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A Preparatively Convenient Ligand-Free Catalytic PEG 2000 Suzuki−Miyaura Coupling

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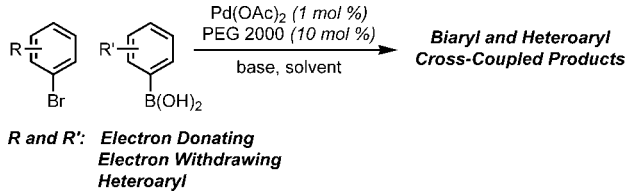

A ligand-free Suzuki−Miyaura reaction for the cross-coupling of aryl and heteroaryl bromides with aryl and heteroarylboronic acids has been developed utilizing catalytic polyethylene glycol 2000 (PEG 2000). This preparatively convenient system afforded the corresponding cross-coupled products in good to excellent isolated yields after a simple aqueous workup. Transmission electron microscopy (TEM) analysis of the Pd-PEG 2000 catalyst system revealed in situ-generated palladium nanoparticles after only 1 min of reaction.

The palladium-catalyzed Suzuki−Miyaura cross-coupling reaction has emerged as an extremely powerful synthetic tool in a broad range of disciplines, ranging from the synthesis of novel materials to industrial manufacturing of pharmaceuticals.[1,2] Significant research has been devoted toward the identification of environmentally friendly cross-coupling protocols. Specifically, low palladium loadings,[3] phosphine-free catalyst systems,[3−7] and microwave irradiation[8] protocols in water have all been demonstrated to actively promote the Suzuki−Miyaura reaction.

Phase-transfer complex (PTC) mediated Suzuki−Miyaura cross-coupling reactions have recently become an area of interest.[9] Used as solvents, the polyethylene glycol (PEG) PTCs promote ligand-free Suzuki−Miyaura reactions through reduction of Pd(II) to Pd(0),[10,11] obviating the need for phosphine reducing agents.[12] Preparative use of the current methods, however, is highly impractical due to the polar nature of PEG. The high viscosity of the reaction mixture renders reaction stirring and monitoring extremely difficult. More importantly, it is prohibitively difficult to isolate all but the most simple biaryl cross-coupled products from the PEG solvent by the standard diethyl ether extraction.[10d,11a,b,12] Thus, a catalytic PEG cross-coupling protocol would minimize these difficulties, while retaining the beneficial metal stabilizing and solubilizing attributes of the PEGs. We report herein a practical ligand-free Suzuki−Miyaura cross-coupling protocol employing 1 mol % of $Pd(OAc)_2$ and 10 mol % of PEG 2000.

We began our investigation by screening the activity of a variety of PTCs under ligand-free reaction conditions (Table 1). To evaluate the relative activity of each PTC, a 1:1 mixture of 4-bromotoluene **1** and 4-methoxyphenylboronic acid **2** with 1 mol % of $Pd(OAc)_2$ was reacted for 12 h. In the absence of a PTC, K_2CO_3 afforded 23% conversion to the cross-coupled product **3** (entry 1). In comparison to the other phase transfer complexes, the higher molecular weight PEG-based PTCs showed improved conversion. Specifically, PEG 2000-K_2CO_3 and PEG 2000-Cs_2CO_3 both delivered 42% conversion while PEG 12000-Cs_2CO_3 and PEG 20000-K_2CO_3 furnished **3** with 46% and 43% conversion, respectively. With these observations, we chose the PEG 2000-K_2CO_3 catalyst system due to its lower molecular weight, low cost, and ease of product isolation relative to the higher order PEG systems.[13]

