What's New in Olefin Metathesis Catalyzed by Molybdenum and Tungsten Complexes?

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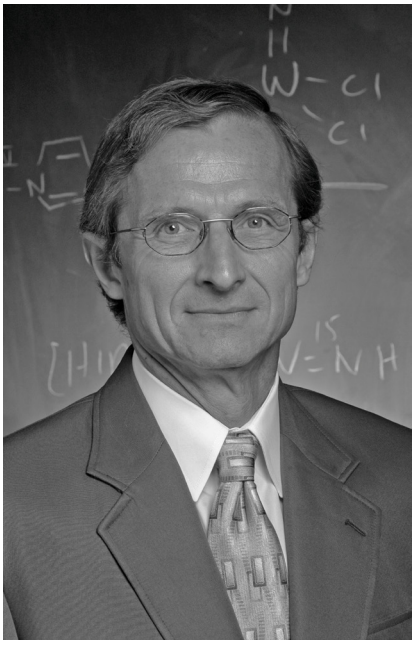
About the Author

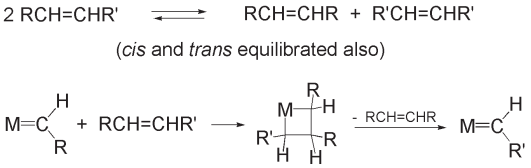


Richard Royce Schrock was born on January 4, 1945, in Berne, Indiana. He is recognized for his contributions to olefin metathesis for which he received the 2005 Nobel Prize in chemistry (with Grubbs and Chauvin). He attended Mission Bay High School in San Diego, holds a BA from the UC-Riverside and a PhD from Harvard University. His postdoctoral period was spent with Lord Jack Lewis at Cambridge. After a spell in industry with DuPont at the Wilmington Experimental Station, he joined the faculty of the Massachusetts Institute of Technology in 1975, became full professor in 1980 and (since 1989) holds the Frederick G. Keyes Professorship in Chemistry there. Schrock is a member of the American Academy of Arts and Sciences, the National Academy of Sciences and was elected to the Board of Overseers of Harvard University in 2007. He is married, has two sons and lives in Winchester, Massachusetts.

On his 8th birthday, Richard's elder brother Theodore presented him with the proverbial chemistry set to help satisfy his love of building things. Thus, began his interest in chemistry. He created a small laboratory at the end of a storage area for canned goods with shelves for the ever expanding collection of test tubes, beakers, and flasks (obtained by mail order with money earned from an early morning paper round). At 13 years, Harry Dailey, the then high school chemistry teacher, stoked his interest in chemistry with more textbooks and discarded equipment and this has continued unabated.

Schrock was the first to elucidate the structure and mechanism of so called 'black box' olefin metathesis catalysts. Initial work at DuPont involved the synthesis of tantalum alkylidenes, alkylidenes being a crucial resting state in the catalytic cycle of olefin metathesis. His work at MIT has led to a detailed understanding of a group of molybdenum alkylidenes and alkylidynes, which are active olefin and alkyne metathesis catalysts, respectively. Schrock has done much work to demonstrate that metallacyclobutanes are the key intermediate in olefin metathesis, with metallacyclobutadienes being the key intermediate in alkyne methathesis. Schrock carbenes are named after him. Richard Schrock's work is ongoing with goals of furthering the understanding of metathesis selectivity and developing new catalyst architectures. His work outside of metathesis includes elucidation of the mechanism of dinitrogen fixation and developing single molecule catalysts which form ammonia from dinitrogen, mimicking the activity of nitrogenase enzymes in biology.

