Discrimination of the mechanistic hypotheses for two- and three-component cross-coupling reactions by using mathematical modeling of the differential selectivity patterns

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Abstract. Distinguishing between several probable mechanistic hypotheses for complex catalytic reactions is a very complicated task. The main cause of such complication is the simultaneous realization of several consecutive-parallel processes under the reactions proceeding including side reactions with the participation of a catalyst. Under these circumstances, using kinetic studies of the reactions can provide unique possibilities to discriminate alternative mechanistic proposals. To achieve the goal, we offer to use the studies of the differential selectivity of such complex reactions by analysing possible correspondence of its patterns to different mathematical models describing alternative mechanistic hypotheses. Using this approach the fine mechanistic details of the catalytic cycles of two-component cross-coupling Suzuki-Miyaura and Mizoroki-Heck reactions as well as of three-component Sonogashira-type reaction coupling have been established.

1. Introduction

Catalytic reactions are the most effective tool for obtaining desired chemical products with high activity (expressed as high reaction rate) and selectivity (that means low concentration of side undesired products formed). As for any other chemical processes, the development of effective procedures for catalytic transformations requires reliable data on the fundamental aspects of the process functioning. However, the revealing of the processes realized in the catalytic system at molecular level is a very complicated scientific task. To clarify catalytic reaction’s mechanism, a set of chemical and physicochemical methods including experimental and theoretical ones is usually used. Note that by the term “reaction mechanism” we will mean hereinafter the set of chemical substances reacting in the definite set of consecutive-parallel steps. Due to the complex character of interconnection between elementary steps of the catalytic cycle and side processes, the search for and development of methods allowing to unambiguously establish the fundamental mechanistic peculiarities of such reactions is the “hot” issue of the catalysis. In the present paper we have attempted to demonstrate that by using simple approach for mathematical description of the reaction differential selectivity based on the experimental data set that does not require expensive equipment it is possible to obtain valid results for complex catalytic reactions. Applications of the approach will be demonstrated below for the family of so-called cross-coupling reactions [1].
2. Theoretical considerations

Schematic representation of catalytic reaction mechanism is presented in figure 1. All catalytic reactions proceed through the formation of intermediates. Therefore, the substances existing in the reaction mixture during the reaction proceeding are to be considered at least as the reactants (including catalyst precursor), intermediates participating in the catalytic cycle, and the reaction products (figure 1). It is well-known that to establish the nature of catalytic reaction intermediates is a very complex task. The matter is that such intermediates are highly reactive substances usually, and, as a result, can be present in the reaction mixture in ultra-low concentrations. However, even hypothetically the situation is realized when all the intermediates participating in the reaction have been experimentally detected and known, such data will be insufficient for establishing the reaction mechanism. The matter is that complete information on the composition and structure of all chemical system components does not allow to construct the mechanistic reaction scheme and only makes it possible to reveal the chemical (or physicochemical) component of the reaction mechanism [2].

![Figure 1. Schematic representation of typical catalytic cycle where Ii is the catalytic reaction intermediate.](image)

This statement has strict mathematical proof. With the data on the composition of all reactants/intermediates in hand, it is possible to unambiguously determine the obligatory set of linearly independent stoichiometric equations (linear algebraic equations) required for finding all possible equations of component material balance, describing the ratios between the amounts of components during the reaction. The mathematical problem of finding linearly independent stoichiometric equations based on the above-mentioned data on the composition of the reaction mixture is reduced to solving a system of linear algebraic equations determining the composition of reaction components, i.e., the following molecular matrix of the system:

\[
B = \begin{bmatrix}
\beta_{11} & \beta_{12} & \ldots & \beta_{1k} \\
\beta_{21} & \beta_{22} & \ldots & \beta_{2k} \\
\vdots & \vdots & \ddots & \vdots \\
\beta_{nk} & \beta_{n2} & \ldots & \beta_{nk}
\end{bmatrix}
\]

where \(k\) is the number of chemical elements being part of the components (i.e. chemical compounds) of the system; \(n\) is the number of the components of the system; \(\beta_{nk}\) – the number of gram-atoms of the element \(k\) in the component \(n\).

The stoichiometric matrix of the system is the following rectangular matrix:

\[
A = \begin{bmatrix}
\alpha_{11} & \alpha_{12} & \ldots & \alpha_{1x} \\
\alpha_{21} & \alpha_{22} & \ldots & \alpha_{2x} \\
\vdots & \vdots & \ddots & \vdots \\
\alpha_{n1} & \alpha_{n2} & \ldots & \alpha_{nx}
\end{bmatrix}
\]
In this case, \( n \), as above, is the number of the components of the system; \( m \) is the number of the stoichiometric equations describing the chemical conversions between components proceeding in the systems; \( \alpha_{n,m} \) is the stoichiometric coefficient of the component \( n \) in the stoichiometric equation \( m \).

Based on the law of conservation of mass, the relation between the \( A \) and \( B \) matrices represents the follows:

\[
A \times B = 0.
\]

If the elements of the \( B \) matrix (i.e. the compositions of the system components) are known, it becomes possible to find one of an infinite number of the linearly dependent variants of the \( A \) matrix, i.e. one of the possible linearly dependent sets of stoichiometric coefficients of the stoichiometric equations describing all the chemical transformations possibly proceeding in the systems [2].

However, the above matrix \( A \) is only one of an infinite number of related linearly dependent matrices that also conforms to the observed component composition. The problem of finding the correct set of stoichiometric equations corresponding to the real reaction mechanism steps based on the knowledge of component composition has no solution. Therefore, the establishing of the composition of the reaction components is insufficient for the clarification of the reaction mechanistic scheme. Thus, additional kinetic data are necessary.

