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Pd-Catalyzed Intramolecular Heck Reaction for the Synthesis of 2-Methylbenzofurans

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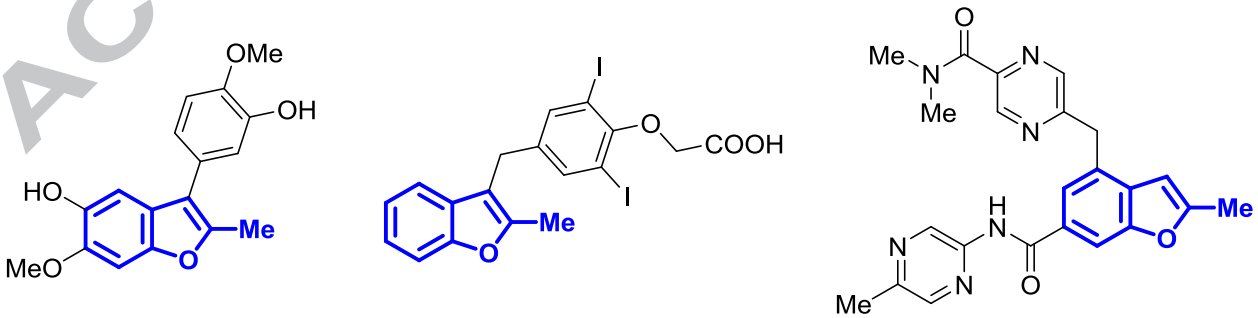
Abstract

A new strategy for the synthesis of 2-Methylbenzofurans via the intramolecular Heck reaction has been developed. This efficient palladium-catalyzed system showed good catalytic activity. Various substituted 2-methylbenzofurans could be afforded in good to excellent yields.

Key words: Intramolecular Heck reaction, Palladium, Cyclization, 2-Methylbenzofurans

Organic molecules containing heteroarenes, such as pyrroles, furans, thiophenes, and their benzo-fused derivatives are quite significant due to their promising properties in pharmacology, catalysis, and application in material science.[1-3] In particular, 2-methylbenzofurans are privileged scaffolds in variety of biologically active compounds, for instance, they were found to demonstrate anti-inflammatory (**1**),[4] anti-arrhythmic (**2**)[5] and anti-diabetic activities (**3**).[6]



Pterolinus A **(1)**
anti-inflammatroy

KB130015 **(2)**
Antiarrhythmic

Glucokinase activator **(3)**
anti-diabetic

Figure 1. Biologically active 2-methylbenzofurans.

Thus, significant efforts to prepare 2-methylbenzofurans have been made and various synthetic

