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Olefin-Metathesis Catalysts for the Preparation of Molecules and Materials (Nobel Lecture 2005)**

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This is a story of our exploration of the olefin-metathesis reaction, a reaction that has been the major emphasis of my independent research. As with all stories of scientific discovery, there are three components: the discoveries, the resulting applications, and, perhaps the most important of all, the people involved. Starting from observations made from seemingly unrelated work, our investigations into the fundamental chemistry of this transformation have been an exciting journey, with major advances often resulting from complete surprises, mistakes, and simple intuition. Ultimately, these efforts have contributed to olefin metathesis becoming the indispensable synthetic tool that it is today.[1]

Much of modern organometallic and polymer chemistry, as we know it, started with a chance observation made in the early 1950s by the Ziegler group in Mülheim, Germany.[2] During this time, Ziegler was continuing work that had been initiated during World War II in exploring the use of alkyl aluminum complexes for the oligomerization of ethylene to produce lubricating oils. On one occasion, it was noted that this reaction produced 1-butene from ethylene instead of the C_{10}–C_{20} hydrocarbons normally observed. Subsequent analysis of the reaction autoclave found the presence of nickel. When nickel salts were deliberately added to this reaction, 1-butene was again observed. This discovery has since served as the foundation for an amazing array of nickel chemistry and catalysis. In addition, as nickel had been found to possess unexpected reactivity, other metal salts were also investigated. In particular, when titanium and zirconium halides were used in combination with alkyl aluminum compounds, a new form of polyethylene was obtained. Natta further demonstrated that similar catalysts could promote the formation of stereoregular polymers from propylene. The 1963 Nobel Prize in Chemistry was awarded to Ziegler and Natta for this work.

The application of Ziegler–Natta-type systems toward the polymerization of cyclic olefins afforded additional unexpected results. A group at DuPont observed that the polymerization of norbornene did not produce a saturated polymer as expected, but instead afforded an unsaturated polymer in which one of the rings had been opened. While surprising, the origin of this unexpected polymeric structure was not to be pursued until later. Natta subsequently observed a similar result when he attempted to polymerize cyclopentene using tungsten and molybdenum halides—he, too, obtained a ring-opened, unsaturated polymer. Finally, Banks and Bailey of Phillips Petroleum Co., while investigating the possible polymerization of propylene over cobalt molybdate, found instead the formation of ethylene and 2-butene. These three observations, seemingly unrelated, were beginning to indicate a fundamentally new olefin transformation.[3]

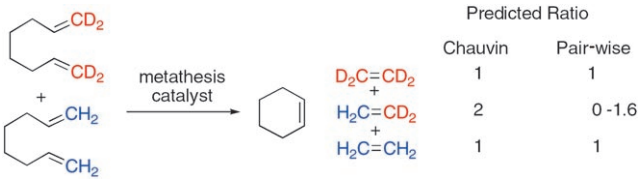
My involvement with this puzzle started in 1967 while I was a postdoctoral fellow at Stanford. Jim Collman, my postdoctoral mentor, had just returned from a trip to Phillips Petroleum, where he had learned of an amazing reaction that converted propylene into ethylene and 2-butene. During a group meeting (Barry Sharpless, Nobel Prize 2001 was also a member of the Collman group at that time), we began to discuss possible mechanisms for this trans-

formation. With my earlier training in mechanistic organic chemistry as an undergraduate and master's student in the laboratories of Merle Battiste, and as a doctoral student with Ron Breslow, I felt this unknown reaction mechanism would be an ideal problem to study.

Around this time, Calderon and his group at Goodyear had developed a soluble catalyst system that could not only induce polymerization via ring-opening, but also convert propylene into ethylene and 2-butene.. Calderon's observations established that the polymerization of cyclic olefins observed by DuPont and Natta and the scrambling of acyclic olefins observed by Banks and Bailey were similar reactions. He also established that the mechanism of this reaction involved the cleavage of carbon–carbon double bonds rather than a transfer of alkyl groups between olefins through single-bond cleavage. This first critical mechanistic observation set the stage for subsequent studies. Banks and Bailey went on to propose a "quasicyclobutane" mechanism to account for their interchange reaction that was also consistent with Calderon's results. Other mechanisms were also proposed to account for this transformation, now termed olefin metathesis. What all these mechanisms had in common was the pair-wise involvement of carbon atoms in reaction intermediates. Theoretical studies of this reaction carried out by Frank Mango at Shell supported this pair-wise exchange of two-carbon fragments.[4]

