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Suzuki Reaction with Aryl Bromides  
at Room Temperature in the Presence  
of a Simple “Ligand-Free” Catalytic System

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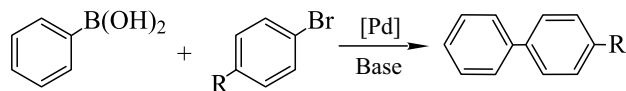
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**Abstract**—Possibility was examined of using the simplest catalytic system (palladium salt and NaOH) in ethanol or in a mixture of ethanol and water as a catalyst precursor in order to obtain high product yields in the Suzuki reaction with nonactivated aryl bromides at room temperature without an inert atmosphere or ligand additives.

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The Suzuki–Miyaura reaction, more frequently named the Suzuki reaction in the literature, is one of the most intensively studied palladium-catalyzed reactions for coupling of aryl halides:



where R = H, C(O)H, OCH<sub>3</sub>.

Owing to the broad spectrum of possible reagents and high selectivity, this reaction has a huge potential for use in the fine organic synthesis and, in particular, in the pharmaceutical industry [1–4].

Despite the large number of publications devoted to the Suzuki reaction, the problem of involving poorly reactive, but accessible aryl bromides and aryl chlorides in the reaction under mild conditions still remains topical. The necessity for performing the reaction under as mild conditions as possible is dictated by the need to reach high selectivities and to enable use of thermally unstable substrates. This problem is mostly solved by making catalytic systems more complex by addition of difficultly accessible donor ligands, which are commonly toxic and highly sensitive to moisture and atmospheric oxygen. More practically attractive in this context are the so-called “ligand-free” catalytic systems, which, in case of a sufficient activity, are capable of

markedly simplifying the conditions in which the reaction is performed (no inert atmosphere is required) and its target products are isolated and substantially diminishing the cost of components of the catalytic system itself.

There is a small number of published examples of carrying out the Suzuki reaction with nonactivated aryl bromides at room temperature by using “ligand-free” catalytic systems [5–10]. However, these systems are not devoid of disadvantages. For example, they use labor-consuming in synthesis and moisture-sensitive alcoholates of alkali metals [7] as a base and ethylene glycol monomethyl ether serving as a solvent does not belong to frequently used solvents [10]. The system suggested in [8] is free of these shortcomings, but a long time (up to 48 h) is required for reaching high product yields.

This communication reports a simple catalytic system based on palladium(II) chloride as the catalyst precursor, technical-grade ethanol as the solvent, and an alkali as the base. With the main factors determining its catalytic activity revealed, it became possible to perform the Suzuki reaction with nonactivated aryl bromides at room temperature in the course of 1 h without using an inert atmosphere or ligand additives.

## EXPERIMENTAL

All the experiments were carried out in air. In a typical

experiment, a glass reactor with a rubber membrane was charged with 10 ml of 95% technical-grade ethanol or its mixture with water (4 : 1 volume ratio), 10 mmol of bromobenzene, 2 mmol of naphthalene (internal standard for GLC), and 13 mmol of NaOH (in the case of ethanol) or 12 mmol of NaOH (in the case of the ethanol–water mixture). To preclude the heating upon addition of NaOH, the reaction vessel was left for a certain time to be agitated with a magnetic rabble in a water bath thermostated at the reaction temperature (22°C). After that the reaction was commenced by addition of 10 mmol of phenylboronic acid and 0.16 mmol (1.6 mol %) of palladium chloride. The experimental conditions different from those described above are specified in the tables and figure captions.

For a GLC analysis, 0.15 ml of a mixture of toluene and water (4 : 1 volume ratio) was added to periodically taken 0.1-ml samples of the reaction solution in order to extract organic substances. The toluene layer was analyzed on an HP-4890 gas-liquid chromatograph with a flame-ionization detector and a 15-m-long capillary column with 15% polyphenylsiloxane as the fixed phase. The analysis was made with programmed heating from 100 to 250°C. The quantitative composition of the samples was calculated by the internal standard method (with naphthalene as the internal standard). The yield of the product was calculated relative to the theoretically possible value. The reaction rate was determined by graphical differentiation of stationary portions of kinetic curves.

