

Kinetic Study of the Heck Reaction by the Method of Competing Reactions

A. F. Shmidt and V. V. Smirnov

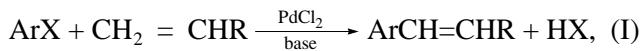
Department of Chemistry, Irkutsk State University, Irkutsk, 664003 Russia

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Abstract—The method of competing reactions is used to measure the isotope effect in styrene phenylation by iodobenzene. The kinetics of styrene, methyl acrylate, and methyl methacrylate phenylation is studied. Experimental data suggest that the step of alkene insertion is relatively fast, while the subsequent step that involves C–H bond dissociation is rate-limiting. The kinetic parameters of the process point to the dependence of the rate-limiting step of the catalytic cycle on the concentrations of base and alkene. These results are consistent with the existing hypothesis that the step of β -elimination of palladium hydride is present in the mechanism.

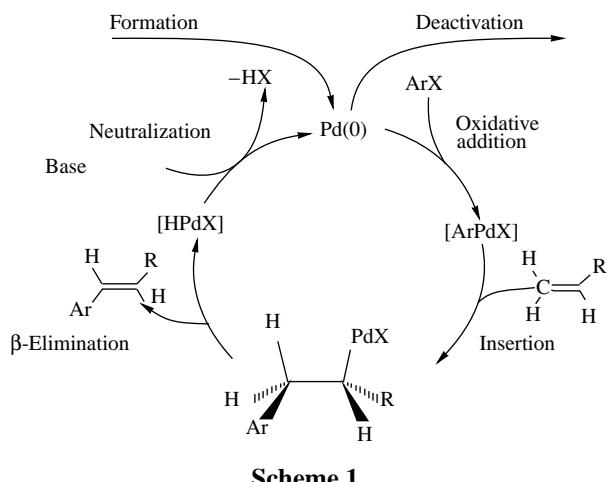
INTRODUCTION

Although almost three decades elapsed since Heck's discovery of the catalytic arylation of alkenes (I), the kinetics of this reaction remains poorly studied. The mechanism of the catalytic reaction (Scheme 1) was proposed by Heck and has not been changed yet.



where $\text{X} = \text{I}, \text{Br}, \text{or Cl}$.

Difficulties in the study of reaction (I) are largely due to the strong effects of catalyst formation, deactivation, and regeneration on the process rate [1]. Thus, the relative reactivity of intermediate palladium complexes in reaction (I) remains unclear. Reliable determination of the rate-limiting step would simplify a further study of reaction kinetics and enable mechanism refinement.



It has been found that the rate of reaction (I) is not determined by the oxidative addition step (Scheme 1) when aryl iodides are used as arylation agents. This

conclusion is based on the opposite effects of aryl substituents on catalytic reaction (I) and the stoichiometric reaction of $\text{Pd}(0)$ with aryl iodides [2]. However, the use of less active ArBr and ArCl makes oxidative addition the slowest step of the catalytic cycle [2]. Taking into account that palladium hydride is unstable under the conditions of reaction (I), it is necessary to determine the relative rates of insertion and β -elimination reactions. This problem can be solved only if active aryl iodides would be used in reaction (I).

Based on the value of the kinetic isotope effect measured by carrying out ethylene and D_4 -ethylene phenylation reactions independently [2], we concluded that the β -elimination of palladium hydride is rate-limiting (Scheme 1). This conclusion should further be confirmed in light of our data on strong relationships between the rates of reaction (I) and catalyst formation, deactivation, and regeneration [1]. Another reason why such confirmation is needed is possibly different effects of admixtures on the catalysis of reactions with deuterated and nondeuterated substrates. In this work, we report the results of kinetic isotope effect measurements and kinetic studies of reaction (I) by the method of competing reactions.

