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A base-free, one-pot diazotization/cross-coupling of anilines with arylboronic acids

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ABSTRACT

anilines and arylboronic acids.

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Suzuki-Miyaura cross-coupling is a powerful tool for the construction of C–C bonds.¹ In general, aryl halides or triflates are used as coupling partners. The search for alternative electrophilic coupling partner continues to attract interests among the synthetic organic community.² Arenediazonium salts represent an attractive alternative due to their high reactivity and easy availability from aniline derivatives.^{3–7} The first utilization of the aryldiazonium salts as electrophiles in palladium-catalyzed Suzuki-Miyaura cross-couplings was achieved independently by Genet⁴ and Sengupta.⁵ These investigations allow biaryls synthesis with moderate to good yields by coupling of aryldiazonium tetrafluoroborates and arylboronic acids in the presence of catalytic amounts of Pd(OAc)₂ and without adding base and ligands. In 2001, Andrus and Song reported a palladium-imidazolium carbene catalyst system for the cross-coupling of arylboronic acid with aryldiazonium tetrafluoroborates. The reaction could be carried out at low temperature (0 °C or room temperature) and afforded the coupling products with high yields.⁶

Although aryldiazonium tetrafluoroborates have been well established as coupling partners in Pd-catalyzed reactions, there are some drawbacks. First, aryldiazonium tetrafluoroborates are generally unstable and only few of them are commercially available. Therefore, they should be newly prepared before use. However, the procedure for the preparation of aryldiazonium tetrafluoroborates is hazardous and tedious due to the use of fluoroboric acid and recrystallization in separation process.⁸ As a result,

* Corresponding author. E-mail address: wangjb@pku.edu.cn (J. Wang). the reaction usually gives low yield especially when carried out in a small scale. Consequently, the advantage of easy availability of aniline starting materials may be counteracted by the lack of efficiency and flexibility in the preparation of aryldiazonium tetrafluoroborates.

Pd-catalyzed one-pot diazotization/cross-coupling is realized for the synthesis of biaryls directly from

We conceived that a one-pot diazotization/cross-coupling would circumvent these setbacks. Such an approach has been pursued first by Fujiwara and coworkers in 1980,⁹ although in their seminal work stoichiometric amount of $Pd(OAc)_2$ was required in order to obtain good yields. Almost at the same time, Matsuda and coworkers described the same coupling reaction but using alkyl nitrite as diazotizing agent and catalytic amounts of $Pd_2(dba)_3$.¹⁰ Andrus and Song have also demonstrated the onepot diazotization/cross-coupling in their catalytic system with palladium-imidazolium carbene as catalyst.⁶ Encouraged by these developments, we wish to report in this Letter an efficient Pdcatalyzed base-free cross-coupling of arylamines and arylboronic acids with *tert*-butyl nitrite as diazotizating agent.¹¹ The reaction does not need to use BF₃-OEt₂ as in the case of Andrus's system.

Initial screening of the reaction conditions with aniline **1a**, *p*-tolylboronic acid **2a**, and *tert*-butyl nitrite revealed that the usual Suzuki–Miyaura coupling protocol [DME, Pd(PPh₃)₄, aqueous Na₂CO₃] failed to afford any desired product. After some experimentations, it was concluded that the desired cross-coupling product **3a** could be obtained in 36% GC–MS yield under a condition with 5 mol % Pd(PPh₃)₄ in CH₃CN at 90 °C (Table 1, entry 1). Encouraged by this initial result, we further proceeded to optimize the reaction conditions. First, different solvents were examined and it was concluded that DMF afforded the best yield of 64%





