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Application of Physical Organic Methods to the Investigation of Organometallic Reaction Mechanisms[†]

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For the past 75 years, physical organic chemistry has been the foundation for the elucidation of mechanisms, and the understanding of structure/activity relationships, in organic chemistry. The rational design of experiments and the critical analysis of data have been the hallmarks of this field. In this Perspective, we revisit some of the studies carried out during the past 30 years in which our group has used the tools of physical organic chemistry to investigate the mechanisms of a variety of organometallic reactions. The Perspective covers a broad spectrum of metal-mediated reactions including organic reductions, alkene, carbon monoxide and nitric oxide migratory insertion reactions, C−H bond activation, and the reactions of metal−heteroatom bonds with organic molecules. These studies, along with similar ones carried out in other groups, have demonstrated that the principles and methods of physical organic chemistry have adapted well to the study of organometallic reaction mechanisms. The understanding obtained in this way has aided the development of useful metal-mediated reactions in a wide range of areas, especially in industrial catalysis and in applications to problems in organic synthesis.

I. Introduction

From its beginnings in the early part of the 20th century, physical organic chemistry has focused on understanding the physical properties and reaction mechanisms of organic compounds. In contrast, in its early years, the focus of academic organotransition metal chemistry was primarily synthetic and structural. This was quite natural, since workers in the field needed to determine the types of metal-containing carbon compounds that were stable enough to isolate and characterize before the reactions in which these molecules participated could be studied carefully. At the same time, chemists interested in homogeneous catalysis were discovering that soluble metal catalysts were a valuable adjunct to their heterogeneous counterparts, especially when high selectivity in commodity chemical transformations was required. However, mechanistic understanding of these industrially important processes was also typically quite limited.[1−4] It was not long before the varied—and often unpredictable—reactions being uncovered by synthetic and industrial organometallic chemists drew the curiosity of scientists intrigued by the possibility of understanding how those transformations worked.[5,6] Because of the extensive study of reaction mechanisms in organic chemistry, it was not surprising that individuals who had received their early training in organic chemistry (such as Halpern, Collman, Whitesides, and Kochi) were among the pioneers of this discipline.[7] The approaches, modes of thinking, and types of experiments devised by physical organic chemists, which were designed to unlock the secrets of organic reaction mechanisms, ultimately proved applicable to understanding many organometallic processes as well.

This paper describes some of the studies in which our group combined the synthetic and exploratory tradition of organometallic chemistry with the mechanistic tools of physical organic chemistry (e.g., kinetic studies and reactivity trends, stereochemical studies, isotope tracer and kinetic isotope effect studies, substituent effects, radical clocks, crossover experiments) to uncover new organometallic transformations and to understand how they work. These studies have been important for the understanding of a number of fundamentally interesting organometallic transformations, some of which are relevant to processes employed in organic synthesis and in the chemical industry.

The application of physical organic experiments to the study of organotransition metal reactions began to influ-

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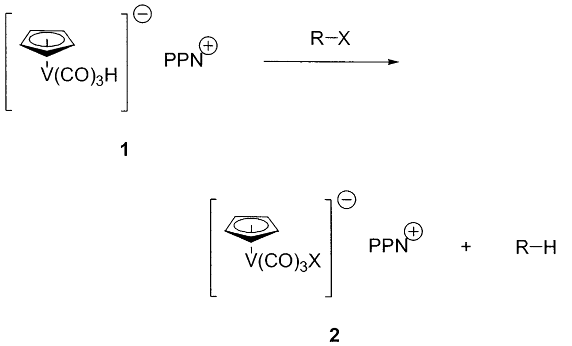
ence our group's research and the education of its members in 1972. At that time, prompted by the contributions of other researchers to this fledgling field, we began to investigate a cobalt-mediated synthesis of benzocyclobutenes,[8] which led to our first contribution to mechanistic organometallic chemistry. In the 30 years since, we have studied the reactivity and mechanisms of many complexes of both early and late transition metals. For this paper we have selected representative examples of these studies, focusing on systems in which early experiments reflecting the traditions of physical organic chemistry provided important milestones along the path to mechanistic understanding. Each section discusses questions that were addressed by researchers in our group, the experiments we designed to answer these questions, and the conclusions we could (or could not) draw from the resulting data. The sections are presented in approximately chronological order to provide a historical perspective. Because of this perspective, many of the studies that are discussed in detail were published some time ago. We have supplemented these with brief references to more recent contributions from our group.

II. Vanadium Carbonyl Hydride Reductions: Reactivity Trends, Stereochemical Probes, and Radical Clocks Identify Organic Radicals as Intermediates

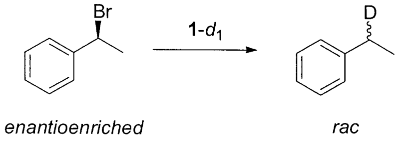
In 1978, we reported the synthesis and reactivity of a new anionic vanadium carbonyl hydride, [PPN][(η^5-C_5H_5)V(CO)$_3$H] (**1**, PPN$^+$ = [$Ph_3P{=}N{=}Ph_3$]$^+$).[9] Complex **1** reduced a wide range of alkyl, vinyl, and acyl bromides and iodides to the corresponding dehalogenated organic compounds, with the concurrent production of [PPN]CpV(CO)$_3$X (**2**), at room temperature (eq 1). We performed three types of experiments to decipher the mechanism of this reduction.



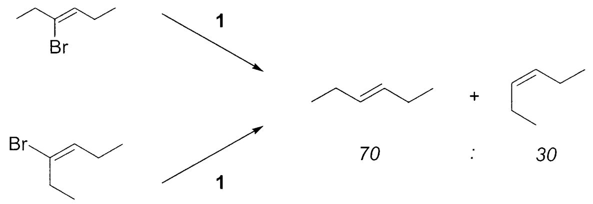
(1)

First, a screen of substrates showed that the reactivity increased in the following order: chlorides < bromides < iodides. Benzylic chlorides reacted at room temperature, but alkyl chlorides and tosylates were only converted at elevated temperatures. Additionally, primary, secondary, and tertiary bromides underwent reduction at comparable rates. These relative reactivities were reminiscent of those previously observed in trialkyltin hydride reductions of organic substrates, suggesting that organic radicals were intermediates in these reactions as well.

Second, results from stereochemical experiments further supported the intermediacy of organic radicals. Reduction of enantioenriched 1-(bromoethyl)benzene with [PPN][(η^5-C_5H_5)V(CO)$_3$D] (**1**-d_1) yielded racemic 1-(deuterioethyl)benzene (eq 2), and reduction of pure *cis*- or pure *trans*-3-bromo-3-hexene gave identical mixtures of *cis*- and *trans*-3-hexenes (30:70) (eq 3). Furthermore, reduction of either stereoisomer of 7-bromo-7-chlorobicyclo[4.1.0]heptane gave the same mixture of products (exo/endo = 10) (eq 4).



