

## **From the Felkin-Anh rule to the Grignard reaction: an almost circular 50 year adventure in the world of molecular structures and reaction mechanisms with computational chemistry.<sup>§</sup>**

<sup>§</sup>This Rosarium is dedicated to the memory of Jack D. Dunitz. I was privileged to spend a year in his laboratory.

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### **Abstract**

This rosarium article relates the adventure started 50 years ago of a computational chemist who was interested in molecules; what are they, what are their shape and how do they react. The story describes results, still valid today, obtained with highly simplified models of chemical reality and elementary computational methods and the gain resulting from the use of better models and more elaborate computational methods. It was necessary to select examples. In this presentation, focus is on hydride and dihydrogen complexes as well as on nucleophiles. Nucleophiles were considered as free hydrides in gas phase at the start of the rosarium while the Grignard reaction is treated with ab initio molecular mechanisms at the end of it.

### **Introduction**

*“The White Rabbit put on his spectacles. ‘Where shall I begin, please your Majesty?’ he asked. ‘Begin at the beginning,’ the King said gravely, ‘and go on till you come to the end: then stop.’”*

Jack Dunitz loved to cite Lewis Carroll whenever he could and this quote from Alice in Wonderland was extensively used. I will follow this advice here, but where is the beginning? Because one’s life and choices are linked to one’s past and one’s family, I will start the story with my parents and notably my mother even before I was born. I am grateful to the format of the rosarium to permit such detour.

### **My luck in life with a bit of background**

Basia Lipkowicz was born in Dolhinow (now Bielorrussia) in 1908 but her childhood was spent in Vilnius (Lithuania). She was the 6<sup>th</sup> daughter of Kaya-Bella and Schmucl Lipkowicz and their last attempt to have a son. The story says that she was thrown on the floor by the frustrated

older sisters when she was born. Was it at this moment that she acquired her survival skill? Let us accept it. Even if her parents were religious, she was educated in a non-religious Jewish gymnasium. She graduated but there was no future for a Jewish girl in Vilnius at the end of the 1920s. *Numerous Clausus* set a very tight limit on the number of Jews who could enter the University and her academic records gave her no hope. Furthermore, her dream was to be on the move and even to travel the world in a caravan like a gipsy. The caravan took the shape of a train and at age 21 she arrived at Gare du Nord in Paris at the end of 1929 with a suitcase containing her feather pillows, 50 dollars in her pocket and the address of a distant relative. She was by herself, a friend who was supposed to join changed her mind at the last moment. She did not stay long with the relative and dived into Paris. She registered as a student at the Sorbonne, the initial excuse for the trip, but immediately looked for a job. After several unsuccessful attempts including a job to make zippers, she read an advertisement in a newspaper "*On demande jeune fille*" (Looking for a young woman). This could have been a trap; it was her luck. The company, involved in international business, needed employees for reading foreign newspapers. Basia whose mother languages were Yiddish at home and Russian at school spoke also reasonable German and some Polish. Her weakest language was French. Basia was hired on the spot as assistant librarian and one of her most enjoyable periods in life started. It did not last too long. She wanted to visit her mother who was not feeling well and she also thought that she could settle in Moscow where one of her sisters lived with her husband and their two children. Thus, she went back East. However, as she said, she was already spoiled by her "good" life in France and the living conditions in Moscow in the mid 1930s were too difficult for her. Thus, again on the move, Basia came back to Paris. Her job was gone and after many years of hardship, alternating short and poorly paid jobs, luck hit again. She became an assistant librarian in an academic institution dedicated to child psychology. Luck was unfortunately not going to last long. In 1941, the head of the institute told her that a pro-Pétain newspaper revealed her name as one of these Jewish immigrants benefiting from a job in an academic institution. He advised her to hide and provided her with several months of salary as support. Life became not only hard again but dangerous. Basia often changed places to spend her nights even if her appartement was rented under the name of a non-Jewish friend. She had a false identity card and, in her own words, she considered herself lucky to have survived. Unfortunately, if Basia was lucky, her companion during the war time, Moishe Gawenski, was not. He was caught by the French police in a raid at Place de la République and deported to Auschwitz in March 1943. During this dark period, there was however one warm event in her life. She was greatly supported by an impressive woman, Geneviève Favre (1855-1943), whom she met through her grand-daughter at the time of the first job. G. Favre, who was the daughter of Jules Favre, one of the founders of the 3<sup>rd</sup> Republic was also one of the first women to divorce at a time when it was simply not acceptable! An

unusual woman from the high bourgeoisie of Protestant faith. Her apartment had been a meeting place for the international intellectual community for years and as the war started, aged over 85 she found ways to help the French resistance. For many years, she held open table once a week and always invited Basia. For many peoples like Basia, it was a moment of relief from hardship. Geneviève Favre was the person I heard the most from Basia. I wanted to acknowledge her courage and pay her credit even if I have no connection to her. At the end of the war, Basia was alive but in desperate mood as she was quite certain that her family had not survived. Vilnius was one of the largest fully eradicated ghettos and the iron curtain imposed by SSSR made any search of survivors essentially impossible. She thus thought she was the survivor from a large family. I was the one who was informed only in 2018 that offspring of two of her five sisters were living, one in Israel and one in USA. And only in 2021, I learned that I have another relative from a third sister of Basia living in Siberia. Basia must have felt very lonely after the war. A man, named Otto Eisenstein, whom she had met before the war had kept her address. He was born in Sadagora, (now Romania) and had spent his childhood in Vienna with his grand-mother. I do not know when he arrived in France. When the war started, Otto registered into the Foreign Legion, which saved his life since he was “only” a war prisoner. When Otto, knocked on the door of Basia after the war, it was the meeting of two lonely persons who had not much in common. They eventually got married and I was born in 1949. They parted soon after my birth and I stayed with Basia in Paris (Figure 1).



**Figure 1:** Basia Lipkowicz, my mother and me at the age of 5-6, picture taken in Luchon, a thermal resort in the Pyrénées (France). Copyright to the author.

Basia understanding and guidance in life were simple: “there is nothing impossible if one tries hard enough”. This was the unique commandment to her daughter. Basia never

understood why I was poor at playing piano, could not sing a note, did not speak Russian through genetic transmission even though she never spoke Russian to me. She just forgave my total inability in the practice of sport related activities where I oscillated between the last and the last-1 ranks during my entire time at school. Education was the solution to any problem and her motto was “study, study, study” and always take the hardest route. Just a bit hard for a young child who was an addicted reader especially of adventure stories. After the *baccalauréat*, I had no clue of what I would do except that I was better in science and especially in physics and chemistry than in humanities. I attempted the competitive exams of the “*Ecoles Normales*” (essentially honor classes for high education, in partnership with universities, providing also a stipend to students) during the spring of 1968. The exams were not interrupted by the events even if reaching the exam places was a challenge with the absence of public transportation. I was not selected for the “*Ecoles Normales*” but my rank was such that I could enter the university at the BA level with a small fellowship. I wanted to study at “Jussieu”. the University, at the center of Paris, also known as University Pierre and Marie Curie and nowadays known as Sorbonne University. It was closer from home but it was slow to reopen after the uprising in the spring of 1968. However, University of Paris-Sud, a newer university set in Orsay, south of Paris, had reopened and most of my schoolmates registered there. I applied a bit late to the Chemical Physics section and I was accepted. This was my lucky card.

### **Outline of this rosarium**

I wish to describe now how I got into the field of computational chemistry and how it changed from 1970 till today. I needed to select topics for this. I am considerably helped by an article published in ACS Catalysis in 2019, with the flattering title of *A Career in Catalysis: Odile Eisenstein*.<sup>1</sup> Five former co-workers who became colleagues and friends, David Balcells, Eric Clot, Stuart A. Macgregor, Feliu Maseras and Lionel Perrin, joined efforts to write this glowing description of my scientific activities in the domain of organometallic chemistry and the relevance to homogeneous catalysis. There is no need to repeat what is so well described in this publication, which I recommend to interested readers. I thus decided to write a personal account of how I evolved as a computational chemist, mostly interested in chemistry, from the early years where only extremely simple methods could be used to the present time where highly elaborate methods and resources are available, opening the possibility to study highly complex chemical situations. I selected topics which illustrate the challenging steps of this progression and my constant interest to interpret the results in terms which could be understood by non-theoreticians. As a guide line, I focus on chemical species and reactions which involve in diverse ways nucleophilic entities that were often hydrides. This topic led me

to study dihydrogen and C-H bond activation. This arbitrary choice illustrates how we have progressed in the last 50 years.

### University of Paris-Sud Orsay

University of Paris-Sud at Orsay was established based on the model of English or American Campuses. Buildings were dispersed over a large area surrounding by trees and even with a “river” (l’Yvette) going through. For someone used to vibrant city, it was very pleasant. But it was the quality of the professors that was essential. During my first year, I was taught structure and bonding by Lionel Salem, kinetics by Michel Magat, thermodynamics by Marcel Fétizon, spectroscopies by Florence Fayard to cite only a few. I was especially fascinated by the approach of Lionel Salem for the presentation of electronic structures of simple molecules. During my second year of studies, I had Nguyen Trong Anh in Organic Chemistry. Anh started his teaching with the Woodward-Hoffmann (WH) rules. I thus discovered that the electronic structure also informed on reactivity. I was fascinated. Since I was doing well in class, Nguyen Trong Anh asked me if I was interested of doing a master degree and even a thesis. I had no clue of what it meant but Anh told me that I could work on extensions of the WH rules. That was enough to convince me. I also badly needed a job since my fellowship was insufficient. I was offered one of the few available teaching assistant positions and I did the problems in organic chemistry for pre-med students. I felt incredibly lucky and happy. (Figure 2)



**Figure 2.** Nguyen Trong Anh and me in the 1970s. Copyright to the author

For my master thesis (thèse 3<sup>ème</sup> cycle) I was suggested to work on the factors that control the rates and regioselectivity of the Diels-Alder reaction. Hückel method was sufficient for this topic in the early 70's. Following the visionary work of Salem on the interactions between conjugated molecules,<sup>2</sup> it was sufficient to search for the greatest stabilizing interactions between the  $\pi$ -orbitals of the two substrates. This was often found to be associated

with the largest interaction between the two frontier  $\pi$ -orbitals closest in energy. It should be noted that we were thus searching for factors which *maximize* the interactions between reacting molecules. These stabilizing interactions were supposed to lower the energy demand to reach the transition state, whose structure and energy we could not determine. This was the state-of-the-art procedure at this time. It went well and it validated the working hypothesis that energy curves associated with different paths would not cross on going from the reagents to the transition states. For dienes and dienophiles, the major regioisomer was proposed correctly in most cases. The rates were more challenging to reproduce but globally it worked, namely the rates of cycloaddition increase by incorporating substituents of opposite electronic demands on the diene and dienophile. Thus, this accounted for the Alder rule (donor on the diene, acceptor on the dienophile) and the inverse Alder rule (reverse distribution), the first one leading, in general, to higher rates. I got my “3<sup>ème</sup> cycle” thesis (equivalent today to a master thesis) with honors and published with Anh several scientific articles, some of them in French.<sup>3</sup> Cycloadditions were in fact extensively studied at the time<sup>4</sup> and it was wiser to move to other topics. We applied the hard and soft acids and bases theory of Pearson to the regioselectivity, C<sub>2</sub> vs. C<sub>4</sub>, for the nucleophilic addition to conjugated enones but success was moderate.<sup>5</sup> It was frustrating not to be able represent LiBH<sub>4</sub>, RMgX, organocopper reagents etc. It will take many years to study properly such reactions. However, in the 1970s, these qualitative studies led to intense discussions with experimental groups. This was essential for my training.

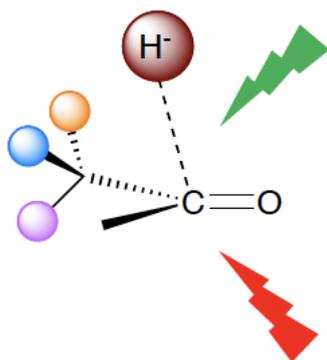
Before I continue further, I need to stress how much I benefited from my supervisor, Nguyen Trong Anh. He was a trained synthetic organic chemist who became very interested in the new ideas associated with the WH rules. He wrote a book “*Les règles de Woodward-Hoffmann*” (Ediscience) in 1970 where the rules were illustrated by numerous experimental examples. Anh had amazing pedagogical talents and was highly appreciated for his ability to explain simply orbital arguments. As I started to work with him, I was quickly introduced to the community of experimental chemists. I am very grateful to Anh to have dragged me along to many highly enjoyable discussions. This gives me the opportunity to acknowledge two persons who were especially important for me, Jacqueline Seyden-Penne and Bianca Tchoubar. I was lucky enough to meet both of them and benefit from their insights.

The topic of my PhD originated from discussions between Nguyen Trong Anh and Jacqueline Seyden-Penne (1930-2018). Jacqueline was a chemist whose main interest was the determination of reaction mechanisms in organic chemistry. She had been trained by Bianca Tchoubar (1910 Kharkov-Ukraine-1990 Paris) a remarkable chemist who basically introduced reaction mechanisms in Organic Chemistry in France and wrote a major textbook

entitled "*Mécanismes Réactionnels en Chimie Organique*". Interested readers can find further information about this impressive person.<sup>6</sup> Back to Jacqueline Seyden-Penne, she was interested in asymmetric induction for which not much was understood at a molecular level. Consequently, the topic of 1,2 asymmetric induction was suggested for my "Thèse d'Etat".

Before getting into the 1,2 asymmetric induction, I wish to devote a few lines to my academic position. Immediately after being a TA in organic chemistry for pre-med students, I was offered a job in the Centre National de la Recherche Scientifique, known under the acronym CNRS. This is certainly surprising for a reader today, and it was indeed an unusual time for this prestigious institution, created in 1939 by Jean Perrin. Those recruited by the CNRS could entirely devote their time to research, had no required teaching, and could work in any academic laboratory in France which had a CNRS label (a proof of high standing). In the early 1970s, hiring very young researchers with good academic records and promising start was a standard. Although it could be considered as difficult to evaluate the quality of a researcher with only two years of research, it was the common attitude at that time. I had not even completed my "thèse 3<sup>ème</sup> cycle" but I had a few publications and a strong determination. Aged 22, I had an academic position in a prestigious research center. Such opportunities did not last long as in the early 1980s it was already difficult to get a position at the CNRS. Today, a PhD and several post-doctoral stays are needed, open positions are rare and the competition is extremely severe. In 1972, I started my study on the asymmetric induction having a comfortable position and time to think about the problem as no time limit was imposed for the duration of the thesis!

