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Preparation of ketones via the palladium-catalyzed cross-coupling of acid chlorides with trialkylboranes

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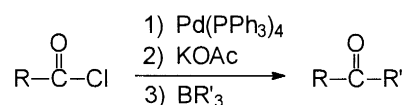
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Abstract

Trialkylboranes react with acid chlorides in the presence of palladium to generate alkyl and aryl ketones in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond-formation via organometallic reactions has been extensively studied.¹ In recent years, numerous transition-metal-catalyzed, cross-coupling reactions of organic halides with organometallic reagents such as organotin,² organoaluminum³ and organoboron⁴ compounds have been reported. Of these, the palladium-catalyzed coupling reactions of organoborane derivatives (the Suzuki–Miyaura Reaction) is playing an ever increasing role in modern organic synthesis.⁵

We recently reported the first coupling of trialkylboranes with acid chlorides using a Suzuki–Miyaura coupling sequence to prepare aliphatic and aromatic ketones via the coupling of trialkylboranes with acyl halides (Scheme 1).⁶ In an earlier study, Negishi had reported that tetraalkylborates will react with acid chlorides to form ketones in the absence of catalysts.⁷ Subsequently, Uemura developed a palladium-catalyzed reaction involving the use of tetraphenylborates with acid chlorides for preparing aryl ketones.⁸ The procedure was later modified and improved by Bumagin.⁹ The preparation of aryl ketones utilizing aryl boronic acids has also been reported.^{9,10}



Scheme 1.

We carried out a study to elucidate reaction conditions which promote maximum product yields. A reaction temperature of 65°C results in convenient reaction times although the reaction does proceed at room temperature (Table 1). The cross-coupling reaction presumably involves an oxidative addition of the acid halide to the palladium(0) catalyst to generate an acyl palladium(II) halide. Treatment of

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the acyl palladium with potassium acetate generates the acyl palladium(II) acetate which undergoes transmetallation with the organoborane reagent. The resultant acyl organopalladium complex then undergoes reductive elimination to generate the ketone product.

Table 1
Reaction of benzoyl chloride with tributylborane to generate valerophenone^a

Pd (PPh ₃) ₄	Temp.	Time	Yield (%) ^b
0.05 mmole	65 °C	3 hr	25
0.1 mmole	65 °C	3 hr	41
0.2 mmole	65 °C	3 hr	74
0.4 mmole	65 °C	3 hr	75
0.2 mmole	21 °C	8 hr	68

^aBenzoyl chloride (1.0 mmole) added to tributylborane (1 mmole) in THF. ^b Isolated

Several features of this reaction make it synthetically useful. These include the fact that reactions can be carried out at moderate temperatures in THF, unlike other transition-metal-catalyzed cross-coupling reactions involving main group organometallics. Most importantly, the reaction is not limited to aromatic acid chlorides, aliphatic acid chlorides also undergo the coupling reaction. The reaction is straightforward and it appears to be generally applicable (Table 2). At present, the reaction involves the transfer of only one of the three alkyl groups and thus is not as efficient as some of the more recent developments using arylboron derivatives which also employ smaller quantities of the palladium reagent.^{9,10} A detailed study of the scope and limitations of the synthesis is in progress.

The synthesis of 1-phenyl-1-pentanone is representative: Benzoyl chloride (1.0 mmol) is added to Pd(PPh₃)₄ (0.2 mmol) and the mixture stirred at room temperature for 10 min. Potassium acetate (2 mmol) and tributylborane (1 mmol) are added to the reaction mixture which is refluxed at 65°C for 3 h. The reaction is quenched with water (10 mL) and the product extracted into ether (3×20 mL). The combined organic extracts are washed with brine and then dried over anhydrous magnesium sulfate prior to solvent removal under reduced pressure. The product is purified by column chromatography (silica gel) using ethyl acetate–hexanes to yield 0.74 mmol (74%) of the desired 1-phenyl-1-pentanone.

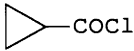
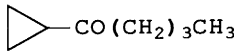
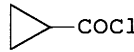
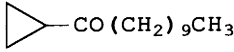
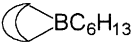
Acknowledgements

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Table 2
Reaction of acid chlorides with trialkylboranes to generate ketones^a

Acid Chloride	Trialkylborane	Product ^b	Yield (%) ^c
PhCOCl	B(C ₄ H ₉) ₃	PhCO(CH ₂) ₃ CH ₃	74
PhCOCl	B(C ₁₀ H ₂₁) ₃	PhCO(CH ₂) ₉ CH ₃	68
CH ₃ (CH ₂) ₈ COCl	B(C ₄ H ₉) ₃	CH ₃ (CH ₂) ₈ CO(CH ₂) ₃ CH ₃	65
CH ₃ (CH ₂) ₈ COCl	B(C ₁₀ H ₂₁) ₃	CH ₃ (CH ₂) ₈ CO(CH ₂) ₉ CH ₃	61
(CH ₃) ₂ CHCH ₂ COCl	B(C ₄ H ₉) ₃	(CH ₃) ₂ CHCH ₂ CO(CH ₂) ₃ CH ₃	56
	B(C ₄ H ₉) ₃		38
CH ₂ =CH(CH ₂) ₈ COCl	B(C ₄ H ₉) ₃	CH ₂ =CH(CH ₂) ₈ CO(CH ₂) ₃ CH ₃	65
CH ₂ =CH(CH ₂) ₈ COCl	B(C ₁₀ H ₂₁) ₃	CH ₂ =CH(CH ₂) ₈ CO(CH ₂) ₉ CH ₃	62
(CH ₃) ₂ CHCH ₂ COCl	B(C ₁₀ H ₂₁) ₃	(CH ₃) ₂ CHCH ₂ CO(CH ₂) ₉ CH ₃	53
(CH ₃) ₂ CHCOCl	B(C ₄ H ₉) ₃	(CH ₃) ₂ CHCO(CH ₂) ₃ CH ₃	34
	B(C ₁₀ H ₂₁) ₃		35
PhCOCl		PhCO(CH ₂) ₅ CH ₃	47

^aAcid chloride (1 mmole) added to the trialkylborane (1 mmole) and Pd(PPh₃)₄ (0.2 mmole) in THF and the mixture refluxed for 3 hours. ^bThe products exhibited physical and spectral characteristics in accord with literature values. ^cIsolated yield.

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