Palladium-Catalyzed Synthesis of Aryl Ketones from Boronic Acids and Carboxylic Acids or Anhydrides **

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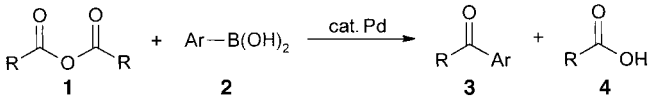
The acylation of carbon nucleophiles with carboxylic acid derivatives is an important C–C bond-forming reaction that is extensively used in the synthesis of natural products and pharmaceutical compounds. Several carboxylic acid derivatives, for example, nitriles, amides, anhydrides, or acid chlorides, can be alkylated or arylated with a variety of organometallic species to produce ketones in moderate to excellent yields.[1]

Carboxylic acids themselves can only be transformed into the corresponding ketones by treatment with lithium, magnesium, or aluminum reagents under rather elaborate conditions that are intolerant of most functional groups.[2] Various procedures have been developed to stop the reaction at the stage of the ketone and avoid the formation of the tertiary alcohols.[3] Milder reagents, for example organotin, -zinc, and -copper compounds or boronic acids, are acylated only by more reactive acid derivatives (usually acid chlorides), which have to be generated in an additional reaction step.[4] Recently, Liebeskind et al. disclosed a versatile, base-free synthesis of aryl ketones by the palladium-catalyzed coupling of thioesters with boronic acids.[5] However, this transformation requires the preformation of the thioester and calls for a stoichiometric amount of copper thiophene carboxylate.

Our target was to develop a convenient preparation of ketones directly from carboxylic acids under mild conditions and with minimal waste production by using a strategy similar to the one that Yamamoto and co-workers utilized for the reduction of carboxylic acids.[6] Boronic acids appeared to be the carbon nucleophiles of choice, as they are readily available,[7] non-toxic, air- and moisture-stable compounds that tolerate the presence of many sensitive functionalities.

Since most carboxylic acids can easily (and potentially in situ) be converted into their anhydrides,[8] our first goal was the development of a catalytic system capable of coupling anhydrides with boronic acids. Although the palladium-catalyzed coupling of the more reactive acid chlorides with boronic acids is known,[9] no reports have been made on whether anhydrides are also suitable for this reaction.[10] In principle, a similar catalytic process for anhydrides that consists of the oxidative addition of the anhydride to an acyl palladium complex, exchange of the carboxylate for the aryl group by transmetallation of the boronic acid, and reductive elimination of the ketone should also be possible.

We chose the reaction of hexanoic anhydride (**1a**, R = *n*-C_5H_{11}) with phenylboronic acid (**2a**, Ar = Ph) as our model system and screened several palladium catalysts under various conditions (Scheme 1). Selected results are shown in Table 1. We initially employed anhydrous conditions to prevent hydrolysis of the anhydrides. However, with various catalytic systems, only sluggish turnovers and moderate yields were observed (Table 1, entry 1). Upon the addition of water, the reaction surprisingly became faster while the competing hydrolysis of the anhydride remained slow, so that high yields of the desired ketone **3a** were obtained.[11] The addition of two equivalents of water with respect to the boronic acid was found to be optimal (Table 1, entries 1–3).



Scheme 1. Coupling of anhydrides with boronic acids (R, Ar: see below).

Table 1. Coupling of hexanoic anhydride with phenylboronic acid.

Entry	Phosphane	Solvent	Water [mmol]	Yield [%]
1	PPh_3	THF	0	29
2	PPh_3	THF	2.5	97
3	PPh_3	THF	10	38
4	PPh_3	DME	2.5	53
5	PPh_3	DMF	2.5	92
6	PPh_3	toluene	2.5	77
7	PPh_3	CH_3CN	2.5	54
8[a]	PPh_3	THF	2.5	92
9	PCy_3	THF	2.5	91
10	P(*o*-Tol)$_3$	THF	2.5	31
11	BINAP	THF	2.5	< 5
12	P(*p*-MeOPh)$_3$	THF	2.5	97
13	DPPF	THF	2.5	< 5
14	P(Fur)$_3$	THF	2.5	46
15	P(*t*Bu)$_3$	THF	2.5	28

Reagents and conditions: hexanoic anhydride (1 mmol), phenylboronic acid (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.07 mmol; 0.035 mmol for chelating phosphanes), 16 h. The yields were determined by using GC. [a] The reaction was performed at 20 °C. DME = 1,2-dimethoxyethane.