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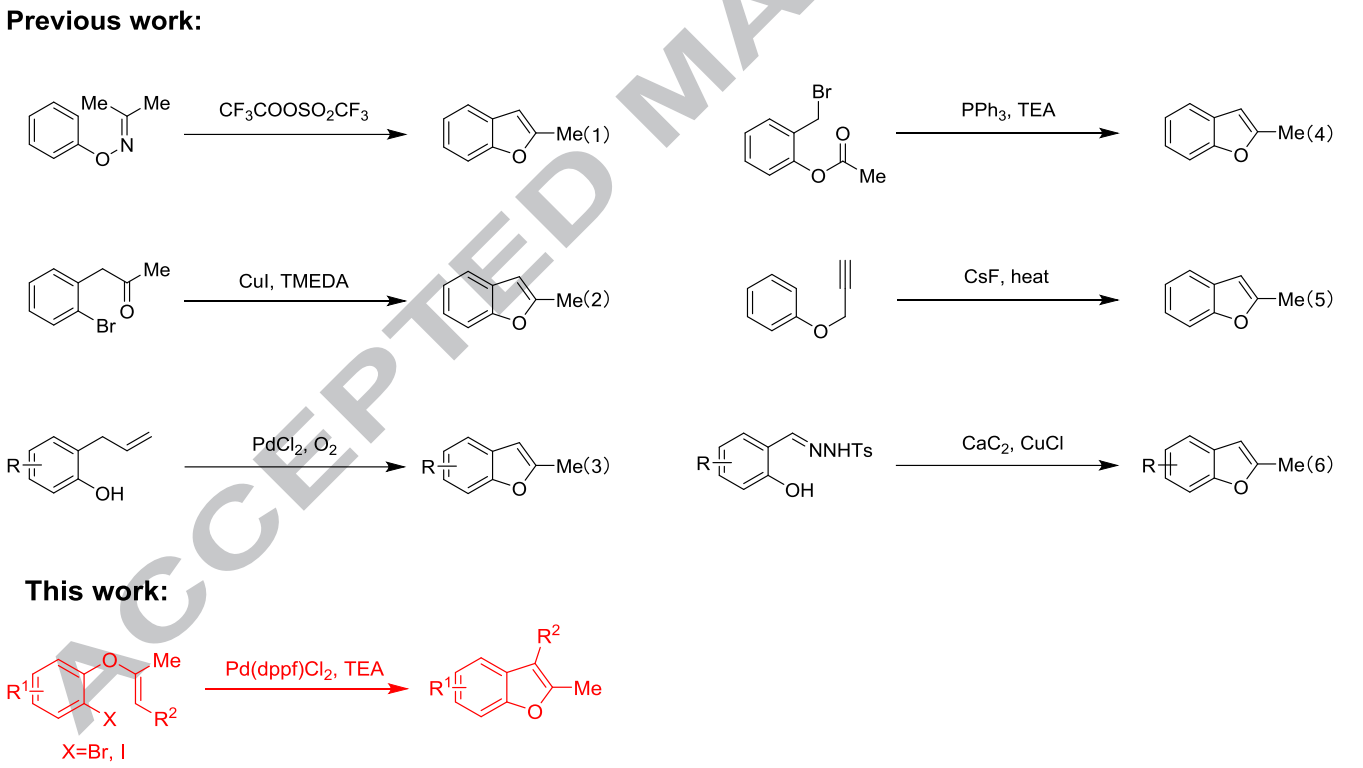
approaches have been published in the past few years. Naito et al. reported a [3,3]-sigmatropic rearrangement reaction during the course of trifluoroacetylation of O-phenyloxime to form 2-methylbenzofurans.[7] Domınguez et al reported a copper-TMEDA complex catalyzed cyclization to form 2-methylbenzofurans from 1-(2-bromophenyl)propan-2-one.[8] Kaneda et al. reported a Wacker type reaction to synthesis of 2-methylbenzofurans.[9] Ghosh et al. reported using a intramolecular photochemical Wittig reaction to prepare 2-methylbenzofurans.[10] Lee et al. reported a CsF catalyzed Claisen rearrangement-cyclization to form 2-methylbenzofurans.[11] Chand et al. reported a palladium nanoparticles catalyzed domino approach to synthesis of 2-substitutedbenzofurans.[12] Recently, Li et al. reported a novel method to synthesis of 2‑ Methylbenzofurans from calcium carbide and salicylaldehyde *p*-tosylhydrazones.[13]

Scheme 1. Preparation of 2-Methylbenzofurans

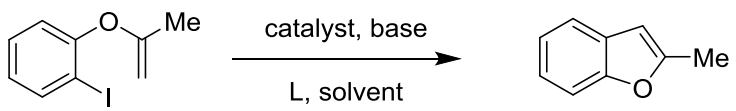


Though numerous approaches access to 2-methylbenzofuran have been disclosed in the literature, some drawbacks still remained for the existing synthetic methods, such as using harsh conditions with limited functional group tolerability. Therefore, the development of novel and efficient synthetic methods for the construction of this fused heterocycle has a special significance to organic chemists, as well as to pharmaceutical chemists.

The Heck reaction is one of the most significant approaches which has proven to be an integral process for the construction of C-C linkages in the organic chemistry, and widely used in organic synthesis, pharmaceutical, and material industries. To the best of our knowledge, however, examples of synthesis of 2-methylbenzofuran via Heck type reaction are not explored. Herein, we report an efficient and practical palladium catalyzed intramolecular Heck coupling reaction for the synthesis of 2-methylbenzofurans. The developed method is applicable to a wide range of 2-methylbenzofurans containing different functional groups, furnishing moderate to excellent yields of the corresponding products.

