

# A new practical ketone synthesis directly from carboxylic acids: first application of coupling reagents in palladium catalysis

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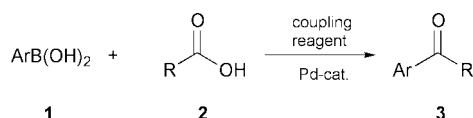
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A new palladium-catalyzed cross-coupling reaction between arylboronic acids and carboxylic acids, activated *in situ* for the oxidative addition to a tricyclohexylphosphine palladium(0) catalyst by treatment with di(*N*-succinimidyl) carbonate (DSC) is disclosed, which allows the high-yielding synthesis of various functionalized arylketones under mild conditions.

The reaction of carboxylic acid derivatives, for example nitriles, Weinreb-amides, anhydrides, or acid chlorides with carbon nucleophiles to the corresponding ketones is an important C–C bond-forming reaction that is commonly used in organic synthesis.<sup>1</sup> Various procedures have been developed to optimize the yield of the ketones and avoid the formation of the tertiary alcohols.<sup>2</sup> Highly reactive acid chlorides can be alkylated with a number of mild carbon nucleophiles, for example organotin, -zinc and -copper compounds or boronic acids.<sup>3,4</sup> Furthermore, ketone synthesis from thioesters<sup>5</sup> has been reported. However, only a few protocols have been disclosed for the highly desirable direct conversion of the plethora of carboxylic acids into ketones and all of these require aggressive lithium, magnesium, or aluminum reagents intolerant of most functional groups.<sup>6</sup> Recently, we reported a novel palladium catalyzed synthesis of arylketones directly from carboxylic acids and boronic acids using pivalic anhydride as an activating agent.<sup>7</sup> This transformation gives good yields for many substrates, however, the reactivity of the pivalic anhydride against basic groups and the inconvenience of the separation of the products from the pivalic acid are still disadvantageous. A milder and more practical ketone synthesis from carboxylic acids and readily available boronic acids,<sup>8</sup> which works under neutral conditions in the presence of many functional groups would be of great value especially for applications in combinatorial chemistry.

The utilization of mild coupling reagents such as DCC–HOBt, CDI (1,1'-carbonyldiimidazole) or DSC for the activation of the carboxylic acids could be the key to a much-improved process (Scheme 1). These compounds are known to cleanly convert carboxylic acids into stable intermediates, which are just reactive enough to ensure smooth conversion to the corresponding amides.<sup>9</sup> Due to their easy handling, their reliability and selectivity combined with an excellent tolerance of functional groups, coupling reagents have become indispensable for most applications in peptide synthesis.

In principle, a catalytic cycle for the palladium-catalyzed reaction of carboxylic acids with boronic acids consisting of the oxidative addition of an activated acid derivative producing an acyl palladium complex, followed by transmetalation of a boronic acid, and reductive elimination of the ketone appeared to be feasible.<sup>10</sup> However, to the best of our knowledge there is



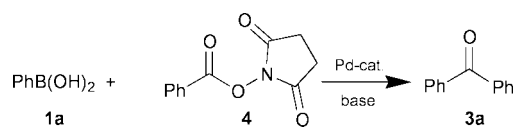
Scheme 1 Cross-coupling of boronic acids and carboxylic acids.

no literature precedent for the use of coupling reagents in transition-metal catalysis.<sup>11</sup>

Due to the high stability and easy handling, we chose phenylboronic acid (**1a**) and *N*-benzoyloxysuccinimide (**4**) as our model substrates and screened various palladium catalysts for activity in the desired conversion (Scheme 2). The catalysts were prepared *in situ* from Pd(II) precursors and two equivalents of different phosphines. Some results are summarized in Table 1.

Whereas no reaction was observed for triarylphosphines, with electron-rich trialkylphosphines moderate yields were obtained (Entries 1–6). This may indicate that the oxidative addition of the *N*-benzoyloxysuccinimide is the rate-determining step which should be facilitated by increasing the electron density on the palladium. Sterically demanding tricyclohexylphosphine gave best results while tri-*tert*-butylphosphine complexes were not stable under the reaction conditions and precipitation of palladium(0) was observed.

THF proved to be the most effective solvent (Entries 6–8). The stability of the catalytic system was significantly enhanced when a mild base was added (Entries 9–13). Best results were obtained with Na<sub>2</sub>CO<sub>3</sub> while the presence of soluble bases appeared to inhibit the reaction. We also investigated the



Scheme 2 Cross coupling of *N*-benzoyloxysuccinimide.

