A Mild and Versatile Method for Palladium-Catalyzed Cross-Coupling of Aryl Halides in Water and Surfactants

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Various aqueous surfactants proved to be excellent media for carrying out palladium-catalyzed Suzuki–Miyaura cross-coupling reactions under mild conditions. The dehalogenation side reaction, which is usually a drawback with the aqueous protocol, was not observed. The concentration of the surfactant in water played a pivotal role for the reaction outcome. Smooth cross-coupling of iodoanisole and a variety of aryl bromides, including electron-rich derivatives, with aryl boronic acids occurred at room temperature in high yields either with $[Pd(PPh_3)_4]$ or Pd/C as catalyst. The water-surfactant Pd/C system combines high activity under ambient conditions (air), easy separation and recyclability. Palladium acetate was found to be effective in cross-coupling of the less reactive aryl chlorides at 100 °C.

Introduction

The palladium-catalyzed cross-coupling reaction of aryl halides and arylboronic acids [the Suzuki−Miyaura reaction (SM reaction)][1−7] is one of the most widely used synthetic protocols in modern chemistry and in industrial applications.[8] The synthesis and utilization of biaryl compounds are implicated in key steps for the building of numerous conducting polymers, molecular wires, liquid crystals, agrochemicals, pharmaceuticals, and chiral skeletons of many asymmetric catalysts.[9,10] In particular, progress in cross-coupling reactions has strongly impacted the pharmaceutical industry[11−13] by accomplishing the preparation of a great diversity of chemical structures for lead identification and optimization of drug candidates. Besides the classic general Ulmann[14] and Stille[15] couplings, the SM synthesis of biaryls is very attractive because organo boronic acids are highly advantageous as reagents in laboratories and industry. They are largely unaffected by the presence of water, tolerate a broad range of functionalities and yield non-toxic by-products which can be readily separated from the desired compound. This is of great importance in the development of more environmentally friendly and economically sound manufacturing processes.[16] The widely employed reaction protocol utilizes aqueous organic solvents in the presence of an inorganic base (typically carbonate, hydrogencarbonate, or hydroxide) and phosphorous derivatives as ligands. In the past few years, great advances have been made in developing active and efficient catalysts by modifying traditional ligands and discovering new ones.[17−24] In the meantime, new types of non-phosphane ligand complexes, such as heterocyclic carbenes,[25,26] oxime palladacycles,[27] imine and amine palladacycles,[28−30] diazabutadienes[31] and 2-aryl-2-oxazolines[32] have also emerged for use in the SM reaction. Regarding industrial applications, however, these ligands and Pd-precursors are expensive. Moreover, homogeneous catalysis presents problems in separation and, furthermore, wasted inorganic materials are difficult to reuse. Deactivation of the soluble palladium catalysts by forming inactive particles is also often encountered at high reaction temperatures. To overcome these problems, heterogeneous palladium catalysts, such as palladium complexes immobilized on polymeric[33] or inorganic supports,[34−37] palladium powder,[38] mixed nanocluster catalysts,[39] cyclodextrin-capped palladium nanoparticles,[40] microencapsulated palladium catalysts,[41] and fluorous biphasic catalysis without perfluorinated solvents,[42] have been developed. In addition to reusable catalysts, from the standpoint of green chemistry, the development of more environmentally benign reaction conditions, for example the use of water instead of organic solvents and the use of non-toxic reagents, would be desirable. Subsequently, SM reactions have been achieved in supercritical carbon dioxide, under solventless conditions,[43] in ionic liquids with methanol as co-solvent under ultrasonic irradiation[44] and in water using microwave and conventional heating.[45] An oxime−carbapalladacycle complex covalently anchored to silica has been used as an active and reusable heterogeneous catalyst for Suzuki cross-couplings in water at reflux.[46] Interestingly, the cheaper Pd/C, one of the most common heterogeneous palladium catalysts, has been found to work efficiently as a reusable catalyst for the coupling reaction of water-soluble iodo- or