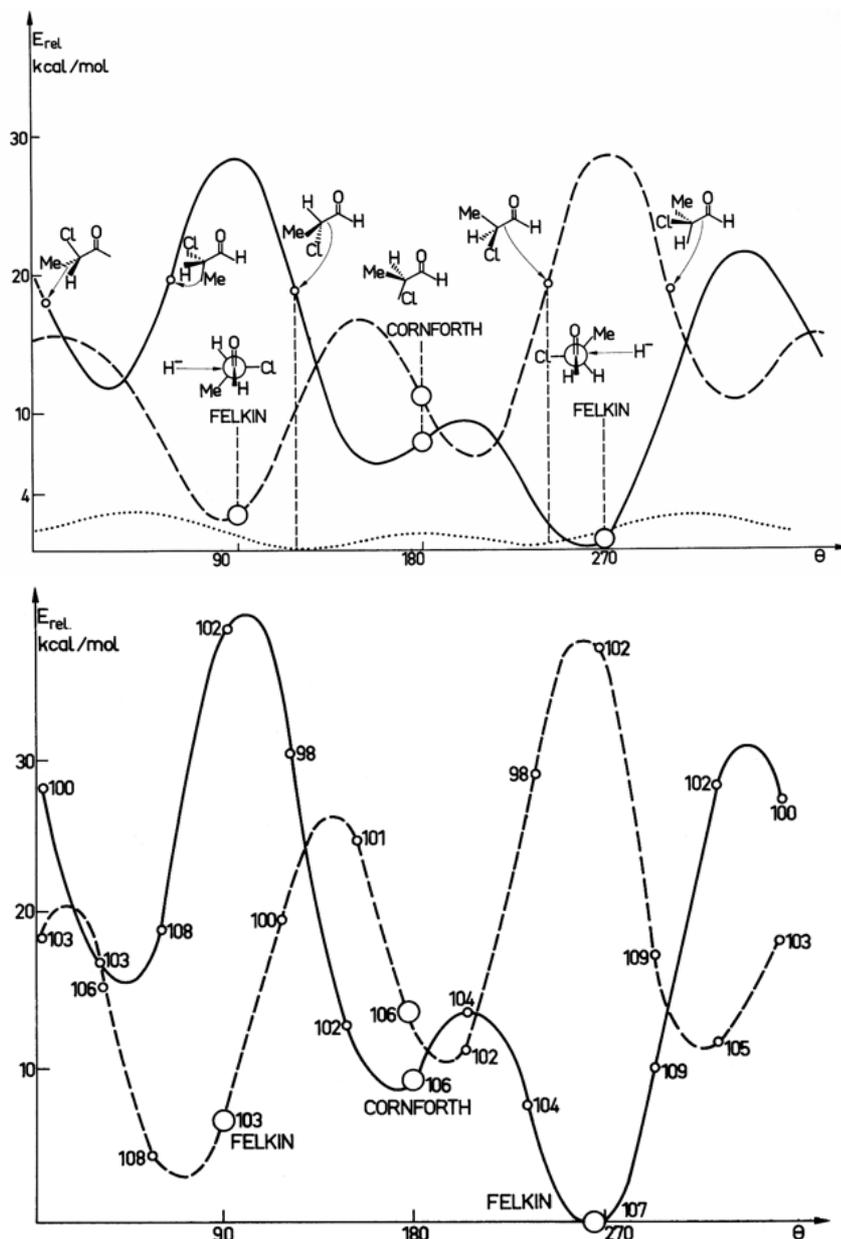
The topic was well defined. Nucleophilic addition to an aldehyde or ketone bearing an  $\alpha$ -chiral carbon gives unequal quantities of the two diastereomers resulting from the approach along the green or the red arrows (Scheme 1). Which factors determined the formation of the major isomer? Empiric rules had been proposed by Cram or Cornforth, Karabatsos and Felkin. The nucleophile added to the least hindered face of the carbonyl in a given conformation of the molecule; the problem was that different conformations had been selected by each author implying different rules (Figure 3). For Cram, the selected conformation was the one where the carbonyl group was flanked by the small and medium groups, the large group being transoid to the carbonyl. Cornforth had the same conformation where the large group was a polar group. Karabatsos selected isomers where either the large or the medium groups eclipsing the carbonyl. Finally, Felkin proposed that the nucleophile enters trans to the large group on the conformation where the medium group was closer to the carbonyl. Which of these models was best and for what reasons? This was the topic of my PhD thesis (thèse d'Etat at this time).



**Scheme 1:** Assumed transition state for nucleophilic addition to a prochiral aldehyde or ketone taken to study 1,2 asymmetric induction (addition along the green or red arrows occurring in unequal quantities). A hydride was used to model the nucleophile.

In my previous studies the reactivity of a given molecule was inferred by analyzing some of its intrinsic properties. We started with a similar hypothesis. We thought that, in a prochiral carbonyl, the electron density of the  $\pi$ -bond of CO should be different on the two diastereotopic faces of the carbonyl. We looked at this through  $\sigma$ - $\pi$  mixing and this led to a preference for the Cram rule.<sup>7</sup> I don't remember what prompted me to pursue further this study. Probably the pioneering studies of Jack Dunitz and Hans-Beat Bürgi on modeling reaction paths, revealed by crystal structures and the inspiring associated theoretical study by Georges Wipff, and Jean-Marie Lehn.<sup>8</sup> Following their studies, I modeled a "transition state" by setting a naked hydride at 1.5 Å from the carbonyl carbon at various  $\text{H}\cdots\text{C}=\text{O}$  angles. (Scheme 1). This setting does not correspond to any experimental situation since there is nothing like a naked hydride but it carried the physics of the nucleophilic addition and such model could be calculated in these years at the Hartree-Fock level with the modest STO-3G basis set for all atoms including the hydride! In the first set of calculations the hydride was set perpendicular to the  $\text{C}=\text{O}$  direction. For this given position of the nucleophile, the chiral group was rotated and the energy reported as a function of the conformation of the chiral carbon (Figure 3 top). This revealed a preference for the Felkin model. In a second set of calculations, the  $\text{H}\cdots\text{C}=\text{O}$   $\alpha$  angle was allowed to vary to take into consideration the preference for an approach direction with  $\alpha > 90^\circ$  as established by Bürgi, Dunitz, Lehn and Wipff.<sup>8</sup> Taking this factor into consideration, the preference the observed major diastereomer increases. Furthermore, the Felkin model becomes even more clearly the preferable model (Figure 3 bottom).<sup>9</sup> Similar results were obtained when Cl is replaced by Et, *i.e.* for the substrate  $\text{H}(\text{CH}_3)(\text{Et})\text{C}(\text{H})=\text{O}$ . These results are now known as the Felkin-Anh rules.

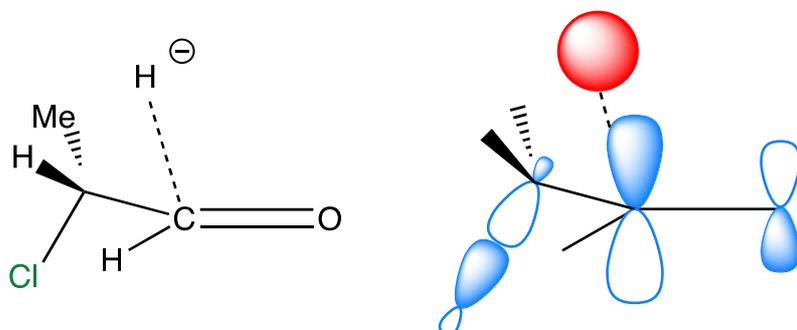




**Figure 3.** Reaction of an hydride with  $\text{H}(\text{CH}_3)\text{ClC}(\text{H})=\text{O}$ . Plots of the energies as a function of the  $\theta$  (Cl-C-C-O) dihedral angle. The full (dashed) line corresponds to the formation of the major (minor) diastereomers. The dotted line corresponds to the energies of isolated  $\text{H}(\text{CH}_3)\text{ClC}(\text{H})=\text{O}$ . Top and bottom parts correspond to approach angles  $\alpha$  ( $\text{H}\dots\text{C}=\text{O}$ ) of  $90^\circ$  and optimized indicated values, respectively. Copyright Nouv. J. Chim.<sup>9</sup>

The preference for the Felkin conformation was interpreted with arguments similar to those used for the anomeric effect<sup>10</sup> and the acidity of alcohols in the gas phase.<sup>11</sup> Spatially properly positioned low-lying empty orbitals stabilize overlapping high-lying occupied orbitals which in turn stabilize the entire system whether it is in a ground state or in a transition state. Thus, the most stable “transition state” for the addition is the one where the C-Cl bond is antiperiplanar to the entering nucleophile. For this conformation, the LUMO, which is the in-phase combination of  $\pi^*_{\text{C}=\text{O}}$  and  $\sigma^*_{\text{C}-\text{Cl}}$ , is the lowest. (Scheme 2). The entry of the nucleophile

with an angle  $\alpha$  around  $110^\circ$  further increases the overlap between the hydride and  $\pi^*_{CO}$ . For this Felkin conformation and angle of reaction, the major diastereomer is obtained when the nucleophile is closer to the smaller group (H in the calculations).<sup>9</sup>



**Scheme 2.** Main orbital interactions between the hydride HOMO (red) and the LUMO (blue) of the pro-chiral aldehyde in the Felkin transition state. The conformation giving the major diastereomer is shown.

Hugh Felkin, who was a CNRS distinguished Director of Research and a group leader in the *Institut de Chimie des Substances Naturelles* (Gif-sur -Yvette), often called ICSN, one of the flagship research institutions in organic synthesis of the CNRS, was pleased with this result even if, with his usual dry sense of humor, he often stated that “*theory was the tunnel after the light*”. The ICSN was three kilometers away from my own laboratory in Orsay and he invited me several times to present seminars in his group and also to attend discussions. It was during these seminars that I met Bob Crabtree. Bob was a CNRS researcher in Felkin group before moving to Yale. About 10 years later Bob and I started to collaborate and established a life-long friendship relation. Hugh Felkin also introduced me to the late Joseph Klein from the Hebrew University of Jerusalem. Joseph Klein was hoping that I could study the stereoselectivity of the nucleophilic addition to double bonds embedded in 6-membered rings, a tricky problem. For this reason, he invited me to spend a month in his laboratory in Jerusalem in July 1974 although I was still a PhD student. I am very grateful for his generosity and it was my first time in Israel. The results of the study were published a few years later reflecting the difficulties of the problem.<sup>12</sup> Overall, the Felkin-Anh rules work well and their interpretation still holds as it appears from the articles published in the topical issue on diastereoselection in *Chemical Reviews* 1999 (issue 5) but exceptions are known.

With my thesis in hands and a permanent position I was really free to establish my own lines of research. I wanted to discover new scientific topics and horizons. Lionel Salem, the head of the laboratory, thought that I could thus go to work with Albert Eschenmoser at the ETH

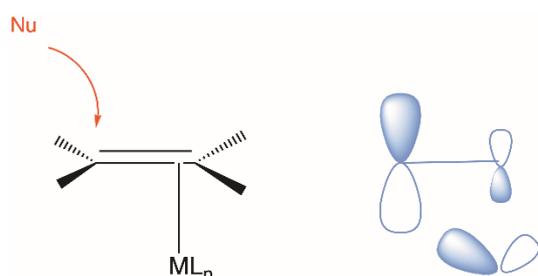
Zurich. We had worked together on the coenzyme B<sub>12</sub> using extended Hückel calculations.<sup>13</sup> It was unrealistic (as obvious today when looking in particular at the work done by Sason Shaik on cytochrome P450)<sup>14</sup> but Lionel was persuaded that we could progress if we understood better the experimental results. For this reason, he wanted me to spend time with Eschenmoser. I went to Zurich in January 1978, met Eschenmoser who kindly suggested that I will probably benefit more to work with Jack Dunitz. Working with the person who mapped reaction paths with crystal structures was very appealing to me and I was delighted that Jack agreed. I used ab-initio method to map the potential energy for the S<sub>N</sub>1 reaction represented by Li<sup>+</sup> interacting with BH<sub>4</sub><sup>-</sup>. The results were published in the Israelian Journal of Chemistry.<sup>15</sup> I also showed that the nucleophilic addition to an alkyne is easier than to a double bond because of the more flexible nature of the former.<sup>16</sup> This one-year period in the group of Jack was very important for my development as a scientist. He broadened my vision of science and life in sometimes unexpected directions. During a discussion with him, I wanted to push the molecular orbital analysis to extreme limits. Jack looked at me and with his wonderful smile said. *“Odile, you can stop here. This is not a Torah commentary”*.

## **Cornell University**

During my stay at the ETH, Roald Hoffmann gave a special topic course on transition metal complexes and I was truly fascinated. I wanted to spend time in his group and I obtained a NATO grant for one year. I arrived in Cornell in the fall of 1979. This was my first time overseas and even my first time flying. My flight from London was delayed and I missed my connection between New York La Guardia and Ithaca. I was put on the next morning flight. I had thus to go late at night from JFK to La Guardia but there was no more airport transportation. A taxi was needed and luckily other travelers offered me to share a taxi. The trip started by a fist fight between two taxi drivers competing for having us as customers. I slept on the floor of La Guardia and I do remember a morning cleaner saying “Don’t worry babe. Nothing will happen to you. I am looking after you”. And then, I was in Ithaca at the best period of the year. Roald picked me up at the airport and showed me around. I admired the landscape of the Finger Lakes district but I could not yet adjust to the open space between buildings in the city center. Why were buildings not always contiguous? Why so much “empty” space? I was a girl from Paris where space is rare and all buildings are closely packed. It did not take me long to fully enjoy Ithaca and the work at Cornell.

I wanted to learn more transition metal chemistry but I was still an “organic chemist” at heart. Thus, my interest went first to understand how a metal influences the reactivity of an organic species. I knew that the extended Hückel (EH) method, which was used for transition metal complexes in the late 1970s, was poorly adapted to the study of reactivity since the

energy variation associated with change in bond distances could not be really used. That did not stop me and I decided to study why a nucleophile adds more easily to an alkene coordinated to a transition metal fragment than to a free alkene, regardless of the global charge of the entire complex.<sup>17</sup> Electrostatic explanation was thus excluded. A first look at the reaction revealed more factors that would favor deactivation than activation. The back-bonding from the metal fragment to the alkene, following the Dewar-Chatt and Duncanson model, pushes up in energy the alkene  $\pi^*$ -orbital, hence decreasing its reactivity toward an incoming nucleophile. So where does the activation come from? We proposed that it was coming from the possibility of changing the coordination of the alkene from  $\eta^2$  in the ground state to a more  $\eta^1$  mode in the activated state. Indeed, moving the metal away from being at equal distance to the two alkene carbon centers, develops the alkene  $\pi^*$ -orbital on the carbon away from the metal. This enhances the electrophilicity of this remote carbon (Scheme 3). This polarization of the  $\pi^*$  orbital applied to all alkene complexes. An experimental confirmation on the possible unsymmetrical coordination of an alkene was given by late Myron Rosenblum from Brandeis.<sup>18</sup> Recently, this shift of the metal away from the  $\eta^2$ -coordination mode was proposed to rationalize the Au(I) and Rh(I) catalyzed anti-Markovnikov hydroamination of alkenes<sup>19</sup> and the inner vs. outer-sphere nucleophilic addition of the Wacker complex studied by ab initio molecular dynamics.<sup>20</sup> It is rewarding when the results obtained by state-of-the-art methods of today can be interpreted by simple orbital arguments derived from EHT calculations. It reinforces the feeling that even the simplest calculations could contain the physics of the chemical systems.



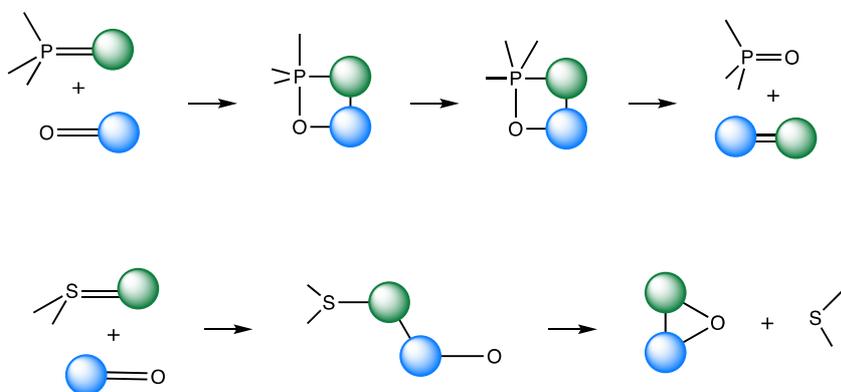
**Scheme 3:** Unsymmetrically coordinated olefin and schematic representation of the associated polarized LUMO.<sup>17</sup>

## The University of Michigan

During my time in Cornell, I admired the energy that emerged from Roald's group and had great appreciation of the scientific and social life within this University. I was nostalgic of the USA when I came back to Orsay. With Roald's advices, I applied to several American universities and I got an offer from University of Michigan at Ann Arbor (UM at A<sup>2</sup>). I had to

teach introductory organic chemistry in addition to establish my own research directions. I arrived in Ann Arbor in January 1982. I was not going to stay long for various reasons but during these two years in A<sup>2</sup> I verified Basia motto. "There is nothing you cannot achieve if you set your mind to it." In fact, UM had a good reason for hiring a computational chemist to teach introductory organic chemistry. The state of Michigan was in bad economical shape due the oil crisis, which had impacted on the car industry notably in Detroit. My initial funding was thus modest. I needed two monitors and I got my two monitors. I also needed access to the University computers and, to my great surprise, computational time was given to me in small amounts, badly adapted to my needs. Without going into details, it took me a while for getting access to large computational resources. Luckily, I had several projects on the fire and I did not waste time. Studies of organometallic species were essentially free of cost with EHT calculations and I increased my knowledge of organometallic chemistry through many collaborations.<sup>21,22</sup> I started to look at one-dimensional systems. I got into this topic with Enric Canadell. Enric had been a post-doc with Lionel Salem and we had shared office. He had returned to Spain where he felt scientifically isolated and had contacted me. I invited him to Ann Arbor. Our first study was under the leadership of Roald. We looked at the thermochromic effect of tetramethyl bistibole, *i.e.* the change of color from solution to solid state.<sup>23</sup> We then explored other one-dimensional systems. It was fun to see how molecular orbitals of individual molecules combine to form the band structures of infinite solids.<sup>24</sup> Enric, who was also a trained molecular computational chemist, was discovering his interested in low dimensional solids, a line of research which he was going to continue for many years. I was going to stay a molecular chemist.

