at 120 °C for 4-6 h.

[b] Isolated yield.

[c] **3kb** contaminated with corresponding β-keto sulfone[16b] (see the Supporting Information).

Next, we sought to evaluate the scope of various substituted 2-bromophenols (**2c-f**) and 1-bromo-2-naphthol (**2g**) under the standard reaction conditions (Scheme 4). The palladium-catalyzed annulation of 2-bromophenols with representative β-iodovinyl sulfones proceeded smoothly under the same reaction conditions. The 5-methyl and 5-chloro derived benzofuran motifs (**3ac**, **3fc**, **3lc, 3ad** and **3fd**) were obtained in good to high yields. In light of the biological significance of organofluoro compounds, we then proceeded successfully to afford the 5-flouro- and 6-flouro benzofuran derivatives (**3ae**, **3oe, 3af**, **3bf** and **3mf**) in 42-76% yields. Further, tandem process progressed with **2g** for the synthesis of naphthofuran analogues (**3ag**, **3bg**, **3fg, 3hg** and **3mg**), pleasingly the desired products were obtained in satisfactory yields. Unambiguously, the structure of **3ag** was confirmed by single-crystal X-ray data analysis (see the Supporting Information).[19]

Scheme 4. Substrate Scope for benzo- and naphtha-furan derivatives.[a,b]

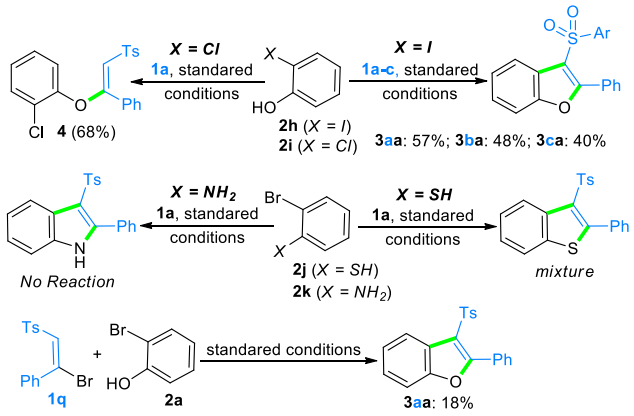


[a] Reactions were performed on a 0.5 mmol scale of **1** (1.0 equiv), **2c-g** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), Cs_2CO_3 (2.0 equiv) in DMF (2.5 mL) under N_2 at 120 °C for 4 h.

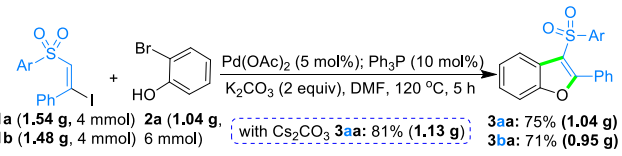
[b] Isolated yield.

As proof of the versatility and applicability of the present methodology, other suitable substrates also examined (Scheme 5). Accordingly, the reactions were carried out between β-iodovinyl sulfones (**1a-c**) and 2-iodophenol (**2h**), surprisingly, the desired products **3(a-c)a** afforded only in modest (40-57%) yields as compared. As expected, the use of 2-chlorophenol (**2i**) resulted in only corresponding enol ether (**4**) in 68% yield. We also verified 2-bromothiophenol (**2j**) and 2-bromoaniline (**2k**), disappointingly the corresponding heterocycles were not formed under the optimal reaction conditions. Additionally, the β-bromovinyl sulfone (**1q**) afforded **3aa** only in 18% yield under standard reaction conditions.

To highlight the viability of the annulation process, the reactions performed in a gram-scale under the similar conditions. As illustrated in Scheme 6, a four mmol reaction scale of β-iodovinyl sulfone **1a** with 2-bromophenol **2a** in the presence 5 mol% of $Pd(OAc)_2$, 10 mol% Ph_3P and Cs_2CO_3 (2 equiv) to produce **3aa** in 81% (1.13 g) yield. An economical point of view, K_2CO_3 is used instead of Cs_2CO_3 yielded **3aa** in 75% (1.04 g) and **3ba** in 71% (0.95 g), respectively with a slight deviation on efficiency.

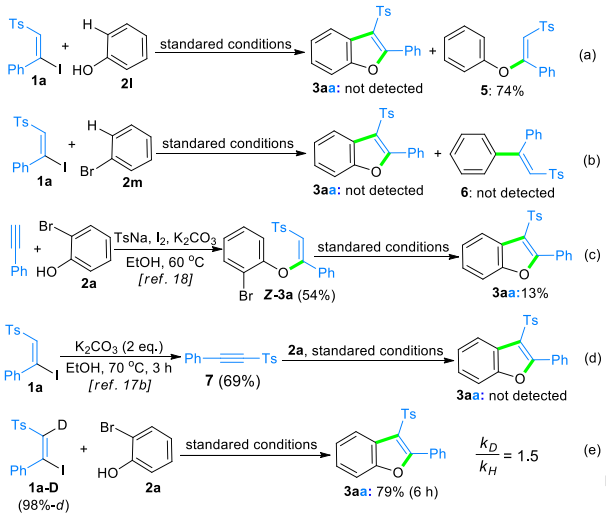


Scheme 5. Study of diverse substrate scope.



