Catalysis of the Suzuki Reaction by Acyclic Diaminocarbene Palladium Complexes Generated In Situ

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Abstract—Acyclic diaminocarbene palladium complexes generated in situ by nucleophilic attack of morpholine, 4-nitrophenylhydrazine, or benzhydrazide on bis(isocyanide) palladium(II) complexes catalyzed the Suzuki reaction of 4-iodo- or 4-bromoanisole with phenylboronic acid. Morpholine turned out to be the best catalyst modifier. The cross coupling reaction under fairly mild conditions (reflux in ethanol in the presence of potassium carbonate) in 2 h afforded 4-methoxybiphenyl whose yield was insignificantly lower than in the presence of preliminarily prepared catalyst. Neither preliminary degassing nor protection from atmospheric moisture and oxygen was necessary.

Keywords: acyclic diaminocarbenes, Suzuki reaction, bis(isocyanide) palladium complexes, in situ catalysis **DOI:** 10.1134/S1070363216090085

Transition metal complexes are extensively used as catalysts in organic reactions. Their catalytic activity can be controlled by variation of the ligand structure, and the complex added to the reaction mixture is often referred to as precatalyst rather than catalyst [1, 2]. Many ligands are capable of reacting with organic and inorganic compounds present in the reaction mixture, thus changing their structure and hence the properties of catalytic center which becomes "true catalyst." Such modifications extend the potential of metal complex catalysis and make it possible to use relatively simple transition metal complexes as precatalysts, so that practical implementation of catalytic reactions is facilitated.

In this connection, of considerable interest are acyclic diaminocarbene palladium(II) complexes (Pd-ADC) that are now among the most efficient cross-coupling catalysts [3, 4]. These complexes are generally synthesized by reaction of various nitrogen nucleophiles with bis(isocyanide) palladium complexes (Scheme 1; R = Alk, Ar) [5–11]. We previously prepared a number of Pd-ADCs which turned out to act as excellent catalysts in Suzuki reactions with haloarenes [12, 13], haloalkenes [14], and benzyl halides [15] and copperfree Sonogashira reactions [16–20]. In all these reactions, the catalyst was synthesized preliminarily by reaction of bis(isocyanide) palladium complexes with

the corresponding nitrogen nucleophile in boiling chloroform or methylene chloride.

Taking into account mild conditions of the formation of these catalysts, we presumed that they can be generated in situ in cross coupling reactions. In the present work we checked this possibility in the Suzuki reaction. As model reaction we selected cross-coupling of 4-haloanisoles 1 and 2 with phenylboronic acid (3) (Scheme 2). Our choice was determined by the fact that the synthesis of methoxybiphenyls is an important field of application of Suzuki reactions [21, 22]; the products are used to monitor decomposition of persistent organic pollutants, polychlorinated biphenyls, in natural environment [23].

The cross coupling reactions were carried out in the presence of different catalytic systems, specifically





 $(CyNC)_2PdCl_2(6) + PhCONHNH_2(8); (CyNC)_2PdCl_2(6) + (CH_2CH_2OCH_2CH_2)NH(9); X = Br(1), I(2).$

acyclic diaminocarbene palladium complex 5 preliminarily prepared as described in [14], dichlorobis (cyclohexyl isocyanide)palladium (6), and mixtures of 6 with nitrogen nucleophiles 7–9. As we showed previously, Pd-ADCs containing fragments of 7 and 8 [13, 14] efficiently catalyzed cross coupling reactions. On the other hand, our attempts to obtain a carbene complex by reaction of morpholine (9) with bis (isocyanide) palladium complexes were unsuccessful, and we failed to isolate the desired complex in the pure state. Therefore, it was interesting to generate the corresponding catalyst in situ. The results of cross coupling of 4-haloanisoles 1 and 2 with phenylboronic acid (3) in the presence of different catalysts are given in table. In all cases, the cross coupling was selective with respect to 4-haloanizole, and the major product was 4-methoxybiphenyl (4); unsubstituted biphenyl (10) was formed as the only by-product. Unreacted phenyl-boronic acid was partially converted to cyclic trimer (PhBO)₃ during the process. 4-Methoxybiphenyl (4) was isolated and characterized by ¹H NMR and mass spectra. The spectral data of 4 coincided with those reported in [24].

As might be expected, 4-iodoanisole (2) was more reactive than 4-bromoanizole (1) in the Suzuki reaction, though the difference in their reactivities tended to decrease in the presence of active catalytic systems

Run no.	ArX	Catalyst, 0.001 mol per mole of ArX	Nitrogen nucleophile 7–9 , mol per mole of ArX	Yield, ^b %	
				4	10
1	1	5	_	>99	5
2	1	6	_	73	5
3	1	6 + 7	0.05	47	26
4	1	6 + 8	0.05	58	5
5	1	6 + 9	0.001	76	5
6	1	6 + 9	0.05	71	7
7	1	6 + 9	0.5	89	6
8	2	5	_	99 (98°)	4
9	2	6 + 7	0.05	87	6
10	2	6 + 7	0.5	7	—
11	2	6 + 8	0.05	53	1
12	2	6 + 9	0.05	87	3
13	2	6 + 9	0.5	95	2

Suzuki cross-coupling reaction of 4-haloanisoles 1 and 2 with phenylboronic acid (3) in the presence of different catalysts^a

^a EtOH, 80°C, 2 h. ^b GC data. ^c Isolated yield.