EXPERIMENTAL

The isotope effect studies were carried out using a constant-temperature vessel with a magnetic stirrer. The reaction mixture was prepared by mixing styrene (0.125 mmol), D_8 -styrene (0.125 mmol), PhI (0.5 mmol), NBu_3 (0.65 mmol), and PdCl_2 (0.08 mmol) in DMF (5 ml). While carrying out the reaction at 80°C, samples were withdrawn for GLC (HP-4890, 15% MePh siloxane, 15 m, 100–200°C) and chromatography/mass spectrometry analyses (MAT-212, an ionization voltage of 70 eV, a cathode current of 0.5 mA, SE-30, 50 m, 100–300°C). The competing phenylation of styrene, methyl acrylate, and methyl methacrylate

was studied at 60°C by mixing two alkenes (10 mmol each), PhI (10 mmol), NaOOCH (13 mmol) and PdCl₂ (0.16 mmol) in DMF (10 ml). The phenylation of individual alkenes was studied in an analogous way in the presence of NBu₃ (13 mmol) as a base or NaOAc (11.2 mmol) with NaOOCH or NBu₃ (1.8 mmol). Samples were analyzed by GLC.

The values of rate constants were calculated by differentiating the stationary portions of kinetic straight lines for alkene phenylation products using a graphical method. The period required for settling the stationary regime was at most 1 min at 3–5% conversion of initial reactants. The values of rate constants were calculated by minimizing the sum of squares of deviations between the calculated and experimental values using the Fletcher–Powell method. Reactants were purified using standard procedures. Deuterated styrene was purchased from Aldrich.

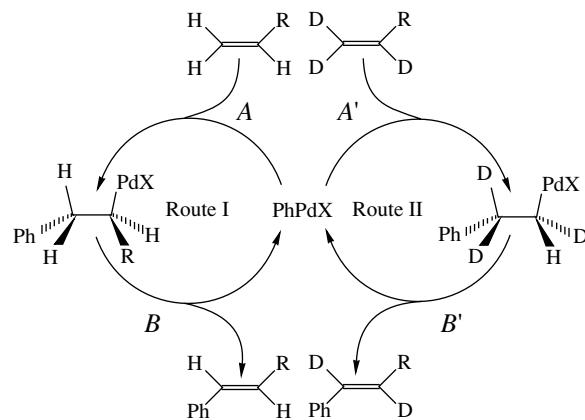
DISCUSSION

Competing Phenylation of Styrene and D₈-Styrene

The isotope effect of reaction (I) was measured by carrying out the phenylation reaction of the equimolar mixture of styrene (ST) and D₈-styrene (DST) by iodo-benzene in the presence of the conventional catalytic system containing the PdCl₂ catalyst and the NBu₃ base. In the samples, the ratio of deuterated and non-deuterated styrenes, as well as the corresponding products of the reaction, was close to unity according to chromatographic/mass spectrometric analyses. This pointed to the equal rates of ST and DST phenylation. At first glance, this result points to the absence of the isotope effect in styrene phenylation as contrasting to ethylene phenylation [2]. However, the overall rate of phenylation of the mixture of ST and DST was two times lower than the rate of ST phenylation. As we will show below, this can be due to the kinetic isotope effect in the step involving C–H bond dissociation, which is next to the irreversible insertion of alkene into a Pd–C bond in Scheme 1. According to the current idea of the Heck reaction mechanism, this is the step of palladium hydride β -elimination (Scheme 1).

Let us consider the scheme of the phenylation of ST + DST mixture with two routes (Scheme 2). As it was shown in [2], the rate of oxidative addition in the phenylation by aryl iodides is rather high. That is, the concentration of Pd(0) in the reaction is insignificant. Therefore, the sequence of steps in Scheme 2 begins with competing irreversible reactions of alkene insertions into a Pd–C bond (A and A' in Scheme 2). The irreversibility of alkene insertion is rather probable because the reverse process would occur with C–C bond scission, which is improbable under the given conditions and has not found experimental support. Further steps of the β -elimination of palladium hydride (B and B' in Scheme 2) is reversible, but they also can be considered irreversible since hydride formed in this

reaction is unstable and acid neutralization occurs at a high rate. Some authors [3, 4] doubt the Heck mechanism and assume that palladium hydride is not formed at all and the hydrogen atom is abstracted directly by the base molecule.



