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Silver Ion Promoted, Pd^{II}-Catalyzed Arylation of Arenes with a Free Amine as Directing Group in Aqueous Medium

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Abstract: Palladium(II)-catalyzed arylation of arenes with aryl boronic acids and a free amine as directing group in aqueous medium has been developed. High reactivity and chemoselectivity for the formation of carbon–carbon bonds were achieved by the use of soluble silver salts. The addition of water is crucial to improve the arylation yield.

Keywords: amines · C–H activation · homogeneous catalysis · palladium · silver

Introduction

The development of general methods for selective transformation of C–H bonds has aroused substantial interest in recent years.[1] Reactivity and selectivity are the most important issues in these transformations. Chelation-assisted strategies using transition metal catalysts have led to spectacular advances in efficiency and selectivity of C–H activation. Nitrogen-containing groups are among the most extensively studied chelating groups, and numerous C–H-activating transformations have been developed by the use of amides,[2] imines,[3] oximes,[4] alkyl amines,[5] and nitrogen-containing heterocycles[6] as directing groups. Despite these important advances, the directing-group limitations remain a challenge in this field.[7] For example, amines are important N-containing functional groups and can be found in many natural products and pharmaceuticals. However, the utilization of amines, especially free amines,[8] as directing groups in transition metal catalyzed C–H activation is often thwarted by catalyst poisoning, which is attributed to the relatively strong bonding of amino groups to metal centers. The excess of the amine is also unfavorable for the cyclometalation process. An equally important challenge for free-amine strategies is to find a way for selective formation of C–C rather than C–N bonds.[9] It is important to develop knowledge and associated strategies for overcoming these hurdles.

In previous studies, extensive efforts were made to adjust the binding ability of the amino group by introducing an acidic medium into the reaction or increasing the acidity of the N–H bond. In 2006, Daugulis and co-workers reported Pd^{II}-catalyzed *ortho* arylation of benzyl amines with aryl iodides.[10] They found that the amount of acid strongly influenced the rate of the arylation reaction, and using five equivalents of trifluoroacetic acid gave the best results, but suffered from spontaneous conversion of free amine to trifluoroacetamide. Later, Shi and co-workers reported an alternative approach using amine derivatives, namely, *N*,*N*-dialkyl amines, as directing groups;[11] the binding ability of the amino group was tuned by means of the acidity of the reaction medium. In 2011, Gaunt et al. demonstrated that aryl–NH is a very effective directing group in Pd^{II}-catalyzed C–H functionalization of β-aryl ethyl amines.[12] They proposed that the introduction of an aryl group into an amine would increase the acidity of the aryl N–H bond and reduce the likelihood of formation of bis-amino Pd^{II} complexes, which is favorable for the formation of the cyclopalladated complex.

We previously investigated free-amine-directed, palladium-catalyzed alkenylation of arenes in the presence of acetic acid, but the free amines subsequently underwent cycloamination with the alkenes to generate phenanthridines as the final products.[13] Given the known strong coordinative interaction between silver ions and amines, we speculated that the binding ability of the amino group could also be tuned by employing the appropriate silver salt, which acts like an acid. Herein, we report a palladium-catalyzed, free-amine-directed Suzuki–Miyaura-type coupling reaction[14] of biaryl-2-amines with aryl boronic acids in the presence of silver nitrate in aqueous media. The free amino groups are not modified in the reaction. In addition to acting as oxidants, two different roles of the silver ion were demonstrated, that is, increasing the reactivity and improving the chemoselectivity. This methodology expands the scope of palladium-catalyzed C–H activation reactions and opens up a new and efficient route for catalytic formation of carbon–carbon bonds for free-amine substrates.

