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Comprehensive Kinetic Screening of Catalysts Using Reaction Calorimetry

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Abstract:

The protocol based on reaction calorimetry which is described in this paper offers a multidimensional kinetic and stability profile of a catalyst candidate in liquid and multiphase reactions. The scale-transparent picture of catalyst properties provided by this method should make it generally useful for rapid screening of candidates for catalytic process steps as well as for fundamental kinetic and mechanistic studies of organic reactions. In the example described here, new Pd complexes with nitrogen-based ligands were found to be more active than phosphapalladacycles in the Heck coupling of aryl halides with olefins.

Introduction

An ever-present problem in pharmaceutical process research and development is the search for reliable methods of choosing a catalyst in cases where the total effort allocated for catalyst discovery, process development, and scale-up of a reaction step must be combined in a rapid timeline. We report here a method for comprehensive catalyst screening for liquid- and multiphase conditions which uses reaction calorimetry to provide a rapid kinetic profile of the catalytic reaction as well as a comprehensive picture of catalyst "lifetime", including initial performance, stability, and deactivation characteristics. These features are important both for fundamental understanding of catalytic mechanisms and for scale-up and commercial use of a catalyst. It may be applied as a general screening protocol to a wide variety of catalysts and catalytic reactions carried out under realistic conditions. In special cases, the method may be used as a rapid "one-pot" screening of multiple catalyst candidates.

Experimental Section

Small aliquots of substrate **A** are injected into a solution in the reaction calorimeter which contains a very small amount of the catalyst and a large excess of substrate **B** in reactions of the type

$$\mathbf{A} + \mathbf{B} \xrightarrow{k} \text{products} \tag{1}$$

For reactions which exhibit a positive order concentration dependence on both substrates **A** and **B**, the use of a large excess of **B** allows establishment of pseudo-zero-order kinetics in **B** ($[\mathbf{B}] \approx [\mathbf{B}_o]$) and may provide an enhanced rate, since the pseudo-zero-order rate constant incorporates the concentration of the excess substrate

$$\mathbf{A} + \mathbf{B} \xrightarrow{k'} \text{products} \tag{2}$$

$$\begin{aligned} \text{rate} &= k'[\mathbf{A}] \\ k' &= k[\mathbf{B}_o]; \quad [\mathbf{B}_o] = \text{large} \end{aligned} \tag{3}$$

The Pd-catalyzed coupling of aryl halides with olefins (Heck reaction[1], Scheme 1) is a powerful method for laboratory-scale and industrial synthesis,[2] and recent research has focused on development of catalysts of improved activity and stability.[3] In this context, we are exploring new Pd complexes with nitrogen-based ligands as phosphine-free alternative catalysts. Our model reaction between typical aryl bromides **4** and olefin **5** is shown in Scheme 1. We compare the catalytic behavior of palladacycles **1**[4] and **2**,[3] dimeric Pd complexes with chelating nitrogen- or phosphorus-based ligands, and a monomeric Pd complex **3**[4] with imine ligands.

Monitoring of the reaction heat flow provides both a rapid activity assessment and a temporal kinetic profile of the catalyst candidate in the reaction of interest. For an isothermal reaction carried out in a batch reactor in the absence of significant side reactions, an enthalpy balance shows that the rate of the reaction is proportional to the heat evolved.

$$q(t) = \Delta H_{\mathrm{rxn}} \frac{\mathrm{d}n}{\mathrm{d}t} \qquad \begin{aligned} q(t) &= \text{instantaneous heat flow, } W \text{ (J/s)} \\ \Delta H_{\mathrm{rxn}} &= \text{heat of reaction, J/mol} \\ \frac{\mathrm{d}n}{\mathrm{d}t} &= \text{reaction rate (mol/s)} \end{aligned}$$

$$\%\ \text{Conversion} = 100 \frac{\int_0^t q(t)\mathrm{d}t}{\int_0^{t_f} q(t)\mathrm{d}t} \qquad \begin{aligned} t &= \text{reaction time} \\ t_f &= \text{time of reaction at 100\% conversion of substrate} \end{aligned} \tag{5}$$

The reaction commences with the injection of a small aliquot of an aryl bromide **4** (typically 5 mmol) to the well-stirred reaction calorimeter (Mettler RC1) containing 500 mL of dimethyl acetamide (DMA) as solvent, a small amount

