



Report on NSF SusChem Workshop and American Chemical Society Symposium

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I. Executive Summary. The NSF SusChem Workshop on Base Metal Catalysis was held in conjunction with a two-day symposium at the 246th National Meeting of the American Chemical Society in Indianapolis, Indiana. The motivation for these events was the recognition that base metal catalysis is an essential component and driver of sustainable chemistry. Catalysis research occurs in many places and with many objectives – the chemical industry, academia, and national laboratories are all home to catalysis research with emphasis on applications ranging from medicines to commodity to materials to energy. The combined event explored contemporary and emerging challenges as well as presented the most recent research findings. Together important areas for future growth in research, outreach, education, and collaboration were identified. For this Workshop, the emphasis was placed on homogenous catalysis with specific emphasis on applications to organic chemistry and fine and commodity chemical synthesis.

II. Background. In the developed world, modern society enjoys unprecedented levels of comfort and convenience enabled by access to medical treatment and prevention, efficient global travel, an abundance of food and energy, and rapid access to information. Catalysis underpins many, if not all, of these technological innovations by providing the new materials, reaction chemistry, and other required building blocks.¹ As global population continues to surge, demands on natural resources and environmental concerns increase, society's dependence on catalysis will also increase.

Because catalysis is a key component of sustainable chemistry it is therefore important to ask – “Is all catalysis as sustainable as possible?” The answer to this question is multifaceted and encompasses issues such as: the availability of elements that required to make the catalyst, catalyst lifetime, durability and recyclability, as well as perhaps less obvious features such as the environmental footprint associated with catalyst preparation and disposal. A workshop to enhance community discussion on the important issue of – base metal catalysis was deemed both timely and important. The National Science Foundation (NSF) sponsored this Workshop in conjunction with an American Chemical Society (ACS) Symposium at the 2013 National Meeting on Base Metal Catalysis.

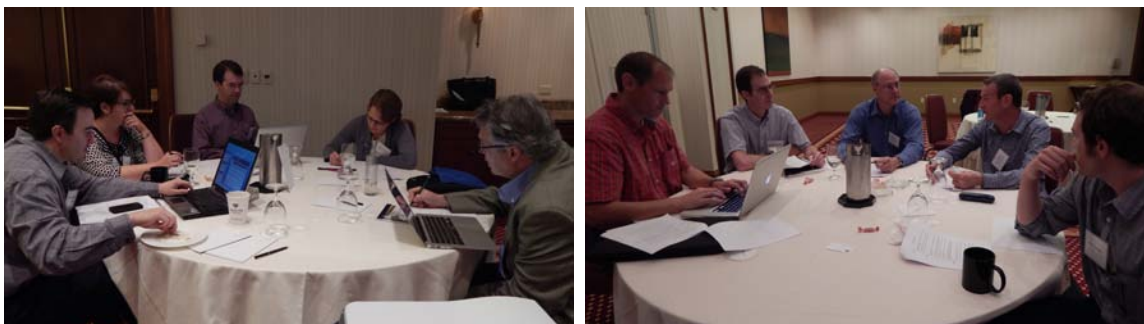


Figure 1. Discussions taking place during breakout sessions during the NSF Workshop on Base Metal Catalysis.

III. Base Metal Catalysis Overview: Opportunities and Impacts.

At outset, it is useful to define what constitutes a base metal. Other important guiding questions include:

- (i) Are all base metals equal in terms of sustainability, toxicity, and environmental compatibility?
- (ii) What metrics are available to distinguish these properties?
- (iii) Are the metrics the same for each application? Why or why not?

Figure 2 presents data on the terrestrial abundance of various elements. As anticipated, first row transition metals such as Ti, Mn and Fe are geologically abundant, found in rock formations. The so-called “precious metals” – Os, Ir, Pd, Pt, Rh, Ru and Au live up to their moniker, being some of the rarest elements in Nature. The data in Figure 2 also establish that among first row metals, some are more abundant than others. Titanium, manganese, and iron are more terrestrially available than nickel and copper. It is also important to note that some metals outside the first row, particularly molybdenum and tungsten, are widely available and may also be considered base metals.

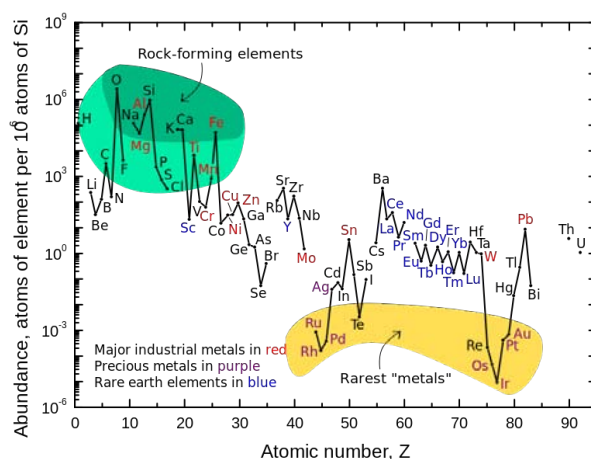


Figure 2. Relative abundance of various elements, including precious and base metals. Taken from: <http://pubs.usgs.gov/fs/2002/fs087-02/>