As a model Suzuki reaction served the reaction of phenylboronic acid with bromobenzene, a typical representative of nonactivated aryl bromides. In all the experiments at 22°C, the conversion of bromobenzene at various instants of time coincided with the yield of diphenyl. This completely rules out any possibility of a reductive homocoupling of aryl bromide and oxidative homocoupling of arylboronic acid, observed under more severe reaction conditions. It should be noted that, owing to the kinetic control over the reaction, the reaction durations represented in the tables correspond to the time during which the concentrations of the reactants and products varied. Thus, it reflects the operation time of the catalytic system.

Analysis of published data shows that alcohols are solvents typically used when performing the Suzuki reaction both under ligand-free conditions [7, 8] and with addition of organic ligands [11, 12]. Therefore,

**Table 1.** Effect of the solvent nature on the catalytic activity in the Suzuki reaction

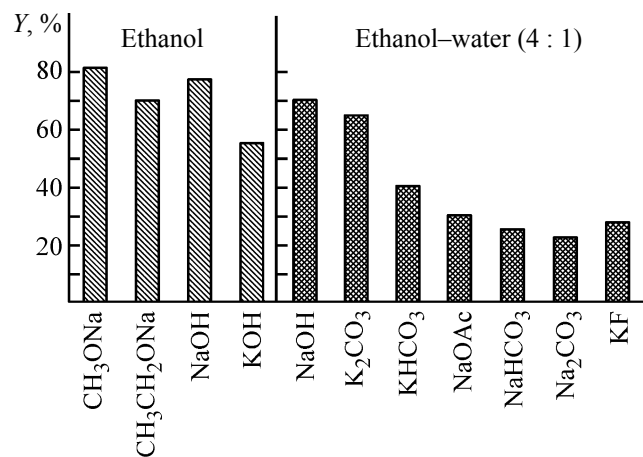
Run no.	Solvent (volume ratio)	Reaction duration, min	Yield of diphenyl, %
1	Ethanol	43	75
2	Ethanol–water (4:1)	55	70
3	Water	90	30
4	DMFA	1000	5
5	DMFA–ethanol (1:1)	1440	22
6	DMFA–ethanol (1:9)	1560	37
7	DMFA–ethanol–water (2:2.5:0.5)	2760	18.8
8	Toluene	1000	
9	Toluene–water–ethanol (5:1:4)	76	56
10	Toluene–water (5:1)	1200	52
11	Toluene–water (1:1)	90	3

the simplest ligand-free catalytic system based of palladium(II) chloride as catalyst precursor and NaOH was tested in ethanol from the very beginning.

The use of ethanol or a mixture of ethanol with water in a 4 : 1 ratio made it possible to obtain the product in high yields (Table 1, run nos. 1 and 2). It should be noted that raising the fraction of water led to stratification of the reaction mixture into two phases, with the yields of the products markedly decreasing. Despite there are reports in the literature about performing the Suzuki reaction with aryl bromides in water [13, 14], it was impossible to obtain the product in high yields by using a ligand-free palladium chloride in an aqueous medium at room temperature (Table 1, run no. 3).

*N,N*-Dimethylformamide (DMFA) is conventionally used as a solvent or a component of a solvent when performing the Suzuki reaction at elevated temperatures [15–17]. In this case, the yield of the coupling product did not exceed 5% even on making the reaction longer. In coupling with ethanol and water, a satisfactory yield was not reached, either (Table 1, run nos. 4–7).

There are published examples of carrying out the Suzuki reaction in toluene [18, 19], including that with addition of water [20–22]. The use of toluene or its mixtures with water as a solvent at room temperature resulted in that the solution became very thick in the first minutes of the reaction. This is possibly due to formation



**Fig. 1.** Effect of the base nature on the product yield  $Y$  in the Suzuki reaction at a reaction duration of 4 h.

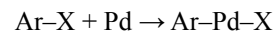
of branched 3D structures containing a B–OH bond. In this case, high conversions or product yields were not observed (Table 1, run nos. 8–11).