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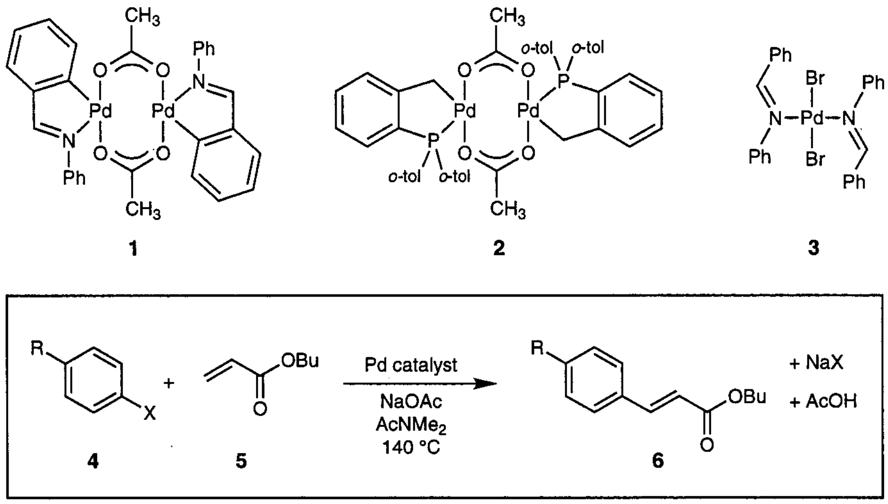
Scheme 1



of catalyst **1**, **2**, or **3** (typically 10−50 μmol), NaOAc as base (typically 200 mmol) and a large excess of **5** (typically 200 mmol). Conversions of the aryl bromide **4** to the corresponding *n*-butyl cinnamate coupling product **6** were found by GLC analysis to be >95%, indicating that the heat flow trace obtained reflects the rate of the reaction of interest.

Results and Discussion

Figure 1 illustrates the form of the heat flow trace for a pulse reaction as described above. The isothermal reaction commences instantaneously upon injection of the substrate. Repetition of this pulse reaction allows a comprehensive picture of catalyst behavior as shown in Figure 2. for catalyst **1**. The height of the consecutive pulses increased at first, indicating that the catalyst exhibited an induction period before reaching its maximum activity. The pulse signal then remained fairly constant for a number of consecutive pulse reactions before finally decreasing.

Consecutive pulses from the multiple-pulse experiment in Figure 2 have been superimposed in Figure 3 to highlight these features. Figure 3a shows the catalyst's induction period, with the reaction rate increasing from the first to the third pulse of reactant shown. After this induction period, several consecutive pulses are shown to give identical heat flow traces, confirming that the catalyst has reached a steady state (Figure 3b). The reaction rate data from this steady-state regime may be used to obtain intrinsic reaction kinetic information with confidence that competing rate processes such as catalyst deactivation are absent. Finally, the rate of catalyst deactivation and the processes by which each catalyst candidate deactivates may be studied by comparing later pulses as shown in Figure 3c.

The catalytic properties of three different catalyst candidates **1**, **2**, and **3** are compared in multiple-pulse reactions shown in Figure 4. Peak heights and peak breadths for a family of pulses combine to provide a rapid visual assessment of both activity and stability for the three catalysts. The results show that the two nitrogen-based catalysts **1** and **3** consistently outperformed the benchmark phosphapalladacycle catalyst[3] in terms of activity. Palladacycle **2** gave peak heights three to four times lower than palladacycle **1**, which exhibited the highest activity. A comparison of peak breadths showed that **2** achieved only one-half the number of pulses that **1** completed in a given time period. Catalyst **3** gave the highest initial activity although **1** was the most active later in the series of pulse reactions. Interestingly, the initial rate comparison from a single pulse reaction would have reversed the order of activity for catalysts **1** and **3** because an induction period was required for **1** to reach maximum activity, ultimately attaining a heat flow nearly 6 times that observed for its initial pulse. By the same token, the multipulse