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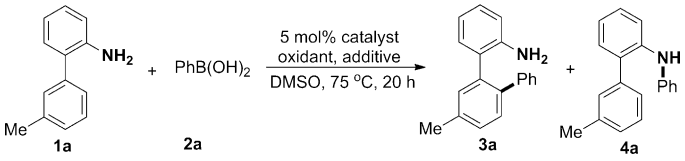
Results and Discussion

We initially employed the reaction conditions of our free-amine-directed alkenylation of C(sp^2)–H by palladium catalysis under acidic condition with copper salts as oxidant. However, all efforts to extend the catalyst system to the arylation of C(sp^2)–H failed, and only the *N*-arylated[15] product **4a** was obtained in almost quantitative yield (Table 1, entry 1). Intriguingly, when AgOAc was used as oxidant, the C(sp^2)–H arylation product **3a** was observed in 8% GC yield and *N*-aryl product **4a** was not found (Table 1, entry 2). The addition of Na_2HPO_4 further improved the reaction to give **3a** in 12% GC yield (Table 1, entry 3). Unexpectedly, $AgNO_3$ showed better efficiency than AgOAc to give **3a** in 25% GC yield (Table 1, entry 4). It is noteworthy that the use of $Na_2HPO_4{\cdot}12H_2O$ led to a sharp increase of the yield to 44% (Table 1, entry 5). It appeared that water might be the key factor in this arylation reaction. Therefore, we carefully examined the effect of the amount of water (Table 1, entries 6–11). Indeed, the incremental addition of water led to a very rapid increase in activity, and a maximum yield (85%) was observed when the amount of water was 0.5 mL (≈28 mmol, Table 1, entry 9). Further addition of water decreased the yield (Table 1, entries 10 and 11). Maybe, the addition of water was favorable to increasing the solubility of aryl boronic acid and $AgNO_3$. Other palladium salts, such as $PdCl_2$, $Pd(TFA)_2$ (TFA = trifluoroacetate) and $Pd(dba)_2$ (dba = *trans*,*trans*-dibenzylideneacetone) were also investigated, and $Pd(OAc)_2$ was clearly the best choice (Table 1, entries 12–14). No reaction took place without catalyst or oxidant in this system (Table 1, entries 15 and 16). Oxygen was found to be ineffective (Table 1, entry 17). The different bases and solvents were also screened; Na_2HPO_4 and DMSO are the most suitable for this transformation (for details, see Supporting Information). Increasing or decreasing the reaction temperature is unfavorable for this reaction. Thus, we established the optimized reaction conditions as follows: 5 mol% of $Pd(OAc)_2$, two equivalents of $AgNO_3$, and two equivalents of Na_2HPO_4 in 1.5 mL of DMSO/H_2O (2:1 v/v) at 75 °C for 20 h.

Table 1. Optimization of reaction conditions.[a]



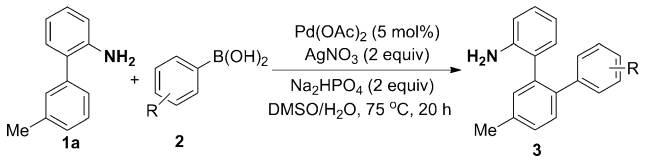
Entry	Catalyst	Oxidant	Additive	Yield [%][b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	HOAc	0 (99)
2	$Pd(OAc)_2$	AgOAc	–	8 (0)
3	$Pd(OAc)_2$	AgOAc	Na_2HPO_4	12 (0)
4	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4	25 (0)
5	$Pd(OAc)_2$	$AgNO_3$	$Na_2HPO_4{\cdot}12H_2O$	44 (0)
6	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (10 mmol)	46 (0)
7	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (20 mmol)	55 (0)
8	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (25 mmol)	69 (0)
9	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (0.5 mL)	85 (0)
10	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (30 mmol)	72 (0)
11	$Pd(OAc)_2$	$AgNO_3$	Na_2HPO_4/H_2O (1.0 mL)	19 (0)
12	$PdCl_2$	$AgNO_3$	Na_2HPO_4/H_2O (0.5 mL)	63 (0)
13	$Pd(TFA)_2$	$AgNO_3$	Na_2HPO_4/H_2O (0.5 mL)	75 (0)
14	$Pd(dba)_2$	$AgNO_3$	Na_2HPO_4/H_2O (0.5 mL)	51 (0)
15	–	$AgNO_3$	Na_2HPO_4/H_2O (0.5 mL)	0 (0)
16	$Pd(OAc)_2$	/	Na_2HPO_4/H_2O (0.5 mL)	0 (0)
17[c]	$Pd(OAc)_2$	O_2	Na_2HPO_4/H_2O (0.5 mL)	0 (0)

