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Palladium-Catalyzed Carbonylative Suzuki Coupling of Benzyl Halides with Potassium Aryltrifluoroborates in Aqueous Media

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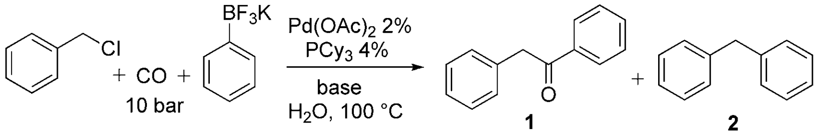
Abstract: A general palladium-catalyzed carbonylative cross-coupling reaction of benzyl chlorides with potassium aryltrifluoroborates in water has been developed. Applying this improved methodology 16 different 1,2-diarylethanones have been synthesized in 40–89% yield.

Keywords: benzyl chlorides; carbonylation; palladium; potassium aryltrifluoroborates; water

Palladium-catalyzed cross-coupling reactions have become one of the most popular tools for the synthesis of novel bio-active compounds and advanced materials.[1,2] Both academic as well as industrial laboratories continuously investigate new applications of the different known methodologies. Thus, this area constitutes one of the major topics in homogeneous catalysis and organic synthesis.[3] Among the different C–C cross-coupling reactions, also three component-type, carbonylations have been developed in the past.[4] These reactions, for example, carbonylative Heck,[5] Suzuki,[6] and Sonogashira reactions[7] allow for the preparation of interesting (hetero)aromatic carbonyl building blocks, which can be easily refined further on.

While carbonylations of aryl halides are well established, and even industrial processes are known,[8] carbonylative coupling reactions of alkyl or benzyl halides have been much less investigated.[9,10] For example in the area of carbonylative Suzuki reactions, until recently only two examples using benzyl halides have been published.[11] This is somewhat surprising considering the importance of the resulting 1,2-diarylethanone motif in known pharmaceuticals and biologically active compounds.[12] Hence, there is still a need to develop convenient and more general methodologies for the synthesis of this class of compounds.

Table 1. Carbonylative Suzuki cross-coupling: model reaction.[a]



Entry	Base	Conversion [%][b]	Yield **1** [%][b]	Yield **2** [%][b]
1	K_3PO_4	100	51	13
2	K_2HPO_4	100	17	16
3	KH_2PO_4	100	4	1
4	K_2CO_3	100	48	11
5	Na_2CO_3	100	36	22
6	$NaHCO_3$	100	56	4
7	$KHCO_3$	100	70	23
14[c]	$KHCO_3$	100	65	6
15[d]	$KHCO_3$	75	17	0

[a] $Pd(OAc)_2$ (2 mol%), PCy_3 (4 mol%), base (2 mmol), H_2O (2 mL), benzyl chloride (1 mmol), $PhBF_3K$ (1 mmol), CO (10 bar), 100 °C, 20 h.

[b] Conversion and yields were determined by GC; with use of hexadecane as internal standard.

[c] 80 °C.

[d] 50 °C.

Based on our interest in novel and improved palladium-catalyzed carbonylations,[13] very recently, we reported the coupling of benzyl chlorides with arylboronic acids to 1,2-diarylethanones in moderate to good yields.[14] Unfortunately, applying arylboronic acids as transfer reagents, the unwanted non-carbonylative coupling is comparably in rate to the carbonylative coupling process. Hence, the substrate scope of this reaction is limited.

Here, we report an improved and more general carbonylative coupling reaction of benzyl halides. Key to success is the use of potassium aryltrifluoroborates as more selective nucleophilic coupling partners.[15]

In our initial experiments, we studied the reaction of potassium phenyltrifluoroborate with benzyl chloride in the presence of carbon monoxide (Table 1).

At the start, we used similar reaction conditions, which have been applied for the carbonylative coupling of benzyl chloride with phenylboronic acid[14] (Table 1, entry 1). To our delight, 51% of 1,2-diphenylethanone **1** was obtained together with 13% of diphenylmethane **2**. It should be noted that phenylboronic acid only gave product **2** under these conditions. We explain this difference due to the increased stability of PhBF$_3$K, while PhB(OH)$_2$ forms more easily benzene.