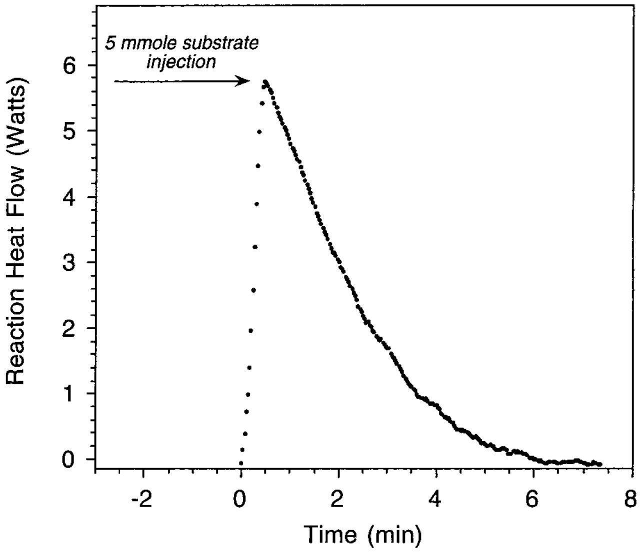


Figure 1. **Heat flow signal for the Heck coupling reaction carried out by injecting 5 mmol of aryl halide 4 (R = -CHO; X = Br) into a solution containing a 40-fold excess of olefin 5 (Y = COOBu) and NaOAc in DMA solvent (500 mL) containing 10 μmol of catalyst 3 (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for the relationship between heat flow and reaction rate.**

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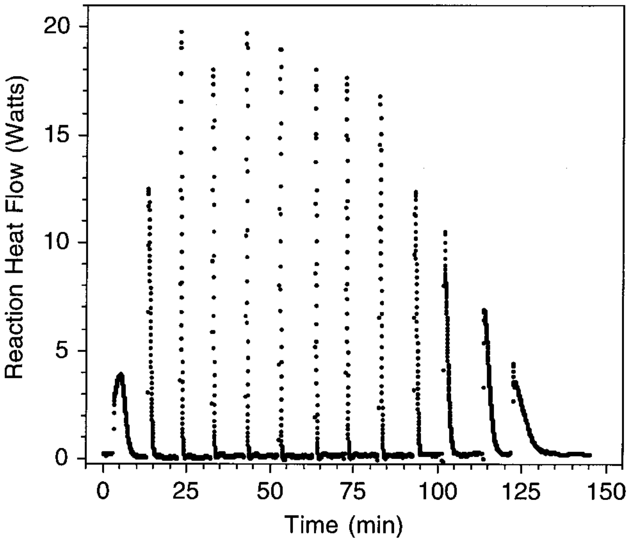

Figure 2. **Heat flow signal for the Heck coupling reaction carried out by injecting consecutive 5 mmol pulses of aryl halide 4 (R = -CHO; X = Br) into a solution containing a 20-fold excess of olefin 5 (Y = COOBu) and NaOAc in DMA solvent (500 mL) containing 50 μmol of catalyst 1 (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for the relationship between heat flow and reaction rate.**

experiment predicts that long-term stability may be better for catalyst **1** than for **3**, since the consecutive pulse heights decrease more rapidly for catalyst **3**.

Activity and stability of catalysts in Heck coupling reactions are commonly reported in terms of integral measures of catalyst activity. Turnover numbers (TON, moles substrate converted/moles catalyst) give a measure of catalyst productivity. Reaction rates are usually calculated in terms of an average turnover frequency (TOF), simply as the total TON divided by the total reaction time. In the Heck coupling reaction studied in this example, TONs in the millions have been reported for palladacycles.[5] The time required to make such measurements on a laboratory scale is on the order of several days per catalyst candidate, and the average rates obtained in such studies tend to minimize differences between catalysts. Indeed, a systematic study of the relative performance of the various catalysts which have been developed for these reactions has not been reported previously.