There is more to base metal catalysis than terrestrial abundance and cost. Table 1 presents data compiled by the pharmaceutical industry comparing the cost, natural abundance, relative toxicity, and carbon footprint of Pd, Ni, Cu and Fe. These metals were selected due to their

widespread utility in catalytic cross coupling.^{2,3,4,5} Not surprisingly, the natural abundance and annual production correlates with cost where the most produced metals have the lowest cost and vice versa. One of the most notable features of the data in Table 1 is the CO₂ footprint associated with each metal. Harvesting metals that are scarcer often results in the use of fossil fuels and generated CO₂ emissions. Of the precious metals, palladium is relatively abundant. Other precious metals such as platinum, rhodium, and iridium are much more scarce in the Earth's crust and their extraction footprint is expected to be considerably larger. Currently, 1 ounce of pure platinum requires extraction of between 10 and 40 tons of raw ore at a depth of up to one mile in the Earth's crust.⁶ This environmental footprint is rarely considered when the sustainability of a given catalyst is evaluated.

Table 1. Metrics comparing the cost, natural abundance, production, oral toxicity, supply risk index, and carbon dioxide footprint of palladium, nickel, copper, and iron.

Metal	Cost (\$/t oz) ^a	Natural Abundance (ppm) ^b	Annual Production (tonnes) ^c	Oral Exposure Limits (ppm) ^d	Supply Risk Index ^{b,e}	CO ₂ Footprint ^f
Pd	746	0.015	24	10	8.5	6649
Ni	0.44	90	1,350,000	25	4.0	7.1
Cu	0.23	68	15,000,000	250	4.5	1.2-3.4
Fe	0.005	56,300	1,200,000,000	1300	3.5	1

^a Metal prices correspond to commodity prices. All prices (\$/troy ounce) from Aug 29, 2013 are taken from <http://www.metalprices.com/dailyexchangedata/Index>. ^b British Geological Survey: Risk List 2011” <http://www.bgs.ac.uk/downloads/start.cfm?id=2063>. ^c Annual 2006 Production accessed Aug 28, 2013: <http://www.worldofwallstreet.us/metals-annual-production-.html> ^d Specific limits for residues of metals (Aug 29, 2013) at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003586.pdf. ^e Supply risk index calculated based on scarcity, production concentration, reserve base distribution, and governance. For details, see footnote b. ^f A carbon dioxide footprint has historically been defined as "the total set of [greenhouse gas](#) (GHG) emissions caused by an organization, event, product or person."

A. Transformations of Interest for Base Metal Catalysis. One of the principal issues in the field is whether all reactions are in need of a base metal catalyst. If not, what are the metrics to make such a determination? Alternatively, is it possible for a precious metal catalyzed reaction to be sustainable? The concept of “distribution entropy” was introduced as a useful guiding principle to evaluate the necessity and potential impact of using a base metal alternative in a given chemical process. This term is a metric associated with catalyst recovery. Heterogeneous reactions conducted in flow over fixed bed catalysts that have minimal metal leaching are an example having low distribution entropy while those such as the crosslinking of silicones where the catalyst is trapped in the product and is not recovered have a high distribution entropy.

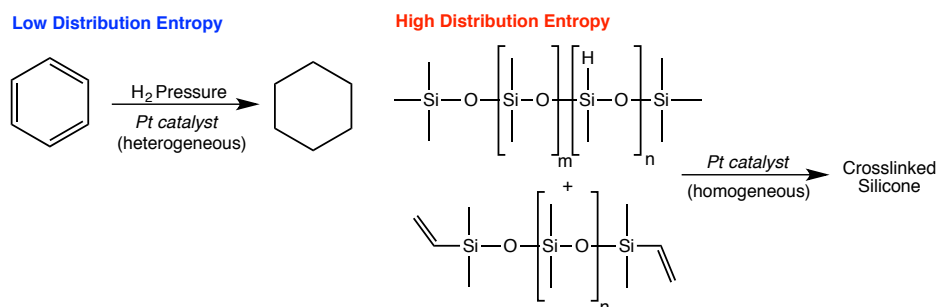


Figure 3. Platinum catalyzed reactions with low and high distribution entropy.

In this context, several reactions and processes were suggested by the Workshop participants as potentially benefitting substantially from base metal catalysis. Transition metal catalyzed cross coupling reactions were identified as a particularly impactful target due to their high volume and impact in the pharmaceutical industry.⁷ Other transformations were discussed and included alkene reductions such as olefin hydrogenation and hydrosilylation, the asymmetric hydrogenation of ketones to provide more value-added alcohols, and the cleavage of C-O bonds that are at the core of biomass processing. Oxidation reactions also present significant opportunities for base metal catalysis. Alkene dihydroxylation, typically performed with OsO₄, various C-H functionalization methods and methods to mimic selective biological pathways are also promising areas for reduction in precious metals usage. The potential impact of base metal catalysis was also deemed high for large scale, high volume processes typically involved in commodity chemical production. Processes such as hydrogen production for ammonia synthesis, fuel cell electrocatalysis, and emission abatement in catalytic converters were identified as areas of particular need, however the expertise of the workshop participants in these areas was somewhat limited, precluding additional discussion on these topics.

