Olefin-Metathesis Catalysts

Molybdenum and Tungsten Imido Alkylidene Complexes as Efficient Olefin-Metathesis Catalysts

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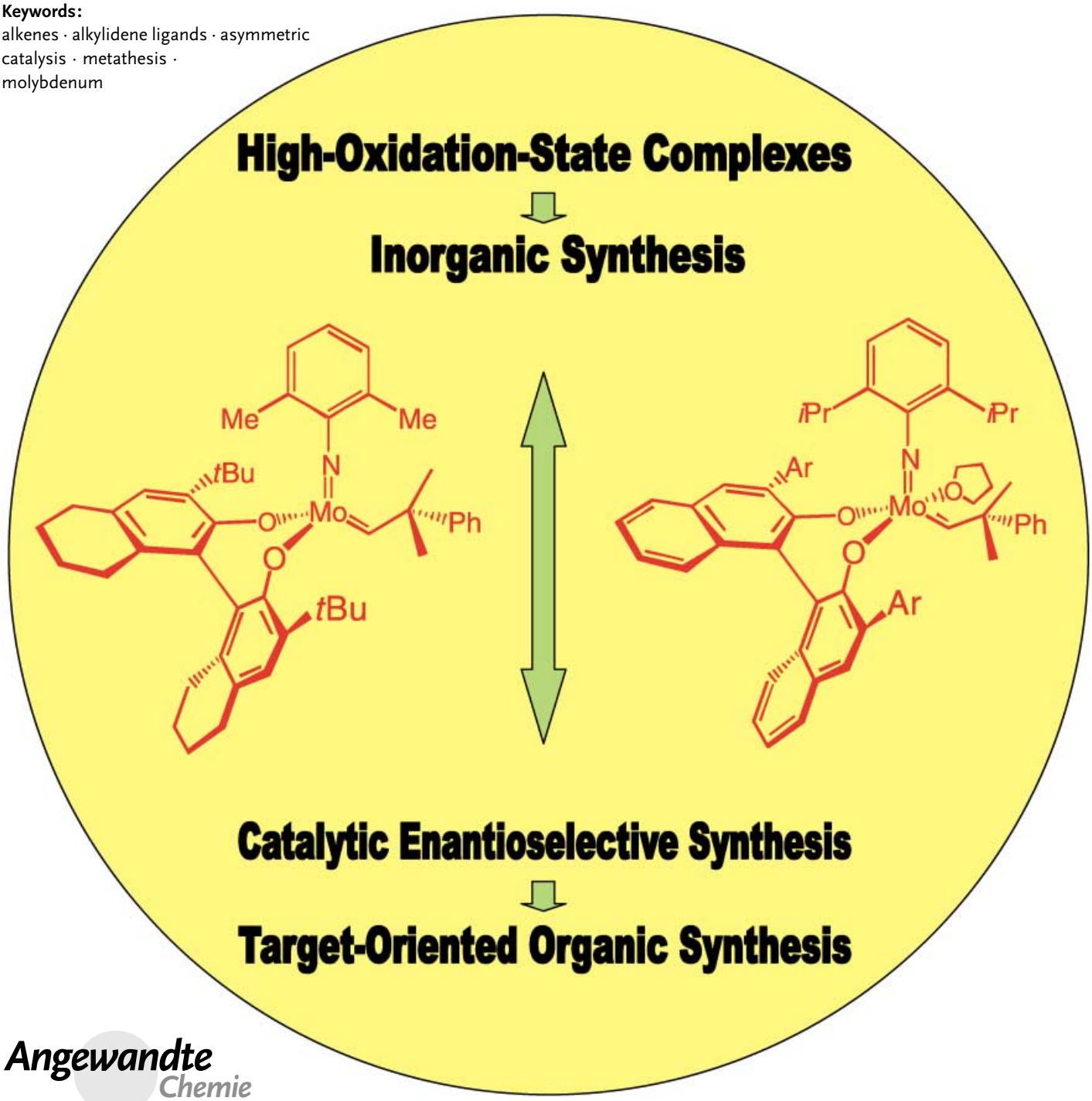
alkenes · alkylidene ligands · asymmetric catalysis · metathesis · molybdenum



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Catalytic olefin metathesis has quickly emerged as one of the most often-used transformations in modern chemical synthesis. One class of catalysts that has led the way to this significant development are the high-oxidation-state alkylidene complexes of molybdenum. In this review key observations that resulted in the discovery and development of molybdenum- and tungsten-based metathesis catalysts are outlined. An account of the utility of molybdenum catalysts in the synthesis of biologically significant molecules is provided as well. Another focus of the review is the use of chiral molybdenum complexes for enantioselective synthesis. These highly efficient catalysts provide unique access to materials of exceptional enantiomeric purity and often without generating solvent waste.

From the Contents

1. Introduction

Metal-catalyzed olefin metathesis has had an enormous impact on organic synthesis. A myriad of small-, medium-, and large-ring carbo- and heterocycles, and a wide assortment of acyclic unsaturated molecules are now readily accessible through this important class of reactions.[1–6] Stereoselective methods that utilize catalytic metathesis and successful complex-molecule total syntheses that have strategically benefited from this remarkable transformation are being disclosed in increasing numbers. Reports of new metal complexes that promote selective metathesis reactions that were not feasible before, catalysts that can be applied to large-scale or combinatorial syntheses, or catalysts that are recyclable or deliver unprecedented levels of efficiency and selectivity continue to adorn our leading journals. Much of this "revolution" in organic synthesis is a consequence of the development of well-defined and functional-group tolerant molybdenum- and ruthenium-based catalysts that are now so widely used.

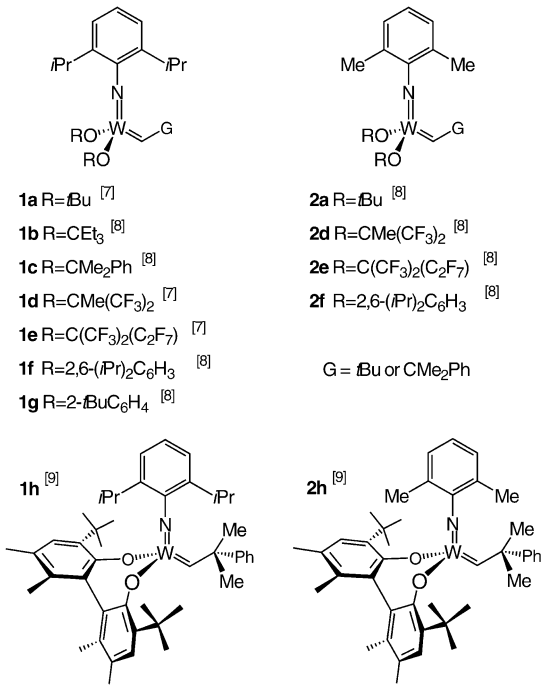

Figure 1. Tungsten-based olefin-metathesis catalysts.

Herein we first provide an account of the journey that eventually resulted in the discovery and development of high-oxidation-state tungsten and then molybdenum imido alkylidene complexes. We will refer to a comprehensive list of tungsten-based (Figure 1[7–9]) and molybdenum-based catalysts throughout this review (Figure 2[10–13] for achiral complexes and Figure 3[14–23] and Figure 4[14–19,24,25] for chiral complexes. In Section 2 of this article we review the design and development of these tungsten and molybdenum-based alkylidene complexes for olefin metathesis, and in Section 3 we discuss the utility of molybdenum-based imido alkylidene

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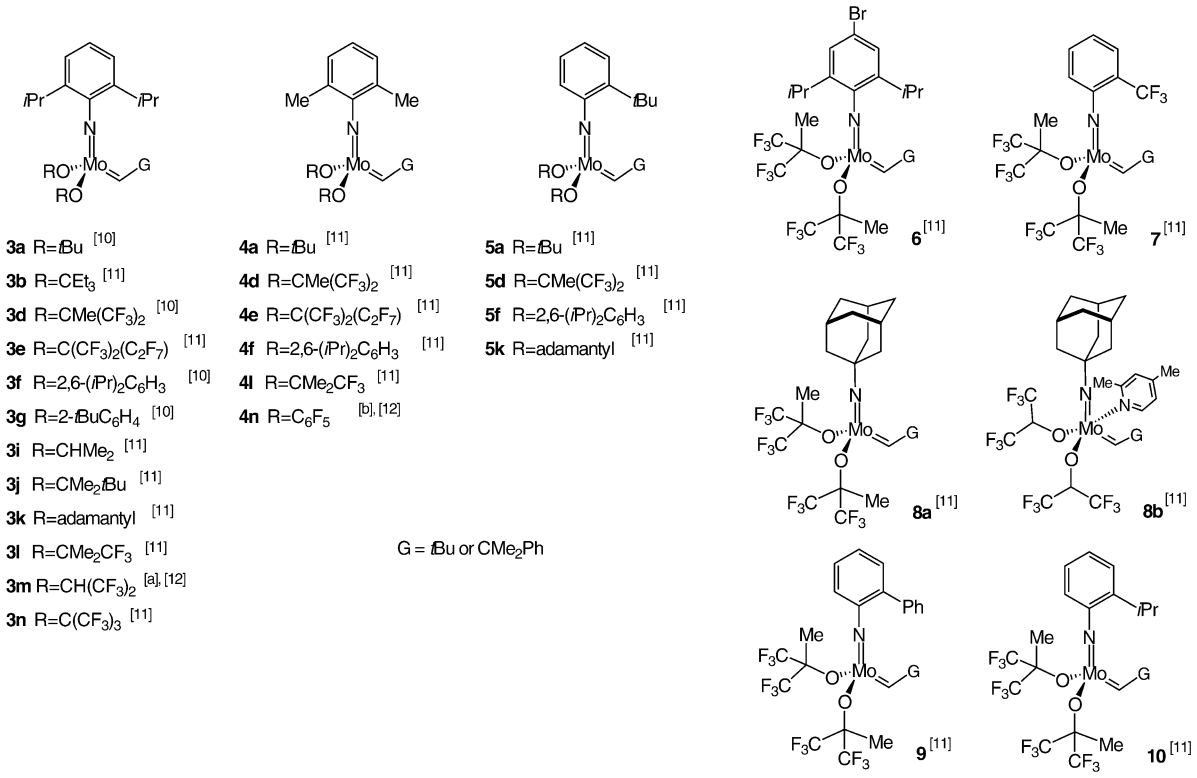

Figure 2. Achiral molybdenum-based olefin-metathesis catalysts. [a] Isolated with an additional 2,4-dimethylpyridine ligand (see **8b**). [b] Isolated with an additional quinuclidine ligand.

complexes as catalysts for ring-opening metathesis polymerization (ROMP). In Section 4, we review the use of achiral molybdenum-based catalysts in the synthesis of relatively complex organic molecules. In Section 5, the ability of enantiomerically pure chiral molybdenum-based catalysts to afford optically pure or enriched organic compounds is presented. When relevant data are available, molybdenum-based and ruthenium-based catalysts will be compared (see also Section 6). For additional details the reader can refer to other articles that cover the discovery and development of high-oxidation-state alkylidene complexes for olefins metathesis[26–33] and their early applications to polymer synthesis.[34–36] The reader may also consult recent reviews concerning olefin metathesis in organic synthesis.[1–6]

1.1. The Basic Process and Key Intermediates in the Catalytic Cycle

The key step in olefin metathesis is a [2+2] addition of an olefin (for example, *trans*-RCH=CHR′; Scheme 1) to a metal–carbon double bond (for example, in **I**) to give a metallacyclobutane complex (for example, **II** in Scheme 1). Metallacyclobutane **II** can decompose in a retro [2+2] reaction either to give **I** and *trans*-RCH=CHR′ again, or to give a new metal alkylidene **I′** and *trans*-R′CH=CHR′, as shown in Scheme 1. Further reaction of **I′** with *trans*-RCH=CHR′ then yields (for example) **II′**, which can decompose to yield *trans*-RCH=CHR and **I**. Metallacycles analogous to **II** (or **II′**) can form in which R′ (or R) substituents on one or both

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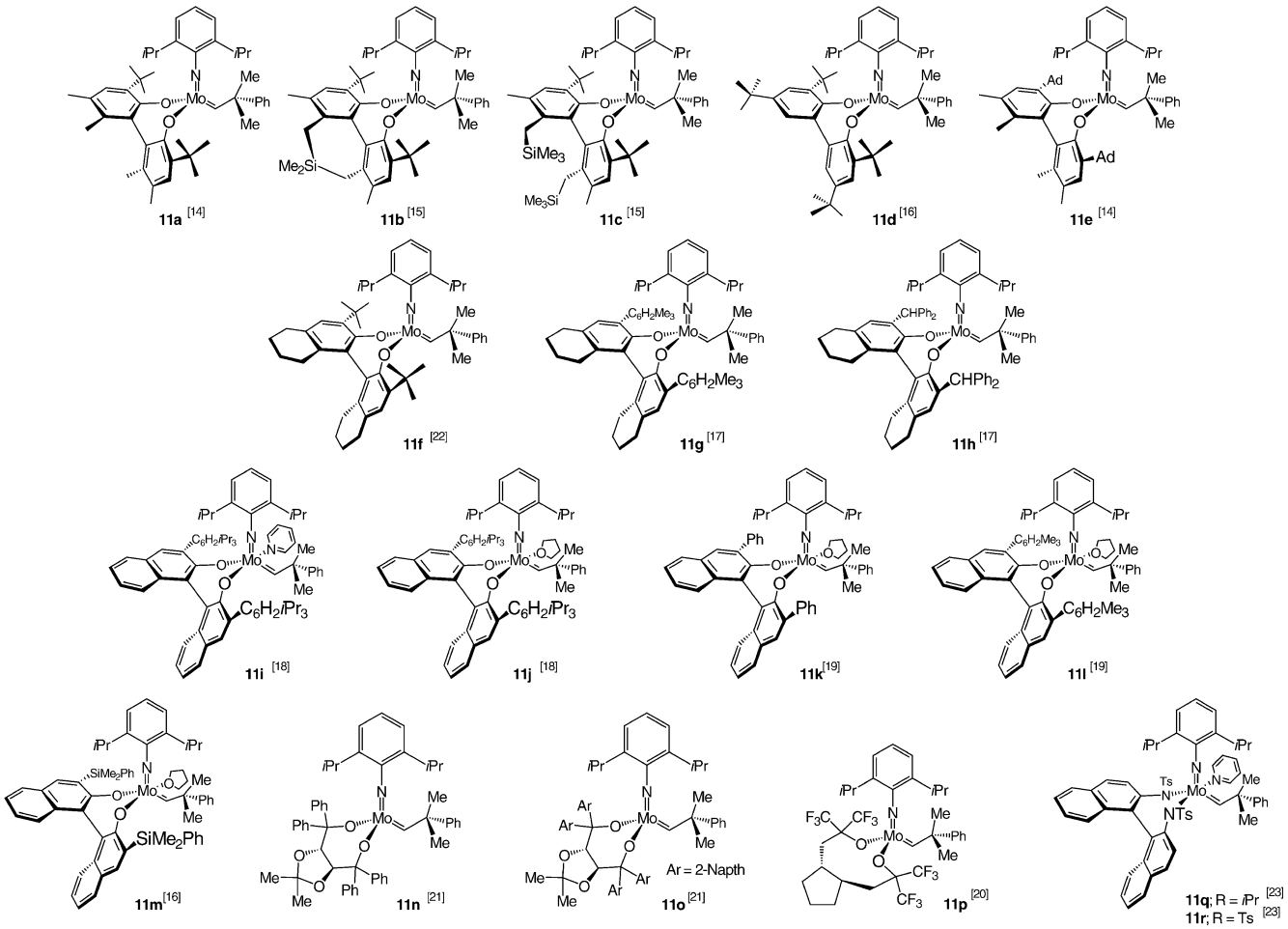


Figure 3. Chiral molybdenum-based catalysts for olefin metathesis bearing a 2,6-diisopropylaryl imido ligand. Complexes **11q** and **11r** to date have not exhibited catalytic metathesis activity and are shown here only for the purpose of discussion. Ad = adamantyl, Ts = tosyl.

α carbon atoms and the β carbon are *cis* to one another. *cis* Olefins can be generated upon cleavage of these metallacycles. Therefore, as shown in Scheme 1, *trans*-RCH=CHR′ would be transformed catalytically into an equilibrium mixture of approximately two parts of RCH=CHR′ (a mixture of *cis* and *trans*) and one part each of R′CH=CHR′ (*cis* and *trans*) and RCH=CHR (*cis* and *trans*).[37–39] Metallacycles that do not lead to new olefins may be formed as well. For example, addition of *trans*-RCH=CHR′ to **I** so that R is on the β carbon atom of the metallacycle and an R′ group is present on each of the α carbon atoms (as opposed to **II** in Scheme 1) would result in a degenerate metathesis reaction, four of which are possible if both *cis* and *trans* olefins are considered. Compounds **I** and **I′** are referred to as the propagating alkylidenes, since they are the two possible alkylidene complexes that can be formed from any alkylidene that initiates the catalytic cycle.

A number of variations of the basic reaction shown in Scheme 1 are known which allow the starting olefin to be converted completely into products. Perhaps the simplest is that in which R′ is a proton, in which case one of the products is ethylene. If ethylene is removed during the reaction, RCH=CH_2 would be consumed completely to give *cis*- and *trans*-RCH=CHR. If an α,ω-diene were employed and if ethylene were removed during the reaction, a cyclic olefin would be formed. These and many other variations form the basic set of transformations that are now used by chemists to access a variety of olefinic products by treatment of readily available alkenes with metal alkylidene initiators.

1.2. A Historical Perspective

1.2.1. Ill-Defined Metathesis Catalysts

Early molybdenum- and tungsten-based homogeneous olefin-metathesis catalysts were prepared in a wide variety of ways from various types of starting materials in which the metal was in an oxidation state between 0 and VI.[37–39] Typical syntheses that began with W^{VI} complexes involved reactions between WCl_6 or $W(O)Cl_4$ in chlorobenzene and an alkylating agent, such as an alkyl aluminum, alkyl lithium, or alkyl stannane. Although such catalytic systems were examined extensively by physical organic techniques (see Section 1.2.2), the oxidation state of the metal and the nature of the ligands were never determined. For this reason, and in contrast to "well-defined" catalysts (isolable and characterizable com-

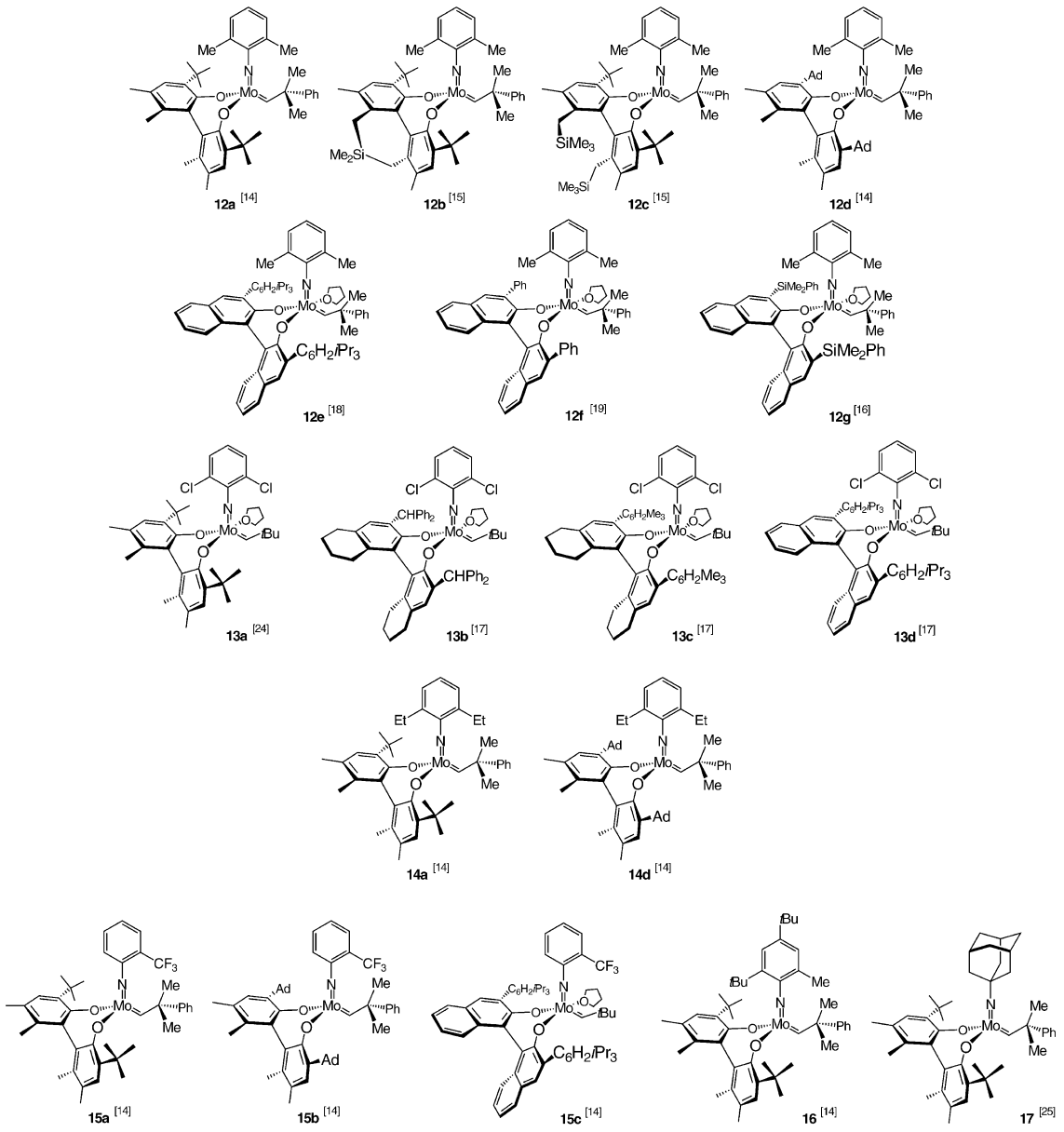
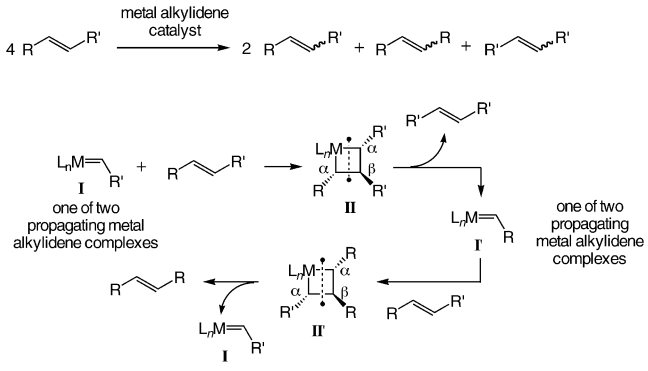


Figure 4. Chiral molybdenum-based catalysts for olefin metathesis bearing various imido ligands.



