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Palladium-catalyzed benzylation of *N*-Boc indole boronic acids

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ABSTRACT

The direct benzylation of indole 2-boronic acid can be efficiently achieved using *trans*-PdBr(*N*-Succ)(PPh_3)$_2$, alleviating the need for strong bases or toxic organotin reagents. Under these reaction conditions substituted indole-2-boronic acids and substituted benzyl bromides are cross-coupled to afford aryl(indolo)methanes in good yield.

Carbon–carbon bond-forming processes catalyzed by palladium species are widely known and applied in organic chemistry.[1] One of the particular utilities is the broadly used and very efficient Suzuki cross-coupling of aryl and heteroaryl boronic acids with aryl bromides or chlorides.[2] A number of catalyst systems have been developed in the laboratories of Buchwald,[3] Fu,[4] Kuwano,[5] and Taylor.[6] However, the cross-coupling of *N*-heterocyclic 2-boronic acids still remains a problem. The main issue with this type of cross-coupling is the reduction of the boronic acid moiety in a process known as protodeboronation.[7]

More specifically, the use of indole-2-boronic acids in Suzuki cross-coupling reactions in combination with activated benzyl groups has not been described in the literature. To accomplish the desired transformation, two alternative methods have been developed. The first involves the deprotonation of the 2-position using lithium diisopropylamide and subsequent quenching with the desired benzyl bromide.[8] The downside of this route is the necessary use of a strong base, which significantly decreases functional group compatibility. The second approach requires the synthesis of the aryl tin species through the same deprotonation sequence as described above, followed by palladium-catalyzed Stille cross-coupling reaction with benzyl bromides.[9] The toxicity associated with organotin species motivated us to investigate an alternative method.

In our initial experiments, different palladium catalysts and pre-catalysts were screened for the formation of the desired coupling product between 6-cyano-indole 2-boronic acid **1** and 3-fluorobenzyl bromide **2**. The results of these reactions are summarized in Table 1.

After screening both palladium(0) and palladium(II) species with different phosphine (mono- and bidentate) and arsine ligands, the first successful reaction was accomplished using an allylpalladium chloride dimer diphenylphosphino-pentane catalyst system and potassium carbonate as a base (entry 5). While this catalyst system generated the desired product **1a**, an equal amount of protodeboronated product **2** was also observed. Similar results were observed when $Pd(PPh_3)_4$ was employed (entry 6). In continuing to profile other palladium(II) catalysts, we investigated *trans*-PdBr(*N*-Succ)(PPh_3)$_2$ in combination with aqueous Na_2CO_3 and, to our delight, a 4:1 ratio of cross-coupling product **1a** to the byproduct **2** was obtained (Table 1, entry 7). In an attempt to better understand the rate of the reaction as well as other factors associated with the protodeboronation event, a kinetic study was conducted.

This investigation was conducted on 6-cyanoindole-2-boronic acid in THF at 60 °C. In order to determine the potential role of *trans*-PdBr(*N*-Succ)(PPh_3)$_2$ in the protodeboronation, the reactions were run with or without the catalyst. In addition, the concentration of aqueous sodium carbonate was varied. The results of this investigation are summarized in Table 2.

Initial experiments revealed that the rate of protodeboronation was not significantly affected by the presence of the catalyst, as both reactions led to similar ratios after 15 min (Table 2, entries 1 and 2). Furthermore, varying the concentration of base had no influence on the formation of **2** (Table 2, entries 1 and 4). The results from the kinetic study indicated that the protodeboronation event is fast with about 30% of **2** after only 5 min (Table 2, entries 3 and 5) and almost complete degradation of the starting material **1a** after 30 min (Table 2, entry 6).

From the brief study of several readily available palladium catalysts and with the knowledge on the stability of the starting material under the reaction conditions, we established that *trans*-PdBr(*N*-Succ)(PPh_3)$_2$ was the most effective catalyst. This palladium source is able to efficiently catalyze the carbon–carbon bond formation at a rate that competes with the protodeboronation pathway.

The scope of the palladium-catalyzed benzylation reaction was explored by using 5% of palladium, 2 M Na_2CO_3 in THF at 60 °C for 1 h. A series of commercially available indole-2-boronic acids were reacted with a variety of substituted benzyl bromides.[10] The

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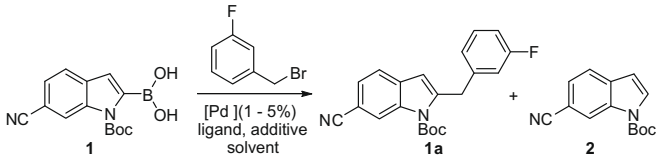
Table 1
Examples of catalysts screened for the palladium-catalyzed cross-coupling of indole 2-boronic acids and benzyl bromides

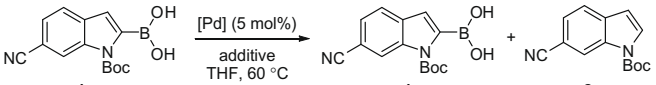


1 1a 2

Entry	Catalyst	Ligand	Additive	Solvent	T (°C)	t (h)	**1a**:2[a]
1	$Pd(OAc)_2$	PPh_3	K_3PO_4	Dioxane	80	12	ND[b]
2	$Pd_2(dba)_3$	PCy_3	K_3PO_4	Dioxane	100	18	0:100
3	$PdCl_2(MeCN)_2$	$AsPh_3$	Ag_2O	Dioxane	80	12	ND[b]
4	$Pd(dba)_2$	DPPPent	Na_2CO_3	THF	60	0.5	0:100
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	DPPPent	K_2CO_3	DMF	60	3	50:50
6	$Pd(PPh_3)_4$	—	K_3PO_4	Dioxane/H_2O	90	3	60:40
7	*trans*-PdBr(Succ)$(PPh_3)_2$	—	2 M Na_2CO_3	THF	60	2	80:20

[a] % Conversion by HPLC.
[b] Uncharacterized byproducts.

