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A Mild, One-Pot Synthesis of Arylamines *via* Palladium-Catalyzed Addition of Aryl Aldehydes with Amines and Arylboronic Acids in Water

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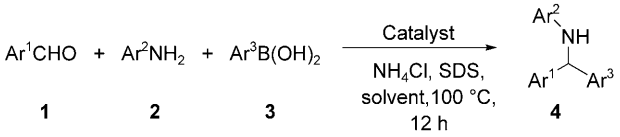
Abstract: A mild, one-pot synthesis of diarylmethylamines *via* the palladium-catalyzed addition of aryl aldehydes with amines and arylboronic acids is reported. Best results were obtained in neat water with ammonium chloride as additive, affording diarylmethylamine derivatives as the main products.

Keywords: aldehydes; amines; arylboronic acids; catalysis; cyclopalladated complexes

Introduction

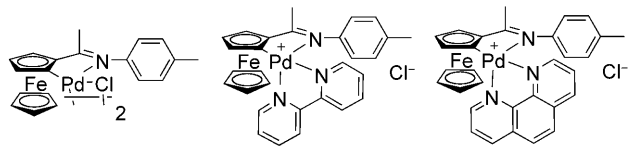
The addition of carbon nucleophiles to carbon-heteroatom multiple bonds such as those of imines is a commonly employed strategy in organic synthesis for the formation of carbon-carbon bonds,[1] as the resulting product amines are important precursors for the synthesis of many pharmacologically active compounds.[2] However, due to the poor electrophilicity of the azomethine carbon, this addition is often plagued by competitive enolization, deprotonation or coupling reactions.[3] Many efforts have been made in the rhodium-catalyzed addition of organometallic reagents to imines.[4] Despite many reports, only recently have several examples of Pd-complex catalysts been developed. Boronic acids have been shown to undergo addition to imines, as demonstrated by Lu's cationic palladium complex-catalyzed addition of arylboronic acids to N-*tert*-butanesulfinyl iminoacetates for the synthesis of arylglycine derivatives,[5] and Hu's phosphinite- and phosphite-based type **I** palladacycle-catalyzed additions of arylboronic acids with aldehydes, α,β-unsaturated ketones, α-keto esters and aldimines.[6] Very recently, Wu[7] described the Pd-catalyzed addition of arylboronic acids to *N*-tosyl-arylimines by employing aminophosphine ligands. Although a variety of methods has been developed, the reaction is not general, and the imine substrates which can be applied in this addition are limited. Our interest focused on the possibility of developing a significant practical improvement over existing conditions and expanding the scope of the substrates for such transformations. Herein, we report the results of our studies regarding the cyclopalladated complexes-catalyzed reaction of aryl aldehydes with arylamines and arylboronic acids in a single-vessel, three-component catalytic procedure that obviates the need to use imines as starting substrates separately synthesized by the reaction of aldehydes with amines (Scheme 1).



Scheme 1.

Results and Discussion

Initial experiments were carried out by the reaction of benzaldehyde, aniline and phenylboronic acid in the presence of **cat. 2** (5 mol%; Scheme 2) in water. Very gratifyingly, the addition product, *N*-phenyl-1,1-diphenylmethylamine **4aaa**, was smoothly obtained in 75% yield (Table 1, entry 1). In addition, when aldimines derived from benzaldehyde and aniline with phenylboronic acid were used as substrates, **4aaa** was also isolated in 75% yield (Table 1, entry 2). Unexpectedly, when diphenylmethanol and aniline were



Scheme 2.

