A Scale-Transparent Reaction Calorimetric Assay For Rapid Catalyst Selection

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Abstract: The use of reaction calorimetry in a "one-pot" catalyst screening protocol provides a rapid route to a scale-transparent picture of catalyst activity when the target reaction is known, the field of catalyst candidates is finite and focused, and the results must be translated efficiently to larger scale reactions. The method is demonstrated for both homogeneous and heterogeneous multi-phase catalytic reactions of interest in the pharmaceutical industry.

Keywords: kinetics; asymmetric catalysis; hydrogenation; catalyst screening; reaction calorimety

Introduction

An important goal for future research in both fundamental and applied catalysis is the development of rapid and reliable methods that allow screening of large numbers of potential catalysts for a particular reaction. This is especially problematic in pharmaceutical process research and development, where the total effort allocated for catalyst discovery, process development, and scale-up is compressed in a rapid timeline. The challenge in these cases can be quite different from that addressed in academic approaches derived from combinatorial chemistry. Combinatorial-based approaches to catalyst discovery have focused on study of the widest possible breadth in chemical structural diversity, motivating the development of methods for synthesis and assay of thousands of candidates.[1] By contrast, the choice of catalyst to effect a particular reaction in the multi-step synthesis of a target drug molecule is often constrained not only by time but also by parameters including compatibility with other steps in the synthesis, the nature of other functional groups present in the target molecule, and scale-up considerations. This translates to a more sharply focused field of candidates, numbering perhaps in the dozens rather than thousands.

A number of innovative approaches to high-throughput catalyst testing have recently been reported for the liquid phase reactions of complex organic molecules.[2] In most examples, however, there remain limitations to general use or, most importantly, questions about the translation of test results to larger scale reactions. Catalyst screening in micro-reactors is carried out under conditions that may deviate widely from those of optimized catalytic processes, and often model compounds are used in place of a more complex drug precursor. The practice of anchoring catalyst candidates to some form of solid support to expedite testing presents further questions about the validity of comparing these results to those of the homogeneous reaction. Thus, the assay used to select catalyst candidates may not reflect the relative performance of the *actual* catalysts in the *actual* reaction of practical interest. A successful approach requires that the ranking of a series of catalysts in a screening test mirror the results which would be obtained in the commercial scale reaction, but few of the reported studies have demonstrated this.

The importance of demonstrating the validity of extending results obtained under one set of reactor conditions has been dramatically illustrated for asymmetric catalytic hydrogenation reactions, where mixing conditions often influence reaction rate and selectivity in ways which are difficult to predict *a priori*. For example, in the Ru(binap)-catalyzed asymmetric hydrogenation of unsaturated alcohols,[3] it has been shown that a four-fold increase in stirring speed resulted in a *decrease* in enantioselectivity from 84% to 31% *S*-citronellol for γ-geraniol as substrate, while for its isomer geraniol as substrate, an *increase* in enantioselectivity from 57% to 85% *R*-citronellol

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was observed under the same conditions. While multi-phase reactions provide an especially vivid example of the importance of controlling reactor conditions, the role of competing heat and mass transfer rate processes may become important in small-scale reactions even in a single phase.[4]

This paper presents a "one-pot" catalyst screening protocol which addresses these issues. Key features of the method include the potential to test catalysts using the target molecule itself and not a model compound, as well as the use of conditions which insure scale-transparent results. In addition, the use of reaction calorimetry provides a rapid "selection by inspection" assay difficult to obtain by *in situ* monitoring techniques which do not measure rate directly. The method is demonstrated for both homogeneous and heterogeneous multi-phase catalytic reactions of interest in the pharmaceutical industry.