Scheme 1. A representative metal-catalyzed olefin-metathesis reaction. Metallacyclobutanes **II** and **II′** and the propagating alkylidene complexes **I** and **I′** are key intermediates for productive metathesis. (Only metathesis of a *trans* olefin to give *trans* products is shown.)

plexes that are essentially identical to intermediates in the catalytic reaction), early catalysts now may be considered "ill-defined." Today, a metal-containing compound that provides catalytic activity, but is not directly related to the catalyst that is actually present in the reaction, would be called a "catalyst precursor" or a "precatalyst."

In virtually all ill-defined systems the percentage of metal that is active at any one time is thought to be small ($< 1\,\%$).[37,38] This is one of the reasons why characterization of the active species in these circumstances has not been possible. Many catalysts have been shown to be exceedingly active (> 100 turnovers per second based on metal added), but they are also generally the shortest-lived (minutes). Ill-defined catalysts often tend to produce side products, or are readily deactivated by common Lewis basic functional groups. As a consequence of these features, the activity of ill-defined

catalysts, even if reproducible, cannot be controlled in a rational manner. In addition, organic molecules frequently undergo side reactions promoted by various requisite metal-containing activators. Therefore, although much was learned about the metathesis reaction, and many applications to polymer synthesis were discovered[37,38] (see Section 3), the use of ill-defined catalysts in the synthesis of organic molecules that contain functional groups is relatively rare.[40–42]

Complications observed in connection with the use of ill-defined catalysts, and the lack of a plausible mechanistic platform that would allow for an interpretation of selectivity and reactivity data, pointed to the preparation of well-defined catalysts as a compelling research objective. Well-defined metathesis catalysts are those that 1) are essentially identical to the active species in terms of metal oxidation state and ligand coordination sphere, 2) react with olefins to yield observable new carbene complexes derived from those olefins, and 3) are stable enough to be characterized through spectroscopic means and preferably also X-ray structural analysis.

1.2.2. Fischer Carbenes as Metathesis Catalysts and Related Mechanistic Studies

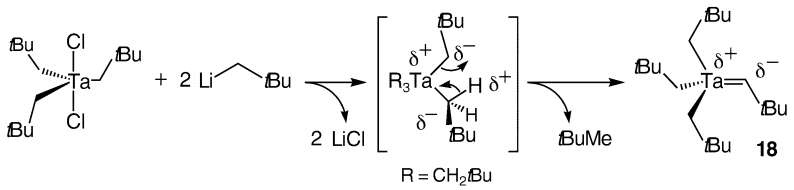
In 1964 Fischer and Maasböl reported the reaction of phenyl lithium with $[W(CO)_6]$ to give an anionic complex which contains an acyl ligand.[43] Protonation followed by treatment with diazomethane yielded the first deliberately synthesized "metal carbene" complex, $[(CO)_5W{=}CPh(OMe)]$. This species contains 18 electrons in metal-based orbitals. Reports of hundreds of compounds that bear a heteroatom-stabilized (usually O or N) carbene ligand soon followed.[44] In such species the heteroatom is believed to stabilize a partial positive charge on the carbene carbon atom, thereby leading to their being characterized as "electrophilic carbenes," since the M=C bond would then be polarized with a partial negative charge ($\delta-$) on the metal center and a relative positive charge ($\delta+$) on the carbene carbon atom, that is, ($\delta-$)M=C($\delta+$). It is appropriate to view a carbene ligand that contains one or two heteroatoms bound to the α carbon atom as being neutral with a metal–carbon bond order between one and two. Therefore, $[(CO)_5W{=}CPh(OMe)]$ contains W(0) and this type of complex falls into the category of a carbene complex in which the metal is in a low oxidation state. In the early 1970s a large volume of research on heteroatom-stabilized carbene complexes was carried out and several comprehensive reviews were published.[44–47] Since many Fischer-type carbene complexes had been prepared when interest in olefin metathesis gathered steam in the late 1960s, Fischer carbenes naturally were scrutinized as possible olefin-metathesis catalysts.

In the 1970s several significant publications concerning the mechanism of olefin metathesis appeared. Some of the most important results were published by the groups of Casey,[48] Chauvin,[49] Dolgoplosk,[50] Grubbs,[51,52] and Katz.[53–55] A detailed discussion of these and related studies can be found in various early reviews[52,55–58] and texts.[37–39] Grubbs et al.,[51] Katz and McGinnis,[53] and Chauvin and Hérisson[49] demonstrated convincingly that metal-catalyzed olefin metathesis is the result of a non-pair-wise exchange of alkylidene fragments. Hérisson and Chauvin are given credit for first proposing in 1971[49,59] the now widely accepted mechanism illustrated in Scheme 1. Casey et al. synthesized $[(CO)_5W{=}CPh_2]$ and showed that it reacts with certain olefins in a manner consistent with the metallacyclobutane mechanism.[48] The expected new carbene could be detected under certain circumstances, but many other products (e.g., cyclopropanes) were also observed, and metathesis products were formed only in substoichiometric quantities. Katz et al.[54] showed that when $[(CO)_5W{=}CPh_2]$ and even $[(CO)_5W{=}CPh(OMe)]$ are added to certain strained cyclic olefins, the cyclic olefins are polymerized slowly to give the polymers expected from ring-opening metathesis polymerization (ROMP; see Section 3 for more details). These investigations collectively provided strong evidence that metal carbene complexes are indeed intermediates in olefin metathesis reactions. However, in spite of the fact that the initial metal complex was well-characterized in many of the above investigations, none rigorously established the nature of the actual catalyst, and no propagating metal carbenes were detected in a catalytic metathesis reaction. Since Casey et al. reported in 1979 that $[(CO)_5W{=}CHPh]$ decomposes above $-60\,^{\circ}C$ and does not yield metathesis products upon reaction with olefins,[60] it seems unlikely that Fischer-type W(0) complexes would be the propagating species in reactions in which some catalytic metathesis activity was observed.[54]

1.3. "High-Oxidation-State" Carbene (or Alkylidene) Complexes of Tantalum

At the time that early examples of metathesis with ill-defined, homogeneous, W and Mo catalysts were known, there were no reports of metathesis reactions promoted by ill-defined tantalum-based catalysts.[37,38] Yet, tantalum-based complexes played a crucial role in our understanding how effective W and Mo catalysts might be designed, since metathesis activity ultimately could be observed with certain newly discovered and carefully tuned "high-oxidation-state" carbene complexes. Therefore, Ta complexes will be considered in this historical perspective.

The events that led to the discovery of the first tantalum-based alkylidene began in 1974 with the synthesis of pentamethyltantalum,[61] the first pentaalkyl complex of Ta. Pentamethyltantalum was found to decompose (sometimes explosively) above $0\,^{\circ}C$ through unidentified intermolecular pathways.[62] To inhibit bimolecular decomposition, attempts were made to synthesize $[Ta(CH_2tBu)_5]$, in which bulky neopentyl groups would replace the much smaller methyl ligands. However, as illustrated in Scheme 2, these attempts did not lead to $[Ta(CH_2tBu)_5]$, but to formation of the tantalum-based carbene **18**, the first example of a stable M=CHR complex, through an intramolecular decomposition of intermediate $[Ta(CH_2tBu)_5]$.[63] The intramolecular decomposition consists of abstraction of an α hydrogen (proton) by a neighboring alkyl group (a base). Compound **18** is unusually robust thermally; it melts at around $70\,^{\circ}C$ and can be distilled



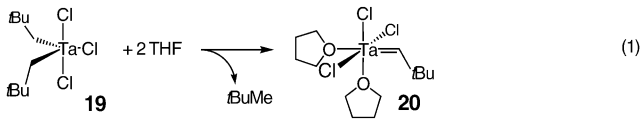
Scheme 2. Formation of the first high-oxidation-state alkylidene complex by α-hydrogen abstraction.

in vacuo. It is sensitive to oxygen, water, and a variety of functionalities, among them ketones and aldehydes, with which it reacts to yield polymeric $[(t\mathrm{BuCH_2})_3\mathrm{Ta{=}O]}_n$ and the expected olefin.[64] Therefore **18** is related to an alkylidene phosphorane,[65] and may be viewed as a Ta(v) alkylidene species. Complex **18** differs sharply in several respects from Fischer-type complexes where a heteroatom is bound to the carbene ligand (see above).[44] Among these differences are the polarities of the M=C bonds (e.g., $(\delta+)\mathrm{Ta{=}C}(\delta-)$ as in Scheme 2 vs. $(\delta-)\mathrm{W{=}C}(\delta+)$ in $[(\mathrm{CO})_5\mathrm{W{=}CPh(OMe)}]$) and the number of electrons in metal-based orbitals (10 for the Ta species versus 18 for the W complex). Note that the 18-electron count in $[(\mathrm{CO})_5\mathrm{W{=}CPh(OMe)}]$ would require that one CO ligand be lost to give a 16-electron species before an olefin can react and form the required metallacyclobutane intermediate. In contrast, no (covalently bound) ligand could be lost from the 10-electron tantalum species under mild conditions, nor would any have to be.

The synthesis of Ta alkylidene **18** established that sterically hindered covalently bound ligands can stabilize electronically unsaturated (< 18 electron) pseudotetrahedral alkylidene complexes towards bimolecular decomposition. Accordingly, further exploitation of the principle of steric protection, and investigation of neopentyl complexes in particular, became critical in the study of high-oxidation-state alkylidene complexes and their development as olefin-metathesis catalysts.

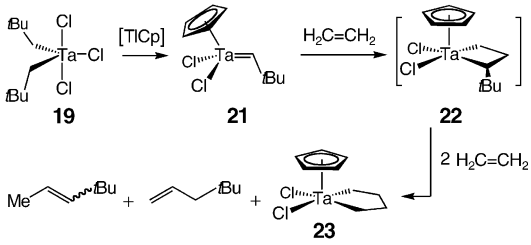
As depicted in Scheme 2, α-hydrogen (proton) abstraction offers an attractive method for the generation of high-oxidation-state alkylidene complexes. In this context, it was demonstrated that such processes can be induced by coordinating solvents.[66] For example, yellow-orange $[\mathrm{Cl_3Ta}(\mathrm{CH_2}t\mathrm{Bu})_2]$[**19**, Eq. (1)] is stable in pentane. In contrast, dissolution of **19** in THF results in formation of purple, 14-electron $[\mathrm{Cl_3(thf)_2Ta{=}CH}t\mathrm{Bu}]$ (**20**).[66]

Compound **19** reacts with [TlCp] (Cp = $\mathrm{C_5H_5}$) to afford $[\mathrm{CpCl_2Ta{=}CH}t\mathrm{Bu}]$ (**21**; Scheme 3), the first of the new alkylidene complexes whose reactivity towards olefins was



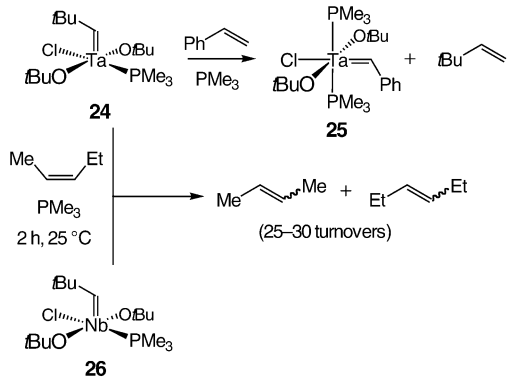
(1)

explored in detail.[67] Complex **21** undergoes reaction with terminal olefins to give products derived from β-hydride rearrangement of a tantalacyclobutane intermediate. As shown in Scheme 3 for the reaction between **21** and ethylene, the intermediate (unobservable) tantalacycle **22** rearranges in the presence of ethylene to yield *cis*- and *trans*-4,4-dimethyl-2-pentene, 4,4-dimethyl-1-pentene, and tantalacyclopentane **23**.[68] It is presumed that: 1) the two observed olefin products are bound to Ta in a $[\mathrm{CpTaCl_2(olefin)}]$ complex immediately upon rearrangement of **22**; 2) olefin products are displaced by ethylene to yield $[\mathrm{CpTaCl_2(ethylene)}]$; 3) $[\mathrm{CpTaCl_2}$-(ethylene)] subsequently reacts with ethylene to yield **23**.[68] Olefin complexes and tantalacyclopentanes ultimately were investigated more extensively in the analogous Cp* (η^5-$\mathrm{C_5Me_5}$) system.[68]



Scheme 3. β-Hydride rearrangement of a tantalacyclobutane formed by reaction of a tantalum-based alkylidene complex with ethylene.

The reactions shown in Scheme 3 suggested that although a metallacyclobutane forms when a Ta neopentylidene reacts with ethylene, it rearranges more rapidly than it converts into *tert*-butylethylene and a Ta methylene complex analogous to **21**. It was subsequently shown that complexes such as $[\mathrm{Cl_3(PMe_3)_2Ta{=}CH}t\mathrm{Bu}]$ react with olefins in a similar fashion to afford olefinic products through rearrangement of unobservable tantalacyclobutanes, and that even **20** [Eq. (1)] is a short-lived metathesis catalyst for *cis*-2-pentene.[69] In an important contrast, however, it was demonstrated that $[(\mathrm{PMe_3})(\mathrm{O}t\mathrm{Bu})_2\mathrm{ClTa{=}CH}t\mathrm{Bu}]$ (**24**) reacts with styrene in the presence of $\mathrm{PMe_3}$ to provide the isolable benzylidene complex, $[(\mathrm{PMe_3})_2(\mathrm{O}t\mathrm{Bu})_2\mathrm{ClTa{=}CHPh}]$ (**25**; Scheme 4). In addition, when treated with *cis*-2-pentene in the presence of $\mathrm{PMe_3}$, Ta complex **24** or the analogous Nb system **26** promote the metathesis of *cis*-2-pentene (25–30 turnovers) at room temperature.[69,70] This was the first time that an alkylidene complex analogous to the initial alkylidene species could be isolated upon reaction with an olefin.[71] However, the ethylidene and propylidene intermediates which were formed in the metathesis of *cis*-2-pentene (Scheme 4), apparently rearranged readily to give ethylene and propylene, respectively, and therefore could not be observed. Rearrangement of ethylidene and propylidene intermediates to olefins is one reason why metathesis by **24** or **26** is not long-lived. It was demonstrated later that some tantalacyclobutane and alkylidene complexes derived from them could be observed if three bulky phenoxide ligands were bound to the Ta center.[72–74] Thus, it was clear that bulky alkoxide ligands are beneficial to sustained metathesis reactions involving Ta or Nb alkylidene complexes.



Scheme 4. The first example of an isolable high-oxidation-state metal alkylidene complex (**25**) formed in a reaction between a well-characterized metal alkylidene catalyst (**24**) and an olefin, and catalytic metathesis with **24** and **26**.

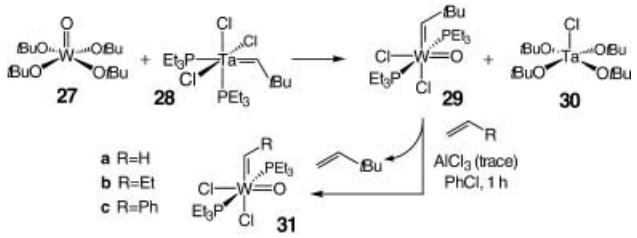
In spite of the above discoveries, the prospects for Ta-based alkylidene complexes as effective catalysts for use in organic synthesis did not appear promising. Tantalum alkylidene complexes do not reform readily from intermediate tantalacyclobutanes relative to the rate at which they rearrange (as shown in Scheme 3), and electron-deficient Ta alkylidene complexes are transformed to an olefin when the alkylidene bears a β proton.[75]

2. Design and Development of Tungsten- and Molybdenum-Based Alkylidene Complexes for Catalytic Olefin Metathesis

Three important findings that emerged from studies involving Ta alkylidene complexes were relevant to alkene metathesis: 1) entirely new (high oxidation state) alkylidene complexes could be prepared and isolated, 2) alkoxides (relative to chlorides as ligands) appeared to promote metathesis, and 3) electron-deficient and sterically crowded pseudotetrahedral alkylidene complexes that contain only covalently bound bulky ligands (including the alkylidene) can be stable. On the basis of the high metathesis activity of ill-defined catalysts described in Section 1.2.1, it seemed likely that some type of high-oxidation-state tungsten- or molybdenum-based alkylidene complexes were the active species. However, exactly what class of metal alkylidene complexes should have been sought or how they might have been prepared was unclear. It was nonetheless appreciated that an alkylidene would have to be stable to bimolecular decomposition if it were to be detected. Moreover, an alkylidene that contains a β proton would have to be stable with respect to rearrangement to an olefin. Finally, loss of an alkylidene α proton to yield an alkylidyne complex, another type of high-oxidation-state species (see Section 2.2),[76] had to be avoided.

2.1. Early Tungsten-Based Metathesis Catalysts

A tungsten-based complex believed to be a plausible target as a well-defined catalyst for olefin metathesis was five-coordinate [(*t*BuO)$_4$W=CH*t*Bu]. (The advantages of a sterically crowded pseudotetrahedral coordination sphere were not appreciated at that time.) The first reaction shown in Scheme 5 (between **27** and **28**) was an attempt to prepare



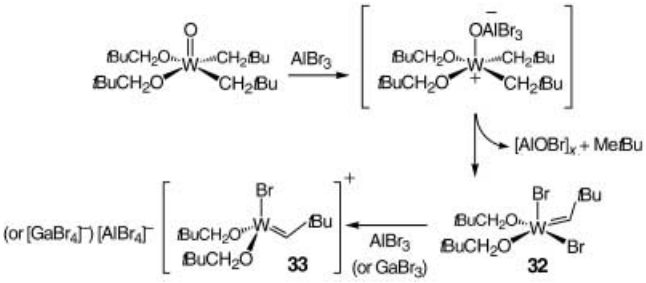
Scheme 5. Synthesis of tungsten-based oxo alkylidene complexes from a tantalum alkylidene complex.

[(*t*BuO)$_4$W=CH*t*Bu] through exchange of an oxo ligand on W with an alkylidene on Ta.[77,78] Instead, the oxo alkylidene [(PEt$_3$)$_2$Cl$_2$W(O)(CH*t*Bu)] (**29**, Scheme 5) and **30** were formed quantitatively. Assembly of **29** suggested that an oxo ligand might help stabilize an alkylidene and that alkylidenes other than a neopentylidene therefore might be observable.

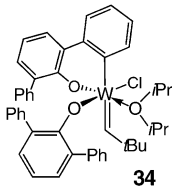
The electron count of the metal center in **29** is 18, since the oxo ligand donates one of its two electron pairs to the metal to create a pseudo triple bond.[79] Therefore it did not seem likely that **29** could react with an olefin unless a phosphane or a chloride ligand were lost to yield a 16-electron species. Nevertheless, it was found that **29** would metathesize terminal and internal olefins very slowly. However, the rate of metathesis was accelerated dramatically in the presence of a trace of AlCl$_3$.[77] It was in this context that the methylene complex [(PEt$_3$)$_2$Cl$_2$W(O)(CH$_2$)] (**31a** in Scheme 5) and new alkylidene complexes that contain β protons, such as **31b**, were observed for the first time.[70] Since it later was demonstrated that addition of one equivalent of AlCl$_3$ (in CH$_2$Cl$_2$) to [(PEt$_3$)$_2$Cl$_2$W(O)(CH*t*Bu)] (**29**, Scheme 5) yielded the 16-electron cationic species [(PEt$_3$)$_2$ClW(O)(CH*t*Bu)][AlCl$_4$],[80] and since [(PEt$_3$)$_2$ClW(O)(CH*t*Bu)][AlCl$_4$] would metathesize terminal and internal olefins (in CH$_2$Cl$_2$; up to ≈100 turnovers in 24 h at room temperature), a small amount of [(PEt$_3$)$_2$ClW(O)(CH*t*Bu)][AlCl$_4$] was believed to be responsible for the metathesis of olefins by [(PEt$_3$)$_2$Cl$_2$W(O)(CH*t*Bu)] in the presence of a trace of AlCl$_3$. Interestingly, the 16-electron complex [(PEt$_3$)Cl$_2$W(O)(CH*t*Bu)] could be isolated and crystallographically characterized and shown to metathesize *cis*-2-pentene for a short time.[77] On the basis of these data, the metal oxidation state that is appropriate for efficient metathesis activity was proposed to be W^{VI}, where the alkylidene is counted as a dianionic ligand. However, it was clear that bimolecular decomposition of alkylidene complexes other than a neopentylidene was still problematic. Decomposition was likely to be most rapid for

methylene complexes, since even 18-electron [$Cp_2MeTa{=}CH_2$] had been found to be unstable towards bimolecular decomposition.[81,82]

Related advances were disclosed by Osborn and co-workers,[83–87] who found that addition of various Lewis acids (such as $AlBr_3$) to [$(OCH_2tBu)_2(CH_2tBu)_2W{=}O$] leads to the formation of metathesis catalysts.[84] Accordingly, it was found that oxo-free alkylidene complexes represented by [$(OCH_2tBu)_2Br_2W{=}CHtBu$] (**32**, Scheme 6) could be isolated,[85] and that **32**, in turn, could be transformed by Lewis acids into cations of the type [$(OCH_2tBu)_2BrW{=}CHtBu)]^+$ (**33**). These cations effectively promoted metathesis of internal olefins and gave rise to observable propagating alkylidenes.[85] It should be noted that the above tungsten-based complexes, along with those later discovered by Basset and co-workers (such as **34**),[88,89] are among the few high-oxidation-state metathesis catalysts that do not contain a second multiply bound ligand in addition to the alkylidene. The neopentoxides were found to be crucial to the preparation and reactivity of the class of tungsten-based catalysts discovered by Osborn and aryloxides were found to be critical to the catalysts prepared by Basset.



