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Pd-catalyzed amidation of aryl(Het) halides with *tert*-butyl carbamate

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ABSTRACT

Pd-catalyzed cross-coupling reaction of *tert*-butyl carbamate with various aryl(Het) halides with Cs_2CO_3 as base in 1,4-dioxane as solvent was investigated, which resulted in the formation of the desired compounds in moderate to excellent yields.

1. Introduction

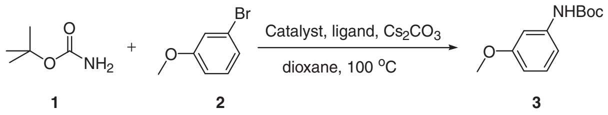
Aryl amines are traditionally valuable in organic synthesis, pharmaceuticals, and materials science.[1–5] The synthesis of arylamines has always been a topic of interest in organic chemistry.[6] In the past years, palladium-catalyzed C–N coupling has received an increased attention.[7] A variety of excellent work has been carried out for this reaction.[8] Lithium bis(trimethylsilyl)amide,[8d] lithium amide,[8e] zinc bis(hexamethyl-disilazide),[8f] and benzophenone imine[8g] have been successfully utilized in this conversion. Hartwig and Buchwald have demonstrated that ammonia can be used as a coupling partner in the Pd-catalyzed conversion of aryl halides to anilines.[8a,c] However, the published ammonia equivalents are not in a conveniently protected form except for *tert*-butyl carbamate. The *tert*-butyloxycarbonyl (Boc) group is a very convenient amine-protecting group because it is easy to be removed. There are only limited examples of *tert*-butyl carbamate reported to be used in the palladium-catalyzed C–N coupling.[6b,9,10] It is reported first time that the Pd-catalyzed amidation of aryl bromides using *tert*-butyl carbamate as substrate by Hartwig in 1999.[9] In 2009, Keith R. Hornberger studied the Pd-catalyzed coupling of aryl bromides with *tert*-butyl carbamate, which gave the desired cross-coupling products in good to excellent yield.[10] However, aryl chlorides were not studied for this type of reaction in the report.[10] We were interested in exploring a broad scope of this type of reaction with a new catalytic system and specially the reaction using aryl chlorides and heteroaryl halides.

2. Optimization of the Pd-catalyzed amidation reactions of aryl bromides

To evaluate the activity of the combination of different catalysts and ligands, *tert*-butyl carbamate **1** and 3-bromoanisole **2** were chosen as model reaction in 1,4-dioxane at 100 °C in the presence of Cs_2CO_3 as base (as shown in Table 1). The combination of $Pd(OAc)_2$ and SPhos, DavePhos, RuPhos, or CyJohnPhos (as shown in Fig. 1) give moderate to good yields (Table 1, entries 1–4). When XPhos was used, 94% yield was offered (Table 1, entry 5). It is reported that the increasing ligand bulk leads to more effective reactions, presumably due to an increase in the rate of reductive elimination.[7a] In the used ligands, XPhos appears to offer the optimal bulk to most efficiently promote the reaction rate (Table 1, entries 1–4 vs 5). Switching the Pd source to $Pd_2(dba)_3{\cdot}CHCl_3$ gives lower yield (Table 1, entry 6). Then the combination of $Pd(OAc)_2$/XPhos was fixed.

To study the effect of solvents and bases on the cross-coupling reaction, *tert*-butyl carbamate **1** and 3-bromoanisole **2** were chosen as the model reaction by fixing 3 mol % $Pd(OAc)_2$ and 9 mol % XPhos (as shown in Table 2). Several bases such as *t*-BuONa, Cs_2CO_3, K_3PO_4, K_2CO_3, and KOAc were examined in the reaction,

Table 1
Screen of catalysts and ligands for the cross-coupling of *tert*-butyl carbamate with 3-bromoanisole[a]



Entry	Catalyst	Ligand	Yield[b] (%)
1	$Pd(OAc)_2$	SPhos	57
2	$Pd(OAc)_2$	DavePhos	66
3	$Pd(OAc)_2$	RuPhos	77
4	$Pd(OAc)_2$	CyJohnPhos	50
5	$Pd(OAc)_2$	XPhos	94
6	$Pd_2(dba){\cdot}CHCl_3$	XPhos	80

[a] All reactions based on 0.25 mmol 3-bromoanisole, 0.3 mmol *tert*-butyl carbamate, 3 mol % catalyst, 9 mol % ligand, 0.35 mmol Cs_2CO_3, 2.0 ml dioxane, 100 °C, 4 h.
[b] The reactions averaged on two runs, isolated yields.

