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Porous Organic Polymer-Derived Nanopalladium Catalysts for Chemoselective Synthesis of Antitumor Benzofuro[2,3-*b*]pyrazine from 2-Bromophenol and Isonitriles

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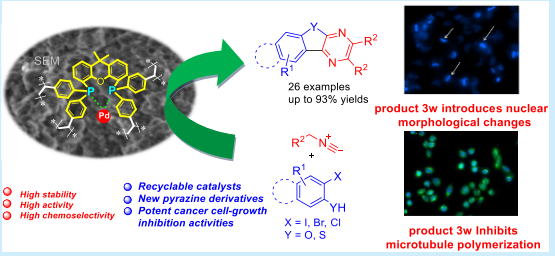
Supporting Information

ABSTRACT: An efficient strategy for the synthesis of benzofuro[2,3-*b*]pyrazines was developed. These tricyclic scaffolds were formed through a multistep cascade sequence, which includes double insertion of isonitriles and chemoselective bicyclization. In this reaction, a nanopalladium was used as a recyclable catalyst. Product **3w** exhibited excellent anticancer activity toward T-24 (IC_{50} = 12.5 ± 0.9 μM) and HeLa (IC_{50} = 14.7 ± 1.6 μM) cells. We also explored the action mechanism of **3w** on T-24 cells.



Polycyclic fused nitrogen-containing heterocycles play an important role in modern organic synthesis due to their ubiquity in many biologically significant natural products and pharmaceuticals and their broad applications in materials science.[1] Among numerous nitrogen-containing aromatic polycyclic compounds, benzofuran-fused N-heterocycles are well-recognized structural units in drug candidates and biologically active compounds (Figure 1). For example,

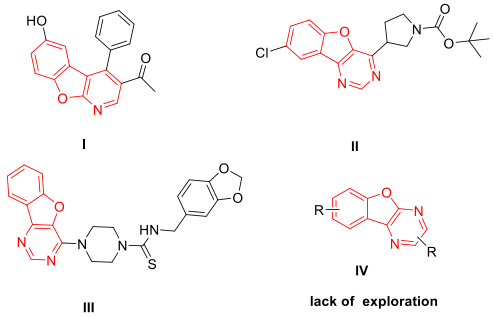


Figure 1. Benzofuran-fused N-heterocycles and their pharmacological activity.

benzofuro[2,3-*b*]pyridine derivatives (**I**) are commonly used as inhibitors of multifarious cyclin-dependent kinases.[2] Benzofuro[3,2-*d*]pyrimidine derivatives (compound **II**) are potent histamine H4 modulators.[3] Compound **III** is a new inhibitor of multitarget tyrosine kinase and is currently undergoing phase I clinical trials.[4] However, few studies have investigated the synthesis method and pharmacological activity of benzofuro[2,3-*b*]pyrazine derivatives (compound **IV**). In recent decades, only a few methods have been reported for the preparation of benzofuro[2,3-*b*]pyrazine.[5] These methods involve multiple steps or prefunctionalization of starting materials. Therefore, scholars must develop facile and efficient approaches for the synthesis of benzofuro[2,3-*b*]pyrazine from commercially available substrates and determine its pharmacological activity.

As important C1 building blocks, isonitriles are useful synthons.[6] Insertions of palladium-catalyzed isonitrile into carbon−heteroatom, carbon−hydrogen, and carbon−halogen bonds have been extensively studied.[7] This strategy has been used to prepare numerous nitrogen-containing compounds with excellent pharmacological activity.[8] However, these homogeneous palladium catalysts are more difficult to recycle from the final products than their corresponding heterogeneous catalytic systems with fixed metal catalysts on large-surface area materials. In view of the highly active and diverse reactivity of isonitriles, controlling their selectivity for participation in chemical reactions is a major challenge. Recent studies have reported on using porous organic polymers (POPs) as catalyst supports and ligands for various metal catalysts to improve reaction selectivity.[9] For example, a series of P-containing POPs with excellent regioselectivity and chemoselectivity were used as recyclable catalysts in hydrogenation, hydroformylation, and decarbonylation.[10] In our previous work,[11] we developed a highly chemoselective method with this type of heterogeneous catalyst for the synthesis of polysubstituted thiazoles from isonitriles.[11b] Thus, we were inspired to develop a new method for the synthesis of benzofuran derivatives **7** from easily available *ortho*-halogenated phenol **1** with isonitriles (Scheme 1). First, substrates **1a** and **2a** were treated with a homogeneous palladium catalyst.