Because the product yields are substantially higher in the case of ethanol or its mixtures with water, compared with other systems of solvents, these two systems were used for further optimization.

As follows from Fig. 1, the base nature can strongly affect the yield of products in the Suzuki reaction with bromobenzene in an ethanolic medium. Good results were obtained in absolute ethanol, with sodium methylate or ethylate as bases. However, as already noted, a disadvantage of bases of this kind is the sensitivity to moisture and need to dry the reagents and solvent. At the same time, using a considerably more accessible and convenient-in-use sodium hydroxide as a base led to comparable product yields not only in nondehydrated 95% technical-grade ethanol, but also in its mixtures with water. It should be noted, in addition, that the true reaction time during which the product was accumulated in the case of NaOH was substantially shorter (40–55 min), compared with other bases.

With palladium chloride and sodium hydroxide used in an ethanolic medium at room temperature, it was impossible to obtain significant conversions of aryl chlorides. However, the reaction with aryl bromides, including those in the deactivated state, provided high yields of the target products (Table 2, run nos. 1–3).

A most important stage of the catalytic cycle of the Suzuki reaction is the oxidative addition of an aryl halide to palladium:



The key importance of this stage is determined by the fact that it is responsible for the competition of the main catalytic cycle of the reaction with the undesirable process of aggregation of unstable Pd compounds. It has been shown previously for the related Heck reaction (coupling of aryl halides with alkenes) that raising the concentration of an aryl halide, which favors a more successful competition of the oxidative addition with the aggregation of palladium, leads to a substantial increase in the yield of products, to the point of its becoming quantitative [23, 24]. Raising the concentration of bromobenzene in the Suzuki reaction in ethanol also led to a rise in the yield of the product (Table 2, run nos. 3–5). In this case, the excess of an aryl halide makes it possible to substantially reduce the load on the catalyst, with the yields remaining high. With, however, the reaction performed in the ethanol–water medium, raising the concentration of an aryl bromide led to only a slight rise in the yield. Moreover, the yield became higher under conditions of aryl bromide deficiency (Table 3). However, this was accompanied by an increase in the reaction duration. This experimental fact is indicative of a possibly weaker adverse effect of the agglomeration of reduced palladium on the catalytic activity of the Suzuki reaction, compared with the Heck reaction, in agreement with the hypothesis of an important contribution by the heterogeneous catalysis mechanism [25].

From the practical standpoint, use of excess amounts of a reagent is undesirable. In this case, it is at least necessary to perform an additional procedure for utilization of the unreacted reagent or to develop methods for its recycling into the reaction. It should be noted, nevertheless, that the sensitivity of the Suzuki reaction to the amount of an aryl halide may be an important

**Table 2.** Effect of the aryl halide nature on the product yield in the Suzuki reaction in ethanol

Run no.	Aryl halide, equiv.	Reaction duration, min	Yield of diphenyl, %
1	<i>n</i> -BrPhC(O)H, 1	60	67
2	<i>n</i> -BrPhOCH <sub>3</sub> , 1	90	54
3	PhBr, 1	43	75
4	PhBr, 2	85	78
5	PhBr, 3	76	100

**Table 3.** Effect of the amount of bromobenzene on the product yield in the Suzuki reaction in the ethanol–water system (4 : 1)

Run no.	PhBr, equiv.	Reaction duration, min	Yield of diphenyl
1	0.5	270	100
2	1	5	70
3	2	90	75
4	3	132	86

**Table 4.** Effect of the catalyst precursor nature on the product yield in the Suzuki reaction in ethanol

Run no.	Catalyst precursor, mol %	Reaction duration, min	Solvent	Yield of diphenyl, %
1	Pd(acac) <sub>2</sub> , 1.6	40	EtOH–H <sub>2</sub> O (4 : 1)	88
2	PdCl <sub>2</sub> , 1.6	55	EtOH–H <sub>2</sub> O (4 : 1)	70
3	PdCl <sub>2</sub> , 0.16	60	EtOH–H <sub>2</sub> O (4 : 1)	50
4	Pd(acac) <sub>2</sub> , 1.6	80	EtOH	62
5	Pd(OAc) <sub>2</sub> , 1.6	50	EtOH	67
6	PdCl <sub>2</sub> , 1.6	43	EtOH	75
7 <sup>a</sup>	PdCl <sub>2</sub> , 0.16	115	EtOH	90
8 <sup>a</sup>	PdCl <sub>2</sub> , 0.016	195	EtOH	62

<sup>a</sup> PhBr, 3 equiv.

factor in optimization of the reaction conditions in the case of other substrates.