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (3.0 mmol), Pd catalyst (0.025 mmol), oxidant (1 mmol, 2 equiv), additive (1.0 mmol), DMSO (1.0 mL), 75 °C for 20 h. [b] GC yields of **3a** based on biphenyl amine **1a**; the yields of **4a** are in parentheses. [c] O_2 (1.0 atm).

Once the optimized reaction conditions were identified, we explored the substrate scope and generality of the arylation reaction (Table 2). The reaction tolerates a wide variety of functional groups, including Me, OMe, F, Cl, CF_3, and OH. Both electron-rich and electron-deficient aryl boronic acids were accommodated with good to excellent efficiency. In general, aryl boronic acids bearing electron-withdrawing groups afforded the arylation products in higher yields (**3d**, **3e**, **3f**, **3j**, and **3k**) than those with electron-donating groups (**3a**, **3b**, **3c**, **3g**, and **3h**). When 4-methoxyphenylboronic acid was used as coupling partner, the corresponding product **3c** was obtained in lower yield, due to the formation of a larger amount of homocoupling product than in the other cases. 3-Hydroxyphenylboronic acid gave the desired product **3i** in moderate yield. 2-Naphthalenylboronic acid reacted smoothly to afford the corresponding product in 78% yield (**3l**).

We next studied the generality of this reaction by varying the electronic and steric properties of the arenes. The electronic property of the arenes had a significant impact on this arylation reaction (Table 3). Arenes with electron-donating substituents (e.g., OMe) at the *meta* position showed better reactivity to deliver the desired product **3m** in moderate yields than those with electron-withdrawing substituents, such as F and Cl (**3n** and **3o**). These results suggested that electrophilic palladation/deprotonation might be involved in this arylation reaction. 2-(Naphthalen-2-yl)aniline could also tolerate the reaction conditions to give **3p** in 64% yield. Moderate yields were obtained for both electron-rich and electron-deficient aniline substrates (**3q** and **3r**). Steric hindrance retarded the reaction. For example, the *ortho*-substituted arene delivered the arylated product **3s** in lower yield than its *meta* analogues. When two *meta* positions were substituted by a methyl group, the reaction failed (**3t**). Biphenyl-2-amine was arylated by phenylboronic acid to give a mixture of mono- and diarylation products in 2:1 molar ratio (**3v**/**3v′**). We got similar results for 4′-substituted biphenyl-2-amines: a mixture of mono- and diarylated products was generated. We also tested a substrates bearing substituents with different electronic properties, but only a moderate yield was obtained (**3u**). In all cases, the substrates underwent direct C(sp^2)–H arylation with complete selectivity over a possible competitive Buchwald–Hartwig *N*-arylation pathway.[9]

Table 2. Arylation of C(sp^2)–H with various aryl boronic acids.[a]