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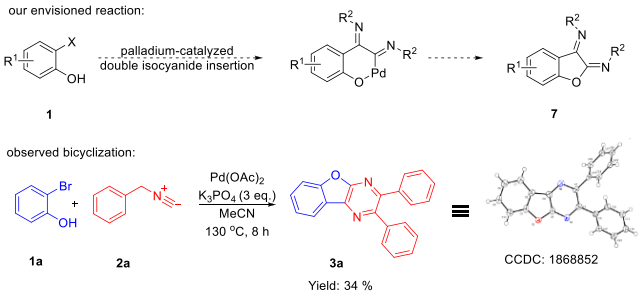
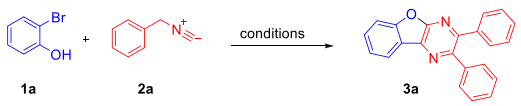
Scheme 1. Possibilities for the Formation of Different Benzofuran Derivatives



Product **7** was not observed, and 2,3-diphenylbenzofuro[2,3-*b*]pyrazine **3a** was obtained in 34% yield. The structure of **3a** was confirmed by single-crystal X-ray analysis. Herein, we report the development of this palladium-catalyzed chemoselective bicyclization reaction for the synthesis of a wide variety of benzofuro[2,3-*b*]pyrazines.

The reaction parameters were comprehensively analyzed, and the results are summarized in Table 1.We used **1a** and **2a**

Table 1. Optimization of the Reaction Conditions[a,b]



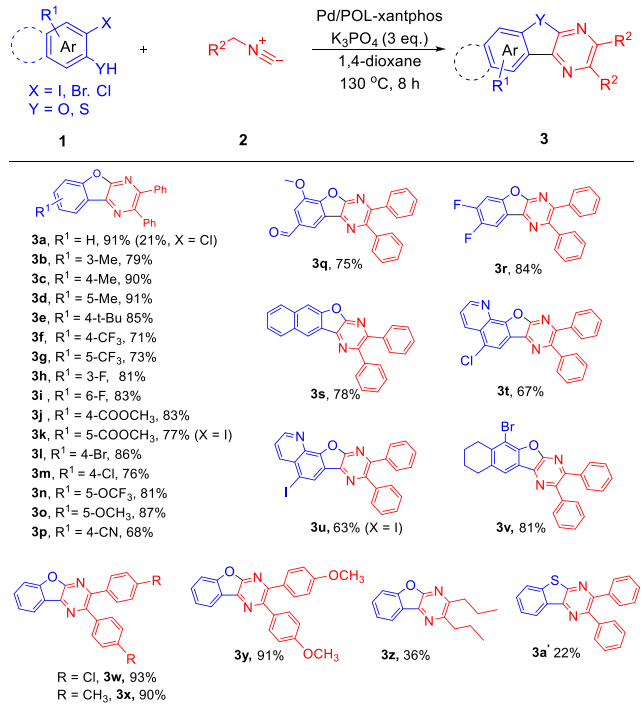
entry	catalyst	ligand	solvent	yield (%)
1	$Pd(PPh_3)_2Cl_2$	–	MeCN	41
2	$PdCl_2$	–	MeCN	47
3	$PdCl_2$	PPh_3	MeCN	53
4	$PdCl_2$	Dppm	MeCN	49
5	$PdCl_2$	Dppe	MeCN	54
6	$PdCl_2$	xantphos	MeCN	56
7	Pd/POL-xantphos	–	MeCN	77[c]
8	Pd/POL-xantphos	–	DMSO	NR[c]
9	Pd/POL-xantphos	–	DCE	47[c]
10	Pd/POL-xantphos	–	1,4-dioxane	91[c]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), homogeneous catalyst (5 mol %), K_3PO_4 (0.45 mmol), ligand (10 mol %), solvent (2 mL), 130 °C, 8 h. [b]Isolated yield. [c]Heterogeneous catalyst (2 mol %).

