

Efficient two-phase Suzuki reaction catalyzed by palladium complexes with water-soluble phosphine ligands and detergents as phase transfer reagents

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Abstract

The coupling reaction of iodoanisole and phenylboronic acid occurs in aqueous medium in presence of palladium complexes with water-soluble phosphine ligands with good yields (> 99%). The complex $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$ is an excellent precursor to catalyze the coupling reactions of aryl halides with arylboronic acid in toluene/ethanol/water with sodium carbonate as base and surfactants as phase transfer reagents between 30°C and 78°C. With increasing concentration of the surfactant the rates of the reactions were increased and the formation of byproducts was suppressed. The catalytic system was active down to the ppm range. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Carbon–carbon coupling; Suzuki reaction; Two-phase system; Water-soluble catalyst; Detergents

1. Introduction

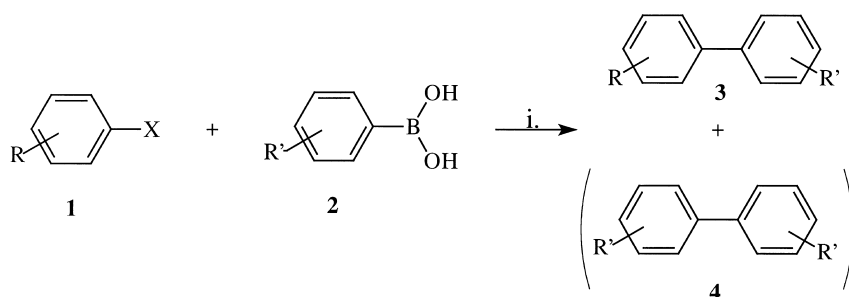
Carbon–carbon bond formation is a general aim in the transition metal catalyzed organic synthetic chemistry [1]. Most reactions were realized as homogeneous systems in organic solvents, but even water is of growing interest as basis for phase separable systems [2]. In accordance with this method, a series of water-soluble phosphines and other hydrophilic ligands was developed [3]. As a typical system, water contains the catalyst and an organic phase

contains educts and products. The transformation of the catalyst into the organic phase can be promoted by a mediator and by a typical phase transfer reagent.

One of the very successful methods of carbon–carbon coupling is the palladium catalyzed reaction of aryl halides, benzyl halides or allyl halides with an aryl- or vinylboronic acid well known as Suzuki coupling [4]. In a review by Miyauri and Suzuki [5] with more than 500 references, we found only three examples for the use of an aqueous phase [6–8].

Recently, Beller et al. [9] published the effectively catalyzed reaction of *p*-bromoacetophenone with phenylboronic acid at 78°C with turnover numbers of up to 9000. Dibowski [10]

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Scheme 1. (i) 15 mmol $\text{PhB}(\text{OH})_2$; 13.5 mmol *p*-iodoanisole; toluene/ethanol/water (15/15/15, v/v/v), substrate/catalyst = 1350; 0.01 mmol $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$; detergents, 45 mmol Na_2CO_3 ; 24 h, 78°C.

in the group of Schmidtchen found that the reaction between iodoisophthalic acid and *p*-methoxyphenylboronic acid can be catalyzed by 5 mol% of a palladium *m*-dialkylguanidinoaryl

phosphine complex under very mild conditions (35°C). Two groups [11–15] submitted excellent Suzuki couplings with ligand-free palladium catalysts in presence of surfactants. Sometimes,

Table 1

Variation of detergents in the Suzuki reaction of 15 mmol phenylboronic acid and 13.5 mmol *p*-iodoanisole (*p*-iodoanisole/detergent = 4; conditions see Scheme 1)