Alkene hydroformylation was discussed as a specific example of a process illustrating the potential complexities associated with identifying the need for base metal catalysis. This reaction is one of the largest scale applications of homogeneous catalysis and finds application in the commercial manufacture of soaps and detergents from commodity terminal olefins. Although the early technology utilized cobalt,⁸ catalyst evolution and improvement has resulted in the development of rhodium compounds that exhibit improved lifetime, selectivity, and activity.⁹ The consensus among the hydroformylation community is that the loadings of the precious metal are sufficiently low, and the rhodium catalyst is suitably robust, that replacement or a return to a base metal is low priority. In these reactions, the catalyst is often recycled suggesting low catalyst distribution entropy. However, return on yield, the energy intensity and inputs, and CO₂ footprint must also be presented with the recovery data in order to make informed decisions on the true need for precious metal catalysts.

The advent of a shale gas domestic energy economy (rather than a petroleum-based economy) is also another potential area of opportunity and growth for base metal catalysis. Inexpensive natural gas is expected to increase the supply of ethylene beyond current commercial polymerization capabilities.¹⁰ A growing frontier for sustainable chemistry will be to expand the number of efficient uses of this hydrocarbon feedstock. First row transition metals such as chromium have been developed for the selective tri- and tetramerization of ethylene to 1-hexene and 1-octene, respectively.¹¹ Other base metals could be explored not only for selective oligomerization reactivity but also for other transformations such as selective oxidation, carbonylation, and carboxylation. Like ethylene, the selective catalytic conversion of methane

into more value-added hydrocarbons and other products, represents a long-standing challenge. The unique properties of base metals may enable new reactivities that have not been discovered due to the traditional reliance on precious metal organometallic compounds.

B. New Opportunities Enabled by Base Metal Catalysis. The one-electron redox chemistry and variable oxidation states available to first row transition metals are often cited as a challenge for promoting catalytic chemistry with these elements.¹² Can these properties be harnessed to enable new chemical reactivities not yet observed with traditional precious metal catalysts? The discovery of new chemistries alleviates comparisons to existing precious metal catalysts, as the route to the desired product is unique. Radical-initiated polymerizations were identified by the Workshop participants as an area of opportunity as were C-H functionalization reactions using sp^3 -hybridized centers as base metal catalysts may impart unique selectivities. For the latter class of reactions, metalloenzymes may serve as guiding inspiration.

Selective oxidations, particularly alkene dihydroxylations, epoxidations, and transformations involving carbon-carbon bonds also present new opportunities for high impact, base metal catalysis. Some successful oxidations have been reported with biomimetic iron complexes.¹³ Small molecule activation reactions such as CO_2 and N_2 functionalization and reduction were also identified as potential new areas for base metal catalysis. As examples of iron-catalyzed hydrogenation to formic acid and reduction of N_2 to ammonia have been recently reported in the literature and the iron-catalyzed Haber-Bosch process has been utilized for over a century, controlled radical chemistry may also enable new routes to using CO_2 and N_2 as building blocks for more value-added organic molecules.

The electronic structures of base metal catalysts also offer the opportunity to enhance existing transformations by new mechanistic pathways. This advantage may, in turn, result in unprecedented selectivities, orthogonal reactivities or expansion of substrate scope beyond what is currently possible with existing precious metal technologies. There was considerable interest from the Workshop participants in developing cross-coupling reactions for the assembly of C-F and other heteroatom-type bonds. Such reactivity may be enhanced by radical type chemistry of the first row transition metals and competing reactions, such as β -hydrogen elimination, may be less problematic.

Tandem reactions were also identified as a potential new opportunity for base metal catalysis. The orthogonal properties of first row metals versus heavier second and third row congeners may allow catalysts to work in concert, enabling new bond constructions and allowing assembly of molecules with a high degree of complexity. First row transition metals are typically “hard” metal ions and likely prefer hard ligands whereas second and third row congeners are softer. These differences in coordination preferences may allow two different catalysts to work in concert, avoiding interference, and possibly enabling multiple bond constructions in a complex environment. Such processes are seen to be valuable in broadening the exploration of known chemical space beyond the existing 0.1% level.¹⁴

C. Metrics for Successful Base Metal Catalyzed Reactions. Base metal catalysis shares many of the metrics such as high activity, turnover frequency, lifetime, thermal stability, recoverability, etc., that are common across the broader field of catalysis. Properties unique to base metals that should gain more attention are the potential reduced environmental and carbon footprints associated with extraction, purification, and disposal of the metal. One challenge is accessing data of this type and having a broader community of chemists appreciate the “hidden”

costs associated with the precious metals. A small sampling of such data is presented Table 1 but there is considerable room for expansion and improvement. It is often assumed that for established reactions such as cross coupling, asymmetric hydrogenation, or olefin metathesis, all of the problems associated with catalyst development are solved. This naïve view must be overcome and cases where base metals expand substrate scope have been reported. Selected examples were presented in the ACS Symposium (*vide infra*).

Challenges particularly relevant to improving base metal catalysis are functional group tolerance and catalyst stability. Currently, precious metal catalysts are more user friendly than base metal catalysts. For example, an array of bench-stable precious metal catalyst precursors are available and allow exploration of reactivity. Development of precatalysts that are straightforward to handle will be required for broad implementation of base metal catalysts, and represents a major frontier for future research. It is important to note that if base metal alternatives are fragile, they in turn become “more expensive” than established precious metal catalysts and barriers to implementation will be high.

