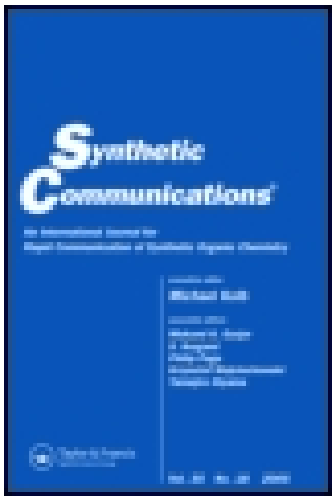

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Phosphine-Free Suzuki Cross-Coupling Reaction Using an Efficient and Reusable Pd Catalyst in an Aqueous Medium Under Microwave Irradiation

Joaquim F. M. da Silva[a], Andres F. Yepes Perez[ab] & Natália P. de Almeida[a]

[a] Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

[b] Facultad de Ciencias Físicas Exactas y Naturales, Universidad de Santander (UDES), Bucaramanga, Colombia

Accepted author version posted online: 11 Jun 2015.

Phosphine-free Suzuki cross-coupling reaction using an efficient and reusable Pd catalyst in an aqueous medium under microwave irradiation

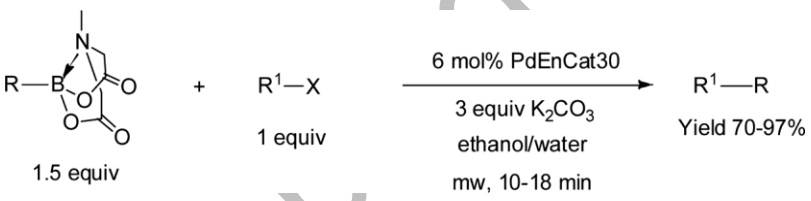
Joaquim F. M. da Silva[1], Andres F. Yepes Perez[1,2], Natália P. de Almeida[1]

[1]Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[2]Facultad de Ciencias Físicas Exactas y Naturales, Universidad de Santander (UDES), Bucaramanga, Colombia

Corresponding author E-mail: joaquim@iq.ufrj.br

Abstract

We report here an improved, highly efficient and general method for the ligand-free Suzuki cross-coupling reaction to the synthesis of biaryls, bipyridyls, thienylpyridine and allylphenols. Microwave irradiation of (het)aryl halides and (hetaryl, allyl)arylboronic acid *N*-methyl-iminodiacetic acid (MIDA) ester, using polyurea microencapsulated palladium catalyst (Pd EnCat 30) gave the coupling adducts **1a**-**x** in excellent yields in just 10-18 min.



KEYWORDS: Suzuki coupling, microwave irradiation Pd EnCat30, phosphine-free reactions, organoboronic acid MIDA ester

INTRODUCTION

The Suzuki reaction is the coupling of an aryl or alkyl boronic acid with an aryl or alkyl halide in the presence of a palladium catalyst. It is a powerful cross-coupling method that allows for the synthesis of conjugated olefins, styrenes and biphenyls.[1] Suzuki coupling

reaction occurs for both aryl iodide and bromide systems in a very efficient way under phosphine-free conditions, what is very important from environmental and economic points of view. Because of the potential advantages of using heterogeneous catalysts for fine chemical synthesis, recently polyurea-encapsulated palladium-catalyzed [PdEnCat™] coupling has been reported. The scope and utility of $Pd(OAc)_2$ encapsulated in polyurea was investigated in a range of synthetically significant applications, including Suzuki-type reactions involving the cross-coupling of aryl boronic acids with aryl bromides. Pd EnCat™ could also be applied to other reactions such as carbonylation reactions, Heck reactions, Stille couplings and hydrogenation reactions.[2-4] We recently reported the Sonogashira coupling for the preparation of arylalkynes using Pd EnCat as catalyst.[5] These transformations are often mediated by Pd species in the presence of phosphine ligands, and this may result in difficulties associated with the removal of homogeneous material from reaction mixtures. In preliminary results[6] we reported the use of Pd EnCat 30 as catalyst in Suzuki coupling reactions using conventional heating (oil bath), and although yields were good, longer reaction times were required, and some yields were not satisfactory. Further, we also wanted to extend our strategy to the preparation of substituted phenols.