We are now well past the 50th anniversary of an observation by H. Eleuterio (in 1956) of a reaction that ultimately came to be known as *olefin metathesis*, a metal-catalyzed reaction that cleaves and rearranges carbon-carbon double bonds.[1] The generic version and the accepted mechanism, which was first proposed by Hérrison and Chauvin,[2] are both shown in Scheme 1. Over the last forty years much research has been directed toward the synthesis and study of metathesis catalysts that are *well-defined*, *i.e.* that are not altered substantially during the reaction and that have been isolated, structurally characterized, and studied in detail. Most of these are either *high oxidation state* catalysts that contain Mo or W, which will be discussed here, or ruthenium-based catalysts.[3]



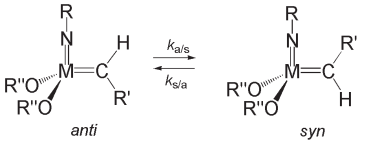
Scheme 1

What could be called first generation Mo and W catalysts have the formula $M(NR)(CHR')(OR")_2$.[4] The first examples were prepared 1986.[5] They are electron deficient (14 electron count) complexes, sensitive to air and water, and thermally unstable when the composite steric crowding (provided by the four ligands) is insufficient to slow bimolecular coupling of alkylidenes. Methylidene

species are especially unstable toward bimolecular decomposition. The challenge has been to design M(NR)(CHR')(OR")$_2$ species or, less commonly, M(NR)(CHR')(OR")$_2$(L) species, in which the donor ligand L is labile but the complex is still capable of isolation and employed as the initial alkylidene species in an alkene metathesis reaction.

The metallacyclobutane intermediate in a metathesis reaction often can be observed and in some cases isolated. Metallacyclobutanes have been found to have either a trigonal bipyramidal structure in which imido and alkoxide groups are in axial positions, or a square pyramidal structure in which the imido ligand is in the apical position.[4d] It is not known whether one of these, or some other metallacyclobutane, is formed initially. In any case, five-coordinate metallacyclobutane species readily interconvert on the NMR time scale, so observed structures may be located in relatively shallow minima on the energy surface.

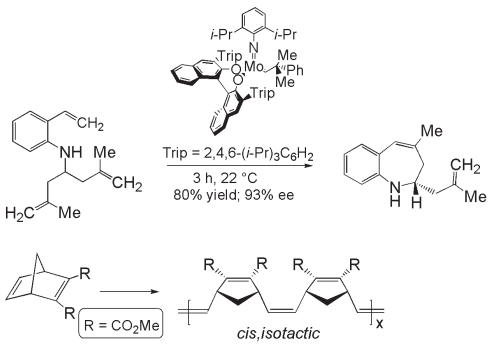
An important feature of M(NR)(CHR')(OR")$_2$ species is the possibility of forming isomers, a *syn*-alkylidene, in which the alkylidene substituent points toward the imido ligand, and an *anti*-alkylidene, in which the alkylidene substituent points away from the imido nitrogen (Scheme 2).[6] The rates of interconversion of these two isomers depend dramatically on the nature of OR" and can vary by as many as six orders of magnitude. The interconversion of *syn* and *anti* isomers is by rotation about the M=C bond in the four-coordinate species. They also interconvert during a metathesis reaction if all possible metallacyclobutanes can form. At first sight, an olefin metathesis reaction is more complicated as a consequence of interconversion of *syn* and *anti* isomers, but since the M=C bond resists rotating in the process of forming a metallacyclobutane intermediate, *Z* (*cis*) selective metathesis reactions become possible.



Scheme 2

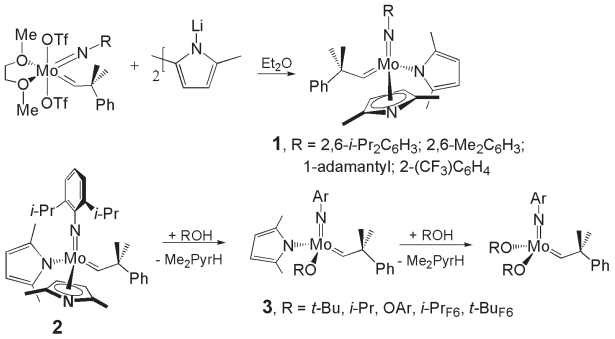
Second generation catalysts were reported in 1993 in the context of controlling the structure of ROMP (Ring-Opening Metathesis Polymerization) polymers[7a] and, in 1998, in the context of enantioselective organic reactions[4a,7b] Second generation catalysts contain a bidentate biphenolate or binaphtholate ligand as shown for an asymmetric ring-closing reaction shown in Scheme 3 (upper).[8] An example of stereoselective ROMP is the synthesis of *cis,isotactic*-poly(dicarbomethoxynorbornadiene) shown in the lower part of Scheme 3. An account of the use of Mo and W catalysts to prepare ROMP polymers stereoselectively has appeared recently.[9]

