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A Forty Year Odyssey in Metallo−Organic Chemistry

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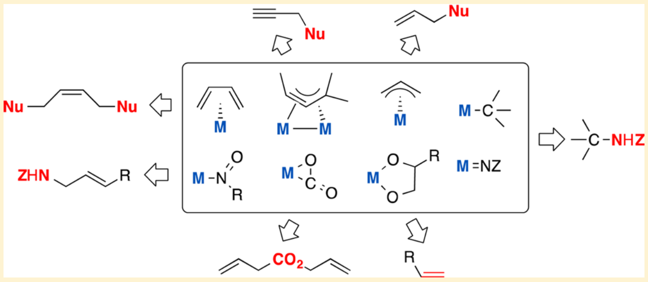

ABSTRACT: In this invited Perspective, I provide a personal account highlighting several of my group's research contributions in metallo−organic chemistry over the past 40 years. Our early work focused primarily in stoichiometric structure/reactivity of transition metal−organic compounds and their use in organic synthesis. More recent efforts have centered on the discovery and development of new metal-catalyzed organic reactions via reactive metal−organic intermediates. The major research findings that are described here include (1) propargylcobalt complexes as electrophilic agents for C−C and C−Nu coupling; (2) the activation of carbon dioxide by metal complexes; (3) metal-promoted C−H nitrogenation reactions; (4) oxo−metal catalyzed deoxygenation reactions; and (5) catalyst discovery via dynamic templating with substrate- and transition-state analogues.

A. INTRODUCTION: THE FORMATIVE YEARS

My fascination with chemistry and chemical research began as a child of the organometallic renaissance that started with the discovery of ferrocene and its remarkable structure and aromatic reactivity.[1,2] My laboratory introduction to the interdisciplinary organometallic world came during an undergraduate research project codirected by two young and engaging professors at SUNY Stony Brook, Robert Kerber, an organic chemist, and Edward Stiefel, an inorganic chemist. From this initial study, we demonstrated the ability of a metal−carbonyl moiety to migrate across the face of a π-ligand, from η^6-arene to η^5-Cp, in (fluorenyl)Mn$(CO)_3^-$.[3] Such haptotropic processes have continued to receive much attention over the intervening years.[4] In graduate school and subsequent postdoctoral work, I was mentored by two inspirational pioneers of organotransition-metal chemistry, Rowland Pettit at the University of Texas[5] and Myron Rosenblum at Brandeis University, both trained as organic chemists, who ventured into the fledgling field organometallic chemistry.[6] During these formative years, my interests and focus turned toward the effects of metal coordination on the stability and reactivity of organic molecules and ions. With Pettit's guidance, I investigated the effects of $-Co_2(CO)_6$ complexation on the reactivity of coordinated alkynes, finding that the metal fragment suppressed reactions with electrophilic reagents at the triple bond, enabling its use as an alkyne protecting group.[7] Early studies showing that π-complexed organometallic species such as $-Cp_2Fe$ and $-(arene)Cr(CO)_3$ could stabilize carbocations as in **1** and **2** (Figure 1)[8] prompted our initial investigations which suggested that the bimetallic $-(alkyne)Co_2(CO)_6$ unit could do the same as in **3**,[9] a phenomenon that I returned to during my independent research career (vide infra). In Rosenblum's laboratory, I was immersed in the chemistry of $CpFe(CO)_2$(=“Fp”)−alkyl and −olefin complexes,[10] discovering an efficient and stereospecific method for carboalkoxylation of the Fe−C bond[11] and seeding ideas about the chemistry and potential synthetic utility of the olefin complexes that would be brought to fruition in my early years at Boston College. It is appropriate here to note a personally influential contribution of A. C. Cope himself to stoichiometric metal−organic chemistry, the resolution of (±)-*trans*-cyclooctene by complexation to a chiral metal fragment, $PtCl_2$(α-methyl benzylamine).[12]

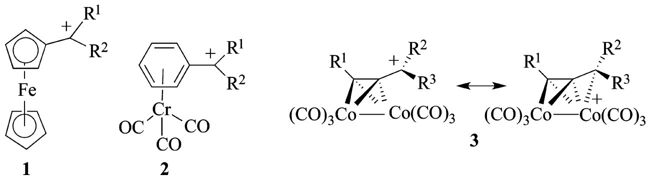

Figure 1. Metal-stabilized carbocations.