My independent career started at Michigan State University in 1968, where I proposed an alternative pair-wise mechanism and initiated experimental work. Shortly thereafter, however, a growing body of evidence against such a mechanism began to appear. While investigating the effect of acyclic olefins in determining the molecular weight of polypentenamers, Chauvin and Hérrison observed products that were not consistent with the diolefin metal complexes proposed in the "quasicyclobutane"-type mechanisms. They instead proposed that the reaction did not go through a diolefin metal complex, but rather via a one-carbon metal carbene complex and metallocyclobutanes; intermediates that contain an odd number of carbon atoms. In a similar study, Katz proposed an analogous mechanism where he was able to rationalize the observations that Chauvin had found to be inconsistent with his non-pair-wise mechanism. Chuck Casey subsequently went on to find a model for this transformation utilizing preformed metal carbene complexes, and Richard Schrock was able to determine that metal carbene complexes could, in fact, be generated under conditions similar to those used to prepare Ziegler–Natta-type catalysts.[5] Incorporating this new information into our mechanistic consideration, we designed an experiment that would allow most of the ambiguities of the Chauvin experiment to be addressed in detail. Rather than using a cross-metathesis reaction that would require us to analyze the role of alkyl groups on the intermediates, we instead selected to study the simplest system possible: isotopic substitution on a ring-closing metathesis (RCM) reaction.

The RCM of 1,7-octadiene generates cyclohexene and ethylene (Scheme 1). Cyclohexene is one of the



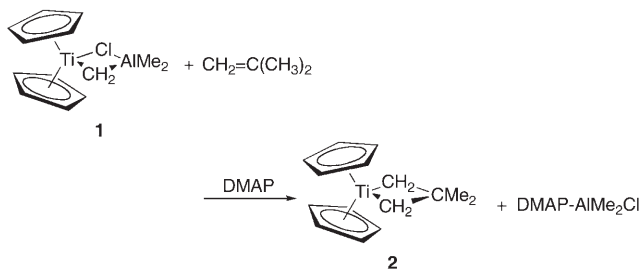
Scheme 1. Ring-closing metathesis of 1,7-octadiene.

few simple cyclic olefins that will not undergo subsequent metathesis reactions. Consequently, the fate of the two olefins in 1,7-octadiene can be determined by examination of the metathesis products. If the pair-wise mechanisms involving even numbers of carbon atoms were involved, the other two carbon atoms would be required to couple together. In contrast, the Chauvin mechanism would be expected to scramble the two terminal carbon atoms. A mixture of 1,1,8,8-tetradeutero-1,7-octadiene and 1,7-octadiene was used to investigate this. In the simplest case, the even-carbon mechanisms should produce only ethylene and tetradeuteroethylene, while the odd-carbon mechanisms should afford a statistical mixture of ethylene, dideuteroethylene, and tetradeuteroethylene in a 1:2:1 ratio. Careful analysis of all of our experiments found that a statistical mixture of ethylene compounds was kinetically formed in this reaction, a result consistent with the prediction made using the Chauvin (odd-carbon) mechanism. Subsequent studies by Katz on related systems provided additional support for this conclusion.[6]

By determining the key reaction intermediates in olefin metathesis, these combined mechanistic studies now enabled the use of rational design for further catalyst optimization. Prior to this time, metathesis catalysts were produced utilizing inconsistent, ill-defined systems. By confirming the non-pair-wise mechanism of Chauvin, the identification of new metal alkylidene (metal carbene) complexes capable of promoting olefin metathesis now became our target for further improving reaction efficiency.

Fred Tebbe, a co-worker of Schrock during his time at DuPont, developed one of the first well-defined metathesis systems. Now known as the Tebbe reagent, titanium complex **1**, a metal carbene precursor, was found to exhibit metathesis activity in addition to its ability to promote Wittig-type reactions on esters. As

the Tebbe catalyst was well-defined, both the starting and propagating carbene species could now be observed during a metathesis reaction, making it an ideal system for mechanistic study. In particular, we became interested in investigating the stereochemistry of the intermediate metallacycle. Our initial efforts to isolate a metallacycle complex proved unsuccessful until Tom Howard was able to serendipitously isolate metallacycle **2** by employing dimethylamino pyridine (DMAP), which facilitated aluminum removal (Scheme 2). Tom was later able to demonstrate this



Scheme 2. Preparation of an isolable metallacycle.

