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A New Method for the Synthesis of Ketones: The Palladium-Catalyzed Cross-Coupling of Acid Chlorides with Arylboronic Acids

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Abstract: The cross-coupling reaction of acid chlorides with arylboronic acids, using catalytic amounts of $Pd(PPh_3)_4$ and five equivalents Cs_2CO_3, under anhydrous conditions provides a new method for the synthesis of ketones in good to moderate yields.

Keywords: Boron and compounds; Ketones; Palladium and compounds: Suzuki reactions.

The Suzuki coupling reaction provides a general method for the formation of carbon-carbon single bonds between boronic acids and alkenyl or aryl halides. Reactions generally proceed in good yield for the synthesis of a wide variety of biphenyl and styrene derivatives.[1] It was of interest to us to explore the condensation of arylboronic acids with acid halides to form ketones since this would be a new method to this important class of compounds. This proposed method would also provide a convenient route to ketones, since a number of organoboronic acids and acid chlorides are commercially available. Miyaura, Suzuki and co-workers have reported a palladium-catalyzed cross-coupling of arylboronic acids with aryl halides and triflates or benzyl halides under an atmosphere of carbon monoxide to prepare benzophenones or aryl benzyl ketones, respectivly.[2] Synthesis of ketones from organometallic reagents and acid chlorides or esters often proceeds in low yield because of the addition of the organometallic reagent to the ketone to form tertiary alcohols.[3] Although the palladium-catalyzed coupling reaction of acid chlorides with organotin reagents has been demonstrated to be an efficient method to form ketones in high yield,[4] organotin reagents are toxic. The Suzuki coupling reaction is generally carried out as a two-phase palladium-catalyzed reaction in ethanol, toluene and water.[5] These conditions would not be suitable for the coupling of acid chlorides with boronic acids. However, it was recently reported that anhydrous CsF can substitute for aqueous bases in the Suzuki coupling reaction performed in a variety of solvents under anhydrous conditions.[6] Herein we reported the first palladium-catalyzed coupling of organoboronic acids with acid chlorides that proceeds under anhydrous reaction conditions (Scheme 1).

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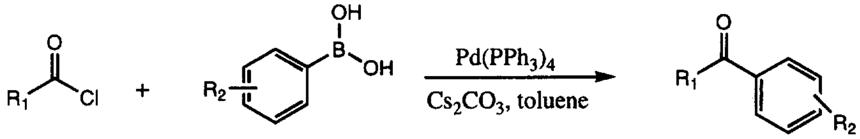
Scheme 1

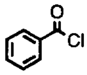
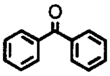
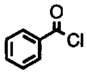
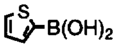
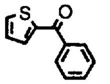
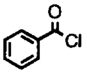
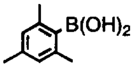
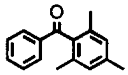
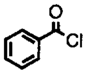
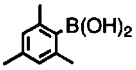
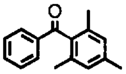
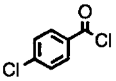
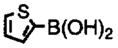
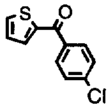
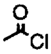
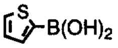
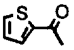
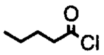
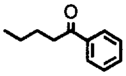
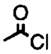
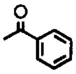
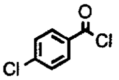
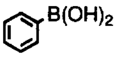
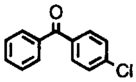
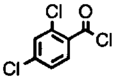
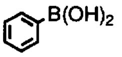
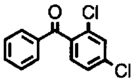
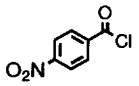
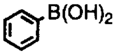
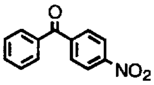
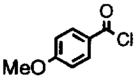
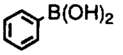
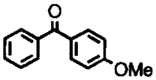
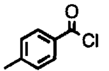
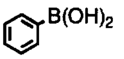
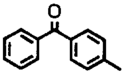
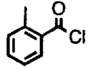
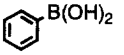
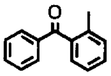