3. The differential selectivity measurements as effective kinetic tool for mechanistic investigations

Kinetic studies of catalytic reactions consisting usually in the establishing of temporal dependences of the concentrations of the substrates, products, and, if possible, the reaction intermediates are one of the most effective tools for mechanistic investigations, as “catalysis is a wholly kinetic phenomenon” [3,4]. The simplest kinetic study is the measurements of the dependence of the reaction rate \( r \) on the concentrations of the reactants and catalyst precursor in accordance with the main postulate of chemical kinetics:

\[
r = C_A^{n_A} C_B^{n_B} C_{Cat}^{n_{Cat}},
\]

where \( C_A \), \( C_B \), and \( C_{Cat} \) are the concentrations of reactants and the catalyst, and \( n_A \), \( n_B \), and \( n_{Cat} \) are the so-called partial kinetic order in correspondent reactants.

The equation (1) described the dependence of overall reaction rate on the concentrations of the reaction participants. However, real catalytic reactions are multistep processes, and particular combination of elementary step proposed as the reaction mechanism leads to the rate dependence with particular meanings of partial reaction orders. For complex reaction such meanings can be integer or fractional, positive or negative. Additionally, partial reaction orders can vary significantly during the reaction proceeding due to the change of the reactants’ concentrations from high to low (to zero when full conversion is observed) [5]. Therefore, the establishing of partial kinetic order of the reaction rates is a popular approach in kinetic investigations, and it is useful for primary assessment of the correspondence of any mechanistic proposal to the reaction under consideration. However, it is well-known that real catalytic processes are nearly always complicated by the processes of side catalyst transformations. Usually, the catalyst compound loaded to the reaction system is not the “true” catalyst but is the catalyst precursor, i.e., it is necessary for some preliminary transformations to produce the species being able to catalyze the reaction spontaneously or by the interaction with the reaction components (figure 1). Additionally, one or more different side reactions with catalyst participation lead to the formation of catalyst forms being inactive in catalysis. Such processes are the catalyst deactivation. In some cases, such inactive forms can regenerate in the course of the reaction, but it is not the obligatory condition (figure 1). All these processes occurring simultaneously with the main catalytic cycle (i.e., the reaction where the substrates loaded convert into the target products) result in the complex character of the dependence of the reaction rate on catalyst concentration due to the non-stationarity of the latter. Therefore, measurements of reaction rates to obtain partial kinetic orders for elucidating mechanistic details of complex catalytic reaction can lead to ambiguous results [6].
As an alternative to the studies of the reaction rates, we proposed to study the reaction differential selectivity (DS). For the reaction where several types of products can form, the differential selectivity of a catalyst on the desired product \((P_1)\) is the ratio of the rate of its formation \((r_{P_1})\) to the sum of the formation rates of all the reaction products \((r_P)\):

\[
Sel_{\text{dif}} = \frac{r_{P_1}}{\sum r_P} = \frac{d[P_1]/dt}{\sum d[P]/dt} = \frac{d[P_1]}{\sum d[P]}
\]  

(2)

where \(r_P\) is the rate of formation of i-th product, \([P]\) is the concentration of i-th product.

For only two products it is possible to assess the differential selectivity using the ratio of the formation rates connected with the differential selectivity by simple dependence:

\[
Sel_{\text{dif}} = \frac{r_{P_1}}{r_{P_1} + r_{P_2}} = \frac{1}{1 + r_{P_2}/r_{P_1}}
\]

\[
r_{P_2} = d[P_2]/dt = d[P_2]/dt = \frac{1 - Sel_{\text{dif}}}{Sel_{\text{dif}}}
\]

(3)

The main advantage of the DS measurements in comparison with the measurements of catalytic activity (i.e., the reaction rate) is the independence of DS on the total concentration of the true catalyst (active species) participating in catalytic cycle (we will demonstrate it below). Indeed, in most cases the concentration of active species is unknown because of the permanent proceeding of their formation, deactivation, and re-activation during the catalytic reaction. Also, as stated above, the active reaction intermediates are highly reactive substances, so their concentrations are usually low and cannot often be detected by routine analytical methods. Additionally, as several forms of catalyst being possibly active are present in the reaction system, one cannot be assured that the form of the catalyst whose concentration is measured is active indeed. Therefore, independence of the DS on the active catalyst concentration allows to overcome these circumstances and apply the method for the reactions accompanied by non-stationarity of active species concentrations.

4. The differential selectivity measurements using phase trajectories

Usually, kinetic studies of the reaction imply the measurements of the concentrations of some of the reaction participants at different time points. Using the data, it is possible to estimate the rates of the products formation \(r_{P_1}\) and \(r_{P_2}\) in the course of the reaction, for instance, by graphical or numerical differentiation of the tabulated dependencies of the products’ concentrations vs. time. However, such way is considerably effortful and may be accompanied by errors resulting from finite periods between two neighboring time points. In order to provide more precise measurements of the reaction rate, special equipment can be used to allow either continuous and accurate measurements of the concentrations of the reactant multiple times per short period or direct evaluation of the rate of the reaction, particularly, the one based on the measurements of instantaneous heat flow of the reaction [5]. However, a substantial shortcoming of the methods is the impossibility of evaluating the kinetics of the formation of several products. In addition, such equipment is rather expensive, so it may not be available. As a result, under kinetic studies there often is a deficiency of kinetic data (component concentrations at different reaction times) and the rate values cannot be calculated exactly.

