

Kinetic Studies of Heck Coupling Reactions Using Palladacycle Catalysts: Experimental and Kinetic Modeling of the Role of Dimer Species

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Abstract: Experimental kinetic studies of the coupling of *p*-bromobenzaldehyde (**1**) with butyl acrylate (**2**) using the dimeric palladacycles complex (**4**) with chelating nitrogen ligands were carried out together with kinetic modeling using a reaction rate expression based on the mechanism shown in Scheme 2. The oxidative addition product of **1** was found to be the resting state within the catalytic cycle. The formation of dimeric Pd species external to the catalytic cycle helped to rationalize a non-first-order rate dependence on catalyst concentration. Theoretical modeling showed how the relative concentrations of the different intermediate species within the catalytic cycle can influence the observed rate dependence on Pd concentration. It was shown how conventional kinetic studies may give reaction orders in substrates which differ from those which would be observed under practical synthetic conditions. Comparison between phosphine- and nonphosphine-based palladacycles suggests that they follow the same reaction mechanism. The role of water in accelerating the initial formation of the active catalyst species is noted.

Introduction

Carbon–carbon coupling reactions have become a versatile tool in organic synthesis.¹ The Heck reaction,^{2,3} the Pd-catalyzed coupling of olefins with aryl or alkenyl halides or triflates, offers tantalizing possibilities for obtaining a wide range of vinylic products used as intermediates in pharmaceuticals and fine chemicals or as building blocks for polymers. Although high turnover numbers and high yields can be obtained with reactive organic halides such as aryl bromides and iodides, the reaction conditions are generally quite harsh. Moreover, the industrially important but less reactive aryl chlorides react very sluggishly with the currently available catalysts. Thus, current research focuses on developing better Pd catalysts for higher activity, stability, and substrate tolerance. Palladium salts combined with coordinating ligands such as sterically demanding triarylphosphines have been found to help increase catalyst efficiency and to suppress the precipitation of Pd metal which results in catalyst deactivation. In particular, cyclometalated dimeric Pd(II) complexes and Pd complexes with chelating diphosphine ligands have received attention.^{4,5} Pd complexes with bulky monodentate phosphorus ligands also successfully effect the reaction.^{6,7}

However, high turnover numbers have also been obtained with simple phosphine-free catalyst systems using special conditions or additives.⁸ Most recently, phosphine-free palladacycles have been shown to be efficient catalysts or catalyst precursors for simple substrates.^{9,10}

Given this extensive interest in the Heck reaction spanning more than 25 years, it is perhaps surprising to consider that few kinetic studies have been carried out, although significant mechanistic questions remain unanswered. Brown and co-workers¹¹ have carried out investigations to identify key intermediates in the reaction using aryl triflates. Beller, Hermann, and co-workers^{4b} noted a dependence of reaction rate on the type of olefin substrate, calling into question the original mechanistic proposition that the rate-limiting step is the initial oxidative addition of the aryl halide. Recently van Leeuwen and co-workers⁶ reported kinetic studies which showed the reaction to be first order in olefin and zero order in aryl halide concentration and the rate-limiting step to be either binding or

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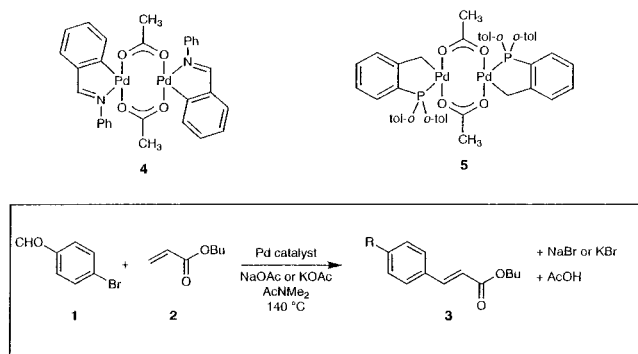
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Scheme 1



insertion of the olefin. Shaw⁵ has proposed an alternative mechanism for aryl halides based on the Pd(II)/Pd(IV) hypothesis put forward earlier by Hermann and Beller.⁴ In this proposal, the olefin binds first, followed by nucleophilic attack by the base on this olefin complex to render it reactive toward subsequent oxidative addition of the aryl halide.

Another interesting feature of Heck reactions carried out using dimeric catalysts has been the observation of a nonlinear dependence of reaction rate on the concentration of Pd. van Leeuwen and co-workers⁶ recently found a half-order dependence on catalyst concentration and attributed this to the formation of a dimeric $[\text{PdLArX}]_2$ species.

Many of the mechanistic questions raised in these studies may be probed effectively via detailed experimental kinetic studies and kinetic modeling. In this paper, theoretical modeling is used to highlight how the subtle interplay between reactions within and without the catalytic cycle may affect the observed reaction order in catalyst concentration. Experimental kinetic studies of the coupling of *p*-bromobenzaldehyde (**1**) with butyl acrylate (**2**) using the dimeric palladacycles complex (**4**)^{12,13} with chelating nitrogen ligands (Scheme 1) and kinetic modeling from in situ measurements over the entire course of the reaction allow greater mechanistic insight than is possible from initial rate kinetic studies. This provides a basis for discussing proposed reaction mechanisms and sheds light on the nature of the rate-limiting step. These studies help to clarify the role of dimeric palladium complexes in stabilizing the active catalytic species. The generality of the proposed reaction mechanism is illustrated by comparing these results to reactions using a phosphapalladacycle as catalyst.

Experimental Section

The reaction rate expression was developed from steady-state treatment of the elementary steps in the mechanism proposed in Scheme 2. Kinetic modeling of the data to fit the proposed rate expression was carried out using the Excel Solver program.

