

# Recyclable palladium catalytic system for sustainable C-C coupling reaction to achieve low palladium contamination of products.

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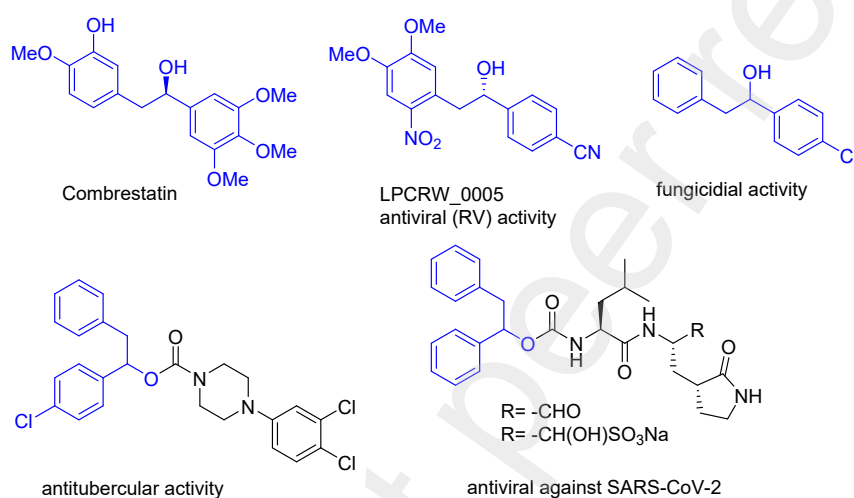
## Abstract

The impact of a palladium species on the 1,2-diarylation reaction course is presented. The application of Pd-dmpzc as a catalyst provides efficient, chemoselective and sustainable protocol for the synthesis of valuable 1,2-diphenylethyl acetates. The reaction is conducted in water under mild conditions. Reaction products can be easily separated from reaction mixture and catalyst by simple extraction. What is more, the rational choice of catalyst significantly reduces the leaching of the metal into product and its contamination (0.1 ppm). Efficient phase separation and ultralow Pd leaching enable the reuse of water medium containing Pd-dmpzc catalyst several times without significant loss of activity and even higher selectivity (from 95% to 100% in third cycle). The recyclability of both the catalyst and the reaction medium together with high chemoselectivity and low palladium leaching reduces the amount of waste and the cost of the process, exhibiting an example of sustainable and green methodology.

## 1. Introduction

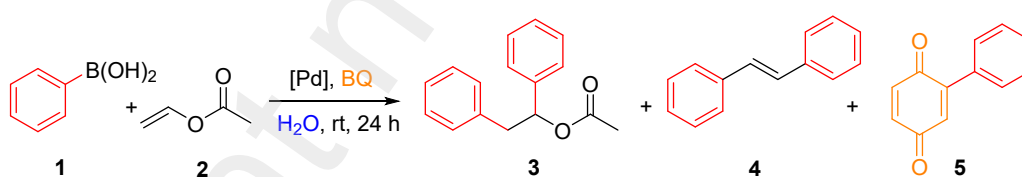
The carbon-carbon cross coupling reactions are one of the most powerful synthetic tools from medicinal chemistry and drug discovery points of view. Most of these transformations are mediated by transition metal catalysts, in particular, palladium-based species as they allow to obtain diverse range of products.[1] However, palladium has an undesired tendency to remain in the final products. Special attention has been paid for the purity of compounds required by pharmacy and medicinal chemistry. Very low limit of heavy metal cations contaminations which is now below 10 ppm and 1 ppm, for oral and parenteral drug substances, respectively excludes most synthetic methods.[2] Such low levels of palladium allowed in pharmaceutically relevant compounds is due to this metal ability to coordinate with proteins, DNA and other macromolecules inhibiting various cellular functions.[3] Therefore, one of the most challenging problems in modern organic chemistry and technology is the design of synthetic methods free from metal impurities.