Scheme 6. Formation of metathesis-active cationic tungsten-based alkylidene complexes.



2.2. Alkylidyne Complexes and Alkyne Metathesis

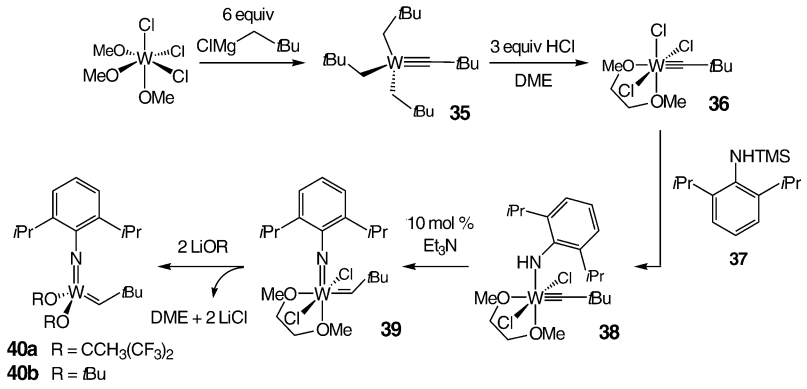
The first reported homogeneous catalysts for alkyne metathesis were prepared from molybdenum hexacarbonyl and a phenol.[90,91] However, reactions promoted by such complexes were slow and the active species and mechanism could not be identified. Katz and McGinnis[53] proposed a catalytic cycle for alkyne metathesis that is analogous to that suggested for alkene metathesis (see Scheme 1), which involves a reversible reaction between a metal–carbon triple bond and an alkyne to give a metallacyclobutadiene. Alkylidyne complexes that were known in the mid 1970s, namely those prepared by Fischer and co-workers,[92,93] such as [$Br(CO)_4W{\equiv}CPh$], did not metathesize alkynes. The discovery of the first high-oxidation-state alkylidynes of Mo and W of the type [$(tBuCH_2)_3M{\equiv}CtBu$] in 1978[94] within a few years led to the development of high-oxidation-state alkylidyne complexes that would metathesize alkynes, and in the process, to an understanding of what might be required to prepare well-defined Mo or W catalysts for olefin metathesis.

The development of well-defined catalysts for alkyne and alkene metathesis took place more or less simultaneously and are strongly linked. For this reason, a brief description of high-oxidation-state Mo and W alkylidyne complexes is provided below.

2.2.1. Synthesis of Well-Defined Tungsten- and Molybdenum-Based Alkylidyne Complexes

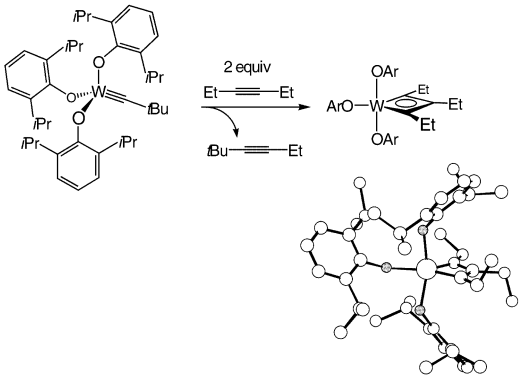
The first practical synthesis of a high-oxidation-state alkylidyne complex of tungsten consists of the reaction between [$W(OMe)_3Cl_3$] and six equivalents of neopentyl magnesium chloride (Scheme 7). Sequential abstraction of two α hydrogen atoms (neopentyl→neopentylidene→neopentylidyne) and complete alkylation at the metal center gives the neopentylidyne complex **35** (Scheme 7).[76,95] The precise sequence of reactions that leads to **35** is not known. Compound **35** is a yellow crystalline compound that melts at approximately 70 °C and can be distilled in vacuo, properties that are reminiscent of [$(tBuCH_2)_3Ta{=}CHtBu$] (**18**, Scheme 2). As shown in Scheme 7, treatment of **35** with three equivalents of HCl in the presence of dimethoxyethane (dme) produces [$(dme)Cl_3W{\equiv}CtBu$] (**36**) quantitatively.

Tungsten-based alkylidyne **36** can be converted readily into a variety of mononuclear compounds with the formula [$(OR)_3W{\equiv}CtBu$], as long as the alkoxide groups are sterically demanding (e.g., OR = O*t*Bu, $OCMe(CF_3)_2$, or O-2,6-$(iPr)_2C_6H_3$).[76,95] Compounds of this type were found to be highly active for alkyne metathesis and were the first well-defined catalysts for this reaction.[29,76,96–98] The expected intermediate alkylidynes could be observed in alkyne meta-



Scheme 7. Synthesis of tungsten-based imido alkylidene complexes from alkylidyne complexes; TMS = Me_3Si.

thesis reactions when bulky electron-withdrawing alkoxides were present, and were isolated and characterized. The structure of intermediate trigonal-bipyramidal (TBP) metallacyclobutadienes could be elucidated by crystallography as well. A representative example of an isolable metallacyclobutadiene is the triaryloxytungstacyclobutadiene shown in Equation (2).[97] This species can act as a catalyst for alkyne



(2)

metathesis since it undergoes a retro [2+2] reaction to yield an alkyne and a triaryloxytungsten alkylidyne complex. Compound **36** (Scheme 7) reacts with an alkyne to afford a five-coordinate trichlorotungstacyclobutadiene analogous to the triaryloxytungstacyclobutadiene shown in Equation (2), but the trichlorotungstacycle reacts further, and irreversibly, with another alkyne equivalent to generate a W^{IV} cyclopentadienyl complex.[99] These studies confirmed that alkoxide ligands promote metathesis-like reactions, while chlorides encourage side reactions that destroy the alkylidyne. On the basis of these studies it was suggested that the most successful tungsten-based olefin-metathesis catalyst might be a pseudotetrahedral species that contains sterically demanding alkoxide ligands.

Pseudotetrahedral molybdenum-based alkylidyne complexes that contain bulky alkoxide ligands were synthesized by techniques similar to those used to prepare the tungsten-based complexes and were shown to be active for alkyne metathesis.[10,95] With alkoxide or phenoxide ligands bound to the Mo center, alkyne metathesis proved to be efficient, while alkyne metathesis could not be detected when halide ligands were present. Intermediate molybdacyclobutadienes appeared to be less stable than the corresponding tungstacyclobutadienes toward loss of alkyne and alkylidyne reformation.

Application of alkyne metathesis to organic synthesis is enjoying increased attention today as a consequence of the development of well-defined high-oxidation-state W and Mo catalysts analogous to those described above.[100] Although alkyne metathesis may not have the scope and potential of alkene metathesis, it is not complicated by the formation of stereoisomers. Controlling the formation of *cis* or *trans* (or *E* or *Z*) isomers in olefin metathesis for the most part remains an unsolved problem.

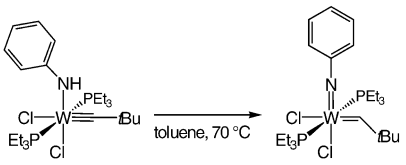
2.3. Development of Imido Alkylidene Complexes as Olefin-Metathesis Catalysts

Tungsten-based complex **29**, shown in Scheme 5, and related systems proved to be fully functional olefin-metathesis catalysts in the presence of $AlCl_3$, which probably removes a chloride to generate an electron-deficient cationic species (< 18 electron). However, metathesis activity was limited by since alkylidene complexes other than the neopentylidene were unstable towards bimolecular decomposition, a process that might include ligand redistribution (e.g., chloride transfer) or alkylidene coupling to give an olefin. The success of using sterically bulky alkoxide ligands in promoting metathesis (of olefins or alkynes) suggested that a complex such as $[W(O)(CHtBu)(OtBu)_2]$ might be a viable target as a well-defined catalyst. Indeed, substitution of the chlorides in **29** with *tert*-butoxide groups led to formation of $[(PEt_3)(OtBu)_2W(O)(CHtBu)]$ but this species decomposed in solution or in the solid state at room temperature.[80] It was thus recognized that an oxo ligand is not sufficiently sterically bulky, that is, it can bridge between metal centers and encourage bimolecular decomposition. Thus, a search for alkylidene complexes that contain an imido ligand in place of an isoelectronic oxo ligand, namely $[W(NR)(CHtBu)(OR')_2]$, was initiated.

To maximize steric protection at the metal center by the imido (NR) group and limit the ability of the imido ligand to bridge between metal centers, complexes bearing N-2,6-$iPr_2C_6H_3$ (NAr) were targeted. Sterically more demanding candidates such as N-2,6-$(tBu)_2C_6H_3$ were rejected on the basis of projected synthetic difficulties. For this reason, a route to $[W(NAr)(CHtBu)(OR')_2]$ species became the immediate goal. An attractive strategy involved alkylidyne complexes, which were being studied intensely at the time. Since neopentylidynes had been prepared by removing two α protons from neopentyl ligands, it seemed possible that one might be able to add a single proton to an alkylidyne to prepare an alkylidene.

2.3.1. Synthesis of Tungsten- and Molybdenum-Based Imido Alkylidene Complexes

The strategy of transferring a proton from an amido nitrogen to an alkylidyne carbon atom was first established in a paper published in 1982.[101] Thus, amido neopentylidyne complexes of the type $[(NHR)Cl_2L_2W{\equiv}CtBu]$ (R = H or Ph; L = PEt_3 or PMe_3) were reported to be transformed into the related imido neopentylidene complexes, $[(NR)Cl_2L_2W{=}CHtBu]$, upon heating or addition of a base, such as triethylamine; an example is shown in Equation (3). Reactions analogous to those in Equation (3) where Ar = 2,6-$iPr_2C_6H_3$ were not attempted. Perhaps the main problem with the



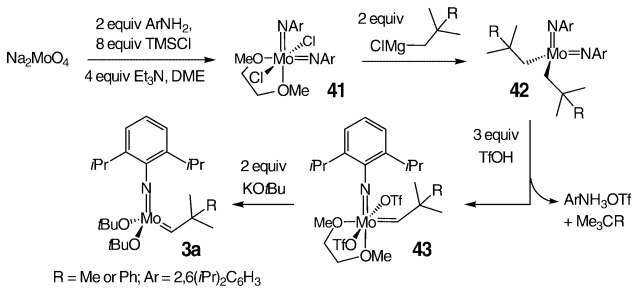
(3)

method shown in Equation (3), as far as preparation of the desired [W(NAr)(CH*t*Bu)(OR′)$_2$] is concerned, is that phosphanes could coordinate to the W center and possibly limit high catalytic activity of the resulting [W(NAr)(CH*t*-Bu)(OR′)$_2$] species.

Six years later it was found that analogous transformations could be carried out on dimethoxyethane complexes, as depicted in Scheme 7. The amido alkylidyne complex **38** was prepared by the reaction of **36** with **37**. Upon treatment with a catalytic amount of Et_3N, **38** was transformed quantitatively into **39**.[7] Miscellaneous observations in the last fifteen years suggest that the type of reaction represented by the conversion of **38** into **39** can proceed in the opposite direction.[14,102] Accordingly, the energetic difference between an amido alkylidyne and an imido alkylidene complex (for example, **38** and **39**, respectively, in Scheme 7) must not be large. Proton migrations between anionic C or N centers in d^0 metal complexes of the type described are related to the α-hydrogen (proton) abstraction (Scheme 2) in which a neopentylidene ligand is formed (irreversibly) from two neopentyl ligands.

When the chloride ligands in tungsten-based alkylidene **39** (Scheme 7) are replaced with sterically demanding alkoxide groups, four-coordinate **40a** and **40b** can be isolated; these should be considered as 14-electron complexes, since the imido ligand donates its electron pair to the metal center to form a pseudo triple bond. Dimethoxyethane, which binds to the metal only as a chelating ligand, does not remain bound to the crowded bis(alkoxide) species for steric reasons. The fact that all four ligands in W alkylidene complexes **40** are sterically demanding and covalently attached to the transition-metal center accounts for their stability toward bimolecular decomposition, a theme that harkens back to the stability of [(*t*BuCH$_2$)$_3$W≡C*t*Bu] (**35**, Scheme 7) and [(*t*BuCH$_2$)$_3$Ta=CH*t*Bu] (**18**).

The Mo alkylidyne complex [(*t*BuCH$_2$)$_3$Mo≡C*t*Bu] is prepared less efficiently than the analogous tungsten-based alkylidyne **35** (Scheme 7). Moreover, the alkylidyne pathway to imido alkylidene compounds (Scheme 7) requires that five out of six neopentyl groups are discarded en route to alkylidyne **36**. Accordingly, an alternative synthesis of molybdenum imido alkylidene complexes was sought. Towards this end, it was established that [Mo(NAr)$_2$(dme)Cl$_2$] (**41**, Scheme 8) can be prepared in large quantities from Na_2MoO_4, two equivalents of $ArNH_2$, eight equivalents of Me_3SiCl, and four equivalents of triethylamine in dimethoxyethane. Alkylation of **41** with neopentyl or neophyl Grignard reagents affords **42**, which upon treatment with three equivalents of triflic acid gives the 18-electron bis(triflate) **43**, in which the Mo=C bond survives further attack by the strong acid (cf. **35**→**36** in Scheme 7). In the presence of various alkoxide or aryloxide salts (Li, Na, or K), including even relatively weak nucleophiles, such as LiOCMe(CF$_3$)$_2$, **43** is converted into Mo alkylidene complexes represented by **3a** in Scheme 8.[13] These molybdenum-based bis(alkoxy)aryl imido alkylidene complexes are stable as long as the alkoxide ligand has sufficient steric bulk to prevent bimolecular decomposition. A complete list of Mo complexes of this general type can be found in Figure 2.



Scheme 8. The route for practical synthesis of molybdenum-based alkylidene complexes; OTf = [CF$_3$SO$_3$]$^-$.

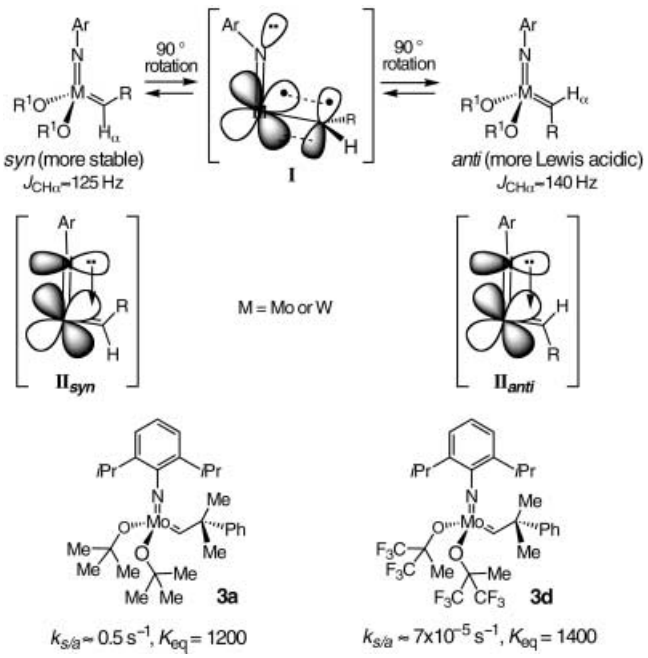
The route outlined in Scheme 8 is the preferred method of synthesizing Mo imido alkylidene complexes. As can be seen from the list in Figure 2, catalysts have been prepared that contain a variety of aryl imido ligands. The only alkyl imido complexes of this general type that have been isolated are 1-adamantylimido species such as **8a** or **8b** (Figure 2). Note that complexes that contain the relatively small OCH(CF$_3$)$_2$ or OC$_6$F$_5$ ligands can be isolated only as adducts with a suitable base (**3m**, **4n**, or **8b**; see also Section 2.3.3). The distinct reactivity and selectivity patterns arising from variations in the aryl imido ligands of molybdenum-based chiral complexes, and the unique attributes of the derived adamantylimido systems, are among the topics discussed below in the context of catalytic asymmetric olefin-metathesis reactions.

Tungsten imido alkylidene complexes can also be prepared by methods related to those shown in Scheme 8, where alkylidyne complexes are not involved.[8]

2.3.2. syn *and* anti *Alkylidene Isomers of Imido Alkylidene Complexes*

In four-coordinate molybdenum- and tungsten-based imido alkylidene complexes (Figures 1–4) the imido ligand is bound to the metal through a pseudo triple bond. That is, the electron pair on the nitrogen atom is donated into an empty d orbital on the metal center. Therefore the M-N-C_{ipso} angle is approximately 180°, and the d orbital on the metal that is involved in the formation of the M=C bond must lie perpendicular to the N-M-C_{ipso} plane. Thus, the metal complex can exist as two stereoisomeric forms. As shown in Scheme 9, one isomer is the *syn* alkylidene, where the substituent R points towards the imido ligand. The other is the *anti* alkylidene, where the substituent points away from the imido nitrogen atom. Studies concerning the structural and reactivity differences of *syn* and *anti* alkylidene complexes of Mo (largely) and W, and the equilibrium between them, have led to a number of important mechanistic insights into olefin metathesis. Selected experimental observations are summarized below. Many of these findings, as well as a number of other details that cannot be explored easily by experimental methods, have been probed by several groups through a variety of theoretical studies.[103]

M=CHR complexes can be detected readily by ^{1}H NMR spectroscopy. In all the complexes in Figures 1–4, the resonance signal of the alkylidene H$_\alpha$ usually is found



Scheme 9. *syn* and *anti* Mo and W alkylidene complexes are interconvertible. The rate constant for *syn* to *anti* conversion ($k_{s/a}$), and the reverse ($k_{a/s}$), are influenced by electronic and steric factors that affect the energy of intermediate **I**.

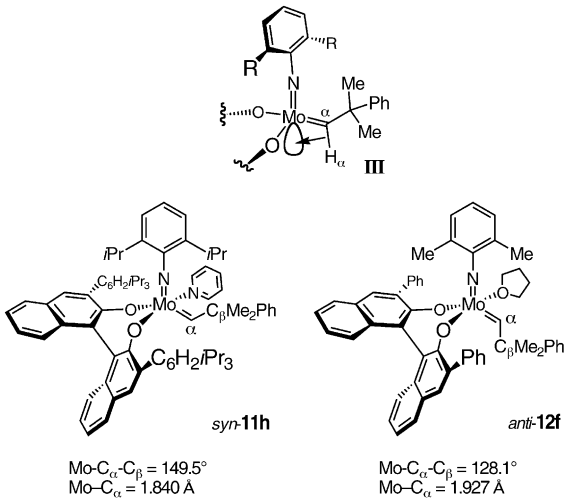
between $\delta = 8$–14 ppm. The resonance that corresponds to the typically minor *anti* isomer, if it can be seen, appears 1–2 ppm downfield of the *syn* H_α resonance. A reasonably reliable method of identifying the isomer is the J_{CH} coupling constant; J_{CH} for the *syn* isomer is typically approximately 125 Hz, while for the *anti* isomer it is typically about 140 Hz. Often only the *syn* isomer can be detected in routine NMR spectra, since so little *anti* isomer is present. However, the minor *anti* isomer is detected in many situations, especially in the aryl oxide complexes shown in Figure 3 and Figure 4.

In 1992, it was demonstrated that Mo complex **3d** (Figure 2, G = CMe_2Ph), which exists almost exclusively as its *syn* isomer at 22 °C, can be transformed into an equilibrium 1:2 mixture of *anti* and *syn* alkylidene complexes upon photolysis (360 nm) of the sample in [D_8]toluene at −78 °C (see Scheme 9).[104,105] When the light is turned off and the temperature raised above −78 °C, the *anti* isomer reverts back to the *syn* form in a reaction that is first order in *anti*-**3d**. In this manner, it was determined experimentally that *anti* alkylidenes can interconvert with their *syn* isomers either thermally or photochemically by rotation about the M=C bond.