The dramatic increase in the number of possible catalysts and the extreme sensitivity of the outcome of a given metathesis reaction to subtle changes in the catalyst requires that catalysts be generated *in situ*, at least for screening purposes. A convenient method would be through addition of an alcohol or diol to an M(NR)(CHCMe$_2$R')X$_2$



Scheme 3

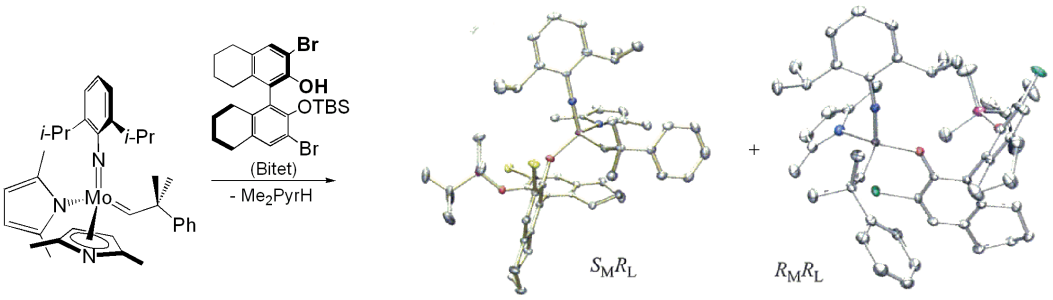
species. The search for M(NR)(CHCMe$_2$R')X$_2$ precursors to catalysts led to the discovery of M(NR)(CHCMe$_2$R')(pyrrolide)$_2$ complexes, *e.g.* **1** shown in Scheme 4. Bispyrrolide species are often found as 18 electron M(NR)(CHCMe$_2$R')(η^1-pyrrolide)(η^5-pyrrolide) species, *e.g.* **2** (Scheme 4), but these are in ready equilibrium with 14 electron M(NR)(CHCMe$_2$R')(η^1-pyrrolide)$_2$ species **3** that can react easily with alcohols or diols (biphenols or binaphthols) to give known catalysts *in situ*. These *in situ* catalysts behave in metathesis reactions as they do when they have been isolated and purified since the pyrrole is relatively innocuous.



Scheme 4

A reaction between the bispyrrolide and a monoalcohol takes place through a monoalkoxide monopyrrolide (MAP) intermediate. In many cases this intermediate forms in good yield and can be isolated and characterized. Crystal structures (see *e.g.* Fig. 1) confirm that the pyrrolide is bound in an η^1 fashion and that the alkylidene is the *syn* isomer. Two of the most important features of MAP species are i) they are highly efficient in olefin metathesis reactions, in fact, much *more* efficient than their bisalkoxide relatives, and ii) the metal itself is a stereogenic centre. There is some indication that the first is a consequence (in part) of the second, according to theoretical studies.[10] The chirality at the metal centre has major implications for reactions with an olefin, since the olefin is likely to approach the tetrahedral metal centre in only one of four ways *for electronic reasons*. Brunner recognized that the metal itself, perhaps, should be the strongest determinant of which of the four approaches to the metal is the lowest energy.[11]

In order to probe the efficiency of the metal's chirality in a metathesis reaction, an enantiomerically pure auxiliary was added (BitetOH = ROH), as shown in Scheme 5. The result is formation of a 7:1 mixture of diastereomers S_MR_L and R_MR_L where L is OBitet. These diastereomers have