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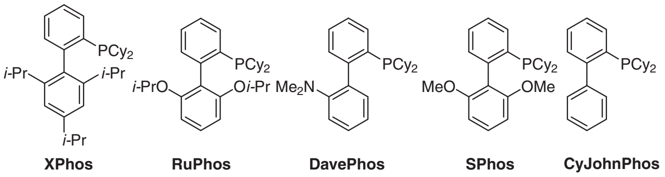


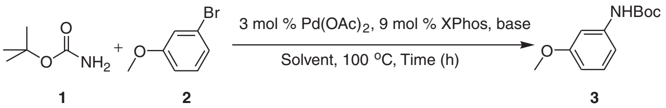
Figure 1. The structure of biarylphosphine ligands.

and an excellent yield was obtained when Cs_2CO_3 was used as base (Table 2, entry 2). Changing the solvent to toluene, *t*-BuOH, or THF did not favor the reaction, even prolonging the reaction time to 24 h (Table 2, entries 6–8). Gothelf and Dallas[11] reported that when cesium carbonate was used as base in 1,4-dioxane, water gives a beneficial effect. When 100 mol % H_2O was added to the mixture the yield was decreased (Table 2, entry 9). Decreasing the reaction temperature from 100 °C to 80 °C or increasing the temperature to 120 °C, the yields were decreased (Table 2, entries 10 and 11). So, the combination of 3 mol % $Pd(OAc)_2$/9 mol % XPhos in 1,4-dioxane in the presence of Cs_2CO_3 at 100 °C is the optimum condition.

3. Substrates scope for the Pd-catalyzed amidation reactions of *tert*-butyl carbamate with aryl(Het) halides

Under the optimized reaction conditions, a series of aryl bromides substrates were investigated for this reaction (as shown in Table 3). Generally, electron-rich and electron-deficient aryl bromides all worked well, providing the corresponding coupling products in moderate to excellent yields. Moreover, a wide variety of functional groups including acetyl, cyano, nitro, keto, ester, trifluoromethyl, and methyl were found to tolerate these conditions (Table 3, entries 1–14). Hornberger and co-workers reported[10] that 4-nitrobromobenzene and 4-bromo-benzoic acid methyl ester decomposed under their reaction condition. In this study the corresponding coupling products were obtained in good to excellent yields from these two substrates (Table 3, entries 4 and 7). Substrates with electron-withdrawing group give higher yields than those with electron-donating group except for 1-(3-bromophenyl)ethanone, which afforded 100% conversion detected by GC–MS but only gives 58% isolated yield (Table 3, entry 2). A side product was detected by GC–MS. Probably because part of 1-(3-bromophenyl)ethanone decomposed under the reaction conditions. Under the same reaction conditions, substrates with substituents at *ortho*-position (Table 3, entries 5 and 10) give lower yields than those at *para*-position (Table 3, entry 4) or *meta*-position (Table 3, entry 11), indicating that the steric hindrance likely has a negative effect on the reaction.

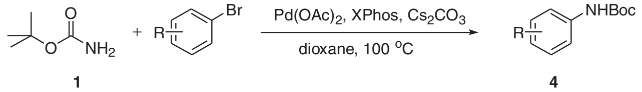
Table 2
Screen of solvents and bases for the cross-coupling of *tert*-butyl carbamate with 3-bromoanisole[a]

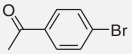
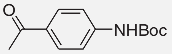
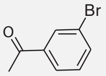
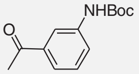
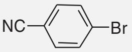
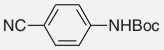
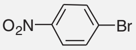
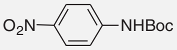
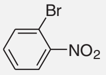
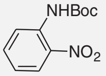
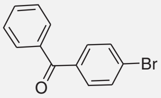
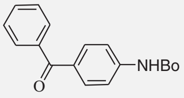
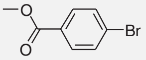
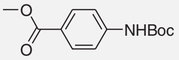
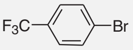
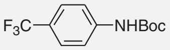
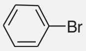
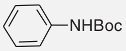
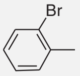
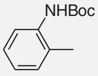
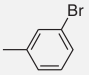
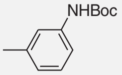
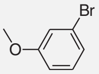
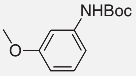
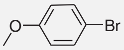
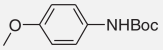
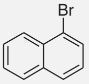
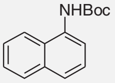


