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Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

Steric Effect of Substituents in Haloarenes on the Rate of Cross-Coupling Reactions

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Abstract—The relative reactivity of *ortho*- and *para*-methyl-substituted iodoarenes in the Sonogashira reaction and palladium-catalyzed methoxycarbonylation, as well as of similarly substituted bromoarenes in the Suzuki reactions and cobalt-catalyzed methoxycarbonylation, was studied. Introduction of a methyl group into the *para* position of aryl halide slows down the cross-coupling. *o*-Methylhaloarenes are less reactive in palladium-catalyzed reactions as compared to both unsubstituted haloarene and *para*-substituted analog. The presence of a methyl group in the *ortho* position with respect to the reaction center accelerates cobalt-catalyzed methoxycarbonylation.

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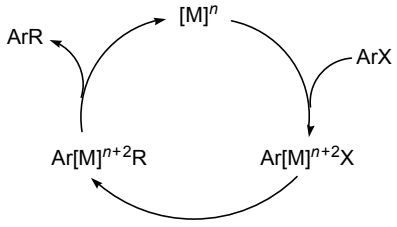
Cross-coupling reactions catalyzed by transition metal complexes justly occupy a prominent place among synthetic methods of organic chemistry [1–11]. These reactions characteristically involve the step of haloarene activation with transition metal complex, i.e., oxidative addition (OxAdd) [5, 11] (Scheme 1). Understanding of general relations holding in that step is quite important for the development of new catalytic processes.

Scheme 1.



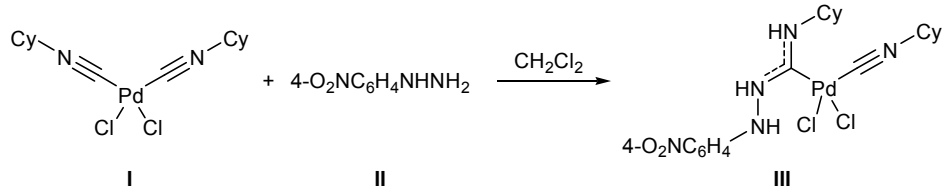
An important factor determining the rate of oxidative addition is the structure of haloarene, in particular, electronic and steric effects of the substituent in the aromatic ring. Insofar as metal complex $[M]^n$ is nucleophilic and haloarene acts as oxidant, electron-withdrawing substituents accelerate oxidative addition, which was noted by all authors who reported on cross-coupling reactions (see, e.g., [11]); moreover, this effect is quite appreciable. In some cases, reactions with less reactive bromoarenes and especially chloroarenes having no electron-withdrawing substituents do not occur at all.

On the other hand, steric effect of substituents in these substrates is not so definite. Some authors believe that Suzuki and Sonogashira reactions [12, 13], as well as palladium-catalyzed alkoxycarbonylation [6], with *ortho*-substituted haloarenes are more difficult than with the corresponding *para*-substituted derivatives. However, there are experimental data demonstrating that such substrates are readily involved in the above reactions [5, 14, 15]. In addition, many *ortho*-substituents containing heteroatoms or multiple bonds make the substrate a chelating ligand and thus facilitate oxidative addition [16, 17].

To elucidate the problem related to steric effect of substituents in haloarenes on the rate of their cross-coupling reactions, systematic study of the relative reactivity of *ortho*-alkyl-substituted substrates is necessary. The difference in the electronic effects of alkyl groups in *ortho* and *para* positions with respect to the reaction center is minimal, and no chelation is possible.

Shilz and Plenio [15] recently reported the results of a qualitative study on substituent effects in the

Scheme 2.

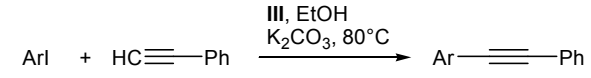


I **II** **III**

Sonogashira cross-coupling reactions. It was shown that alkyl substituents in the *ortho* position relative to halogen hamper the reaction, but their effect was not so strong as it was believed previously. Furthermore, the substituent effect depended on the size of phosphine ligand used. No quantitative data on the relative reactivity were given. There are no analogous published data on other cross-coupling reactions.

