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Comparative Activity of Aryl, Alkyl, and Cycloalkyl Halides in the Suzuki Reaction Catalyzed with Acyclic Diaminocarbene Complex of Palladium

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Abstract—Relative activity of halogenated arenes, alkanes, and alkanes in the Suzuki reaction catalyzed with acyclic diaminocarbene complex of palladium has been investigated. Under all the investigated conditions, 4-iodoanisole has been more active than the alkyl halides. The reaction with 4-methyl-1-(chloromethyl)benzene has afforded the target 4-methyl-1-(phenylmethyl)benzene along with significant amount of by-products; other alkyl and cycloalkyl halides do not participate into the cross-coupling reaction. Ethanol has been found the most suitable solvent for the reaction. The reaction in acetonitrile provides noticeable yield of the products only in the presence of polyethylene glycol and water.

Keywords: the Suzuki reaction, acyclic diaminocarbene complex of palladium, organic halide

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Over the recent decade, acyclic diaminocarbene complexes of palladium (Pd-ADC) have attracted emerging attention as catalysts [1, 2]: they have appeared a suitable alternative to the well known heterocyclic carbene complexes (Pd-NHC) [3] due to simplicity of their one-step preparation from bis(isocyanide) palladium complexes and *N*-nucleophiles [1, 4, 5]. The Pd-ADC complexes catalyze various cross-coupling reactions of aryl halides, such as the Suzuki reaction [6–8], the Sonogashira reaction [6, 9–13], the Heck reaction [6, 14], and the Buchwald–Hartwig reaction [14].

The Suzuki reaction is among the most important reactions of C–C cross-coupling in organic synthesis [15–19]. It is most often used for synthesis of unsymmetrical biaryls. Alkyl halides have been rarely used in this reaction as substrates [20, 21], and the information on this reaction involving cycloalkyl halides has been lacking. On top of that, data on comparative activity of aryl and alkyl halides is absent in the literature to the very best of our knowledge. In view of that, the present work aimed to compare the activity of various organic halogenated derivatives **1**–**7** in the Suzuki reaction catalyzed with acyclic diaminocarbene complex of palladium(II) **8** (Scheme 1).

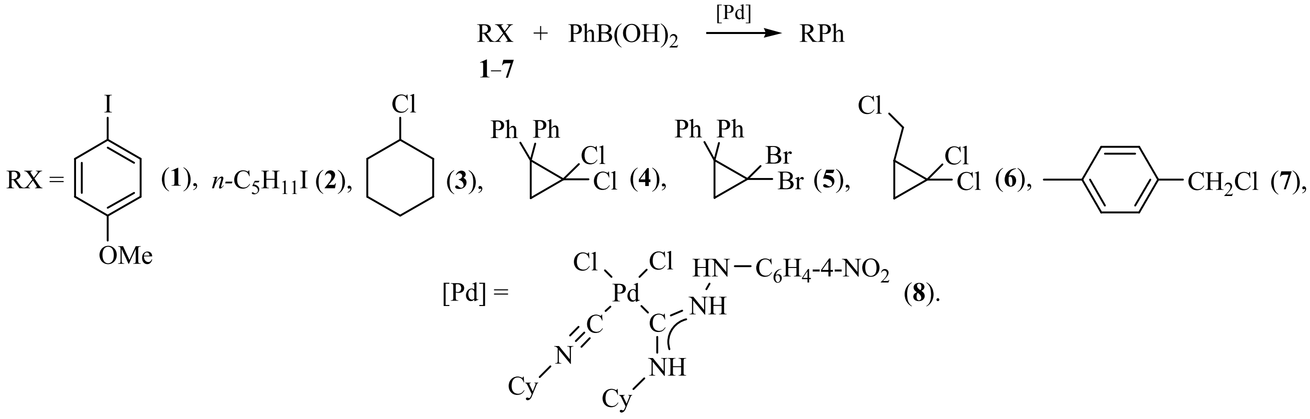
The catalyst was prepared via the method elaborated in [22, 23], the reaction of bis(cyclohexylisocyanide)palladium(II) chloride **9** with 4-nitrophenylhydrazine **10** in CH_2Cl_2 at room temperature (Scheme 2).

