

# Resolving Heterogeneity Problems and Impurity Artifacts in Operationally Homogeneous Transition Metal Catalysts

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## 1. INTRODUCTION

Although already established as distinct areas of practice by chemists by the late 19th century, a formal distinction between homogeneous and other types of catalysis was only made by Ostwald in 1901. The key passage of his paper, published in its English version in *Nature* in 1902, runs as follows:<sup>1</sup>

Catalytic actions may be divided into four classes: (1) Release in supersaturated systems. (2) Catalysis in homogeneous mixtures. (3) Heterogeneous catalysis. (4) Enzyme actions.

What Ostwald meant by “release” in his first category was crystallization. Ostwald's proposal is understandable because crystallization is indeed often initiated by a substoichiometric quantity of seed crystals or even by dust particles. We exclude this category today because crystallization is a physical not a chemical change, a distinction that was not understood in its modern form by Ostwald.<sup>2</sup>

### 1.1. Blurred Distinctions

The sharp distinction between homogeneous and enzyme catalysis—Ostwald's classes 2 and 4—that seemed so obvious in 1901 has now been blurred by advances in bioorganic and bioinorganic chemistry. Amino acid and oligopeptide organocatalysts<sup>3,4</sup> clearly constitute a bridge between homogeneous and enzyme catalysis. A number of small-molecule metal complexes also do a remarkably good job of reproducing the salient features of certain metalloenzyme active sites.<sup>5–7</sup> Nor can we think of enzymes as being restricted to natural products, because the study of artificial mutants is a central aspect of modern enzymology.<sup>8</sup>

The distinction between homogeneous and heterogeneous catalysis—Ostwald's classes 2 and 3—then considered sharp, has also been blurred by work on clusters, metal nanoparticles (NPs), and nanomaterials. All of these intermediate forms between small molecules and extended solids have shown catalytic activity in a variety of cases, some of which are discussed below. Influential reviews of the field are available from Lewis,<sup>9</sup> Aiken and Finke,<sup>10a</sup> and Astruc.<sup>11,12</sup> Of particular interest in the present context, Finke<sup>10</sup> has recommended a powerful strategy that emphasizes a suite of kinetic and spectroscopic measurements that has proved robust for resolving the title problem in a number of different and very challenging cases. This involves determining both the speciation of the precatalyst and the contribution of each species to the overall catalytic kinetics. Jones and co-workers<sup>13</sup> have reviewed their work on this problem for the important case of Pd-catalyzed C–C coupling. Striking classic work from Schmid,<sup>14</sup>

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Finke,<sup>10a</sup> and Moiseev, Zamaraev, and co-workers<sup>15</sup> involved the deliberate synthesis of giant clusters with more or less well-defined stoichiometry and having as many as ~560 metal atoms.

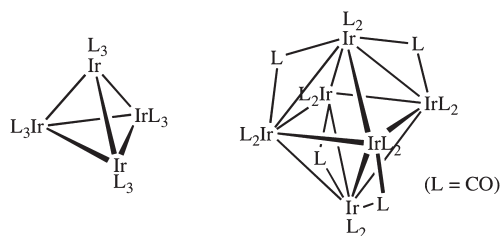
The term “nanoparticle” refers to metal-containing particles in the nanometer size range, most often 1 to at least 10 and in some cases up to 100 nm. These normally remain suspended in solution and are usually stabilized by appropriate surface adsorbates. The density of the material is of course a big factor in deciding the speed of precipitation of the largest particles from the nanoparticle suspension, sometimes termed a “colloid” or “sol”; however, these two terms are more often seen in the older than in the recent literature. In any one preparation, the particles have a range of sizes, narrow or broad, depending on the synthetic method, and they do not precipitate other than by forming larger particles. The term “nanocluster” is coming into common use<sup>13,16–18</sup> in this context to denote particles at or below the 1 nm end of the size range that may or may not have a precisely defined molecular structure but are lightly stabilized so as to give rise to catalytic activity; a striking example is a Rh<sub>4</sub> cluster identified by Finke and co-workers<sup>10c</sup> as the active species in catalysts formed from a [Cp\*RhCl<sub>2</sub>]<sub>2</sub> precursor. Being so small, these are harder to securely identify as active catalysts than larger NPs.

Polynuclear complexes with three or more metal atoms have traditionally been considered as metal clusters. These are typically isolable materials that are saturated with ligands such as CO and show good catalytic activity only in a very restricted number of cases.<sup>19</sup> A number of authors distinguish highly catalytically active, lightly stabilized metal clusters as a distinct category. For example, Gates<sup>20</sup> considers particles in the size range below 1 nm are of particular interest for their distinct reactivity patterns when supported on surfaces such as oxides. Lewis,<sup>9</sup> Finke,<sup>10,11</sup> and Astruc<sup>12</sup> have all shown how small metal clusters can form and be the active catalysts in operationally homogeneous solution-phase catalysts. Gas-phase studies have also been informative. For example, Bohme and Schwarz<sup>21</sup> have looked at an extensive series of highly reactive small metal cluster ions by mass spectrometry and consider them “the ultimate single-site catalysts”.

Because the classical homogeneous/heterogeneous distinction is based on the phases involved, it stands or falls on the definition of a phase. When does a growing metal cluster M<sub>n</sub> in solution become a new phase? The properties of the extended phase M<sub>∞</sub> grow in only slowly with increasing *n*, and different properties each grow in in different ways with increasing *n*, so no sharp onset of a distinct new heterogeneous phase can ever be identified for the growing particle in solution.<sup>11,12</sup> Lewis,<sup>9</sup> for example, cites data showing how the ionization thresholds of bare metal clusters M<sub>n</sub> only slowly approach the bulk value as *n* rises. For Fe, Ni, Cu, and Nb, the ionization threshold is still hundreds of millivolts above the bulk value when *n* is as high as 25. This means that no clear distinction can be drawn between homogeneous and heterogeneous catalysts in this intermediate size range, not just in practice but also in principle. We can still consider a catalyst as being operationally homogeneous or heterogeneous, perhaps depending on whether the catalytic activity resides in the filtrate or else is retained by the filter in a Maitlis hot filtration test,<sup>22</sup> a procedure to be described in more detail below.

In many cases, nanoparticulate catalysts have been deliberately prepared for use in operationally homogeneous catalysis. To prevent aggregation of the particles with consequent loss of surface area, a variety of stabilizers have been recommended. Starkey-Ott and

Scheme 1. Structures of [Ir<sub>4</sub>(CO)<sub>12</sub>] and [Ir<sub>6</sub>(CO)<sub>16</sub>]



Finke<sup>23</sup> have discussed nanocluster stabilizers, providing a list of the ones that gave the best combination of stabilization and catalytic activity for Ir(0)<sub>n</sub> nanoparticles. Dendrimers have also found application as NP stabilizers.<sup>24</sup> The stabilizer must bind sufficiently strongly to fulfill its function, but not so strongly as to block catalytic active sites. It may well be easier for catalytically active NPs to form, as opposed to formation of a metallic precipitate, when stabilizers, either adventitious or intentionally added, are present.

In some cases, operationally heterogeneous catalysts have been obtained from well-defined metal clusters supported on classical heterogeneous catalyst support materials by removal of the cluster ligands. For example, Gates<sup>20</sup> reported that removal of CO from [Ir<sub>4</sub>(CO)<sub>12</sub>] and [Ir<sub>6</sub>(CO)<sub>16</sub>] (Scheme 1) gave the corresponding bare Ir<sub>4</sub> and Ir<sub>6</sub> clusters supported on γ-Al<sub>2</sub>O<sub>3</sub> for which catalytic activity for toluene hydrogenation was monitored. Core–shell nanoparticles have also attracted recent interest as catalysts. For example, core–shell Au/Pd NPs with Pd rich surfaces were extremely active for crotyl alcohol oxidation at room temperature with good selectivity for the formation of crotonaldehyde.<sup>20b</sup>

Another bridge between homogeneous and heterogeneous catalysis comes from work on surface-bound molecular species as catalysts. These are clearly chemically molecular, and so are mechanistically homogeneous, but operationally heterogeneous.<sup>25–27</sup> Numerous supports, solid, liquid, and polymeric, have also been used for easy recycling of the associated “homogeneous” catalysts.<sup>28</sup>

## 1.2. Ambiguity of Catalyst Mechanism

It is one thing to deliberately make nanoparticles to study their catalytic activity, but it is quite another to be misled by unsuspected nanoparticle formation in an operationally homogeneous catalyst. Early concern about the possible heterogeneity of what were assumed to be homogeneous catalysts was expressed by the groups of James,<sup>29</sup> Maitlis,<sup>22</sup> Whitesides,<sup>30</sup> Collman,<sup>31</sup> and in our own work,<sup>32,33</sup> but the most extensive study, lasting over decades, has come from Finke.<sup>10</sup> Nanoparticle preparations can appear completely clear by eye and have a color that mimics a metal complex; for example, nanoparticulate Ir in water at relevant concentrations can have a very light straw color. In a supposedly homogeneous catalyst, the active catalyst may therefore be nanoparticulate metal, perhaps formed from the decomposition of only a small fraction of the total metal content of the solution, leaving the precatalyst largely unchanged. The nanoparticles formed can show exceptionally high catalytic activity, so even a small degree of speciation into NPs can have a big effect on the catalytic reaction.<sup>10</sup> Likewise, in a supposedly heterogeneous catalyst, a fraction of the metal may dissolve under the reaction conditions and the true catalyst may thus be homogeneous. The

metal can even redeposit on the catalyst support when the reaction is over, leaving no clue as to the true nature of the catalyst. In only a few such cases has the true catalyst been unmasked by detailed study—in the great majority of literature reports, the nature of the active catalyst is merely assumed from the nature of the precatalyst employed. It is not yet clear whether the fraction of misleading cases is small or whether it is much larger than currently believed, with many wrongly interpreted cases having escaped detection.

Finally, conditions and time scale both matter a great deal. A catalyst may operate under one mechanism under one set of conditions but quite another under different—perhaps even only slightly different—conditions. The presence or absence of certain ligands can strongly influence the tendency of monometallic complexes to form NPs and for NPs to fragment into monometallic units.<sup>10b,34</sup> Most homogeneous catalysts decompose at some point, and if catalytically active NPs are produced in the decomposition, the catalyst may switch mechanism from homogeneous to heterogeneous during the decomposition phase, hence providing the potential for time-dependent behavior.

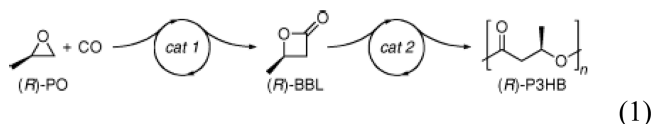
### 1.3. Ambiguity of Catalyst Terminology

The terms homogeneous and heterogeneous have been used to mean quite different things by different authors. One usage follows Ostwald's original vision, based on phases. In other papers, homogeneous and heterogeneous are considered as mechanistic categories, depending on whether the catalyst has a single molecular active site or is instead a collection of adjacent sites on a surface. Schwartz<sup>35</sup> seems to have been the first to draw attention to the unsatisfactory usage of the homogeneous/heterogeneous nomenclature in catalysis, suggesting instead that these two terms should be distinguished mechanistically depending on the nature of the catalytic site, not on the phases involved; this approach was also recommended by Lin and Finke.<sup>36</sup> In spite of these recommendations, authors in general continue to use the terms in both senses, often without any indication of which sense is meant. Some authors have even gone so far as to use the term "quasi-homogeneous". This can only lead to confusion, not just of expression but also of thinking.

Because the distinction between homogeneous and heterogeneous catalysts is most often based on the phases involved, it is not only intrinsically flawed for the reasons already mentioned but also fails to address the mechanistic distinction that lies at the heart of the problem. For greater clarity, this review adopts a slightly different terminology to denote the mechanistic distinction. Retaining the linguistic link to the established terms, substitution of the suffix *-topic* (Greek *topos*, site) for *-geneous* (*genos*, type) seems the most conservative change that allows unambiguous discussion of the mechanistic distinction. This homotopic/heterotopic terminology makes it no easier to tell if a single site or a variety of sites is in fact present in any given case, of course, but it does allow the distinction to be expressed succinctly and considered in a more orderly way. A heterotopic catalyst would be one such as Pd/C with a "cocktail of sites" available for catalysis. The term homotopic only includes catalysts that have a single type of site, whether they are homogeneous or heterogeneous on the phase-based definition. Examples would include molecular catalysts grafted onto polymer beads<sup>28</sup> or an organometallic center supported on a metal oxide as described by Copéret and Basset.<sup>37</sup> On the other hand, a nanoparticulate

metal, while it could be operationally homogeneous, would nevertheless be heterotopic.

Even so, difficulties can arise with the advent of multicomponent tandem catalysis, a rapidly advancing topic in which much useful work is currently emerging: for example, Dunn and Coates<sup>38a</sup> have shown how two different single-site, molecular catalysts can cooperate in a one-pot procedure to bring about a series of useful transformations (eq 1), so we have to expand the definition of homotopy to include reactions involving catalysts with multiple sites, each of which would be considered homotopic if they acted alone. A homotopic catalyst would be one that has a single type of site, or a small number of multiple sites, each being molecularly well-defined. Bare or lightly stabilized metal clusters with a well-defined, regular structure and a small number of metal atoms, such as a tetrahedral M<sub>4</sub> unit, would therefore also be homotopic in this sense.



In other homotopic cases, two sites are needed to promote a single reaction, as in the hydrolytic kinetic resolution of terminal epoxides with Co-salen catalysts by Jacobsen and co-workers.<sup>38b</sup> Here, the precatalyst forms two different catalytic species in solution, a nucleophile-activating species and an electrophile-activating species. These two species work in concert in a reaction that is second order in cobalt.

### 1.4. Should We Care?

Before going further, we need to establish if it really matters whether the active species of an operationally homogeneous catalyst is in fact a homotopic molecular catalyst or a heterotopic nanoparticle suspension and, if so, in what context. The answer depends on the circumstances. If we merely want to make a sample of a needed compound via a "homogeneous" metal-catalyzed route, then the true nature of the catalyst could at first sight be thought to be a matter of indifference. Nevertheless, problems could arise even here if the true catalyst, say a nanoparticle, is not reproducibly formed from a given precursor each time the reaction is run. Nanoparticle synthesis can be very sensitive to conditions and the presence or absence of traces of surface-active stabilizers.<sup>39</sup> As materials, NPs are not normally single pure compounds. They are often surface-capped with extraneous species such as surfactants or adsorbed ions; indeed some such capping is required to stabilize the resulting sol. Syntheses are subject to modification by trace amounts of surface-active materials, and the NP surface might easily be poisoned by different amounts of trace materials present in different runs or batches of reagents. Nanoparticles also differ in size and shape, a factor that leads to a change in the area of faces and the number of edge and corner sites. Of the two possibilities, a truly homotopic catalyst is therefore more likely to have reproducible characteristics and be more reproducibly scaleable for large-scale work.

Unintended heterotopy with loss of all the ligands initially present in the precatalyst also nullifies the effect of sophisticated ligand design such as in the multifunctional ligands<sup>40</sup> needed for molecular-recognition catalysis.<sup>41</sup> The same problem arises for heterogenized homogeneous catalysts,<sup>42–44</sup> where one of the precatalyst ligands is covalently grafted onto a support such as polystyrene. If that ligand decomposes or dissociates, leaching of



the metal can occur. Complexes with ligand-based redox activity<sup>45,46</sup> likewise rely on the ligands remaining bound. Conversely, retention of the ligand-based characteristics under catalytic conditions is preliminary evidence for homotopy. Exceptions can still arise if the ligand affects the structure and properties of the nanoparticle either by affecting the mode of nanoparticle formation or growth or by binding to it in the final structure.