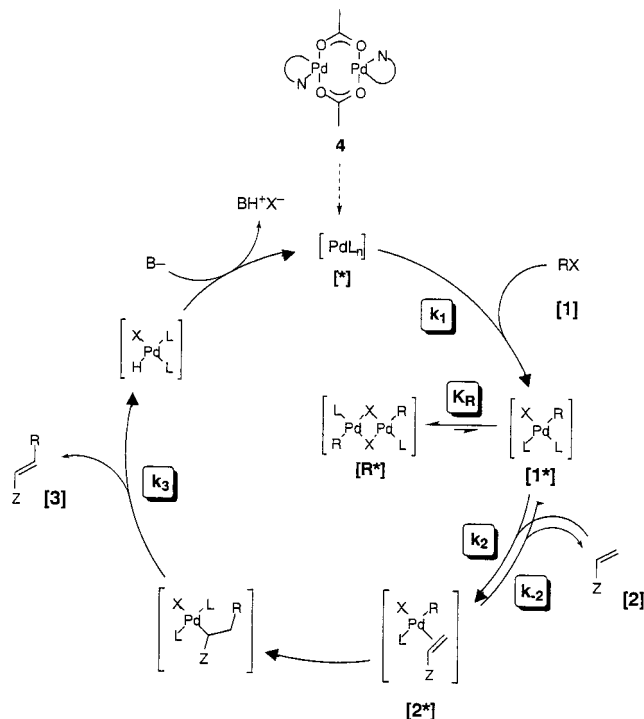
Synthesis and structural characterization of the nitrogen-based palladacycle was carried out as described in ref 13. *p*-Bromobenzaldehyde, butyl acrylate, and dimethylacetamide were distilled and dried prior to use. KOAc was used both as received and after extensive drying before use.

Kinetic measurements were made in a reaction calorimeter (Mettler RC1) using a 1 L jacketed glass vessel with a Hasteloy head and impeller shaft. A reaction rate datum point was obtained typically every 2 s over the course of the reaction, providing ca. 1000 data points for a 30-min reaction. The reaction calorimeter is capable of minimizing

(12) Granell, J.; Sainz, D.; Sales, J.; Solans, X.; Font-Alba, M. *J. Chem. Soc., Dalton. Trans.* **1986**, 1785.

(13) For earlier studies using **4**, see ref 10 and the following: Schmees, N. Dissertation, University of Köln, 1998. Complex **4** was synthesized as described in ref 12 and purified by recrystallization from chloroform/heptane.

Scheme 2



and accounting for any heat losses attendant to the process under study. An energy balance around a batch isothermal reactor shows that in the absence of side reactions or other heat effects, the measured heat flow is directly proportional to the reaction rate, as shown in eq 1

$$q(t) = \Delta H_{\text{rxn}} V \frac{dC}{dt} \quad (1)$$

where $q(t)$ = instantaneous heat flow (W), ΔH_{rxn} = heat of reaction (J/mol), V = reactor volume (l), and dC/dt = reaction rate (M/s). A two-part calibration experiment conducting an energy balance around the outer surface of the reactor is used to determine the heat transfer properties of the reactor and its contents, giving the two parameters U and C_p (eq 2).

$$q = UA(T_R - T_j) + mC_p \frac{dT_R}{dt} \quad (2)$$

A precision heating probe providing a known heat flow value q was immersed in the reactor contents under isothermal conditions ($dT_R/dt = 0$), and the reactor and jacket temperatures T_R and T_j were measured in order to solve for the heat transfer coefficient U . The reactor was then subjected to a known temperature ramp during which the heat flow through the reactor walls equaled the enthalpy accumulation ($q = 0$), allowing determination of the heat capacity of the solution C_p . This calibration was carried out in the absence of a catalytic reaction, typically in the reaction medium prior to adding catalyst or after the reaction has reached 100% conversion, and comparison of the two was used to ensure that significant changes in U and C_p did not occur over the course of the reaction.

The conversion over the course of the reaction may be determined from the partial heat flow or the area under the heat flow curve at any time t divided by the total heat flow for the entire reaction time from $t = 0$ to $t = t_f$ (eq 3).

$$\% \text{ conversion} = 100 \frac{\int_{t_0}^t q(t) dt}{\int_{t_0}^{t_f} q(t) dt} \quad (3)$$

Since the reaction calorimetric experiment monitors the sum of the heat flow for all reactions occurring in the reaction vessel, it is important

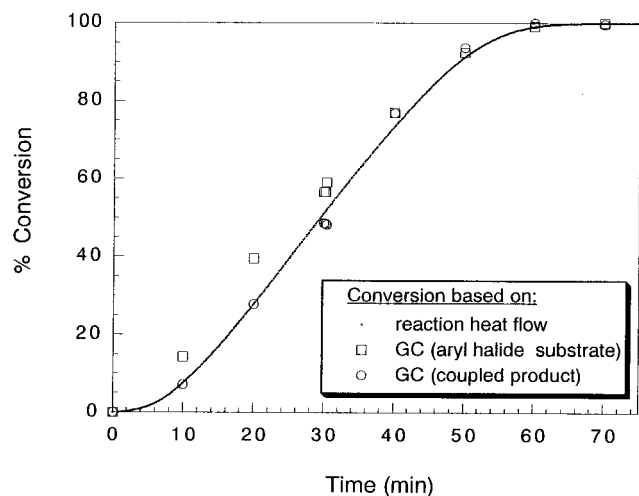


Figure 1. Correlation between reaction heat flow and analytical measurements of reaction conversion as a function of time in the Heck coupling of *p*-bromobenzaldehyde with butyl acrylate using palladacycle catalyst **4**, as described in Scheme 1 and in the Experimental Section.