B. EXPLORING AND EXPLOITING THE REACTIVITY OF π-COMPLEXED SPECIES

1. Carbocations and Unsaturated Hydrocarbons. At Boston College, we focused our efforts on exploring the reactivity of several cationic, electrophilic π-complexes, especially the (propargyl)$Co_2(CO)_6^+$ species **3**. The remarkable thermodynamic and kinetic stability of **3** is evidenced by pK_R^+ values comparable to that of the trityl cation, Ph_3C^+[13] and their convenient isolation and long-term storability as salts (see photo below).[14] These features, together with the IR and NMR spectra of **3**, indicate a highly delocalized charge, the powerful electron-donating ability of the

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$-Co_2(CO)_6$ unit, and an unsymmetrical η^2–η^3 structure.[15] Over the course of several years at Boston College and continuing at the University of Oklahoma, we established that the propargyl−cobalt complexes **3** react efficiently and *regiospecifically* with a variety of carbon and heteroatom nucleophiles,[16] producing the corresponding (μ–η^2,η^2-alkyne)$Co_2(CO)_6$ complexes **4** (Figure 2), free from the allenyl byproducts which often accompany substitution reactions of uncomplexed propargyl electrophiles.[17] The facile and efficient generation of **3** and their coupling/demetalation reactions provides a useful method for introducing the synthetically versatile propargyl unit, leading to its appelation by Shreiber as the Nicholas reaction.[18] We and several others expanded the scope of these coupling reactions by exploring a range of nucleophilic partners, including both conventional heteroatomics (e.g., ROH, RNH_2, RSH, PR_3), and, more usefully, mild carbon nucleophiles such as aromatics, allyl−metaloids, and enol derivatives (Figure 3). Various precursors to the reactive **3** were also established, including acetylenic acetals, aldehydes, epoxides, and enynes. The bent geometry of the coordinated propargyl unit in **3** and **5** (Figure 4) facilitates *intramolecular* Nu-propargyl coupling reactions to produce cyclic products, including macrocyclic alkynes.[19]

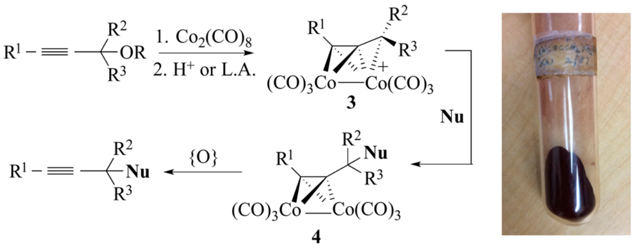

Figure 2. Cobalt-mediated propargylation.

The diverse reactivity of both the free and the coordinated C−C triple bond, particularly in the Pauson−Khand [2 + 2 + 1] cycloaddition,[20] has drawn many chemists to employ the Co-mediated propargyl−Nu coupling reactions in organic synthesis.[21,22] Indeed, this reaction has been employed (mostly by other groups) in dozens of total syntheses of natural and unnatural products and bioactive compounds. It is noteworthy that catalyzed propargylic coupling reactions also have been reported (with Ru and Au, but not Co),[23] but these thus far have seen relatively little synthetic use. During the latter years of our studies of the propargyl−cobalt complexes, we also found, in part serendipitously, that the corresponding (propargyl)$Co_2(CO)_6$ *radicals* **6** are easily generated and have distinctive carbon-centered reactivity, enabling efficient intra- and intermolecular C−C coupling (Figure 5).[24] This chemistry has been further studied by my former research associate Gagik Melikyan,[25] but is little known for other π-coordinated radicals.

