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Mechanistic Study of Direct Arylation of Indole Using Differential Selectivity Measurements: Shedding Light on the Active Species and Revealing the Key Role of Electrophilic Substitution in the Catalytic Cycle

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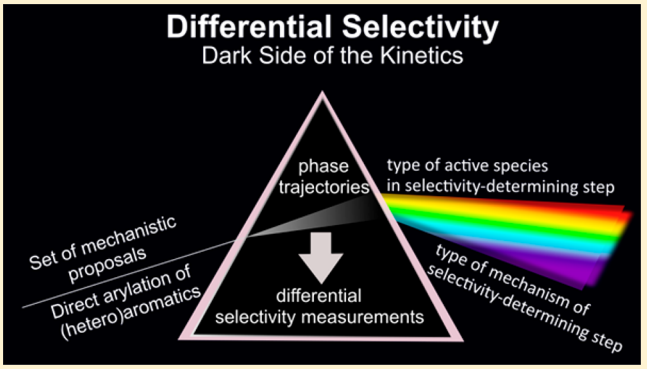
Supporting Information

ABSTRACT: Differential selectivity of the direct arylation of indole with aryl halides under competing and noncompeting conditions with a varying set of reaction parameters was determined using phase trajectories. The results described herein allow for conclusions to be drawn regarding the character of active complexes (cationic, neutral, or anionic) as well as realization of the indole electrophilic substitution in the catalytic cycle using the ligand-free catalytic system.



INTRODUCTION

Direct arylation of C−H bonds in (hetero)aromatics by aryl halides is an attractive synthetic methodology for obtaining building blocks for the synthesis of biologically active substances.[1] Despite significant progress in synthetic procedures using direct arylation, many "blank spots" remain from a mechanistic viewpoint. To date, a comprehensive description of the reaction mechanism of direct C−H arylation of heteroaromatics has not been reported. To the best of our knowledge, all mechanistic hypotheses that have been proposed so far can be categorized in two distinct mechanistic proposals. We attempted to present all mechanistic possibilities using the most common mechanistic scheme (Scheme 1). There is a general consensus regarding the participation of aryl halides in the direct arylation of heteroaromatics via oxidative addition to Pd(0) (Scheme 1a, **A**). Therefore, both mechanistic hypotheses for the formation of C2- and C3-arylated indoles being the most common products of the reactions, including C−H activation of indole molecule with aryl halide,[2−4] include the oxidative addition of aryl halides to Pd(0). If only one regioisomer formation is considered (for instance, the C2-arylated indole), then the first variant of the mechanism involves one of the following sequences: **A** ⇒ **B** ⇒ **C**′ ⇒ **H**′ or **A** ⇒ **B** ⇒ **D**′ ⇒ **F**′ ⇒ **I**′ or **A** ⇒ **B** ⇒ **E**′ ⇒ **I**′ (Schemes 1a, b, and d). All the sequences mentioned apply to the so-called noncooperative reaction mechanism (can be also called a linear mechanism from a kinetic viewpoint). Accordingly, the indole and product of oxidative addition **3** (R = Ar) generate π-complex **4** (Scheme 1b, **B**). In addition, three alternative pathways for indole conversion may proceed as follows: (i) formation of σ-complexes **5** and **5**′ via Heck-type carbopalladation (Scheme 1b, **C**, **C**′); (ii) formation of σ-complexes **7** and **7**′ via electrophilic substitution (Scheme 1b, **D**, **F** and **D**′, **F**′); (iii) formation of σ-complex **7**′ via concerted nonelectrophilic metalation−deprotonation (CMD, Scheme 1b, **E**′)[2,3] that should lead to the prior formation of C2-palladated intermediates following the formation of the C2-arylated products.[3,5,6] Intermediates **5**, **5**′ or **7**, **7**′ are then converted to C2- or C3-arylated products (Scheme 1d, **H**, **H**′ or **I**, **I**′) accompanied by the regeneration of Pd(0) **1**, which can react with aryl halide in the next catalytic cycle (Scheme 1a, **A**). Efforts to verify the noncooperative mechanism, including the alternative possibilities of indole activation (Scheme 1b, **C**, **C**′, **D**, **D**′, **E**′), have been reported for several types of aromatic and heteroaromatic substrates, and conflicting results have been obtained.[3,5−11]

The second mechanistic proposal includes the cooperation of two distinct metal fragments generated in merging catalytic cycles, as proposed by Hartwig et al. based on the results of extensive study of the direct arylation of pyridine *N*-oxide.[12] This proposal was supported by the studies of the direct arylation of simple arenes,[13] as well as their oxidative coupling.[14] When considering the formation of only one

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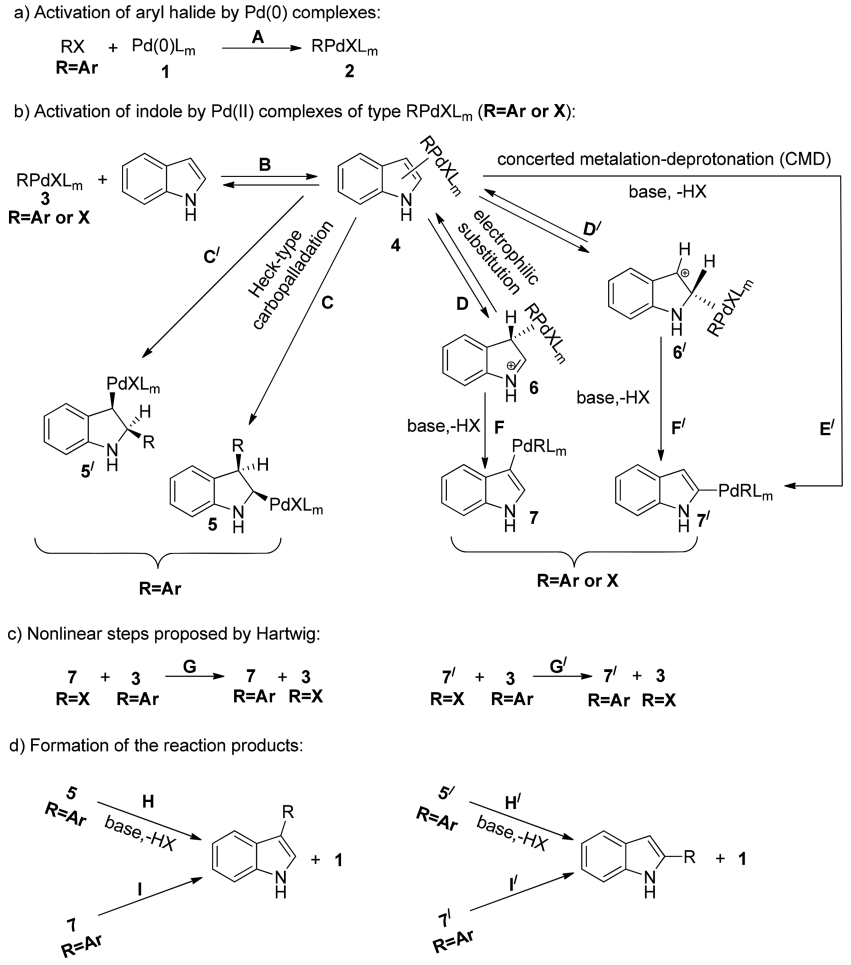
Scheme 1. Alternative Mechanistic Hypotheses for the Formation of C2- and C3-Arylated Products (Where L Represents Neutral or Anionic Ligands)



