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Synthesis of diarylmethane derivatives from Pd-catalyzed cross-coupling reactions of benzylic halides with arylboronic acids

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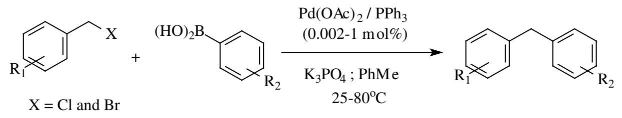
Abstract—A simple catalyst precursor prepared in situ from palladium acetate and triphenylphosphine shows high activity for the Suzuki cross-coupling reaction of benzylic bromides and chlorides with aryl boronic acids. The reaction can be carried out at low catalyst loading (0.002–1 mol%) and under mild conditions (room temperature to 80 °C) furnishing diarylmethane derivatives in high yields (86–99%).

The palladium-catalyzed cross coupling of aryl halides with arylboronic acids (Suzuki reaction) is a well established and efficient method for the construction of C_{aryl}–C_{aryl} bonds and has found widespread use in organic and polymer synthesis.[1] Diarylmethane derivatives, which are important building blocks in organic synthesis, can also be obtained by a Suzuki reaction by using benzyl halides in the place of aryl halides. For instance, Suzuki reactions employing a benzyl halide have been exploited to produce a macrobicycle and antagonists of the human EP3 receptor[2] and polybenzyls[3]. However, compared with aryl halides, few examples exist in which a benzylic halide is coupled under Suzuki conditions. Most of the Suzuki coupling reactions of benzyl halides were described with benylic bromides and $Pd(PPh_3)_4$ as catalyst (3–10 mol%).[2–4] $PdCl_2(dppf)$ [dppf = 1,1′-bis(diphenylphosphino)ferrocene] was also used for the Suzuki coupling reaction of cyclopropylboronic acids and esters with benzyl bromide using Ag_2O with KOH as the base.[5] Recently, it was reported that the tetrapodal phosphine ligand tedicyp [*cis*,*cis*,*cis*-1,2,3,4-tetrakis (diphenylphosphinomethyl) cylopentane] in conjunction with $[PdCl(C_3H_5)]_2$ is an efficient system for the coupling of benzylic chlorides and bromides with arylboronic acids.[6] On the other hand phosphine-free oxime-derived palladacycles were used as catalyst precursors for the cross-coupling reaction of benzylic chlorides with arylboronic acids in acetone–water at room temperature.[7] Over the last years, we have successfully applied Pd and Ni based catalyst systems for the Suzuki reactions of aryl halides and tosylates with arylboronic acids.[8] More recently we have used a mixture of $Pd(OAc)_2$ and PPh_3 as a catalyst precursor in a successful homogeneous and recyclable Suzuki cross-coupling reaction, and during these studies we have found that this system is also active for the coupling of benzyl halides with arylboronic acids.[9] In this paper, we wish to report that a simple system such as palladium acetate and triphenylphosphine is able to perform the Suzuki cross-coupling reaction of benzylic bromides and chlorides under mild conditions and with low loadings of catalyst.[10]



A set of experiments was performed in order to establish the best catalyst precursor, solvent, and base. Initially, we investigated the coupling of benzyl bromide with phenylboronic acids using different catalyst precursors (palladacycle $\{PdCl[o\text{-}C_6H_4CH(Me)StBu]\}_2$, $Pd(OAc)_2$/PPh_3, $NiCl_2(PCy_3)_2$, bases (K_3PO_4 and K_2CO_3), and solvents (THF, toluene, and DMA) under reaction conditions previously studied in our group.[8,9] Although all catalyst precursors gave the expected coupling product, palladium acetate in the presence of triphenylphosphine using toluene as solvent at 80 °C and K_3PO_4 as base was

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Keywords: Benzylic halides; Suzuki cross-coupling reaction; Diarylmethanes.

