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A convenient method for preparing aromatic ketones from acyl chlorides and arylboronic acids via Suzuki–Miyaura type coupling reaction

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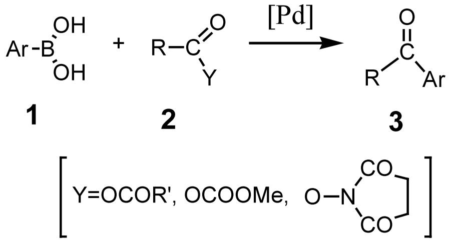
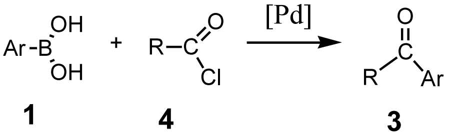
Abstract—Aromatic ketones are synthesized efficiently via palladium-catalyzed cross-coupling reaction of boronic acids with acyl chlorides in the presence of K_3PO_4 hydrate in toluene. This allows the use of aliphatic acyl chlorides as the starting material. Hydrated water plays a significant role as an H_2O source to activate the catalytic system. © 2002 Elsevier Science Ltd. All rights reserved.

Many synthetic methods have been developed for the synthesis of aromatic ketones, which are important building blocks included in a large number of natural products and active pharmaceutical ingredients (APIs). Recently, palladium-mediated cross-coupling between a boronic acid (**1**) and an activated derivative (**2**) of an acid has been reported to be effective for synthesizing functionalized benzophenones (Eq. (1)).[1,2] The activated derivatives (**2**) have to be formed either prior to the reaction or in situ by an activator such as pivalic anhydride or dimethy dicarbonate.



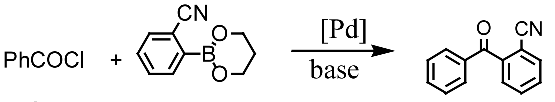
1 **2** **3** (1)

From the point of view that the reaction is performed in a large (or industrial) scale, acyl chlorides (**4**) are preferred as the activated derivative of an acid because they are widely available. Haddach[3] and Bumagin[4] reported the ketone synthesis via palladium-catalyzed cross-coupling of arylboronic acid (**1**) and acyl chloride (**4**) under aqueous conditions (in acetone–water (3:1)) and anhydrous conditions (in toluene), respectively. The former reaction can be performed insofar as the acid chloride is not susceptible to water. The latter conditions required an elevated temperature and a longer reaction time. The yield of the product (**3**) was relatively low (19–80%). Here we wish to report that a hydrated base can accelerate the palladium-catalyzed reaction of **1** with **4** to provide an efficient route leading to symmetrical and asymmetric ketones (Eq. (2)).



1 **4** **3** (2)

Since we needed *o*-cyanobenzophenone derivatives that are useful synthetic intermediates for some pharmaceuticals, our initial attempt was to couple benzoyl chloride with 2-(1,3,2-dioxaborinan-2-yl) benzonitrile (**5**) that was selected instead of (*o*-cyanophenyl)boronic acid. This is because boronic acids are known to undergo intermolecular condensation under anhydrous conditions.[5] However, we obtained the expected product (**3a**) in 26% yield under the anhydrous conditions reported by Haddach (Cs_2CO_3, toluene). Under Bumagin's aqueous conditions, **3a** was formed in 23% yield (Eq. (3)).



4a **5** **3a** (3)

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Table 1. Palladium-catalyzed reaction of benzoyl chloride (**4a**) with **5**[a]

Entry	Base	Solvent	Yield of **3a** (%)[b]
1	Na_2CO_3	Toluene	0
2	$Na_2CO_3 \cdot H_2O$	Toluene	2
3	KF	Toluene	7
4	$KF \cdot 2H_2O$	Toluene	25
5	K_3PO_4	Toluene	11
6	$K_3PO_4 \cdot nH_2O$[c]	Toluene	70 (70)[e]
7	$K_3PO_4 \cdot nH_2O$[c]	NMP	3
8	$K_2CO_3 \cdot 1.5H_2O$	Toluene	11
9	$K_3PO_4 + 1.5H_2O$[d]	Toluene	53

[a] For typical reaction conditions, see Ref. 7.
[b] Yield was calculated by HPL assay of reaction mixture.
[c] Actual number of '*n*' was 1.5 in this lot.
[d] Water (1.5 mol equiv. to K_3PO_4) was added to the reaction system..
[e] Isolation yield after column chromatograph.

