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Approach to the determination of kinetic order of catalyst deactivation: observation of unusual kinetics in the Suzuki–Miyaura reaction

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Using of a new approach to estimate the kinetic orders of catalyst transformations in the Suzuki–Miyaura reaction allowed us to establish that the catalytic reaction and catalyst deactivation are of nearly first orders, and this fact contradicts the current view on the nature of an active catalyst.

The Suzuki–Miyaura reaction is one of the most studied catalytic processes in cross-coupling reactions.[1] However, in spite of considerable attention paid to the optimization of its catalytic systems from a practical viewpoint,[2,3] fundamental aspects of this reaction remain unidentified. Contradictory results on the nature of active species in this reaction have been reported.[4,5] A kinetic study can provide important information on the mechanism of this reaction. We used kinetic data to demonstrate that the Suzuki–Miyaura reaction catalyst is heterogeneous; this result is inconsistent with the accepted view on the nature of active species in this reaction.

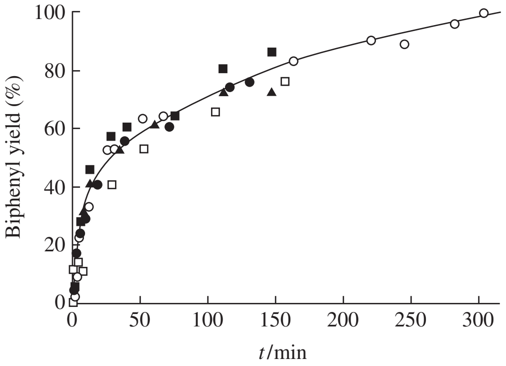
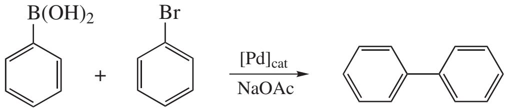


Figure 1 Biphenyl yield *vs.* time in the Suzuki–Miyaura reaction at 60 °C at different degrees of reaction mixture dilution with the solvent: (▲) standard experiment (without dilution); dilution ratios of (■) 1 : 2, (○) 1 : 10, (●) 1 : 20 and (□) 1 : 40. Solid curve is plotted based on equation (2) ($k_{\mathrm{cat}} = 281\ \mathrm{min}^{-1}$, $k'_{\mathrm{cat}} = 8.36\ \mathrm{min}^{-1}$, and $k_{\mathrm{deact}} = 0.073\ \mathrm{min}^{-1}$).

The Suzuki–Miyaura reaction (Scheme 1)[†] is characterized by the occurrence of numerous complex catalyst transformations, including nonlinear kinetics processes.[6] However, in this study, the kinetic curves of yield *vs.* time were found to remain unchanged upon varying the solvent quantity (Figure 1). Such a behavior is unusual for a complex catalytic system; nevertheless, it was observed over a wide range of temperatures (22, 60, and 140 °C) and should be attributed to the reaction mechanism.



Scheme 1 Suzuki–Miyaura reaction.

It is well known that, only in the case of the overall first order of reaction, the time of attainment of the same product yield in reaction with different dilutions does not depend on the initial component concentrations. Therefore, Figure 1 indicates that the Suzuki–Miyaura reaction exhibits overall first-order kinetics. However, partial orders with respect to the reagents of catalytic reactions are variables that depend on the rate constants of elementary steps and on the reagent concentrations.[7] Since the first-order kinetics was observed at different temperatures, the overall first order of the reaction (*i.e.*, the sum of the partial orders in reagents) is an extraordinary result. The sole rationale for this phenomenon may be that all the rate-determining elementary steps of the test reaction are first-order kinetics. However, when the catalyst transformations occurring outside the catalytic cycle (*e.g.*, the formation and/or deactivation of the active catalyst) influence the reaction rate, the rate-determining steps of these processes should also be first-order reactions.

Two nearly linear segments with different catalyst activities are clearly visible in the kinetic curves (Figure 1), indicating the deactivation of the active species to a less active form or its total deactivation. Since this process manifests itself clearly as a sharp drop in the reaction rate (at approximately 30–40 min, Figure 1), the deactivation along with the catalytic cycle is capable of affecting the reaction rate; thus, it is the rate-determining step of the Suzuki–Miyaura reaction. Therefore, this process should be a first-order reaction.

[†] A glass reactor fitted with a rubber septum and a magnetic stirrer was charged with bromobenzene (5 mmol), PhB(OH)$_2$ (5 mmol) and naphthalene (1 mmol) as an internal standard for gas chromatography (GC); NaOAc (6.5 mmol) was used as a base, and PdCl$_2$ (0.08 mmol Pd) was used as a catalyst precursor; a DMF–water mixture (4:1, 5 ml) was used as a reaction medium. The reactions were conducted at 22, 60 or 140 °C with stirring (477.5 rpm). To perform experiments with different degrees of dilution of the reaction mixture, the amounts of all reagents (except for the solvent) were decreased by factors of 2, 5, 10, 20 and 40. The reaction was monitored by GC and GC-MS.