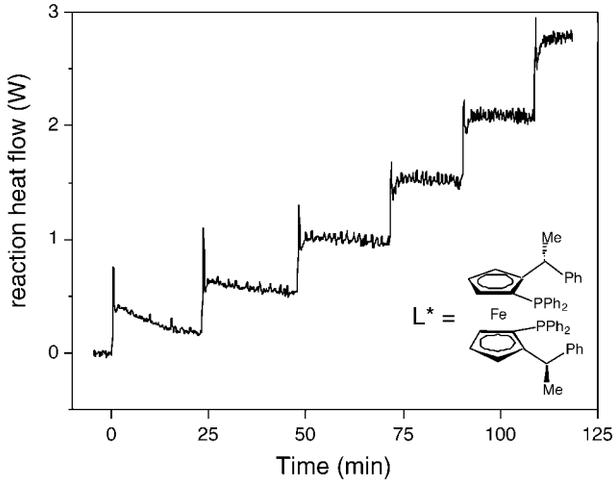


Figure 1. Reaction heat flow vs. time for consecutive injections of 10 μmole aliquots of Rh/ferriphos(methyl) catalysts into a reaction mixture of 0.65 M (*Z*)-α-acetamidocinnamic acid in methanol under 1 bar hydrogen pressure at 293 K.

Description of the Method

The catalyst screening reaction is carried out in an automated reaction calorimeter which also provides the primary assay *via* an instantaneous measure of reaction rate. Consider the reaction between two substrates, **A** and **B**, to form a product or products. When high substrate concentrations allow establishment of pseudo-zero-order kinetics, a plot of reaction rate vs. time will appear as a horizontal line with its magnitude related to the pseudo-zero-order rate constant, k′ (Equation 1). This rate constant k′ will be amplified over the intrinsic rate constant k since it incorporates the excess initial concentrations of the substrates, $[\mathbf{A_o}]$ and $[\mathbf{B_o}]$.

$$A + B \xrightarrow{k} products$$

$$rate = k' = k[A_o]^x[B_o]^y[cat] \quad (1)$$

Under these pseudo-zero-order conditions, the sequential injection of small aliquots of different catalysts into the reaction mixture will yield a rate curve which thus appears as a series of steps representing the linear addition of each catalyst's contribution to the overall reaction rate. The relative reactivity of each catalyst may then be discerned from the relative size of the steps representing each catalyst injection.

The key to obtaining a rapid assessment of catalyst properties from this sequential screening lies in the ability to obtain a rapid and direct measure of reaction rate. Reaction calorimetry is a tool increasingly being used in pharmaceutical research.[5,6] 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 flow (Equation 2). This rapid and accurate *in situ* measurement of the reaction heat flow thus provides an instantaneous and virtually continuous measure of reaction rate as a function of reaction progress. Because the heat and mass transfer properties of the calorimeter are well-characterized, results obtained in this system are kinetically transparent to the scale of the reaction. Thus, a result obtained for a catalyst candidate on a μmole-scale in this system is meaningful for the same reaction carried out in a different reactor at orders of magnitude larger scale.

$$q(t) = \Delta H_{rxn}\frac{dn}{dt} \quad (2)$$

n = *moles substrate*
t = *reaction time*
q = *reaction heat flow (J / s)*
ΔH_{rxn} = *heat of reaction (J / mole)*
dn/dt = *reaction rate (moles / s)*

This concept of multiple catalyst screening is illustrated with experimental data in Figure 1. This figure shows the heat flow trace for the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid under 1 bar hydrogen pressure, a reaction which is discussed in more detail in a later section. The reaction rate obtained from consecutive injections of 10 μmole aliquots of one catalyst Rh/L* [see Equation 5, L* = ferriphos(methyl)[7]] is manifested as a series of approximately equal size steps for each injection.

It may not always be possible to carry out reactions in the pseudo-zero-order kinetic regime as discussed above. For reactions which exhibit more complex power law or Langmuir-Hinshelwood kinetics, the heat flow trace for each catalyst injection may be fit to a kinetic model to determine rate constants and hence relative catalyst activities. Alternatively, the initial step height might be used, or an average rate for each injection may be used.[8] This average may be

calculated by comparing the conversion for a given injection time and subtracting the reaction history previous to that injection. Conversion may be calculated from the partial heat flow at any time (Equation 3). As an example, Equation 4 calculates the average rate for the second catalyst injection in a sequence. This equation assumes that equal amounts of catalyst are used in each injection; however, differing catalyst concentrations are easily taken into account in this analysis.

$$\textit{partial heat flow} = \textit{fractional conversion at time } t = \frac{\int_0^t q(t)dt}{\int_0^{t_f} q(t)dt} \quad (3)$$

$$rate_{ave}\ (pulse\ 2) = \left(\frac{\int_{t_2}^{t_3} q(t)dt}{t_3 - t_2}\right) - \left(\frac{\int_{t_1}^{t_2} q(t)dt}{t_2 - t_1}\right) \quad (4)$$

