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Preparation of *N*-alkylpyridinium aryl ketone derivatives via the surfactant promoted cross-coupling reaction of *N*-alkylpyridiniumboronic acids with carboxylic anhydride in water at room temperature

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The palladium (II) chloride catalyzed coupling reaction of *N*-alkylpyridiniumboronic acids with benzoic anhydride was carried out smoothly in water to give high yields of ketones without the use of a phosphine ligand. The reaction was conducted under mild conditions at room temperature. In this article, by focusing on the Suzuki reaction, it is shown how this method can impact modern synthetic chemistry, making reactions faster, easier and cleaner. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: *N*-alkylpyridinium ketone; *N*-alkylpyridiniumboronic acids; carboxylic anhydride; palladium catalysis

Introduction

The use of catalytic cross-coupling methods for preparing aryl functionalized heterocycles with pharmaceutical, agrochemical, materials and supramolecular applications is a burgeoning field of study.[1] In the context of biaryl and heterobiaryl synthesis, metal-mediated cross-coupling reactions continue to be of paramount importance. Within this field the Suzuki–Miyaura protocol for palladium-catalyzed cross-coupling of aryl/heteroaryl boronic acids with aryl/heteroaryl halides is particularly versatile. Although the use of halopyridines as cross-coupling partners is widespread[2] in Suzuki reactions, there are only isolated examples of the use pyridylboronic acids or esters.[3–7] This is no doubt partly due to the difficulties of purifying parent pyridylboronic acids, which are highly polar water-soluble molecules, although a new and efficient synthesis of 3-pyridylboronic acid has been developed.[8–10]

Most reactions have been carried out as homogeneous systems in organic solvents, but recently, aqueous transition metal catalysis has gained popularity as a method for generating complex organic molecules with reduced environmental impact.[11–13] Water, being cheap, readily available, nontoxic and nonflammable, has clear advantages for use as a solvent in chemistry.[14,15] For instance, phase separation is easier because most organic compounds are lipophilic and are easily separated from the aqueous phase. The possible benefits of aqueous catalytic systems include easier product separation, decreased cost and increased reactivity.[16,17] Water is compatible with most of the known palladium-catalyzed reactions,[18] but the low solubility of the majority of organic compounds in water is a major problem.[19]

Yamamoto *et al*.[20], Ghosh *et al*.[21] and Patil *et al*.[22] independently reported a new method for obtaining aryl ketones under mild conditions, based on the cleavage of the C–O bond of carboxylic anhydrides or acyl chlorides in the presence of palladium catalysts. Nevertheless less active carboxylic derivatives, or carboxylic acids, require activation by phosphine ligands.[23]

Recently, Xin *et al*.[24] published the surfactant-improved palladium-catalyzed cross-coupling reaction of arylboronic acids with carboxylic anhydrides or acyl chlorides in water in the presence of surfactants. The use of surfactants has considerably extended organic chemistry in water and has had a notable effect on reactions rates[19] Sodium dodecyl sulfate (SDS), inexpensive and widely used in industry, has been found to be a good promoter of the coupling reaction and good yields of aryl ketones have been obtained without the use of phosphine ligands.[20]

Herein, we report the evaluation of palladium-catalyzed cross-coupling of *N*-alkylpyridiniumboronic acids and benzoic anhydride in the absence of phosphine ligands in water. The method is straightforward, and the ketones can be synthesized under mild reaction conditions, with high yields and short reaction times.

Our work required 3- and 4-pyridylboronic acids on a multigram scale but, owing to their high cost, we sought to prepare them ourselves following a recently reported procedure[10] using pyridyl Grignard reagent and trimethylsilylborate. The isomeric surfactants (bromide salts) were prepared by direct quaternization of pyridineboronic acids. Equimolar quantities of the appropriate pyridineboronic acid and alkyl bromide were dissolved in nitromethane and heated to 73 °C for 7 days. Physical and micellar properties of four compounds are listed in Table 1. Using spectrophotometric methods, the dissociation

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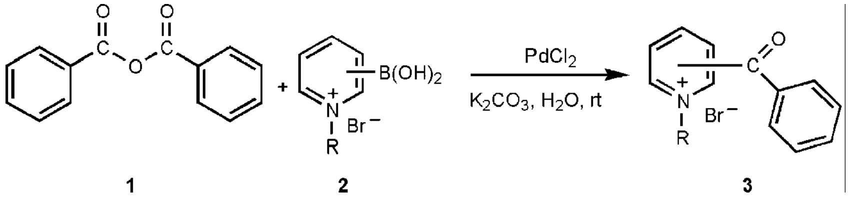


Scheme 1. Palladium-catalyzed cross-coupling of carboxylic anhydride with *N*-alkylpyridiniumboronic acids.

$$PdX_2 \xrightarrow{\text{in situ}} Pd(0)L_n$$
$$L_n = H_2O,\ OH,\ HCO_3$$

Scheme 2. Reduction of Pd (II) to Pol (0).

