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Mild and Ligand-Free Palladium-Catalyzed Cross-Couplings between Aryl Halides and Arylboronic Acids for the Synthesis of Biaryls and Heterocycle-Containing Biaryls

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Ligand-free palladium-catalyzed Suzuki–Miyaura cross-couplings between aryl halides and arylboronic acids performed at room temperature are presented. It was found that both solvent and base had a fundamental influence on the reaction, and the most effective system in terms of yield and rate was observed to be the combination of $Pd(OAc)_2$ with MeONa and alcohols. In the presence of $Pd(OAc)_2$ and MeONa, a variety of aryl halides reacted very rapidly with arylboronic acids in good to excellent yields at room temperature in EtOH as the solvent. Moreover, the $Pd(OAc)_2$/MeONa catalytic system could also be applied in couplings between heteroaryl halides and arylboronic acids to provide satisfactory results in MeOH as the solvent after prolonged reaction times. It is noteworthy that the reactions were conducted under mild, aerobic, and ligand-free conditions.

Introduction

Biaryls are important intermediates broadly used in synthetic organic chemistry and found in many naturally occurring and biologically valuable molecules.[1] Accordingly, substantial attention has been paid to the development of efficient methods for the synthesis of biaryls, one of the best known methods for the construction of such biaryl compounds being the Suzuki–Miyaura cross-coupling reaction.[2–8] The original and general Suzuki–Miyaura coupling procedure involves the use of palladium–ligand (often a phosphane ligand) complexes as catalysts, and the reactions are performed at high temperature and under oxygen-free conditions to avoid side reactions. In addition, long reaction times are usually required. Impressive progress in the development of efficient catalytic systems to achieve this reaction under mild conditions has been made in the last several years,[3,4] but there still exists considerable room for further exploration, as only a few methods for palladium-catalyzed Suzuki–Miyaura coupling at room temperature without the aid of any ligands have been developed.[5–7] Among those ligand-free and room temperature Suzuki–Miyaura coupling transformations, many methods have still required other additional promoters,[5] such as phase-transfer catalysts (usually nBu$_4$NBr), supramolecular reactors [amphiphilic rod-coil molecules consisting of poly(ethylene oxide)], and others, to provide the best results. Sajiki and co-workers[6] recently found that Pd/C-catalyzed Suzuki–Miyaura cross-couplings between aryl bromides and arylboronic acids could be carried out smoothly without the aid of any ligands and promoters at room temperature, but long reaction times (24 h) were still necessary to ensure complete conversion under oxygen-free conditions. To the best of our knowledge, only one paper[7] has demonstrated that palladium-catalyzed Suzuki–Miyaura cross-couplings between aryl bromides and arylboronic acids can be carried out rapidly (20 min to 60 min) in aqueous acetone under ligand-free and aerobic conditions, but the procedure was performed with heating in order to complete the conversion of aryl iodides and bromides rapidly (35 °C). In addition, no reactions involving the synthesis of heterocycle analogues were reported. The development of mild, rapid, ligand-free, and aerobic procedures for palladium-catalyzed Suzuki–Miyaura cross-couplings is therefore still a topic of unparalleled important in organic synthesis and industry.

Serendipitously, we found that couplings between various aryl halides and arylboronic acids could be carried out very rapidly (4–30 min) at room temperature in good to excellent yields in the presence of $Pd(OAc)_2$ (1 mol-%), NaOMe (1 mmol), and EtOH (1 mL). In addition, the catalytic system could also be applied for couplings between heteroaryl halides and arylboronic acids, with satisfactory results still being achieved at room temperature in MeOH as the solvent after prolonged reaction times. Here we wish to report our results in detail [Equation (1)].