As a possible way to overcome these difficulties, we proposed another approach for measurements of the reaction differential selectivity using the integral kinetic data on the reactants/products concentrations at different times of the reaction [7]. For the reaction when the formation of two products \(P_1\) and \(P_2\) occurs, it is possible to plot the so-called phase trajectories, i.e., the interdependence of the concentration of \(P_2\) vs. \(P_1\), and the tangent slope to any point of such curve is the ratio of the rates of the formation of \(P_1\) and \(P_2\) (see equation (3)). Therefore, with only integral data in hand (dependencies of the concentrations vs. time), it is possible to check at qualitative (by
coincidence or non-coincidence of the phase trajectories) or quantitative (by comparison of the slopes of the phase trajectories) level the probable preservation or change of the reaction DS under change of the reaction conditions. Thus, the reaction DS can be easily studied by plotting phase trajectories at the variations of the reaction system aimed at the changes of a particular reaction parameter. Overlap of the phase trajectories points to the constancy of the DS under varying the reaction conditions, while difference of phase trajectories unambiguously indicates a change of the DS.

5. Application of mathematical modeling of the differential selectivity patterns for mechanistic studies of cross-coupling reactions

5.1. The studies of the differential selectivity in the processes with “natural multi-routeness”

As follows from the definition of DS, its application implies the formation of several (at least, two) reaction products. Please note that hereinafter we will mean the ratio of the rates of two products formation as the DS (3).

Nearly always for thermodynamic reasons, catalytic reactions feature parallel routes leading to the formation of several reaction products. Formation of two or more products in a reaction catalyzed by one catalyst implies the existence of multi-route reactions occurring through common intermediates. These intermediates turn into two (or more) parallel or competitive (with the participation of additional reagents) steps being the parts of the so-called conjugation nodes (i.e., the fragments of a mechanism involving three (or more) steps related to the same intermediate) [2]. The situation when several reaction products form from one set of reactants can be characterized as “natural multi-routeness” as it does not need any additional substances for several products to be formed. The simplest situation is realized when two products form from one substrate in parallel reactions. The principal scheme of the process is represented in figure 2. Substrate S reversibly reacts with active catalyst X with the formation of intermediate Xs followed by its conversion into products P1 and P2 and catalyst X. Such mechanism of typical catalytic process corresponds to so-called Michaelis-Menten kinetics that has been used for catalytic reaction for more than 100 years [8]. The sole distinction for figure 2 is the parallel formation of two products from one substrate. However, it does not lead to any principal difference in the sum rate of the conversion of the substrate to the products.

![Figure 2. Schematic representation of two products (P1 and P2) formation in a parallel reaction.](image)

Based on the law of mass action, it is possible to obtain the equations for the rates of the formation of products P1 and P2 (figure 2) by using quasi-equilibrium approximation for interaction of the catalyst X with the substrate S [2]. Such approximation permits the concentrations of the intermediates to be excluded from the rate equation, so that only the sum of intermediate concentration, i.e., the total amount of active species ([Cat]e), remains in the equation:

\[
\frac{d[P1]}{dt} = \frac{k_{P1}K[S][Cat]_e}{1 + K[S]} ,
\]

\[
\frac{d[P2]}{dt} = \frac{k_{P2}K[S][Cat]_e}{1 + K[S]} ,
\]

where \( r_{P1} \) and \( r_{P2} \) are the rates of formation of P1 and P2 products, \( K \) is the equilibrium constant, i.e., the ratio of the rate constant of the S and X interaction in forward and reverse directions, \( k_{P1} \) and \( k_{P2} \) are the rate constants of the elementary steps where the formation of corresponding products occurs, \([Cat]_e=[X]+[X_s]\).
Note that rate constants and equilibrium constants are the values whose meanings are determined by the nature of the interacting substances and temperature but they are insensitive to the concentrations of the substances. As was stated above, the total amount of active species is unknown for most of the catalytic reactions due to the complex character of the processes with the participation of the catalyst including its side transformations (figure 1). Therefore, using total concentration of catalyst precursor (loaded into the reaction system) is highly probable to be incorrect. However, the DS of the catalyst (i.e., the ratio of the rates of \( P2 \) and \( P1 \) formation) does not contain the concentration of active species at all:

\[
\frac{r_{r2}}{r_{r1}} = \frac{d[P2]}{d[P1]} = k_{r2}/k_{r1}.
\]

Therefore, even if the concentration of active species changes during the reaction proceeding, the value of the reaction DS will be unchanged. Consequently, the corresponding phase trajectory (interdependence of \([P2]\) vs. \([P1]\)) should have the constant slope, i.e., to be the line. As follows from (5), the DS is determined only by the ratio of the rate constants depending on the nature of common intermediate \( X_S \), whose nature, in its turn, is determined by the natures of substrate \( S \) and catalyst \( X \) (figure 2). Therefore, if the nature of active species responsible for the formation of the reaction products (\( X \) and \( X_S \)) is unchanged in the course of the reaction, the rate constants \( k_{r1} \) and \( k_{r2} \) should also be unchanged resulting in the constancy of the rate ratio \( r_{r2}/r_{r1} \). As stated above, permanent change of the concentration of different forms of catalyst being present in the reaction systems (both active and inactive) always accompanies catalytic reactions [2,9]. Moreover, several types of catalyst can be active in the reaction (see, for instance, [10]). All these circumstances lead to the following: the concentration of active species becomes non-stationary and application of the equations of the reaction rate (being of equation (1) type) containing this concentration for unambiguously elucidating mechanistic details becomes impossible. However, as follows from the equation (5), the expression for the DS of the reaction does not contain the concentration of active species at all. Such peculiarity of the DS also remains when much more complex mechanisms are realized in a catalytic system, and we will demonstrate it below. Therefore, the studies of the DS are applicable for any catalytic reaction. The sole condition that must be strictly followed is the formation of the products whose concentrations are used for the measurements of DS through the identical reaction mechanisms on identical type of active species (reaction intermediates). Otherwise, the rate equations for the formation of the reaction products will contain different rate constants and the concentrations of different reaction intermediates, so any simplification by dividing the equations against each other will have no sense.