Scheme 2.

It is reasonable to assume that the insertion step does not reveal the isotope effect because hydrogen does not break any bond in this step. Thus, if it were rate-limiting in reaction (I), the rates of ST and DST phenylation would be equal. This agrees with the experiment, but we did not observe a decrease in the overall rate of reaction. On the other hand, it is clear that palladium hydride β -elimination must have a kinetic isotope effect because it breaks the C–H bond [5].

The pseudo-steady-state rate laws of two competing routes of styrene (S1) and D₈-styrene (S2) phenylation (Scheme 2) for the equal initial concentrations of alkenes are

$$w_{S1} = \frac{k_{S1}^{\text{ins}} [\text{Pd}]_{\Sigma}}{1 + \frac{k_{S1}^{\text{ins}}}{k_{S1}^{\text{el}}} + \frac{k_{S2}^{\text{ins}}}{k_{S2}^{\text{el}}}}; \quad w_{S2} = \frac{k_{S2}^{\text{ins}} [\text{Pd}]_{\Sigma}}{1 + \frac{k_{S1}^{\text{ins}}}{k_{S1}^{\text{el}}} + \frac{k_{S2}^{\text{ins}}}{k_{S2}^{\text{el}}}}, \quad (1)$$

where w_{S1} and w_{S2} are the rates of routes S1 and S2; k_{S1}^{ins} and k_{S2}^{ins} are the rate constants of insertion steps (A and A', Scheme 2), k_{S1}^{el} and k_{S2}^{el} are the rate constants of elimination steps (B and B', Scheme 2), and $[\text{Pd}]_{\Sigma}$ is the total concentration of palladium. In this case, k_{S1}^{ins} and k_{S2}^{ins} also involve the concentrations of the corresponding alkenes.

If elimination is a rate-limiting step in either route (B or B', Scheme 2), the following inequalities are fulfilled:

$$\frac{k_{S1}^{\text{ins}}}{k_{S1}^{\text{el}}} \gg 1, \quad \frac{k_{S2}^{\text{ins}}}{k_{S2}^{\text{el}}} \gg 1.$$

If we neglect the unity in the denominators of Eqs. (1), then we obtain

$$w_{S1} = \frac{Lk_{S1}^{\text{el}}k_{S2}^{\text{el}}[\text{Pd}]_{\Sigma}}{Lk_{S2}^{\text{el}} + k_{S1}^{\text{el}}}; \quad w_{S2} = \frac{k_{S1}^{\text{el}}k_{S2}^{\text{el}}[\text{Pd}]_{\Sigma}}{Lk_{S2}^{\text{el}} + k_{S1}^{\text{el}}}, \quad (2)$$

where $L = k_{S1}^{\text{ins}}/k_{S2}^{\text{ins}}$ is the ratio of the rate constants of insertion steps (A and A' , Scheme 2).

Thus, ST and DST would react at the same rates because $k_{S1}^{\text{ins}} = k_{S2}^{\text{ins}}$ and $L = 1$. If the rate limiting step is elimination, the rate of styrene phenylation is determined by the rate of this step and described by the equation

$$w_{S1} = k_{S1}^{\text{el}}[\text{Pd}]_{\Sigma}. \quad (3)$$

By dividing Eq. (3) by the sum of Eqs. (2), we arrive at the ratio of styrene phenylation rate w_{S1} to the overall rate for the mixture of styrenes w_{S1+S2} :

$$N = \frac{w_{S1}}{w_{S1+S2}} = \frac{k_{S2}^{\text{el}} + k_{S1}^{\text{el}}}{2k_{S2}^{\text{el}}}. \quad (4)$$

It follows from Eq. (4) that $w_{S1} > w_{S1+S2}$ if $k_{S1}^{\text{el}} > k_{S2}^{\text{el}}$. This condition is expected to be fulfilled when there is a kinetic isotope effect, which is responsible for the apparent decrease in the overall phenylation rate in the case of the mixture of styrenes.