(2)



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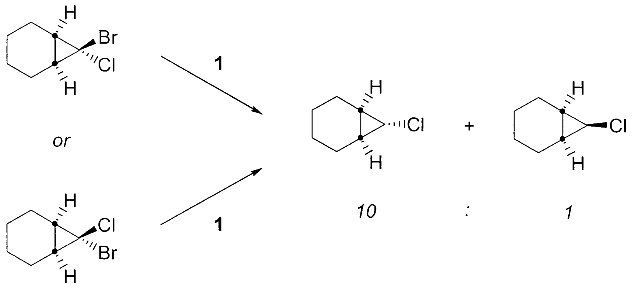
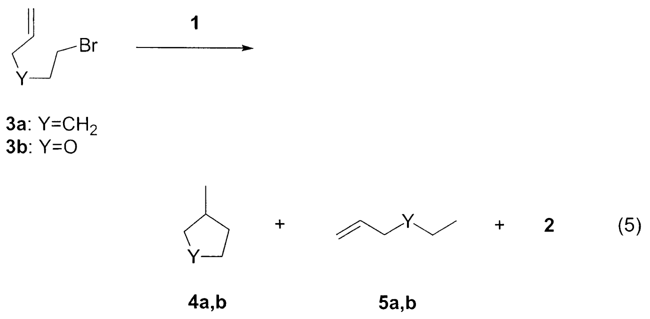


(4)

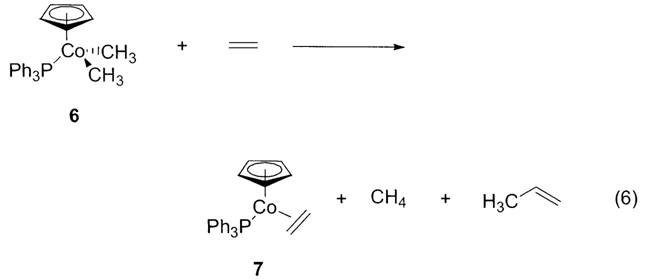
Third, rearrangement and trapping studies provided critical tests of the radical hypothesis. To the best of our knowledge, this experiment represented one of the earliest examples of a radical clock used to probe the intermediacy of organic radicals in organotransition-metal reactions. Radical clock studies of transition-metal reaction mechanisms have since been used frequently; notably, they played an important role in establishing and understanding the radical mechanism of cytochrome P450-catalyzed hydroxylation of alkanes.[10] The cyclization of the 1-hexenyl-5-radical had been used previously to explore radical intermediates in a number of organic systems, and so we first studied the reduction of 6-bromo-1-hexene (**3**) by **1** (eq 5). Surprisingly, this resulted in only small quantities of the expected radical cyclization product **4a** even at low concentrations of **3a** and **1**. Since the rate constant for cyclization of **3a** was known to be about 10^5 s^{-1}, if radicals were involved in this reduction, they must have been reduced with a rate constant $k >$ 10^5 s^{-1}. We therefore next examined the cyclization of the related radical **3b** because it was known to proceed an order of magnitude more rapidly. In this case, substantial amounts of cyclization product **4b** were observed, supporting the radical hypothesis. This established hydride **1** as an exceptionally rapid hydrogen atom donor toward organic radicals.



III. Reaction of Ethylene with CpCo(PPh$_3$)(CH$_3$)$_2$: Deuterium Isotope Tracer Studies Establish the Mechanism of an Alkene Migratory Insertion

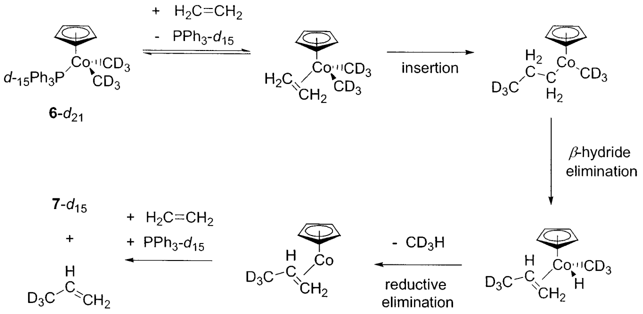
Our early studies of cobalt-catalyzed alkyne trimerization reactions, in which we found that certain diynes could be used to synthesize benzocyclobutenes,[8] produced a natural interest in reactions that take place at the cobalt−carbon bond. In an effort to prepare complexes in which reactions of such bonds might be studied directly, we chose the cyclopentadienyl group as an ancillary ligand. We used precursors bearing this fragment to develop simple mono- and binuclear cobalt complexes with metal−carbon bonds and began to examine their reactions with small organic compounds.

The first simple mononuclear alkylcobalt complex that drew our attention, CpCo(PPh$_3$)(CH$_3$)$_2$, **6**, provided a means of studying the migratory insertion of alkenes into the metal−carbon bond. Interest in this process was stimulated to some extent by Ziegler−Natta polymerization of ethylene and other olefins which was at the time, and continues to be, an important industrial catalytic process. This class of reactions had been assumed to involve insertion of an olefin into the metal−carbon bond of an intermediate metal alkyl species.[11−13] In 1978, however, Green and co-workers pointed out that no examples had been reported in which a well-characterized metal−alkyl−olefin compound had been observed to undergo such an insertion reaction.[14,15] The authors therefore suggested that an alternative mechanism should be considered which involved an α-elimination to form a transient carbene complex. In 1979, we reported our studies on the well-characterized cobalt complex (**6**) (eq 6) that reacted cleanly with ethylene, yielding propylene and methane as the products.[16]

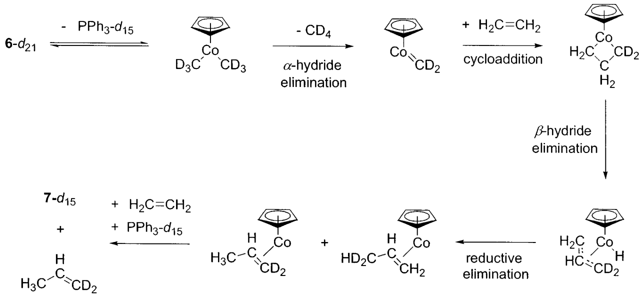


To elucidate the mechanism of the insertion process, labeled compound **6**-d_{21} (fully deuterated phosphine and methyl groups) was synthesized. If the insertion mechanism were operative, **6**-d_{21}, when treated with unlabeled ethylene, would produce methane-d_3 and propene-d_3 (Scheme 1). In the alternative carbene mechanism, however, **6**-d_{21} would produce methane-d_4 and propene-d_2 under the same conditions (Scheme 2).

SCHEME 1. Alkene Insertion Mechanism for the Generation of Propene in Eq 6, Showing Expected Isotope Distribution



SCHEME 2. α-Elimination Mechanism for the Generation of Propene in Eq 6, Showing Expected Isotope Distribution



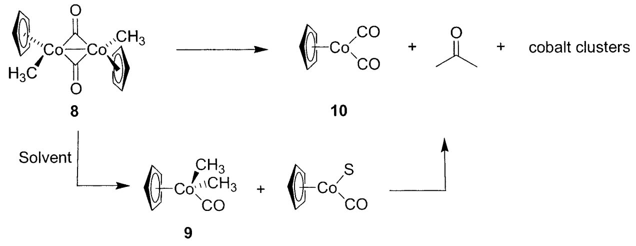
Mass spectral analysis of the methane produced showed that it was CD$_3$H. Similar analysis of the propene produced showed it to be ≥96% propene-d_3. Furthermore, in a second experiment, reaction of **6**-d_{21} with ethylene-d_4 gave 95% CD$_4$. These results demonstrated that (a) the new methane hydrogen is derived from ethylene and from no other hydrogen source in the system (cyclopentadienyl ring, solvent, phosphine) and (b) an entire methyl group is transferred to the ethylene. These results clearly supported (in agreement with the classical view) that insertion, rather than α-elimination, was the critical stepin the mechanism of ethylene methylation by cobalt complex **6**.