Applying more acidic potassium phosphates as base gave lower yields (4–17%; Table 1, entries 2 and 3). On the other hand carbonates and bicarbonates led to comparable results to potassium phosphate, and up to 70% of product **1** is produced (Table 1, entries 4–7). The use of potassium or sodium acetate resulted in the formation of benzyl acetate, while benzyl alcohol was formed as the major product when potassium hydroxide was employed as base. Notably, in the presence of organic bases (DABCO, DMAP, and pyridine) no carbonylation product **1** is obtained, instead homo-coupling of benzyl chloride took place. Among all tested bases, KHCO$_3$ proved to be optimal yielding 70% of the desired product (Table 1, entry 7).

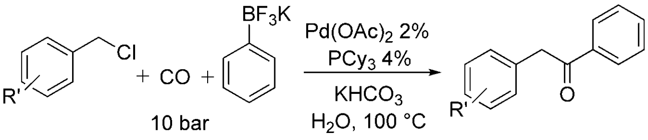
Next, several organic solvents (DMSO, DMF, and NMP) were tested in the presence of KHCO$_3$ as base. Unfortunately, only traces of product **1** and 40–50% of benzyl phenylacetate as a result of the corresponding alkoxycarbonylation were detected. To our surprise, running the model reaction in water worked well, despite the potential formation of the corresponding carboxylic acids.

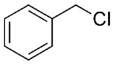
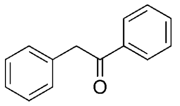
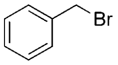
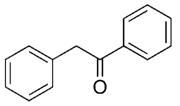
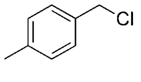
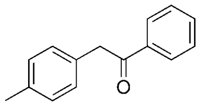
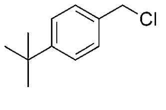
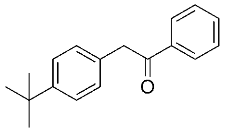
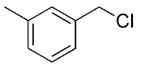
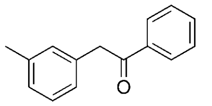
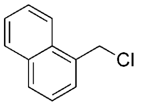
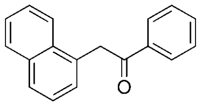
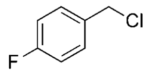
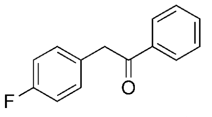
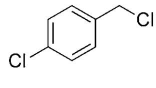
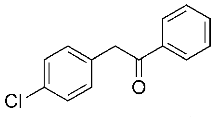
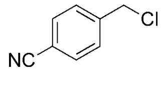
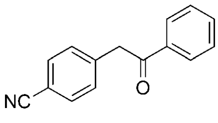
With respect to the CO pressure, 10 bar of carbon monoxide gave best results: Higher pressures (20 bar) inhibited the reactivity of palladium catalyst; lower pressures (5 bar) gave more non-carbonylation cross-coupling product **2.**

After having found suitable conditions for the model reaction, we explored the scope and limitations of our protocol. As shown in Table 2 and Table 3, the generality and versatility of the current methodology is proven by synthesizing 16 different 1,2-diarylethanones in moderate to good yields. More specifically, 9 different benzyl halides were reacted with potassium phenyltrifluoroborate to give the corresponding products in 55–89% yield (Table 2). Both electron-rich and electron-withdrawing substituted benzyl chlorides were successfully transformed (Table 2, entries 3–9).

Variations of the aryltrifluoroborates showed that different functional groups are tolerated (Table 3).