Where the homotopic/heterotopic distinction makes the biggest difference is in catalyst development. If we assume that active catalyst is molecular because the catalyst precursor is molecular, then both mechanistic understanding and catalyst optimization will be hindered if the active catalyst is in fact nanoparticulate. Optimization of homogeneous catalysts is best done by varying the ligand set and conditions with mechanistic notions as a guide. If our mechanism is wrong, our guide will be false and we may be misled into moving in unhelpful directions such as designing ever more elaborate ligands for testing. Furthermore, selectivity, activity, lifetime, poison-sensitivity, and catalyst recovery and regeneration are also likely to behave completely differently for the two classes of catalyst. Computational mechanistic work is also playing a larger role in guiding catalyst research.<sup>47</sup> With the wrong model for the active catalyst, computation is at least severely hampered, if not doomed to failure.

### 1.5. Lack of Exchange between Catalyst Subfields

Everyone now agrees that the same fundamental physical and chemical principles govern all three classes of chemical catalysis—Ostwald's classes 2, 3, and 4—so it might at first seem strange that these three classes have continued to develop as largely independent fields. One honorable exception here is the long running series of conferences entitled "International Symposium on Relations between Homogeneous and Heterogeneous Catalysis" (ISHHC) that brings together workers in homogeneous, heterogeneous, and enzyme catalysis. This separation no doubt arises because each requires entirely different experimental methods, creating three separate groups of practitioners who rarely exchange ideas. As a result, workers in homogeneous catalysis may not always be fully alert to the possibility of artifacts, notably that heterotopic catalysts might be the true actors in particular systems under study. The converse is in principle possible—heterogeneous catalysts could owe their activity to molecular compounds formed in solution under the catalytic conditions or to quasi-molecular specific sites on the surface.

## 2. TESTS FOR MOLECULAR VERSUS PARTICULATE CATALYSIS IN AN OPERATIONALLY HOMOGENEOUS CATALYST

First we look at the situation in which homotopic catalysis was intended but heterotopy is suspected. Because the formation of a metallic deposit is easy to detect and therefore raise suspicion, the usual, more subtle question to be resolved is whether or not activation of a molecular catalyst precursor gives catalytically active metallic nanoparticles that remain in suspension. Within this group, most studies by far refer to reduction catalysis, and the established tests have therefore been devised with this application in mind. Only recently has the same problem come to the fore in the case of oxidation catalysis, where the corresponding risk is formation of metal oxide nanoparticles that act as oxidation catalysts. We defer discussion of this aspect to a later section, in

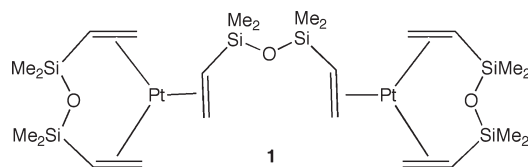
part because it is not yet possible to cover the oxidation problem beyond a few brief remarks, because it is at such an early stage of development.

The central problems in determining the topicity of a catalytic reaction are easily stated but difficult to resolve. As most strongly emphasized by Finke,<sup>10</sup> this requires determining the speciation of the precatalyst under reaction conditions (in operando) and identifying the contributions of the different species present to the overall process. This in turn requires that kinetic studies take a leading role, as is indeed appropriate for this problem, because catalysis is a predominantly kinetic phenomenon.

### 2.1. Suspicious Circumstances

Before heroic methods are applied, we need some indication that all might not be well and that our homotopic molecular precatalyst has formed a heterotopic catalyst as the true active species (Table 1). The strongest such indication is deposition of a metallic precipitate or mirror on the tube walls, isolation of which allows testing for catalytic activity. If the deposit is itself a catalyst, then its contribution to the overall activity can be estimated. Even if the deposit is not a catalyst, or only weakly so, it is still possible that the precursor metal complex is continuously decomposing during the reaction and that a catalytically active cluster or nanoparticulate form of the metal is a precursor to the inactive metallic deposit; indeed to go from a mononuclear complex to a metal deposit implies the intermediacy of small clusters at some point. Once the NPs have aggregated and precipitated, the catalytic rate may drop off sharply or go to zero. The mere presence of an inactive precipitate, such as a metal, need not necessarily be an indication of heterotopy—it may simply constitute a catalyst deactivation product. Failure to precipitate is not definitive, either, because some nanoparticulate suspensions can be very robust and resist agglomeration. Instead they may be stable under the conditions and mimic a homotopic catalyst. Finke's Ir<sub>~300</sub> nanoparticulate preparations even retain activity after evaporation of the solvent and subsequent redissolution,<sup>10</sup> unlike classical preparations that tend to agglomerate and lose activity.<sup>48</sup> Maitlis and co-workers<sup>22</sup> considered the formation of dark-colored reaction mixtures as a suspicious indication.

Another classic sign of potential trouble is an unexplained induction period before catalysis begins, sometimes followed by sigmoidal reaction kinetics. A lag phase does not always mean a heterotopic catalyst is formed, however, because a metal complex could easily require slow conversion to a still-homotopic active form under the reaction conditions. Catalyst precursors often undergo a change before they participate in the catalytic cycle, and so a lag phase may just involve this conversion. Such a case was identified by Stein, Lewis, and co-workers<sup>49</sup> for Karstedt's hydrosilylation catalyst (1).



Nanoparticle syntheses can be very sensitive to small quantities of adventitious material and so irreproducibility may legitimately raise suspicion, but certain nanoparticulate catalysts can give very reproducible catalytic results.<sup>36</sup> However, Narayanan et al.<sup>50</sup> have shown that nanoparticle shape and size can strongly affect

**Table 1. Suspicious Circumstances Suggesting a Need for Further Study of an Operationally Homogeneous Metal Catalyst System**

circumstance	comment
unexplained lag time before onset of catalysis	conversion of molecular precursor to an active catalyst, possibly nanoparticulate
catalyst properties, such as selectivity, closely resemble the properties of the appropriate analogous conventional heterogeneous catalyst	nanoparticle (NP) catalysis possible
ligand (L) effects are minimal; all active catalysts have similar rates and properties	all catalysts may convert to NPs having similar catalytic properties whatever the nature of L, but ligands can modify NP synthesis and so ligand-dependent activity cannot eliminate the possibility that NPs are the active species <sup>60</sup>
transmission electron microscopy shows electron-dense particles	the particles may not be active and may even have formed only during sample preparation <sup>49,55</sup>
catalytic activity is halted by a selective poison for the heterotopic catalyst	Hg(0) is most common but precautions are needed <sup>49,68</sup>
kinetic irreproducibility	nanoparticle synthesis can be very dependent on conditions
reaction mixture turns dark in color <sup>22</sup>	possible indication of NPs
metal-containing deposit or mirror formed <sup>130</sup>	possible indication of intermediacy of NPs, and the deposit itself may be catalytically active
harsh conditions <sup>a</sup>	ligands may degrade and release metal

<sup>a</sup>For example, >150 °C or strong oxidants, acids, or bases.

activity. In the case of Pt nanoparticles catalyzing the reaction between hexacyanoferrate(III) ions and thiosulfate, the higher the fraction of atoms at edges and corners of the NP, the greater the activity found. Tetrahedral particles that maximized corners and edges gave the highest activity. The nature of the stabilizing groups at the surface of the NP also had a big effect.

Some workers have been tempted to think that, if the catalyst can be reisolated in some molecular form in good yield at the end of the reaction, the mechanism must be homotopic. Unfortunately, it only needs a small amount of the molecular catalyst precursor to transform into a highly active NP for the catalytic reaction to be dominated by the heterotopic component.<sup>22</sup> For example, Lin and Finke<sup>36</sup> find that, after 6 h, 85% of their cyclohexene substrate has been hydrogenated by Ir NPs but only 45% of the expected cyclooctane is seen, with cyclooctane being an indicator for catalyst activation because it is derived from hydrogenation of the (cod)Ir-containing catalyst precursor. Likewise, palladacycle catalysts can sometimes be partially recovered after a Heck coupling when other indications suggest heterotopy.<sup>13</sup>

Finally, harsh conditions are a factor to consider. For example, if a supposedly homotopic reaction only goes above 150 °C or only goes with harsh reagents such as powerful oxidants or reductants, then special vigilance is indicated.

## 2.2. Controls

No single criterion can be considered definitive, however, so a battery of tests has been devised by different authors over the years. The first line of defense is running a full series of controls, such as omission of the catalyst, having the appropriate metal salt without the ligand and the ligand without the metal. Also relevant is the role of air versus an inert atmosphere and even, on occasion, sunlight versus dark conditions.

A particularly simple control is to run the reaction with the authentic heterogeneous catalyst best adapted to mimic the case under study. For example, in the case of a Pd coupling reaction with a molecular catalyst precursor, a good control would be Pd/C.

A further clue is evident if the selectivity of the Pd/C reaction is very similar to the operationally homogeneous case. Even if Pd/C gives catalysis, this is not definitive evidence of heterotopy, because of the possible dissolution of Pd under the reaction conditions to form an active homotopic catalyst. Indeed, Pd/C is thought to operate via a homotopic route in this chemistry, so the interpretation of these controls is not always straightforward.

If a nanoparticulate catalyst is suspected, an obvious control is to make the NP in question by a literature route and test its catalytic activity and selectivity. Unfortunately, although molecular compounds made in different laboratories can normally be relied upon to behave in the same way, NP preparations do not always have the same properties from one procedure to another. Even with a standard procedure, differences may arise from one preparation to another because in some cases even slight variations in the procedure can produce differences in the size and shape of the particles, differences that can lead to different catalytic behavior. For example, heterotopic catalysts can be poisoned by small amounts of materials that might be present as impurities in the reactants for the catalytic reaction under study. In other cases, good reproducibility is possible, however.

## 2.3. Selectivity

In the case of hydrogenation reactions, certain substrates are more rarely reduced by authentic homotopic catalysts but are readily reduced by many heterotopic metals, including NP versions. Such is the case<sup>51</sup> for reduction of C<sub>6</sub>H<sub>6</sub> to C<sub>6</sub>H<sub>12</sub> and of PhNO<sub>2</sub> to PhNH<sub>2</sub>. Seeing either of these products from a "homotopic" catalyst automatically raises suspicions of heterotopy. For example, benzene is fully reduced both by nanoparticulate Ir(0)<sup>52</sup> and by Rh(0)<sup>53</sup> but not yet by any authentically mononuclear Ir or Rh hydrogenation catalyst. Presumably a single metal is less effective for these harder substrates. In exceptional cases, homotopic catalysts have been found that reduce C<sub>6</sub>H<sub>6</sub> to C<sub>6</sub>H<sub>12</sub>, but in some authentically homotopic cases, unlike the heterotopic examples, the product of deuteration is predominantly the all-cis isomer of C<sub>6</sub>H<sub>6</sub>D<sub>6</sub>,<sup>54</sup> compared

with the formation of multiple isotopomers,  $C_6H_xD_{12-x}$ , having no special stereochemical arrangement, more often found for heterotopic catalysts.<sup>53</sup> Deuteration might therefore qualify as a candidate test to help distinguish the two situations, but exceptions exist. Dyson has reviewed the extant catalysts and has suggested homo- or heterotopic activity for them from the available evidence.<sup>51</sup>

The Maitlis arene hydrogenation precatalyst,  $[Cp^*RhCl_2]_2$ , has proved to be one of the most difficult and challenging cases for resolution of the title problem.<sup>10c,55</sup> In initial work, Maitlis, Finke, and co-workers<sup>55a</sup> found good evidence for both types of catalysis, homotopic and heterotopic, depending on exactly how the precursor is activated; harsh conditions and thus nanoparticles were required for benzene reduction, but a homotopic catalyst formed via activation under slightly milder conditions was viable only for cyclohexene reduction.

Finke and co-workers<sup>10c</sup> have now modified their conclusions for the Maitlis catalyst and find in operando X-ray absorption fine structure (XAFS), kinetic, and kinetic poisoning evidence for the predominant species and active catalyst being subnanometer  $Rh_4$  clusters. They found no  $Rh(0)$  NPs, except after exposure to air. A useful poison in these studies proved to be 1,10-phenanthroline (phen). Addition of phen up to a 0.5 phen/Rh ratio gave no poisoning effect, whereas 1–5 phen/Rh ratios led to progressive poisoning. A quantitative treatment suggested that four Rh sites were susceptible to poisoning, consistent with the proposal that  $Rh_4$  clusters are involved. In contrast, authentic  $Rh(0)$  NPs behaved differently and were poisoned with phen/Rh ratios much less than 1. Interestingly, the clusters, like  $Rh(0)$  NPs, are poisoned by  $Hg(0)$ , so this test cannot distinguish between  $Rh_4$  clusters and  $Rh_n$  NPs.

In a similar vein, the Finke strategy<sup>10</sup> has led to a reassignment<sup>55b</sup> from homotopic to heterotopic of the active species from the  $[Ru_3(\mu^2-H)_3(\eta^6-C_6H_6)(\eta^6-C_6Me_6)_2(\mu^3-O)]^+$  benzene hydrogenation precatalyst, via a combination of kinetic studies, Hg poisoning experiments, NMR data, as well as related experiments. A number of authentic homotopic catalysts reduce related but less challenging substrates than benzene itself—these include multinuclear arenes and heterocyclic aromatics—so these cases should raise no undue suspicion of heterotopy.<sup>31,56</sup>

It might be thought that successful asymmetric catalysis with a homochiral ligand would be a good indication of homotopy, because the ligand must presumably be interacting with the metal in such a case, but this is not a reliable indicator. For example, Abley and McQuillin<sup>57</sup> found up to ca. 60% asymmetric induction in the reduction of methyl 3-phenylbut-2-enoate by  $RhCl_3py_3/NaBH_4$  with (+)-*N*-(1-phenylethyl)formamide as homochiral ligand, and homotopicity was thus assumed. Indeed, given the very early date, 1971, no suspicions had yet been raised against any ostensibly homogeneous catalyst, so this assignment was reasonable at the time. We revised this assignment<sup>33</sup> and proposed nanoparticulate catalysis on a number of grounds. The active “solution” was very dark, dynamic light scattering indicated the presence of particles,  $Hg(0)$  poisoning was complete, reduction of  $PhNO_2$  to  $PhNH_2$  was fast, but the particles were small enough to defy attempts at filtration because activity always appeared in the filtrate (under Maitlis<sup>22</sup> conditions) and the activity proved even higher after filtration than before, for reasons not yet clarified. This is a clear limitation of the filtration test. Izumi<sup>58</sup> had already shown that modest enantiomeric excess (ee) values were accessible in hydrogenation by modifying Raney Ni with a wide variety of homochiral modifiers. The Izumi catalyst

was also stable to recycling, including maintaining its asymmetric activity, so the ligands remained firmly bound. In work remarkable for its early date (1956), Izumi and co-workers even used Raney Ni on silk in the first asymmetric hydrogenation ever reported, with the silk being conceived as a model for the polypeptide matrix of enzymes.<sup>58</sup>

More recently, a vibrant field has developed involving surface modification of heterogeneous catalysts for asymmetric reactions.<sup>59</sup> To take just one modern example, Bönemann and Braun<sup>60</sup> found that a platinum sol stabilized by the protonated alkaloid, dihydrocinchonidine, can bring about the enantioselective hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate with ee values up to 78%. This clearly indicates that ligands can bind firmly to nanoparticles so as to give marked ligand-specific effects in catalysis.