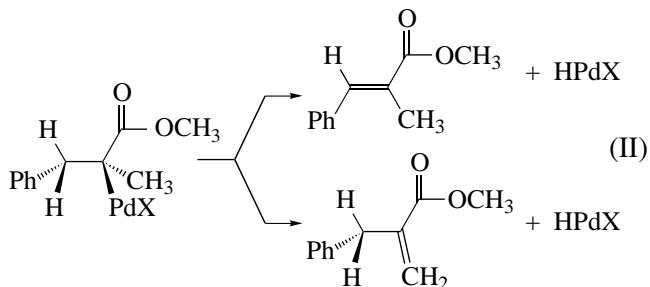
The ratio $k_{S1}^{\text{el}}/k_{S2}^{\text{el}}$ can be expressed using Eq. (4) and thus, we derive the relationship between the kinetic isotope effect of palladium hydride β -elimination step and the value of N :

$$\frac{k_{S1}^{\text{el}}}{k_{S2}^{\text{el}}} = 2N - 1. \quad (5)$$

For the experimentally observed value of $N = 2.0$, the value of the kinetic isotope effect calculated from Eq. (5) is 3.0, which is very close to that obtained for ethylene phenylation (3.2 [2]) and that reported in [6] for stoichiometric β -elimination (2.28). This fact supports the idea that this step is rate-limiting in Scheme 1.

Competing Phenylation of Other Substrates

To find evidence that elimination is the rate-limiting step for a variety of alkenes, we used different substrates: styrene, methyl acrylate (MA), and methyl methacrylate (MMA). All reactions were carried out in the catalytic system $\text{PdCl}_2 + \text{NaOOCH}$ [7]. The choice of this system is stipulated by the high rate of the *in situ* formation of the catalytically active complexes of reduced palladium from initial Pd(II) . This high rate makes the catalytic activity independent of this process. Reactions of ST and MA occur according to Scheme 1. In the case of MMA, additional β -H atoms are available, and two regiomers can be formed by β -elimination:



The constant ratio of the concentrations of these products during the reaction points to the fact that these processes are parallel to each other. This allowed us to approach CT and MMA processes in a similar way. In the latter case, the rate constant of elimination is the sum of the rate constants for two regiomers in reactions (II).

The results of experiments confirm, even at a qualitative level, that elimination is a rate-limiting step. For instance, MMA phenylation is much faster (w_{S2}) than ST phenylation (w_{S1}) (no. 1, Table 1). However, in the phenylation of the MMA + ST, styrene reacted four times more rapidly than MMA ($L = 4$), whereas the overall rate of phenylation (w_{S1+S2}) was close to the phenylation rate of styrene alone (no. 1, Table 1). If the insertion step were rate-limiting, the selectivity in the competing process would be higher in the case of the more active substrate (MMA). On the other hand, if the hypothesis that elimination is rate-limiting is true, the

Table 1. Rates of the competing phenylation of ST, MA, and MMA

No.	Substrate		Rate $\times 10^2$, mol l ⁻¹ min ⁻¹			Selectivity $L = \frac{k_{S1}^{\text{ins}}}{k_{S2}^{\text{ins}}}$	Calculated $k_{S1}^{\text{el}}/k_{S2}^{\text{el}}$ from		
	S1	S2	w_{S1+S2}	w_{S1}	w_{S2}		$\frac{w_{S1}}{w_{S2}}$	$\frac{w_{S1}}{w_{S1+S2}}$	$\frac{w_{S2}}{w_{S1+S2}}$
1	ST	MMA	3.9	3.4	9.0	4.00	0.38	0.35	0.38
2	ST	MA	4.0	3.4	5.0	0.91	0.68	0.71	0.66
3	MA	MMA	5.1	5.0	9.0	5.65	0.57	0.87	0.53

selectivity in the phenylation of two substrates, as in the case of ST and DST, is determined by the ratio of the rate constants of insertion steps L (see Eqs. (2)), but the overall rate of the process depends both on the rate constants of elimination steps k_{S1}^{el} and k_{S2}^{el} and L rather than on L only.