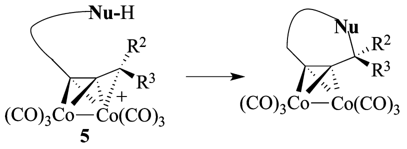

Figure 4. Intramolecular propargyl−nucleophile reactions.

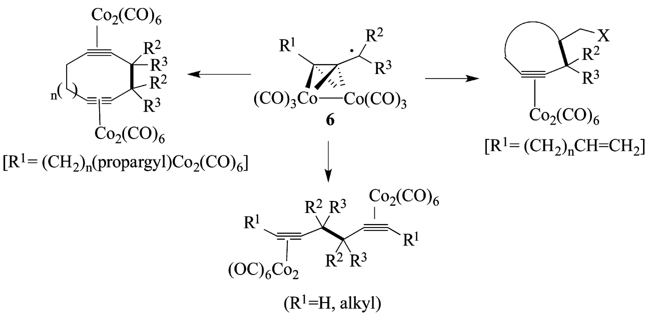

Figure 5. Coupling reactions of propargyl−cobalt radicals.

During this period, we also explored the reaction chemistry of other electrophilic π-complexes, including $CpFe(CO)_2(\eta^2\text{-olefin})^+$ (**7**), (η^3-allyl)$Fe(CO)_4{}^+$ (**8**), and (η^4-diene)$Co(CO)_3{}^+$ (**9**) (Figure 6). The high reactivity of the iron−olefin$^+$ complexes **7** with various nucleophiles[9] prompted us to show that nucleophilic attack on the coordinated olefin occurs stereospecifically *anti* (opposite) to the $CpFe(CO)_2$ (=Fp) unit,[26] a feature now recognized to be typical of 18-electron (closed valence shell) complexes. Conversely, we demon-

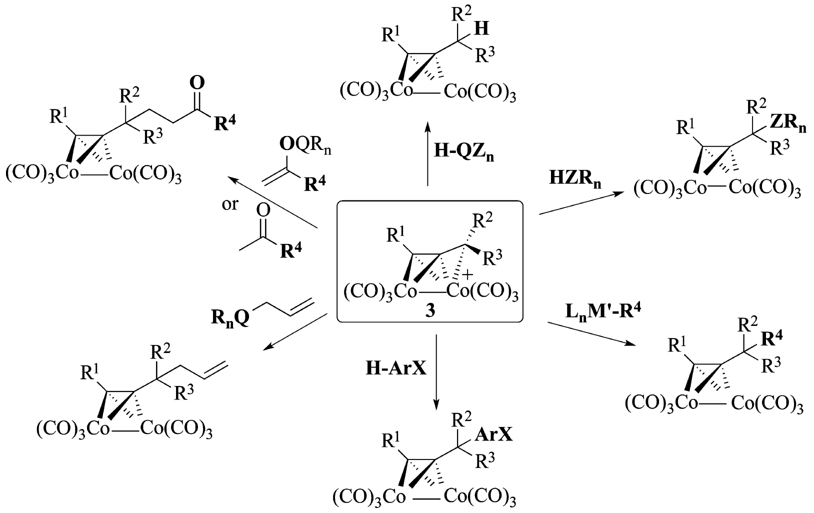

Figure 3. Nucleophilic partners in cobatlt-mediated propargylation.