to correlate the heat flow measured with analytical data to ensure that the heat flow may be used as a measure of the reaction of interest, without interference from side reactions. Figure 1 shows the results of a typical Heck reaction, where conversion measured by heat flow was compared to conversion measured from gas chromatographic analysis on the basis of the two substrates and on the product. The excellent agreement confirms that the calorimetric method provides a valid and accurate measure of the reaction rate for this reaction.¹⁴

Results and Discussion

Kinetic Model of the Reaction Network. Scheme 2 presents a mechanism for the Heck coupling reaction which served as the basis for our kinetic modeling. We assume that the dimeric palladacycle **4** is converted to an active monomeric Pd(0) complex by dissociation and a reductive step presumably involving the olefinic substrate. We consider this process to be essentially irreversible under the reaction conditions (although when the catalytic reaction is over, it is possible that the palladacycle may form again by reaction of the remaining Pd species with the arylimine ligand). We have no information about the nature of the ligands (L) bound to Pd during the catalytic cycle. L could be a solvent molecule, an arylimine ligand derived from **4**, or in some of the intermediates an acetate or bromide.

The catalytic cycle is initiated by oxidative addition of the aryl halide [1] to the Pd(0) catalyst [*], resulting in the four-coordinate aryl-Pd(II) complex [1*]. This complex reacts with the olefin to form the π -complex [2*]. Insertion of the olefin into the Pd-R bond leads to a Pd-alkyl species which undergoes β -hydride elimination, followed by dissociation to the product **3** and a Pd-hydride complex. The catalytic cycle is completed by base-assisted reductive elimination of HX regenerating the catalytically active Pd(0) complex [*]. Since in our studies the reaction rate was found to be independent of base concentration, we assume that base addition occurs after the rate-limiting step. The olefin insertion and product forming steps are not distinguishable from one another in the kinetic experiments carried out in this work, and hence the sequence of steps after formation of [2*] is combined into one step characterized by the rate constant k_3 . We consider that spectator dimeric Pd

species such as [R*] may form during reaction, as has been noted by van Leeuwen and co-workers.⁶

Using the steady-state approximation for the catalytic species **1*** and **2***, and assuming the dimeric R* species to exist in equilibrium with **1***, a reaction rate expression may be written to describe the mechanism shown in Scheme 2. This rate expression has fewer adjustable parameters than it does unknowns, and hence a unique solution for the five rate constants and one equilibrium constant shown in Scheme 2 is not possible from reaction rate data alone. With the assumption that the reverse reaction of oxidative addition of aryl halide is negligible, the equation may be simplified as shown in eq 4.¹⁵ [Pd] is the total concentration of Pd atoms, or twice the number of moles of original palladacycle **4** added to the reactor. All other rate constants and concentrations are as given in Scheme 2. Data obtained by following the course of the reaction with at least two different ratios of the initial concentrations of aryl halide to olefin and two different catalyst concentrations suffice to provide a unique fit to the kinetic model of eq 4.

$$r = 2k_1k_2k_3[1][2][Pd] / \{k_2k_3[2] + k_1(k_2 + k_3[1] + k_1k_2[2]) + (k_2k_3[2] + k_1(k_2 + k_3[1] + k_1k_2[1][2]))^2 + 8K_R(k_1(k_2 + k_3)[1])^2[Pd]^{1/2}\} \quad (4)$$

The denominator of the rate equation describes the ways in which the catalyst distributes itself between different species within and without the catalytic cycle. The concentrations of all catalytic species acting *within* the cycle of Scheme 1 ([*], [1*], and [2*], respectively, eq 5) are contained in what is known as the adsorption term, borrowing from the terminology of heterogeneous catalysis.

$$\text{adsorption term} = k_2k_3[2] + k_1(k_2 + k_3[1] + k_1k_2[1][2]) = ([*] + [1*] + [2*]) \quad (5)$$

However, when a reaction network involves catalyst species which do not themselves participate in the catalytic cycle but which react with active catalytic intermediates, the denominator of the rate expression must also account for the concentrations of dimer species. In this case we have extended the Langmuir-Hinshelwood expression to include a further "dimer term" to account for the concentration of inactive dimeric species [R*] (eq 6).

$$\text{dimer term} = (\text{dimer coefficient})[Pd] = 8K_R(k_1(k_2 + k_3)[1])^2[Pd] \quad (6)$$

Complex catalytic reaction networks involving dynamic equilibria between monomeric and dimeric species are a feature of a number of important catalytic reactions. Noyori and co-workers recently presented a theoretical treatment of the nucleophilic addition of diethylzinc to benzaldehyde using chiral amino alcohols which participate in a monomer-dimer equilibrium, with implications for nonlinear effects of catalyst enantiopurity.¹⁶ Sharpless and co-workers have observed both first- and half-order kinetics in the Ti-tartrate catalyst in asymmetric epoxidation of allylic alcohols, and molecular weight measurements revealed the presence of dimer species.¹⁷ While these examples

(15) Oxidative addition of aryl halides is usually considered to be essentially irreversible under Heck reaction conditions. Treatment of this step as a "quasi-equilibrium" in modeling of our experimental data suggested that the reverse reaction is at least 200 times slower than the forward step and may be neglected in the present kinetic treatment.

(16) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.

(14) For other kinetic studies using reaction calorimetry, see: (a) Sun, Y.; LeBlond, C.; Wang, J.; Forman, A.; Larsen, R.; Orella, C.; Blackmond, D. G. *Thermochim. Acta* **1996**, *289*, 189. (b) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511.

are analogous in some respects to the Heck reaction network presented here, in our case neither enantioselectivity nor nonlinear effects of catalyst enantiopurity is a relevant parameter, and we may focus here on reaction rate behavior alone.