Let us demonstrate the powerful methodology of DS measurements by using the phase trajectories on the example the Mizoroki-Heck reaction (figure 3). Two \( \alpha \)- and \( \beta \)-regioisomeric products (i.e., the molecules being distinct in the position of the substituent appearing as a result of the reaction) form from aryl halide and alkene [11,12]:

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\( M = \text{Li, Na, NBu}_4 \)

\( X = \text{Cl, Br, I} \)

\( \text{PdCl}_2 \)

\( \text{MX, NMP, } 140^\circ\text{C} \)

\( \text{Ph} \quad \text{Ph} \)

\( \beta \)-product

\( \text{Ph} \quad \text{Ph} \)

\( \alpha \)-product

**Figure 3.** Scheme of Pd-catalyzed Mizoroki-Heck reaction.

Based on the accepted view on the mechanism of the Mizoroki-Heck reaction [13], the selectivity on \( \alpha \)- and \( \beta \)-regioisomeric products (3 and 4, figure 3) is determined in the elementary step of so-called migratory insertion of alkene (steps C, \( C' \), figure 4). Using quasi-equilibrium approximation for \( \pi \)-complex formation (step B, figure 4) and steady-state approximation for other catalytic cycle intermediates [2], the rates of the formation of \( \alpha \)- and \( \beta \)-regioisomeric products will be as follows:
The changes of the rate constants can any unknown quantities of the rate constants in the equations for mathematical modeling where $k_i$ and $K$ are the rate and equilibrium constants of elementary steps in figure 4, $[Cat]_e = [Pd(0)L_α]+[ArPdL_βX]+[\sigma\text{-complex}]+[\sigma\text{-complex}]+[\sigma\text{-complex}]+[HPdL_αX]$.

As can be seen, a very complex character of equations (6) does not allow analyzing them and using the equations for mathematical modeling as they contain too many unknown quantities of the rate constants of elementary steps that cannot be reliably estimated by using experimental data. At the same time, the ratio of the rates of $\alpha$- and $\beta$-regioisomeric products formation (the differential selectivity of the reaction) is substantially simpler:

\[
\frac{d[P_α]}{d[P_β]} = \frac{k_{pα}}{k_{pβ}}.
\]  

Figure 4. Accepted mechanistic scheme of $\alpha$- and $\beta$-regioisomeric products $(P_α$ and $P_β$) formation in the Mizoroki-Heck reaction.

Therefore, if varying the reaction parameters leads to a change of rate constants $k_{pα}$ and $k_{pβ}$, the differential selectivity of the reaction should also change visualizing by a change of the slope of the phase trajectory. Additionally, as follows from (7), the phase trajectories plotted in the coordinates of $[P_α]$ vs. $[P_β]$ should be strictly linear in the course of the reaction because the rate constants in the equation (7) should be invariable in time. Indeed, the phase trajectories of the Mizoroki-Heck reaction plotted by using the concentrations of $\alpha$- and $\beta$-regioisomeric products represented linear dependences with different slope when different inorganic salts were used as additives to the catalytic system (figure 5). This experimental result unambiguously pointed to the change of the ratio of the rate constants $k_{pα}$ and $k_{pβ}$ under varying the nature of the additive. The changes of the rate constants can result only from a change in the nature of reagents participating in the particular selectivity-
determining step (C, C', figure 4). As the same alkene was used in the set of experiments presented in figure 5, the sole reagent able to influence the rate constants \( k_{P\alpha} \) and \( k_{P\beta} \) is ArPdX intermediate. Based on the common view of organometallic chemistry, the most probable explanation of the observed phenomenon lies in the varying of X counterion in ArPdX when Cl\(^-\), Br\(^-\), or I\(^-\)-containing salts were added. Taking into account the dependence of phase trajectories on the nature of salt cation (compare experiments with LiCl and NaCl in figure 5), such active intermediates should be anionic and consequently form ion pairs with cations present in the reaction system. The experimental result obtained under real catalytic conditions without any simplifications is the clear evidence for the possibility to collect data about composition of the reaction intermediates without using any complex physical-chemical analytical methods.

Much more interesting pattern was obtained when we analyzed differential selectivity in related C-H direct arylation of indoles with aryl iodide (figure 6). As a result of the reaction, two regioisomers – C2- and C3-arylated indoles (7 and 8 in figure 6) – formed from the same reactants [14].

The reaction mechanism for the formation of the regioisomeric products in direct C-H arylation of indole differs from the mechanism of Mizoroki-Heck reaction. In accordance with the existing mechanistic hypotheses [14,15], the parallel formation of C2- and C3-arylated indoles (marked as C2-Ar-Ind and C3-Ar-Ind in figure 7) proceeds in the step (reversible or irreversible) directly following the step where common reagent, i.e., base, participates.
Figure 7. Common mechanistic scheme of C2- and C3-arylated indoles (C2-Ar-Ind and C3-Ar-Ind) formation in the reaction of indole and iodobenzene with base as common reagent.

It is possible to deduce the equation (8) describing the ratio of the rates of C2- and C3-arylated indoles formation, i.e., the reaction differential selectivity.

\[
\frac{d[C2 - ArInd]}{d[C3 - ArInd]} = \frac{k'_{C2} \cdot k_{C3} \cdot (k'_{C3} + k_{C3}[\text{base}])}{k'_{C3} \cdot k_{C2} \cdot (k'_{C2} + k_{C2}[\text{base}])}
\] (8)

Analyzing the equation (8), three cases are possible with different influence of the base on the reaction differential selectivity.