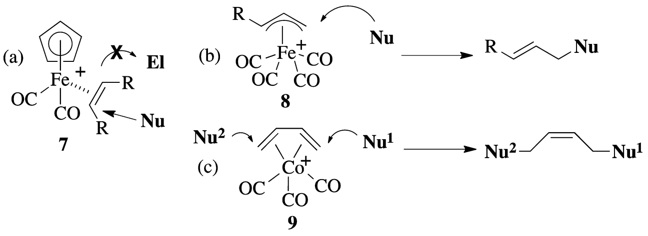

Figure 6. Nucleophilic reactions of other metal−π complexes.

strated that the easily installed and removed electron-withdrawing Fp^+ moiety could be used as a protecting group for the normally addition-prone C−C double bond.[27] The related allyl−iron complexes **8** were found to be highly reactive toward nucleophiles, even electron-rich aromatics (Figure 6b).[28] Regioselective attack by nucleophiles at the less substituted site of unsymmetrical allyl units provided a stoichiometric forerunner of the widely utilized Pd-catalyzed allylic substitutions.[29] The (η^4-diene)$Co(CO)_3{}^+Z^-$ complexes **9** received our initial attention at the University of Oklahoma and were shown to be extraordinarily reactive toward a variety of nucleophiles, making it possible to sequentially add two nucleophiles in a selective 1,4-fashion to produce the *Z*-functionalized olefin (Figure 6c).[30]

2. Carbon Dioxide Activation by Coordination. During the 1980s and 1990s, motivated in part by the potential practical benefits of the chemical utilization of the earth's most abundant and simplest carbon resource, CO_2, we began to probe the reactivity of coordinated CO_2 in discrete metal complexes and, subsequently, through metal-catalyzed transformations. From these efforts, we helped to establish the propensity of coordinated CO_2 to transfer an oxygen/oxide, either: (1) to another CO_2, to produce CO and carbonate, as in the photoreaction of $Cp_2Mo(\eta^2\text{-}CO_2)$[31] (**10**, Figure 7a); (2) to an oxophilic metal, e.g., $Cp_2NbR(\eta^2\text{-}CO_2) \rightarrow Cp_2Nb(O)R + CO$;[32] or (3) to external electrophilic reagents (Figure 7a).[33] A catalytic *O*-transfer counterpart was established in the CO_2-driven phosphine oxidation catalyzed by Wilkinson's complex (Figure 7c).[34] With the goal of incorporating the entire CO_2 molecule into value-added products, we found that Rh−phosphine complexes catalyze CO_2 hydrogenation to formic acid through rhodium formate intermediates (Figure 7b),[35] a transformation whose efficiency has since been improved upon by several other groups.[36] Our later efforts in the CO_2 activation arena yielded catalytic reactions for the carboxylation of metal−alkyls, e.g., in the palladium-catalyzed carboxylation of allyl-SnR_3[37] and allyl−allyl carboxylative coupling (Figure 7d).[38] It is exciting and gratifying to see a recent resurgence of research activity in this area that carries such important technological, environmental, and societal impacts.[39]

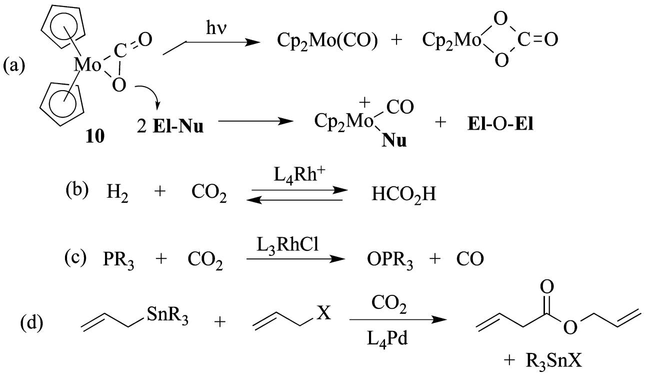

Figure 7. Metal-promoted reactions of carbon dioxide.