Rate constants for conversion of the *anti* into the *syn* isomer ($k_{a/s}$) have been determined at temperatures between −78 °C and 22 °C for a variety of Mo complexes. Once the location of the *anti* H_α resonance signal was determined, the equilibrium constant between *syn* and *anti* isomers could be measured at room temperature, although in some cases with difficulty on account of the large magnitude of K_{eq} (K_{eq} = [*syn*]/[*anti*]). From K_{eq} and $k_{a/s}$ at 22 °C values (measured or calculated from temperature studies), $k_{s/a}$ may be determined at 22 °C ($K_{eq} = k_{a/s}/k_{s/a}$). Values for K_{eq} usually range from approximately 20 to around 2000 and both $k_{a/s}$ and $k_{s/a}$ tend to vary significantly as a function of the alkoxide and the imido ligand. For example, comparison of $k_{s/a}$ for **3a** and **3d**, which have nearly the same K_{eq} values (toluene, 22 °C; Scheme 9), reveals that the *syn* isomer of the *tert*-butoxide complex converts into the *anti* isomer $\approx 10^4$ times more rapidly than in the hexafluoro-*tert*-butoxide analogue.

As illustrated in **I** in Scheme 9, the d orbital in the N-M-C plane, which is involved in the formation of the pseudo triple bond between the imido nitrogen atom and the metal center, also participates in the formation of a M=C bond in the rotated alkylidene. The M-N-C_{ipso} angle therefore is likely to decrease in **I**, although it is not clear whether the imido substituent would point away or towards the alkylidene.[103f] A plausible model that explains the difference in $k_{s/a}$ for **3a** and **3d** is that the electron-withdrawing alkoxide groups in **3d** strengthen the M–N pseudo triple bond, thereby rendering access to the rotated alkylidene **I** (Scheme 9) energetically more costly. The rate of interconversion of *syn* and *anti* isomers often changes with the nature of the imido group, the alkylidene ligand, and the metal center (W versus Mo).[104] If photolysis in [D_8]toluene at −78 °C does not establish an equilibrium between *anti* and *syn* isomers, then spin saturation transfer is a possible alternative method of determining the rate of interconversion of *anti* and *syn* isomers. Spin saturation transfer has been employed in studies involving aryloxide complexes.[14,15]

Stereoelectronic factors are at least partially responsible for the fact that *syn* alkylidenes are energetically favored. As illustrated in **III** in Scheme 10, and supported by theoretical studies,[103] an agostic interaction[106] is proposed to exist between the C_α–H_α bond and the transition-metal center. Such a stabilizing hyperconjugation ($\sigma_{C-H} \rightarrow \sigma^*_{Mo-N}$) increases the π character of the C_α–H_α bond, thereby lowering J_{CH} and increasing the triple-bond character of the Mo=C_α bond. Crystallographic studies support the validity of such interactions. As an example, as illustrated in Scheme 10, the X-ray



Scheme 10. Hyperconjugative effect proposed to be present in the *syn* alkylidene complexes and representative structural consequences.

structure of *syn*-**11h**[18] is comparable to that of the closely related *anti*-**12f**,[16] except for two significant differences: 1) *anti*-**12f** contains a smaller Mo=C_α–C_β bond angle (128.1(6)°) than *syn*-**11h** (149.5(10)°), and 2) *anti*-**12f** has a longer Mo–C_α bond (1.927(9) Å) than *syn*-**11h** (1.840(12) Å). Such differences can be explained in terms of the aforementioned agostic interaction.

On the basis of the structural differences between *syn* and *anti* isomers discussed above, it is not surprising that the two isomers exhibit disparate reactivity profiles, at least when determination of a difference is possible. For instance, in the case of Mo complex **3d** the *anti* isomer is estimated to be at least 100-times more reactive than the corresponding *syn* alkylidene toward 2,3-bis(trifluoromethyl)norbornadiene ($NBDF_6$) at −78 °C. In contrast, it has been estimated that *anti*-**3a** is possibly 10^5-times more reactive than *syn*-**3a** towards $NBDF_6$ at 22 °C.[104] It is generally presumed that an alkylidene/olefin complex is a transition state on the pathway to formation of a metallacyclobutane intermediate. Accordingly, the lower reactivity of the *syn* isomer might result in part from steric interactions between the alkylidene substituent and the aryl imido groups in **IV** depicted in Figure 5, as compared to those in the *anti* isomer **V**. (See below for further discussion and evidence.) *anti* Alkylidenes may exhibit higher reactivity owing to the increased Lewis acidity of the metal center (more effective association with the π-donor olefin substrate), which is consistent with the hyperconjugative interactions mentioned above (Scheme 10), and the strength of the interaction between the metal center in *anti* alkylidenes and two-electron-donor ligands such as phosphanes (see Section 2.3.3).

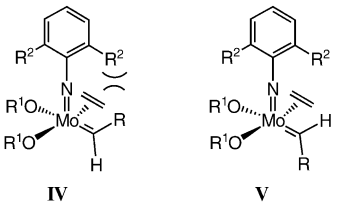
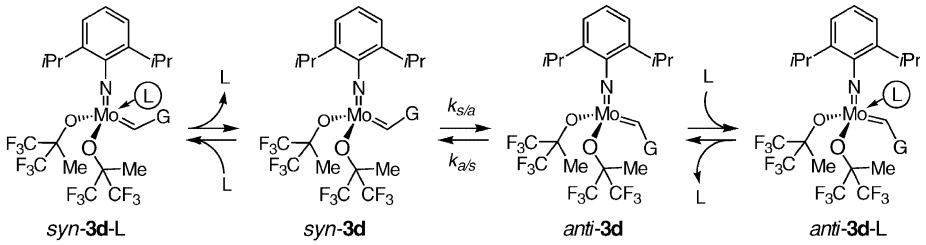


Figure 5. Steric interactions in the square-pyramidal (SP) complex formed upon coordination of olefin substrate may be partly responsible for lower reactivity of *syn* alkylidenes towards an olefin (ethylene used as example).

2.3.3. *Molybdenum and Tungsten Imido Alkylidene Complexes with Various Donor Ligands: Mechanistic Implications*

In general, four-coordinate Mo and W imido alkylidene complexes can form monoadducts with good two-electron-donor ligands, such as THF, PMe_3, pyridine, or quinuclidine (see Figures 3 and 4 and Scheme 10 for THF and pyridine adducts).[107] In all cases reported to date, the donor has been found to add to a CNO tetrahedral face (one of two pseudotetrahedral faces with the imido nitrogen, the alkylidene C_α, and an alkoxide oxygen atom at the corners), to afford a trigonal bipyramidal complex in which the new ligand is bound in the axial position (Scheme 11). When the alkoxide groups are electron-withdrawing, as in **3d** (Scheme 11), and the donor (L) is PMe_3, then the initial adduct contains the alkylidene in the *syn* orientation (e.g., *syn*-**3d**-PMe_3). This is because the phosphane ligand binds tightly to the perdominating *syn* isomer ($K_{eq} \approx 1400$ for **3d**). With time, as illustrated in Scheme 11, the *syn* adduct loses the phosphane to give a small concentration of the base-free species, the alkylidene rotates about the M=C bond (*syn*-**3d**→*anti*-**3d**) in the base-free form, and the phosphane binds again to yield the thermodynamically more stable adduct of the *anti* isomer. Note that the *syn* alkylidene is favored ($K_{eq} = 1400$) in base-free **3d**, while the *anti* alkylidene is the predominant adduct in **3d**-PMe_3. Coordinating bases bind strongly to electron-poor metal centers, as in hexafluoro-*tert*-butoxides, and weakly to relatively electron-rich metal centers, as in *tert*-butoxide complexes; however, the strength of the metal–donor-ligand interactions have not yet been quantified.



Scheme 11. *syn* and *anti* metal alkylidene complexes form adducts with various donor ligands (L). Interconversion between the two isomers, however, requires loss and reassociation of the donor ligand (G=CMe_2Ph).

The crystal structure of *syn*-**3d**-PMe_3 shown in Figure 6 reveals a significant steric repulsion between the *t*Bu group of the alkylidene and one of the *o*-*i*Pr groups of the imido ligand; such a claim is based on essentially identical values (≈156°) for the Mo-N-C_{ipso} angle in the imido ligand, which is normally about 180°, and the Mo-C_α-C_β angle in the neo-

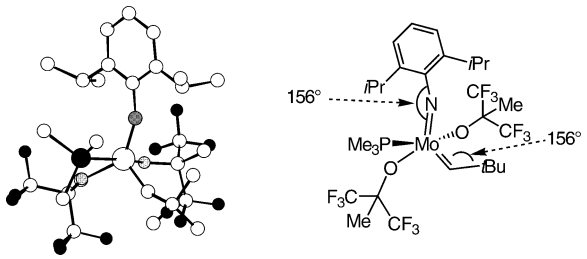


Figure 6. Structure of the PMe_3 adduct of [(NAr){$OCMe(CF_3)_2$}$_2$Mo=CH*t*Bu].

pentylidene ligand, which is typically around 140°. This effect is the same interaction discussed in Section 2.3.2 and presented in Figure 5. Interaction between an *o*-*i*Pr group and the *syn* alkylidene substituent is probably at least partially responsible for destabilizing the *syn*-L adduct, thus lowering the reactivity of the *syn* alkylidene complex towards two-electron donors, which include olefins. Reactivity differences therefore can depend dramatically on the nature of the substituent on the alkylidene and the nature of the imido ligand. For example, there is evidence that *syn* and *anti* isomers of the 1-adamantylimido Mo complex **8a** (Figure 2) are approximately equally reactive towards $NBDF_6$.[104]

When the alkoxide ligand is relatively small and electron-withdrawing, the derived neopentylidene or neophylidene complex is stable toward bimolecular decomposition only as a Lewis base adduct. As an example, Mo alkylidene **3m** (see Figure 2), where OR = $OCH(CF_3)_2$, can be isolated only as its 2,4-dimethylpyridine complex.[12] Similarly, bis(hexafluoroisopropoxide) Mo alkylidene **8b**, bearing the relatively small adamantylimido ligand, is isolated only as a 2,4-dimethylpyridine complex.[12]

A number of enantiomerically pure Mo systems exist as THF adducts (Figure 3 and Figure 4). It is noteworthy that a base adds to the same diastereotopic CNO face of a complex, regardless of the diolate, imido group, alkylidene isomer, or the donor molecule (see the pyridine complex **11h** in Scheme 10).[17] This trend suggests that one face of an enantiomerically pure catalyst is sterically more accessible (see Section 5 for a detailed discussion).

Among THF-bound chiral Mo complexes are those that bear an electron-withdrawing 2,6-dichlorophenylimido ligand (e.g., **13a–d** in Figure 4). The smaller size of the 2,6-dichlorophenylimido group (compared to the NAr ligand) in combination with its greater electron-withdrawing ability encourages the donor molecule to coordinate to the more electron-poor and sterically accessible metal center. In a similar fashion, complexes that bear diolate ligands which provide a significant amount of space in their chiral pocket (as judged by examination of molecular models) are isolated as pyridine or THF complexes. Representative examples of the latter type are substituted binaphtholate Mo complexes **11i–m** in Figure 3 and **12e** in Figure 4.

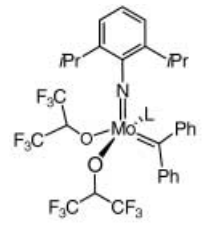
In the presence of coordinating solvents, such as THF (especially at low temperatures), *syn* and *anti* complexes in which the donor solvent is bound to the metal center can usually be detected.[16,18,19,25] In some cases all four diastereomeric solvent adducts can be detected at low temperature, where exchange of the bound THF is slow.[9,19,25] At elevated temperatures, NMR spectroscopic evidence suggests that donor solvent molecules (usually THF) first begin to dissociate from the less Lewis acidic *syn* complexes (see Scheme 9) and subsequently from the more Lewis acidic *anti* complexes.[18] Dissociation of donor solvent molecules is more facile in the case of sterically more demanding chiral ligands, or when bulky and more electron-donating imido groups are present.

If a coordinating solvent dissociates readily from *syn* and *anti* isomers, then interconversion of the two alkylidenes may proceed through rotation about the Mo=C bond. In connection with the effect of a Lewis basic ligand on the efficiency of alkylidene isomerization, it has been determined that the rate of interconversion between *syn* and *anti* isomers of **3d**, a Mo complex that bears electron-withdrawing alkoxide ligands, is significantly slower in $[D_8]$THF than in $[D_8]$toluene.[104] Whereas for most Mo alkylidene complexes the value for $\Delta S^{\neq}$ is aproximately 0 in $[D_8]$toluene, the relatively large and positive value for $\Delta S^{\neq}$ obtained in $[D_8]$THF ($+20$ to $25\ cal\ mol^{-1}\ K^{-1}$) is consistent with a process that requires rate-limiting loss of Lewis basic THF from the metal center.[104] These values also suggest that the alkylidene rotates in four-coordinate species, not five-coordinate base adducts.

On the basis of the discussion so far, one might suspect that five-coordinate base adducts of imido alkylidene complexes cannot react directly with olefins, since the donor ligand effectively blocks coordination of the olefin. All evidence to date suggests that this is the case.

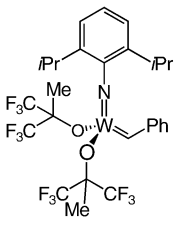
One might question whether an olefin adduct of an alkylidene complex is observable. An alkylidene/olefin complex, distinct from a metallacycle, has been detected in NMR spectra at low temperatures in only one instance, one which involves cationic catalysts of the type studied by Osborn and Kress (see Scheme 6 and the related discussion).[108] Alkylidene/olefin intermediates have not been observed in any imido alkylidene bis(alkoxide) complexes of Mo or W.

The strength of coordination of a base to an imido alkylidene bis(alkoxide) complex, and the degree to which the base stabilizes that alkylidene complex towards bimolecular decomposition (see Section 2.4.2), depend on the size and electronic characteristics of the alkylidene, alkoxide, and imido ligands, and, of course, the Lewis base. We have discussed primarily adducts of neopentylidene or neophylidene complexes in which the alkoxides and imido ligands are sterically demanding and are inherently relatively stable toward bimolecular coupling of alkylidenes to form a disubstituted olefin (e.g., *trans*-di-*tert*-butylethylene). Therefore, complexes that contain disubstituted alkylidenes should be even more stable toward bimolecular alkylidene coupling. For example, diphenylmethylene complexes (such as **45**[12] that contain small alkoxide groups) which in solution are largely base-free at concentrations of approximately 10 mM, can be isolated. At the other end of the steric scale are methylene complexes, no base-free example of which has been isolated. Thus, while complex **46** has been isolated and characterized,[7] the corresponding methylene species has only been detected as a Lewis base adduct, phosphane complex **47** being one example.[7]

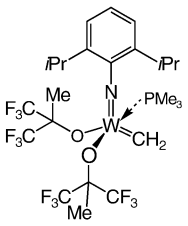


45 L = 2,4-dimethylpyridine

The base adducts of alkylidene complexes can still be reactive, if the base is labile enough to provide a significant concentration of the free alkylidene, under conditions where the alkylidene does not decompose bimolecularly. For example, the 2,4-dimethylpyridine complex **8b** (Figure 2)



46



47

readily polymerizes (*o*-TMS)phenylacetylene.[12,109] When the base is pyridine, the adduct is virtually inactive toward (*o*-TMS)phenylacetylene, while the 2,5-dimethylpyridine complex analogous to **8b** is unstable as a consequence of the high concentration of the base-free species formed in solution which then decomposes bimolecularly.

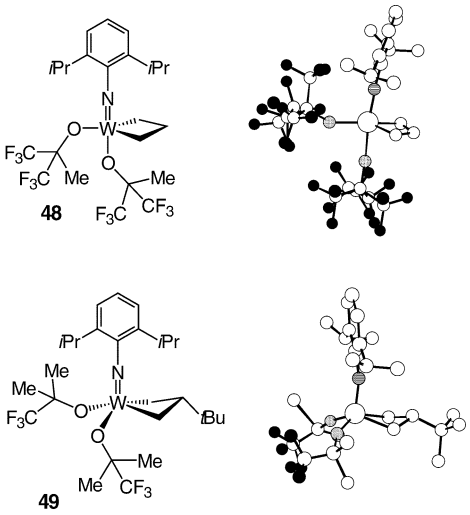


Figure 7. Tungstacycobutanes have been isolated, characterized, and shown to exist as trigonal-bipyramidal (TBP; **48**) or square-pyramidal (SP; **49**) complexes.

2.4. Olefin Metathesis Catalyzed by Imido Alkylidene Complexes

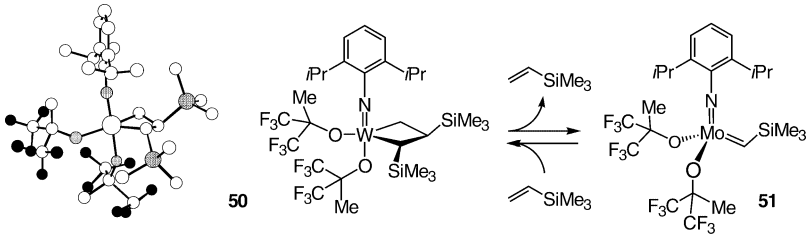
2.4.1. Reactions of Tungsten- and Molybdenum-Based Alkylidene Complexes with Olefins

Alkoxide-bearing W imido alkylidene complexes, such as those illustrated in Figure 1, are highly active catalysts for the metathesis of internal olefins.[7,28,32] Catalyst activity for metathesis of an unfunctionalized internal alkene, such as *cis*-2-pentene (to generate 2-butenes and 2-hexenes), is higher with W complex **1d**, which bears $OCMe(CF_3)_2$ ligands, than with **1a**, which contains O*t*Bu groups. Differences in catalyst activity can be attributed in a general sense to the increased electrophilicity of the metal center in a given isomer (*syn* or *anti*), although the rate of equilibration of *syn* and *anti* isomers, and their relative reactivities are also important aspects of overall reactivity (see Scheme 9 and related discussion).

Two types of tungstacyclobutanes, each of which has distinctive ^1H and ^{13}C NMR spectra, have been observed under a variety of conditions.[7,28] Crystallographic studies indicate that these metallacyclobutanes possess either a trigonal-bipyramidal (TBP, **48**, Figure 7) or a square-pyramidal geometry (SP, **49**, Figure 7). In certain instances, both geometries have been observed in solution and found to interconvert without loss of an olefin. In each type of metallacycle (SP or TBP) the $W-C_\alpha$ bond lengths are relatively short (2.05–2.15 Å) compared to typical $W-C_\alpha$ bond lengths in ordinary W^{VI} alkyl complexes (2.20–2.25 Å). Moreover, it was established that SP complexes are more stable towards loss of olefin when they contain a relatively electron-donating alkoxide group (e.g., O*t*Bu) and TBP systems are most stable when their alkoxide ligands are relatively electron-withdrawing (e.g., $OMe(CF_3)_2$). However, it has not been determined which metallacycle, if either, is formed directly upon reaction of the alkylidene complex with an olefin.

Unsubstituted tungstacycles (illustrated by **48** in Figure 7), can be formed under conditions where ethylene is generated. More unsubstituted than substituted metallacycles have been isolated and characterized, since loss of ethylene occurs more readily from unsubstituted metalacycles than the rate with which substituted metalacyclcles loses alkenes.[28,110] Therefore, unsubstituted metallacycles may be the dominant and detectable species in solution whenever ethylene is generated.[19] Like five-coordinate base adducts of alkylidenes, five-coordinate metallacycles are relatively stable towards bimolecular decomposition and thus can serve as reservoirs for reactive alkylidenes.

Isolation and study of tungstacyclobutanes revealed another noteworthy mechanistic principle: formation of a metallacyclobutane does not necessarily guarantee that an olefin undergoes metathesis. For example, reaction of tungsten-based complexes **1d** with $TMSCH{=}CH_2$ leads to the formation of TBP metallacyclobutane **50** (Scheme 12) which has been isolated and structurally characterized.[7] Complex **50** contains *trans* TMS groups, rendering it a possible intermediate en route to the formation of *trans*-1,2-bis(trimethylsilyl)ethylene (*trans*-TMSCH=CHTMS). Nevertheless, as illustrated in Scheme 12, metallacycle **50** selectively loses vinyltrimethylsilane to afford **51** (not TMSCH=CHTMS and the tungsten-based methylidene species); therefore vinyltrimethylsilane is not metathesized by **1d** to generate



50 51

Scheme 12. Bis(trimethylsilyl)tungstacyclobutane **50**, isolated and characterized by X-ray crystallography, breaks up to afford silylalkylidene complex **51** (not TMSHC=CHTMS), which suggests that not all metallacyclobutanes lead to productive metathesis.

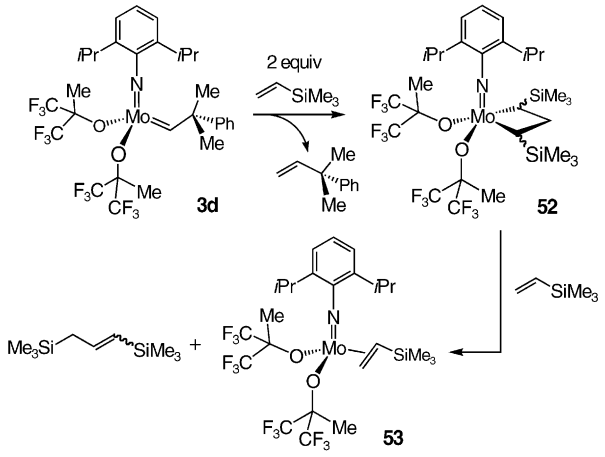
ethylene and TMSCH=CHTMS. This result suggests that transformations between certain terminal olefins might prove to be selective in favor of formation of cross-metathesis products versus those derived from homometathesis reactions.[111–113]

Similar to tungsten-based systems, molybdenum-based complexes (Figures 2–4) are highly active olefin-metathesis catalysts, particularly when electron-withdrawing alkoxide groups are present (e.g., **3d**, Figure 2).[32,33] One advantage of molybdenum-based catalysts is that molybdacyclobutane intermediates appear to break up more readily than their tungsten counterparts. Thus, in a molybdenum-catalyzed metathesis process, an unsubstituted metallacyclobutane is less likely to serve as a reservoir of a Mo=CH_2 complex.

