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Palladium catalyzed Suzuki cross-coupling of benzyltrimethylammonium salts *via* C–N bond cleavage†

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A palladium catalyzed Suzuki cross-coupling for construction of Csp^3–Csp^2 bond *via* Csp^3–N bond activation of benzyltrimethyl-ammonium salt is described. This reaction not only offered a highly efficient approach to diarylmethanes but also paved the way for the application of benzyltrimethylammonium salts in the palladium catalyzed cross coupling reactions.

Palladium catalyzed cross-coupling reactions between various electrophiles and nucleophilic metal reagents are highly practical methodologies for C–C bond formation.[1] They are one of the significant accomplishments of last century's chemistry and their significance has been recognized by the 2010 Nobel Prize in Chemistry. Among these cross coupling reactions, the Suzuki reaction, the coupling between organoborane reagents and electrophiles, is the most popular one because of the inherent advantages of organoboron reagents, such as air- and moisture-stability, good functional group tolerance, low toxicity and wide availability. A variety of electrophiles such as aryl halides,[2] triflates,[3] mesylates/tosylates,[4] esters,[5] ethers,[6] and phosphates[7] have been developed for this reaction. Very recently, the transition metal catalyzed Suzuki coupling reactions involving the C–N bonds cleavage have attracted much attentions.[8] Quaternary ammonium salts[9] are the most important C–N bond containing electrophiles due to their wide availability and high reactivity. Macmillan and co-workers reported the first Ni catalyzed Suzuki cross-couplings of aryltrimethylammoniums.[8i] Watson extended this concept to benzyltrimethyl ammoniums and realized the stereospecific preparation of enantioenriched diarylethanes.[8j] However, both cases involved the using of air and moisture sensitive Ni catalysts which limited their practical application. Compared with Ni catalyzed reactions carried out under inert atmosphere, palladium catalyzed coupling reactions are relatively easy to handle. However, the palladium catalyzed cross-coupling reactions involving C–N bond cleavage of quaternary ammonium salts remained rare. Recent studies demonstrated that palladium could be used as valid catalyst for cross-coupling reaction of quaternary ammonium salts. Wang and co-workers reported a palladium catalyzed C–H arylation of oxazoles with aryltrimethyl-ammonium salts.[10] Reeves developed the palladium catalyzed cross-coupling between aryltrimethylammonium salts and Grignard reagents.[11] However, palladium catalyzed Suzuki cross-coupling of quaternary ammonium salts is still kept untouched. In addition, considering the diversity of palladium catalyzed organic transformations, establishment of robust palladium catalyst systems for activating the C–N bond of quaternary ammonium salts would be valuable for exploring their application in organic synthesis. In such context, we herein reported the first palladium catalyzed Suzuki coupling with benzyltrimethylammoniums as the electrophile partner.

Diarylmethane derivatives have been widely used in pharmaceuticals and materials (Fig. 1).[12] Very recently, Rhee disclosed that the synthesis of diarylmethanes could be accomplished by palladium catalyzed Suzuki cross-coupling of *N*,*N*-ditosylbenzylamines[13] *via* C–N bond activation. We envisioned that palladium catalyzed Suzuki cross-coupling of benzylammonium salts with aryl boronic acids would be an effective approach to diarylmethanes. It is initiated by investigating the crossing coupling of 4-cyanophenyl boronic acid with benzylammonium salt **1a**, which is readily prepared

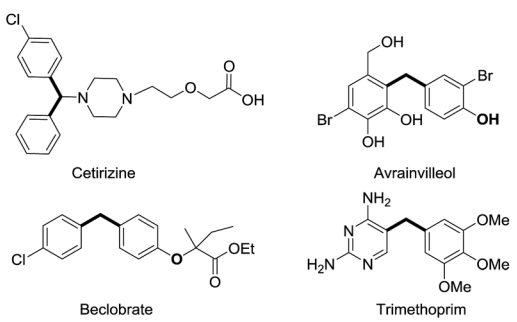

Fig. 1 Drugs containing diarylmethane motif.

