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Palladium-catalyzed carbonylative coupling of benzyl chlorides with aryl boronic acids in aqueous media

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ABSTRACT

A novel chemoselective protocol for the carbonylative Suzuki coupling of benzyl chlorides with aryl boronic acids at low pressure of carbon monoxide has been developed. Applying a commercially available palladium acetate/PCy_3 catalyst system in the presence of potassium phosphate as the base and water as the solvent the coupling reactions proceeded smoothly. To demonstrate the general applicability 12 different α-arylated acetophenones have been synthesized in moderate to good yields (41–78%) under mild conditions.

Palladium-catalyzed coupling reactions have become a true power tool for advanced organic chemistry.[1,2] In particular, the formation of C–C-, C–O-, and C–N-bonds of aryl, heteroaryl, benzyl, and vinyl halides in the presence of homogeneous palladium complexes is frequently applied for the synthesis of pharmaceuticals, agrochemicals, as well as advanced materials. Due to the importance of these reactions both academic as well as industrial laboratories continuously investigate and develop new applications.

Among the different known palladium-catalyzed coupling processes, reactions with carbon monoxide create interesting benzoic acid-based building blocks. Already in the mid-1970s, Heck and co-workers described pioneering work on the alkoxy-, hydroxyl-, and aminocarbonylation of aryl iodides and bromides.[3] Since then, numerous applications in organic synthesis have been reported and even industrial processes were developed.[4] As an example, the more challenging reductive carbonylation of aryl halides forming aldehydes has become an industrial process in 2006.[5] Herein, the key to success is the employed ligand (*n*-butyl-diadamantylphosphine, cata*CX*ium A®), which has also been applied successfully in alkoxycarbonylations[6] and in the aminocarbonylation of aryl halides with ammonia gas to give primary amides.[7]

More recently, we became interested in three component carbonylation reactions, such as the carbonylative Suzuki,[8] carbonylative Sonogashira,[9] and carbonylative Heck reactions,[10] which allow for a significant increase in molecular complexity.

Based on this work, we got attracted by related carbonylations of benzyl halides. While the carbonylative coupling of benzyl halides in the presence of O- and N-nucleophiles is well known,[11,12] apart from only two examples similar reactions of benzyl chlorides with phenyl boronic acid in the presence of carbon monoxide are not described.[8c] This is somewhat surprising considering the importance of the resulting 1,2-diarylethanone motif in known pharmaceuticals and biologically active compounds.[13] Hence, there is still a need to develop convenient and more general methodologies for the synthesis of this class of compounds.

Herein, we present a novel procedure for carbonylative coupling reactions of benzyl chlorides with phenyl boronic acids under mild conditions in aqueous media. Initially, the carbonylation of inexpensive benzyl chloride with phenyl boronic acid in the presence of different palladium catalysts was tested as a benchmark reaction. Selected results are shown in Table 1. In general, catalytic experiments were performed in toluene using K_3PO_4 as the base at low carbon monoxide pressure (10 bar). Applying $Pd(OAc)_2/PPh_3$ as the catalyst system 26% of the desired carbonylative product **1** was formed together after 20 hours along with 12% of the non-desired Suzuki coupling by-product **2** (Table 1, entry 1). Employing PCy_3 as the ligand, an improved yield and chemoselectivity is obtained (Table 1, entry 2). On the other hand using sterically more hindered alkylphosphines such as *n*-butyl-diadamantylphosphine or tri-*tert*-butylphosphine gave only low yields of carbonylation products (Table 1, entries 6 and 7). Similarly, various bidentate phosphines as well as one example of a carbene ligand [1,3-bis(2,6-diisopropylphenyl) imidazolium chloride] led to significantly lower activity in this reaction.

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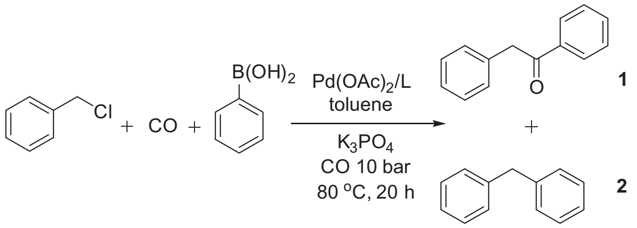
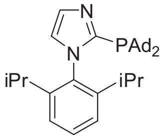
Table 1
Carbonylative Suzuki coupling of benzyl chloride: variation of ligands[a]



