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Synthesis of Biaryls and Polyaryls by Ligand-Free Suzuki Reaction in Aqueous Phase

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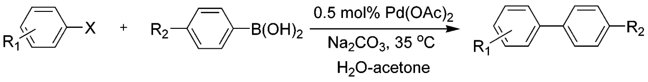

A highly efficient palladium acetate-catalyzed ligand-free Suzuki reaction in aqueous phase was developed in short reaction times (0.5−1 h) at 35 °C in air. The key for such a successful catalytic system was the use of a suitable amount of cosolvents in the aqueous phase. The method could be extended to the consecutive multi-Suzuki coupling, and polyaryls were prepared in a single one-pot step in high selectivity and excellent yield under mild reaction conditions (60 °C).

The Suzuki cross-coupling reaction is one of the most important methods for the selective construction of biaryls,[1] which has found extensive use in the synthesis of natural products, pharmaceuticals, and advanced materials.[2] The utility of the Suzuki reaction comes from its high stability, broad functional group tolerance, as well as low toxicity associated with boron compounds. Recently, the use of water as solvent for the Suzuki reaction received much attention.[3] Water has clear advantages as a solvent in organic synthesis considering its safety, cost, and significance to environmentally benign processes.[4] Although many additives and water-soluble ligands have been successfully applied in the Suzuki reaction as useful promoters,[5] the Suzuki reaction in the absence of additives and ligands is greatly limited by the substrate solubility and reactivity in aqueous media.[6] For example, Belestkaya and co-workers reported the Suzuki reaction in water with water-soluble aryl halides with the catalyzing of a simple palladium salt, but the reaction was sluggish with water-insoluble aryl halides under the reaction conditions.[7]

Wallow and co-workers[8] have reported an improved method for ligandless Suzuki coupling using 1:1 acetone/water as solvent. However, the attractiveness of their protocol is limited by the painstaking measures used to exclude oxygen, including a total of 15 freeze−pump−thaw degassing cycles at various stages of the reaction.[8a] In our previous studies, we found that the amount of water was crucial to the success of the Suzuki coupling reaction in aqueous media in the presence of PEG and ionic liquid.[9] Herein we present the reassessment of the ligand-free Suzuki reaction in water−cosolvent. We have reinvestigated the procedure with respect to four key variables: (1) solvent composition, (2) nature of the base, (3) catalyst loading, and (4) reaction temperature. During the course of these studies, we have discovered that the reaction can be run *in air* thus improving its operational simplicity. Moreover, we have extended the scope of useful coupling partners to di- and trihaloaromatics, providing an improved synthesis of polyaryls. Polyaryls are of current interest,[10−12] and their synthesis by conventional means is often inefficient.[13,14] Recently, polyaryls have been prepared via Suzuki coupling using palladium phosphine complexes.[15,16] However, to the best of our knowl-

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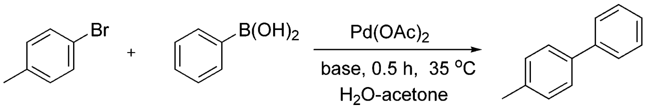
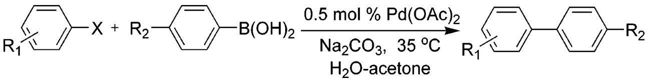
TABLE 1. Effect of Solvent, Base, and Amount of Catalyst on the Suzuki Coupling Reaction[a]



entry	base	solvent (mL)	catalyst (mol %)	yield[b] (%)
1	Na_2CO_3	pure H_2O (6)	0.5	9
2	Na_2CO_3	acetone/H_2O (3:6)	0.5	93
3	Na_2CO_3	acetone/H_2O (3:4)	0.5	97
4	Na_2CO_3	acetone/H_2O (3:3.5)	0.5	98
5	Na_2CO_3	acetone/H_2O (3:3)	0.5	97
6	Na_2CO_3	acetone/H_2O (3:1)	0.5	73
7	Na_2CO_3	pure acetone (6)	0.5	7
8	K_2CO_3	acetone/H_2O (3:3.5)	0.5	97
9	NaOH	acetone/H_2O (3:3.5)	0.5	97
10	KOH	acetone/H_2O (3:3.5)	0.5	97
11	K_3PO_4	acetone/H_2O (3:3.5)	0.5	95
12	Na_2CO_3	ethanol/H_2O (3:3.5)	0.5	97
13	Na_2CO_3	propanol/H_2O (3:3.5)	0.5	96
14	Na_2CO_3	DMF/H_2O (3:3.5)	0.5	96
15	Na_2CO_3	acetone/H_2O (3:3.5)	0.25	94
16	Na_2CO_3	acetone/H_2O (3:3.5)	0.002 (6 h)	68
17	Na_2CO_3	acetone/H_2O (3:3.5)	0.0002 (10 h)	72
18	Na_2CO_3	acetone/H_2O (3:3.5)	0.000 02 (24 h)	66

[a] Reaction conditions: bromotoluene (1 mmol), $PhB(OH)_2$ (1.5 mmol), base (2 mmol). [b] GC yields based on bromotoluene.