IV. New Challenges Associated with Base Metals. First row transition metals present a rich coordination chemistry largely enabled by the array of oxidation states available by kinetically and thermodynamically accessible one-electron redox changes. While this is an opportunity for synthesis and electronic structure determination, it is nevertheless a significant challenge for characterization. This area was addressed through both breakout sessions and panel discussion at the workshop. For those trained to deal with more traditional diamagnetic organic or organometallic compounds, working with paramagnetic molecules can be intimidating. The challenge is therefore both technical and pedagogical. Many techniques such as EPR, paramagnetic NMR, Mössbauer and X-ray absorption and Emission spectroscopies are available to characterize these compounds yet many researchers not trained in physical inorganic chemistry are not familiar with them. To compound matters, many universities and industrial labs do not have EPR or Mössbauer facilities, requiring collaboration and sample shipping. There is a tremendous opportunity to bring this instrumentation into more widespread use. Instrument purchase is one obvious solution, other more subtle methods are those that provide networks and incentives for collaboration and funds for students and postdocs to travel to collaborators’ laboratories to learn new techniques and make measurements.

Accessible pedagogical materials for learning these techniques and analyzing data associated with odd electron species or one electron transfers are lacking. These techniques are often not part of the standard curriculum for undergraduate and graduate students and many synthetic chemists simply lack exposure and education. Areas for growth and broader impacts include preparation of websites and instructional videos and even workshops to familiarize a broader cross section of chemists with these techniques. A more systematic way to identify collaborators was also noted as being needed, especially for techniques like X-ray Absorption Spectroscopy (XAS) and X-ray Emission Spectroscopy (XES) that require synchrotron radiation. The facilitation of a “collaboration matrix” to seed interactions between collaborators and their students would be a benefit to the community.

Another important area related to characterization somewhat unique to base metal catalysis is the detection of precious metal impurities. Palladium, for example is well known to be extremely active for certain classes of cross coupling reactions; likewise rhodium and iridium operate effectively at parts-per-million level concentrations in asymmetric hydrogenation of certain substrates. Attention must therefore be paid to establishing that the base metal catalyst is

indeed the active catalyst. Atomic absorption and inductively coupled plasma spectroscopies are established methods for detecting sub-parts per million concentrations of virtually any element. These techniques alone are insufficient; reproducibility from batch to batch of catalyst should also be reported.

V. Base Metal Catalysis: An Industrial Perspective. An industrial perspective was provided by the second panel discussion and was valuable for placing many of the issues relevant to base metal catalysis into a practical context. Each industrial panelist was asked to use the following three questions to frame the discussion:

- (i) *What do you see as the top 5 (or so) challenges in applying base metal catalysts?*
- (ii) *What is different between academics and industry?*
- (iii) *What would you, as an industrial chemist, like your academic colleagues to know that might surprise them?*

Several challenges were identified that serve as important targets and metrics for the development of base metal catalysts. To date, the selectivity, scope, and generality of first row metal catalysts lag behind their precious metal counterparts to the point where most chemists are not willing to explore or adopt them. It is therefore key to develop a synthetic rather than cost or environmental incentive as the driver to the use and widespread adoption of new base metal catalysts. If such compounds offer unique selectivity, complementary reactivity, or altogether new transformations then interest in using base metals in catalysis will increase and possibly supplant precious metals. Reactions that have a low impurity profile are also attractive and as base metal catalysts can be discovered that minimize side products, this too will offer an advantage over precious metal catalysts.

Chemistry that is recognized as established often has limitations that are not well articulated in the literature. In the case of palladium catalyzed cross coupling, for example, failure rates as high as 20-60% were cited by the industrial panelists representing the medicinal chemistry community. It was suggested that publications on new catalytic methods, either precious or base metal-based, identify the limitations of the method, as well as attempt to explore substrates that more accurately mimic the functional group density encountered in typical medicinal chemistry molecules. Along these lines, claims to functional group tolerance are often restricted to a single example. It was recommended that publications recognize the importance and potential impact of follow-up studies that expand the substrate scope of previously reported reactions.

Methods for the discovery of base metal catalysts are also less developed than those now well established for heavy transition metal based catalysis and therefore, present a barrier for adoption. High throughput experimentation is now commonplace but requires reproducible and high yielding reactions to be practical and accessible. Key to this technology is the availability of precursors. In precious metal catalysis, there are excellent and widely adopted rhodium, iridium and palladium precursors that are commercially available. These precursors undergo predictable, well-established coordination chemistry that, in turn, allows rapid evaluation of libraries of ligands and associated reaction optimization. In base metal catalysis, the precursor options are fewer and evaluation of ligand libraries and reaction optimization is less mature. There is considerable opportunity for the exploration and understanding of fundamental coordination chemistry to discover base metal catalyst precursors that can be widely adopted. Ease of synthesis and air stability are both important design criteria.

In addition to scientific issues, the industrial panel also addressed important aspects of collaboration between academia and industry. The industrial scientists agreed that in general, industry is interested in collaboration and can offer academicians access to more practical insight, advanced technology, and unique opportunities for student and postdoctoral training. Key aspects to optimizing these interactions are negotiable intellectual property positions from both the academic and industrial partners. Working in so-called “pre-competitive space”, free of any restrictions, was deemed to be the most straightforward path forward even though it is not likely to be broadly acceptable to most universities or companies.

VI. Broader Impacts and Opportunities for Outreach. In addition to technological needs, the Workshop participants identified several opportunities for broader impacts and outreach. Many of the broader impacts of base metal catalysis are immediate: replacing precious metal catalysts with more abundant base metal variants would enable more sustainable chemical processes and provide greater domestic security for natural resources by reducing reliance on foreign sources for “conflict elements”.