regioisomer (for instance, the C2-arylated indole as before), the second variant of the reaction mechanism includes two (instead of one) sequences to form the catalytic cycle (Scheme 1): (i) **A** ⇒ **G**′ ⇒ **I**′; (ii) **B** ⇒ **D**′ ⇒ **F**′ ⇒ **G**′ or **B** ⇒ **E**′ ⇒ **G**′. Intermediates **3** (R = Ar) and **7**, **7**′ (R = X) are generated in separate catalytic cycles and react with each other in steps **G**, **G**′ (Scheme 1c), corresponding to the so-called cooperative mechanism (can be also called as nonlinear from kinetic viewpoint due to interaction of two different palladium-containing intermediates). In this hypothesis, as for the noncooperative mechanism, the aryl halide is activated by Pd(0) complex **1** (Scheme 1a, **A**), and the indole is activated by the Pd(+2) complex **3** (R = X, Scheme 1b, **B**). Complex **3** (R = X) in this mechanism does not contain the C-bound aryl ligand. After the sequential transformation of **3** into **7** or **7**′ without aryl ligands (R = X, Scheme 1b), the reaction proceeds with the aryl-containing complex **3** (R = Ar) (Scheme 1c, **G**, **G**′) forming complex **7** or **7**′ again, but with the aryl ligand (R = Ar) accompanied by the regeneration of the Pd(+2) complex **3** (R = X), which can react in the next catalytic cycle with indole (Scheme 1b, **B**).

Complexes **7** and **7**′ (R = Ar) transform into C2- and C3-arylated products and regenerate Pd(0) **1** (Scheme 1d, **I**, **I**′), which can react in the subsequent catalytic cycle with ArX. The important observation supporting cooperative mechanism proposed by Hartwig et al. is the experimental detection of the second (or intermediate between 1 and 2) reaction order in the catalyst precursor concentration.[13,14] It should be noted that for the reaction of indoles with aryl iodides considered in this study, the reaction order in [Pd] was considerably higher than unity (1.6). However, high reaction order in the catalyst precursor concentration can arise from nonlinearity of the catalytic cycle steps (in accordance to Hartwig's mechanism, the step **G** and **G**′ where two palladium-containing intermediates react) and from nonlinear processes occurring outside the catalytic cycle, such as the in situ formation of catalytically active Pd nanoparticles. It should be noted here that we did not aim to discriminate cooperative and noncooperative mechanisms by the approach used. The kinetic approach described herein based on the measurements of differential selectivity allows for information to be obtained regarding particular steps of the catalytic reaction irrespective of any distinct hypothesized sequence of steps and exact nature of active species.

It should also be noted that few reports have been published regarding the nature of the active Pd complexes responsible for product formation. A report considered ligand-free active species in the related reaction of benzene arylation when phosphine-containing catalytic systems are used.[15] A more recent paper[16] suggested the cationic character of the active species in the direct arylation of imidazole by aryl halides and displacement of phosphine ligands as a component of catalytic

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system with active Pd complexes. In our opinion, opportunities for mechanistic investigations, including clarification of the character of the active species and elementary steps, can be realized using a set of approaches based on differential selectivity of the reaction.[17,18]

Herein, we present the results of intensive kinetic studies of the direct arylation of indole by aryl iodides through analysis of the differential selectivity of the reaction. Differential selectivity was measured in two types of experiments: under competition of two similar substrates (aryl iodides or indoles) monitoring the products formed by competing substrates, and under noncompetitive conditions, examining the differential regioselectivity of the C2- and C3-arylated products.

EXPERIMENTAL DETAILS

General Considerations. The quantitative compositions of the samples were determined using gas chromatography (GC) (Chromatec Crystal 5000.2 instrument fitted with a flame ionization detector [FID] and 15-m HP-5 methyl phenyl siloxane capillary column) and GC−mass spectrometry (MS) (Shimadzu GC−MS QP-2010 Ultra, ionization energy of 70 eV, 0.25 μm × 0.25 mm × 30 m GsBP-5MS column, He as the carrier gas) analyses. The recorded mass spectra were compared with those available in the literature (Wiley, NIST, and NIST05 comparison libraries).

Samples for GC and GC−MS analyses were collected at different reaction time points. To estimate the reproducibility of the data, each experiment was performed three times. For phase trajectories plotted, the appropriate polynomial fitting of the experimental data was used to be convinced in phase trajectories overlapping/changing.

Competing Direct Arylation of Indole by Iodobenzene and 4-Iodoanisole. Iodobenzene and 4-iodoanisole (1.25 mmol each), indole (2.5 mmol), $PdCl_2$ (0.04 mmol, 1.6 mol %), base (1.625 mmol), and naphthalene (0.5 mmol) as an internal standard for GC and GC−MS analyses were added to 5 mL of DMF−H_2O mixture (4/1) in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a preheated oil bath (140 °C), and the reaction mixture was stirred.

Competing Direct Arylation of Indole and *N*-Methylindole by Iodobenzene. Indole and *N*-methylindole (1.25 mmol each), iodobenzene (2.5 mmol), $PdCl_2$ (0.04 mmol, 1.6 mol %), base (1.625 mmol), and naphthalene (0.5 mmol) as an internal standard for GC and GC−MS analyses were added to 5 mL of DMF−H_2O mixture (4/1) in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a preheated oil bath (140 °C), and the reaction mixture was stirred.

