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RESEARCH ARTICLE

Analysis of phase trajectories for studying the operational evolution of catalytic systems

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Abstract

Objectives. *To establish details of catalytic systems operation using the kinetic method with no needs for the differentiation of primary experimental kinetic data.*
Methods. *Analysis of the time patterns of differential selectivity and relative reactivity of substrates in parallel or competing reactions was used.*
Results. *For various coupling reactions of aryl halides and nucleophiles, the possibility to obtain the data about the evolution of the catalytic systems and patterns of the changes of catalytically active species under dynamic transformations of several active and inactive catalyst forms was demonstrated.*
Conclusions. *The analysis of the evolution of differential selectivity and relative reactivity under competing or parallel reactions is the useful tool for discrimination between probable hypotheses of complex catalytic process operation.*

Keywords: *kinetics, catalysis, palladium, differential selectivity, reaction mechanism*

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НАУЧНАЯ СТАТЬЯ

Анализ фазовых траекторий реакций в исследованиях эволюции функционирования каталитических систем

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Аннотация

Цели. *Определение деталей механизмов функционирования каталитических систем с помощью кинетического метода, не требующего дифференцирования первичных экспериментальных кинетических данных.*
Методы. *Анализ закономерностей изменения дифференциальной селективности и относительной реакционной способности субстратов в параллельных и конкурирующих реакциях во времени.*
Результаты. *На примерах различных реакций сочетания арилгалогенидов с нуклеофилами показана возможность получения данных об эволюции каталитических систем и закономерностях изменений природы каталитически активных соединений в условиях динамических превращений нескольких активных и неактивных форм катализатора.*
Выводы. *Эволюционный анализ величин дифференциальной селективности и относительной реакционной способности в ходе конкурирующих или параллельных реакций является эффективным инструментом дискриминации гипотез механизмов сложных каталитических процессов.*

Ключевые слова: *кинетика, катализ, палладий, дифференциальная селективность, механизм реакции*

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INTRODUCTION

In the 1960s, as a result of the intensive development of the chemistry of coordination compounds of transition metals, the scientific direction of liquid-phase catalysis of metal complexes was formed. This term was introduced by Academician I.I. Moiseev, one of the founders of this field of research, who made a huge contribution to its formation and development [1].

Today's chemical industry cannot be imagined without the use of catalysts based on transition metals [2, 3]. An obvious condition for the successful development of synthetic catalytic methods is the establishment of the regularities of catalyst transformations occurring over the course of the used processes. Since "no hypothesis of the mechanism can be considered as proven if it does not correspond to the observed kinetics of the process" [4], kinetic methods can be effectively used for studying the mechanisms of catalytic reactions.

A characteristic feature of reactions involving transition metal complexes is the so-called multirouteness, the concepts of which were developed in the works of I.I. Moiseev, O.N. Temkin, L.G. Brook *et al.* [5–8]. Multirouteness refers to the simultaneous occurrence of several processes coupled to each other with the participation of a catalyst. Kinetic studies with an analysis of the regularities determined in the so-called conjugation nodes of multipath reactions are an extremely effective tool for discriminating between probable hypotheses of the mechanisms of complex catalytic processes [5–8].

Among the kinetic methods for studying the mechanisms of catalytic reactions, approaches based on estimating the differential selectivity (DS) of a catalyst for a certain product as a parameter that does not depend on the concentration of active species can be singled out. This concentration is typically nonstationary and changes significantly during a catalytic reaction due to the course of formation-deactivation (poisoning) processes. However, when combined with the need to differentiate kinetic data to calculate the DS value as the ratio of product accumulation rates to the total rate of all processes involving a catalyst, the complexity of kinetic studies in general leads to the fact that DS is extremely rarely used in studies of reaction mechanisms. To overcome the described difficulties, a method was developed for estimating the DS value using the so-called phase trajectories, which require exclusively integral kinetic data [9, 10]. Subsequently, this approach, proposed for the first time to distinguish cases of catalysis of the Mizoroki–Heck and Suzuki–Miyaura cross-coupling reactions by dissolved palladium molecular complexes in solution or compounds in a heterogeneous phase [9], was developed for solving a wide range of problems related to the determination of the structure and composition of catalytically active compounds and mechanisms (stages) of their transformation inside and outside the main catalytic cycle in various catalytic processes [9–18].

In the present work, we attempted to demonstrate the possibilities of developing this approach for analyzing the genesis of a catalytic system in time using the example of a number of aryl halide coupling reactions catalyzed by Suzuki–Miyaura and Mizoroki–Heck palladium compounds, as well as in the direct arylation of heteroaromatic compounds.