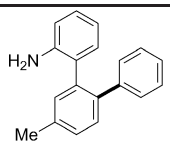
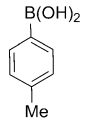
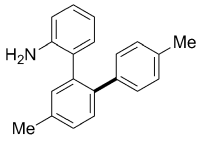
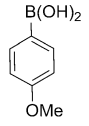
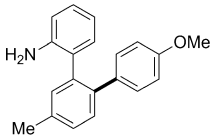
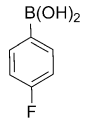
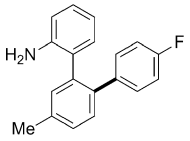
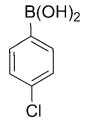
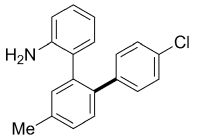
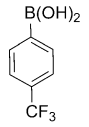
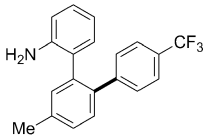
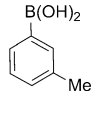
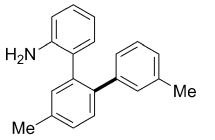
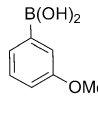
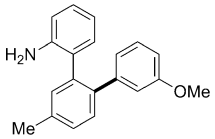
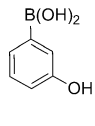
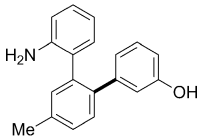
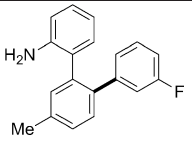
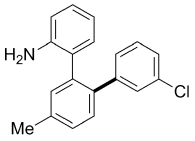
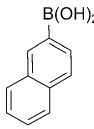
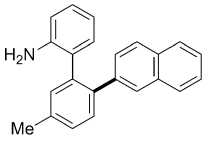
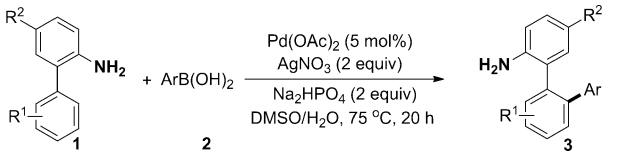
Entry	ArB(OH)$_2$ **2**	Product **3**	Yield [%][b]
1	 **2a**	 **3a**	83
2	 **2b**	 **3b**	77
3	 **2c**	 **3c**	42
4	 **2d**	 **3d**	87
5	 **2e**	 **3e**	84
6	 **2f**	 **3f**	90
7	 **2g**	 **3g**	83
8	 **2h**	 **3h**	85
9	 **2i**	 **3i**	68

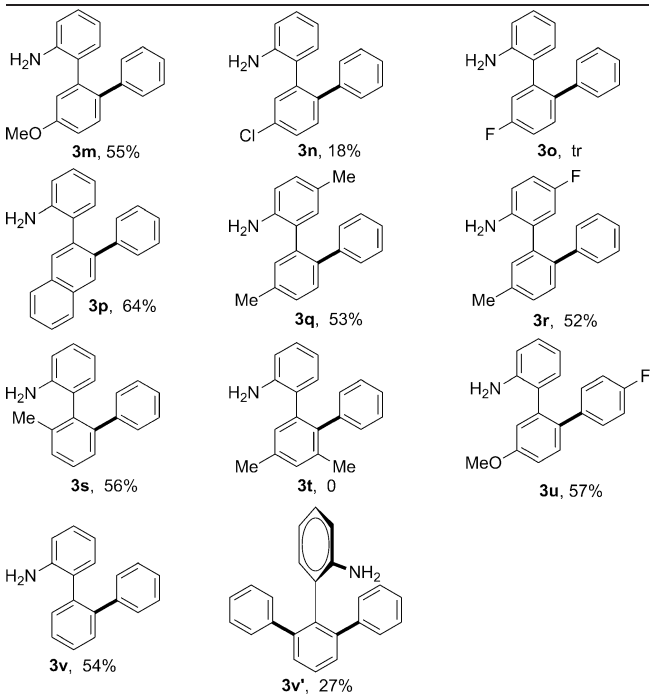
Table 2. (Continued)

Entry	ArB(OH)$_2$ **2**	Product **3**	Yield [%][b]
10	 **2j**	 **3j**	91
11	 **2k**	 **3k**	82
12	 **2l**	 **3l**	78

[a] Reaction conditions: **1a** (0.5 mmol), **2** (3.0 mmol), Pd(OAc)$_2$ (0.025 mmol), $AgNO_3$ (1.0 mmol), Na_2HPO_4 (1.0 mmol), DMSO (1.0 mL), H_2O (0.5 mL), 75 °C, 20 h. [b] Yields of isolated compounds, based on biphenyl amine **1a**.