As with all rapid screening methods, important considerations must be addressed before deciding if it may be applied successfully in a particular case. For example, this method may be used to test either homogeneous or heterogeneous catalysts, as long as the different catalysts do not interact with each other in solution in a way which will change their individual performance. This is likely to rule out homogeneous catalytic reactions where an excess of ligand is used and ligand exchange is thought to occur.[9] Further, any deactivation processes should be slow compared to the time scale of the experiment. The time allowed between injections of catalyst aliquots must be long enough so that the steady-state behavior[10] of the candidate may be observed. In addition, the presence of side reactions which may contribute to the overall heat flow must be considered. For cases where these problems can be surmounted, each catalyst aliquot added in turn to the reaction mixture may be assumed to operate independently from the others and the signal obtained may be correlated with reaction rate.

Interestingly, it may be shown that this catalyst screening protocol can in fact also be used as a probe to study more complex types of catalytic behavior as described above. In these cases, the combination of *in situ* experimental tools and kinetic modeling of the extensive high-quality data available from these tools, deconvolution of the separate contributions for consecutive injections of different catalyst candidates may be possible.

While high reaction rate may be the starting point for selection of a catalyst for further development, consideration of product selectivity is also crucially important for catalyst selection. In this screening protocol, selectivity may be determined from analytical samples taken during each injection. Although samples may be collected for each candidate, only candidates selected from evaluation of the rate measurement need be subjected to a time-consuming analysis procedure.[11] This highlights an advantage of using a relatively large-scale, automated laboratory reactor: the larger volume and ease of operation allow sampling during the reaction so that product selectivity may be determined without disturbing the ongoing reaction. Thus, the number of catalysts which may be tested in a given time depends on how fast the reaction proceeds and how rapidly consecutive catalyst injections may be made.

Experimental Results and Discussion

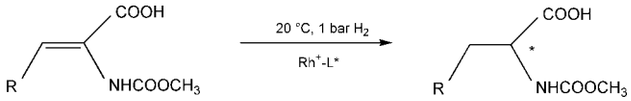
The catalyst screening protocol described above is demonstrated here using two reactions of interest in pharmaceutical research. The first is the asymmetric hydrogenation of enamides using homogeneous Rh^+ catalysts with a variety of chiral diphosphine ligands. Asymmetric catalysis is rapidly gaining commercial importance as a tool for producing highly enantiopure drugs, and significant advances in catalysis design and discovery continue to widen the field of catalyst choices. The second reaction is the heterogeneously catalyzed hydrogenation of nitrobenzene using commercial Pd catalysts supported on carbon. These are workhorse catalysts in the pharmaceutical industry due to their ease of recovery and recyclability and are used for a variety of transformations, including the removal of protecting groups in hydrogenation or hydrogenolysis steps.

Both hydrogenations were carried out at ambient temperature and 1 bar H_2 pressure in an automated reaction calorimeter with 500 mL reaction volume. Reactions were stirred at 2000 rpm, and mass transfer coefficients were measured under these conditions to insure that the reactions were not limited by the transfer of hydrogen from the gas to liquid phase. The highest reaction rate measured was thus more than ten times lower than the maximum rate of gas-liquid mass transfer. Reactions were continuously monitored by three separate methods: reaction calorimetry (Mettler-ASI RC1), FTIR spectroscopy (Mettler-ASI ReactIR), and the uptake of hydrogen (Büchi gas flow controller). Selected sample analysis was made using a Chiracel ODH LC column for the hydrogenation of enamides and a polysiloxane OV-1 GC column for nitrobenzene hydrogenation.

Asymmetric Hydrogenation using Rh-Diphosphine Complexes

The hydrogenation of α-(acylamino)acrylic acids and esters to the corresponding amino acid derivatives, used in the production of Monsanto's drug L-Dopa

for treatment of Parkinson's disease,[12] was the first significant asymmetric catalytic process and is one of the most extensively investigated (Equation 5).