Application of various palladium salts as the catalyst precursor for the Suzuki reaction in ethanol or aqueous-ethanolic medium affected the yield of the product only slightly. The somewhat higher yield of the product with palladium bisacetylacetonate [Pd(acac)<sub>2</sub>] as the catalyst precursor was obtained because of the higher reaction rate (Table 4, run no. 1), which may be due to the ease of Pd(acac)<sub>2</sub> reduction in an ethanolic solution of the alkali.

Making smaller the amount of the catalyst caused a decrease in the yield (Table 4, run no. 3). However, the yield of the reaction at an excess of bromobenzene was satisfactory even with 0.016 mol % palladium (Table 4, run nos. 7 and 8). Thus, taking a smaller amount of the catalyst made it possible to raise both the catalyst turnover frequency (TOF) and turnover number (TON).

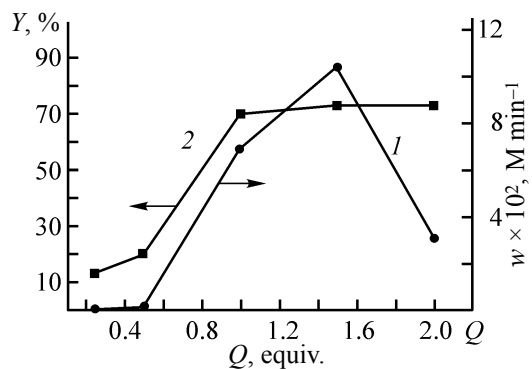
It was found that varying the amount of phenylboronic acid even within a comparatively narrow range of

concentrations affects the catalytic activity in the Suzuki reaction. For example, changing the amount of the acid from 0.5 to 1.5 equiv. resulted in that the reaction rate increased nearly 100-fold, which approximately corresponds to a fourth kinetic order of the reaction with respect to phenylboronic acid. At the same time, further increase in the amount of the acid led to a sharp decrease in the reaction rate and, consequently, to a negative reaction order (Fig. 2).

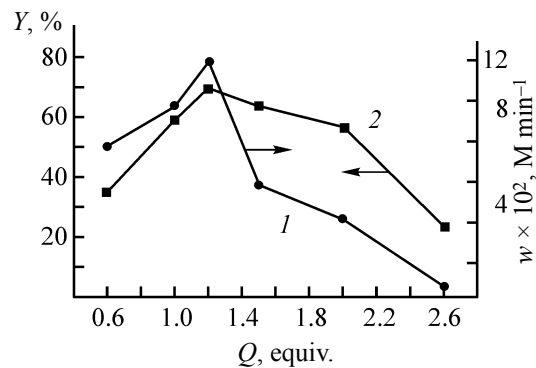
The so high sensitivity of the reaction rate to the amount of the acid cannot be accounted for only by its effect in the stage of the main catalytic cycle and, in all probability, is due to involvement of phenylboronic acid in catalyst conversion processes outside this cycle (formation and deactivation of the active catalyst).

As demonstrated by analysis of the available published data, the overwhelming majority of researchers used a considerable excess of the base with respect to the substrate (2–3 equiv. and more). However, it follows from Figs. 3 and 4 that, with sodium hydroxide used as a base at room temperature, the optimal amount of the base is substantially lower (1.2–1.3 equiv.). The dependences of both the reaction rate and the product yield on the amount of the base pass through a maximum. It is important to note that use of sodium hydroxide from different manufacturers resulted in a certain variation of the amount of the base, necessary for reaching the maximum reaction rate and product yield. However, its optimal value never exceeded a value of 1.5 equiv. in terms of the substrate.

