Kinetic investigation of cross-coupling reaction steps by advanced competing reaction methods

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ABSTRACT

Investigating the mechanism of a complex catalytic reaction is usually quite complicated because many processes, such as active catalyst formation and deactivation, are linked to the main catalytic cycle. Using artificial multi-route reactions with similar competing substrates is a unique way to elucidate the fine details of a reaction mechanism. Applying such multi-route reaction-based methods to the cross-coupling of alkynes with aryl halides (Cu-free Sonogashira reaction) and alkenes with aromatic carboxylic anhydrides (modified Heck reaction) catalysed by ligand-free Pd allowed us to elucidate the fast, reversible, and rate-determining steps involved in the relevant catalytic cycles.

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1. Introduction

Pd-catalysed cross-coupling reactions currently constitute one of the most intensively studied catalytic processes because of their attractiveness for fine organic synthesis. The range of substrates and catalytic systems for these processes has been considerably extended because of the substantial research attention dedicated to them [1]. However, relatively few investigations of the mechanisms of these catalytic cycles have been performed, resulting in sparse knowledge about this topic, especially for ligand-free catalytic systems. In general, most mechanistic studies have focused on the well-known Heck and Suzuki-Miyaura reactions, and other cross-coupling processes have been far less studied. We have attempted to elucidate the mechanisms of the catalytic cycles for two ligand-free Pd-catalysed cross-coupling reactions that are also widely used in organic synthesis: the reaction of aromatic carboxylic anhydrides with alkenes (modified Heck reaction) [2] and that of aryl halides with alkynes, which is known as the Sonogashira reaction [3]. We used the advanced artificial multi-route reactions methods developed for and tested with the Suzuki-Miyaura and Heck reactions with aryl halides to establish the fast, reversible, and rate-determining steps of catalytic cycles [4,5]. The integral kinetic curves of competing substrate consumption were analysed to determine the natures of the fast and rate-determining steps.

Studying the dependence of the differential selectivity of competing reactions on various parameters, such as the ratio of the competing substrates and the nature and concentration of the coupling partner, clarified the degrees of reversibility of the steps in which two substrates compete. Based on the data obtained, mechanistic schemes for the reversible, fast, and rate-determining steps of the catalytic cycles of the Heck reaction with aromatic carboxylic anhydrides and the Sonogashira reaction are proposed.

It should be noted that in spite of visible complications of a reaction arising when additional substrate is introduced, the artificial multi-route character has some advantages for the mechanistic investigation of a complex catalytic reaction. The competing substrates can be distinguished by varying the nature of the substituents and their separation from the reaction centre. In this sense, competitive reactions of such substrates are completely sufficient to assume that the natures of the catalytically active compounds are the same. Additionally, the assumption regarding identical products formation sequences (from a mechanistic point of view) becomes more valid in this case in comparison with the formation of the main and side products of a catalytic reaction. The latter is very important because it leads to a rather simple mathematical description of differential selectivity (vide infra), that can be important in the correct interpretation of experimental data. Therefore, the suggested approach can be applied for more complex catalytic systems possessing complicated transformations of a catalyst and wide set of products formed.

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2. Experimental

2.1. General considerations

The quantitative compositions of the samples were determined using gas chromatography (GC) (HP 4890 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). In order to verify the formation of particular products **2**-**9**, their authentic samples (analogous to that obtained in the reaction with unsubstituted phenyl acetylene and iodobenzene) were obtained.

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.

The reaction selectivity values were estimated using the slopes of phase trajectories (Section 3). The instantaneous rates of competing substrate consumption and corresponding product accumulation (Sections 3.3 and 3.4) were estimated by graphical differentiation of the region of each kinetic curve over the relevant time period.

2.2. Heck reaction with competing alkenes

Two competing alkenes (2.5 mmol each), an aromatic carboxylic anhydride (5 mmol), $PdCl_2$ (0.08 mmol, 1.6 mol%), LiCl (0.5 mmol) and naphthalene (1 mmol) as an internal standard for GC and GC–MS analyses were added to 5 mL of N-methyl-2-pyrrolidone (NMP) in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a pre-heated oil bath (140 °C), and the reaction mixture was stirred.