(5)

Kagan's introduction of the chelating chiral diphosphine ligand DIOP[13] (Equation 6) in the early 1970's sparked a maelstrom of activity in ligand design which continues to this day. Although substrate tolerance varies with ligand type, product enantioselectivities in the high 90's are now commonly achieved with a large number of different ligands under optimized conditions. Extensive tables may be found in a number of reviews detailing the product enantioselectivity which may be expected in hydrogenation of a range of olefin substrates for literally dozens of different ligands of this type.[14] Interestingly, however, none of these references provides significant information about the relative *activity* of these catalysts. Yet the choice of catalyst for practical implementation of an asymmetric hydrogenation might well rest on the question of relative productivity, especially for systems which give similar selectivity profiles.

The hydrogenation of (*Z*)-α-acetamidocinnamic acid (0.94 M in methanol) was carried out under 1 bar hydrogen pressure at 293 K, catalyzed by 22 consecutive injections of RhL* (of 5–10 μmol), where L* represents a chiral diphosphine ligand. Table 1 lists the ligands used and the order of injections. A total of ten different ligands were used, and all ligands were injected at least twice. All ligands give the *R*-(+)-*N*-acetylphenylalanine product preferentially, except Deguphos which gives the opposite product.

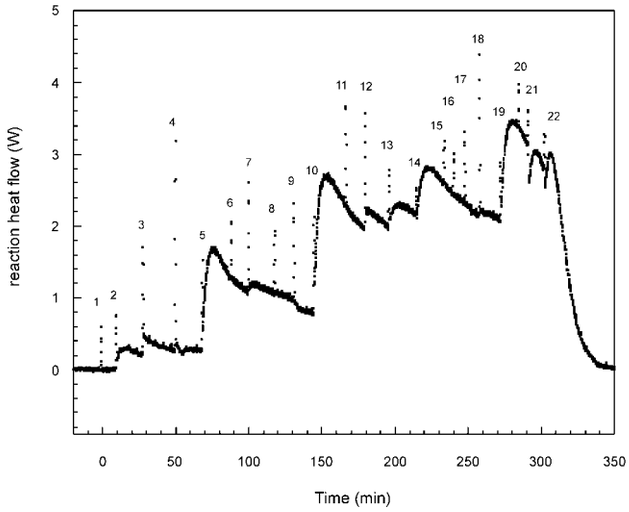


Figure 2. Reaction heat flow vs. time for consecutive Rh/L* catalyst injections as given in Table 1 into a reaction mixture of of 0.94 M (*Z*)-α-acetamidocinnamic acid in methanol under 1 bar hydrogen pressure at 293 K. A heat flow datum point was collected every two seconds. Injections are noted by the number corresponding to that given in Table 1. The point of each injection may also be noted by the transient positive perturbation in the heat flow signal.

Figure 2 shows the reaction heat flow trace as a function of time for the series of injections described in Table 1. Clear differences in activity may be seen for the different catalysts. The activities for the individual catalysts were evaluated according to Equation 4. The comparison of the average reaction rate for each injection is shown in Figure 3. The reaction exhibits more complex kinetics than simple pseudo-zero-order, but the data show that the screening method successfully differentiates between active and inactive catalysts. The ligands BPPM and DIOP, shown in Equation 6, proved to be the most active in

Table 1. Screening of diphosphine ligands for asymmetric hydrogenation[a]

Injection No.	Ligand	μmoles Rh	Injection No.	Ligand	μmoles Rh
1	Deguphos	9.86	12	Ferriphos (methyl)[b]	9.92
2	Duphos (benzene methyl)	10.10	13	Duphos (benzene methyl)	10.10
3	Ferriphos (methyl)[b]	9.92	14	BPPM	4.96
4	Ph-β-Glup[c]	9.92	15	Deguphos	9.86
5	BPPM	9.92	16	Duphos (benzene ethyl)	9.27
6	Duphos (benzene ethyl)	10.30	17	Norphos	9.92
7	Ferriphos (*N*-methyl)[b]	9.92	18	Ph-β-Glup[c]	9.92
8	Duphos (ethane methyl)	10.40	19	DIOP	4.96
9	Norphos	9.92	20	Duphos (benzene methyl)	10.4
10	DIOP	9.92	21	BPPM[d]	4.96
11	Ferriphos (methyl)[b]	9.92	22	DIOP[d]	4.96

[a] Structural and other information about ligands not specifically cited here may be found in Refs. [11,12].
[b] Ref. [7].
[c] A. Borner, *Chim Oggi*, **2000**, *18*, 48.
[d] Uncertainties in Equation 4 at very high conversion of substrate made activity of these two final samples difficult to assess.

