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Very Fast Suzuki–Miyaura Reaction Catalyzed by $Pd(OAc)_2$ under Aerobic Conditions at Room Temperature in EGME/H_2O

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The results of a ligand-free $Pd(OAc)_2$-catalyzed Suzuki–Miyaura C–C coupling performed at room temperature under aerobic conditions are presented. It was found that the use of an ethylene glycol monomethyl ether/H_2O mixture as the solvent resulted in very rapid reactions of aryl bromides with arylboronic acids. As a matter of fact, under optimized conditions, some substrates were converted quantitatively in less than 1 min with exceptionally high TOF values. For example, the reaction between 4-methoxyphenylboronic acid and bromobenzene afforded 4-methoxybiphenyl in 30 s with TOF = 180000 h^{-1}. Furthermore, the reaction tolerates a wide range of functional groups and can be successfully applied to heteroaryl bromides such as 2-bromopyridine and 5-bromopyrimidine. Interestingly, also an activated aryl chloride such as 1-chloro-4-nitrobenzene reacted quantitatively with phenylboronic acid at 373 K.

Introduction

The Suzuki–Miyaura reaction is one of the most powerful methods for the synthesis of functionalized biaryl compounds through the C–C coupling of two aryl units. Since the first reports in 1979,[1,2] this type of palladium-catalyzed process, based on the reaction of aryl halides with aryl boronic acids (or esters), has shown an explosive growth.[3–21] Generally, the efficiency of the Pd^{II}-based catalyst is strongly dependent on the nature of the coordinated ligands and a variety of catalysts have been prepared and screened for activity in the reaction, in particular phosphane and N-heterocyclic carbene complexes. Recently, methods for palladium-catalyzed Suzuki–Miyaura coupling without the aid of any ligands have also been reported, and it was generally found that both solvent and base had a fundamental influence on the reaction.[22–41] Effective systems in terms of yield and rate are, for example, $Pd(OAc)_2$/Na_2CO_3 in acetone/H_2O[37] and $Pd(OAc)_2$/MeONa in alcohols.[38] However, the development of mild, rapid, low-cost, and aerobic ligandless-based procedures is still a topic of considerable interest in organic synthesis and industry.

Very recently, we reported that ligand-free $Pd(OAc)_2$ behaved as an efficient precatalyst for the Heck reaction of bromobenzene and styrene at 120 °C when a H_2O/ethylene glycol monomethyl ether (EGME) mixture was employed as the solvent.[42] Thus, nearly quantitative formation of *trans*-stilbene and high TOFs[43] were observed by using $Pd(OAc)_2$ in a 3:1 EGME/H_2O solution. Encouraged by these findings, we decided to test the effectiveness of the ligandless Pd^{II}/EGME/H_2O catalytic system in the formation of biaryls starting from aryl halides and boronic acids. Herein we report an optimized protocol applied to aryl bromides as starting material. As a matter of fact, we succeeded in obtaining a very rapid and quantitative conversion of aryl bromides into a variety of coupling products under mild catalytic conditions, such as working at room temperature and without exclusion of air, with a relatively low catalyst loading. The coupling was effective for both activated and deactivated substrates by using catalyst amounts in the range 0.01–1 mol-%, and TOFs up to 180000 h^{-1} were reached. With respect to previously reported Suzuki–Miyaura couplings run in alcohols at room temperature[38] or in acetone/H_2O at 35 °C[37] under aerobic conditions and by using ligandless $Pd(OAc)_2$, our catalytic system often showed higher reaction rates. Noticeably, in some cases quantitative yields of the coupling product were obtained within less than 1 min.

Results and Discussion

The high catalytic activity of $Pd(OAc)_2$ for the Heck reaction in EGME/H_2O solution was previously shown by us.[42] In the first part of this study, the method was applied to the Suzuki–Miyaura coupling of bromobenzene (**1**) and 4-tolylboronic acid (**2**) as model substrates. Thus, 0.5 mmol of the aryl halide was treated with the boronic acid (0.6 mmol) and K_2CO_3 (0.6 mmol) in the presence of 1 mol-% of catalyst, in EGME (1.5 mL)/water (0.5 mL) mixture. The 3:1 ratio between the two solvents was that previously optimized for the Heck coupling,[42] and the reaction was conveniently performed at 21 °C under aerobic conditions.

