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Cross coupling of benzylammonium salts with boronic acids using a well-defined N-heterocyclic carbene–palladium(II) precatalyst†

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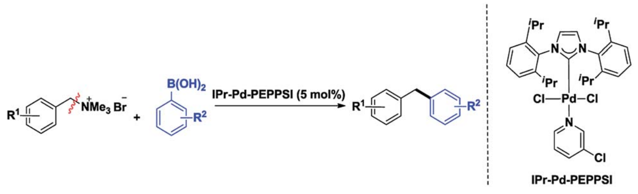
N-heterocyclic carbene–palladium(II)-catalyzed cross-coupling of benzylammonium salts with arylboronic acids for the synthesis of diarylmethane derivatives *via* C–N bond activation has been developed. Notably, in the presence of the easily prepared and bench-stable Pd-PEPPSI precatalyst, the Csp^3–N bond activation of the benzylammonium salt even proceeded smoothly in isopropanol at room temperature.

Studies on synthetic methods of diarylmethane derivatives have attracted considerable attention because the compounds are important structural units in organic synthesis, materials science and pharmaceutical development.[1] Among the synthetic approaches explored, transition metal catalyzed Suzuki coupling is one of the most important and frequently used methods. Over the past decade, the most popular strategies for the cross coupling of benzyl halides[2] and benzyl sulfonates[3] with aryl boric acid using Pd-catalysis have been reported. Disappointingly, some obvious drawbacks are involved with the use of benzyl halides and benzyl sulfonates as the electrophiles. These reagents are sometimes difficult in terms of substrate tolerance and storage. During recent years, the transition metal catalyzed Suzuki coupling reactions by the C–N bonds cleavage have been developed.[4] Among them, the cross coupling of quaternary ammonium salts has been quite well explored because they are more easily available from amine precursors or benzyl halides and they are also stable to long-term storage. Since the pioneering work of MacMillan and co-workers in 2003,[5] with aryltrimethylammonium salts as the electrophiles in various catalytic reactions such as cross-coupling,[6] C–H arylation,[7] borylation[8] and reductive carboxylation reactions[9] have been carried out. Although excellent results have been obtained, the optimization and development of cross-coupling reactions involving Csp^3–N bond cleavage of benzylammonium salts under mild conditions, such as in aqueous media or at room temperature, are still worthwhile projects.[10] In this present contribution, we have developed efficient catalytic systems[11–13] for the Suzuki–Miyaura coupling of benzyl chlorides with arylboronic acids, producing the corresponding diarylmethane derivatives in high yields. In a recent communication, the N-heterocyclic carbene–palladium(II) complexes were also found to be active catalysts for the Suzuki–Miyaura cross-coupling of *N*-acylsuccinimides with arylboronic acids *via* C–N bond activation.[14] Considering our successful experience with the applications of this complexes in the cross-coupling reaction, we then turned our recent interest to the coupling reaction between benzylammonium salt and arylboronic acids for the formation of diarylmethane derivatives. In such context, we herein report the first example of NHC–Pd-PEPPSI catalyzed coupling reactions of benzylammonium salts with arylboronic acids *via* Csp^3–N bond activation under mild conditions (Scheme 1).

It is initiated by investigating the crossing coupling of 4-methoxyphenyl boronic acid with benzyltrimethylammonium bromide **1a**, which is readily prepared quantitatively *via* the reaction of trimethylamine and benzyl bromide. The details were shown in Table 1. The choice of base is crucial to the yield of the reaction (Table 1, entries 1–9).[15] In the presence of the IPr–Pd-PEPPSI complex **4a** as the catalyst, $K_3PO_4 \cdot 3H_2O$ as the base in isopropanol at 70 °C, we were delighted to observe that the reaction gave the corresponding diarylmethanes



Scheme 1 NHC–Pd(II) catalyzed coupling reactions of benzylammonium salts with arylboronic acids *via* Csp^3–N bond activation.