The Suzuki cross-coupling was investigated under the convenient conditions described in [7], the most efficient in the cases of the reactions with aryl halides. The reactions were carried out in refluxing ethanol in the presence of K_2CO_3. The following compounds were used as substrates: aryl halide **1**, alkyl halide **2**, cycloalkyl halides **3**–**6**, and benzyl halide **7** (Scheme 1). The obtained results are given in Table 1.

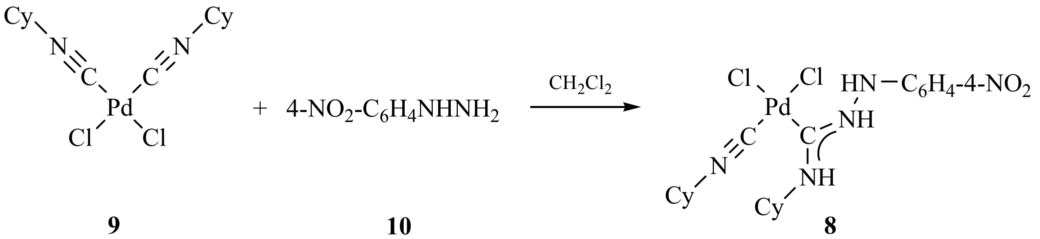
It was demonstrated that under the studied conditions only aryl halide **1** and benzyl halide **7** formed the cross-coupling products **11** and **12**; other alkyl and cycloalkyl halides did not participate in the Suzuki reaction even in the presence of KI as additive, facilitating the *in situ* formation of alkyl iodides from chlorine and bromine derivatives.

Compounds **3** and **6** underwent partial chlorine–iodine exchange in the presence of KI. However, *gem*-dihalocyclopropanes **4** and **5** were inert under the applied conditions; the corresponding iodocyclo-

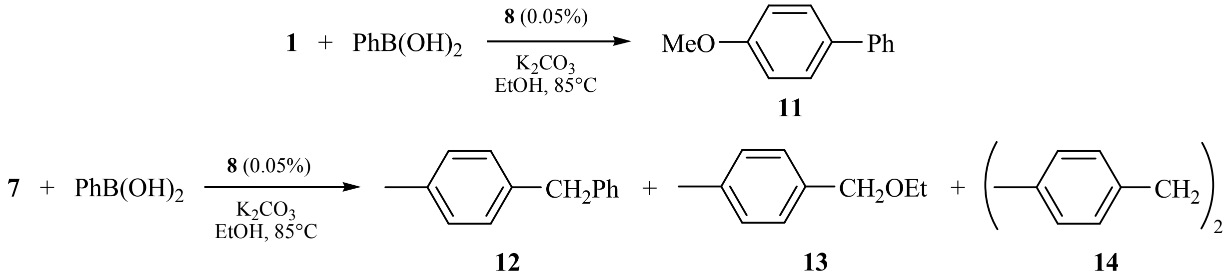
Scheme 1.



Scheme 2.



Scheme 3.

