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Expedient carbonylation of aryl halides in aqueous or neat condition

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ABSTRACT

An expedient and versatile, microwave-assisted procedure for the carbonylation of aryl halides with boronic acids, alcohols or amines in water or under neat conditions has been developed. The reaction is catalyzed by fluorous, oxime-based palladacycle **1** that shows an excellent recyclable property and low levels of Pd leaching. To demonstrate the usefulness of the protocol, we applied it to the preparation of compounds of pharmaceutical interest, including a precursor of the reverse transcriptase inhibitor, niacin, benzocaine and butamben.

1. Introduction

Palladium-catalyzed carbonylation reactions are a versatile tool for the synthesis of amides, esters, ketones, carbamates, etc., which are important functional groups found in dyes, pharmaceuticals and other industrial products. These reactions require the insertion of CO into the substrate and are typically carried out with carbon monoxide gas as it is readily available.[1–5] During these reactions, a constant stream of carbon monoxide gas has to be supplied into the reaction system whose reaction times could range from 1 to 60 h, which reduces the expediency in combinatorial chemistry and drug-discovery.[3,6–9] To provide a more expedient reaction, molybdenum hexacarbonyl, $Mo(CO)_6$, has been used as a solid carbon monoxide source.[10] With $Mo(CO)_6$, the carbon monoxide gas is released in situ during the reaction thus making it possible for the reaction to be carried out in a closed vessel under microwave irradiation.[11–14] The ease of handling makes $Mo(CO)_6$ an appealing carbon monoxide source for lab-scale synthesis where parallel synthesis methods are favoured especially in medicinal chemistry applications and could be beneficial to high-throughput applications in small-scale protocols where the introduction of gaseous reactants is problematic.

Recently, there has been a growing trend of performing microwave-assisted C–C bond forming reactions in aqueous medium.[13] To this effort, we have previously developed a fluorous oxime-based palladacycle **1** (Fig. 1), which was shown to be a very efficient and versatile precatalyst for a wide range of carbon–carbon bond formation reactions (Suzuki–Miyaura, Sonogashira, Stille, Heck, Glaser-type and Kumada) in either aqueous or organic medium under microwave irradiation.[15–17] In addition, palladacycle **1** possessed an excellent recyclable property and produces only low levels of Pd leaching. These features are important for medicinal chemistry applications as the tolerance for heavy metal impurities is very low. To date, carbonylative Suzuki–Miyaura coupling and alkoxycarbonylation reactions with $Mo(CO)_6$ has been only carried out in organic solvents.[18,19] Therefore, in this study we further extend the use of palladacycle **1** and evaluate its performance in the microwave-assisted carbonylative Suzuki–Miyaura coupling, alkoxycarbonylation and aminocarbonylation reactions with $Mo(CO)_6$ in aqueous medium. To demonstrate the usefulness of the protocol, we applied it to the preparation of compounds of pharmaceutical interest, including a precursor of the reverse transcriptase inhibitor, niacin, benzocaine and butamben.

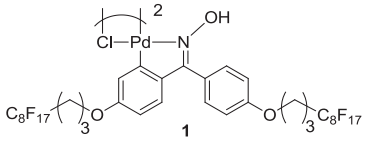

Fig. 1. Structure of fluorous palladacycle **1**.

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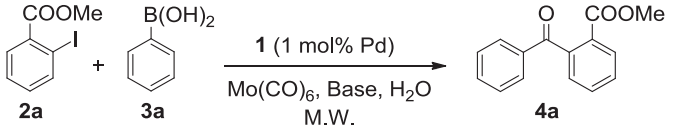
0040-4020/

2. Results and discussion

2.1. Carbonylative Suzuki–Miyaura coupling of aryl halides and arylboronic acids

Initial assessment of the carbonylative Suzuki-Miyaura reaction for the formation of asymmetrical biaryl ketones was conducted using methyl 2-iodobenzoate **2a** and phenylboronic acid **3a** with palladacycle **1** as precatalyst, *N*,*N*-diisopropylethylamine (DIPEA) as base, water as solvent and $Mo(CO)_6$ as the carbon monoxide source under microwave irradiation at 130 °C. The desired biaryl ketone **4a** was obtained after 20 min in 72% yield (Table 1, entry 1). To optimize the reaction, we varied the base and found that the reaction proceeded most efficiently with DIPEA (entries 1–6). Next, we investigated the effect of the amount of palladacycle **1** on the reaction and found that 1 mol % Pd provided the best yield of the desired product (entries 1, 7–9).