Noncompeting Direct Arylation of Indole by Iodobenzene. Indole and iodobenzene (2.5 mmol each), $PdCl_2$ (0.04 mmol, 1.6 mol %), base (1.625 mmol), and naphthalene (0.5 mmol) as an internal standard for GC and GC−MS analyses were added to 5 mL of DMF−H_2O mixture (4/1) in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a preheated oil bath (140 °C), and the reaction mixture was stirred.

RESULTS AND DISCUSSION

Competing reaction methods are widely used as a mechanistic tool for investigation of complex reactions.[19] In spite of visible complications of the reaction arising when additional substrate is introduced, the artificial multiroute character with measurements of differential selectivity have distinct advantages over noncompeting one-route reactions with corresponding measurements of catalytic activity (for a detailed description of the advantages, see ref 17). Thus, experimental detection and kinetic control of active species is usually complicated task that, in addition, cannot be solved unambiguously due to a role of species detected by any physic-chemical technique can be as positive (catalytically active) as negative (inactive). In addition, it cannot be ruled out that true catalytic species may present in ultralow concentration being substantially lower than detection limit of particular analytical method. Independence of differential selectivity on the active species concentration allows to not measuring such concentration at all because of changes of the differential selectivity (or its invariability) varying the reaction conditions unambiguously point to the change (or, correspondingly, constancy) of active species nature that does not need any additional experimental evidence.

In addition, the identical nature of active species and sequences of elementary steps leading to the formation of products under similar substrates competition as well as fewer number of steps (and, consequently, rate constants) influencing the differential selectivity allow to considerably simplify mathematical description of differential selectivity, which can be important in the correct interpretation of experimental data (see ref 17 for details). Therefore, in spite of complication of the reaction system, the results of differential selectivity investigations can be analyzed with more certainty.

We proposed and tested in cross-coupling reactions earlier the approaches for determining the degree of reversibility of the catalytic cycle steps by measuring the differential selectivity dependence on the nature and concentrations of competing substrates and common reagents used.[17,20] It should be noted that hereafter the rate ratio of competing reactions is used as a measure of the reaction differential selectivity (see ref 17 for extensive validation of this method).

Two alternatives (Schemes 2a and b) were considered for the conjugation of reversible and irreversible steps in the two competing catalytic cycles: (i) common reagent (*R* at Scheme 2) reacts in the step (Scheme 2a, **Y**) directly following the competitive step (Scheme 2a, **X**); (ii) steps including the competing substrates (Scheme 2b, **X**) and common reagent (Scheme 2b, **Y**) are separated by several other steps in the catalytic cycle. It can be concluded that the nature and/or concentration of any common reagent can influence the differential selectivity of the reaction products, *P*1 and *P*2, only if all steps in the catalytic cycle beginning with the step where competition occurs (step **X** in Schemes 2a and b) and up to the step where the common reagent participates (step **Y** in Schemes 2a and b) are substantially reversible. If even one virtually irreversible step is present between them (any step marked with a dashed arrow in Schemes 2a and 2b), the common reagent cannot affect the observed differential selectivity of the reaction products (*P*1 and *P*2) formed in the two competing catalytic cycles. The kinetic equations describing differential selectivity and corresponding mechanistic hypotheses from the literature regarding the catalytic cycle of direct arylation (Scheme 1) were derived (see Supporting Information, equations S1−S13). It should be noted that all variants of conjugation in the reversible and irreversible catalytic cycle steps where competing substrates participate assumed the linearity of differential selectivity with respect to the ratio of competing substrate concentrations. Therefore, as the initial stage of hypothesis verification, the linearity of the differential selectivity dependence on the ratio of concentrations of competing substrates is determined (see Sections 3.1.1 and 3.2.1 in the Supporting Information). All equations obtained demonstrated that influence of the nature and/or concentration of the common reagent on the differential selectivity is only achieved when reversible steps exist (Schemes 2a and b). Thus, measurements of differential

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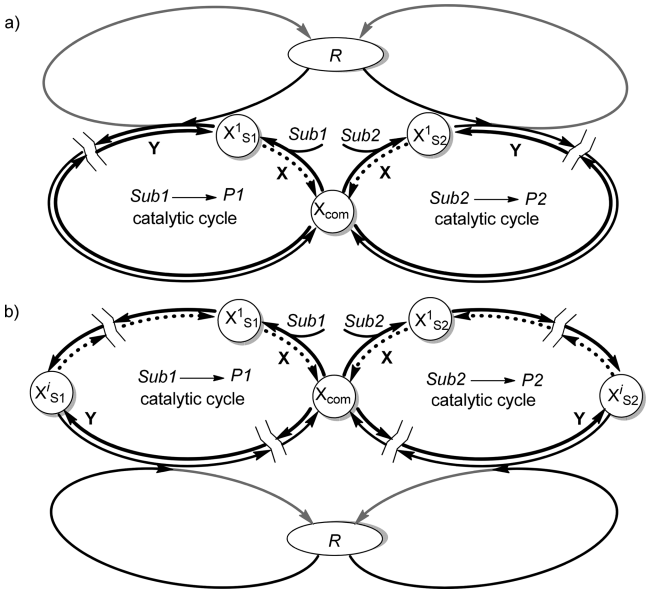
Scheme 2. Catalytic Reactions between Common Reagent (*R*) and Two Similar Substrates (*Sub*1 and *Sub*2) Competing for the Common Catalyst (X_{com}) and Formation of Products *P*1 and *P*2[a]



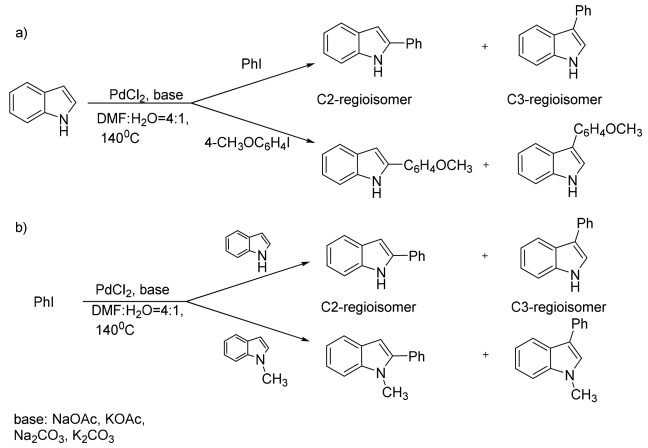
[a]The common reagent (*R*) (loaded to the reactor or generated in situ by the additional catalytic cycle (marked by grey) participates (a) in the catalytic cycle step directly following the step where *Sub*1 and *Sub*2 compete or (b) in the catalytic cycle step that is distant from the *Sub*1/*Sub*2 competition step. Dashed arrows indicate the step reversibility where the nature and/or concentration of reagent *R* can influence the differential selectivity of the reaction products.

selectivity of competing reactions with varying natures and concentrations of common reagents can yield information about the degree of reversibility of particular catalytic cycle steps.