It is already clear that no one test can be used alone and in difficult cases, a final decision may come down to a question of probabilities rather than of certainties. The process may therefore resemble a legal trial, where a majority verdict of the scientific community can raise suspicion but quasi-unanimous agreement is required to convict. Heraclitus' classic dictum, “Nature loves to hide”, particularly applies to this problem.

#### 2.4. Kinetics

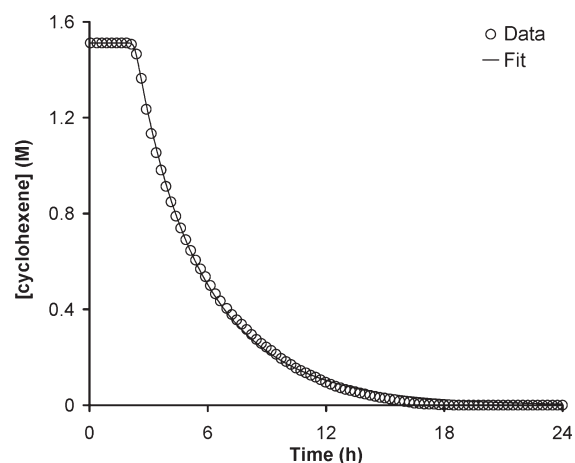
The classic paper by Watzky and Finke<sup>61</sup> perhaps did the most to clarify this aspect of the problem. This work involved the catalyst precursor  $[Bu_4N]_5Na_3[(cod)Ir(POM)]$  where POM is a polyoxometallate anion, originally introduced in the form of the  $[Bu_4N]_9[P_2W_{15}Nb_3O_{62}]$  salt. Hydrogenation led to loss of cyclooctane and formation of a neutral  $\sim 20$  Å diameter  $Ir_n$  nanoparticles ( $n \approx 300$ ), stabilized by associated POM,  $Na^+$ , and  $Bu_4N^+$ . The NP formation kinetics were followed from the hydrogen uptake during cyclohexene hydrogenation. A classic sigmoidal curve was seen, with no  $H_2$  absorption for the first  $\sim 2$  h, followed by onset of rapid catalysis that terminated with the exhaustion of the reactant alkene. Similar kinetics are seen for oxide-supported Pt NP formation from chloroplatinic acid, also reported by the Finke group.<sup>62</sup>

The Watzky–Finke model<sup>61</sup> describes the growth process<sup>63</sup> for metal NPs, which tends to produce near-monodisperse particles. Indeed, the standard deviation of the initial size distribution of the  $Ir_{\sim 300}$  NPs was quite low: 2.8 Å.<sup>64</sup> A four-step mechanism for the formation of NPs, recently introduced by Finney and Finke,<sup>65</sup> leads to a very characteristic type of curve, illustrated for  $Pt(cod)Cl_2$  hydrogenation in Figure 1.

The particle size seen for  $Ir_{\sim 300}$  shows close correspondence with one of the “magic numbers” (13, 55, 147, 309, 561, 923) that refer to the total numbers of atoms in successive closed-shell, close-packed shell structures. For example, a single atom can have 12 neighbors; hence, the number 13 initiates the series. Each successive number corresponds to adding one new shell of close-packed atoms. When the shells are not yet fully formed, the remaining vacancies provide active defect sites that are catalytically active but preferentially filled in during autocatalytic growth. By filling all these vacancies, the more stable closed-shell structure is attained. Lacking defect sites, the closed-shell structure is a less effective autocatalyst for nanoparticle growth and growth halts, at least for a time. The authors obtained excellent quantitative fits for a three-regime kinetic model that involved nucleation, particle growth, and substrate hydrogenation.<sup>66</sup>

Another useful point these authors established is that addition of  $Ir_{\sim 300}$  NPs to the catalyst precursor solution at the outset





**Figure 1.** Typical kinetic curve for the reduction of  $\text{Pt}(\text{cod})\text{Cl}_2$ , in the presence of 2 equiv of proton sponge and 2 equiv of  $\text{Bu}_3\text{N}$ , with cyclohexene hydrogenation as the concomitant reporter reaction. The data are fit to the four-step mechanism of ref 65a. The steps are  $\text{A} \rightarrow \text{B}$  (rate constant  $k_1$ ),  $\text{A} + \text{B} \rightarrow 2\text{B}$  ( $k_2$ ), bimolecular agglomeration  $\text{B} + \text{B} \rightarrow \text{C}$  ( $k_3$ ), and autocatalytic agglomeration  $\text{B} + \text{C} \rightarrow 1.5 \text{C}$  ( $k_4$ ). In the last step, the smaller (B) and larger (C) nanoparticles agglomerate with their own rate constants, often with the order  $k_4 > k_3$ .<sup>65</sup> Reprinted with permission from ref 65a. Copyright 2008 American Chemical Society.

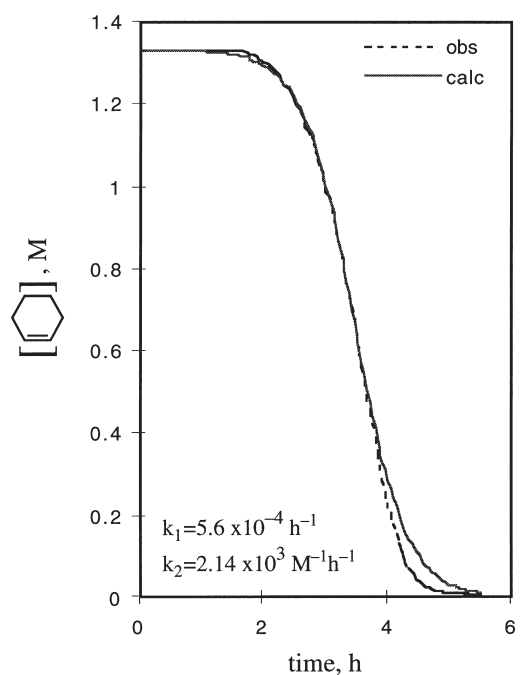
shortens the lag phase by  $\sim 40\%$  because the added particles can catalyze hydrogenation of the molecular precursor complex and mediate NP formation. This finding means that, if any lag phase is significantly shortened by deliberate inoculation of a small aliquot of a spent catalyst solution into a fresh sample of the precursor complex solution, this can provide an indication of NP formation.<sup>61</sup> Whitesides and co-workers<sup>67</sup> earlier found that  $[\text{Pt}(\text{cod})\text{Me}_2]$  could only be hydrogenated to  $\text{Pt}(0)$  in the presence of  $\text{Pt}(0)$  nanoparticles as catalyst. Finney and Finke<sup>68</sup> looked at  $[\text{Pt}(\text{cod})\text{Cl}_2]$  and found that it could also be hydrogenated to  $\text{Pt}(0)$  NPs, but only after a lag time of 7 h.

There is also recent XAFS and kinetic evidence that the most active component of an iridium-based Ziegler-type hydrogenation catalysts made from  $[(\text{cod})\text{Ir}(\mu\text{-O}_2\text{C}_8\text{H}_{15})_2]$  and  $\text{AlEt}_3$  is also nanoparticulate  $\text{Ir}(0)$  formed via the intermediacy of subnanometer clusters.<sup>69</sup>

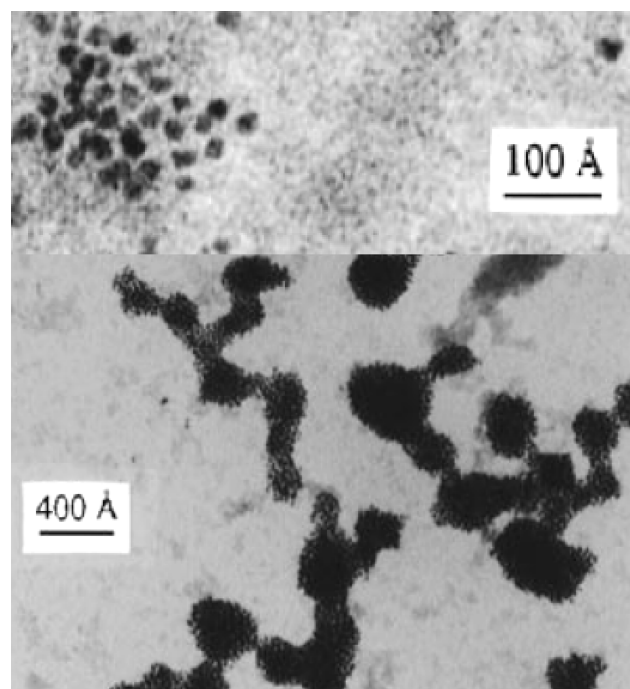
## 2.5. Microscopy

Transmission electron microscopy (TEM) has given valuable information in a number of cases. The TEM data from Watzky and Finke<sup>61</sup> showed that the NPs in fresh  $\text{Ir}_{\sim 300}$  preparations are uniform and well-dispersed but that they change over weeks in acetonitrile (Figure 2), becoming much bigger as well as developing an irregular size distribution. The changes presumably result from agglomeration.

In “ligand-free” Mizoroki–Heck<sup>70</sup> reactions (eq 2) of aryl iodides with  $\text{Pd}(\text{OAc})_2$ , Jeffery<sup>71</sup> suggested using tetraalkylammonium salts as additives to act as phase-transfer catalysts. Since these salts are also known<sup>72</sup> to stabilize Pt nanoparticles, Reetz and co-workers<sup>73,74</sup> looked into the problem with TEM and scanning tunneling microscopy (STM), among other methods, and gathered evidence for the presence of 1–5 nm Pd nanoparticles. Even though pure  $\text{Pd}(\text{OAc})_2$  is known to decompose at  $100^\circ$  to palladium black, solvent-stabilized 8–10 nm  $\text{Pd}(0)$  nanoparticles are formed simply by heating  $\text{Pd}(\text{OAc})_2$  in a polar



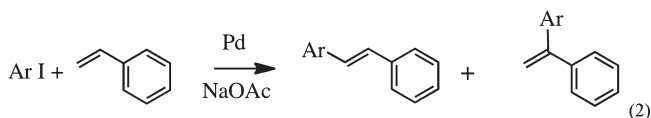
**Figure 2.** Watzky and Finke's cyclohexene hydrogenation data and the excellent fit of their kinetic model for nanoparticle nucleation and growth, quantified<sup>61</sup> by rate constants  $k_1$  and  $k_2$ . Reprinted with permission from ref 61. Copyright 1997 American Chemical Society.



**Figure 3.** TEM data for fresh  $\text{Ir}_{\sim 300}$  nanoparticles (upper) versus a 6-week-old sample that shows agglomeration (lower). Reprinted with permission from ref 61. Copyright 1997 American Chemical Society.

solvent such as propylene carbonate, with no tendency to form Pd black even after several days at  $120^\circ$ .<sup>75</sup> Palladacycles of various types have been shown to be excellent precatalysts for the Heck

reaction, but Rocaboy and Gladysz<sup>76</sup> proposed from TEM and related studies that these merely act as a source of Pd nanoparticles; a complicating feature in this case is the fact that many of these palladacycles can be in part recovered after the reaction, a point that might lead one to believe that they are the true catalysts. This study emerged from an attempt to design a fluorous-phase catalyst that would be readily recyclable. The nanoparticulate form of the catalyst, having lost its fluorous ligands, failed to recycle with the fluorocarbon phase, as expected because it no longer had the physical properties of the precursor. This is another illustration of the idea that, in work with a multifunctional ligand, the topicity of the catalyst does matter.



A significant limitation of TEM studies was identified by Stein, Lewis, and co-workers.<sup>49</sup> They found that, in a Pt hydrosilylation in which only mononuclear Pt species were present at the end of the reaction, mere evaporation of the solution was sufficient to induce NP formation. Methods are therefore to be preferred in which there is no sample preparation (in operando) or at least in which the sample preparation is minimal to ones where sample preparation is such that significant changes may occur. This also raises the question of time scale: nanoparticles observed by TEM subsequent to catalysis may be required from the outset for catalysis to occur or they may be formed during the course of the catalysis or subsequent treatments and not be essential for catalysis. Finally, very small clusters may escape detection by TEM; although no general rule can be posited from literature data, a lower limit of 5–10 Å diameter seems to apply. New methods are continually becoming available, and these may prove useful in future; for example, high-angle annular dark field scanning transmission electron microscopy (HAADF-STEM), also known as Z-contrast microscopy, has shown recent promise for detecting small metal particles in the subnanometer range.<sup>77</sup>

Potential limitations of TEM include the possibility that the electron beam might initiate particle formation.<sup>10c</sup> Finally, TEM cannot be considered a bulk method or an in operando method as is kinetics or dynamic light scattering.

## 2.6. Dynamic Light Scattering<sup>78</sup>

This less-common technique has been applied to the topicity problem.<sup>9,32,33,49,79,80</sup> It can detect nanoparticles and establish a mean radius for the ensemble. Given the minimal sample preparation relative to microscopy, light scattering has the advantage of working on the catalytic solution itself, ideally in operando. Light scattering can in principle also detect smaller particles than standard TEM, and it may prove useful in these roles in future. Neither light scattering nor microscopy can establish if the nanoparticles detected are directly involved in the catalysis or merely act as bystanders. Only kinetic and quantitative kinetic poisoning experiments<sup>10c</sup> can establish which of the species present is the true, most active catalyst.

## 2.7. X-ray Methods

Small angle X-ray scattering (SAXS) gave very useful information in the Stein–Lewis<sup>49</sup> study of Pt hydrosilylation catalysis. In the case of the classic chloroplatinic acid precatalyst, 20 Å particles were detected after HSi(OEt)<sub>3</sub> treatment; in contrast, Karstedt's catalyst (**1**) formed no particles during catalysis, at least with substrates that are good ligands. Confirmatory data was

obtained by EXAFS on frozen solutions, where Pt–C (2.18Å) and Pt–Si (2.32Å) bonds were identified, but no Pt–Pt bonds. The active Pt catalyst was also trapped in a silicone glass that permitted X-ray photoelectron spectroscopy (XPS) analysis of the trapped Pt. This gave a Pt (4f<sub>7/2</sub>) binding energy of 73.1 eV, compared to Karstedt's precatalyst at 72.4 eV, which suggests that the trapped Pt catalyst was in the Pt(II) oxidation state. In a related technique, Bradley et al.<sup>81</sup> have used electron diffraction to identify the crystalline forms of various poly(*N*-vinyl-2-pyrrolidone) (PVP)-stabilized Pd NPs, which proved either to be amorphous or face-centered cubic (fcc), depending on the synthetic method.

XAFS has also given useful in operando structural information on the Rh clusters present in catalytic dehydrocoupling of amine boranes. Rh<sub>4</sub> and Rh<sub>6</sub> clusters are identified as the major (>99%) Rh-containing species during and after the reaction.<sup>82</sup> This work emphasizes that we can no longer consider that the possible categories of active catalysts to be identified are limited to the nanoparticulate and monometallic types—catalysis may also occur via nanoclusters M<sub>n</sub>, having a small number of metal atoms. It is too early to say for sure, but we may eventually find examples across the whole range of possible *n* values.