Table 1. pK_a and cmc values of *N*-alkypyridiniumboronic acids determined at 25 °C

Compounds	pK_a	Cmc (M)
N-dodecylpyridinium-3-boronic acid bromide	4.09	2.86×10^{-4}
N-hexadecylpyridinium-3-boronic acid bromide	4.09	7.35×10^{-5}
N-dodecylpyridinium-4-boronic acid bromide	5.91	1.24×10^{-4}
N-hexadecylpyridinium-4-boronic acid bromide	5.91	7.51×10^{-5}

constant of *N*-alkylpyridiniumboronic acids bromides (*N*-APBABr) was determined. It is reasonable to assume that, in neutral aqueous solutions, the boronic groups of *N*-alkylpyridiniumboronic acids bromides will be ionized and the surfactant will be present in zwitterionic form.[25] The critical micellar concentration (cmc) was measured by surface tension and fluorescence probe methods. The agreement between the two methods was quite good. Because of its simplicity and the unambiguous determination of the cmc, the fluorescence probe method works very well with the zwitterionic micelles.

The general process involves formation of *N*-alkylpyridinium aryl ketone **3** (Scheme 1) from the parent benzoic anhydride (Bz_2O) **1**, *N*-alkylpyridiniumboronic acids surfactant **2**, base and Pd catalyst in aqueous solution (Scheme 1).

It is important to note that the end of all these reactions was clearly visualized since palladium metal precipitated as soon as all of the carboxylic anhydride was consumed and pale yellow-brown mixtures became dark. Pd was separated by simple filtration and the reaction products were easily separated by liquid–liquid extraction with dichloromethane.

All reactions were performed using a 1 : 1 stoichiometric ratio of benzoic anhydride and *N*-alkylpyridiniumboronic acid bromide surfactant, as compared with the 1:1.2 or 1:1.5 ratios often used in aqueous Suzuki reactions. In addition, the reactions were performed in air without degassing the water prior to use. The results of the coupling reaction are collected in Tables 2 and 3 and discussed below.

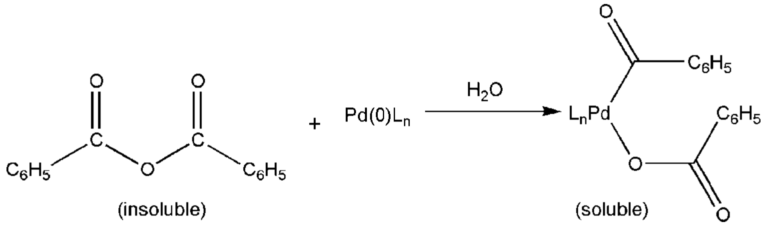
The concentration of the bromide *N*-alkylpyridiniumboronic acid surfactant in water played a pivotal role for the reaction outcome. Higher yields were obtained at [*N*-PBABr] well above cmc. Presumably the increase of the reaction yields can be attributed to the easy formation of the *N*-alkylpyrdiniumboronate [*N*-alkylpyridinium$B(OH)_3]^-$, the key intermediate at the transmetallation step.[26] A large excess of *N*-alkylpyridiniumboronic acid did not improve the yield of coupling product. In addition, the formation of byproduct *N*,*N*-dialkypyridinium, which is generated by self-coupling of *N*-alkylpyridiniumboronic acid bromide, was also obviously depressed at this concentration. Palladium (II) chloride was shown to be an excellent catalyst in this system, while palladium (II) acetate gave moderate yields (Table 4).

Thus, the aqueous surfactant systems proved to be excellent media for carrying out palladium-catalyzed reactions. These systems have the following advantages in comparison with more conventional procedures: no organic solvent is needed; ultra-low surface tension allows fast and easy mixing of reagents; the systems are formed spontaneously and vigorous mechanical stirring is not needed to obtain and maintain the systems.

The reaction proceeded rapidly at room temperature in the presence of different palladium catalysts. Palladium salts PdX_2 (X = Cl, OAc) were found to be the most effective catalysts for cross-coupling with *N*-alkylpyridiniumboronic acids. It can be assumed that, under such conditions, palladium intermediates act not only as catalysts but also as phase transfer agents.