It should be noted that this method is valid for verifying mechanistic hypotheses irrespective of the number of catalytic cycles (only one for noncooperative mechanism or several cycles for cooperative mechanism). In the latter mechanism, the common reagent is not loaded into the reactor but is generated in situ from the additional catalytic cycle (marked by gray in Schemes 2a and b). If any changes occur in this cycle under the varying reaction conditions resulting in changes of concentration and/or nature of the generated common intermediate, the influence on the reaction differential selectivity becomes possible only if the all steps in the competing catalytic cycles (beginning at the steps where competition occurs up to the steps where the generated common intermediate participates) are substantially reversible, as for the mechanistic hypotheses based on the noncooperative mechanism.

It should be noted also that measurement of differential selectivity is a complicated task because of the differentiation of integral data regarding substrates or products concentrations needs for obtaining reaction rates at each reaction moment. The problem can be solved by using special equipment that allows for the direct measurement of reaction rates.[21] However, this equipment is expensive and cannot measure the rates of consumption/accumulation of several substrates/products. A more simple approach, allowing for the estimation of differential selectivity is achieved using integral kinetic data regarding the concentration of reactants.[17] The approach consists of plotting so-called phase trajectories of competing reaction considering the dependences of one product yield versus another. The slope of the tangent to any point of the phase trajectory represents the ratio of the rates of competing reactions, which is also the parameter describing the differential selectivity (for a detailed substantiation, see 17). Therefore, any discrepancy in the trajectories of the reaction when a parameter is changed unambiguously indicates the differential selectivity variation. On the other hand, coincidence of phase trajectories indicates a constant differential selectivity at each moment of the reaction proceeding. It is important that phase trajectories coincidence (i.e., have the same differential selectivities) becomes possible along with considerable changes in the rates of competing reaction product formation resulting from changes in active species concentration. Therefore, by comparing phase trajectories, it is possible to estimate the influence of individual factors on the differential selectivity of the reaction. When two similar substrates (i.e., aryl iodides or indoles) were used (Scheme 3) to measure the differential selectivity of competing

Scheme 3. Competing Direct Arylation of (a) Indole by Iodobenzene and 4-Iodoanisole and (b) Indole and *N*-Methylindole by Iodobenzene



substrates, the phase trajectories could be plotted using the sums of the corresponding C2- and C3-arylated products. The differential selectivity of the regioisomer formation can be measured by plotting the phase trajectories using the corresponding C2- and C3-arylated products in competing and noncompeting reaction conditions.

Differential Selectivity in the Competition Reaction of Two Aryl Halides with Varying Concentration and Nature of the Indole. All direct arylation mechanistic hypotheses include the oxidative addition of the aryl halide to palladium (**A**). The virtually irreversible oxidative addition in direct arylation of simple arenes[13] and cross-coupling reactions[17,20] was previously demonstrated. However, for the direct arylation of heteroaromatics, irreversibility has not yet been unequivocally demonstrated. To determine the reversibility of the oxidative addition step, a set of experiments using competing iodobenzene and 4-iodoanisole with varying nature and concentrations of common reactants was performed (Scheme 3a). To measure the differential selectivity of aryl halides, the phase trajectories should be plotted using the sums of C2- and C3-arylated indoles forming from each competing

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aryl halide. It means that C2- and C3-arylated products formation proceeds after the selectivity-determining step where aryl halides compete (regularities of the reaction selectivity in C2- and C3-arylated indoles see below in corresponding section).

As in all mechanistic hypotheses (Scheme 1), the step directly following (**A**) includes the interaction of an arylpalladium intermediate **3** (R = Ar) with indole (common reagent, noncooperative mechanism (**B**), Scheme S1 in the Supporting Information) or with intermediates **7**, **7′** (R = X) generated in the additional catalytic cycle (common reagent, cooperative mechanism **G**, **G′**) Scheme S2). Both variants are described by Scheme 2a and eqs S1−S3. According to eq S1 and eq S2, the reversibility of the catalytic cycle steps where competing aryl halides participate (**A**) becomes possible only when the concentration and/or nature of the common reagent (indole in noncooperative or indole-containing intermediates **7**, **7′** (R = X) in cooperative mechanisms) influences differential selectivity. To assess the possible reversibility of aryl halide oxidative addition, experiments with varying concentrations of indole (0.5−1 M) and its nature (indole was substituted with 5-methoxyindole) were performed. For all experiments, the phase trajectories coincided (Figure S2 in the Supporting Information), indicating independence of differential selectivity on concentration and nature of the common reagent, validity of eq S3, and virtual irreversibility of the oxidative addition (**A**). The conclusion is valid not only for noncooperative but also for cooperative mechanisms because changes in the concentration and/or nature of the indole (common reagent in noncooperative mechanism) should lead to changes in the concentration/nature of the indole-containing intermediates **7** and **7′** (R = X) (common reagent in cooperative mechanism), which reacts with intermediates of the competing catalytic cycles. Thus, lack of such influence is in agreement with the virtual irreversibility of the oxidative addition. Note, that despite complete coincidence of the phase trajectories (and, consequently, the differential selectivities), the reaction rates considerably differed (from 1.1×10^{-2} to 2.0×10^{-2} M/min). These results highlight the advantages of using differential selectivity over catalytic activity measurements, which are traditionally used for kinetic studies.