It follows from Eqs. (2) that for $L \neq 1$, we can obtain by analogy with Eq. (5)

$$\frac{k_{S1}^{\text{el}}}{k_{S2}^{\text{el}}} = N(L + 1) - L. \quad (6)$$

If one knows w_{S1} and $w_{S1 + S2}$, it is possible to predict the rate of phenylation of the second substrate w_{S2} . That is, we can check the conjecture that the β -elimination of palladium hydride is rate-limiting.

The calculated ratios of the rate constants of elimination steps from the rates of the phenylation of three substrates and all their possible combinations are shown in Table 1. The coincidence of these values for each pair of substrates is rather good. This means that Eq. (6) derived assuming that the β -elimination of palladium hydride is rate-limiting in the Heck reaction is adequate to the experiment.

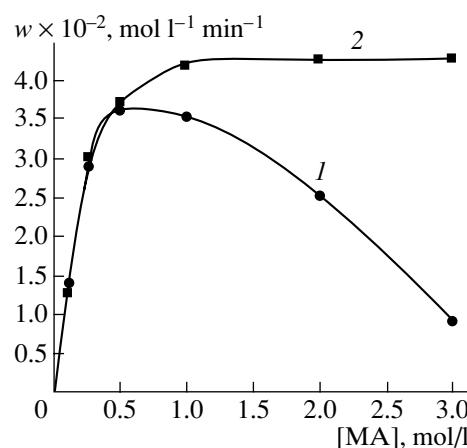
The same experimental data were used to calculate the absolute values of rate constants. The least-squares method for the set of three equations was used to calculate three rate constants of elimination steps. The set of equations contained equations like Eq. (7), which described the rate of the competing phenylation of ST, MA, and MMA in different combinations. Equation (7) can be derived from Eqs. (2) and (6). The rate constants of elimination reactions thus calculated and the same values calculated from Eq. (3) from usual, "non-competing" experiments agree well with each other (see Table 2).

$$w_{S1 + S2} = [\text{Pd}]_2 \left(k_{S1}^{\text{el}} \left(\frac{L}{N(L + 1)} \right) + k_{S2}^{\text{el}} \left(1 - \frac{L}{N(L + 1)} \right) \right). \quad (7)$$

Formal-Kinetics Parameters of the Heck Reaction

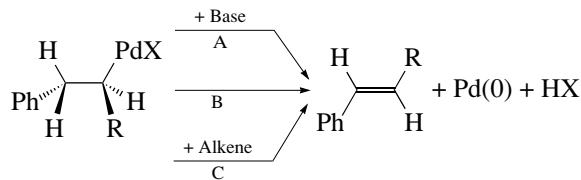
Proceeding from the fact that the elimination step in reaction (I) is rate-limiting, one should expect from Eq. (3) that the orders with respect to reactants are equal to zero. However, in the phenylation of ST, MA, MMA, and ethylene in the presence of different catalytic systems, the values of reaction orders differed substantially from zero (Table 3). These results agree with the available hypothetical mechanisms of the elimination steps that were proposed without kinetic data.

For instance, the sensitivity of reaction (I) to the concentrations of the base and alkene can be due to their participation in the elimination step. The hypotheses that the base directly participates in the elimination



Dependence of the rate of reaction (I) on the concentration of MA at [PhI] equal to (1) 1 and (2) 2 mol/l.

reaction (step A, Scheme 3) was advanced by Deeth *et al.* [3] based on DFT calculations and NMR monitoring of MA phenylation and by Beller and Riermeier [4] based on the dependence of the regioselectivity of MMA arylation on the choice of a base.