A number of single-crystal X-ray studies on molecules in the size range of interest are relevant, but we look at just two recent examples here. In one case, a well-defined Au<sub>102</sub> nanoparticle stabilized with 44 mercaptobenzoic acid groups has been isolated and fully characterized by single-crystal X-ray structural work at 1.1 Å resolution. Although not having a magic number of Au atoms, the authors believe that the structure can be explained in terms of 44 surface AuAr groups stabilizing an inner Au<sub>58</sub> core. If each core Au contributes its one valence electron, the authors regard the total of 58 electrons of the core as constituting a closed shell, a factor that is also believed to account for the high stability of Au<sub>58</sub> clusters in the gas phase.<sup>83</sup>

Turning to metal oxides, Benedict and Coppens<sup>84</sup> have characterized a series of nanocluster-sized titanium oxides<sup>85</sup> by single-crystal X-ray diffraction, with the aim of helping to understand interfacial electron transfer in TiO<sub>2</sub> based solar cells. For example, in Ti<sub>17</sub>(μ<sup>4</sup>-O)<sub>4</sub>(μ<sup>3</sup>-O)<sub>16</sub>(μ<sup>2</sup>-O)<sub>4</sub>(cat)<sub>4</sub>(OPr<sup>i</sup>)<sub>16</sub>, four surface Ti atoms have bound catecholates; the same linkers are sometimes used to bind to TiO<sub>2</sub> NP surfaces in solar cells.

## 2.8. Infrared Studies

Bradley et al.<sup>81</sup> also trapped Pd NP preparations of diameter 25, 40, and 60 Å (TEM) with CO and showed how the CO IR spectral bands of the resulting materials responded to the size of the NP. Small particles showed strong terminal (~2050 cm<sup>-1</sup>) as well as bridging CO bands, while the large particles showed essentially only bridging bands (~1935 cm<sup>-1</sup>). Terminal CO is thought to prefer the edges and vertices of the NPs, locations that constitute a greater fraction of available sites in smaller particles. No applications to the homogeneous catalyst topicity problem have been reported as yet, however.

## 2.9. Selective Poisons

If we had a set of poisons selective for homotopic catalysts and another set for heterotopic ones, we could assay any given reaction by applying each type of poison in turn. Unfortunately, once again we meet difficulties. Mercury and CO were already recognized in early work as powerful poisons for both heterogeneous and colloidal catalysts.<sup>86,87</sup> The earliest application to the present problem was the Hg test<sup>30</sup> in which Hg(0) is proposed to act as a selective poison for Pt group metal nanoparticles while



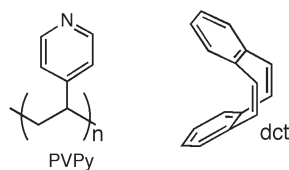
leaving homogeneous catalysts largely unaffected. By Hg(0) suppression of unwanted heterotopic platinum(0)-catalyzed side reactions via poisoning in systems involving competing homotopic reactions of soluble organoplatinum species, Whitesides and co-workers were able to identify the homotopic component of a reaction under study. Whitesides<sup>88</sup> was unable to identify the original source of the Hg(0) poisoning method and considered that the technique was a part of the oral tradition of organometallic experimental practice. We also found this test useful to help eliminate the possibility that Ir(0) NPs were the active species in our early alkane activation work.<sup>32,33</sup> The method is likely to poison nanoparticle-based catalysts, even where a homotopic catalyst is formed by dissolution of the metal from the particle under the reaction conditions, as sometimes happens for Pd catalyzed reactions. Finney and Finke<sup>68</sup> have recommended another precaution to be taken in applying the test: excess Hg(0) is best added to the catalyst with efficient stirring but only after the catalyst has been activated. This gives an internal control in that the catalytic reaction is in progress when the Hg(0) is added. Adding Hg(0) from the outset may also inhibit the catalyst-activation step. It is sometimes said that the Hg(0) amalgamates the surface, but this is by no means required; the Hg(0) atoms merely have to adsorb at the active sites to poison the catalyst. At least in one case, Hg(0) can also poison Rh<sub>4</sub> nanoclusters.<sup>10c</sup>

Stein, Lewis, and co-workers<sup>49</sup> have identified a case of mistaken application of the test in which the Hg(0) was incubated with Karstedt's Pt precatalyst (1) for 7 h before commencement of a catalytic hydrosilylation run. No catalysis was observed with Hg(0), contrary to the situation in its absence, and heterotopy was originally suggested. The authors were able to show that in fact the Hg(0) slowly but completely decomposed the catalyst during the incubation time. After 7 h, no Pt remained in solution, as determined by atomic absorption spectroscopy. They found that Hg(0) addition without any incubation delay gave active catalysis, suggesting that Karstedt's catalyst is homotopic, reversing the prior interpretation.

Dyson<sup>51</sup> considers it unsafe to exclude the possibility that Hg(0) may poison an authentically homotopic catalyst, and so only if Hg(0) fails to poison the system is it safe to conclude that the system is homotopic. Controls are also needed to see if Hg(0) inhibits the appropriate heterogeneous catalyst that is suspected to be present, such as Rh/alumina for a operationally homogeneous Rh catalyst. Exceptionally, one case of acceleration of a presumably heterotopic reaction by Hg(0) has been reported.<sup>89</sup> Manners and co-workers<sup>90</sup> successfully applied the Hg(0) test, among other methods, in the analysis of a catalytic dehydrocoupling of the phosphine–gallane adduct with a [(cod)RhCl]<sub>2</sub> precursor, where Rh NPs were identified as the active catalysts.

Polymer-bound phosphines have been suggested as selective poisons for molecular catalysts. Lipshutz et al.<sup>91</sup> added polymer-bound PPh<sub>3</sub> to a Kumada coupling with a Ni/C catalyst with the result that only 42% conversion of aryl halide occurred as compared to 100% without polymer-bound PPh<sub>3</sub>. In combination with results from other tests, molecular catalysis by dissolved Ni was suggested.

Weck, Jones, and co-workers<sup>92a,b,e</sup> found evidence that SCS pincer complexes of Pd(II) are merely precatalysts in Heck reactions by a variety of tests including a series of poisoning experiments; for example, Hg(0) suppressed the reaction. When the catalyst was immobilized on silica, significant leaching of the Pd took place and, after filtering off the silica particles, the filtrate still showed significant catalytic activity. Recycling of the silica-bound Pd catalyst was also affected: although the product yield in



**Figure 4.** Two materials recommended for selective catalyst poisoning.

the second run was essentially the same as in the first, the rates were much reduced, and in each case a sigmoidal rate curve was apparent, consistent with autocatalytic growth of NPs.<sup>61</sup> Polyvinylpyridine (PVPy, Figure 4) was suggested as a specific poison for operationally homogeneous Pd, whether present as a sol or as molecular complexes. Indeed, PVPy poisoned the catalysis, even when the Pd complex was supported on silica, consistent with a homogeneous component of the system being required for catalysis. Numerous other controls and tests were also performed. The same group came to the same conclusion in the case of PCP pincers,<sup>93</sup> and Bergbreiter et al.<sup>94</sup> came to similar conclusions in a related SCS pincer case.

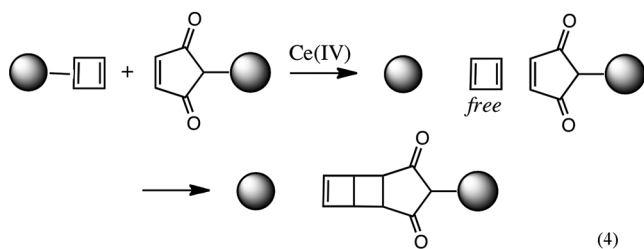
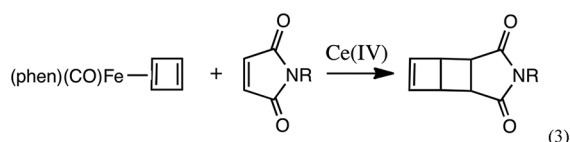
An important aspect of poisoning is its stoichiometry. If the catalyst is poisoned with PPh<sub>3</sub>, for example, then a homotopic, mononuclear catalyst should require at least 1 equiv, if not more, to shut down all the sites. Nanoparticles can be poisoned with less than this, for example, only 0.2 equiv PPh<sub>3</sub> per Ir for the Ir<sub>~300</sub> case mentioned above.<sup>36</sup> This arises from the fact that the NPs have some significant fraction of their M atoms in the interior of the NP and because bulky PPh<sub>3</sub> has a big footprint on the NP surface. Other poisons such as CS<sub>2</sub> have been suggested, but the stoichiometry in this case is more variable, because the CS<sub>2</sub> may be cleaved on adsorption, with each atom, no doubt bridging, poisoning several sites. Finke and co-workers<sup>95</sup> note that the number of metal active sites poisoned per CS<sub>2</sub> molecule can be estimated based on the available literature to lie between 1.5 and 10. However, they also emphasize that a more precise, experimentally determined value would greatly aid and improve the use of CS<sub>2</sub> as a way to determine the number of nanoparticle active sites. Poisoning stoichiometry can be grossly affected by speciation, however. If only a small part of the total metal is in the catalytically active form, the poisoning stoichiometry may not be helpful. Again, one needs to know the number of species present in operando, and their relative kinetic contributions, as emphasized by Finke.<sup>10</sup>

Huang and co-workers<sup>92b,d</sup> have compared resin- and silica-bound thiol scavengers for the removal of Pd to help determine the true catalytic species in Heck coupling of bromobenzene and styrene. Elemental analysis and TEM data indicate that silica-bound thiols have an advantage over resin-bound thiols in selective removal of soluble Pd from a Heck reaction solution in that they efficiently poison the catalytic species but hardly affect Pd clusters in solution, even ones as small as 1 nm. From catalyst poisoning by the scavengers, filtration data, and TEM studies, Pd clusters were shown to be inactive for the Heck reaction with Pd(0)/SiO<sub>2</sub>, with dissolved Pd(0) being the sole active species. [a,e]-Dibenzocyclooctatetrene (dct, Figure 4) has been suggested as a selective poison for homotopic hydrogenation catalysts,<sup>33</sup> but its synthesis is tedious and the method has not been widely invoked.

### 2.10. Three-Phase Test

The three-phase test used to probe this problem was originally developed by Rebek and Gavina<sup>96</sup> to probe the presence of a free

intermediate in a reaction. It harks back to Paneth and Hofeditz's<sup>97</sup> classic work showing that free methyl radicals formed by decomposition of  $\text{PbMe}_4$  at a hot spot in a tube could be transported for a distance by a flowing gas to a cool zone where the radicals reacted with a previously formed Pb mirror to give back  $\text{PbMe}_4$  and etch away the mirror. In the Rebek experiment,<sup>96</sup> the question to be solved for the reaction of eq 3 is whether the cyclobutadiene—a species that is far too reactive to be isolated—is ever truly free or if it instead remains metal-bound during the Diels–Alder reaction. In an experiment where the two reactants were covalently bound to separate beads of Merrifield resin (eq 4), the reaction was shown to proceed normally. This result argues for the intermediacy of free, relatively long-lived cyclobutadiene because the free diene has to have enough time to travel through the solution from one bead to another.



Collman and co-workers<sup>98</sup> showed that Merrifield-type cross-linked polymers with unsaturation act as viable substrates for hydrogenation reactions in the presence of homotopic catalysts, but not heterotopic ones, such as metal sols or heterogeneous catalysts.  $[\text{Ir}(\text{cod})\text{L}_2]\text{PF}_6$  was shown to be homotopic but  $[\text{Cp}^*\text{RhCl}_2]_2$  proved to be heterotopic, at least under the conditions employed for the test.

In the catalytic arena, the question becomes whether a soluble catalyst detaches from the solid-phase heterogeneous catalyst, say Pd/C, and contributes to the activity. Following the logic of eq 4, the reaction is run with a reactant attached to a polystyrene bead. If a soluble Pd species is active, then it can enter the bead and carry out the reaction. If there is no soluble fraction or if the soluble Pd species is inactive, catalyst cannot enter the reactant bead and no reaction product will be seen in the bead. Of course, this does not rule out the formation of Pd nanoclusters because if these were to detach from the Pd/C catalyst and enter the pores of the bead, which can have pore sizes in the nanoparticle range, then the reaction can occur and the test fails.<sup>99</sup> The three-phase test thus only distinguishes whether operationally homogeneous components are formed from a heterogeneous catalyst precursor. Any release of Pd or any metal into the products can also be of significance in commercial production. At the simplest level, precious metal is lost from the catalysts, increasing process costs and contaminating the product. Contamination is a particular concern in pharmaceutical production, where regulatory limits on metallic impurities in the final product are very strict.

There are numerous cases where the three-phase test has given useful information. In an early study,<sup>100a</sup> Davies et al. asked if

heterogeneous catalysts can be precursors to homogeneous catalysts. Indeed, in a commercially significant synthesis using Pd/C for alkoxy-carbonylation of a vinyl halide (Vi-X), as much as 25% of the Pd was detected in the process stream. The three-phase test proved positive for a truly homogeneous catalyst only when vinyl halide was present, suggesting that Vi-X reacts with Pd/C to produce a soluble Vi-Pd-X species. The authors found similar results for a Heck mechanism, again only when the organic halide was present. Shmidt and Mametova<sup>100b</sup> seem to have been the first to make this causal connection between Pd leaching and the presence of the halide reactant.

Some limitations apply to the three-phase test.<sup>101a</sup> The catalyst may not be active in immobilized form, so a control is needed to check that a soluble substrate is indeed converted normally. The polymer substrate may be unsuitable for the dissolved catalyst, as revealed by a control reaction with the soluble form of the catalyst and the immobilized form of the substrate. Crudden and co-workers report further precautions and limitations associated with the three-phase test.<sup>101b</sup>

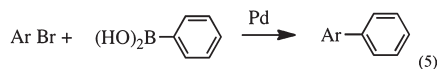
### 2.11. Maitlis' Hot Filtration Test

In this test,<sup>22</sup> sometimes known as a “split test”, the reaction mixture involving a nominally homogeneous catalyst is passed through a glass frit with a filter aid such as “Hyflo Super Cel” (Aldrich), ensuring the appropriate reaction temperature is maintained during the procedure. The catalytic activity of the filtrate is then assayed. The filter pad and any entrained particles are then rinsed and returned to the original vessel, also previously rinsed. After the vessel is charged with fresh substrate and reactants, the catalytic activity of the resulting mixture is checked. Any filterable material retained by the filter aid endows it with catalytic activity, and reaction products are observed. Depending on the effective pore size of the filter aid, particles below a certain size may not be held back, so small nanoparticles may escape detection by this means. Conversely, in running the test on a nominally heterogeneous catalyst, any soluble material released from the catalyst should pass through the filter, in which case catalytic activity also appears in the filtrate. For reactants with low solubility, care must be taken to ensure they have successfully passed through the filter. It is hard to maintain in operando conditions during the whole procedure, but the method is relatively easy to apply and needs no special instrumentation or apparatus.

In a recent example, Biffis and co-workers<sup>102</sup> came to similar conclusions as others in the case of a nominally heterogeneous Pd catalyst precursor for the Heck reaction. They found activity resided in the filtrate and identified the halide component of the reactant mixture as the solubilizing agent.