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$$Ar{-}X + Ar'{-}B(OH)_2 \xrightarrow[ROH,\ r.t.]{Pd(OAc)_2/NaOMe} Ar{-}Ar'$$

Ar, Ar' = aryl, heteroaryl
X = I, Br, Cl

(1)

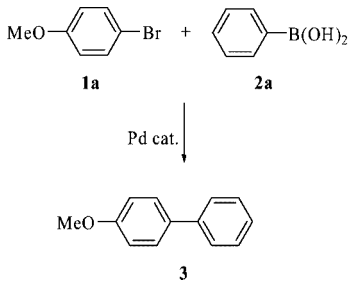
Results and Discussion

Coupling between *p*-bromoanisole (**1a**) and phenylboronic acid (**2a**) was chosen as a model reaction for screening of the conditions, and the results are summarized in Table 1. Initially, a number of solvents were examined, and preliminary experiments showed that solvents had a fundamental influence on both rate and yield of the reaction: treatment of substrate **1a** with **2a**, $Pd(OAc)_2$ (1 mol-%), and NaOMe (1 mmol) in MeOH had afforded the corresponding product **3** in quantitative yield after 10 h (Entry 1), whereas in EtOH substrate **1a** had been completely consumed after 6 min, to provide results otherwise identical to those obtained in MeOH (Entry 2). Other solvents, including *n*PrOH, *i*PrOH, *n*BuOH, *i*BuOH, *t*BuOH, and acetone, however, decreased both rate and yield of the reaction (Entries 3–8). Encouraged by these results, we therefore performed the reaction with other Pd catalysts, including $Pd_2(dba)_3$, $PdCl_2$, and $PdCl_2(MeCN)_2$, in EtOH. Unfortunately, though, they were less effective than $Pd(OAc)_2$ in terms of both yield and rate (Entries 2 and 9–11). A series of other bases was also investigated, and it was found that results identical to those seen with NaOMe was obtained with NaOEt as the base (Entries 2 and 12), but that the yields of the target product **3** were reduced to some extent when NaOMe was replaced by other bases, such as Na_2CO_3, Cs_2CO_3, Na_3PO_4, NaOH, and Et_3N (Entries 13–17). The yield of **3** was reduced to 86%, for example, when Cs_2CO_3 was used as the base (Entry 14). Et_3N, an organic base, gave the corresponding product **3** in a rather low yield (Entry 17). Gratifyingly, we observed that satisfactory results were still obtained at 0.1 mol-% loading of Pd (89% yield in 30 min; Entry 18), although only a low yield was isolated after 22 h when the loading of $Pd(OAc)_2$ was reduced to 0.01 mol-% (Entry 19). It is noteworthy that the reaction between 5 mmol of substrate **1a** and 6 mmol of **2a** in the presence of 1 mol-% of $Pd(OAc)_2$, and 10 mmol of NaOMe could also be conducted smoothly in EtOH to produce the desired product **3** in a 98% yield after 30 min (Entry 20).

With the standard reaction conditions to hand, we next set out to examine the scope of the reaction. As shown in Table 2, substrate **1a** had been consumed completely in the presence of boronic acids **2a** or **2b**, $Pd(OAc)_2$, and NaOMe after 5 min, affording the corresponding products **4** and **5** in 99% and 81% yields, respectively, in EtOH as the solvent (Entries 1 and 2). Substrate **1b**, a deactivated aryl iodide, also underwent the coupling with **2a**, rapidly providing the biaryl product **3** in excellent yield under the same conditions (Entry 3). It was found that different substituents were tolerated well in the reaction, and a wide range of other aryl bromides, whether electron-rich or electron-deficient, all worked well with arylboronic acids, $Pd(OAc)_2$, and NaOMe in EtOH at room temperature under ligand-free and aerobic conditions to provide the target products in good to excellent yields. The reactions between bromide **1c** and **2a**–**2d**, for example, gave the corresponding products **13**–**17** in good to excellent yields (Entries 4–7). However, the reaction between **1c** and **2e**, another heteroarylboronic acid, was unsuccessful (Entry 8). Substrates **1d**–**1f**, bearing carbonyl and cyano groups, also underwent the reactions in good yields under the standard conditions (Entries 9–11). We were happy to observe that high yields were still achieved in EtOH after 30 min from the couplings of the bulky aryl bromide **1i** in the presence of $Pd(OAc)_2$ and NaOMe (Entry 15), although another bulky aryl bromide (**1k**) and the activated chloride **1l** were not suitable substrates for the reaction even in the presence of 3 mol-% of $Pd(OAc)_2$ (Entries 17 and 18).