In an attempt to boost reaction conversion, lithium halides[14] (LiCl, LiBr, and LiI), solvent, and boronic acid stoichiometry were evaluated with the PEG 2000-K_2CO_3 catalyst system. LiBr afforded no change in conversion (ca. 42%) while LiCl and LiI delivered much lower yields of **3**. Acetonitrile, methanol, and ethanol offered no advantage over tetrahydrofuran, however, a more concentrated THF and H_2O reaction solution offered a substantial boost in reaction conversion (entries 15 and 16). Increasing the boronic acid stoichiometry to 1.3 equiv in conjunction with 1 mol % of $Pd(OAc)_2$, 10 mol % of PEG 2000, 2 equiv of K_2CO_3, and a 1:1 ratio of THF and H_2O at reflux delivered the highest conversion to cross-coupled product **3** (entry 16). Upon reaction completion, dilution with ethyl acetate

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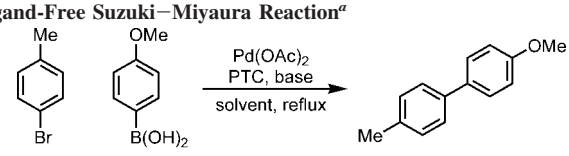
TABLE 1. Evaluation of Phase Transfer Complexes (PTCs) in the Ligand-Free Suzuki−Miyaura Reaction[a]

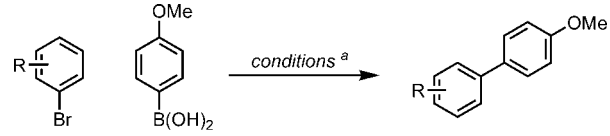


1 2 3

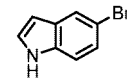
entry	PTC	base	solvent	additive	conv, %
1		K_2CO_3	THF/H_2O		23
2[b]	OABCDBr	K_2CO_3	THF/H_2O		2.5
3[c]	BCDBr	K_2CO_3	THF/H_2O		9.4
4[d]	ANCDCl	K_2CO_3	THF/H_2O		18
5	Bu_4NI	$NaHCO_3$	THF/H_2O		33
6	18-c-6	K_2CO_3	THF/H_2O		39
7	PEG 600	Cs_2CO_3	THF/H_2O		37
8	PEG 2000	K_2CO_3	THF/H_2O		42
9	PEG 2000	Cs_2CO_3	THF/H_2O		42
10	PEG 12000	Cs_2CO_3	THF/H_2O		46
11	PEG 20000	K_2CO_3	THF/H_2O		43
15[e]	PEG 2000	K_2CO_3	ACN/H_2O		29
16	PEG 2000	K_2CO_3	MeOH/H_2O		34
17	PEG 2000	K_2CO_3	EtOH/H_2O		31
12	PEG 2000	K_2CO_3	THF/H_2O	LiCl	25
13	PEG 2000	K_2CO_3	THF/H_2O	LiBr	43
14	PEG 2000	K_2CO_3	THF/H_2O	LiI	14
15[f]	PEG 2000	K_2CO_3	THF/H_2O		88
16[g]	PEG 2000	K_2CO_3	THF/H_2O		98

[a] Conditions: 4-bromotoluene **1** (1.0 mmol), 4-methoxyphenylboronic acid **2** (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), PTC (0.1 mmol), base (2.0 mmol), solvent (5.0 mL), H_2O (5.0 mL), reflux, 12 h. [b] *O*-Allyl-*N*-benzylcinchonidinium bromide (OABCDBr). [c] *N*-Benzylcinchonidinium bromide (BCDBr). [d] *N*-(9-Anthracenylmethyl)cinchonidinium chloride (ANCDCl). [e] Acetonitrile (ACN). [f] 4-Bromotoluene (1.0 mmol), 4-methoxyphenylboronic acid (1.2 mmol), THF (1.6 mL), H_2O (1.6 mL). [g] 4-Bromotoluene (1.0 mmol), 4-methoxyphenylboronic acid (1.3 mmol), THF (1.6 mL), H_2O (1.6 mL).