PHASE TRAJECTORIES AS A TOOL FOR A COMPARATIVE INVESTIGATION OF RESPONSE OF THE REACTION TO CHANGING CONDITIONS

The originally proposed version of the analysis of phase trajectories in studies of the mechanisms of catalytic reactions assumed that the reaction was carried out under conditions of the so-called artificial multirouteness [5], i.e., when using several (at least two) similar competing substrates [9]. In this case, the concentrations of competing substrates or products formed from them (total concentrations of product groups) are plotted on the axes of phase trajectories. In this case, the slope of the phase trajectory at any of its points is the ratio of the rates of consumption of competing substrates or accumulation of the corresponding products, which unambiguously characterizes the DS value [10].

By comparing the phase trajectories of series of experiments carried out under varying process conditions, it is possible to obtain an unambiguous answer to the question of the effect or absence of the effect of variable parameters on the DS value. The principal advantage of the approach with the analysis of the DS of the reaction using phase trajectories consists in the possibility of its application under the conditions of a real catalytic process without involving the results of model (with the exclusion of one or several components of the reaction systems) and stoichiometric (at low substrate/catalyst ratios) experiments.

ANALYSIS OF THE EVOLUTION OF THE DS OF CATALYTIC REACTIONS

The above-described approach involves comparing phase trajectories in a series of experiments with different initial conditions. However, the analysis of an individual phase trajectory obtained in the course of one experiment can also be used in studies of the mechanisms of catalytic reactions, in particular, to study the transformation dynamics of the active catalyst during the reaction.

In the general case of the transformation of a pair of substrates competing for a common intermediate (Fig. 1a), the shape of the phase trajectory, which describes the change in the ratio of the rates of competing reactions with time, is different from linear. This is due to a change in the ratio of the concentrations of competing substrates during the reaction due to their different reactivity [10]. At the same time, if the phase trajectory is constructed from the concentrations of the products of not competitive, but parallel reactions (Fig. 1b), whose rate is determined solely by the reactivity and concentration of the common intermediate of the parallel reaction, the ratio of the accumulation rates of such products, provided that the nature of the common intermediate remains unchanged, should be constant during the reaction and, therefore, the phase trajectory must be strictly linear.

Situations of parallel reactions of catalytic cycle intermediates arise in reactions involving the formation of isomeric products (regioisomers, stereoisomers, enantiomers, etc.). Thus, the

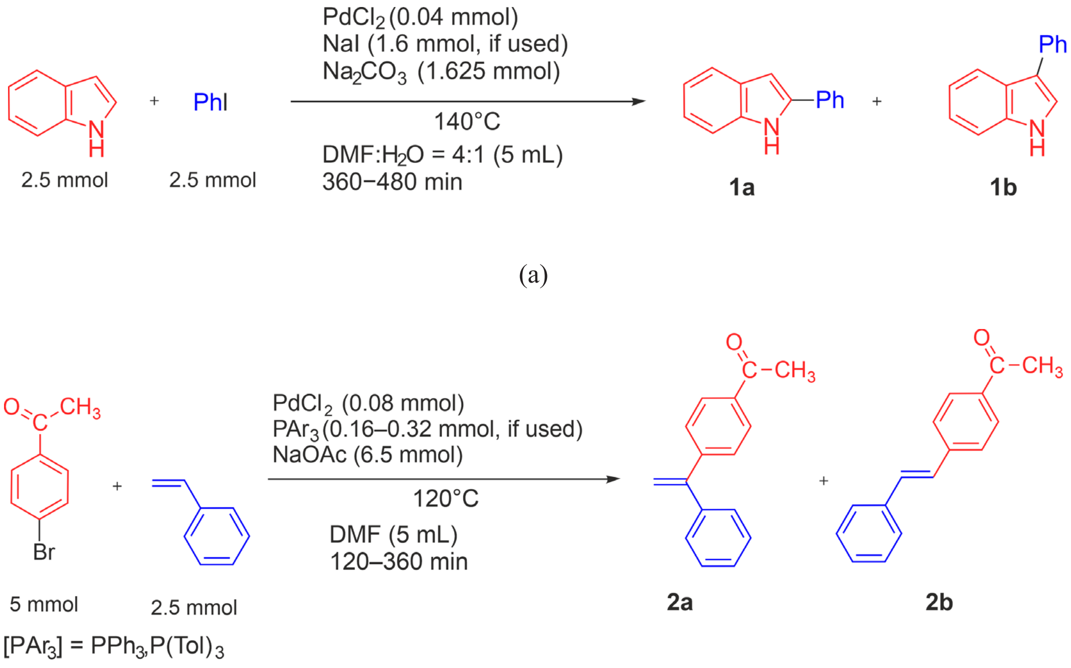
(a) (b)

Fig. 1. General scheme of the reaction with the formation of two products P1 and P2 as a result of:
(a) competitive reaction of two substrates S1 and S2 with common intermediate (X_{com});
(b) two parallel reactions of the common intermediate (X_{com}) (monomolecular, or due to the interaction with the one substrate S).

experimentally observed deviations of phase trajectories from linearity are direct evidence of changes in the nature of the common intermediate in the course of the reaction.