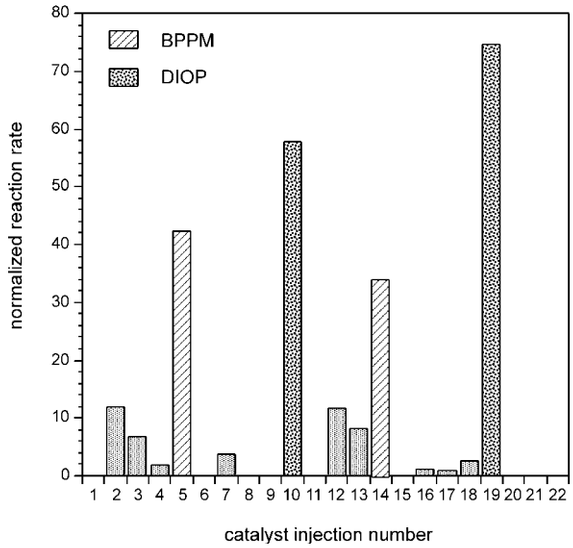


Figure 3. Average reaction rate for each catalyst injection shown in Figure 2 as calculated using Equation 4. Rates are normalized to the rate of the catalyst showing the lowest (non-zero) rate.

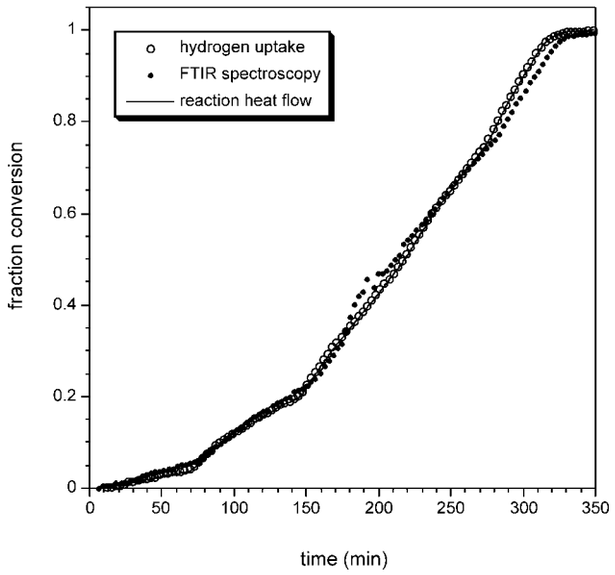
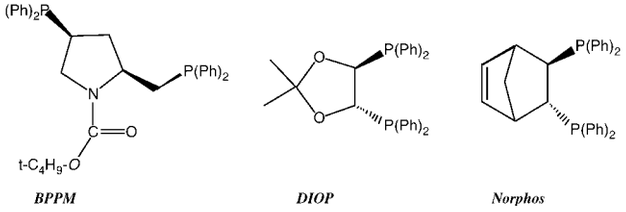


Figure 4. Fraction conversion vs. time for the reaction shown in Figure 2. Conversion is measured in three ways:
1) hydrogen uptake (open circles, every third data point only shown for clarity);
2) FTIR spectroscopy (absorbance at 1254 cm^{-1}, filled circles, every third data point only shown for clarity);
3) partial heat flow (from Equation 3, solid line).

this reaction under the conditions employed. For example, reactions with DIOP (injections **5** and **14**) and BPPM (**10** and **19**) were ca. 70 and 40 times faster than the reaction using Norphos (**9** and **17**). Reproducibility of repeat injections of ligands was ca. ±15–20% and consistently demonstrated gross differences between the ligands, as is the aim in a rapid screening prototocol.



(6)

Enantioselectivities for the reactions using DIOP and BPPM showed that while the reaction was fastest with DIOP, the product enantioselectivity (69% ee) was lower than that found with BPPM (80% ee) under these conditions. Interestingly, however, the greater rate achieved with DIOP more than offsets this selectivity difference. In a given reaction time, DIOP gives more than 50% higher yield of the *major* enantiomer, albeit at lower selectivity, than does BPPM. The ultimate choice of catalyst will depend on whether overall productivity or selectivity is more important. The relative importance of these parameters may vary from case to case, and this catalyst screening protocol provides a simultaneous window onto each.