Our ongoing interest in the design of environmentally benign protocols for the synthesis of biologically relevant compounds [4, 5] led us the development of palladium-catalyzed 1,2-diarylation of vinyl esters in aqueous medium.[6] This protocol utilizes sustainable arylboronic acids and inexpensive palladium acetate as a catalyst and offers ready-made one-step access to 1,2-diarylethyl esters. These products and their derivatives are important class of compounds for medicinal chemistry (Figure 1). This includes antineoplastic combretastatin [7] and some other molecules with antiviral (against Rhinovirus (RV) [8] and SARS-CoV-2[9]), antitubercular [10] or fungicidal [11] properties. However, the previously developed protocol does not fulfil the requirements of limits of palladium contamination. Thus, to overcome these limitations we decided to study the impact of a ligand structure on the leaching of palladium into the products and the reaction course. The rational design of catalyst where the ligand prevents from metal leaching into products, can also enable the reuse of a catalyst.



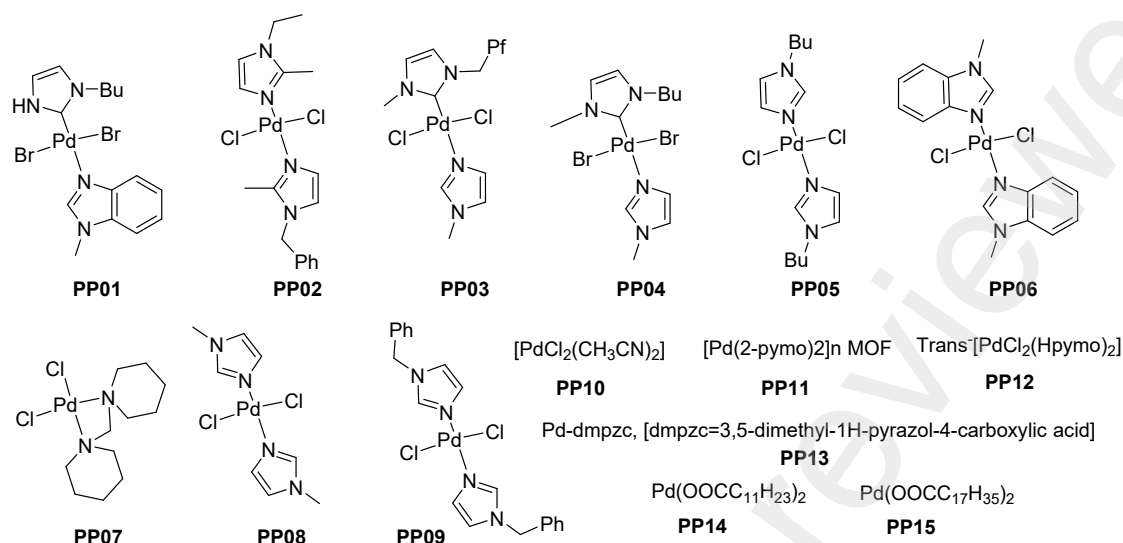
**Figure 1.** Representative structures of 1,2-diarylethanol derivatives.

## 2. Results and Discussion



**Scheme 1.** The palladium-catalyzed diarylation of vinyl esters.

To study the efficiency of various palladium catalysts and palladium leaching in products, we choose previously developed diarylation reaction [6] (Scheme 1). As model substrates we



choose phenylboronic acid (**1**) and vinyl acetate (**2**). The reaction was conducted in water at room temperature in the presence of 1,4-benzoquinone (BQ) as a re-oxidant and a palladium catalyst during 24 hours. At first we have tested the impact of various palladium species on the reaction course. We have tested 15 different complexes of palladium (Figure 2) [12-19] and previously used palladium (II) acetate.

**Figure 2.** The structures of tested palladium catalysts.

Based on the previously obtained data [6], the studied reaction led to the formation of 1,2-diphenylethyl acetate (**3**) as a main product and two by-products – stilbene (**4**) and 2-phenyl-1,4-benzoquinone (**5**). The majority of a re-oxidant – benzoquinone is reduced to hydroquinone, which remains in water phase after extraction of reaction products by ethyl acetate. Herein we investigated the chemoselectivity of studied catalysts as well as their efficiency. The results are presented in Table 1.