For example, for the reaction of direct arylation of indole with an aryl halide (Fig. 2a), the phase trajectories in the coordinates of the concentrations of C2- and C3-regioisomeric products of indole arylation deviated from linearity (Fig. 3a, curve 1), indicating a change in the composition of catalytically active complexes during the reaction. The change in the catalytic system was also found to be caused by the ratio of the concentrations of base anions capable of being coordinated to palladium and endogenous halide ions [19] that accumulate as a result of the conversion of the initial aryl halide, which changes during the process. This hypothesis was confirmed by the "straightening" of phase trajectories with an increase in the addition of iodide salt, which simulates the effect of endogenous halide ions (Fig. 3a, curve 2) [13].

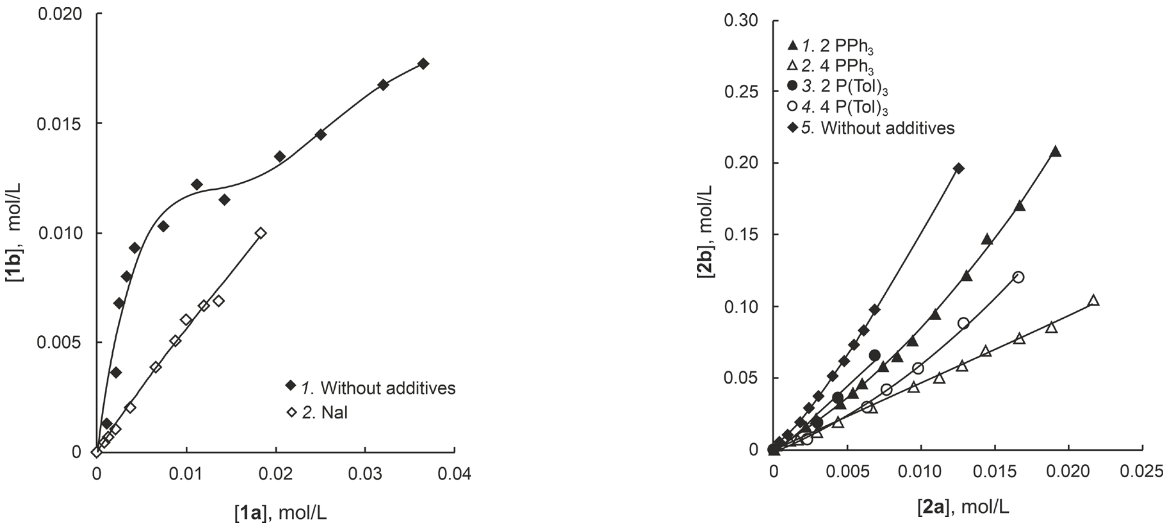
In the Mizoroki–Heck reaction, a comparison of the phase trajectories in the coordinates of concentrations of α- and β-regioisomeric products of styrene arylation (Fig. 2b) indicated the sensitivity of differential regioselectivity to the introduction



(a)

(b)

Fig. 2. Scheme of: (a) reaction of direct arylation of indole,
(b) Mizoroki–Heck reaction with the formation of regioisomeric products.



(a) (b)

Fig. 3. Phase trajectories plotted by using the concentrations of regioisomeric products formed in the following reactions: (a) direct arylation of indole with iodobenzene (Fig. 2a); (b) styrene arylation with 4-bromoacetophenone (Fig. 2b).

of tertiary phosphine additives into the reaction system (Fig. 3b), indicating its entry into the composition active complexes of palladium. In this case, the deviation of the phase trajectory from linearity observed in some cases (Fig. 3b, curves 1, 4, 5) also indicated a change in the composition of such complexes during the reaction.

In special experiments, deviations from linearity were found to be due to a change in the ratio of the concentrations of tertiary phosphine and endogenous halide ions accumulated during the reaction, which compete for inclusion in the composition of active complexes [14].