Initially, 1-iodo-2-(prop-1-en-2-yloxy)benzene (**1a**) was chosen as the model substrate to test intramolecular Heck reaction (Table 1). As expected, the desired product **2** was obtained in 23% yield in the presence of $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2.0 equiv) at 100 °C in DMF (0.25 M) for 24 h (Table 1, entry 1). After screening kinds of base (Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, ^{t}BuOK and Et_3N), we found that Et_3N was more efficient than the others (Table 1, entries 6). A range of solvents, such as CH_3CN, 1,4-dioxane, toluene and THF were also tested and CH_3CN showed the best efficiency, which could give **2** in 61% yield (Table 1, entry 7). The use of a ligand was also essential for the reaction. Different ligands, including POT, dppb, dppf, SPhos and XPhos, were investigated, and dppf performed best with a yield of 72% (Table 1, entries 13). Prompted by these results, further investigations on the Palladium catalyst, such as Pd_2dba_3, $PdCl_2$ and $Pd(dppf)Cl_2$ were conducted and $Pd(dppf)Cl_2$ performed best with a yield of 91% (Table 1, entries 18). Finally, the optimal conditions involved the following parameters: 10 mol% of $Pd(dppf)Cl_2$ and 2 equiv of Et_3N in 4 mL of CH_3CN at 82°C under nitrogen.[14]

Table 1. Optimization of Reaction Conditions[a]



1a **2**

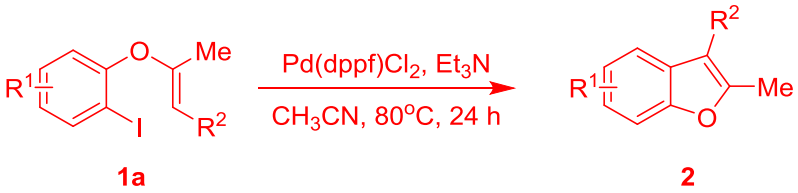
Entry	Catalyst	Ligand	Base	Solvent	*T* (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	100	23
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	100	46
3	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	100	42
4	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMF	100	44
5	$Pd(OAc)_2$	PPh_3	^{t}BuOK	DMF	100	27
6	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	100	60
7	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN	80	61
8	$Pd(OAc)_2$	PPh_3	Et_3N	1,4-dioxane	100	44

9	$Pd(OAc)_2$	PPh_3	Et_3N	toluene	100	49
10	$Pd(OAc)_2$	PPh_3	Et_3N	THF	70	28
11	$Pd(OAc)_2$	POT	Et_3N	CH_3CN	80	58
12	$Pd(OAc)_2$	dppb	Et_3N	CH_3CN	80	44
13	$Pd(OAc)_2$	dppf	Et_3N	CH_3CN	80	72
14	$Pd(OAc)_2$	SPhos	Et_3N	CH_3CN	80	56
15	$Pd(OAc)_2$	XPhos	Et_3N	CH_3CN	80	61
16	$Pd_2(dba)_3$	dppf	Et_3N	CH_3CN	80	63
17	$PdCl_2$	dppf	Et_3N	CH_3CN	80	67
18	$Pd(dppf)Cl_2$	—	Et_3N	CH_3CN	80	91

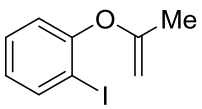
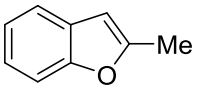
[a]Reaction conditions: **1a** (1 mmol), catalyst (10 mol%), ligand (20 mol%) and base (2 mmol) in solvent (4 mL) was heated for 24 h. [b]Isolated yield.