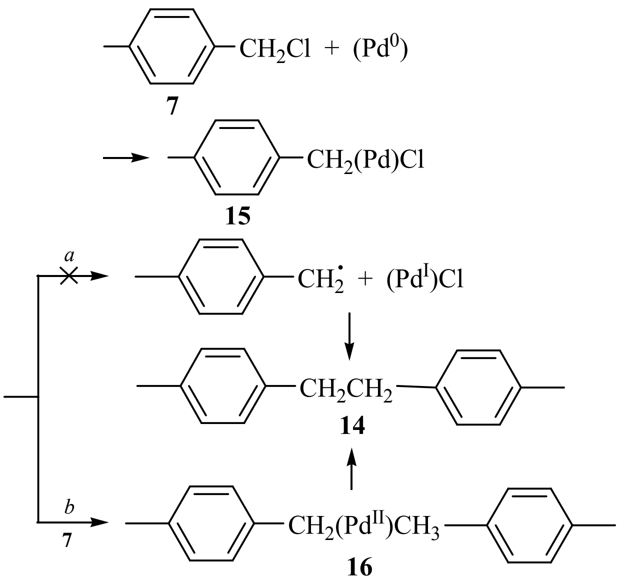


propanes were not found in the reaction mixture (Table 1). Substitution of the chlorine with iodine in compound **6** has been observed earlier when performing the reaction in DMF at 50–55°C [24].

In the case of aryl iodide **1**, the reaction proceeded selectively: 4-methoxybiphenyl **11** was the only product. Halide **7** provided exclusively 4-methyl-1-(ethoxymethyl)benzene **13** formed as a result of ethanolysis of the starting compound. Along with the target compound **12** and the ethanolysis product **13**, compound **14** was formed via the homo coupling of halide **7** (Scheme 3). The reference experiment demonstrated that in the absence of the palladium catalyst the product **14** was not formed. That evidenced that compound **14** could be formed only through the benzyl palladium complex **15** either due to homolysis of complex **15** followed by recombination of benzyl radicals (direction *a,* Scheme 4) or via its reaction with the second molecule of benzyl halide followed by reductive elimination of compound **14** from dibenzyl complex of palladium(II) **16** (direction *b*, Scheme 4).

The absence of *para*-xylene (the possible product of halide **7** reduction) in the reaction mixture proved that direction *a* was not operative under the investigated conditions. The fact that the yield of compound **14** was significantly increased when adding KI to the reaction mixture also confirmed its formation through dibenzylpalladium complex **16**, since that complex should be formed much more easily in the reaction of complex **15** with 1-(iodomethyl)-4-methylbenzene

Scheme 4.



formed *in situ* in the presence of KI than in that with the starting halide **7**.

Note that ethanolysis of halide **7** proceeded significantly slower than the cross-coupling at the initial stage of the reaction. In detail, the conversion of compound **7** within 10 min was of 20%, the cross-coupling product **12** yield being of 13%. Hence, the catalytic system was not stable under the reaction conditions; the target product was formed within the first 30–40 min of the reaction, and later the catalyst became inactive.

The reactivity of aryl iodide **1** and alkyl halide **7** in the Suzuki reaction catalyzed with complex **8** was compared taking advantage of the competitive reactions method. Halide **1** occurred to be somewhat more reactive than compound **7**; the relative rate constant k_1/k_7 determined by measuring the yield of the cross-coupling products **11** and **12** at low conversion of the starting halides was of 1.4.

Taking into account that the cross-coupling reaction of halide **7** with phenylboronic acid in ethanol afforded by product of the solvolysis, it seemed interesting to investigate the use of less nucleophilic medium. To do so, we performed the Suzuki reaction catalyzed with complex **8** in propan-2-ol and acetonitrile. 4-Iodo-1-(methoxy)benzene **1** and 4-methyl-1-(chloromethyl)benzene **7** were used as the model halides. The obtained results are given in Table 2.

Table 1. Reactivity of halogenated arenes, alkanes, and cycloalkanes in the Suzuki reaction catalyzed with acyclic diaminocarbene complex of palladium in ethanol[a]

RX	KI (mol/mol RX)	Reaction mixture composition after the reaction completion[b] (mol %)[c]				
		RX	RPh	ROEt	R_2	RI
1	–	33	67	–	–	33
2	–	100	–	–	–	100
3	–	100	–	–	–	–
3	0.5	95	–	–	–	5
4	–	100	–	–	–	–
	0.5	100	–	–	–	–
5	–	100	–	–	–	–
	0.5	100	–	–	–	–
6	–	100	–	–	–	–
	0.5	76	–	–	–	24
7	–	–	26	71	3	–
[d]	–	80	13	7	–	–
	0.5	–	18	59	19	4

[a] Reaction conditions: EtOH, 85°C, molar ratio **1** : RX : $PhB(OH)_2$: K_2CO_3 = 0.0005 : 1 : 1 : 2, 2 h. [b] By GLC–MS. [c] By GLC. [d] Reaction time 10 min.