Entry	Detergent	Abbreviation	Yield (%)	
			60 (min)	360 (min)
1	Without	D = 0	65	75
2	Benzyltrimethylammonium bromide	BzMe ₃ NBr	70	86
3	Tetra- <i>n</i> -butylammonium bromide	Bu ₄ NBr	73	88
4	Cetylammonium tetrafluoroborate	CNH ₃ BF ₄	20	47
5	Polyoxyethylen(16)methyl ester C ₁₂	E ₁₆ OMe	74	95
6	Dodecyltrimethylammonium bromide	DTAB	84	94
7	3-Dodecyldimethylammonium propane sulfonate	C ₁₂ Me ₂ N(CH ₂) ₃ SO ₃	89	94
8	<i>N</i> -Dodecylpyridinium chloride	C ₁₂ PyCl	80	95
9	Sodium dodecansulfate	SDS	86	92
10	<i>N</i> -Lauroyl-alanine, sodium salt	<i>N</i> -Lau-ala	85	89
11	<i>N</i> -Lauroyl-proline, sodium salt	<i>N</i> -Lau-pro	84	89
12	Polyoxyethylen(20)sorbitanmonolaurate	Tween 20	78	86
13	Polyoxyethylen(6)lauryl ether	E ₆ C ₁₂	67	75
14	Polyoxyethylen(10)lauryl ether	E ₁₀ C ₁₂	70	78
15	Polyoxyethylen(23)lauryl ether C ₁₆	E ₂₃ C ₁₂	88	91
16	Cetyltrimethylammonium bromide	CTAB	98	99
17	Cetyldimethylethylammonium bromide	CMe ₂ EtNBr	89	94
18	Cetyltrimethylammonium tetrafluoroborate	CMe ₃ NBF ₄	77	92
19	Cetyltrimethylammonium sulfate	CMe ₃ NSO ₄ H	78	91
20	3-Cetyldimethylammonium propane sulfonate	CMe ₂ N(CH ₂) ₃ SO ₃	90	98
21	Sodium hexadecyl sulfate	SCS	85	88
22	Sodium hexadecansulfonate	CSO ₃ Na	81	91
23	<i>N</i> -Cetylpyridinium chloride	CPyCl	72	90
24	<i>N</i> -Cetylpyridinium bromide	CPyBr	77	92
25	Polyoxyethylen(23)hexadecyl ether	E ₂₃ C ₁₆	81	86

the surfactants formed microemulsions and, in other cases, the amphiphile had the function as phase transfer reagent. In a paper by Darses et al. [16], highly activated phenyldiazonium tetrafluoroborates were used instead of haloarenes. One example is given with palladium(II) acetate as precursor of a catalyst and water as medium. The reaction occurs at ambient temperature with 100% conversion and 45% yield of the target product. In several groups, the cross-coupling reactions of phenylboronic acid and bromoarenes or chloroarenes were carried out in polar organic solvents with nickel(0) or palladium(0) catalysts and sometimes in the presence of amphiphilic [17,18]. As a rule, chloroarenes are easily available as technical products but are less active in C–C coupling reactions [19–21].

In a first communication [22], we presented some results about Suzuki cross-coupling reactions in a micellar and alternatively in a two-

phase system. The micellar system could be optimized with tetraalkylammonium hydroxides as base but the two-phase system was superior with respect to activity and selectivity [23].

Now, we want to submit investigations under the two-phase conditions (water/ethanol/toluene = 1/1/1; v/v/v) with a water-soluble palladium phosphine complex as catalyst.

2. Experimental

The chemicals were purchased from Aldrich, Fluka or Lancaster. All preparations were performed in oxygen-free solvents under an argon atmosphere.

The ^1H and ^{13}C NMR spectra were recorded on Bruker Spectrometer AC 250 and ARX 300 in CDCl_3 as solvent. IR spectra were obtained on a Nicolet Magna 550 as KBr disk or in nujol