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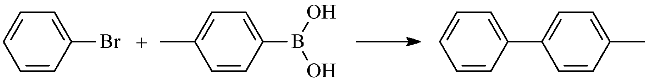
As reported in Table 1, complete formation of 4-methylbiphenyl (**3**) was observed within 4 min, as indicated by GC monitoring of the reaction mixture (Table 1, entry 1), showing a very high TOF (49200 h^{-1}).

Table 1. Activity of Pd^{II}-based catalysts in the model reaction between bromobenzene (**1**) and 4-tolylboronic acid (**2**).[a]



1 **2** **3**

Entry	Catalyst	Base	Yield (%)[b]	Time (min)	TOF (h^{-1})[c]
1	$Pd(OAc)_2$	K_2CO_3	>99	4	49200
2	$Pd(TFA)_2$	K_2CO_3	98	40	16200
3	$Pd(acac)_2$	K_2CO_3	>99	30	1900
4	Na_2PdCl_4	K_2CO_3	>99	25	13600
5	Na_2PdBr_4	K_2CO_3	>99	25	9800
6	PdI_2	K_2CO_3	>99	40	320
7	$PdCl_2(PhCN)_2$	K_2CO_3	97	20	13800
8	$Pd(OAc)_2$	*t*BuOK	>99	8	43300
9	$Pd(OAc)_2$	NaOAc	53	180	20
10	$Pd(OAc)_2$	KF	66	30	1580

[a] Reaction conditions: bromobenzene (0.5 mmol), 4-tolylboronic acid (0.6 mmol), base (0.6 mmol), catalyst (1 mol-%), EGME/H_2O (3:1, 2 mL), T = 294 K. [b] Determined by GC. [c] Turnover frequency (mols of substrate per mol of complex per hour) at 50% conversion.

Searching for more efficient catalysts, the next step was the examination of other simple Pd^{II}-based species. Thus, $Pd(TFA)_2$ (TFA^- = trifluoroacetate), $Pd(acac)_2$, Na_2PdX_4 (X = Cl or Br), PdI_2, and $PdCl_2(PhCN)_2$ were analyzed in the same experimental conditions as for $Pd(OAc)_2$ (Table 1, entries 2–7). None of these catalysts was as good as palladium acetate, as indicated by the TOF values, even though all promoted the almost quantitative formation of **3**. A similar finding was reported by Li and coworkers, who observed, however, a less neat difference between the activity of $Pd(OAc)_2$ and that of $PdCl_2$ and $PdCl_2(MeCN)_2$ in ethanol.[38] For all species, with the exception of $Pd(acac)_2$, the formation of palladium black was observed, despite the fact that the catalytic runs were performed at room temperature. A comparison between the catalytic activity of $Pd(acac)_2$ and $Pd(OAc)_2$ is reported in Figure 1. The lower efficiency of the former along with the apparent lack of formation of palladium black are clearly indicative of its high stability towards decomposition, which most probably arises from the strong chelation of the two $acac^-$ ligands.

The choice of the base was found to be crucial for the reduction of catalyst degradation with enhancement of the reaction rate. For instance, the replacement of K_2CO_3 with *t*BuOK resulted in only a slightly lower TOF value, but much more time was needed to reach the complete conversion of the substrates into **3** (Table 1, entry 8 vs. entry 1). By contrast, largely incomplete reactions and very low TOFs were observed by using NaOAc or KF (Table 1, entries 9 and 10).

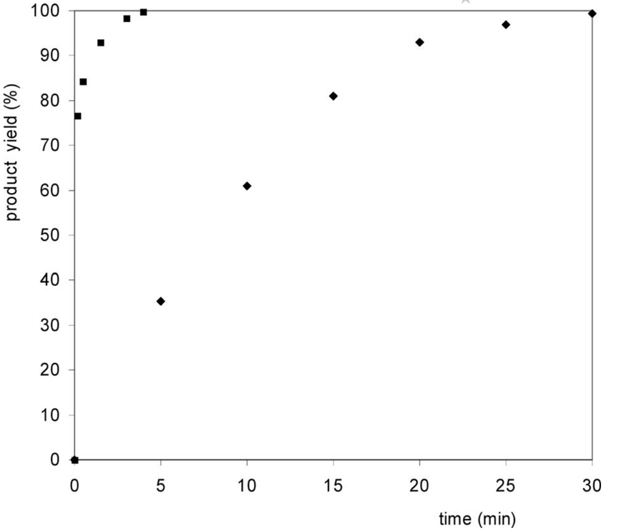
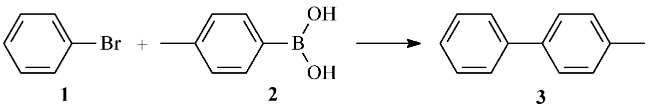