While the α-elimination mechanism did not operate in our cobalt-based system, it was possible that it still operated in other apparent insertion reactions. Subsequently, the discovery of soluble early transition-metal single-site Ziegler−Natta catalysts that exhibit very high selectivities and activities has produced a major revolution in alkene polymerization chemistry and stimulated a substantial effort in understanding their mechanisms. Currently, there are two leading mechanistic hypotheses for this class of Ziegler−Natta polymerizations: (1) a direct insertion of a coordinated olefin and (2) an α-agostic-assisted olefin insertion.[17]

IV. Dialkyldicobalt Complexes: Crossover Experiments Provide Information about the Relationship between the Nuclearity of a Starting Material and of a Reaction Intermediate

During the course of the studies on alkylcobalt complexes described above, we were able to prepare and

SCHEME 3. Reaction of Alkylcobalt Complex Dimer with CO



investigate the reactions of a novel alkylcobalt complex **8** that contained two metal centers, each with a simple metal−carbon bond. This provided our first opportunity to test the idea that the presence of two metals located in close proximity to one another would give rise to chemistry not observed with analogous mononuclear systems. We therefore investigated the thermal decomposition of compound **8** in organic solvents and in 1979 uncovered a rapid first-order reaction in which acetone was formed as the sole organic product at 25 °C.[18,19]

It was tempting to conclude that this was an example of two adjacent metals simultaneously donating their attached methyl groups to a coordinated or incoming CO molecule. However, as we and others have ultimately found to be true of many organometallic reactions, the actual reaction mechanism is more complicated than the composition of the starting materials may imply. Monitoring the reaction by ^{1}H NMR spectroscopy showed that acetone formation was not the first observable step in this reaction. Instead, a monomeric intermediate cobalt dialkyl complex, **9**, formed initially and then appeared to decompose to acetone (Scheme 3).[20]

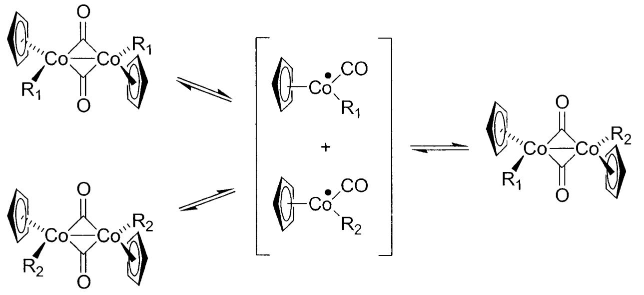
Crossover experiments had been performed previously by physical organic chemists to differentiate between intra- and intermolecular reactions, and we employed them here to test our hypothesis that the key step in this reaction was monomeric, despite the dimeric starting material. Thus, compounds **9**-$(CH_3)_2$ and **9**-$(CD_3)_2$ were synthesized separately and then mixed. Mass spectral analysis of the product acetone revealed an isotope distribution of 47% d_0, 45% d_6, and 7% d_3. This lack of significant scrambling showed that decomposition of the monomer **9** to form acetone was indeed intramolecular.[21]

Since it was shown to be the key intermediate, we desired an increased understanding of the formation of **9**. We postulated that **9** was itself formed in a two-step process, in which a rapid dissociation/recombination reaction first equilibrated dimer **8** with two 17-electron mononuclear CpCo(CO)R fragments. Subsequently, these fragments underwent alkyl radical transfer to produce **9** and a CpCo(CO) fragment.

To test for the rapid dissociation/recombination reaction, another crossover experiment was performed. In this case, differently substituted symmetrical dialkyl complexes were mixed together. The alkyl groups were found to scramble, consistent with the rapid dissociation and recombination of the dimers illustrated in Scheme 4.

The nature and rapid rate of this process were ultimately confirmed by an unusual variable-temperature ^{1}H NMR spectroscopic observation.[18b] A solution of the bis-CH_2CF_3 analogue of **8** (which undergoes rearrangement to $CpCo(CO)(CH_2CF_3)_2$) exhibited no observable resonances at ambient temperature, but when the sample was cooled, resonances for the dimer appeared. The reversible dissociation of the dicobalt complex into the paramagnetic monomeric alkylcobalt fragments at ambient temperature produced paramagnetic broadening, and this accounted for the lack of signals.

SCHEME 4. Crossover Experiment To Test for Rapid Dissociation/Recombination Reaction



This study provided a clear warning that the presence of linked metals in a starting material does not necessarily mean that the metal centers in the product-forming intermediates are also linked. Analogous studies carried out subsequently in our laboratory and others have demonstrated that transient changes in nuclearity are a hallmark of many organometallic transformations.

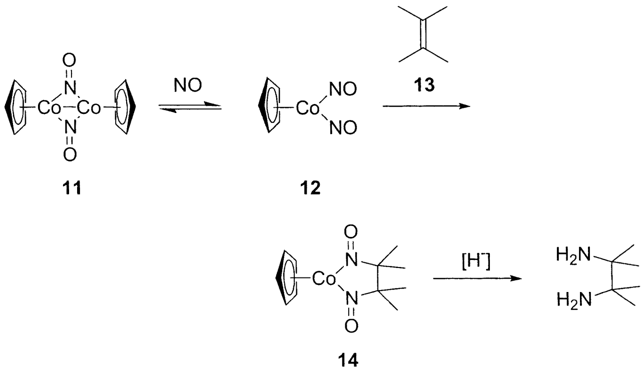
V. Cobalt Dinitrosyl Complexes: Kinetic and Substituent Effect Experiments Identify a Complex That Behaves Like an Organometallic "1,3-Dipolarophile"

At the time of the early studies summarized above, the migratory insertion of carbon monoxide into metal−carbon bonds had been extensively studied. However, although many metal nitrosyl complexes were known, similar insertions of NO into metal−carbon bonds had not been directly observed. In 1981, we demonstrated the first observable nitrosyl alkyl migratory insertion reaction.[22] The need to generate starting materials for this reaction drew our interest to the chemical properties of cobalt nitrosyl dimer **11**, a reaction precursor. In 1983, our studies of **11** led to the discovery of, and mechanistic insight into, a new cycloaddition reaction.

Following up earlier hints in the literature, we found that exposure of **11** to excess nitric oxide and alkenes (e.g., **13**) led to novel adducts having structure **14**.[23] It seemed likely that the unknown cobalt dinitrosyl complex $CpCo(NO)_2$, **12**, was the critical intermediate in these reactions. (Eventually we were able to observe **12** by in situ IR studies and examine the rates of its reaction with alkenes directly.) The NO groups in **14** could subsequently be reduced, leading to a stoichiometric synthesis of 1,2-diamines (Scheme 5).