Differential Selectivity in the Competition Reaction of Two Aryl Halides with Varying Concentration and Nature of the Base. Because the direct arylation of indole requires a base to proceed, it should be considered as an essential common reagent for the reaction with aryl halides competition. According to the mechanistic hypotheses (Schemes 1b and c), in the noncooperative mechanism, the base is necessary in the catalytic cycle step that proceeds after the indole enters the catalytic cycle (**F**, **F′**, **E′**, **H**, **H′**) and does not participate in oxidative addition (**A**). As per Hartwig's hypothesis, changes in differential selectivity with competing aryl halides could arise from changes in the concentration/nature of common intermediate **7** or **7′** (R = X) (Scheme S2) due to variation in the base concentration/nature. Thus, the possible influence of the base concentration and nature on the differential selectivity with competition of two aryl halides was investigated. The phase trajectories did not change with varying concentration of NaOAc (Figure S3) but changed when it was replaced with carbonates (Figure 1). These changes were slight but reproducible (each experiment was repeated for three times). In addition, the phase trajectories obtained needed different polynomials to be described.

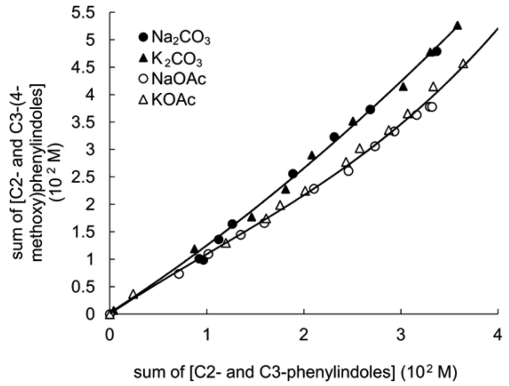

Figure 1. Phase trajectories of the reaction of indole with competing iodobenzene and 4-iodoanisole (Scheme 3a) varying the base nature ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 4−6 h).

Interestingly, the use of acetates and carbonates of Na and K suggested that differential selectivity is sensitive only to the anion of the base and not to the cation. Based on the data obtained upon varying the nature and concentration of the indole, virtual irreversibility of the oxidative addition was established. Consequently, there is a minimum of one virtually irreversible step (i.e., oxidative addition) between the aryl halides competition step (**A**) and those in which the base participates (**F**, **F′**, **E′**, **H**, **H′**). Thus, the base cannot influence the differential selectivity of the competing aryl halides because of the reversibility of the catalytic cycle steps. The observed changes in differential selectivity of indole arylation with competing aryl halides upon changing the anion of the base can be explained by changes in the nature of the active species. The base anions enter the coordination sphere of the Pd(0) **1** complex participating in oxidative addition (**A**). The possibility of forming a Pd(0) anionic complex in related cross-coupling reactions was demonstrated under model experimental conditions by Amatore and Jutand[22,23] and under real catalytic conditions.[24] In such case, the nature of the active species and, consequently, the differential selectivity should be sensitive to presence of other anions, including those with low basicity that can coordinate to Pd(0). Indeed, even when only moderate amounts of NaBr or NaCl (20 equiv to Pd) were added to the reaction vessel, differential selectivity was changed slightly but reproducibly (each experiment was repeated for three times). Changes of the phase trajectories were confirmed by the fact that different polynomials were needed to describe them (Figure 2). In our opinion, this indicated the entrance of the halide anion presenting in the catalytic system or forming from aryl halide conversion (endogenous halide anions) in the active Pd complex that can be either soluble molecular compounds or situated at the surface of heterogeneous catalyst (including nanoparticles) and its participation in the catalytic cycle step where two aryl halides competed, i.e., their oxidative addition to Pd(0) complexes.

Differential Selectivity in the Competition Reaction of Two Indoles with Varying the Concentration and Nature of Aryl Halide. All mechanistic hypotheses for direct arylation include π-complex formation via reaction of intermediate **3** with the indole molecule (**B**). Experiments with competing indole and *N*-methylindole (Scheme 3b) with varying nature and concentrations of the common reactants were performed. To measure differential selectivity of indoles, the phase trajectories should be plotted using the sums of C2-

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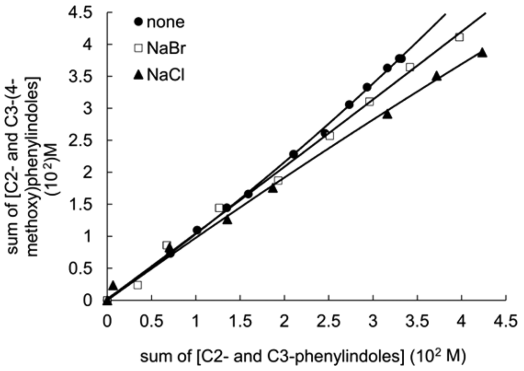

Figure 2. Phase trajectories of the reaction of indole with competing iodobenzene and 4-iodoanisole (Scheme 3a) using NaOAc as the base without (●) and with additives of NaCl (▲) or NaBr (□) (20 equiv to Pd) ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 3−6 h).

and C3-arylated indoles forming from each competing indole. As for two aryl halides competition C2- and C3-arylated products formation proceeds after the selectivity-determining step where indoles compete which, accordingly to all mechanistic hypotheses, is the π-complex formation (**B**) (regularities of the reaction selectivity in C2- and C3-arylated indoles, see below in corresponding section).

In accordance with all mechanistic hypotheses (Scheme 1b), the step directly following that where indoles participate (**B**) does not include the interaction of the π-complex **4** with aryl halide (common reagent, noncooperative mechanism, Scheme S3) or with intermediate **3** (R = Ar) generated in the additional catalytic cycle (common reagent, cooperative mechanism, Scheme S4). Both variants are described by Scheme 2b and eqs S4−S6. According to eqs S4 and S5, the considerable reversibility of all the steps in the catalytic cycle between the indole competition (**B**) and the step where the common reagent (aryl halide or intermediate **3** (R = Ar)) participates (**A** or **G**, **G**′, respectively) influences differential selectivity. By varying the concentration of the aryl halide (0.25−0.75 M) and its nature (iodobenzene was replaced by 4-iodoanisole), it was shown that the phase trajectories coincided (Figure S5). This indicates the independence of differential selectivity with respect to the concentration and nature of the aryl halide and validates eq S6. The results also indicate the presence of at least one virtually irreversible step in the catalytic cycle between the steps where the indole and common reagent (or common intermediate) participate (Scheme 2b). This agrees with the possible irreversibility of one or more steps (**C** − **I**, **C**′ − **I**′). In the noncooperative mechanism, the irreversible step(s) should be where stable arylated indoles are formed (**H**, **H**′, or **I**, **I**′). However, in Hartwig's mechanism (cooperative mechanism), the irreversible steps should be accompanied by the formation of arylated products realized in the additional catalytic cycle (where the common intermediate is generated) separate from the competing catalytic cycles (Scheme S4). Consequently, phase trajectory coincidence in Hartwig's mechanism should arise from the irreversibility of another step. As such, the virtually irreversible step with excess base is the formation of σ-complexes **7** and **7**′ via the CMD step (**E**′) or electrophilic substitution (**F**, **F**′).