Scheme 5

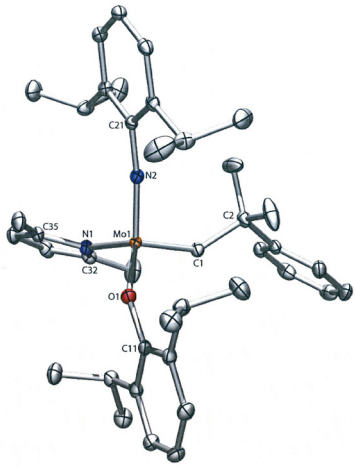


Fig. 1. The structure of Mo(NAr)(CHCMe$_2$Ph)(Me$_2$Pyr)(OAr)..

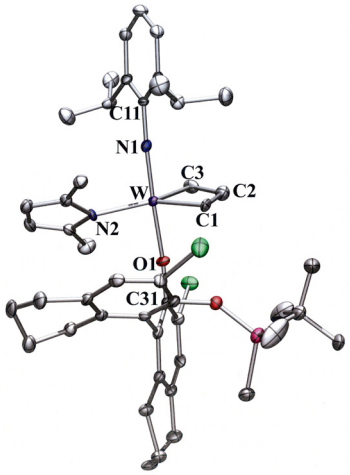
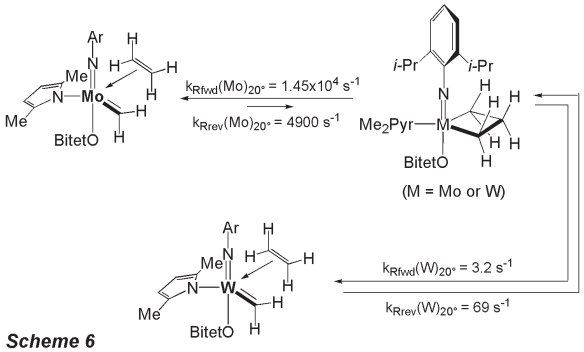


Fig. 2. The structure of W(NAr)(CH$_2$CH$_2$CH$_2$)(Me$_2$Pyr)(OBitet).

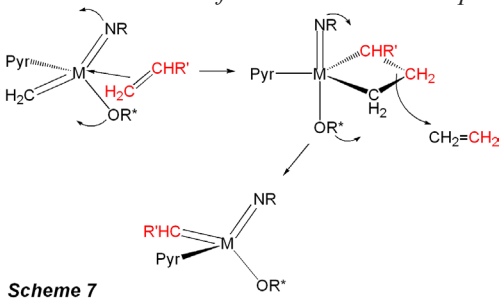
been isolated and characterized. They are configurationally stable in the absence of an olefin. However, in the presence of an olefin, such as ethylene, they interconvert rapidly (~100 s^{-1}) to form a 2:1 equilibrium mixture of methylene complexes that are themselves in equilibrium with unsubstituted TBP metallacyclobutane species, several of which have been structurally characterized; an example is shown in Fig. 2.

In the process of studying the interconversion of metallacyclobutane species of the type shown in Fig. 2, where the metal is Mo or W, it was found that they are in equilibrium with ethylene/methylidene species of unknown geometry, that the rate of *opening* the metallacyclobutane to the ethylene/methylidene species when M = Mo is ~4500 times faster than when M = W, and that the equilibrium toward the metallacyclobutane is much larger when M = W than when M = Mo (Scheme 6). These studies help explain what had been observed qualitatively, namely that Mo systems turn over much more rapidly under ethylene than analogous W systems.