No other anionic ligands in Mo and W imido alkylidene complexes to date have proven to be as successful as alkoxides for sustained metathesis activity.[29] This situation arises either because alternative ligands are not bulky enough to stabilize an electron-deficient metal center and prevent decomposition (e.g., halides) or because such ligands donate too much electron density to the metal in a σ and/or π fashion (e.g., amides). Recent examples of the latter effect are complexes **11q** and **11r** (Figure 3); no reaction was observed between **11q** or **11r** and ethylene or even benzaldehyde.[23]

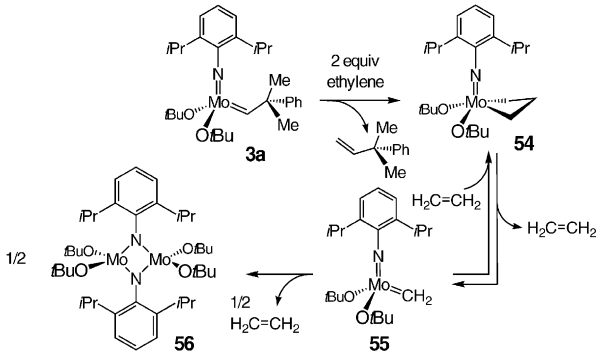
2.4.2. *Pathways that Lead to Catalyst Decomposition*

Two main mechanistically elucidated routes lead to a depletion of catalyst concentration during a typical metathesis reaction; in each of these processes, reduced (Mo^{IV} or W^{IV}) species are generated. Such decomposition pathways are the following: 1) Rearrangement of metallacyclobutanes to olefins. For example, the reaction shown in Scheme 13



Scheme 13. One pathway that results in decomposition of molybdenum-based metathesis catalysts leads to molybdenum(IV) olefin complexes, such as **53**.

involving **3d**, leads to formation of a Mo^{IV} olefin complex **53** as a consequence of β-hydride rearrangement of an intermediate α,α′-disubstituted metallacyclobutane (**52**).[114] 2) Bimolecular decomposition of alkylidene complexes. This pathway, which is fastest for methylene complexes, leads to the formation of olefins as a result of coupling of two alkylidenes (Scheme 14). The *tert*-butoxide complex **3a** upon



Scheme 14. Pathways that lead to the generation of dimeric complexes, such as **56**, also account for decomposition of molybdenum-based metathesis catalysts.

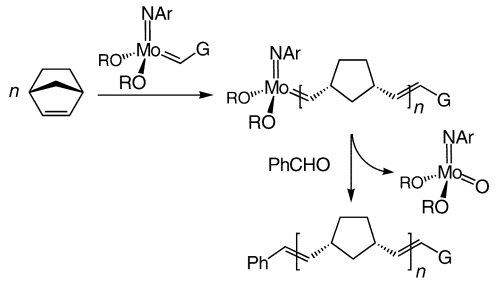
reaction with ethylene is converted into a detectable (by ^{1}H NMR spectroscopy) SP metallacyclobutane (**54**), which in turn decomposes to afford imido-bridged dimeric system **56** via methylene complex **55**.[114] It has been proposed that **56** is formed via an intermediate that contains two bridging methylenes, which subsequently loses ethylene.[114] Bimolecular decomposition of methylene complexes was demonstrated most convincingly for the 18-electron species [$Cp_2(CH_3)Ta{=}CH_2$] early in the development of high-oxidation-state alkylidene complex chemistry.[82]

More recent studies involving the enantiomerically pure binaphtholate complexes **11j**, **11k**, and **11l** (see Figure 3) indicate that some propylene is formed as well upon decomposition of unsubstituted molybdacyclobutane species.[19] These investigations suggest that decomposition of unsubstituted molybdacyclobutane compounds derived from binaphtholate complexes is faster in the absence or the presence of ethylene. Accelerated decomposition in the absence of ethylene can be ascribed to displacement of the equilibrium between an unsubstituted metallacyclobutane and a methylene complex (for example, between **54** and **55** in Scheme 14) in favor of the latter, which subsequently decomposes bimolecularly. However, decomposition of an unsubstituted metallacyclobutane to give propylene in the presence of ethylene was unexpected. Clearly, additional mechanistic studies will be required to elucidate decomposition pathways of imido alkylidene complexes and their metallacyclobutane counterparts. Regardless of various mechanistic intricacies, the above findings indicate that since ethylene is generated in a metathesis reaction involving a terminal olefin, it is especially important to consider carefully the conditions under which the transformation is carried out (for example, whether a closed or open vessel is employed).

3. Ring-Opening Metathesis Polymerization (ROMP) Catalyzed by Molybdenum-Based Imido Alkylidene Complexes

Olefin metathesis has many variations, among them reactions that lead to polymers. Examples include the ring-opening metathesis polymerization (ROMP) reaction,[37,38] polymerization of terminal alkynes,[12,36,115,116] step-growth polymerization of dienes,[117,118] and cyclopolymerization of 1,6-heptadiynes.[119,120] Studies concerned with ROMP of norbornenes has led to an elucidation of the reactivity patterns of *syn* and *anti* alkylidenes. The results of these investigations are detailed below.

ROMP reactions were of great interest to polymer chemists long before questions regarding the exact nature of the active catalyst began to be addressed rigorously.[37,38] The development of well-defined catalysts provided new opportunities for increasing our understanding of the mechanism of ROMP. As illustrated in Scheme 15 for norbornene, in

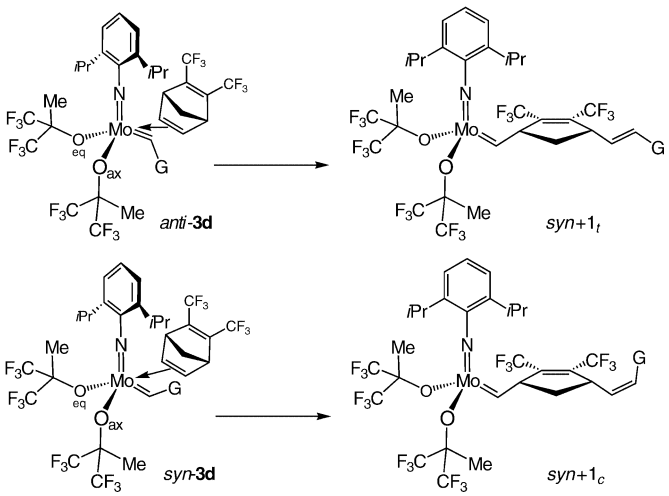


Scheme 15. ROMP and cleavage of the polymer with benzaldehyde in a Wittig-like reaction.

ROMP reactions a cyclic olefin reacts with the alkylidene to give a metallacyclobutane that is ruptured to afford a new alkylidene into which the cyclic species has been incorporated.[34,35,121,122] The new alkylidene may continue to react with the cyclic olefin in a similar manner to form a polymer with repeating units consisting of the "opened" alkene. If intermediates of this type escape decomposition during the process, and if the ring-opening step is irreversible, then such ROMP reactions are referred to as living; another monomer can be added after consumption of the first, which results in the formation of block copolymers. Alternatively, the polymer may be cleaved from W or Mo through reaction with a benzaldehyde. In processes that are not living, ROMP products can equilibrate to deliver mixtures that contain other cyclic or linear olefins formed by secondary metathesis processes.

3.1. Effect of Catalyst Structure (syn and anti Alkylidenes) on Rate of Polymerization and Olefin Stereoselectivity

At −78 °C the *anti* alkylidene isomer of Mo complex *anti*-**3d** (Scheme 16) has been demonstrated to react selectively with 2,3-bis(trifluoromethyl)norbornadiene ($NBDF_6$) to produce the racemic *syn* "first insertion product" bearing a *trans*



Scheme 16. Different alkylidene isomers can lead to polymeric structures with varying backbone olefin stereochemistry (C=CMe$_2$Ph).

olefin (*syn* + 1_t in Scheme 16). This outcome can be explained if $NBDF_6$ approaches one CNO face of the catalyst in the manner illustrated in Scheme 16 (through the *exo* face of the C=C bond), where the bridgehead methylene group of the olefin substrate lies approximately over the "flattened" aryl imido ring and the C=C and Mo=C bonds are approximately parallel to one another.[104] Formation of the derived metallacycle and subsequent ring-opening would then deliver a *trans* alkene. Note that the *syn* + 1_t product now contains a chiral β carbon atom, and that subsequent reaction of the monomer at one or the other CNO face will not be energetically equivalent. It is estimated that $NBDF_6$ reacts with *anti*-**3d** at least 100-times faster than with *syn*-**3d** at −78 °C.

As depicted in Scheme 16, the *syn* alkylidene isomer of the same Mo complexes (*syn*-**3d**) reacts with $NBDF_6$ to afford selectively a *syn* Mo alkylidene that carries a *cis* alkene (*syn* + 1_c). This reaction takes place readily only above 0 °C.

The importance of these findings was underlined by the subsequent discovery of the high *cis* content (≈95 %) of the polymer derived from $NBDF_6$ when **3d** is employed as an initiator.[123] (For **3d** $K_{eq} = [syn]/[anti] = 1400$ at 22 °C in toluene, the *anti* form of the first insertion product, *anti* + 1_c, is not detected in routine NMR spectra; that is, K_{eq} was estimated to be > 100 for *syn* + 1_c and subsequent insertion products.) Accordingly, *syn* alkylidene species are likely to be responsible for the polymerization process. (*anti* Alkylidene propagating species would deliver *trans* alkenes). The near exclusive involvement of the *syn* isomer is the result of two circumstances: 1) The *anti* isomer is not readily accessed through rotation about the Mo=C bond on the time scale of polymerization ($k_{s/a} = 7\text{x}10^{-5}\ s^{-1}$ at 22 °C). 2) Addition of $NBDF_6$ to a *syn* isomer yields another *syn* isomer and a *cis* alkene. Even though the *anti* isomer is the more reactive at ambient temperature by at least two orders of magnitude, it cannot be accessed rapidly and its concentration is low. The modes of approach of substrate to a CNO face shown in Scheme 16 are preferred in aryl imido complexes because the flat aryl ring is expected to lie approximately in the trigonal plane of the TBP transition state (where the incoming olefin

occupies an axial position) and steric interaction between the incoming substrate and alkoxide ligands can be minimized. Addition of $NBDF_6$ to the Mo=C bond in an orientation 180° to that shown in Scheme 16 would lead to significant interaction of the $NBDF_6$ with the alkoxide ligands. Similar arguments would apply to any alkylidenes formed in the course of the polymerization process.

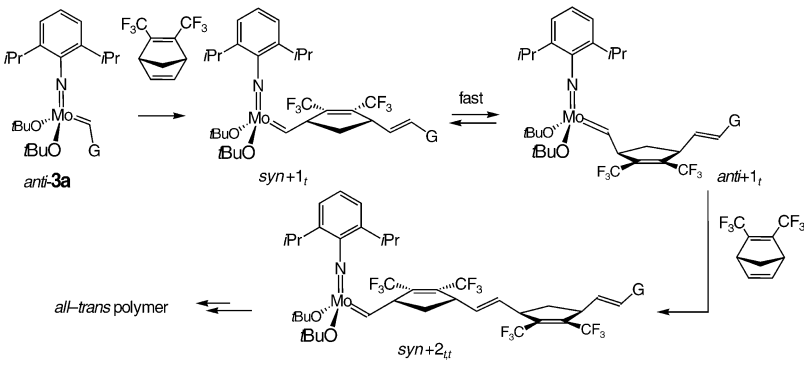
Polymerization of $NBDF_6$ by the less Lewis acidic Mo complexes **3a** (bearing O*t*Bu ligands) affords a polymer in which approximately 98% of its backbone alkene units are *trans*.[124] *trans* Linkages can be formed through reactions involving only *anti* alkylidenes (Scheme 17), if the following assumptions hold:

1) The mode of approach of a monomer to an *anti* alkylidene (Scheme 17) is the same as the proposed mode of approach to a *syn* alkylidene (Scheme 16)
2) The *tert*-butoxide ligands in **3a** deactivate the metal to the point where the *syn* alkylidenes do not react with $NBDF_6$ before the kinetically accessible ($k_{s/a} = 1\ s^{-1}$) *anti* isomer does, in spite of the fact that the concentration of the *syn* alkylidene is nearly a thousand-times higher than the *anti* isomer. Thus, if we assume that $k_a[anti] = 100\ k_s[syn]$ and $K_{eq} = 10^3$, then $k_a = 10^5 k_s$, which indicates that the *anti* alkylidene can be approximately five orders of magnitude more reactive than the corresponding *syn* isomer toward $NBDF_6$.

For a more reactive monomer, such as norbornene, the above mechanistic scenario may not hold and more *cis* linkages can form.

It also has been demonstrated that when Mo complexes **8** are used instead of **3d** (i.e., changing the aryl imido ligand to an adamantylimido group), the initial *syn* and *anti* metal alkylidene complexes appear to be approximately equally reactive toward $NBDF_6$. These findings suggest that the steric and electronic properties of the imido ligand are of fundamental importance in determining polymer *cis*/*trans* structure.

In 1994, Feast, Gibson, and co-workers disclosed an intriguing result demonstrating that the mechanistic pathway for polymerization reactions catalyzed by molybdenum-based catalysts might vary dramatically based on the nature of the substrate.[125,126] These researchers established that 1,7,7-trimethylnorbornene is polymerized slowly by the complexes **3d** in CH_2Cl_2 to give an *all-trans* polymer (not *all-cis* as with $NBDF_6$) at a rate that is independent of substrate concentration and with a rate constant that is essentially equal to the $k_{s/a}$ value measured for the catalyst at 22°C ($7x10^{-5}\ s^{-1}$). These findings are consistent with a rate-limiting conversion of *syn* into *anti* alkylidene. The *anti* alkylidene in turn reacts relatively rapidly with the substrate monomer to afford a *syn* insertion product with a *trans* alkene. Reaction of 1,7,7-trimethylnorbornene with *syn* Mo alkylidenes, even highly reactive **3d**, essentially does not take place, presumably for steric reasons.



Scheme 17. In spite of predominance of the *syn* molybdenum-based alkylidene complexes, the substantially higher reactivity of the *anti* isomers leads to the formation of *all-trans* polymers (G=CMe_2Ph).

3.2. Effect of Catalyst Structure on Polymer Tacticity

3.2.1. Achiral Catalysts and Chain-End Control of Stereochemistry

The ability to control *cis*/*trans* selectivity as well as the relative stereochemistry between monomer units (tacticity) are important features of ROMP with well-defined catalysts. In ROMP reactions of norbornenes or norbornadienes that contain a mirror plane, four stereoregular polymers can be formed, as shown in Figure 8 for a generic disubstituted

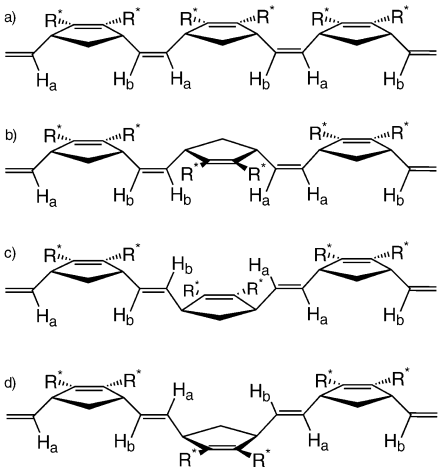
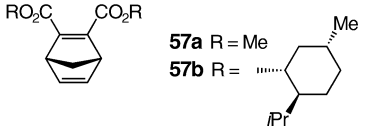


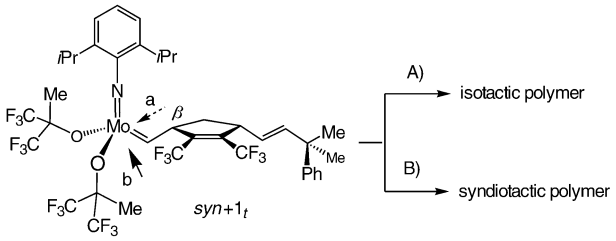
Figure 8. The four possible regular structures of 2,3-disubstituted norbornadienes and the effect of enantiomerically pure auxiliary R* (from reactions of **57b**) on the chemical environments of the inequivalent protons H_a and H_b; a) *cis*, isotactic (*cc*,*mm*), b) *cis*, syndiotactic (*cc*,*rr*), c) *trans*, syndiotactic (*tt*,*rr*), d) *trans*, isotactic (*tt*,*mm*).

norbornadiene (such as **57a** or **57b**). In a triad, which is a three-monomer unit within the polymer as shown in Figure 8, the central monomer unit in a *cis*, isotactic polymer is flanked by *cis* double bonds and a mirror plane relates the central unit



to the unit on each side. That is, the polymer has a *cc*,*mm* (*cis*,*cis*,*meso*,*meso*) structure at the triad level of analysis. Therefore, as shown in Figure 8, the *cis*, syndiotactic polymer has a *cc*,*rr* structure (*cis*,*cis*,*racemic*,*racemic*).

The *all-trans* product derived from polymerization of $NBDF_6$ catalyzed by Mo complex **3a** is highly tactic (according to ^{13}C NMR spectroscopy; see below).[124] In contrast, the high *cis* polymer obtained from the reaction of $NBDF_6$ with **3d** (G = *t*Bu) has been shown to be biased toward one tacticity (≈75%, ^{13}C NMR spectroscopy). Any tacticity control under either set of conditions must arise through chain-end control. That is, the chirality of the β carbon atom in the first insertion product determines which diastereotopic face of the M=C bond is approached by the next equivalent of monomer. As summarized in Scheme 18, if the same CNO face is approached in each step in the polymerization process, an isotactic polymer is formed. If alternating CNO faces are approached in each step in the polymerization process, then a syndiotactic polymer is generated. If monomers add randomly to diastereotopic CNO faces then there is no stereocontrol and an atactic polymer results.



Scheme 18. Approach from the two diastereotopic faces of a chiral alkylidene intermediate determines the tacticity of the polymer product. A) monomer approaches one CNO diastereoface (a or b) in each step, B) monomer approaches alternating CNO diastereofaces a and b.

The tacticity of *all-cis*- or *all-trans*-poly($NBDF_6$) is determined by evaluating the C(7) resonance(s) in ^{13}C NMR spectra.[21] As shown in Figure 9a the C(7) resonance in the *all-cis* polymer prepared by treatment of $NBDF_6$ with achiral Mo complex **3d** (G = CMe_2Ph) was found to consist of three resonances at δ = 38.4, 37.6, and 36.5 ppm, with the dominant one being at 38.4 ppm. In atactic, *all-cis* poly($NBDF_6$), the resonances at δ = 38.4, 37.6, and 36.5 ppm would be found in a 1:2:1 ratio, since the center resonance can be ascribed to the C(7) resonance in a *cis*,*cis*,*meso*,*racemic* (*cc*,*mr*) triad. Therefore, the polymer whose C(7) resonance is shown in Figure 9a is biased toward one tacticity that gives rise to the C(7) resonance at approximately δ = 38.4 ppm. However, the tacticities that give rise to C(7) resonances at δ = 38.4 and 36.5 ppm (*cc*,*mm* = isotactic or *cc*,*rr* = syndiotactic; Figure 8) cannot be assigned a priori.

3.2.2. *Chiral Catalysts and Stereochemical Induction by Metal-Complex Asymmetry*

A potential disadvantage of chain-end control is that an error in a tactic polymer can control the next insertion. Such an error is said to be propagated (not corrected). In contrast, the asymmetric nature of a chiral catalyst may control the stereochemistry of monomer addition more efficiently compared to a chiral β carbon atom in a chain-end (Scheme 18), and higher tacticity polymers would be expected. If a chiral metal complex forces the monomer to add to the same CNO face in each ROMP step, an isotactic polymer will be formed.

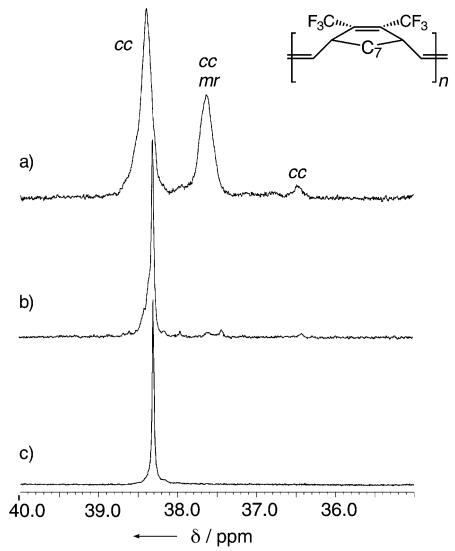


Figure 9. The C(7) resonance(s) in the ^{13}C NMR spectra of *cis* polymers obtained from reactions of $NBDF_6$, where molybdenum-based complexes **3d** (G = CMe_2Ph); spectrum a), **11o** (spectrum b), and **12g** (spectrum c) are used as the catalyst. (*cc mr* = *cis*,*cis*,*meso*,*racemic*; see text for explanation.)