TABLE 2. Suzuki Cross-Coupling Reaction of Aryl Halides with Arylboronic Acid[a]



entry	X	R_1	R_2	time (min)	yield[b] (%)
1	I	4-CH_3	H	20	97
2	I	4-OCH_3	H	30	90
3	I	4-NO_2	H	20	98
4	Br	4-Cl	H	30	98
5	Br	4-$COCH_3$	H	20	98
6	Br	4-CN	H	20	98
7	Br	4-Me	H	30	97
8	Br	2-Me	H	30	94
9	Br	3-OH	H	30	97
10	Br	4-OMe	H	40	98
11	Br	H	4-OCH_3	30	97
12	Br	H	4-CF_3	45	94
13	Br	4-CH_3	4-OCH_3	30	98
14	Br	4-CH_3	4-CF_3	45	81
15	Br	4-OCH_3	4-OCH_3	45	94
16	Br	4-OCH_3	4-CF_3	60	92
17	Br	4-Cl	4-CF_3	45	91
18	Br	4-Cl	4-OCH_3	30	98
19	Br	4-CN	4-OCH_3	30	98
20	Br	4-CN	4-CF_3	45	98

[a] Reaction conditions: aryl halide (1 mmol), $ArB(OH)_2$ (1.5 mmol), Na_2CO_3 (2 mmol), H_2O/acetone = 3.5:3 mL, 35 °C (external temperature). [b] Isolated yields.

edge, ligand-free one-pot consecutive cross-couplings in aqueous media have not yet been reported.

We initially studied the effect of acetone as a cosolvent on the Suzuki reaction in water. We employed the coupling reaction of 4-bromotoluene with phenylboronic acid as a model reaction to study the effect of acetone on the reaction. The reactions were carried out using Na_2CO_3 as base in the presence of 0.5 mol % $Pd(OAc)_2$ at 35 °C (external temperature) in air. As is evidenced from Table 1, the reaction in pure water afforded 4-methylbiphenyl in a very low yield after 0.5 h (Table 1, entry 1). However, the addition of incremental amounts of acetone led to a very rapid increase in the activity, and nearly quantitative yield was obtained when the ratio of water and acetone was between 3:3 and 4:3 mL (Table 1, entries 3−5). The reaction in pure acetone was sluggish (Table 1, entry 7). These results suggest that the ratio of water and acetone plays the key role in the ligand-free Suzuki reaction. Different bases, including Na_2CO_3, K_2CO_3, K_3PO_4, NaOH, and KOH, delivered the desired product in high yields (Table 1, entries 4, 8−11). In addition, a profound solvent effect on the reaction was observed. The use of ethanol, propanol, and DMF as cosolvent gave almost identical results as acetone (Table 1, entries 12−14), whereas toluene, CH_2Cl_2, dioxane, DMSO, THF, and CH_3CN delivered very low yields ($<40\%$).

The efficiency of the catalytic system was evaluated by the coupling of 4-bromotoluene and phenylboronic acid in a 3.5:3 mixture of water and acetone in the absence of any ligand or additive (Table 1, entries 15−18). A quantitative yield of desired product was obtained in the presence of 0.5 mol % $Pd(OAc)_2$ for 0.5 h. Decreasing the catalyst loading to 0.25 mol % gave a respectable 94% yield of the product for 0.5 h. $Pd(OAc)_2$ in the amount of 0.002 mol % was found to be sufficient to give a moderate conversion with a 68% isolated yield of the product after 6 h. A yield of 66% was obtained after 24 h when the loading of Pd was decreased to 0.000 02 mol %, which corresponds to a turnover number of 3 000 000, indicating that the $Pd(OAc)_2$−H_2O−acetone catalytic system is highly active for the mono-Suzuki coupling reaction.

The catalytic system was applicable to a wide range of aryl iodides and bromides (Table 2). The coupling of aryl iodides was superior and afforded the desired product in excellent yields (Table 2, entries 1−3). The electron-deficient aryl bromides showed an excellent reactivity and furnished the products in high yields in short reaction times (Table 2, entries 4−6). A little prolongation of the reaction time was required for the electron-rich aryl bromides (Table 2, entries 7−10). It is worth noting that the catalytic system was tolerant to a broad range of functional groups, such as NO_2, OMe, OH, COMe, and CN. The coupling of 4-bromochlorobenzene with the phenylboronic acid gave exclusively 4-chlorobiphenyl in 98% yield, showing good selectivity (Table 2, entry 4). Both the electron-rich and the electron-deficient arylboronic acids delivered the products with high yields (Table 2, entries 11−20). The sterically demanding aryl bromide also gave a high yield (Table 2, entry 8), but the aryl chlorides were almost inactive.