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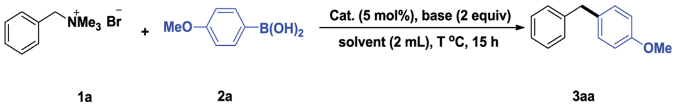
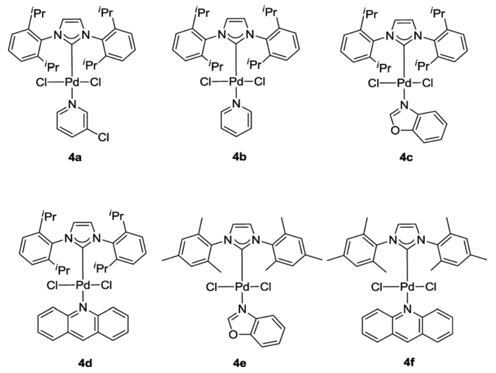
Table 1 Optimization of the cross-coupling reaction on substrate **1a**[a]

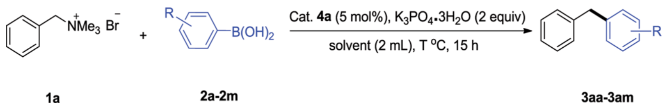


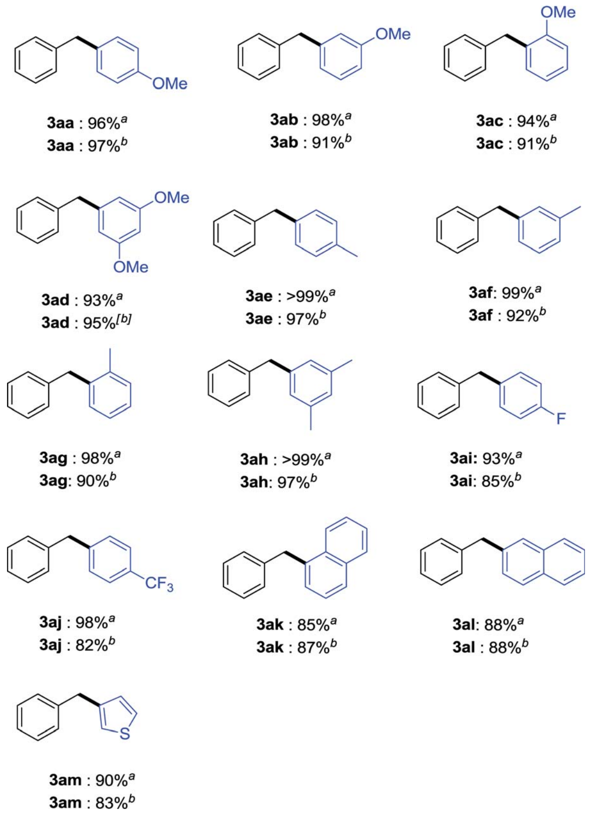


Entry	Cat.	Base	Solvent	Temp (°C)	Yield[c] (%)
1	**4a**	KO^{t}Bu	^{i}PrOH	70	89
2	**4a**	Na_2CO_3	^{i}PrOH	70	Trace
3	**4a**	K_2CO_3	^{i}PrOH	70	91
4	**4a**	$NaHCO_3$	^{i}PrOH	70	Trace
5	**4a**	K_3PO_4	^{i}PrOH	70	70
6	**4a**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	70	>99
7	**4a**	NaOAc	^{i}PrOH	70	Trace
8	**4a**	NaOH	^{i}PrOH	70	90
9	**4a**	KOH	^{i}PrOH	70	98
10	**4a**	$K_3PO_4\cdot 3H_2O$	THF	70	47
11	**4a**	$K_3PO_4\cdot 3H_2O$	1,4-Dioxane	70	98
12	**4a**	$K_3PO_4\cdot 3H_2O$	EtOH	70	88
13	**4a**	$K_3PO_4\cdot 3H_2O$	Toluene	70	30
14	**4a**	$K_3PO_4\cdot 3H_2O$	CH_3CN	70	59
15	**4a**	$K_3PO_4\cdot 3H_2O$	H_2O	70	54
[b]16	**4a**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	70	82
17	**4a**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	50	99
18	**4a**	**$K_3PO_4\cdot 3H_2O$**	**^{i}PrOH**	**rt**	**96**
19	**4b**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	rt	92
20	**4c**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	rt	90
21	**4d**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	rt	22
22	**4e**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	rt	42
23	**4f**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH	rt	16
24	**4a**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	rt	75
25	**4a**	**$K_3PO_4\cdot 3H_2O$**	**^{i}PrOH : H_2O (1 : 1)**	**50**	**97**
26	**4b**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	50	91
27	**4c**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	50	90
28	**4d**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	50	86
29	**4e**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	50	6
30	**4f**	$K_3PO_4\cdot 3H_2O$	^{i}PrOH : H_2O (1 : 1)	50	Trace