One of my interests in these years was to look for mechanistic analogies between organic and organometallic reactions. Roald had designed the isolobal analogy which describes the bonding analogies between organic and organometallic species.<sup>25</sup> Could a related analogy exist for reactions pathways? Metathesis and small ring formation was a reaction that occurred with and without metals. Thus, phosphonium and sulfonium ylids react differently with carbonyl groups. While the phosphonium ylide yields an olefin and a phosphine oxide in the reaction with a carbonyl (Wittig reaction), the sulfonium ylide yields an oxirane and a thioether (Corey-Chaykovsky reaction), Scheme 4. With metal carbenes complexes, olefin metathesis and cyclopropane formation were two possible products in the reaction with an alkene.



**Scheme 4:** Top) Wittig reaction. Bottom) Corey-Chaykovsky reaction. The blue and green circle are carbene type groups.

Was there any common factor which could determine the preference for group exchange (metathesis reaction) versus group transfer (3-member ring formation)? We thus determined the reaction pathways for the two types of reaction with and without metal. For the organic systems, we used Hartree-Fock on the simplest possible models for the reagents,  $\text{PH}_3=\text{CH}_2$ ,  $\text{H}_2\text{S}=\text{CH}_2$  and formaldehyde. We found that the four-member ring formation was energetically easy for both ylids but that the pseudo rotation at P or S, needed to yield the olefin and the oxide, had a lower barrier for phosphorus. In parallel, the nucleophilic addition of the ylid to an aldehyde was possible with the two reagents but only  $\text{H}_2\text{S}$  was a good leaving group to yield oxirane in a ring closing reaction.<sup>26</sup> In these years, locating a transition state even for such reaction was demanding. Preceding collaboration with Berny Schlegel on the addition of borohydride anion to formaldehyde (in absence of  $\text{Li}^+$  and solvent!) had shown that finding transition states was a painful but feasible task.<sup>27</sup> My first PhD student François Volatron, who started to work with me while I was still in France, was skilled at this work. But what was doable for P and S containing systems,<sup>26</sup> could not be done with transition metal complexes. Even if we looked at cyclopropanation with EHT calculations,<sup>28</sup> it was thus not possible to extract information that could help to compare pathways for organic and organometallic reactions. However, this work had very nice secondary benefit. Late Keiji Morokuma had visited UM and following our discussions invited me to his laboratory provided that I could finance my travel. UM generously paid the trip and I benefitted from Keiji advices on scientific matters and Japanese culture, as well as a very generous time on the computer center of the Institute for Molecular Science in Okasaki. Japan is still today one of my countries of choice.

### Back to France

In 1984, I had a dilemma. During my time as assistant professor at University of Michigan, I was on leave of absence from my position in the CNRS. This was very comfortable but could not last forever. The CNRS asked me to decide: coming back or resigning from the CNRS.

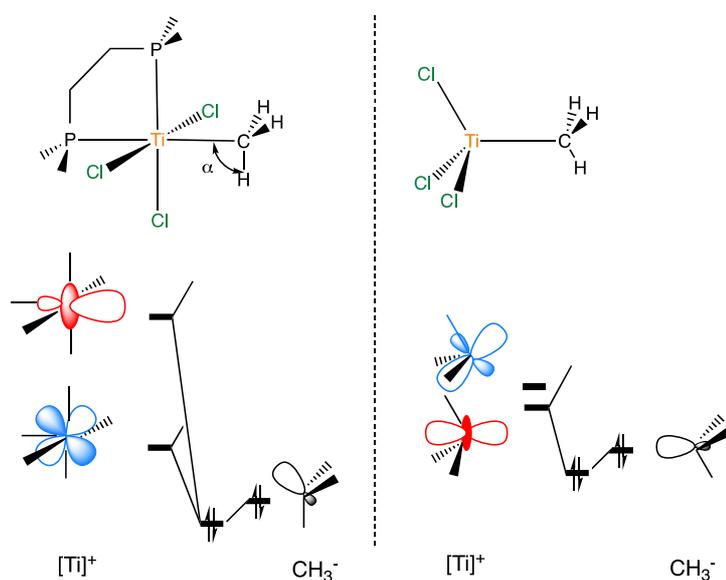
Even if my working conditions had significantly improved in the second year in Michigan, I did not feel that it was the right place for me and I decided to return to France. This was a wise choice since I got rapidly promoted to Research Director. In addition, Enric was also offered a research position at the CNRS.

The long study of the reactivity with ylids had been educational to me. I wanted to move away from organic chemistry and get into organometallic chemistry. It was an open field for exploration. It was also a place where EHT calculations were still acceptable even if it was clear that better methods were soon to become operative. EHT was a fantastic playground with many attractive ways to test interpretations. It had drastic limitations but I felt I knew them well. I had just to choose the right topics. In addition, several colleagues of the group of theoretical chemistry at Paris-Sud Orsay wanted to join efforts in exploring organometallic chemistry. This was in particular the case of Professor Yves Jean. The resulting collaboration was highly enjoyable.

#### 1) *Electron deficient complexes and agostic interaction.*

C-H bond activation had been an important topic to chemists and determining some controlling factors was an exciting line of research. In line with the reaction path mapping from Dunitz and Bürgi, I got fascinated by the publications of Maurice Brookhart and Malcolm Green on agostic interaction.<sup>29</sup> A C-H bond of a ligand coordinated to a metal center was approaching this metal center without being cleaved. The complexes displaying this interaction could be viewed as snapshots on the path to C-H activation. Understanding why the C-H bond was getting close to the metal center at the expense of significant geometrical distortions was appealing. I got especially fascinated by two closely related Ti(IV) methyl complexes which displayed striking structural differences (Figure 4). Thus, in the hexacoordinated Ti(IV) methyl complex, the methyl group was strongly distorted with an Ti-C-H angle of  $93.7^\circ$  suggesting an attraction between the C-H bond and the Ti center. In contrast in the corresponding tetracoordinated methyl complex, there was no abnormal Ti-C-H angle suggesting the absence of Ti...C-H attraction.<sup>30</sup> We decided to understand the origin of these remarkable differences. EHT calculations reproduced nicely the structural features. A fragment molecular orbital analysis provided a very simple interpretation based on the shape and energy of the titanium-based orbitals which were available to form the Ti-CH<sub>3</sub> bond in each complex. In both complexes, the metallic fragment has an empty fragment orbital (red in Figure 4) which overlaps best with the sp<sup>3</sup> hybrid HOMO of CH<sub>3</sub><sup>-</sup> for a "normal" geometry (Ti-C-H = 109°) However, in the pentacoordinated square based pyramidal fragment Ti has an energy *lower* empty orbital (blue in Figure 4 left) which can overlap with the CH<sub>3</sub><sup>-</sup> group HOMO only when this orbital tilts away from the Ti-C direction (Ti-C-H < 109°). Tilting of the methyl group can be energetically

beneficial if the blue orbital is low enough in energy. This is what happens in the hexacoordinated complex where the Ti-C-H angle is  $93.7^\circ$ . In the tetraordinated complex, there is no tilt of the methyl group because the Ti blue and red empty orbitals are at the same energy (Figure 4 right). This led us to propose that the  $\alpha$ -agostic interaction could be in part driven by changing the nature of the Ti-C bond and not only by the C-H $\cdots$ Ti interaction.<sup>31</sup> Many studies of agostic interactions followed involving either  $\alpha$ ,  $\beta$  or more remote C-H (or even C-C) bonds. In all cases, the nature of this agostic interactions is not simple and not limited only to a metal $\cdots$ C-H interaction.<sup>32</sup>

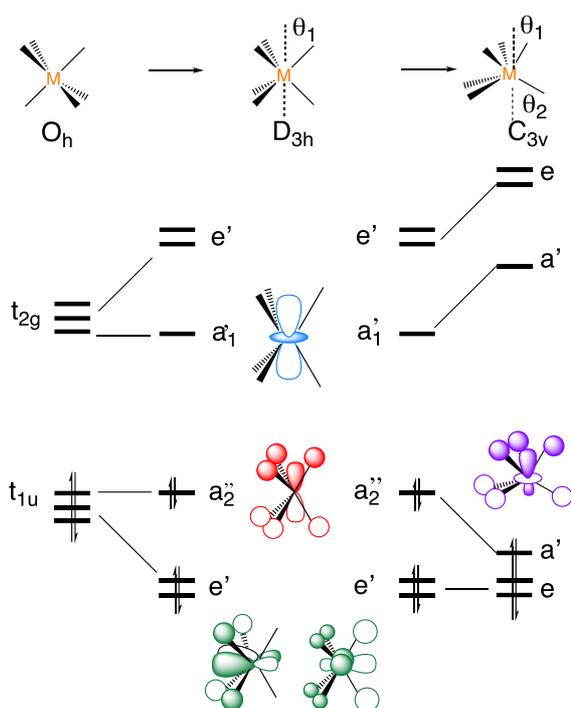


**Figure 4:** Top. Left) Hexacoordinated Ti(IV) complex with  $\alpha = 93.7^\circ$ . Right) Tetrahedral Ti complex with  $\alpha$  around  $109^\circ$ . Bottom: The interaction diagram of the metal fragment [Ti]<sup>+</sup> with the CH<sub>3</sub><sup>-</sup> group. Adapted from reference 31.

After exploring the  $\alpha$ -agostic interaction in the methyl titanium complex, it was natural to look at the  $\beta$ -agostic one in the corresponding ethyl complex. Furthermore, neutron diffraction structures giving the position of all hydrogen atoms were available for both species.<sup>30</sup> The study of the ethyl was expected to be an extension of that of the methyl complexes but, it opened new horizons. A change of bond angles at the metal was needed to approach a C <sub>$\beta$</sub> -H bond of the ethyl group to Ti. The complex could not stay octahedral but to our great surprise moving bond angles away from  $90^\circ$  had a global stabilizing effect. The analysis of the results showed all empty d orbitals of Ti could participate in the six Ti-ligand



bonds and thus strengthen these bonds in a non-octahedral coordination. After publication of these results in *Organometallics*<sup>33</sup> I was contacted by Tom Albright, another past member of Roald Hoffmann scientific family. He found our results interesting but surprising and was ready to check if they will survive with different methods of calculations. Was I interested? Yes, I was. At the same time (1986), I was invited as speaker at the Gordon Conference of Organometallic chemistry. The story of the distortion of the coordination sphere away from octahedral, which I presented in my lecture, was met with considerable skepticism by a large part of the audience. Was it an artefact of EHT calculations? How to prove or disprove it? The calculations with Tom Albright were not yet finished. This Gordon Conference was a bit difficult for me. Finally, SCF and MP2 calculations on CrH<sub>6</sub> and CrF<sub>6</sub> were finalized.<sup>34</sup> CrH<sub>6</sub> was the best model of the experimental neutral titanium complex shown in Figure 4, and CrF<sub>6</sub> was included because its structure was unknown. CrH<sub>6</sub> prefers a non-octahedral structure but the more ionic CrF<sub>6</sub> prefers an octahedral structure (today, I believe that the fluorine lone pairs also favor the octahedral structure). Other computational studies gave similar results.<sup>35</sup> In octahedral d<sup>0</sup> MR<sub>6</sub> (R = H, Me), *only two* empty metal d orbitals participate into the six M-R bonds but *all* metal d orbitals participate into the six M-R bonds in non-octahedral geometry (Figure 5). Thus, the results of the EHT calculations were not an artefact. Experimental support came later with ZrMe<sub>6</sub><sup>(2-)</sup> and WMe<sub>6</sub>.<sup>36</sup> The case of WMe<sub>6</sub> merits a specific mention. Arne Haaland from Oslo had informed me in advance that he was going to look at it with electron diffraction spectroscopy even though this red blood colored complex was explosive. Later, during the welcome mixer of an international meeting, I saw him walking towards me. With a large smile on his face, he shook my hand and said “*Odile, you were right*”. No more was needed. Case closed? Almost. The electron diffraction study gave a *D*<sub>3h</sub> structure because the method could not be more accurate.<sup>36b</sup> Later X-Ray diffraction study by Konrad Seppelt at TU Berlin gave a *C*<sub>3v</sub> structure very close to that calculated by T. Albright.<sup>36c</sup> Neon matrix Infra-red spectroscopy study of WH<sub>6</sub> gave similar results.<sup>36d</sup> Then even later, computational studies of the general class of d<sup>0</sup> MX<sub>n</sub>, showed that these complexes do not obey the Gillespie structural rules notably when X has no lone pairs.<sup>35</sup>



**Figure 5:** Orbital correlation diagram for a trigonal twist from  $O_h$  to a  $D_{3h}$  geometry and a pyramidalization to  $C_{3v}$  geometry. Electron occupancy correspond to  $d^0 MX_6$ . Adapted from Inorganic Chemistry.<sup>34</sup>

## 2) The first study on dihydrogen complex.

One day Yves Jean stormed into my office very excited by having read the communication of a tungsten dihydrogen complex.<sup>37</sup> I listened to him and replied: “*Oh yes sure, it is like an olefin complex because the frontier orbitals of ethylene and  $H_2$  have similar topology*”. Yves replied: “*Yes Odile, but  $H_2$  is not ethylene!*” Yves was correct. Thus, we looked at  $trans-W(PR_3)_2(CO)_3(H_2)$  and in particular why  $H_2$  coordinates in the plane of the two cis large phosphine ligands. Conformational issues in the metal coordination sphere are usually well reproduced with EHT calculations. Indeed, calculations of the model  $trans-W(PH_3)_2(CO)_3(H_2)$  reproduces the experimental structure because back-donation into  $\sigma^*_{H_2}$  is stronger in the plane containing the phosphine ligands.<sup>38</sup> Furthermore, the calculated rotational barrier of  $H_2$  of around 1 kcal/mol in the model was close to that measured by Inelastic Neutron Scattering (INS). In these years, Hartree-Fock calculations on a similar model were not giving better results.<sup>39</sup> Furthermore, EHT calculations easily showed that increasing back donation into  $\sigma^*_{H_2}$  favors a dihydride complex relative to a dihydrogen complex. Thus, replacing CO by phosphine ligands induces a cleavage of the H-H bond. While such trends could be easily understood, the computational community would need a few more years to provide reliable calculated structural parameters for complexes of this type.<sup>40</sup>

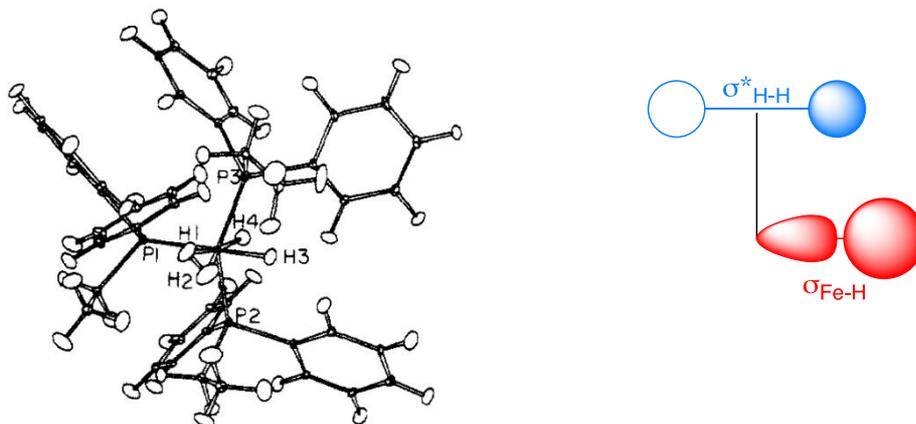
## New topics, new collaborations

At the end of the 1980s I received two offers which were going to have great influence on my life. Both arrived in ways hard to forget. Malcolm Chisholm from Indiana University called in the middle of the night (for me). When he realized he had miscalculated the time zone he apologized but still asked me if I was interested to be visiting professor in his department. The other one came from Martyn Poliakoff from Nottingham. We met at JFK while waiting for our respective overseas flights to Europe. Martyn was ready to board his flight to London when he asked me if I was interested in teaching a special graduate course at Nottingham. These two offers were of interest to me. I wanted to go back to USA and I was interested in knowing better the British chemical community. The invitation to Indiana led to the collaboration with Ken Caulton and Malcolm Chisholm. The invitation to Nottingham led to the collaboration with Robin Perutz from York and a long-term honorary professor position at his university. It is also during this period that I started to collaborate with Bob Crabtree from Yale. These collaborations were fruitful and enjoyable since experiments and calculations were done in parallel.