C. STOICHIOMETRIC TO CATALYTIC CHEMISTRY

1. Metal-Promoted Hydrocarbon Nitrogenation. In the 1990s, we expanded our research studies to include metal-promoted reactions that involve the direct formation of C−N bonds from hydrocarbons, i.e., nitrogenation. At the time, very few such transformations were known aside from olefin aziridination[40] and the industrially practiced propylene ammoxidation to acrylonitrile.[41] We envisioned that complexes of organonitrogen species, e.g., of nitroso alkanes[42] and nitrenes (Figure 8), could promote C−N bond-forming reactions via C−H and/or C−C activation. First, we found that $LMo^{VI}O_2$ complexes catalyze *allylic amination* of olefins by hydroxylamine derivatives[43] via $LMoO(\eta^2\text{-}ArNO)$ intermediates.[44] The distinctive and synthetically valuable regioselectivity of these reactions (*N*-attack at less substituted olefinic carbon), however, was shown to be the result of the intermediacy of free ArNO, which undergoes a regioselective ene reaction to the allyl hydroxylamine followed by Mo-promoted deoxygenation.[45] Subsequent studies led to our discovery of allylic amination reactions catalyzed by other redox-active metal salts and complexes, e.g., by $Fe^{II/III}$[46] and $Cu^{I/II}$.[47] Although both sets of reactions show the same ene-reaction-type regioselectivity, the Fe-promoted reactions apparently involve RN transfer by a *coordinated N*-species, i.e., a novel iron−azodioxide complex **12**, which we could isolate/characterize. The nature of the reactive *N*-species involved in the Cu-catalyzed reactions, still being investigated and developed by former research associate R. Srivastava,[48] is less certain.

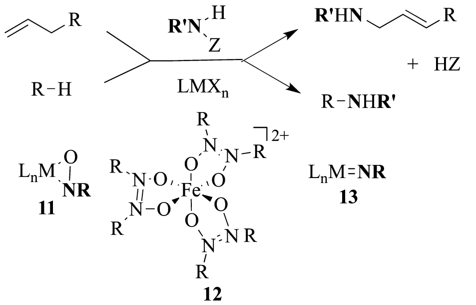

Figure 8. Metal-promoted nitrogenation of hydrocarbons.

We then extended our nitrogenation efforts to other classes of hydrocarbons and *N*-reagents. While seeking to effect the nitrogenation of alkynes via $[CpM(CO)_2]_2$-promoted nitroarene deoxygenation with CO, we were surprised and delighted to discover that 3-substituted indoles are produced instead (Figure 9a).[49] Mechanistic studies indicate that, as with the olefin aminations by ArNHOH/ML, the catalyst serves as a redox shuttle, deoxygenating $ArNO_2$ to ArNO, which then cycloadds to the alkyne to give the *N*-hydroxyindole (a previously unknown organic transformation), which in turn, is deoxygenated to the indole.[50] The scope and synthetic utility of this very direct route to typically bioactive indoles[51] and *N*-hydroxyindoles[52] has been inves-

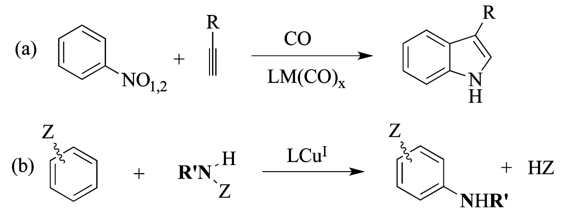

Figure 9. Metal-catalyzed nitrogenation of alkynes and arenes.

tigated, in collaboration with my former research associate, Andrea Penoni.[53]

Turning to benzylic substrates, copper complexes and salts were shown to catalyze intermolecular nitrogenation by commercial TsNNaCl (Figure 10)[54] and efficient intramolecular reactions as well.[55] Several mechanistic probes, including isotope effects, stereoselectivity, and computational modeling with Kendall Houk,[56] support the intermediacy of a (diimine)$Cu(NSO_2Me)^+$ species with substantial *N*-centered radical character, which undergoes stepwise C—H insertion via transition state **14**. Unfortunately, this limits the prospect for enantioselective *N*-functionalization.[57]