An assessment of the degree of deviation of the phase trajectory from linearity as a criterion for changing the nature of the active catalyst during the process, which can be carried out both visually and using the tools of linear regression analysis, can be used not only for the case of parallel reactions of catalytic cycle intermediates (Fig. 1b), but also in the case of their competitive transformations in the presence of several substrates/reagents (Fig. 1a). To do this, the change in the concentrations of competing substrates that affect the value of DS in the course of the reaction should be insignificant, that is, to create conditions for the pseudo-zero order reaction to proceed through competing substrates. The traditional technique for implementing pseudo-zero order conditions for substrates involves the use of their excess concentrations. From a mathematical point of view, this means that (as in the case of phase trajectories of parallel reactions of the transformation of a common intermediate) the ratio of the rates of competing reactions of a common intermediate during the reaction, i.e., the slope of the phase trajectory should remain practically unchanged with the constancy of the nature of the intermediate, which should lead to a linear phase trajectory (1).

If the conditions $[S1]_0 >> [\mathrm{P1}]$ и $[S2]_0 >> [\mathrm{P2}]$ are satisfied, then the equation:

$$\frac{r_{\mathrm{S2}}}{r_{\mathrm{S1}}} = \frac{d[S2]/dt}{d[S1]/dt} = \frac{k_{\mathrm{S2}}[X_{\mathrm{com}}]^{n_{\mathrm{cat}}}[S2]^{n_{\mathrm{S}}}}{k_{\mathrm{S1}}[X_{\mathrm{com}}]^{n_{\mathrm{cat}}}[S1]^{n_{\mathrm{S}}}} = = \frac{k_{S2}([S2]_0-[P2])^{n_{\mathrm{S}}}}{k_{S1}([S1]_0-[P1])^{n_{\mathrm{S}}}} \approx \frac{k_{\mathrm{S2}}}{k_{\mathrm{S1}}}\left(\frac{[S2]_0}{[S1]_0}\right)^{n_{\mathrm{S}}}, \qquad (1)$$

where r_{S1} and r_{S2} are the rates of conversion of competing substrates S1 and S2 into the corresponding products P1 and P2 with effective rate constants k_{S1} and k_{S2}, respectively (Fig. 1a); $[X_{\mathrm{com}}]$ is the concentration of the total catalytic cycle intermediate; $[\mathrm{S1}]_0$ and $[\mathrm{S2}]_0$ are the initial concentrations of competing substrates; n_{S} and n_{cat} are the reaction orders with respect to the substrate and catalyst, respectively.

For example, in the Suzuki–Miyaura reaction (Fig. 4), the use of a pair of competing aryl chlorides at concentrations exceeding the concentration of their common reagent—arylboronic acid—by a factor of 6 led to linear phase trajectories (Fig. 5a), confirming the value expected based on the equation (1). This result allows us to confidently state that no changes in the nature of the catalytically active compound responsible for the activation of competing aryl halide substrates occur during the reaction. At the same time, under conditions of equimolar ratios of competing aryl chlorides and arylboronic acid (Fig. 5b), the phase trajectory had a typical nonlinear character, which is to be expected for the case of competition of substrates differing in reactivity.

It is not always possible to carry out a reaction with an excess of competing substrates to linearize phase trajectories in order to test the hypothesis of the invariance of the nature of the compounds responsible for catalysis. However, it is also possible to obtain information about the patterns of evolution of the catalytic system for a competitive reaction under conditions of substrate concentrations close to equivalent amounts. In the case of competition between substrates for a common intermediate of the catalytic cycle, the reaction should proceed as one having first order with respect to competing substrates. In this case, integration of Eq. (1) under the condition of the first order in substrates ($n_S = 1$) leads to an equation of the following form:

$$\ln\left(\frac{[S2]}{[S2]_0}\right)=\frac{k_{S2}}{k_{S1}}\ln\left(\frac{[S1]}{[S1]_0}\right)=k_{\text{rel}}\ln\left(\frac{[S1]}{[S1]_0}\right), \tag{2}$$

where k_{rel} is the relative reactivity of competing substrates.

By using logarithmic coordinates corresponding to Eq. (2) it becomes possible to return to the linear forms of phase trajectories for estimating deviations from linearity as a result of evolutionary changes in the behavior of the catalytic system for most catalytic reactions. The degree of deviation from linearity can be assessed both visually and using linear regression analysis.