The application of the above optimized reaction conditions to the corresponding treatment of heteroaryl halides in order to construct heterocycle-containing biaryl systems was also studied (Table 3).[8] The results showed that EtOH

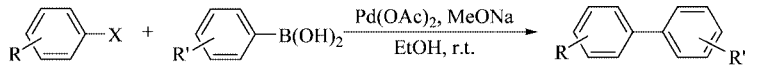
Table 1. Screening conditions for palladium-catalyzed Suzuki–Miyaura cross-coupling reactions between *p*-bromoanisole (**1a**) and phenylboronic acid (**2a**).[a]

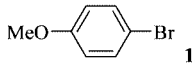
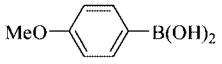
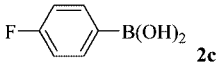
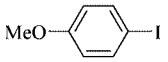
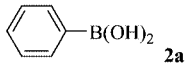
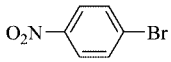
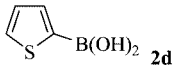
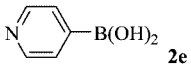
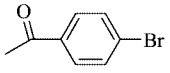
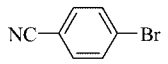
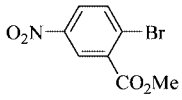
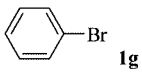
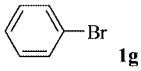
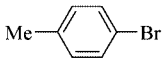
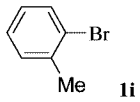
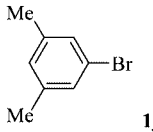
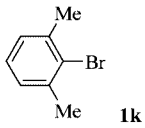
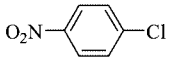


Entry	[Pd]	Base	Time	Solvent	Isolated yield (%)
1	$Pd(OAc)_2$	NaOMe	10 h	MeOH	100
2[b]	$Pd(OAc)_2$	NaOMe	6 min	EtOH	100
3	$Pd(OAc)_2$	NaOMe	30 min	*n*PrOH	69
4	$Pd(OAc)_2$	NaOMe	30 min	*i*PrOH	20
5	$Pd(OAc)_2$	NaOMe	30 min	*n*BuOH	59
6	$Pd(OAc)_2$	NaOMe	30 min	*i*BuOH	trace
7	$Pd(OAc)_2$	NaOMe	30 min	*t*BuOH	57
8	$Pd(OAc)_2$	NaOMe	10 h	acetone	43
9	$Pd_2(dba)_3$	NaOMe	30 min	EtOH	trace
10	$PdCl_2$	NaOMe	8 min	EtOH	80
11	$PdCl_2(MeCN)_2$	NaOMe	8 min	EtOH	66
12[b]	$Pd(OAc)_2$	NaOEt	9 min	EtOH	98
13	$Pd(OAc)_2$	Na_2CO_3	30 min	EtOH	33
14	$Pd(OAc)_2$	Cs_2CO_3	7 min	EtOH	86
15	$Pd(OAc)_2$	K_3PO_4	30 min	EtOH	58
16	$Pd(OAc)_2$	NaOH	30 min	EtOH	11
17	$Pd(OAc)_2$	Et_3N	30 min	EtOH	18
18[c]	$Pd(OAc)_2$	NaOMe	30 min	EtOH	89
19[d]	$Pd(OAc)_2$	NaOMe	22 h	EtOH	23
20[e]	$Pd(OAc)_2$	NaOMe	30 min	EtOH	98

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (1 mol-%), base (1 mmol), and solvent (1 mL) at room temperature. [b] The reaction was monitored by GC-MS and TLC over two runs. [c] $Pd(OAc)_2$ (0.1 mol-%). [d] $Pd(OAc)_2$ (0.01 mol-%). [e] **1a** (5 mmol), **2a** (6 mmol), base (10 mmol), and solvent (5 mL).