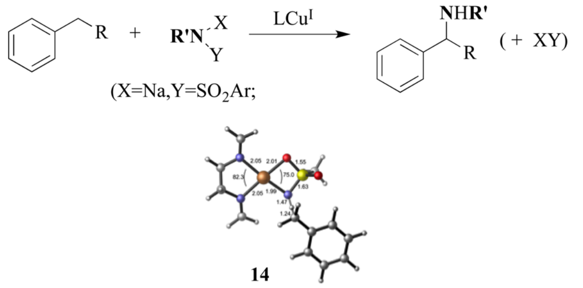

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Figure 10. Copper-catalyzed benzylic amination and calculated transition state.

Our most recent nitrogenation activities have explored reagent/catalyst systems that effect *N*-functionalization of the most challenging substrates, alkanes and arenes, which have the strongest C—H bonds. We uncovered a novel (admittedly nonmetal promoted) iodine-catalyzed *N*-functionalization of weaker C—H bonds (tertiary, secondary and benzylic) by imidoiodinanes, PhI═NZ.[58] Metal-promoted aromatic C—H nitrogenation has been achieved most commonly with arenes sporting substituents that enable coordinative *ortho*-*N*-functionalization,[59] as we found with simple Pd and Cu catalysts (Figure 11a).[60] We recently achieved rare *N*-functionalization of simple (noncoordinating) arenes via (phenanthroline)Cu-catalyzed reactions with hydroxylamine derivatives, RNHZ (Figure 11, R = $Cl_3CH_2OC(O)$—, Z = $TolSO_3$), with regioselectivity suggestive of a radical substitution process.[61,62] The reactive *N*-species responsible for these transformations is as yet unknown. The field of C—H *N*-functionalization has exploded in recent years, both in terms of synthetic scope and mechanistic understanding, through the efforts of numerous creative researchers.[63]

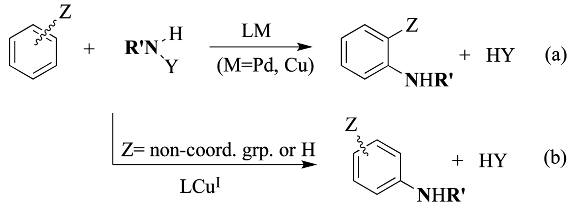

Figure 11. Metal-catalyzed arene C—H amination.

D. TURNING THE TABLES: METAL-PROMOTED DEOXYGENATION OF POLYOXYGENATES

After many years of seeking to activate/functionalize hydrocarbon substrates with low oxidation state metal species, we recently turned our attention to de-/refunctionalizing highly oxygenated substrates to produce hydrocarbons through the agency of high oxidation state metal species. Stimulated in part by real-world concerns about the sustainability of our chemical and energy resources and motivated as always to explore the reactivity of less studied transition metal—organic compounds, we recently initiated a new project seeking to develop and to better understand metal-promoted *deoxygenation* reactions. These reactions could be valuable for the conversion of biomass-derived oxygenates, e.g., carbohydrates and other polyols, to value-added products. Early studies by Andrews[64] and Gable[65] on the oxo—rhenium promoted, phosphine-driven glycol to olefin reaction, termed deoxydehydration (DODH, Figure 12), prompted us to explore the scope and utility of this reaction and to understand more deeply its mechanism.[66] We have been able to discover more practical reductants for the DODH reaction, including Na_2SO_3,[67] $ArCH_2OH$,[68] reducing elements (Zn, Fe, C),[69] dihydroarenes,[70] and most recently, CO.[71] From our experimental[72] and computational studies[73] of the $ZReO_x$-promoted reactions, a dual pathway catalytic cycle generally appears to be viable (Figure 13), with the preferred path (1 or 2) and the turnover-limiting step both dependent on the reductant and the catalyst. Our ongoing search for nonprecious (cheap) transition-metal reagents and catalysts has been rewarded with the discovery of vanadium—oxo complexes that are also effective catalysts for DODH.[74]

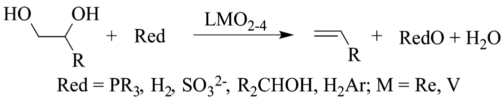

Figure 12. Oxo—metal-catalyzed deoxydehydration.