Scheme 6

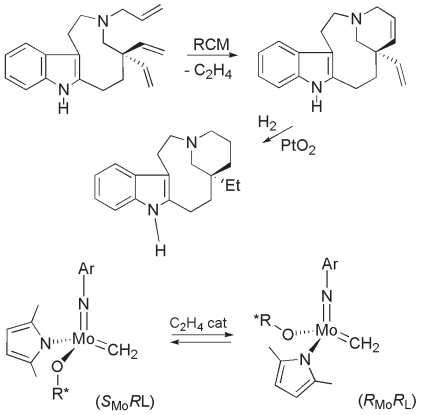
Detailed studies have led to several key proposals as to how MAP species react with olefins. As shown in Scheme 7, it is proposed that i) metallacyclobutanes that contain *axial imido and alkoxide* ligands (as in Fig. 2) are the crucial metathesis intermediates in MAP catalyst systems, ii) an olefin arrives on the CNO face (and therefore leaves) *trans* to the pyrrolide, and iii) the configuration at the metal *inverts with each forward metathesis step*.



Scheme 7

Two dramatic results led to a focus on MAP species since *ca*. 2007. The first is a synthesis of (+)-quebrachamine that involves the desymmetrization ring-closing reaction shown in Scheme 8. This reaction was found to be catalyzed by Mo(NAr)(CHCMe$_2$Ph)[OCMe(CF$_3$)$_2$]$_2$ (15 mol%, 12 h, 98% conversion; 71% yield), but by *no* second generation asymmetric Mo catalyst that was tried. Yet the *7:1 mixture* of Mo(NAr)(CHCMe$_2$Ph)(OBitet)(Me$_2$Pyr) diastereomers (see Scheme 5) was found to give rise to an efficient ring-closing reaction (2 mol%, 1 h, 98% conversion; 75% yield, 95%ee)[12,13] This finding was explained in terms of the unusually high reactivity of MAP species in general, a rapid equilibrium between diastereomers in the presence of ethylene, and the low reactivity of *one* of the two diastereomers.[14] It is proposed that the reaction proceeds *via* the ($S_{Mo}R_L$) methylidene diastereomer (Scheme 8) in a two-step ring-closing process that

leads to overall retention of configuration at the Mo center. Any ($R_{Mo}R_L$) methylidene diastereomer that is present is a much poorer catalyst for this particular ring-closing reaction. Therefore, the reaction proceeds efficiently to give product in high ee.



Scheme 8

The second finding is that shown in Scheme 9. The ring-opening cross-metathesis reaction proceeds rapidly and efficiently to give the expected product in high % ee. Most importantly, the phenyl substituted double bond is >98% *Z*. This finding gave rise to the proposal that the *large* aryloxide in combination with the *small* imido substituent allows only the *all cis* metallacyclobutane and, therefore, only the *Z* product, to form (Scheme 10). Achiral phenoxides were also efficient for *Z* selective reactions, especially the O-2,6-(2,4,6-*i*-$Pr_3C_6H_2)_2C_6H_3$ (OHIPT) ligand. A space-filling model of the TBP structure of W(NAr)($CH_2CH_2CH_2$)(Pyr)(OHIPT) (Fig. 3) reveals that the three *anti* protons (those opposite the imido ligand) of the metallacyclobutane are in contact with the methyl protons in the *ortho*-isopropyl groups of the OHIPT ligand. Therefore, no substituent is likely to be found in an *anti* position in a metallacyclobutane intermediate of this type. If secondary isomerization of the *Z* product into the *E* product can be avoided, then *Z* selective processes should prevail.

