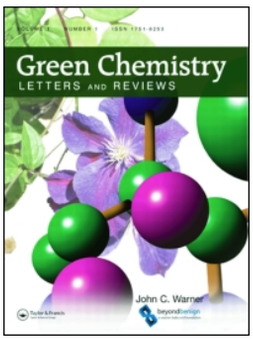

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Novel animal-bone-meal-supported palladium as a green and efficient catalyst for Suzuki coupling reaction in water, under sunlight

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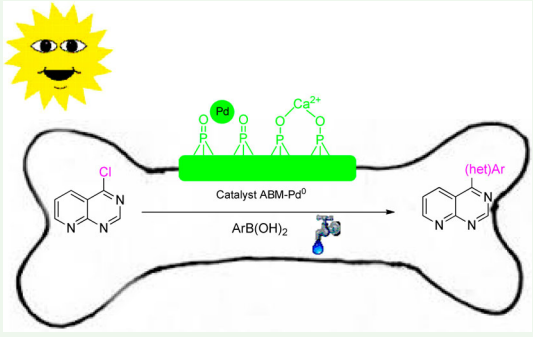
ABSTRACT

Animal-bone-meal-supported palladium (0) was prepared and used as catalyst in the Suzuki coupling reaction in water, under sunlight as an alternative source of energy. This palladium has showed a high catalytic activity than tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) in the Suzuki cross-coupling reaction (the reaction of 4-halogenopyridopyrimidine with boronic acids) in water via sunlight as the light source, with no addition of ligands. This green method affords heteroaryls with excellent yields in comparison with the classical method using tetrakis (triphenylphosphine) palladium. The green catalyst did not show any significant loss of activity, even when used up to five times.



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Animal bone meal; palladium; pyridopyrimidines; Suzuki coupling; sunlight

1. Introduction

The development of heterogeneous catalysts (*1–3*) has gained much attention because of their simple isolation of products, easy recovery, recyclability, and efficiency. Residual metal contamination in the isolated product is a serious problem in the use of homogeneous transition metal catalysts. The use of a heterogeneous catalyst can minimize the residual metal (i.e. palladium [Pd]) catalyst loading, which is economically desirable and leads to the reduction of Pd contamination in the final drug product (*4*).

The Suzuki cross-coupling reaction is a palladium-catalyzed selective construction of carbon–carbon bonds, and is one of the most versatile and utilized reactions for the preparation of many important compounds, such as pharmaceuticals, polymers, and agrochemicals (*5*).

The presence of a pyridopyrimidine scaffold in more complex structures has led to a variety of bioactive molecules that can be used as antimicrobial agents (*6*), antibacterial agents (*7*), antifolates (*8, 9*), anti-inflammatory agents (*10, 11*), insecticides (*12*), antivirals (*13*), anticanceragents (*14*), antihypertensives (*15*), antileishmanials (*16*), anticonvulsants (*17*), diuretics, potassium-sparing activity agents (*18, 19*), anti-aggressive agents (*20, 21*), tyrosine kinases (*22*), and antitumor derivatives (*23*) with selective pro-apoptotic activity (*24*).

Reactions mediated by the photoredox catalyst have become a useful and green strategy in designing radical reactions under mild reaction conditions, that is, visible light (sunlight) irradiation at room temperature (*25*).

The Suzuki–Miyaura reaction is a universal reaction since it allows the coupling of the derivatives boron aryl,

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heteroaryl, vinyl, or even alkyl with all types of halogenated, triflates, or diazoniums compounds. Therefore, the preparation of easy, inexpensive catalysts and an environmentally benign methodology to replace the utilization of a toxic and costly process is highly desirable.

Previously, different heterogeneous catalyst-supported palladiums have been reported for the Suzuki coupling reaction in water (*26–29*), and among them, hydroxyapatite, a source of apatite, has been used by Jamwal and co-workers (*30*). Many solid supports have been used for the preparation of heterogeneous catalysts, and among them, animal bone meal (ABM), a source of biogenic apatite, has received much more attention in last decade (*31*).