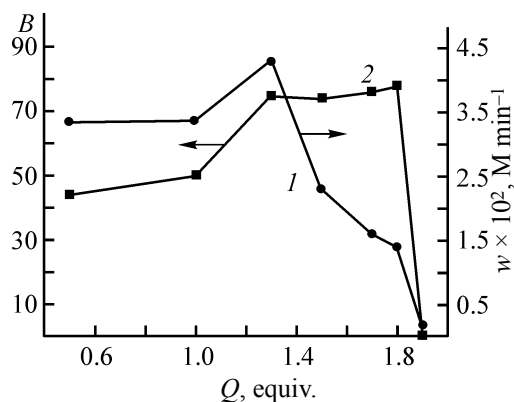
It follows from the data presented above that slight changes in the amount of the base relative to the optimal value may lead, among other things, to a full termination of the reaction. As also in the case of the effect of the



**Fig. 2.** (1) Suzuki reaction rate  $w$  and (2) product yield  $Y$  vs. the amount  $Q$  of phenylboronic acid in the ethanol–water medium (4 : 1).



**Fig. 3.** (1) Suzuki reaction rate  $w$  and (2) product yield  $Y$  vs. the amount  $Q$  of NaOH in the ethanol–water medium (4 : 1).

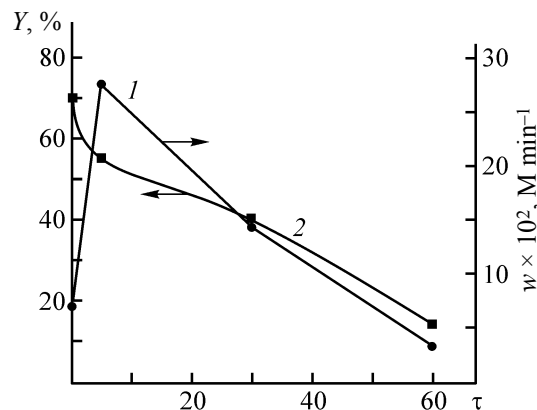


**Fig. 4.** (1) Suzuki reaction rate  $w$  and (2) product yield  $Y$  vs. the amount  $Q$  of NaOH in ethanol.

amount of phenylboronic acid on the reaction rate, the high sensitivity of the catalytic activity to the amount of the base can hardly be due only to its influence on stages of the catalytic cycle.

As evidence in favor of this conclusion can be regarded results of experiments in which the catalyst precursor ( $\text{PdCl}_2$ ) was for a certain time agitated in an ethanolic solution of the alkali and then all the remaining components of the Suzuki reaction were added to the solution. The dependence of the reaction rate on the time of preliminary mixing of palladium chloride with the alkali passed through a maximum, whereas the yield of the reaction product steadily decreased (Fig. 5).

Thus, the base can adversely affect the catalytic activity. The rise in the rate upon a 5-min contact with the alkali solution can be attributed to an increase in the amount of the active catalyst that is formed by the time of introduction of the rest of the reagents. However, the large amount of the active catalyst also objectively promotes, especially in the absence of a substrate, development of deactivation processes. As a result,



**Fig. 5.** (1) Suzuki reaction rate  $w$  and (2) product yield  $Y$  vs. the time  $\tau$  of preliminary mixing of  $\text{PdCl}_2$  with NaOH in the ethanol–water medium (4 : 1).

on making longer the time of contact with the alkali solution, the concentration of the active catalyst may decrease by the instant of the reaction onset, which affects the reaction rate and yield of the products.

## CONCLUSIONS

(1) Use of a simple ligand-free catalytic system makes it possible to perform the Suzuki reaction with nonactivated aryl bromides under mild conditions.

(2) The main factors determining the catalytic activity in the system under study are the amounts of arylboronic acid and a base. The optimal amount of the base is as small as 1.2–1.5 equiv., whereas using 2 equiv. of the base and more, commonly reported in the literature, results in a sharp decrease in activity, to the point of complete termination of the reaction.

## ACKNOWLEDGMENTS

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