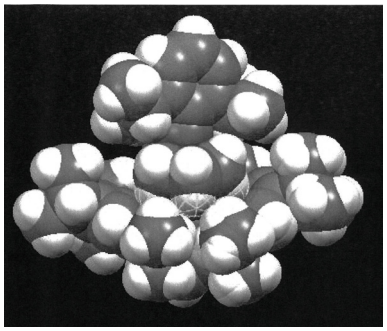
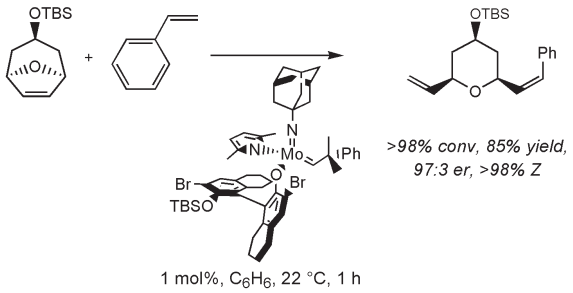
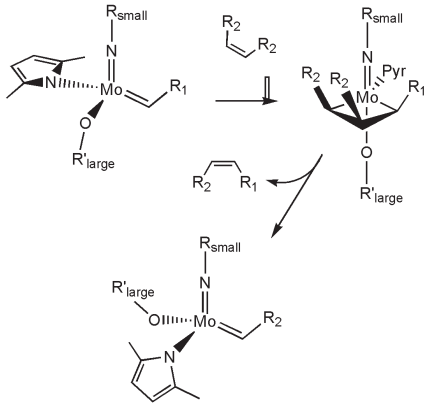


Fig. 3. A space filling model of the TBP structure of W(NAr)($CH_2CH_2CH_2$)(Pyr)(OHIPT).

Z-selective metathesis homocoupling of terminal olefins has been a long-sought goal of olefin metathesis. It should proceed as shown in Scheme 11, especially with complexes that have a *large*/*small* combination of aryloxide and imido substituent, respectively. *Z*-selective metathesis homocoupling of terminal olefins was found to proceed with high efficiency with the appropriately designed *tungsten* catalysts, either at elevated temperatures (80-120 °C)[15]

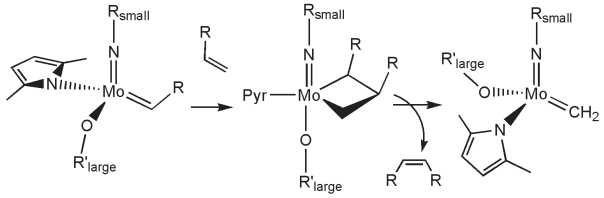


Scheme 9



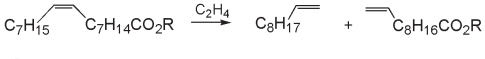
Scheme 10

or room temperature.[16] Most molybdenum-based catalysts that have been tried appear to be less efficient that tungsten-based catalysts, possibly because of secondary rapid isomerization of the initial *Z* product. The relatively high molecular weight of the product allows the starting material to be removed readily and the desired product to be isolated in relatively pure form. It is preferable to remove ethylene from the reaction as efficiently as possible in order to minimize secondary reactions of methylidene species, including decomposition.



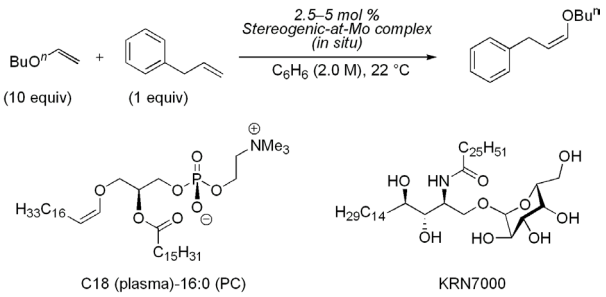
Scheme 11

Ethenolysis is a reaction in which ethylene is added to an internal olefin to yield (ideally) a mixture of the two terminal olefin products. Clearly ethenolysis catalysts must be stable to ethylene, and unsubstituted metallacyclobutane species cannot be too stable toward loss of ethylene. Ethenolysis is especially important in terms of obtaining useful chemicals from renewable feedstocks such as oleic acid esters (Scheme 12). Mo(NAr)($CHCMe_2Ph$)(Me_2pyr)(OBitet) has been shown to catalyze ethenolysis of methyl oleate at room temperature and 10 atm of ethylene with a high selectivity (>99%) to 1-decene and methyl-9-decenoate in high yield (95%).[17] Turnover numbers currently are in the range of 5000-10000, a number that is likely to depend critically upon the purity of the oleate. Tungsten catalysts are not as efficient as molybdenum catalysts for ethenolysis as a consequence of the stability of the unsubstituted metallacyclobutane, as noted earlier.