Recently, we reported that ABM, a cost-effective material, can be used as a catalyst in several reactions. It was a good candidate as it contains a natural apatite for an inorganic support material since it possesses a large specific surface (*32*). Consequently, along with our experience with the synthesis of heteroaromatic rings via the Suzuki coupling reaction (*33*), we decided to extend a methodology toward the synthesis of isomeric position 4-monosubstituted pyrido[2,3-*d*]pyrimidines via cross-coupling reactions using ABM-catalyst-supported palladium.

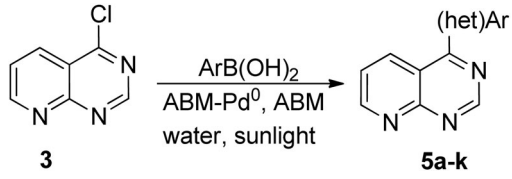
2. Results and discussion

In this experiment, an attempt was made to prepare ABM-supported palladium (0) and its subsequent application for the synthesis of new monosubstituted pyrido [2,3–*d*] pyrimidines **5** via the Suzuki coupling reaction between 4–chloropyrido[2,3–*d*] pyrimidines **3** and heteroaryl boronic acids using ABM as the base and water as the solvent (Scheme 1).

4-Chloropyrido[2,3-*d*]pyrimidines **3** was prepared from nicotinic acid **1** by cyclization and chlorination to obtain the halogenated product **3** in 89% yield (Scheme 2).

2.1. Protocol for the preparation of ABM-supported palladium (0) catalyst

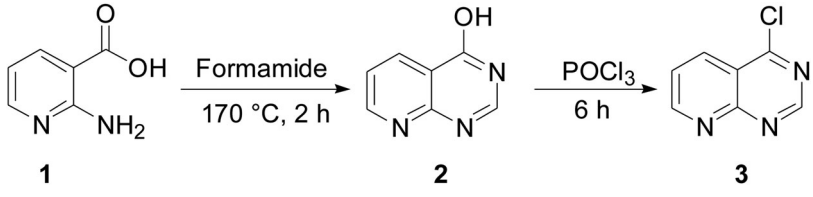
ABM (10.0 g) in ethanol (50 mL) and $PdCl_2$ (200 mg) was poured into a round-bottom flask (100 mL), and the resulting mixture was stirred constantly at room temperature for 5 h. A dropwise addition of hydrazine hydrate (6 mL of 80%) was carried out over a period of 30 min, with further stirring at room temperature for 8 h. A dark-gray product was obtained during this period. The catalyst (ABM–Pd^0) so obtained was filtered and washed with ethanol (20 mL) and acetone (5 × 20 mL). The catalyst was refluxed continuously for 8 h in ethanol and acetonitrile, respectively, to avoid any residual $PdCl_2$, each for 4 h. Further, the ABM–Pd^0 was dried in an oven for 8 h and stored in a desiccator.



Scheme 1. Preparation of monosubstituted pyrido[2,3-*d*]pyrimidines **5**.

2.2. General protocol for the Suzuki coupling reaction

Double-distilled water (6 mL) was added to a mixture of 4-chloropyrido[2,3–*d*] pyrimidines **3** (1 mmol), heteroaryl boronic acid (1.1 mmol), ABM–Pd^0 (0.2 g, 0.25 mol% Pd), and ABM (50 mg) in a round-bottom flask (25 mL). The reaction mixture was stirred under sunlight as the light source until complete conversion of the starting materials (monitored by Thin-layer chromatography [TLC], 100% Dichloromethane [DCM]). After confirmation of reaction completion, it was cooled to room temperature and filtered, and the residue was washed with hot dichloromethane (3 × 10 mL) followed by double-distilled water (3 × 50 mL). A heavy shower of water was washed over the reaction mixture to remove the organic layer and dried with anhydrous sodium sulfate. Furthermore, the product was received after removal of the solvent under reduced pressure. The crude material was purified by column chromatography (100% DCM) to afford compounds of type **5**, which was identified by IR, ^{1}HNMR, ^{13}C NMR ($CDCl_3$), and mass spectral data. ABM was prepared for the utilization of the catalyst (ABM–Pd^0) as per the literature method (*34–36*).