If the catalytic cycle step where parallel formation of \( \sigma \)-complexes leading to the formation of C2- and C3-phenylindoles correspondingly is reversible (that means the implementation of the conditions \( k'_{C3} >> k_{C3}[\text{base}] \) and \( k'_{C2} >> k_{C2}[\text{base}] \)), the differential selectivity will be as follows:

\[
\frac{d[C2 - ArInd]}{d[C3 - ArInd]} = \frac{K'_{C3} \cdot k_{C2}}{K'_{C2} \cdot k_{C3}}
\] (9)

where \( K'_{C3} \) and \( K'_{C3} \) are the equilibrium constants of the steps of two \( \sigma \)-complexes formation. Such situation leads to the differential selectivity becoming dependent on the ratio of the rate constants of the steps with common reagent participation (\( k_{C2} \) and \( k_{C3} \)), therefore, on the nature of common reagent \( \text{base} \). The selectivity, however, should not depend on its concentration.

The inverse situation when the steps where parallel formation of \( \sigma \)-complexes leading to the formation of C2- and C3-phenylindoles correspondingly is virtually irreversible (i.e., \( k'_{C3} << k_{C3}[\text{base}] \) and \( k'_{C2} << k_{C2}[\text{base}] \)) lead to the selectivity is determined only by the ratio of rate constants of the step where these parallel formations of two \( \sigma \)-complexes proceed. Such case excludes any influence of the step of the catalytic cycles where common reagent participates and, as a consequence, its nature on the selectivity:

\[
\frac{d[C2 - ArInd]}{d[C3 - ArInd]} = \frac{k'_{C2}}{k'_{C3}}
\] (10)

If none of two utmost cases realized allowing to neglect one of two summands of \( (k'_{C3}+k_{C3}[\text{base}]) \) and \( (k'_{C2}+k_{C2}[\text{base}]) \), the differential selectivity becomes dependent on both the nature and concentration of common reagent \( \text{base} \) (accordingly to equation (8)).

The set of experiments was carried out when the differential selectivity patterns were studied under varying the nature and concentration of base [14]. It was demonstrated that the differential selectivity...
on C2- and C3-arylated indoles characterized by using phase trajectories plotted by [C2-arylated indole] vs. [C3-arylated indole] was insensitive to the concentration of base that allowed to discard the validity of the equation (8). The change of the nature of base used led to the change of the differential selectivity pointing to the validity of the equation (9). As can be seen, the equation (9) implies that the phase trajectories plotted by using the concentrations of C2- and C3-arylated indoles should be also linear analogously to those of Mizoroki-Heck reaction described above (figure 5). However, the data obtained contradicted this statement. Even when the phase trajectories coincided under varying the reaction conditions, i.e., the differential regioselectivity of C2- and C3-arylated indoles remained unchanged, they never were linear. For instance, when additives of different inorganic salts were used, the phase trajectories had two close to linear segments at different stages (figure 8). The non-linearity of the phase trajectories cannot be explained by the equation (9). The simplest explanation of two different slopes of the phase trajectories with clear transition between them is the functioning of two different active species with different rate constants $K_{C2}^M, K_{C3}^M, k_{C2}^M$ and $k_{C3}^M$ at different periods of the reaction proceeding. Taking into account high probability of catalytic activity of anionic Pd complexes in the reaction of direct C-H arylation of indole [14], these complexes having different anions should possess different selectivities. At the reaction beginning, only anions from base were present in the reaction system, while endogenous iodide anions accumulated further as a result of aryl iodide conversion into the reaction products. Therefore, the transformation of active Pd complexes containing base anions to active iodide-containing ones should proceed in the course of the reaction resulting in the change of the corresponding rate constants of their conversion and, consequently, the differential selectivity. As follows from the equation (9), the participation of sole active catalyst can result in strictly linear phase trajectories, while their non-linearity unambiguously points to the products formation through two (at least) types of active species whose relative contribution changes directly under the reaction proceeding.

Figure 8. Phase trajectories of the reaction of iodosobenzene and indole (figure 6) plotted by using concentrations of C2- and C3-phenylindoles employing $K_2CO_3$ as the base and additives of halide salts.

5.2. The studies of the differential selectivity in the processes with “artificial multi routeness”.
As was stated above, the formation of two products through the same reaction mechanism is the requirement for the implementation of the DS for making valid mechanistic conclusions for complex catalytic reaction. In order to be confident of the identity of the mechanisms of two products formation it is optimal to measure the differential selectivity by using several (at least a pair) similar competing substrates creating a so-called artificial multi routeness [2]. The variant of DS studies using products of the conversion of competing substrates of the same type (for instance, differing in a substituent remote from the reaction center) provides the possibility to claim the validity of the postulate about the identical nature of the active species responsible for the formation of products [2] and the same mechanisms of product formation used in the estimates of the DS value. In this case, identical
mechanisms are understood to be analogous sequences of elementary steps leading to the formation of products, including the same orders of these processes with respect to the catalyst.

Let us consider typical catalytic reaction mechanism (similar to those depicted in figure 2) complicated by participation of two substrates $S1$ and $S2$ competing for common reaction intermediate $X_{com}$ in the reaction with common reagent $R$ (figure 9) [5]. The principal difference between the formation of two reaction products in figure 2 and figure 9 is that in the latter case these products form from different substrates.