TABLE 2. Substrate Scope of Aryl and Heteroaryl Bromide 4 in the Reaction with 4-Methoxyphenylboronic Acid 2



4 2 5

entry	arylbromide (R)	time,h	yield[b]
1	4-Me	5	97% (**3**)
2	2-Me	10	98% (**5a**)
3	2,6-Me	19	22% (**5b**)
4	4-OH	9	92% (**5c**)
5	4-NH_2	8	98% (**5d**)
6	3-SMe	10	97% (**5e**)
7	4-CF_3	6	98% (**5f**)
8	4-Cl	7	98% (**5g**)
9	3-SO_2Me	11	99% (**5h**)
10		13	94% (**5i**)
11		10	97% (**5j**)
12		15	84% (**5k**)
13		19	41% (**5l**)[c]

[a] General reaction conditions: aryl and heteroaryl bromide **4** (1.0 mmol), 4-methoxyphenylboronic acid **2** (1.3 mmol), $Pd(OAc)_2$ (0.01 mmol), PEG 2000 powder (0.1 mmol), K_2CO_3 (2.0 mmol), THF (1.6 mL), H_2O (1.6 mL), reflux. [b] Isolated yields. [c] 5-Bromoindole and **2** were recovered in 29% and 15% yield, respectively.

followed by an aqueous brine wash enabled the efficient extraction of the product with no observable loss to the aqueous and PEG 2000 layers. Zhang[10d] and Liu[11a,b] have reported that oxygen can promote PEG-mediated Suzuki−Miyaura cross-coupling of simple aryl chlorides and bromides, respectively. In contrast, our reaction conducted open to the air resulted in the formation of homodimerization byproducts derived from the arylboronic acid in up to 12% yield. Presumably, air oxidation of Pd(0) to Pd(II) induces this dimerization pathway, which was not observed in the previous reports.[15] An inert atmosphere of nitrogen completely suppressed the boronic acid dimerization and delivered the cross-coupled products in high yield.

With conditions in hand, we explored the electronic and steric effects of various substituents in the cross-coupling of aryl and heteroaryl bromide coupling partner **4** with 4-methoxyphenylboronic acid **2** (Table 2). Aryl bromides with diverse electron-donating and electron-withdrawing substituents delivered the cross-coupled products in high yields (entries 1 to 9). Of note, 3-bromothioanisole (entry 6), a potentially difficult substrate due to palladium coordination, furnished the cross-coupled product **5e** in 97% yield.[16] The sterically demanding 2,6-tolylbromide (entry 3), however, proved to be a difficult substrate. After extended reaction times, product **5b** was isolated in modest 22% yield with 61% and 53% recovery of the starting aryl bromide and boronic acid, respectively.

Heteroaryl halides have rarely been employed in ligand-free Suzuki−Miyaura cross-coupling protocols.[17] Typically, high catalyst loading (5 mol %) is required to overcome catalyst deactivation through heteroatom coordination.[18] With the 1 mol % of $Pd(OAc)_2$ and catalytic PEG 2000 conditions, pyridine, pyrimidine, and pyrazole substrates all afforded their cross-coupled products in high isolated yields (entries 10 to 12). Modest conversion with 5-bromoindole, however, furnished **5l** in 41% isolated yield, presumably due to palladium coordination by the indole nitrogen.

In a similar fashion, the steric and electronic tolerance of the aryl and heteroarylboronic acid fragments were evaluated against 4-bromoanisole **6** (Table 3). Both electron-rich and electron-deficient arylboronic acids performed well under the reaction conditions (entries 1 to 7). Of note, Boc-protected 4-aminophenylboronic acid (entry 4) furnished **5p** in 79% isolated yield as well as 15% yield of the des-Boc product. Presumably, des-Boc **5p** arises from basic hydrolysis of **5p**, not from the starting boronic acid, as 4-aminophenylboronic acid was not observed

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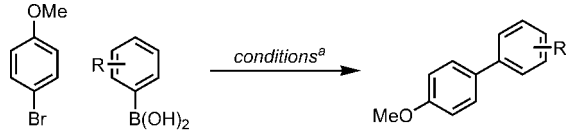
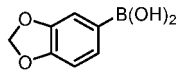
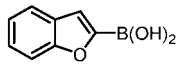
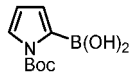
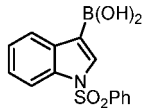
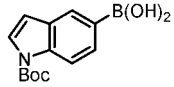
TABLE 3. Substrate Scope of Aryl and Heteroarylboronic Acids 7 in the Reaction with 4-Bromoanisole 6