Entry	Ligand	Conv.[b] (%)	Yield **1**[b] (%)	Yield **2**[b] (%)
1	PPh_3	85	26	12
2	PCy_3	70	38	2
3	TFP	84	26	10
4	DPPF	15	1	3
5	DPPP	20	1	2
6	$BuPAd_2$	80	19	5
7	$P^tBu_3 \cdot HBF_4$	18	0	0
8	$Me(^tBu)_2P \cdot HBF_4$	50	27	0
9		10	0	0
10	P(*o*-Toyl)$_3$	50	1	8
11	IPr·HCl	9	0	0

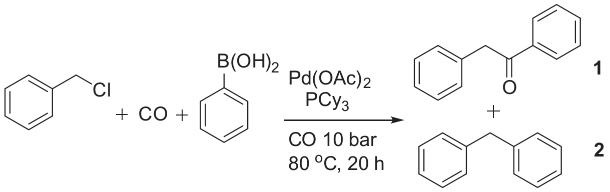
[a] $Pd(OAc)_2$ (2 mol %), L (4 mol %), K_3PO_4 (2 mmol), toluene (2 ml), benzyl chloride (1 mmol), phenyl boronic acid (1.5 mmol), CO (10 bar), 80 °C, 20 h.

[b] Conversion and yields were determined by GC using hexadecane as internal standard. TFP = tri-2-furylphosphine; IPr·HCl = 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride.

Next, we tested different bases and solvents using $Pd(OAc)_2/PCy_3$ as our standard catalyst system (Table 2). While K_3PO_4 and K_2CO_3 gave comparable results (Table 1, entry 2 and Table 2, entry 1; 35–38%), Na_2CO_3 and Cs_2CO_3 resulted in lower yields (Table 2, entries 2 and 3; 3–10%).

In the presence of organic bases such as DMAP and DABCO no product was observed at all; instead only trimerization of phenyl boronic acid was detected (Table 2, entries 4 and 5). Among the different organic solvents, dioxane proved to be the best giving 95% conversion and 68% yield of product **1** (Table 2, entries 6–11). To our delight only 2% of the direct coupling product was obtained (Table 2, entry 6). Notably, running the model reaction in water gave an even better yield (Table 2, entry 11; 73%). Clearly, water is the most abundant, green, cheap, and environmental benign solvent, which has attracted significant attention in the last decade.[14] However, the use of water as solvent in carbonylation reactions has

Table 2
Carbonylative Suzuki coupling of benzyl chloride: testing of solvents and base[a]



Entry	Solvent	Base	Conv.[b] (%)	Yield **1**[b] (%)	Yield **2**[b] (%)
1	Toluene	K_2CO_3	85	35	2
2	Toluene	Na_2CO_3	78	10	1
3	Toluene	Cs_2CO_3	75	3	1
4	Toluene	DMAP	0	0	0
5	Toluene	DABCO	0	0	0
6	Dioxane	K_3PO_4	95	68	2
7	THF	K_3PO_4	88	39	2
8	Heptane	K_3PO_4	86	27	5
9	DMF	K_3PO_4	96	16	6
10	NMP	K_3PO_4	90	21	10
11	H_2O	K_3PO_4	100	73	7
12[c]	H_2O	K_3PO_4	100	48	24

[a] $Pd(OAc)_2$ (2 mol %), PCy_3 (4 mol %), base (2 mmol), solvent (2 ml), benzyl chloride (1 mmol), phenyl boronic acid (1.5 mmol), CO (10 bar), 80 °C, 20 h.

[b] Conversion and yield were determined by GC using hexadecane as internal standard.

[c] CO (5 bar).

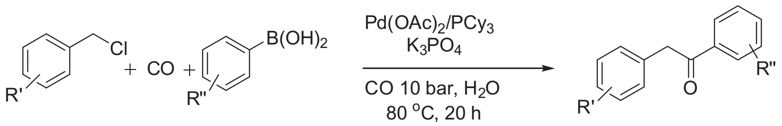
been largely neglected because it reacts preferentially as a nucleophile forming the corresponding carboxylic acids. To the best of our knowledge this is the first example using water as the single solvent in carbonylative Suzuki reactions.