![Mechanistic scheme of competitive reaction between two competing substrates (S1, S2) and one common reactant (R)](image)

Figure 9. Mechanistic scheme of competitive reaction between two competing substrates ($S1$, $S2$) and one common reactant ($R$)

Using steady-state approximation, the rate equations for two reaction products $P1$ and $P2$ from two competing substrates $S1$ and $S2$ will be as follows:

$$
\frac{d[P1]}{dt} = \frac{k^1_{s1}k_{s1}[S1][R][Cat], a'}{a' + k^1_{s1}[S1]a' + k^1_{s2}[S2]a} ,
$$

$$
\frac{d[P2]}{dt} = \frac{k^1_{s2}k_{s2}[S2][R][Cat], a}{a' + k^1_{s2}[S1]a' + k^1_{s2}[S2]a},
$$

where $a = k^1_{s1} + k^1_{s1}[R]; a' = k^1_{s2} + k^1_{s2}[R]$ and \([Cat]_x = [X] + [X_{S1}] + [X_{S2}]\).

However, the rate ratio which characterizes the differential selectivity of a common catalyst is substantially simplified because of the identical denominators in (11). Moreover, the total amount of active catalyst is also absent in this case:

$$
\frac{d[P2]}{d[P1]} = \frac{k^1_{s2}k_{s2}[S2][S1]}{k^1_{s1}k_{s1}[S1]a'} = \frac{\left(\frac{k^1_{s1}k_{s1}}{k^1_{s2}k_{s2}}\right)[S2]}{\left(\frac{k^1_{s2}k_{s2}}{k^1_{s1}k_{s1}}\right)[S1]}.
$$

(12)

Depending on the degree of reversibility of the step where substrates $S1$ and $S2$ compete for common reaction intermediate $X_{com}$, two utmost cases are possible:

If the catalytic cycles’ steps A and B (figure 9) are reversible (that means the implementation of the conditions $k_{s1}>>k_{S1}[R]$ and $k_{s2}>>k_{S2}[R]$), the DS will be as follows:

$$
\frac{d[P2]}{d[P1]} = \frac{\left(\frac{k_{s1}k_{s1}}{k_{s2}k_{s2}}\right)[S2]}{\left(\frac{k_{s2}k_{s2}}{k_{s1}k_{s1}}\right)[S1]},
$$

(13)

where $K_{s1}$ and $K_{s2}$ are the equilibrium constants of the steps A and B (figure 9).

If the catalytic cycles’ steps A and B (figure 9) are virtually irreversible (that means the implementation of the conditions $k_{s1}<<k_{S1}[R]$ and $k_{s2}<<k_{S2}[R]$), the DS will be as follows:

$$
\frac{d[P2]}{d[P1]} = \frac{k_{s2}[S2]}{k_{s1}[S1]},
$$

(14)

If one compares the equations (8)-(10) and (12)-(14), it can be seen that they differ only by the ratio of concentrations of the competing substrates $[S2]/[S1]$ present in the equation (12)-(14) (taking into account that base acts as common reagent $R$ in (8)). Correspondingly, all conclusions about
sensitivity of DS to varying the nature and concentration of common reagent described by one of the equations (12)-(14) is the same as for the differential selectivity of regioisomers (i.e., differential regioselectivity) described by equations (8)-(10). However, one principal difference of the phase trajectories corresponding to the differential regioselectivity and differential selectivity of competing substrates appears. As in the most common case two competing substrates have different reactivity, i.e., react with the same catalyst with higher or lower rate, the ratio of their concentrations \([S2]/[S1]\) will change in the course of the reaction leading to a change of the slope of the phase trajectory plotted by using the concentrations of the products formed from these substrates and, consequently, to its non-linearity. However, these non-linear phase trajectories should also coincide under varying the reaction conditions when the nature of active common intermediate reacting with the competing substrates remains unchanged due to constancy of the rate constants in equation (12)-(14) in such situation.

The wide set of fine mechanic details of cross-coupling reactions has been studied by our group by using this kinetic approach considering the degree of reversibility and possible rate-determining character of particular catalytic cycle steps \([14,16,17]\), the nature (homogeneous or heterogeneous) \([7,18]\) and type (anionic, cationic, or neutral) of active species responsible for the reaction products formation \([14,19]\). Here we will demonstrate novel experimental data on the nature and type of active species in cross-coupling reactions obtained for the most promising reaction systems including simple catalysts and available substrates by using the phase trajectories analysis.

5.2.1. The differential selectivity measurements for elucidating fine mechanistic details in Suzuki-Miyaura reaction.

The Pd-catalyzed Suzuki-Miyaura cross-coupling reaction between aryl halides and arylboronic acid is one of the most effective tools for obtaining unsymmetrical biaryls used in drug synthesis, optoelectronics, and agro chemistry \([20]\). Being a typical catalytic process, the reaction is accompanied by the interconversions of several forms of Pd being potentially catalytically active \([9,10]\) resulting in non-stationary concentrations of all these forms. However, the studies of DS allow obtaining valid data irrespective of the complex character of catalyst interconversions.

We used two aryl chlorides as the competing substrates in the reaction with phenylboronic acid (figure 10a). Note that using pair of competing substrates provides a unique opportunity to study the particular reaction intermediates involved in the conjugation node with participation of these substrates. Therefore, choosing the appropriate pair of competing substances one can study the nature of active intermediates participating at different steps of the catalytic reaction. By using two competing aryl chlorides, the nature of Pd(0) complexes reacting with the substrates in oxidative addition elementary step (figure 11a, A) can be investigated.

**Figure 10.** Scheme of Pd-catalyzed Suzuki-Miyaura reaction under competition of two aryl chlorides (a) and of two arylboronic acids (b).
Figure 11. Accepted mechanistic scheme of Suzuki-Miyaura reaction.