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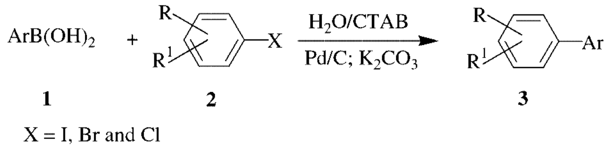
bromophenols and arylboronic acids in aqueous media at room temperature.[47] The development of water-based organic transformations is growing in importance in chemistry. Its low cost and lack of inflammable, explosive, mutagenic and carcinogenic properties makes water the most suitable solvent for the production of fine chemicals. In addition, several synthetic advantages are expected using water as the solvent. Among others, phase separation is easier because most organic compounds are lipophilic and are easily separated from the aqueous phase. Provided that the heterogeneous catalysts exhibit high catalytic activity in water, the catalysis would represents an almost ideal synthetic process. Water is compatible with most of the known palladium-catalyzed reactions.[48] The low solubility of the majority of organic compounds in water is a great problem.[49] This should be addressed by using surfactants in concentrations above the cmc (critical micelle concentration) level, which for common surfactants are in the range of 10^{-3} to 10^{-2} M. It has recently been shown[50] that formation of C−C and C−O bonds occurs efficiently in water in the presence of surfactants. In this work we prepared biaryls in good yields from aryl halides and arylboronic acids using water as solvent, various surfactants and $[Pd(PPh_3)_4]$, Pd/C or $Pd(OAc)_2$ as catalyst. The obvious advantages of working in aqueous suspensions are that water-insoluble reaction products can be isolated by simple liquid-liquid extraction and that Pd/C can be separated by simple filtration. Ultra filtration could lead to recovery of the surfactants. The dehalogenation side reaction, which is usually a drawback with the aqueous protocol of SM coupling, was not observed.[51]

Results and Discussion

The general process involves formation of biaryl **3** (Scheme 1) from the parent aryl halide **2** (0.2−2.0 mol·dm^{-3}), K_2CO_3 (0.4−4.0 mol·dm^{-3}) in an aqueous solution of 0.15 mol·dm^{-3} surfactant, Pd catalyst (6.25 10^{-3} mol·dm^{-3}), and aryl boronic acid **1** (0.10−1.0 mol·dm^{-3}).



Scheme 1

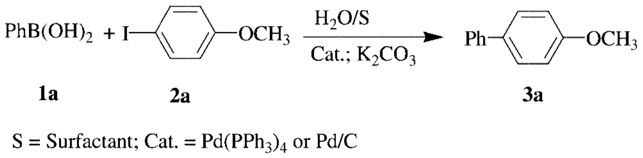
The surfactants concentration are, in all reactive cases, at least one order of magnitude (two orders for CTAB) higher than their cmc levels and the reactants concentrations are equal to or in excess of that of the surfactants.

The results of coupling reactions are collected in Tables 1−3 and are discussed below.

The various factors which affect the investigated reaction can be analyzed separately, as follows:

Type of Surfactant

The effect on varying the surfactant structure can be interpreted in the light of the results obtained for reactions of 4-iodoanisole **2a** with phenyl boronic acid **1a**, using a solution 0.15 M of a surfactant in water/1-butanol (8:1) as the reaction medium, $[Pd(PPh_3)_4]$ or Pd/C as the palladium source and potassium carbonate as the base. We chose to start with an aryl iodide, since the large difference in the coupling rate of iodo- versus bromo- and chloro-functions in the SM cross-coupling reaction should have presented some advantages in the optimization studies. In the preliminary experiments a small amount of butanol was added to the reaction mixtures in order to obtain more stable systems. In fact, the presence of surfactants in amounts far exceeding the cmc could lead to the formation of complex systems, like gels, that are not desirable as media for reactions. Under the above conditions, the reaction product 4-methoxybiphenyl (**3a**) was isolated in high yields, at room temperature, in the presence of cationic, anionic, zwitterionic, and non-ionic surfactants (Scheme 2, Table 1). Very likely, the moderate yields of **3a** obtained in the presence of cetyltrimethylammonium iodide (CTAI) and cetylpyridinium chloride (CPyCl) were due to the low solubility, at room temperature, of the former surfactant and base-promoted decomposition of the latter.