The stereochemistry, kinetic behavior, and substituent effects exhibited by these reactions followed almost exactly those established earlier for organic 1,3-dipolar cycloadditions of compounds such as alkyl and aryl azides to alkenes. For example, reactions with *E* or *Z* alkenes occurred with complete retention of alkene stereochemistry. Additionally, the alkene fragment in complex **14** exchanged with other alkenes photochemically and thermally.[24] In the thermal reaction, treatment of **14** with

SCHEME 5. Cycloaddition Reaction of Dinitrosyl Complex with Alkenes



SCHEME 6. Kinetic Study of Retrocyclization/Cyclization Reaction

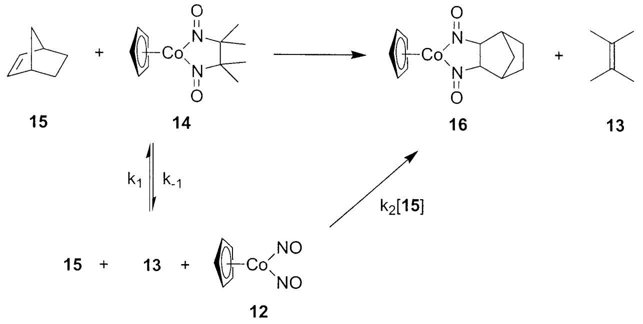
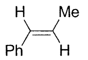
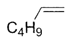
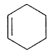
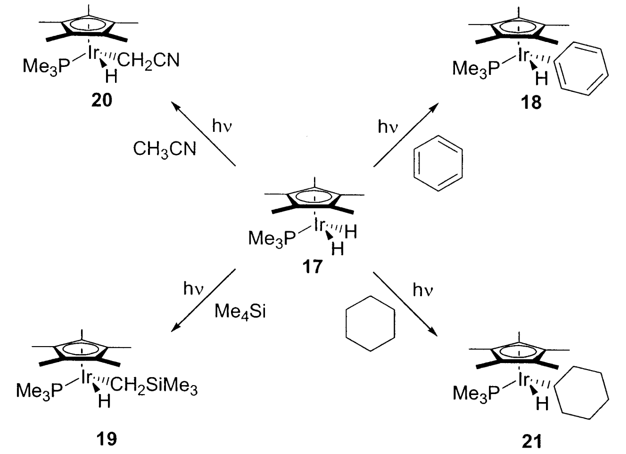


TABLE 1. Relative Rates of Cycloaddition Reactions of $CpCo(NO)_2$ with Alkenes

					
PhN_3, CCl_4, 25 °C	5700	56	12	7.3	1
$CpCo(NO)_2$, C_6H_{12}, 20 °C	1960	59	13	2.3	1

SCHEME 7. C−H Bond Activation Reactions of $Cp^*(PMe_3)IrH_2$



an excess of norbornene (**15**) led to the quantitative release of **13** and the formation of the new adduct **16** (Scheme 6). Added **13** inhibited the reaction, and added **15** accelerated it. Quantitative kinetic studies using varying (excess) concentrations of these alkenes established that the reaction exhibited saturation kinetics and followed the rate law in eq 7. A plot of $1/k_{\mathrm{obs}}$ vs the [**13**]/[**15**] ratio was linear, providing convincing evidence for this mechanism.

$$\mathrm{Rate} = \frac{k_1k_2[\mathbf{14}][\mathbf{15}]}{k_{-1}[\mathbf{13}] + k_2[\mathbf{15}]} = k_{\mathrm{obs}}[\mathbf{14}] \Longrightarrow \frac{1}{k_{\mathrm{obs}}} = \frac{k_{-1}[\mathbf{13}]}{k_1k_2[\mathbf{15}]} + \frac{1}{k_1} \qquad (7)$$

Another dramatic example of the parallelism of this new reaction with organic 1,3-dipolar cycloadditions is illustrated by the relative rate data in Table 1: over nearly 3 orders of magnitude, the relative reactivity of $CpCo(NO)_2$, **12**, toward differently substituted alkenes corresponds almost exactly to the relative reactivity of phenyl azide toward these organic substrates. This relationship between physical organic and organometallic data provided strong evidence that the addition of **12** to alkenes is a concerted process, with a transition state that must be electronically very similar to that identified earlier in mechanistic studies of organic 1,3-dipolar cycloaddition reactions. Even today, the $CpCo(NO)_2$ addition remains novel because there are very few known organometallic reactions in which two metal-bound ligands simultaneously attack the termini of an unsaturated organic compound, without entrance of the organic substrate into the inner coordination sphere of the metal. The osmium tetraoxide/alkene reaction is, of course, the most well-known of these processes.

VI. Alkane C−H Bond Activation by "16-Electron" Ir and Rh Complexes: Traditional and Ultrafast Kinetics, Isotope Effects, Crossover Experiments, and Intramolecular Competition Experiments Provide an Intimate Picture of the Mechanism

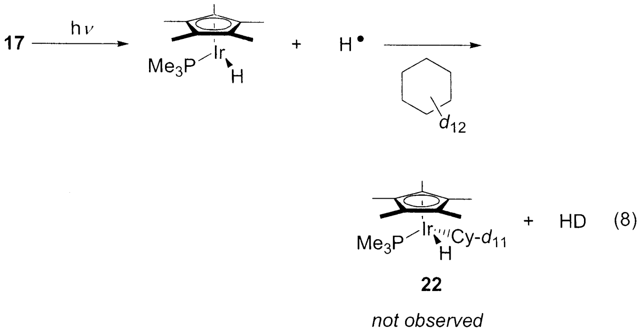
The C−H bond activation research in our group began with the investigation of the mechanism of hydrogenolysis of $CpCo(PPh_3)Me_2$, which we believed produced $CpCo(PPh_3)H_2$.[25] We were unable to isolate this proposed complex, however. This led us to synthesize and fully characterize the more stable analogous dihydrides $Cp^*Rh(PPh_3)H_2$ and $Cp^*Ir(PPh_3)H_2$ ($Cp^* = \eta^5$-C_5Me_5). At the same time, we noted that Green had observed arene and tetramethylsilane C−H bond activation by a structurally similar tungstenocene dihydride after photolysis.[26]

To see if we could extend Green's arene C−H bond activation chemistry to late transition metals, we irradiated $Cp^*(PMe_3)IrH_2$ (**17**) in a variety of solvents. We expected that we would be able to use ^{1}H NMR spectroscopy to observe the C−H bond activation products of the solvents, based on the diagnostic upfield chemical shifts of the metal hydrides.

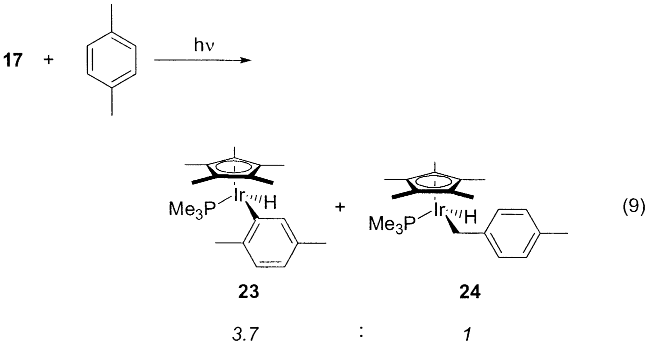
Gratifyingly, irradiation of **17** in benzene yielded a single hydride resonance in the ^{1}H NMR spectrum. This product was assigned as phenyl hydride complex **18** (Scheme 7). Photolysis in tetramethylsilane and acetonitrile yielded different hydride resonances, supporting our hypothesis that in each case the desired intermolecular C−H activation of the respective solvent had occurred. These products were assigned as complexes **19** and **20**, respectively.[27]

In a reaction with no precedent at the time,[28,29] carrying out the irradiation of Cp*$(PMe_3)IrH_2$ in cyclohexane proceeded as in the above cases to produce a new high-field hydride resonance. We tempered our growing excitement until full characterization, including X-ray crystallography, established that we had indeed observed the first known case of intermolecular C−H oxidative addition of an unactivated alkane, producing cyclohexyl hydride complex **21**.[30−32]

Having characterized the C−H activation products, we proceeded to investigate the mechanism of this reaction. Though it was likely that initial photolysis caused reductive elimination of H_2, producing a reactive 16-electron complex, we considered a possible hydrogen atom abstraction pathway.[27] However, this radical pathway was ruled out by the following isotope labeling and intramolecular competition experiments. In the labeling experiment, the photolysis was carried out in cyclohexane-d_{12}. If hydrogen atom abstraction had occurred, the product (**22**) would have exhibited one hydride resonance. However, only the deuteride Cp*$(PMe_3)Ir(C_6D_6)D$ was observed (eq 8).