The competing Suzuki-Miyaura reaction with two aryl halides corresponds to figure 9 where Pd(0) is common intermediate (X<sub>com</sub> in figure 9) reacting with two competing aryl chlorides (S1 and S2 in figure 9) converting further to the reaction products P1 and P2 in the reaction with common reagent – phenylboronic acid (R in figure 9). Therefore, the DS of competing aryl chlorides is described by one of the equations (12)-(14). In special experiments with varying the nature and concentration of common reagent (arylboronic acid) it was demonstrated that equation (12) is valid for the reaction with two competing aryl chlorides, i.e., the oxidative addition elementary step (figure 11a, A) is substantially reversible. In accordance with common view on the mechanism of Suzuki-Miyaura reaction, base molecules present in the reaction system do not participate in oxidative addition step, but can possibly influence the DS by the entrance of its anion in the coordination sphere of Pd(0) active complexes. If such possibility is realized, DS value and, consequently, phase trajectories plotted by using the concentrations of the reaction products formed from competing aryl chlorides should be sensitive to varying the base nature because of change of the rate constants <i>k</i><sub>S1</sub>, <i>k</i><sub>-S1</sub>, <i>k</i><sub>S2</sub>, and <i>k</i><sub>-S2</sub> in (12) depending on the composition of common intermediate. To check this supposition, we carried out the set of experiments where the nature of base was varied in the reaction with competing 4-chloroacetophenone and 1,4-dichlorobenzene (figure 12a). The resulting phase trajectories also pointed to absence of any influence of base on the DS of competing aryl chlorides and, consequently, on the common intermediate X<sub>com</sub> (figure 9). The data obtained indicated that base molecules (or its anions) did not enter the coordination sphere of Pd(0) active complexes (figure 11a).
Figure 12. The phase trajectories of Suzuki-Miyaura reaction with two competing aryl chlorides (figure 10) under varying the base nature (a) or with two competing arylboronic acids under varying the base nature (b).

Note that the phase trajectories in figure 12a are linear while it follows from equation (12) that due to different reactivity of competing substrates such linearity should not be observed. In this particular case the sum concentration of competing aryl chlorides was twofold higher than concentration of phenylboronic acid that is the common reagent. Therefore, the degree of competing substrates’ conversion was far from complete, therefore, the different drop in the concentrations of competing substrates did not become sufficient to give rise to non-linearity of the phase trajectories. Such variant of the DS studies under high concentrations of competing substrates lead to the possibility of neglecting the effect of the concentrations’ change in the course of the reaction on the DS value and, consequently, to linear phase trajectories. Therefore, the resulting phase trajectories allow analyzing possible changes of active species nature in a simple way similarly to the DS of regioisomers.

If we carry out Suzuki-Miyaura reaction under competition of two arylboronic acids (figure 10b), it provides the opportunity to study the nature of Pd(II) active complexes reacting in the transmetalation elementary step (figure 11b, B). In a similar manner to the experiments under competition of two aryl chlorides, the base present in the reaction mixture can influence the DS of competing arylboronic acids by the entrance of its anions or hydroxo-anions formed in the reaction medium [21-25]. It should result in a change of the rate constants $k_{S1}$, $k'_{S1}$, $k_{S2}$, and $k'_{S2}$ in (12) describing the interaction of competing arylboronic acids with the common intermediate ArPdX due to a change of the nature of the latter. Indeed, the phase trajectories plotted by the concentration of the reaction products formed from competing arylboronic acids were sensitive to the varying of the base nature (figure 12b) pointing to the change of common intermediate X$_{con}$ (figure 9), i.e., ArPdX intermediate in this particular case (figure 11b). Thus, the studies of DS allowed not only to unambiguously establish the change of the active reaction intermediate, but also to make it for particular elementary step by using the appropriate pairs of competing substrates.

5.2.2. The differential selectivity measurements for elucidating fine mechanistic details in Mizoroki-Heck reaction.

The DS studies by the phase trajectories under competition of two substrates were also applied for Mizoroki-Heck reaction. We discussed above the regularities of the differential regioselectivity arising
from the “natural multirotueness” with the formation of α- and β-regioisomers from one alkene and one arylating agent characterizing active Pd(II)-σ-complexes (Section 5.1). Along with that, by creating the “artificial multirotueness” it is possible to study another conjugation node of the reaction mechanism. We carried out a set of experiments using two competing aryl chlorides (figure 13) to study the properties of common reaction intermediate participating in the elementary step where these substrates are activated, i.e., Pd(0) complexes being active in the oxidative addition step (figure 4, A).

Figure 13. Scheme of Pd-catalyzed Mizoroki-Heck reaction under competition of two aryl chlorides.

As for Suzuki-Miyaura reaction, mechanistic scheme of Mizoroki-Heck reaction also corresponded to figure 9, where S1 and S2 were competing aryl chlorides, Pd(0) is common intermediate (X$_{com}$) and alkene was common reagent (R). Therefore, probable changes of the nature of common intermediate can be assessed by the studies of DS for the reaction under varying the reaction conditions possibly influencing the nature of common intermediate. Coincidence or non-coincidence of the phase trajectories plotted by the sum concentrations of two regioisomeric products formed from each of competing substrates will mean corresponding constancy or variation in the rate constants $k_{S1}$, $k'_{S1}$, $k_{S2}$, and $k'_{S2}$ in (12)-(14) that characterize the interaction of Pd(0) with competing aryl chlorides in this particular case. As follows from figure 14, the phase trajectories remained unchanged under varying the base nature, thus pointing to absence of any influence of the base molecules on the composition of common intermediate, i.e., Pd(0) active complexes. The observed linearity of the phase trajectories under competition of aryl chlorides arose from their higher concentrations in comparison with concentration of common reagent (alkene) similarly to the same competition experiments for Suzuki-Miyaura reaction (figure 12a). Taking into account the data obtained under competition of two aryl chlorides in Suzuki-Miyaura reaction (figure 12a), it is possible to conclude that for these two related cross-coupling reactions using identical type of arylating agents (aryl chlorides) the independence of Pd(0) active complexes on the base nature has the same character.
5.2.3. The differential selectivity measurements for elucidating fine mechanistic details in three-component coupling reaction.