Scheme 12

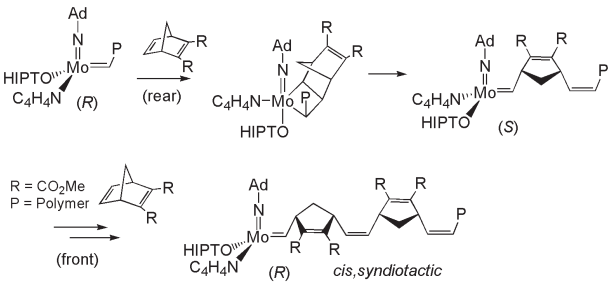
It has been demonstrated that MAP catalysts are efficient for the stereoselective synthesis of *Z*-olefins through catalytic *cross*-metathesis reactions. One of many potentially important classes of desirable cross-metatheses is one that employs an enol ether, as shown in Scheme 13.[18] This type of reaction has allowed a dramatically improved diastereoselective and enantioselective synthesis of the antioxidant plasmologen C18 (plasm)-16:0 (PC), a phospholipid derivative that is found in electronically active brain and heart tissues and which has been implicated in Alzheimer's disease.[19,20] A second example is the anti-tumor agent KRN7000 (Scheme 13).[21] Ethylene is detrimental to the rate cross-metathesis and also diminishes *Z*-selectivity by increasing methylidene concentration and consequent isomerization of *Z*-product to *E*-product.



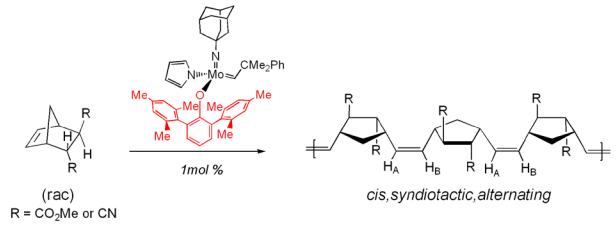
Scheme 13

MAP catalysts have also had an impact on ROMP chemistry. As mentioned earlier, the *cis,isotactic*-poly(2,3-dicarbomethoxynorbornadiene) is obtained through enantiomorphic site control employing biphenolate and binaphtholate catalysts (see Scheme 3). In the case of MAP initiators, the required approach of an olefin *trans* to the pyrrolide in a *Z*-selective manner followed by inversion of the configuration at the metal automatically forms a *cis,syndiotactic* polymer from the same monomer, as shown in Scheme 14.[22] Effectively, the monomer is forced to add sequentially to *opposite* sides of the M=C bond. This *stereogenic metal control* appears to be a new method of controlling polymer structure. New structures become possible. For example, racemic 2,3-dicarbomethoxynorbornene is polymerized by the hexamethylterphenoxide catalyst shown in Scheme 15. Since the metal inverts with each insertion, the enantiomers assemble in a perfectly alternating manner to give a *cis,syndiotactic* polymer in terms of the basic structure, or *cis,syndiotactic,alternating*. The only other polymer of this type is prepared through polymerization of *rac*-1-methylnorbornene by $ReCl_5$, a catalyst whose detailed mode of reaction has not been elucidated.[23]

Stereogenic-at-metal (SAM) MAP species are opening up many new possibilities in the area of olefin metathesis. It is not yet known to what degree the pyrrolide ligand is necessary for the high reactivity and efficiency of MAP species; MAP species could be only a subset of a larger class of SAM species that are as efficient or even more efficient than MAP catalysts. Although more time will be required and methods devised to prepare new SAM species, we can look forward to an increasingly bright future for olefin metathesis with Mo and W catalysts in organic and polymer chemistry.



Scheme 14



Scheme 15

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