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Palladium-catalyzed tandem reaction of 2-hydroxyarylacetonitriles with sodium sulfinates: one-pot synthesis of 2-arylbenzofurans†

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The first example of the palladium-catalyzed one-pot synthesis of 2-arylbenzofurans in moderate to excellent yields *via* a tandem reaction of 2-hydroxyarylacetonitriles with sodium sulfinates is reported. A plausible mechanism for the formation of 2-arylbenzofurans involving desulfinative addition and intramolecular annulation reactions is proposed. Moreover, the present synthetic route to benzofurans could be readily scaled up to the gram quantity without any difficulty. Thus, the method represents a convenient and practical strategy for synthesis of benzofuran derivatives.

The benzofuran ring is among the most prevalent heterocyclic structural motifs that occur in a wide variety of isolated natural products[1] and is extremely important in medicinal chemistry[2] and functional materials.[3] Among the numerous benzofuran derivatives known, 2-arylbenzofurans have recently attracted considerable attention due to their versatile pharmaceutical activities, such as $S1P_1$ receptor agonists,[4] and their antitumor,[5] antiviral,[6] antioxidative,[7] and antifungal properties.[8] Recently, Ono and Saji reported that ^{18}F or ^{99m}Tc-labeled benzofuran derivatives were investigated by positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging for β-amyloid plaques in Alzheimer's brains.[9] The importance of 2-arylbenzofurans has resulted in the development of two types of synthetic methods. One type involves the introduction of substituents by direct arylation of a preexisting benzofuran ring *via* the palladium-catalyzed cross-couplings of 2-halobenzofurans with arylmetallic reagents,[10] or 2-benzofuryl organometallics with aryl halides.[11] Recently, Wang[12] and Rao[13] independently reported palladium-catalyzed direct tandem reaction of 2-(*gem*-dibromovinyl)phenols with arylation reagents such as phenyl(trialkoxy)silanes,[12a] sodium arylsulfinates,[12b] and triarylbismuth.[13] Whereas the other predominant type involves the assembly of the functionalized furan nucleus on a benzenoid scaffold, which mainly includes annulation of *o*-alkynylphenols,[14] cyclization of *o*-halobenzyl ketones,[15] cyclodehydration of *o*-hydroxybenzyl ketones,[16] Suzuki coupling/arylation,[17] decarboxylative/coupling of 3-arylcoumarins,[18] C–H activation/oxidative cyclization of 2-(1-arylvinyl)phenols with iodobenzenes,[19] oxidative cyclization of *o*-vinylphenols,[20] Wittig reaction,[21] and [3,3]-sigmatropic rearrangement of oxime ethers.[22] Recently, transition-metal-catalyzed direct tandem reactions using phenols as starting materials have been reported.[23]

Transformations of nitriles play an important role in both the laboratory and industry due to their well-recognized chemical versatility.[24] However, the nitrile group is generally inert in organometallic reactions, and thus acetonitriles or benzonitriles usually participate as solvents or ligands[25] in metal-catalyzed reactions. The addition of arylpalladium species to the cyano group, pioneered by the Larock group[26] and elegantly employed in recent years,[27] provided a conceptual basis for our approach. Lu's group[28] and our group[29] have also developed the palladium-catalyzed one-pot synthesis of benzofurans by addition of organoboron reagents to functionalized nitriles.

To the best of our knowledge, synthesis of benzofurans with the use of sodium sulfinates as coupling partners has rarely been reported,[12b,30] even though sodium sulfinates are generally used as the aryl source in transition-metal-catalyzed desulfinative reactions.[31] As part of the continuing efforts in our laboratory toward the development of novel transition metal-catalyzed coupling reactions with arylation reagents,[32] herein we report a simple and efficient protocol for the synthesis of 2-arylbenzofurans by palladium-catalyzed tandem reaction of 2-hydroxyarylacetonitriles with sodium sulfinates (Scheme 1).