Table 3. Arylation of various biaryl-2-amines.[a]





[a] Reaction conditions: **1** (0.5 mmol), **2** (3.0 mmol), Pd(OAc)$_2$ (0.025 mmol), $AgNO_3$ (1.0 mmol), Na_2HPO_4 (1.0 mmol), DMSO (1.0 mL), H_2O (0.5 mL), 75 °C, 20 h. Yields of isolated products based on biphenyl amine **1**.

To understand the mechanism of this new C–H arylation reaction, the effect of silver salts was first examined in some detail (Figure 1). Ag_2O and Ag_2CO_3, which are commonly used in C–H activation showed, very poor effects on the arylation reaction. In contrast, $AgNO_3$, which is rarely used in these transformations, exhibited the best efficiency and afforded **3a** in high yield. AgF and $AgSbF_6$ also worked under the reaction conditions, but delivered lower yields. AgOTf gave the arylated product in moderate yield. AgTFA and AgOAc showed good efficiency. In general, the effect of silver salt is in accordance with their relative solubilities.

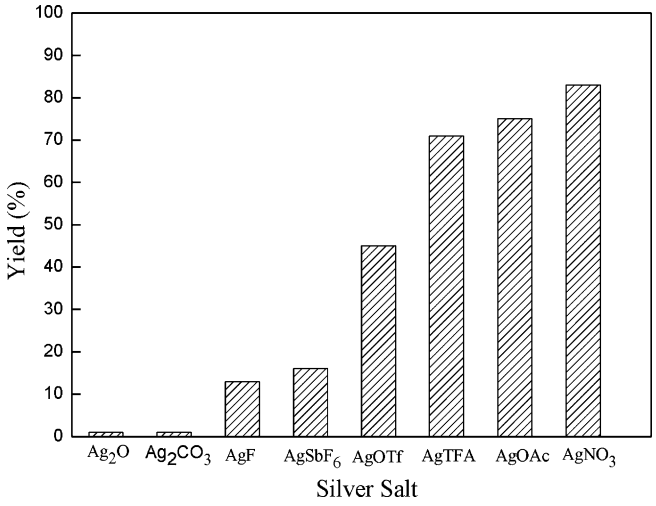


Figure 1. The effect of various silver salts. Reaction conditions: **1a** (0.5 mmol), **2a** (3.0 mmol), $Pd(OAc)_2$ (0.025 mmol), silver salt (1.0 mmol), Na_2HPO_4 (1.0 mmol), DMSO (1.0 mL), H_2O (0.5 mL), 75 °C, 20 h.

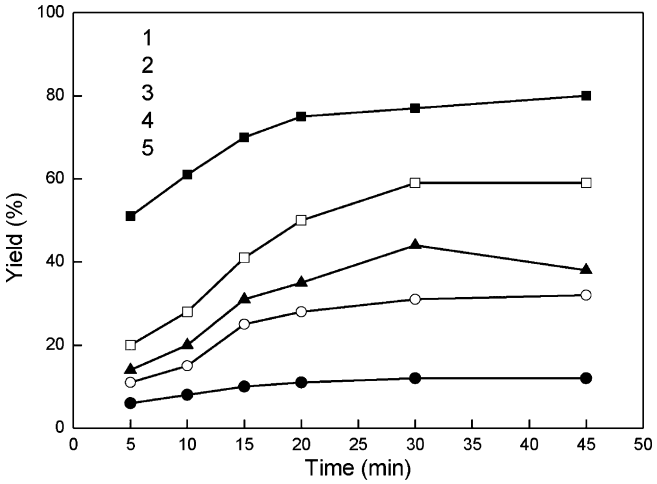
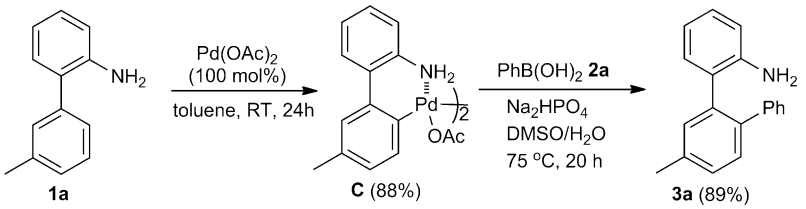


