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Synthesis of benzofurans in ionic liquid by a $PdCl_2$-catalyzed intramolecular Heck reaction

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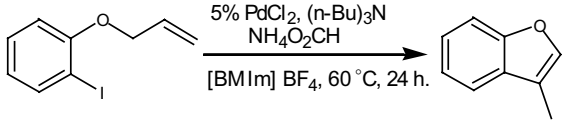
Abstract—$PdCl_2$-catalyzed intramolecular Heck reaction was conducted in ionic liquid, 1-*n*-butyl-3-methylimidazolium tetraborate ([BMIm] BF_4), substituted benzofurans were obtained in modest to satisfactory yields. The ionic liquid containing Pd catalyst can be used four times with a little loss of activity.

One of the prime principles of green chemistry is to develop an alternative reaction medium, which is the basis for the development of many cleaner chemical technologies. Particularly, ionic liquids have recently gained recognition as possible environmentally safe alternatives to volatile organic solvents. Ionic liquids, especially those based on the 1-*n*-alkyl-3-methyl imidazolium cation, have shown great promise as novel reaction medium for various catalytic processes.[1] And these types of ionic liquids have been demonstrated to be ideal immobilizing agents for various 'classical' transition-metal catalyst precursors in reactions to enhance the reaction rate and selectivity.[2] In addition the products can be extracted by *n*-hexane or diethyl ether, or simply be distilled from the reaction mixture, and this made the workup very easy to conduct. Moreover, the ionic liquids with the metal catalyst can be recovered and recycled without any loss of activity for several times. Due to these advantages, ionic liquids have been recognized as the optimal green reaction medium in laboratories and factories.

It remained a problem to construct the framework of benzofuran in synthesizing of natural products and pharmaceutical products.[3] Pd-catalyzed intramolecular Heck reaction of *ortho*-iodo aryl allyl ether is an attractive method to synthesize benzofurans.[4] It is needed to maintain the reaction mixture at 80 °C for a comparatively long time (2 days), and additional $(Bu)_4NCl$ was needed to activate the catalyst $Pd(OAc)_2$. However, the yields of benzofurans were not very satisfactory. Probably due to the low reaction efficiency, the reaction was scarcely used in practice.

Considering the unique property of ionic liquids, the reaction may proceed well in ionic liquid in the absence of the additional $(Bu)_4NCl$. This prompted us to have a try. 1-*n*-Butyl-3-methyl imidazolium tetrafluoroborate [BMIm] BF_4 was a popular and available ionic liquid and it has shown enhanced reactivity and selectivity in several Pd-catalyzed reactions.[5] But according to our knowledge, it has not been applied to this type of reaction, so it was chosen as reaction medium. *ortho*-Iodo benzyl allyl ether was chosen as the first reactant and a more available and economic Pd source, $PdCl_2$ as catalyst. When *ortho*-iodo benzyl allyl ether was treated with 5 mol% $PdCl_2$, 1.5 equiv $(n\text{-}Bu)_3N$ and 1 equiv NH_4OOCH at 60 °C for 24 h, it disappeared completely and the product 3-methyl benzofuran was obtained in 71% isolated yields (Scheme 1). The yield was much higher than its initial yield in DMF (47%).[4] After the reaction, the product was extracted by diethyl ether and purified by column chromatography on silica gel as usual. Since the catalyst remained completely in the



Scheme 1.

Keywords: Intramolecular Heck reaction; Benzofurans; Ionic liquid.
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Table 1. Recycle of the catalyst system[a]

Run	Isolated yield (%)[b]
1	71
2	66
3	60
4	57

[a] All the experiments were done according to Ref. 6.
[b] The products were identified by 200 M ^{1}H NMR and mass spectrometry.