Therefore, the goal of the present work was to study the relative reactivity of *ortho*-alkyl-substituted iodo- and bromoarenes in several C–C bond-forming reactions: Sonogashira and Suzuki cross-couplings and carbonylation. For this purpose, competitive reactions were performed. The Sonogashira and Suzuki reactions were catalyzed by the palladium complex with acyclic diaminocarbene ligand (complex **III**, Scheme 2). In recent time, complexes like **III** are increasingly used to catalyze organic reactions [18] due to their stability toward atmospheric oxygen and synthetic accessibility. In particular, complex **III** was synthesized by nucleophilic addition of 4-nitrophenylhydrazine (**II**) to *cis*-dichlorobis(cyclohexyl isocyanide)palladium (**I**) in methylene chloride (Scheme 2). The use of complex **III** made it possible to conduct the Sonogashira reaction under experimentally convenient conditions, by heating in boiling ethanol on exposure to air without addition of copper compounds. Potassium carbonate was selected as base. Under these conditions we examined reactions of alkyl-substituted iodobenzenes **IV**–**VIII** with phenylacetylene (**IX**) (Scheme 3).

Scheme 3.



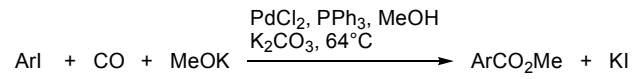
IV–VIII **IX**

IV, Ar = Ph; **V**, Ar = 2-MeC_6H_4; **VI**, Ar = 4-MeC_6H_4; **VII**, Ar = 2,4-$Me_2C_6H_3$; **VIII**, Ar = 2,4,6-$Me_3C_6H_2$.

The relative rate constants of competitive reactions were determined following the consumption of initial iodoarenes. ^{1}H NMR analysis of the reaction mixtures after complete consumption of acetylene (**IX**) (iodoarenes were taken in excess) showed the absence of side transformations of the initial iodoarenes. The results are collected in Table 1. It is seen that introduction of methyl groups into both *ortho* and *para* positions with respect to the iodine atom hampers the cross-coupling reaction and that the effect of *ortho*-substitution is stronger. Moreover, the effect of the second methyl group is stronger than that of the first one. Such cumulative action is typical of steric effects. Thus our results obtained in the copper-free reaction are consistent with published data [15] according to which *ortho*-alkyl substituents slightly decelerate Sonogashira reaction under its classical conditions implying the use of phosphine ligand and copper salts.

We also examined another palladium-catalyzed C–C bond-forming reaction with the same substrates, namely methoxycarbonylation. The reactions were carried out under analogous conditions, by heating in boiling methanol in the presence of K_2CO_3 as base and $Pd(OAc)_2/PPh_3$ as catalyst (Scheme 4). The relative rate constants were determined as above. In this case, we also observed inhibitory steric effect of methyl substituents (Table 2).

Scheme 4.



IV–VI

With a view to elucidate whether the effect of *ortho*-substitution in the palladium-catalyzed reactions of haloarenes depends on the size of the halogen atom,

Table 1. Relative reactivity of iodoarenes in the Sonogashira cross-coupling

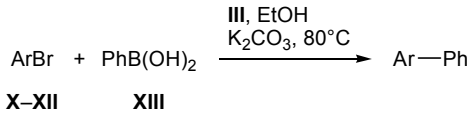
Iodoarene no.	Relative rate constant
IV	1.0
V	0.77
VI	0.84
VII	0.65
VIII	0.39

Table 2. Relative reactivity of iodoarenes in the palladium-catalyzed methoxycarbonylation

Iodoarene no.	Relative rate constant
IV	1.0
V	0.61
VI	0.75

we compared the reactivities of bromobenzene (**X**), *o*-bromotoluene (**XI**), and *p*-bromotoluene (**XII**). Taking into account low rates of both Sonogashira and carbonylation reactions with these substrates, as model reaction we selected the Suzuki cross-coupling with phenylboronic acid (**XIII**). The reactions were carried out in the presence of palladium complex **III** and K_2CO_3 in boiling ethanol (Scheme 5).

Scheme 5.



X, Ar = Ph; **XI**, Ar = 2-MeC_6H_4; **XII**, Ar = 4-MeC_6H_4.