The application of the above aqueous catalytic systems in the synthesis of polyaryls was studied, and the results are summarized in Table 3. Among the solvents tested, DMF afforded the best selectivity to the product of terphenyl as the cosolvent in the coupling of 1-bromo-2-iodobenzene with phenyl

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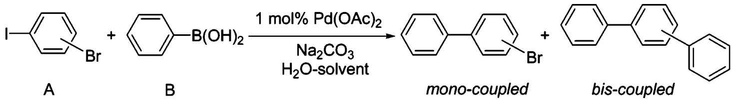
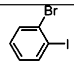
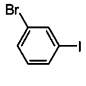
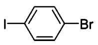
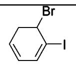
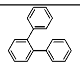
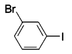
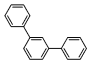
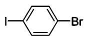
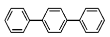
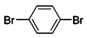
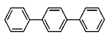
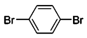
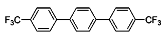
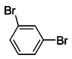
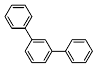
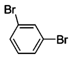
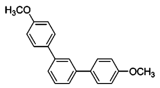
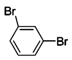
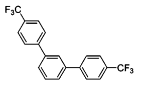
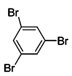
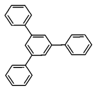
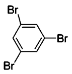
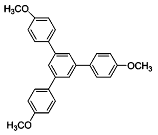
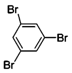
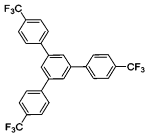
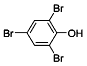
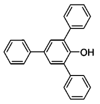
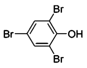
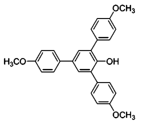
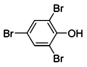
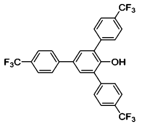
TABLE 3. Double Coupling of Dihaloaryls with Phenyl Boronic Acid[a]



entry	A	B (mmol)	temp (°C)	time (h)	ethanol		acetone		DMF	
					yield[b]	mono:bis	yield[b]	mono:bis	yield[b]	mono:bis
1		4	35.	3	99	64:35	100	44:56	100	33:67
2		6	35	12					100	31:69
3		6	60	12					100	2:98
4		4	35	3	99	52:47	100	31:69	100	14:86
5		6	35.	12					100	9:91
6		6	60	12					100	0:100
7		4	35	3	99	55:44	100	24:76	98	19:79
8		6	35	12					100	15:85
9		6	60	12					100	1:99

[a] Reaction conditions: dihalide (1 mmol), PhB(OH)$_2$ (4−6 mmol), Na$_2$CO$_3$ (4 mmol), H$_2$O/solvent = 3.5:3 mL. [b] GC yield based upon dihalide.

TABLE 4. Coupling of Di- and Trihaloaryls with Phenyl Boronic Acids

entry	halide	aryl boronic acid	product	yield[a]
1		Ph-B(OH)$_2$		96[b]
2		Ph-B(OH)$_2$		98[b]
3		Ph-B(OH)$_2$		98[b]
4		Ph-B(OH)$_2$		96[b]
5		4-F$_3$C-Ph-B(OH)$_2$		95[b]
6		Ph-B(OH)$_2$		96[b]
7		4-MeO-Ph-B(OH)$_2$		90[b]
8		4-F$_3$C-Ph-B(OH)$_2$		95[b]
9		Ph-B(OH)$_2$		97[c]
10		4-MeO-Ph-B(OH)$_2$		97[c]
11		4-F$_3$C-Ph-B(OH)$_2$		90[c]
12		Ph-B(OH)$_2$		96[c]
13		4-MeO-Ph-B(OH)$_2$		97[c]
14		4-F$_3$C-Ph-B(OH)$_2$		85[c]

[a] Isolated yield. [b] Reaction conditions: dihalide (1 mmol), ArB(OH)$_2$ (6 mmol), Na$_2$CO$_3$ (4 mmol), Pd(OAc)$_2$ (1 mol %), H$_2$O/DMF = 3.5:3 mL, 60 °C (external temperature), 12 h. [c] Reaction conditions: trihalide (1 mmol), ArB(OH)$_2$ (9 mmol), Na$_2$CO$_3$ (6 mmol), Pd(OAc)$_2$ (1.5 mol %), H$_2$O/DMF = 3.5:3 mL, 60 °C (external temperature), 12 h.