Here, we explore, under microwave heating conditions, the catalyst charge, the volume ratio of aqueous medium and the use of different bases, in order to find optimal reaction conditions to obtain higher yields. Furthermore, we explored if with this new heating condition, it is possible to recycle the catalyst without losing its activity. The strategy was also extended to use halophenols as precursors and allyl MIDA ester as organoboronic

reagent, in order to evaluate if these phenolic precursors coupled effectively using water as solvent.

We used our methodology that involves phosphine-free, supported Pd catalyst entrapped in a polyurea matrix and microwave as heating source, with potential for both economic and environmental advantages. Pd EnCat™ 30 has proven to be effective as recyclable catalysts for use in Suzuki type cross-coupling reactions and do not require expensive and toxic phosphines as co-ligands.[7-9] Secondly, microwave irradiation has emerged as a powerful technique for promoting a variety of chemical reactions.[10] Reactions performed under microwave irradiation conditions benefit from significant enhancements in rate and product yields. In recent years, we have developed some new methods for the efficient synthesis of heterocyclic compounds under microwave irradiation.[5,11,12]

Our continued interest in PdEnCat chemistry have led us to investigate the catalytic activity of PdEnCat30 towards C–C cross-coupling reaction. Herein we report the PdEnCat-catalyzed Suzuki cross-coupling reaction between organoboronic MIDA ester and (hetaryl)aryl halides, under microwave irradiation in the absence of ligands, and under mild and environmentally friendly conditions.

RESULTS AND DISCUSSION

C–C Cross-Coupling Reaction

In a first approach, to develop an optimal catalytic system for the Suzuki cross-coupling reactions, various parameters such as temperature, % catalyst, solvent, base and reaction

time were studied, always under microwave irradiation and without using any ligand. As a part of our ongoing research programme in the development of new ecofriendly protocols, the coupling reaction was studied initially using only ethanol as solvent, K_2CO_3 (3 mmol) as base and PdEnCat30™ (10 mol%) as the catalyst, under microwave irradiation (10-20 min at 100 °C to 140 °C). We isolated the Suzuki product in very low yields, the majors products being the homocoupling and the dehalogenation products, alongside with the formation of black palladium. However, yields increased substantially when significant volumes of water were added to the reaction.

Then, for the optimization of our conditions we selected as model the reaction of 4-bromoacetophenone with 2-formylphenylboronic acid MIDA (1.5 mmol). Table 1 shows the effect of different volumetric ratios of solvent and loadings of the catalyst used on the Suzuki coupling between 2-formylphenylboronic acid MIDA and 4-bromoacetophenone. We have used some EtOH:H_2O mixtures (1:1, 2:1, 3:1, 4:1, 6:1, 8:1) and different decreasing amounts of Pd EnCat30™ (1, 2.5, 6, 8 and 10%mol, respectively) with an irradiation time of 10 min, at 120 °C.

In Table 1 it is possible to see that the highest conversion to **1a** was observed using EtOH:H_2O in a 4:1 ratio, probably because it better dissolves both organic reagents and the inorganic base, and 6 mol% catalyst, together with the lowest occurrence of the debrominated or homocoupling side products, while the formation of black palladium was not observed. The isolated yield of Suzuki-product **1a** was 95%. In the other ratios tested, the coupling reactions were accompanied by different extents of

hydrodehalogenation or homocoupling, and in some these cases the formation of black palladium was observed. In order to investigate the role of the base and using the model selected, four bases were investigated, namely KF, K_3PO_4, $NaHCO_3$ and K_2CO_3. The results show that K_2CO_3 was the optimum base under microwave irradiation at 120°C. (Table 2)

Recycling investigations (Table 3) were carried out using PdEnCat30™ 6 mol% in the reaction between 2-formylphenylboronic acid MIDA and 4-bromoacetophenone. The heterogeneous catalyst allows efficient recycling by filtration. Indeed, the catalyst was reused for three cycles, and after each run the reaction mixture was centrifuged and the liquid mixture was decanted. The residual solid catalyst was employed again with fresh solvent, substrates and base. The results showed that when the catalyst was recycled 3 times at the reaction conditions established no significant loss of activity or yield occurred. During these reactions, the formation of black palladium was not observed (Table 3).