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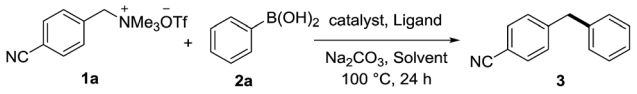
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (3 mol%)	Ligand (10 mol%)	Solvent	Yield[b] (%)
1	$PdCl_2$	—	Mixture	—
2	$PdCl_2$	dppf	Mixture	—
3	$PdCl_2$	dppp	Mixture	—
4	$PdCl_2$	Xantphos	Mixture	Trace
5	$PdCl_2$	PPh_3	Mixture	67(65)
6	$Pd(acac)_2$	PPh_3	Mixture	65
7	$Pd_2(dba)_3$	PPh_3	Mixture	63
8	$Pd(TFA)_2$	PPh_3	Mixture	57
9	$PdCl_2(PPh_3)_2$	PPh_3	Mixture	55
10	$Pd(PPh_3)_4$	PPh_3	Mixture	54(50)
11	$PdCl_2(dppf)_2$	PPh_3	Mixture	50
12	$Pd(OAc)_2$	PPh_3	Mixture	20
13	$PdCl_2$	PPh_3	PhMe	34
14	$PdCl_2$	PPh_3	DMSO	18
15	$PdCl_2$	PPh_3	DMF	54
16	$PdCl_2$	PPh_3	CH_3CN	43
17	$PdCl_2$	PPh_3	THF	32
18	$PdCl_2$	PPh_3	EtOH	75
19[c]	$PdCl_2$	PPh_3	EtOH	99(98)
20[d]	$PdCl_2$	PPh_3	EtOH	97
21[e]	$PdCl_2$	PPh_3	EtOH	96

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (3 mol%), ligand (10 mol%) and Na_2CO_3 (2 equiv.) in solvent (1 mL) at 100 °C. Mixture: toluene : DMSO = 9 : 1. [b] GC yield, isolated yield was indicated parentheses. [c] EtOH (3 mL). [d] Potassium phenyltrifluoroborate was used in place of boronic acid. [e] Phenylboronic acid pinacol ester as the boron reagent.

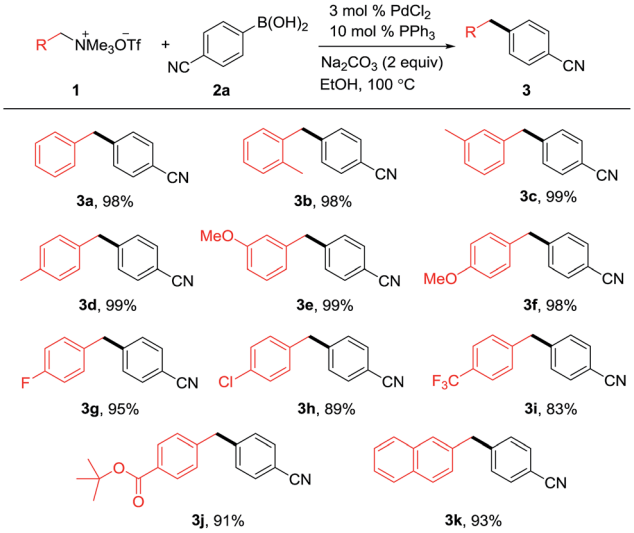
quantitatively *via* methylation of 4-cyano-*N*,*N*-dimethylbenzylamine. As shown in Table 1, the reaction is sensitive to ligand. Only the monodentate PPh_3 ligand afforded moderate yield of target diarylmethane accompanied by significant amount of homo coupling product of boronic acid when $PdCl_2$ was used as the catalyst. Although further screening of palladium catalysts did not offer any improvement, a dramatic solvent affect was observed (Table 1, entries 13–18). In particularly, homo coupling of boronic acid, the notorious issue of Suzuki cross-coupling, could be suppressed significantly by using ethanol as the solvent. We were delighted to observe that the homo coupling could be suppressed completely when more ethanol was used (Table 1, entry 19). In turn, the yield of cross coupling product was increased up to quantitative. The similar reaction efficiencies were observed when potassium phenyltrifluoroborate and phenylboronic acid pinacol ester were used as the boron reagent (Table 1, entry 20 & 21).

