



# A highly efficient heterogeneous palladium-catalyzed carbonylative annulation of 2-aminobenzamides with aryl iodides leading to quinazolinones

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## ABSTRACT

The first heterogeneous carbonylative annulation of 2-aminobenzamides with aryl iodides was achieved in *N,N*-dimethylformamide (DMF) at 120 °C under 10 bar of carbon monoxide by using an MCM-41-immobilized bidentate phosphine palladium(II) complex [MCM-41-2P-Pd(OAc)<sub>2</sub>] as catalyst and 1,8-diazabicycloundec-7-ene (DBU) as base, yielding a wide variety of quinazolinone derivatives in good to excellent yields. The new heterogeneous palladium catalyst can easily be prepared by a simple procedure from commercially readily available reagents, and recovered by filtration of the reaction solution, and recycled up to eight times without significant loss of activity.

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## 1. Introduction

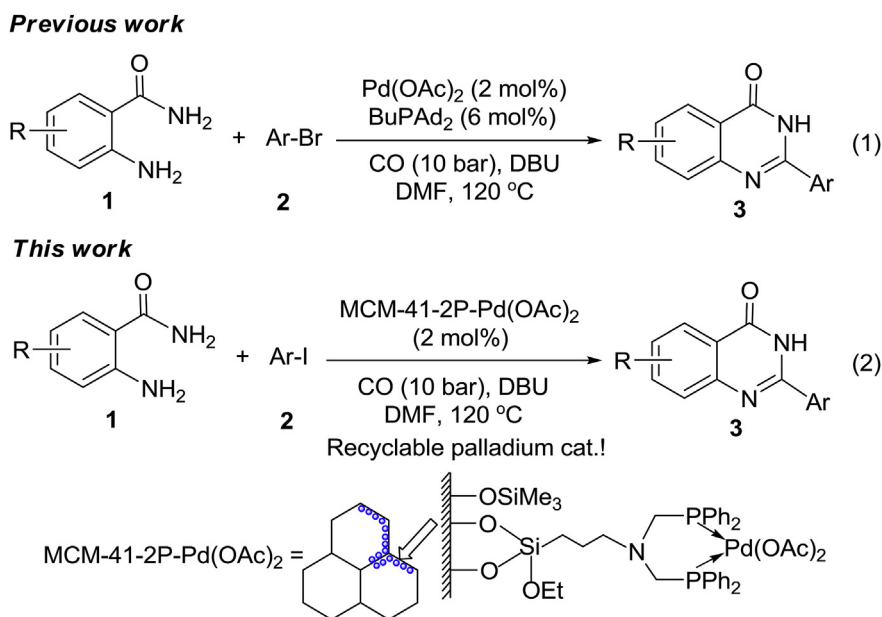
Quinazolinones, existing in many natural alkaloids and pharmaceuticals [1,2], are a significant class of annulated six-membered nitrogen heterocycles. They are endowed with numerous pharmacological and biological activities, including anticancer [3,4], antibacterial [5], antifungal [6], antimalarial [7], antihypertensive [8], antitubercular [9], inhibitors of derived growth factor receptor phosphorylation [10], anticonvulsant [11], and other activities [12–14]. Additionally, quinazolinones are also important building blocks in the synthesis of natural products and bioactive compounds [15,16]. As a result, a number of methods have been developed for construction of quinazolinones [17]. Conventionally, such a structure is synthesized by the condensation of 2-halobenzoic acids, 2-halobenzamides, 2-aminobenzamides, 2-aminobenzoic acids with amidines, benzyl alcohols, benzylamines, acid amides or amino acids [18–21]. However, these known methods generally suffer from certain disadvantages, such as multistep synthesis, low yields, limited substrate scope, and/or

harsh reaction conditions. These problems have stimulated several groups to apply transition metal-catalyzed reactions for the development of new protocols to substituted quinazolinones, using Cu [22], Ir [23], Pt [24], and Pd [25–27] as catalysts.

Since the pioneering work of Heck and co-workers in 1974 [28], palladium-catalyzed carbonylative transformation of organohalides has become a powerful tool in modern organic synthesis [29–31]. The advantages of carbonylation reactions are (i) it is the most potent methodology in the construction of carbonyl-containing compounds, which increases the carbon number at the same time, and (ii) carbon monoxide (CO) can be used as a cheap and readily available C1 source, which is also in agreement with the green chemistry principles. Recently, palladium-catalyzed carbonylative annulation reactions have been successfully applied in the synthesis of furanones, benzoxazinones, flavones, and other heterocycles [32–35]. Wu and coworkers reported a palladium-catalyzed carbonylative synthesis of quinazolinones from 2-aminobenzamide and aryl bromides with expensive BuPAd<sub>2</sub> (di-1-adamantyl-*n*-butylphosphine) as the ligand [36] [Eq. (1), in Scheme 1]. Although these palladium-catalyzed carbonylative annulation reactions are highly efficient for the construction of heterocycles, industrial applications of these homogeneous palladium complexes remain a challenge because they are quite expensive, cannot be recycled, and difficult to

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**Scheme 1.** Palladium-catalyzed carbonylative synthesis of quinazolinones.

separate from the product mixture, which is a particularly significant drawback for their applications in the pharmaceutical industry. Immobilization of the existing homogeneous palladium catalysts on porous materials with high surface areas could be an attractive solution to these problems since the immobilized catalysts can be facily separated from the reaction mixture by a simple filtration process, and recycled for several times. There has been considerable interest in the development of heterogeneous palladium catalytic systems that can be efficiently recycled whilst maintaining the inherent activity of the catalytic centre [37].