[a] All reactions were carried out using **1a** (0.20 mmol), **2a** (0.40 mmol), base (2.0 equiv.), cat. (5.0 mol%) in solvent (0.1 M) for 15 h. [b] Cat. (2.0 mol%). [c] Isolated yields.

Table 2 Scope of the coupling reaction with respect to the arylboric acid





3aa : 96%[a]
3aa : 97%[b]

3ab : 98%[a]
3ab : 91%[b]

3ac : 94%[a]
3ac : 91%[b]

3ad : 93%[a]
3ad : 95%[b]

3ae : >99%[a]
3ae : 97%[b]

3af: 99%[a]
3af : 92%[b]

3ag : 98%[a]
3ag: 90%[b]

3ah : >99%[a]
3ah: 97%[b]

3ai: 93%[a]
3ai: 85%[b]

3aj : 98%[a]
3aj : 82%[b]

3ak : 85%[a]
3ak : 87%[b]

3al: 88%[a]
3al : 88%[b]

3am : 90%[a]
3am : 83%[b]

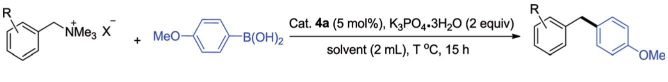
[a] All reactions were carried out using **1a** (0.20 mmol), **2** (0.40 mmol), $K_3PO_4\cdot 3H_2O$ (2.0 equiv.), cat. **4a** (5.0 mol%) in ^{i}PrOH (0.1 M) at room temperature for 15 h. [b] All reactions were carried out using **1a** (0.20 mmol), **2** (0.40 mmol), $K_3PO_4\cdot 3H_2O$ (2.0 equiv), cat. **4a** (5.0 mol%) in mixture solvent (^{i}PrOH : H_2O [v / v] = 1 : 1, 0.1 M) at 50 °C for 15 h.

quantitatively. Several other solvents including THF, EtOH, 1,4-dioxane, toluene, CH_3CN and H_2O were tested, and the yield was not enhanced further (Table 1, entries 10–15). When 2.0 mol% of complex **4a** was tested, the yield of cross coupling product was obtained in 82% yield (Table 1, entry 16). It is worth mentioning that the IPr–Pd-PEPPSI complex **4a** still gave good yield at room temperature (Table 1, entry 18). Further screening of NHC–Pd(II) catalysts demonstrates that the coordination environment of the NHC–Pd(II) complexes had an obvious effect on the yield (Table 1, entries 18–23). When a solvent mixture of isopropanol and water was tested, the yield of the product reduced to 76% (Table 1, entry 24). In this case, heating to 50 °C was found to be necessary (Table 1, entry 25). Then the performance of the other five NHC–Pd(II) complexes **4b–f** in this reaction condition was examined, and IPr–Pd-PEPPSI complex **4a** was found to be optimal (Table 1, entry 25 *vs.* entries 26–30).