If the value of the correlation coefficient of the linear dependence according to Eq. (2) decreases during the reaction, this is unambiguous evidence of the evolution of the catalytic system in a direction not described by this equation. Thus, when performing the Suzuki–Miyaura reaction under the conditions of competition of a pair of arylboronic acids (Fig. 6), a decrease in the value of the correlation coefficient of the linear dependence (2) was found to occur with an increase in the depth of the reaction. The deviation of the experimental phase trajectory from that expected in the approximation of the constant nature of the active catalyst can be demonstrated by comparing it with the phase trajectory obtained by calculation using a constant value of k_{rel}, which is estimated from the slope of linear dependence (2) at the initial stage of the reaction (Fig. 7a). This pattern can also

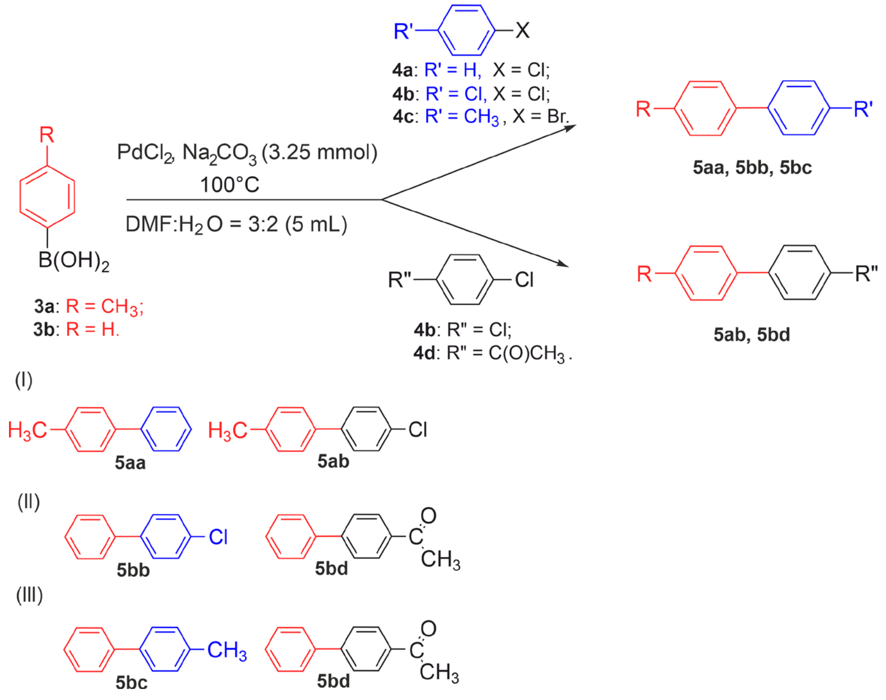
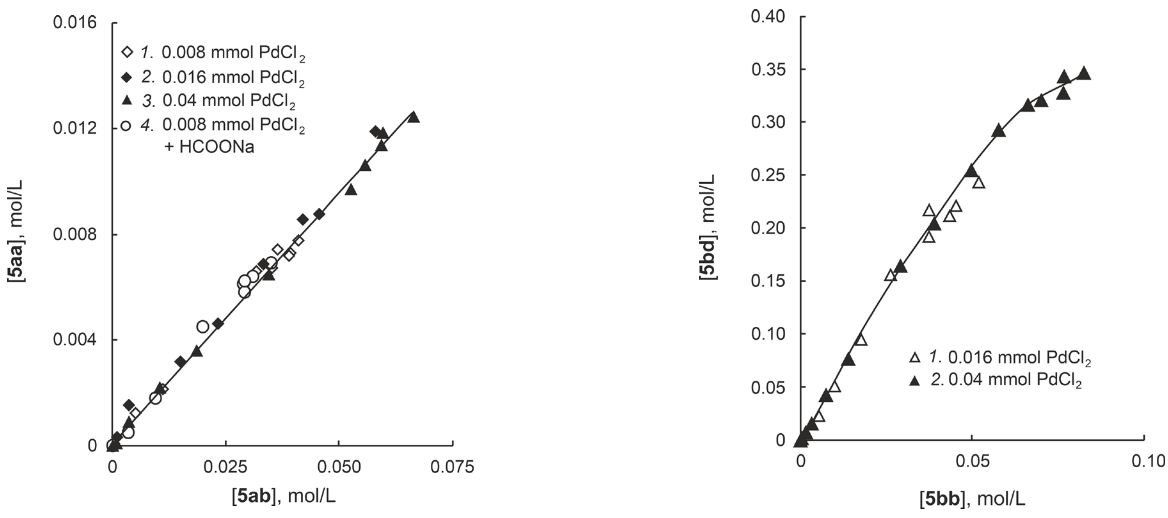


Fig. 4. Suzuki–Miyaura reaction under competition of two aryl halides.
Reaction conditions: (I) **3a** (0.4 mmol), **4a** (2.5 mmol), **4b** (2.5 mmol), $PdCl_2$ (0.008–0.04 mmol), HCOONa (0.1 mmol, if used), 30–140 min, products **5aa**, **5ab**;
(II) **3b** (2.5 mmol), **4b** (2.5 mmol), **4d** (2.5 mmol), $PdCl_2$ (0.016–0.04 mmol), 120–220 min, products **5bb**, **5bd**;
(III) **3b** (2.5 mmol), **4c** (1.25 mmol), **4d** (10 mmol), $PdCl_2$ (0.008 mmol), NBu_4Br (1.15 mmol, if used), 120–230 min, products **5bc**, **5bd**.