Scheme 2. Preparation of 4-chloropyrido[2,3-*d*]pyrimidines **3**.

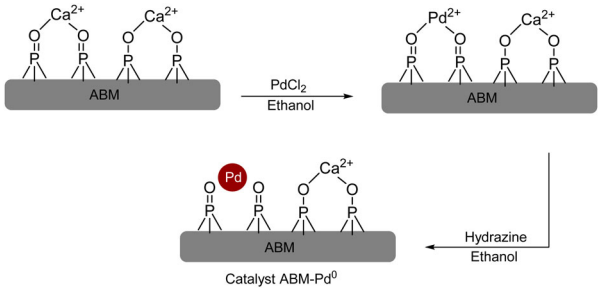


Figure 1. The synthetic outline of ABM–Pd^0.

Stirring of the ABM–$PdCl_2$ mixture in ethanol, followed by a dropwise addition of hydrazine hydrate (80%) and afforded the catalyst (ABM–Pd^0). Figure 1 shows the synthetic outline of ABM–Pd^0.

The characterization of ABM–Pd^0 was done by XRD and TEM. Powder XRD diffraction patterns of ABM–Pd^0 (Figure 2) show three additional reflections ($2\theta = 40°$, 48°, and 67°), which could be attributed to Pd(0).

The TEM micrograph (Figure 3) shows a clear distribution of palladium into ABM, with an average diameter of 20 nm.

2.3. Catalyst optimization for the Suzuki reaction

The reaction toward product **5** was first optimized using phenylboronic acid **4d** (1.1 equiv.) and 4-chloropyrido[2,3-*d*]pyrimidines **3** in the presence of ABM–Pd^0 (Scheme 3). The obtained results are shown in Table 1.

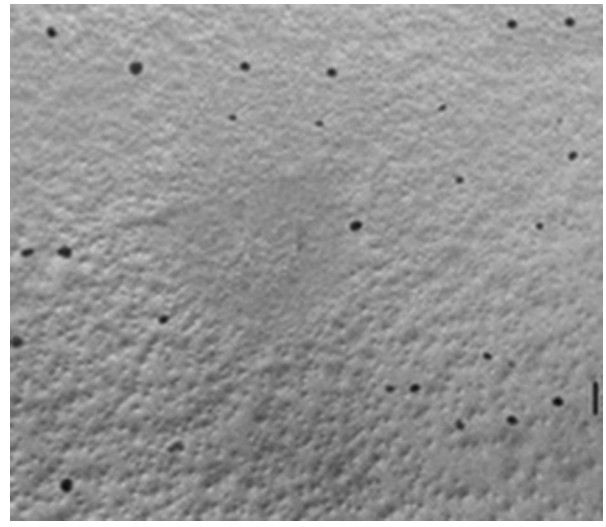


Figure 3. TEM micrographs of ABM–Pd^0.

In either toluene or water, without the catalyst, no reaction was observed in the presence of K_2CO_3 as the base (Table 1, entries 1 and 2). With $PdCl_2$ in presence of K_2CO_3 as the base and toluene or water as the solvent, the product **5d** was obtained with a low yield (entries 3 and 4). In the presence of ABM alone, product **5d** was not detected (entry 5). When using ABM–Pd^0 in toluene, the product was obtained with an excellent yield in the presence of K_2CO_3 as the base (entry 6). Under the same condition in entry 6 when only using ABM as the base, product **5d** was obtained with a slightly improved yield (entry 7).