When the possibility of dimer formation is vanishingly small, the expression reduces to that of conventional steady-state kinetics with first-order dependence on catalyst concentration. When dimeric species dominate, the reaction rate will be proportional to the square root of the total Pd concentration (eq 7). It is also interesting to note that in this limiting case the

$$r = \frac{k_2 k_3}{\sqrt{2K_R(k_{-2} + k_3)}} [2][Pd]^{1/2} \quad (7)$$

reaction rate will show first-order dependence on the concentration of olefin, [B], but will be independent of that of the aryl halide, [1]. However, because the rate constants in eq 7 are lumped together, this limiting case cannot provide information about the rate-limiting step in the catalytic cycle. van Leeuwen and co-workers⁶ used this limiting case to rationalize their recent observations in Heck reactions using dimeric Pd catalysts with phosphorus amidite ligands.

Between these two limiting cases, the rate may be expected show some dependence on the amount of Pd between half and first order, depending on the substrate concentrations and the values of the various rate constants in the catalytic network. Figures 2 and 3 show theoretical calculations to illustrate the relationship between rate and catalyst concentration for a variety of model reaction conditions. In these plots, "normalized rate" is defined as the rate calculated from the full rate expression in eq 4 for different magnitudes of K_R divided by the conventional steady-state expression in the absence of dimer species. This is given by eq 8.

$$\text{normalized rate} = \frac{\{2(k_2 k_3 [2] + k_1(k_{-2} + k_3[1]) + k_1 k_2 [1][2])\}}{\{k_2 k_3 [2] + k_1(k_{-2} + k_3[1]) + k_1 k_2 [1][2] + (k_2 k_3 [2] + k_1(k_{-2} + k_3[1]) + k_1 k_2 [1][2])^2 + 8K_R(k_1(k_{-2} + k_3[1])^2 [Pd])^{1/2}\}} \quad (8)$$

Equation 8 provides a measure of the contribution of the dimer term to the reaction rate. If dimer species are negligible, the reaction will exhibit simple first-order kinetics in catalyst concentration and the normalized rate should be a horizontal line equal to 1 as a function of catalyst concentration. Deviations from this horizontal line help us to examine the variables which affect the reaction order in catalyst.

One important conclusion which may be reached upon examination of Figure 2 is that the relative concentrations of the different intermediate species within the catalytic cycle will have an influence on the observed dependence on Pd concentration. These intermediate species concentrations depend on the relative magnitudes of the rate constants in the reaction network (which may vary with the nature of the substrates and catalysts) as well as the substrate concentrations. Figures 2a–c reveal that under typical Heck coupling conditions deviation from first-order kinetics in catalyst concentration is slight when the concentration of the oxidative addition product [1*] is low, which occurs when the reaction to form this intermediate is slow. This provides the practical diagnostic that Heck coupling reactions following this mechanism will show deviations from first-order kinetics in catalyst concentration *only* if a step *other*

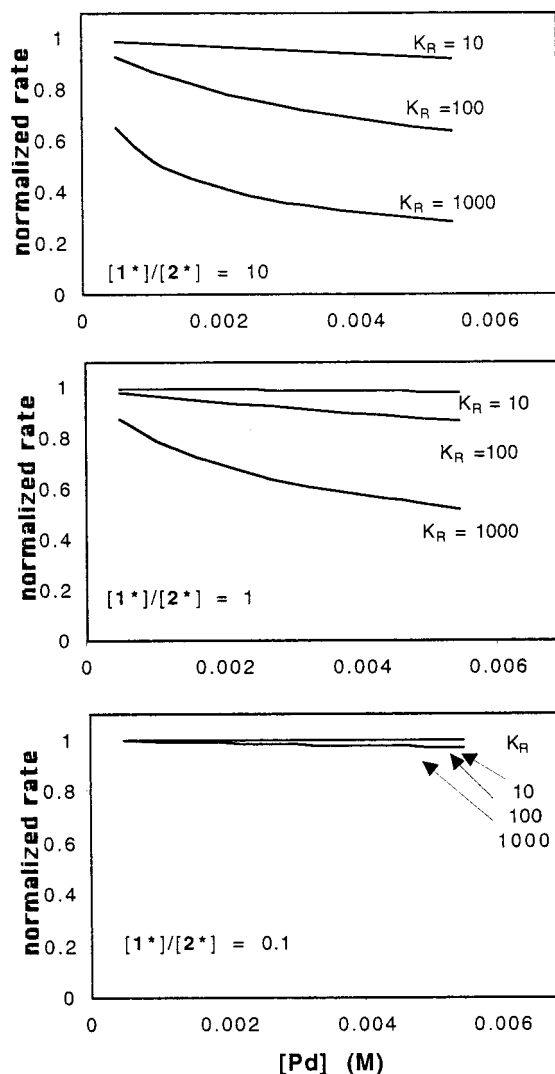


Figure 2. Theoretical curves for reaction rate as a function of Pd concentration for different distributions of intermediate species in the catalytic cycle shown in Scheme 2. Normalized rate is calculated as given in eq 8. The extent of deviation from a horizontal line equal to 1 indicates the extent of contribution from dimer species in the reaction mechanism. All symbols are as shown in Scheme 2. K_R = equilibrium constant for dimer formation, [1*] = oxidative addition product, [2*] = product of olefin addition and insertion. (a) [1*]/[2*] = 10. (b) [1*]/[2*] = 1. (c) [1*]/[2*] = 0.1.

than oxidative addition of aryl halide is rate-limiting. However, a strong deviation from first-order kinetics in catalyst concentration is not sufficient to distinguish which of the steps after oxidative addition is rate-limiting.