Figure 2. Performance of silver ions. Reaction conditions: (■) Pd^{II} intermediate **C** (0.15 mmol), **2a** (1.8 mmol), DMSO/H_2O (2:1 v/v, 1.0 mL), 75 °C, no $AgNO_3$; (□) $Pd(OAc)_2$ (0.3 mmol, 1.0 equiv), **1a** (0.3 mmol), **2a** (1.8 mmol), $AgNO_3$ (0.6 mmol), DMSO/H_2O (2:1 v/v, 1.0 mL), 75 °C; (▲) Pd^{II} intermediate **C** (0.15 mmol), **2a** (1.8 mmol), $AgNO_3$ (0.6 mmol), DMSO/H_2O (2:1 v/v, 1.0 mL), 75 °C; (○) $Pd(OAc)_2$ (0.6 mmol, 2.0 equiv), **1a** (0.3 mmol), **2a** (1.8 mmol), DMSO/H_2O (2:1 v/v, 1.0 mL), 75 °C, no $AgNO_3$; (●) $Pd(OAc)_2$ (0.3 mmol, 1.0 equiv), **1a** (0.3 mmol), **2a** (1.8 mmol), DMSO/H_2O (2:1 v/v, 1.0 mL), 75 °C, no $AgNO_3$.



Scheme 1. Study on the key palladacyclic intermediate.

We suppose that silver ions could influence this arylation in two ways: 1) by acting as an oxidant to complete the Pd^{II}/Pd^0 catalytic cycle (see Figure 3 below); 2) by serving as a promoter to facilitate the cyclopalladation process (Figure 3, Path b). Under our standard reaction conditions, silver ion is in equilibrium with the amine. Formation of silver amine complex **F**[16] can decrease formation of Pd^{II} amine complex **A**. This is favorable to the formation of Pd^{II} amino complex **B**, which is a required precursor of the cyclopalladation intermediate.[17]

Firstly, we prepared palladacyclic complex **C** according to ref. [18] and treated it with phenylboronic acid (**2a**) under standard reaction conditions in the absence of Ag salts. Indeed, we obtained the arylated product **3a** in 89% yield (Scheme 1), which indicated that the palladacyclic complex **C** is a key intermediate during this catalytic cycle. Next, we examined the effect of silver ions on the reductive-elimination process. Perhaps they can facilitate the interaction between palladium and free amine in intermediate **E** to make the reductive-elimination process easier (Figure 3, Path I). We performed the arylation reaction of 0.15 mmol of palladacyclic intermediate **C** with and without $AgNO_3$ (Figure 2). Surprisingly, the reaction without $AgNO_3$ is much faster than that with 2.0 equivalents of silver nitrate (Figure 2, plots 1 and 3). The results clearly demonstrated that silver ions have very limited impact on improving the transmetalation and reductive elimination process.