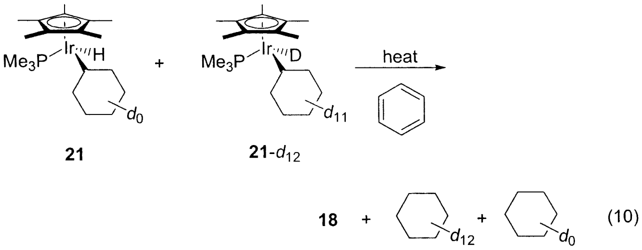


In the intramolecular competition experiment, **17** was photolyzed in *p*-xylene. The kinetic product ratio of 3.7:1 (**23**/**24**) showed that the aromatic C−H bond reacted faster than the benzylic C−H bond (eq 9). If a radical mechanism were operative, the reverse selectivity would have been expected due to the lower bond energy of the benzylic C−H bond relative to the aromatic C−H bond. Similar "anti-radical" reactivity was observed during the activation of propane, in which the primary C−H bond reacted twice as fast as the secondary,[27] and in the successful activation of cyclopropane, despite its high bond dissociation energy.[33]



Because the data from both experiments were consistent with a mechanism that involved initial reductive elimination of H_2 followed by oxidative addition of the C−H bond, we decided to study the reaction mechanism of the microscopic reverse of the oxidative addition.[34] Kinetic studies of the thermal conversion of cyclohexyl hydride **21** to phenyl hydride **18** in benzene via initial reductive elimination followed by oxidative addition of benzene revealed that the reaction was inhibited by added cyclohexane, and showed saturation kinetics when the observed pseudo-first-order rate constant was plotted against the benzene/cyclohexane concentration ratio. At high benzene concentration, the reaction was zero order in the concentration of benzene and showed no benzene/benzene-d_6 isotope effect; the activation parameters measured under these conditions were $\Delta H^{\ddagger} = 35.6 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = 10 \pm 2$ e.u. These observations provide strong evidence that the initial step involves reductive elimination of cyclohexane, and the benzene C−H activation reaction takes place in a subsequent step.

The molecularity of the reaction was studied next. A crossover experiment with a mixture of **21** and **21**-d_{12} thermalized in benzene produced >90% cyclohexane-d_0 and -d_{12} along with phenyl hydride **18**. The negligible amount of products with scrambled labels indicated a highly intramolecular mechanism for the cyclohexane elimination (eq 10).



The rate of the reductive elimination of cyclohexane from **21** and **21**-d_{12} was examined, and an unexpected inverse isotope effect of $k_{H-12}/k_{D-12} = 0.7 \pm 0.1$ was found. The inverse isotope effect was in sharp contrast to the normal isotope effect of 2.2−3.3 observed for most other reductive eliminations of alkanes at the time.[35−37] However, Jones and co-workers had observed an inverse isotope effect in the reductive elimination of benzene from a rhodium arene hydride. They proposed that the effect arose from an equilibrium isotope effect in a preequilibrium step rather than from an intrinsic inverse isotope effect in the reductive elimination transition state.[38,39] In our case, an equilibrium isotope effect required the existence of an intermediate on the reaction path between the cyclohexyl hydride **21** and the 16-electron intermediate Cp*$IrPMe_3$. Therefore, we proposed that the newly formed C−H bond on the cyclohexane remained datively bonded to the iridium center, in an intermediate complex after reductive elimination (eq 11).[40]

Consistent with this proposal, compound **21a**-d_1, labeled specifically with a single deuteride, exhibited interconversion with **21b**-d_1 competitive with formation of **18**, as observed by ^1H NMR spectroscopy (Scheme 8).

The more reactive Rh analogue exhibited similar scrambling at lower temperature. In a careful double-labeling experiment, complex **25a** was synthesized with

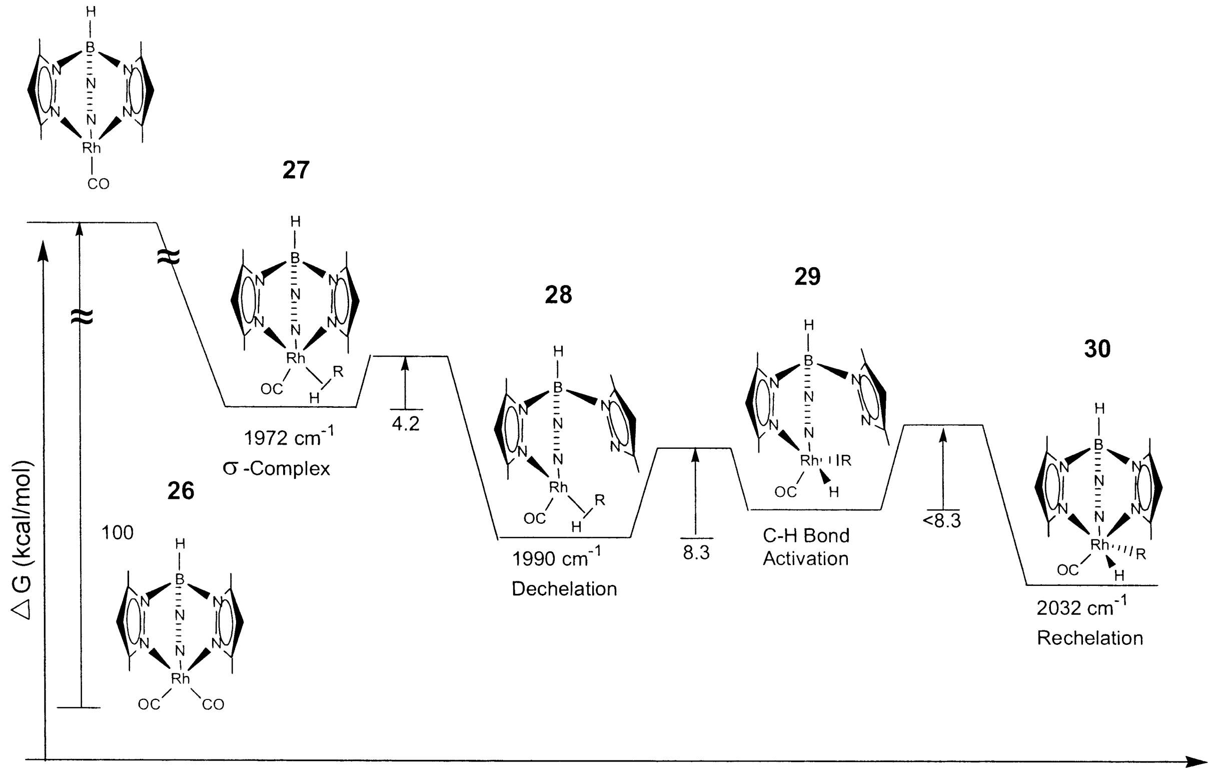
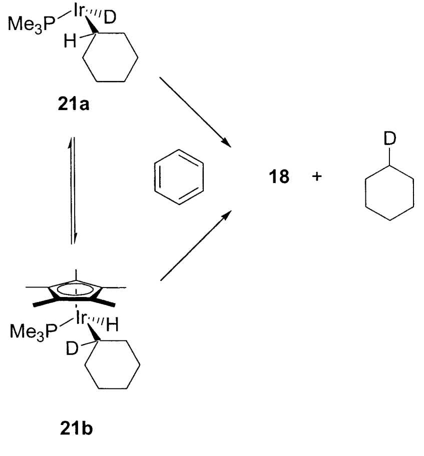
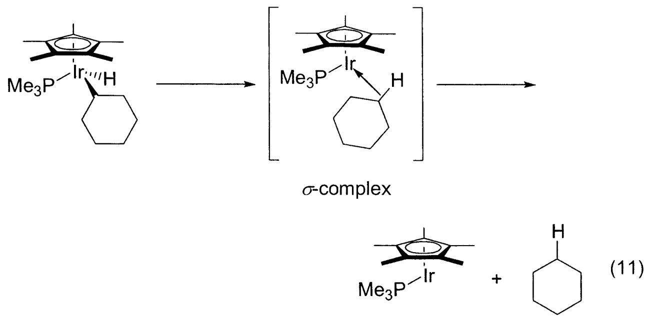