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[complex 5, system 6 + 9)]. The obtained data indicated that cross-coupling catalysts can be formed in situ from all nucleophiles 7–9; however, their catalytic activity was lower than the activity of preliminarily synthesized carbene complex 5. Bis(isocyanide) complex 6 is capable of catalyzing the Suzuki reaction in the absence of nucleophile. This may be due to generation in situ of aminooxycarbene complex 11 (Scheme 3). The formation of such complexes via nucleophilic addition of alkoxide to coordinated isocyanide was described in [25, 26], but these complexes were poorly studied.

On the whole, among the catalysts generated in situ, those based on morpholine showed the best catalytic activity (see table; run nos. 7, 13).

The dependence of the catalytic activity on the nucleophile concentration was interesting. Raising the amount of 4-nitrophenylhydrazine (7) was accompanied by sharp reduction of the catalytic activity instead of expected increase. These findings suggest some inhibitory effect of 4-nitrophenylhydrazine on the generated catalyst. No analogous inhibitory effect was observed with morpholine (9). By contrast, the best results were obtained using a large excess of morpholine with respect to bis(isocyanide) palladium complex.

Thus, we have demonstrated the possibility for carrying out Suzuki reaction in the presence of acyclic diaminocarbene palladium complexes generated in situ by nucleophilic attack of 4-nitrophenylhydrazine, benzhydrazide, or morpholine on a bis(isocyanide) palladium(II) complex. The latter was shown to catalyze the Suzuki reaction in alcoholic solution in the absence of a nitrogen nucleophile. Among the examined nucleophiles, morpholine taken in a large excess turned out to be the best modifier. The cross coupling reaction is complete in 2 h under mild conditions (reflux in ethanol in the presence of potassium carbonate) with formation of 4-methoxybiphenyl. The yield is insignificantly lower than the yield in the reaction catalyzed by preliminarily prepared catalyst. The reaction requires neither preliminary degassing nor protection from atmospheric moisture and oxygen.

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EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded at room temperature on a Bruker Avance II+ spectrometer at 400.13 and 100.61 MHz, respectively, using CDCl₃ as solvent. Gas chromatographic–mass spectrometric analyses were obtained on a Shimadzu GCMS QP-2010 SE instrument [electron impact, 70 eV; a.m.u. range 35–500; detector temperature 200°C; Rtx-5MS column, 30 m×0.32 mm×0.25 μ m; carrier gas argon, flow rate 0.8 mL/min; oven temperature programming from 50°C (2 min) to 250°C at a rate of 25 deg/min, 20 min at 250°C].

GC analysis was performed on a Khromatek Kristall 5000.2 instrument equipped with a flame ionization detector and an Optima 1 capillary column, $25 \text{ m} \times 0.32 \text{ mm} \times 0.35 \text{ µm}$.

Suzuki reaction catalyzed by preliminarily prepared complex 5. A screw-cap ampule equipped with a magnetic stirrer was charged with 2 mL of ethanol, 0.2 mmol of 4-haloanisole 1 or 2, 1.1 equiv of phenylboronic acid (3), and 1.5 equiv of K₂CO₃. The mixture was heated to 80°C with stirring, and 0.1 mL of a 2×10^{-3} M solution of complex 5 [12] (2×10^{-7} mol) in ethanol was added. The mixture was heated for 2 h at 80°C on an oil bath, cooled to room temperature, and diluted with 2 mL of water. The product was extracted into hexane–methylene chloride (1:1, 2×5 mL), and the combined extracts were dried over anhydrous Na₂SO₄ and analyzed by GC ad GC/MS. The solvent was removed, and the residue was weighted and analyzed by ¹H NMR.

Suzuki reaction in the presence of catalysts generated in situ (general procedure). A screw-cap

ampule equipped with a magnetic stirrer was charged with 2 mL of ethanol, 0.2 mmol of 4-haloanisole 1 or 2, 1.1 equiv of phenylboronic acid (3), 1.5 equiv of K_2CO_3 , and a required amount of nucleophile 7–9. The mixture was heated to 80°C with stirring, and 0.1 mL of a 2×10⁻³ M solution of complex 6 (2×10⁻⁷ mol) in ethanol was added. The mixture was then heated for 2 h at 80°C on an oil bath (80°C) and treated as described above.

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