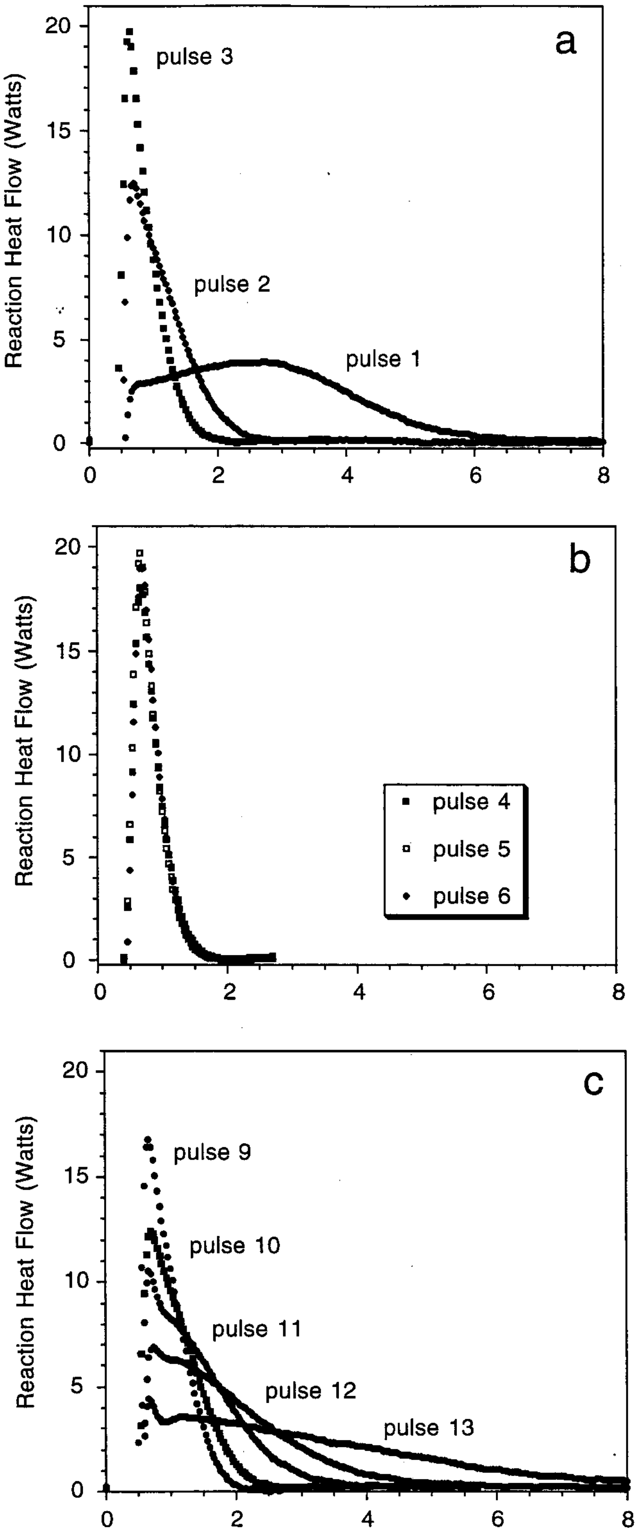

Figure 3. **Heat flow pulses from Figure 2 superimposed to illustrate (a) catalyst induction period, pulses 1, 2, and 3; (b) steady-state catalyst behavior, pulses 4, 5, and 6; and (c) catalyst deactivation, pulses 9−13.**

Kinetic monitoring of reactions carried out under typical reaction conditions (where the aryl halide/olefin concentration ratio is 1:1.4 instead of a 20- to 40-fold excess of olefin as in the rapid screening experiment) confirmed the conclusions of the screening experiments. Figure 5 shows heat flow traces for Heck coupling reactions carried out with a substrate: catalyst ratio of 10000:1. The induction period noted for catalyst **1** in the multi-pulse experiment of Figure 4 is clearly visible in Figure 5. Catalyst **2** was significantly less active than either **1** or **3**, requiring a much longer reaction time (>6 h compared to <2 h) to achieve full conversion. This experiment confirmed the conclusion of the screening experiments, which demonstrated that neither phosphine ligands nor a palladacycle structure is necessary for development of an efficient Heck coupling catalyst.

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(7) The extremely high activity of catalysts **1** and **3** in this reaction made it unfeasible to compare these catalysts under the zero-order protocol described here.