Mesoporous MCM-41 materials have recently been shown to be powerful supports for immobilization of homogeneous catalysts due to their outstanding advantages, such as extremely high surface areas, large and defined pore sizes, big pore volumes and the presence of a large number of silanol (Si–OH) groups on the inner surface in comparison with other solid supports [38–40]. So far, some palladium [41–44], rhodium [45], molybdenum [46], gold [47–49] and copper [50–52] complexes immobilized on MCM-41 have been successfully used as highly active and recyclable catalysts in organic reactions. As a part of our continuing interest in the development of efficient heterogeneous catalysts for organic synthesis [43,49–52], herein we report the synthesis of an MCM-41-immobilized bidentate phosphine palladium(II) complex [MCM-41-2P-Pd(OAc)<sub>2</sub>] and its successful application to carbonylative annulation of 2-aminobenzamides with aryl iodides under 10 bar of CO leading to a wide variety of 2-aryl-substituted quinazolinones in good to excellent yields [Eq. (2), in Scheme 1]. The new heterogeneous palladium catalyst exhibits high catalytic activity in the reaction and can be facily recovered via a simple filtration process after the reactions, and its catalytic efficiency remains unchanged even after recycling eight times.

## 2. Results and discussion

### 2.1. Synthesis and characterization of MCM-41-2P-Pd(OAc)<sub>2</sub> complex

The MCM-41-immobilized bidentate phosphine palladium(II) complex [MCM-41-2P-Pd(OAc)<sub>2</sub>] was synthesized starting from

mesoporous material MCM-41, *N,N*-bis((diphenylphosphino)methyl)-3-(triethoxysilyl)propan-1-amine, and Pd(OAc)<sub>2</sub> according to the procedure summarized in Scheme 2. Firstly, the condensation of *N,N*-bis((diphenylphosphino)methyl)-3-(triethoxysilyl)propan-1-amine with MCM-41 in toluene at 100 °C for 24 h, followed by the silylation with Me<sub>3</sub>SiCl in toluene at room temperature for 24 h gave a bidentate phosphino-functionalized MCM-41 material (MCM-41-2P). The latter was subsequently reacted with Pd(OAc)<sub>2</sub> in acetone under reflux for 72 h to generate the MCM-41-immobilized bidentate phosphine palladium(II) complex [MCM-41-2P-Pd(OAc)<sub>2</sub>] as a light yellow powder. The palladium content of this complex was determined to be 0.36 mmol/g (3.83 wt%) by ICP-AES. The energy dispersive X-ray spectroscopy (EDS) shows the elements present in the material. EDS analysis of fresh MCM-41-2P-Pd(OAc)<sub>2</sub> complex (Fig. 1) shows the presence of Si, O, C, N, P, and Pd elements, confirming the successful anchoring of the palladium-phosphine complex onto the MCM-41. The silanization of MCM-41 was further confirmed by FTIR spectroscopy (Fig. 2). The FTIR spectrum (Fig. 2a) of MCM-41 shows the Si–O stretching absorption around 1095 cm<sup>-1</sup>. In the FTIR spectrum (Fig. 2b) of MCM-41-2P-Pd(OAc)<sub>2</sub> absorptions at 1630, 1572 and 1413 cm<sup>-1</sup> (benzene ring) were observed, indicating the presence of silylated palladium(II)-phosphine groups.

Fig. 3 shows the XRD patterns for the parent MCM-41 and the MCM-41-2P-Pd(OAc)<sub>2</sub> complex. Small angle X-ray diffraction pattern of the parent MCM-41 showed three peaks corresponding to hexagonally ordered mesoporous phases. For the MCM-41-2P-Pd(OAc)<sub>2</sub>, the (100) reflection of the parent MCM-41 was maintained after introduction of the palladium complex, but the intensity decreased apparently, while the (110) and (200) reflections became weak and diffuse, which may be mainly due to contrast matching between the silicate framework and organic moieties which are located inside the channels of MCM-41. These results indicate that the structure of the mesoporous MCM-41 remains intact through the functionalization procedure, and the formation of the catalyst has taken place preferentially inside the pore system of MCM-41.

Morphological changes of MCM-41 and MCM-41-2P-Pd(OAc)<sub>2</sub> were investigated by scanning electron microscopy (SEM). As shown in Fig. 4, the morphology of MCM-41-2P-Pd(OAc)<sub>2</sub> (Fig. 4b

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