Figure 1. Comparison between the efficiency of $Pd(OAc)_2$ (■) and $Pd(acac)_2$ (◆) in the reaction between bromobenzene (**1**) (0.5 mmol) and 4-tolylboronic acid (**2**) (0.6 mmol) in the presence of K_2CO_3 (0.6 mmol). Reaction conditions: EGME (1.5 mL), H_2O (0.5 mL), T = 294 K.

In order to evaluate the potential and limits of the catalytic system, the standard reaction between **1** and **2** was also run with catalyst amounts decreased by one and two orders of magnitude, and the data are shown in Table 2. The use of 0.1 mol-% of $Pd(OAc)_2$ resulted in a noticeably increase in the TOF value to 105700 h^{-1}, with only a negligible decrease in the yield of **3** (from >99 to 98%; Table 2, entry 2). By contrast, **3** was formed very slowly (95% yield in 24 h) in the presence of 0.01 mol-% of catalyst (Table 2, entry 3). It is well known that addition of tetrabutylammonium bromide (TBAB) can increase the rate of reaction, as it acts not only as a phase-transfer agent, but it is also capable of activating the arylboronic acid. Unexpectedly, we found that addition of TBAB (in a 1:1 molar ratio with respect to **1**) caused a neat slow down of the reaction (Table 2, entry 4; Figure 2). The efficiency of $Pd(OAc)_2$ in solvents structurally related to EGME was also examined, in particular the

Table 2. Activity of $Pd(OAc)_2$ in the model reaction between bromobenzene (**1**) and 4-tolylboronic acid (**2**).[a]



1 **2** **3**

Entry	mol-% Pd	Solvent[b]	Yield (%)[c]	Time	TOF (h^{-1})[d]
1	1.0	EGME/H_2O	>99	4 min	49200
2	0.1	EGME/H_2O	98	2 min	105700
3	0.01	EGME/H_2O	95	24 h	1000
4	1.0[e]	EGME/H_2O	97	6 min	12100
5	1.0	EG[f]/H_2O	>99	6 h	900
6	1.0	DME[g]/H_2O	93	4 h	6900
7	1.0	ethanol/H_2O	>99	1 h	11500
8	1.0	2-propanol/H_2O	>99	6 h	4900

[a] Reaction conditions: bromobenzene (**1**) (0.5 mmol), 4-tolylboronic acid (**2**) (0.6 mmol), $Pd(OAc)_2$, K_2CO_3 (0.6 mmol), solvent (2 mL), T = 294 K. [b] Organic solvent/H_2O (3:1). [c] Determined by GC. [d] Turnover frequency (mols of substrate per mol of complex per hour) at 50% conversion. [e] TBAB (0.5 mmol) was added. [f] EG = ethylene glycol. [g] DME = 1,2-dimethoxyethane.

catalyst was tested in 3:1 mixtures of ethylene glycol/H_2O and 1,2-dimethoxyethane/H_2O. Interestingly, in both cases (Table 2, entries 5 and 6) the catalytic activity of Pd$(OAc)_2$ was much lower than that shown in EGME/H_2O, thus confirming the peculiar role played by EGME in the C–C coupling reaction promoted by palladium(II) compounds.[42] As $Pd(OAc)_2$ showed good activity for the Suzuki reaction performed in pure ethanol,[38] we were intrigued to examine its efficiency in ethanol/H_2O (3:1). Surprisingly, the formation of **3** starting from **1** and **2**, although quantitative, was very slow (Table 2, entry 7). The rapid decomposition of the catalyst with formation of palladium black may account for this finding. A 2-propanol/H_2O (3:1) mixture behaved similarly (Table 2, entry 8). However, the yield was quantitative and this contrasts with previous findings showing a 100% yield in methanol and ethanol, which decreased to 20% in 2-propanol.[38]