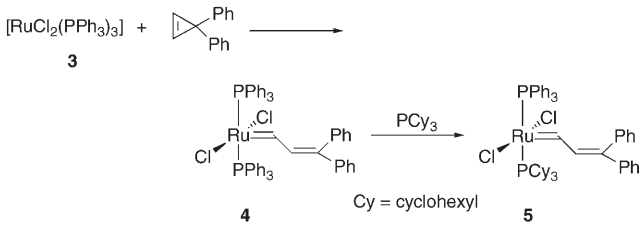
metallacycle to be the low-energy state for this catalyst system. In addition, **2** was found to be an active metathesis catalyst. This observation provided the first example of a metallacycle intermediate and demonstrated that metallacycles could function as kinetically competent catalysts for olefin metathesis.[7]

Utilizing the well-defined Tebbe system, additional mechanistic and synthetic studies were carried out. Laura Gilliam found that metathesis conducted using this system was inherently "living," allowing for the preparation of polymers with defined structures. Polymer preparation and analysis consequently became a major focus within my group to further explore these observations. It was during this period that Richard Schrock spent a four-month sabbatical at Caltech, where we co-authored a paper demonstrating that one of his tantalum catalysts could also serve as a living initiator.. In fact, it is now well established that virtually all defined metathesis initiators can be used to generate polymer structures through living polymerization.[8]

Subsequent studies by the Schrock group resulted in the design and synthesis of a number of very efficient molybdenum and tungsten metathesis catalysts, the historical development of which are discussed in his lecture (see the preceding article in this issue). Despite the activity of Schrock systems, the use of these early-transition-metal catalysts had a major limitation: the oxophilicity of the metal center afforded poor functional-group tolerance and necessitated catalyst preparation and handling under an inert atmosphere. To fully exploit the potential of metathesis, we believed that the development of new, functional-group-tolerant catalysts would be crucial. Once again, serendipity would play a role in achieving this objective.

The development of ruthenium-based metathesis catalysts started with the goal of preparing interesting polymeric structures. Polymer chemistry provides an excellent means of studying metathesis catalysts: miniscule catalyst loadings have the capacity to generate large amounts of polymeric material, the structure of which can provide a historical record of catalyst activity. The polymer program within my group was focused on understanding the basic principles of living metathesis polymerization. From this knowledge, we hoped to develop novel polymers that possessed interesting structures and physical properties. During the course of this work, model building had suggested that the ring-opened polymer from 7-oxo-norbornenes could be used to produce ionophoric membranes for selective ion transport. Bruce Novak took on the challenge of making these desired polymers. Much to our dismay, however, none of the available catalysts was found to promote this reaction. Examining the literature, Bruce came upon reports by Michelotti[9] and later Natta, where late-transition-metal catalysts had been used to polymerize strained olefins in protic media. In the laboratory, Bruce was able to demonstrate that these systems could also effectively promote the formation poly-7-oxo-norbornenes. More importantly, he went on to discover that ruthenium(II) complexes could serve as much more active polymerization catalysts. The outcome of Bruce's investigations resulted in the development of a robust catalyst system that tolerated most functional groups and aqueous media. Despite the activity of these ruthenium salt catalysts, however, only a small percentage of the ruthenium added to a reaction was found to produce an active catalytic center. In addition, as the structure of the active catalysts was totally undefined, it was impossible to make rational changes for further improvements.[10] However, this work defined the path forward; a ruthenium(II) complex and a strained olefin were found to be required to form an active catalyst system.