As mentioned in previous sections there is considerable need for pedagogical tools in all aspects of base metal catalysis. The field is broad and requires expertise across disciplines. The creation of pedagogical resources in the form of review articles, online tutorials and books that are accessible to those with diverse backgrounds is an area of need. An online tutorial, the webPCET maintained by Professor Hammes-Schiffer, was presented as an example.¹⁵

VII. The Outlook for Base Metal Catalysis.

The final sessions of the workshop focused on developing a more general outlook for base metal catalysis. The first group of questions, shown below, focused on defining metrics for establishing successful base metal catalyzed reactions and criteria for evaluation:

- (i) *What are currently the most successful base metal catalyzed reactions? Why? And what improvements could/should be made?*
- (ii) *What features (aside from terrestrial abundance) of a base metal catalyzed reactions need to be considered to maximize sustainability?*
- (iii) *What current precious metal-catalyzed processes are the least sustainable? Why?*
- (iv) *What features (aside from terrestrial abundance) of base metal catalyzed reactions need to be considered to maximize sustainability?*

Several current processes were identified as excellent examples of base metal catalyzed reactions. Most notable is the Haber-Bosch reaction for the industrial synthesis of ammonia. The original discovery required a precious metal, osmium, for N₂ hydrogenation but subsequent catalyst optimization has resulted in the currently deployed, supported iron catalyst. The activity of these catalysts is remarkable. In some cases, up to one ton of ammonia can be produced per minute! Other examples of successful base metal catalyzed reactions included methane steam reforming (Ni), the Ziegler-Natta polymerization of olefins (Ti, Zr, Cr, Ni), the cobalt-catalyzed oxo process, the Shell Higher Olefins (SHOP) process (Ni), and DuPont’s butadiene hydrocyanation with Ni. These processes were deemed successful not only because of their use of a base metal but also because of their large scale and industrial fidelity.

At the opposite end of the spectrum are reactions that were identified as the least sustainable and in greatest need for base metal catalysis. Process such as industrial silicone synthesis are particularly noteworthy, as platinum-catalyzed hydrosilylation is performed on large scale, generates waste by-products through imperfect selectivity, and has a high distribution entropy due to entrapped metal in the final product. Other processes such as OsO₄-catalyzed dihydroxylations are no longer performed on scale because of concerns about heavy metal exposure. Related transformations include the Captiva Process that currently consumes approximately three metric tons of iridium annually.¹⁶ Emerging catalytic reactions such as C-H functionalization are both exciting and promising from a synthetic standpoint, but adoption may ultimately be limited due to current reliance on iridium. There are similar concerns with rhodium-catalyzed reactions. It is estimated that 28 metric tons of rhodium are used in catalytic hydroformylation and hydrogenation reactions.

Evaluation of the sustainability of a process must be multifaceted and take into consideration numerous criteria. These issues extend beyond science and technology and include business and societal sustainability. For chemical catalysis, factors such as supply and source risks, which include reserve base distribution, the global distribution of currently untapped sources, and governance, the political stability of producing countries,¹⁷ are important for precious metals yet often not considered in life cycle analyses. As mentioned in Table 1, the carbon footprint associated with precious metal extraction and purification should also be considered. The solvent requirements for precious versus base metal catalysis may also be a factor in implementation of new catalytic processes. For example, in rhodium and iridium-catalyzed asymmetric hydrogenation reactions, dichloromethane is often required to provide synthetically useful activity and selectivity. Recent examples of base metal catalyzed reactions operate optimally in neat substrate, presenting a distinct advantage by minimizing waste. The recoverability and recyclability of base and precious metal catalysts should also be taken into account when selecting the best possible synthetic design.

The final discussion in the workshop sought to provide an outlook for base metal catalysis and was framed by the following questions:

- (i) *What lessons have we learned about applying base metal catalysts?*
- (ii) *What synthetic methods need to be developed to better enable broad implementation of base metal catalysis?*
- (iii) *What are the potential guiding principles for assessing the value of base metal catalysis research?*
- (iv) *What long-term questions remain?*

The field of base metal catalysis remains in its infancy. It is clear that base metal catalyzed reactions are highly meritorious. The challenges associated with the synthesis, mechanism, characterization, and theoretical modeling of first row transition metal complexes present new opportunities for growth and development, largely requiring new fundamental chemistry. As the field matures, there are also opportunities for new ligand development, as existing designs and libraries have largely been evolved for precious metals.

VIII. State of the Art in Base Metal Catalysis: Summary of the Presentations from the ACS Symposium.

To engage researchers at every level, from undergraduate students to faculty, workshop participants gave research presentations at the National ACS meeting at the symposium, “Non-Precious Metal Catalysts: Opportunities and Impacts.” The symposium provided conference attendees with representative snapshots of cutting edge research in base metal catalysis, exemplified by the expertise of the invited speakers. The symposium was intended to highlight a series of representative examples, and not to serve as a comprehensive summary of the field. For example, recent advances in C–H activation were not included. Throughout the symposium, the unique advantages and challenges presented by base metal catalysts were illustrated. The following is a very brief summary of the symposium presentations.



Figure 4. A selection of participants from the ACS symposium “Non-Precious Metal Catalysis: Opportunities and Impacts”.