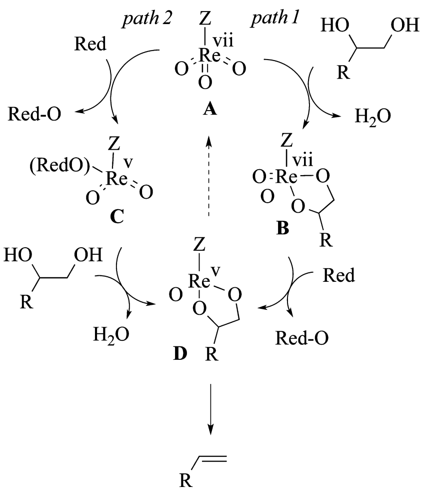

Figure 13. Catalytic pathways for deoxydehydration.

The DODH reaction has also attracted the attention of several other groups, who have contributed importantly to expanding its substrate and reductant scope,[75] defining its selectivity, and elucidating other reductions promoted by oxo−metal complexes.[76] We are now investigating tandem atom-economical DODH/olefin-transforming reactions (e.g., DODH/hydroformylation, etc.) and other selective deoxygenation and coupling reactions of alcohols, which could be useful in the chemical or biorefinery[77] and in fine chemical synthesis.

E. NEW APPROACH TO COORDINATION CATALYST DESIGN/SELECTION

I would like to conclude this Perspective by briefly describing a very different "new direction" that we have taken recently.

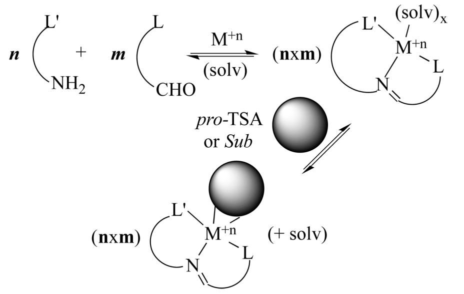

Figure 14. Dynamic templating of Schiff base complexes with transition-state analogues.

Rather than seeking new types of metal-promoted reactions, our objective here is to establish a new approach to the discovery of highly active and/or selective catalysts for a given reaction of interest. We take a page from the concepts and methods of eliciting catalytic antibodies,[78] which I first became conversant with during a sabbatical at the Scripps Research Institute with Kim Janda.[79] In this approach to catalyst discovery, the potential catalysts are elicited/selected on the basis of their binding affinity for transition state analogs (TSA). According to the Pauling−Jenks adaptation of transition-state theory for enzyme/antibody catalysis,[80] the "best catalyst", i.e., most active or selective, will be the one that has the highest relative binding affinity for the TSA versus the substrate. To achieve diversity and high throughput for a library of metal−ligand precatalysts, LM, instead of using the immune system's costly and laborious protein factory, we produce a synthetic equilibrating, combinatorial library of imine−metal complexes from a set of aldehydes, amines, and a metal salt (Figure 14). The library is then templated against the TSA (and substrate) to identify the best binder(s) and, in principle, the best catalyst.

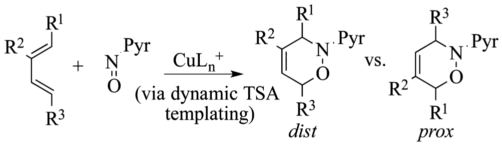

Figure 16. Copper-catalyzed hetero-Diels−Alder reactions.