as model substrates. When the reaction proceeded with 5 mol % $Pd(PPh_3)_2Cl_2$ in CH_3CN at 130 °C, we obtained the desired 2,3-diphenylbenzofuro[2,3-*b*]pyrazine **3a** in 41% yield (Table 1, entry 1). When homogeneous $PdCl_2$ was used, product **3a** was isolated in 47% yield (Table 1, entry 2). In addition, the use of PPh_3 ligands increased the yield of **3a** to 53% (Table 1, entry 3). Ligand screening revealed that xantphos was better (Table 1, entries 4–6). According to our previous reports, palladium-metalated porous organic polymers can significantly increase the selectivity and catalytic activity in the reaction for the synthesis of heterocycles. Thus, we attempted to optimize the reaction conditions with this method. When the heterogeneous catalyst Pd NPs/POL-xantphos was used,[12] the yield of **3a** improved to 77% (Table 1, entry 7). Further results suggested that 1,4-dioxane was the optimal solvent (Table 1, entries 8–10). Using bipyridine or phenanthroline as the ligand did not improve the yield (Scheme S1). Therefore, the optimal conditions for preparing **3a** were as follows: heterogeneous Pd (2 mol %) as a catalyst in 1,4-dioxane and reaction at 130 °C in air for 8 h (Table 1, entry 10).

We then extensively evaluated the substrate scope of this chemistry (Scheme 2) under the conditions described above.

Scheme 2. Synthesis of Benzofuro[2,3-*b*]pyrazines from *o*-Halophenols with Diverse Isonitriles[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), K_3PO_4 (0.45 mmol), Pd/POL-xantphos (2 mol %), 1,4-dioxane (2 mL), 130 °C, 8 h. Unless otherwise noted, all X groups of substrates **1** are Br groups. [b]Isolated yields.

o-Bromophenols with various aromatic substituents reacted smoothly to afford the target products in moderate to good yields. When the Br group was replaced with the Cl group, we isolated product **3a** in 21% yield (Scheme 2, **3a**). *o*-Bromophenol with alkyl groups reacted smoothly, and target products **3** were isolated in high yields (Scheme 2, **3b–3e**). The 3, 4, and 5 substitutions on the phenyl ring of *o*-bromophenol did not significantly affect the product yield. *o*-Halophenols with various substituents and electronic properties at the phenyl ring (R = 5-CF_3, 4-CF_3, 3-F, 6-F, 4-$COOCH_3$, 5-$COOCH_3$, 4-Br, 4-Cl, 5-OCF_3, 5-OCH_3, or 4-CN) reacted smoothly to afford the target products in moderate to good yields (Scheme 2, **3f–3r**, respectively). Other special substrates, including 3-bromo-2-naphthol, 7-bromo-5-chloro-8-hydroxyquinoline, 5,7-diiodo-8-hydroxyquinoline, and 1,3-dibromo-5,6,7,8-tetrahydronaphthalen-2-ol, were tolerated (Scheme 2, **3s–3v**, respectively). In the isonitrile moiety, benzyl isocyanides with different groups were suitable substrates (Scheme 2, **3w–3y**). Alkyl isocyanides also reacted with *o*-bromophenol to afford product **3z** in 36% yield. By replacing the oxygen atom with the sulfur atom, we isolated 2,3-diphenylbenzo[4,5]thieno[2,3-*b*]pyrazine **3a′** in 22% yield.

When 2-bromo-1-phenylethan-1-one, which is similar to *o*-bromophenol, was used as the reaction substrate, 2,3,6-triphenylfuro[2,3-*b*]pyrazine **6** was obtained in 28% yield.