### 1) Hydride and di-hydrogen interaction

Ken Caulton was looking at hydride complexes and also at diverse  $\pi$ -bonded species, two topics of interest to me. I present the most representative cases in the hydride complexes, and I don't describe further the studies of the  $\pi$ -metal complexes.<sup>41</sup>

The group of Ken Caulton succeeded in getting neutron quality crystal of  $\text{FeH}_4(\text{PEtPh}_2)_3$ , originally reported by Aresta. This gave us access to the positions of the hydrogen atoms in the complex. The neutron diffraction revealed a cis,mer- $\text{Fe}(\text{H})_2(\text{H}_2)(\text{PEtPh}_2)_3$  structure (Figure 6).<sup>42</sup>

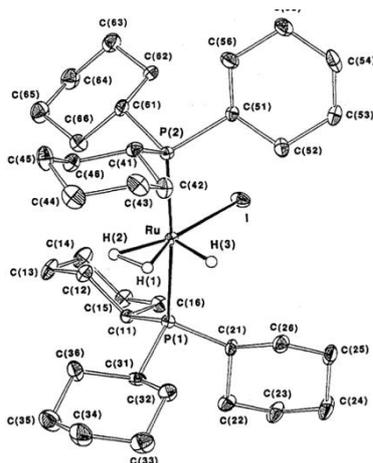


**Figure 6:** Left) ORTEP drawing of  $\text{Fe}(\text{H})_2(\text{H}_2)(\text{PEtPh}_2)_3$  as revealed by neutron diffraction. Copyright from J. Am. Chem. Soc.<sup>42</sup> Right) a schematic representative of the orbital interactions in the cis-effect.

In this structure determined at 27K, the dihydrogen ligand is staggered relative to the cis ligands, which is an unusual orientation as back-bonding is maximized when  $\text{H}_2$  is in the P3-Fe-P2 plane. Since steric effects are unlikely, the only rationale for the observed orientation of  $\text{H}_2$  is an *attractive interaction* from the cis hydride. EHT calculations express such interaction in terms of nucleophilic/electrophilic interaction between the high-lying occupied orbital characteristic of the electron rich hydride and the empty low-lying  $\sigma^*_{(\text{H-H})}$  orbital characteristic of a Lewis acidic coordinated  $\text{H}_2$ . (Figure 6 right) This interaction between two cis ligands creates an incipient bond between the hydride and the closest H of  $\text{H}_2$  which can assist the H-H exchange between the two ligands. This anticipates the  $\sigma$ -cam mechanism of Sabo Etienne and Perutz.<sup>43</sup> The calculations reproduce also correctly the very low rotational barrier of the coordinated  $\text{H}_2$  ligand measured by INS.<sup>42</sup> Attempts to study the same system with *ab initio* calculations were moderately successful.<sup>44</sup> The available computational level was still too modest for representing bonding and non-bonding interactions. Calculations in these times also suffered from the obligation to replace any large ligand by a smaller analogue ( $\text{PH}_3$  for  $\text{PEt}_2\text{Ph}$ ). Despite these limitations, the proposal of through space attractions between chemical systems deprived of lone pairs, as in the hydrogen bond, caught the attention of chemists. Several other cases of attraction involving hydrides were noted.<sup>45</sup> This was of special interest to Jeremy Burdett, a close friend and an original very creative mind.<sup>46</sup> We collaborated on other dihydrogen complexes,<sup>47</sup> and we were not the only ones.<sup>40</sup>

One central question was to determine by computations the relative stabilities of dihydrogen  $[\text{M}](\text{H}_2)$  and corresponding dihydride  $[\text{M}](\text{H})_2$  isomeric forms. In most cases, the calculations identified correctly the observed isomers. Thus, the hexacoordinated  $\text{OsH}_3\text{XL}_2$  (X = halide, L = phosphine) was found to be a 16e non-octahedral trihydride  $d^4$  Os(IV) complex.<sup>48</sup> It has an unusual NMR signature, a topic to be developed below. In contrast, computations on  $\text{PtH}_3\text{L}_2^+$  (L = phosphine) showed a clear preference for a square planar  $\text{Pt}(\text{II})(\text{H})(\text{H}_2)\text{L}_2^+$  structure.<sup>49</sup> The calculations were carried out by Joe Rambo, a post-doctoral fellow from Indiana University. His MP2/DFT optimized structure gave a dihydrogen-hydride complex. Ken Caulton at Indiana was skeptical but further hydrogen isotope labelling and low temperature NMR measurements supported our proposal. I will not forget the large smile of Joe Rambo when we learned that we had predicted correctly the structure. Cationic  $\text{PtH}_3\text{L}_2^+$  was thus a dihydrogen complex whereas the isoelectronic neutral  $\text{IrH}_3\text{L}_2$  was calculated to be a mer trihydride in a square based pyramidal coordination.<sup>50</sup> Ir(III) is an easily accessible oxidation

state for iridium while Pt(IV) is not so favored for platinum. The ability for calculations to determine the preference for either the polyhydride or the dihydrogen isomers run into an obstacle with  $\text{RuH}(\text{H}_2)\text{X}(\text{PCy}_3)_2$ . This complex, made in the group of Bruno Chaudret in Toulouse and characterized by NMR and low temperature X-Ray diffraction had an unusual square based pyramid with a basal  $\text{H}_2$  ligand eclipsing the apical Ru-H bond due to cis H/H<sub>2</sub> attraction, Figure 7.<sup>51</sup>

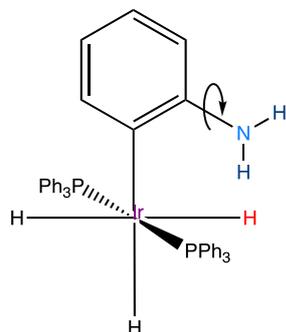


**Figure 7:** ORTEP Plot of  $\text{RuH}(\text{H}_2)\text{Cl}(\text{PCy}_3)_2$ . Copyright from J. Am. Chem. Soc.<sup>51</sup>

Ab initio calculations never reproduced this hydride-dihydrogen structure and always gave a preference for trihydride isomer. This Ru complex was going to be a thorn in my side for many years. However, despite some difficulties there was more successes than failures and we wrote a review on transition metal hydrides complexes for the special issue of Chemical Reviews on Theoretical Inorganic Chemistry (2000) upon the invitation of Ernest Davidson.<sup>40</sup>

I had already started to collaborate with Bob Crabtree,<sup>52</sup> who has been always deeply interested in understanding why chemical systems had the structures and properties they had as he nicely illustrates in his book now in its 7<sup>th</sup> edition.<sup>53</sup> Bob Crabtree was exploring “*a new type of intermolecular interaction, the H···H or dihydrogen bond, which operates between a conventional hydrogen bond donor such as an NH or OH bond as the weak acid component and a element hydride bond as the weak base component, where the elements in question can be a transition metal...*”.<sup>54</sup> The cis-interaction, presented above in  $\text{Fe}(\text{H})_2(\text{H}_2)\text{L}_2$ , was one of the first examples of an intramolecular dihydrogen interaction. Other species were studied with Bob. Thus, NMR temperature dependent measurements and calculations of the dynamics

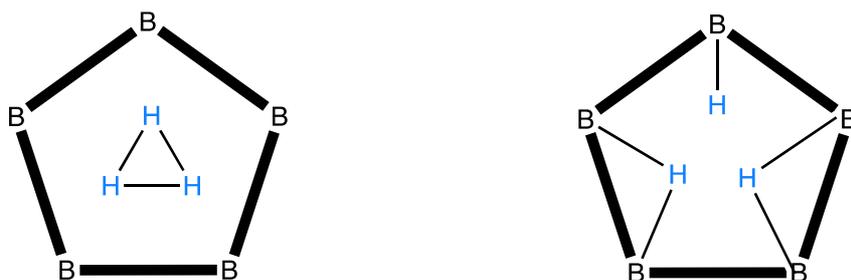
in  $\text{IrH}_3(\text{PPh}_3)_2(2\text{-amino-pyridine})$  (Figure 8) led to an estimation of a 5 kcal/mol attractive interaction between the acidic H of  $\text{NH}_2$  and hydridic H of Ir-H.<sup>55</sup>



**Figure 8:**  $\text{IrH}_3(\text{PPh}_3)_2(2\text{-amino-pyridine})$  used to evaluate the strength of the intramolecular dihydrogen bond between H of  $\text{NH}_2$  and H of the cis Ir-H bond. Adapted from reference 55.

The intermolecular interaction was a problem of another dimension. Bob Crabtree and Per Siegbahn had succeeded to reproduce with DFT calculations the  $\text{B-H}^{\delta-} \dots \delta^+\text{H-N}$  interaction seen in the solid-state structure of  $\text{H}_3\text{BNH}_3$ .<sup>54</sup> In contrast, reproducing the interaction between  $\text{ReH}_5(\text{PPh}_3)_3$  and indole in their co-crystal was a challenge. Thus, the distance between the two partners had to be fixed and within this constraint the relative orientation of the two molecules was properly reproduced.<sup>56</sup>

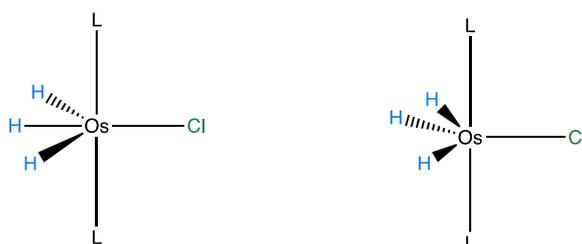
In most transition metal polyhydride complexes, the hydrides are exchanging coordination sites. Comparing calculated values and experimental data helped to understand the role of ligands and coordination mode on this dynamics such as  $\text{ReH}_5(\text{PPh}_3)_2\text{L}$  (L = pyridine type ligand).<sup>57</sup> A related result was obtained in the case of the long-standing puzzle of the structure of  $\text{B}_{11}\text{H}_{14}^-$  and the mechanism for the fast exchange between the endo hydrogens observed by NMR.<sup>58</sup> Lipscomb has earlier proposed that  $\text{B}_{11}\text{H}_{14}^-$  could be viewed as the formal union of  $\text{H}_3^+$  and  $\text{B}_{11}\text{H}_{11}^{2-}$  (Figure 9 left) and Jeremy Burdett has proposed that complexes of  $\text{H}_3^+$  could exist.<sup>59</sup> However, solid state NMR and Hartree-Fock calculations were consistent with a classical structure (Figure 9 right).



**Figure 9:** The non-classical (left) and classical structure (right) of  $B_{11}H_{14}^-$ . Adapted from Reference 57.

## 2) The Quantum exchange NMR phenomenon

During this period, a very unusual spectroscopic phenomenon was discovered in transition-metal polyhydride complexes. Abnormally large temperature dependent NMR H-H coupling were reported notably in trihydride complexes.<sup>60</sup> Observed first in the 1970s and rediscovered independently by Bercaw, Chaudret and Heinekey, modeled by Zilm and by Weitekamp *et al*, this coupling was different from the usual magnetic coupling. It was named exchange coupling and was shown to be due to a tunneling effect of the hydrogen centers, *i.e.* a pair-wise quantum mechanical exchange of two protons in a double-well potential. Calculations from first principles of this quantum exchange coupling was challenging because tunneling is highly sensitive to the height of the barrier for the physical exchange of protons and the path-length (*i.e.* the distance between the two wells) as shown by the pioneering calculations carried out independently by Chaudret, Daudey *et al.* and Lledós, Lluch *et al.*<sup>61</sup> We decided to calculate directly the coupling constants by way of a full determination of the ro-vibrational levels involved in the tunneling effect. The study was carried on  $OsH_3Cl(PH_3)_2$ , a model of  $OsH_3XL_2$  ( $X = Cl, OR, L = phosphine$ ) (Figure 10). A PhD student, Eric Clot, with good background in quantum theory, was in charge of this project with the help of a colleague Claude Leforestier, expert in quantum dynamics. The main difficulty was the accuracy of the potential energy surface, namely the height of the barrier for the physical exchange between two hydrogens (Figure 10 right). The calculated energy barrier was too high and thus, the exchange coupling was too small but the temperature dependence was nicely reproduced.<sup>62</sup> Eric presented this work for this PhD thesis. Interestingly, Eric told me that he had enjoyed this project but was frustrated by the time needed to calculate energies. However, as he took a position of CNRS research associate professor in 1996, the computer facilities were improving immensely and soon Eric was calculating reaction pathways for large and complex systems. We did not invest more into quantum exchange which was pursued by Lluch and Lledós,<sup>63</sup> Soon, the excitement about this phenomenon, which was rare and not associated with other chemical properties, declined. This period will still be remembered as an exciting time for both experimentalists and theoreticians.



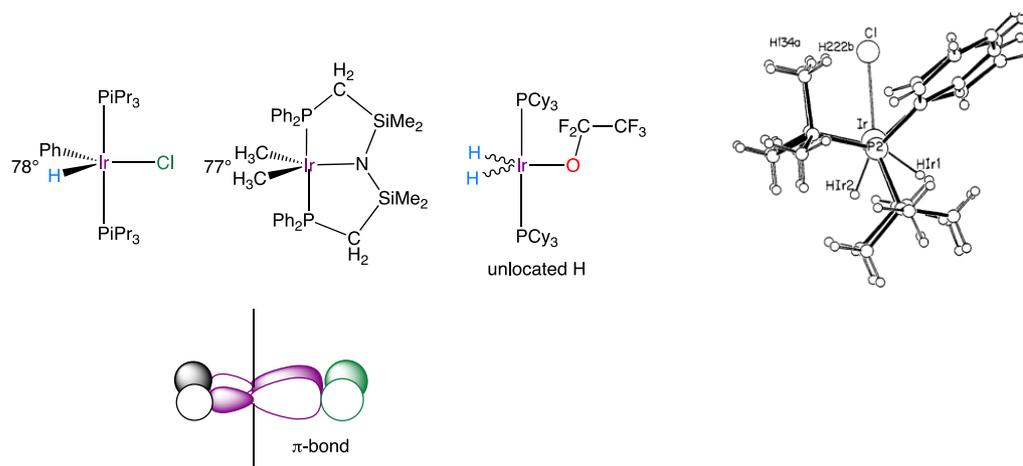
**Figure 10:** Left) Optimized structure of  $d^4$   $\text{OsH}_3\text{ClL}_2$  ( $L = \text{phosphine}$ ), Right) Transition state for pairwise exchange between two of the three hydrogen atoms. Tunneling occurs below this physical barrier associated with this transition state.<sup>62</sup>

### 3) Structures of electron deficient complexes

Electron deficient complexes were models of reactive intermediates which could inform on reaction pathways. Thus, the activation of the C-H bond by transition metal in an approach “à la Bürgi-Dunitz” was analyzed.<sup>64</sup> Understanding the structures of electron deficient complexes was also of great interest because of the great diversities in structures.

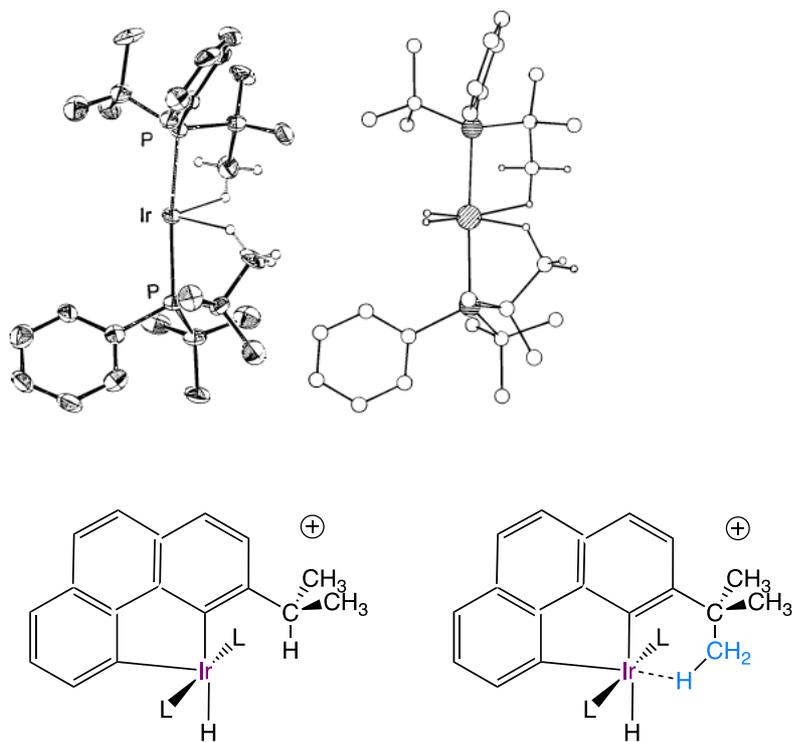
Pentacoordinated  $16e$   $d^6$   $\text{ML}_5$  complexes have predominantly a square pyramidal shape such as  $\text{M}(\text{CO})_5$  ( $M = \text{W}, \text{Mo}, \text{Cr}$ ) obtained by photolysis of  $\text{M}(\text{CO})_6$  and studied by IR spectroscopy and analyzed by the angular overlap method.<sup>65</sup> Complexes like  $\text{RuCl}_2(\text{PPh}_3)_3$  are also square pyramid.<sup>66</sup> However, another structure appeared in the literature around the 1990s. This new structure is a strongly distorted trigonal bipyramid in which the bond angle between two equatorial ligands is  $80^\circ$ -  $90^\circ$  resulting in the equatorial ligands arranged in form of a Y shape (Figure 11). The interpretation of this acute bond angle was unclear. Thus, the H-Ir-C(Ph) angle of  $78^\circ$  in  $\text{Ir}(\text{H})(\text{Ph})\text{Cl}(\text{PiPr}_3)_2$  was interpreted as a weak attractive interaction between H and Ph.<sup>67</sup> However, the Me-Ir-Me angle of  $76^\circ$  in the PNP pincer Ir complex, negated such interpretation.<sup>68</sup> The neutron diffraction structure of  $\text{IrH}_2\text{Cl}(\text{PtBu}_2\text{Ph})_2$  gave a H-Ir-H angle of  $72.7^\circ$  but the associated distance of  $1.82 \text{ \AA}$  between the two hydrides is too long to suggest an attraction between them.<sup>69</sup> Another strange feature was noted. In  $\text{Ir}(\text{H})_2(\text{OCF}_2\text{CF}_3)(\text{PCy}_3)_2$ , the fluoroalkoxy group prefers a conformation maximizing the steric interactions.<sup>70</sup> EHT calculations and HF calculations alike confirmed the existence of a Y shaped trigonal pyramidal structure as a minimum and the presence of a  $\pi$ -bond M-X bond (Figure 11) to stabilize it.<sup>50</sup> This explained why the Y structure is observed only with ligands like OR,  $\text{NR}_2$  or halide. It should be stressed that the ideal trigonal bipyramidal structure with angles of  $120^\circ$  between the three equatorial ligands is not a stable structure for a  $d^6$   $\text{ML}_5$  species. It is a Jahn Teller unstable structure that distorts toward a square based pyramid or a Y structure. For an orbital correlation diagram of these distortions see reference 50 and a summary in reference 1.