Reductions. The enantioselective reduction of alkenes and carbonyl derivatives is a hotbed of activity in catalyst development. Early studies employing precious metal catalysts resulted in hydrogenations that revolutionized preparation of compounds in the pharmaceutical industry and were eventually awarded the 2001 Nobel Prize. In recent years, important efforts to move beyond the precious metals to base metals have been reported.¹⁸ Exciting new base metal catalyzed transfer hydrogenation reactions of carbonyl compounds were described. **Professor Morris** (University of Toronto) reported on highly enantioselective iron-catalyzed transfer hydrogenation reactions of ketones and imines.¹⁹ **Dr. Hanson** (Los Alamos National Laboratory) presented research on cobalt-catalyzed transfer hydrogenation of ketones and alkenes and dehydrogenation reactions of alcohols.²⁰ In both the Morris and Hanson systems, mechanistic evidence is consistent with Noyori-type mechanisms for the reduction of ketones, where the amine ligand cooperates in the hydrogenation step, demonstrating that precious and base metals can operate by similar mechanistic pathways. Enantioselective alkene hydrogenation is typically accomplished using chiral rhodium, iridium, or ruthenium complexes. **Professor Chirik** (Princeton University) presented research on new cobalt catalysts for highly enantioselective reduction of alkenes.²¹ A critical aspect of this work was the identification of suitable catalyst

precursors, a challenge frequently associated with the evaluation of new ligands for base metal catalysts.

Additions to electrophiles. Several exciting applications of base metals for 1,2- and 1,4-addition reactions with electrophiles were presented at the symposium. **Dr. Fandrick** (Boehringer Ingelheim Pharmaceuticals) presented research on the zinc-catalyzed diastereoselective propargylation of ketones.²² This method has been employed in large scale for the preparation of the glucocorticoid agonist BI-653048, a candidate for the treatment of rheumatoid arthritis. Use of zinc catalysts provided a more selective, as well as less toxic, alternative to use of organotin reagents. Design of transformations that take advantage of the tendency of organonickel complexes to react with unsaturated electrophiles was presented by **Professor Montgomery** (University of Michigan) and **Professor Weix** (University of Rochester). In contrast to traditional transition-metal catalyzed 1,2-addition reactions of nucleophiles, these reactions are initiated by oxidative cyclization or oxidative addition. This strategy can achieve selectivity and reactivity patterns that are unique to the base metal catalyzed reaction. They present an advantage or a complementary approach to the traditional precious metal-catalyzed transformation. Professor Weix demonstrated reductive coupling of enones with arylhalides, whereby selectivity for heterocoupling over homocoupling is governed by the rapid oxidative addition of the nickel catalyst with the enone to form MacKenzie complexes.²³ Professor Montgomery presented results on a broad range of reductive couplings of electrophiles with alkynes that are initiated by oxidative cyclization of the alkyne, electrophile, and nickel catalyst.²⁴

Cross-coupling reactions to form C–N bonds. Copper-catalyzed coupling of amines with aryl halides, the Evans-Chan-Lam reaction, provides a practical method for the synthesis of anilines. This transformation is a base metal catalyzed alternative to the popular palladium-catalyzed Buchwald-Hartwig amination reactions with the added benefit that aryl halides, instead of aryl boronic acids, are the requisite starting materials. Recent advances have continued to improve both the scope and our understanding of the mechanistic details of the reaction. **Dr. Tedrow** (Amgen) presented his research on the advances toward cross coupling of less basic nucleophiles, specifically sulfonamides, as a key reaction in a synthetic route for a lead compound for asthma treatment, AMG-853.²⁵ This application provided an opportunity to contrast the relative merits of the palladium- and copper-catalyzed coupling reactions, illustrating metrics that can be used to evaluate whether the base- or precious-metal catalyzed reaction provides the better solution to a given problem. **Professor Stahl** (University of Wisconsin) presented mechanistic experimental results that refine our understanding of the role of the copper catalyst.²⁶ These studies highlighted the mechanistic challenges associated with base metal catalysts, including determining relevant catalyst oxidation states and distinguishing organometallic reactions from outer sphere single electron transfer.

Cross coupling reactions to form C–C bonds. Cross coupling reactions, particularly palladium-catalyzed reactions to prepare biaryl linkages, have transformed the types of compounds that can be synthesized by medicinal chemists. Base metals, particularly nickel, iron, and copper, bring unique reactivity patterns that could complement those observed with palladium complexes. The discovery of such reactions is a highly active area of research. For example, nickel catalysts are considered to be highly reactive toward oxidative addition. Aryl-aryl coupling of traditionally unreactive aryl carbamates that take advantage of the increased reactivity of organonickel catalysts was described by **Professor Garg** (University of California, Los Angeles).²⁷ The factors that determine whether or not a new reaction should be considered

“green” were presented. Nickel catalysts have also shown promise for cross-coupling reactions of alkyl electrophiles. Their advantage over the corresponding palladium catalysts is attributed, in part, to an increased activity toward oxidative addition and a decreased propensity for β -hydride elimination. Other differences between nickel and palladium catalysts must also be considered in the development of such reactions. For example, the increased tendency of nickel catalysts to participate in single electron reactions have important stereochemical consequences. **Professor Jarvo** (University of California, Irvine) reported on stereospecific cross-coupling reactions of alkyl ethers and esters with Grignard and organozinc reagents.²⁸ **Professor Tilley** (University of California, Berkeley) presented the synthesis of a two-coordinate nickel(I) complex and a stoichiometric two-electron oxidative addition reaction with an alkylhalide to provide a T-shaped alkylnickel(III) complex.²⁹

Critical to the further development of base metal catalyzed cross coupling reactions are detailed studies of the mechanisms of the transformations. These studies must address the ambiguity with respect to the oxidation state of the active catalyst. **Professor Bedford** (University of Bristol) presented research on iron-catalyzed cross-coupling reactions of aryl and alkyl halides with organozinc reagents, along with evidence that supports an iron(I) active catalyst.³⁰ The importance of using experimental methods to distinguish between catalysis by homogenous organometallic complexes and iron nanoparticles was discussed by both Professor Bedford and Professor Morris and will likely remain an important theme in future catalysis research.