Table 2. Rapid palladium-catalyzed Suzuki–Miyaura cross-couplings between aryl halides (**1**) and arylboronic acids (**2**) at room temperature.[a]

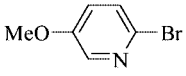
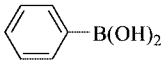
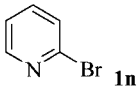
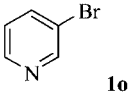
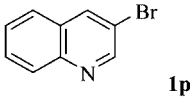
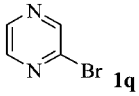
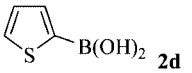
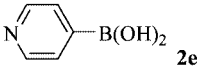
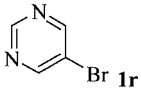
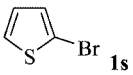
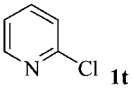
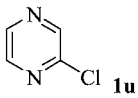
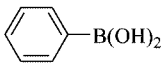
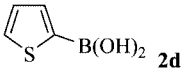
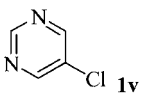


Entry	ArX	Ar′B(OH)$_2$	Time (min)	Yield (%)[b]
1	 **1a**	 **2b**	5	99 (**4**)
2	**1a**	 **2c**	5	81 (**5**)
3	 **1b**	 **2a**	4	100 (**3**)
4	 **1c**	**2a**	25	99 (**6**)
5	**1c**	**2b**	5	99 (**7**)
6	**1c**	**2c**	9	92 (**8**)
7	**1c**	 **2d**	15	88 (**9**)
8	**1c**	 **2e**	15	trace (**10**)
9	 **1d**	**2a**	5	99 (**11**)
10	 **1e**	**2a**	30	80 (**12**)
11	 **1f**	**2a**	30	65 (**13**)
12	 **1g**	**2a**	3	100 (**14**)
13	 **1g**	**2d**	30	55 (**15**)
14	 **1h**	**2a**	4	98 (**16**)
15	 **1i**	**2a**	30	93 (**17**)
16	 **1j**	**2a**	30	96 (**18**)
17[c]	 **1k**	**2a**	60	9 (**19**)
18[c]	 **1l**	**2a**	60	10 (**6**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Pd(OAc)$_2$ (1 mol-%), MeONa (1 mmol), and EtOH (1 mL) at room temperature. [b] Isolated yield. [c] Pd(OAc)$_2$ (3 mol-%).

was not an effective solvent for couplings of heteroaryl halides: in EtOH, for example, only a moderate yield of the corresponding heteroaryl-aryl product **20** was isolated after 24 h when 2-bromo-5-methoxypyridine (**1m**) was treated with **2a**, $Pd(OAc)_2$, and NaOMe at room temperature (Entry 1). To our delight, though, the yield of **20** was enhanced

Table 3. $Pd(OAc)_2$-catalyzed Suzuki–Miyaura cross-couplings of heteroaryl halides.[a]

Entry	ArX	$Ar'B(OH)_2$	Time (h)	Yield (%)[b]
1[c]	 **1m**	 **2a**	24	55 (**20**)
2	**1m**	**2a**	24	100 (**20**)
3[d]	**1m**	**2a**	36	20 (**20**)
4[e]	**1m**	**2a**	24	46 (**20**)
5	 **1n**	**2a**	23	53 (**21**)
6[f]	**1n**	**2a**	21	80 (**21**)
7	 **1o**	**2a**	22	80 (**22**)
8	 **1p**	**2a**	20	76 (**23**)
9	 **1q**	**2a**	5	98 (**24**)
10	**1q**	 **2d**	5	75 (**25**)
11	**1q**	 **2e**	5	55 (**26**)
12	 **1r**	**2a**	22	72 (**27**)
13[f]	 **1s**	**2a**	24	60 (**15**)
14[f]	 **1t**	**2a**	24	trace (**21**)
15	 **1u**	 **2a**	5	81 (**24**)
16	**1u**	 **2d**	5	trace (**25**)
17[f]	**1u**	**2d**	5	trace (**25**)
18[f]	 **1v**	**2a**	28	18 (**27**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (1 mol-%), MeONa (1 mmol), and MeOH (1 mL) at room temperature. [b] Isolated yield. [c] EtOH (1 mL) instead of MeOH. [d] MeOH/DMF (2:1, 1 mL) as the solvent. [e] Na_2CO_3 (1 mmol) and H_2O/acetone (3.5:3, 1 mL) instead of MeONa (1 mmol) and MeOH (1 mL), ref.[7]. [f] $Pd(OAc)_2$ (3 mol-%).