6 7 5

entry	boronic acid (R)	time,h	yield[b]
1	3-OH	5	91% (**5m**)
2	3-NH_2	12	87% (**5n**)
3	3-OTBS	11	95% (**5o**)
4	4-NHBoc	12	79% (**5p**)[c]
5	4-Cl	10	93% (**5q**)
6	4-CO_2Me	12	88% (**5r**)
7	3-COMe	9	88% (**5s**)
8		8	94% (**5t**)
9		13	71% (**5u**)
10		15	61% (**5v**)[d]
11		20	– (**5w**)
12		19	21%(des-Boc **5x**)[e]

[a] General reaction conditions: 4-bromoanisole (1 mmol), boronic acid (1.3 mmol), $Pd(OAc)_2$ (0.01 mmol), PEG 2000 powder (0.1 mmol), K_2CO_3 (2.0 mmol), THF (1.6 mL), H_2O (1.6 mL), reflux. [b] Isolated yields. [c] 15% of the des-Boc coupled product was also isolated. [d] Des-Boc **5v** was isolated in 22% yield. [e] Des-Boc **5x** was isolated in 21% yield with 51% and 47% recovery of **6** and *N*-Boc-5-indoleboronic acid, respectively.

during the course of the reaction. Heteroarylboronic acids have had limited utility in the Suzuki−Miyaura coupling, primarily due to their difficult preparation, poor solubility, and low reactivity.[19] Recently, the judicious choice of ligand, base, and solvent have been shown to have a dramatic effect on the reaction's outcome.[20] Evaluation of our Pd-catalytic PEG 2000 protocol against challenging heteroarylboronic acids revealed encouraging results. Specifically, coupling of 3,4-methylenedioxyphenylboronic acid (entry 8), benzofuran 2-boronic acid (entry 9), a substrate prone to proto-deborylation, and *N*-Boc-pyrrole 2-boronic acid (entry 10) with **6** afforded the corresponding products **5t**, **5u**, and **5v** in good yield. Cross-coupling of indoleboronic acid substrates, however, did not perform as well (entries 11 and 12). Multiple products were observed in the coupling of *N*-phenylsulfonyl-3-indoleboronic acid (entry 11), with no appreciable isolation of **5w**. In the case of *N*-Boc-5-indoleboronic acid (entry 12), only 21% of the des-Boc product was isolated with recovery of both the starting halide and boronic acid.

Suzuki−Miyaura protocols employing a PEG solvent system have been shown to form palladium nanoparticles possessing high catalytic activity.[11a,b,12,21,22] Although such nanoparticles are normally prepared through the premixing of a palladium source and PEG at elevated temperatures, followed by the introduction of substrates and base after an induction period,[10d,12,23] we set out to verify the involvement of palladium nanoparticles in our catalyst system.

Indeed, examination of the catalytic PEG 2000 cross-coupling between 4-bromotoluene **1** and 4-methoxyphenylboronic acid **2** with transmission electron microscopy (TEM) revealed the presence of in situ-generated palladium nanoparticles (Figure 1). At 23 °C, 1 min after combining the reaction components, 10−20 nm palladium nanoparticles embedded upon the surface of a 200 nm PEG 2000 sphere were formed. At 5 min, the PEG 2000 sphere collapsed into well-dispersed 10−20 nm sized Pd-PEG 2000 nanoparticles with high surface area. At 30 min and 2 h, the nanoparticles began to cluster, forming agglomerates, with less surface area and presumably less catalytic activity.