Scheme 2

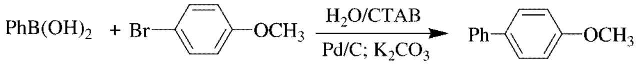
Table 1. Reaction of **1a** with **2a** in the presence of surfactants

Entry	Surfactant	Time [h]	Catalyst	Product **3a**[a] Yield [%]
1	SDS	3	$[Pd(PPh_3)_4]$[b]	80
2	CTAB	3	$[Pd(PPh_3)_4]$[b]	96
3	CTAB	3	$[Pd(PPh_3)_4]$[b][c][d]	98
4	None	3	$[Pd(PPh_3)_4]$[b]	26
5	CTAB	24	Pd/C	95
6	CTAB	24	Pd/C[c]	95
7	SB3−14[e]	3	$[Pd(PPh_3)_4]$[b]	77
8	BHDC[f]	3	$[Pd(PPh_3)_4]$[b]	85
9	CTAI	3	$[Pd(PPh_3)_4]$[b]	33
10	TritonX 100[g]	3	$[Pd(PPh_3)_4]$[b]	85
11	CpyCl	3	$[Pd(PPh_3)_4]$[b]	47
12	TBAB	27	Pd/C[c]	5

[a] Typical experimental procedure: 0.60 mmol of surfactant, 4 mL of water, 0.5 mL of butanol, 0.5 mmol of **1a**, 1.0 mmol of **2a**, 2.0 mmol of K_2CO_3 were mixed together by gentle stirring until an optically isotropic system was obtained. Palladium catalyst (0.025 mmol) was then, added. [b] The reaction was carried out under nitrogen atmosphere. [c] The reaction was carried out without butanol. [d] At room temperature the system has a milk-like appearance. [e] 3-(Dimethyltetradecylammonium)propane sulphonate. [f] Benzyldimethylhexadecylammonium chloride. [g] Ethoxylated octylphenol.

In contrast to results obtained in the pioneering work on the palladium-catalyzed carbonylation of iodoarenes in aqueous solubilized systems,[52] the reaction gave the best yield in the presence of CTAB, even without adding butanol as co-solvent (Table 1, entries 2 and 3). Using this surfactant, the coupling proceeded readily in the presence of Pd/C or [Pd(PPh_3)$_4$] as catalyst. The same result was observed with or without adding the co-solvent (Table 1, entries 5 and 6). The formation of **3a** (26% yield) using [Pd(PPh_3)$_4$] as the catalyst in water/butanol (8:1), without surfactant, shows that butanol also facilitates the dissolution of the reactants and the catalyst in the reaction medium (Table 1, entry 4). The failure to form **3a** using tetrabutylammonium bromide[53] (TBAB) (Table 1, entry 12) should rule out the use of CTAB as a phase-transfer catalyst.

The concentration of the surfactant in water played a pivotal role for the reaction outcome. Taking the coupling of phenylboronic acid **1a** with 4-bromoanisole **2b** as a model system, we performed the reaction on a 0.5 mmol scale of **1a** using different concentrations of CTAB and constant quantities of **1a**, **2b**, K_2CO_3, and Pd/C. An increase in the yield of **3a**, from 5% to 93%, was observed on changing the concentration of CTAB from 10^{-4} to 0.1 mol·dm^{-3} (Scheme 3, Table 2, entries 2−5). Higher yields were obtained at [CTAB] well above cmc. We next turned our attention to a larger scale reaction. We performed the coupling on a 5 and 10 mmol scale of **1a**, by placing **1a** in 4 mL of an aqueous solution of 0.15 M CTAB, a proportional amount of **2b** and K_2CO_3, and exactly the same amount of Pd/C catalyst used in the runs carried out on the 0.5 mmol scale. Again, we obtained impressive yields (73−99%) of biaryl **3a**. Of course, with a lower loading of the catalyst, longer reactions times were required when the reactions was carried out at room temperature. An increase in the turnover frequency (TOF, number of moles of aryl boronic acid converted/moles of Pd per hour) was accomplished by increasing the reaction temperature (Table 2, entries 6−8). The ratio [CTAB]/aryl halide did not seem to have any significant effect on the reaction outcome if the [CTAB] was greater than 100 times its cmc.



1a **2b** **3a**

Scheme 3

Table 2. Reaction of **1a** with **2b** at variable [CTAB]

Entry	[CTAB], M 10^2	[CTAB]/[**2b**] 10^2	Product **3a**[a] Yield [%]
1	0	0.0	2[b]
2	0.01	0.04	5[b]
3	0.1	0.40	50[b]
4	1	4.0	70[b]
5	10	40	93[b]
6	15	6.0	73[c] [d]
7	15	6.0	98[c] [e]
8	15	3.0	99[f]

[a] Experimental procedure: CTAB, **1a**, **2b**, and K_2CO_3 are mixed together in 4 mL of water by gentle stirring. Palladium catalyst (0.025 mmol) was then added. [b] 0.5 mmol of **1a**, 1.0 mmol of **2b** and 2.0 mmol of K_2CO_3, at room temperature for 24 h. [c] 5.0 mmol of **1a**, 10.0 mmol of **2b** and 20.0 mmol of K_2CO_3. [d] Room temperature for 72 h. [e] 40 °C for 24 h. [f] 10.0 mmol of **1a**, 20.0 mmol of **2b** and 40.0 mmol of K_2CO_3, at 60 °C for 24 h.