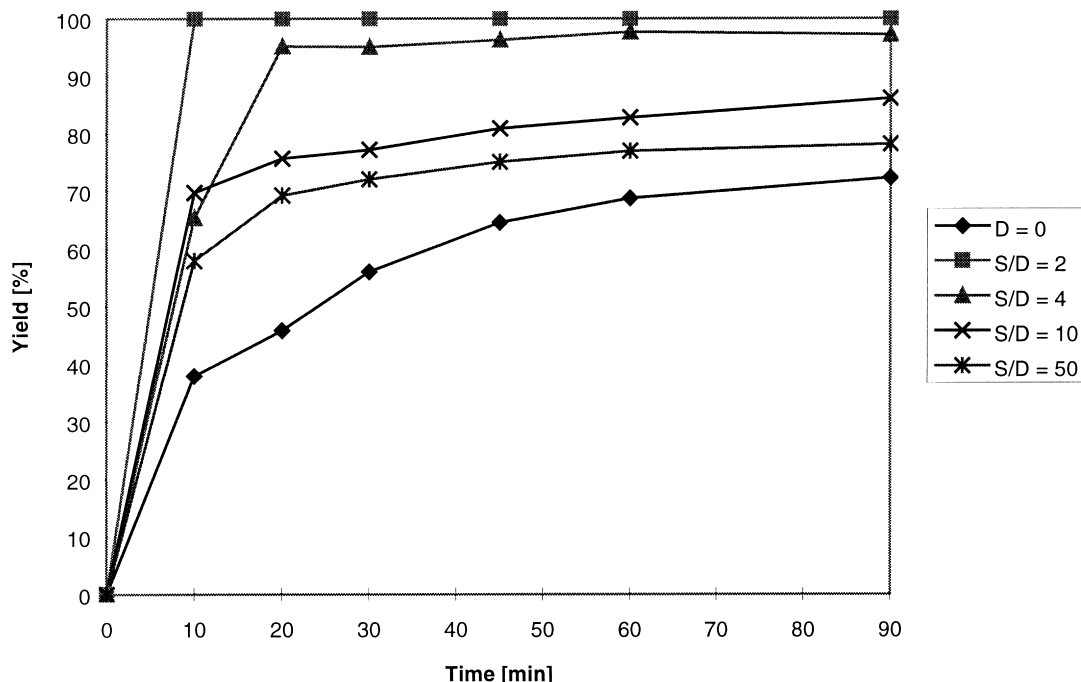


Fig. 1. Dependence on the CTAB concentration (Suzuki reaction of 15 mmol phenylboronic acid and 13.5 mmol *p*-iodoanisole with 0.01 mmol $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$ at 78°C in toluene/ethanol/water = 15/15/15 (v/v/v) as well as different ratios of *p*-iodoanisole/CTAB = S/D and 45 mmol Na_2CO_3).

mult. The mass spectrometry was performed on an AMD 402/3.

2.1. Example of the procedure of C–C-coupling

In two separate Schlenk tubes, *p*-iodoanisole (3.20 g, 13.5 mmol) was dissolved in 15 ml toluene and phenylboronic acid (1.83 g, 15 mmol) was dissolved in 15 ml ethanol. Sodium carbonate decahydrate (11.6 g, 45 mmol) and cetyltrimethylammonium bromide (1.27 g, 3.38 mmol) were placed in a 100 ml water thermostatted flask and dispersed in 15 ml of water. The solutions of *p*-iodoanisole and phenylboronic acid were added and the first sample was taken. Then, the reaction mixture was heated at 78°C and the catalyst $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$ (9 mg, 0.01 mmol) was added under vigorous stirring (> 1000 r.p.m.). 0.20 ml samples were taken after 10, 20, 30, 45, 60, 90, 120, 180... min, diluted with 0.8 ml toluene,

dried with sodium sulfate, analyzed by GLC (column HP 1; program: 2 min at 50°C then 10°C/min up to 260°C) [22].

After the reaction was finished, the mixture was extracted with toluene, the organic phase was dried with sodium sulfate, the solvent removed and the residue dissolved in hexane. The product was purified by column chromatography (silica gel, e.g., *n*-heptane/ethyl acetate = 7/1). All products were analytically characterized [23] with elementary analysis, GC, GC–MS, IR, ^1H NMR and ^{13}C NMR and also compared with commercially available compounds.

3. Results and discussion

We used a palladium complex of the type PdCl_2L_2 either in an isolated and well characterized form or prepared in situ. The ligand L was preferably the phosphine $\text{Ph}_2\text{P}(\text{CH}_2)_4$ -