The optimized protocol [aryl bromide (1 equiv.); arylboronic acid (1.2 equiv.); K_2CO_3 (1.2 equiv.); $Pd(OAc)_2$; EGME/H_2O, 3:1; room temperature; reaction under air] was then applied to a series of different aryl bromides and boronic acids, which led to monosubstituted biaryls. For

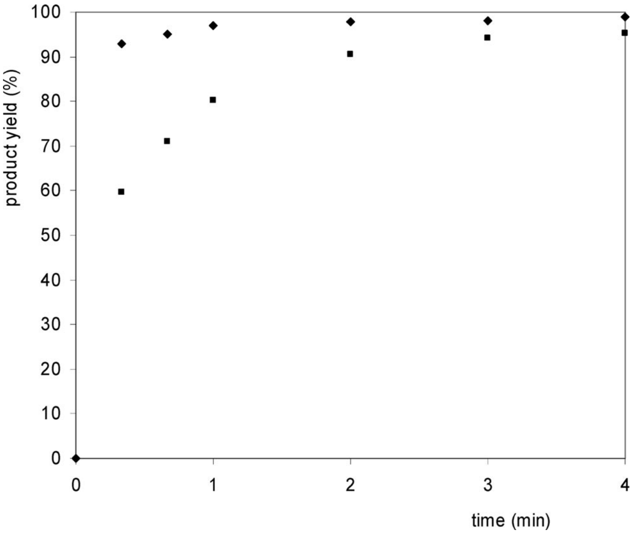
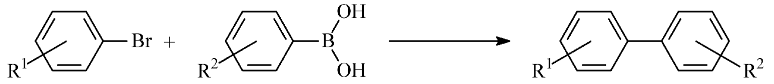


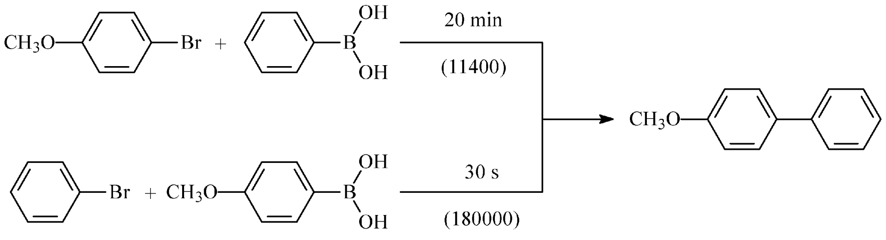
Figure 2. Yield of 4-methylbiphenyl (**3**) from bromobenzene (**1**) and 4-tolylboronic acid (**2**); (■) 0.5 mmol of TBAB added, (♦) without TBAB. Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), K_2CO_3 (0.6 mmol) EGME (1.5 mL), H_2O (0.5 mL), T = 294 K.

Table 3. Reaction between different aryl bromides and arylboronic acids.[a]