Thus, the aqueous surfactant systems proved to be excellent media for carrying out palladium-catalyzed reactions. These systems have the following advantages in comparison with more conventional procedures: no organic solvent is needed; ultra low surface tension allows fast and easy mixing of reagents; the systems are formed spontaneously and vigorous mechanical or ultrasonic agitation is not needed to obtain and maintain these systems.

Structure of the Aryl Halide

We studied the SM cross-coupling reaction of phenylboronic acids with aryl iodides, bromides, and chlorides. Although aryl iodides, bromides, and triflates are most commonly used, recently aryl chlorides, hitherto regarded as inert to palladium-catalyzed cross-coupling reactions, have been shown to be effective participants, provided that there is an electron-withdrawing group on the aryl ring and/or a basic phosphane ligand on the palladium. Representative cross-coupling reactions using both electron-rich and electron-poor haloarenes were investigated. The results are summarized in Table 3.

All the experiments were performed on 0.15 M aqueous solutions of CTAB. In all cases a small amount of biphenyl (1−6%) was formed as a by-product from the homocoupling reaction of phenylboronic acid. The phenylboronic acid/aryl halide ratio greatly influenced the yield of this latter by-product, which could become relevant in the presence of an excess of the arylboronic acid with respect to the aryl halide. In a number of cases, the comparison of the catalytic activity of palladium-phosphane complexes with ligand-free palladium catalysts, in the presence of surfactants, was the key to obtaining useful results from a synthetic point of view.

It is clear that the cross-coupling is efficient over a broad spectrum of *ortho*- and *para*-substituted aryl halides and that variations in the electronic nature of the substituents are well tolerated. The SM coupling of heteroaryl bromides with phenylboronic acid also occurs in good yields. Application of the general conditions developed, allowed for smooth coupling of iodoanisole and a variety of aryl bromides, including electron-rich derivatives with arylboronic acids at room temperature in high yields. Although steric hindrance of aryl halides is not a major factor for the formation of substituted biaryls, the cross-coupling reaction of *ortho*-substituted aryl bromides required heating at 60 °C for 24 h to give the expected biaryl derivatives in high yields. Competitive deboronation was not observed. As expected, aryl chlorides were less reactive than iodides and bromides. Nevertheless, high conversions of the activated aryl chlorides were achieved at 100 °C in the presence of Pd/C as catalyst and K_2CO_3 as base. Encouraged by these results

Table 3. Cross-Coupling of aryl halide with aryl boronic acids in 0.1 m aqueous CTAB