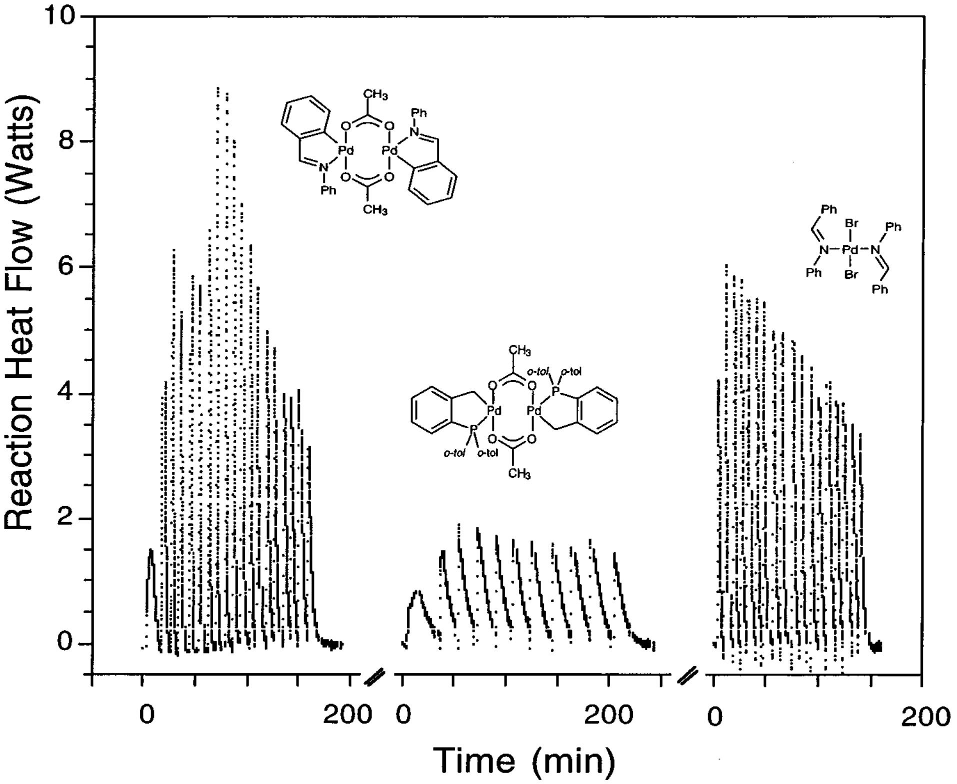

Figure 4. **Comparison of catalysts 1, 2, and 3 in separate multiple pulse reaction experiments. Heck coupling reactions carried out by injecting consecutive 5 mmol pulses of aryl halide 4 (R = -CHO; X = Br) into a solution containing a 40-fold excess of olefin 5 (Y = COOBu) and NaOAc in DMA solvent (500 mL) containing 10 μmol of catalyst (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for the relationship between heat flow and reaction rate.**

Screening for Substrate Tolerance. Figure 6 shows that this screening method may also be used to probe functional group tolerance in catalytic reactions. In this case, we make consecutive injections of small aliquots of different aryl halides **4** where the R-group (R_1) or the halogen (X) has been changed. Clear differences in reactivity may be observed between electron-rich and electron-poor aryl bromides. Re-injection of a "control" substrate may be used to provide information about how different substrates influence catalyst deactivation. A recent paper[6] described a "one-pot" screening method to compare different substrates in a catalytic reaction by designing analytical protocols for deconvoluting the products from the different reactions. That concept could be coupled with the approach described here to assess both reaction rate and product selectivity in a "one-pot" scheme for investigating substrate tolerance to investigate the generality of a particular catalyst candidate for effecting a particular class of reaction.

Extension to "One-Pot" Catalyst Screening. The ultimate goal for rapid catalyst screening would be the development of a method to screen multiple catalysts with consecutive injections into the same reaction mixture. For cases where alteration of catalytic properties through interaction between different catalyst species in solution can be ruled out, the calorimetric method described here may also be extended to a "one-pot" screening of multiple catalyst candidates. A slightly different protocol is used in this case. When the reaction is carried out in a large excess of *both* reactants, the reaction rate may be made to exhibit overall pseudo-zero-order kinetics, and the corresponding heat flow trace will appear as a constant horizontal signal as a function of reaction time

$$\mathbf{A} + \mathbf{B} \xrightarrow{k''} \text{products} \tag{6}$$

$$\text{rate} = k''$$

$$k'' = k[\mathbf{A}_o][\mathbf{B}_o] \qquad [\mathbf{A}_o],\quad [\mathbf{B}_o] = \text{large} \tag{7}$$

If consecutive small aliquots of different catalysts are injected into this reaction mixture, the heat flow curve will appear as a series of steps representing the linear addition of the rates of reaction of each catalyst species present in the mixture. The relative reactivity of each catalyst would be discerned from the relative size of the step for each injection. This concept is illustrated in principle in Figure 7, where consecutive injections of equal aliquots of the same catalyst, $Pd(OAc)_2$, resulted in a heat flow trace with constant step sizes, demonstrating the accuracy of the method.[7] When this protocol is carried out with different catalysts, candidates exhibiting either much higher or much lower activity may easily be selected by inspection of the size of each step in the resulting heat flow trace.