Molybdenum-based complexes **11d**, **11m**, **11n** (enantiomerically pure), and **12g** were employed to examine the control of polymer tacticity by a chiral catalyst (see Figure 3 and Figure 4).[16,21] Except for **11d**, all the other Mo catalysts were obtained and used as their THF-coordinated complexes. The *all-cis* polymers obtained from polymerization of $NBDF_6$ catalyzed by complex **11o** (Figure 9, spectrum b) or especially **12g** (Figure 9, spectrum c) were found to be highly tactic (>99%), with only the δ = 38.4 ppm resonance being visible. The results shown in spectrum c of Figure 9 are particularly striking compared to the low tacticity of the polymer product obtained by chain-end control from reaction of $NBDF_6$ in the presence of **3d** (G = CMe_2Ph) as the catalyst (Figure 9, spectrum a). When **11m** is employed as the catalyst (wherein the N-2,6-$Me_2C_6H_3$ imido ligand of **12g** is replaced with N-2,6-$i Pr_2C_6H_3$), the resulting polymer contains ≈25% *trans* olefins, and therefore is highly irregular with a complex and broad set of resonances (not shown) for C(7). It is likely that additional steric crowding in the *syn* alkylidene isomer of the more sterically hindered **11m** shifts some chain propagation to the *anti* isomer, which promotes the generation of *trans* alkenes. Surprisingly, with biphenolate **11d**, which is used as a base-free complex and bears a ligand that is achiral in its metal-free form, *cis*, tactic poly($NBDF_6$) is again obtained. One would expect that a chiral catalyst encourages monomer addition to the same diastereotopic CNO face and therefore promotes the formation of an isotactic polymer. Therefore

one would expect the $\delta = 38.4$ ppm resonance to be due to *all-cis*-poly($NBDF_6$). However, it is not feasible to prove the tacticity of the *all-cis*, tactic poly($NBDF_6$) made from **12g**, or the *all-trans*, tactic poly($NBDF_6$) made from **3a** (see Section 3.2.1.)

It would be possible to demonstrate the tacticity of *all-cis* or *all-trans* tactic polymers if they were to contain an enantiomerically pure group (R* in Figure 8) in place of the trifluoromethyl group. Fortunately, 2,3-dicarboalkoxynorbornadienes **57a** and **57b** (which contain the required enantiomerically pure group) can be polymerized to give *all-trans*, tactic polymers with catalyst **3a**, and *all-cis*, tactic polymers with **12g**; their ^{13}C NMR spectra are analogous to those discussed for poly($NBDF_6$). As in the case of poly($NBDF_6$) samples, the olefinic region of the ^1H NMR spectra of *all-cis*, tactic poly(**57a**) is sharp and well-resolved. This circumstance made it possible to determine tacticity through analysis of the ^1H NMR spectra of poly(**57b**). Thus, as shown in Figure 8, the two inequivalent olefinic protons (H_a and H_b) in the four regular structures are bound to adjacent olefinic carbon atoms in isotactic, but not syndiotactic, polymers. Therefore, if two olefinic resonances are observed and if the two olefinic protons are coupled, the polymer is isotactic; if the protons are not coupled, the polymer is syndiotactic. As illustrated in Figure 10, the COSY spectra for a product obtained by

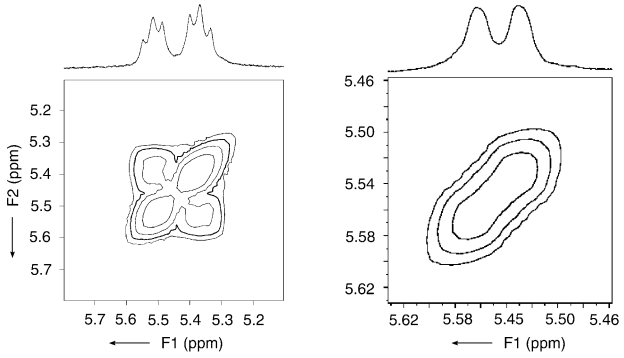


Figure 10. The olefinic regions of the 300 MHz homonuclear COSY NMR spectra of *all-cis*, isotactic (left) and *all-trans*, syndiotactic (right) polymers obtained from polymerization of **57b** ($CDCl_3$ at 25 °C) with **12g** and **3a** as the catalysts, respectively.

polymerization of **57b** show that the olefinic protons are coupled in the *cis* (prepared with **12g** as the catalyst), and not in the *trans* polymer (prepared with **3a** as the catalyst). These findings are consistent with *all-cis*, isotactic polymer being generated through enantiomorphic site control imposed by chiral Mo complex **12g** and *all-trans*, syndiotactic polymer being formed by chain-end control in the presence of **3a**. Although it is not possible to demonstrate the tacticity of *trans* and *cis* poly($NBDF_6$), it seems likely that they are also syndiotactic and isotactic, respectively.

4. Achiral Molybdenum-Based Olefin-Metathesis Catalysts in Stereoselective Synthesis

Only a few years ago incorporation of a transformation involving olefin metathesis in a total synthesis scheme was viewed as a daring application of an interesting but unproven process. Today, metathesis-based approaches, particularly ring-closing metathesis (RCM), are employed with such regularity that their use in a large number of contexts is considered routine.[1–4] In this section, we provide an overview of the use of achiral molybdenum-based complex **3d** in modern organic synthesis. In instances where the use of ruthenium-based catalysts **58**[127] (shown in Figure 11) has also been explored, comparative data are presented.

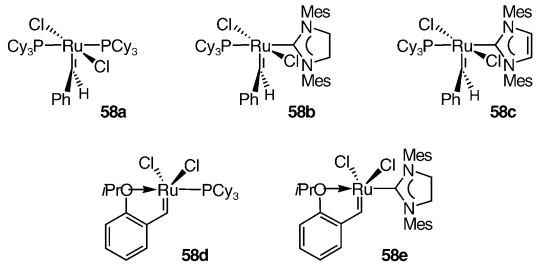
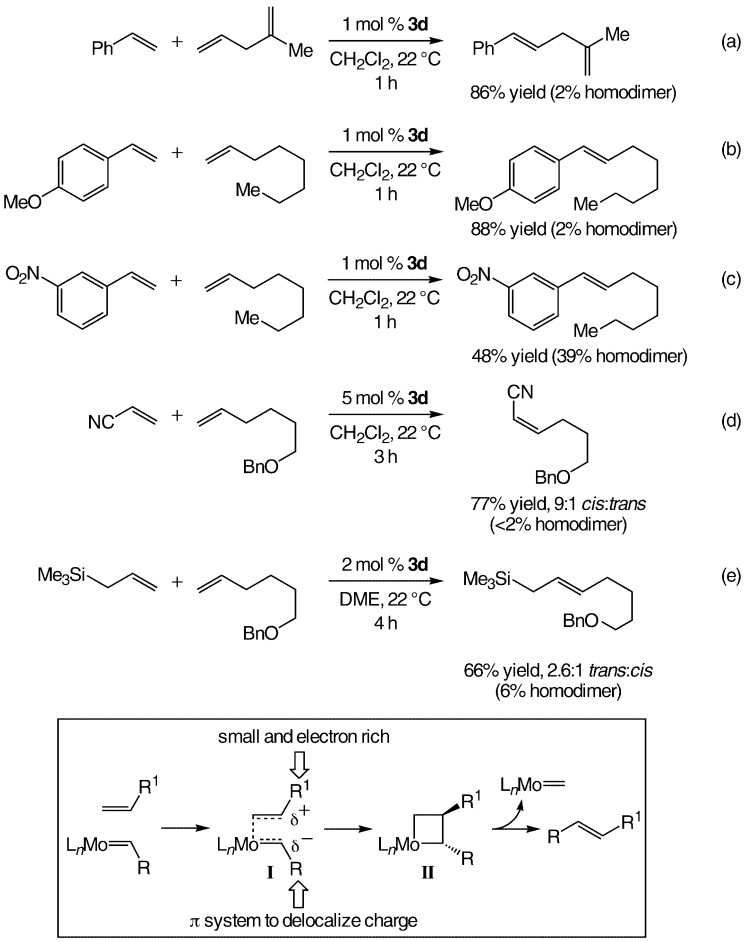


Figure 11. Achiral ruthenium-based olefin-metathesis catalysts. Mes = 2,4,6-$Me_3C_6H_2$.

4.1. Molybdenum-Catalyzed Cross-Metathesis Reactions

One of the earlier applications of Mo catalysts was reported by Crowe and Zhang in 1993 in the context of stereoselective cross metathesis (CM).[111] As the examples in Scheme 19 illustrate [Eq. (a)–(c)], styrenes and terminal aliphatic alkenes undergo CM promoted by Mo complex **3d** (G = CMe_2Ph). Transformations proceed with varying efficiency, depending on the electronic attributes of the aryl olefin. The electron-rich alkene in Equation (b) of Scheme 19 delivers a significantly higher yield of the desired CM product than the electron-poor nitrostyrene [Eq. (c)], with which nearly 40% homodimer is generated. Based on these and additional data, Crowe and Goldberg proposed a model for the molybdenum-catalyzed CM (Scheme 19, bottom).[112] It was suggested that reactions are more efficient when one olefin partner bears a substituent that stabilizes the partial negative charge at the carbon atom of the Mo alkylidene and the other olefin has an electron-donating substituent that can stabilize the developing electron deficiency at the β carbon atom of the incipient metallacyclobutane. The ability of acrylonitrile to participate effectively in molybdenum-catalyzed CM is consistent with this postulate [Eq. (d), Scheme 19]. However, subsequent studies provided instances that cannot be rationalized by the mechanistic picture in Scheme 19; one such case is the efficient catalytic CM between allylsilane and terminal alkenes [Eq. (e) of Scheme 19].[113,128]



Scheme 19. Top: Molybdenum complex **3d** used in some the first examples of efficient catalytic and stereoselective cross metathesis, bottom: proposed molybdenum-catalyzed cross-metathesis mechanism.

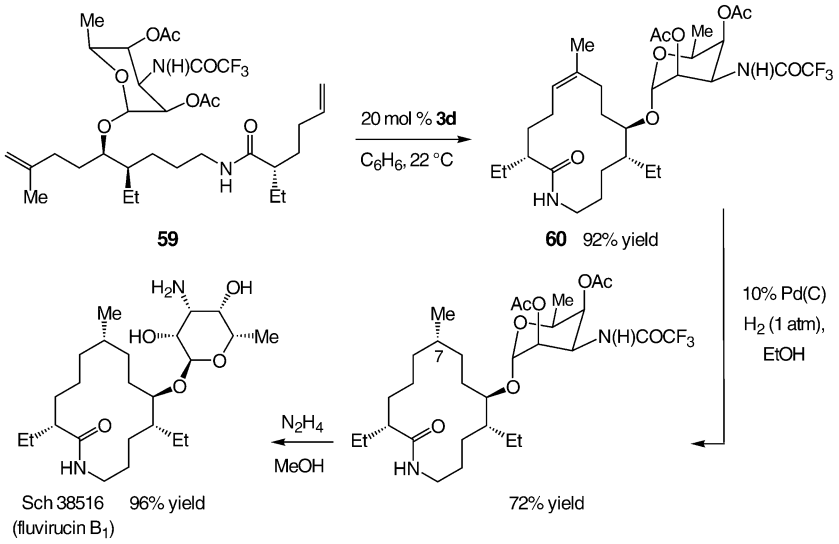
Molybdenum-catalyzed CM was later used by Barrett and co-workers to access optically pure *trans*-disubstituted homoallylic ethers, where the requisite terminal homoallylic alcohol was prepared through enantioselective allylation of aldehydes by an optically pure allylboronate.[129] These researchers later illustrated that, in contrast to ruthenium-based catalyst **58a**, complex **3d** (G = CMe2Ph) does not effect CM reactions with allenes.[130]

4.2. Molybdenum-Catalyzed Ring-Closing Metathesis (RCM) Reactions

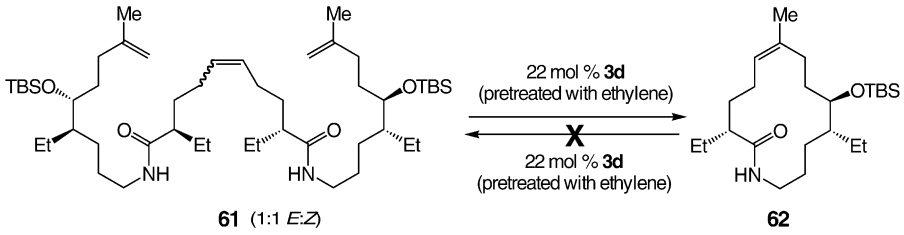
4.2.1. Synthesis of Macrocycles by Molybdenum-Catalyzed RCM

In 1995, in the context of the enantioselective total synthesis of fluvirucin B_1 (or Sch 38516), an efficient molybdenum-catalyzed ring-closing metathesis (RCM) leading to the formation of the desired fourteen-membered lactam was reported (Scheme 20).[131] The catalytic ring closure of fully functionalized diene **59** to afford macrocycle **60** was effected in 92% yield.[132] Facile formation of **60** illustrated that Mo complex **3d** can be employed to prepare macrocyclic structures in the presence of a variety of Lewis basic functional groups. The stereoselective formation of the trisubstituted olefin (> 95% *Z*) proved critical, as the subsequent catalytic hydrogenation of the alkene could then be used to establish the remote C7 stereochemistry (> 98% *de*).

Subsequent studies[133] demonstrated that efficient generation of the fourteen-membered macrolactam and the absence of homodimeric products is probably the result of the reversible nature of metal-catalyzed metathesis.[134] As depicted in Equation (4) (where TBS = *t*BuMe$_2$Si) treatment of homodimeric triene **61** (1:1 *E*:*Z*, obtained from reaction of monomer with Ru catalyst **58a**) with 22 mol% **3d** (G = CMe$_2$Ph) in the presence of ethylene led to the formation of macrolactam **62**. Ethylene was used to ensure exact reaction conditions through generation of the corresponding molybdenum methylidene complex. Furthermore, subjection of **62** to the above conditions did not deliver any monomeric or homodimeric adducts, which suggests that stereoselective olefin formation is kinetically controlled and not a result of a thermodynamic preference for the *Z* alkene. Follow-up investigations showed that conformational preorganization imposed by stereogenic centers in **59** or **61** (1:1 *E*:*Z*) is critical to the efficiency of the catalytic RCM. Removal of stereogenic sites resulted in substantial amounts of homodimers. It would be intriguing to establish the effectiveness of some of the more reactive and



Scheme 20. A key step in the total synthesis of fluvirucin B_1 is the molybdenum-catalyzed RCM that forms a trisubstituted olefin **60** with > 98% *Z* selectivity and generates a fourteen-membered cyclic lactam.

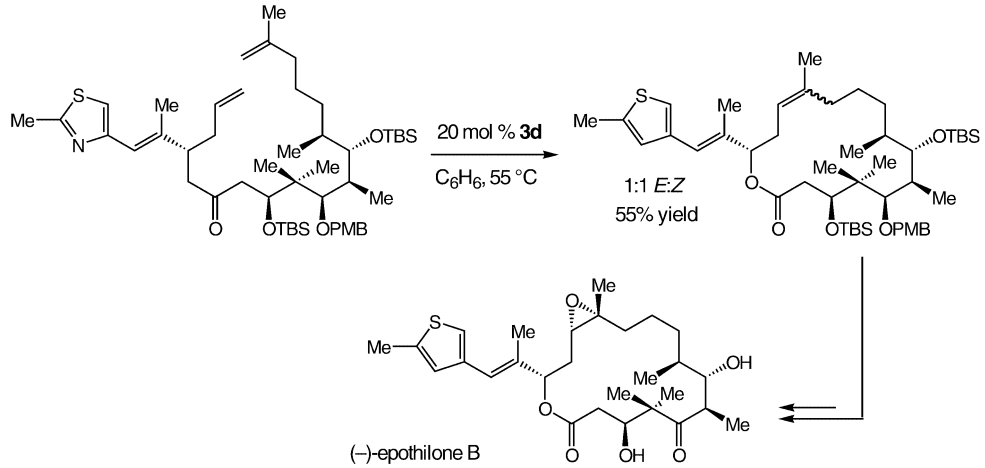


(4)

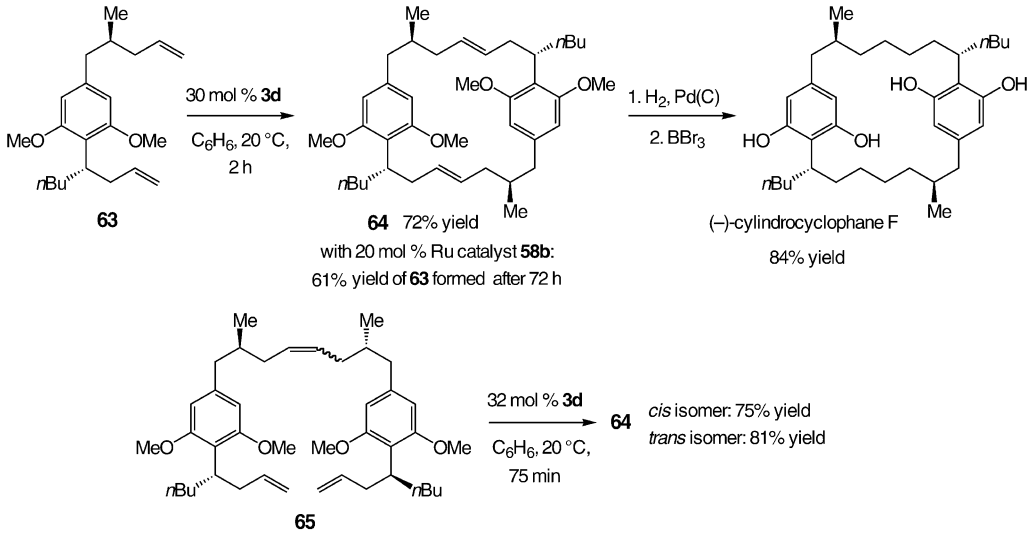
recently developed Ru-based catalysts, such as **58b–d** (Figure 11), in promoting the formation of such trisubstituted cyclic olefins. In general, the same question can be posed in connection to a number of olefin-metathesis processes discussed below.

A more recent molybdenum-catalyzed RCM reaction, where the target is a trisubstituted olefin within a macrolactone olefin, was reported in 1998 in the context of the total synthesis of (−)-epothilone B.[135] As illustrated in Scheme 21, in the presence of 20 mol% **3d** (Figure 2, $G = CMe_2Ph$), the desired product was generated in 55% yield. Unlike the fluvirucin B_1 synthesis, a mixture of *E* and *Z* isomers (1:1) was produced (separated through chromatography on silica gel). Subsequent functional-group manipulations, including oxidation of the appropriate alkene isomer, led to the isolation of the target molecule.

Molybdenum-catalyzed metathesis reactions have been investigated by Smith and co-workers in the context of the total syntheses of (−)-cylindrocyclophanes A and F.[136] Through a tandem molybdenum-catalyzed CM/RCM, as depicted in Scheme 22, acyclic diene **63** is converted into



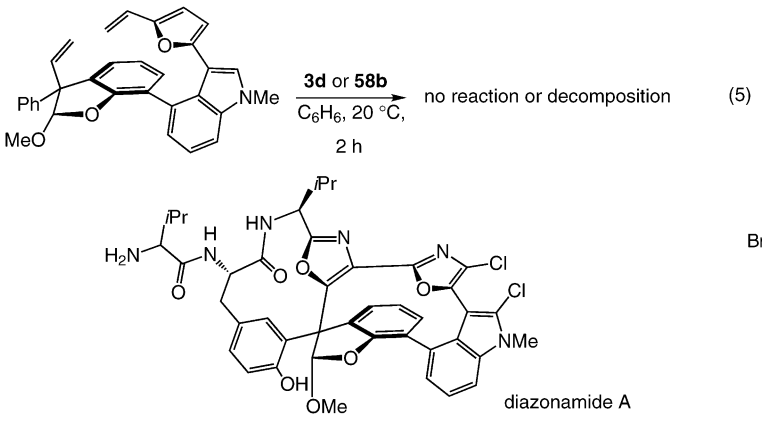
Scheme 21. Molybdenum-catalyzed RCM affords a macrocyclic lactone bearing the trisubstituted olefin used at a later stage to install the requisite epoxide in the total synthesis of (−)-epothilone B. PMB = *p*-methoxybenzyl.



Scheme 22. The molybdenum-catalyzed tandem CM/RCM reaction leads to a regioselective dimerization that serves as the foundation of a total synthesis of (−)-cylindrocyclophanes; control experiments indicate that the initial CM is reversible, which allows the predominant formation of the lower energy head-to-tail macrocycle.

macrocyclic diene **64** with complete regiocontrol (head-to-tail). The same transformation proved significantly less efficient with Ru catalyst **58b** (Figure 11). The reversible nature of alkene metathesis plays a critical role here as well. As shown by transformation of the head-to-head CM product **65** to **64**, the higher energy pathway required for the RCM of intermediates such as **65**, causes reversion to monomeric compounds.[137,138] Regeneration of the head-to-tail CM adduct and a facile RCM leads to the desired macrocycle.