Our preliminary studies focused on the reaction between 2-hydroxyphenylacetonitrile (**1a**) and sodium benzenesulfinate (**2a**) to obtain the optimal reaction conditions (Table 1). On the basis of the previous addition protocol of organoborons to nitriles,[29a] a test reaction with $Pd(O_2CCF_3)_2$ and 2,2′-bipyridine (**L1**) as the catalytic system was performed under an air

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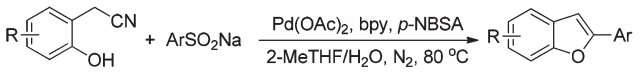
† Electronic supplementary information (ESI) available: Analytical data and spectra (^1H, ^{13}C NMR) for all products. See DOI: 10.1039/c4ob00575a



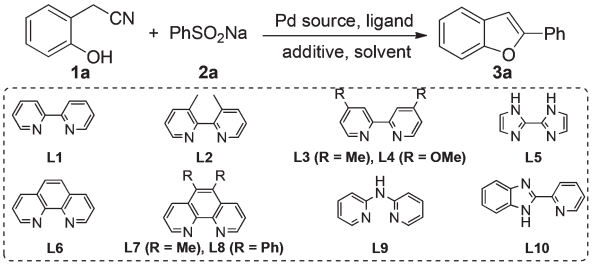
1a: R = H **2a**: Ar = Ph
1b: R = 4-OMe **2b**: Ar = *p*-MeC_6H_4
1c: R = 3-OMe **2c**: Ar = *o*-MeC_6H_4
1d: R = 5-Me **2d**: Ar = *p*-$OMeC_6H_4$
1e: R = 5-Cl **2e**: Ar = *p*-$^tBuC_6H_4$
1f: R = 5-Br **2f**: Ar = *p*-FC_6H_4
2g: Ar = *p*-ClC_6H_4
2h: Ar = *o*-ClC_6H_4
2i: Ar = *p*-$CF_3C_6H_4$
2j: Ar = 2-naphthyl

Scheme 1 Palladium-catalyzed one-pot synthesis of 2-arylbenzofurans.

atmosphere. To our delight, the desired product 2-phenylbenzofuran (**3a**) was isolated in 22% yield (entry 1). Encouraged by this promising result, reaction parameters including palladium sources, ligands, additives, and solvents were adjusted. Among the palladium sources used, $Pd(OAc)_2$ exhibited the highest catalytic reactivity in 31% yield (entries 1–12). Considering that additives always played important roles in organic reactions, subsequently various additives were examined for this transformation (entries 3, 13–21). The reaction yield improved to 74% when *p*-toluenesulfonic acid (*p*-TSA) was used (entry 15). However, the best yield was obtained with *p*-nitrobenzenesulfonic acid (*p*-NBSA) as the additive (79%, entry 16). While $MeSO_3H$, CF_3SO_3H, and H_2SO_4 were less efficient, CH_3CO_2H, $PhCO_2H$, HCl and HNO_3 were unsuitable additives and prohibited the reaction. Replacement of 2,2′-bipyridine (**L1**) with other ligands, such as **L2–L10**, resulted in slightly lower yields (entries 16 and 22–30). The influence of the solvent on the reaction was also noteworthy. Screening revealed that the use of THF or 2-MeTHF greatly increased the yield of **3a** (entries 16 and 31–37). 2-MeTHF[33] offers both economical and environmentally friendly advantages over THF. The yield of **3a** improved to 92% when the model reaction was performed under a N_2 atmosphere (entry 38).

With the optimized reaction conditions in hand, the tandem reactions between 2-hydroxyphenylacetonitrile (**1a**) and various sodium arylsulfinates (**2a–2j**) were investigated (Table 2). The steric effects of substituents had an obvious impact on the yield of the reaction. For example, reaction of **1a** with *para*- and *ortho*-tolylsulfinate (**2b–2c**) provided 89% of **3b**, while the yield of **3c** was decreased to 62% (entries 2 and 3). The same phenomenon was observed in the reaction of **1a** with *para*- and *ortho*-chlorobenzenesulfinates (**2g–2h**) (entries 7 and 8). The electronic properties of the substituents on the phenyl ring of the sodium arylsulfinates affected the yields of the reaction to some extent. In general, the sodium arylsulfinates bearing an electron-donating substituent (*e.g.*, –OMe and –^{t}Bu) produced slightly higher yields than those analogues bearing an electron-withdrawing substituent (*e.g.*, –F and –Cl) (entries 4–7). However, sodium arylsulfinates bearing a strong electron-withdrawing substituent (*e.g.*, –CF_3) at the *para* position, such as sodium 4-(trifluoromethyl)benzenesulfinate (**2i**), led to the corresponding 2-(4-(trifluoromethyl)phenyl)benzofuran (**3i**) in slightly lower yield (entry 9). To specially mention, only trace amounts of **3i** were observed by GC/MS analysis when arylboronic reagents, such as (4-(trifluoromethyl)phenyl)-boronic acid, were used as the substrates under the same reaction conditions (see Scheme S1 in ESI†). It is noteworthy that an excellent yield of 2-(naphthalen-2-yl)benzofuran (**3j**) was obtained when sodium naphthalene-2-sulfinate (**2j**) was used as the substrate (entry 10).