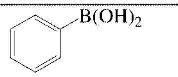
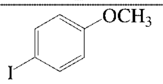
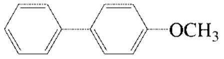
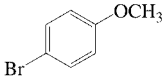
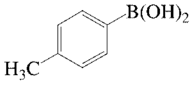
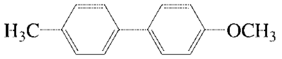
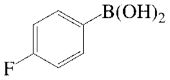
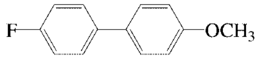
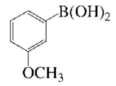
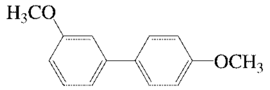
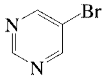
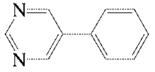
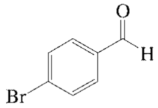
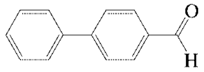
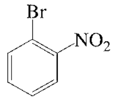
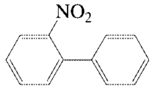
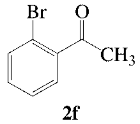
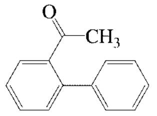
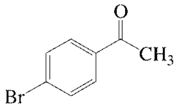
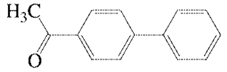
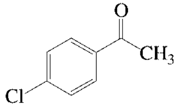
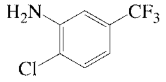
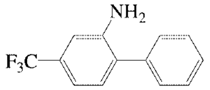
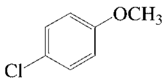
Entry	Compound **1**	Compound **2**	Procedure	T [°C]	Time [h]	Product **3** (%)	Conversion to biphenyl (%)
1	 **1a**	 **2a**	A[a]	rt	3	 **3a** (96)	1
2	**1a**	**2a**	B[b]	rt	24	**3a** (95)	1.5
3	**1a**	 **2b**	A	rt	3	**3a** (90)	2.5
4	**1a**	**2b**	B	rt	24	**3a** (94)	2
5	 **1b**	**2b**	B	rt	24	 **3b** (96)	
6	 **1c**	**2b**	B	rt	24	 **3c** (89)	
7	 **1d**	**2b**	B	rt	24	 **3d** (65)	
8	**1a**	 **2c**	A	rt	24	 **3e** (52)	5
9	**1a**	**2c**	A	40	4.5	**3e** (65)	4
10	**1a**	**2c**	B	rt	24	**3e** (65)	6
11	**1a**	 **2d**	A	rt	24	 **3f** (75)	3
12	**1a**	**2d**	B	rt	24	**3f** (74)	5
13	**1a**	 **2e**	B	60	24	 **3g** (95)	3.5
14	**1a**	 **2f**	B	60	4	 **3h** (89)	2.5
15	**1a**	 **2g**	A	rt	3	 **3i** (89)	3
16	**1a**	 **2h**	A	60	24	**3i** (-)	
17	**1a**	**2h**	A	100	24	**3i** (-)	
18	**1a**	**2h**	C[c]	100	24	**3i** (-)	
19	**1a**	**2h**	D[d]	100	24	**3i** (-)	
20	**1a**	**2h**	B	100	24	**3i** (85)	
21	**1a**	**2h**	E[e]	100	24	**3i** (-)	

Table 3. *(Continued)*

Entry	Compound **1**	Compound **2**	Procedure	T [°C]	Time [h]	Product **3** (%)	Conversion to biphenyl (%)
22	**1a**	 **2i**	B	100	24	 **3j** (96)	
23	**1a**	 **2j**	B	100	24	**3a** (6)	
24	**1a**	**2j**	F[f]	100	20	**3a** (22)	10
25	**1a**	**2j**	G[g]	100	20	**3a** (9)	20
26	**1a**	**2j**	H[h]	100	22	**3a** (65)	9

Typical procedure: 0.60 mmol of CTAB, 4 mL of water, 0.5 mmol of 1, 1.0 mmol of 2 and 2.0 mmol of an inorganic base were mixed together by gentle stirring until an optically isotropic system was obtained; catalyst (0.025 mmol) was then added, unless specified. [a] Procedure A: under a nitrogen atmosphere with 0.5 mL of butanol as co-solvent, K_2CO_3 as inorganic base and $[Pd(PPh_3)_4]$ as catalyst. [b] Procedure B: K_2CO_3 as inorganic base and Pd/C as catalyst. [c] Procedure C: under a nitrogen atmosphere with 0.5 mL of butanol as co-solvent, Cs_2CO_3 as inorganic base and $[Pd(PPh_3)_4]$ as catalyst. [d] Procedure D: under a nitrogen atmosphere, 0.5 mL of butanol as co-solvent, KF as inorganic base and $[Pd(PPh_3)_4]$ as catalyst. [e] Procedure E: without surfactant, K_2CO_3 as inorganic base and Pd/C as catalyst. [f] Procedure F: under a nitrogen atmosphere, 1.9 mmol of NaOH as inorganic base and $[Pd(PPh_3)_4]$ as catalyst. [g] Procedure G: under a nitrogen atmosphere, 1.9 mmol of NaOH as inorganic base and $Pd_2(dba)_3$ and 0.050 mmol of 1,2-bis(diphenylphosphino)ethane as catalyst. [h] Procedure H: under a nitrogen atmosphere, 1.9 mmol of NaOH as inorganic base and $Pd(OAc)_2$ as catalyst.