Entry	Solvent	Base	Time (h)	Yield[b] (%)
1	Dioxane	*t*-BuONa	4	10
2	Dioxane	Cs_2CO_3	4	94
3	Dioxane	K_3PO_4	4	36
4	Dioxane	K_2CO_3	4	66
5	Dioxane	KOAc	4	Trace
6	Toluene	Cs_2CO_3	24	65
7	*t*-BuOH	Cs_2CO_3	24	63
8	THF	Cs_2CO_3	24	20
9	Dioxane + 100 mol % H_2O	Cs_2CO_3	24	63
10	Dioxane	Cs_2CO_3	4	44[c]
11	Dioxane	Cs_2CO_3	4	77[d]

[a] All reactions based on 0.25 mmol 3-bromoanisole, 0.3 mmol *tert*-butyl carbamate, 3 mol % $Pd(OAc)_2$, 9 mol % XPhos, 0.35 mmol base, 2.0 ml solvent and the reactions averaged on two runs.
[b] Isolated yields.
[c] Reaction temperature 80 °C.
[d] Reaction temperature 120 °C.

Table 3
Pd-catalyzed cross-coupling of *tert*-butyl carbamate with aryl bromides[a]

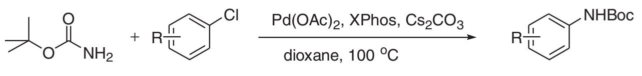


Entry	ArBr	Product	Time (h)	Yield[b] (%)
1			1.5	93
2			1.5	58
3			1.5	86
4			1.5	97
5			2	87
6			1.5	90
7			2	87
8			2	96
9			4	66
10			4	80
11			4	89
12			4	94
13			4	75
14			4	83

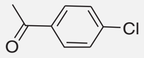
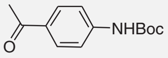
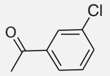
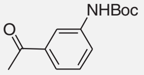
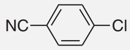
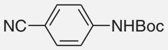
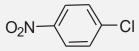
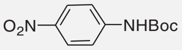
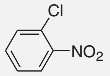
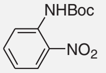
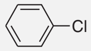
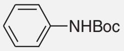
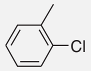
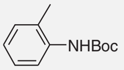
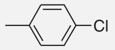
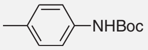
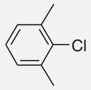
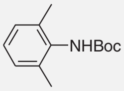
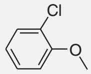
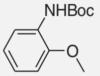
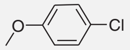
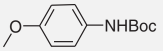
[a] Reaction conditions: 0.25 mmol aryl bromides, 0.3 mmol *tert*-butyl carbamate, 3 mol % $Pd(OAc)_2$, 9 mol % XPhos, 0.35 mmol Cs_2CO_3, 2.0 ml dioxane, 100 °C.
[b] Isolated yields; average of two runs.

Aryl chloride is one kind of attractive substrates due to being less expensive and more readily available. The encouraging results from aryl bromides prompted us to check if the coupling of aryl chlorides with *tert*-butyl carbamate could work at the same catalytic system. As shown in Table 4, under the optimized reaction conditions, a series of aryl chlorides substrates were successfully converted to the corresponding products. However, the reactions were influenced by electron effect and steric effect of the substituent. Aryl chlorides with electron-withdrawing group give higher yields than those with electron-donating group (Table 4, entries 1–5 vs 6–10). 4-Chloroanisole only gave 25% yield presumably due to the electron-donating effect. Increasing the catalyst to 4 mol %, a 76% yield was obtained (Table 4, entry 11). Due to the steric effect, when 2-chloroanisole reacted with *tert*-butyl carba-

Table 4
Pd-catalyzed cross-coupling of *tert*-butyl carbamate and aryl chlorides[a]

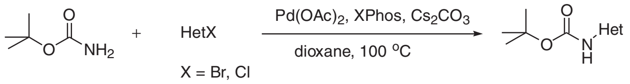


1 5

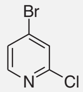
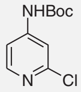
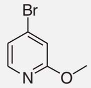
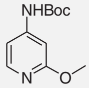
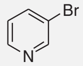
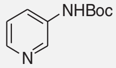
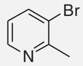
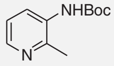
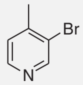
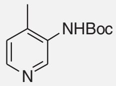
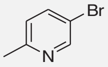
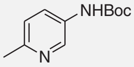
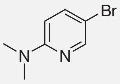
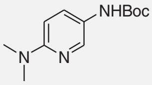
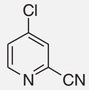
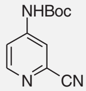
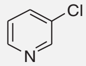
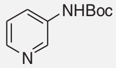
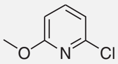
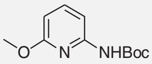
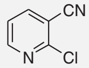
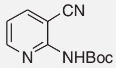
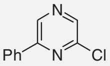
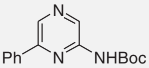
Entry	ArCl	Product	Time (h)	Yield[b] (%)
1			2.5	86
2			2.5	49
3			2.5	90
4			2.5	92
5			4	85
6			4	59
7			4.5	70
8			4	73
9			24	10[c]
10			24	10 (27[d])
11			6	25 (76[d])