**Figure 11:** Top) Representative examples of 16e  $d^6$   $MR_2XL_2$  ( $R = H$ , alkyl, aryl;  $X = Cl$ ,  $NR_2$ , OR) with a Y type trigonal bipyramidal structure. Bottom) The metal-X  $\pi$ -bond in these species.

Highly electron deficient 14e complexes were isolated in the group of Ken Caulton. This project was driven by Feliu Maseras. Feliu, who got his PhD with Agusti Lledós, had been a long term post-doctoral fellow with Keiji Morokuma. He returned to Spain in a non-satisfying position. Keiji contacted me with very strong recommendation about Feliu. I had just moved to Montpellier and I needed someone to help me setting the group. The CNRS was responsive and Feliu came with a position of associate scientist and two years after was offered a position at ICIQ. He also came with his expertise on IMOMM, which he had developed with Keiji. This was a fantastic opportunity to look at large complexes. A representative example was  $Ir(H_2)(PtBu_2Ph)_2^+$ .<sup>71</sup> It had a butterfly shape derived from an octahedral complex deprived of two cis-ligands (Figure 12 top). The empty coordination sites were occupied by two agostic C-H interactions, one from each phosphine ligands. Such interaction was expected but DFT and IMOMM calculations indicated that the C-H bonds of the tBu ligands were held in the proximity of the metal by the steric bulk of the PtBu<sub>2</sub>Ph ligands.<sup>71</sup> This led to a detailed analysis of the interactions disfavoring and favoring the agostic interaction. This is no surprise today but, in these years, the interactions in competition with agostic interactions were not understood. We had a related case in a collaboration with Bob Crabtree. Solid state structures and NMR spectroscopy of 2-substituted benzoquinoline Ir(III) complexes show that the pendant group G does not necessarily become agostic despite an available nearby empty coordination at the Ir center (Figure 12 bottom).<sup>72</sup> Thus, for  $G = tBu$ , the agostic interaction is observed but for  $G = iPr$ , the potentially agostic iPr methyl groups point away from the metal. Computations revealed the diversity of attractive and repulsive interactions at play resulting in the observed structures.



**Figure 12:** Top) ORTEP (left) and calculated (right) structure of IrH<sub>2</sub>(PPh<sub>4</sub>tBu)<sub>2</sub><sup>+</sup>. The hydrogen atoms were not located by X-ray diffraction. Copyright from J. Am. Chem. Soc.<sup>71b</sup> Bottom) Ir(III) complexes with non agostic iPr and agostic tBu group. Adapted from reference 72.

## Understanding reaction pathways

### 1) A tough start

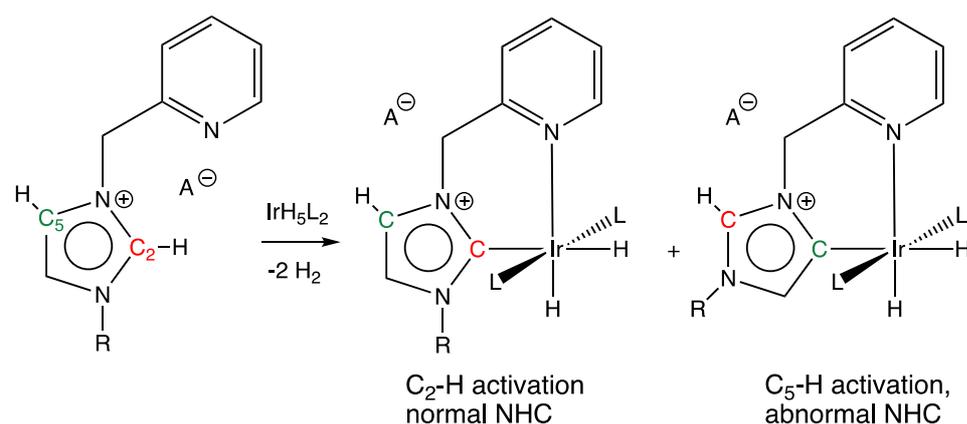
I wanted to get back into reaction mechanism with appropriate methods and this was becoming possible for reactions with organometallic complexes at the end of 20<sup>th</sup> century. However, we picked a rather difficult problem as first study: the oxidative addition of H<sub>2</sub> and addition of CO to highly reactive d<sup>8</sup> (M(dmpe)<sub>2</sub>, dmpe = Me<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>PMe<sub>2</sub>), M = Ru, Fe). The experimental results indicated essentially zero energy barrier for the reaction with Ru and Fe, which contrasted with the case of the corresponding cation rhodium complex, where an energy barrier for oxidative addition is expected. Stuart Macgregor, who was post-doctoral fellow at this time, was interested in the project and went to the group of E. J. Baerends to learn using the ADF program. The study was challenging.<sup>73</sup> Since there was no transition state, we looked for approach pathways. We showed that H<sub>2</sub> approaches end-on and becomes side-on close to products for Fe and Ru and at the transition state for Rh<sup>+</sup>. We accounted properly for the lack of energy barrier for Ru and Fe and the existence of a transition state for Rh<sup>+</sup>. We learned

that it is probably easier to study a reaction mechanism when transition state(s) existed. Stuart, who has become professor at Heriot-Watt had a tough start. I am grateful for his persistence.

## 2) Importance to represent the experimental systems

Representing properly the experimental situation and doing the right of calculations has been a permanent concern of computational chemists and numerous articles and reviews are published on this topic, a selection of which are given in the references.<sup>74</sup> We are presenting below two examples of this problem focusing on the proper representation of the chemical systems present in the reactive media.

Excluding chemical groups which were considered as only spectators in a reaction has been the traditional choice in the past. This is in particular the case of non-coordinating counter ions. However, counterion effects have taken recently a more prominent role in organometallic chemistry.<sup>75</sup> In 2005, together with Bob Crabtree, we studied the origin of an unexpected counter-ion effect on the selectivity of C-H bond activation. The selectivity of the reaction of 2 pyridylmethyl imidazolium with  $\text{IrH}_5(\text{PPh}_3)_2$  to give chelating NHC complexes bonded at  $\text{C}_2$  (normal carbene) or  $\text{C}_5$  (abnormal carbene) depends on the counter anion (Figure 13). Thus, with bromide, activation at  $\text{C}_2$  is observed, while with  $\text{BF}_4^-$ , activation occurs at  $\text{C}_5$ .<sup>76</sup> The reaction was shown to be under kinetic control so that the counter anion has to be explicitly present in the determination of the reaction pathways. This was hard work for Eric Clot but he did not give up.



**Figure 13:** The two products that can be formed in the reaction of 2 pyridylmethyl imidazolium with  $\text{IrH}_5\text{L}_2$  ( $\text{L} = \text{PPh}_3$ ). For  $\text{A} = \text{Br}$ , the normal NHC is formed, while for  $\text{A} = \text{BF}_4$  the abnormal one is preferred. Adapted from reference 76.

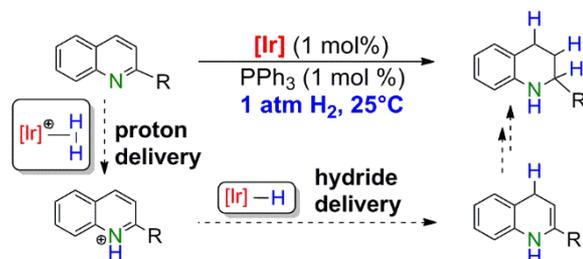
The computational study confirmed the anion effect. A key point is that the acidity of the imidazolium is higher at  $\text{C}_2$  than  $\text{C}_5$  and thus, ion-pairing is also stronger at  $\text{C}_2\text{-H}$ .

Consequently, despite the abnormal free NHC being nearly 15 kcal/mol less stable than the normal one, the two possible products are of similar energies upon carbene coordination and ion-pair formation. Activation of the C<sub>2</sub>-H and C<sub>5</sub>-H bonds has similar barriers but occurs by way of different mechanisms. The activation at the weakly polar C<sub>5</sub>-H bond goes via oxidative addition and shows little ion pair dependence because there is no large variation in the charge distribution during the reaction. In contrast, the activation of the polar C<sub>2</sub>-H bond goes via an heterolytic mechanism and shows strong ion-pair effect. The Br<sup>-</sup> anion assists the proton motion in what can be termed an anion-coupled transfer, yielding the normal NHC. The counter anion BF<sub>4</sub><sup>-</sup> cannot assist the proton motion, because it cannot approach close enough to the metal. It can only remain H-bonded to unactivated C<sub>2</sub>-H bond while the Ir center cleaves the C<sub>5</sub>-H bond by oxidative addition, yielding the abnormal NHC. The preference for an oxidative addition at the C<sub>5</sub>-H bond is due to the strong donor character of the abnormal carbene which favors an Ir(V) oxidation state in the transition state.

This study could only be solved with elaborate computational methods able to represent at a sufficiently accurate level a large range of interactions for already large systems. The importance of including the apparently innocent counter ions in the calculations is now recognized as described in a recent review.<sup>77</sup> In addition, the abundant literature in the domain of the computational studies of C-H activation has been collected by us in a review<sup>78</sup> and the continuum of C-H activation mechanisms and terminology presented in a recent paper by J. Love.<sup>79</sup>

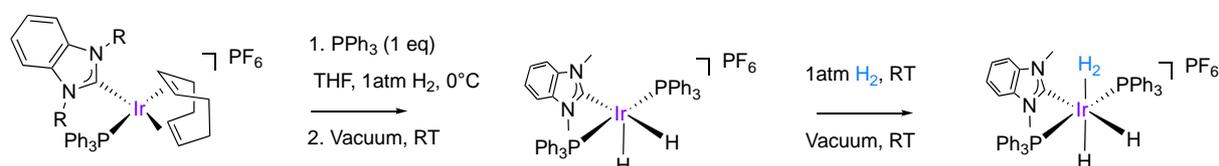
The other reaction concerns hydrogenation and dehydrogenation of organic substrates. This topic and related transfer hydrogenation reaction have attracted considerable attention as shown by selected references mostly focused on mechanistic and computational aspects.<sup>80</sup> The mechanisms are very sensitive to the nature of the coordinated ligands, to the second sphere of coordination and to the solvent. Indeed, most of the reactions involve a transfer of an ionic pair H<sup>+</sup>/H<sup>-</sup> between the catalyst and the substrate. While H<sup>-</sup> is usually “stored” by the metal center, there is a high diversity of ways for assisting the proton transfer through use of non-innocent ligand, substrate itself or solvent notably protic solvent. In addition, the second sphere can also be involved or simply stabilizes the ionic transfer through weak interactions.

Our contribution to this topic concerned an iridium catalyzed hydrogenation of N-heterocyclic compounds by molecular dihydrogen, the interesting aspect being that the reaction worked better with more hindered substrates (Figure 14).<sup>81</sup>



**Figure 14:** Iridium catalyzed hydrogenation of quinoline by molecular dihydrogen. Copyright from J. Am. Chem. Soc.<sup>81</sup>

Experimental studies identified all intermediates. Thus, the cationic 16e Ir hydride, which was isolated and characterized by X-Ray diffraction, was shown to be in equilibrium with the cationic trans hydride-dihydrogen complex, which itself was characterized by NMR spectroscopy (Figure 15). Computations showed that the dihydride complex could not



**Figure 15:** Formation of the trans hydride-dihydrogen intermediate which is the catalyst for hydrogenation of substituted quinoline. Copyright from J. Am. Chem. Soc.<sup>81</sup>

hydrogenate the substrate and thus the reactive species is the dihydrogen-dihydride complex. We established a preference for an outer-sphere mechanism, which starts by protonation of the quinoline by the acidic cationic dihydrogen complex followed by a relatively easy hydride transfer from the neutral mer-trihydride complex to the activated quinoline. The fact that hindered quinoline such as 2-methyl quinoline is more easily hydrogenated is fully consistent with this outer-sphere mechanism and the essential role of coordinated H<sub>2</sub> complex to provide the proton and then the hydride. The damaging role of non-substituted quinoline, which competes efficiently with H<sub>2</sub> for coordination at Ir is understood. The full mechanism of hydrogenation of quinoline, is shown in Figure 16. Outer-sphere hydrogenation is frequent,<sup>80</sup> but not, to our knowledge, with a coordinated H<sub>2</sub> complex as intermediate.

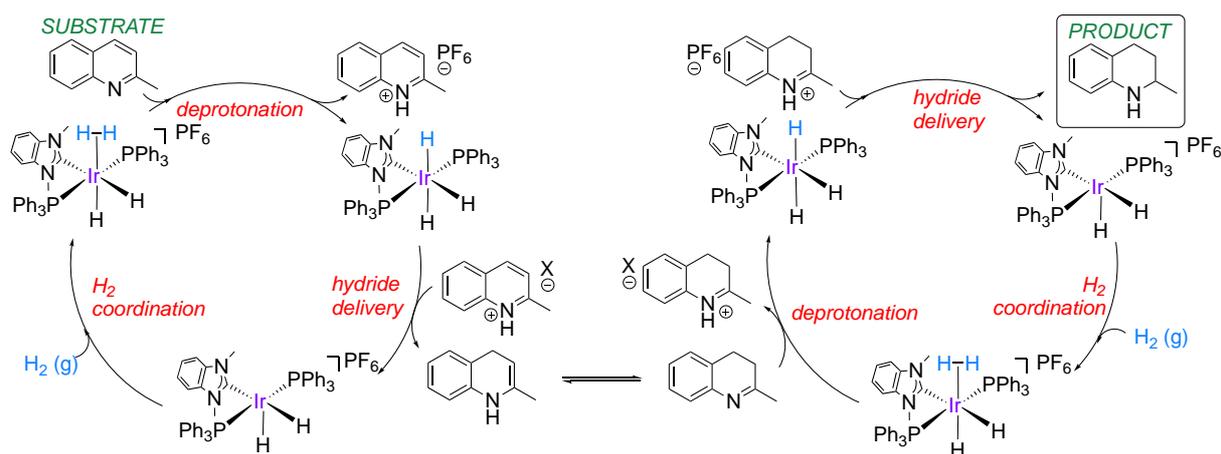
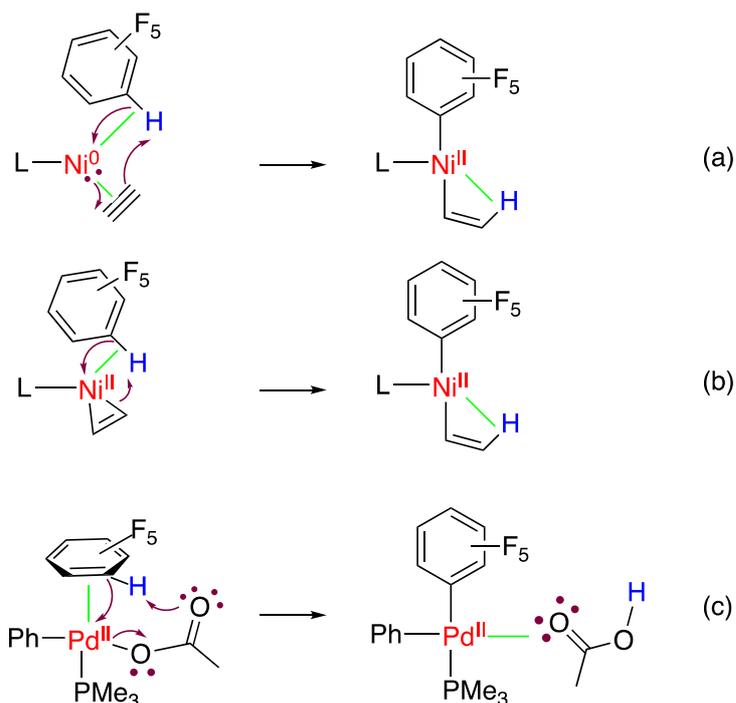