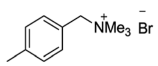
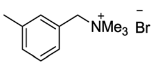
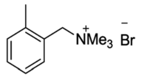
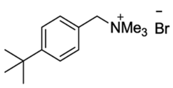
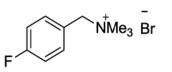
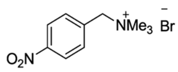
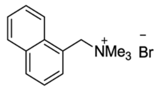
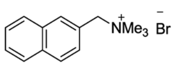
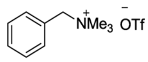
Since the reaction was performed in isopropanol at room temperature as well as in a solvent mixture consisting of isopropanol (1.0 mL) and water (1.0 mL) at 50 °C rather well, they were both applied as the reaction conditions in the following experiments to explore the scope of the cross coupling. As shown in Table 2, a series of aromatic boronic acids with benzyltrimethylammonium bromide were investigated in ^{i}PrOH in the presence of 5.0 mol% complex **4a** and 2.0 equiv. $K_3PO_4\cdot 3H_2O$ at room temperature for 15 h. Gratifyingly, most of the coupling reaction proceeded rapidly and efficiently to provide the corresponding diarylmethane derivatives in excellent yields. It seems that the electronic effect and the steric effect of the substituents on the aromatic boronic acids have little effect on the reaction efficiency. No matter electron-donating (**3aa–3ah**) or -withdrawing (**3ai–3aj**) groups on the phenyl ring of boronic acids, good to excellent yields were obtained. The reaction was quite feasible with benzyltrimethylammonium bromide when the *ortho*-substituted aryl boronic acid was used (**3ac** and **3ag**). In addition, in the case of 1-naphthylboronic acid or 2-naphthylboronic acid afforded in high reaction efficiency under the present reaction conditions (**3ak–3al**). Particularly, when heteroaromatic boronic acid, such as thienyl, was used as the substrate, high yield of the corresponding product was always observed (**3am**). Subsequently, a series of aromatic boronic acids with benzyltrimethylammonium bromide were investigated in ^{i}PrOH–H_2O in the presence of 5.0 mol% complex **4a** and 2.0 equiv. $K_3PO_4 \cdot 3H_2O$ at 50 °C for 15 h. All of the above substrates still worked well to afford the desired products in good to almost quantitative yields.

Inspired by these results and our attention was next turned to the cross coupling reaction of benzylammonium salts with 4-methoxyphenyl boronic acid. As shown in Table 3, the reactions proceed smoothly to afford diarylmethanes in excellent yields. Roughly, the electron-donating group in the phenyl ring of benzylammonium salts showed some beneficial effect on the yields of the catalysis products. Benzylammonium salts bearing fluorine substituent showed good reactivity in this transformation (**3be**). Substrate **1** having naphthalene ring substituent was also suitable for such transformation to afford products **3bg** and **3bh** in good yields under appropriate conditions. In addition, when benzyltrimethylammonium triflate was used as the substrate, high yield of the corresponding product was always observed (**3bi**).

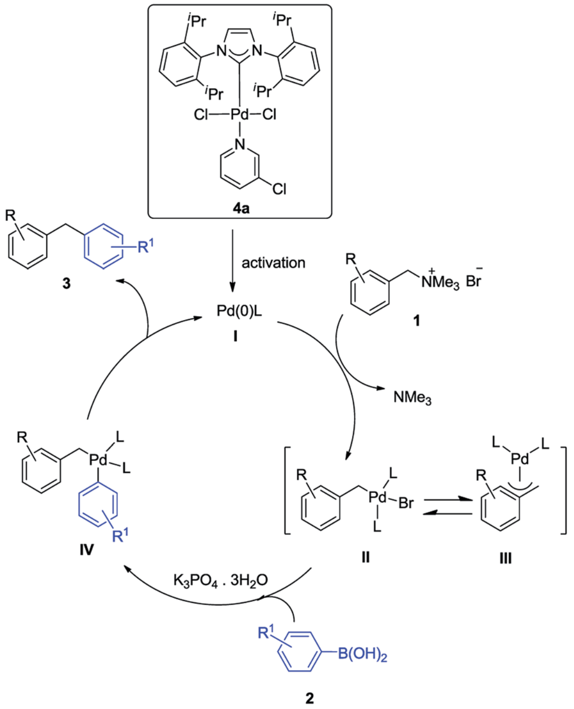
Table 3 Scope of the coupling reaction with respect to the benzylammonium salts