we decided to see whether the CTAB-based reaction medium was suitable to activate the electronically challenging 4-chloroanisole with Pd/C as catalyst. Many of the approaches for the activation of aryl chlorides in the SM reaction rely on the development of either new ligand sets or new pre-catalyst types, both of which require a substantial degree of synthetic elaboration.[10] Interestingly, it was recently reported[54] that "ligand-free" TBAB-Pd systems, using $Pd(OAc)_2$ as Pd source, are capable of showing good activity in the Suzuki coupling, even of electronically deactivated aryl chlorides, provided that the reactions are performed in the presence of water. So, we performed a concise base/catalyst screening. The use of Pd/C as catalyst, in aqueous CTAB and variation of the base (K_2CO_3, KF, Cs_2CO_3, K_3PO_4, and NaOH) gave disappointing results. In fact, the highest level of cross-coupling derivative (6%) was observed when NaOH was employed as base. In contrast with the CTAB/H_2O/NaOH system, species formed from $Pd(OAc)_2$ were capable of catalyzing efficiently the cross-coupling process and we obtained results similar to that reported in the coupling of aryl chlorides in TBAB-water mixtures.[54] We failed to obtain the cross-coupling derivative omitting CTAB from the system. The disappointing results obtained on adding phosphorous ligands to $Pd(OAc)_2$ gives support to the hypothesis that the true active catalysts are palladium colloids. The in situ reduction of Pd^{II} species can generated Pd nanoparticles which would be uniformly dispersed and mixed with the reactants resembling a homogeneous catalytic system.[55]

Structure of the Arylboronic Acid

We evaluated the influence of the substituents of the boronic acid on the outcome of the reaction by investigating the cross-coupling of 4-fluoro-, 4-methyl-, and 3-methoxyphenylboronic acids with 4-bromoanisole **2b**. The corresponding biaryl derivatives **3b−d** were isolated in high yields. Usually, slightly lower conversions were observed when electron-donating substituents were present on the aryl moiety of the boronic acid derivatives. Under our conditions the results seem to indicate that the reaction outcome is not affected by electronic factors.

Catalyst

We chose to investigate heterogeneous Pd/C as catalyst to build-up a novel SM reaction system based on surfactant/water mixtures. These new systems should present notable features including fast and efficient reactions in air, catalyst/CTAB recyclability, and total catalyst stability under the reaction conditions. This system should not only solve the basic problems with catalyst separation and recovery but should also avoid the need for phosphane ligands. In contrast, homogeneous catalysts require air-sensitive ligands (usually phosphanes) with removal of the catalyst from the product being difficult, this applies to the ligand as well as the expensive precious metal. A specially optimized air-stable Pd on activated carbon catalyst[56] was shown to be a highly active, selective, and convenient heterogeneous catalyst for SM reactions in *N*-methylpyrrolidone (NMP)/water (10:3) system at 120 °C. Furthermore, these ligand-less heterogeneous Pd catalysts[57] showed the unique ability to activate aryl chlorides for SM cross-couplings. The choice of solvent system was the determining factor for obtaining the SM cross-coupling product selectively and for blocking the homo-coupling pathway. Based on the concept that dispersing metal catalysts utilizing microemulsion as the reaction medium could improve the effectiveness of the catalyst for the SM cross-coupling reaction, we found that Pd/C could represent a convenient air stable, phosphanefree catalyst for SM reactions in a water-surfactant system. Recently, ultrafine Pd particles have been prepared in a water/AOT/*n*-hexane microemulsion by hydrogen gas reduction of $PdCl_4^{2-}$, and their efficiency has been evaluated for hydrogenation reactions of olefins.[55] As stated in related studies[58] on the correlation of activity, catalyst properties and palladium leaching of Pd/C catalysts, the reaction should be accompanied by a Pd dissolution/precipitation process. Thus in the presence of surfactant aggregates, a fresh catalyst exhibiting a higher Pd dispersion and more uniform distribution than the starting Pd/C can be generated in situ. The mechanism of the Pd-catalyzed SM reaction of aryl halides with boronic acids involves oxidative addition of Pd^0 to aryl halide, transmetallation of Ar−Pd−X with $Ar'B(OH)_3^-\ M^+$ and reductive elimination to give Ar−Ar′. The presence of positive R_4N^+ ions at the surface of the surfactant aggregates could enhance the synergistic anchimeric and electronic effects occurring upon anchoring the arylboronate intermediate close to a Pd site. In the presence of microemulsions in water the transmetallation step seemed to be rate-determining.[59] The cooperative anchimeric and electronic effects are absent with $[Pd(PPh_3)_4]$ which explains the excellent reactivity of Pd/C catalyst with electron-poor aryl chlorides. When we investigated the coupling of the electronically very deactivated substrate 4-chloroanisole, the formation of the cross-coupling derivative was observed only with $Pd(OAc)_2$ as catalyst. The different reactivity of $Pd(OAc)_2$ could be due to Pd dispersion and the uniform distribution of palladium nanoparticles giving the most active catalyst. It is noteworthy that the water−surfactant Pd/C system combines high activity, under ambient conditions (air), easy separation and recyclability. The experimental procedure is very simple. Liquid-liquid extraction with common organic solvent, such as diethyl ether, allows the quantitative recovery of the product from the water-surfactant Pd/C system. The activity of the recovered water-surfactant Pd/C system was monitored using the reaction of 4-bromoanisole with $PhB(OH)_2$. Although the catalytic activity gradually diminished (yield of **3a**: 1st reuse 95%, 2nd reuse 88%, 3rd reuse 85% and 4th reuse 80%), the yield was still 80% even after the fourth reuse.