In the Suzuki–Miyaura reaction, the conversion of bromobenzene at different reaction times coincides with the sum of biphenyl and benzene yields indicating that the homocoupling of bromobenzene or phenylboronic acid does not proceed. In all runs, the benzene yield in a side reaction of bromobenzene reduction was 3–10%.

The conversions were examined by GC (HP-4890, FID and 15 m HP-5 column). The products were characterized by GC-MS (Shimadzu GCMS 2010 Ultra, 30 m GsBP-5MS column, He as a carrier gas, electron impact ionization, electron energy of 70 eV, and *m/z* range of 40–350). Comparative experiments with iodobenzene (Suzuki–Miyaura reaction) and styrene (Heck reaction) were carried out in the same manner; the only difference was that PhBr and PhB(OH)$_2$ were replaced with PhI and styrene, respectively (see Online Supplementary Materials).

To validate the above speculation, let us consider the system of differential equations (1) that correspond to three first-order reactions:

$$\begin{cases} \dfrac{\mathrm{d[P]}}{\mathrm{d}t} = k_{\mathrm{cat}}[\mathrm{Pd}] + k'_{\mathrm{cat}}[\mathrm{Pd}'], \\ \dfrac{\mathrm{d[Pd]}}{\mathrm{d}t} = -k_{\mathrm{deact}}[\mathrm{Pd}]. \end{cases} \tag{1}$$

The first equation of the system describes the rate of product formation ([P]) as an operation result of two catalysts (Pd and Pd′) with different activities (k_{cat} and k'_{cat}, respectively) under the assumption of pseudo-zero-order kinetics in the substrate. The second equation describes the rate of transformation of catalyst Pd to the less active catalyst Pd′. The solution of equations (1) is the following equation, which describes the product yield as a function of time:

$$\frac{[\mathrm{P}]}{[\mathrm{S}]_0}\times 100 = \frac{[\mathrm{Pd}]_0}{[\mathrm{S}]_0}\left[\left(\frac{k_{\mathrm{cat}}}{k_{\mathrm{deact}}} - \frac{k'_{\mathrm{cat}}}{k_{\mathrm{deact}}}\right)(1 - \mathrm{e}^{-k_{\mathrm{deact}}t}) + k'_{\mathrm{cat}}t\right]\times 100, \tag{2}$$

where $[\mathrm{Pd}]_0$ is the concentration of a loaded catalyst and $[\mathrm{S}]_0$ is the initial concentration of the substrate limiting the product yield.

It is obvious from equation (2) that the right-hand member is independent of reaction mixture dilution. Note that the observed kinetics (Figure 1) is fitted well by equation (2) at not only 60 °C but also at the other temperatures. According to the results of the performed analysis, the yield *vs.* time kinetic curves should depend on the reaction mixture dilution when catalyst deactivation exhibits zero- or second-order kinetics (see Online Supplementary Materials). Thus, only the first-order deactivation agrees with the overlaid kinetic curves (Figure 1). Therefore, performing experiments at different degrees of reaction mixture dilution can provide information on the orders of the rate-determining steps of the catalytic cycle and the orders of the catalyst transformation processes occurring outside the catalytic cycle.

The first order of catalyst deactivation in the Suzuki–Miyaura reaction revealed by the proposed approach contradicts the widely accepted view that the agglomeration of dissolved $\mathrm{Pd^0}$ complexes is the main path of catalyst deactivation. It is unlikely that the agglomeration kinetics would correspond to simple first-order kinetics.[8]

The proportions of dissolved $\mathrm{Pd^0}$ complexes and agglomerated particles in the reaction depend significantly on the nature of aryl halide because it is responsible for the oxidation and subsequent dissolution of palladium metal. In particular, on replacing aryl bromides with aryl iodides, which are more reactive compounds, no palladium black precipitate is visually observed in the Suzuki–Miyaura reaction. In order to demonstrate the sensitivity of suggested approach to fine details of the mechanisms of complicated catalytic processes, we carried out similar experiments for the Suzuki–Miyaura reaction with iodobenzene and obtained quite different results. The kinetic curves for this reaction carried out at different degrees of dilution did not overlap (see Online Supplementary Materials). Further, a distinct increase in product yield with an increase in the reaction mixture dilution was observed. This increase in product yield was in excellent agreement with the non-first-order kinetics of catalyst deactivation and was indicative of the aggregation of catalytically active dissolved $\mathrm{Pd^0}$ compounds, which was previously assumed for the Suzuki–Miyaura reaction with aryl iodides.[5,9]

The dissolved $\mathrm{Pd^0}$ compounds were also supposed as an active species in the Heck reaction.[6,10,11] Actually, the kinetic curves obtained at different degrees of dilution of the Heck reaction mixture between bromobenzene and styrene did not overlap (see Online Supplementary Materials). This suggests the catalytic activity of dissolved Pd species, which are deactivated by agglomeration according to non-first-order kinetics.

Therefore, we conclude that the experimental data obtained in the Suzuki–Miyaura reaction with non-reactive aryl halides give evidence for the existence of active species other than dissolved $\mathrm{Pd^0}$ compounds. In our opinion, these active species are most probably *in situ* formed heterogeneous palladium particles (including palladium nanoparticles) supposed as an active catalyst in a number of publications.[9,12–14]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.02.010.

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