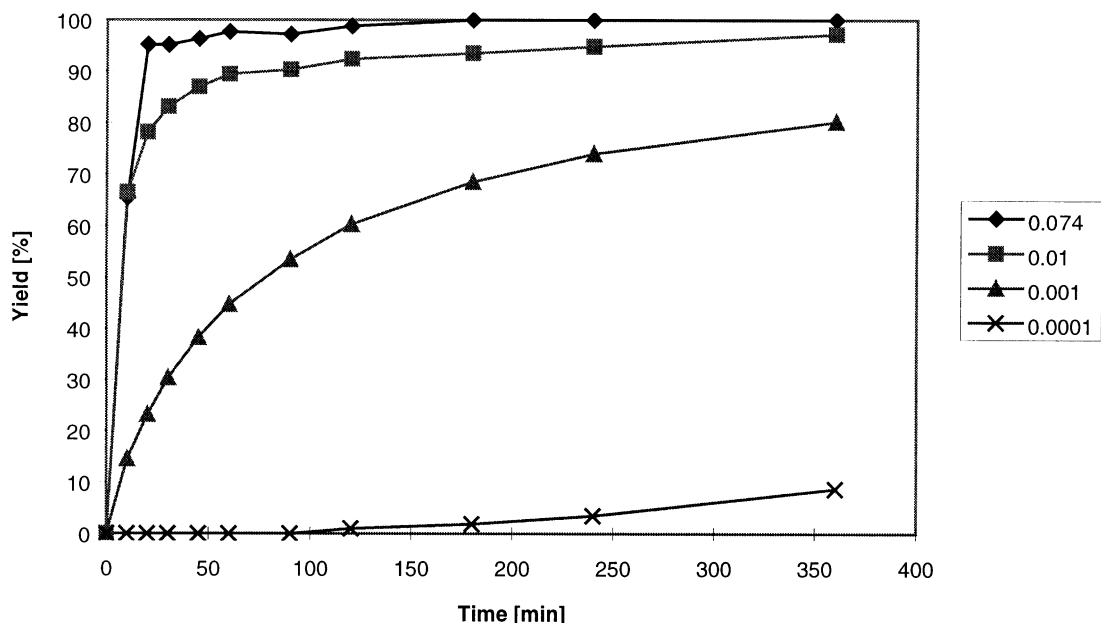


Fig. 2. Variation of the catalyst concentration (Suzuki reaction of 15 mmol phenylboronic acid and 13.5 mmol *p*-iodoanisole with different mmol $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$ at 78°C in toluene/ethanol/water = 15/15/15 (v/v/v) as well as *p*-iodoanisole/CTAB = 4 and 45 mmol Na_2CO_3 . The relative concentration of catalyst is given in mol percent with respect to *p*-iodoanisole).

SO₃K, which was synthesized in our laboratory some years ago [24] but used in comparison to the well known trisulfonated triphenylphosphine (TPPTS) and the monosulfonated triphenylphosphine (TPPMS). All three phosphines gave almost similar results. A systematic investigation of the influence of different water-soluble phosphines will be given in a subsequent paper.

The coupling of phenylboronic acid with *p*-iodoanisole in accordance to Scheme 1 without any surfactant leads to 70% *p*-methoxybiphenyl and 10 to 5% biphenyl after 24 h at 78°C.

We found an acceleration of the reaction by the use of typical phase transfer reagents and other amphiphiles [23]. An effect could be indicated by cationic, anionic, zwitterionic and non-ionic detergents. Table 1 displays the conversion in dependence on the type of the detergent at 78°C. We selected amphiphiles with C₁₂ and C₁₆ hydrocarbon chains, although even tetrabutylammonium bromide and benzyltrimethylammonium bromide gave an effect.

Obviously, all amphiphiles promoted the reaction. The efficiency is given in Table 1 as conversion after 60 min and after 360 min. Most of the amphiphiles finally gave yields of > 90% except cetyltrimethylammonium tetrafluoroborate (entry 4) which inhibits the reaction. Even the short chain amphiphiles (entries 2 and 3) and amphiphiles with low HLB (hydrophilic lipophilic balance) (entries 5, 10–14) gave lower activities. In the case of tetraalkylammonium salts, there is a dependence on the anion (entries 6, 7, 16–20). In our investigations, the cetyltrimethylammonium bromide was favored as phase transfer reagent (entry 16), but also zwitterionic amphiphiles, e.g., alkyldimethylammonium propane sulfonates (entries 7 and 20) are excellent promoters.

Besides, an activation as a second achievement has been observed as an enhancement of the selectivity by the addition of detergents. The formation of the side product biphenyl **4** was almost suppressed and could not be detected.