Conlon and co-workers<sup>103</sup> come to a similar conclusion for the Suzuki–Miyaura reaction (eq 5) catalyzed by Pd/C by estimating the solution levels of Pd by hot filtration followed by high-performance liquid chromatography (HPLC) analysis for the organics and inductively coupled plasma–mass spectrometry (ICP-MS) analysis for the palladium. Other workers have come to similar conclusions. For example, a palladium(II)–SCS–pincer complex has been covalently immobilized on porous silica and polynorbornene supports and evaluated in the Mizoroki–Heck reaction.<sup>104</sup> Kinetics and poisoning studies show that the pincer complexes decompose to liberate active Pd(0) species. There was no evidence for catalysis by

the intact Pd(II) pincer complex, ruling out a Pd(II)–Pd(IV) cycle that had been postulated for such catalysts under the conditions used.



Obviously if the active catalyst is nanoparticulate, formed by dissolution and reprecipitation from the reaction mixture, it could still pass through the filter and produce a catalytically active filtrate. Lipshutz and co-workers<sup>91</sup> describe the case of Ni/C catalyzing aromatic aminations and Kumada coupling, where dissolution of the Ni occurs but its subsequent re-deposition is so fast that very little dissolved Ni is ever present in solution and the Ni/C is largely recovered at the end of the reaction. Nevertheless, spectroscopic analyses (TEM, energy-dispersive X-ray spectrometry (EDX), inductively coupled plasma atomic emission spectrometry (ICP-AES), and React-IR data) suggest that the true catalyst is most likely homogeneous rather than heterogeneous. Other limitations of hot filtration have been discussed by Sheldon and Schuchardt and their co-workers.<sup>105</sup>

Heterogeneous Pd catalysts may not always leach easily. Kobayashi and co-workers<sup>106,107</sup> have reported a “polymer-incarcerated” preparation of palladium nanoparticles that seems to show very low leaching in reactions such as the Suzuki–Miyaura coupling.

In a much more sophisticated version of the filtration test, Rothenberg and co-workers<sup>107</sup> looked at leaching of Pd from Pd nanoparticles under both Heck and Suzuki C–C coupling conditions in a special membrane reactor. The membrane allowed passage of species smaller than ca. 5 nm, and the results suggested that catalysis is carried out by either Pd(0) or Pd(II) that leaches into solution.

Centrifugation does not seem to have been used in the context of separating a heterogeneous from a homogeneous phase for separate testing of each phase for catalytic activity, probably because this room-temperature procedure would only give post operandum information, gathered after the reaction mixture had been cooled down from the reaction temperature. Catalysts that operate at room temperature are much more common in oxidation chemistry (section 2.13), where we may see in operando centrifugation employed in future.

A related procedure, sometimes termed Sheldon’s<sup>108</sup> hot filtration test, involves filtration of a heterogeneous catalyst from the reaction mixture partway through a reaction, followed by continuation of the reaction in the absence of the solid catalyst. If the reaction comes to a halt, heterogeneous catalysis is considered to be confirmed.

Because of their simplicity, there may be an over-reliance on filtration tests for identifying the topicity of catalytic reactions. The standard review by Jones and co-workers<sup>13</sup> contains an extended discussion of this point.

## 2.12. UV–Visible Spectroscopy

In the catalytic dehydrocoupling of the amine boranes and phosphine boranes with a variety of Rh precatalysts such as [Rh(cod)Cl]<sub>2</sub>, Rh/Al<sub>2</sub>O<sub>3</sub>, an authentic Rh-colloid, and [Rh(cod)<sub>2</sub>]-OTf, Jaska and Manners<sup>109</sup> tried to determine whether the dehydrocoupling proceeds by a homogeneous or heterogeneous mechanism. A combination of standard methods, such as TEM and the Hg(0) test, gave useful information. The presence of Rh

colloids in solution was also indicated from UV–visible spectroscopy. Ten nm Rh colloids exhibit a continuous absorption in the visible range due to a surface plasmon resonance, with a steep rise in absorbance at short wavelengths. Lag times were seen in some cases, followed by sigmoidal kinetics. The results obtained suggest that the catalytic dehydrocoupling of amine boranes is heterotopic, involving Rh(0) colloids, while that of phosphine boranes is homotopic even when starting with Rh(0) precursors such as Rh/Al<sub>2</sub>O<sub>3</sub>. An active heterotopic Rh catalyst for dimethylamine borane dehydrogenation was later reported by Zahmakiran and Özkar.<sup>110</sup> The same conclusion was reached by Andrews et al.<sup>111</sup> for palladium-containing perovskite catalysts in the Suzuki reaction. This work included a catalyst-poisoning study.

It seems that both soluble Pd and insoluble Pd species are in principle accessible whether we start from a homogeneous or a heterogeneous catalyst precursor. This means that formation of Pd nanoparticles in a given reaction that starts from a homogeneous catalyst precursor does not necessarily mean that the active catalyst is heterogeneous. Pd may be unusual in this respect among precious metals but it is also the Pt group metal with the greatest number of applications in organic chemistry, so the necessary studies have yet to be carried out for the less common Pt metals. If Pd can dissolve under the catalytic conditions, less noble metals are even more likely to do so, and this possibility may need to be taken into consideration more often.<sup>10b</sup>

## 2.13. Oxidation Catalysis

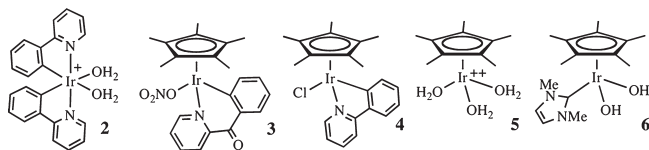
The mechanisms<sup>112–115</sup> of homogeneous, transition metal catalyzed oxidation catalysis tend to be less well developed, more complex, and more difficult to define than for the case of reduction or redox-neutral catalysis. Numerous papers and reviews<sup>116–119</sup> have reported the activity of deliberately prepared metal or metal oxide nanoparticles in oxidation catalysis. It is too early to say anything general about possible heterotopic contributions in supposedly homogeneous catalysts, but a few initial observations have appeared.<sup>135,138c</sup>

Water oxidation catalysts<sup>120,121</sup> are attracting increased interest in connection with alternative energy strategies, but in relatively few cases has the possibility of heterotopy been carefully examined. Modeling the Mn<sub>4</sub>O<sub>4</sub>Ca water oxidation cluster of Photosystem II, a synthetic tetramanganese cluster, [Mn<sub>4</sub>O<sub>4</sub>L<sub>6</sub>]<sup>+</sup> (L = diarylphosphinate),<sup>122</sup> was introduced into a Nafion matrix and shown to give efficient water oxidation catalysis. X-ray absorption spectroscopy and transmission electron microscopy suggested, however, that the cluster acts in the Nafion as merely a source of Mn(II), which is then reoxidized to form nanoparticles of Birnessite, a mixed Mn(III/IV) oxide. Cycling between the photoreduced product and the Birnessite was proposed to be responsible for the photochemical water oxidation catalysis. If so, the original manganese cluster is therefore only a precursor to the true catalyst.<sup>123–125</sup> Nocera<sup>126</sup> and co-workers’ amorphous cobalt phosphate material is electrodeposited from cobalt salts in solution and is of particular importance as an efficient, base metal heterogeneous catalyst.

Iridium complexes can be homogeneous catalyst precursors for water oxidation driven by ceric ammonium nitrate (CAN) as primary oxidant or electrochemically. The use of Ir in this field seems to go right back to early Soviet work<sup>127</sup> (1965). Recent work has emphasized organometallic complexes. For example,



precatalysts **2**,<sup>128</sup> **3**,<sup>129</sup> and **4**, among others, have proved active for water oxidation.

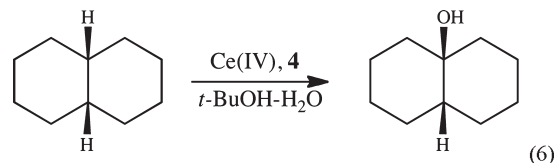


Because  $\text{IrO}_2$  is a known water oxidation catalyst and harsh primary oxidants such as CAN are often used to bring about the reaction, the possibility exists that all the ligands are oxidatively removed and the true catalyst is nanoparticulate  $\text{IrO}_2$ . Beyond  $\text{IrO}_2$  itself, amorphous electrochromic mixed-valent iridium oxide  $\text{IrO}_x \cdot n\text{H}_2\text{O}$  is also a candidate catalyst material, as shown by the facile anodic deposition of highly catalytically active, dark blue form of this material from precursors such as **5**.<sup>130</sup> In a particularly informative electrochemical quartz crystal nanobalance study, Schley et al.<sup>131</sup> quantitatively determined the deposition of a material that we call the “blue layer” (BL) on a gold electrode attached to the quartz crystal. A distinction was noted between precursors such as **5**, which deposit BL, and precursors such as **4**, which do not, at least on the experimental time scale of minutes. One might think that, even if a deposit is absent, as in the case of **4**, particles might still form in solution, but we rely on the observations by Murray and co-workers<sup>132</sup> and Yagi et al.<sup>133</sup> that  $\text{IrO}_2$  NPs deposit anodically from solution; assuming this also applies to BL, as it may well do because **5** indeed yields a deposit, heterotopy can be eliminated for **4**. These measurements only apply to the first minute or so of reaction, but they seem to imply that both homotopic and heterotopic materials can act as catalysts in this case. The N-heterocyclic carbene (NHC)-substituted complex **6** seems to be the fastest yet reported in the  $\text{Cp}^*$  series.<sup>134</sup> Formation of the BL, a material that no longer contains  $\text{Cp}^*$  Me groups (IR and NMR), means that the  $\text{Cp}^*\text{Ir}$  unit can be oxidatively degraded without too much difficulty to give a highly active, heterotopic water oxidation catalyst. This behavior raises a red flag for such systems in general, and close scrutiny will be needed to define their topicity and how it may vary with change of ligands, change of conditions, and the time scale considered. Other ligand sets may prove more suitable than Cp and  $\text{Cp}^*$ . This work also emphasizes the importance of controlling for the homogeneity of electrocatalysis by rinsing the electrode and then checking its catalytic activity in pure electrolyte. Of course, this test still does not eliminate the possibility that heterotopic catalysts are formed that do not deposit on the electrode.

Beller and co-workers<sup>135</sup> reported that simple Ir salts, such as  $\text{IrCl}_3 \cdot x\text{H}_2\text{O}$ , were even more active than **1–5**, thus ruling out the need for organometallic ligands. Because of the very slow dissolution kinetics of  $\text{IrCl}_3$ , the dissolution process was left to continue for 15 days to obtain the maximum rates. The TOF activities they observe for the best catalysts are better than for conventional  $\text{IrO}_2$  and do not show the very rapid drop in TOF seen for the  $\text{IrO}_2$  over time. Critically for the mechanistic interpretation,  $\text{IrCl}_3$ –CAN was shown by HAADF–STEM imaging to contain 12.5 Å particles containing iridium in a ceria matrix. Such very small nanoclusters might easily escape<sup>10</sup> detection by conventional TEM.

Zhou et al.<sup>136</sup> looked at CH hydroxylation with precatalyst **4** and Ce(IV) and showed retention of configuration at carbon in

cases such as eq 6. Stereoretention seems more plausibly associated with homotopic than heterotopic catalysis, but a UV band near 580 nm, possibly associated with formation of an iridium oxide material, is seen under certain conditions and the long time scale of the reactions, hours, raises concerns. Isolated bulk BL itself does not seem to have good activity for CH hydroxylation and did not show retention of configuration, but the bulk material may well be deactivated relative to the active species in the reaction of eq 6. Although TEM does not show NPs under the conditions employed, small particles, best viewed as nanoclusters, could still form, as in the Beller study, and could easily be competent to give stereoretentive reactions like eq 6. Both a mononuclear and a multinuclear nanocluster could be homotopic in the sense of having a single type of metal active site. Much more work is needed, however, before the active catalysts can be securely identified.



A homogeneous precursor,  $\text{Au}(\text{OAc})_3$ , gave selective oxidation of dibenzylamine to dibenzylimine with  $\text{O}_2$  as the oxidant. The nature of the active catalyst was suggested by in situ X-ray absorption spectroscopy (XANES) and by TEM. In an early stage of the reaction, dissolved  $\text{Au}(\text{OAc})_3$  is reduced by the amine in situ and the resulting  $\text{Au}(0)$  nanoparticles were considered to be the true active catalyst for the reaction.<sup>137</sup> Palladium oxide NPs, and not as previously believed  $\text{Pd}(0)$  NPs, are now thought to be responsible for the aerobic oxidation of benzyl alcohol.

A recent report<sup>138a</sup> of a cobalt polyoxometalate (POM) catalyst for water oxidation with chemical oxidants attracted attention for its use of Earth-abundant metals rather than Ru or Ir. In this work, a  $[\text{Co}_4(\text{H}_2\text{O})_2(\text{PW}_9\text{O}_{34})_2]^{10-}$  precatalyst in pH 8.0 sodium phosphate buffer was shown to act as a water oxidation catalyst (WOC) with an appropriate  $[\text{Ru}(\text{bipy})_3]^{3+}$  oxidant. Kanan and Nocera<sup>126,138b</sup> had previously reported a cobalt oxide material ( $\text{CoO}_x$ ) formed from Co(II) salts by anodic deposition in buffers such as phosphate as an active WOC, so the possibility that the POM complex released cobalt and deposited  $\text{CoO}_x$  under operating conditions could not be excluded. Indeed, electrochemical, kinetic, UV–vis, scanning electron microscopy (SEM), EDX, and related work by Stracke and Finke<sup>138c</sup> suggests that the POM complex may be only a precatalyst for a heterotopic  $\text{CoO}_x$  WOC. UV–vis and electrochemical data show that the 500  $\mu\text{M}$  POM complex slowly releases 58  $\mu\text{M}$  Co(II) into the phosphate buffer, and an active  $\text{CoO}_x$  WOC was detected on the anode after the electrochemical runs. Finally, authentic 58  $\mu\text{M}$  Co(II) was shown to give an active  $\text{CoO}_x$  WOC under the appropriate buffered conditions without any POM present.

## 2.14. Possible Future Studies

The remarkable recent advances in electrospray mass spectral methods suggests that the post operandum speciation of precatalysts might be accessible in this way. A referee has suggested that for NMR-active metals like platinum or rhodium, a small molecular cluster would be likely to have a well-defined solution NMR, but failure to observe a metal NMR signal could be a clue that single molecular species are not present.

Table 2. Tests That Can Be Useful in Helping to Distinguish Molecular (Homotopic) from Multisite (Heterotopic) Catalysts<sup>a</sup>

test	comment	classification <sup>b</sup>
kinetics	unexplained lag time and sigmoidal kinetics may indicate heterotropy <sup>c</sup>	IO, MP, AF
selectivity	selectivity may match a relevant catalyst of known topicity <sup>d</sup>	IO, MP, AF
poisoning	choice of poison has to be appropriate for the case in question	IO, MP, AP
3-phase	with several possible failure modes, a positive outcome <sup>e</sup> is more persuasive than a negative one	IO, MP, AP
hot filtrate (split test)	the soluble catalyst must persist long enough for its activity to be apparent in the filtrate	PO <sup>f</sup> , MP, AP <sup>f</sup>
microscopy	particles may be inactive or only formed in sample preparation or observation	PO, SP, AF
asymmetric catalysis with appropriate ligand	heterotopic as well as homotopic catalysts can show high ee's <sup>g</sup>	IO, MP, AF
spectroscopy	observable species may not be active species	IO, SP, AF
electrochemical	the catalytic activity of the rinsed electrode in pure electrolyte may result from a catalytic deposit	PO, SP, AF
inoculation	addition of an aliquot of the final reaction mixture to the starting catalyst solution may abolish any lag phase, <sup>61</sup> suggesting heterotropy	IO, MP, AP

<sup>a</sup> Abbreviations: IO = in operando; PO = post operandum; MP = mechanistic probe; SP = speciation probe; AF = additive-free; AP = additive present.