Table 1. Optimization of reaction conditions for the addition of benzaldehyde and aniline to phenylboronic acid.[a]

Entry	Pd catalyst	Solvent	Yield[b] [%]
1	**cat. 2**	H_2O	75
2[c]	**cat. 2**	H_2O	75
3[d]	**cat. 2**	H_2O	trace
4	**cat. 2**	THF	16
5	**cat. 2**	CH_3NO_2	NR
6	**cat. 2**	HOAc	NR
7	**cat. 2**	dioxane	NR
8	**cat. 2**	*i*-PrOH	trace
9	**cat. 2**	DMF	trace
10	**cat. 2**	DMSO	trace
11	**cat. 2**	CH_3NO_2/dioxane (8:1, v/v)	trace
12	**cat. 1**	H_2O	NR
13[e]	**cat. 1**	H_2O	22
14	**cat. 3**	H_2O	8
15[f]	$Pd(OAc)_2$	H_2O	54

[a] *Reaction conditions:* PhCHO 0.5 mmol, $PhNH_2$ 0.5 mmol, $PhB(OH)_2$ 1.5 mmol, PhOH 1.5 mmol, sodium dodecyl sulfonate 0.5 mmol, 5.0 mol% of catalyst in 2.0 mL of solvent at 100 °C for 12 h.
[b] Isolated yield.
[c] *N*-Benzylideneaniline and phenylboronic acid (1:1) were used as the substrates. *N*-Benzylideneaniline was derived from benzaldehyde and aniline in water.
[d] Diphenylmethanol and aniline (1:1) were used as the substrates. Diphenylmethanol was derived from benzaldehyde and phenylboronic acid under these reaction conditions.
[e] **Cat. 1**:bpy (1:2) was used as the catalyst.
[f] $Pd(OAc)_2$:bpy (1:2) was used as the catalyst.

subjected to our reaction conditions, only a trace amount of **4aaa** resulted (Table 1, entry 3). The rigorous exclusion of air/moisture was not required in these transformations. The results of this initial solvent screening are summarized in Table 1.

After screening the solvents, we found that the neat water appeared to be the best among the common solvents. The aldimine which was formed from benzaldehyde and aniline was the main product, which became substantial when the reaction was carried out in solvents other than water (Table 1, entries 4–11). When the **cat. 1**was used in this reaction, the reaction mixtures became dark quickly and no reaction was observed (Table 1, entry 12). However, when **cat. 1** with bipyridine or **cat. 3** was subjected to the reaction, low yields of the products were obtained (Table 1, entries 13 and 14). It is worth noting that $Pd(OAc)_2$ combined with bipyridine could be used for this transformation (Table 1, entry 15), but the yield is lower. So **cat. 2** emerged as the best choice of catalyst precursors.

A variety of acids (e.g., acetic acid, benzoic acid, phenol, ammonium chloride and $NaH_2PO_4{\cdot}2H_2O$) were investigated, and NH_4Cl was found to give the best yields (Table 2, entries 1–5). A series of bases was also examined, and the results were not satisfactory (Table 2, entries 6–10). The addition of NH_4Cl to the reaction mixture is not essential for the transformation to proceed, but the reproducibility in the chemical yield of **4aaa** was higher in the presence of ammonium chloride than in its absence (Table 2, entry 11). The weak acid, NH_4Cl, may be the effective protonolysis reagent for the palladium amide species in water.[8] The influence of the loading of **cat. 2** could be reduced to 3.0 mol% with no change in the yield (Table 2, entries 12–14). When reducing the reaction temperature, the yield dropped sharply (Table 2, entry 15). In addition, the yields of amine decreased with decreasing amount of phenylboronic acid (Table 2, entry 16). The excess amounts of phenylboronic acid were consumed due to the homo-coupling reaction to form the biphenyl. Thus, PhCHO (0.5 mmol), $PhNH_2$ (0.5 mmol), $PhB(OH)_2$ (1.5 mmol), **cat. 2** (3.0 mol%), NH_4Cl (1.5 mmol) and

Table 2. Screening of the reaction conditions.[a]