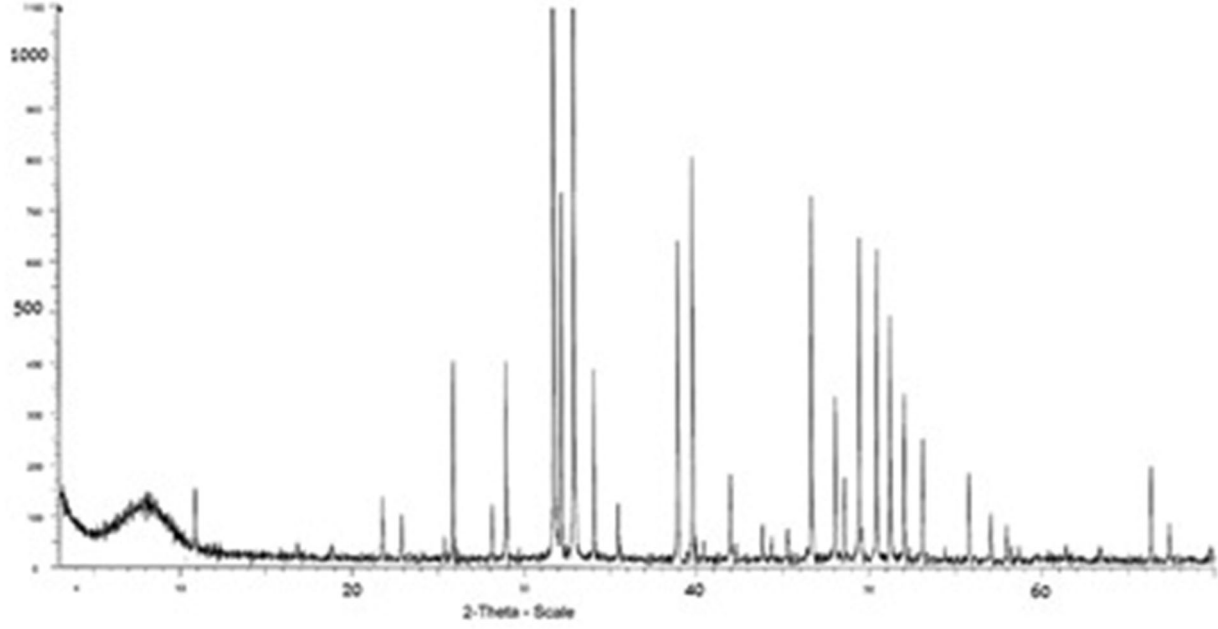
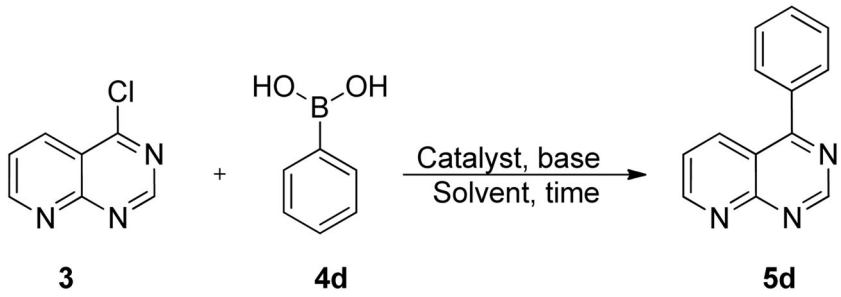


Figure 2. XRD diffraction patterns of ABM–Pd^0.



Scheme 3. The first optimization of the Suzuki coupling reaction.

Table 1. Optimization of the Suzuki coupling reaction.

Entry	Solvent	Catalyst	Base	Time	Yield (%)[a]
1	Toluene	No	K_2CO_3	24 h	NR[b]
2	Water	No	K_2CO_3	24 h	NR[b]
3	Toluene	$PdCl_2$	K_2CO_3	24 h	10
4	Water	$PdCl_2$	K_2CO_3	24 h	18
5	Water	ABM	K_2CO_3	24 h	NR[b]
6	Toluene	ABM–Pd^0	K_2CO_3	7 h	86
7	Water	ABM–Pd^0	ABM	7 h	96

[a]Yields in pure isolated products.
[b]NR: No reaction.