DMF (*N*,*N*-dimethylformamide) and THF proved to be the most effective solvents (Table 1, entries 2, 4–7). Owing to its lower toxicity, we considered THF to be more convenient. The choice of phosphane also has a significant effect on the reaction outcome (Table 1, entries 9–15). The optimum reaction temperature was 60 °C, but reasonable yields were also obtained at lower temperatures (Table 1, entry 8).

To study the scope of this transformation, we varied both the boronic acids and the anhydrides. A few representative results are shown in Table 2. We found that for best results, different phosphanes need to be chosen with regard to the steric and electronic properties of the anhydrides. Tri-*p*-methoxyphenylphosphane is generally suitable for all carboxylic acid anhydrides and the superior choice for most alkyl derivatives. For more electron-poor aryl derivatives, however, triphenylphosphane or diphenylferrocenylphosphane are more effective.

Most substrates gave excellent yields, and even sensitive compounds such as furaneboronic acid were smoothly converted. Alkyl, vinyl, and aryl anhydrides are equally suitable

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Table 2. Synthesis of aryl ketones according to Scheme 1.

Entry	R	Ar	Yield [%]
1	n-C_5H_{11}	*o*-tolyl	98
2	n-C_5H_{11}	*p*-MeO-phenyl	91
3[a]	n-C_5H_{11}	*p*-CH_3CO-phenyl	96
4	n-C_5H_{11}	*m*-Cl-phenyl	97
5	n-C_5H_{11}	2-furyl	84
6	n-C_5H_{11}	3-thienyl	88
7	CH_3	phenyl	98
8	*sec*-butyl	phenyl	98
9	-$C(CH_3)$=CH_2	phenyl	71
10[b]	*p*-MeO-Ph	phenyl	90
11[b]	phenyl	phenyl	96
12	*tert*-butyl	phenyl	0

Reagents and conditions: anhydride (1 mmol), boronic acid (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), P(*p*-MeOPh)$_3$ (0.07 mmol), 16 h, 60 °C; all yields refer to isolated products. [a] PCy_3 (0.07 mmol) was used as ligand. [b] PPh_3 (0.07 mmol) was used as ligand.

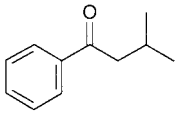
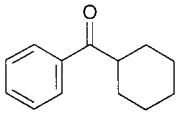
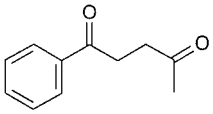
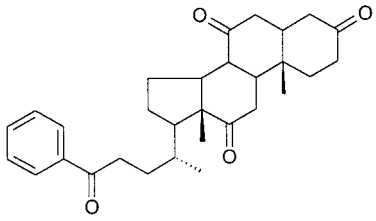
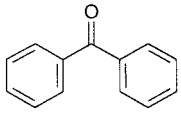
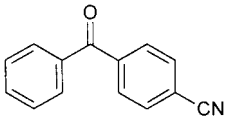
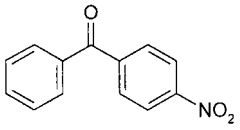
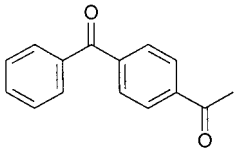
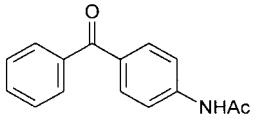
for this transformation (Table 2, entries 1, 7–11). However, no reaction was observed for the sterically demanding pivalic anhydride (Table 2, entry 12).