[a] Reaction conditions: 0.25 mmol aryl chlorides, 0.3 mmol *tert*-butyl carbamate, 3 mol % Pd(OAc)$_2$, 9 mol % XPhos, 0.35 mmol Cs$_2$CO$_3$, 2.0 ml dioxane, 100 °C.
[b] Isolated yields; average of two runs.
[c] Estimated by GC–MS prior to isolation of the desired product.
[d] 4 mol % Pd(OAc)$_2$ and 12 mol % XPhos.

Table 5
Pd-catalyzed cross-coupling of *tert*-butyl carbamate and heteroaryl halides[a]



1 6

Entry	HetX	Product	Time (h)	Yield[b] (%)
1			24	49
2			24	42
3			24	38
4			24	62
5			24	27
6			24	55
7			24	38
8			24	88
9			24	36
10			24	48
11			24	Trace
12			24	91

[a] Reaction conditions: 0.25 mmol heteroaryl halides, 0.3 mmol *tert*-butyl carbamate, 3 mol % Pd(OAc)$_2$, 9 mol % XPhos, 0.35 mmol Cs$_2$CO$_3$, 2.0 ml dioxane, 100 °C.
[b] Isolated yields; average of two runs.

mate, only 10% yield was obtained, and the more steric hindered 2-chloro-1,3-dimethylbenzene just give 10% yields detected by GC (Table 4, entries 9 and 10).

Heteroaryl halides are widely used in synthetic pharmaceutical research. However, to the best of our knowledge, there are only two reports on the successful combination of heteroaryl halides with *tert*-butyl carbamate.[6b,10] We proceeded to study the amidation reactions of various heteroaryl halides with *tert*-butyl carbamate under our optimized reaction conditions. The results are summarized in Table 5. The amidation reaction preferred to occur at the bromo position other than chloro position (Table 5, entry 1). 4-Bromo-2-methoxypyridine gave lower yield than 4-bromo-2-chloropyridine (Table 5, entry 2). The corresponding product was obtained in 38% yield from 3-bromopyridine (Table 5, entry 3). The substrates with methyl group in 2- or 6-position gave higher yields than those with methyl group in 4-position (Table 5, entries 4, 6 vs 5). 5-Bromo-*N*,*N*-dimethyl-2-pyridinamine was successfully converted into the corresponding product (Table 5, entry 7). The 88% corresponding product was obtained from 2-cyano-4-chloropyridine (Table 5, entry 8). 3-Chloropyridine and 2-chloro-6-methoxy-pyridine could be applied to this cross-coupling reaction to get the corresponding coupling products (Table 5, entries 9 and 10). Presumably due to the low activity of 2-chloro and steric effect between 3-cyano and BocNH$_2$, the corresponding product was detected with only trace amount by GC–MS in the case of 3-cyano-2-chloropyridine (Table 5, entry 11). 2-Chloro-6-phenylpyrazine gave an excellent yield of 91% (Table 5, entry 12).

In summary, we developed an efficient catalytic system for Pd-catalyzed cross-coupling reaction of *tert*-butyl carbamate with aryl(Het) halides. The catalyst and ligand are commercially available. A wide range of substrates could be used to this system. Aryl bromides and aryl chlorides with electron-donating, electron-neutral, and electron-withdrawing substituents all work well and heteroaryl halides give moderate yields in this system.

4. General procedure of amidation

A dried glass reaction tube equipped with a magnetic stir bar was charged with Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol, 3 mol %), XPhos (11 mg, 0.0225 mmol, 9 mol %), Cs$_2$CO$_3$ (114.3 mg, 0.35 mmol, 1.4 equiv), *tert*-butyl carbamate (35.1 mg, 0.3 mmol, 1.2 equiv), and aryl(Het) halides (0.25 mmol, 1.0 equiv); anhydrous 1,4-dioxane (2.0 mL) was added and the mixture was charged with nitrogen gas three times. Then the reaction mixture was stirred at 100 °C under nitrogen gas until aryl halides were consumed. The reaction progress was monitored by TLC and GC–MS. The reaction mixture was poured into H_2O after cooling down to room temperature and extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography to produce the desired product. The products were characterized by melting point, ^1H NMR, and GC–MS/LC–MS/MS.

Acknowledgments

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