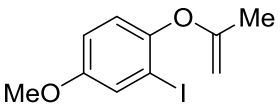
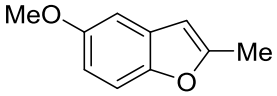
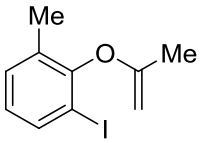
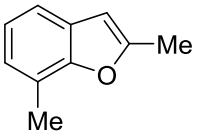
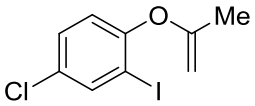
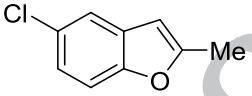
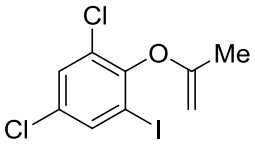
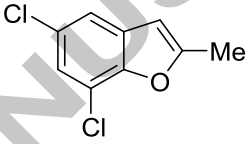
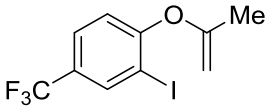
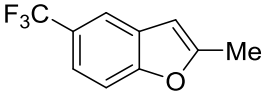
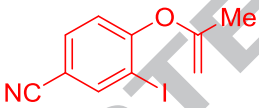
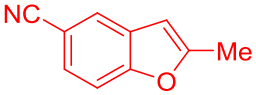
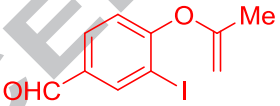
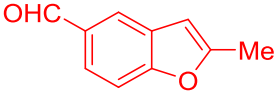
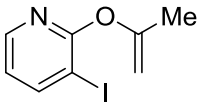
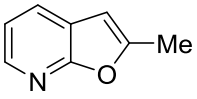
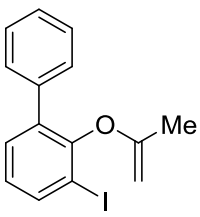
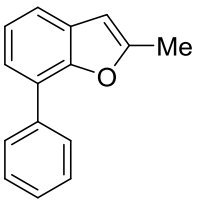
With the optimized reaction condition in hand, the substrate scope toward this palladium-catalyzed intramolecular Heck-type reaction was further investigated, the results are listed in Table 2. A wide range of aryl iodides were examined in the reaction, and moderate to excellent yields were obtained in producing the corresponding 2-methylbenzofuran (Table 2). Iodobenzene derivatives, which bear substituted groups on their aromatic rings, such as methoxyl, methyl and Cl, gave the corresponding products in excellent yield (Table 2, Entry 2~5). However, the substrates, bearing electron-withdrawing groups on their aromatic rings, could also afford the desired corresponding products but in lower yield (Table 2, Entry 6~9). It is noteworthy that the substrate including biphenyl and naphthyl groups were fairly compatible with these conditions to afford desired product in satisfactory yield (Table 2, Entry 10, 11). In addition, 3-substituted-2-methylbenzofurans could also be synthesized by this intramolecular Heck reaction in good yield (Table 2, Entry 12, 13).

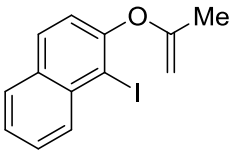
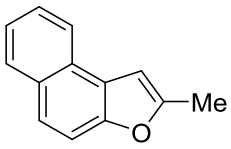
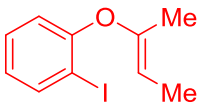
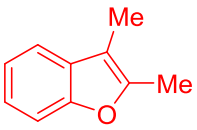
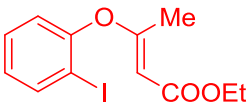
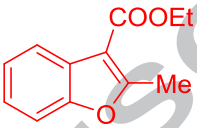
Table 2. Scope of Iodobenzene Substrates[a]



1a **2**

Entry	Iodobenzene	Product	Yield [%][b]
1	 **1aa**	 **2a**	91%

2	 **1ab**	 **2b**	96%
3	 **1ac**	 **2c**	90%
4	 **1ad**	 **2d**	94%
5	 **1ae**	 **2e**	90%
6	 **1af**	 **2f**	52%
7	 **1ag**	 **2g**	64%
8	 **1ah**	 **2h**	78%
9	 **1ai**	 **2i**	83%
10	 **1aj**	 **2j**	91%