Microwave heating has been reported to increase reaction rates as well as often to avoid by-products formation as compared with conventional heating.[13–15] Therefore, Suzuki cross-coupling reactions were also attempted under microwave irradiation using other (*orto- meta- para-*)-aryl halides and heteroaryl halides in the ethanol/H_2O (4:1) mixture.

A comparative analysis of the results in Table 1 and 4, allows to conclude that microwave heating dramatically improves the rate of reaction for all reactions performed,

corresponding sometimes even to a 54-fold increase in reaction rate, compared with conventional heating. Interestingly, microwave heating appears to be particularly beneficial in the cross-coupling of *p*-bromoacetophenone and *p*-iodoanisol with significantly improved conversions as compared with 1-bromo-4-methylbenzene (*p*-bromotoluene). (Table 4, entries: 1, 4, 5).

Our studies on the Suzuki reaction coupling were performed using aryl halides bearing both electron-donating and electron-withdrawing groups and the results were comparable. Therefore, under the defined conditions, reactions did not show any sensitivity to electronic effects; for example, 4-iodoanisole or 4-chloro-3-methylphenol has a comparable result to 4-bromobenzaldehyde or 1-iodo-4-nitrobenzene (Table 4, entries: 2, 3, 4, 10).

In Table 4 are shown the data obtained using the catalytic system for Suzuki cross-coupling reaction of different types of aryl bromides, iodides and less reactive aryl chlorides, using three different boronic acid MIDA esters under microwave irradiation at 120 °C.

Our protocol showed that the reaction successfully occurred without any phosphine ligand to give the corresponding Suzuki coupling products **1a–x** in good to excellent yields. Also, the Suzuki coupling reaction of aryl halides with 2-formylphenylboronic acid MIDA ester and 6-methoxy-2-pyridylboronic acid MIDA ester or allylboronic acid MIDA ester, respectively, occurred efficiently to provide the corresponding products. For

example, 2-bromobenzaldehyde and 4-chloro-3-methylphenol reacted with 2-formylphenylboronic acid MIDA ester to yield in 88% (**1i**) and 84% (**1j**), respectively. 1-Iodo-4-nitrobenzene and 4-bromobenzaldehyde reacted with 6-methoxy-2-pyridylboronic acid MIDA ester to yield in 84% (**1m**) and 90% (**1o**), respectively, and 4-chlorophenol reacted with allylboronic acid MIDA ester to yield in 75% (**1w**).

With the optimized reaction conditions in hand, the coupling reactions of a variety of hetaryl halides and 2-formylphenylboronic acid MIDA ester or 6-methoxy-2-piridylboronic acid MIDA ester were carried out. As shown in Table 4, significant structural variations in the (hetero)aryl halides components were well tolerated and afforded the corresponding heteroaromatic functionalized compounds (**1f-h**, **1q-v**) in good yields.