In the above examples, where catalytic metathesis is used to prepare complex macrocycles, experimental evidence points to the influence of ring size and substrate stereochemistry in reaction efficiency. In this vein, it should be noted that, in the context of the total synthesis of diazonamide A, Nicolaou and co-workers attempted to effect the RCM transformation in Equation (5) with **3d** (Figure 2, G = CMe_2Ph), or various Ru-based catalysts to no avail. This lack of reactivity is likely to be a result of the ring strain associated with the desired target structure.[139]



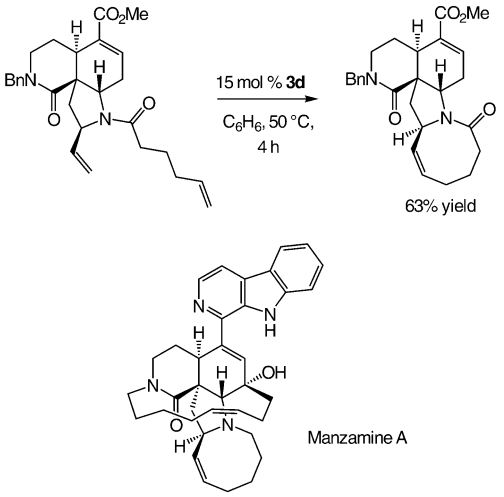
(5)

4.2.2. *Synthesis of Medium Rings by Molybdenum-Catalyzed RCM*

Since a considerable number of medicinally important agents bear seven- and eight-membered-ring carbo- and heterocycles, efficient and selective synthesis of medium rings has been, and remains, a long-standing goal in modern organic synthesis. In this arena also, molybdenum-catalyzed olefin metathesis has made a significant impact.

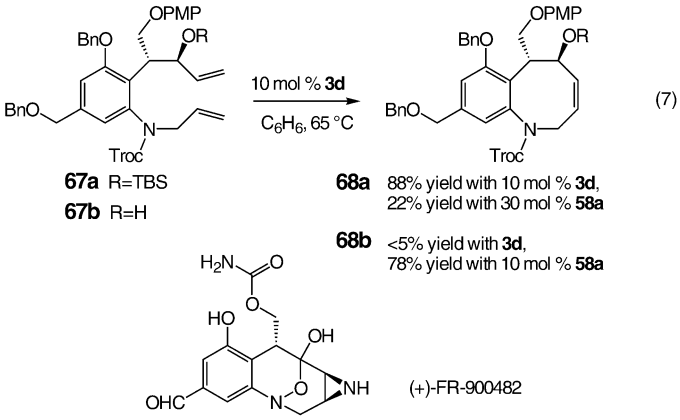
One of the earliest examples (1994) of the use of olefin metathesis to access a medium ring is the molybdenum-catalyzed transformations reported by Martin and co-workers. As depicted in Equation (6) (**3d** Figure 2, G = CMe_2Ph), synthesis of the desired tetracycle, including an eight-membered unsaturated amide proceeds in 63% yield.[140]

Another important early example, disclosed in the context of the total synthesis of antitumor antibiotic (+)-FR900482, is shown in Equation (7).[141] This study is noteworthy as it provides an early illustration of the complementarity of the molybdenum- and ruthenium-based catalysts. Catalytic RCM was effected by 10 mol% **3d** (Figure 2, G = CMe_2Ph), to afford **68a** in 88% yield. When Ru complex **58a** (Figure 11) was used (30 mol%), the desired product was generated in



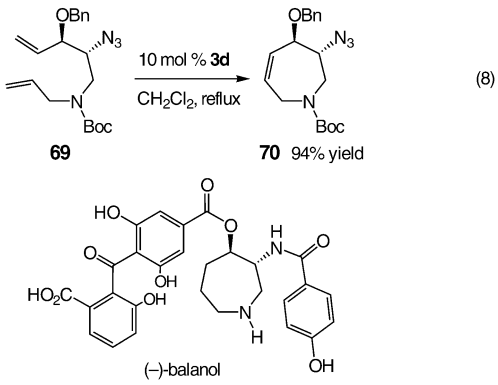
(6)

22% yield (48% recovered starting material). Mo complex **3d** (G = CMe_2Ph) cannot be used with substrates that bear sterically unprotected hydroxy units. However, reaction of the allylic alcohol **67b** was readily promoted by 10 mol% **58a** to provide **68b** in 78% yield. Bicyclic amide **68b** was subsequently utilized to complete the total synthesis.



(7)

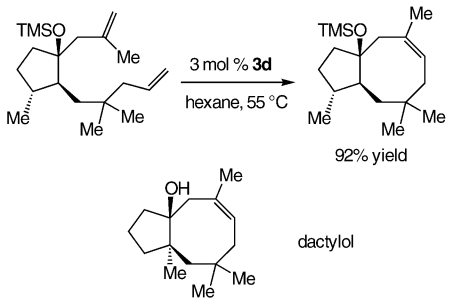
In the course of studies towards the total synthesis of balanol [Eq. (8); Boc = 1,1-dimethylethoxycarbonyl], RCM of diene **69** was effected at 70°C in the presence of Ru complex **58a** (Figure 11), to give a thermally induced non-metathesis product.[142] However, in the presence of 10 mol%



(8)

3d (refluxing CH_2Cl_2), the desired unsaturated seven-membered-ring amine **70** was isolated in 94% yield.

The formation of the trisubstituted olefin in Equation (9) was later disclosed to proceed in 92% yield in the presence of

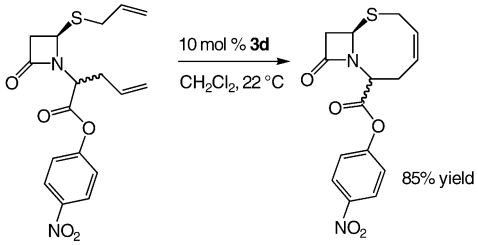


(9)

3 mol % **3d**.[143] The desired bicyclic adduct was subsequently transformed to the target sesquiterpene dactylol.

As depicted in Scheme 23, in the course of synthetic and structure determination of liverwort diterpenes (such as **73**), RCM of **71** was effected by Mo complex **3d** (Figure 2), leading to functionalized cycloheptene **72**. Since the same process was effected with 10 mol % **58a** (Figure 11), it is likely that such high loadings of **3d** are not necessary.[144] As also illustrated in Scheme 23, initial attempts to promote the RCM of the parent ketone was unsuccessful with catalysts **3d** and **58a**; Mo complex **3d** (Figure 2, $G = CMe_2Ph$) is usually incompatible with carbonyl groups[145] and the reaction of **58a** is probably retarded by coordination of the ruthenium carbene unit with the oxygen atom of the neighboring carbonyl group. In support of the latter hypothesis, in the presence of Lewis acidic $Ti(OiPr)_4$ and 30 mol % **58a** some of the desired product was obtained.[146,147]

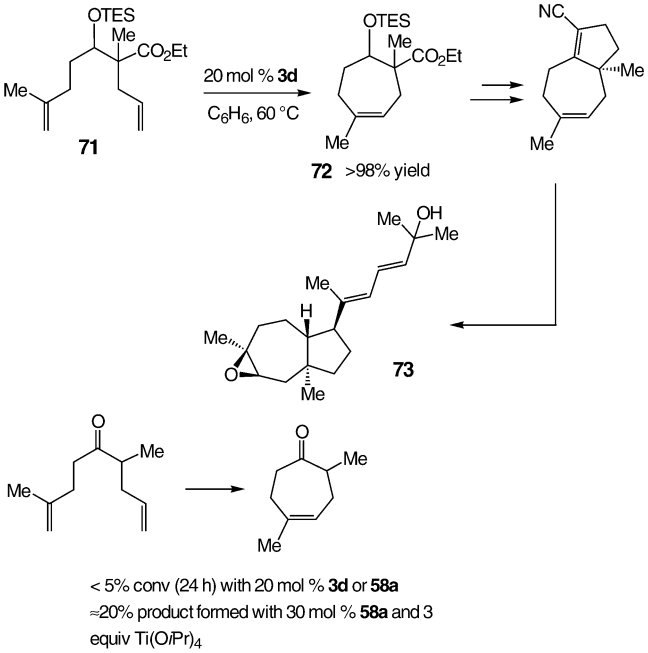
A variety of β-lactam carbocyclic esters have been synthesized by tandem Ireland–Claisen rearrangement/catalytic RCM methods. A notable advantage of molybdenum-based catalysts (versus Ru complexes) was demonstrated in the context of this investigation.[148] Thus, the sulfur-containing diene, shown in Equation (10), was readily converted into



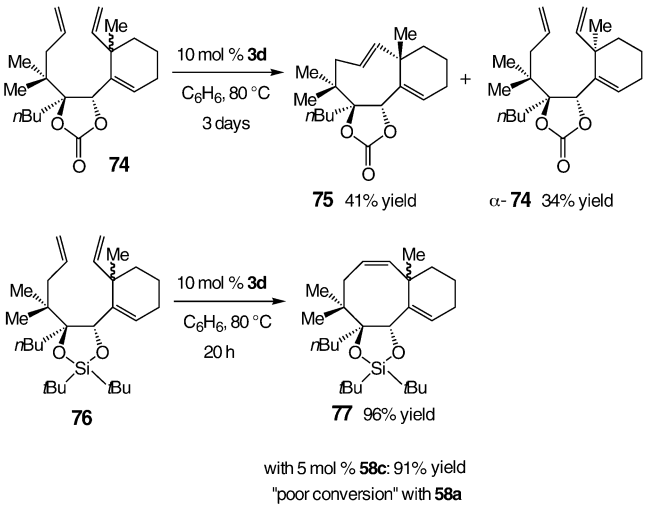
(10)

the desired cyclic product. In contrast, ruthenium-based catalyst **58a** (Figure 11) rapidly decomposes upon exposure to the same substrate.

More evidence regarding the influence of a substrate's stereochemical identity and its conformational properties on the facility of catalytic metathesis was provided in a study by Prunet and co-workers (Scheme 24).[149] Molybdenum-catalyzed RCM of a mixture of two diastereomers of **74** leads to the conversion of only one isomer to provide **75** and recovered α-**74**. Furthermore, it is the *trans* alkene that is generated preferentially; subsequent treatment of *trans*-**74** with **3d** (Figure 2, $G = CMe_2Ph$), and diallyl ether leads to the formation of the thermodynamically favored *cis* alkene through sequential ROM/RCM. The same RCM was effected by Ru complex **58a**, albeit at a slower rate (8 days vs. 3 days



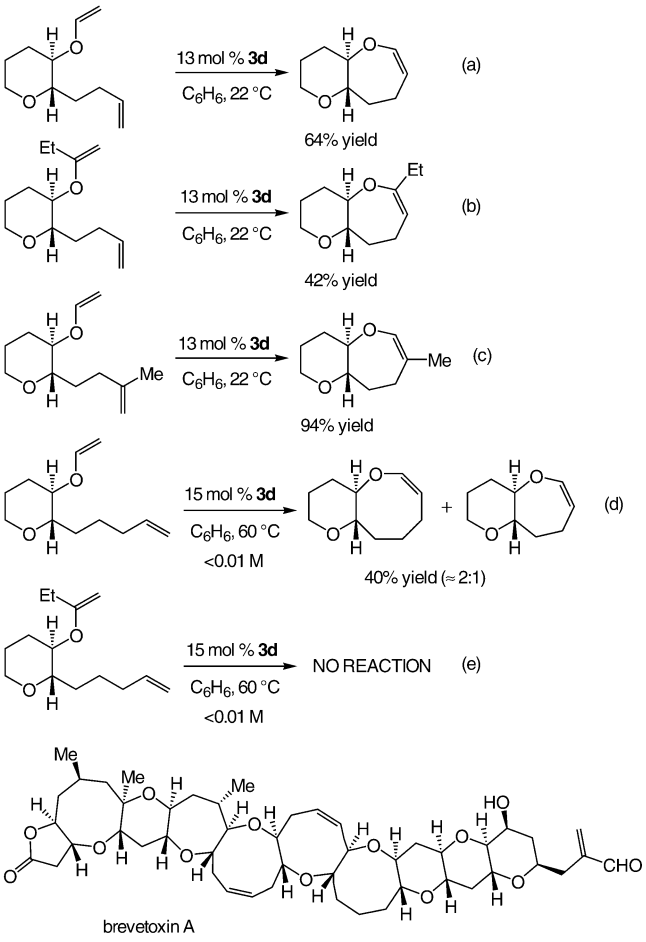
Scheme 23. Molybdenum-catalyzed RCM affords medium-ring carbocycles that can be used in the total synthesis of terpenes such as **73**; TES = Et_3Si.



Scheme 24. Functionalities within a substrate and conformational preferences can be critical to the outcome of RCM reactions that afford medium rings.

for **3d**). In contrast, when the cyclic carbonate of **74** was exchanged with a cyclic silyl ether (**76**, Scheme 24), the molybdenum-catalyzed RCM proceeded to completion to afford **77** in 96% yield;[150] Ru complex **58a** delivers "poor conversions," while the more active **58c** (Figure 11) affords **77** in 91% yield.

The discovery of medicinally significant and structurally complex molecules, such as marine neurotoxin brevetoxin A (Scheme 25), has given rise to a number of investigations aimed at the development of efficient syntheses of these polycyclic ethers. Given the remarkable ability of catalytic



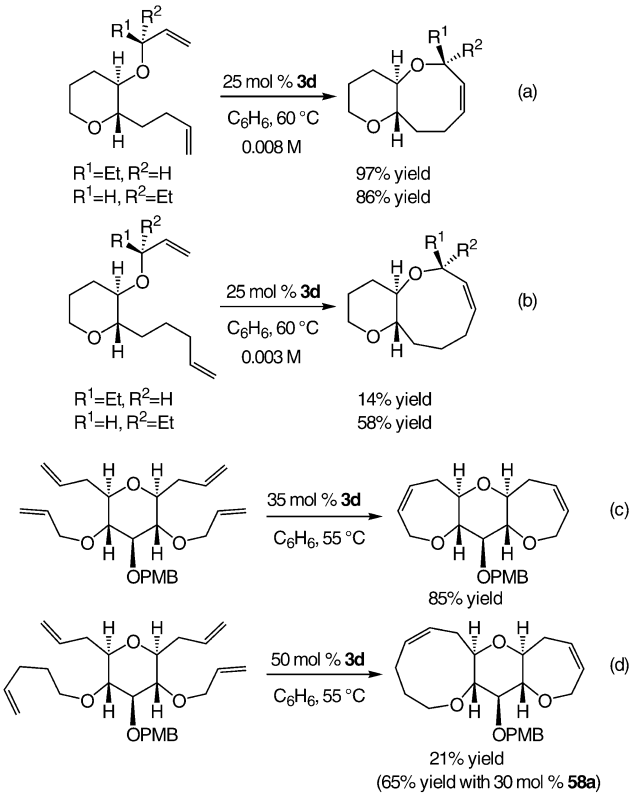
Scheme 25. Molybdenum-catalyzed RCM delivers medium-ring enol ethers that may be used as building blocks in the total synthesis of ichthyotoxins, such as brevetoxin A (**3d**, Figure 2, G = CMe_2Ph).

RCM in yielding medium rings that are otherwise difficult to access, it is not surprising that a number of key studies in this area are based on olefin metathesis.

Some of the more revealing disclosures in this connection are by Clark and Kettle.[151–153] As the results summarized in Scheme 25 indicate, seven- and some eight-membered cyclic enol ethers are accessible through molybdenum-catalyzed RCM. As reactions in Equations (a)–(c) of Scheme 25 illustrate, seven-membered ring enol ethers that bear di- and trisubstituted olefins were synthesized at ambient temperature with 13 mol% **3d**. The efficiency of RCM does vary depending on the substitution pattern of the substrate alkene and enol ether moieties. As illustrated in Equations (d) and (e) of Scheme 25, reactions that lead to eight-membered rings were less efficient; not only were higher dilution conditions required, significant amounts of a seven-membered-ring enol ether were generated as well [Eq. (d) in Scheme 25]. The latter complication presumably involves initial olefin isomerization to the disubstituted internal alkene,[154] followed by RCM.

RCM reactions involving enol ethers cannot typically be promoted by ruthenium-based catalysts. Recent strategies to access such structures through ruthenium-catalyzed RCM of allylic ethers followed by olefin isomerization, although effective in certain settings, may prove to be synthetically limited, particularly in light of mechanistic uncertainties regarding the nature of the isomerization catalyst. Moreover, the latter strategy imposes limitations regarding the presence of other olefin units that might also undergo adventitious isomerization or metathesis reactions.[155]

Related molybdenum-catalyzed RCM of allylic ethers have been outlined by Clark et al. as well (Scheme 26).[156,157] In these transformations, in contrast to the processes involving enol ethers (Scheme 25), eight-membered systems can be prepared efficiently [Eq. (a), Scheme 26]. The difference in the outcome between RCM of the two substrates in Equa-

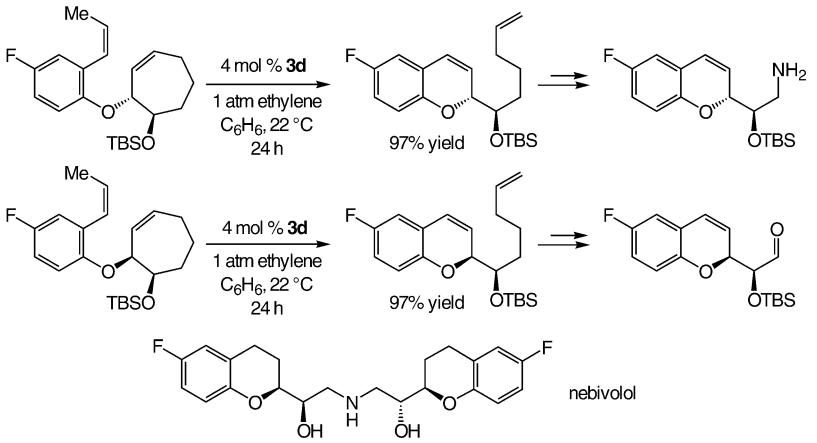


Scheme 26. Molybdenum-catalyzed RCM affords eight- and nine-membered-ring allylic ethers; reaction facility depends on the relative stereochemistry of substrate structures (**3d**, Figure 2, G = CMe_2Ph).

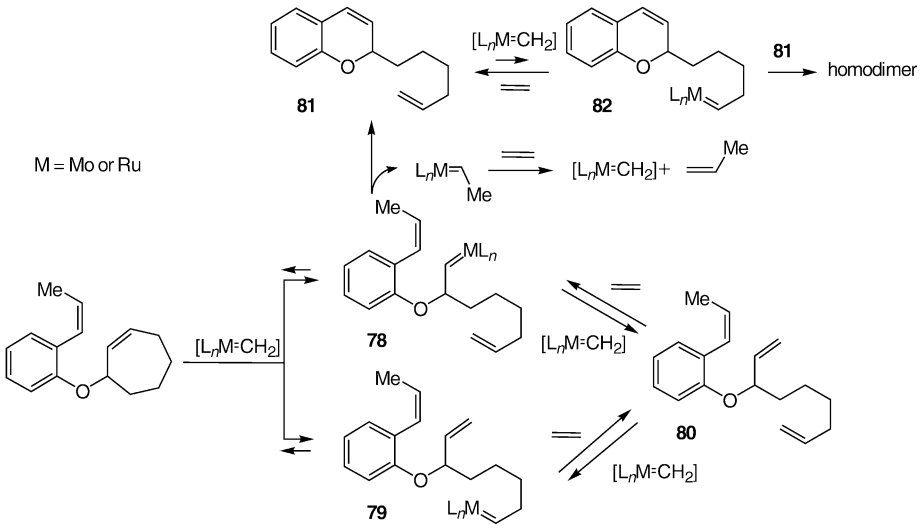
tion (b) of Scheme 26 provides another illustration of the significance of a substrate's stereochemical identity on reaction efficiency. Also noteworthy is the formation of the nine-membered ring [Eq. (d) of Scheme 26]; this product can be accessed more efficiently in the presence of Ru complex **58a**.

4.2.3. *Synthesis of Five- and Six-Membered Rings by Molybdenum-Catalyzed Metathesis*

Catalytic olefin metathesis has made a significant impact on methods for synthesis of five- and six-membered rings. As the examples below illustrate, the availability of Mo complex **3d** (Figure 2 G = CMe_2Ph) has led to the development of effective strategies that have allowed for unorthodox retrosynthetic analyses, which give rise to substantially more concise synthesis routes.In 1997, a catalytic conversion of various carbocyclic styrenyl ethers into the corresponding 2-substituted chromenes, building blocks found in a wide range of medicinally important agents, was reported (Scheme 27).[127f] These ring-opening/ring-closing metathesis (ROM/RCM) transformations proceed effectively with substrates bearing a terminal styrene with both **3d** and Ru catalyst **58a** (Figure 11). However, with disubstituted styrenes, such as those shown in Scheme 27, only **3d** is sufficiently reactive. It should be noted that disubstituted styrenes are required for effective zirconium-catalyzed kinetic resolutions[158,159] that deliver the requisite disubstituted styrenes in the optically pure form (terminal styrenes cannot be resolved by the same method). The tandem zirconium-catalyzed kinetic resolution/molybdenum-catalyzed ROM/RCM was subsequently employed in the enantioselective total synthesis of antihypertensive agent nebivolol.[160]



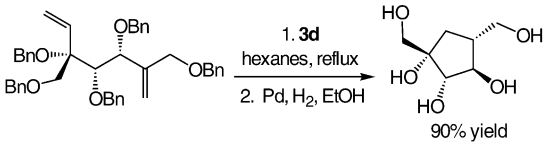
Scheme 27. Molybdenum-catalyzed ROM/CM used to prepare functionalized chromenes en route to the total synthesis of antihypertensive agent nebivolol (**3d**, Figure 2, G = CMe_2Ph).



Scheme 28. Reaction pathway for the molybdenum-catalyzed (or ruthenium-catalyzed) reactions of disubstituted styrenyl ethers in the presence of ethylene atmosphere.