(a) (b)

Fig. 5. Phase trajectories of Suzuki–Miyaura reaction with competing:
(a) chlorobenzene and 1,4-dichlorobenzene in the reaction with 4-tolylboronic acid (Fig. 4, conditions (I));
(b) 1,4-dichlorobenzene and 4-chloroacetophenone in the reaction with phenylboronic acid (Fig. 4, conditions (II)).

be visualized by plotting the deviations of the experimentally observed and calculated using the constant k_{rel} value of the concentrations of the product of one of the competing reactions from the concentration of the product of the second competing reaction (Fig. 7b).

The change in the nature of Pd(II) compounds active in the selectivity-determining step [20, 21] was due to a change in the ratio between the concentrations of the base anions capable of coordinating with palladium and the accumulated endogenous halide ions [19].

Evolutionary changes in the catalytic system can also be evaluated for hypotheses of mechanisms that are more complex in comparison with Eq. (2). Under the competition between aryl chloride and aryl bromide in the Suzuki–Miyaura reaction, the kinetics of the reaction are affected by the significant reversibility of the stage in which the competition of substrates occurs [10, 17] (Fig. 8). In this case, the DS is described by Eq. (3) that is more complicated than Eq. (2) and not amenable to linearization. Here, numerical methods for simulating the reaction kinetics can become useful. For example, as the depth of the reaction increases, the phase trajectory (Fig. 9a) is observed to deviate from the calculated dependence obtained by numerical integration of Eq. (3) under the assumption of the unchanged nature of catalytically active species, i.e., unchanged values of the rate constants for the elementary steps presented in Eq. (3)). This is confirmed by the increase in the deviation of the experimental values of the concentrations of one of the competitive reaction products from those calculated by Eq. (3) observed with increasing reaction depth (Fig. 9b).

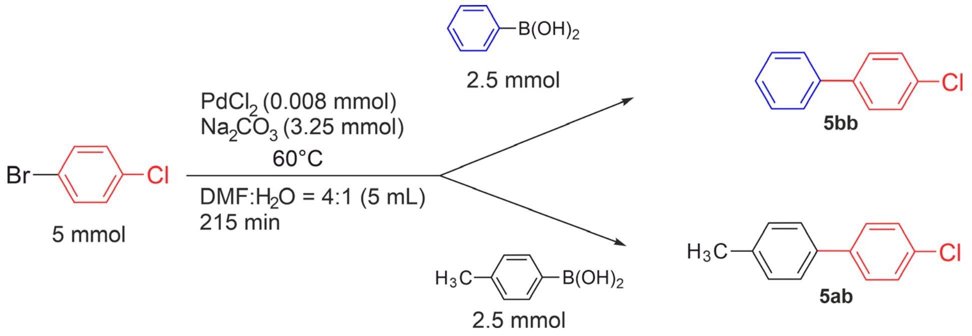
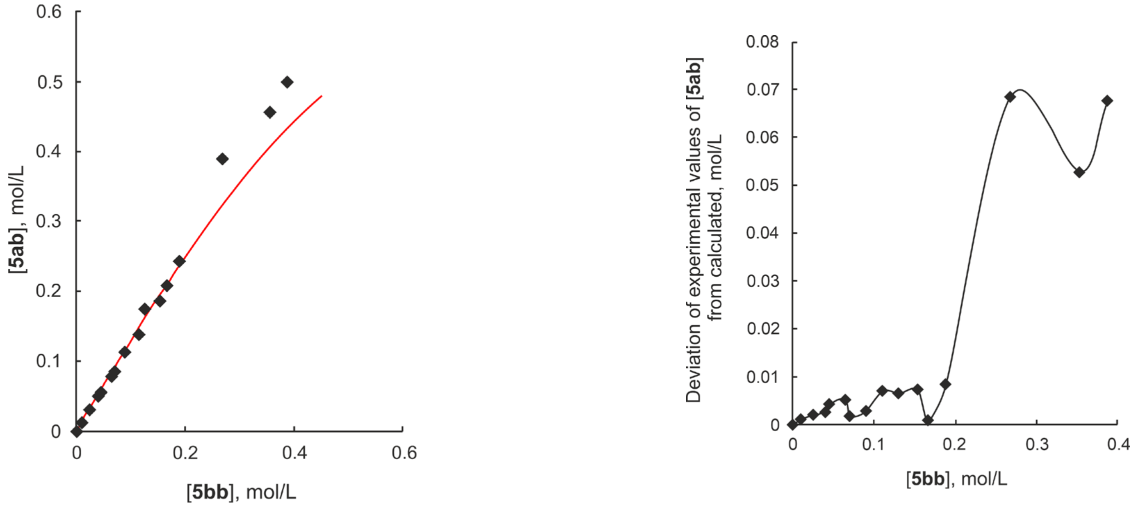


Fig. 6. Suzuki–Miyaura reaction under competition of two arylboronic acids.