As we apply of base metal catalysts to ever more complicated reactions, finding catalysts with suitable activity may not be as straightforward as it might be to pull a “privileged” noble metal and known phosphine ligand off the shelf. However, these challenges can often be met by rapid and systematic evaluation of a broad range of catalysts, ligands, additives, and reaction conditions. **Dr. Tudge** (Merck Research Laboratories) illustrated that this high throughput strategy is feasible using low-tech microscale multiparallel chemistry equipment, where a single chemist can evaluate ~500 reaction conditions in a single day. Nickel-catalyzed cyanation of aryl tosylates used in the synthesis of MK-0633 required systematic evaluation of multiple reaction parameters and presented significant advances over the palladium-catalyzed method. The copper-catalyzed pyrimidine synthesis used in HIV Integrase inhibitors such as Isentress was also discovered by a high throughput approach.³¹

Materials: Synthesis of monomers and polymers. Base metal catalysts have a key role to play in synthesis of polymers for small- and large-scale applications and in conversion of biopolymers to chemical feedstocks. **Dr Weller** (Momentive Performance Materials) presented an example of a large-scale application of base metal catalysis in the synthesis of high performance materials. Automotive vehicle tires contain silicones that are prepared by hydrosilation. An iron catalyst was shown be more selective and practical for the desired hydrosilation reaction than the corresponding platinum catalyst. Another large-scale application of base metal catalysts is the Shell higher olefin process (SHOP). **Professor Zubris** (Villanova University) presented the synthesis of new nickel catalysts for ethylene polymerization. Arylation of imidoyl chlorides proceeded cleanly to generate a library of ligands where steric parameters were systematically varied.³² **Professor Ladipo** (University of Kentucky) presented methods for the conversion of renewable feedstocks, such as cellulose and glucose, to a valuable building block, 5-hydroxymethylfurfural. Such transformations often employed chromium and molybdenum based-catalysts; Professor Ladipo presented bimetallic aluminum Lewis acid catalysts.

Characterization and Theoretical Methods. Design of new catalysts requires detailed understanding of their structure so that structure-activity correlations may be identified. The traditional characterization tools, NMR spectroscopy and X-ray crystallography, may not provide assistance when paramagnetic complexes or unstable catalytic intermediates are to be examined. Furthermore, much of our chemical intuition with respect to structure and stability of organometallic complexes is based on the chemistry of noble metal complexes. **Professor Holland** (Yale University) illustrated this point by discussing the chemistry of a stable 12 electron iron(II) alkyl complex. Conventional wisdom would suggest that β -hydride elimination from this complex should be slow, based on the absence of empty d orbitals. However, β -hydride elimination was observed, and DFT calculations are consistent with spin crossover en route to the transition state.³³

Characterization of the coordination sphere and electronic structure of base metal complexes will continue be refined by the development and incorporation of new experimental and theoretical techniques. **Professor DeBeer** (Max-Planck-Institut for Chemical Energy Conversion) described the application of valence-to-core X-ray emission spectroscopy (XES) in determining the electronic structures of base metal complexes. By exciting a core electron and looking at the emission spectrum one can interpret the energy levels of the molecular orbitals and determine oxidation states that can be challenging to assign by x-ray crystallographic analysis. This method was applied to small and large molecules, including the intact nitrogenase MoFe protein.³⁴ **Professor Hammes-Schiffer** (University of Illinois, Urbana Champaign) presented her research on the theoretical methods for characterizing proton-coupled electron transfer in solar cells and metalloenzymes. The hydrogen evolution performed by the cobalt complexes was also characterized computationally to explain unexpected reactivity trends. It was found that protonation of the ligand modulates electrocatalytic activity.³⁵

Appendix I. Workshop Schedule

Schedule: Saturday September 7, 2013

Conrad Hotel, Room TBA

- | | |
|-------------|---|
| 8:30-8:40 | Welcoming Remarks, Chirik and Jarvo |
| 8:40-8:45 | NSF Remarks |
| 8:45-10:00 | Participant Introductions
Slide: "My interest in base metal catalysis is..." |
| 10:00-10:45 | Breakout I. |
| 10:45-11:00 | Coffee Break. |
| 11:00-11:30 | Breakout summary. Discussion leader: Shannon Stahl |
| 11:30-12:00 | Panel Discussion I: Spectroscopy and Theory
(Pat Holland, Serena DeBeer, Sharon Hammes-Schiffer) |
| 12:00-1:00 | Breakout II. <i>Working lunch, Conrad Hotel</i> |
| 1:00-1:15 | Breakout summary. Discussion leader: Sharon Hammes-Schiffer |
| 1:15-2:00 | Panel Discussion II: Industrial Perspectives
(Matt Tudge, Dan Fandrick, Jason Tedrow, Keith Weller) |
| 2:00-2:45 | Breakout III. |
| 2:45-3:00 | Breakout summary. Discussion leader: Jason Tedrow |
| 3:00-3:30 | Coffee Break. |
| 3:30-4:30 | Breakout IV: Summary and roadmap. |
| 4:30-5:00 | Breakout summary. Discussion leader: Deanna Zubris. |
| 5:00-5:15 | Closing Remarks, Chirik and Jarvo |
| 5:15-6:00 | Organizers meeting Appendix II. Guiding Questions for Breakout Sessions. |

Breakout I:

- (i) What current transformations would benefit the most from replacing a precious metal with a base metal and why?
- (ii) What new reactions can be enabled by the unique properties of base metals

- (iii) What are the metrics for a successful base metal catalyst?