The data demonstrated that the change of EtOH with *i*-PrOH was not rational since it led to significant reduction of the cross-coupling products yield both for aryl iodide **1** and chloride **7**. On the other hand, solvolysis of aryl halide **7** was impeded insignificantly. While MeCN was used as solvent, the reaction was even more decelerated. Addition of PEG-1500 as a phase-transfer catalyst (the technique often used for the reactions in the presence of K_2CO_3 in organic solvents [25]) did not cause appreciable increase of the cross-coupling products yield. Addition of water (only 10%) to the mixture of MeCN and PEG-1500 significantly promoted the reaction, and the product yields were comparable to those obtained in the reaction performed in ethanol. However, in the case of alkyl halide **7** it resulted in hydrolysis of significant fraction of the starting substrate.

In summary, 4-iodoanisole was found to be more reactive in the Suzuki reaction catalyzed with acyclic diaminocarbene complex of palladium than alkyl halides. The reaction with 4-methyl-1-(chloromethyl)benzene provided the target 4-methyl-1-(phenylmethyl)benzene along with noticeable amount of by-

Table 2. Reactivity of 4-iodo-1-(methoxy)benzene **1** and 4-methyl-1-(chloromethyl)benzene **7** in the Suzuki reaction catalyzed with acyclic diaminocarbene complex of palladium in propan-2-ol and acetonitrile[a]

RX	Solvent	KI (mol/mol RX)	Reaction mixture composition after the reaction completion[b] (mol%)[c]					
			RX	product of solvolysis	RPh	R_2	RH	RI
1	*i*-PrOH	0.5	82	–	18	–	–	82
	MeCN	0.5	97	–	3	–	–	97
	MeCN + 10% PEG-1500	0.5	93	–	7	–	–	93
	MeCN + 30% PEG-1500 + 10% H_2O	0.5	34	–	61	–	5	34
7	*i*-PrOH	0.5	52	41 (*i*-ROPr)	3.5	–	0.5	3.0
	MeCN	0.5	92	–	5.1	2.4	0.5	–
	MeCN + 10% PEG-1500	0.5	86	–	9.5	4.0	0.5	–
	MeCN + 30% PEG-1500 + 10% H_2O	0.5	–	65 (ROH)	18	8	9	–

[a] Reaction conditions: 85°C, molar ratio **1** : RX : $PhB(OH)_2$: K_2CO_3 = 0.0005 : 1 : 1 : 2, 2 h. [b] By GLC–MS. [c] By GLC.

products; the other studied alkyl and cycloalkyl halides did not participate in the cross-coupling reaction. Ethanol was found the most suitable solvent for the studied reaction. The reaction in acetonitrile proceeded with appreciable yield only in the presence of PEG and water. It was reasonable to suppose that the true catalyst was formed from acyclic diaminocarbene complex of palladium in its reaction with a protic solvent in the presence of a base.

EXPERIMENTAL

^{1}H NMR spectra were registered using a Bruker AvanceII+ spectrometer at 400.13 MHz at room temperature. Gas–liquid chromatography analysis was performed using a Khromatek Kristal 5000.2 instrument equipped with a flame ionization detector; capillary column VRKh-1 (10 m × 0.53 mm × 2.65 μm). Analysis by means of GLC–MS was performed with a Shimadzu GCMS QP-2010 SE instrument (electron impact ionization; an Rtx-5MS capillary column, 30 m × 0.32 mm × 0.25 mm).