FIGURE 1. Reaction coordinate diagram for the C−H activation reaction of Tp*Rh(CO)$_2$ in alkane solution.

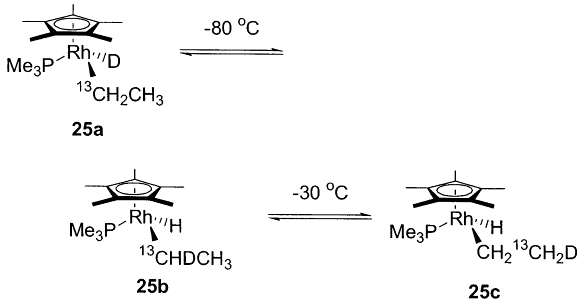
SCHEME 8. Isotope Scrambling through σ-Complex Competitive with Trapping by Benzene



the hydride position labled with deuterium and with the α-carbon enriched in ^{13}C (eq 12).[41] At −80 °C the deuteride was found to exchange with hydrogen on the labeled carbon (**25b**); furthermore, upon warming to −30 °C the deuteride migrated to the β-position, *while remaining attached to the labeled carbon* (**25c**). This concomitant migration of the labeled atoms was consistent with an intermediate σ-complex, and it cast doubt on alternate mechanisms that required a β-hydride elimination.



(11)



(12)

With the preponderance of evidence in our system as well as in other systems pointing toward the existence of σ-alkane complexes in late-transition-metal C−H bond activation, we sought spectroscopic and flash kinetic means to observe these species directly. Because all organic solvents react, the use of noble gases as solvents (e.g., liquefied xenon or krypton) was required to observe the activation of alkanes that were difficult to liquefy or use as solvents (such as cubane, adamantane, and methane).[42] Most importantly, though, these inert solvents also allowed us to carry out flash kinetic experiments providing direct evidence not only for the existence of metal−alkane but also metal−noble gas complexes.[43−45]

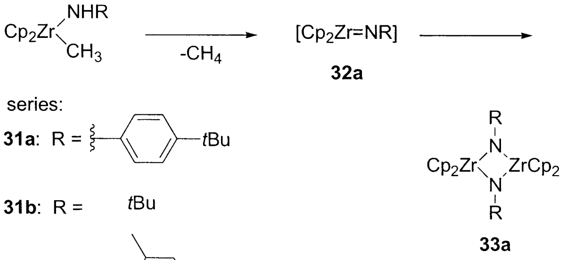
In collaboration with the Moore, Frei, and Harris groups, we were able to study the oxidative addition reaction in alkane solution using ultrafast spectroscopy on the microsecond, nanosecond, and picosecond time scales.[46] One important change in the picosecond study was the use of the complex Tp*Rh(CO)$_2$ (**26**), which was chosen because it had a relatively high quantum yield of ~30% compared to the quantum yield of ~1% for CpM(CO)$_2$ (M = Rh, Ir). Additionally, the presence of CO ligands provided a convenient and sensitive way to monitor the progress of the reaction. Upon irradiation of complex **26**, two intermediates were observed on the picosecond time scale, one with a CO resonance at 1972 cm^{-1} and the other with a CO resonance at 1990 cm^{-1} (Figure 1). The 1972 cm^{-1} transient was assigned as the initial σ-complex (**27**) and had a lifetime of 200 ps. The second intermediate was concluded to be a σ-complex in which one of the three Tp* arms had dissociated (**28**). Nanosecond IR experiments revealed that the formation of the σ-complex was followed by an oxidative addition of the alkyl C−H (**29**) bond and rapid reassociation of the Tp* arm (**30**). The barrier heights included in Figure 1 were estimated from the decay rates of the intermediates.

After this work, our group found systems in which the C−H activation chemistry of alkanes can be extended from Ir(I) complexes to include Ir(III) complexes.[47] The mechanism that operates in these higher-valent systems could involve an oxidative addition/reductive elimination pathway in which Ir(III) is oxidized to an Ir(V), analogous to that which occurs with the Ir(I) complexes discussed above, or a σ-bond metathesis transition state. Our synthesis of stable Ir(V) complexes as models for oxidative-addition intermediates lends support to the oxidative addition pathway.[48] We have most recently identified reactive Ir(III) complexes that can be used to carry out catalytic H/D exchange from benzene-d_6 and even D$_2$O into organic compounds through this reactivity.[49,50]

VII. Group IV Imido, Sulfido, and Oxo Complexes: C−H and N−H Bond Activation, Cycloaddition, and Dative Ligand Coordination Allow for Trapping of Reactive Intermediates

Prior to 1988, many metal−oxo (M = O) and −imido (M = NR) complexes were known, but in most the M = X double bonds were notoriously inert. Our group noticed an absence in the literature of monomeric group IV metallocene complexes of this class. This suggested to us that if these species could be generated, they might exhibit more extensive chemistry than the oxo and imido complexes that were known at the time. In 1988, we reported the generation and a variety of trapping reactions of the first monomeric imidozirconocene (Cp$_2$Zr=NR) complexes.[51]

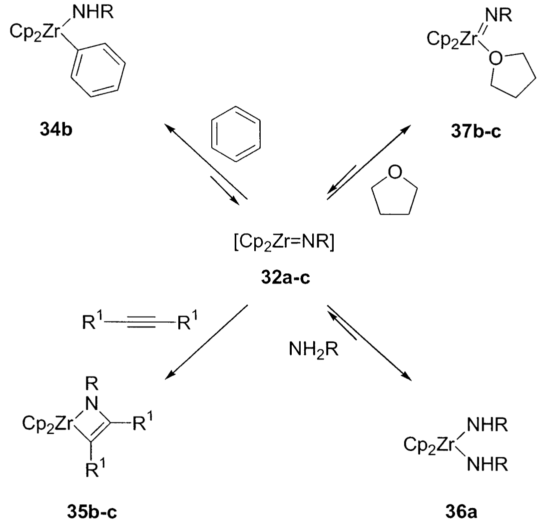
Thermolysis of methyl 4-*tert*-butylanilide complex **31a** in benzene led to the formation of dimerized imido complex **33a**, which was characterized by X-ray crystallography. This seemed consistent with formation and subsequent dimerization of the desired transient imido complex **32a** (eq 13) and provided our first insight into the reactivity of these complexes.



