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A rapid, solvent-free, ligandless and mild method for preparing aromatic ketones from acyl chlorides and arylboronic acids via a Suzuki–Miyaura type of coupling reaction

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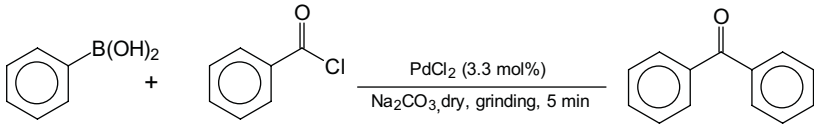
Abstract—Aromatic ketones were synthesized via a palladium catalyzed cross-coupling reaction of boronic acids with acyl chlorides in the presence of Na_2CO_3 at room temperature under solvent-free conditions. The ligand-free and mild reaction conditions, highly rapid reaction rate and good to excellent yields are important features of this method.

The conversion of carboxylic acid derivatives into aryl ketones is an important transformation often employed in the synthesis of complex organic molecules such as natural products and pharmaceuticals.[1] Many methods have been developed for the synthesis of aromatic ketones. Most common is the Friedel–Crafts acylation of an arene.[2] However, due to limited regioselectivity, the products of this reaction are usually obtained as hard-to-separate isomeric mixtures. Furthermore, the reaction conditions tend to be incompatible with certain functional groups. Alternatively, a variety of aryl metal species can be acylated with a wide range of carboxylic acid derivatives leading to single regioisomers of the desired aryl ketones.[3–5] Palladium-catalyzed cross-coupling reactions between acid chlorides and boronic acids are also important for the regioselective synthesis of ketones.[6–10] However, long reaction times and drastic reaction conditions are disadvantages associated with most of the reported Suzuki cross-coupling methods. Homo-coupling is also an important limitation associated with these methods. Consequently, there remains the opportunity for further development of milder conditions and ligand-free procedures, with increased variation of the component substituents and better yields.

In this communication, we report a rapid, ligand-free and mild protocol for preparing aromatic ketones from

Table 1. Study of the catalytic Suzuki cross-coupling reaction between benzeneboronic acid (1 mmol) and benzoyl chloride (1.5 mmol)

Entry	Catalyst $PdCl_2$ (mol %)	Reaction time (min)	Yield (%)
1	0	60	—
2	0.5	5	20
3	1.0	5	35
4	1.5	5	47
5	2.0	5	50
6	3.0	5	80
7	3.3	5	90
8	4.0	5	90
9	4.0	10	90



Scheme 1.

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Table 2. Palladium catalyzed Suzuki cross-coupling reactions of boronic acids with acyl chlorides

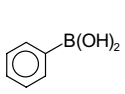
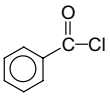
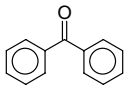
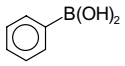
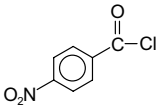
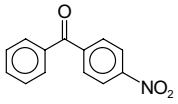
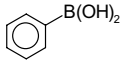
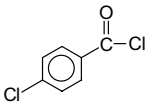
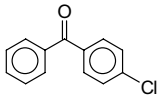
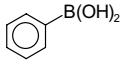
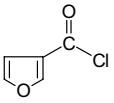
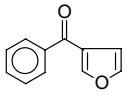
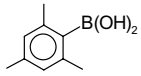
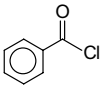
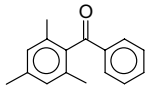
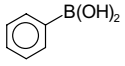
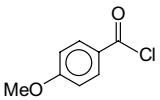
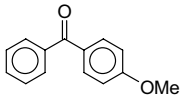
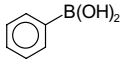
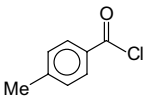
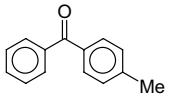
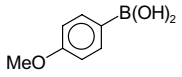
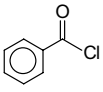
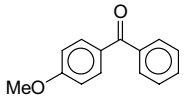
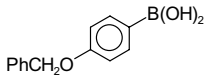
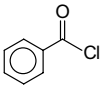
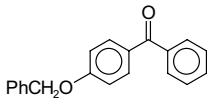
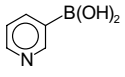
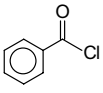
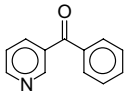
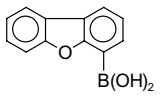
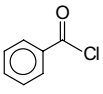
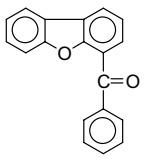
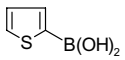
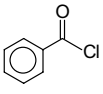
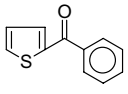
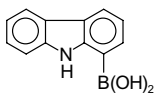
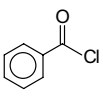
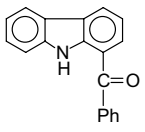
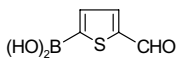
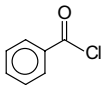
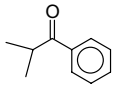
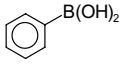
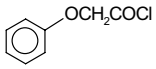
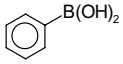
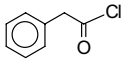
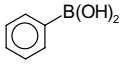
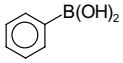
Entry	Arylboronic acid	Acid chloride	Ketone	Time (min)	Yield[a,b] (%)
1				5	90
2				5	82
3				5	80
4				5	78
5				5	80
6				5	90
7				5	88
8				5	92
9				5	92
10				5	90
11				5	95
12				5	95
13				5	93
14				5	90