Figure 3 shows that the relative concentrations of the two substrates may also influence the observed order in catalyst concentration. While Heck coupling reactions are typically carried out under a slight excess of olefin in order to avoid a second coupling reaction of the aryl halide, kinetic studies are often carried out at artificially high concentrations of one substrate to provide pseudo-zero-order conditions. We demonstrate here, however, that such conditions for making conventional kinetic measurements may themselves influence the observed reaction rate law. Figure 3 reveals that a large excess of olefin will diminish deviations from first-order kinetics in catalyst concentration observed in the same catalyst system at lower olefin concentration. This may be rationalized by recognizing that an increase in the olefin concentration drives the distribution of catalyst species toward a higher fraction of

(17) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106–113.

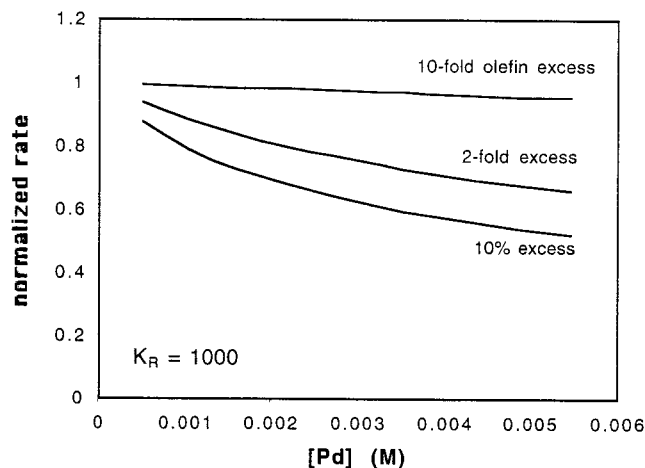


Figure 3. Theoretical curves for reaction rate as a function of Pd concentration for different amounts of excess olefin in the catalytic cycle shown in Scheme 2 for the case of dimerization equilibrium constant $K_R = 1000$.

the olefin addition/insertion product species $[2^*]$. Since the formation of dimer species depends on the fraction of $[1^*]$, a change in $[1^*]$ influences the balance between monomer and dimer species and hence also the observed reaction order in catalyst concentration. The consequence is that when kinetic experiments are carried out using concentrations far removed from those of the conventional catalytic reactions in a complex network such as this, reaction orders may differ from those observed under practical synthetic conditions.

It is interesting to note that for this type of reaction network lower absolute concentrations of catalyst result in higher catalytic efficiency. The molecularity of the dimerization reaction is two, and therefore a larger percentage of the total Pd will be present as the inactive dimer at higher catalyst concentrations. Conversely, the fraction of dimer species drops at low catalyst concentrations. Investigations of Heck chemistry in the literature over the years have reported on reactions carried out using a wide range of Pd concentrations, and often comparisons are made without reference to these differences. In systems where dimerization or formation of higher order Pd species is possible, the driving force for such processes will be a sensitive function of the Pd concentration. It is therefore wise to exhibit caution in extending conclusions reached under one set of conditions to those obtained with widely different catalyst concentrations.¹⁸

These brief model cases demonstrate that the reaction rate expression corresponding to the catalytic network in Scheme 2 describes an intricate interplay between reactions within and without the catalytic cycle. The complexity of the system and the range of variables which may influence observed reaction orders suggest that a simple assessment of the reaction behavior under a limited set of conditions may not be sufficient to offer meaningful mechanistic insight. Monitoring reaction progress from beginning to end offers the opportunity to obtain a continuous rate/concentration profile for assessing the full rate law. Therefore, in situ kinetic methods are particularly well-suited to the study of reaction mechanisms of this complexity, as is demonstrated in the next section.

(18) In this context a recent report speculating on the role of agglomerated Pd species in Heck reactions with phosphine-free catalysts may be mentioned: Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–68. This work employed Pd concentrations ca. 10 000 times greater than those reported in recent studies such as refs 4b, 6, and 9 and the current work.

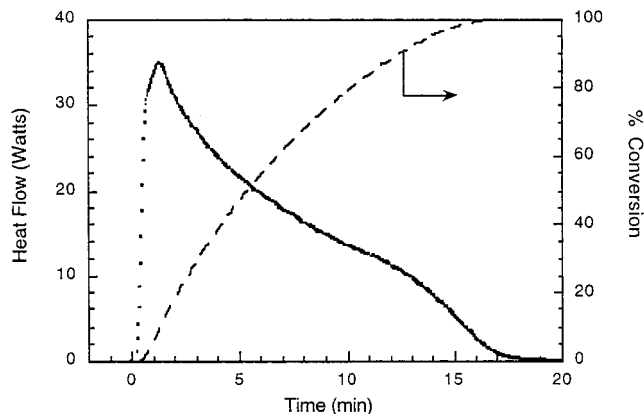


Figure 4. Reaction heat flow as a function of time for the Heck coupling of *p*-bromobenzaldehyde (**1**, 0.2 M) with butyl acrylate (**2**, 0.28 M) using palladacycle catalyst **4**, as described in Scheme 1 and in the Experimental Section. Dashed line shows conversion calculated from heat flow using eq 3.

Experimental Studies and Kinetic Modeling. The progress of the Heck coupling reaction shown in Scheme 1 was monitored using reaction calorimetry. A typical reaction heat flow curve is shown in Figure 4 for the reaction using the dimeric palladacycle **4** as a catalyst. This nitrogen-based palladacycle is extremely active for the reaction of this activated bromide, exhibiting turnover frequencies of ca. 50 000 h^{-1} even at substrate concentrations as low as 0.2 M. The plot also reveals several interesting features about the rate behavior. The reaction exhibits an induction period before a maximum in rate is reached at ca. 15% conversion of the aryl halide. After the rate maximum, the reaction follows positive order throughout the reaction, exhibiting a characteristic shoulder in the rate vs time curve at high conversion.