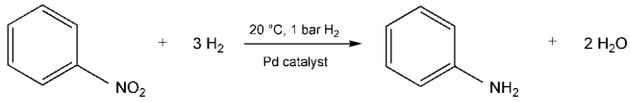
In order to assure that the reaction heat flow indeed corresponded to that of the reaction of interest, the reaction was also monitored *in situ* using FTIR spectroscopy to follow the disappearance of the substrate, and by measuring the hydrogen consumed by the reaction as a function of time. Figure 4 plots fraction conversion vs. time for data from these two methods compared with data from the calorimetric measurement (converted to conversion using Equation 3). The striking agreement between these three methods, which monitor different physical and chemical properties of the system, allow us to conclude that the heat flow trace provides a valid measure of the progress of the reaction of interest.

A further point of importance to this catalyst screening method concerns the difference between *direct* and *indirect* measurements of reaction rate. Changes in a reacting system as a function of time are more readily noted from measurements of *differential* properties of the system, such as rate (given by the reaction heat flow, Equation 2), than from measurements of *integral* properties, such as are obtained from integrating the heat flow curve (Equation 3) to give conversion, or by methods which monitor concentrations as a function of time, such as FTIR spectroscopy. Thus, the data points of the heat flow trace in Figure 2 are represented by the instantaneous slope of the line in Figure 4. Although rate differences for the most active catalysts may be discerned from

breaks in the data shown in Figure 4, "selection by inspection" is more readily made from the heat flow assay of Figure 2.

Hydrogenation of Nitrobenzene

The hydrogenation of nitrobenzene catalyzed by Pd supported on carbon is used as a standard test reaction to evaluate catalysts (Equation 7). Catalyst suppliers often characterize different Pd/carbon catalysts by their "aniline number", which is a measure of product formation in a given time period under prescribed conditions in this reaction.



(7)

Pd/carbon catalysts are available in a range of preparations in which the metal is present as a salt or as a passivated reduced metal, evenly dispersed throughout the porous carbon or as an "eggshell" layer on external carbon surfaces, with acid- or base-treated carbon, and with the carbon possessing special albeit ill-defined properties related to the wood whence it originated. All of these features may affect the activity and selectivity of the Pd/carbon catalysts for nitrobenzene hydrogenation as well as for reactions using other substrates. Thus performance in a particular reaction is difficult to predict from the simple designation of a catalyst as "Pd/carbon".

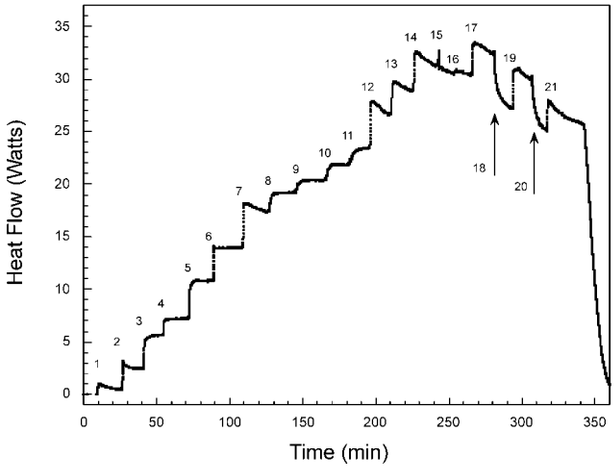


Figure 5. Reaction heat flow vs. time for 21 consecutive injections of 5–10 μmoles of different Pd catalysts into a reaction mixture of 5 M $PhNO_2$ in methanol under 1 bar hydrogen pressure at 293 K. 16 different catalysts were screened, with five catalysts injected twice during the screening.