Bipyridines have been extensively used.[16]. Hosseini *et al*. and Sadimenko's showed their use as organometallic ligands.[17,18] In particular, the 2,4-, 2,2-, and 2,3-bipyridyl such as collismycins and cytosine, have been used as antibiotics and to help with smoking cessation, and 4,6-diaryl-2,4'-bipyridines for cancer treatment.[19] (Scheme 1)

Typically, the 2-pyridyl–boron bond is exquisitely sensitive to protodeborylation, making most 2-pyridyl boranes unstable. In contrast, 2-pyridyl *N*-methyliminodiacetic acid (MIDA) boronate (Table 4) is the first 2-pyridylborane derivative that is both air stable and commercially available.[20]

The coupling reactions of representative heteroaromatic halides (Entry 17-22) with 6-methoxypiridylboronic acid MIDA ester proved to be effective with our new protocol using microwave. It was also observed that the chemical yields of bipyridines and 2-thienyl-pyridine systems from the Suzuki-Miyaura coupling reaction were 77-87% after 10-min when the microwave irradiation were used. Furthermore, in a first approach to produce allyl-substituted phenolic, allylphenols **1w** and **1x** were prepared by reaction of 4-chlorophenol or 2-iodo-4-nitrophenol and allylboronate acid MIDA ester respectively. The results showed that the Suzuki products were obtained in good yields (75% and 70% respectively). It is important to note that our methodology opens a new possibility for the preparation of allylphenols without using excessive heating and excessive reaction times via the well-known Claisen-rearrangement, and can be used in the synthesis of allylphenols for pharmaceutical industry such as alprenolol, and the Eugenol-Niacin hybrids[21,22]. (Figure 1)

Moreover, further experiments conducted in our laboratory showed that the reaction can be scaled up without compromising the yield. The reaction of 4-bromoacetophenone, 4-iodoanisol, 4-bromotoluene, 4-bromopyridine and 2-bromothiophene, respectively, with 2-formylphenylboronic acid MIDA and 6-methoxy-2-piridylboronic acid MIDA ester (1.5 mmol) were repeated on a 3 mmol scale (Table 4, entry: 1,4,5,6,8,14,16,20,22) using microwave irradiation. The isolated yield of products were **1a** (93%), **1d** (81%), **1e** (79%), **1f** (92%), **1h** (84%), **1n** (77%), **1p** (85%), **1t** (80%) and **1v** (73%), respectively, almost identical to that when the reactions were performed on a 1 mmol scale.

CONCLUSIONS

In summary, we have developed a general, rapid and eco-friendly method for the synthesis of functionalized biaryls (**1a-e**, **1i-l**), (hetaryl)aryls (**1f-h**, **1m-p**), (hetaryl)pyridines (**1q-v**) and allylphenols (**1w**, **1x**) from (heteroaryl)aryl halides and three *N*-methyliminodiacetic acid (MIDA) boronates by using microwave-assisted Suzuki cross-coupling reactions mediated by the Pd-encapsulated PdEnCat^{TM} 30. The reactions are applicable to a wide range of substrates, avoiding the use of toxic eco-unfriendly solvents. Furthermore, most of the reactions involved are efficient, giving the desired compounds in high yields within short reaction time. Our new protocol could be directed to the synthesis of compounds with potential biological activity. In general, our methodology has the advantage of low catalyst loadings, rapid reaction times, ease of reaction (no need for anaerobic conditions), and the most important, the reactions occur without presence any phosphine-ligand and in aqueous medium or in water.

EXPERIMENTAL

General Procedure For The Microwave-Assisted Suzuki Reactions.

In a 10 mL glass tube were placed halide (1.0 mmol), 2-formylphenyl or 2-pyridyl MIDA boronate (1.5 mmol) or allyl MIDA boronate, K_2CO_3 (3.0 mmol), Pd EnCat30 (6 mol %) and ethanol:H_2O (4:1 v/v) or water, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. The temperature being ramped from rt to 120 °C or 135°C. Once the reaction temperature was reached, the reaction mixture was held at this temperature for 10-18 min. After the mixture was allowed to cool to room temperature, the reaction vessel was opened and the contents were poured into a

separating funnel. Water and ethyl acetate (3 x10 mL) were added. The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The organic residue was adsorbed onto silica gel, and then purified by column flash chromatography (hexane/ethyl acetate as eluent) to afford the desired product **1a-x**. The biaryls, bipyridines or allylphenols prepared are known compounds.[23-45] The products were confirmed by comparing the ^{1}H NMR and mass spectral data with authentic samples reported in the literature.