2.3. Heck reaction with competing aromatic carboxylic anhydrides

Two competing aromatic carboxylic anhydrides (2.5 mmol each), an alkene (5 mmol), $PdCl_2$ (0.08 mmol, 1.6 mol%), LiCl (0.5 mmol) and naphthalene (1 mmol) as an internal standard for GC and GC–MS analyses were added to 5 mL of NMP in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a pre-heated oil bath (140 °C), and the reaction mixture was stirred.

2.4. Sonogashira reaction with competing alkynes

Two competing alkynes (5 mmol each), an aryl iodide (5 mmol), Pd(OAc)₂ (0.08 mmol, 1.6 mol%), NBu₃ (6.5 mmol) as a base, and naphthalene (1 mmol) as an internal standard for GC and GC–MS analyses were added to 5 mL of N,N-dimethylformamide (DMF) in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a pre-heated oil bath (80 °C), and the reaction mixture was stirred.

2.5. Sonogashira reaction with competing aryl iodides

Two competing aryl iodides (2.5 mmol each), an aryl acetylene (10 mmol), Pd(OAc)₂ (0.08 mmol, 1.6 mol%), NBu₃ (6.5 mmol) as a base, and naphthalene (1 mmol) as an internal standard for GC and GC–MS analyses were added to 5 mL of DMF in a glass reactor equipped with a magnetic stir bar and a septum inlet. The reactor was placed into a pre-heated oil bath (80 °C), and the reaction mixture was stirred.

3. Results and discussion

Mechanistic investigations of complex catalytic reactions are usually quite difficult because many processes are directly and indirectly involved in the catalytic cycle. For cross-coupling reactions with aryl halides, particularly the Heck and Sonogashira reactions, dynamic interconversions of different forms of Pd (i.e., mono- and polynuclear complexes in solution, nanoparticles, and bulk aggregates) during the catalytic reaction have been observed many times [6–9]. This peculiarity led to the failure of many standard procedures used to establish the mechanistic details of reactions to obtain reliable results for cross-coupling reactions. Thus, the most attractive methods for establishing the mechanistic details of such reactions are kinetic studies. Just imagine that the structure and composition of all the reaction intermediates is established (that is, of course, impossible due to the concentration of reactive intermediates (including active species) can be too small to be detected by any method used). However, even in this improbable situation, the appearing of a compound in the reaction mixture does not give any information about its role in the reaction itself. Thus, the kinetic study analysing an accumulation or consumption of any reaction intermediates, substrates and products can be the only tool for determine the catalytic role of different species. In our previous works, we attempted to develop methods to unambiguously elucidate the mechanistic features of the catalytic cycles of complex catalytic reactions, including the rate-determining steps and the degrees of reversibility of the steps. These aims were achieved by using a set of approaches based on the competing reaction method [4,5]. The competing reaction method, or, to be more precise, artificial multi-routeness is exactly intend for studying mechanisms of complex catalytic reactions. This approach let one to investigate the properties of concrete step of catalytic cycle where two substrates compete (by measurements of differential selectivity) irrespective to complexity of whole reaction mechanism and amount of elementary steps. In addition, creation of artificial multi-routeness by introduction of several reactants interacting with one of the intermediates becomes the sole method to get information about elementary steps if they occur after the rate-limiting step of catalytic cycle. Thus, we demonstrated that measuring the dependence of the differential selectivity of competing reactions using two (or more) competing substrates on various parameters (such as the concentration ratio of the competing substrates and the concentration and nature of the coupling partner) allowed the reversibility of a catalytic cycle's steps to be examined. This information is very important from both fundamental and applied perspectives because it facilitates the effective selection of optimal reaction conditions [5]. Additionally, analysing the integral kinetic curves of competing substrates over the course of the reaction provides unambiguous information about the natures of the fast and rate-determining steps [4]. Our success testing the proposed approaches in quite simpler and well-studied traditional Suzuki-Miyaura and Mizoroki-Heck reactions with aryl halides characterized by high selectivity (minor products are virtually absent) [4,5] has demonstrated the possibility of suggested approaches to determine reversible, fast, and rate-determining steps of complex catalytic reactions accompanied with different transformations of a catalyst.

It should be noted that to characterize the differential selectivity (Sel_{dif}), we use the ratio of competing reaction rates (i.e., the product-formation rates corresponding to each competing substrate). The 'classical' equation for differential selectivity (the ratio of the rate of formation of one product to the sum of the rates of formation of all possible reaction products) is clearly related to the