Entry	Catalyst loading [Pd mol%]	Additive	Temperature [°C]	Yield[b] [%]
1	5.0	CH_3COOH	100	49
2	5.0	PhCOOH	100	5
3	5.0	PhOH	100	75
4	5.0	NH_4Cl	100	79
5	5.0	$NaH_2PO_4{\cdot}2H_2O$	100	42
6	5.0	$KF{\cdot}2H_2O$	100	69
7	5.0	Na_2CO_3	100	NR
8	5.0	K_2CO_3	100	14
9	5.0	$K_3PO_4{\cdot}7H_2O$	100	15
10	5.0	*t*-BuONa	100	NR
11	5.0	–	100	58
12	4.0	NH_4Cl	100	79
13[c]	3.0	NH_4Cl	100	**79**
14	2.5	NH_4Cl	100	65
15	3.0	NH_4Cl	80	36
16[d]	3.0	NH_4Cl	100	56

[a] *Reaction conditions:* PhCHO 0.5 mmol, $PhNH_2$ 0.5 mmol, $PhB(OH)_2$ 1.5 mmol, additive 1.5 mmol, sodium dodecyl sulfonate 0.5 mmol, **cat. 2** in 2.0 mL of water for 12 h.
[b] Isolated yield.
[c] The expected product **4aaa** was obtained along with biphenyl in 8% yield.
[d] The amount of $PhB(OH)_2$ was 1.0 mmol.

Table 3. Pd-catalyzed addition of aryl aldehydes with aniline and phenylboronic acid.[a]

Entry		Ar^1		Ar^2		Ar^3	Product	Yield[b] [%]
1	**1a**	Ph	**2a**	Ph	**3a**	Ph	**4aaa**	79
2	**1b**	2-ClC_6H_4	**2a**		**3a**		**4baa**	68
3	**1c**	2-BrC_6H_4	**2a**		**3a**		**4caa**	64
4	**1d**	4-FC_6H_4	**2a**		**3a**		**4daa**	50
5	**1e**	4-ClC_6H_4	**2a**		**3a**		**4eaa**	61
6	**1f**	4-BrC_6H_4	**2a**		**3a**		**4faa**	62
7	**1g**	2-$O_2NC_6H_4$	**2a**		**3a**		**4gaa**	74
8	**1h**	3-$O_2NC_6H_4$	**2a**		**3a**		**4haa**	96
9	**1i**	2-$MeOC_6H_4$	**2a**		**3a**		**4iaa**	46
10	**1j**	4-$MeOC_6H_4$	**2a**		**3a**		**4jaa**	37

[a] *Reaction conditions:* aryl aldehyde 0.5 mmol, $PhNH_2$ 0.5 mmol, $PhB(OH)_2$ 1.5 mmol, NH_4Cl 1.5 mmol, sodium dodecyl sulfonate 0.5 mmol, 3.0 mol% of **cat. 2** in 2.0 mL of water for 12 h.
[b] Isolated yield.

sodium dodecyl sulfonate (0.5 mmol) in water (2.0 mL) at 100 °C for 12 h were chosen as the optimized conditions (Table 2, entry 13).

With the optimized conditions in hand, the reactions of different aryl aldehydes and arylamines with various arylboronic acids were examined to explore the scope of the reaction. First, we examined the benzaldehyde derivatives with electron-withdrawing substituents in this catalytic system. To our delight, the reaction proceeded smoothly in the presence of a variety of functional groups including fluoro, chloro, bromo and nitro groups (Table 3, entries 1–8). However, the reaction yields were sensitive to electronic effects on the benzaldehyde, and electron-donating groups at the *ortho* or *para* position of aryl aldehydes gave much lower yields (Table 3, entries 9 and 10).