Table 2. Palladium-catalyzed carbonylative coupling of benzyl chlorides with potassium phenyltrifluoroborate.[a]



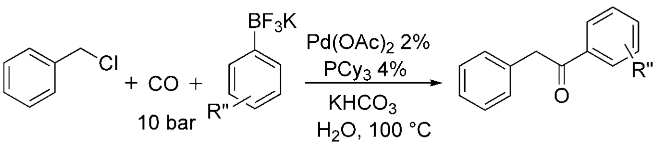
Entry	Benzyl chloride	Product	Yield [%][b]
1			70; 68;[c] 73[14]
2			62
3			72; 78[14]
4			85; 80[c]
5			80
6			89; 88[c]
7			55; 47[14]
8			63
9			60

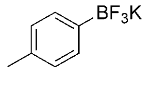
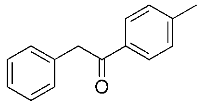
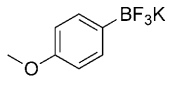
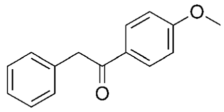
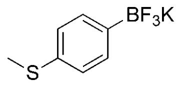
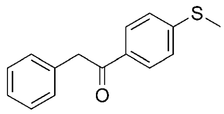
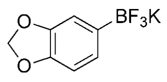
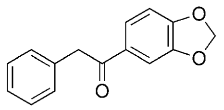
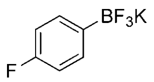
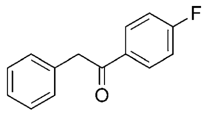
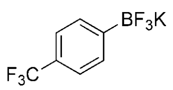
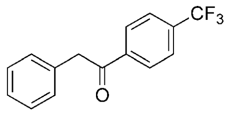
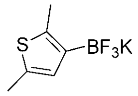
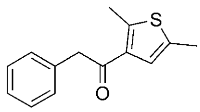
[a] Pd(OAc)$_2$ (2 mol%), PCy$_3$ (4 mol%), KHCO$_3$ (2 mmol), H$_2$O (2 mL), benzyl chlorides (1 mmol), PhBF$_3$K (1 mmol), CO (10 bar), 100 °C, 20 h.

[b] Yields were determined by GC.

[c] Isolated yield.

Table 3. Palladium-catalyzed carbonylative coupling of benzyl chloride with potassium aryltrifluoroborates.[a]



Entry	Arylborates	Product	Yield [%][b]
1			68
2			75; 75[c]
3			48
4			55
5			88; 85[c]
6			63
7			40

[a] $Pd(OAc)_2$ (2 mol%), PCy_3 (4 mol%), $KHCO_3$ (2 mmol), H_2O (2 mL), benzyl chloride (1 mmol), $ArBF_3K$ (1 mmol), CO (10 bar), 100 °C, 20 h.

[b] Yields were determined by GC.

[c] Isolated yield.

Hence, MeO, MeS, dioxole, F, and CF_3 substituted phenyltrifluoroborates gave the corresponding 1,2-diarylethanones in 48–88% yields (Table 3, entries 2–6). Moreover, 2,5-dimethylthiophenetrifluoroborate as an example of a heterocyclic borate gave 40% of the desired coupling product (Table 3, entry 7).

In conclusion, an improved method for the palladium-catalyzed carbonylative Suzuki coupling of benzyl chlorides with potassium aryltrifluoroborates has been developed. The reactions proceeds at low carbon monoxide pressure in water as benign solvent. Compared to previously known methods both electron-rich and electron-withdrawing substituted benzyl halides and arylborates are transformed into the corresponding 1, 2-diarylethanones in moderate to good yields.

Experimental Section

Typical Reaction Procedure for the Carbonylative Cross-Coupling of Benzyl Chloride and Potassium Phenyltrifluoroborate

A 4-mL vial was charged with $Pd(OAc)_2$ (2 mol%), PCy_3 (4 mol%), $KHCO_3$ (2 mmol), $PhBF_3K$ (1.0 mmol) and a stirring bar. Then, 2 mL H_2O (distilled, then degassed with argon within one hour) and 1 mmol of benzyl chloride were injected by syringe. The vial (or several vials) was (were) placed in an alloy plate, which was transferred into a 300-mL autoclave of the 4560 series from Parr Instruments® under an 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 100 °C. After the reaction had 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. The product was isolated as a white solid; yield: 133 mg (68%); $R_f = 0.27$. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 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, $CDCl_3$): $\delta = 197.7$, 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).

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