Using the examples of two-component Suzuki-Miyaura and Mizoroki-Heck reactions we demonstrated above that relatively simple equations describing DS of appropriate pair of competing substrates allowed to make conclusions about the nature of active reaction intermediates. This methodology can be applied also to a more complicated reaction system. Let us use the example of Pd-catalyzed reaction being related to Sonogashira-type cross-coupling where three components – aryl halide, arylacetylene, and arylboronic acid – react to each other with the formation of several reaction products [26]. As to Mizoroki-Heck reaction, there is a possibility to study the reaction selectivity using both “natural” and “artificial” multi routeness. In order to demonstrate once more how the application of DS can simplify the task of establishing the mechanistic details for complex catalytic processes, we used the three-component coupling reaction under competition of two aryl halides (figure 15).

![Figure 15](image)

**Figure 15.** Scheme of Pd-catalyzed three-component coupling of arylacetylene and arylboronic acid with two competing aryl iodides.

The mechanistic scheme for this competing reaction (figure 16) is more complex in comparison with the above-mentioned scheme for two-component one (figure 9). However, it can be demonstrated that DS of competing reaction is also described by relatively simple equations.
Taking into account the probable reversible interaction of competing aryl halides (S1 and S2 in figure 16) with common intermediate and reversible involvement of unsaturated substrate – tolane (21 in figure 15, R in figure 16) – characterized by equilibrium constants in the catalytic cycle followed by irreversible interaction with the third component – nucleophile PhB(OH)$_2$ (9 in figure 15, R in figure 16) – it is possible to obtain the equation for DS of products from each of the two competing substrates (15):

$$
\frac{d[P2]}{d[P1]} = \frac{K_{S1}K_{S2}k_{R2}}{K_{S1}K_{S2}k_{R1}} \frac{[S2]}{[S1]},
$$

where $K_{S1}$, $K_{S2}$ and $K_{S1}$, $K_{S2}$ are the equilibrium constants of the steps with participation of competing substrates S1, S2, and common reactant R (figure 16).

It follows from equation (15) that studying the DS of competing substrates allows to detect any possible changes of active reaction intermediates resulting in the changes of the equilibrium constants $K_{S1}$, $K_{S2}$, $K_{S1}$, and $K_{S2}$ and rate constants $k_{R1}$ and $k_{R2}$ in (15). It is well-known that two-component cross-coupling reactions of aryl halides are accompanied by the interconversions of several soluble and insoluble forms of Pd being probably catalytically active in homogeneous (both reactants and catalyst are dissolved in the reaction medium) and heterogeneous (dissolved reactants interact with solid surface of the catalyst) manner, correspondingly [9,10]. In order to distinguish these two mechanistic possibilities, we proposed earlier to study the DS of the reaction under varying the conditions influencing the structure and/or composition of solid forms of Pd particles while keeping that of dissolved Pd complexes in solution unchanged [7,9]. Any changes of the phase trajectories in such set of experiments will indicate direct involvement of heterogeneous Pd forms in catalysis. The nature and concentration of catalyst precursor can be considered as the parameters being able to influence the structure and/or composition of solid forms of Pd particles. The data obtained with some concentrations of soluble precursor PdCl$_2$ and insoluble deposited on the solid support Pd/C as well as with different additives influencing the structure of heterogeneous Pd particles pointed to the constancy of DS of three-component coupling reaction with two competing aryl halides (figure 17). Note that in this particular case the concentrations of competing substrates instead of the concentrations of competing reactions products were used for plotting phase trajectories. Due to the material balance of the reagents (i.e., the sum concentrations of the substrates and all products formed from them) remaining constant during the reaction proceeding, it is valid to use the concentrations of competing substrates to measure the DS.

The coincidence of the phase trajectories under varying such wide set of precursors became possible only if all the rate constants in equation (15) remained unchanged. In accordance with the view on the interconversions of homogeneous and heterogeneous Pd forms and the above reasoning [7,9,10], such result pointed to the reaction proceeding through homogeneous mechanism in the solution phase resistant to the changes of the varied parameters. Note that the development of the
methods allowing to unambiguously distinguish between homogeneous and heterogeneous catalysis for cross-coupling reactions has been an urgent scientific task for the latest 20 years due to high complexity of the mutual influence of the main catalytic reaction and the accompanying catalyst transformations [27]. As can be seen, studying the reaction DS by the phase trajectories is a simple and simultaneously reliable kinetic approach to solving the problem.

![Figure 17. The phase trajectories of three-component reaction with two competing aryl halides (figure 15) under varying the nature and concentration of catalyst precursor.](image)

6. Conclusions
The data on the differential selectivity of competing substrates under “artificial multirouteness” and the differential regioselectivity under “natural multirouteness” presented here demonstrated only several particular cases of solving various scientific tasks in the field of complex catalytic reactions. The key feature of the independence of DS on active species concentrations (none of the equations for DS or differential regioselectivity presented in the paper contain the catalyst concentration in any form) defines the convenience and reliability of this approach for the reactions where the concentration (and very often the nature) of active species cannot be determined exactly. The DS is determined by the strictly limited set of the rate constants, therefore the investigations of the patterns of DS under varying the reaction conditions allow to make an unambiguous conclusion about the structure and/or composition of a particular reaction intermediate. In our opinion, application of the reaction DS studies with mathematical modelling of possible mechanistic hypothesis (see review [28] for details) is a promising approach to the investigations of the properties of complex chemical processes.

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