Figure 4 also plots the conversion of the aryl halide substrate as a function of time derived from the heat flow as given in eq 3. It is interesting to note that the induction period is much more difficult to discern from the data plotted in this way, as is the rate transition at the end of the reaction. Subtle changes in a reacting system as a function of time are more readily observed from measurements of *differential* properties of the system than from *integral* properties, highlighting an advantage of reaction calorimetry over spectroscopic and analytical in situ methods which monitor concentrations as a function of time.

Figures 5 and 6 show the results of the reaction in Scheme 1 carried out with different concentrations of palladacycle catalyst **4** (Figure 5) and different initial concentrations of aryl halide and olefin substrates (Figure 6). Figure 5 plots the rate as the turnover frequency (mol substrate/molcatalyst/h) at 50% conversion of substrate vs catalyst concentration. The data in Figure 6 are plotted as reaction rate vs olefin concentration over the course of the reaction in order to allow comparison to rate expressions such as those developed in the previous section, where substrate concentration is given as the independent variable. Therefore, the progress of the reaction runs from right to left in this figure.

Reactions were carried out using different concentrations of the palladacycle catalyst (Figure 5) and different initial concentrations for the aryl halide **1** and olefin **2** (Figure 6). These data were fit simultaneously to the general kinetic model rate expression given in eq 4 on the basis of the mechanism in Scheme 2. This fit is shown as the dashed line in Figure 5 and the solid lines in Figure 6, and the rate constants as estimated by the model fit are given in Table 1.

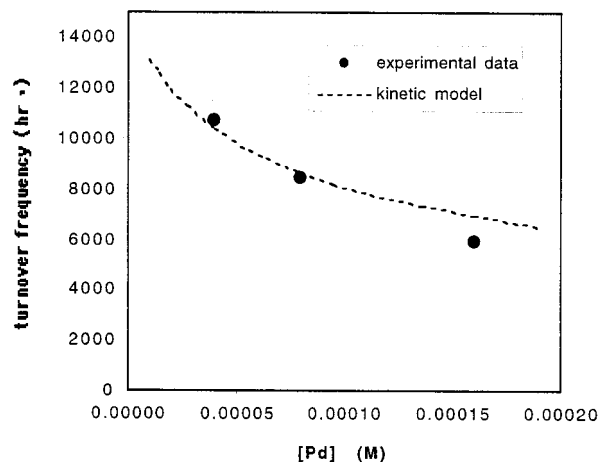


Figure 5. Reaction rate as a function of Pd concentration for the Heck coupling of *p*-bromobenzaldehyde (**1**, 0.2 M) with butyl acrylate (**2**, 0.28 M) using palladacycle catalyst **4**. Filled circles are experimental data points taken at 50% conversion. Dashed line represents the kinetic model with normalized rate calculated at 50% conversion using eq 8.

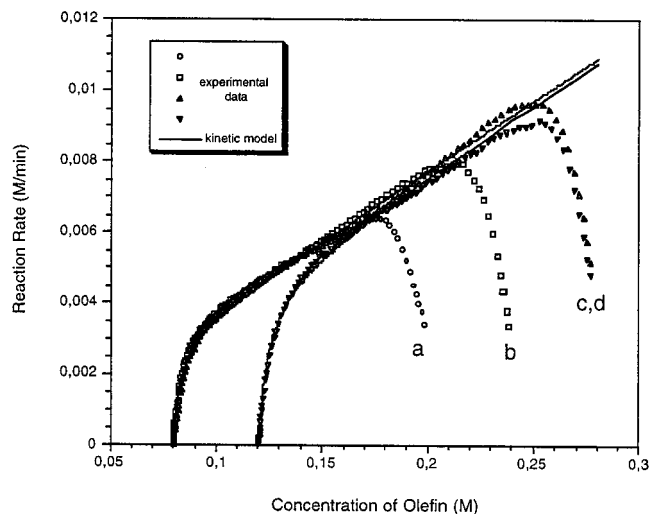


Figure 6. Reaction rate in M/min as a function of olefin concentration for the Heck coupling of *p*-bromobenzaldehyde (**1**) with butyl acrylate (**2**) using palladacycle catalyst **4**. The progress of the reaction runs from right to left in this figure. Symbols are experimental data points (only 1 out of 10 data points is shown for clarity). Solid lines represent the kinetic model given in eq 4. (a) (○): initial olefin concentration $[2]_0 = 0.20$ M; initial aryl halide concentration $[1]_0 = 0.12$ M. (b) (□): initial olefin concentration $[2]_0 = 0.24$ M; initial aryl halide concentration $[1]_0 = 0.16$ M. (c) (△): initial olefin concentration $[2]_0 = 0.28$ M; initial aryl halide concentration $[1]_0 = 0.20$ M. (d) (▽): initial olefin concentration $[2]_0 = 0.28$ M; initial aryl halide concentration $[1]_0 = 0.16$ M.

Figure 5 shows that the reactions did not follow first-order kinetics in [Pd]. The effect of Pd concentration on rate shown in Figure 5 is reminiscent of the theoretical cases shown in Figures 2a and 2b with a large dimerization equilibrium constant. The model predicts that more than 99% of the Pd is diverted toward dimer formation. The strong deviation from first-order behavior in catalyst concentration is in agreement with other studies which have shown similar deviations in reactions carried out at low catalyst concentrations.^{4b,6} Thus, the reported turnover numbers and turnover frequencies for these reactions would appear even more remarkable if based on the amount of Pd actually present in the catalytic cycle.¹⁹ This may provide insight concerning the special stability that has often been associated

Table 1. Kinetic Rate and Equilibrium Constants Determined from the Fit of eq 4 to the Experimental Data of Figures 5 and 6^a

k_1 (L/mol/h)	363
k_2 (L/mol/h)	34.2
k_{-2} (/h)	114
k_3 (/h)	374
K_R (L/mol)	9990

^a These values represent the best fit to eq 4 in which all constants in the table are simultaneously floated. Rate constants in reaction networks such as that presented in eq 4 may be highly coupled, however, especially in the case where an equilibrium constant such as K_R is part of the network. Therefore, the absolute value of at least one constant should, if possible, be verified in an independent experiment. The relative values of the constants remains accurate, as do the groupings in eq 5 which lead to the distributions of catalyst species shown in Figure 7.

with dimeric palladacycle catalysts. Pd lost via deactivation processes may be replaced by Pd metered into the cycle from the reservoir of dimer species to maintain the dimer–monomer equilibrium. This feature may become increasingly important in reactions of more demanding substrates where catalyst deactivation is a greater concern.