to 100% when MeOH was used as the solvent in place of EtOH (Entry 2). However, two solvent mixtures, including the previously reported effective aqueous acetone,[7] were not suitable solvents for the reaction. Subsequently, couplings of the other heteroaryl bromides **1n**–**1s**, including nitrogen-containing and sulfur-containing halides, with arylboronic acids were conducted smoothly in the presence of $Pd(OAc)_2$ and NaOMe in MeOH at room temperature, affording the corresponding heteroaryl-aryl and heteroaryl-heteroaryl products in moderate to excellent yields (Entries 5–13). The nitrogen-containing heteroaryl bromide **1q**, for example, coupled with arylboronic acid **2a** to provide the corresponding product **24** in a 98% yield (Entry 9). In addition, the optimized reaction conditions were also effective for the reactions between substrate **1q** and sulfur-containing or nitrogen-containing boronic acids in good yields (Entries 10 and 11). The catalytic efficiency of the $Pd(OAc)_2$/NaOMe/MeOH system was less, however, for couplings of heteroaryl chlorides. Only 2-chloropyrazine (**1u**) was able to undergo coupling with boronic acid **2a** to generate the corresponding desired product smoothly in satisfactory yield (Entry 15), but with heteroarylboronic acid **2d** this was unsuccessful even in the presence of 3 mol-% of $Pd(OAc)_2$ (Entry 16). Other chlorides **1t** and **1v** were also found to be less active for the reaction (Entries 14 and 18).

Conclusions

In summary, we have demonstrated a simple, mild, and rapid method for palladium-catalyzed cross-couplings between aryl halides and arylboronic acids for the synthesis of biaryls and heterocycle-containing biaryls. In relation to previously reported results,[3–7] several interesting features are obvious for this reaction. Firstly, the reaction is very rapid with aryl iodides and aryl bromides. Secondly, several functional groups – such as carbonyl, cyano, methoxy and fluoro groups – could be tolerated in this system. In addition, the scope of the reactions was extended to heteroaryl halides and heteroarylboronic acids. Finally, the reactions could be conducted at room temperature under ligand-free and aerobic conditions. Further applications of the system in other coupling transformations are under investigation.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded with an INOVA-400 or INOVA-500 (Varian) spectrometer or a Bruker AMX 300 spectrometer in $CDCl_3$ as the solvent. All reagents were directly used as obtained commercially. All products were determined by GC-MS (SHIMADZU GCMS-QP2010). All the solvents were dried by standard procedures and the other reagents were used directly from commercial sources. Analytical data and spectra (^1H and ^{13}C NMR) for all products are available in the Supporting Information. Supporting Information for this article is available on the WWW under http://www.eurjoc.org. or from the author.

Typical Experimental Procedure for the Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction: A mixture of aryl halide **1** (0.5 mmol), arylboronic acid **2** (0.6 mmol), $Pd(OAc)_2$ (1 mol-%), NaOMe (1 mol) and MeOH or EtOH (1 mL) was stirred at room temperature for the indicated time until complete consumption of starting material as monitored by TLC. After the mixture had been filtered and concentrated, the residue was then purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the corresponding coupled product.

2-Methoxy-5-phenylpyridine (17): Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 7.79 (d, J = 2.8 Hz, 1 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.35 (dd, J = 7.6 Hz, 7.2 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 1 H), 3.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 145.0, 137.9, 137.4, 130.1, 128.9, 127.3, 126.7, 110.8, 53.5 ppm. LRMS (EI, 20 eV): *m/z* (%): 185 (100) $[M]^+$. HRMS (EI) for $C_{12}H_{11}NO$ (M^+): calcd. 185.0841; found: 185.0840.

2-(Pyridin-4-yl)pyrazine (23): Light yellow solid, m.p. 87.6–88.4 °C (uncorrected). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 8.79 (d, J = 6.0 Hz, 2 H), 8.72 (s, 1 H), 8.64 (s, 1 H), 7.93 (d, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 150.1, 144.7, 144.6, 143.5, 142.3, 120.9; LRMS (EI, 20 eV) *m/z* (%): 157 (100) $[M^+]$. HRMS (EI) for $C_9H_7N_3$ (M^+): calcd. 157.0640, found 157.0640.

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