Chloromethyl-*gem*-dichlorocyclopropane 6 was prepared via dichlorocarbeniation of allyl chloride according to the known procedure; its physicochemical parameters coincided well with the literature [26].

Synthesis of complex 1 [22, 23]. A mixture of bis(cyclohexylisocyanide)palladium(II) chloride (40 mg, 0.10 mmol) and 4-nitrophenylhydrazine (16 mg, 0.10 mmol) in 2 mL of CH_2Cl_2 was incubated at room temperature for 48 h. Then the reaction mixture was diluted with 2 mL of *n*-hexane; white precipitate was filtered off, washed with anhydrous Et_2O (3 mL), and dried in air. Yield 43 mg (76%), white crystalline compound, mp >160°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24–2.20 m (20H, 10CH$_2$), 3.85–4.15 m (1H, CHNC), 4.25–4.67 m (1H, C$\underline{\text{H}}$NH), 6.90 d (2H$_{\text{Ar}}$, *J* 8.7 Hz), 7.05 br.s (1H, NH), 7.75 s (1H, ArNH), 8.10 d (2H$_{\text{Ar}}$, *J* 8.7 Hz), 9.90 br.s (1H, NH).

Experimental procedure for the Suzuki reaction. An appropriate organic halide (0.5 mmol), phenylboronic acid (61 mg, 0.5 mmol), K_2CO_3 (140 mg, 1.0 mmol), KI (when need, 41 mg, 0.25 mmol), PEG-1500 (when needed, 150 mg) were placed into an ampoule with twisted stopper equipped with magnetic stirrer, and the appropriate solvent (2 mL) was added. The reaction mixture was heated at stirring to start refluxing (heating bath temperature was 85°C for all the used solvents), and 0.1% solution of complex **1** (0.14 mL) in the used solvent was added; the stopper was closed, and heating was continued. The solution got immediately brown-reddish, then in few minutes the color turned to orange-yellowish; the color in the course of the reaction gradually disappeared changing to greyish due of the metallic palladium particles formed at the catalysis decomposition. The reaction mixture was heated during 2 h and cooled; the specimen for the analysis was sampled (0.2 mL), diluted with *n*-hexane (2 mL) and water (1 mL), and shaken; the hexane layer was separated and analyzed by GLC and GLC-MS.

Preparative procedure for Suzuki reaction (in ethanol). 4-Methyl-1-(chloromethyl)benzene (703 mg, 5.0 mmol), phenylboronic acid (610 mg, 5.0 mmol), and K_2CO_3 (1.38 g, 1.0 mmol) were placed into a 50 mL round-bottom flask equipped with magnetic stirrer and a condenser; ethanol (20 mL) was added to the mixture. The reaction mixture was heated at stirring till beginning of reflux (bath temperature 85°C), and 0.1% solution of complex **1** in ethanol (1.35 mL, 1.35 mg, 2.5μmol) was added through the condenser. The solution was refluxed during 2 h. Then the reaction mixture was cooled, diluted with *n*-hexane (10 mL) and water (5 mL), and stirred during 10 min. The upper hexane layer was separated, and the rest of the reaction mixture was washed with *n*-hexane (10 mL). The combined hexane fractions were washed with 1% solution of KOH in MeOH (20 mL), then with water (20 mL), and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure; the residue was distilled in vacuum, discharging the first portion of the distillate (≈ 20%).

4-Methyl-1-(phenylmethyl)benzene [27]. Yield 160 mg (18%, purity 90% by ^1H NMR), yellowish oily liquid, bp 90°C (0.5 mbar). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.47 s (3H, CH_3), 4.66 s (2H, CH_2), 7.22 t ($1H_{Ar}$, *J* 8.7 Hz), 7.29–7.33 m ($4H_{Ar}$), 7.36–7.41 m ($4H_{Ar}$).

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