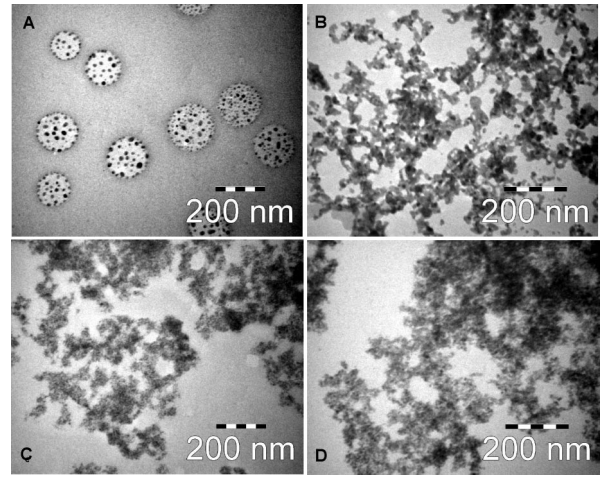


FIGURE 1. TEM imaging of the Pd-PEG 2000 catalyst at (A) 1 min, (B) 5 min, (C) 30 min, (D) and 2 h.

To our knowledge, this represents the first observation of the changing nanoparticle agglomeration landscape over the course of a cross-coupling reaction. Interestingly, all reactions reported herein turned black within 1 min, indicating the precipitation of palladium from solution. Possibly, the larger chain length of PEG 2000 is the cause of the palladium black precipitation as the smaller PEG 400 has been reported to remain in solution with no observable palladium black formation for months.[11b] Currently, we are examining whether homogeneous or heterogeneous catalysis is operative with catalytic PEG 2000 and the effect the Pd-PEG 2000 nanoparticle agglomeration has on the reaction kinetics. In addition, evaluation of alternative cross-coupling partners such as aryl and heteroaryl chlorides and

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(23) References 11a and 11b describe one of the first examples of in situ-generated nanoparticles.

iodides as well as potassium trifluoroborate salts and boronate esters is ongoing and will be reported in due course.

In summary, we have developed a practical reaction protocol for the ligand-free, catalytic PEG 2000 Suzuki−Miyaura cross-coupling. Advantages of our new method include the facile isolation of polar cross-coupled products, low cost of PEG 2000, and the ability to promote the cross-coupling of heteroaryl bromides and heteroarylboronic acids. For the first time with catalytic PEG-based Suzuki−Miyaura reactions, we have observed the rapid formation (<1 min) of in situ-generated palladium nanoparticles and their decreasing surface area over the course of a reaction by TEM analysis.

Experimental Section

General Procedure for the Catalytic PEG 2000 Mediated Cross-Coupling of Aryl Bromides and Arylboronic Acids. 4-Bromotoluene **1** (0.171 g, 1 mmol) was added to a nitrogen-purged 20 mL scintillation vial equipped with a stir bar. 2-Methoxyphenylboronic acid **2** (0.197 g, 1.3 mmol) was then added, followed by solid potassium carbonate (0.276 g, 2.0 mmol), polyethylene glycol powder (PEG 2000, 0.199 g, 0.10 mmol), and palladium acetate (0.002 g, 0.01 mmol). Tetrahydrofuran (1.6 mL, 0.6 M) followed by water (1.6 mL, 0.6 M) was added to the scintillation vial via syringe and the vial was capped and brought to reflux. After the reaction was deemed complete (5 h, TLC), the black reaction mixture was cooled to rt, diluted with ethyl acetate (10 mL), and introduced into a separatory funnel. The triphasic solution was separated and the combined PEG 2000 and aqueous phases were extracted with ethyl acetate (5 mL, 2×). The combined organic extracts were washed with saturated aqueous sodium chloride (10 mL, 2×), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude material was purified via silica gel chromatography (5% EtOAc/hexane) to afford 4-methoxy-4′-(methyl)-1,1′-biphenyl **3** (0.28 g, 97%) as a white solid. Mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 6.6, 2.1 Hz, 2H), 7.29 (dd, J = 6.4, 1.7 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 6.81 (dd, J = 6.7, 2.1 Hz, 2H), 3.68 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 137.9, 136.4, 133.7, 129.4, 127.9, 126.6, 114.2, 55.4, 21.0.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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