Limitations of the Method. It is important to note that the general exploitation of this calorimetric method for catalyst screening relies on a number of important conditions being met. The test reaction must exhibit a heat of reaction large enough and a reaction rate fast enough to afford a reasonable heat flow signal. The existence of side reactions must also be considered, since the global measurement of the heat flow will include any and all reactions taking place simultaneously in the system. When these conditions are met,

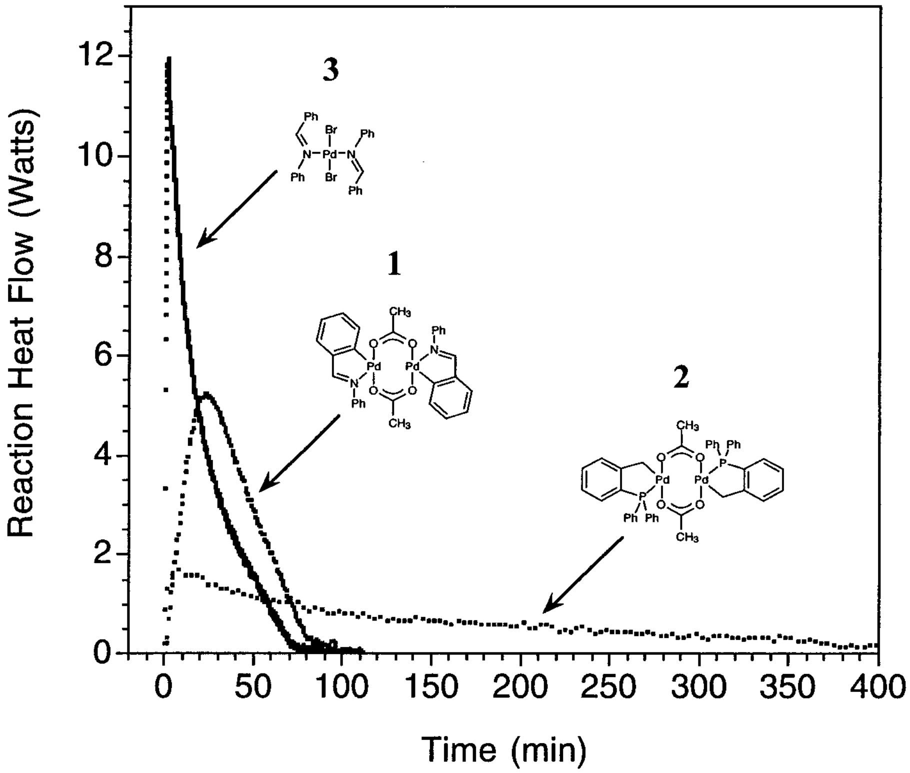

Figure 5. **Heat flow signal for the Heck coupling reaction carried out with all components added prior to start of the reaction. 100 mmol of aryl halide 4 (R = -CHO; X = Br), 140 mmol of olefin 5 (Y = COOBu) and NaOAc in DMA solvent (500 mL), 10 μmol of catalyst 3 (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for relationship between heat flow and reaction rate.**