Differential Selectivity in the Competition Reaction of Two Indoles with Varying the Concentration and Nature of the Base. In accordance with all mechanistic hypotheses, the base (the common reagent) participates in a step (**F**, **F**′ or **H**, **H**′) separate from that where the two indoles compete (**B**). This is described by Schemes 2b and S3 and eqs S4−S6. Additionally, for the mechanistic hypothesis including the CMD step, the base participates in step (**E**′) directly following the step where the two indoles compete (**B**), as described in Schemes 2a and S5 and eqs S7−S9. It should be emphasized that the influence of the nature of the base on differential selectivity can arise from changes in the additional catalytic cycle where the common reagent is generated for the cooperative mechanism (Scheme S4). However, if changes in the base lead to changes in the concentration of common reagent **3** (R = Ar), it would be unable to influence the differential selectivity of the competing indoles. Otherwise, a change in differential selectivity of the competing indoles should be observed under varying aryl halide concentration and nature (see above section). Consequently, if the base influences the steps of the additional catalytic cycle where common intermediate **3** forms (sequence of the steps **A** ⇒ **G** ⇒ **I** or **A** ⇒ **G**′ ⇒ **I**′), no influence on the proceeding of the cycles where indoles compete for **3** (R = X) should be observed. Therefore, all the above reasoning is valid for both the cooperative and noncooperative mechanisms.

Differential selectivity was not sensitive to base concentration (Figure S6) but was extremely sensitive to its nature (Figure 3). Using carbonates instead of acetates led to the formation of phenylindoles dominating compared to that of *N*-methylphenylindoles. The differential selectivity was also dependent on the base anion but not on its cation, as observed for the aryl halide competition. The observed changes in differential selectivity with variation of the base anion can be explained by changes of the nature of the active species through the coordination of base anions to Pd(+2) complex **3.** The complex **3** then reacts with the competing indoles (**B**), similar to the above-mentioned situation where the base influenced the reaction selectivity of the aryl halides competition. The differential selectivity could also be influenced by the reversibility of the catalytic cycle steps between the indoles competition and base participation. In the former case the nature of active species should be sensitive to the presence of other anions in the catalytic systems, including those with low basicity that can coordinate to Pd(+2). Indeed,

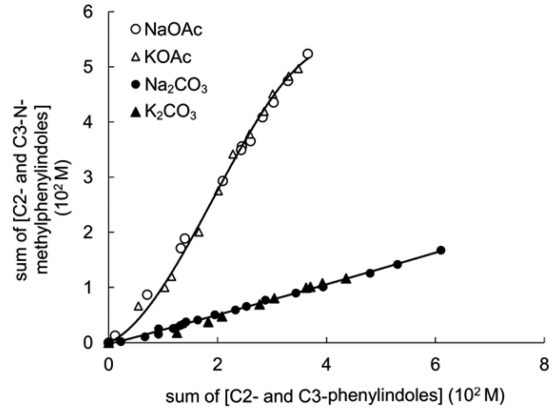

Figure 3. Phase trajectories of the reaction of iodobenzene with competing indole and *N*-methylindole (Scheme 3b) varying the base nature ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 4−6 h).

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it was established that adding halide salts to the indole competition reaction resulted in changes in the differential selectivity (Figure 4). This indicates the presence of halide

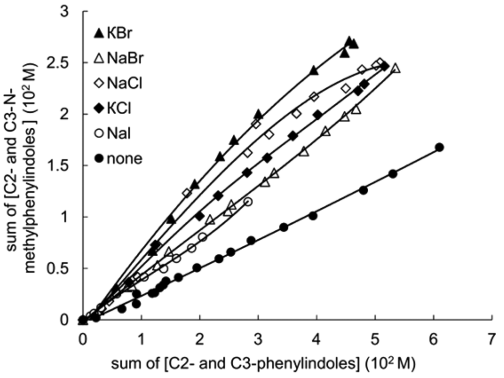


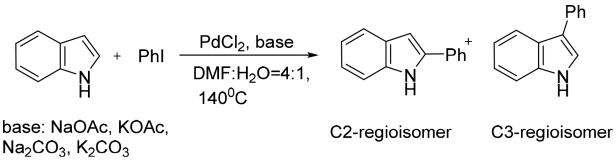
Figure 4. Phase trajectories of the reaction of iodobenzene with competing indole and *N*-methylindole (Scheme 3b) using Na_2CO_3 as the base without (●) and with additives of NaCl (◊), NaBr (△), KCl (♦), KBr (▲), and NaI (○) (40 equiv to Pd) ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 5−8 h).

anions (including endogenous iodide anions released from aryl iodide conversion) in the Pd(+2) active complex **3** that reacts with the indole molecule (**B**). Moreover, it was revealed that the differential selectivity of the indoles competition reaction was sensitive to the nature of the halide salt cation (Figure 4, experiments with additives NaBr and KBr). Because the alkali-metal cation cannot directly coordinate with the Pd center, the most reasonable explanation of their influence on the relative reactivity of the active species becomes possible when these species are anionic through electrostatic interaction in the ion pairs formed (i.e., tight ion pairs). Therefore, the rationale for the influence of both the cation and anion of the inorganic salt on the reaction selectivity when two indoles compete can be the anionic nature of active Pd species (that also can be either soluble molecular compounds or situated at the surface of heterogeneous catalyst) in the step where indole reacted (**B**). It should be noted that the anionic character of the Pd(+2) active species was previously reported for the catalytic systems of the related Mizoroki−Heck reaction under model[25] and catalytic conditions.[24] At first glance, participation of anionic Pd complexes in the steps where indole reacts as C-nucleophile can seem not so probable (from formal viewpoint). However, it was demonstrated earlier that anionic Pd(+2) complexes were active ones in related cross-coupling reactions where electrophilic interaction between anionic Pd(+2) and C-(sp^2)=C(sp^2) bond realized.[24,25] Of course, one can suppose that cationic or neutral Pd(+2) complexes may be more reactive in such reactions; however, the regularities of differential selectivity indicated that due to the presence of endogenous and exogenous (added to catalytic cycle) halide anions in the catalytic system, cationic and neutral Pd(+2) complexes just cannot exist, and the reaction proceeded via anionic species.