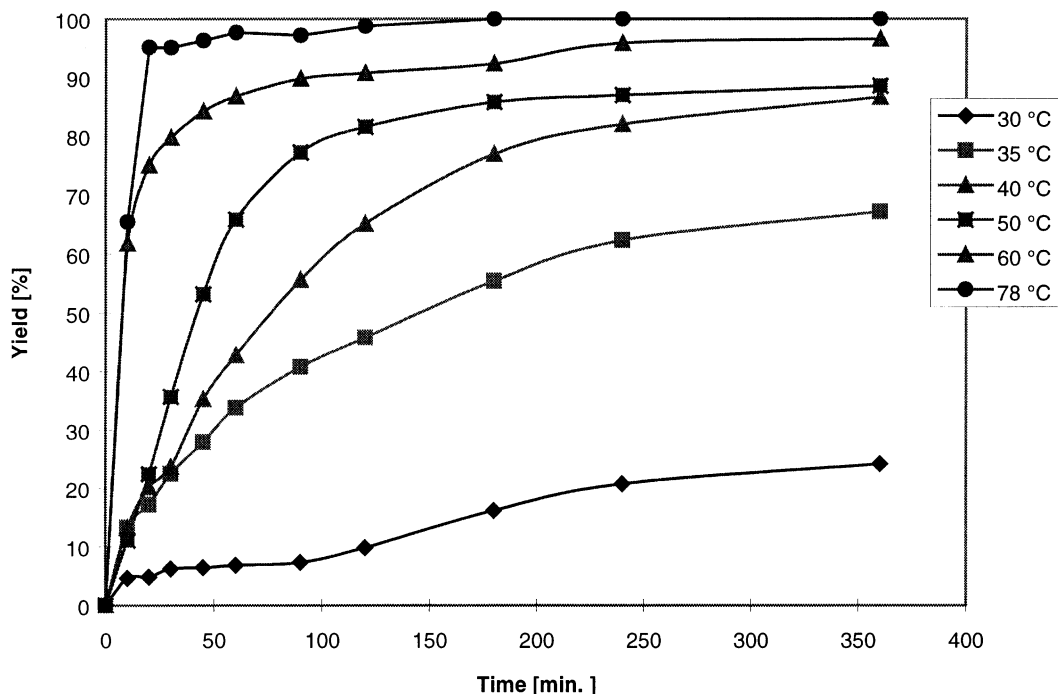


Fig. 3. Dependence on the temperature (Suzuki reaction of 15 mmol phenylboronic acid and 13.5 mmol *p*-iodoanisole with 0.01 mmol PdCl₂[Ph₂P(CH₂)₄SO₃K]₂ at different temperature in toluene/ethanol/water = 15/15/15 (v/v/v) as well as *p*-iodoanisole/CTAB = 4 and 45 mmol Na₂CO₃).

The reproducibility was determined with CTAB in four runs (substrate/detergent = 4) and gave about 10% deviation during the first 10 min and less than 5% after 30 min.

The dependence of the conversion on the time and on the ratio substrate/detergent (S/D) in the Suzuki coupling of **1** and **2** is shown in Fig. 1. Already, 2 mol% (S/D = 50) of CTAB has an effect in comparison to the experiment without detergent (D = 0) and there is an increase of the reaction rate with increasing amounts of detergent.

With 50 mol% of CTAB (S/D = 2), the reaction is almost finished after 10 min and gave a conversion to more than 99% Suzuki product. No biphenyl **4** could be observed, but it should be mentioned that the isolation of the product is more difficult in the presence of high concentration of the detergent. The best separation was attained by chromatography over a short column with silica. But we will rationalize this problem in the future.

Fig. 2 demonstrates the reaction rate in the presence of different amounts of the palladium

Table 2

Variation of educts in the Suzuki reaction (halogene compound/CTAB = 4; conditions see Scheme 1)

Entry	Educts 1	Arylboronic acid 2	Time (min)	Yield 3 (%)	Ref.
1	Iodobenzene	Phenylboronic acid	90	99	
2	2-Iodotoluene	Phenylboronic acid	180	99	
3	3-Iodotoluene	Phenylboronic acid	60	99	
4	4-Iodotoluene	Phenylboronic acid	10	99	
5	4-Iodohydroxybenzene	Phenylboronic acid	1440	99	
6	4-Iodoaniline	Phenylboronic acid	360	98	
7	2,6-Dimethyliodobenzene	Phenylboronic acid	480	99	
8	4-Iodonitrobenzene	Phenylboronic acid	60	99	
9	4-Iodoanisole	Phenylboronic acid	180	99	
10	Allyliodide	Phenylboronic acid	240	99	
11	2-Bromopyridine	Phenylboronic acid	1440	88	
12	Bromobenzene	Phenylboronic acid	180	99	
13	2-Bromotoluene	Phenylboronic acid	1440	98	
14	3-Bromotoluene	Phenylboronic acid	240	99	
15	4-Bromotoluene	Phenylboronic acid	360	99	
16	4-Bromoanisole	Phenylboronic acid	360	99	
17	4-Bromoaniline	Phenylboronic acid	480	73	
18	4-Bromoacetophenone	Phenylboronic acid	20	99	
19	Allylbromide	Phenylboronic acid	240	99	
20	4-Chlorobenzotrifluoride	Phenylboronic acid	1440	24	
21	Benzylchloride	Phenylboronic acid	60	99	
22	2-Chloropyridine	Phenylboronic acid	1440	59	
23	1-Chloromethylnaphthaline	Phenylboronic acid	360	89	
24	3-Chlorobenzonitrile	Phenylboronic acid	2880	10	[25]
25	2-Chlorobenzonitrile	Phenylboronic acid	1440	7	[26]
26	Allylchloride	Phenylboronic acid	360	17	
27	4-Iodoanisole	Phenylboronic acid	180	99	
28	4-Iodoanisole	2-Tolylboronic acid	90	99	[27]
29	4-Iodoanisole	4-Tolylboronic acid	360	99	[27]
30	4-Iodoanisole	3-Nitrophenylboronic acid	1440	99	[28]
31	4-Iodoanisole	3-Fluorophenylboronic acid	120	99	[29]
32	4-Iodoanisole	2,4-Dichlorophenylboronic acid	10	99	
33	4-Iodoanisole	1-Naphthylboronic acid	10	99	[30]
34	4-Iodoanisole	Butylboronic acid	1440	no reaction	