Conclusion

In summary we have demonstrated that the water-surfactant palladium-catalyst system can accomplish the SM cross-coupling in milder and more environmentally friendly conditions. CTAB aggregates could generate in situ (on their surfaces?) highly dispersed palladium nanoparticles from simple Pd/C and $Pd(OAc)_2$. Additional ligands are unnecessary. Surface effects could explain the excellent reactivity of heterogeneous Pd catalysts with aryl chlorides. These effects are absent with homogeneous catalysts. Our water-surfactant Pd/C system could solve the basic problems of catalyst separation and recovery. Other notable features include efficient reactions, recyclability, and catalyst stability in air.

Experimental Section

General Remarks: All starting materials and surfactants [dodecyl sulfate sodium salt (SDS), cetyltrimethylammonium iodide (CTAI), cetylpyridinium chloride (CPyCl), benzyldimethylhexadecylammonium chloride (BHDC), ethoxylated octylphenol (TritonX 100)] are commercially available and were used as purchased without further purification, unless otherwise stated. 3-(Dimethyltetradecylammonium)propane sulfonate (SB3−14) and cetyltrimethylammonium bromide (CTAB) were purified by recrystallization from acetone and ethanol/diethyl ether respectively. Solutions were made with redistilled, deionized water. The products, after conventional workup, were purified by flash chromatography on silica gel, eluting with *n*-hexane/ethyl acetate mixtures. Products are all known and were identified by comparison of physical and spectroscopic data with those given in the cited references: **3a**,[60] **3b** and **3c**,[61] **3d**,[62] **3e**,[63] **3f**,[64] **3g**,[65] **3h**,[66] **3i**,[67] and **3j**.[68]

Typical Experimental Procedure: Surfactant (0.60 mmol), arylboronic acid (0.5, 5.0 or 10.0 mmol), aryl halide (1.0, 10.0 or 20.0 mmol), and an inorganic base (2.0, 20.0, or 40.0 mmol) were dissolved in 4 mL of water (in some experiments 0.5 mL of butanol was added as co-solvent) and mixed together by gentle stirring (under a nitrogen atmosphere with homogeneous catalysts) until an optically isotropic system was obtained. A palladium-based catalyst (0.025 mmol) was then added. The reaction was monitored by TLC or GC-MS. After completion, the solvent was removed, and the reaction mixture was purified by flash chromatography (silica gel, *n*-hexane/ethyl acetate mixtures).

Recycle Procedure: CTAB (2.73 g, 7.5 mmol), phenylboronic acid (0.76 g, 6.25 mmol), *p*-bromoanisole (1.55 g, 10.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) were dissolved in 50 mL of water and mixed together by gentle stirring, until an optically isotropic system was obtained. Pd/C (10% Pd) (0.068 g, 0.06 mmol) was then added and the mixture stirred for 72 h at room temperature. At the end of each reaction cycle the product was recovered from the water-surfactant Pd/C catalyst by a liquid-liquid extractor using, as solvent, diethyl ether. To the recovered system was then added all the starting reagents, except surfactant and Pd/C catalyst, for a new reaction cycle. The recovered organic solvent was evaporated and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 99:1).

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