The concentrations of both substrates decrease continually over the course of the reaction. Reactions with different amounts of olefin excess ($[2]_0 - [1]_0$) will have different aryl halide concentrations at a given olefin concentration and will come to an end at different final concentrations of **2**. The fact that the data from different initial concentrations of **1** and **2** shown in Figure 6 fall on the same straight line for most of the reaction indicates that the reaction follows first-order kinetics in olefin concentration and zero-order kinetics in aryl halide concentration until high conversion rates occur. This dependence on the concentration of the olefin, as well as the strong deviation from first-order kinetics in [Pd], indicates that the initial oxidative addition of the aryl halide cannot be considered as rate-limiting. The large value for K_R indicates that for most of the reaction the data are described by the limiting case of eq 7. The sharp bend at low concentration of **1** indicates where the observed zero-order kinetics in aryl halide concentration collapses in the final stages of the reaction, as the rate expression then approaches the limiting case of low **1** (eq 9), where rate depends linearly on the concentrations of both substrates and the catalyst concentration and is inversely proportional to the amount of excess olefin (solid lines in Figure 6). The transition between the limiting cases of eqs 7 and 10 allow us to determine the rate constants for the full expression given in eq 4. The kinetic model predicts that the rate-limiting step is the initial binding of the olefin to form the π -complex **2**.

$$r_{\text{low}[1]} = \left(\frac{k_1}{[2]_0 - [1]_0} \right) [1][2][\text{Pd}] \quad (9)$$

Determination of the constants in the reaction network allows us to predict the concentrations of all catalyst species as a function of reaction progress, as described in eq 5. This is shown in Figure 7. The dominant species participating in the catalytic cycle is **1***, the oxidative addition product, which is present in ca. 50 times the concentration of **2***, the bound olefin complex. The theoretical plots in Figure 2 showed that strong deviation from first-order kinetics in catalyst concentration may occur in two separate cases: when **1*** is dominant and when **1*** and **2*** are more evenly distributed within the cycle. The

(19) This helps to rationalize how Heck reactions may be effected using what Beletskaya and Cheprakov have called “homeopathic doses” of Pd (see ref 3d).

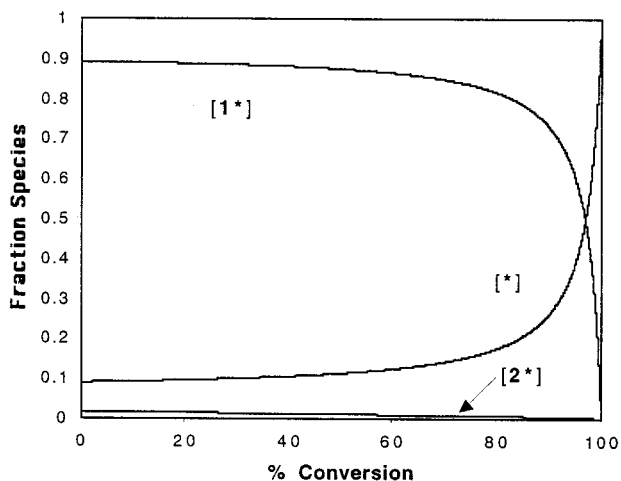


Figure 7. Distribution of catalyst species within the cycle as a function of reaction progress for the Heck coupling of *p*-bromobenzaldehyde (**1**, 0.2 M) with butyl acrylate (**2**, 0.28 M) using palladacycle catalyst **4** (40 μ M Pd).

limiting case of eq 7 used by van Leeuwen and co-workers cannot distinguish between these two possibilities. Kinetic modeling based on the full rate law establishes that it is the former possibility which holds in the system studied here.

It is interesting to note that data from the relatively modest concentration range used in our study suffice to provide a full description of the kinetic model. In particular, accurate and plentiful data from the *last* stages of the reaction, where very low substrate concentrations cause the zero-order approximation in [1] to collapse, provide the key to extracting distinguishing detail from the kinetic model. This is in contrast to most conventional kinetic studies, which make use of initial rate data.

Initial rate measurements may be problematic in cases where the catalyst exhibits transient behavior at the beginning of the reaction. In our experimental studies, we observed that the amount of water in the reaction mixture influenced the initial rate significantly. Reactions were normally carried out with a nominal amount of water in the system derived from the hygroscopic base KOAc. Under these conditions, the reaction rate rose until ca. 10–20% conversion, after which the system exhibited positive order kinetics in substrate. However, when the base was dried prior to addition to the reaction mixture,²⁰ the reaction proceeded very slowly and the induction period was significantly more pronounced, as shown in Figure 8. By contrast, the presence of a noncatalytic amount of water in the reaction mixture resulted in the disappearance of the induction period and a significant increase in initial rate, as is also shown in Figure 8. Addition of the reaction products acetic acid and/or NaBr to the dry system did not change the nature of the induction period. It was also observed that the inorganic base was not completely solubilized under very dry conditions. However, no dependence of the reaction rate on base concentration was observed under either wet or dry conditions. The amount of water present may influence the rate at which the active monomeric Pd catalyst is produced from the dimeric palladacycle precursor. Small differences in the amount of water present may result in irreproducible initial reaction rates, making quantitative kinetic information difficult to derive from such measurements. Further studies of the induction period in these reactions will be presented separately.²¹

(20) Dry conditions: KOAc or NaOAc was dried overnight in a vacuum oven at 110 °C before addition to the reaction mixture.