(a) (b)

Fig. 7. Experimental (dots) and simulated (red line) phase trajectories of Suzuki–Miyaura reaction with 1-chloro-4-bromobenzene and competing phenyl- and 4-tolylboronic acids (a), and the plot of the deviations between experimental and calculated values of the 1’-chloro-4-methylbiphenyl concentrations (**5ab**) *vs*. increasing 4-chlorobiphenyl concentrations (**5bb**) under the reaction proceeding (b) (Fig. 6).

$$\frac{r_{S2}}{r_{S1}} = \frac{(k'_{S2}k_{S2})(k'_{-S1}+k_{S1}[\mathrm{ArB(OH)_2}])[\mathrm{Ar_2X}]}{(k'_{S1}k_{S1})(k'_{-S2}+k_{S2}[\mathrm{ArB(OH)_2})[\mathrm{Ar_1X}]}, \qquad (3)$$

where r_{S1}, r_{S2} are the conversion rates of competing aryl halides; $[Ar_1X]$ and $[Ar_2X]$ are the concentrations of aryl halides; $[ArB(OH)_2]$ is the concentration of arylboronic acid. The constants k'_{S1}, k'_{-S1}, k_{S1}, k'_{S2}, k'_{-S2}, k_{S2} correspond to the rate constants of the elementary stages given in Fig. 8. The obtained data represent an additional demonstration of the possibilities of analyzing the nature of catalytically active compounds using phase trajectories under conditions of complex dynamic transformations of the catalyst, which are characteristic of cross-coupling reactions of aryl halides [19, 22–24].