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Table 1. Pd-catalyzed Suzuki cross coupling reaction of benzyl bromide and chloride with phenylboronic acid[a]

Entry	X	Pd (mol%)	PR_3	*T* (°C)	Conv (%)	Yield[b] (%)
1	Br	1	—	80	23	17
2	Br	1	PCy_3	80	100	94
3	Br	1	PCy_3	25	93	83
4	Cl	1	PCy_3	80	62	44
5	Br	1	PPh_3	80	100	100
6	Br	1	PPh_3	25	100	100
7	Cl	1	PPh_3	80	100	100
8	Cl	1	PPh_3	25	100	100
9	Cl	0.1	PPh_3	80	100	100
9	Cl	0.02	PPh_3	80	94	94
10	Cl	0.002	PPh_3	80	60	60
11	Br	0.002	PPh_3	80	66	54

[a] Reaction conditions: benzyl halide (1 mmol), phenylboronic acid (1.5 mmol), K_3PO_4 (2 mmol), $Pd(OAc)_2/PR_3$ ratio = 2, toluene (3 mL), 15–19 h (reaction times were not optimized).

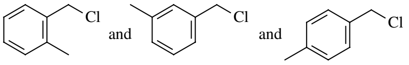
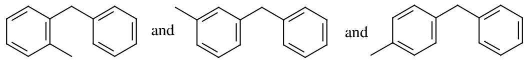
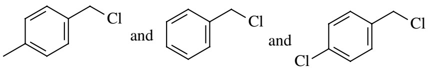
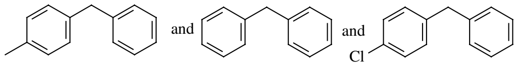
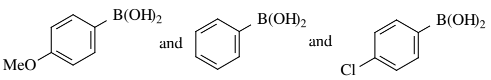
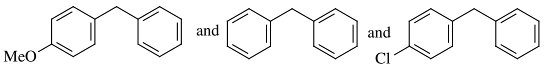
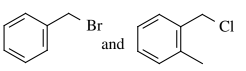
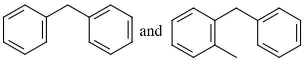
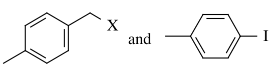
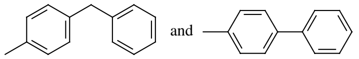
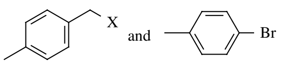
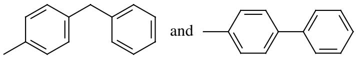
[b] GC yields.

the most effective system, and was chosen for further optimization studies (Table 1). Low conversion was obtained in the absence of phosphine ligand (Table 1, entry 1). Although PCy_3 is known to give very active palladium-based catalytic systems for the coupling of aryl chlorides,[11] incomplete conversion for the coupling of benzyl bromide at room temperature and for the coupling of benzyl chloride was obtained using tricyclohexylphosphine as ligand (entries 2–4). We were delighted to see that not only benzyl bromide but also benzyl chloride could be quantitatively coupled at room temperature by using 1 mol% of $Pd(OAc)_2$ and triphenylphosphine as ligand (entries 5–8) and 0.1 mol% catalyst loading at 80 °C (entry 9). The coupling reaction of benzyl chloride and bromide could be performed even at 0.002 mol% catalyst loading with a TON of 3000 (entries 10 and 11) but no conversion of the substrates was observed at 0.0002 mol% catalyst loading. Although the reactions were carried out overnight, we observed a complete conversion of benzyl chloride after 3 and 11 h, when 1 mol% and 0.1 mol% catalyst loading were used, respectively (entries 7 and 9).

In order to gain some insight into the effect of the ring substituents and the nature of the leaving group on the reaction outcome, a number of competitive experiments were performed (Table 2). No significant effect was observed by changing the position of a methyl group in the ring (Table 2, entry 1) or the substituent group on the aromatic ring of benzyl chloride and arylboronic acid (Table 2, entries 2 and 3). These results indicate that the cross-coupling reaction of benzyl chlorides is much less sensitive to steric and electronic effects than we have observed for the reaction of aryl halides.[8] On the other hand, as observed for aryl halides, bromide is a better leaving group than chloride, and the cross-coupling reaction of benzyl bromide is five times faster than the coupling of *o*-methylbenzyl chloride (Table 2, entry 4).