Table 1
Reaction condition study using methyl 2-iodobenzoate **2a** and phenylboronic acid **3a**[a]



2a 3a 4a

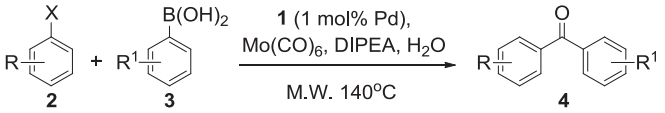
Entry	Base	Temp (°C)	Time (min)	Yield of **4a**[b] (%)
1	DIPEA	130	20	72
2	DBU	130	20	0
3	TEA	130	20	47
4	K_2CO_3	130	25	55
5	KOAc	130	25	35
6	Pyridine	130	20	13
7[c]	DIPEA	140	20	18
8[d]	DIPEA	130	25	62
9[e]	DIPEA	130	13	68
10	DIPEA	120	35	68
11	DIPEA	140	12	73
12[f]	DIPEA	140	12	69
13[g]	DIPEA	140	17	70
14[h]	DIPEA	140	15	57
15[i]	DIPEA	140	12	64
16[j]	DIPEA	140	12	56
17[k]	DIPEA	140	12	63
18[l]	DIPEA	140	12	73

[a] Reaction condition: methyl 2-iodobenzoate (0.6 mmol), phenylboronic acid (2.5 equiv), **1** (1 mol % Pd), $Mo(CO)_6$ (1.5 equiv), base (3.0 equiv), H_2O (1.0 mL).
[b] Isolated yields.
[c] Absence of palladacycle **1**.
[d] Pd (0.5 mol %).
[e] Pd (2 mol %).
[f] Reaction concentration 1.0 M.
[g] Reaction concentration 0.3 M.
[h] Phenylboronic acid (1.5 equiv).
[i] Phenylboronic acid (2.0 equiv).
[j] $Mo(CO)_6$ (0.5 equiv) was used.
[k] Base (2.0 equiv) was used.
[l] TBAB (1.0 equiv) was added.

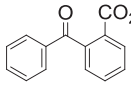
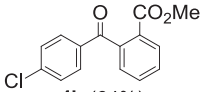
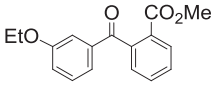
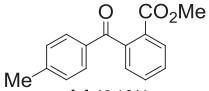
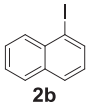
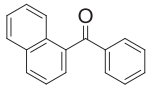
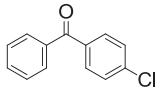
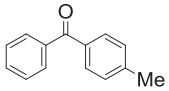
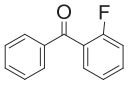
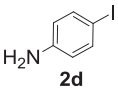
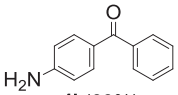
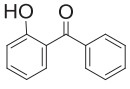
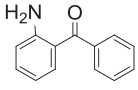
We have also examined the effect of temperature on the reaction. Lowering the temperature to 120 °C lengthened the reaction time and provided compound **4a** in a slightly lower yield whilst increasing the temperature to 140 °C enabled the reaction to be completed in half the time and provided compound **4a** in comparable yield (entries 10 and 11). Other variations, like changing the concentrations of **2a**, **3a**, $Mo(CO)_6$ or base or adding tetra-*n*-butylammonium bromide (TBAB) as an additive to the reaction did not provide any significant improvement in the yield of compound **4a** (entries 12–18).

The generality of the reaction condition was examined using various aryl halides and arylboronic acids, which gave the desired biaryl ketone in moderate to good yields (Table 2). The aqueous protocol was compatible with aryl halides bearing acidic protons (entries 9–11),

Table 2
Carbonylative Suzuki–Miyaura coupling of aryl halides and boronic acids[a]



2 3 4
(X= I or Br)

Entry	Aryl halide	R^1	Time (min)	Product (yield[b])
1	 **2a**	**3a**: H	12 (12 h[c])	 **4a** (73%,60%[c], 51%[d])
2		**3b**: 4-Cl	15	 **4b** (64%)
3		**3c**: 3-OEt	12	 **4c** (83%)
4		**3d**: 4-Me	15	 **4d** (91%)
5	 **2b**	**3a**	10 (12 h[c])	 **4e** (80%,83%[c])
6	 **2c**	**3b**	20 (12 h[c])	 **4f** (76%,81%[c])
7		**3d**	20 (12 h[c])	 **4g** (84%,79%[c])
8		**3e**: 2-F	20	 **4h** (73%)
9	 **2d**	**3a**	15	 **4i** (60%)
10	 **2e**	**3a**	20	 **4j** (54%)
11	 **2f**	**3a**	12	 **4k** (66%)