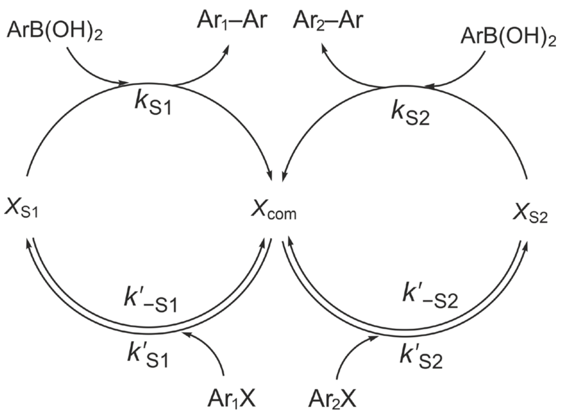


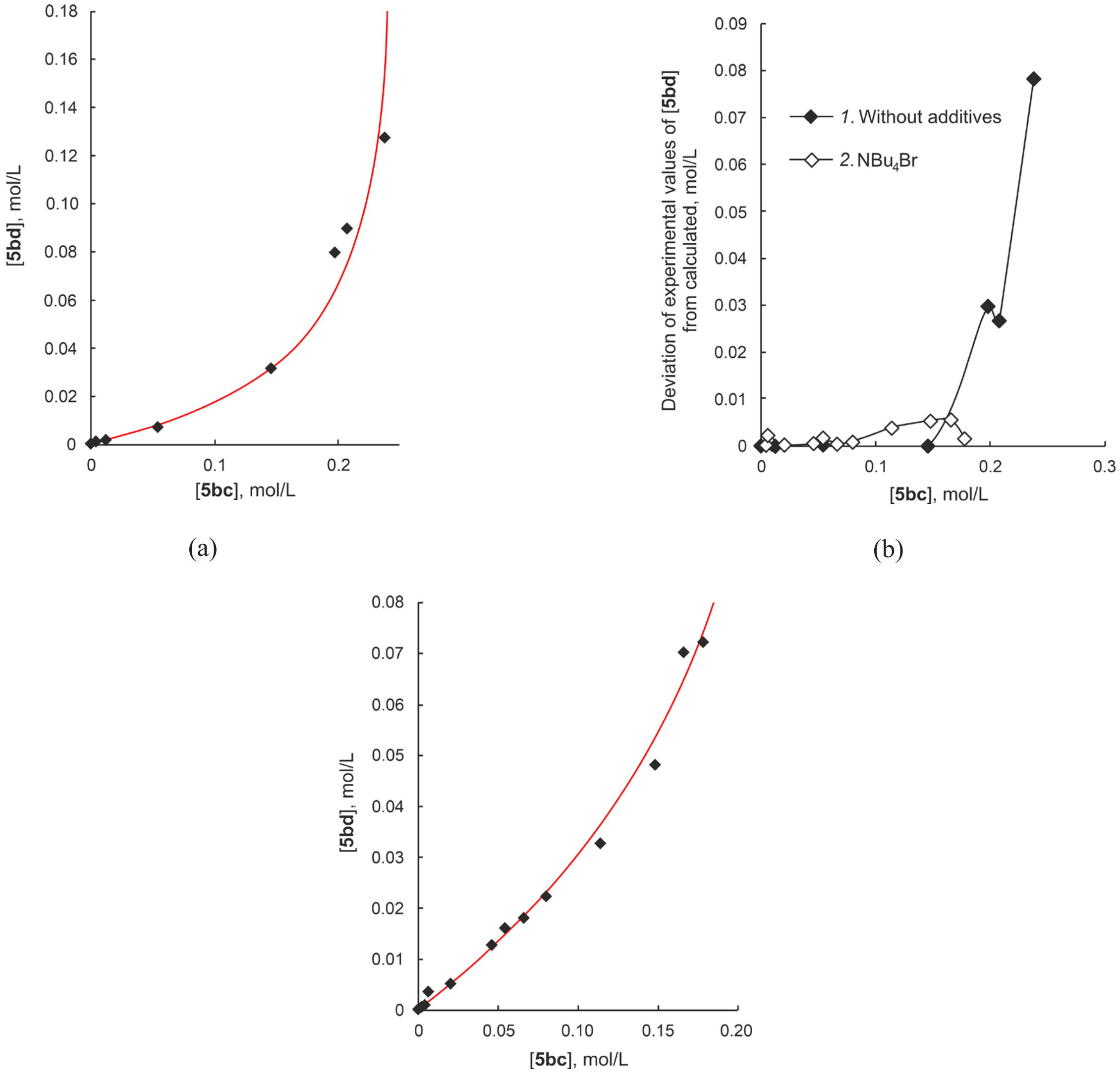
Fig. 8. Scheme of the competitive Suzuki–Miyaura reaction with arylboronic acid, considering reversible character of the elementary step where two aryl halides (Ar_1X, Ar_2X) compete.

The deviations again turned out to be explainable in terms of the accumulation of endogenous halide ions during the reaction [19], leading to a change in the ratio between the catalytically active dissolved and inactive solid forms of the catalyst, which are converted into each other during the reaction [9, 18]. As confirmation of this hypothesis, we can consider the decrease in the deviations of the experimental and calculated phase trajectories at the late stages of the reaction when using additives of halide salts that simulate the effect of endogenous halide ions as significant in terms of reducing the effect of the accumulation of endogenous halogen anions on the distribution of palladium between different types of active particles in the course of the reaction (Fig. 9c).

CONCLUSIONS

The presented examples demonstrate the possibilities of a simple kinetic method using exclusively primary experimental data on the accumulation of products of parallel or competing reactions for studying evolutionary changes during the functioning of catalytic systems.

By constructing phase trajectories of competing or parallel reactions in different coordinates to linearize the dependences of the concentrations



(a)

(b)

(c)

Fig. 9. Experimental (dots) and simulated (red line) phase trajectories of Suzuki–Miyaura reaction with phenylboronic acid and competing 4-chloroacetophenone and 4-bromotoluene with no additives (a), and the plot of the deviations between experimental and calculated values of the 4-acetylbiphenyl concentrations (**5bd**) *vs*. increasing 4-methylbiphenyl concentrations (**5bc**) under the reaction proceeding without additive and with NBu_4Br additive (b). At part (c) the phase trajectories for the reaction with NBu_4Br additive are plotted (Fig. 4, conditions (III)).

of the products of these reactions on each other, it becomes possible to track possible changes in the nature of the active catalyst by visual estimation or linear regression analysis. When the complex nature of the conjugation of the elementary stages of competing catalytic cycles does not permit a linearization of the phase trajectory, the assessment of possible changes in the nature of the catalyst during the reaction can be carried out by simulating phase trajectories using numerical integration procedures for differential equations that describe the ratios of the rates of competing processes.

The analysis of changes in DS or relative reactivity carried out in this way as a result of the spontaneous evolution of the catalytic system can be especially useful for discriminating between possible hypotheses of the mechanism in reactions whose characteristic feature is the dynamic nature of the transformations of various potentially active forms of the catalyst.

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Authors' contribution

All authors equally contributed to the research work.

The authors declare no conflicts of interest.

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