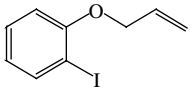
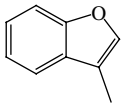
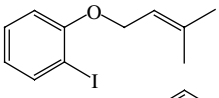
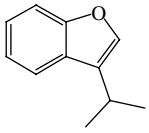
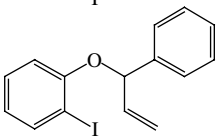
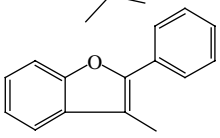
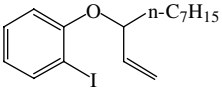
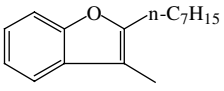
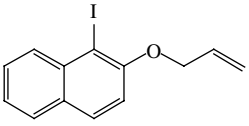
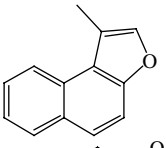
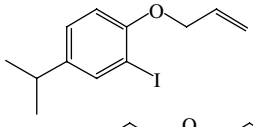
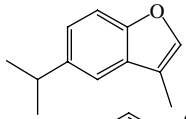
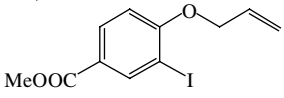
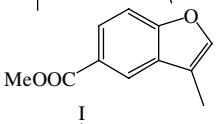
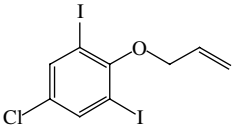
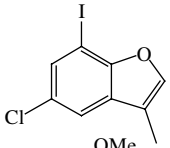
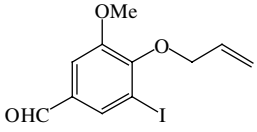
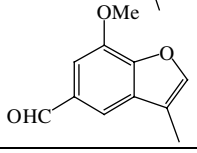
ionic liquid, the catalyst system can be reused. Then another partial of substrate, $(n\text{-Bu})_3N$ and NH_4OOCH were added and the reaction was repeated. As shown in Table 1, the catalyst system still kept high activity after recycling four times. It proceeded in 66%, 60% and 57% yields when it was used in the following three runs.

To extend the scope of this methodology, we applied it to other *ortho*-iodo aryl allyl ether (Scheme 2) and the

Scheme 2.

results were summarized in Table 2. As exhibited in Table 2, all the substrates proceeded well and modest to satisfactory yields were obtained. And it seemed that the less hindered the double bond (entry 1) or the better the aryl leaving group (entry 5), the lower the yield of benzofuran. This observation was in agreement with the original paper.[4] And the yields of the substrates with a substituent on the aryl group were lower, respectively. However, the character of the substituent did not have a significant effect on the reaction yields (entries 6–8). When it was concerned with entry 9, a mixture was obtained in which the desired product was obtained only

Table 2. Cyclization of other *ortho*-iodo aryl allyl ether

Entry[a]	Substrate	Product[b]	Isolated yield (%)
1			71
2			87
3			85
4			78
5			45
6			54
7			51
8			43
9			21

[a] All experiments were done according to Ref. 6.
[b] The products were identified by 200 M ^{1}H NMR and mass spectrometry.[7]

in 21% yields probably due to the affection of methoxy group and aldehyde group on the aryl group.

In summary, we have developed an environmentally friendly method to synthesize benzofurans. One major advantage of our protocol is that the catalyst system can be recycled and the green character of the ionic liquid. This lowered the reaction temperature and shortened the reaction time with satisfying yields. So the reaction efficiency was greatly improved and it may have great potential to construct the framework of benzofuran in synthesizing of natural products and pharmaceutical products.

Acknowledgements

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6. General procedure: 1 mmol *ortho*-iodo aryl allyl ether, 1.5 mmol $(n\text{-Bu})_3N$ and 1 mmol NH_4OOCH and 0.05 mmol $PdCl_2$ were added to 1.5 mL $[BMIm]BF_4$. The mixture was heated to 60 °C and maintained for 24 h. When the mixture was cooled to room temperature, it was extracted by diethyl ether (15 mL×3). The Pd catalyst was kept and suspended in the ionic liquid layer. The diethyl ether layers were collected and concentrated in vacuum. Then the crude mixture was purified by column chromatography on silica gel to give the pure benzofurans.
7. The spectral data of some products. Product **1**: ^1H NMR(200 M, $CDCl_3$): $\delta = 2.23$(s, 3H), 7.18–7.53(m, 5H). MS (EI): $m/z(\%) = 132(70)$, 131(100), 103(43), 77(56). Product **4**: ^1H NMR(200 M, $CDCl_3$): $\delta = 0.85$(t, $J = 4.3$ Hz, 3H), 1.27(m,10H), 1.67(t, $J = 3.0$ Hz, 2H) 2.63(s, 3H) 7.22–7.52(m,4H). MS (EI): $m/z(\%) = 358(100)$, 297(18), 233(22). Product **6**: ^1H NMR(200 M, $CDCl_3$): $\delta = 1.29$ (d, $J = 3.5$ Hz, 6H), 2.23(s, 3H), 3.02(m, 1H), 7.14–7.38(m, 3H). MS (EI): $m/z(\%) = 174(35)$, 159(100), 131(11). Product **7**: ^1H NMR(200 M, $CDCl_3$): $\delta = 2.25$(s, 3H), 3.91(s, 3H), 7.44–8.01(m,3H), 8.26(s, 1H). MS (EI): $m/z(\%) = 190(50)$, 159(100), 131(36), 103(14). Product **8**: ^1H NMR(200 M, $CDCl_3$) $\delta = 2.19$(s, 3H), 7.24–7.46(m, 2H), 7.62(s, 1H). MS (EI): $m/z(\%) = 292(100)$, 165(15), 137(14), 127(27).