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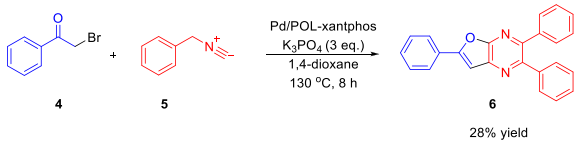
Hence, the proposed method has a wide substrate scope (Scheme 3).

Scheme 3. Synthesis of 2,3,6-Triphenylfuro[2,3-*b*]pyrazine from 2-Bromo-1-phenylethan-1-one and Benzyl Isocyanide



To evaluate the reusability of Pd NPs/POL-xantphos, we selected the reaction of **1a** and benzyl isocyanide **2a** as an example. After each run, the heterogeneous catalyst Pd NPs/POL-xantphos was recovered through filtration and washed with water, 1,4-dioxane, and acetone. This catalyst was effectively used for at least 10 cycles without a loss of efficiency (Figure 2a). The TEM images show the formation of

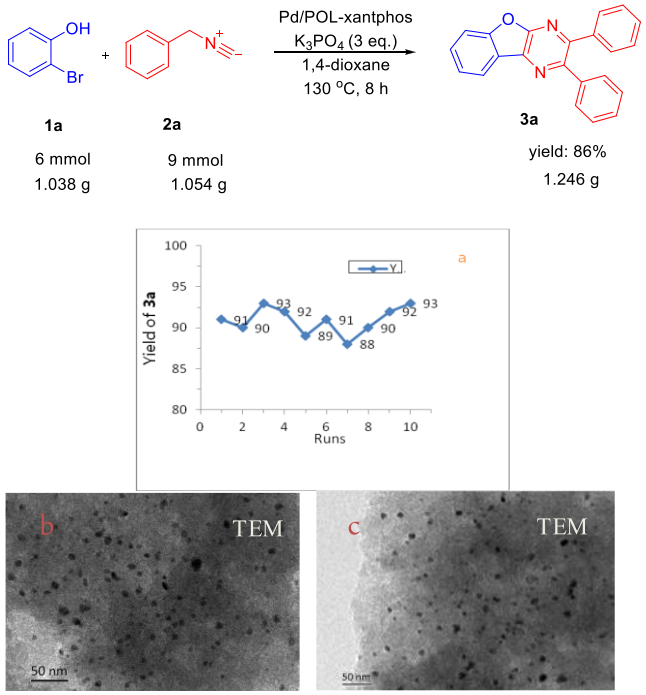
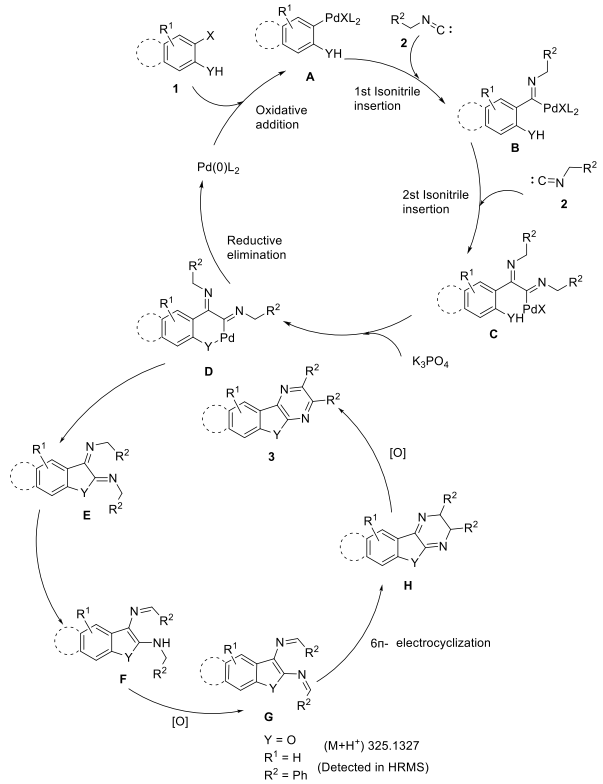


Figure 2. (a) Recycling experiments. (b) TEM characterization of our fresh Pd nanocatalyst. (c) TEM characterization of our used Pd nanocatalyst.

a heterogeneous Pd catalyst without obvious aggregation after the 10th run (Figure 2b,c). More importantly, ICP-MS showed that the Pd metal can be stably fixed on POP materials (<2 ppb in the filtrate) during the recycling, which is perfect for the synthesis of drug intermediates. These results explain the recyclability and high activity of the prepared catalyst. The reaction of 1.038 g of *o*-bromophenol **1a** with isonitriles **2a** produced **3a** in 86% yield (1.246 g).