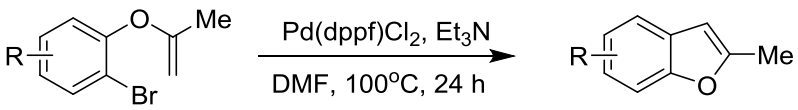
11	 **1ak**	 **2k**	96%
12	 **1al**	 **2l**	90%
13	 **1am**	 **2m**	86%

[a] Reaction conditions: **1a** (1 mmol), $Pd(dppf)Cl_2$ (10 mol%) and Et_3N (2 mmol) in CH_3CN (4 mL) was heated at 80°C for 24 h.

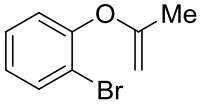
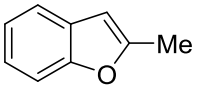
[b] Isolated yield.

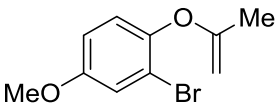
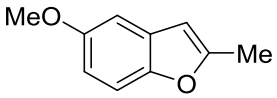
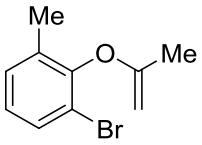
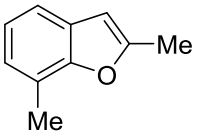
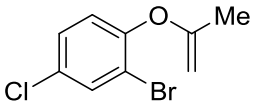
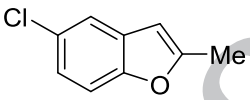
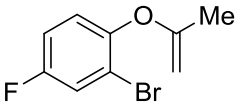
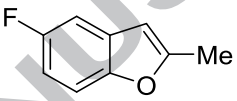
To our delight, the reaction on aryl bromides could also proceed smoothly at slightly higher temperature (100°C), and the results were shown in Table 3. However, in comparison with the aryl iodides, only electron-donating substituents on aromatic ring could maintain the excellent yield (Table 3, Entry 2, 3). Substrate bearing F, Cl or without substitution gave desired product in moderate yield (Table 3, Entry 1, 4 and 5).

Table 3. Scope of Bromobenzene Substrates[a]



1b **2**

Entry	Iodobenzene	Product	Yield [%][b]
1	 **1ba**	 **2a**	67%

2	 **1bb**	 **2b**	99%
3	 **1bc**	 **2c**	90%
4	 **1bd**	 **2d**	64%
5	 **1bn**	 **2n**	63%

[a]Reaction conditions: **1b** (1 mmol), $Pd(dppf)Cl_2$ (10 mol%) and Et_3N (2 mmol) in DMF (4 mL) was heated at 100°C for 24 h.

[b] Isolated yield.

In summary, we have developed an efficient method for the synthesis of 2-methylbenzofurans by intramolecular Heck reaction. A variety of substituted 2-methylbenzofurans could be successfully synthesized according to this approach in satisfactory yield. The new methodology provides an efficient and alternative strategy for natural and unnatural compounds containing the 2-methylbenzofuran skeleton and will find its potential applications in organic synthesis.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found. This material includes detailed experimental procedures and NMR data (^1H and ^{13}C NMR data).

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14. General procedure for the preparation of 2-methylbenzofurans **2**: A pre-dried screw-capped tube was charged with **1** (1 mmol, 1 eq), Pd(dppf)Cl_2 (0.1 mmol, 0.1 eq) and Et_3N (2 mmol, 2 eq) in MeCN (5 mL) under N_2 atmosphere. The reaction mixture was heated to 82℃ under stirring for 24 hours. The mixture was concentrated in vacuo and purified by column chromatography (100% petroleum ether) to afford the pure products.

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Highlights

- An efficient method was established for the synthesis of 2-methylbenzofurans.
- Palladium-catalyzed intramolecular Heck reaction was performed under mild condition.
- Broad substrate scope and good functional compatibility.
- Good to excellent yields.

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Graphical abstract