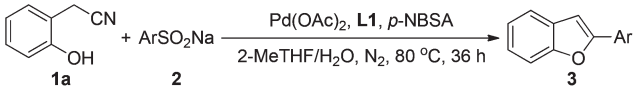
Table 1 Optimization of the reaction conditions[a]



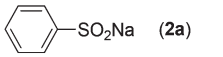
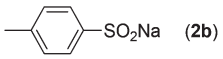
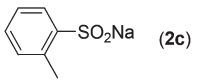
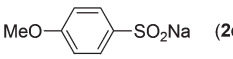
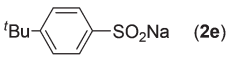
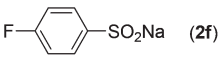
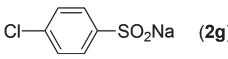
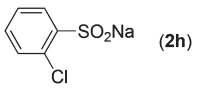
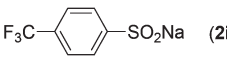
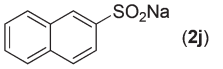
Entry	Pd source	Ligand	Additive	Solvent	Yield[b] (%)
1	$Pd(CF_3CO_2)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	22
2	$PdCl_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	19
3	$Pd(OAc)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	31
4	$Pd(OH)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	29
5	$PdCl_2(PPh_3)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	12
6	$PdCl_2(Py)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	17
7	$PdCl_2(NH_3)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	Trace
8	$Pd(acac)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	26
9	$Pd(PPh_3)_4$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	Trace
10	$PdCl_2$(dppe)	**L1**	CF_3CO_2H	2-MeTHF–H_2O	0
11	$PdCl_2$(cod)	**L1**	CF_3CO_2H	2-MeTHF–H_2O	0
12	$Pd(dba)_3$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	18
13	$Pd(OAc)_2$	**L1**	CF_3CO_2H	2-MeTHF–H_2O	Trace
14	$Pd(OAc)_2$	**L1**	$PhCO_2H$	2-MeTHF–H_2O	Trace
15	$Pd(OAc)_2$	**L1**	*p*-TSA[c]	2-MeTHF–H_2O	74
16	$Pd(OAc)_2$	**L1**	*p*-NBSA[d]	2-MeTHF–H_2O	79
17	$Pd(OAc)_2$	**L1**	$MeSO_3H$	2-MeTHF–H_2O	63
18	$Pd(OAc)_2$	**L1**	CF_3SO_3H	2-MeTHF–H_2O	52
19	$Pd(OAc)_2$	**L1**	H_2SO_4	2-MeTHF–H_2O	22
20	$Pd(OAc)_2$	**L1**	HCl	2-MeTHF–H_2O	Trace
21	$Pd(OAc)_2$	**L1**	HNO_3	2-MeTHF–H_2O	Trace
22	$Pd(OAc)_2$	**L2**	*p*-NBSA	2-MeTHF–H_2O	62
23	$Pd(OAc)_2$	**L3**	*p*-NBSA	2-MeTHF–H_2O	61
24	$Pd(OAc)_2$	**L4**	*p*-NBSA	2-MeTHF–H_2O	31
25	$Pd(OAc)_2$	**L5**	*p*-NBSA	2-MeTHF–H_2O	Trace
26	$Pd(OAc)_2$	**L6**	*p*-NBSA	2-MeTHF–H_2O	68
27	$Pd(OAc)_2$	**L7**	*p*-NBSA	2-MeTHF–H_2O	51
28	$Pd(OAc)_2$	**L8**	*p*-NBSA	2-MeTHF–H_2O	17
29	$Pd(OAc)_2$	**L9**	*p*-NBSA	2-MeTHF–H_2O	71
30	$Pd(OAc)_2$	**L10**	*p*-NBSA	2-MeTHF–H_2O	14
31	$Pd(OAc)_2$	**L1**	*p*-NBSA	Toluene–H_2O	37
32	$Pd(OAc)_2$	**L1**	*p*-NBSA	Xylene–H_2O	34
33	$Pd(OAc)_2$	**L1**	*p*-NBSA	Dioxane–H_2O	51
34	$Pd(OAc)_2$	**L1**	*p*-NBSA	DMF–H_2O	Trace
35	$Pd(OAc)_2$	**L1**	*p*-NBSA	THF–H_2O	73
36	$Pd(OAc)_2$	**L1**	*p*-NBSA	^{i}PrOH–H_2O	34
37	$Pd(OAc)_2$	**L1**	*p*-NBSA	H_2O	25
38	$Pd(OAc)_2$	**L1**	*p*-NBSA	2-MeTHF–H_2O	92[e]