Initial attempts to couple acid chlorides with arylboronic acids using the conditions reported by Wright and co-workers[6a] for the Suzuki coupling reaction (CsF, DME) provided ketones in low yield (entry 3). Increasing the amount of catalyst to 10 mol % did not improve the yield. Substitution of toluene for DME as the reaction solvent failed to give ketones, which was attributed to the insolubility of CsF. Recently, Buchwald et al. reported the palladium(0) coupling of amines and aryl bromides using Cs_2CO_3 as the base.[7] We applied these conditions to the coupling of arylboronic acids and acid chlorides using $Pd(PPh_3)_4$ as the catalyst. The best results were obtained with 5 mol % of palladium catalyst and 5 equivalents of Cs_2CO_3 in toluene. This reaction was studied with several acid chlorides and boronic acids and provided biaryl ketones and acetophenones in good yields (Table 1). Deletion of the $Pd(PPh_3)_4$ catalyst from the reaction mixture for entry 9 (Table 1) yielded no 4-chlorobenzophenone, confirming the requirement for a palladium(0) catalyst. For the synthesis of the acetophenones, (entries 6-8) the reaction mixtures required extensive flushing with nitrogen (15 minutes) before the addition of 3 equivalents of acid chloride for optimum yields. The synthesis of benzophenones required only one to two equivalents of acid chloride and complete removal of oxygen was not as critical. An illustrative example is as follows:

To a mixture of phenylboronic acid (32 mg, 0.26 mmole) and anhydrous cesium carbonate (222 mg, 0.65 mmol) in anhydrous toluene (5 mL) under nitrogen, was added tetrakis(triphenylphosphine) palladium(0) (4 mg) followed by benzoyl chloride (70 mg, 57.8 μL, 0.5 mmol). The reaction mixture was heated at 100° C for 16 hours and diluted with ethyl acetate (20 mL). The solution was washed successively with water, a saturated solution of sodium bicarbonate, and brine, dried over sodium sulfate and concentrated in *vacuo*. The resulting material was purified by preparative TLC (silica gel, 1:9 ethyl acetate–hexanes) to give benzophenone (35 mg, 80%) identical with authentic material from Aldrich; mp 47-49 °C; ^1H NMR ($TMS/CDCl_3$): 7.48 (t, J = 7.5 Hz, 4H); 7.59 (t, J = 7.5 Hz, 2H); 7.81 (d, J = 7.5 Hz, 4H).

Thus, reaction conditions developed for this facile synthesis of ketones tolerate the use of acid chlorides in contrast to the standard Suzuki reaction protocol.[5] It is important to note that the cross-coupling of the arylboronic acids and acid chlorides were not affected by *ortho* substituents or electronic effects on either the aryl acid chlorides or boronic acids. The yields for the *para* substituted isomers were only slightly better than the corresponding *ortho* isomers (entries 9 vs. 10 and 13 vs. 14). Good yields of ketones were obtained with a heteroarylboronic acid as well (entries 2 and 6).

Table 1. Palladium-catalyzed cross-coupling of arylboronic acids with acid chlorides

Entry	Acid Chloride	Boronic Acid	Product[a)]	%Yield[c)]
1				80
2				70
3[b)]				19
4				50
5				78
6				47
7				40
8				50
9				70
10				60
11				55
12				40
13				76
14				70

[a)] 5 mol% of $Pd(PPh_3)_4$, 5 equiv. Cs_2CO_3 in toluene at 100°C, except entry (3). [b)] CsF in DME at reflux. [c)] Yields reported are based on isolated ketone[8] after column chromatography.

In summary, the synthesis of ketones from acid chlorides and boronic acids under anhydrous Suzuki cross-coupling reaction conditions with tetrakis(triphenylphosphine)palladium(0) and cesium carbonate in toluene is reported. This provides a new alternative method for the synthesis of ketones.

References and Notes

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8. Literature compounds were characterized by ^{1}H-NMR and GC/MS. All boronic acids and acids chlorides are from commercial sources.