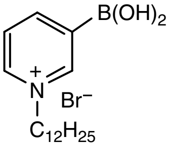
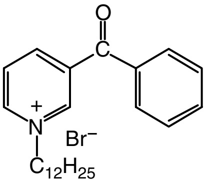
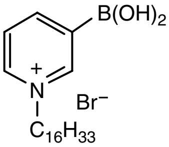
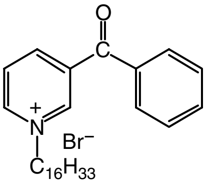
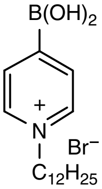
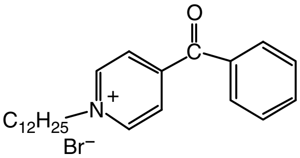
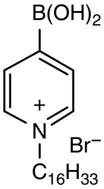
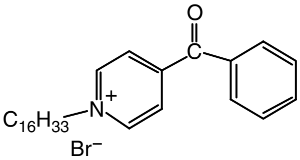
The Pd(0) materials were more active than their corresponding Pd(II) precursors, presumably because the latter need to be reduced *in situ* before entering the catalytic cycle.

The solubility of $[(Bz)_2OPdL_n]$-complex in water is due to the hydrophilicity of the ligand (L). Water-insoluble carboxylic anhydride can react easily with *N*-alkylpyridiniumboronic acids at room temperature in aqueous media. The reaction is also facilitated by the presence of the bases Na_2CO_3 and K_2CO_3. These facts can be accounted for by the formation of palladium with oxygen-containing $(Bz)_2OPdL_n$ (L_n = OH, HCO_3, H_2O etc.) which



Scheme 3. The (acyl) (aryl) palladium (II) intermediate.

Table 2. Suzuki coupling of *N*-alkylpyridiniumboronic acids (*N*-APBABr) with benzoic anhydride (Bz_2O) in water[a]

Entry	Boronic acid	Product	Conditions	Yield (%)[b]
1			RT, 12 h 60 °C, 4 h	99 (81) 99 (81)
2			RT, 12 h 60 °C, 4 h	99 (78) 99 (78)
3			RT, 12 h 60 °C, 4 h	99 (84) 99 (82)
4			RT, 12 h 60 °C, 4 h	99 (86) 99 (76)

[a] Typical experimental procedure: 1 mmol of Bz_2O, 1 mmol of *N*-APBABr and 1.6 mmol of K_2CO_3, were mixed together in 10 ml of water by gentle stirring. $PdCl_2$ (1.7 mol%) was then added.

[b] HPLC yields based on benzoic anhydride, isolated yields in parentheses.

are more reactive towards boronic acids in the transmetallation step. In other studies in aqueous micelles and similar association colloids[27] it was assumed that, in the present system, the transfer of reactants was a crucial but fast equilibrium process[28] and that the reaction region was the micellar aqueous solution. Consequently, the results obtained can be interpreted in the light of current ideas on micellar catalysis.[29] Acylation in the absence of phosphine ligands in water is thought to proceed through the mechanism described by Yamamoto[20] and Ghosh.[21]

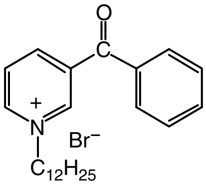
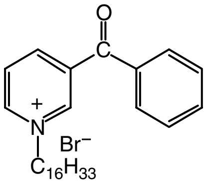
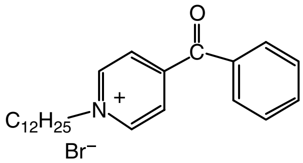
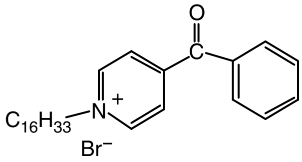
In conclusion, we have revealed an efficient and convenient system for the Suzuki coupling of carboxylic anhydrides with various *N*-alkylpyridiniumboronic acid bromides using $PdCl_2$ as catalyst and water as the solvent at room temperature. This methodology has the advantage of low catalyst loading, rapid reaction times, ease of reaction (no need for anaerobic conditions), and use of nontoxic, nonflammable solvent. This mild and environmentally friendly reaction is suitable for the preparation of *N*-alkypyridinium aryl ketone. Further research is in progress in our laboratory to use these catalytic systems in broader synthesis applications. Chemists are increasingly using it for their chemical transformations in the laboratory. There is little doubt that interest will continue to grow, with an increasing number of reports of reactions that work in water but not in common organic solvents appearing in the literature. Also, within the chemical industry, there are financial benefits to be drawn from using water as a solvent, especially given the more stringent environmental laws that are being passed every year.[30,31]

Experimental

Typical Procedure for the Coupling Reactions

A mixture of benzoic anhydride (1 mmol), *N*-dodecylpyridinium-3-boronic acid bromide (1 mmol), K_2CO_3 (1.6 mmol), $PdCl_2$ (1.7 mol %) and water (10 ml) was added to a 50 ml flask and stirred as indicated in the conditions given (Table 2). After the reaction had been completed, the mixture was acidified and the product extracted by dichloromethane. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to afford *N*-dodecylpyridinium-3-aryl ketone with a yield of 81% ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.13 (dd, 1H, H-6), 8.98 (d, 1H, H-2), 8.95 (dd 1H, H-4), 8.49 (dd, 1H, H-5), 7.79 (dd, 1H, H′-2), 7.79 (dd, 1H, H′-6), 7.63 (dd 1H, H′-4), 7.54 (dd, 1H, H′-3), 7.54 (dd, 1H,