<sup>b</sup> Definitions from section 2.14: homotopic = mechanistically homogeneous (single type of active site); heterotopic = mechanistically heterogeneous (multisite). <sup>c</sup> Or the precatalyst may be undergoing a conversion to a different, but still homotopic, active form. <sup>d</sup> It can be difficult to choose appropriate comparison catalysts, however. <sup>e</sup> That is, catalytic activity is observed. <sup>f</sup> IO filtration is hard to carry out. The additive is the filter aid. <sup>g</sup> See section 2.3.

### 2.15. Hierarchy of Tests

Not all tests have equal value (Table 2). The best mechanistic evidence is expected to come from measurements on the reaction mixture itself during the catalytic reaction (in operando) rather than on a sample of the reaction mixture that has been subjected to sample preparation (post operandum), as in microscopy. Similarly, measurements that directly probe mechanism, such as kinetics and poisoning, are likely to be more relevant than measurements that establish phase relationships, again as in microscopy. Finally, measurements that do not require additives, such as kinetics, may be more reliable than tests in which additives are needed, such as in poisoning experiments. The Finke strategy<sup>10</sup> is an example of how one can combine complementary experiments to obtain reliable information.

## 3. MOLECULAR CATALYSIS IN OPERATIONALLY HETEROGENEOUS CATALYSTS

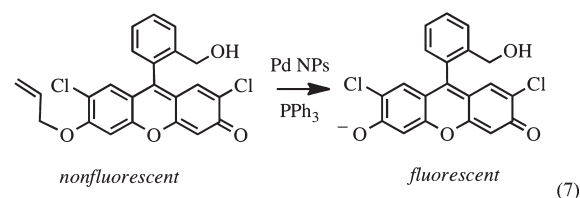
When operationally heterogeneous catalysts are exposed to reagents in solution, a question naturally arises: do they stay heterogeneous<sup>138</sup> or is the active catalyst a soluble metal complex formed by reaction with the reactants? This is just the converse of the concern discussed above on the homogeneity of operationally homogeneous catalysts. A few examples will illustrate the problem.

### 3.1. Mizoroki–Heck Catalysis

The recent reviews by Jones and co-workers<sup>13,92</sup> cover this area in such depth that we do no more than mention leading aspects here. To take the most important case first, Pd/C is one commercially useful catalyst for a series of solution-phase C–C coupling reactions, the importance of which was emphasized by the recent award of the Nobel Prize in this area. Catalytic activity can arise from some of the Pd becoming soluble by reaction with the aryl halide reactant, and it is often the resulting soluble molecular species that is the true catalyst, responsible either for some or all of the overall activity.<sup>13,92</sup> This can have serious implications for the design of commercial processes: for example, in the case of Mizoroki–Heck couplings of aryl iodides and bromides with nominally heterogeneous Pd/C as catalyst, excessive catalyst loss was seen in a flow reactor for this reason. Apart from loss of activity, the Pd released evidently also risks contaminating the product, a particularly serious problem in

pharmaceutical production.<sup>139</sup> de Vries<sup>140</sup> argues that all Heck reactions that go at the usual high temperatures (120–160 °C) are nanoparticle-based whatever the precursor, but that these particles act as precursors to molecular species that act as intermediates. If so, this would seem to be a borderline case between homo- and heterotopicity with easy transformation from one to the other.

Dupont and co-workers<sup>141a</sup> came to very similar conclusions for Heck reactions in ionic liquids. Pd(0) nanoparticles of 2 nm diameter, in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ionic liquid, were catalyst precursors for Heck coupling of aryl halides with *n*-butylacrylate. In situ TEM analysis after the catalytic reaction shows the formation of larger nanoparticles (6 nm). ICP-AES data show significant metal leaching (up to 34%) from the ionic phase to the organic phase at low substrate conversions, which drops to 5–8% leaching at higher conversions. These results strongly suggest that the Pd(0) nanoparticles serve as a reservoir of homotopic catalytically active species. A similar borderline situation is proposed for Pd NPs of 2.4 and 3.8 nm diameter in a Tsuji–Trost cleavage of an allyl group that “turns on” fluorescence in the product (eq 7). Pd leaching was considered to arise from oxidative addition of the reactant to a NP-based Pd, leading to a molecular phosphine-containing Pd complex being liberated. Ostwald ripening occurs, in which atoms preferentially detach from smaller nanoparticles and reattach to bigger particles; in this way, redeposition of the Pd led to NP growth during the reaction.<sup>142</sup> Köhler and co-workers<sup>141b</sup> came to similar conclusions.

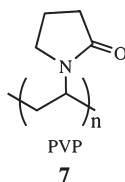


### 3.2. Other Reactions

Numerous other cases of commercial importance are known. For example, Sheldon and co-workers<sup>105</sup> found that intended heterogeneous catalysts consisting of Mo(VI), W(VI), or V(V), supported on silica, all gave rapid leaching of the metal ion in the epoxidation of propylene with ethylbenzene hydroperoxide; only

Ti(IV) gave a stable, nonleaching catalyst. The hydroperoxide was identified as the reagent that solubilized some of the labile metals. Likewise, in the transesterification of triglycerides with methanol to produce biodiesel, catalyzed by solid CaO, extensive leaching under certain operating conditions threatened the viability and sustainability of the process.<sup>143</sup>

In what was intended as a nanoparticle-catalyzed Monsanto reaction with poly(*N*-vinyl-2-pyrrolidone) (PVP, 7)-stabilized Rh nanoparticles, a number of tests including filtration suggested that Rh leaching took place under the reaction conditions to give the conventional homotopic catalyst,  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$ . Closer study suggested that the MeI present in the reaction medium is the reactant that drives the conversion of the Rh(0) to the soluble catalyst. The reaction mixture remained clear and deposit-free by visual inspection even when Rh nanoparticles were known to be present.<sup>144</sup>



In the catalytic formylation of 3-methoxypropylamine with hydrogen and supercritical carbon dioxide, carbon dioxide acts as both reactant and solvent. Ru/Al<sub>2</sub>O<sub>3</sub> modified by 1,2-bis-(diphenylphosphino)ethane (dppe) showed a high formylation activity comparable to those of the known homotopic catalysts RuCl<sub>2</sub>(dppe)<sub>2</sub> and RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>. Analysis of the reaction mixture by inductively coupled plasma optical emission spectrometry (ICP-OES) and structural studies by in situ X-ray absorption spectroscopy led to the proposal that the presence of the phosphine modifier led to the formation of a homotopic ruthenium catalyst.<sup>145</sup>

### 3.3. Implications for Catalyst Recycling

The possibility that some operationally heterogeneous catalysts, including heterogenized catalysts, gradually lose metal to the solution over time, or lose activity while remaining bound to the support, raises issues about assessing recoverability of catalysts.<sup>92c</sup> In a key study, Gladysz<sup>146</sup> has pointed out that many papers on recoverable catalysts report reaction yields as a function of number of recycles. A constant value is held to be proof of recyclability. As Gladysz says:

Suppose an arbitrary decision has been made to let each cycle run one hour. However, under the conditions of cycle 1, product formation is in fact complete after one minute. Suppose that half the catalyst is lost in the first recycling operation. Cycle 2 could still give complete product formation in two minutes (given reasonable rate law assumptions, etc.). Suppose half the catalyst is lost on each succeeding cycle. No major yield deterioration would be noted until cycle 8! However, the rate of product formation or turnover frequency (TOF) would decrease markedly from cycle to cycle.

Gladysz therefore recommends comparing TOF data from successive cycles as a better figure of merit for assessing recyclability. He also recommends other, more searching criteria for assessing recyclability:

High-quality studies will seek a complete mass balance for the catalyst precursor. In addition to recovered catalyst,

three other quantities may be defined: (a) the amount of active catalyst that is leached during reaction or recycling (note that each species on the catalytic cycle is an independent candidate for leaching); (b) the amount of decomposed inactive catalyst that is leached during reaction or recycling; (c) the amount of decomposed inactive catalyst that is recycled. Depending upon quantities and conditions, it may not be practical to measure all of these.

In addition, Jones<sup>92c</sup> recommends full kinetic studies as a means for assessing recyclability. Because a longer-lived catalyst is often more practically useful than a recyclable catalyst, it may be a better allocation<sup>146</sup> of effort in future to look more closely into ways of extending catalyst lifetime rather than concentrating on adding to the growing universe of literature on different modes of catalyst recycling, particularly as so few examples have yet proved commercially viable.<sup>92c</sup>

## 4. HOMEOPATHIC EFFECTS AND IMPURITY ARTIFACTS IN CATALYSIS

The term “homeopathic” refers to the remarkably low levels of metal that seem to be involved in many of the cases discussed in this section. Particularly where the catalyst is a precious metal, this raises the possibility of using that metal much more efficiently if the homeopathic effects can be controlled and exploited. When very low concentrations of metal can give highly efficient catalysis, impurity artifacts can be a problem. Impurity artifacts lead to misassignment of a catalytic mechanism as a result of the unanticipated catalytic activity of an undetected impurity present in the system. This misassignment, if not unmasked, may also lead to a misassignment of the type of catalysis involved, homotopic or heterotopic, hence the relation to the present topic.

Such problems are not restricted to homogeneous catalysts. Although enzyme work—Ostwald’s class 4—is unlikely to be affected by topicity problems, impurity artifacts can still occur in that field.<sup>147</sup>

### 4.1. Palladium Coupling

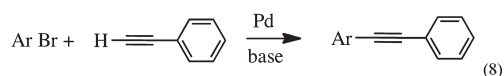
In an important review, Beletskaya and Cheprakov<sup>148</sup> call attention to the extremely low Pd loadings, which they term “homeopathic”, that can give acceptable reactivity in the Mizoroki–Heck reaction under what are often called “ligand-free” or, more properly, “lightly ligand-stabilized” conditions. They also document the high sensitivity of the catalyst to initial conditions, a feature that can translate into irreproducibility. They ascribe this to the difficulty of making reproducible nanoparticle preparations in the absence of surface-active stabilizing additives. Once again, the Jones reviews<sup>13,92</sup> give very useful coverage of this field.

Reetz and de Vries<sup>149</sup> have recommended loadings in the range of 0.01–0.1 mol % Pd(OAc)<sub>2</sub> in ligand-free Mizoroki–Heck reactions. In view of the cost of Pd, this may provide industrially important variants of these classic and highly useful reactions. The argument in favor of this specific range of loadings is that higher metal loadings lead to deposition of Pd black with loss of activity because most of the Pd is no longer accessible, but lower loadings lead to lower activity because of the low Pd concentration.

The effectiveness of Pd for coupling reactions at extremely low loadings leads directly into the topic of impurity artifacts.



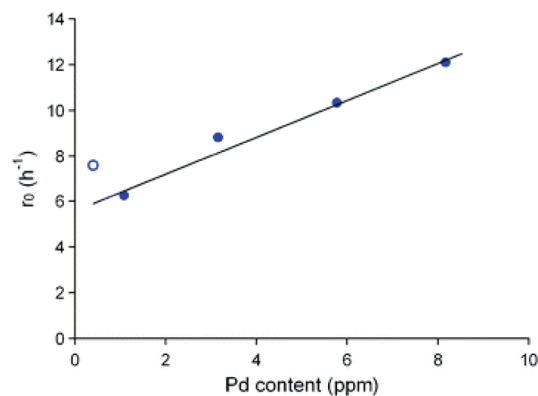
Two recent examples illustrate the extreme difficulty of determining the true catalyst at work in a given system. In a recent report,<sup>150</sup> a homogeneous cross-coupling, a reaction best known with Pd catalysts but also known for Cu, was proposed to be iron-catalyzed. Astonishingly, according to later work, a few ppm trace impurity of Cu in the Fe was the true catalyst.<sup>151</sup> In an example of microwave activation of Suzuki cross-coupling, Leadbeater and co-workers<sup>152,153</sup> found a positive result for an apparently “metal-free” reaction mixture. In this case, it later transpired that 50 ppb of Pd present in a reactant was sufficient to bring about the coupling. In another case of what was intended to be a Pd-free Sonogashira coupling (eq 8), Pd was identified as an impurity in the CsCO<sub>3</sub> base.<sup>154</sup> In what was originally thought to be a La-catalyzed C–N cross coupling, arguments have been made that trace Cu is the true catalyst.<sup>155</sup> An important clue to the resolution of this case was that the “La-catalyzed” reaction showed the same selectivity characteristics as previously seen for the previously known copper catalyst; in particular, the *N,N'*-dimethylethylenediamine (DMEDA) ligand proved best for both.



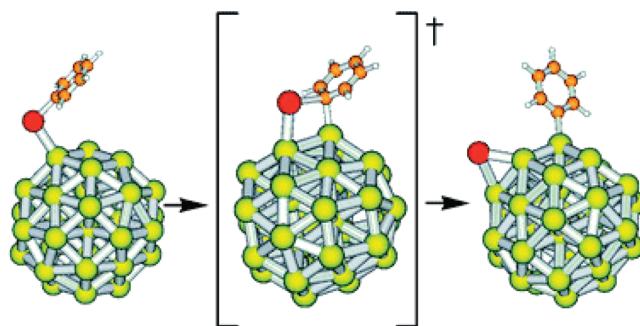
These are just the examples where clarification has been achieved—and even then only recently. There must be numerous similar undiscovered cases in the literature. It is a real challenge to identify contaminant metals in such low amounts. Inductively coupled plasma mass spectrometry (ICPMS) has been suggested by Novák<sup>156</sup> as a good procedure for doing this because it is good down to ppb or even ppt levels, but it is hardly feasible to subject all catalytic results to such intensive analysis.

An example of the complications involved comes from recent Spanish work. The story starts with the report by Corma and co-workers<sup>157</sup> that Au supported on CeO<sub>2</sub> nanoparticles catalyzes the Sonogashira coupling of terminal alkynes with aryl iodides. Because Au nanoparticles were less efficient on their own, the activity was ascribed to molecular Au(I) species on the CeO<sub>2</sub> nanoparticles. In support of this interpretation, Au(I) complexes were prepared and shown to be active. Espinet, Echevarren, and co-workers<sup>158</sup> found that a series of molecular complexes were inactive except in the presence of Pd impurity and suggested that an impurity artifact might have affected the prior work. They pointed out that even high-purity Au can contain traces of Pd. Corma and co-workers<sup>159</sup> reexamined their work in the light of the suggestion by Espinet and Echevarren. The state of our understanding at the time of writing is as follows—an induction period is needed before the homogeneous Au complexes become active, which is now ascribed to the formation of Au NPs that are considered the true active species. The role of Pd was examined by deliberate addition of Pd with the result that the rate is indeed enhanced by Pd but the essentially Pd-free Au nanoparticle already has a substantial activity (Figure 5).