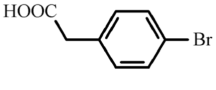
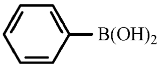
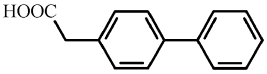
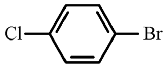
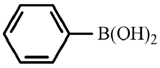
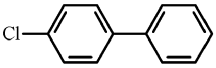
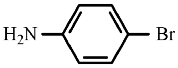
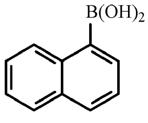
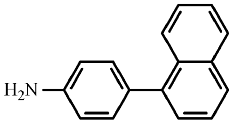
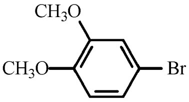
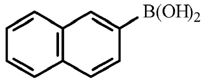
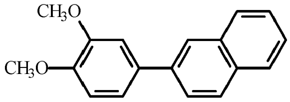
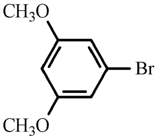
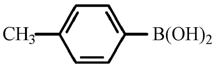
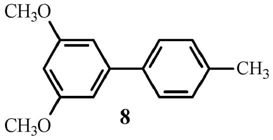
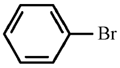
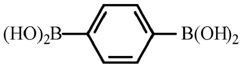
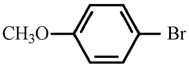
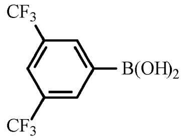
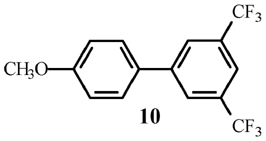
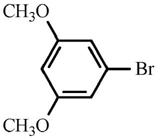
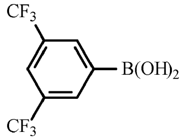
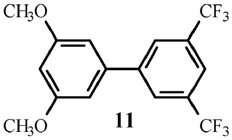
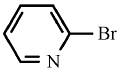
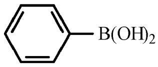
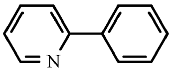
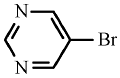
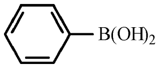
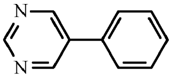
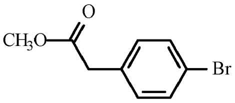
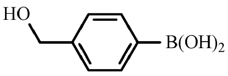
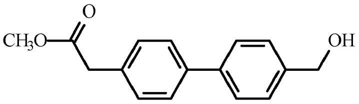
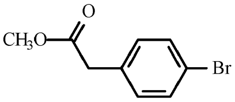
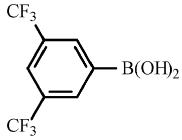
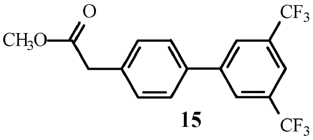
Entry	R^1	R^2	Catalyst amount (%)	Yield[b] (%)	Time	TOF[c] (h^{-1})
1	4-$CH_2CO_2CH_3$	H	1	>99	10 min	16500
2	4-$CH_2CO_2CH_3$	H	0.1	>99	30 min	60000
3	4-CN	H	1	>99	1 min	22500
4	4-CN	H	0.1	>99	15 min	98600
5	4-NO_2	H	1	98	40 s	19000
6	4-NO_2	H	0.1	>99	10 min	39000
7	4-OCH_3	H	1	>99	20 min	11400
8	4-OCH_3	H	0.1	92	4 h	8300
9	H	4-CF_3	1	98	1 h	13900
10	H	4-CF_3	0.1	93	4 h	1800
11	H	3-$COCH_3$	1	94	24 h	400
12	H	3-$COCH_3$	0.1	88	24 h	800
13	H	4-OCH_3	1	>99	30 s	180000
14	H	4-OCH_3	0.1	>99	1 h	66700
15	H	4-CH_2OH	1	>99	30 min	20200
16	H	4-CH_2OH	0.1	97	1.5 h	6700
17	4-NO_2[d]	H	1	>99[e]	24 h	30

[a] Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (0.6 mmol), $Pd(OAc)_2$, EGME/H_2O (3:1, 2 mL), T = 294 K. [b] Determined by GC. [c] Turnover frequency (mols of substrate per mol of complex per hour) at 50% conversion. [d] 1-Chloro-4-nitrobenzene was used as the substrate. [e] At 373 K.



Scheme 1. Alternative paths for the formation of 4-methoxybiphenyl. Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (0.6 mmol), $Pd(OAc)_2$ (1 mol-%), EGME/H_2O (3:1, 2 mL), T = 294 K. TOFs (in h^{-1}) are reported in parenthesis.

Table 4. Reaction between different aryl bromides and arylboronic acids.[a]

Entry	Aryl bromide	Arylboronic acid	Product	Yield (%)[b]	Time
1			 **4**	79	3 h
2			 **5**	> 99 (95)	2 min
3			 **6**	99	6 h
4			 **7**	58	1 h
5			 **8**	90	30 min
6			 **9**	98	15 min
7			 **10**	98	1 h
8			 **11**	79	8 h
9			 **12**	67	22 h
10			 **13**	98	23 h
11			 **14**	97 (96)	3 h
12			 **15**	99 (98)	1.5 h

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[a] Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (0.6 mmol), $Pd(OAc)_2$ 1 mol-%, EGME/H_2O (3:1, 2 mL), $T = 294$ K. [b] Determined by GC, isolated yield in parenthesis.