On the basis of our previous work,[11] a rational mechanism of this reaction can be proposed (Scheme 4). An oxidative addition reaction of *o*-halophenol **1** with the Pd(0) catalyst will generate Pd(II) species **A**. Then, intermediate **A** reacts with two molecules of isonitriles **2** to afford **C**. Cyclization of **C** will produce six-membered cyclic compound **D**. Reductive elimination of **D** will afford benzofuran derivative **E**. The

Scheme 4. Proposed Mechanism



reaction proceeds through isomerization to give intermediate **F** and oxidation to give intermediate **G**. Analysis of the reaction mixture by LC-MS showed the presence of intermediate **G**. Then, intermediate **G** transforms into **H** through a 6π-electrocyclic ring closure and oxidation sequence to give compound **3**.

We conducted the methylthiazolyltetrazolium (MTT) assay to evaluate the antitumor activity of products **3a**−**3z** against four human tumor cell lines (MGC-803, T-24, HeLa, and HL-7402) and one normal cell line (WI-38). 5-FU and cisplatin were used for comparison. Compound **3w** exhibited preferential cytotoxicity toward MGC-803, T-24, HeLa, and HL-7402 cells, with IC_{50} values of 20.2 ± 1.4, 12.5 ± 0.9, 14.7 ± 1.6, and 25.4 ± 0.9 μM, respectively (Table 2). These results indicate that product **3w** displayed better antiproliferative activity toward tumor cells than toward WI-38 cells. Compound **3w** exhibited better antitumor activity on HeLa cells but lower cytotoxicity against WI-38 cells compared with 5-FU and cisplatin. Confocal microscopy analysis was conducted to investigate the cytotoxicity mechanisms of compound **3w** in T-24 cells. The results suggested that compound **3w** inhibited tubulin polymerization, induced apoptosis, increased the rate of intracellular Ca^{2+} release, and supported ROS regulation in T-24 cells (Supporting Information).

In conclusion, we developed an efficient and chemoselective one-step method for the synthesis of benzofuro[2,3-*b*]-pyrazines by using recyclable heterogeneous catalysts. The Pd NPs/POL-xantphos was effectively used for at least 10 cycles without a loss of efficiency. The in vitro antitumor activity of the products was studied. Product **3w** exhibited satisfactory anticancer activity toward T-24 (IC_{50} = 12.5 ± 0.9 μM) and HeLa (IC_{50} = 14.7 ± 1.6 μM) cells. Furthermore, we also explored the mechanism of action of **3w** on T-24 cells.

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Table 2. IC_{50} (micromolar) Values of Compound 3w, 5-FU, and Cisplatin against Five Cell Lines

compound	MGC-803	T-24	HeLa	HL-7402	WI-38
3w	20.2 ± 1.4	12.5 ± 0.9	14.7 ± 1.6	25.4 ± 0.9	>40
5-FU	32.5 ± 1.1	37.6 ± 0.8	>40	>40	>40
cisplatin	8.9 ± 0.9	9.6 ± 1.3	16.1 ± 0.8	11.7 ± 1.5	10.5 ± 0.5

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01230.

Experimental procedures and characterization of compounds **3a**−**3z** and **6** and antitumor mechanism of compound **3w** on T-24 cells (PDF)

Accession Codes

CCDC 1868852 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(12) The synthesis and characterization of the Pd NPs/POL-xantphos catalyst have been reported in our previous work.[10a] We used the same catalyst in this study.

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