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A General and Highly Efficient Method for the Construction of Aryl-Substituted N-Heteroarenes

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A general, simple and highly efficient method has been developed for the $Pd(OAc)_2$-catalyzed ligand-free and aerobic Suzuki reaction of N-heteroaryl halides, which is strongly dependent on the molecular structure of solvent.

Introduction

After the development of three decades, the Suzuki reaction has become one of the most useful methods for the construction of biaryls.[1] To date, this chemistry is still full of challenges and attracts attention of researchers from a wide range of disciplines.[2] For example, the formation of aryl-substituted N-heteroaryl compounds is of great importance in the synthesis of pharmaceuticals, natural products and advanced functional materials.[3] However, N-heteroaryl halides are difficult substrates for the Suzuki reaction due to the potential coordination of the nitrogen to the active palladium species.[4] In recent years, the groups of Buchwald,[5] Fu,[6] Plenio[7] and others[8] have reported a variety of ligand-promoted protocols to activate these substrates successfully.

Attempts have also been made to develop ligand-free approaches for such a transformation in an aqueous media,[9] in which the nitrogen atoms are proposed to prefer to engage in hydrogen bonding with water rather than coordinate to the palladium.[7]

However, the water-involved ligand-free protocol usually encounters with either a low reactivity or a narrow scope with respect to N-heteroaryl halides.

To the best of our knowledge, a general and highly efficient approach for the construction of N-heterobiaryls via the palladium-catalyzed ligand-free and aerobic Suzuki reaction has not been reported. We describe herein a simple, general and highly efficient method for the $Pd(OAc)_2$-catalyzed Suzuki reaction of N-heteroaryl halides in the absence of a ligand in short reaction time under air in neat ethylene glycol (EG).

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Results and Discussion

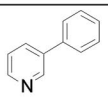
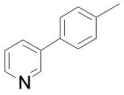
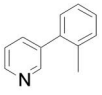
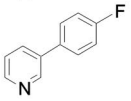
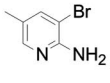
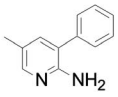
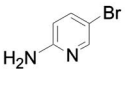
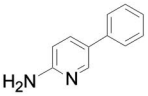
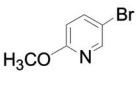
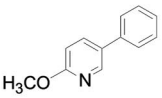
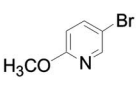
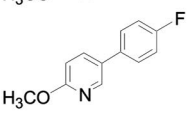
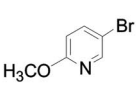
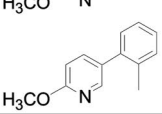
As aryl-substituted pyridines are the most common N-heteroaryl units in pharmaceutically active compounds,[10] we first investigated the Suzuki reaction of pyridyl bromides.

According to the literature reports, 3-pyridyl bromides are more reactive than the corresponding 2-pyridyl bromides in the palladium-catalyzed ligand-free protocols.[9c–9e] This reactivity difference has also been observed in the bromine/magnesium exchange reactions.[11] Therefore, we started the study of the cross-couplings of 3-pyridyl bromides with arylboronic acids using 0.5 mol-% $Pd(OAc)_2$ in ethylene glycol at 80 °C under air. The results are collected in Table 1. The cross-coupling of 3-bromopyridine with phenylboronic acid completed in 15 min, resulting in a TOF of 784 h^{-1} (Table 1, entry 1), which is the fastest and most efficient example among the reported ligand-free approaches.[9c,12]

The Suzuki reactions of 3-bromopyridine with arylboronic acids containing either electron-donating or electron-withdrawing groups provided excellent yields in short time (Table 1, entries 2–4). Excitingly, the cross-couping of *o*-tolylboronic acid with 3-bromopyridine proceeded quantitatively over 3 h, which is the first example that this coupling reaction could complete in a ligand-free protocol (Table 1, entry 3). Noticeably, 2-amino-3-bromo-5-methyl- or 2-amino-5-bromopyridine, which is generally protected prior to the cross-coupling reaction due to the retarding effect of the amino group on the organometallic reaction,[13] reacted with phenylboronic acid to afford the desired biaryls in high yields, respectively (Table 1, entries 5 and 6). To our delight, 2-methoxy-5-bromopyridine exhibited high activity in the $Pd(OAc)_2$/EG system even in the presence of a 0.05 mol-% palladium loading (Table 1, entries 7–9), providing a previously unreported high TOF up to 23520 h^{-1} (Table 1, entry 7).