Table 2 (*continued*)

Entry	Arylboronic acid	Acid chloride	Ketone	Time (min)	Yield[a,b] (%)
15				5	90
16			NR	20	—
17			NR	20	—
18			NR	20	—
19			NR	20	—
20			NR	20	—

NR: No reaction.
[a] Yields of pure isolated products.
[b] Products were characterized by ^{1}H NMR, IR, elemental analysis and by comparison with authentic samples.

acyl chlorides and arylboronic acids under solvent-free conditions (Scheme 1 and Table 2).

The catalytic activity of $PdCl_2$ was investigated with respect to loading. After screening different amounts of the $PdCl_2$ catalyst, we found that 3.3 mol % of $PdCl_2$ worked remarkably well. The results are presented in Table 1.

This study (Table 1) showed that in the absence of catalyst, there was no reaction. The yield of ketone was increased on increasing the amount of catalyst and was found to be optimal with 3.3 mol % of a catalyst.

The generality of this method is indicated by the results presented in Table 2. The recently reported $Pd(PPh_3)_4$ catalyzed synthesis of ketones involved five mole equivalents of $CsCO_3$, elevated temperatures (100 °C) and long reaction times (16 h) under anhydrous conditions and a nitrogen atmosphere.[6] Attempts to couple benzoyl chloride with 2,4,6-trimethylbenzeneboronic acid using the conditions reported by Wright et al.[11] for the Suzuki coupling reaction (CsF, DME) provided the ketone in low yield (19%)[6] whereas the conditions reported by Haddach and McCarthy[6] furnished the corresponding ketone in only a slightly improved yield (50%). In this context, the present methodology was found to be superior as it provided an excellent yield of the corresponding ketone (80%) (Table 2, entry 5) in a very short time (5 min) under mild conditions (25 °C). Similarly, cross-coupling of 4-nitro-, 4-chloro-, 4-methoxy- and 4-methyl-benzoyl chlorides with benzeneboronic acid using the present method furnished excellent yields of ketones as compared to the low yields of the corresponding ketones using Haddach's harsher conditions (100 °C). The method reported by Bumagin and Korolev[10] can be performed only insofar as the acid chloride is not susceptible to water. The low yields of ketones in polar solvents, drastic conditions and hydrolysis of acid chlorides with hydrated base were the limitations associated with a more recently reported method.[8]

Most of the reported Suzuki-coupling reactions for the synthesis of aryl ketones from arylboronic acids and acyl chlorides require the use of a ligand and elevated temperatures.[6–9] However, ligandless palladium species give fast coupling reactions[12] and phosphine related side reactions can be suppressed.[13] Therefore, the present methodology is superior in terms of the excellent yields of ketones under solvent-free, ligand-free and mild conditions in very short reaction times without formation of a trace amount of any biaryls. It is important to note that various aryl (Table 2, entries 1–9), heteroaryl (Table 2, entries 10–14) and aliphatic (Table 2, entry 15) boronic acids underwent smooth cross-coupling with a variety of acyl chlorides under ligandless and solvent-free conditions at room temperature. It is important to mention that aliphatic (Table 2, entries 16–20), even aryloxylalkyl (Table 2, entry 16) and arylalkyl (Table 2, entry 17) acyl chlorides did not couple with aryl boronic acids (Table 2, entries 16–19) even after grinding the reaction mixture for a longer time (20 min) under the present reaction conditions. The reaction is not affected by substituents located either on the boronic acids or on the acyl chlorides, which opens the way to a general synthesis of ketones. Further work on the synthesis of natural chalcones using this novel methodology is under investigation in our laboratory.

Typical procedure: To a mixture of benzeneboronic acid (122 mg, 1 mmol), sodium carbonate (212 mg, 2 mol) and 4-methoxybenzoyl chloride (0.174 ml, 1.5 mmol) in a mortar, palladium chloride (6 mg, 3.3 mol %) was added with continuous grinding with a pestle at 25–30 °C. The reaction was monitored by TLC. After com-

pletion of the reaction, ether (10 ml) was added and the mixture was washed with sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to furnish the crude product, which was further purified by column chromatography (pet. ether/ethyl acetate = 9:1) and the product was characterized from spectroscopic data.[14]

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