SUPPLEMENTAL MATERIAL

Full experimental procedures and characterization data for all synthesized compounds for this article can be accessed on the publisher's website.

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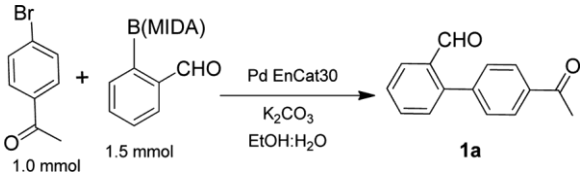
Table 1. Optimization of solvent and catalyst loading for Suzuki cross-coupling reaction under microwave irradiation.[a]

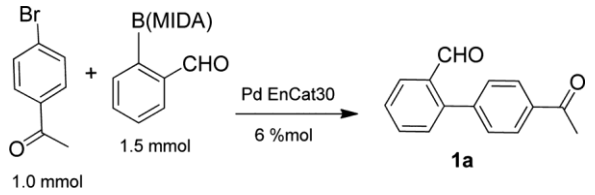


Entry	Volumetric ratios EtOH:H_2O	Catalyst Loading (mol%)	Suzuki-coupling product (**1a**) % yield[b]
1	1:1	10 %mol	60
2	2:1	10 %mol	68
3	3.1	10 %mol	72
4	4:1	10 %mol	82
5	4:1	8 %mol	89
6	**4:1**	**6 %mol**	**95**
7	4:1	2.5 %mol	77
8	4:1	1 %mol	74
9	6:1	10 %mol	70
10	8:1	10 %mol	67

[a] 3.0 equiv of K_2CO_3 were used, microwave 120°C.

[b] isolated yield

Table 2. Optimization of base for Suzuki cross-coupling reaction.[a]

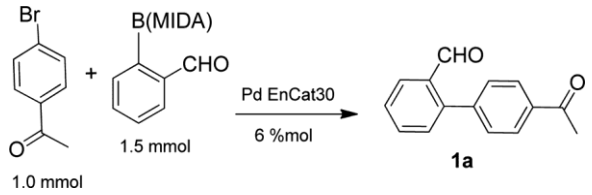


Entry	Base	Suzuki-coupling product (**1a**) % yield[b]
1	KF	83
2	K_3PO_4	80
3	$NaHCO_3$	70
4	K_2CO_3	95

[a] Reaction conditions: **1a** (1.0 mmol), phenylboronic acid MIDA (1.5 mmol), base (3.0 mmol), EtOH:H_2O (4:1).

[b] microwave, 10 min, 120°C

Table 3. Recycling investigations.[a]

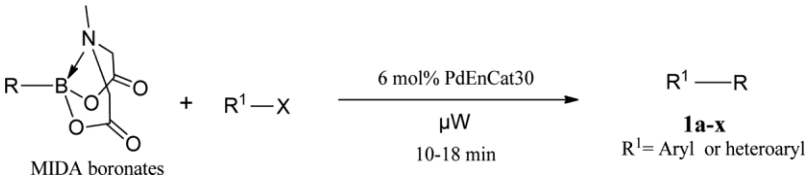


Entry	Cycle	% yield[b] (**1a**)
1	1	92
2	2	87
3	3	81

[a] Reaction conditions: **1a** (1.0 mmol), phenylboronic acid MIDA (1.5 mmol), K_2CO_3 (3.0 mmol), EtOH:H_2O (4:1).