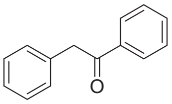
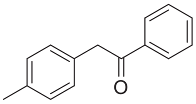
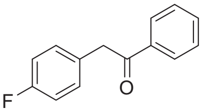
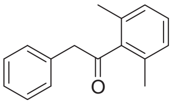
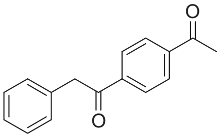
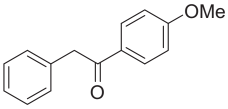
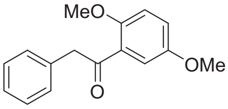
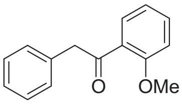
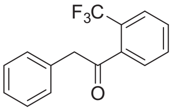
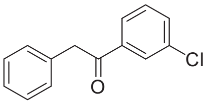
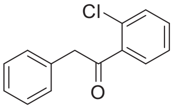
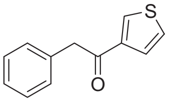
In the presence of quaternary ammonium salts, for example, TBAF or TBAB the direct Suzuki coupling is favored. Similarly, addition of 18-crown-6 led preferentially to the direct coupling by-product **2**.

Once optimized reaction conditions were identified, we investigated the influence of substituted benzyl chlorides and aryl boronic acids in this reaction.[15] As shown in Table 3 the palladium-catalyzed carbonylative Suzuki reaction took place under

Table 3

Palladium-catalyzed Suzuki carbonylation of different benzyl chlorides[a]



Entry	Product	Yield[b] (%)
1		73
2		78
3		47
4		58
5		54
6		55
7		41
8		58
9		53
10		58
11		69
12		50

[a] $Pd(OAc)_2$ (2 mol %), PCy_3 (4 mol %), K_3PO_4 (2 mmol), H_2O (2 ml), benzyl chlorides (1 mmol), phenyl boronic acids (1.5 mmol), CO (10 bar), 80 °C, 20 h.

[b] Isolated yields.

mild conditions (80 °C, 10 bar CO) in water. *Ortho*-, *meta*-, and *para*-substituted aryl boronic acids gave the corresponding products in moderate to good yields (Table 3, entries 4–11; 41–69%). There is no problem using sterically hindered 2,6-dimethyl phenyl boronic acid (Table 3, entry 4). In addition, 3-thiophenyl boronic acid as an example for a heterocyclic substrate works equally well in this system yielding 50% of the desired product (Table 3, entry 12).

It should be noted that in some cases (Table 3, entries 3–10) a significant amount of the direct Suzuki product was formed (30–45%) parallel to the carbonylation reaction. Especially, for activated benzyl chlorides, for example, *para*-nitro-substituted benzyl chloride, the direct coupling with phenyl boronic acid prevailed. In contrast more difficult coupling substrates, for example, *ortho*-substituted aryl boronic acids hampered the Suzuki reaction due to steric reasons and favored the desired carbonylation reaction.

In conclusion, we have developed novel carbonylative Suzuki reactions of benzyl chlorides and aryl boronic acids. This methodology allows for the straightforward synthesis of 1,3-diarylethanones, which represent useful building blocks for organic synthesis. Starting from inexpensive and easily available benzyl chlorides the corresponding ketones are obtained in moderate to good yields. Notably, these carbonylations can be performed in water as the solvent.

Acknowledgments

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13. See for example β-blocker Budavari; *The Merck Index*, 11th ed., Merck, Rahway, USA, 1989.
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15. *General reaction procedure for model reaction:* A 12 ml vial was charged with $Pd(OAc)_2$ (2 mol %), PCy_3 (4 mol %), K_3PO_4 (2 mmol), $PhB(OH)_2$ (1.5 mmol) and a stirring bar. Then, 2 ml H_2O (distilled, then degassed with argon within 1 h) and 1 mmol of benzyl chloride were injected by syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 ml autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO and adjusting the pressure to 10 bar, the reaction was performed for 20 h at 80 °C. After the reaction is finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The solution was extracted 3–5 times with 2–3 ml of ethyl acetate. After evaporation of the organic solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using *n*-heptane/AcOEt (50:1) as eluent. White solid (143 mg) was obtained as product, $R_f = 0.27$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91–7.98 (m, 2H), 7.44–7.52 (m, 1H), 7.34–7.42 (m, 2H), 7.13–7.30 (m, 5H), 4.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 136.6, 134.6, 133.2, 129.5, 128.73, 128.69, 128.67, 126.9, 45.6; GC–MS (EI, 70 eV): $m/z(\%) = 196$ (M+5), 105 (100), 91 (10), 77 (20), 65 (5), 51 (10).