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Table 1

Pd-catalyzed cross-coupling of aniline **1a** and *p*-tolylboronic acid **2a**^a



Entry	Cat. (mol %)	Solvent (mol %)	Additive	Temp (°C)	Yield ^b (3a , %)
1	$Pd(PPh_3)_4(5)$	MeCN	_	90	36
2	$Pd(PPh_3)_4(5)$	DCE	_	90	8
3	$Pd(PPh_3)_4(5)$	Toluene	_	90	17
4	$Pd(PPh_3)_4(5)$	DMSO	_	90	52
5	$Pd(PPh_3)_4(5)$	DMF	_	90	64
6	_	MeCN	_	90	0
7	$Pd(PPh_3)_4(5)$	DMF	K ₂ CO ₃ (200)	90	8
8	$PdCl_2(PPh_3)_2(5)$	DMF	_	90	12
9	$Pd(P^tBu)_3(5)$	DMF	_	90	32
10	$Pd(OAc)_2(5)$	DMF	_	90	17
11	$Pd(PPh_3)_4(5)$	DMF	_	90	49
12	$Pd(PPh_3)_4(5)$	DMF	AcOH (100)	90	70
13	Pd ₂ dba ₃ (2.5)/P(2-furyl) ₃ (15)	DMF	_	90	74
14	Pd ₂ dba ₃ (2.5) P(2-furyl) ₃ (15)	DMF	AcOH (100)	90	91

^a Reaction conditions: aniline **1a** (0.5 mmol); **1a**:**2a**:^tBuONO = 1:1.3:1.2; solvent 2 mL, under N₂.

^b GC-MS yield using mesitylene as internal standard.

Tab1e 2

The scope of the one-pot diazotization-coupling reaction^a



3a'-n

Entry Arylamines 1a-n Products 3a'-n Yield^b (%) OMe NH₂ 81 1 3a' 1a NH₂ OMe 2 77 1b 3b NH₂ OMe 3 73 1c **3**c OMe NH₂ 4 52 1d 3d OMe CI NH₂ С 5 75 1e 3e CI C CI NH₂ С OMe 56 6 1f 3f

(continued on next page)

Tab1e 2 (continued)



 $^{^{}a}\,$ Reaction were carried out in 1 mmol scale, DMF 4 mL under N_{2} atmosphere. $^{b}\,$ Isolated vield.

(entries 2–5). Control experiment indicated that without palladium catalyst, the reaction failed to give any coupling product (entry 6). Besides, the reaction could not be improved by adding a base (entry 7). Next, we examined other palladium catalysts; however, the reaction could not be improved (entries 8–10). The reaction became sluggish when the temperature decreased from 90 to 70 °C. To our delight, it was noted that the reaction could be significantly improved when catalyzed by a combination of Pd₂dba₃ (2.5 mol %) and P(2-furyl)₃ (15 mol %) (entry 13). Finally, adding 1 equiv of acetic acid was found to further improve the reaction (entry 14). The positive effect of acetic acid in one-pot diazotization-coupling reaction has also been observed by Matsuda¹⁰ and Beller.¹² We reasoned that acetic acid not only accelerated the diazotization process but also influenced the transmetallation step by anion exchange with ^rBuO⁻.

With $Pd_2dba_3/P(2-furyl)_3$ catalytic system, the scope of the onepot diazotization/coupling reaction was examined by a series of arylamines **1a–n** and 4-methoxyphenylboronic acid **2b**¹³ The results are summarized in Table 2. For a wide range of arylamines, the reaction afforded the biaryl products **3a'–n** in moderate to good yields. Substrates with weak electronic effect generally gave good yields, as shown by methyl and halide substituted arylamines (entries 1–5). However, it was noted that the steric hindrance significantly diminished the yield (entry 4). It is also worthy to note that the reaction tolerates a wide range of subtituents, wheather it is of electron withdrawing or electron donating.