The relative rate constants were determined by the competitive reaction method, following the consumption of initial bromoarenes. Analysis of the reaction mixtures by ^{1}H NMR spectroscopy after complete consumption of phenylboronic acid (**XIII**) (whose amount was less than stoichiometric) showed the absence of by-products that could be formed from bromotoluenes. We presumed that bromobenzene also does not give rise to by-products under the given conditions. The results presented in Table 3 indicated that replacement of iodine by bromine does not change the character of substituent steric effect in the palladium-catalyzed cross-coupling of haloarenes.

Table 3. Relative reactivity of bromoarenes in the Suzuki cross-coupling

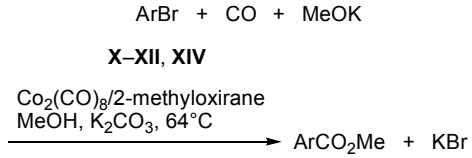
Bromoarene no.	Relative rate constant
X	1.0
XI	0.41
XII	0.58

Table 4. Relative reactivity of bromoarenes in the cobalt-catalyzed methoxycarbonylation

Bromoarene no.	Relative rate constant
X	1.0
XI	1.3
XII	0.60
XIV	2.2

Taking into account our results and published data on *ortho*-directing effect of halogen in methoxycarbonylation reactions catalyzed by cobalt complexes [19], we examined the effect of *ortho*-alkyl substitution in the reaction catalyzed by $Co_2(CO)_8$/2-methyloxirane [7, 19] in methanol in the presence of K_2CO_3 (Scheme 6).

Scheme 6.

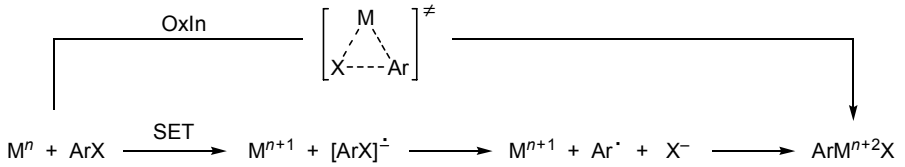


X, Ar = Ph; **XI**, Ar = 2-MeC_6H_4; **XII**, Ar = 4-MeC_6H_4; **XIV**, Ar = 2,4,6-$Me_3C_6H_2$.

According to our previous data [20], cobalt-catalyzed methoxycarbonylation of substituted bromoarenes is accelerated by electron-withdrawing substituents in the aromatic ring. If only electronic effect of methyl group is considered, the reactivity of substrates should decrease in the series **X** > **XI** ≈ **XII**. However, experiments showed a different reactivity series (Table 4). Our results indicated an appreciable positive effect of *ortho*-methyl substitution like that observed previously in the methoxycarbonylation of dichlorofluorobenzenes [19]. "Moving" of methyl group, which possesses a pronounced positive inductive effect, closer to the reaction center accelerates the carbonylation rather than decelerates it. Moreover, introduction of two methyl groups into the *ortho* positions with respect to bromine in molecule **XII** (compound **XIV**) makes the substrate even more reactive [k_{rel}(**XIV**/**XII**) = 3.7].

Thus opposite steric effects of *ortho*-methyl substituents are observed in the examined reactions of haloarenes. The presence of a methyl group in the *ortho* position with respect to the halogen atom hampers palladium-catalyzed reactions of haloarenes but accelerates methoxycarbonylation in the presence of cobalt catalyst. Such dependence of the substituent effect on the metal nature may be rationalized in terms of different activation paths of haloarene. Oxidative addition of organic halides may follow several mechanisms [21]; among these, the following two paths are generally typical of aromatic substrates: oxidative insertion

Scheme 7.

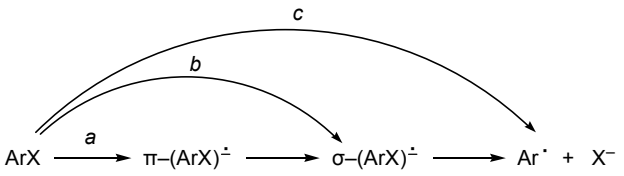


(OxIn) [22–25] and, more rarely, radical anion activation via single-electron transfer (SET) [20, 26] (Scheme 7).