[a] *Reaction conditions*: **1a** (0.3 mmol), **2a** (0.6 mmol), indicated Pd source (10 mol%), ligand (20 mol%), additive (10 equiv.), solvent (2 mL), H_2O (1 mL), 80 °C, 36 h, air. [b] Isolated yield. [c] *p*-TSA = *p*-toluenesulfonic acid. [d] *p*-NBSA = *p*-nitrobenzenesulfonic acid. [e] Under a N_2 atmosphere.

Table 2 Reaction of **1a** with various sodium sulfinates[a]



1a 2 3

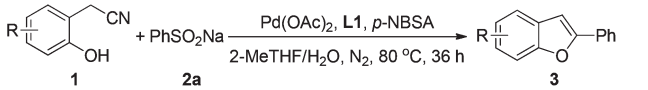
Entry	$ArSO_2Na$ (2)	Product (3)	Yield[b] (%)
1	 (**2a**)	**3a**	92
2	 (**2b**)	**3b**	89
3	 (**2c**)	**3c**	62
4	 (**2d**)	**3d**	85
5	 (**2e**)	**3e**	84
6	 (**2f**)	**3f**	76
7	 (**2g**)	**3g**	81
8	 (**2h**)	**3h**	41
9	 (**2i**)	**3i**	56
10	 (**2j**)	**3j**	94

[a] *Reaction conditions*: **1a** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), **L1** (20 mol%), *p*-NBSA (10 equiv.), 2-MeTHF (2 mL), H_2O (1 mL), 80 °C, 36 h, N_2. [b] Isolated yield.

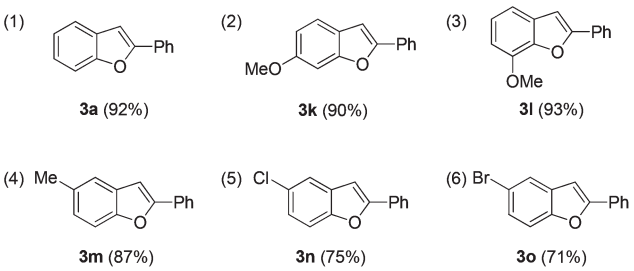
We next turned our attention to the effect of the reactions of sodium benzenesulfinate (**2a**) with various 2-hydroxyarylacetonitriles (**1a–1f**) under the optimized conditions (Table 3). As expected, the groups on the phenyl ring of 2-hydroxyarylacetonitriles, such as methyl, methoxy, chloro, and bromo, were quite compatible. The electronic properties of the groups on the phenyl ring moiety of 2-hydroxyarylacetonitriles had some effects on the reaction. Generally, 2-hydroxyarylacetonitriles with an electron-donating substituent on the phenyl group gave slightly higher yields. Substrates **1b** and **1c** bearing a methoxy group, for example, were treated with **2a** to afford 90% and 93% yields of **3k** and **3l**, respectively (runs 2 and 3). While the yields of **3n** and **3o** were decreased to 75% and 71% from substrates **1e** and **1f** possessing a halogen group, respectively (runs 5 and 6).

It is noteworthy that the chloro, fluoro, and bromo moieties (commonly used for cross-coupling reactions) in substrates were all tolerated and afforded several halogen-containing

Table 3 Reaction of **2a** with various 2-hydroxyarylacetonitriles[a]



1 2a 3

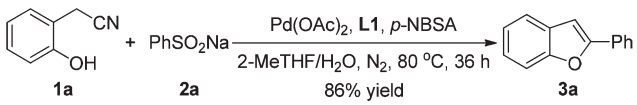


[a] *Reaction conditions*: **1** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), **L1** (20 mol%), *p*-NBSA (10 equiv.), 2-MeTHF (2 mL), H_2O (1 mL), 80 °C, 36 h, N_2. The isolated yield is given in parentheses.

products **3f–3h** (Table 2, entries 6–8) and **3n–3o** (Table 3, runs 5 and 6) in moderate to good yields, making further elaborations of the corresponding biaryl products possible.