Table 3. Effect of the concentration of *N*-alkylpyridiniumboronic Acids (*N*-APBA) on the coupling reaction in water

Entry	*N*-Alkylpyridiniumboronic acids	[M]	Ratio *N*-APBA : Bz_2O	Yield (%)[a]
1		1.43×10^{-5}	0.05	15
		1.43×10^{-4}	0.5	30
		2.86×10^{-4}	1	99
		1.43×10^{-3}	5	99
2		3.68×10^{-6}	0.05	17
		3.88×10^{-5}	0.5	33
		7.35×10^{-5}	1	99
		3.68×10^{-4}	5	99
3		6.20×10^{-6}	0.05	14
		6.20×10^{-5}	0.5	32
		1.24×10^{-4}	1	99
		6.20×10^{-4}	5	99
4		3.76×10^{-6}	0.05	12
		3.76×10^{-5}	0.5	31
		7.5110^{-5}	1	99
		3.76×10^{-4}	5	99

[a] Typical experimental procedure: 1 mmol of Bz_2O, 1 mmol of *N*-APBABr and1.6 mmol of K_2CO_3, were mixed together in 10 ml of water by gentle stirring. $PdCl_2$ (1.7 mol%) was then added.

[b] HPLC yields based on benzoic anhydride.

Table 4. Effect of base and catalysts on the cross-coupling reaction[a]

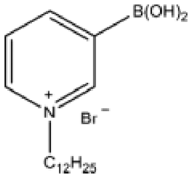
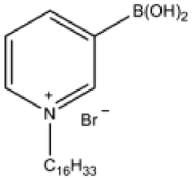
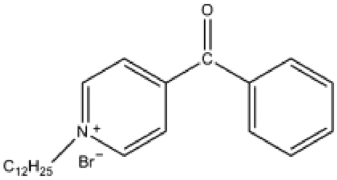
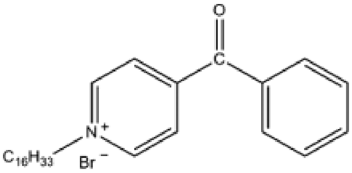
Entry	*N*-Alkylpyridiniumboronic acids	Base	Catalyst (1.7 mol%)	Yield (%)[b]
1		K_2CO_3	$PdCl_2$	99
		K_2CO_3	$Pd(OAc)_2$	63
		Na_2CO_3	$PdCl_2$	97
		Na_2CO_3	$Pd(OAc)_2$	61

Table 4. (*Continued*)

Entry	*N*-Alkylpyridiniumboronic acids	Base	Catalyst (1.7 mol%)	Yield (%)[b]
2		K_2CO_3	$PdCl_2$	99
		K_2CO_3	$Pd(OAc)_2$	59
		Na_2CO_3	$PdCl_2$	97
		Na_2CO_3	$Pd(OAc)_2$	61
3		K_2CO_3	$PdCl_2$	99
		K_2CO_3	$Pd(OAc)_2$	62
		Na_2CO_3	$PdCl_2$	98
		Na_2CO_3	$Pd(OAc)_2$	58
4		K_2CO_3	$PdCl_2$	99
		K_2CO_3	$Pd(OAc)_2$	61
		Na_2CO_3	$PdCl_2$	97
		Na_2CO_3	$Pd(OAc)_2$	59

[a] Typical experimental procedure: 1 mmol of Bz_2O, 1 mmol of *N*-APBABr and1.6 mmol of base were mixed together in 10 ml of water by gentle stirring. Catalyst (1.7 mol%) was then added.

[b] HPLC yields based on benzoic anhydride.

H′-5) 4.70 (t, 2H, $-N-CH_2-$), 1.30 (m, 2H, $-N-C-CH_2-C-$), 1.29 [m, 18H, $-(CH_2)_9-$], 0.88 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 149.9 (C-6), 147.3 (C-4), 145.7 (C-2), 137.6 (C-3), 129.4 (C-5), 196.3 (C=O), 133.8 (C′-1), 132.6 (C′-4), 129.8 (C′-2), 129.7 (C′-6), 128.8 (C′-3), 128.8 (C′-5), 71 ($-N-C_1-$), 30.4 (C_2), 28.0 (C_3), 29.3 (C_4), 29.6 (C_5, C_6, C_7, C_8), 29.3 (C_9), 31.9 (C_{10}) 22.7 (C_{11}), 14.1 (C_{12}). IR (KBr): ν (cm^{-1}) = 1685 (C=O). ESI MS (*m/z*) 352 (M^+).

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