(13)

Increasing the steric bulk of the R group by using *tert*-butyl (**31b**) or 2,6-dimethylphenyl (**31c**) prevented dimerization and allowed us to explore the chemistry of the desired intermediate through additional trapping reactions. Thermolysis of **31b** in benzene gave methane and Cp$_2$Zr(NH-*t*-Bu)(Ph) (**34b**), the product of C−H activation of the benzene solvent by the reactive intermediate **32b** (Scheme 9). Alkynes also served to trap the free imido complexes **32b** and **32c** efficiently via cycloaddition, yielding metallacycle products **35b** and **35c**. Amines reacted with the free imido complexes, as exemplified by the thermolysis of methyl amide **31a** in the presence of 4-*tert*-butylaniline, which produced bis-amide **36a**. Finally, intermediates **32b** and **32c**[52] could be trapped by THF to give the simple adducts **37b** and **37c**. To our knowledge, **37b** was the first crystallographically characterized monomeric group IV imido complex. Heating these THF-trapped products in the presence of alkynes led to the formation of metalacycles **35b** and **35c**, implying THF dissociated to generate the reactive free imido complexes.

SCHEME 9. Reactions of Cp$_2$Zr=NR



Kinetic evidence provided further support for the generation of a discrete transient imido intermediate. Cycloaddition of phenyl amide **34** with 1-phenyl-1-propyne in cyclohexane-d_{12} at 85 °C exhibited clean first-order dependence on the concentration of **34** but no dependence on the concentration of the alkyne.[51] Similarly, thermolysis of **31a** in the presence of 4-*tert*-butylaniline exhibited first-order dependence on concentration of **31a** but no kinetic dependence on the con-

TABLE 2. Equilibrium Constants for Nickel Amide/Amine Exchanges (eq 14)

X	K_{eq} (est error)	$\Delta G°$ (est error) (kcal/mol)
p-NMe$_2$ (**38b**)	0.21 (0.02)	+0.9 (0.1)
p-OMe (**38c**)	0.50 (0.05)	+0.4 (0.1)
p-Me (**38a**)	1	0
p-F (**38d**)	2.2 (0.3)	−0.5
p-CF$_3$ (**38e**)	400 (50)	−3.5 (0.1)
p-Ac (**38f**)	$2 (1) \times 10^3$	−4.5 (0.3)
m-NMe$_2$ (**38g**)	1.1 (0.2)	−0.1 (0.1)

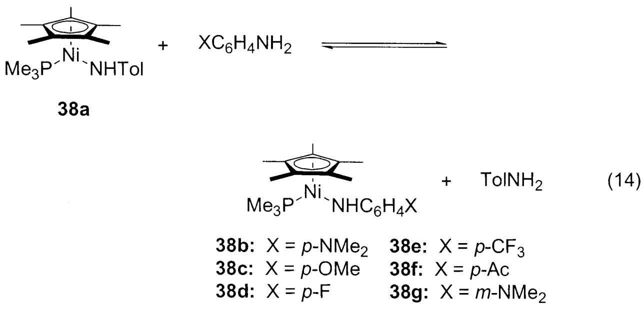
centration of amine. These experiments were consistent with a rate-determining methane elimination to generate the free imido intermediate $Cp_2Zr{=}NR$. A similar experimental approach led to the successful generation and study of the analogous complexes $Cp^*{}_2Zr{=}O$, $Cp^*{}_2Zr{=}S$,[53,54] and $Cp^*{}_2Ti{=}S$,[55] and to the generation and study of the enantioselective reactions of (ebthi)Zr=NR (ebthi = ethylenebis(tetrahydroindenyl)).[56] Most recently, the enantioenriched ethylenebis(tetrahydroindenyl)zirconocene analogue (ebthi)Zr=NR was found to undergo cycloaddition with allenes with high enantioselectivity, leading to a kinetic resolution of racemic allenes.[56]

VIII. Cyclopentadienylnickel Amido Complexes: Equilibrium Studies and E/C Analysis Reveal the Balance between Electrostatic and Covalent Contributions to Metal−Heteroatom Bond Strength

Late-transition-metal compounds with monoanionic nitrogen and oxygen ligands are important intermediates in industrial[57,58] and biological[59] processes. While many new complexes of this type had been synthesized in the mid-1990s, the factors controlling the strengths and reactivity of M−N and M−O bonds were not well understood.

In 1997, we presented the synthesis, characterization, and study of new monomeric nickel amido and alkoxo complexes.[60] In this paper, we discussed equilibrium studies and substituent effects that we had used to gain insight into the electronic nature of the Ni−X bond. Importantly, our results ran counter to the then-current model for predicting late transition metal−X bond energies. We therefore offered a more general qualitative model based on electrostatic−covalent (E−C) theory.[61]

The equilibrium constants for the reactions indicated in eq 14 were measured at room temperature by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy in benzene-d_6 and are presented in Table 2. These data showed that, within this series, a more electron-withdrawing X substituent resulted in a stronger Ni-X bond, assuming that the entropy remained constant.



38b: X = p-NMe$_2$ **38e:** X = p-CF$_3$
38c: X = p-OMe **38f:** X = p-Ac
38d: X = p-F **38g:** X = m-NMe$_2$

The use of exchange reactions to derive the relative bond dissociation energies of late metal−ligand bonds had been employed most extensively in work by Bryndza and Bercaw.[62] By measuring K_{eq} for a large series of X ligands for which the H−X bond energies were known, a scale of relative M−X bond energies could be devised.[63] Two of their systems are shown in eqs 15 and 16.

$$Cp^*Ru(PMe_3)X^1 + HX^2 \xrightleftharpoons{K_{eq}} Cp^*Ru(PMe_3)X^2 + HX^1 \qquad (15)$$

X = OH, OMe, $CH_2C(O)Me$, NHPh, NMePh, NPh_2

$$(DPPE)Pt(Me)X^1 + HX^2 \xrightleftharpoons{K_{eq}} (DPPE)Pt(Me)X^2 + HX^1 \qquad (16)$$

X = OH, OMe, CCPh, $CH_2C(O)Me$, NHPh

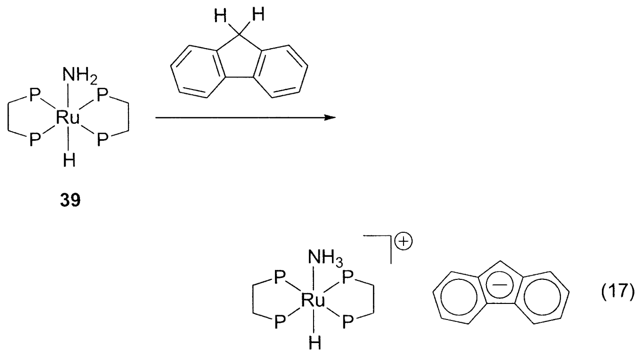
In Bryndza and Bercaw's study, the equilibrium constants for all of the reactions were found to be near unity. This correlation implied a model for bonds between late transition metals and anionic ligands in which the trend in H−X bond energies directly matched the trend in M−X bond energies. In our system, however, a plot of relative Ni−N bond energies versus H−N bond energy had a slope of 1.9. That is, much larger differences in M−X bond energies were observed compared to those predicted by the Bryndza/Bercaw model.