To probe the effect of silver ion further, we performed the reaction between substrate **1a** and phenylboronic acid (**2a**) in the presence of a stoichiometric amount of $Pd(OAc)_2$ with and without $AgNO_3$ (Figure 2, plots 2 and 5). A prominent effect of silver ions was noted in this reaction. In the absence of silver nitrate, the efficiency of the transformation was much lower than with 2.0 equivalents of $AgNO_3$. In addition, the nitrate anion may also influence the reaction. We performed reactions with one equivalent of $Pd(OAc)_2$ in the presence of 2.0 equiv $NaNO_3$ and without $NaNO_3$, which resulted in almost the same yields of the arylated products (Scheme 2). These results showed that the re-

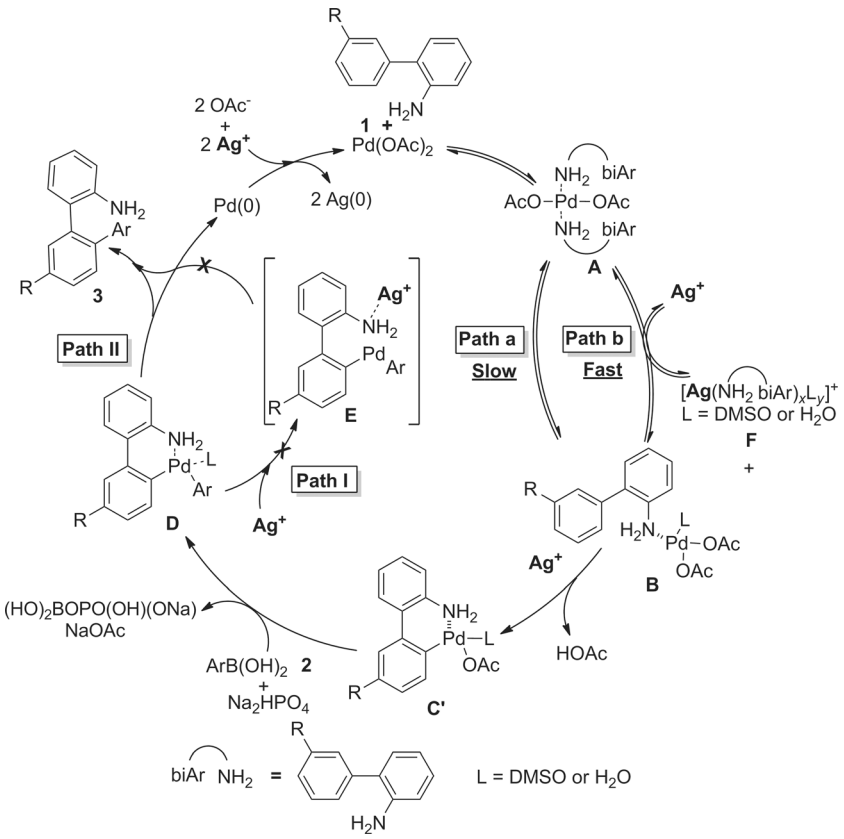
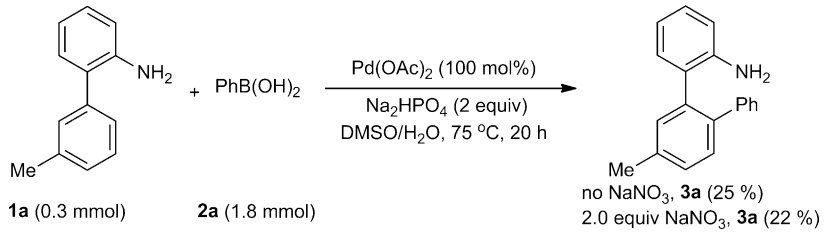


Figure 3. A plausible mechanism.