Assuming that olefin metathesis must occur via the formation of metal carbenes, we felt that the development of well-defined ruthenium carbene complexes was vital for further catalyst optimization. It took a few years, but eventually graduate student SonBinh Nguyen was able to prepare air-stable carbene complex **4** from the reaction of ruthenium(II) phosphine complex **3** with cyclopropene (Scheme 3). To our surprise, complex **4** was found to be an effective catalyst for the polymerization of norbornenes in protic media. Although **4** was not very active, its structure was well-defined, finally providing us with a scaffold by which to make structural changes for catalyst optimization. While many modifications have since been



Scheme 3. Preparation of the first well-defined ruthenium carbene catalyst.

made (e.g. ligand exchange using tricyclohexylphosphine to generate the more active catalyst **5**), the basic structure of our catalyst systems still resembles that of our original "SonBinh Catalyst." This well-defined family of catalysts is distinguished by its amazing tolerance to oxygen and water, making it ideal for application to organic synthesis.[11]

In the early 1990s, Greg Fu joined our group as a postdoctoral scholar from Dave Evan's group at Harvard and began investigating the activity of various metathesis polymerization catalysts in organic synthesis. Relatively quickly, he was able to demonstrate that the Schrock molybdenum catalysts were effective for a number of important organic transformations, particularly those involving ring-closing reactions. Just prior to leaving the group to join the faculty at MIT, he was able to demonstrate that our newly prepared ruthenium systems could perform the same transformations on the benchtop without the use of a glovebox. In addition, many previously unreactive substrates were found to readily undergo ruthenium-catalyzed olefin metathesis in high yields.[12]

In our earlier work with the Tebbe reagent, we had found that its general use had been limited because of its air sensitivity and difficult preparation. In contrast, our user-friendly ruthenium catalysts were in high demand, and efforts now had to be made to make them readily available. Unfortunately, the SonBinh synthesis was difficult to run on large scale. Eventually, building off of work performed by Marcia France, Peter Schwab was able to develop a method based on the use of a diazo precursor. Although this reagent is potentially explosive, Mike Giardello developed a procedure to tame this reagent, allowing complex **6** to be commercially made on multikilogram scales (Figure 1).[13] With commercial sources, the organic synthetic community found a wide array of creative uses of olefin-metathesis catalysts in the synthesis of complex structures.

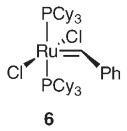


Figure 1. First-generation commercial catalyst.

Ruthenium's preference for soft Lewis bases and π-acids, such as olefins, over hard bases, such as oxygen-based ligands, is responsible for its high tolerance to air and water. It also makes ruthenium catalysts fundamentally different from titanium-, tungsten-, and molybdenum-based systems. Consequently, the rules learned in the development of early-transition-metal catalysts no longer applied: for example, as ruthenium possesses a metal center rich in d electrons, strongly electron-donating ligands, rather than electron-poor ones, are required for high catalyst activity. Detailed mechanistic studies to obtain an understanding of the catalyst's structure–activity profile were therefore required. During the course of such investigations, we found that five-coordinate complexes, such as **5** and **6**, are catalytic precursors. To generate the metathesis-active species, one of the neutral ligands must be lost. The remaining neutral ligand of the resulting 14-electron complex is responsible for catalyst turnover. This knowledge was used to rationalize why bulky, basic tricyclohexylphosphine ligands are more effective than triphenylphosphine ligands in the ruthenium-catalyzed metathesis of cyclooctene.[14]

Further catalyst tuning through the substitution of one of the phosphine ligands on **6** with an N-heterocyclic carbene (NHC) ligand resulted in a series of highly active catalysts (e.g. catalyst **7**; Figure 2). This

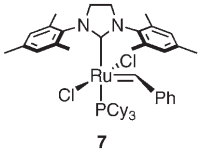


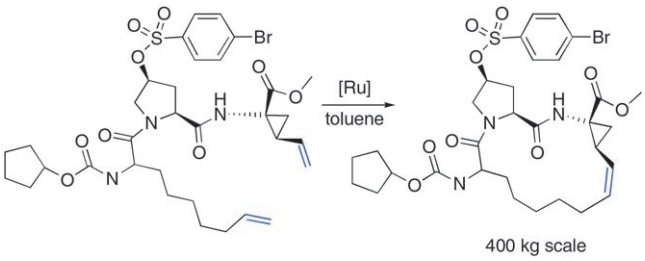
Figure 2. Second-generation commercial catalyst.

increase in metathesis activity was attributed to an increased rate of catalyst turnover owing to the favorable electron donation and steric bulk of the NHC ligand. Additional modification by replacing the phosphine in **7** with a weaker ligand, such as pyridine, resulted in an increase in activity up to a factor of 10^4 relative to catalyst **6**.[15] A number of other research groups have played a role in further optimizing these catalytic systems.

