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Palladium-catalyzed cross-coupling reaction of aryldioxaborolane with 2-bromo-*N*,*N*-dimethylacetamide

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Abstract—A Suzuki-type cross-coupling of aryldioxaborolane with 2-bromo-*N*,*N*-dimethylacetamide in the presence of a catalytic amount of tricyclohexylphosphine as the ligand and hydroquinone as the free-radical scavenger has been demonstrated as a convenient and simple way for the synthesis of α-arylacetamide.

α-Arylamides have potential medical and agricultural applications,[1] but few general methods for their preparation have been reported. Classical methods for the α-arylation of amide have involved Friedel–Crafts or photostimulated reaction of amide enolate with haloarenes via $S_{RN}1$ mechanism.[2] Recently, inter- and intramolecular palladium-catalyzed α-arylation of *N*,*N*-dimethylamides by using aryl halides and silylamide base have been reported by Hartwig's group.[3] It is known that the cross-coupling reactions of phenylboronic acid with aryl bromide in the presence of palladium catalysts and base, Suzuki reaction,[4] have many attractive features, such as good yields, mild conditions, tolerant to several functional groups and the ability to remain unaffected in the presence of water. However, despite the wide variety of organic halides which mediate these types of cross-coupling reactions, examples of the synthesis of α-arylacetamide via Suzuki-type reaction have very limited scope.[5] In view of the limited number of methodologies for the synthesis of α-arylamides, herein, we wish to report the cross-coupling of aryldioxaborolane and 2-bromo-*N*,*N*-dimethylacetamide in the presence of $Pd(dba)_2$ catalyst, a catalytic amount of tricyclohexylphosphine as the ligand, and 3.4 equiv. of K_3PO_4 as the base in THF at 70°C could give α-aryl-*N*,*N*-dimethylacetamide in moderate to good yields.

Initially, we started to use phenylboronic acid to couple with 2-bromo-*N*,*N*-dimethylacetamide in the presence of 3 mol% of $Pd(PPh_3)_4$ and 3% of Cu_2O as the co-catalyst[5a] and 3.4 equiv. of K_2CO_3 as the base in toluene at 80°C for 12 h. However, we only obtained very low yield of the cross-coupling product along with 35% of biphenyl. Attempts to use K_3PO_4 or Cs_2CO_3 as the base did not get any improvement in the yields. Using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane as the substrate did not improve the yields. However, when we used 2-phenyl-1,3,2-dioxaborolane as organoborane species and used THF as the solvent in the above mentioned reaction conditions, the yields may reach up to 42%. Running the reaction at rt or using just 1 equiv. of K_3PO_4 only gave very low yields. We also found that using other kinds of base such as K_2CO_3, $Ba(OH)_2$, NEt_3, CsF,[6] or KF[6] could give only low to moderate yields. Using cuprous halides instead of Cu_2O did not improve the yields. No reaction was occurred when the reaction was running in the absence of palladium catalyst or base. These results indicated that the coupling product was really obtained via the Suzuki-type reaction. Interestingly, in contrast to the previous report,[5a] we found that the co-catalyst, Cu_2O, is totally unnecessary. Thus, the reaction yield could reach to 44% in the absence of Cu_2O. We then tried to study the cross-coupling reaction by using different palladium catalysts or in the presence of ligands as commonly reported in the literature.[6,7]

Changing the palladium catalyst from $Pd(PPh_3)_4$ to palladacycle, $PdCl_2(PPh_3)_2$, or $Pd(dba)_2$, while used K_3PO_4, Cs_2CO_3, NEt_3, or $^iPr_2NEt$ as the base and THF or DMF as the solvent, could not greatly improve the

Keywords: Suzuki coupling reactions; aryldioxaborolane; 2-bromo-*N*,*N*-dimethylacetamide.