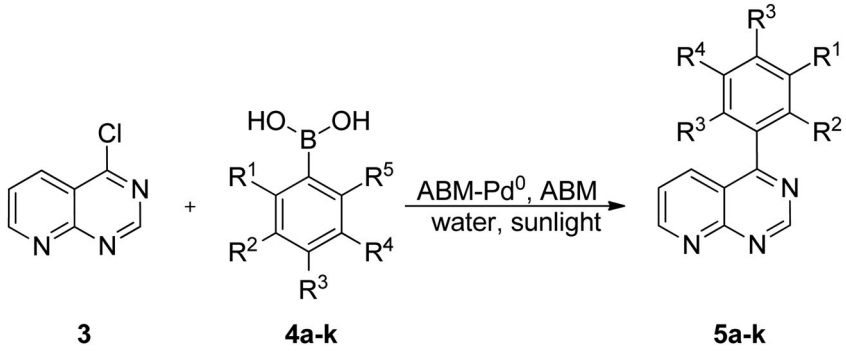
2.4. Extension of the methodology

The methodology was extended in order to form a small library of heterocycles type **5**. Therefore, the reaction of 4-chloropyrido[2,3-*d*]pyrimidines **3** with a slight excess of boronic acids **4a**-**k** (1.1 equiv.) was investigated in water in the presence of the ABM–Pd^0 catalyst with ABM as the base and sunlight as the light source (Scheme 4). The optimized results are shown in Table 2, with a comparison of $Pd(PPh_3)_4$ as the catalyst.

Full conversions afforded substituted pyrido[2,3-*d*]pyrimidines **5a**–**k** with excellent yields after 6–10 h, and they were obtained with good yields. All aromatic boronic acid reactions carried out with **3**, having electron-donating groups and electron-drawing groups in water with doped ABM, as shown in Table 2 (entries 1–10). A remarkable decrease in reaction time was achieved along with good to excellent yields of the product by using ABM–Pd^0 compared to tetrakis(triphenylphosphine)-palladium. Structures of the desired products **5a**–**k** were established by physical and spectral characterizations (M.P., ^{1}H NMR, ^{13}C NMR, and IR).

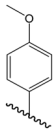
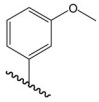
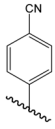
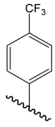
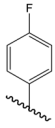
Recyclability of the catalyst is an important point when using a supported metal catalyst. Therefore, to test the recyclability of our catalyst, the coupling between 4–chloropyrido[2,3–*d*]pyrimidines and phenylboronic acid in the presence of ABM–Pd^0 was performed for five consecutive rounds (1st round: 96% after 4 h; 2nd round: 93% after 4 h; 3rd round: 92% after 4 h; 4th round: 90% after 6 h). The recovery remained stable until the fifth reaction.

In summary, to the best of our knowledge, we have presented the simple preparation of an ABM-supported palladium (0) catalyst and its effective application for the Suzuki coupling reaction under atmospheric air, using water as the solvent and sunlight as the energy source. The use of easily available starting materials, easy reaction conditions, and clean and environmentally friendly catalytic processes combined with high yields of products are the main outcome of this green method. A highly efficient, simple accomplishment makes this eco-friendly method



Scheme 4. Investigation of the reaction of 4-chloropyrido[2,3-*d*]pyrimidines **3** with boronic acids **5a**–**k** in water.

Table 2. Reaction of halogenated product **3** with boronic acids **4a–k** in the presence of ABM–Pd^0 catalyst, in comparison with $Pd(PPh_3)_4$.

Entry	(het)Ar	Products	Yields[a] (Time)	
			$Pd(PPh_3)_4$	ABM–Pd^0
1		**5a**	92% (10 h)	94% (7 h)
2		**5b**	86% (10 h)	89% (8 h)
3		**5c**	84% (10 h)	87% (8 h)
4		**5d**	93% (10 h)	96% (7 h)
5		**5e**	84% (10 h)	88% (8 h)
6		**5f**	83% (10 h)	86% (8 h)
7		**5g**	90% (8 h)	94% (6 h)
8		**5i**	91% (6 h)	93% (4 h)
9		**5j**	90% (6 h)	94% (4 h)
10		**5k**	NR[b]	NR[b]

[a]Yield of pure isolated products. Reaction conditions: $ArB(OH)_2$, ABM–Pd^0 (0.25 mg) or $Pd(PPh_3)_4$(5 mol%), ABM (50 mg), water, and sunlight.
[b]NR: No reaction.

attractive for potential applications in various other organic reactions.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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