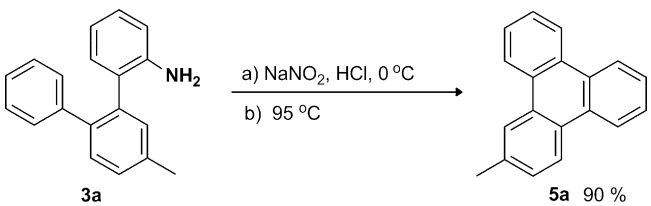


Scheme 2. The action of $NaNO_3$.

action was not influenced by the addition of NO_3^-. In the Pd^{II}/Ag^I system, silver nitrate may oxidize the Pd^0 and thus makes the concentration of Pd^{II} higher than that without Ag^I. To investigate the effect of Pd^{II} concentration, we performed the reaction in the presence of two equivalents of $Pd(OAc)_2$ without $AgNO_3$ (Figure 2, plot 4). The reaction was faster than with one equivalent of $Pd(OAc)_2$ (Figure 2, plot 5), but much lower than with a combination of one equivalent of $Pd(OAc)_2$ and 2.0 equivalents of $AgNO_3$ (Figure 2, plot 2). All of these results demonstrated that silver ions play a key role in the reaction besides acting as an oxidant.

Based on these preliminary results and related studies on the *ortho* metalation of primary amines,[17] a plausible reaction mechanism was proposed (Figure 3). First, $Pd(OAc)_2$ coordinates with substrate amine **1** to give palladium amine complex **A**, which is known to be stable due to the strong binding ability of the amino group. The subsequent formation of intermediate **B**, which is relatively active, may proceed in two ways. One is the direct formation of intermediate **B**, which is not favored in the absence of silver ion (Figure 3, Path a). In this regard, we demonstrated that the arylation reaction was sluggish without the use of $AgNO_3$ (Figure 2, plots 4 and 5). In the presence of silver ion, the formation of intermediate **B** is promoted by the formation of silver amine complex **F**[18] (Figure 3, Path b). We indeed found that the arylation reaction was much faster in the presence of $AgNO_3$ (Figure 2, plot 2). The electrophilic cyclopalladation[19] occurs at the less hindered *ortho* position of the arenes to generate the intermediate **C′**,[17c] which undergoes transmetalation with the aryl boronic acid to produce intermediate **D** with the assistance of Na_2HPO_4. Reductive elimination results in the arylated product and liberates Pd^0, which is oxidized to Pd^{II} by silver salt to restart the cycle.

Polycyclic aromatics have been widely studied for their unique properties in material science;[20] for example, they are important δ-conjugated functional materials.[20a] The arylated product **3a** can be easily transformed into triphenylene derivative **5a** by diazotization and subsequent removal of nitrogen by heating (Scheme 3).[21]



Scheme 3. Synthesis of triphenylene **5a**.

Conclusion

We have developed an efficient free-amine-directed arylation reaction of arenes by palladium catalysis in aqueous medium. By employing soluble silver salt, the poisoning effect of the free amine on Pd^{II} is eliminated, which allows significant improvement of regioselectivity and reactivity to give the $C(sp^2)$–H arylation products in high yields. Further mechanistic investigations to reveal the detailed effects of silver salts and application of this new protocol to other amine-directed C–H activations are currently ongoing.

Experimental Section

General procedure for arylation of biaryl-2-amines with various phenylboronic acids: A round bottom flask (10 mL) with a magnetic stir bar and reflux condenser was charged with $Pd(OAc)_2$ (0.025 mmol, 6 mg, 5 mol%), $AgNO_3$ (1.0 mmol, 171 mg, 2.0 equiv), Na_2HPO_4 (1.0 mmol, 142 mg), biaryl-2-amine **1** (0.5 mmol, 1.0 equiv), phenylboronic acid **2** (3.0 mmol, 6.0 equiv), DMSO (1.0 mL), and H_2O (0.5 mL). The mixture was stirred at 75 °C for 20 h. After cooling to room temperature, the mixture was filtered through a plug of Celite and the residue washed with ethyl acetate (2×20 mL). Then saturated Na_2CO_3 (30 mL) was added, and the organic layer was collected. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluent to afford the corresponding products.

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