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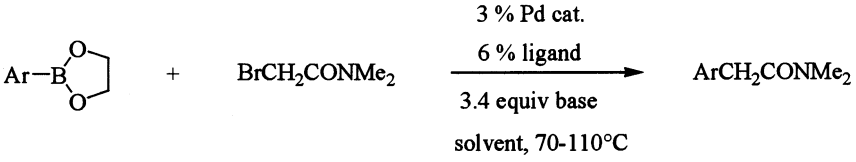
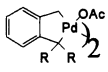
yields (entries 1–8, Table 1). However, we found that the sterically hindered chelating phosphine ligand, PCy_3, furnished good yield in the above Suzuki-type reaction to afford up to 68% yield of desired product by using $Pd(dba)_2$ as the catalyst (entry 15, Table 1). Using other ligands such as PPh_3 or $P(o\text{-tol})_3$ proceeded in somewhat lower yields (entries 9–14, Table 1). $Pd(dba)_2$ seems to be the pertinent catalyst than palladacycle or $Pd(PPh_3)_4$ in the above PCy_3-assisted Suzuki-type cross-coupling reaction (entries 16 and 17, Table 1). When we run the above reaction in the presence of 10 mol% of hydroquinone, the yield may reach to 89% (entry 18, Table 1). The use of other free-radical scavengers such as Galvinoxyl or TEMPO still gave biphenyl as the major by-product in 35–43% yield. The formation of biaryls may be attributed to the transmetallation between palladium enolate species and arylboronates, suggesting the possibility that some bases generated from hydroquinone and K_3PO_4 enhances the transmetallation process. Thus, the Suzuki-type cross-coupling of various aryldioxaborolanes with 2-bromo-*N*,*N*-dimethylacetamide can proceed smoothly under the similar reaction conditions to give the desired coupling products in moderate to good yields as shown in Table 2. The structure of the cross-coupling products were ascertained by ^1H and ^{13}C NMR and mass spectral analysis. We have attempted to do the coupling reaction of 2-(1,3,2-dioxaborolan-2-yl)thiophene with 2-bromo-*N*,*N*-dimethylacetamide under the same reaction conditions, but failed. Only bithiophene was isolated in 54% yield along with a trace amount of the desired cross-coupling product as detected in GC–MS spectral analysis. Running the above coupling reaction in the presence of 3.4 equiv. of water gave 35% yield of the desired product. The coupling reaction of phenylmagnesium bromide or phenylzinc chloride with 2-bromo-*N*,*N*-dimethylacetamide did not give any detectable amount of the desired product. Attempts to add *n*-butyllithium to phenyldioxaborolane to form a borate complex before running the coupling reaction gave only 10% yield of the desired product.

Based on the known studies of the mechanisms for Suzuki-type cross-coupling reaction reported in the literature,[8] we proposed the mechanism as shown in Scheme 1. Thus, dibenzylideneacetone was replaced initially by tricyclohexylphosphine as the ligand to the palladium(0) catalyst, after oxidative addition with 2-bromo-*N*,*N*-dimethylacetamide to form bromopalladium enolate complex, the palladium complex was activated by the presence of base. Another equivalent of base was activated the aryldioxaborolane to form a borate complex, which underwent transmetallation with the activated palladium species to form arylpalladium enolate complex and a stablilized borate complex. Reductive elimination of the arylpalladium enolate complex afforded the cross-coupling product and regenerate Pd(0) catalyst.

Table 1. The cross-coupling reaction of phenyldioxaborolanes with 2-bromo-*N*,*N*-dimethylacetamide