Scheme 3.

The effect of alkene concentration on the rate of the stoichiometric elimination reaction has been known for the complexes of some metals. Thus, Kochi [8] observed the autocatalytic acceleration, which was stipulated by the unimolecular reaction (analogous to step B in Scheme 3) in the beginning of the process and by an increase in the rate of the bimolecular reaction (analogous to step C in Scheme 3) with an increase in the concentration of alkene formed in the reaction. For reaction (I), the fact that the decomposition of the corresponding σ -alkyl complex occurs only in the presence of MA [9] proves the participation of alkene in the elimination step.

Table 2. Rate constants of the elimination step for various substrates

Substrate	k^{el} calculated from the rate of single substrate phenylation	k^{el} calculated from the rate of competing phenylation
ST	2.13	2.11
MA	3.13	3.11
MMA	5.63	5.63

Table 3. Partial orders with respect to the reactants of reaction (I) for different catalytic systems: (A) $\text{PdCl}_2 + \text{NBu}_3$, (B) $\text{PdCl}_2 + \text{NaOOCH}$, (C) $\text{PdCl}_2 + \text{NaOOCH} + \text{NaOAc}$, and (D) $\text{PdCl}_2 + \text{NBu}_3 + \text{NaOAc}$

No.	Alkene	Catalytic system	$T, ^\circ\text{C}$	Partial orders with respect to reactants*		
				PhI	alkene	base
1	MA	A	50	0.80	**	0
2	ST	A	80	0.30	0.60	0.30
3	Ethylene	A	80	0.30	0.24***	0
4	MA	B	70	0.70	**	0.54
5	ST	B	80	0.47	0.38	0.13
6	T	B	60	0.26	0	0
7	MA	C	70	0.77	**	0
8	ST	C	80	0.10	0.10	0
9	Ethylene	D	80	0.00	0.39***	0

* The partial orders were measured in the same range of component concentrations (0.25–2.5 mol/l).

** The rate-vs.-concentration curve had the form of a maximum analogous to that shown in the figure.

*** Because of the low solubility of ethylene, its concentration was varied in the range from 0.0183 to 0.183 mol/l.

Thus, the values of the partial orders of reaction (I) with respect to the alkene and base ranging from 0 to 1 (Table 3) can be due to the occurrence of elimination via both the unimolecular mechanism (step B, Scheme 3) and the bimolecular mechanism with the participation of the alkene and base (steps A and C, Scheme 3).

Unlike the alkene and base, the reason for the dependence of the rate of reaction (I) on the concentration of PhI is not the participation of PhI in the rate-limiting step. No matter what the rate-limiting step, the concentration of PhI can affect the total amount of palladium over all intermediate complexes in the catalytic cycle. It is known [1] that reaction (I) is accompanied by catalyst deactivation due to the aggregation of catalytically active $\text{Pd}(0)$ (Scheme 1). The order with respect to $\text{Pd}(0)$ in the process of aggregation is higher than in the oxidative addition step (Scheme 1) [1]. That is why more active alkenes will be able to cause an increase in the concentration of $\text{Pd}(0)$ at any moment in time and the elimination of palladium from the catalytic cycle due to aggregation. This is evidenced by the form of the dependence of the MA phenylation rate on the concentration (see the figure). At a high concentration of this substrate, we observed palladium black sedimentation, the virtually complete discoloration of reaction solution, and the cessation of the reaction at relatively low conversions. However, with an increase in the concentration of PhI, the rate-vs.-MA concentration curve had a usual form with saturation (see the figure) and the yield of phenylation products increased substantially.

CONCLUSION

Thus, we showed that the elimination step is rate-limiting in the catalytic cycle of the Heck reaction.

Kinetic parameters of this process allow us to refine the mechanism of this step by supplementing it with the bimolecular interaction of the palladium complex with the base or alkene molecules.

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