Breakout II:

- (i) What compounds are the most difficult to characterize or observe? What are the challenges?
- (ii) What are the challenges associated with characterizing paramagnetic compounds?
- (iii) What techniques are underutilized or emerging that would be of value to those using base metal catalysts?
- (iv) What are the best pedagogical materials for new scientists seeking to learn these techniques?
- (v) Are there specific examples, especially for the non-expert, that successfully demonstrate the appropriate application of theoretical chemistry in base metal catalysis?

Breakout III:

- (i) If successfully replaced would the base metal catalysts be expected to operate by the same mechanistic pathway/catalytic cycle?
- (ii) What are the unique properties of base metals that give them advantages for new catalytic reactions?
- (iii) What are the unique properties of base metals that address sustainability?
- (iv) What are the most successful base metal catalyzed reactions? Why?
- (v) Are their precious metal reactions that are particularly unsustainable?

Breakout IV:

- (i) What synthetic methods need to be developed to better enable broad implementation of base metal catalysis?
- (ii) What lessons have we learned about applying base metal catalysis?
- (iii) What long-term questions are on the horizon?
- (iv) Can we formulate guiding principles of base metal catalysis?
- (v) Are there new opportunities for collaboration based on interdisciplinary discussions?

Appendix III: Presentations by participants during the ACS Symposium, “Non-Precious Metal Catalysts: Opportunities and Impacts”

Participant	Institution	Title of Presentation
Robin Bedford	University of Bristol	Iron catalyzed C–C bond-formation with Zn and with Group 13 nucleophiles
Paul Chirik	Princeton University	Base Metal Catalysis for Organic Synthesis: Mechanism and Applications
Serena DeBeer	Max Planck Institute for Chemical Energy Conversion	X-ray spectroscopic studies of biological catalysis
Daniel Fandrick	Boehringer-Ingelheim	Zinc and Copper Catalyzed Asymmetric Propargylations with a Propargyl Boronate
Neil Garg	University of California – Los Angeles	Development of Nickel-Catalyzed Cross-Couplings
Sharon Hammes-Schiffer	University of Illinois	Proton-coupled electron transfer mechanisms of hydrogen-producing cobalt and nickel molecular electrocatalysts
Susan Hanson	Los Alamos National Laboratory	Cobalt-Catalyzed Hydrogenation and Dehydrogenation Reactions
Patrick Holland	Yale University	Challenges and opportunities in high-spin organometallic complexes of iron and cobalt
Elizabeth Jarvo	University of California – Irvine	Mechanism-Based Design and Development of Catalyzed Reactions Stereospecific C–C Reactions
Folami Ladipo	University of Kentucky	Catalytic conversion of saccharides into 5-hydroxymethylfurfural using aluminum Lewis acid catalysts
John Montgomery	University of Michigan	Discovery and application of nickel-catalyzed couplings and cycloadditions
Robert Morris	University of Toronto	Iron Catalysts for the Asymmetric Reduction of Ketones and Imines
Shannon Stahl	University of Wisconsin	Cu-catalyzed aerobic oxidation reactions: How does a metal that undergoes one-electron redox chemistry mediate two-electron oxidation reactions with a four-electron oxidant?
Jason Tedrow	Amgen	Replacing Palladium: Development of a General Copper-Catalyzed Sulfonamide Coupling Under Mild Conditions
T. Don Tilley	University of California – Berkeley	Bond activations and catalytic transformations for organosilanes with more earth-abundant metals
Matthew Tudge	Merck	Base metal catalysis in drug development
Daniel Weix	University of Rochester	Precious reactivity from abundant metals: Nickel mediated conjugate addition, allylic substitution, and ketone synthesis

Keith Weller	Momentive	Highly RegioSelective Bis(imino)pyridine Iron Catalysts for the Hydrosilylation of 1,2,4-Trivinylcyclohexane
Deanna Zubris	Villanova University	Structural analysis of mono(imino)pyridine ligands for Ni(II): Precatalysts for the oligomerization of ethylene

Evening poster session

E. Jarvo, P. Chirik, *Organizers*

6:00 - 8:00

- . Chemical transformations of alkene and alkyne using tungstic acid as a catalyst: kinetics and reactions mechanisms. **A. Alothman**, A. Apblett
- . Mechanistic studies of catalytic aerobic alcohol oxidation using a copper/azodicarboxylate catalyst system. **S. D. McCann**, S. S. Stahl
- . Investigation of axial ligand exchange as related to the immobilization of cobaloxime catalysts on a carbon surface. **K. Hauser**, C. Eubanks, M. Freer, D. Wheeler, M. Hambourger

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