We next explored the generality of the coupling reactions between 2-pyridyl bromides and various arylboronic acids

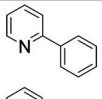
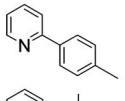
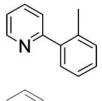
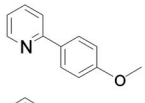
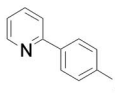
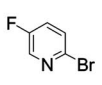
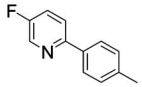
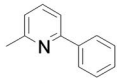
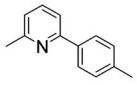
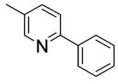
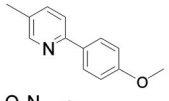
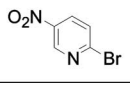
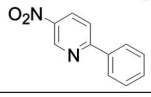
Table 1. The Suzuki reaction of 3-pyridyl bromides with arylboronic acids.[a]

Entry	3-Pyridyl bromides	Product	Time/min	Yield (%)[b]
1			15	98
2			15	99
3			180	96
4			35	96
5			240	93
6			300	80
7			5	98[c]
8			12	99[c]
9			25	96[c]

[a] Reaction conditions: 3-bromopyridine (0.5 mmol), arylboronic acids (0.75 mmol), $K_3PO_4{\cdot}7H_2O$ (1 mmol), $Pd(OAc)_2$ (0.5 mol-%), ethylene glycol (4 mL), 80 °C, under air. The reaction was monitored by TLC. [b] Isolated yields. [c] $Pd(OAc)_2$ (0.05 mol-%).

in ethylene glycol. The results are summarized in Table 2. A quantitative yield of 2-phenylpyridine was obtained in the presence of 0.5 mol-% $Pd(OAc)_2$ at 80 °C for 30 min in air, resulting in a TOF of 396 h^{-1} (Table 2, entry 1). Although this coupling provided a nearly half of the TOF value with respect to that between 3-bromopyridine and phenylboronic acid, it is the most efficient ones under ligand-free conditions.[9a–9d,9f,12,14] It is noteworthy that the reaction between 2-bromopyridine and *o*-tolylboronic acid could be conducted in 94% yield after 60 min (Table 2, entry 3), which is far more efficient than that carried out in an aqueous system.[9a,9f] Arylboronic acids with electron-deficient or electron-rich groups reacted smoothly with 2-bromopyridine, affording high isolated yields in short time (Table 2, entries 2–5). For example, 4-fluorophenylboronic acid, with an electron-withdrawing group, completed the reaction with 2-bromopyridine in 20 min with 99% yield (Table 2, entry 5). The cross-coupling reactions between arylboronic acids and 2-pyridyl bromides bearing electron-donating or electron-withdrawing groups were carried out rapidly with excellent yields (Table 2, entries 6–11). The coupling of 2-bromo-5-fluoropyridine with *p*-tolylboronic acid gave exclusively 5-fluoro-2-(*p*-tolyl)pyridine in 96% yield after 10 min, showing high efficiency and good selectivity (Table 2, entry 6). To our surprise, 2-bromo-6-methylpyridine, an inactive substrate in aqueous system,[9a] exhibited high activity in ethylene glycol (Table 2, entries 7 and 8).

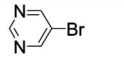
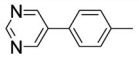
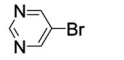
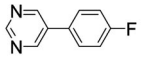
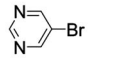
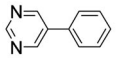
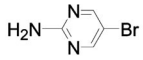
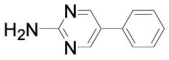
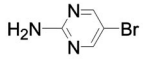
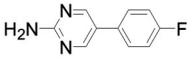
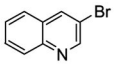
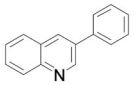
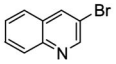
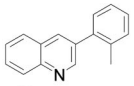
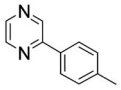
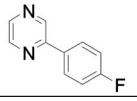
Table 2. The Suzuki reaction of 2-pyridyl bromides with arylboronic acids.[a]

Entry	2-Pyridyl bromides	Product	Time/min	Yield (%)[b]
1			30	99
2			15	97
3			60	94
4			40	98
5			20	99
6			10	96
7			20	92
8			15	91
9			35	99
10			60	84
11			20	98

[a] Reaction conditions: 2-bromopyridine (0.5 mmol), arylboronic acids (0.75 mmol), $K_3PO_4{\cdot}7H_2O$ (1 mmol), $Pd(OAc)_2$ (0.5 mol-%), ethylene glycol (4 mL), 80 °C, under air. The reaction was monitored by TLC. [b] Isolated yields.