The interpretation was supported by density functional theory (DFT) calculations on a model Au NP (Figure 6) that shows cooperation of adjacent metal sites in the key C–I cleavage step of the overall PhI/alkyne coupling reaction. The interpretation is also consistent with temperature-programmed high vacuum reaction data by Lambert and co-workers<sup>160</sup> for phenylacetylene and iodobenzene reacting on a Pd-free Au(111) surface to give the Sonogashira coupling product at temperatures comparable to those seen in the operationally homogeneous catalysts.



**Figure 5.** Plot of the initial reaction rate ( $r_0$ ) for diphenylacetylene formation as a function of Pd impurities in the presence of Au/CeO<sub>2</sub>. The empty circle corresponds to an Au/CeO<sub>2</sub> catalyst made from 99.999% pure Au. Reprinted with permission from ref 160. Copyright 2011 Royal Society of Chemistry.



**Figure 6.** Calculated pathway for the rupture of the C–I bond in iodobenzene on a Au<sub>38</sub> nanoparticle. Au atoms are yellow, C atoms are orange, H atoms are white, and I atoms are red. Reprinted with permission from ref 161. Copyright 2010 American Chemical Society.

Lambert and co-workers have also looked at Au NPs on both SiO<sub>2</sub> and TiO<sub>2</sub> in this connection and have identified size-dependent behavior for PhI/PhCCH coupling. Greater selectivity for PhCCH, the desired heterocoupling product, was found for the largest 23 nm NPs versus the smaller ones of 12 and 2.8 nm diameter, which gave increasing amounts of diphenyl, the undesired homocoupling product. A possible origin for the size effect was also discussed. Small particles are less likely to have well-developed Au(111) faces, and if these are the only faces that are active for the heterocoupling, then the size effect on selectivity is understandable. Significant leaching of some of the Au into solution also occurred, but the leachate had negligible activity.<sup>161</sup>

The extended discussion of this system has therefore been very fruitful not only in enhancing our understanding of this particular system but also in emphasizing the complexities of the general problem of mechanism in operationally homogeneous catalysts. Dupont and co-workers<sup>162</sup> reported a dangerous variant of this problem in that even ppt amounts of residual Pd remaining from glassware previously used for the Pd-catalyzed Mizoroki–Heck reaction can be sufficient, even after cleaning the glassware, to catalyze a subsequent “Pd-free” reaction. Heidenreich, Köhler, and co-workers<sup>163</sup> find that extremely

low loadings of a specially prepared Pd/C catalyst can give extraordinarily high activity in Heck, Suzuki, and Sonogashira reactions. Turnover numbers of up to 36 000 and turnover frequencies of up to 18 000 h<sup>-1</sup> are achieved with Pd loadings as low as 0.0025 mol %.

#### 4.2. Electrocatalysis

Impurity problems are not just an issue for thermal catalysis. Sodium tungsten bronze, Na<sub>x</sub>WO<sub>3</sub> (0 < x < 1), was reported to be as good a catalyst for electrochemical reduction of O<sub>2</sub> as Pt.<sup>164</sup> Unfortunately, the activity later proved to arise from traces of Pt in the bronze as a result of the synthetic history of the particular sample of the bronze, notably its formation in a Pt crucible.<sup>165</sup> Again, homeopathic levels of Pt seem to have been involved.

Recent electrocatalytic examples have come from Compton and co-workers<sup>166</sup> and Pumera and co-workers.<sup>167–169</sup> These authors suggested that the electrocatalytic activity ascribed to nanotube-modified electrodes is actually dominated by contributions from metal impurities in the nanotubes. For example, such is the case for the electrocatalytic oxidation of hydrazine by carbon NTs, where multicomponent Co/Mo/Fe impurities were identified as the active species in double-walled carbon nanotubes.<sup>167b</sup> Similarly, bimetallic nickel–iron impurities in single-walled carbon nanotubes are responsible for the oxidation of amino acids.<sup>167c</sup> Recent work shows how samples of NTs from different suppliers can have very different impurity profiles, which would affect reproducibility of impurity-based catalysis.<sup>170</sup>

#### 4.3. Rosenberg's Pt Study

A classic example of a closely related artifact that was turned to good effect by careful subsequent analysis was the discovery of the antitumor activity of Pt(II) amine complexes. As Rosenberg relates in a review<sup>171</sup> that emphasizes the historical development of the field, the effect turned up unexpectedly in an attempted electrolysis of tumor cells with Pt electrodes. "Extensive detective work" showed that the antitumor activity that was identified was entirely due to the trace (~10 ppm) of Pt(II) that dissolved under the conditions of the study and reacted with trace components of the system to give the active *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] complex. This eventually appeared in clinical practice with the result that hundreds of thousands of patients have now benefited. Sadly, pharmaceutical companies have not examined many other metal complexes for biological activity, presumably because they do not resemble standard "drug-like molecules".

### 5. CONCLUSION

Catalyst topicity can be one of the hardest problems to resolve in the field of homogeneous catalysis. At least now with such a wide array of methods to apply, the clear cases where concordant testing results are obtained should be relatively easily classified. Hardest are cases where indications are mixed or where small nanoclusters<sup>10c</sup> are involved.

Critical thinking is necessary to raise the topicity question in the first place, and early resolution of problematic cases is highly desirable to avoid time being wasted following up inappropriate experiments. To take an operationally homogeneous catalyst that proves to be heterotopic, covalent attachment to a surface or elaborate ligand design are clearly less likely to be fruitful than in a homotopic case.

The related problem of impurity artifacts again poses major problems. The phenomenally low loadings of metal that can give high activity is a major hazard in this area. With the recent sharp

price rises of the Pt metals, base metal catalysis is gaining attention as a greener alternative. With an intrinsically less active metal, harsher reaction conditions will doubtless be needed, and impurity artifacts are therefore likely to be even more troublesome in future. On the positive side, we may be able to learn how to reproducibly obtain rapid catalysis from homeopathic levels of precious metal catalyst.

In Ostwald's time, the practical aspects of catalysis were emphasized over the mechanistic ones, justifying his phase-based classification. With the rise of interest in mechanism in our own time, a mechanistic classification seems an appropriate adjunct, as indeed was previously recommended by Schwartz<sup>35</sup> and by Lin and Finke.<sup>36</sup>

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Bob Crabtree, educated at New College, Oxford, with Malcolm Green, did a Ph.D. with Joseph Chatt at Sussex and spent four years in Paris with Hugh Felkin at the CNRS, Gif. At Yale since 1977, he is now Whitehead Professor. He has been ACS and RSC organometallic chemistry awardee, Baylor Medallist, Mond lecturer, Kosolapoff awardee, and Stauffer Lecturer, has chaired the ACS Inorganic Division, and is the author of an organometallic textbook. Early work on catalytic alkane C–H activation and functionalization was followed by work on H<sub>2</sub> complexes, dihydrogen bonding, and catalysis for green and energy chemistry. He is an ACS Fellow and a Fellow of the American Academy of Arts and Sciences.

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## REFERENCES

- (1) Ostwald, W. *Nature* **1902**, *65*, 522.
- (2) *Principles of Inorganic Chemistry*; Ostwald, W., Ed.; Macmillan: London, 1914; p 6.
- (3) *Organocatalysis*; Reetz, M.T., Ed.; Springer: Berlin and New York, 2008.
- (4) List, B. *Chem. Rev.* **2007**, *107*, 5413.
- (5) *Bioinorganic chemistry: Cellular systems and synthetic models*; Long, E. C., Baldwin, M. J., Eds.; American Chemical Society: Washington, DC, 2009.
- (6) van Eldik, R. *Chem. Rev.* **2005**, *105*, 1917.
- (7) Holm, R. H. *Chem. Rev.* **2004**, *104*, 347.
- (8) *Molecular Cell Biology*, 4th ed.; Lodish, H., Berk, A., Zipursky, S. L., Matsudaira, P., Baltimore, D., Darnell, J., Eds.; W. H. Freeman: New York, 2000.
- (9) Lewis, L. N. *Chem. Rev.* **1993**, *93*, 2693.
- (10) (a) Aiken, J. D.; Finke, R. G. *J. Mol. Catal., A* **1999**, *145*, 1. (b) Widegren, J. A.; Finke, R. G. *J. Mol. Catal., A* **2003**, *198*, 317. (c) Bayram, E.; Linehan, J. C.; Fulton, J. L.; Roberts, J. A. S.; Szymczak, N. K.; Smurthwaite, T. D.; Özkaz, S.; Balasubramanian, M.; Finke, R. G. *J. Am. Chem. Soc.* **2011**, DOI: dx.doi.org/10.1021/ja2073438.
- (11) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852.
- (12) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884.
- (13) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.
- (14) Schmid, G. *Polyhedron* **2321**, *7*, 1988.
- (15) Vargafik, M. N.; Zagorodnikov, V. P.; Stolarov, I. P.; Moiseev, I. I.; Kochubey, D. I.; Likhoholobov, V. A.; Chuvilin, A. L.; Zamaraev, K. I. *J. Mol. Catal.* **1989**, *53*, 315.
- (16) Schmid, G. *Endeavour* **1990**, *14*, 172.
- (17) (a) Gao, Y.; Shao, N.; Pei, Y.; Zeng, X. C. *Nano Lett.* **2010**, *10*, 1055. (b) Shimizu, K.-i.; Shimura, K.; Ohshima, K.; Tamurab, M.; Satsumab, A. *Green Chem.* **2011**, DOI: 10.1039/c1gc15835j.
- (18) (a) Finney, E. E.; Finke, R. G. *J. Colloid Interface Sci.* **2008**, *317*, 351. (b) Özkaz, S.; Finke, R. G. *Langmuir* **2003**, *19*, 6247.
- (19) *Catalysis by Di- and Polynuclear Metal Cluster Complexes*; Adams, R. D., Cotton, F. A., Eds.; Wiley-VCH: New York, 1998.
- (20) Gates, B. C. *J. Mol. Catal., A* **2000**, *163*, 55. (b) Balcha, T.; Strobl, J. R.; Fowler, C.; Dash, P.; Scott, R. W. *J. ACS Catal.* **2011**, *1*, 425.
- (21) Bohme, D. K.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 2336.
- (22) Hamlin, J. E.; Hirai, K.; Millan, A.; Maitlis, P. M. *J. Mol. Catal.* **1980**, *7*, 543.
- (23) Starkey-Ott, L.; Finke, R. G. *Coord. Chem. Rev.* **2007**, *251*, 1075.
- (24) Bronstein, L. M.; Shifrina, Z. B. *Chem. Rev.* **2011**, *111*, 5301.
- (25) Copéret, C. In *Handbook of Green Chemistry*; Anastas, P., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Vol. 2.
- (26) Basset, J. M.; Gates, B. C.; Candy, J.-P.; Choplin, A.; Leconte, M.; Quignard, F., and Santini, C., Eds. *Surface Organometallic Chemistry: Molecular Approaches to Surface Catalysis*; Kluwer: Dordrecht, The Netherlands, 1988.
- (27) Marks, T. J. *Acc. Chem. Res.* **1992**, *25*, 57.
- (28) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215.
- (29) James, B. R. *Homogeneous Hydrogenation*; Wiley-Interscience: New York, 1973.
- (30) Foley, P.; Dicosimo, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6713.
- (31) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 549–556.
- (32) (a) Crabtree, R. H.; Mellea, M. F.; Mihelcic, J. M.; Quirk, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 107. (b) Crabtree, R. H.; Demou, P. C.; Edén, D.; Mihelcic, J. M.; Parnell, C.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994.
- (33) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855.
- (34) See, for example, section 4.7 in ref 10b.
- (35) Schwartz, J. *Acc. Chem. Res.* **1985**, *18*, 302.
- (36) Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891.
- (37) Copéret, C.; Basset, J. M. *Adv. Synth. Catal.* **2007**, *349*, 78.
- (38) (a) Dunn, E. W.; Coates, G. W. *J. Am. Chem. Soc.* **2010**, *132*, 11412. (b) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.
- (39) Ott, L. S.; Finke, R. G. *J. Nanosci. Nanotechnol.* **2008**, *8*, 1551.
- (40) Crabtree, R. H. *New J. Chem.* **2011**, *35*, 18.
- (41) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941 and refs cited therein.
- (42) Bergbreiter, D. E.; Tian, J. H.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530.
- (43) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275.
- (44) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
- (45) Allgeier, A. M.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 894.
- (46) (a) Chirik, P. J.; Wieghardt, K. *Science* **2010**, *327*, 794. (b) Bart, S. C.; Chlopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13901.
- (47) Davidson, E. R. *Chem. Rev.* **2000**, *100*, 351.
- (48) Cardenas-Trivino, G.; Klabunde, K. J.; Dale, E. B. *Langmuir* **1987**, *3*, 986.
- (49) Stein, J.; Lewis, L. N.; Gao, Y.; Scott, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 3693.
- (50) Narayanan, R.; Tabor, R.; El-Sayed, M. A. *Top Catal.* **2008**, *48*, 60.
- (51) Dyson, P. J. *Dalton Trans.* **2003**, 2964.
- (52) Bayram, E.; Zahmakiran, M.; Özkaz, S.; Finke, R. G. *Langmuir* **2010**, *26*, 12455.
- (53) Weddle, A. S.; Aiken, J. D.; Finke, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 5653.
- (54) Muetterties, E. L.; Bleeke, J. R. *Acc. Chem. Res.* **1979**, *12*, 324.
- (55) (a) Hagen, C. M.; Widegren, J. A.; Maitlis, P. M.; Finke, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 4423. (b) Hagen, C. M.; Vieille-Petit, L.; Laurenczy, G.; Süß-Fink, G.; Finke, R. G. *Organometallics* **2005**, *24*, 1819.
- (56) Dobereiner, G.; Nova, A.; Schley, N.; Hazari, N.; Miller, S.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7547 and refs cited therein.
- (57) Abley, P.; McQuillin, F. J. *J. Chem. Soc., C* **1971**, 844.
- (58) (a) Izumi, Y. *Angew. Chem., Int. Ed.* **1971**, *10*, 871. (b) Akabori, S.; Izumi, Y.; Fujii, Y.; Sakurai, S. *Nature* **1956**, *178*, 323.
- (59) Indra, A.; Doble, M.; Bhaduri, S.; Lahiri, G. K. *ACS Catal.* **2011**, *1*, 511 and refs cited therein.
- (60) Bönemann, H.; Braun, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1992.
- (61) Watzky, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 10382.
- (62) Mondloch, J. E.; Yan, X.; Finke, R. G. *J. Am. Chem. Soc.* **2009**, *131*, 6389.
- (63) (a) Besson, C.; Finney, E. E.; Finke, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 8179. (b) Besson, C.; Finney, E. E.; Finke, R. G. *Chem. Mater.* **2005**, *17*, 4925. (c) Finney, E. E.; Finke, R. G. *Chem. Mater.* **2008**, *20*, 1956. (d) Finney, E. E.; Finke, R. G. *Chem. Mater.* **2009**, *21*, 4468.
- (64) Aiken, J. D.; Lin, Y.; Finke, R. G. *J. Mol. Catal., A* **1996**, *114*, 29.
- (65) (a) Finney, E. E.; Finke, R. G. *Chem. Mater.* **2008**, *20*, 1956. (b) Finney, E. E.; Finke, R. G. *Chem. Mater.* **2010**, *22*, 2687 and refs cited therein.
- (66) Widegren, J. A.; Aiken, J. D.; Özkaz, S.; Finke, R. G. *Chem. Mater.* **2001**, *13*, 312.
- (67) Miller, T. M.; Izumi, A. N.; Shih, Y.-S.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 3146.
- (68) Finney, E. E.; Finke, R. G. *Inorg. Chim. Acta* **2006**, *359*, 2879.