each pair of reagents, the catalytic experiments were run with the use of 1 and 0.1 mol-% of $Pd(OAc)_2$. The results are collected in Table 3. The reaction between a 4-substituted bromobenzene and phenylboronic acid (Table 3, entries 1–8) was quantitative and faster with the use of 1 mol-% of catalyst. By contrast, higher was the TOF value obtained with a lower catalyst amount,[44] in accord with the presence of nanosized colloidal palladium(0) species as effective precatalysts.[18,44b,44c,45] Only the reaction given by 4-bromoanisole in the presence of 0.1 mol-% of $Pd(OAc)_2$ was very slow and incomplete (Table 3, entry 8). It is worth noting that the most electron-poor aryl bromides (4-bromobenzonitrile and 4-nitrobromobenzene) quantitatively gave the coupling product in less than 1 min (Table 3, entries 3 and 5). To the best of our knowledge, no other catalytic system is capable of such performances at room temperature. As reported in Table 3 (entry 7), 4-bromoanisole and phenyboronic acid completely formed 4-methoxybiphenyl within 20 min. Noticeably, the same product was otherwise quantitatively formed within only 30 s starting from bromobenzene and 4-methoxyboronic acid (Scheme 1), and the relative TOF value (180000 h^{-1}) was the highest found in this study.

Several other combinations between aryl bromides and arylboronic acids were examined to afford products **4**–**15**, which are depicted in Table 4. Biphenyls **14** and **15**, obtained by starting from methyl 4-bromophenylacetate, are novel compounds, which were fully characterized by NMR spectroscopy. With a few exceptions, the yield of the coupling product was always almost quantitative. In this context, it should be stressed that large amounts of palladium black were observed for those products showing rather low yield (Table 4, entries 4 and 7). The synthesis of 4-biphenylacetic acid (**4**) (a NSAI drug known as *felbinac*®) (Table 4, entry 1) can be accomplished in one step by treating 4-bromophenylacetic acid with phenylboronic acid, but the yield was not satisfactorily high (79%). However, the corresponding methyl ester can be obtained quantitatively by starting from methyl 4-bromophenylacetate with the use of 0.1 mol-% of $Pd(OAc)_2$ (Table 3, entry 1). As an example of double coupling useful for the synthesis of symmetric terphenyls, the reaction between bromobenzene and benzene-1,4-diboronic acid was also performed, which resulted in the almost quantitative formation of 1,4-diphenylbenzene (**9**) within 15 min (Table 4, entry 6).

The protocol was also conveniently applied to the synthesis of heterocyclic compounds. Thus, 2-phenylpyridine (**12**) and 5-phenylpyrimidine (**13**) were formed in 67 and 98% GC yield, respectively (Table 4, entries 9 and 10). These results, when compared with that found with the use of the $Pd(OAc)_2/CH_3OH/CH_3ONa$ system,[38] evidence that the present protocol gives much better results, especially in the case of **13**.

The catalytic method can be successfully applied to activated aryl chlorides by using higher temperatures. For example, at 373 K, 1-chloro-4-nitrobenzene reacted with phenylboronic acid to afford quantitatively 4-nitrobiphenyl after 48 h (Table 3, entry 17). In this case, the immediate formation of palladium black was observed and a noticeable amount of the homocoupling product was present at the end of the reaction.

Finally, a ^1H NMR spectroscopic investigation was undertaken to possibly shed light into the role of EGME in the formation of the catalytically active species. Two samples were prepared by dissolving $Pd(OAc)_2$ into an EGME/D_2O mixture. To one of the two samples was added K_2CO_3. The samples gave identical ^1H NMR spectra showing the presence of EGME and the OAc^- ion only. No appreciable signals due to oxidation products derived from EGME were observed, although reduction of Pd^{II} to Pd^0 occurred, as palladium black was slowly formed. A third sample, prepared by mixing and heating $Pd(OAc)_2$, K_2CO_3, and bromobenzene in EGME/D_2O solution, again did not show the presence of new signals. Thus, apparently EGME seems not to be involved in a redox process that leads to formation of catalytically active Pd^0 species. It is likely that both EGME and water could help to stabilize the Pd^0 colloidal nanocluster by strong solvation, and the nanocluster, most probably, acts as a precursor to the true catalyst.[45b,46] The influence of water on the rate of formation of the active catalyst has been well established.[44a]