Figure 16: Proposed outer-sphere hydrogenation mechanism of 2-methyl-quinoline. Copyright from J. Am. Chem. Soc.<sup>81</sup>

### 3) Proposing new reaction mechanisms

Proposing new reaction pathways by way of computational studies is now standard. While it is well known that one cannot prove a mechanism but only disprove it, support by experiments is essential. Thus, with Robin Perutz, we proposed that C-H activation occurs via a ligand-ligand hydrogen transfer (LLHT) in place of an oxidative addition in the hydrofluorination of alkyne with Ni catalyst.<sup>82</sup> This mechanism agrees with the lack of H/D kinetic isotope effect. Figure 17 illustrates the differences between the oxidative addition (**a**) and the LLHT(**b**). In the first one, the alkyne is  $\pi$ -bonded and considered as neutral. In the latter, the alkyne complex is represented as a Ni(II) metallacyclopropene (due to the strong back-donation from Ni(0)) and the reaction is a  $\sigma$ -bond metathesis between the C-H and M-C bonds. It is a variant of a  $\sigma$ -cam reaction.<sup>43</sup> Thus, one key factor in the LLHT is the electron density accumulation in the alkyne. In this way, LLHT has analogy with the activation of fluoroarenes assisted by the acetate ligand, described independently as the Concerted Metalation Deprotonation (CMD),<sup>83</sup> the Ambiphilic Metal-Ligand Activation (AMLA).<sup>84</sup> A review on this topic has been published,<sup>85</sup> and an interesting discussion of the subtle difference between CMD and AMLA is presented in reference 79. An LLHT mechanism was also established in the hydroarylation of unactivated alkene with trifluoro substituted arenes in collaboration with John Hartwig.<sup>86</sup> However, LLHT is not favored for Pd and Pt where oxidative addition is systematically preferred as we showed in collaboration with Shigeyoshi Sakaki.<sup>87</sup>



**Figure 17:** Representations of the C–H activation for the hydrofluoroarylation of alkyne (a) as an oxidative cleavage and (b) as a  $\sigma$ -complex reaction and (c) palladium C–H activation in fluoroarenes assisted by the acetate Ligand. Copyright Organometallics.<sup>82</sup>

### Organolanthanide complexes

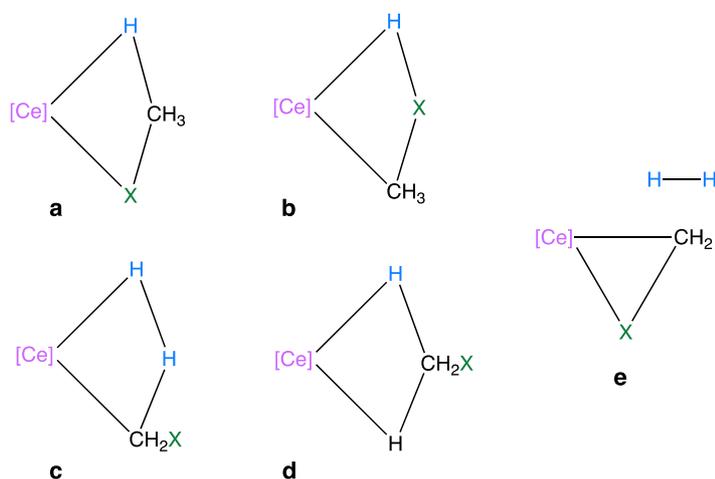
The study of the reactions of organolanthanide complexes with a diversity of substrates which was carried out over a 20-year period illustrates well how a research theme evolves. This line of research was carried out in collaboration with late Richard (Dick) Andersen from UC Berkeley and Laurent Maron, who was a post-doctoral fellow in our group at the start of the project and a full professor at the University of Toulouse when it ended. We were also greatly helped by Lionel Perrin who was a PhD student with Laurent and I early in the project. I limit myself here to the mention of the work on reaction mechanisms.<sup>88</sup> References to the studies of the unusual electronic states of some lanthanide complexes and actinide complexes are not included because they are the work of Laurent.

This research line started before I met Dick Andersen. Laurent was an expert in the calculations of heavy elements and we decided to study together the chemistry of lanthanide complexes.<sup>89</sup> We established that the 4f Ln shell is not playing a major role in the Ln-ligand bond in  $\text{LnX}_3$  ( $X = \text{H}$  and  $\text{SiH}_3$ ). We also showed that the structure of the complexes is consistent with some covalent contribution in the Ln-ligand bond. We determined that

lanthanide hydrides react with simple molecules like H<sub>2</sub>, CH<sub>4</sub>, SiH<sub>4</sub>, CF<sub>4</sub> by  $\sigma$ -bond metathesis mechanism. Lionel Perrin gives a nice summary of our studies in reference 1.

I met Dick Andersen by chance in early September 2001 at the gate of Latimer building at UC Berkeley. I had met him briefly at an organometallic meeting in Spain in 2000. I was on my way back to France after an around-the-world trip and I was looking for a place to look at my mail before spending three days sight-seeing in the bay of San Francisco. Dick invited me to come to his office. When I was ready to leave, he asked me if I would have time for some discussions on chemistry. Yes, I had. The discussion continued over lunch and then over dinner. I came back the day after and in fact till the last minute before leaving for the east coast of USA. As I told Ernesto Carmona<sup>90</sup> “*my three-day vacation had evaporated in thin air but a scientific venture, whose amplitude was still unknown to me, was starting*”.

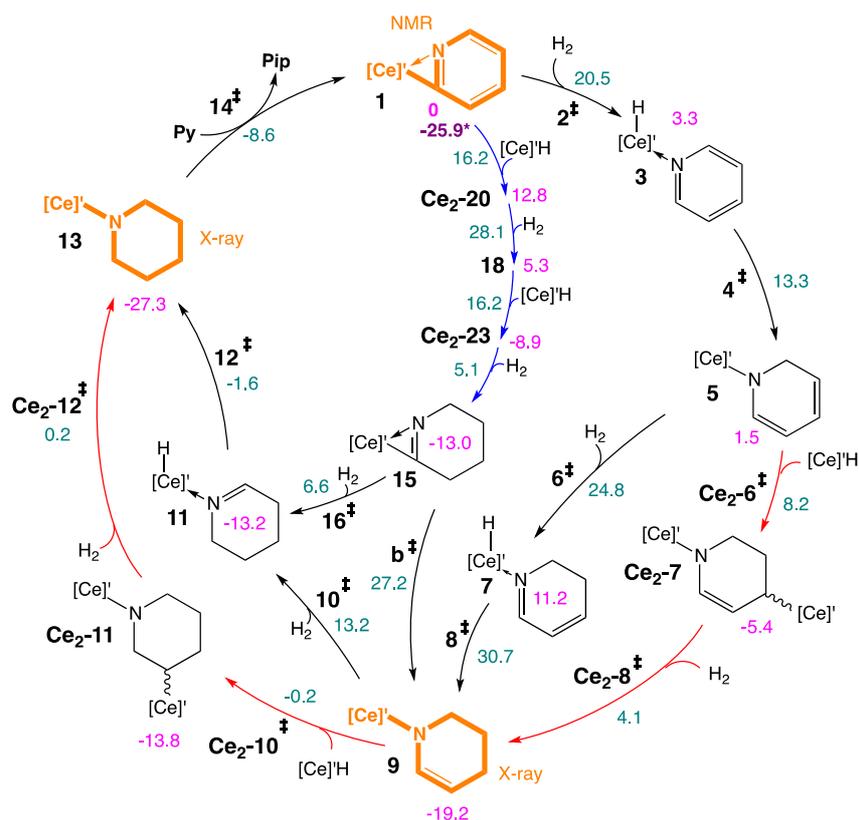
The goal of this long collaboration was to establish the general principles that govern the reactivity of lanthanide complexes. Towards this goal, Dick Andersen had studied the reaction of simple organic molecules with a given lanthanide, which was most of the time [1,2,4-(Me<sub>3</sub>C)<sub>3</sub>C<sub>5</sub>H<sub>2</sub>]<sub>2</sub>CeH, named Cp'<sub>2</sub>CeH. The substrates were alkanes, arenes substituted by chemical groups like halide, OR, NR<sub>2</sub>, OSiMe<sub>3</sub>, OSO<sub>2</sub>R etc. CO, H<sub>2</sub> were also considered. The calculations showed that the reaction mechanisms were highly diverse, supporting the hypothesis of some covalent character in the lanthanide-ligand bond. One remarkable reaction was Cp'<sub>2</sub>CeH with CH<sub>3</sub>X (X = F, OR, NR<sub>2</sub>), which yields Cp'<sub>2</sub>CeX and CH<sub>4</sub> for X = F and OMe but not for X = NMe<sub>2</sub>.<sup>88d,f</sup> Pathways, typical of  $\sigma$ -bond metathesis were considered (Figure 18). Calculations indicated that the direct formation of the products (via **a**) was highly disfavored energetically and gave a preference for a transition state of type **c**, yielding a carbenoid reacting with H<sub>2</sub> as shown in **e** to form the products. The bonding within this carbenoid determines its reactivity and we reproduced well the experimental trends. This reaction pathway is supported by the isolation and characterization by solid-state diffraction of the carbenoid complex for X = OMe.





**Figure 18:** Schematic possible 4c-4e transition states (**a-d**) for the reaction of [Ce]-H with CH<sub>3</sub>X. (X = F, OMe, NMe<sub>2</sub>. [Ce] = Cp'<sub>2</sub> = [1,2,4-(Me<sub>3</sub>C)<sub>3</sub>C<sub>5</sub>H<sub>2</sub>]<sub>2</sub>Ce. The favored path via **c** forms a carbenoid which reacts with H<sub>2</sub> via transition state **e** to form the products [CeX] + CH<sub>4</sub> for X = F and OMe but not for NMe<sub>2</sub>. Adapted from 88d.

Interestingly, the modelling of the lanthanide complexes evolved drastically during this 20 years collaboration. In the early 2000, a lanthanocene was represented by replacing the cyclopentadienyl ligand by chloride! Then, C<sub>5</sub>H<sub>5</sub> was used. It gave better results but was found also not sufficient and introducing the substituents on the Cp type ring, present in the experimental systems, was needed. One of our last studies summarizes it all. The reaction pathway of the hydrogenation of pyridine by [1,2,4-(Me<sub>3</sub>C)<sub>3</sub>C<sub>5</sub>H<sub>2</sub>]<sub>2</sub>CeH and H<sub>2</sub> could only be explained by considering the real lanthanide complex in the calculations.<sup>88f</sup> The rather elaborate multistep mechanism, based on computations, presented in Figure 19, involving even two Ce complexes at some steps, explains all observed facts and the final paragraph of the article published in 2014 represents the philosophy of this collaboration. “*The experimental results outlined in this manuscript were obtained several years ago. The computational results using C<sub>5</sub>H<sub>5</sub> as a substitute for 1,2,4-(Me<sub>3</sub>C)<sub>3</sub>C<sub>5</sub>H<sub>2</sub> gave results in contradiction with the experimental ones and calculations with the full ligands were not possible. Specifically, the size and conformational ambiguity of the full system prevented a complete exploration of the potential energy surfaces, which was the case with one Cp'<sub>2</sub>CeH molecule; two were inconceivable. Today, this is not true due the dramatic advances in computational power and this long-standing problem waited patiently for the necessary computational advances. The reactivity studies and associated mechanistic questions, which originated when the two senior authors were speakers at the Spanish Organometallic group meeting in Valladolid in 2000, are outlined in this forum article.*”



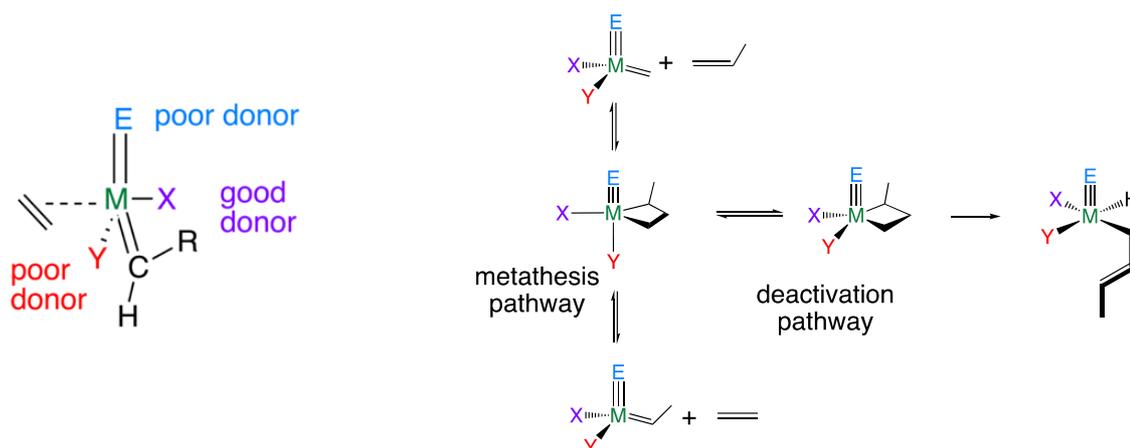
**Figure 19:** Reaction pathways for the catalytic hydrogenation of pyridine, **py**, to piperidine, **pip**, with  $[\text{Ce}]^{\text{H}}$ . All extrema are labeled in bold black and transition states, are labeled with a dagger sign and all energies are in  $\text{kcal mol}^{-1}$  relative to **1**. Values for minima and transition states are in pink and teal, respectively. The free energy of the reaction is given in purple. Copyright Inorganic Chemistry.<sup>88l</sup>

### Alkene metathesis catalysis and analysis of $^{13}\text{C}$ NMR chemical shift tensor

In the early 2000s, we started to collaborate with Christophe Copéret (in Lyon at the start of the collaboration, at the ETH Zurich at the end). He had contacted us because there was no understanding of why the Schrock metathesis catalysts,  $d^0 \text{MXY}(\text{E})=\text{CHR}$  ( $\text{M} = \text{Mo}, \text{W}$  with  $\text{E} = \text{NR}'$ ;  $\text{M} = \text{Re}$  with  $\text{E} = \text{CR}'$ ;  $\text{X}, \text{Y} = \text{hydrocarbyl}, \text{OR}, \text{OSiR}_3, \text{pyrrolyl}$  etc) were more efficient in their reaction with alkenes when they were grafted on amorphous silica.<sup>91</sup> This was one of the many interesting examples of surface organometallic chemistry, which is an area of catalysis at the frontier between homogeneous and heterogeneous catalysis initiated by Jean-Marie Basset.<sup>92</sup> Studying reaction pathways for catalysts grafted on amorphous silica was not easy even if methods to represent amorphous silica are known. Since silica is chemically inert and since the grafted catalysts are highly dispersed on the surface, we decided to use a molecular approach.<sup>93</sup> Xavier Solans-Monfort, who started as a post-doctoral fellow on the

project, is now a faculty member at the UAB near Barcelona. He has now kept this topic as one of his lines of research in his independent position.<sup>94</sup>