With the optimized reaction conditions in hand, we next set out to evaluate the generality of benzylammonium salts with 4-cyanophenyl boronic acid as a model substrate. As shown in Scheme 1, a broad substrate scope of benzylammonium salts was observed. It seems that the electronic effect and the steric effect of the substituents on the benzylammonium salts have little effect on the reaction efficiency. No matter electron-donating (**3b–f**) or -withdrawing (**3g–j**) groups on the phenyl ring of benzylammonium salts, good to excellent yields were obtained. The *ortho* methyl substituent could be tolerated (**3b**). Notably, the C–N bond could be selectively cleaved in the presence of ether (**3e** & **3f**), fluoro (**3g**) and chloro (**3h**) groups albeit bromo and iodo-substituted benzylammonium salts did not offer the target cross coupling products.

The substrate scope of boronic acids had also been investigated and the results are summarized in Scheme 2. Moderate electron-withdrawing and -donating groups were tolerated while their stronger congeners cause slight decrease in yield. Even the steric demanding 2,6-dimethyl substituents were tolerated (**3aa**). It is noted that a series of functional groups such as carbonate (**3ag**), aldehyde (**3ai**) and ester (**3aj**) were compatible. In addition, diarylmethanes containing heterocycles such as pyridine (**3ak**), furan (**3al**) and thiophene (**3am**) could also be prepared by this method. Styrylboronic acid also proceeded smoothly to furnish the cross coupling product in excellent yield (**3ao**). No evidence of Heck coupling was observed when (4-vinylphenyl)boronic acid was employed as the substrate (**3an**). Interestingly, for some cases (**3a–d**, **3f–i**), we could get the same products with that of Scheme 1 from different set of starting materials by employing the standard reaction conditions. This advantage will be more prominent when one of the starting material is more expensive or not available.

A significant functional group orthogonality to chloride, fluoride, ether and amine for benzylammonium salts as well as boronic acids was observed in this methodology. For example, the chloro group was kept intact in both cases (**3h**) and thus affording an opportunity for further functionalization. This feature was exemplified by sequential Suzuki-cross couplings (Scheme 3).

A plausible reaction mechanism was proposed in Scheme 4. The oxidative addition of Pd(0) **A** formed *in situ*, with



Scheme 1 Palladium-catalyzed reaction of 4-cyanophenyl boronic acid with various benzylammonium salts. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (3 mol%), PPh_3 (10 mol%) and Na_2CO_3 (0.4 mmol) in ethanol (3 mL) at 100 °C for 18–24 h. Isolated yields were given.