To further investigate the scope and limitations of this methodology, we carried out cross-couplings of other nitrogen-based heteroaryl halides with various arylboronic acids. As shown in Table 3, 5-bromopyrimidine reacted smoothly with arylboronic acids bearing different electronic effect groups using 0.1 mol-% $Pd(OAc)_2$ (Table 3, entries 1–3). Obviously, it took much longer reaction time to complete the Suzuki reaction of 2-amino group substituted 5-bromopyrimidine requiring an increased palladium loading of 0.5 mol-%, highlighting the retarding effect of the amino group on the coupling reaction.

Table 3. The Suzuki reaction of N-heteroaryl halides with arylboronic acids.[a]

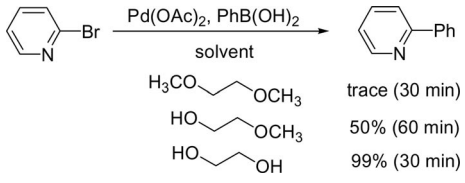
Entry	Ar-X	Product	Time/min	Yield (%)[b]
1			7	99[c]
2			30	98[c]
3			20	98[c]
4			120	95
5			180	95
6			25	93
7			85	80
8			20	99
9			95	88

[a] Reaction conditions: N-heteroaryl halides (0.5 mmol), arylboronic acids (0.75 mmol), $K_3PO_4 \cdot 7H_2O$ (1 mmol), $Pd(OAc)_2$ (0.5 mol-%), ethylene glycol (4 mL), 80 °C, under air. The reaction was monitored by TLC. [b] Isolated yields. [c] $Pd(OAc)_2$ (0.1 mol-%).

The reaction of 3-bromoquinoline with phenylboronic acid provided the product in 93% yield within 25 min (Table 3 entry 6), much more efficient than that performed in a silica-assisted aqueous protocol.[9c]

The steric effect on the arylboronic acid usually decreased the reactivity, therefore, only an 80% isolated yield was obtained after 85 min in the case of *o*-tolylboronic acid (Table 3, entry 7). It is noteworthy that 2-chloropyrazine is a good coupling partner in the $Pd(OAc)_2$/EG system (Table 3, entries 8–9).

To understand the high efficiency of the $Pd(OAc)_2$/EG system for the Suzuki reaction of N-heteroaryl halides, the cross-coupling of 2-bromopyridine with phenylboronic acid was chosen to study the effect of solvent molecular structure on the reactivity under air using 0.5 mol-% $Pd(OAc)_2$ at 80 °C. The results are illustrated in Scheme 1.



Scheme 1. Effect of the solvent molecular structure on the reactivity.

It is clear that the hydroxy groups of solvent play an important role in the reactivity of the Suzuki reaction. Using methoxyl group instead of one of the hydroxy groups of ethylene glycol resulted in obviously decreased reactivity, thus, only 50% isolated yield of the 2-phenylpyridine was reached after 60 min. Further replacing both hydroxy groups of ethylene glycol with methoxyl groups provided trace cross-coupling product in 30 min, while a quantitative yield was reached in 30 min in ethylene glycol. Therefore, ethylene glycol functions not only as a solvent but also as a promoter in the Suzuki reaction of N-heteroaryl halides. Although the nature of ethylene glycol as a promoter is unclear, we propose that an active palladium complex could be formed in the catalytic cycle via hydroxy groups of the solvent.

Conclusions

In conclusion, we have developed a general, ligand-free, aerobic and very fast protocol for the constuction of N-heterobiaryl derivatives via the Suzuki reaction of N-heteroaryl halides in ethylene glycol. Further investigation on the reaction mechanism and synthetic application of this protocol are ongoing in our laboratory.