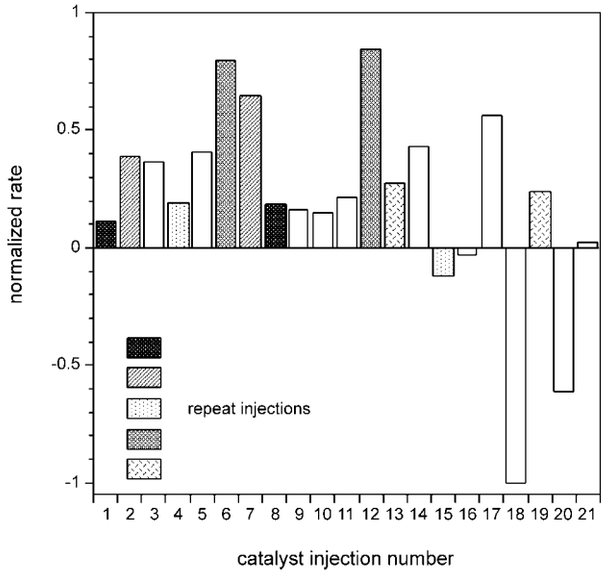


Figure 6. Average reaction rate for each catalyst injection shown in Figure 5 as calculated using Equation 4. Rates are normalized to the rate of the catalyst showing the lowest (positive) rate. All candidates were commercial 5 wt% Pd/carbon catalysts except injections 18 and 20, which were 1 wt% colloidal Pd catalysts stabilized with polyvinylpyrrolidone with 3.3 nm and 1.8 nm particle sizes, respectively.

Figure 5 shows the heat flow curve resulting from 21 consecutive additions of catalyst aliquots, each containing ca. 5–10 μmoles of Pd, to a 5 M solution of $Ph(NO_2)$ in methanol under 1 bar H_2 pressure. Since the reaction approximates zero-order kinetics for most catalysts, each addition appears as a instantaneous increase in the reaction rate visible as steps in the heat flow curve. Clear differences between the catalysts are illustrated by the differences in step heights. GC analysis of conversion of substrate agreed quite well with that calculated from the heat flow.

Figure 6 compares the relative activities of the catalysts in this sequence using average rates for each injection from Equation 4. Repeat injections of a particular candidate gave fair to excellent reproducibility. Thus the original field of 16 different Pd catalysts has been narrowed to three to be subjected to further study, if we take a normalized rate greater than 0.5 as a threshold for acceptable performance.

Interestingly, catalyst injection numbers **18** and **20** gave *negative* rates, as may be seen in Figure 5 (injections marked by arrows) and Figure 6. These two injections represent the only catalyst candidates which are not heterogeneous Pd/carbon samples. These samples are Pd colloids with well-defined nano-scale metal particle sizes (respectively, 3.3 and 1.8 nm) stabilized by the homopolymer polyvinylpyrrolidone. Colloidal catalysts of this type have been shown to be

highly active in the Heck coupling of aryl halides.[15] However, it is clear that their inclusion in this screening reaction had a negative effect on the activity of other catalysts in the series. The stabilizing polymer may adsorb and block active Pd sites on the Pd/carbon samples, resulting in a strong suppression of reaction rate. Thus this catalyst screening method not only helps to differentiate catalyst candidates of high activity, but it may also be used to obtain information about potentially deleterious interactions between catalyst samples.

Scope of the Catalyst Screening Method

While numerous discussions of combinatorial methods have noted parallels between drug discovery and the discovery of new catalysts for pharmaceutical applications, it is perhaps important to note, in the context of this screening protocol described here, that there are also intrinsic differences between the two. Investment in combinatorial chemistry techniques reflects the potential financial rewards for discovery of new pharmaceutical target molecules, which may be in the billions of dollars. On the other hand, identification of an efficient new catalyst will result in a less lucrative payoff, since a catalyst's contribution is typically made in reducing manufacturing costs of one step in the multi-step synthesis of the identified drug molecule. Further, optimization of the catalytic process may make as great or greater contribution to the overall efficiency of a drug synthesis as does the initial catalyst discovery.

Any rapid screening protocol necessarily sacrifices something in the interest of high throughput, and judicious decisions about this trade-off must be made. This catalyst screening approach provides a rapid route to a scale-transparent and gross picture of catalyst activity when the target reaction is known, the field of catalyst candidates is finite and focused, and the main objective is the timely implementation of a target catalytic reaction in a commercial process. It should therefore be reiterated that the method described in this paper differs in important ways from the development and testing of very large scale catalyst libraries, which has been the focus of most work in the area of high-throughput screening to date. Those approaches have significant merit for academic discovery of new catalytic reactions or new classes of catalysts, both in aiding our mechanistic understanding and in potential future application. However, they may play less of a role in day-to-day, real-time pharmaceutical process research and development.