Table 1 Effects of the reaction conditions on the yield<sup>a</sup>

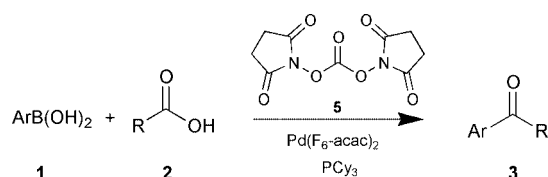
	Ligand	Pd-source	Solvent	Base	Product (%) <sup>b</sup>
1	PPh <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	—	< 2
2	DPPF	Pd(OAc) <sub>2</sub>	THF	—	< 2
3	P( <i>o</i> -Tol) <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	—	< 2
4	P( <i>t</i> Bu) <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	—	< 2
5	P( <i>n</i> Bu) <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	—	19
6	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	—	33
7	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	DMF	—	6
8	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	Toluene	—	12
9	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	K <sub>2</sub> CO <sub>3</sub>	48
10	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	CS <sub>2</sub> CO <sub>3</sub>	< 2
11	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	KF	40
12	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	NEt <sub>3</sub>	41
13 <sup>c</sup>	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	64, <sup>e</sup> 76, 98 <sup>f</sup>
14 <sup>d</sup>	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	74
15	PCy <sub>3</sub>	Pd(OAc) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	48
16	PCy <sub>3</sub>	dba <sub>3</sub> Pd <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	5, <sup>e</sup> 36, 45 <sup>f</sup>
17	PCy <sub>3</sub>	Pd(NO <sub>3</sub> ) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	70, <sup>e</sup> 92, 97 <sup>f</sup>
18	PCy <sub>3</sub>	PdCl <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	15, <sup>e</sup> 25, 26 <sup>f</sup>
19	PCy <sub>3</sub>	Pd(acac) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	2, <sup>e</sup> 80, 98 <sup>f</sup>
20	PCy <sub>3</sub>	Pd(F <sub>6</sub> -acac) <sub>2</sub>	THF	Na <sub>2</sub> CO <sub>3</sub>	67, <sup>e</sup> 81, 97 <sup>f</sup>

<sup>a</sup> Conditions: 1 mmol *N*-benzoyloxysuccinimide, 1.2 mmol phenylboronic acid, 3 mol% Pd, 7 mol% ligand, 2 mmol base, 60 °C, 14 h. <sup>b</sup> Yields determined by GC. <sup>c</sup> 1 mmol water added. <sup>d</sup> 10 mmol water added. <sup>e</sup> 3 h; <sup>f</sup> 36 h.

influence of the counter ion on the palladium pre-catalyst and observed faster reactions with weakly coordinating counterions such as  $\text{NO}_3^-$  or  $\text{F}_6\text{-acac}$  than with stronger coordinating  $\text{Cl}^-$  (Entries 16–20).<sup>10</sup> Under the reaction conditions, the boronic acids act as the reducing agents for the palladium so that biaryls are formed in small quantities. With  $\text{dba}_3\text{Pd}_2$  as a pre-catalyst, lower yields were observed, which may be due to an insufficient dissociation of the dba from  $\text{Pd}(0)$ . The presence of small quantities of water has little effect on the reaction outcome so that it is not necessary to dry the reagents or solvents, however, the presence of a large excess of water was found to lower the yields (Entries 13–15).

We then set out to combine the activation of the carboxylic acid with di(*N*-succinimidyl) carbonate and the transformation to the ketone into a convenient one-pot procedure (Scheme 3).<sup>†</sup> Since the activation of the acid was found to proceed smoothly within a few minutes in THF in the presence of  $\text{Na}_2\text{CO}_3$ , this was easily accomplished: in a typical procedure, all reagents except the boronic acid are dissolved in THF and the mixture is stirred until the  $\text{CO}_2$  evolution has ceased. Then, the boronic acid is added and the reaction is heated until complete conversion. Under these conditions  $\text{F}_6\text{-acac}$  gave best results, and it is beneficial to add a slight excess of the phosphine to make up for losses during the first reaction step. The water-soluble by-products *N*-hydroxysuccinimide and boric acid are easily removed by a single water wash.

In order to test the generality of this protocol, we applied it to a variety of different substrates. Table 2 shows the broad scope of the new transformation. Both electron-rich and electron-poor aryl, aryl and even heteroaryl carboxylic acids work equally well, many functional groups such as keto, cyano, ester, nitro, amido and even hydroxy groups are tolerated, and no side products arising from enolisation of the keto groups were observed in significant quantities.



Scheme 3 One-pot synthesis of arylketones from carboxylic acids.