In our qualitative model, factors that stabilize the partial negative charge on the N, O, or S atom would stabilize the metal complex. This was conveniently analyzed using the E−C substituent constants of Drago,[61] which indicated that electrostatic factors play a much larger role in the Ni−X bond energy than covalent factors, particularly for N and O monoanionic ligands. Thus, we proposed amending the late-metal bonding model put forward by Bryndza and Bercaw, in which the proton and the transition metal bind to X with similar covalent versus electrostatic contributions, to incorporate more electrostatic contribution in the M−N and M−O bonds relative to the respective H−N and H−O bonds in at least the nickel systems and potentially in other systems as well.

IX. Ruthenium Amido Complexes: Reactivity Trends and Hydrogen/Deuterium Exchange Rates Establish Its Unusually High Basicity

When late transition metal−heteroatom bonds react with organic molecules, an important question concerns whether the transformation takes place via odd- or even-electron intermediates. For example, many late metal alkoxides undergo overall even-electron RO-transfer reactions with electrophiles.[64−66] In other cases, metal−oxygen bonds have been proposed to react by initial hydrogen atom abstraction, an odd-electron process.[67,68] In 2000, as part of our research into the synthesis and reactivity of late-transition-metal amido complexes (see also section VIII), we reported[69,70] a study on the preferred reactivity mode of the well-characterized[71] parent amido complex *trans*-$(DMPE)_2(H)Ru(NH_2)$ (**39**).

Complex **1** reacted cleanly with organic compounds having C−H bonds characterized by a wide range of bond dissociation energies and acidities. Three interrelated modes of reactivity were observed. The first was the generation of a stable ion pair formed by overall proton transfer from the carbon to ruthenium-bound nitrogen, as exemplified by the reaction of the hydrocarbon fluorene with **39** to form ion pair **40** (eq 17), which was isolated and characterized by X-ray diffraction. The second mode of reactivity involved proton transfer to nitrogen followed by displacement of the resulting ammonia ligand from the Ru center, as exemplified by the reaction of cyclobutanone with **39**. In this case ^{1}H NMR spectroscopy provided evidence for an intermediate ion pair, **41**, which then underwent the second displacement step to form covalent enolate complex **42** (eq 18). The third mode of reactivity was observed with exceedingly weakly acidic compounds, as exemplified by the reaction of **39** with excess toluene-d_8. In this case, the Ru−NH_2 group was (surprisingly) basic enough to induce exchange of deuterium for hydrogen in the toluene methyl group and, ultimately, the DMPE ligands of the ruthenium amide complex itself (eq 19). However, intermediate ion pairs could not be spectroscopically observed in this case, probably because of the greater endothermicity of the initial proton-transfer reaction.



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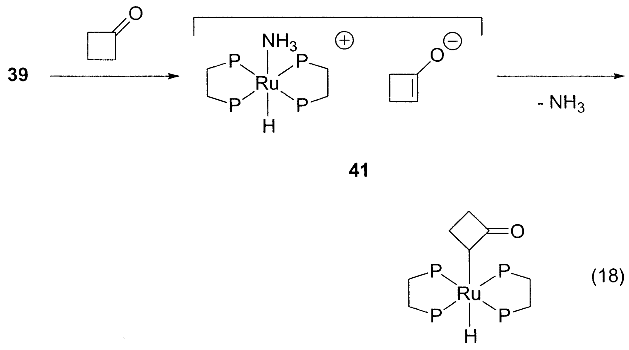
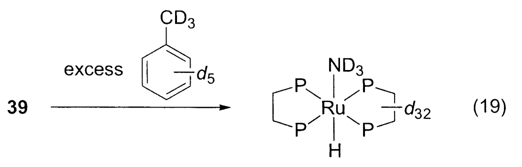


42



39-*d*$_{34}$

Monitoring the rate and reactivity of H/D exchange for a series of substrates helped to decipher whether these reactions proceeded via one- or two-electron processes. In all cases, the pK_a and *not* the bond dissociation energy of the substrate appeared to be the physical property that controlled the reactivity, including the rate of H/D exchange. For example, no H/D exchange was observed with the benzyl methyl hydrogens of *N*,*N*-dimethyl-*p*-toluidine, even though they have aromatic methyl C−H bond dissociation energies similar to those of toluene. This lack of reactivity is most adequately explained by the assumption of a proton-transfer mechanism for the exchange and thus by the lower acidity of the benzyl protons in *N*,*N*-dimethyl-*p*-toluidine.[72,73] Similarly, amido complex **39** undergoes H/D exchange with ammonia, despite the exceptionally high NH_3 bond dissociation energy (107.4 kcal/mol). Treatment of **39** with a variety of poorly acidic substrates that possess particularly weak C−H bonds, such as cycloheptatriene (73 kcal/mol), led to H/D exchange; however, no products from radical dimerization were observed. These results provided strong support for a two-electron pathway for the hydrogen transfer reactions and also attested to the high basicity of the ruthenium amide complex. It is still not clear, however, why ammonia is displaced by the anion formed on proton transfer in some of these reactions, but not in others.

X. Conclusions

The wide variety of unknown organometallic reaction mechanisms (and, as it turned out, organometallic reactions) in the 1970s challenged our group to apply traditional physical−organic experiments to aid in the understanding of these processes. During the last 30 years, these studies have helped us provide insight into a number of important organometallic systems, including reduction, polymerization, C−H bond activation, metal−ligand multiple bonds, and metal−ligand bond energies and basicities. Over this time, these techniques have also been adopted by many other research groups, and mechanistic studies are now an important part of organometallic research. They have also been employed extensively by investigators who apply organometallic compounds in the development of new applications, especially in industrial catalysis and synthetic organic chemistry, and they have yielded insights into the operation of reactions that take place in heterogeneous systems. We expect that the tradition of using physical organic concepts, supplemented by the increasing breadth of experimental and computational techniques that have become available for mechanistic studies, will provide even more intimate pictures of organometallic processes in the future.

Acknowledgment. The research described in this Perspective would not have been possible without the talent and dedication of the large number of student and postdoctoral co-workers who participated in it, many of whom are listed in the references. In addition, many insights and directions were provided by faculty colleagues and spectroscopic service directors who assisted, both with and without formal acknowledgment, in many aspects of the work. Finally, on behalf of everyone who contributed to the research achievements described here and benefited from the training that took place during all aspects of this work, we acknowledge support from the agencies, companies, and nonprofit organizations that supported it financially. These include the California Institute of Technology, the University of California, the National Science Foundation, the Department of Energy through the Lawrence Berkeley National Laboratory, the National Institutes of Health, the Chevron, Dow, and E. I. DuPont companies, the Camille and Henry Dreyfus Foundation, and the American Chemical Society.

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