The reaction was not significantly affected by the electronic effect of the amines because both electron-rich and electron-deficient arylamines could give similarly moderate or good results (Table 4, entries 1–6). No reaction was observed when a *p*-toluenesulfonamide was subjected to our optimized reaction conditions (Table 4, entry 7), which is in sharp contrast to the existing reports.[4–7]

A contrasting electronic effect was observed when substituted arylboronic acids were used. Arylboronic acids with electron-donating substituents, which are more nucleophilic, and hence transmetalate more quickly than electron-neutral analogues, are not prone to homocoupling and protodeboronation side reactions,[9] and gave excellent yields of the addition products (Table 5, entries 2–6). However, the sterically hindered *ortho*-substitued arylboronic acid was proved to be problematic for this catalyst system (Table 5, entry 1). For arylboronic acids with electron-withdrawing groups, lower yields of addition products

Table 4. Pd-catalyzed addition of benzaldehyde with arylamines and phenylboronic acid.[a]

Entry	Ar^1		Ar^2	Ar^3	Product	Yield[b] [%]
1	**1a**	**2b**	3-MeC_6H_4	**3a**	**4aba**	50
2	**1a**	**2c**	4-MeC_6H_4	**3a**	**4aca**	75
3	**1a**	**2d**	4-$MeOC_6H_4$	**3a**	**4ada**	79
4	**1a**	**2e**	3-BrC_6H_4	**3a**	**4aea**	77
5	**1a**	**2f**	4-ClC_6H_4	**3a**	**4afa**	81
6	**1a**	**2g**	3-$O_2NC_6H_4$	**3a**	**4aga**	58
7	**1a**	**2h**	4-$MeC_6H_4SO_2$	**3a**	**4aha**	0

[a] *Reaction conditions:* benzaldehyde 0.5 mmol, arylamine 0.5 mmol, $PhB(OH)_2$ 1.5 mmol, NH_4Cl 1.5 mmol, sodium dodecyl sulfonate 0.5 mmol, 3.0 mol% of **cat. 2** in 2.0 mL of water for 12 h.
[b] Isolated yield.

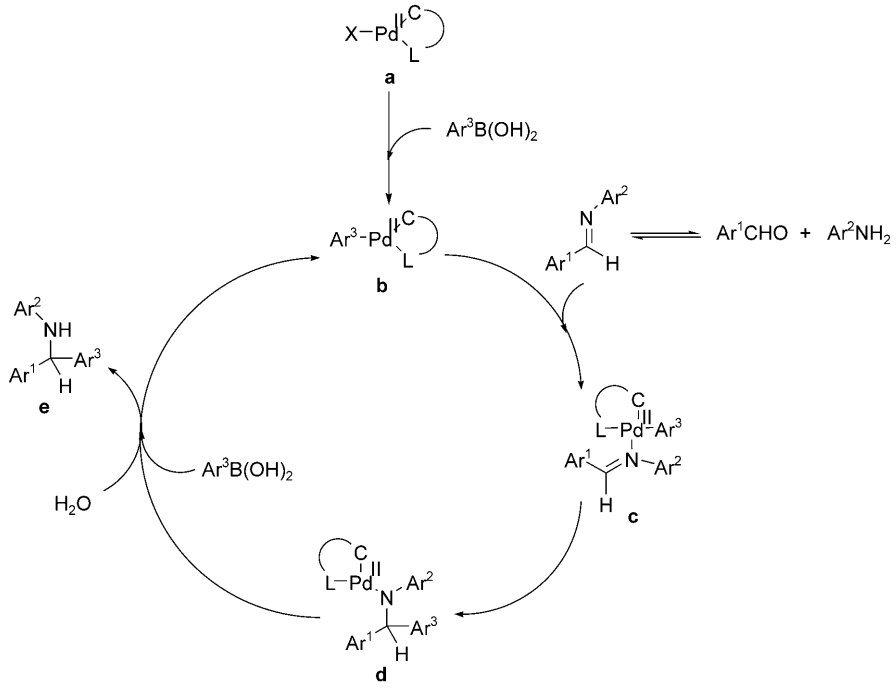
Table 5. Pd-catalyzed addition of benzaldehyde with arylamines and arylboronic acids.[a]