Palladium complexes activate haloarene according to a concerted mechanism (OxIn) [27], whereas catalysis by cobalt complexes involves electron transfer [20]. Our results indicate deceleration of the OxIn stage upon introduction of an alkyl group into the *ortho*-position with respect to halogen. This is quite explainable in terms of generally accepted views on steric hindrances in the transition state as compared to the initial state in reactions with a larger nucleophile (in our case, palladium complex). Acceleration of the radical anion substitution is more difficult to interpret since the transition state theory is hardly applicable in this case. Presumably, the positive effect of *ortho*-substitution is related to specificity of SET activation of bromobenzene and its methyl-substituted derivatives.

Depending on the substrate structure, radical anion activation of haloarenes may include different numbers of steps (paths *a*, *b*, and *c* in Scheme 8).

Scheme 8.



Unlike other haloarenes, aryl iodides generally give rise to fairly stable σ-radical anions, for the σ* orbital of the C–I bond in their molecules has relatively low energy [28]. Therefore, path *b* predominates in radical anion substitution in aryl iodides. Bromoarenes and especially chloroarenes with electron-withdrawing substituents in the aromatic ring, as well as polynuclear aromatic systems, possess low-lying π* orbitals, so that radical anion substitution therein follows mainly path *a* [29, 30]. Non-activated bromoarenes and chloroarenes react most typically according to synchronous mechanism *c* [31]. Thus the substituent effects on the reactivity of haloarenes may differ utterly depending on the haloarene nature.

We performed a theoretical simulation of a probable radical anion activation path for substrates **X**, **XI**, and **XIV**. In all cases, no clearly defined minimum was observed on the potential energy surface cross section along the reaction coordinate; as the latter we selected stretching of the C–Br bond in the presumed haloarene radical anion. This means that the process follows a synchronous mechanism without intermediate formation of radical anion. In the C–Br bond length range from 1.83 to 2.20 Å, i.e., in the initial part of the reaction path characterized by the highest energy, the optimized model structures were not planar, and the bromine atom deviated from the benzene ring plane. Therefore, factors that cause deviation of the bromine atom from the benzene ring plane favor the reaction. The presence of a substituent in the *ortho* position with respect to the reaction center is just a factor destabilizing the planar structure due to van der Waals repulsion.

On the whole, our results suggest that steric effect of *ortho*-substituent on the rate of transition metal-catalyzed cross-coupling reactions of haloarenes depends on the metal nature. Palladium-catalyzed reactions, such as Sonogashira and Suzuki cross-couplings and methoxycarbonylation, become slightly slower when a methyl group is introduced into the *ortho* position with respect to the halogen atom. The opposite effect is observed in the cobalt-catalyzed methoxycarbonylation, where *ortho*-methyl-substituted substrates are considerably more reactive. The influence of the metal nature may be rationalized by different mechanisms of oxidative addition of haloarene.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker DPX 300 spectrometer operating at 300.13 (^{1}H) and 75.03 MHz (^{13}C). The mass spectra were recorded on a Bruker micrOTOF instrument (electrospray ionization, solvent MeOH, a.m.u. range 50–3000). GLC analysis was performed on a Tsvet-104 chromatograph equipped with a flame ionization detector and 2500 × 3-mm glass columns packed with 10% of SE-30 on Chromaton N-Super (80–100 mesh). The elemental compositions were determined on a Hewlett Packard 185B analyzer. Com-

mercial inorganic reagents of analytical grade were used without additional purification; the purity of commercial organic reagents was checked by GLC and ^{1}H NMR. Potassium carbonate of analytical grade was calcined for 6 h at 150°C. Dicobalt octacarbonyl $Co_2(CO)_8$ was commercial product (Merck). The solvents used were purified and (if necessary) dried according to standard procedures.

Quantum-chemical calculations were performed using Gaussian 03 [32] in terms of the spin-unrestricted density functional theory with the UB3LYP hybrid functional and 6-31+G(*d*) basis set; geometric parameters were optimized at each step of potential energy surface scan. Solvation effects were taken into account according to the polarizable continuum model (PCM).