These considerations may help forge a balance between the degree of effort expended in developing methods to find large numbers of catalyst candidates and the effort put towards rapid, quantitative, and scale-transparent assessment of a restricted field of catalyst candidates.

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References and Notes

[1] For recent reviews, see: (a) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem. Int. Ed.* **1999**, *38*, 2495; (b) R. H. Crabtree, *Chem. Commun.* **1999**, 1611; (c) P. P. Pescarmona, J. C. van der Waal, I. E. Maxwell, T. Maschmeyer, *Catal. Lett.* **1999**, *63*, 1; (d) T. Bein, *Angew. Chem. Int. Ed.* **1999**, *38*, 323.

[2] See Ref. [1d] for general methods; for thermal detection methods for liquid-phase reactions in particular see: (a) M. T. Reetz, M. H. Becker, K. M. Kuhling, A. Holzwarth, *Angew. Chem. Int. Ed.* **1998**, *37*, 2647; (b) M. T. Reetz, M. H. Becker, M. Liebl, A. Furstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 1236; (c) S. J. Taylor, J. P. Morken, *Science*, **1998**, *280*, 267.

[3] (a) Y. Sun, J. Wang, C. LeBlond, J. Laquidara, J. R. Sowa, Jr., D. G. Blackmond, *J. Am. Chem. Soc.* **1995**, *117*, 12647; (b) Y. Sun, J. Wang, C. LeBlond, J. Laquidara, J. R. Sowa, Jr., D. G. Blackmond, *J. Organomet. Chem.* **1997**, *548*, 65.

[4] Recent research has compared the efficiency of liquid-liquid mixing in microreactors and conventional scale reactors: W. Ehrfeld, K. Golbig, V. Hessel, H. Löwe, T. Richter, *Ind. & Eng. Chem. Res.* **1999**, *38*, 1075.

[5] W. Regenass, *ACS Symp. Ser.* **1978**, *65*, 37–42 .

[6] Y. Sun, C. LeBlond, J. Wang, A. Forman, R. Larsen, C. Orella, D. G. Blackmond, *Thermochim. Acta* **1996**, *289*, 189.

[7] (a) European Patent, EP 0967015; (b) J. J. A. Perea, M. Lotz, P. Knochel, *Tetrahedron Asymmetry* **1999**, *10*, 375.

[8] The approximation of using an initial rate or an average rate will be a good one when the substrate is present in large excess.

[9] The processes of dynamic binding-dissociation of ligands or ligand exchange in homogeneous catalytic systems do not in themselves preclude use of the method if the ligands are not used in excess, the same metal is employed in all catalyst samples, and the ratio of catalytic metal to ligand is the same for each catalyst tested in a series.

[10] The term "steady-state" is taken in the context of a batch or semi-batch reaction to mean a steady-state concentration of catalytic species within the reaction network (subsequent to any induction periods due to transformation of a catalyst precursor species).

[11] Enantioselectivities determined from samples taken before ($ee_{i-1,meas}$) and after ($ee_{i,meas}$) a given injection may be used to calculate the enantioselectivity achieved by a given catalyst during a given reaction time. Because the enantioselectivity of the mixture changes as a function of time, this is an approximate calculation which may be expected to hold over short conversion intervals.

$$ee_{injection\ i} = \frac{\left(ee_{i,meas} - \frac{\sum rate_{i-1}}{\sum rate_{i-1} + \sum rate_i} \cdot ee_{i-1,meas} \right)}{\frac{\sum rate_i}{\sum rate_{i-1} + \sum rate_i}}$$

[12] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106.
[13] H. B. Kagan, in *Asymmetric Synthesis*, Vol. 5: Chiral Catalysis (Ed.: J. D. Morrison), Academic Press, New York, Ch. 1.
[14] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience, New York, Ch. 2.
[15] J. Le Bars, U. Specht, J. S. Bradley, D. G. Blackmond, *Langmuir* **1999**, *17*, 7621.