boronic acid (Table 3, entry 1). Acetone and ethanol also presented high activity as cosolvents, but showed relatively lower selectivity to terphenyl (Table 3, entry 1). An increase in the amount of phenyl boronic acid and the prolongation of the reaction time have a slight impact upon the selectivity toward terphenyl (Table 3, entry 2). The temperature was found to be the strongest effect on the selectivity, and the excellent yield and selectivity to terphenyl was obtained when the temperature was increased to 60 °C (Table 3, entry 3). Changes to the aromatic substituent location have little function to the activity and selectivity (Table 3, entries 4−9). In all cases, the mixture of water and DMF afforded the best selectivity to terphenyls (Table 3).

In the study of single and double Suzuki couplings with dihalobenzene, Sinclair and Sherburn[15a] reported that the halogen was the major factor in determining the selectivity for the coupling of aryl boronic ester in the presence of $Pd(PPh_3)_4$ and Ag_2CO_3. They found that diiodobenzenes were the best choice for the double coupling and that dibromobenzenes mainly delivered the single coupling products. In the case of the $Pd(OAc)_2-H_2O-DMF$ system, the identity of the halogen presented little effect on the selectivity, as shown in Table 4. For each di- or trihalobenzene substrate examined, regardless of the halide substituent location and type, the major products resulted from the multiple coupling under the reaction conditions (Table 4, entries 1−14). The electron-rich, electron-poor, and electron-neutral aryl boronic acids presented essentially the same reactivity and selectivity patterns.

In conclusion, we have developed a general and high-yielding methodology for the Suzuki reaction in aqueous phase in a short reaction time under mild conditions. The high efficiency and use of only cosolvent without other additives and ligands make the method useful and attractive for the synthesis of biaryls. Furthermore, the method can be extended to the consecutive multi-coupling Suzuki reaction involving di- and trihaloaromatics, which allows the access of a variety of polyaryls in high selectivity and high yield under mild aqueous reaction conditions.

Experimental Section

General Procedure for the Suzuki Reaction: A mixture of Na_2CO_3 (0.212 g, 2 mmol; for dihalides, 4 mmol; for trihalides, 6 mmol), $Pd(OAc)_2$ (1 mg, 0.5 mol %; for dihalides, $Pd(OAc)_2$ = 1 mol %; for trihalides, $Pd(OAc)_2$ = 1.5 mol %), aryl halides (1 mmol), arylboronic acid (1.5 mmol; for dihalides, boronic acid was 6 mmol; for trihalides, boronic acid was 9 mmol), distilled water (3.5 mL) and solvent (3 mL) was stirred for the indicated time. Afterward, the reaction solution was extracted four times with diethyl ether (4 × 10 mL). The combined organic phase was analyzed by GC and GC/MS. The further purification of the product was achieved by flash chromatography on a silica gel column.

4,4″-Trifluoromethyl-1,1′:3′,1″-terphenyl [**T4−8**]: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.79 (s, 1H), 7.73 (m, 8H), 7.64−7.56 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 140.9, 130.0 (q, J = 32.3 Hz), 129.9, 127.8, 127.4, 126.6, 126.1 (q, J = 3.8 Hz), 124.5 (q, J = 270.3 Hz). MS (EI, %) m/z: 366 (100) [M^+], 347 (12), 296 (10), 228 (10), 183 (8); HRMS (EI) calcd for $C_{20}H_{12}F_6$, 366.0838; found, 366.0835; IR (KBr) υ 1616, 1573, 1482, 1410, 1389, 1323, 1249, 1173, 1126, 1070, 1059, 1023, 844, 796, 755, 737, 698, 601, 430 cm^{-1}.

2,4,6-Tris(4-trifluoromethylphenyl)phenol [**T4−14**]: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.79 (d, 4H, J = 8.5 Hz), 7.73 (d, 4H, J = 8.0 Hz), 7.70 (s, 4H), 7.55 (s, 2H), 5.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 143.7, 140.9, 133.3, 130.6 (q, J = 32.3 Hz), 130.0, 129.6 (q, J = 32.3 Hz), 129.6, 128.7, 127.3, 126.3 (q, J = 3.4 Hz), 126.1 (q, J = 3.6 Hz), 124.5 (q, J = 270.1 Hz), 124.3 (q, J = 270.9 Hz). MS (ESI) m/z: 525.0 ([M − H]$^+$). HRMS (ESI) calcd for $C_{27}H_{15}F_9O$, 525.0895; found, 525.0893. IR (KBr) υ 3447, 1617, 1394, 1328, 1228, 1164, 1112, 1067, 837 cm^{-1}.

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Supporting Information Available: The experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, and MS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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