**Table 1.** The impact of palladium catalyst on a reaction course.<sup>a</sup>

Entry	Catalyst	Yield of <b>3</b> [%] <sup>b</sup>	Yield of <b>4</b> [%] <sup>b</sup>	Yield of <b>5</b> [%] <sup>b,c</sup>	Selectivity [%]
1	Pd(OAc) <sub>2</sub>	70	13	1	83
2	<b>PP01</b>	32	17	6	58
3	<b>PP02</b>	5	2	5	42
4	<b>PP03</b>	49	13	3	75
5	<b>PP04</b>	17	7	1	68
6	<b>PP05</b>	65	14	3	79
7	<b>PP06</b>	47	16	1	73
8	<b>PP07</b>	38	7	10	69
9	<b>PP08</b>	85	6	9	85

10	<b>PP09</b>	54	13	2	78
11	<b>PP10</b>	65	10	1	86
12	<b>PP11</b>	14	2	1	82
13	<b>PP12</b>	12	16	1	41
14	<b>PP13</b>	76	4	0	95
15	<b>PP14</b>	53	7	1	87
16	<b>PP15</b>	73	12	1	85

<sup>a</sup> Reaction conditions: **1** (4 equiv., 3 mmol), **2** (1 equiv., 0.75 mmol), Pd catalyst (5 mol %, 0.0375 mmol), BQ (1.2 equiv., 0.9 mmol), H<sub>2</sub>O (3 mL). <sup>b</sup> Yield of isolated product. <sup>c</sup> Yield was calculated in reference to BQ amount.

To develop the sustainable process, the application of environmentally friendly reaction conditions is not sufficient enough. Thus, in the next step of the studies, we have focused our attention on the impact of palladium catalyst structure on the contamination of product by metal. As 1,2-diphenylethyl acetate and its derivatives are pharmaceutically relevant compounds,<sup>[7-11]</sup> it is important to develop the synthetic protocol that allows to obtain low contaminated products by palladium species. For the most efficient catalysts, the leaching of palladium in product **3** was analyzed *via* ICP-MS/MS (Table 2).

**Table 2.** The palladium leaching.<sup>a</sup>

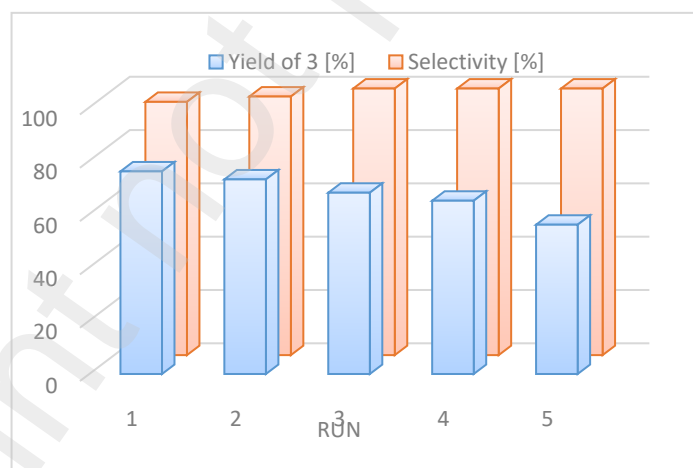
Entry	Catalyst	Palladium content [ppm]
1	Pd(OAc) <sub>2</sub>	26
2	<b>PP05</b>	4
3	<b>PP08</b>	0.3
4	<b>PP10</b>	12
5	<b>PP13</b>	0.1
6	<b>PP15</b>	17

<sup>a</sup> Determined by ICP-MS/MS.

The obtained results show that the type of ligand used has a crucial impact on the palladium leaching in the final product **3** (Table 2). The highest leaching of palladium (26 ppm) was observed for previously used palladium (II) acetate (Table 2, entry 1) and structurally similar palladium (II) stearate **PP015** (17 ppm, Table 1, entry 6). The stability of these complexes is lower, thus the leaching of palladium into solution is observed. Also the application of bis(acetonitrile)palladium dichloride (**PP10**) does not fulfill the pharmacopeia requirements (12 ppm, Table 1, entry 4). The change of ligand significantly reduces the palladium leaching in product. The best results (below 5 ppm) were obtained for catalyst **PP05**, **PP08** and **PP13** (Table 1, entries 2, 3, 5). However, the ultralow levels of metal impurities (below 0.5 ppm)