We established a proof-of-concept and successfully applied this strategy for the identification of Zn(imine) catalysts for pyridine ester hydrolysis with a *gem*-diol TSA **14** (Figure 15 a,b).[81] To enable high-throughput catalyst selection, we have shown the viability of MS analysis of metal complex mixtures for semiquantitative TSA−ML_n binding[82] and we have evaluated the dynamic templating approach for the identification of metal catalysts for the kinetic resolution of esters[81] and regioselective nitroso-arene hetero-Diels−Alder reactions (Figure 16).[83] A simple affinity chromatographic method for metal-complex catalyst selection is currently being investigated in which the TSA or a substrate analogue is bound to the chromatographic support.[84] We hope the initial promising results from these studies will encourage others to employ the dynamic templating method to discover metal catalysts for their reactions of interest.

F. CONCLUSIONS AND FUTURE PROSPECTS

I have highlighted here several of my research group's contributions to metallo-organic chemistry and its application to organic synthesis and catalysis. Our efforts in the future will continue to draw on the theme of exploring and exploiting the unique reactivity of metal-coordinated organic species. With my recent retirement from classroom teaching, gaining Emeritus status, I look forward to new and exciting adventures in transition metal−organic chemistry, both in the laboratory and in silico, a tool which I think will be increasingly valuable for predicting the viability of new metal-promoted reactions.

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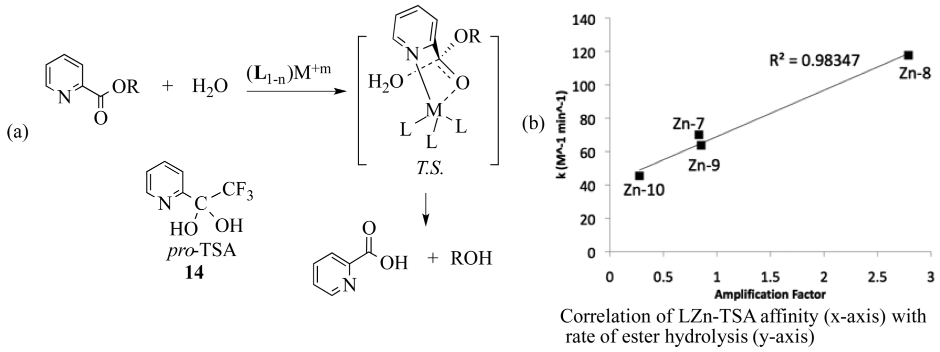
Notes

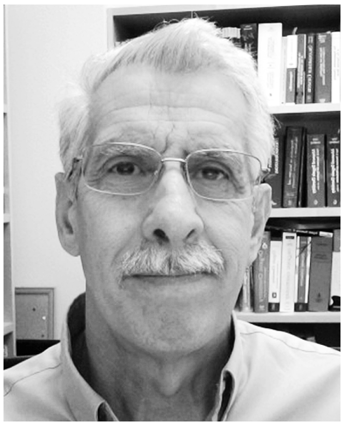
The authors declare no competing financial interest.



Correlation of LZn-TSA affinity (x-axis) with rate of ester hydrolysis (y-axis)

Figure 15. Metal complex catalyzed ester hydrolysis.

Biography



Kenneth Nicholas received his B.S. in Chemistry from SUNY Stony Brook in 1969 and his Ph.D. in Organic and Inorganic Chemistry under the direction of Rowland Pettit at the University of Texas (Austin) in 1972. After a Postdoctoral position in organometallic chemistry with Myron Rosenblum at Brandeis University, he joined the faculty at Boston College in 1973. In 1984, he relocated to the University of Oklahoma where he has continued to the present and is now George Lynn Cross Research Professor Emeritus. His research interests have centered on the discovery, development, and mechanistic elucidation of transition-metal-promoted organic reactions. He is the recipient of a 2015 A. C. Cope Senior Scholar Award administered by the American Chemical Society.

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(14) This sample of $[(HC_2CH_2)Co_2(CO)_6]BF_4$ photographed in 2014 was prepared in 1987 and shows no significant decomposition when stored under a dry nitrogen atmosphere.

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