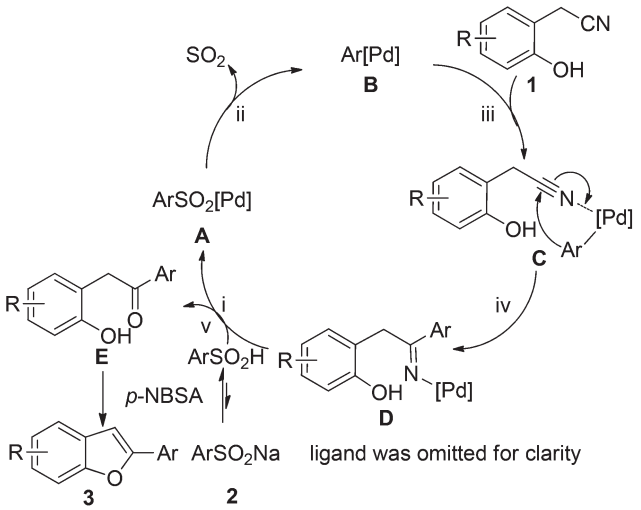
Finally, the present synthetic route to 2-arylbenzofurans could be readily scaled up to the gram quantity without any difficulty. For instance, the reaction at the 20 mmol scale afforded the corresponding product 2-phenylbenzofuran (**3a**) in 86% yield (Scheme 2).

To elucidate the mechanism of formation of 2-arylbenzofurans, we performed control experiments (see Schemes S2–S4 in ESI†). Reaction of 2-phenylacetonitrile (**4**) with sodium benzenesulfinate (**2a**) was examined under the standard conditions, affording the corresponding product 1,2-diphenylethanone (**5**) in 89% yield. However, no desired product **4** was observed in the absence of the palladium catalyst and the ligand (see Scheme S2 in ESI†). The desired product **3a** could not be detected and when 2-hydroxyphenylacetonitrile (**1a**) was treated with **2a** in the absence of the palladium catalyst and the ligand, almost 90% of **1a** was recovered (see Scheme S3 in ESI†). We found that **3a** was obtained in 89% yield when the intramolecular annulation of 2-(2-hydroxyphenyl)-1-phenylethanone (**6**) was performed in the absence of the palladium catalyst and the ligand, while a trace yield of the desired product **3a** was observed in the absence of *p*-NBSA (see Scheme S4 in ESI†). These results showed that the addition reaction depends on the palladium catalyst and the ligand, whereas the intramolecular annulation is independent of the addition reaction and does not depend on the palladium catalyst and the ligand, but it depends on the additive.



1a 2a 3a
2.66 g 6.56 g 3.34 g

Scheme 2 Gram-scale synthesis of **3a**.



Scheme 3 Plausible mechanism.

On the basis of the above experimental results, a plausible mechanism for the formation of 2-arylbenzofurans is proposed in Scheme 3. The following key steps are included in the catalytic pathway: (i) coordination of $Pd(OAc)_2$ with arylsulfinic acid (or sodium arylsulfinate **2**) to afford a palladium species **A**; (ii) the desulfination of the arylsulfinic acid to give aryl-palladium species **B**, which was followed by (iii) the coordination of 2-hydroxyarylacetonitriles **1** to generate intermediate **C**; (iv) carbopalladation of the 2-hydroxyarylacetonitriles **1** to form the corresponding ketimine complex **D**; (v) protonation of the ketimine complex **D** by *p*-NBSA to afford the free ketimine, which undergoes hydrolysis to form the corresponding 2-(2-hydroxyphenyl)-1-arylethanones **E** under acidic conditions and regenerates an active palladium species. Finally, intramolecular annulation of 2-(2-hydroxyphenyl)-1-arylethanones **E** under acidic conditions readily delivers 2-arylbenzofurans **3** as the desired products.

In summary, we have developed a new strategy for constructing 2-arylbenzofurans in moderate to excellent yields from the palladium-catalyzed tandem reaction of 2-hydroxyarylacetonitriles with sodium sulfinates. Further efforts to extend this catalytic system to the preparation of other useful heterocycles are currently underway in our laboratories.

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