Conclusions

A simple protocol for the $Pd(OAc)_2$-catalyzed cross-coupling of aryl bromides with boronic acids has been developed. Notably, the reaction is performed at room temperature under aerobic conditions and with the use of a ligand-free cheap catalyst. The key for achieving a very rapid and often quantitative coupling is the use of a EGME/H_2O (3:1) mixture, which seems to be preferable to acetone/water[37] or to alcohols[38] for a wide range of substrates. In some cases we observed complete conversion of aryl bromides and boronic acids into the C–C coupling product within 1 min. It is noteworthy that all functional groups present in the aryl bromide and arylboronic acid ($-NO_2$, $-CN$, $-NH_2$, $-OH$, $-OCH_3$, $-CF_3$, $-COOH$, $-COOCH_3$) could be tolerated. Furthermore, we found that the protocol can be successfully applied to an electron-poor aryl chloride such as 1-chloro-4-nitrobenzene, which can be quantitatively transformed into 4-nitrobiphenyl by reaction with phenylboronic acid at 373 K. This subject is part of a current investigation focused on the application of Pd^{II}-based compounds to the Suzuki–Miyaura reaction between aryl chlorides and arylboronic acids.

Experimental Section

Materials and Methods: All reagents and solvents were purchased from Aldrich and used without further purification. The ^1H, ^{19}F, and ^{13}C NMR spectra (at 200.13, 188.31, and 50.32 MHz, respectively) were recorded with a Bruker AC 200 F QNP spectrometer. Chemical shifts were referenced to $SiMe_4$ for ^1H and ^{13}C nuclei, whereas for the ^{19}F nucleus the reference was $CFCl_3$. The GC–MS analyses, run to control the identity of the compounds obtained in the catalytic trials, were carried out with a Fisons TRIO 2000 gas chromatograph–mass spectrometer working in the positive ion 70 eV electron impact mode. Injector temperature was kept at 250 °C and the column (Supelco® SE-54, 30 m long, 0.25 mm i.d., coated with a 0.5 µm phenyl methyl silicone film) temperature was programmed from 50 to 310 °C with a gradient of 12 °C min^{-1}. The GC analyses were run with a Fisons GC 8000 Series gas chromatograph equipped with a Supelco® PTA-5 column [30 m long, 0.53 mm i.d., coated with a 3.0 µm poly(5% diphenyl/95% dimethylsiloxane) film] Injector and column temperatures were 250 and 60–300 °C, respectively.

General Procedure for the GC Monitoring of the Suzuki Reaction

Method A. Using 1 mol-% of Catalyst: In a thermostatted bath at 21 °C, a 25-mL Schlenk flask was charged with the palladium compound (5 µmol), the boronic acid (0.6 mmol), the base (0.6 mmol), and the solvents (EGME, 1.5 mL; H_2O, 0.5 mL). Then the reaction was started by addition of the aryl bromide (0.5 mmol). The reaction mixture was extracted from the flask by syringe (the volume of the extracted sample was ca. 0.1 mL), and the reaction was immediately quenched by adding the sample to water (0.5 mL). In this manner, the organic compounds separated, which were extracted with dichloromethane (2 mL). The solution was dried with $MgSO_4$ and analyzed by GC after purification on a microcolumn filled with silica gel or Celite®, depending on the sample. The method was slightly modified when using an aryl chloride as precursor: the temperature of the bath was settled at 100 °C and the catalyst $Pd(OAc)_2$ was added after the mixture reached the desired temperature.

Method B. Using 0.1 mol-% of Catalyst: The first part of the above-described procedure was slightly modified as follows: a solution of the catalyst was prepared by dissolving the palladium compound (5 µmol) into a mixture of EGME (15 mL) and H_2O (5 mL). After stirring for a few minutes, the solution (2 mL) was introduced into the flask charged with all other chemicals. Further workup was as described above.

A set of extractions of samples from the reaction mixture (which were performed in steps of 10 s in the case of the faster reactions) allowed the construction of the aryl halide conversion versus time curve, from which we obtained the time value X corresponding to 50% conversion of the aryl halide. Such a value was used to calculate the desired TOF according to the equation: TOF (h^{-1}) = $50 \times 3600/X(s)$ (for a reaction run in the presence of 1 mol-% of catalyst).