In our previous report, the Suzuki–Miyaura reaction of **5** with an aryl bromide was shown to be promoted by water.[6] Hence, we chose the hydrated bases that are commercially available, insoluble in organic solvents, and weak in basicity. With these weak bases in organic solvents, the decomposition of acyl chlorides and the boronate (**5**) would be suppressed. As summarized in Table 1, the addition of hydrated bases gave better results (entries 2, 4, 6 versus entries 1, 3, 5, respectively). Among the hydrated bases examined herein, K_3PO_4 hydrate afforded the best yield in toluene (entry 6).

The use of a polar solvent (1-methyl-2-pyrrolidinone: NMP) resulted in lowering the yield (entry 7). In this case, the formation of benzoic acid was detected by HPLC analysis. It is likely that benzoyl chloride is easily hydrolyzed with a hydrated base that is more soluble in NMP than in toluene. It should be noted that the addition of water to anhydrous K_3PO_4 lowered the yield (entry 9). This is largely due to the characteristic tendency of hygroscopic bases to aggregate and solidify in the presence of additional water, as reported previously.[6] This is an important factor to be considered in realizing reproducibility in large-scale synthesis.

Next, we applied the optimized conditions to the preparation of various ketones from boronic acids (**1**) and acyl chlorides (**4**). To our surprise, various ketones were formed in from good to excellent yields as summarized in Table 2. Although K_3PO_4 hydrate was used, aliphatic acid chlorides react smoothly to afford the corresponding ketones in good yields (entries 7 and 8). Under the present heterogeneous conditions, competitive hydrolysis of the acyl chloride is minimized. Probably, the reaction takes place at the surface of the solid base and the amount of free water in toluene is controlled to be minimal. For the synthesis of an *ortho*-substituted benzophenone, the use of the corresponding *ortho*-substituted phenylboronic acid gave a better yield (entry 11 versus entry 4).

The reaction mechanism is thought to be the same as that of the well-established Suzuki–Miyaura cross-coupling reaction, in which water plays a significant role as an activator for boronic acid and/or palladium catalyst.[8] In the present reaction using K_3PO_4 hydrate under heterogeneous conditions, it is concluded that the hydrated water cannot hydrolyze the acyl chloride, but activates the boronic acid. In entry 2, the yield of the ketone decreased to 66% when $Pd(OAc)_2$–PPh_3 was used.

In summary, palladium-catalyzed cross-coupling reaction of boronic acids with acid chlorides was achieved by using K_3PO_4 hydrate as a base to afford symmetrical and asymmetric ketones in good to excellent yields. The concept employed herein seems to be applicable to the Suzuki–Miyaura cross-coupling reactions using various moisture-sensitive starting materials. Further studies on the mechanism and the scope of this reaction are in progress.

Table 2. Palladium-catalyzed reaction of acyl chlorides (**4**) with boronic acids (**1**) in the presence of K_3PO_4 hydrate

Entry	R	Ar	Temp. (°C)/time (h)	Products	Yield (%)[a]
1	Phenyl	Phenyl	110/4	Benzophenone	91
2	4-Tolyl	Phenyl	110/4	4-Methylbenzophenone	95
3	3-Tolyl	Phenyl	110/4	3-Methylbenzophenone	94
4	2-Tolyl	Phenyl	110/4	2-Methylbenzophenone	82
5	4-Methoxyphenyl	Phenyl	110/4	4-Methoylbenzophenone	90
6	4-Nitrophenyl	Phenyl	110/4	4-Nitrobenzophenone	70
7	Ethyl	Phenyl	80/4	Propiophenone	71
8	Methyl	Phenyl	40/6	Acetophenone	68
9	Phenyl	4-Tolyl	110/4	4-Methylbenzophenone	97
10	Phenyl	3-Tolyl	110/4	3-Methylbenzophenone	91 (90)[b]
11	Phenyl	2-Tolyl	110/4	2-Methylbenzophenone	95

[a] Yield was calculated by HPL assay of the reaction mixture.
[b] Isolation yield after column chromatograph.

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7. *Typical procedure*: To a mixture of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (224 mg, 1.2 mmol), dicholorobis-(triphenylphosphine)palladium (14 mg, 0.02 mmol) and hydrated K_3PO_4 (360 mg, 1.5 mmol) in toluene (5 mL) under nitrogen was added benzoyl chloride (141 mg, 1.0 mmol). The reaction mixture was heated at 110°C for 4 h and diluted with toluene (10 mL). The solution was washed successively with a saturated solution of sodium bicarbonate, water, and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting material was purified by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) to give 2-cyanobenzophenone (145 mg, 70%) identical with authentic material purchased from Aldrich.
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