Since aryl halides have been extensively studied in the Suzuki coupling reaction, we tried to establish a relative

Table 2. Competitive Pd-catalyzed Suzuki cross coupling reactions with phenylboronic acids[a]

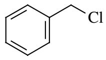
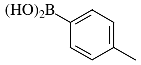
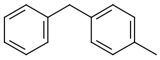
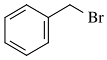
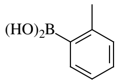
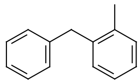
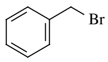
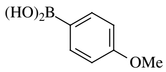
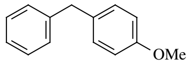
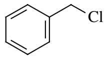
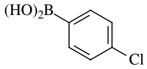
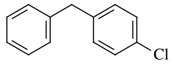
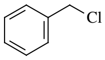
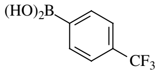
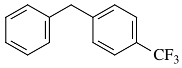
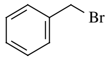
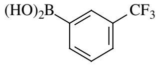
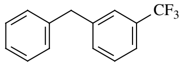
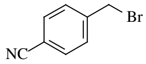
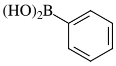
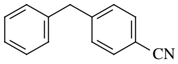
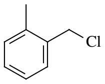
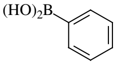
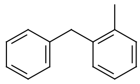
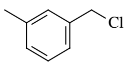
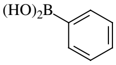
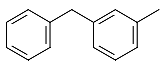
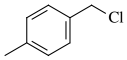
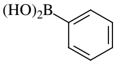
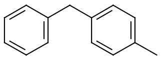
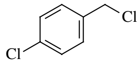
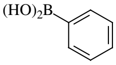
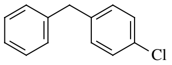
Entry	Benzyl or aryl halides	Coupling products (relative ratio)[b]
1		 42 36 22
2		 37 25 39
3[c]		 35 29 36
4		 83 17
5 (X = Br) 6 (X = Cl)		 X = Br 3 97 X = Cl 0 100
7 (X = Br) 8 (X = Cl)		 X = Br 100 0 X = Cl 88 12

[a] Reaction conditions: benzylic or aryl halides (0.5 mmol each), phenylboronic acid (0.05 mmol), K_3PO_4 (1 mmol), $Pd(OAc)_2$ (0.0005 mmol), PPh_3 (0.0015 mmol), toluene (3 mL), 1 h, 80 °C.

[b] Average of two or three runs (determined by GC).

[c] $PhCH_2Cl$ (0.05 mmol), arylboronic acids (0.5 mmol each).

Table 3. Pd-catalyzed Suzuki cross coupling reaction of benzylic halides with arylboronic acids[a]

Entry	ArX	$ArB(OH)_2$	Biaryl	Yield (%)[b]
1				97
2				93
3				96
4				91
5				86
6				96
7				99
8				91
9				96
10				90
11				96

[a] Reaction conditions: benzylic halide (1 mmol), arylboronic acid (1.5 mmol), K_3PO_4 (2 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.02 mmol), toluene (3 mL), 19 h (reaction times were not optimized).

[b] Isolated yields.

order between the halide substrates. Using $Pd(OAc)_2$/PPh_3 under the optimized conditions obtained in this work the reactivity order found was: aryl iodide > benzyl bromide > benzyl chloride > aryl bromide (Table 2, entries 3–6).

Encouraged by these results we applied the optimized conditions for the Suzuki coupling reactions of a range of benzylic and arylboronic substrates (Table 3).[12] As anticipated from the competitive reactions, all the substrates investigated gave the diarylmethane products in good yields (86–99%).

In summary, we have found that simple catalyst precursor prepared in situ from palladium acetate and triphenylphosphine can be used for the Suzuki cross-coupling reaction of benzylic bromides and chlorides with arylboronic acids. The reaction can be carried out at low catalyst loading (0.002–1 mol%) and mild conditions (room temperature to 80 °C) furnishing diarylmethane derivatives in high yields (86–99%). From a synthetic point of view this protocol is a cheap and easy alternative for the synthesis of diarylmethanes from benzylic halides and arylboronic acids.

Acknowledgements

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12. In a typical experiment an oven-dried resealable Schlenk flask was evacuated and back filled with argon and charged with $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.02 mmol), arylboronic acid (1.5 mmol), and K_3PO_4 (2 mmol). The flask was evacuated and back filled with argon, and then the benzyl halide (1 mmol) and toluene (3 mL) were added. The reaction mixture was stirred at the desired temperature for 19 h. The solution was then taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 5 mL) and brine (2 × 5 mL), and then dried over $MgSO_4$. After purification by flash chromatography the diarylmethane product was characterized by ^1H and ^{13}C NMR, IR, and GC–MS.