Table 2
Kinetic study on the effects of catalyst and base present on protodeboronation side reaction



1 1 2

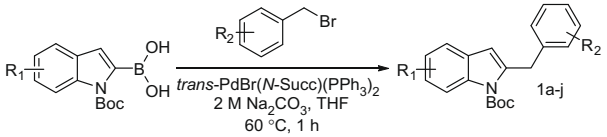
Entry	Catalyst	Additive	t (min)	Ratio (1:2)[a]
1	NONE	2 M Na_2CO_3	10	23:77
2	*trans*-PdBr(N-Succ)$(PPh_3)_2$	2 M Na_2CO_3	10	36:64
3	NONE	4 M Na_2CO_3	5	67:33
4	NONE	4 M Na_2CO_3	20	11:89
5	*trans*-PdBr(N-Succ)$(PPh_3)_2$	4 M Na_2CO_3	5	72:28
6	*trans*-PdBr(N-Succ)$(PPh_3)_2$	4 M Na_2CO_3	30	10:90

[a] Ratio determined by HPLC (λ = 254 nm).

results of these experiments are shown in Table 3. The transformation appears to be compatible with many functional groups; electron-donating as well as electron-withdrawing groups were equally tolerated on both the indole and benzyl bromide reaction partner. It should be noted that esters were also allowed, resulting in clean conversion to the desired products (Table 3, entries 1g and 1j) without any hydrolysis. Ketones (Table 3, entry 1d) and silyl-protected phenols (Table 3, entry 1i) were also used as successful coupling partners, further expanding the toleration of base-sensitive functionality. An aryl bromide moiety was introduced in an attempt to invoke cross reactivity within the palladium catalytic cycle. Interestingly, the reaction appears to be highly selective for reaction with a benzyl bromide rather than an aryl bromide (Table 3, entries 1c and 1d). The position of the benzyl group was verified via 2-D NMR NOESY experiments. It should be noted that the reaction of an indole-2-boronic acid with α-bromoethylbenzene under typical reaction conditions afforded only the protodeboronation product, suggesting that substitution at the α-position impedes the catalytic cycle, permitting uncontrollable side reaction.

In summary, the Suzuki cross-coupling reaction of substituted indole-2-boronic acids with substituted benzyl bromides has been reported. This reaction eliminates the need for strong bases or toxic reagents. Conditions that tolerate a variety of sensitive functional groups and minimize protodeboronation were identified. The benzylated indole products are formed in moderate to high yields while retaining the *N*-Boc functionality, thus allowing for further manipulation.

Table 3
The palladium-catalyzed cross-coupling of indole-2-boronic acids and benzyl bromides



Entry	R_1	R_2	Yield[a] (%)
1a	6-CN	3-F	60
1b	H	3-F	55
1c	4-Br	3-F	60
1d	4-Br	4-COMe	60
1e	7-OMe	2-Me	77
1f	7-OMe	4-OMe	79
1g	6-CO_2Me	H	82
1h	6-Cl	4-CF_3	62
1i	5-OTBS	3-Cl	85
1J	6-OBn	4-CO_2Me	58

[a] Isolated yield.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.124.

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10. *General procedure for the benzylation of N-Boc-protected indoles*. 6-Cyano-2-(3-fluoro-benzyl)-indole-1-carboxylic acid *tert*-butyl ester (**1a**): To a 20 mL scintillation vial containing a stir bar was added 1-Boc-6-cyanoindole-2-boronic acid (286 mg, 1 mmol) and *trans*-bromo(*N*-succinimidyl)-bis(triphenylphosphine)palladium(II) (purchased from Aldrich Chemical Co.) (40 mg, 0.05 mmol) followed by the addition of anhydrous THF (2.5 mL). Upon dissolution, 3-fluorobenzyl bromide (122 μL, 1 mmol) was added as a single portion via syringe. The pale orange reaction mixture was diluted with 2.0 M Na_2CO_3 (1.25 mL) to form a biphasic reaction mixture that was warmed to 60 °C and allowed to stir for 1 h. Analytical methods (TLC, HPLC) showed complete consumption of the starting boronic acid, the reaction was then cooled to room temperature and diluted with water (10 mL). The resulting solution was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford the crude product as an orange oil. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes) to afford the pure indole product as an oil (148 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.46 (dt, J = 8.1, 4.7, 2H), 7.33–7.27 (m, 1H), 7.01–6.93 (m, 2H), 6.93–6.87 (m, 1H), 6.22 (s, 1H), 4.39 (s, 2H), 1.61 (s, 9H). HPLC R_f = 3.4 min, 92% purity. MS (ESI) mass calcd for $C_{21}H_{19}N_2O_2F$, 350.39; m/z found, 351.0 $[M+H]^+$.