The yields of this one-pot diazotization/coupling reaction were moderate to good and the main byproduct is homo coupling of arylboronic acids. Control experiment showed that tert-butyl nitrite could function as an oxidant in homo coupling of arylboronic acid catalyzed by Pd(0). The advantage of this one-pot reaction lies in its operational simplicity and convenience. It is important to note that the aryldiazonium salts are formed very quickly for some substrates, such as ethyl p-aminobenzoate. For this type of substrates, we have applied an alternative procedure in which the diazotization is carried out first and the cross-coupling with boronic acid is then performed upon the completion of the diazotization, namely a one-pot, two-step process. This procedure was then applied to the coupling of arylboronic acids with arylamines (Table 3). In a typical experiment, arylamine and tert-butyl nitrite were first mixed with a ratio of 1:1.05 and set to react at room temperature. The diazotization was complete within 5 min as monitored by TLC analysis. Then Pd(0) catalyst, P(furyl)₃, and boronic acid were added and the reaction was carried out at 90 °C. For a wide range of arylboronic acids, the reaction afforded products 30-z in moderate yields.

The mechanism of this diazotization-coupling is proposed to be the standard oxidative addition-reductive elimination mechanism of Pd-catalyzed cross-coupling (Scheme 1). The first-step is diazotization of arylamine to form corresponding aryldiazonium salt. It is known that aryldiazonium salt cations can coordinate transition metals to give species like **A**, in which the metal has increased its

Table 3

Cross-coupling of arylamines with arylboronic acids by one-pot, two-step process¹⁴



^a Isolated yield.

oxidation number by two units.¹⁵ Alternatively, this process could also be considered as an oxidative addition of $Pd(0)L_n$ with aryldi-



Scheme 1. Possible reaction mechanism.

azonium salt to afford Pd(II) intermediate. Extrusion of dinitrogen from intermediate **A** leads to the formation of complex **B**, from which transmetallation to form **C**. Reductive elimination is followed to afford the final biaryl product.

In conclusion, we have developed a convenient Pd-catalyzed one-pot diazotization/cross-coupling of arylamines and arylboronic acids. Since arylamines are abundant and easily available, this transformation provides an efficient and economic approach for the preparation of biaryl products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.099.

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- 13. General procedure. Pd₂dba₃ (23 mg, 2.5 mol %), P (2-furyl)₃ (46 mg, 20 mol %), 4-methoxybenzeneboronic acid **2b** (182 mg, 1.2 equiv), and *p*-toluidine **1b** (107 mg, 1 mmol) were weighed in a 25 mL Schlenk round bottle flask under nitrogen atmosphere. The system was degassed four times by oil pump. DMF (4 mL), 'BuONO (134 mg, 1.3 equiv), and HOAc (60 mg, 1.0 equiv) were then added in succession by syringe. The resulting reaction mixture was allowed to stir at 90 °C for 8 h. The solution was then concentrated under reduced pressure and the crude residue was purified by flash column chromatography with petroleum ether to give 4-methoxy-4'-methylbiphenyl **3b** (152 mg, 77%).
- General procedure. Pd₂db₃ (23 mg, 2.5 mol %), P (2-furyl)₃ (46 mg, 20 mol %), and benzeneboronic acid 2c (146 mg, 1.2 equiv) were weighed in a 25 mL

Schlenk round bottle flask under nitrogen atmosphere. The system was degassed four times by oil pump. Ethyl 4-aminobenzoate **1n** (165 mg, 1 mmol) was weighed in another 25 mL Schlenk round bottle flask under nitrogen atmosphere. DMF (2 mL), 'BuONO (108 mg, 1.05 equiv), and HOAC (60 mg, 1.0 equiv) were added in succession by syringe and this reaction mixture was stirred for 5 min. Then the solution containing the newly generated diazonium salt was transferred to the above Schlenk round bottle by syringe. In the course of this transfer, another 2 mL DMF was added to the reaction system. The resulting reaction solution was stirred and the resultion was then concentrated under reduced pressure and the crude residue was purified by flash column chromatography (petroleum ether/EtOAc = 30:1) to afford the product ethyl biphenyl-4-carboxylate **30** (113 mg, 50%).

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