Palladium complex III. A solution of 40 mg (0.10 mmol) of palladium complex **I** and 16 mg (0.10 mmol) of 4-nitrophenylhydrazine (**II**) in 2 ml of methylene chloride was kept for 48 h at room temperature, 2 ml of hexane was added, and the precipitate was filtered off, washed with 3 ml of anhydrous diethyl ether, and dried in air. Yield 47 mg (84%), white crystals, decomposition point 165°C. IR spectrum, ν, cm^{-1}: 2934–2856 (C–H), 2230 (C≡N), 1330 (NO_2). ^{1}H NMR spectrum, δ, ppm: 1.24–2.20 m (20H, CH_2), 3.85–4.15 m (1H, CH), 4.25–4.67 m (1H, CH), 6.90 d (2H, H_{arom}, J = 8.7 Hz), 7.05 d (1H, NH, J = 10.2 Hz), 7.75 s (1H, ArNH), 8.10 d (2H, H_{arom}, J = 8.7 Hz), 9.90 s (1H, C=NH). Mass spectrum (ESI$^+$): *m*/*z* 512.1088 [M – Cl]$^+$. Found, %: C 43.42; H 5.50; N 12.75. $C_{20}H_{29}Cl_2N_5O_2Pd$. Calculated, %: C 43.77; H 5.33; N 12.76. M 512.1045.

Competitive Sonogashira reactions (*general procedure*). A solution of 1.0–2.0 mmol of a 1:1 mixture of the corresponding haloarenes, 0.5–1.0 mol of phenylacetylene (**IX**), and GLC internal standard in 2 ml of ethanol was stirred, a sample was withdrawn for GLC analysis, 0.2 g (1.4 mmol) of K_2CO_3 was added, the mixture was heated under stirring to 80°C, 0.10 ml of a 2×10^{-3} M solution of complex **III** in ethanol was added, and the mixture was stirred for 2 h at 80°C. The mixture was cooled, a 0.5-ml sample was withdrawn and treated with 2 ml of water and 2 ml of a 1:1 methylene chloride–hexane mixture, and the organic phase was separated and analyzed by GLC.

Competitive palladium-catalyzed methoxycarbonylations. A glass reactor was charged with 1.5–2.0 mmol of a 1:1 mixture of the corresponding haloarenes, GLC internal standard, and 10 ml of methanol. A sample for GLC analysis was withdrawn, 2.0 g (14 mmol) of K_2CO_3, 0.25 mol of triphenylphosphine, and 0.13 mol of $PdCl_2(NCCH_3)_2$ were added, and carbon(II) oxide was passed through the mixture over a period of 15 min under vigorous stirring. The mixture was then heated at 63°C until 40–70% conversion with respect to the total substrate amount (the conversion was monitored by the consumption of CO), 2.0 g of potassium hydroxide was added to hydrolyze esters, and the mixture was stirred for 2 h at that temperature. The mixture was cooled, and a 1.0-ml sample was withdrawn, treated as described above, and analyzed by GLC.

Competitive Suzuki reactions. A solution of a 1:1 mixture of the corresponding haloarenes, 0.5–1.0 mmol of phenylboronic acid. and GLC internal standard in 2 ml of ethanol was stirred, a sample for GLC analysis was withdrawn, the mixture was heated to 80°C, 0.2 g (1.4 mmol) of K_2CO_3 and 0.10 ml of a 2×10^{-3} M solution of **III** in ethanol were added, and the mixture was stirred for 1 h at 80°C. The mixture was cooled, and a 0.5-ml sample was withdrawn, treated as described above, and analyzed by GLC.

Competitive cobalt-catalyzed methoxycarbonylation. A glass reactor was charged with 1.5–2.0 mmol of a 1:1 mixture of the corresponding haloarenes, GLC internal standard, and 10 ml of methanol, the mixture was stirred, a sample for GLC analysis was withdrawn, 2.0 g (14 mmol) of K_2CO_3 was added, and carbon(II) oxide was passed through the mixture over a period of 15 min at room temperature under vigorous stirring. Dicobalt octacarbonyl, 0.035 g (0.10 mmol), was then added in a stream of CO, the mixture was heated to 63°C, 0.26 g (0.3 ml, 4.5 mmol) of 2-methyloxirane was added, the mixture was heated until 40–70% conversion of the substrates in total (the conversion was monitored by the consumption of CO), 2.0 g of potassium hydroxide was added to hydrolyze esters, and the mixture was stirred for 2 h at that temperature. The mixture was cooled, and a 1.0-ml sample was withdrawn, treated as described above, and analyzed by GLC.

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