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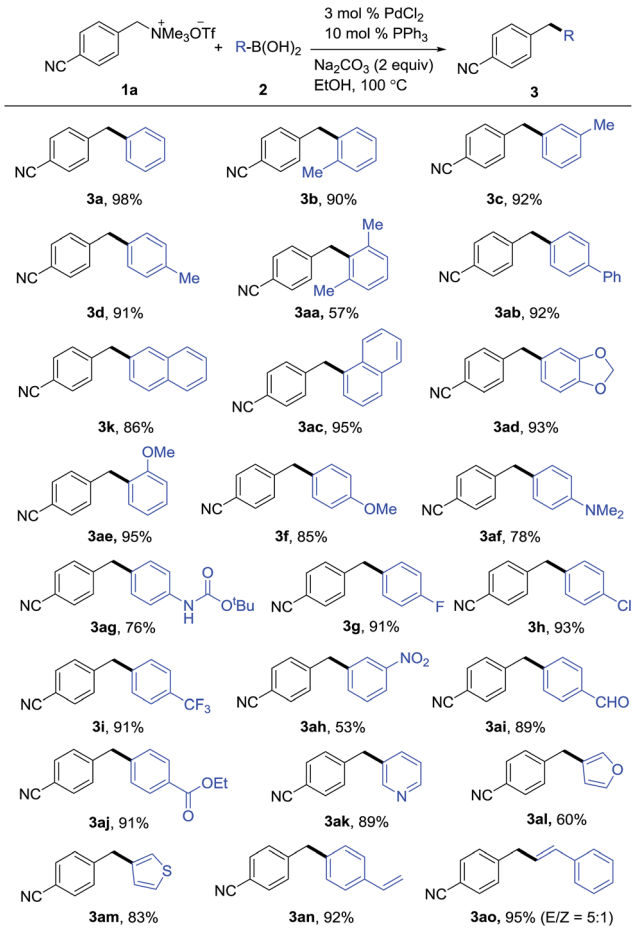
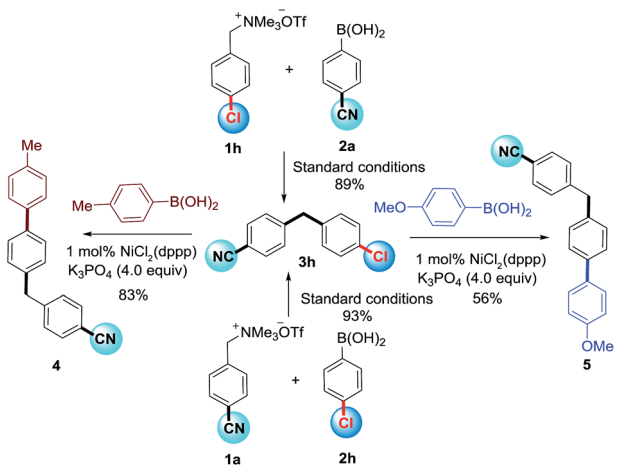
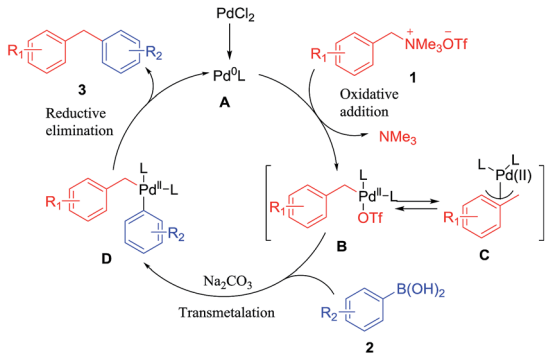


Scheme 2 Palladium-catalyzed reaction of 1-(4-cyanophenyl)-*N*,*N*,*N*-trimethylmethanaminium trifluoromethanesulfonate reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $PdCl_2$ (3 mol%), PPh_3 (10 mol%) and Na_2CO_3 (0.4 mmol) in ethanol (3 mL) at 100 °C for 18–24 h. Isolated yields were given.

benzyltrimethylammonium salt **1** produced C–Pd complex **B** with the release of trimethylamine. Followed by a transmetalation with boronic acid, the palladium complex **B** afforded



Scheme 3 Sequential Suzuki crossing couplings.



Scheme 4 Proposed reaction mechanism.

a new complex **D**, which upon reductive elimination furnished the cross coupling product **3**.

In summary, we have developed the first palladium catalyzed Suzuki cross-coupling reaction of quaternary ammonium salts. This reaction represented the first example of palladium catalyzed Csp^3–Csp^2 coupling of benzyltrimethylammonium salts *via* C–N bond activation. It not only offered an effective synthetic strategy to diarylmethane derivatives but also paved the way for the unprecedented palladium catalyzed cross-coupling of benzyltrimethyl ammonium salts. Further application of the catalyst system to other palladium catalyzed cross-coupling reactions of benzyltrimethyl ammonium salts are undergoing in our laboratory and the results will be reported in due course.

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