Experimental Section

Materials and Methods: All N-heteroaryl bromides and arylboronic acids were used as received (Alfa Aesar, Avocado). All other chemicals were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts were reported in ppm relative to TMS. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. Mass spectroscopy data of the products were collected on a MS-EI instrument. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by ^{1}H NMR spectra to reported data.

General Procedure for the Suzuki Reaction of 3-Pyridyl Bromides or Other N-Heteroaryl Halides with Arylboronic Acids: A mixture of 3-pyridyl bromide or other heteroaryl halides (0.5 mmol), arylboronic acid (0.75 mmol), $Pd(OAc)_2$ (0.5 mol-%, 0.56 mg), $K_3PO_4 \cdot 7H_2O$ (1 mmol, 338.4 mg) and ethylene glycol (4 mL) was stirred at 80 °C for indicated time. The mixture was added to brine (10 mL). The mixture was extracted with diethyl ether (10 mL). Sodium hydroxide (10 mmol, 400 mg) was added to neutralize the superfluous arylboronic acid. The mixture was transferred into brine (10 mL) in order to extract the impurity which dissolved in the aqueous solution and dissolve the superfluous base. The abovementioned three steps were repeated for three times. The solvent was concentrated in vacuo and the product was isolated by short chromatography on a silica gel (200–300 mesh) column.

General Procedure for Suzuki Reaction of 2-Pyridyl Bromides with Arylboronic Acids: A mixture of 2-pyridyl bromide (0.5 mmol), arylboronic acid (0.75 mmol), $Pd(OAc)_2$ (0.5 mol-%, 0.56 mg), $K_3PO_4 \cdot 7H_2O$ (1 mmol, 338.4 mg) and ethylene glycol (4 mL) was stirred at 80 °C for indicated time. The mixture was added to brine (10 mL) and extracted four times with diethyl ether (4 × 10 mL).

The solvent was concentrated in vacuo and the product was isolated by short chromatography on a silica gel (200–300 mesh) column.

5-(4-Fluorophenyl)-2-methoxylpyridine: Yield 99% (100.5 mg), m.p. 75 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.33 (d, J = 2.4 Hz, 1 H, Py), 7.74 (dd, J = 8.4, 2.4 Hz, 1 H, Py), 7.49–7.45 (m, 2 H, Ph), 7.15–7.11 (m, 2 H, Ph), 6.81 (d, J = 8.4 Hz, 1 H, Py), 3.98 (s, 3 H, OCH_3), ppm. ^{13}C NMR: δ = 163.6 [d, $^1J(^{13}C,^{19}F)$ = 8.0 Hz, C*i*], 161.2 (C*i*), 144.8 (C_{Py}), 137.4 (C*i*), 134.1 [d, $^3J(^{13}C,^{19}F)$ = 3.0 Hz, C_{Ph}], 129.2 (C_{Py}), 128.3 [d, $^5J(^{13}C,^{19}F)$ = 8.0 Hz, C*i*], 115.9 [d, $^2J(^{13}C,^{19}F)$ = 22.0 Hz, C_{Ph}], 110.9 (C_{Py}), 53.57 (OCH_3), ppm. MS (EI): *m*/*z* (%) = 204, 203 (100) [M^+], 175, 172, 146, 133, 132, 107, 83, 63.

2-Methoxy-5-(2-methylphenyl)pyridine: Yield 96% (95.5 mg), light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.13 (d, J = 2.8 Hz, 1 H, Py), 7.54 (dd, J = 8.8, 2.4 Hz, 1 H, Py), 7.28–7.19 (m, 4 H, Ph), 6.79 (d, J = 8.4 Hz, 1 H, Py), 3.98 (s, 3 H, OCH_3), 2.27 (s, 3 H, CH_3), ppm. ^{13}C NMR: δ = 163.3 (C*i*), 146.7 (C_{Py}), 139.7 (C_{Py}), 138.3 (C_{Ph}), 135.9 (C*i*), 130.7 (C_{Ph}), 130.6 (C_{Ph}), 130.1 (C*i*), 127.8 (C_{Ph}), 126.2 (C*i*), 110.3 (C_{Py}), 53.6 (OCH_3), 20.6 (CH_3), ppm. MS (EI): *m*/*z* (%) = 200, 199 (100) [M^+], 198, 170, 169, 167, 154, 141, 128, 127, 115, 102, 89, 77, 63, 48, 39.

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