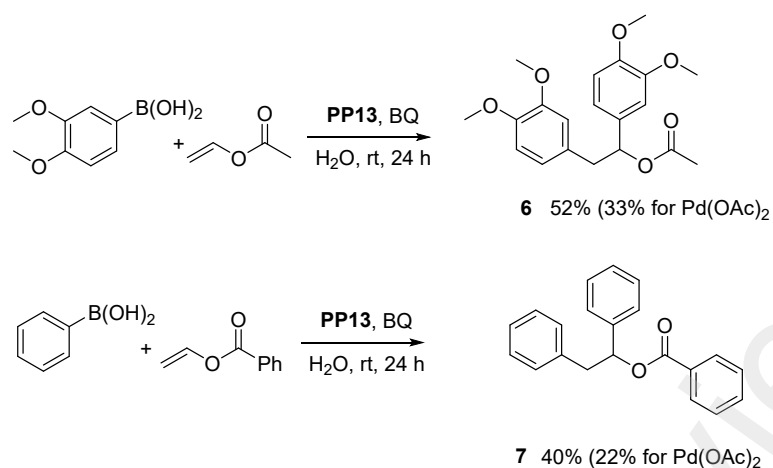
were measured for **PP08** and **PP13** (Table 1, entries 3, 5). What is more, the catalyst **PP13** not only the most chemoselective catalyst (Table 1, entry 14), but also provides products with ultralow level of palladium content. The intermolecular hydrogen bonds, responsible for the formation of the network structure of catalyst **PP13**, can have a stabilizing effect. This may favor more persistent binding of palladium, which limits its leaching. The stability of the complex (which limits leaching) also sustains catalytic activity and results in higher yields. The reduction of metal impurities as well as side products simplify the purification procedures and significantly reduces the amount of wastes and costs.

As Pd-dmpzc catalyst (**PP13**) revealed the lowest metal leaching into product, we also investigated the possibility to reuse the **PP13** catalyst (Figure 3). The studied 1,2-diarylation reaction is conducted in water and the products are separated from reaction mixture by simple extraction with ethyl acetate. It is important to note, that the catalyst **PP13** remains in water phase, what enables the reuse of medium containing catalyst. The studied catalytic system was reused in 5 cycles for diarylation reaction of vinyl acetate with phenylboronic acid. After each catalytic cycle, the products were separated *via* extraction with organic solvent, and the fresh portion of substrates was added to aqueous phase containing a catalyst. It is also worth to note, that the amount of by-product **4** decreased with each cycle, in the second run only 2% of stilbene was formed, to disappear completely in subsequent cycles. The recyclability studies revealed a slight decrease in product **3** yield what can be caused by the remaining reagents in water phase (such as hydroquinone, boric acid or unreacted substrates). It is worth to note, that the selectivity of the reaction increases in subsequent cycles up to 100% in 3<sup>rd</sup> run (Figure 3).



**Figure 3.** The recycling efficiency of reaction medium containing catalyst **PP13**.

Finally, to prove the generality of presented catalyst, the additional experiments were performed (Scheme 2). When 3,4-dimethoxyphenylboronic acid and vinyl acetate were used as substrates, the diarylation product **6** was obtained with 52% (33% for previously used palladium acetate). Then, we have changed the vinyl ester from acetate to benzoate obtaining product **7** with nearly twofold higher yield than for Pd(OAc)<sub>2</sub>. These results indicate that catalyst **PP13** is not only chemoselective, high active and recyclable but also works well for various substrates.



**Scheme 2.** The palladium-catalyzed diarylation of vinyl esters.

### 3. Conclusion

In conclusion, here we presented the studies on the impact of structure of palladium ligand on the chemoselectivity of vinyl esters diarylation reaction and metal leaching into product. The reaction is conducted at room temperature in water under mild conditions what makes it attractive from environmental point of view. The application of Pd-dmpzc (**PP013**) as a catalyst not only provides the best chemoselectivity (elimination of by-products) but reduces the leaching of palladium into product to ultralow level (0.1 ppm), what considerably diminishes the amount of generated wastes and cost of whole procedure. It is also worth to note that the change of ligand from previously used acetate to dmpzc resulted in great decrease of metal contamination in final product. This and water solubility of complex PP13 allow us to develop the methodology based on the recyclability of the catalyst and water medium several times without significant loss in yield. Reaction products were easy separated from reaction mixture containing catalyst and other reagents by simple extraction with ethyl acetate what also simply the purification procedure. It is important to note the selectivity of reaction catalyzed by **PP13** increases in subsequent cycles reaching 100% in 3rd cycle. The use of an aqueous medium and the recyclability of the catalyst and medium at least five times reduces the amount of generated wastes and the cost of the process, exhibiting an example of sustainable and green methodology.

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### Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at

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