catalyst $\text{PdCl}_2[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{SO}_3\text{K}]_2$. The relative concentration is given in mol percent with respect to *p*-iodoanisole as educt. A significant effect could be found already below 0.001 mol%. Our standard amount is 0.01 mol% and would be sufficient for an optimized process. The turnover number (TON) was 9,500 in this system, in the diluted system with 0.001 mol% > 78,000. In our experience, the ligand-free palladium-catalyzed Suzuki coupling is less active than our system.

The reaction strongly depends on the temperature (Fig. 3). We decreased the temperature stepwise down to 30°C and conclude in accordance with Fig. 3 the need for at least 50°C for a successful progress. A reaction temperature above 78°C demands another alcohol than ethanol as phase mediator.

Table 2 contains all educt combinations investigated in our laboratory. Basis of these data are time-conversion curves as given in Figs. 1–3. We measured the shortest time to attain the maximum yield. In contradiction to Badone et al. [15], we found the best reactivity for iodocompounds as aromatic and unsaturated haloeducts. All of the products are known, but the less-common compounds were characterized by a reference [25–30].

Iodotoluenes (entries 2–4) are more reactive than iodobenzene (entry 1) and even 4-iodonitrobenzene (entry 8), that means there is no activation according to Hammett's σ -constants. Beller et al. [9] made a similar observation and concluded that the oxidative addition of the halogenoarenes to the palladium catalyst cannot be the rate determining step. 4-Iodophenol (entry 5) reacted slowly with phenylboronic acid and the Suzuki product had to be converted with trimethylsilyldiazomethane for the detection in glc. Even 2,6-dimethyliodobenzene (entry 7) is decreased in the reactivity, probably because of the steric effect.

Allyliodide, allylbromide and allylchloride (entries 10, 19, 26) were successful as educts but with clearly decreasing activity and conversion. Most of the bromocompounds gave good con-

versions but lower rates than the analogous iodocompounds.

Obviously, most interesting as educts in an industrial scale are the chlorocompounds. Unfortunately, only benzylchlorides (entries 21 and 23) gave satisfying results, whereas allylchloride (entry 26) and chloroarenes (entries 20, 24 and 25) led to low conversions.

2-Chloropyridine (entry 22) was slightly less active than 2-bromopyridine (entry 11). Therefore, this could be a convenient way to substituted 2-phenylpyridines.

The last part of Table 2 (entries 27–34) shows some results with modified phenylboronic acids. Most combinations with 4-iodoanisole were successful except butyl boronic acid (entry 34), which gave no reaction. Surprisingly, no dependence of the reactivity on sterical or electronic effects is perceptible, and perhaps the distribution between aqueous and organic phases plays a decisive role.

4. Conclusions

The carbon–carbon bond formation starting from haloarenes, benzylhalides or allylhalides, and different kinds of arylboronic acids gave, in the presence of water-soluble palladium complexes as catalysts and amphiphiles as phase transfer reagents, satisfying or excellent results in a two-phase system containing water and toluene as phases and ethanol as phase mediator. The reactivity sequence of the halocompounds is $\text{I} > \text{Br} \gg \text{Cl}$. Also, the aryl boronic acids show a dependence on the structure of the aryl group. Whereas the water-soluble palladium complex was in most experiments dichloro-bis[diphenyl-4-(potassium butane sulfonato)-phosphine]palladium(II), the type of the investigated surfactants was varied in a wide range. The method can compete with the reaction in a homogeneous system and gives more convenience in the separation of products and catalyst. In comparison to two-phase systems with ligand-free catalysts, we observe a higher activ-

ity and selectivity with respect to the Suzuki coupling product (suppressing of self coupling of the arylboronic acid).

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