In contrast to low-basic halide anions, the influence of base anions on the differential selectivity (Figure 3) of the two indoles competition results from the effect on the nature of the active species in step **B**. Also, the reversibility of the catalytic cycle steps where the C2- and C3-phenylated indoles are formed can influence the differential selectivity.

Regioselectivity of the C2-/C3-Arylated Indoles in the Reaction of Indole with Iodobenzene. Verification of the hypotheses proposing the reversibility of the C2- and C3-phenylated indole formation steps was performed using analysis of the differential selectivity of C2- and C3-arylated indoles formed from one indole and one aryl halide (instead of on the sums of the products formed from two competing indoles (Schemes 4 and S6)). It should be noted that using

Scheme 4. Noncompeting Direct Arylation of Indole by Iodobenzene



competing conditions for this purpose should lead to the same differential selectivity of the C2- and C3-arylated indoles obtained under noncompeting conditions in the absence of the second indole. This assumption was experimentally verified by the good coincidence of the phase trajectories of the C2- and C3-phenylated indoles under competing and noncompeting conditions (Figure S7). The result also suggests the absence of influence of the second indole (used under competing conditions) on the formation of the active species responsible for the parallel formation of the C2- and C3-phenylindoles.

In contrast to the indoles competition, where the formation of π-complex **4** (**B**) is the selectivity-determining step, the differential selectivity in noncompeting reaction is determined by the parallel formation of C2- or C3-arylated σ-complexes **5**, **5′**, **6**, **6′**, or **7**, **7′** (depending on the hypothesis, steps **C**, **C′**, or **D**, **D′**, or **E′**). Measurements of differential selectivity of the C2- and C3-arylated indoles upon varying the nature of the base allowed the determination of the (ir)reversible character of the step where base reacts as a common reagent directly following the parallel formation of C2- and C3-arylated intermediates. Thus, it is valid for the hypotheses, including carbopalladation (**C**, **C′**) or electrophilic substitution (**D**, **D′**) as described by Scheme S6 and eqs S10, S12, and S13. The CMD step reveals that the base directly influences the rates of the parallel formation of C2- and possible C3-arylated intermediates (Scheme 1b, **E′**, Scheme S6) that are described by eqs S11−S13. The analysis of differential selectivity of C2- and C3-products in the noncompeting reaction of iodobenzene and indole indicated that it was dependent on the nature of the base and, more specifically, on the nature of both its anion and cation (Figure 5). It should be noted that when Na and K carbonates were used, the differential selectivity significantly changed during the reaction. Initially, the formation of the C3-arylated product dominated, and the selectivity clearly switched over to subsequently favor the formation of the C2-arylated product. As it was observed for differential selectivity in the indoles competition, the use of halide salt additives influenced the differential selectivity of the C2-/C3-phenylindoles (Figures 6 and S8). Additionally, increasing KBr when K_2CO_3 was used as the base resulted in a gradual reduction of the curve of the phase trajectories where the formation of the C3-arylated product dominated. The addition of 40 equiv of NaI (using Na_2CO_3 as the base) led to substantial suppression of the reactions forming the C3-arylated product, and the formation of the C2-arylated product dominated the reaction

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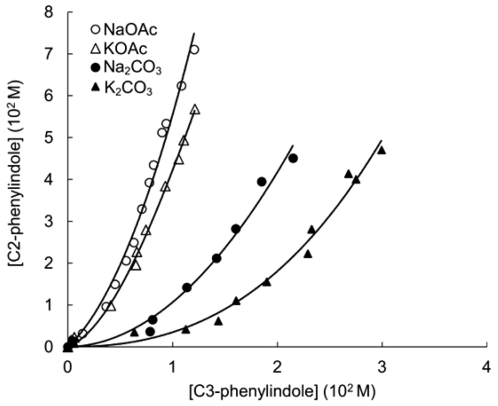

Figure 5. Phase trajectories of the reaction of iodobenzene and indole (Scheme 4) plotted by using concentrations of C2- and C3-phenylindoles varying the base nature ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 4−6 h).

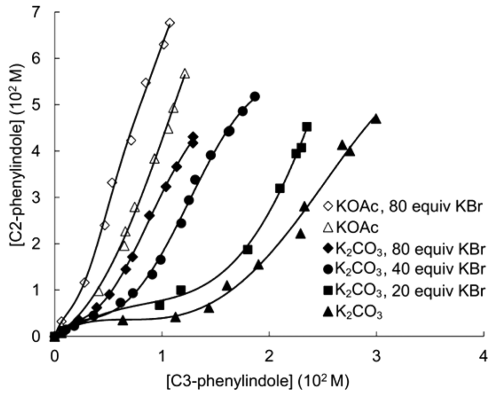

Figure 6. Phase trajectories of the reaction of iodobenzene and indole (Scheme 4) plotted by using concentrations of C2- and C3-phenylindoles employing K_2CO_3 as the base without additives (▲) and with 20 (■), 40 (●), 80 (◆) equivalents of KBr and KOAc as the base without additives (△) and with 80 equiv of KBr (◇) ($PdCl_2$, DMF−H_2O = 4/1, 140 °C, reaction time 3−6 h).

from the beginning (Figure S8). These observations indicated that the changes in the nature of the active species, namely by additive and endogenous iodide ions coordinating the Pd active complexes, induced major selectivity toward the C2-arylated indole. The effect of endogenous iodide ions conformed to the differential selectivity changes over the course of the reaction where carbonate bases were used without addition of halide salts (Figure 5). Here, the endogenous iodide anions released as the result of aryl halide conversion caused changes in the coordination sphere of the Pd active complexes that led to increasing relative rate of C2-arylated product formation (manifesting as an increase of the phase trajectory slope). The initial dominant C3-arylated product formation contradicts the mechanistic hypothesis that includes the direct metalation of the indole via a non-electrophilic CMD because it should lead to the prior formation of C2-palladated intermediates (Scheme 1, **E**′) followed by the formation of C2-arylated products.[3,5,6] Therefore, the reaction mechanism proceeding through the CMD step is unlikely.