(21) Rosner, T.; Pfaltz, A.; Blackmond, D. G. Submitted for publication.

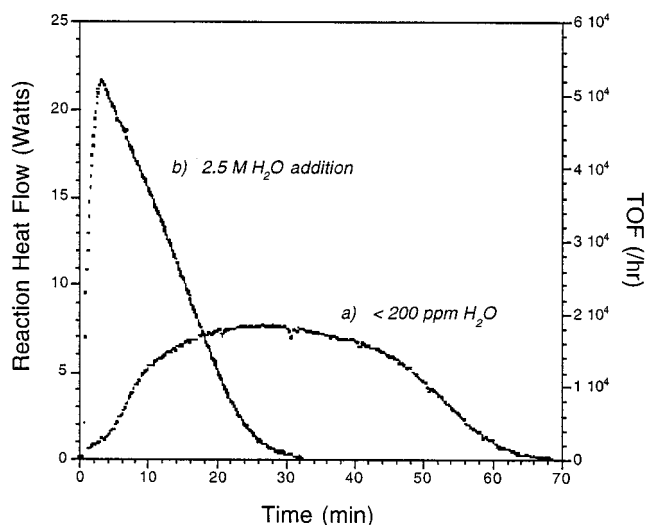


Figure 8. Effect of dry conditions and of added water on reaction rate in the Heck coupling of *p*-bromobenzaldehyde (**1**, 0.24 M) with butyl acrylate (**2**, 0.4 M) using palladacycle catalyst **4** (20 μ M Pd) (TOF = turnover frequency, mol 1/mol Pd/h): (a) < 200 ppm water; (b) ca. 2.5 M water added.

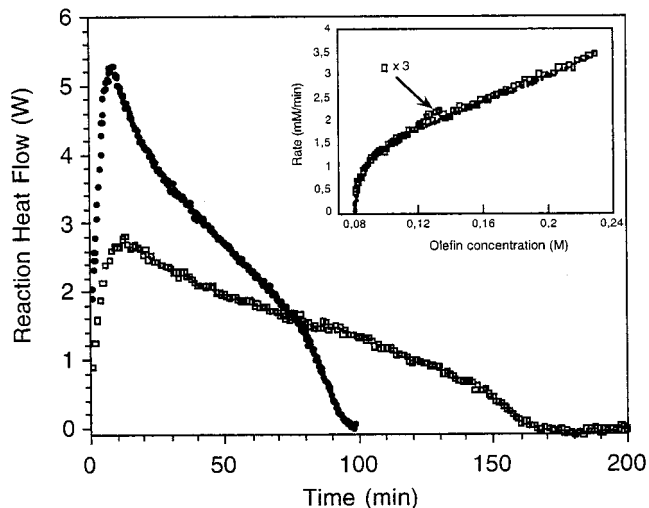


Figure 9. Reaction heat flow vs time for the Heck coupling of *p*-bromobenzaldehyde (**1**, 0.2 M) with butyl acrylate (**2**, 0.28 M) using 20 μ M Pd palladacycle catalysts: **4** (●) and **5** (□). Inset shows reaction rate (M/min) vs olefin concentration for the same two experiments, with the rate for catalyst **5** multiplied by a factor of 3.

Comparison to Other Palladacycle Catalysts. The behavior of palladacycle **4** in the reaction shown in Scheme 1 was also compared to that of phosphapalladacycle **5**, as shown in Figure 9. The form of the rate curves was identical, although reaction with the phosphapalladacycle was ca. 3 times slower than that for the nitrogen-based palladacycle. This strikingly similar fit for palladacycle catalysts with different types of ligands supports the generality of the kinetic model for this set of substrates, with an outstanding feature being the oxidative addition product [1*] as the resting state of the catalyst within the catalytic cycle.

Conclusions

Theoretical kinetic modeling combined with in situ experimental studies revealed a complex kinetic rate law in a catalytic reaction network where the active monomeric species exists in equilibrium with a dimer species. The observed rate behavior results from a subtle interplay between reactant and catalyst

concentrations and the rate and equilibrium constants for the elementary steps in the network. The dependence of rate on the catalyst concentration may be altered by the presence of dimeric species. Conventional kinetic experiments which employ artificially high substrate concentrations to determine reaction orders may skew the distribution of intermediate species in such a system and may give misleading information about reaction orders in catalyst. Accurate rate measurements over a range of substrate concentrations combined with global kinetic modeling allow the rate constants to be estimated in cases where transitions between dominant terms in the reaction rate law occur.

The fact that the catalytic efficiency increases at lower catalyst concentration has important practical implications. In the case of unreactive substrates, the addition of more catalyst may not have the desired strong effect on the rate as in other processes where dimer formation does not play a role, and catalytic efficiency may in fact remain surprisingly high even at extremely low catalyst/substrate ratios. The concentration dependence of

catalyst has to be taken into account when comparing different catalyst systems.

In the case of the Heck reaction of *p*-bromobenzaldehyde and butyl acrylate discussed in this paper, kinetic studies show that the resting state of the catalyst within the catalytic cycle is the intermediate derived from oxidative addition, while the majority of Pd exists outside the catalytic cycle as a dimer in equilibrium with this oxidative addition species. This finding is general for palladacycle complexes with phosphine- and nonphosphine-based ligands. The role of water in accelerating the initial preparation of the active catalyst species was highlighted. Thus, the combination of continuous kinetic measurements and global kinetic modeling offers an opportunity for expanded mechanistic insight into complex catalytic reaction networks.

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