Entry	Ar^1	Ar^2		Ar^3	Product	Yield[b] [%]
1	**1a**	**2f**	**3b**	2-MeC_6H_4	**4afb**	31
2	**1a**	**2f**	**3c**	3-$MeOC_6H_4$	**4afc**	74
3	**1a**	**2a**	**3d**	4-MeC_6H_4	**4aad**	94
4	**1a**	**2f**	**3e**	4-$MeOC_6H_4$	**4afe**	89
5	**1a**	**2f**	**3f**	4-$Me_3CC_6H_4$	**4aff**	95
6	**1a**	**2f**	**3g**	4-$F_3COC_6H_4$	**4afg**	66
7	**1a**	**2f**	**3h**	3-ClC_6H_4	**4afh**	45
8	**1a**	**2f**	**3i**	4-BrC_6H_4	**4afi**	55
9	**1a**	**2f**	**3j**	3-thienyl	**4afj**	47
10	**1a**	**2a**	**3k**	1-naphthyl	**4aak**	52

[a] *Reaction conditions:* benzaldehyde 0.5 mmol, arylamine 0.5 mmol, arylboronic acid 1.5 mmol, NH_4Cl 1.5 mmol, sodium dodecyl sulfonate 0.5 mmol, 3.0 mol% of **cat. 2** in 2.0 mL of water for 12 h.
[b] Isolated yield.

were obtained (Table 5, entries 7 and 8). 3-Thienylboronic acid **3j** still worked smoothly in this procedure, although the yield of **4afj** was decreased to 47%, which may be ascribed to the fact that heteroatoms in the heteroarylboronic acid could coordinate to the transition metal (Table 5, entry 9).[10] The steric hindrance in arylboronic acid **3k** had also little negative effect on the reaction, and **4aak** was obtained in 52% yield (Table 5, entry 10).

The possible mechanism for the addition of aryl aldehydes with amines and arylboronic acids was proposed as shown in Scheme 3. First, the Pd(II) complex was pre-activated to form **a**. Transmetalation will generate the arylpalladium species **b**. Because of the vacant coordination site on the palladium, the aldimine could coordinate with it very easily to generate intermediate **c**. It was followed by insertion of the C=N bond into the palladium-carbon bond to produce **d**.



Scheme 3.

The protonolysis of **d** gave **e** and regenerated the palladium catalyst **a**.

Conclusions

In summary, a highly practical method for the synthesis of α-branched amines has been developed. Imine synthesis and arylboronic acids addition can be accomplished in one pot. The procedure is very simple, cheap and offers other distinct advantages over the existing methods. Further studies on probing the detailed mechanism and the application to asymmetric synthesis are currently underway.

Experimental Section

Materials

All the chemicals are commercially available. Aniline and organic solvents have been purified prior to use. The catalysts **cat. 1** to **cat. 3** were prepared according to our previous work.[11]

Typical Procedure for the Addition of Aryl Aldehydes with Amines and Arylboronic Acids

A reaction vessel was charged with benzaldehyde (0.5 mmol, 53 mg), aniline (0.5 mmol, 47 mg), phenylboronic acid (1.5 mmol, 183 mg), NH_4Cl (1.5 mmol, 81 mg), sodium dodecyl sulfonate (0.5 mmol, 136 mg), and Pd **cat. 2** (0.015 mmol, 9.2 mg) in 2.0 mL of water and the mixture incubated in a oil bath at 100 °C for 12 h. After cooling, the reaction mixture was diluted with 10 mL brine. The aqueous layer was extracted with dichloromethane and dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to TLC (petroleum-dichloromethane) to give the product **4aaa**; yield: 79%.

Analyses

Melting points were measured on a WC-1 microscopic apparatus and are uncorrected. IR spectra were recorded on a Bruker VECTOR22 spectrophotometer. ^{1}H NMR, and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were measured on a Waters Q-T of Micro spectrometer.

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