The observed changes of differential selectivity upon changing the base cation (Figure 5) suggest that an anionic Pd(+2) active species participates in steps **C**, **C**′ or **D**, **D**′. To confirm that the base influence can originate from the reversibility of the catalytic cycle steps also (Scheme 2a), it is necessary to exclude the influence of the base as a ligand in the Pd(+2) active species. This can be achieved by using concentrations of additives of halide salts that are able to fully displace the base anions from the Pd coordination sphere. The experimental data indicate good stability of the halide palladium complexes compared to those formed with acetate (under similar conditions of phosphine-free cross-coupling reactions).[23,26]

Additionally, taking into account the dependence of differential selectivity on the nature of cations present (possibly resulting from formation of tight ion pairs with anionic Pd(+2) active complexes), any difference in base and additive salt cation should also be excluded. Therefore, we compared differential selectivity of the C2- and C3-phenylindoles in noncompeting indole arylation by iodobenzene by adding K_2CO_3 and KOAc as the base with excess of KBr additive (Pd/additive/base = 1/80/65). The data obtained indicated that under conditions where all base anions should be displaced from the Pd coordination sphere by bromide ions, the differential selectivity differed when various bases were used (Figure 6). This indicates the reversibility of the catalytic cycle step where parallel formation of C2- and C3-arylated indoles proceeds (Schemes 2a and S6 as well as eq S12).

Considering the low probability of the CMD pathway (**E**′) due to the domination of C3-arylated products initially during

Table 1. Summarized Data of Experiment Sets on the Influence of Common Reagents and Additives on the Differential Selectivity and the Conclusions Drawn[a]

				conclusions	
row	selectivity-determining step	conditions/differential selectivity measurement	common reagent and additives (influence)	reversible or irreversible	active species
1	oxidative addition (Scheme 1a, **A**)	competing (two aryl iodides)/on sums of arylated indoles	indole (−) base (+) salt (+)	irreversible	anionic
2	indole coordination (Scheme 1b, **B**)	competing (two indoles)/on sums of arylated indoles	aryl iodide (−) base (+) salt (+)[b]	impossible to make a conclusion[c]	anionic
3	electrophilic substitution (Scheme 1b, **D**, **D**′)[d] or Heck-type carbopalladation (Scheme 1b, **C**, **C**′) or CMD (Scheme 1b, **E**′)	noncompeting and competing (two indoles)/on C2- and C3-regioisomers	base (+)[b] salt (+)	reversible	anionic
4	electrophilic substitution (Scheme 1b, **D**, **D**′)[d] or Heck-type carbopalladation (Scheme 1b, **C**, **C**′) or CMD (Scheme 1b, **E**′)	noncompeting and competing (two aryl iodides)/on C2- and C3-regioisomers	base (+)[b] salt (+)	reversible	anionic

[a]The extensive discussion of these conclusions can be seen in appropriate sections of the paper. [b]Influence of both anion and cation. [c]Making a conclusion is impossible due to the competing steps and steps where common reagent participants are separated by several steps (Scheme 2b). [d]Most likely because it is in accordance with the revealed reversibility.

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the reaction (Figures 5 and 6), other hypotheses regarding the mechanism of C2- and C3-arylated product formation (**C**, **C**$^{/}$, or **D**, **D**$^{/}$) are more plausible. Based on the results obtained the electrophilic substitution of the hydrogen atom in indole (**D**, **D**$^{/}$) seems to be the most probable. Heck-type carbopalladation (**C**, **C**$^{/}$) accompanied by the formation of a new C-C bond as a result of addition of an aryl moiety to the carbon atom of the pyrrole ring under relatively mild reaction conditions does not possesses a sufficient degree of reversibility, implying C—C bond breakage. Thus, if the reaction proceeds through virtually irreversible carbopalladation, the base reacting in the following steps (**H**, **H**$^{/}$) cannot influence the ratio of the reaction rates of the parallel formation of C2- and C3-arylated indoles. Consequently, the base would also not be able to influence the differential selectivity of the C2- and C3-arylated indoles under the reaction conditions when the base influence on the active species is excluded. Therefore, the data obtained allow discriminating of hypothesis including direct arylation proceeding through Heck-type carbopalladation.

CONCLUSION

In summary, analyses of differential selectivity of competing and noncompeting reactions determined using phase trajectories of the reactions irrespective of the proposed mechanistic hypotheses (cooperative and noncooperative) were performed. These experiments allowed establishing the degree of reversibility of selectivity-determining catalytic cycle steps and the type of active species involved. The summarized experimental data and the corresponding conclusions based on them are presented in Table 1 (the extensive discussion of these conclusions see in appropriate sections of the paper). For the direct arylation of indoles by aryl iodides, it was demonstrated that oxidative addition of the aryl halide is virtually irreversible (row 1, Table 1), while the parallel formation of C2- and C3-arylated indoles possesses substantial reversibility (rows 3 and 4, Table 1). Considering proposals regarding the reaction mechanism, the results presented herein are fully consistent with the electrophilic substitution of the indole. In contrast, mechanisms including irreversible Heck-type carbopalladation are unlikely. Detecting changes in differential selectivity during the reaction indicated the domination of C3-arylated product formation at the reaction beginning. This observation excluded mechanisms involving direct metalation of the indole via nonelectrophilic CMD. The type of active species participating in the selectivity-determining step was also elucidated. The dependence of differential selectivity of the competing aryl halides on the base and halide anions (added to the catalytic system or endogenous anions formed by aryl halide conversion, row 1, Table 1) indicates the anionic nature of the Pd(0) active complexes. The dependence of the differential selectivity of competing indoles (row 2, Table 1) or of parallel C2-/C3-arylated product formation (rows 3 and 4, Table 1) on the cation and anion of the base or halide salt indicates the anionic character of the active Pd(+2) species containing anions from base and/or added halide salt in its coordination sphere. These active species participate in the catalytic cycle steps where activation of indole occurs (rows 2−4, Table 1).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00216.

Mechanistic schemes, differential selectivity equations, and experimental dependences (PDF)

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Notes

The authors declare no competing financial interest.

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