To our great satisfaction, the calculations on molecular catalysts reproduced the “silica effect” on the energy profile of the reaction.<sup>93b,f</sup> This suggested that a siloxy ligand could have an effect similar to amorphous silica which was indeed verified by experiments.<sup>95</sup> The reaction mechanism of alkene metathesis remains the one proposed by Yves Chauvin but we discovered that coordination of the alkene to the metal center needed an activation energy. Indeed, the originally tetrahedral catalyst, is strongly distorted to a trigonal pyramidal geometry at the transition state for alkene coordination. The lowest transition state is found when the X and Y ligands have different electronic properties. The stronger electron donor ligand (alkyl), is at the apical site of the trigonal pyramid while the weaker electron donor ligand (OSiR<sub>3</sub>), is at a basal position (Figure 20). This rationalizes the “silica effect” on the reaction rate. Furthermore, this transition state is prochiral, which was used Schrock and Hoveyda to design highly efficient and enantioselective catalysts.<sup>96</sup> We also studied other factors that influence the reaction efficiency.<sup>93g,h</sup> In particular, deactivation processes and off-cycles reactions had been neglected, notably by computational studies, but their importance in catalyst design is now recognised.<sup>97</sup> It is however demanding to determine the deactivation pathways because the products resulting from these paths are often unknown. We established that the trigonal bipyramidal metallacycle intermediate is on the metathesis pathway while its square based pyramidal isomer leads to catalyst deactivation (Figure 20).<sup>93g,h</sup> Interestingly, we had to use highly simplified models of the catalysts at the start of the project but the full identity of the experimental catalysts was considered 10 years after.<sup>93k</sup>



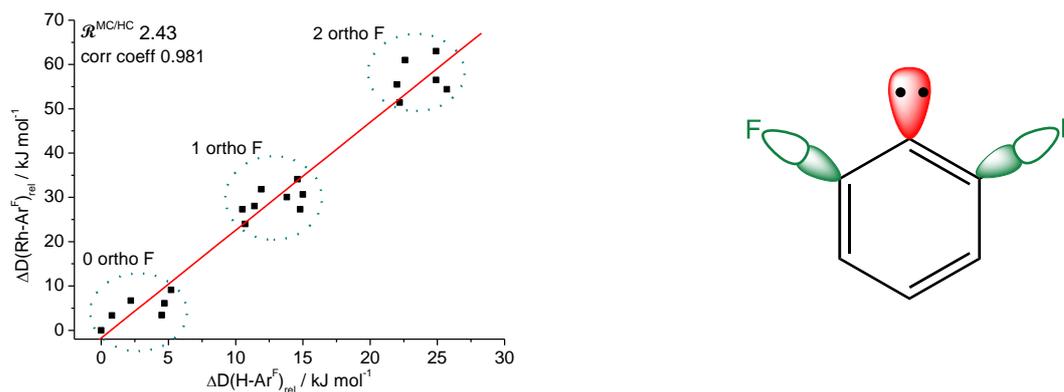
**Figure 20:** Left) Schematic representation of the key transition state in alkene metathesis with Schrock catalysts.<sup>93b,f</sup> The alkene being far from the metal center, the energy of this TS is essentially that needed to distort the catalyst from a tetrahedral to a trigonal pyramidal shape. Right) the competing pathways for productive metathesis and deactivation. MXY(E)(=CHR) (M = Mo, W with E = NR'; M = Re with E = CR'; X, Y = hydrocarbyl, OR, OSiR<sub>3</sub> pyrrolyl).<sup>93g,h</sup>

This study of the alkene metathesis reaction with Schrock catalysts was followed by a study of the  $^{13}\text{C}$  NMR chemical shifts of the metal-bonded carbon in a variety of organometallic complexes in collaboration with Christophe Copéret and Christophe Raynaud.<sup>98</sup> This was initiated because solid-state NMR spectroscopy is an essential tool of characterization for surface grafted species. This NMR method has the advantage to inform on the anisotropy of the chemical shift (chemical shift tensor) at the active nucleus. The calculated tensor components, which were in good agreement with the measured values, gave interesting information on the metal-carbon bonds in metal-alkyl, metal-alkylidene and metal-alkylidyne complexes. By analyzing the relation between the chemical shift tensor components, and the frontier orbitals of the organometallic complexes, we showed how the reactivity at the carbon is encoded in its chemical shift tensor. These studies are not easy to summarize in a couple of paragraphs and we refer interested readers to the Account of Chemical Research article which we published.<sup>98g</sup> These studies were enjoyable in that they highlighted how chemical bonding in organometallic complexes, as originating from the Roald Hoffmann school and described into the book of Tom Albright, Jeremy Burdett, and Mike Whangbo<sup>99</sup> were useful to understand trends in NMR chemical shifts.

### **Energetics of metal-carbon bonds**

The knowledge of the energetics of bonds that are cleaved and formed is essential to understand a chemical processes. Unfortunately, determination of absolute values of metal-ligand bond enthalpies in polyatomic transition metal complexes is exceptionally difficult.<sup>100</sup> However, only relative values are usually needed and, in few cases, it is possible to employ kinetic and equilibrium methods to determine free energies for a series of related reactions. Thus, assuming that entropic factors are constant, bond enthalpies for M-X bond can be estimated relative to a standard (*e. g.* metal-phenyl). Henry Bryndza *et al.* noticed that a series of relative M-X bond enthalpies correlates with H-X bond enthalpies.<sup>101</sup> Two studies followed focusing on M-C and H-C bond enthalpies. Bill Jones *et al.* published correlations between Rh-C bond enthalpies and H-C bond enthalpies of alkanes, alkenes, and benzene for the case of  $\text{Rh}(\text{H})(\text{R})(\text{Tp}')(\text{CNCH}_2\text{CMe}_3)$  [ $\text{R}$  = hydrocarbyl,  $\text{Tp}' = \text{HB}(3,5\text{-dimethylpyrazolyl})_3$ ],<sup>102</sup> while Bennett and Wolczanski reported similar studies for Ti-C bonds of  $\text{Ti}(\text{R})(\text{silox})_2(\text{NHSitBu}_3)$  ( $\text{silox} = \text{OSitBu}_3$ ).<sup>103</sup> Both studies show a linear correlation between M-C and HC relative bond energies with a slope  $R^{\text{M-C/H-C}}$  that is larger than 1. Bergman, Andersen *et al.* examined NHar ligands bound to  $\text{Ni}(\eta^5\text{-C}_5\text{Me}_5)(\text{PEt}_3)$  and found a slope of 1.9.<sup>104</sup> The fact that the value of  $R^{\text{M-C/H-C}}$  is larger than 1 has important consequence on the selectivity of H-C bond activation. There is a thermodynamic advantage in cleaving a stronger C-H bond.

Computational studies are ideal to analyze this topic for many organometallic complexes including those which are not amenable to experimental studies. We carried out this project in collaboration with Robin Perutz. The validation step was successful and the correlations observed by Jones and Wolzancski were reproduced with good accuracy even though absolute values of BDE could differ from observed values.<sup>105</sup> We then explored the correlations in the full series of fluorinated benzenes  $C_6F_nH_{6-n}$ , ( $n = 0-5$ ) including all isomers, to better understand the widely observed preference for activating a C-H bond adjacent to a fluorine atom in fluoroarenes and analogues.<sup>106</sup> The calculations found a linear correlation between relative H-C and M-C bond dissociation energies with a slope  $R^{M-C/H-C}$  ranging from 2 to 3 depending on the metal center. The surprising high value of  $R$  was confirmed by further experimental studies by Bill Jones for  $Tp^*Rh(CNneopentyl)$  and fluoroarenes with an observed and calculated  $R^{M-C/H-C}$  around 2.<sup>107</sup> The key point is that the slope of the correlation is essentially determined by the number of ortho fluorine atoms, the meta and para fluorine atoms having only modest and comparable influences. The correlation shown in Figure 21 is thus made of three well separated domains, defined by the number of fluorine ortho to the activated C-H bond. Inside each domain are all isomers with diverse numbers of meta and para fluorine substituents. Rationalizing this trend was only partly successful. An influence of the  $\pi$ -system of the aryl can be eliminated since meta and para fluorines have similar effect on the M-C bond strength. Focus was put on the M-C and C-H  $\sigma$ -bonds. It is recognized that a M-C bond has a larger ionic component than a C-H bond. There is thus a larger contribution of the  $\sigma$ -aryl  $C_6F_nH_{5-n}^-$  anionic valence bond form in the electronic description of the metal-aryl complex than in the corresponding arene. Increasing the ionic contribution of the M-C bond contributes to its strengthening as shown by Pauling. Thus, ortho fluorine atoms, which stabilize this anionic form through hyperconjugation of the  $\sigma$ -lone pair with the  $\sigma^*_{C-F}$  orbitals (Figure 21 right), contribute to a larger bond strengthening in the metal-aryl complex than in the arene. Unfortunately, it is not yet possible to evaluate in a quantitative manner the anionic and covalent contributions to the metal-carbon bond. Another territory to explore is the effect of the metal. Calculations indicate that the ratio  $R^{M-C/H-C}$  decreases down a column of the periodic table as we found for the triad Ni, Pd, and Pt.<sup>106b</sup> Recent experiments by Paul Chirik point to the same results in the case of Co relative to Rh and Ir.<sup>108</sup> We are presently looking at this question. We have also looked at the importance of these correlations in the kinetics of the reactions.<sup>109</sup>



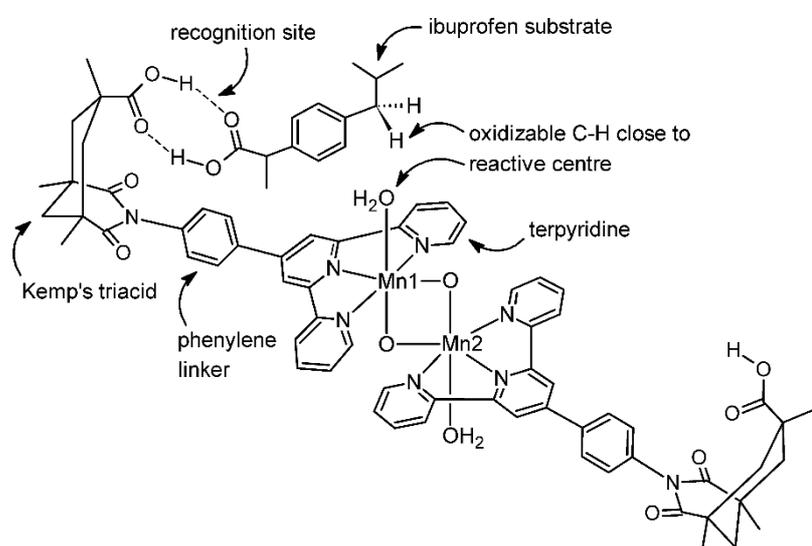
**Figure 21.** Left) Correlation between the Rh-C bond dissociation energies of  $\text{Rh}(\eta^5\text{-C}_5\text{H}_5)(\text{H})(\text{Ar}^{\text{F}})(\text{PH}_3)$  with the H-C bond dissociation energies of fluorobenzenes. The zero corresponds to the values for H-Ph and Rh-Ph bond energies. Copyright J. Am. Chem. Soc.<sup>106b</sup>. Right) Schematic representation of the hyperconjugative stabilizing effect of ortho  $\sigma^*_{\text{C-F}}$  orbitals in  $1,3\text{-C}_6\text{F}_2\text{H}_3^-$  anion.

Thus, if computations cannot yet provide quantitative values for metal-ligand bond strength, they give already reliable trends and relative values at reasonable computational cost. It is thus with confidence that we also contributed to compare C-H and C-F activation, a topic which was mostly led by Robin Perutz, notably in collaboration with Stuart Macgregor and John McGrady.<sup>110</sup> Even if the C-F bond is strong it can be activated and great insights have been already gained on this topic.

### C-H oxidation reaction

We engaged into a study of the metal-catalyzed oxidation reaction in collaboration with Bob Crabtree. This project was entirely under the responsibility of David Balcells who kept this important topic in his research lines when he moved to Oslo after a highly productive post-doctoral stay in our group. DFT calculations were the essential access to the mechanism of these reactions which involve unstable intermediates with the metal center in high oxidation. This was a domain well explored by Sason Shaik but we took the case of the manganese porphyrin complexes, which had not been explored.<sup>111</sup> We knew that using DFT for looking at the spin states of these species had to be done with care and we benefited from discussions with Jeremy Harvey who was on sabbatical in our laboratory. We showed that the hydroxylation reaction is related to the degree of oxyl character on the oxygen center of the Mn-oxo bond and we analyzed how this character is influenced by the coordination sphere of the Mn. We established that Mn-hydroxyl is competent in C-H activation,<sup>112</sup> and this led to

propose an interpretation for the experimentally observed competition between hydroxylation and dehydrogenation of 9,10-dihydrophenanthrene.<sup>113</sup> We also looked at how molecular recognition could influence the selectivity of the C-H activation.<sup>114</sup> Selectivity in C-H activation and functionalization is especially challenging when the substrate contains multiple reactive functional groups that can take part in the reaction and decrease the selectivity. This question was tackled by a bio-inspired approach and by using a catalyst in which the recognition site is bound to the reactive center through a linker as shown in Figure 22. The manganese had a judiciously positioned carboxyl group, which could recognize ibuprofen. The selective hydroxylation of ibuprofen at the benzylic site is reproduced by the computations, in which the experimental system was simplified by including only one Kemp's triacid.



**Figure 22:** Molecular recognition model for selective oxidation of ibuprofen. Copyright to Dalton Transaction.<sup>114</sup>

We continued this research direction with some calculations on water oxidation by iridium oxo complexes also in collaboration with Bob Crabtree and Gary Brudvig.<sup>115</sup> It is my great pleasure to acknowledge the remarkable work of David Balcells in these studies. It was really his own line of research and I am very happy that this served him well to get to his present position as group leader in Oslo. I encourage the interested reader to read a more detailed summary of this section in several reviews he contributed to.<sup>1,78, 116</sup>

### Grignard Reagent and Reaction

When I started research, I was forced to represent a nucleophilic reagent by a hypothetical chemical species with a high-lying occupied orbital. This was conceptually correct but deeply frustrating. In 2014, I gave a lecture at University of Oslo and Mats Tilset asked me to comment

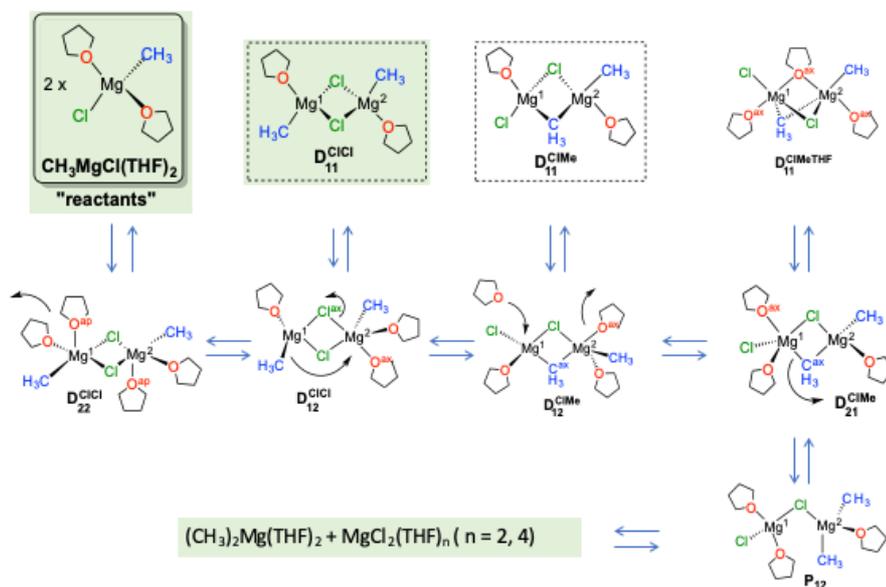
on poorly understood chemical reactions which would be worth studying by computations. I named the Grignard reagent and associated Grignard reaction which plays a central role in synthesis and is widely used in research and industry. Michele Cascella, a physicist by training with interest in computational structural biology and expertise in multiscale modelling, recently hired as a faculty member in Oslo, was present in the audience. He was intrigued by my statement and we agreed to collaborate. The project was put in the hands of a PhD student, Raphael Peltzer.

In 1900 a young French chemist Victor Grignard working on his doctorate discovers the a reaction for which he was awarded the Nobel prize of Chemistry in 1912. In this reaction, the so-called Grignard reagent, an organomagnesium species, promotes the addition of R, an organic residue, to an electrophilic substrate. Thus, the addition of RMgX to carbonyl moieties,  $R_1R_2(C=O)$ , yields a magnesium alcoholate that gives  $R_1R_2COH$  after hydrolysis. Despite more than 100 years of extensive studies the mechanism of this reaction remains elusive. Difficulties in elucidating the mechanism are mainly related to the fact that ethereal solutions of Grignard reagent contain a high variety of species. As written by Seyferth, RMgX (R = hydrocarbyl, X = halide) “*is more complicated than this simple formula indicates*”.<sup>117</sup> Many species are coexisting in ethereal solution and little is known about their nature at the molecular level and associated reactivity. Thus, despite numerous experimental studies and a few computational studies one of the most famous and first made organometallic species remains mysterious. We decided to tackle this “cold case” by first identifying the species in solution<sup>118</sup> and then studying how they react with a carbonyl substrate.<sup>119</sup> We used the ab initio molecular dynamics (AIMD) method to represent properly the dynamic of the solvent.