Table 2 Pd-catalyzed synthesis of arylketones<sup>a</sup>

Comp.	Ar	R	Yield (%) <sup>b</sup>
3a	Phenyl	Phenyl	90
3b	Phenyl	2-Phenylethyl	95
3c	<i>o</i> -Tolyl	2-Phenylethyl	90
3d	1-Naphthyl	2-Phenylethyl	90
3e	<i>p</i> -Methoxyphenyl	2-Phenylethyl	91
3f	<i>p</i> -Acetylphenyl	2-Phenylethyl	56
3g	3-Thienyl	2-Phenylethyl	88
3h	2-Furyl	2-Phenylethyl	55
3i	Phenyl	2-Methoxycarbonylethyl	51
3k	Phenyl	<i>m</i> -Acetoxyphenyl	42
3l	Phenyl	4-Pyridyl	42
3m	Phenyl	<i>p</i> -Methoxycarbonylphenyl	53
3n	Phenyl	3-Thienyl	49
3o	Phenyl	3-Furyl	48
3p	Phenyl	<i>p</i> -Acetylphenyl	88
3q	Phenyl	Cyclohexyl	81
3r	Phenyl	<i>p</i> -Nitrophenyl	37
3s	Phenyl	<i>p</i> -Methoxyphenyl	68
3t	Phenyl	<i>p</i> -Cyanophenyl	95
3u	Phenyl	<i>p</i> -Trifluoromethylphenyl	89
3v	Phenyl	<i>p</i> -Acetamidophenyl	86
3w	Phenyl	<i>m</i> -Cyanophenyl	90
3x	Phenyl	$\text{HO-C}_{11}\text{H}_{22}$	78

<sup>a</sup> Conditions: 1 mmol carboxylic acid, 1.2 mmol boronic acid, 1.3 mmol DSC, 3 mol%  $\text{Pd}(\text{F}_6\text{-acac})_2$ , 9 mol%  $\text{PCy}_3$ , 2 mmol  $\text{Na}_2\text{CO}_3$ , 60 °C, 20 h.

<sup>b</sup> Isolated yields.

In summary, the introduction of easy-to-handle coupling reagents as activating agents for acids in transition-metal catalysis led to the discovery of a convenient new ketone synthesis from carboxylic acids and boronic acids. Further applications of this new concept, for example, in the reduction of carboxylic acids to aldehydes or the Heck reaction of benzoic acid derivatives are under current investigation.

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## Notes and references

<sup>†</sup> Synthesis of 2-(4'-methoxyphenyl) ethylphenyl ketone (3e): a 100 mL flask was charged with palladium hexafluoroacetylacetonate (156 mg, 0.30 mmol), tricyclohexylphosphine (252 mg, 0.90 mmol), 3-phenylpropionic acid (2e) (1.50 g, 10.0 mmol),  $\text{Na}_2\text{CO}_3$  (2.08 g, 20.0 mmol), and di(*N*-succinimidyl) carbonate (3.33 g, 13.0 mmol). The reaction vessel was purged with argon and degassed THF (30 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to RT, a solution of 4-methoxyphenylboronic acid (1a) (1.82 g, 12.0 mmol) in THF (30 mL) was added and the purple reaction mixture was stirred at 60 °C overnight. The reaction slurry was then poured into water (300 mL) and extracted 3 times with 100 mL portions of ethyl acetate. The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the volatiles were removed *in vacuo*. The residue was adsorbed on a plug of  $\text{Al}_2\text{O}_3$ . Nonpolar impurities such as the phosphine or the biaryl were removed by elution with hexane. The product (2.19 g, 91%) was then eluted with 20% ethyl acetate in hexane. <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ , 25 °C, TMS):  $\delta$  = 7.93 (d, <sup>3</sup>J (H,H) = 9 Hz, 2H), 7.23–7.19 (m, 5H), 6.92 (d, <sup>3</sup>J (H,H) = 9 Hz, 2H), 3.85 (s, 3H), 3.24 (t, <sup>3</sup>J (H,H) = 7 Hz, 2H), 3.06 (t, <sup>3</sup>J (H,H) = 7 Hz, 2H) ppm; <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ , 25 °C, TMS):  $\delta$  = 197.8, 163.5, 141.5, 130.3, 130.0, 128.5, 128.4, 126.1, 113.7, 55.5, 40.1, 30.3 ppm; MS (70 eV): *m/z* (%): 240 (33) [ $\text{M}^+$ ], 135 (100), 121 (2), 107 (6), 92 (8), 77 (13); HRMS: calcd. for  $\text{C}_{16}\text{H}_{16}\text{O}_2$  [ $\text{M}^+$ ]: 240.115029; found: 240.115132; anal. calcd. for  $\text{C}_{16}\text{H}_{16}\text{O}_2$  (240.30): C, 79.97; H, 6.71; N, 0.0; found: C, 80.12; H, 6.78; N, 0.0. The reactions in Table 1 and Table 2 were performed on a 1 mmol scale using 50 mg tetradecane as an internal GC standard. The products were isolated by column chromatography ( $\text{Al}_2\text{O}_3$  hexane–ethyl acetate 10:1) and characterized by means of <sup>1</sup>H and <sup>13</sup>C NMR as well as by GC-MS and HRMS.

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