[b] microwave, 10 min, 120°C

Table 4. Suzuki coupling reaction between (het)aryl halides and 2-formylphenylboronic MIDA ester.[a]



Entry[c]	R^1X	R-MIDA boronate	Reaction time	Yield[b] (%)
1	4-bromoacetophenone	2-formylphenyl-MIDA	10 min.	**1a** (95)
2	1-iodo-4-nitrobenzene	=	10 min.	**1b** (89)
3	4-bromobenzaldehyde	=	10 min.	**1c** (97)
4	4-iodoanisole	=	10 min.	**1d** (83)
5	1-bromo-4-methylbenzene	=	10 min.	**1e** (80)
6[d]	4-bromopyridine	=	10 min.	**1f** (95)
7	3-bromopyridine	=	10 min.	**1g** (95)
8	2-bromothiophene	=	10 min.	**1h** (90)
9	2-bromobenzaldehyde	=	10 min.	**1i** (88)
10[e]	4-chloro-3-methylphenol	=	16 min.	**1j** (84)[f]
11[e]	2-bromo-5-hydroxybenzaldehyde	=	16 min.	**1k** (75)[f]
12[e]	2-iodo-4-nitrophenol	=	16 min.	**1l** (70)[f]
13	1-iodo-4-nitrobenzene	6-methoxypiridyl-MIDA	10 min.	**1m** (84)
14	4-bromoacetophenone	=	10 min.	**1n** (81)
15	4-bromobenzaldehyde	=	10 min.	**1o** (90)

16	4-iodoanisole	=	10 min.	**1p** (87)
17	2-bromopyridine	=	10 min.	**1q** (80)
18	2-chloro-5-nitropyridine	=	10 min.	**1r** (78)
19	3-bromopyridine	=	10 min.	**1s** (87)
20[d]	4-bromopyridine	=	10 min.	**1t** (81)
21	2-bromoquinoline	=	10 min.	**1u** (84)
22	2-bromothiophene	=	10 min.	**1v** (77)
23	4-chlorophenol	allyl-MIDA	18 min.	**1w** (75)[f]
24	2-iodo-4-nitrophenol	=	18 min.	**1x** (70)[f]

[a] Reaction conditions: halide (1.0 mmol), 1.5 equiv of MIDA boronate, 6 mol % Pd EnCat30, 3.0 equiv of K_2CO_3, 0.1 M in 4:1 ethanol/H_2O.

[b] isolated yield.

[c] Cross-couplings were run at 120°C.

[d] 4-bromopyridine hydrochloride was used.

[e] pure water as solvent was used.

[f] cross-couplings were run at 135°C.

Scheme 1. Structure of some bipyridines of biological interest that can be prepared using our protocol.

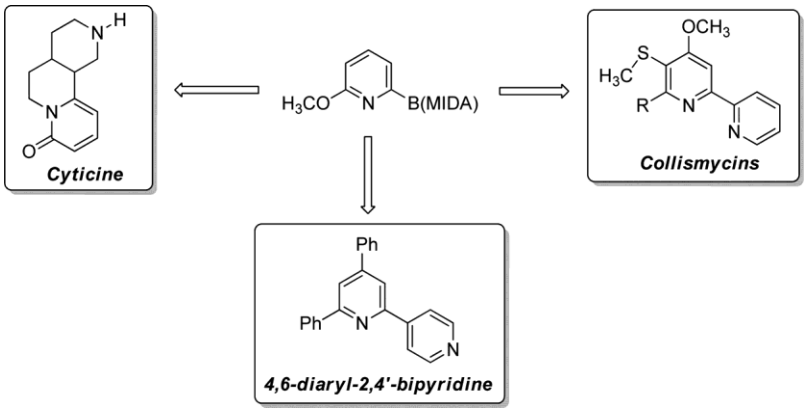
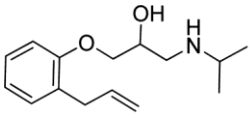
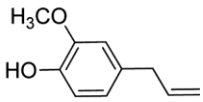


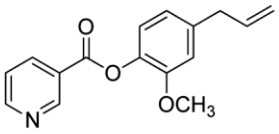
Figure 1. Some allyl-substituted phenolic compounds of medicinal interest that can be prepared using our protocol.



Alprenolol
Antihypertensive agent



Eugenol



Niacin-Eugenol hybrid
Potential Alzheimer's drug