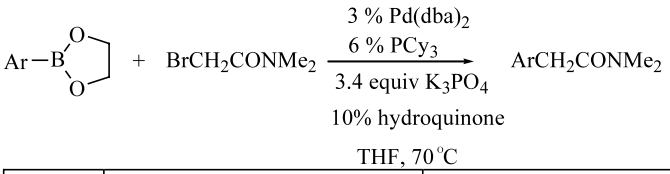


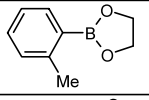
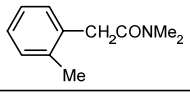
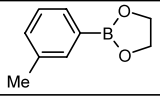
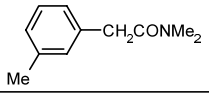
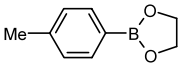
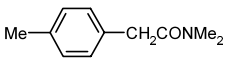
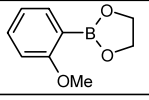
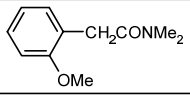
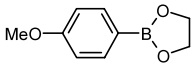
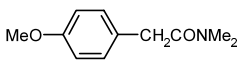
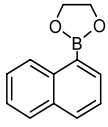
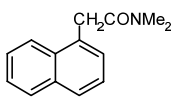
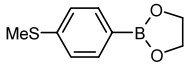
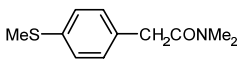
Entry	Catalyst	Ligand	Base	Solvent	Temp. (°C)	Yield (%)
1	$Pd(dba)_2$	–	K_3PO_4	THF	70	20
2	Palladacycle[a]	–	K_3PO_4	THF	70	33
3	Palladacycle	–	K_3PO_4	DMF	110	Trace
4	Palladacycle	–	Cs_2CO_3	THF	70	50
5	Palladacycle	–	$^iPrNEt_2$	THF	70	Trace
6	Palladacycle	–	$^iPrNEt_2$	DMF	110	48
7	$PdCl_2(PPh_3)_2$	NEt_3	Cs_2CO_3	THF	70	48
8	$PdCl_2(PPh_3)_2$	$^iPrNEt_2$	Cs_2CO_3	THF	70	42
9	$PdCl_2(PPh_3)_2$	$P(o\text{-tol})_3$	Cs_2CO_3	THF	70	30
10	$Pd(PPh_3)_4$	$P(o\text{-tol})_3$	K_3PO_4	THF	70	26
11	$Pd(OAc)_2$	$P(o\text{-tol})_3$	Cs_2CO_3	THF	70	23
12	$Pd(dba)_2$	$P(o\text{-tol})_3$	K_3PO_4	THF	70	30
13	$Pd(dba)_2$	PPh_3	K_3PO_4	THF	70	26
14	$Pd(dba)_2$	PPh_3	NEt_3	THF	70	Trace
15	$Pd(dba)_2$	PCy_3	K_3PO_4	THF	70	68
16	Palladacycle	PCy_3	K_3PO_4	THF	70	60
17	$Pd(PPh_3)_4$	PCy_3	K_3PO_4	THF	70	22
18[b]	$Pd(dba)_2$	PCy_3	K_3PO_4	THF	70	89

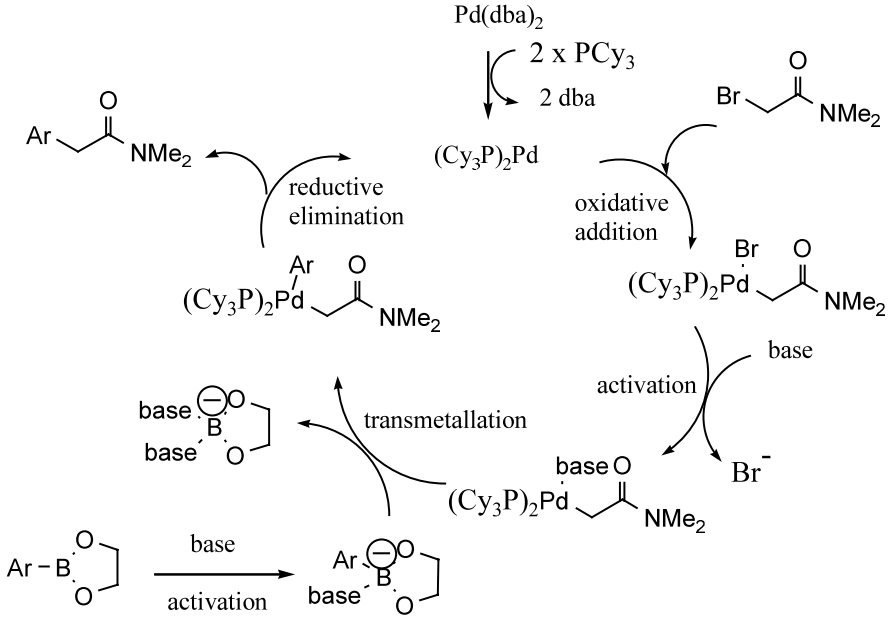
[a] Palladacycle =  R = *o*-tolyl

[b] In the presence of 10 mol% of hydroquinone.

Table 2. Suzuki-type cross-coupling of aryldioxaborolanes with 2-bromo-*N*,*N*-dimethylacetamide



Entry	Aryldioxaborolane	Product	Yield (%)
1			72
2			73
3			76
4			62
5			71
6			67
7			42



Scheme 1. Plausible mechanism of the Suzuki-type reaction to form α-arylamide.

In conclusion, a palladium-catalyzed cross-coupling of aryldioxaborolane with 2-bromo-*N*,*N*-dimethylacetamide in the presence of a catalytic amount of tricyclohexylphosphine as the ligand and 10 mol% of hydroquinone as the free-radical scavenger has been demonstrated as a convenient and simple way to the synthesis of α-arylacetamide. The sterically hindered ligand as well as the nature of the palladium catalyst influenced tremendously the efficiency of the cross-coupling reaction.

Acknowledgements

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