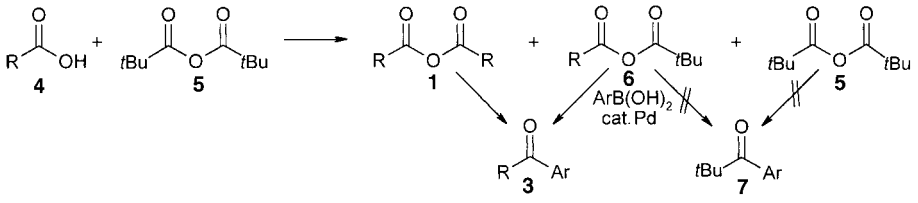
The low reactivity of pivalic anhydride (**5**) opened up an opportunity for achieving an in situ activation of sterically less hindered carboxylic acids **4** by the generation of the corresponding mixed anhydrides **6** (Scheme 2).

We tested our hypothesis on the reaction of 3-phenylpropionic acid (**4b**) with phenylboronic acid (**2a**) (Scheme 3, R = 3-phenylpropyl, Ar = Ph) and indeed observed the desired conversion exclusively into 3-phenylpropyl phenyl ketone **3b**.

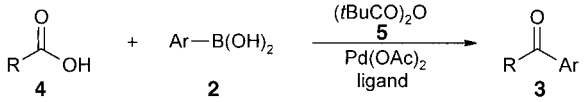
The optimum reaction conditions for the one-pot reaction were found to be similar to the best conditions for the homoanhydrides. The influence of the water content is profound: in the absence of water, less than 1% of the ketone was obtained. However, with two equivalents of water more than 90% of the ketone was formed, but with ten equivalents less than 80% was produced. P(*p*-MeOPh)$_3$ (65%), PPh_3 (68%), DPPF (91%; DPPF = 1,1′-bis(diphenylphosphino)ferrocene), and PCy_3 (55% yield) were found to be effective ligands on palladium. The scope of the one-pot reaction was investigated by using different combinations of carboxylic acids and boronic acids. Selected results are displayed in Table 3. P(*p*-MeOPh)$_3$ is most effective for alkyl carboxylic acids (Table 3, entries 1–5), whereas PPh_3 or DPPF are usually superior for aryl derivatives (Table 3, entries 1–10). For aryl alkyl derivatives such as 3-phenylpropionic acid, the properties of the boronic acids also have to be taken into account when choosing the ligand (Table 3, entries 12–18).

Table 3. Synthesis of aryl ketones from carboxylic acids and aryl boronic acids.

Entry	Product[a]	Ligand[b]	Yield [%]
1		A	90
2[c]		A	60
3		A	65
4		A	81
5		C	68
6		B	80
7		C	75
8		D	54
9		B	85



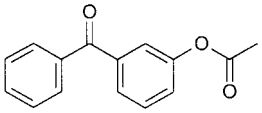
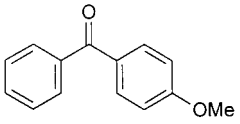
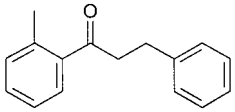
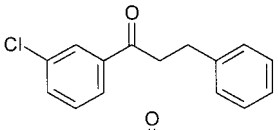
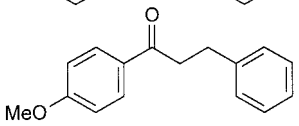
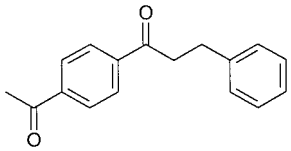
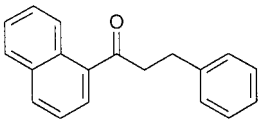
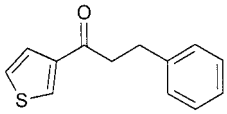
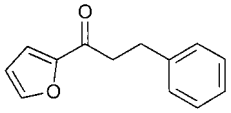
Scheme 2. In situ activation of carboxylic acids.