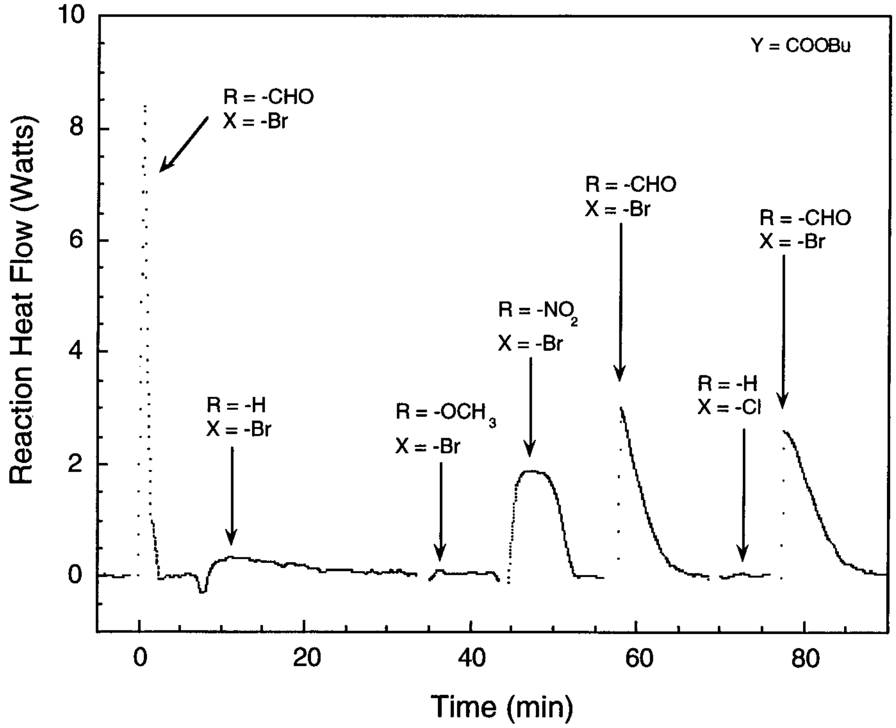

Figure 6. **Heat flow signal for the Heck coupling reaction carried out by injecting consecutive 5 mmol pulses of aryl halides 4 with R and X groups as shown into a solution containing a 20-fold excess of olefin 5 (Y = -COOBu) and NaOAc in DMA solvent (500 mL) containing 50 μmol of catalyst 1 (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for relationship between heat flow and reaction rate.**

this calorimetric method provides one of the most rapid and quantitative measurements of reaction rate available for liquid- and multiphase reactions.

Conclusions

A rapid screening protocol necessarily sacrifices detail in the information obtained in the interest of throughput, and

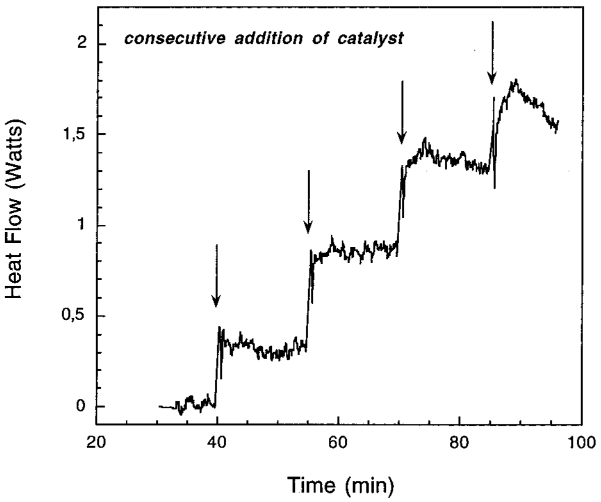

Figure 7. **Heat flow signal for the Heck coupling reaction carried out under pseudo-zero-order conditions with consecutive injections of 0.44 mmol $Pd(OAc)_2$ catalyst. 200 mmol of aryl halide 4 (R = -CHO; X = Br), 280 mmol of olefin 5 (Y = COOBu) and NaOAc in DMA solvent (500 mL) (See Scheme 1). Reaction temperature is 413 K. A heat flow datum point is collected every 2 s. See eqs 1 and 2 for relationship between heat flow and reaction rate.**

judicious decisions about this trade-off must be made. The protocol described here based on reaction calorimetry offers a multidimensional kinetic and stability profile in a matter of hours. These experiments helped to identify new Pd complexes with nitrogen-based ligands as catalysts which are efficient, relatively stable, and more active than the catalysts based on phosphine ligands which are traditionally employed in Heck coupling reactions. This catalyst-screening approach provides a rapid route to a comprehensive and scale-transparent picture of catalyst properties and should find widespread use for comprehensive catalyst screening as well as for detailed kinetic and mechanistic studies of catalytic organic reactions.

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