Identifying the nature of the species in solution was approached by looking at the Schlenk equilibrium. In this equilibrium, discovered by Wilhelm Schlenk and his son, RMgX in ethereal solution is in equilibrium with  $MgR_2$  and  $MgX_2$ .  $CH_3MgCl$  in tetrahydrofuran (THF) was used as representative case. The simulations confirmed the co-existence of several mono- and bimetallic magnesium species bonded mostly via the chloride atoms but also via the methyl groups. These numerous species rapidly exchange the methyl and chloride groups with a low activation energy of less than 10 kcal/mol under the influence of the dynamics of the solvent (Figure 23). Remarkably, the most stable dichloro-bridged dimagnesium species,  $D_{11}^{ClCl}$ , is rather inert but a change in solvation to  $D_{12}^{ClCl}$  makes it more dynamic. We thus identified the path that exchanges the chloride and methyl groups ( $D_{12}^{ClCl}$ ,  $D_{12}^{ClMe}$ ,  $D_{21}^{ClMe}$ , and  $P_{12}$ ), and showed that solvation at the two magnesium varies during the exchange.<sup>118</sup> The key role of the dynamics of the solvent in the equilibrium between the various species in solution is likely to



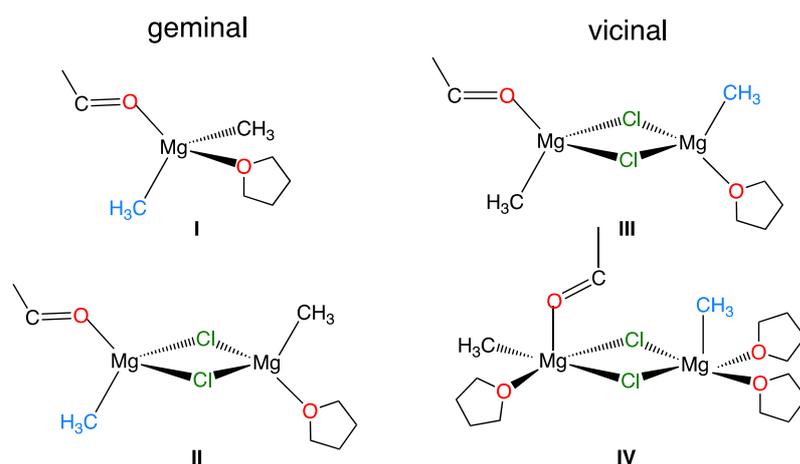
occur with any Grignard reagent and related systems even if the nature of the species in solution should depend on R and X.



**Figure 23:** Chemical species involved in the Schlenk equilibrium obtained by AIMD calculations. Green colored boxes indicate the most stable species. In  $\text{D}_{np}^{\text{XY}}$  the superscripts XY indicate the nature of the bridging X and Y groups or atoms and the subscripts indicate the number n and p of THF bonded to the left and right Mg centers, respectively. Adapted from reference 118.

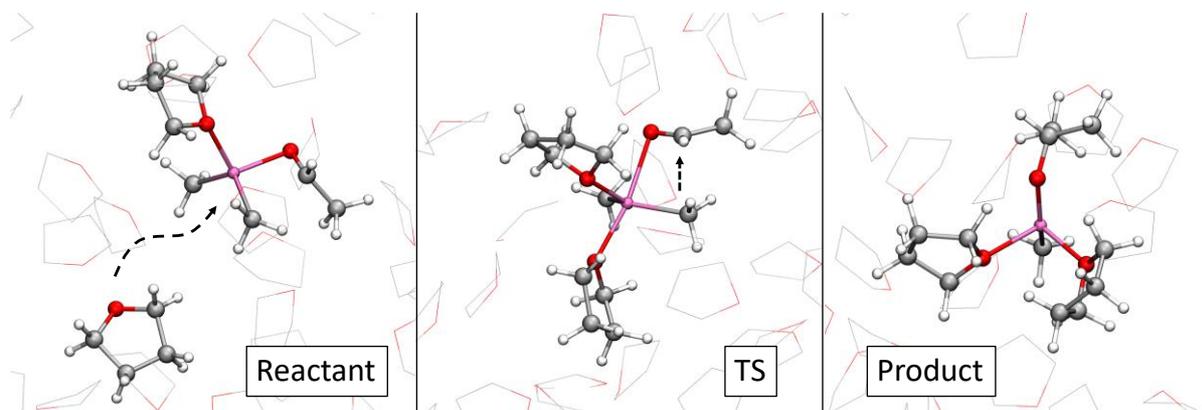
In studying the Grignard reaction, our purpose was twofold. We wanted first to determine which of the Mg species identified in solution were active in the C-C bond formation with the substrate (selected to be acetaldehyde). In addition, we wanted to understand what favors the single electron transfer (SET) mechanism which was found to occur for substrates with low reduction potential.<sup>119</sup>

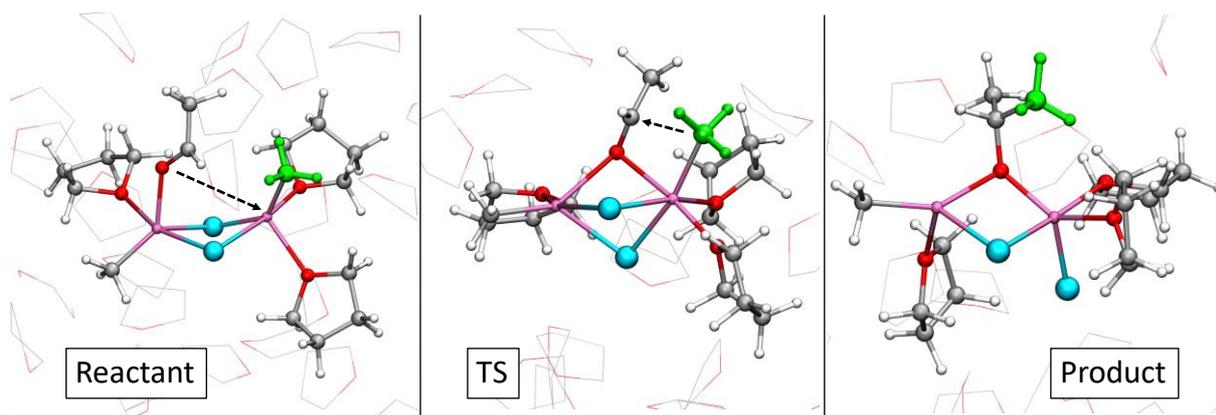
Coordination of the substrate to a Mg atom was considered as a requisite because it provides the needed electrophilic activation of the substrate for the nucleophilic addition. Thus, to determine the most reactive species, one of the coordinated THF was replaced by acetaldehyde in all species previously identified. This replacement can be done in two ways – with the acetaldehyde and methyl group on the same magnesium (geminal reaction) or on different magnesium atoms (vicinal reaction). The most representative species are represented in Figure 24.



**Figure 24:** Most representative species considered for the nucleophilic addition mechanism of the Grignard reaction. The methyl group considered as the nucleophile is colored in blue. Adapted from 119.

The AIMD calculations revealed that all species are competent in the C-C bond formation and that the range of activation energies is relatively small. However, two species, **IV** and **I**, are found to be associated with lowest free energy of activation. The most active species is the dimagnesium species **IV** showing that initial proximity between the substrate and the nucleophile is not a prerequisite for a low-lying activation energy. The pathway followed is shown at the bottom of Figure 25. At the transition state, the electrophilicity of acetaldehyde, which bridges the two magnesium centers is significantly enhanced. The nucleophilicity of the “blue” methyl group is enhanced by the increased coordination at the Mg center to which the “blue” methyl group is coordinated. Finally, the reaction occurs without additional entropy penalty because no additional solvent enters the coordination sphere of this dimagnesium species during C-C bond formation. In contrast the reaction for species **I** requires the assistance of an entering THF (Figure 25 top) and this makes **I** slightly less reactive than **IV**.





**Figure 25:** The pathways for Grignard reaction obtained by AIMD calculations for species **I** and **IV** of Figure 24. Copyright J. Am. Chem. Soc.<sup>119</sup>

The single electron transfer mechanism was limited to calculate the  $\text{CH}_3\text{-Mg}$  bond dissociation energy (BDE) of the methyl-magnesium bond in various complexes by static DFT calculations validated by CCSD(T) benchmark. The BDE in  $\text{CH}_3\text{MgCl}(\text{THF})_2$  is calculated to be 66 kcal/mol in close agreement with the experimental value for  $\text{CH}_3\text{MgBr}$  in diethyl ether. Furthermore, the solvent coordination and nature of the halide were found to have little influence on this value. The SET reaction in such condition cannot compete with the nucleophilic reaction. However, the SET transfer is only mentioned to occur in presence of the substrate. Therefore, the  $\text{CH}_3\text{-Mg}$  BDE was calculated for Mg complexes with the carbonyl substrate as one of the coordinated ligands. The BDE drops drastically and an analysis of the spin density reveals that the single electron is fully located in the LUMO of the coordinated substrate and not on the magnesium center. Thus, the substrate assists the homolytic cleavage of the  $\text{R-Mg}$  bond in  $\text{RMgX}$  and it was verified that lowering the reduction potential of the substrate also lowers the  $\text{CH}_3\text{-Mg}$  BDE. It was then possible to verify that the SET mechanism is preferred to the nucleophilic mechanism in the case of fluorenone in good agreement with experiments.

We thus now understood why this reaction was puzzling for so long. The coexistence of multiple species in rapid exchange due to the Schlenk equilibrium and the evidence that the range of activation energies of all possible reactions is relatively modest indicate that the Grignard reaction should not be described by an individual process. Instead, it should rather be thought as an ensemble of transformations that can occur simultaneously in solution. We are now using this acquired knowledge to widen the study to closely related reactions and in particular to understand the observed impressive increase of rate when salts like LiCl are added to the solution. This is known as the turbo Grignard. This is on-going research done with Michele Cascella at the University of Oslo.

## Conclusion and Perspective

Fifty years have passed since I entered Nguyen Trong Anh group to study the Diels-Alder reaction. Probably young readers of today would have a hard time to imagine what it was to study a chemical problem with the modest computational methods and relatively slow computers of these times. It is probably nicely illustrated by the following anecdote: Lionel Salem had in mind a project involving Grignard reagents (already) and was discussing the issue with Henri Kagan, one of our contemporary giants in organic chemistry and asymmetric catalysis. Lionel wanted to represent the Grignard and the coordinating solvent and proposed to use water as model of solvent. Henri Kagan was horrified, and it was a learning experience for me to see how Lionel had to explain that the oxygen atom in H<sub>2</sub>O and any ether has similar lone pairs and thus similar properties towards an electrophile, *on first approximation!* This anecdote exemplifies the situation in these years. We were forced to select for each chemical transformation the atoms or group of atoms which were absolutely essential to the question of study. Thus, any ether or alcohol could be replaced by H<sub>2</sub>O if only the oxygen atom was (or thought to be) involved in the study. This time is completely gone and we are well aware of how important are chemical groups who look like spectators and are finally far to be innocent. Each group of a chemical systems involved in a reaction plays a role. This is not a theater with actors on a stage and silent and peacefully seated spectators. The spectators are part of the show. Thus, the complexity is immense and the number of possibilities is essentially infinite. It is not surprising that automatic search and machine learning has started to play a role in determining reaction pathways and catalyst design. This is a research theme that is growing very quickly. Focusing on the topic of molecular chemistry and homogeneous catalysis, I cite some recent selective reviews and perspectives on this topic.<sup>74k,121,122</sup> Other improvements will certainly occur in the field of computational methods, programs, and hardware, to make calculations faster and more accurate. It is not my intention to discuss this further. Thus, it is quite likely that in 50 years, people might smile at what is done today. This is the normal evolution of science. I still view myself as privileged for having had computational tools which gave me the possibility to provide simple interpretations of chemical facts and helped to establish concepts applicable to a large number of systems. Old concepts may remain valid, new concepts will be proposed. This should stimulate the dialog between computational and experimental chemists. I welcome an even more efficient and integrated experimental/computational approach of chemistry.

## Acknowledgements

First of all, I would like to thank the CNRS who offered me a position from 1971 to 2014. I am grateful to University of Paris-Sud Orsay (now University of Paris-Saclay) and University of

Montpellier where I worked with my CNRS position. I thank also the CNRS and the University of Montpellier for the present Emeritus status. In 2012, I became adjunct professor at the University of Oslo, first in the Center for Theoretical and Computational Chemistry (CTCC) and then in the Hylleraas Center. I am very grateful to Trygve Helgaker for having invited me to this position. This opened new routes and this is how I started to collaborate with Michele Cascella. Consequently, this work is supported by the Research Council of Norway (RCN) through the CoE Hylleraas Center for Quantum Molecular Sciences (Grant number 262695). Some of the studies cited in this work were supported by the Norwegian Supercomputing Program (NOTUR) (Grant number NN4654K).

I had the immense chance to be mentored by Nguyen Trong Anh and Lionel Salem during my PhD time and by late Jack D. Dunitz and then by Roald Hoffmann during my post-doctoral positions. Their enthusiasm for research was contagious and their advices were precious. It was a great benefit to collaborate with colleagues of my own institution, Yves Jean, Michel Pélissier, Claude Leforestier and Christophe Raynaud. I had the immense luck to establish long-term collaborating with many experimental chemists. I would like to acknowledge specifically Bruno Chaudret, late Jeremy Burdett, Ken Caulton, Bob Crabtree, Robin Perutz, late Dick Andersen, Bill Jones, Christophe Copéret, and Don Tilley to cite only a few. I benefited from the energy and creativity of students, post-doctoral fellows and short time visitors. Many of them took academic positions and became colleagues. The PhD students, some of them, marked as # co-supervised with colleagues, are in approximate chronological orders F. Volatron, A. Demolliens, # P. Sautet, D. Cauchy, # I. E. I. Rachidi, # C. Chardon, J. F. Riehl, # E. Clot, # D. Cauchy, # H. Gérard, L. Perrin, # C. Mégret, J. Guihaumé, S. Halbert, # and R. Peltzer#. Post-doctoral fellows and short time visitors, also in approximate chronological order, were S. A. Jackson, J. R. Rambo, M. Sigalas, G. Sini, S. A. Macgregor, S. Fantacci, R. Bosque, J. J. Carbó, late N. Gallego-Planas, G. Ujaque, M. Besora, J. E. McGrady, L. Maron, D. Balcells, X. Solans-Monfort, Ainara Nova, A. Poater, A. Poblador-Bahamonde, V. Postils, and P. Ludwig. I have very special gratitude to Feliu Maseras who, as associate scientist, helped me making the transition from Université Paris-Sud to Université de Montpellier in 1996. This also initiated a regular flow of young scientists, named above, from Spain and notably Catalonia. Special thanks also to Jeremy Harvey who spent a sabbatical with us and stimulated new scientific directions in the group, which were in particular taken by D. Balcells. Late Bertrand Castro was our most unusual collaborator. Synthetic organic chemist, former professor at University of Nancy and Scientific Director of SANOFI, he was fascinated by computational chemistry. With his support, David Balcells was paid by SANOFI for 3 years as post-doc with total freedom for his projects. When Bertrand retired from SANOFI, he became a post-doctoral fellow in our group and we started to collaborate on the project concerning the

synthesis of the artemisinic acid. Sadly, he passed away before he could read the proofs of the article resulting from this collaboration.<sup>123</sup> He is sadly missed. So are Jeremy Burdett and Dick Andersen who had become friends during the long, pleasant and highly productive collaborations.

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## Biography



Odile Eisenstein is Research Professor Emeritus from the CNRS and the University of Montpellier. She is also adjunct Professor at the Hylleraas Centre for Quantum Molecular Science at the University of Oslo. Odile Eisenstein is a computational chemist who has worked

in very strong symbiosis with leading experimental chemists to address questions on structures, properties and reactivity of complex molecular species. Her research concerns molecular organic and organometallic chemistry often with direct impact in homogeneous catalysis. She has received many awards including the Silver Medal from the CNRS, the Prix Le Bel from the French Chemical Society, the ACS Organometallic award, the Frankland and Centenary awards from the RSC. She holds honorary degrees from the Universities of Indiana, Laval, Oslo, and York and the Technion. She is a member and presently the President of the IAQMS. She is a member of the French “Académie des sciences”, and Academia Europea and foreign member of the Academy of Arts and Science of Norway, the North Rhine Westphalian Academy, the American Academy of Arts and Sciences and the US National Academy of Science. She has received the titles of « Officier de l’Ordre du Mérite » et « Officier de l’ordre de la Légion d’Honneur ».

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