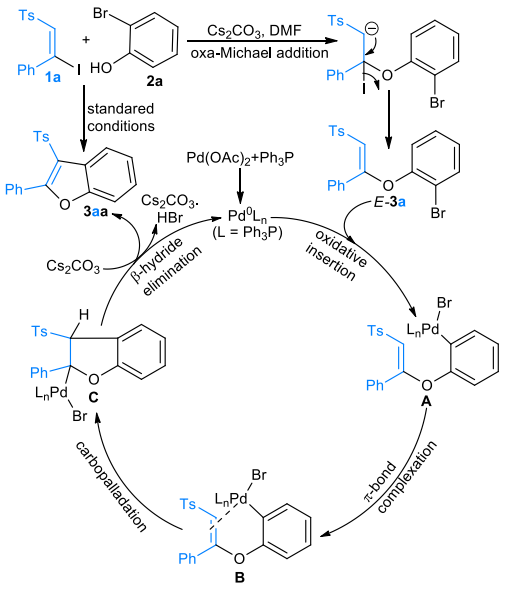
Scheme 6. Gram-scale reactions for the synthesis of 3-sulfonyl benzofurans.

To gain valuable insight into understanding the reaction mechanism, we performed a few control experiments (Scheme 7). Initially, the reaction employed with phenol **2l** under the standard reaction conditions provided phenoxy vinylsulfone **5** in 74% yield; however, the desired product **3aa** was not detected (Scheme 7a). The reaction of **1a** with aryl bromide **2m** was not afford either **3aa** or cross-coupling product **6** (Scheme 7b). According to known procedure, the *Z*-enol ether (**3a**)[18] was prepared and subjected to cyclopalladation process (Scheme 7c). To our surprise, the desired benzofuran **3aa** was formed in 13% yield. Thus, it was assumed the coordination of palladium to alkene moiety through π-system complexation may allow to partial isomerization (*Z* to *E*) (see the Supporting Information).[20] Moreover, the reaction between alkynyl sulfone (**7**)[17b] and 2-bromophenol **2a** under the same conditions, unsuccessful to provide **3a** or **3aa** (Scheme 7d). Further, we have successfully prepared the desired deuterated starting material **1a-D** (98%-*d*) to perform isotopic experiments (see the Supporting Information). The rate of the reaction slow as compared and the reaction completed in 6 h under standard conditions (Scheme 1 e). Overall, these control experiments evidenced that the 2-bromo functionality and the geometry of **3a** would be indispensable for cyclopalladation process.



Scheme 7. Control experiments.

Based on the above experimental results and the literature precedent,[14,20,21] a plausible mechanism for this tandem process is proposed (Scheme 8). Firstly, base-promoted oxa-Michael addition of β-iodovinyl sulfone (**1a**)[16b,17f] with 2-bromophenol **2a** could form enol ether (***E*-3a**). Secondly, the mechanism starts with the consist of oxidative insertion of ***E*-3a** to the *in situ* generated zerovalent palladium (PdL_n) species to form the arylpalladium complex (**A**).[14,21] The intra-molecular coordination with olefin moiety *via* π–bond complexation to form the intermediary (**B**).[21a] Subsequent carbopalladation generates the organo-palladium species (**C**)[20,21] followed by β-hydride elimination lead to desired product **3aa** and active palladium(0)catalyst would be regenerated in the presence of base for the further catalytic process.



Scheme 8. Plausible mechanism for tandem process.

In summary, we have successfully developed a general and efficient method for the construction 3-sulfonyl benzofuran derivatives from readily available starting materials. For the first time, the new tandem conjugate addition and cyclopalladation resulted in accessing three types of fused furan analogues: benzofurans, naphtho[2,1-*b*]furans and furo[3,2-*b*]pyridines in moderate to high yields, which were difficult prepare by other methods. Notably, the efficacy of the process proved at gram-scale reactions. The synthetic exploration of β-iodovinyl sulfones and 3-sulfonyl benzofurans[22] being in progress in our laboratory.

Experimental Section

General procedure for synthesis of 3-sulfonyl benzofurans: A heat gun-dried Schlenk tube was charged β-iodovinyl sulfones **1a-q** (0.5 mmol, 1.0 equiv), 2-halophenols **2a-h** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), Ph_3P (0.1 mmol, 20 mol%) and Cs_2CO_3 (1.0 mmol, 2 equiv) in DMF (2.5 mL) under nitrogen atmosphere. The mixture was stirred at 120 ºC for 4 h and monitored by TLC either complete or appeared to be proceeding no further progress. The mixture was quenched by addition of water (20 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were washed with brine (2x30 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel 100-200 mesh, eluted with 15% to 20% ethyl acetate/petether) to afford desired 3-sulfonyl benzofuran derivatives.

Acknowledgements

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