1a-i **2a** **3ba-3bi**

 **3ba** : 97%[a] **3ba** : 96%[b]	 **3bb** : 96%[a] **3bb** : 96%[b]	 **3bc** : 88%[a] **3bc** : 86%[b]
 **3bd** : 88%[a] **3bd** : 83%[b]	 **3be** : 96%[a] **3be** : 88%[b]	 **3bf**: 70%[a] **3bf**: 67%[b]
 **3bg** : 89%[a] **3bg** : 80%[b]	 **3bh** : 92%[a] **3bh** : 85%[b]	 **3bi** : 95%[a] **3bi** : 95%[b]

[a] All reactions were carried out using **1** (0.20 mmol), **2a** (0.40 mmol), $K_3PO_4 \cdot 3H_2O$ (2.0 equiv.), cat. **4a** (5.0 mol%) in ^{i}PrOH (0.1 M) at room temperature for 15 h. [b] All reactions were carried out using **1** (0.20 mmol), **2a** (0.40 mmol), $K_3PO_4 \cdot 3H_2O$ (2.0 equiv.), cat. **4a** (5.0 mol%) in mixture solvent (^{i}PrOH : H_2O [v / v] = 1 : 1, (0.1 M)) at 50 °C for 15 h.



Scheme 2 Proposed reaction mechanism.

On the basis of the mechanism of previous reports[10b] and our results, a putative reaction mechanism was then proposed in Scheme 2. First, oxidative addition of Pd(0) I produced *in situ*, with benzyltrimethylammonium salt 1 formed intermediate II with the release of trimethylamine. Then a transmetalation reaction of the intermediate II with aryl boronic acid converted to intermediate IV, which followed by reductive elimination to the product 3 with simultaneous regeneration of the Pd(0) catalyst.

Conclusions

In summary, we have developed the first example of NHC–Pd(II) catalyzed cross-coupling of benzylammonium salts with arylboronic acids to form diarylmethane derivatives, a very important skeleton in synthetic chemistry. The current process tolerates broad scope with respect to both the boronic acid and benzylammonium salts under mild conditions. Further exploration of these N-heterocyclic carbene–palladium(II) complexes and their catalytic applications in other reactions is in progress.

Experimental

General remarks

The catalytic reactions were carried out under a nitrogen atmosphere. Benzylammonium salts were prepared according to the literature method.[16] The N-heterocyclic carbene–

palladium(II) complexes were synthesized according to our previous report.[11b] Solvents were dried by standard methods and freshly distilled prior to use. All other chemicals were used as purchased. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 instrument using TMS as an internal standard.

General procedure for the cross-coupling of benzylammonium salts with arylboronic acids

A Schlenk flask was charged with the required benzylammonium salts **1a** (0.20 mmol, 46.0 mg), (4-methoxyphenyl)boronic acid (0.40 mmol, 60.8 mg), N-heterocyclic carbene–palladium(II) complex **4a** (5 mol%, 6.8 mg), $K_3PO_4\cdot 3H_2O$ (2.0 equiv., 106.5 mg), and ^{i}PrOH (0.1 M) [or ^{i}PrOH : H_2O [v / v] = 1 : 1, 0.1 M]. The mixture was stirred at room temperature [or 50 °C] for 15 h under N_2. After cooling, the mixture was evaporated and the product was isolated by by preparative TLC on silica gel plates eluting with CH_2Cl_2/petroleum ether to afford the diarylmethane. The purified products were identified by NMR spectra and their analytical data are given in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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