14: A mixture of methyl 4-bromophenylacetate (573 mg, 2.5 mmol), 4-(hydroxymethyl)phenylboronic acid (456 mg, 3.0 mmol), K_2CO_3 (415 mg, 3.0 mmol), and $Pd(OAc)_2$ (5.6 mg, 25 µmol) in EGME (7.5 mL) and H_2O (2.5 mL) was stirred at room temperature for 6 h. To the resulting mixture was added water (5 mL), and the product was extracted with dichloromethane (2 × 5 mL). The mixture, after treatment with $MgSO_4$, was purified by passing through a Celite® column. Elimination of the solvent in vacuo gave **14** (616 mg, 96%) as a colorless solid. $C_{16}H_{16}O_3$ (256.30): calcd. C 74.98, H 6.29; found C 74.81, H 6.37. ^1H NMR (200.13 MHz, $CDCl_3$, 295 K): δ = 7.59–7.27 (m, 8 H, *Ph*), 4.68 (s, 2 H, CH_2), 3.69 (s, 3 H, CH_3), 3.65 (s, 2 H, CH_2), 2.32 (br. s, 1 H, O*H*) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$, 295 K): δ = 172.0 (*C*O), 140.0 (*Ci*), 139.9 (*Ci*), 139.6 (*Ci*), 132.9 (*Ci*), 129.6 (C_{Ph}), 127.3 (C_{Ph}), 127.1 (C_{Ph}), 127.0 (C_{Ph}), 64.8 (CH_2), 52.0 (CH_3), 40.7 (CH_2) ppm.

15: A procedure similar to that described above for the synthesis of **14** was adopted by using 3,5-bis(trifluoromethyl)phenylboronic acid (774 mg, 3.0 mmol) and stirring the mixture for 2 h. Analogous workup afforded **15** (890 mg, 98%) as a colorless oil. ^1H NMR (200.13 MHz, $CDCl_3$, 295 K): δ = 8.04–7.81 (m, 3 H, *Ph*), 7.59–7.38 (m, 4 H, *Ph*), 3.72 (s, 3 H, CH_3), 3.69 (s, 2 H, CH_2) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$, 295 K): δ = 171.7 (*C*O), 142.8 (*Ci*), 137.1 (*Ci*), 134.9 (*Ci*), 132.1 [q, $^2J(^{13}C,^{19}F)$ = 33.2 Hz, *Ci*], 130.2 (C_{Ph}), 127.4 (C_{Ph}), 127.1 [sym m, $^3J(^{13}C,^{19}F)$ = 2.4 Hz, $^5J(^{13}C,^{19}F)$ = 1.2 Hz C_{Ph}], 123.4 [q, $^1J(^{13}C,^{19}F)$ = –272.6 Hz, CF_3], 120.9 [hept., $^3J(^{13}C,^{19}F)$ = 3.8 Hz, C_{Ph}], 52.1 (CH_3), 40.7 (CH_2) ppm. ^{19}F NMR (188.31 MHz, $CDCl_3$, 295 K): δ = –63.3 ppm.

^{1}H NMR Studies: An NMR tube was charged with $Pd(OAc)_2$ (27 mg, 0.12 mmol), EGME (19 µL, 0.24 mmol), and D_2O (0.4 mL). The tube was gently warmed for 20 min at 40 °C, during which time small amounts of palladium black formed. After cooling, it was put into the probe of the NMR spectrometer to record the ^1H spectrum. The spectrum showed signals at δ = 3.73 (m), 3.59 (m), 3.42 (s, EGME), 2.06 (s, OAc^-) ppm.

A second sample was prepared in the same manner and before heating K_2CO_3 (21 mg, 0.15 mmol) was added. The spectrum showed signals at δ = 3.69 (m), 3.54 (m), 3.36 (s, EGME), 2.05(s, OAc^-) ppm.

A third sample was prepared as the second one and bromobenzene (19 mg, 0.12 mmol) was also added before heating. The spectrum showed signals at δ = 3.71 (m), 3.58 (m), 3.39 (s, EGME), 2.06 (s, OAc^-), 7.4–6.7 (m, C_6H_5Br) ppm.

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