Scheme 3. One-pot synthesis of aryl ketones.

Many functional groups are tolerated: carboxylic acids and boronic acids that contain halo, keto, cyano, ester, nitro, or protected amino groups were successfully converted. Some heteroyclic ketones were synthesized as well. However, alkylboronic acids were not converted under any of the given conditions.

Table 3. (Continued).

Entry	Product[a]	Ligand[b]	Yield [%]
10		D	48
11		D	55
12		C	65
13		C	55
14		A	78
15		D	55
16		C	75
17		A	72
18		B	47

Reagents and conditions: carboxylic acid (1 mmol), boronic acid (1.2 mmol), pivalic anhydride (1.5 mmol), $Pd(OAc)_2$ (0.03 mmol), ligand (0.07 mmol; 0.035 mmol for DPPF), solvent (4 mL), H_2O (2.5 mmol), 60 °C, 16 h; all yields refer to isolated products. [a] Aryl groups that originate from the boronic acids are drawn on the left side of the keto groups. [b] Ligands: A = P(*p*-MeOPh)$_3$; B = PPh_3; C = DPPF; D = PCy_3. [c] DME was used as solvent.

In summary, the palladium-catalyzed cross-coupling reaction disclosed herein represents a one-step, high-yielding synthesis of aryl ketones directly from the plethora of available carboxylic acids and boronic acids. The reaction is easily performed with many functionalized derivatives, requires only commercially available nontoxic chemicals, and produces a minimum amount of waste. It is thus a valuable alternative to the standard procedures, especially for applications in drug discovery or combinatorial chemistry.

Experimental Section

3b: A 100-mL round-bottomed flask equipped with a pressure equalizer and a magnetic stirring bar was charged with palladium acetate (67.3 mg, 0.30 mmol), diphenylferrocenylphosphane (194 mg, 0.35 mmol), 3-phenylpropionic acid (1.50 g, 10 mmol), and phenylboronic acid (1.46 g, 12 mmol). Subsequently, THF (40 mL), water (45 mg, 2.5 mmol), and pivalic anhydride (2.79 g, 15 mmol) were added through a syringe. The reaction vessel was purged with argon and the brown reaction mixture was heated at 60 °C overnight. After removal of the volatiles under vacuum, the residue was taken up in a minimum amount of hexane and filtered through aluminum oxide (10 cm) by using a hexane/MTBE (MTBE = *tert*-butyl methyl ether) gradient as eluent. The first fraction contained mainly biphenyl formed during the reduction of the palladium(II) precatalyst. The second fraction, which eluted with 10% MTBE in hexane, contained the almost pure product. After the removal of the volatiles and crystallization of the residue from hexane, 3-phenylpropyl phenyl ketone (1.73 g, 83%) was obtained as colorless crystals. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.95$ (m, 2H), 7.61–7.19 (m, 8H), 3.32 (t, ^3J(H,H) = 6 Hz, 2H), 3.13 (t, ^3J(H,H) = 6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 198.8$, 141.0, 136.5, 132.7, 128.3, 128.2, 128.1, 127.7, 125.8, 40.1, 29.8; MS (70 eV): *m*/*z* (%): 210 (53) [M^+], 105 (100), 77 (46), 51 (17); HR-MS: calcd for $C_{15}H_{14}O$ [M^+]: 210.104465; found: 210.10447; Elemental analysis calcd for $C_{15}H_{14}O$ (210.3): C 85.68%, H 6.71%, N 0.00%; found: C 85.37, H 6.67, N 0.00%.

The reactions in Tables 1–3 were performed on a 1-mmol scale, with tetradecane (0.05 mL) as an internal GC standard. The products were isolated by column chromatography (basic Al_2O_3 or SiO_2, ethyl acetate/hexane 1:30–1:10) and characterized by means of ^{1}H and ^{13}C NMR spectroscopic analysis as well as by GC-MS and HR-MS.

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