- (69) Alley, W. M.; Hamdemir, I. K.; Wang, Q.; Frenkel, A. I.; Li, L.; Yang, J. C.; Menard, L. D.; Nuzzo, R. G.; Özkaz, S.; Johnson, K. A.; Finke, R. G. *Inorg. Chem.* **2010**, *49*, 8131.
- (70) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
- (71) Jeffery, T. *Chem. Commun.* **1984**, 1287.
- (72) Kiwi, J.; Grätzel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7214.
- (73) Reetz, M. T.; Helbig, W.; Quaiser, S. A.; Stimming, U.; Breuer, N.; Vogel, R. *Science* **1995**, *267*, 367.
- (74) Reetz, M. T.; Winter, M.; Breinbauer, R.; Thurn-Albrecht, T.; Vogel, W. *Chem.—Eur. J.* **2001**, *7*, 1084.
- (75) Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921.
- (76) Rocaboy, C.; Gladysz, J. A. *New J. Chem.* **2003**, *27*, 39.
- (77) Zhang, B.; Zhang, W.; Su, D. S. *ChemCatChem* **2011**, *3*, 965.
- (78) Pecora, R. *J. Nanoparticle Res.* **2000**, *2*, 123.
- (79) Lewis, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 743.
- (80) Lewis, L. N.; Lewis, N. J. *Am. Chem. Soc.* **1986**, *108*, 7228.
- (81) Bradley, J. S.; Hill, E. W.; Behal, S.; Klein, C.; Duteil, A.; Chaudret, B. *Chem. Mater.* **1992**, *4*, 1234.
- (82) Fulton, J. L.; Linehan, J. C.; Autrey, T.; Balasubramanian, M.; Chen, Y.; Szymczak, N. K. *J. Am. Chem. Soc.* **2007**, *129*, 11936.
- (83) Jadzinsky, P. D.; Calero, G.; Ackerson, C. J.; Bushnell, D. A.; Kornberg, R. D. *Science* **2007**, *318*, 430.
- (84) Benedict, J. B.; Coppens, P. *J. Am. Chem. Soc.* **2010**, *132*, 2938.
- (85) Steunou, N.; Kickelbick, G.; Boubekeur, K.; Sanchez, C. *Dalton Trans.* **1999**, 3653.
- (86) Paal, C.; Hartmann, W. *Chem. Ber.* **1918**, *51*, 711.
- (87) Pease, R. N.; Stewart, L. *J. Am. Chem. Soc.* **1925**, *47*, 1235.
- (88) Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J. P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819.
- (89) Georgiades, G. C.; Sermon, P. A. *Chem. Commun.* **1985**, 975.
- (90) Clark, T. J.; Jaska, C. A.; Turak, A.; Lough, A. J.; Lu, Z. H.; Manners, I. *Inorg. Chem.* **2007**, *46*, 7394.
- (91) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem.* **2003**, *68*, 1177.
- (92) (a) Yu, K.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161. (b) Jones, C. W.; Richardson, J. M. In *Catalysis of Organic Reactions*; Prunier, M. L., Ed.; CRC Press: Boca Raton, FL, 2009; pp 193–202. (c) Jones, C. W. *Top. Catal.* **2010**, *53*, 942. (d) Huang, L.; Ang, T. P.; Wang, Z.; Tan, J.; Chen, J.; Wong, P. K. *Inorg. Chem.* **2011**, *50*, 2094. (e) Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *46*, 1865.
- (93) Sommer, W. J.; Yu, K.; Sears, J. S.; Ji, Y.; Zheng, X.; Davis, R. J.; Sherrill, C. D.; Jones, C. W.; Weck, M. *Organometallics* **2005**, *24*, 4351.
- (94) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. *Adv. Synth. Catal.* **2005**, *347*, 172.
- (95) Hornstein, B. J.; Aiken, J. D.; Finke, R. G. *Inorg. Chem.* **2002**, *41*, 1625.
- (96) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112.
- (97) Paneth, F.; Hofeditz, W. *Chem. Ber.* **1920**, *62*, 1335.
- (98) Collman, J. P.; Kosydar, K. M.; Bressan, M.; Lamanna, W.; Garrett, T. *J. Am. Chem. Soc.* **1984**, *106*, 2569.
- (99) Hori, M.; Gravert, D. J.; Wentworth, P., Jr.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2363.
- (100) (a) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (b) Shmidt, A. F.; Mametova, L. V. *Kinet. Catal.* **1996**, *37*, 406.
- (101) (a) Richardson, J. M.; Jones, C. W. *J. Catal.* **2007**, *251*, 80. (b) Webb, J. D.; MacQuarrie, S.; McEleney, K.; Crudden, C. M. *J. Catal.* **2007**, *252*, 97.
- (102) Biffis, A.; Zecca, M.; Basato, M. *Eur. J. Inorg. Chem.* **2001**, 1131.
- (103) Conlon, D. A.; Pipik, B.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R., Jr.; Izzo, B.; Collins, P.; Ho, G.-J.; Williams, M.; Shi, Y.-J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931.
- (104) Yu, K.; Sommer, W.; Weck, M.; Jones, C. W. *J. Catal.* **2004**, *226*, 101.
- (105) Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485.
- (106) (a) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412. (b) Inasaki, T.; Ueno, M.; Miyamoto, S.; Kobayashi, S. *Synlett* **2007**, 3209.
- (107) Gaikwad, A. V.; Holuigue, A.; Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Chem.—Eur. J.* **2007**, *13*, 6908.
- (108) Lempers, H. E. B.; Sheldon, R. A. *J. Catal.* **1998**, *175*, 62.
- (109) Jaska, C. A.; Manners, I. *J. Am. Chem. Soc.* **2004**, *126*, 9776.
- (110) Zahmakiran, M.; Özkaz, S. *Inorg. Chem.* **2009**, *48*, 8955.
- (111) Andrews, S. P.; Stepan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.* **2005**, *347*, 647.
- (112) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds*; Academic Press: New York, 1981.
- (113) Meunier, B., Ed. *Biomimetic oxidations catalyzed by transition metal complexes*; Imperial College Press: London, 2000.
- (114) Griffith, W. P. *Ruthenium Oxidation Complexes*; Springer: Dordrecht, The Netherlands, 2011.
- (115) Meyer, F.; Limberg, C. *Organometallic Oxidation Catalysis*; Springer: Berlin, 2007.
- (116) Hughes, M. D.; Xu, Y. J.; Jenkins, P.; McMorn, P.; Landon, P.; Enache, D. I.; Carley, A. F.; Attard, G. A.; Hutchings, G. J.; King, F.; Stitt, E. H.; Johnston, P.; Griffin, K.; Kiely, C. J. *Nature* **2005**, *437*, 1132.
- (117) Tian, N.; Zhou, Z. Y.; Sun, S. G.; Ding, Y.; Wang, Z. L. *Science* **2007**, *316*, 732.
- (118) Avelino, C.; Hermenegildo, G. *Chem. Soc. Rev.* **2008**, *37*, 2096.
- (119) Shiju, N. R.; Gulianti, V. V. *Appl. Catal., A* **2009**, *356*, 1.
- (120) Ruttiger, W.; Dismukes, G. C. *Chem. Rev.* **1997**, *97*, 1.
- (121) Geletii, Y. V.; Yin, Q. S.; Hou, Y.; Huang, Z. Q.; Ma, H. Y.; Song, J.; Besson, C.; Luo, Z.; Cao, R.; O'Halloran, K.; Zhu, G. B.; Zhao, C. C.; Vickers, J. W.; Ding, Y.; Mohebbi, S.; Kuznetsov, A. E.; Musaev, D. G.; Lian, T. Q.; Hill, C. L. *Israel J. Chem.* **2011**, *51*, 238.
- (122) Ruettinger, W.; Yagi, M.; Wolf, K.; Bernasek, S.; Dismukes, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 10353.
- (123) Hocking, R. K.; Brimblecombe, R.; Chang, L.-Y.; Singh, A.; Cheah, M. H.; Glover, C.; Casey, W. H.; Spiccia, L. *Nature Chem.* **2011**, *3*, 461.
- (124) Brimblecombe, R.; Koo, A.; Dismukes, G. C.; Swiegers, G. F.; Spiccia, L. *J. Am. Chem. Soc.* **2010**, *132*, 2892 and refs cited therein.
- (125) Young, K. J.; Gao, Y.; Brudvig, G. W. *Aust. J. Chem.* **2011**, *64*, 1.
- (126) Kanan, M. W.; Surendranath, Y.; Nocera, D. G. *Chem. Soc. Rev.* **2009**, *38*, 109.
- (127) Ginzburg, S. I.; Yuz'ko, M. I. *Russ. J. Inorg. Chem.* **1965**, *10*, 444.
- (128) McDaniel, N. D.; Coughlin, F. J.; Tinker, L. L.; Bernhard, S. *J. Am. Chem. Soc.* **2008**, *130*, 210.
- (129) Savini, A.; Bellachioma, G.; Ciancaleoni, G.; Zuccaccia, C.; Zuccaccia, D.; Macchioni, A. *Chem. Commun.* **2010**, 9218.
- (130) (a) Blakemore, J. D.; Schley, N. D.; Olack, G.; Incarvito, C. D.; Brudvig, G. W.; Crabtree, R. H. *Chem. Sci.* **2011**, *2*, 94. (b) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301.
- (131) Schley, N. D.; Blakemore, J. D.; Subbaiyan, N. K.; Incarvito, C. D.; D'Souza, F.; Crabtree, R. H.; Brudvig, G. W. *J. Am. Chem. Soc.* **2011**, *133*, 10473.
- (132) Nakagawa, T.; Beasley, C. A.; Murray, R. W. *J. Phys. Chem. C* **2009**, *113*, 12958. Nakagawa, T.; Bjorge, N. S.; Murray, R. W. *J. Am. Chem. Soc.* **2009**, *131*, 15578.
- (133) Yagi, M.; Tomita, E.; Sakita, S.; Kuwabara, T.; Nagai, K. *J. Phys. Chem. B* **2005**, *109*, 21489.
- (134) Hettterscheid, D. G. H.; Reek, J. H. N. *Chem. Commun.* **2011**, 2712.
- (135) Marquet, N.; Gärtner, F.; Losse, S.; Pohl, M.-M.; Junge, H.; Beller, M. *ChemSusChem* **2011**, DOI: 10.1002/cssc.201100217.
- (136) Zhou, M.; Schley, N. D.; Crabtree, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 12550.
- (137) Aschwanden, L.; Mallat, T.; Grunwaldt, J. D.; Krumeich, F.; Baiker, A. *J. Mol. Catal., A* **2009**, *300*, 111.
- (138) (a) Yin, Q.; Tan, J. M.; Besson, C.; Geletii, Y. V.; Musaev, D. G.; Kuznetsov, A. E.; Luo, Z.; Hardcastle, K. I.; Hill, C. L. *Science* **2010**, *328*, 342. (b) Kanan, M. W.; Nocera, D. G. *Science* **2008**,

- 321, 1072. (c) Stracke, J. J.; Finke, R. G. *J. Am. Chem. Soc.* **2011**, *133*, 14872.
- (139) Glasnov, T. N.; Findenig, S.; Kappe, C. O. *Chem.—Eur. J.* **2009**, *15*, 1001.
- (140) de Vries, J. G. *Dalton Trans.* **2006**, 421.
- (141) (a) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 3298. (b) Köhler, K.; Heidenreich, R. A.; Soomro, S. S.; Pröckl, S. S. *Adv. Synth. Catal.* **2008**, *350*, 2930.
- (142) Yang, Y. W.; Unsworth, L. D.; Semagina, N. J. *Catal.* **2011**, *281*, 137.
- (143) Granados, M. L.; Alonso, D. M.; Sadaba, I.; Mariscal, R.; Ocon, P. *Appl. Catal., B* **2009**, *89*, 265.
- (144) Lui, H.; Wang, Q.; Jiang, D.; Li, X.; Han, M. *J. Mol. Catal., A* **1997**, *118*, 145.
- (145) Rohr, M.; Grunwaldt, J. D.; Baiker, A. *J. Catal.* **2005**, *229*, 144.
- (146) Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319.
- (147) Dwyer, M. A.; Looger, L. L.; Hellinga, H. W. *Science* **2008**, *319*, 569.
- (148) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
- (149) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559.
- (150) Bolm, C.; Gladysz, J. A. *Chem. Rev.* **2003**, *103*, 2761.
- (151) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.
- (152) (a) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407. (b) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.
- (153) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.
- (154) Gonda, Z.; Tolnai, G. L.; Novák, Z. *Chem.—Eur. J.* **2010**, *16*, 11822.
- (155) Fors, B. P.; Buchwald, S. L. *Adv. Synth. Catal.* **2010**, *352*, 3119.
- (156) Crow, J. M. *Chem World*; Royal Society of Chemistry: Cambridge, UK, 2011; p 46.
- (157) González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536.
- (158) Lauterbach, T.; Livendahl, M.; Rosellon, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006.
- (159) Corma, A.; Juárez, R.; Boronat, M.; Sanchez, F.; Iglesias, M.; Garcia, H. *Chem. Commun.* **2011**, *47*, 1446.
- (160) Kanuru, V. K.; Kyriakou, G.; Beaumont, S. K.; Papageorgiou, A. C.; Watson, D. J.; Lambert, R. M. *J. Am. Chem. Soc.* **2010**, *132*, 8081.
- (161) Kyriakou, G.; Beaumont, S. K.; Humphrey, S. M.; Antonetti, C.; Lambert, R. M. *ChemCatChem* **2010**, *2*, 1444.
- (162) Gruber, A. S.; Pozebon, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2001**, *42*, 7345.
- (163) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118.
- (164) Sepa, D. B.; Damjanovic, A.; Bockris, J. O'M. *Electrochim. Acta* **1967**, *12*, 746.
- (165) Bockris, J. O'M.; McHardy, J. J. *Electrochem. Soc.* **1973**, 61.
- (166) Banks, C.; Crossley, A.; Salter, C.; Wilkins, S. J.; Compton, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2533.
- (167) (a) Pumera, M.; Iwai, H. *Chem. Asian J.* **2009**, *4*, 554. (b) Pumera, M.; Hidai, H. *J. Phys. Chem. C* **2009**, *113*, 4401. (c) Pumera, M.; Iwai, H.; Miyahara, Y. *ChemPhysChem* **2009**, *10*, 1770.
- (168) Ambrosi, A.; Pumera, M. *Chem.—Eur. J.* **2010**, *16*, 10946.
- (169) Stuart, E. J. E.; Pumera, M. *Chem. Asian J.* **2011**, *6*, 1019.
- (170) Ge, C. C.; Li, W.; Li, Y. F.; Li, B.; Du, J. F.; Qiu, Y.; Liu, Y.; Gao, Y. X.; Chai, Z. F.; Chen, C. Y. *J. Nanosci. Nanotechnol.* **2011**, *11*, 2389.
- (171) Rosenberg, B. *Platinum Metals Rev.* **1973**, *15*, 42.