One of the most rewarding aspects of my research has been the opportunity to study the potential applications of a new catalyst. The facile preparation of our ruthenium catalysts, coupled with their functional-group tolerance and environmental stability, enabled olefin metathesis to finally realize its broad potential. Although this reaction was already commercially utilized in the processing of hydrocarbons, the application of olefin metathesis in organic synthesis

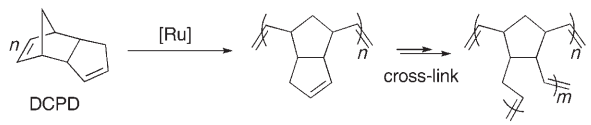
and in the preparation of highly functionalized polymers had yet to be fully developed.

Most commercial products that contain organic molecules possess at least one carbon–carbon double bond or, if one is not present, it is likely that an olefin was used in its preparation. This being the case, the potential applications of olefin metathesis are endless. To date, commercial products range from a wooden baseball bat, treated with metathesis-based polymers to improve durability, to the preparation of highly functionalized pharmaceutical agents, many of which are in the advanced stages of testing. For example, Boehringer Ingelheim recently reported the use of olefin metathesis for the commercial preparation of 400 kg of a compound under investigation to treat hepatitis C (Scheme 4).[16]



Scheme 4. Commercial application of ring-closing metathesis.

Some of the earliest commercial applications of olefin metathesis involved the ring-opening metathesis polymerization (ROMP) of monomers containing strained, unsaturated rings. The polymerization of dicyclopentadiene (DCPD) is one of the best-known examples of this (Scheme 5). DCPD is an attractive monomer for polymer production, as it is inexpensive, and the resulting polymer products are useful for a variety of applications. Hercules and Goodrich developed one of the first commercial processes for this reaction, where early-transition-metal complexes were combined with alkylaluminum to form catalysts to produce DCPD polymers by injection molding. Unfortunately, the extreme sensitivity of these catalysts toward air and water mandated the use of rigorous processing conditions and highly purified monomers. In contrast, the functional and environmental tolerance of the ruthenium catalysts enables DCPD polymerization to be carried out in open molds in the presence of numerous additives. In addition, DCPD monomers bearing functional groups for further synthetic elaboration can also be utilized. A wide variety of products, such as the composite baseball bats discussed previously, as well as bathroom fixtures, ballistic panels, and large equipment body parts, are currently in/or being developed for production utilizing ruthenium-catalyzed ROMP.[17]



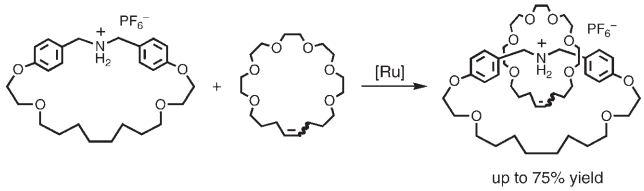
Scheme 5. Ring-opening metathesis polymerization for the preparation of dicyclopentadiene (DCPD) polymers.

The ruthenium systems can also be used to prepare polymers with well defined structures. Like the Tebbe complex, ruthenium olefin-metathesis catalysts can be used for the production of living polymers. In these cases, strained olefins are ring open polymerized by the metal center to produce a polymer that contains an active ruthenium alkylidene at the end of the polymer chain. After the first monomer added to the catalyst is consumed, a second monomer can be added and the polymers start to grow again. If the monomers contain different functional groups, the different segments of the polymer will have different properties and functions. Since the systems are living, if all the chains are initiated at the same time, the length of the chain and therefore the molecular weight is controlled by statistics and produces a very narrow distribution of chain lengths. Consequently, both the functionality and molecular weight of polymers produced using the ruthenium systems can be controlled. Since the ruthenium systems have been demonstrated to tolerate many functional groups on other applications, the polymers prepared using ruthenium initiators can contain many functionalities for use in a wide variety of applications. For example, if one of the blocks of the polymer is water soluble and the other is insoluble, the block copolymers form micelles (that are nanoparticles) that are being explored for applications in medical diagnostics. If the two blocks are incompatible, the solids formed from the block copolymers will have microphase separated structures that are important for a number of applications in materials science.

Ring-closing metathesis (RCM) and, to a lesser extent, cross metathesis (CM) have now become standard transformations in organic synthesis. As ruthenium catalysts will tolerate most functional groups, protection–deprotection strategies—which often hinder the application of other reaction methodologies—are seldom required. In addition, ruthenium-catalyzed olefin metathesis is ideal for use during the late stages of a total synthesis owing to the chemoselectivity exhibited by the catalyst and the mild reaction conditions required. Ruthenium metathesis catalysts are also ideally suited for use in tandem reactions involving acetylene derivatives and ring systems, as they are stable toward a variety of reaction conditions and reagents and, often, their presence will not impede subsequent reaction transformations. This favorable combination of reactivity and functional-group compati-

bility has resulted in the extensive use of olefin metathesis, which is reflected in large number of citations to the use of ruthenium-based metathesis catalysts.

A useful feature of olefin metathesis lies in the reaction's reversibility. Olefin metathesis is a thermodynamically controlled reaction; therefore, the self-assembly of the most stable product of a metathesis reaction can be attained by simply allowing the reaction to reach equilibrium. This feature has proven to be advantageous for a variety of applications, particularly in the use of RCM to produce interlocked, "magic" ring systems in high yield (Scheme 6).[18]



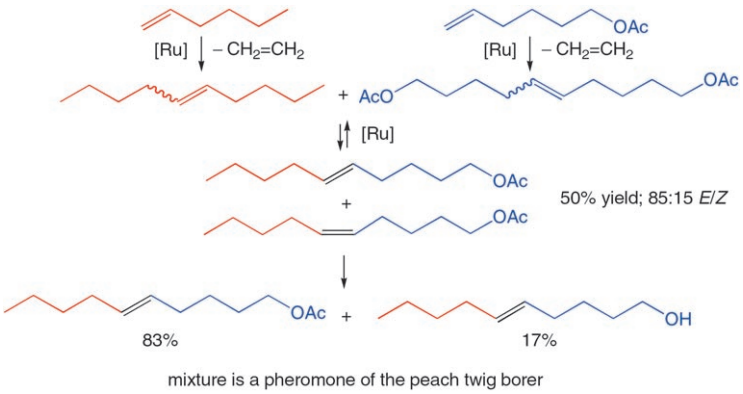
Scheme 6. Olefin metathesis for the preparation of "magic" rings.

In a modern industrial setting, the use of efficient chemical processes, preferably those with minimal impact on the environment, is essential. The term "green chemistry" has evolved as an umbrella concept to represent this general approach of conducting reactions. Metathesis attains the goals of green chemistry in three ways: 1) by providing a more efficient route over traditional methods to carbon-carbon bond formation and avoiding by-product formation; 2) through enabling the use of renewable resources; and 3) by providing a means to attain environmentally friendly products. For instance, the processing of seed oils represents an excellent example of the first two goals. Using solvent-free conditions, olefin metathesis enables vegetable oils to be efficiently processed into compounds that can serve as renewable sources of petroleum product alternatives.[19]

The solvent-free CM of 1-hexene with hexenylacetate (Scheme 7) represents an example of the use of metathesis to generate environmentally friendly products. The product of this reaction can be readily converted into a pheromone of the peach twig borer moth, which can be used as an environmentally friendly means of insect control in lieu of the use of broad-spectrum pesticides. CM is currently under investigation for the commercial preparation of other pheromones, as this route represents an efficient means to generate these compounds starting from inexpensive starting materials.[20]

Beginning as merely an interesting anomaly over forty years ago, the olefin-metathesis reaction has transitioned into one of chemistry's most valuable reactions for carbon–carbon bond formation. In the early days of trying to understand this fundamental process, we never envisioned that this reaction would one day achieve the import that it has today. Our exploration of this reaction has been a fascinating journey, and it is one that is ongoing. As work on olefin metathesis continues in both industry and academia, we can look forward to exciting future developments.

I would like to thank the over 200 co-workers who have contributed to my work, as well as all the other interesting people I have interacted with during my career in chemistry. I would also like to thank the group at Materia Inc. who has played a significant role in making this technology available for many commercial applications. You have all made the journey very interesting. I especially want to thank my wife Helen and the kids (Barney, Brendan and Katy) who have provided the support that has made it all possible and worthwhile.



Scheme 7. Commercial application of cross-metathesis in the production of "green" compounds.

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