In the course of the total synthesis of nebivolol, it was established that unless the ROM/CM reactions are carried out under an atmosphere of ethylene (with both Mo- and Ru-based catalysts), products would be obtained in low yield along with formation of significant amounts of homodimeric compounds. Mechanistic studies[127g] indicated that the presence of ethylene is critical to efficiency of metathesis reactions for three reasons: 1) Ethylene rapidly converts the initial metal complexes into the more reactive methylidene complexes ([$L_nMo{=}CH_2$] in Scheme 28), thus enhancing initiation rates. 2) Rapid reaction of the metal alkylidene derived from the terminal alkene of **82** (Scheme 28) with ethylene leads to minimization of dimerization products. 3) Since reactions have been shown to be initiated at the cycloalkene site (versus the styrene olefin) and such ROM processes are not likely to be regioselective (**78** and **79** in Scheme 28 are formed nonselectively), ethylene converts the "wrong" metal alkylidene **79** into an olefin **78** which can then be converted into the desired chromene. This simple but effective strategy has been subsequently adopted successfully in a number of other related studies.[161]

Molybdenum complex **3d** has been employed in the synthesis of highly functionalized smaller ring structures. One example is illustrated in Equation (11) (**3d**, catalyst loading

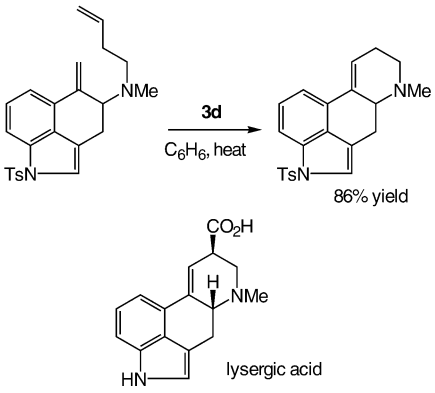


(11)

and reaction temperature not specified), where catalytic RCM occurs efficiently between a 1,1-disubstituted olefin and

a sterically hindered terminal alkene. The resulting product was subsequently transformed to a fructofuranose derivative.[162]

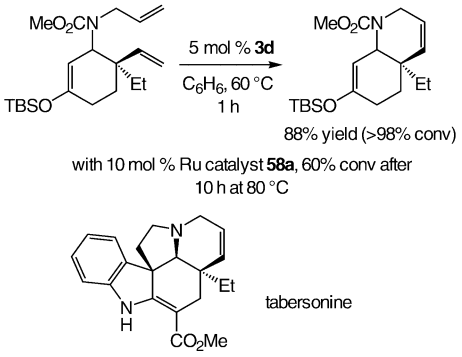
Molybdenum-based catalysts are tolerant of amine functional groups, as demonstrated in the transformation in Equation (12) (**3d** Figure 2, $G = CMe_2Ph$; catalyst loading



(12)

and reaction temperature not specified). These studies were disclosed by Martin and co-workers in the context of the total synthesis of the *ergot* alkaloid lysergic acid.[163] In contrast, use of the ruthenium-based catalyst **58a** provided "small quantities" of the desired product. (For studies regarding enantioselective olefin metathesis involving tertiary amines, see Section 5).

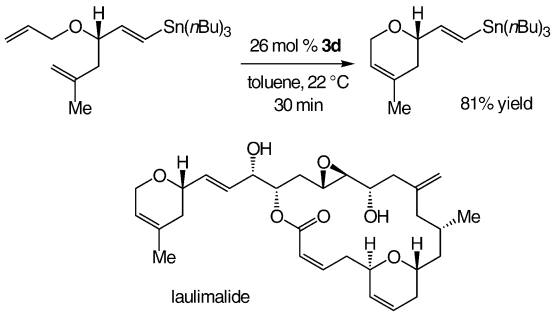
A trademark of molybdenum-based metathesis catalysts is their often unparalleled reactivity. One telling recent example is the RCM reaction reported by Rawal in the course of the total synthesis of tabersonine. As illustrated in Equation (13) (**3d** Figure 2, $G = CMe_2Ph$) an allylic amide



(13)

and a sterically encumbered terminal olefin adjacent to a quaternary carbon center undergo efficient ring-closure to deliver the desired compound.[164,165]

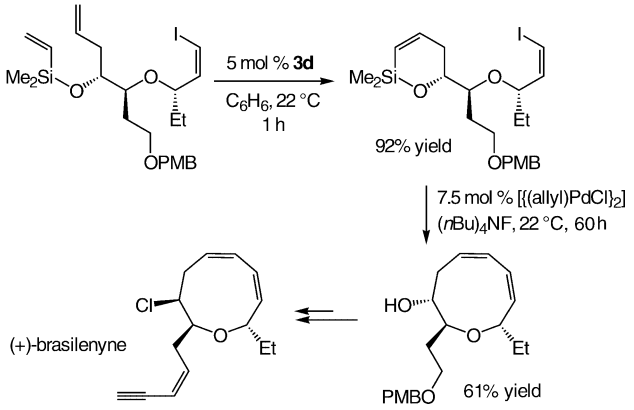
Although highly reactive, Mo complex **3d** can be used to promote site-selective transformations. A revealing example is shown in Equation 14, involving a regioselective process that excludes participation by the more hindered vinyl stannane.[166] The unreacted C–Sn bond was subsequently converted into the derived Grignard reagent and used by



(14)

Nelson et al. in a key diastereoselective C–C bond-forming reaction en route to the total synthesis of laulimalide.

Another site-selective molybdenum-catalyzed RCM has recently been reported by Denmark and Yang in the context of the total synthesis of antifeedant (+)-brasilenyne (Scheme 29).[167] The vinyl iodide moiety, used in the follow-

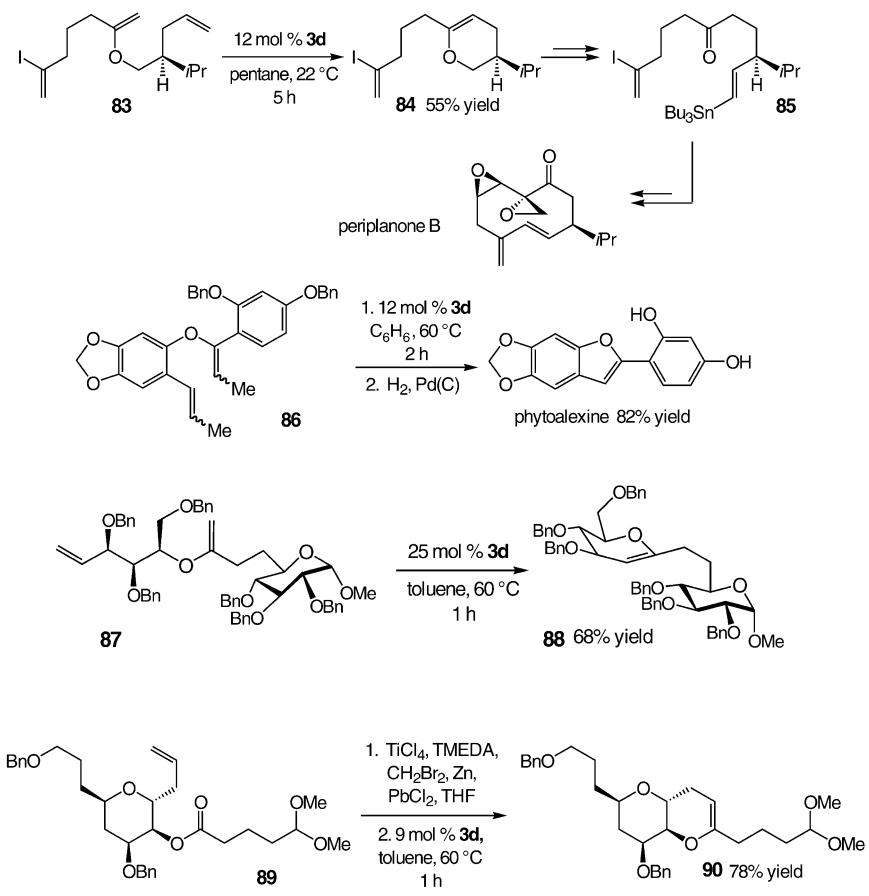


Scheme 29. Cyclic vinylsilane obtained from molybdenum-catalyzed RCM is used in a subsequent palladium-catalyzed intramolecular cross-coupling to afford a nine-membered-ring structure en route to the total synthesis of brasilenyne.

up palladium-catalyzed cross-coupling, does not participate in the catalytic RCM process.

A variety of small-ring enol ethers have been accessed through molybdenum-catalyzed RCM. Four examples are depicted in Scheme 30. The first instance involves the regioselective ring-closure of **83** to afford vinyl iodide **84** in the course of synthetic studies towards periplanone B.[168] Similar to the case in Scheme 29 or analogous to the vinyl stannane in Equation (14), the vinyl iodide moiety was later utilized to effect an intramolecular Stille coupling (via **85**). The molybdenum-catalyzed RCM involving **86** proceeds smoothly with two highly congested olefin partners to deliver phytoalexine.[169]

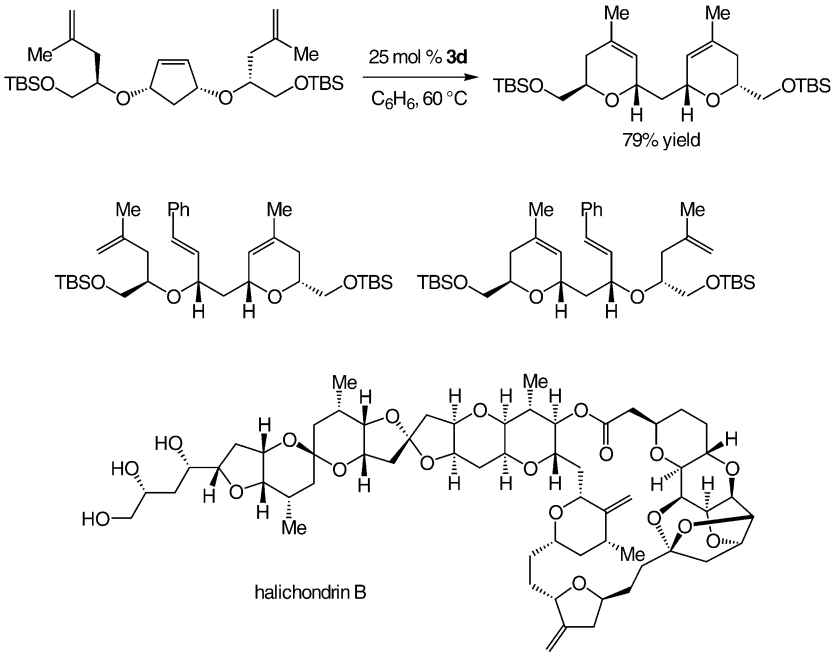
Another RCM transformation that underlines the unique reactivity and functional group compatibility of **3d** (Figure 2, $G = CMe_2Ph$) is the conversion of **87** into β-C-disaccharide **88**.[170–172] Note that formation of compounds such as **88** are inefficient with Ru catalyst **58a**. With the more reactive complexes **58b** or **58c** (see Figure 11) similar loadings are



Scheme 30. Molybdenum-catalyzed RCM can be used in target-oriented synthesis to access a variety of complex cyclic enol ethers; TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl 1,2-ethanediamine. Compound **88** is also formed with 25 mol% **58b** (added in portions under Ar).

required but catalysts must be added in portions (under Ar) to drive the reaction to completion. The last example shown in Scheme 30 (**89**→**90**) has been reported by Rainier et al. who has utilized catalytic RCM of highly functionalized enol ethers to access intermediates to be used in the total synthesis of brevitoxins.[173–175]

The molybdenum-catalyzed transformation illustrated in Scheme 31 is an efficient sequential ROM/RCM/RCM reported by Burke et al. as part of studies aimed at the total synthesis of halichondrin B.[176] Attempts to effect this transformation with Ru complex **58a** resulted in the formation of monopyrans shown in Scheme 31. These undesired compounds are likely derived from a ROM/RCM process, where the initial transformation deposits the benzylidene of the catalyst structure within the product. Addition of ethylene to circumvent the above complication proved unsuccessful.



Scheme 31. Molybdenum-catalyzed (**3d** Figure 2, G = CMe_2Ph) ROM/RCM provides access to bis(dihydropyran) structures that may be used as intermediates in the total synthesis of halichondrin B. With 25 mol% of Ru complex **58a** as the catalyst (80 °C, C_6H_6) the two byproducts shown in the middle of the scheme are formed in 21% yield.

5. Enantiomerically Pure Chiral Molybdenum-Based Olefin-Metathesis Catalysts in Asymmetric Synthesis

With regard to the synthesis of optically pure materials, catalytic olefin metathesis has generally served a supporting role. In cases where RCM is required, as the examples discussed in Section 4 illustrate, an already optically pure diene is treated with an achiral metal catalyst so that a nonracemic product is isolated (e.g., Scheme 20, Scheme 21, Scheme 22). Alternatively, there are examples where optically enriched cyclic alkenes are employed in instances where ROM is needed (e.g., Scheme 27). Although such strategies have led to noteworthy accomplishments, there are several unique attributes of olefin metathesis that can only be realized with chiral optically pure catalysts.

One of the most useful characteristics of metathesis reactions is their ability to promote skeletal rearrangements, where simple achiral substrates are transformed into more complex chiral molecules. As will be seen below, in numerous instances, products that are rendered available by a chiral

metathesis catalyst would only be accessible, and often less selectively, by a longer route if alternative synthetic methods were to be used.

5.1. The First Enantiomerically Pure Chiral Catalysts for Olefin Metathesis

As mentioned before (Section 3.2.2), the first enantiomerically pure chiral metathesis catalysts were molybdenum-based complexes **11 m**, **11 n**, and **12 g** (Figure 3 and Figure 4), which were synthesized to address tacticity control in ROMP processes.[16,21] The eventual application of such catalysts to enantioselective synthesis of small organic molecules was adumbrated in a statement that appeared in the 1993 publication that such chiral catalysts "could selectively …. ring close one enantiomer in a racemic mixture."[21]

The constitution of molybdenum-based catalysts, such as those shown in Figure 2, provides an attractive opportunity for development of chiral metathesis catalysts. In addition to their high activity, these complexes possess a modular structure involving imido and alkoxide moieties that do not dissociate from the metal center during the catalytic cycle. Structural alterations may therefore be implemented so that the desired effect on selectivity and reactivity is attained. As with the first chiral complexes mentioned above, alkoxide moieties offer an excellent opportunity for incorporation of chirality.

5.2. Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis (ARCM)

5.2.1. Catalytic Kinetic Resolution with a Chiral Hexafluoro Molybdenum Catalyst[177]

The preparation and utility of chiral complex **11p** (Figure 3) in kinetic resolution of various dienes was disclosed in 1996 by Grubbs and Fujimura.[178–180] As the case regarding the resolution of shown in Figure 12 indicates, levels of enantiodifferentiation proved to be low ($k_{rel} < 3$).

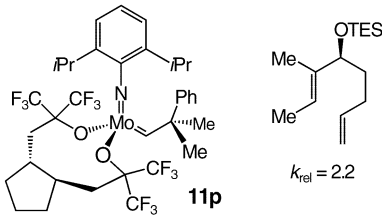


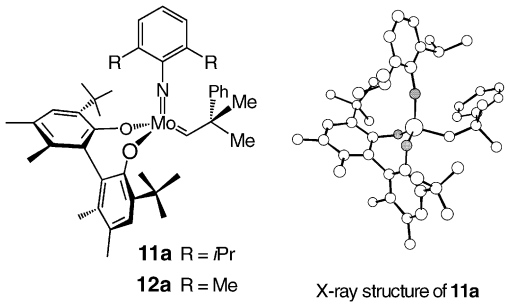
Figure 12. The first attempt at kinetic resolution through molybdenum-catalyzed ARCM.

5.2.2. The First Effective Chiral Metathesis Catalysts

During the past seven years, numerous chiral Mo catalysts and two chiral tungsten-based complexes (Figure 1, Figure 3, and Figure 4), have been developed for use in asymmetric RCM (ARCM).[181] As will be discussed below, the structural modularity of these chiral high-oxidation-state alkylidene complexes has proven critical to their potential utility in organic synthesis; preparation and screening of catalyst pools can thus be carried out,[182] so that optimal reactivity and selectivity levels are identified.

5.2.3. Chiral biphen Molybdenum Catalysts

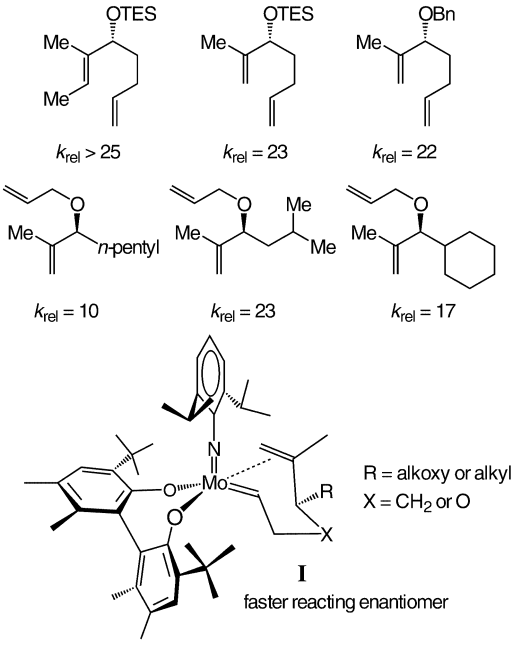
Enantiomerically pure chiral Mo complexes **11a** and **12a** were synthesized in 1997 and their ability to effect ARCM was probed.[14,183] It was established that these Mo catalysts



initiate olefin metathesis with excellent asymmetric induction owing to their rigidity and the sterically based differentiation imposed on the binding pocket of the chiral complex. Complexes **11a** and **12a** are orange solids and indefinitely stable when kept under an atmosphere of N_2.

5.2.4. Catalytic Kinetic Resolution by Molybdenum-Catalyzed ARCM

Catalytic kinetic resolution of various dienes through ARCM can be carried out efficiently at 22 °C in the presence of 5 mol % **11a**.[183] As the data in Scheme 32 illustrate, 1,6-



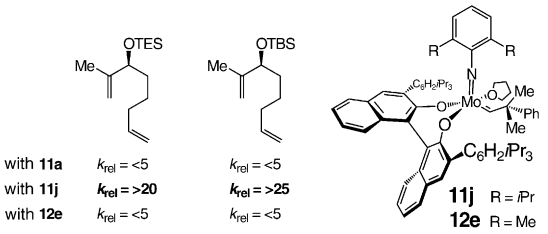
Scheme 32. Effective molybdenum-catalyzed kinetic resolution of 1,6-dienes through ARCM promoted by **11a**.

dienes[184] and allylic ethers[185] that afford five-membered-ring structures upon ring closure have been resolved with levels of enantioselectivity ($k_{rel} > 10$, see Scheme 32) that are superior to those observed with **11p** (see Figure 12).

The high levels of enantioselectivity attained with chiral Mo complex **11a** (vs. **11p**) are likely to be due to the intermediacy of the more reactive *anti* alkylidenes, such as **I** (Scheme 32; see Section 2.3.2 for reactivity of *syn* versus *anti* alkylidenes[104]). The stereochemistry of the metal–olefin complex arises from coordination of the Lewis basic olefin to the CNO face,[28] so that the olefinic π orbital can properly overlap with the molybdenum-centered LUMO (see Figure 5).[103] Moreover, this mode of olefin–metal association is consistent with the stereochemistry of coordination of various donor ligands with Mo complexes shown in Figures 6, 3, and 4 (see Section 2.3.3). The 1,1-disubstituted olefin thus interacts with the metal center while pointing away from the protruding diolate *t*Bu and the *i*Pr groups of the imido ligands.

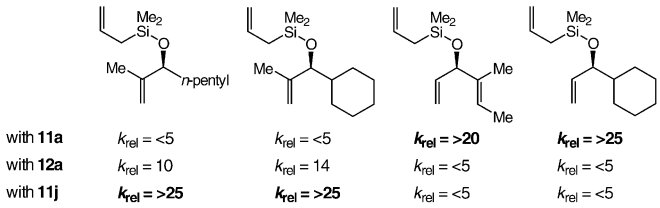
5.2.5. Modularity of Chiral Molybdenum Complexes and Optimization of Catalytic ARCM Reactions

In spite of the high enantioselectivity observed in the molybdenum-catalyzed ARCM of 1,6-dienes, when **11a** and **12a** are used in transformations involving 1,7-dienes, inferior asymmetric induction is obtained ($k_{rel} < 5$). Representative examples are shown in Scheme 33. To address this shortcoming, the modular character of the Mo complexes was exploited and a range of chiral complexes were synthesized and tested as catalysts. It was accordingly discovered (Scheme 33) that binol (2,2′-dihydroxy-1,1′-biphenyl) based complex **11j** promotes the RCM of 1,7-dienes with outstanding selectivity ($k_{rel} > 20$).[18] Binol-based catalyst **12e**, bearing the (dimethyl)phenylimido ligand, appears to be less efficient in promoting the resolution of this class of substrates.



Scheme 33. Molybdenum-catalyzed kinetic resolution of 1,7-dienes and the importance of structural modification of the chiral catalysts.

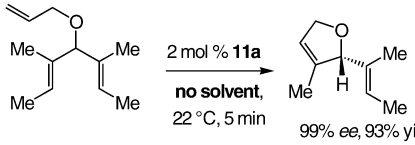
The above findings underline the significance of the availability of a diverse set of chiral catalysts. It should however be noted that, as the data in Scheme 34 illustrate, although binol-based complexes (e.g., **11j**) typically promote ARCM of 1,7-dienes with higher selectivity than the biphen-based catalysts (e.g., **11a**), such a trend does not always hold. Thus, each catalyst may not be optimal in every instance, but efficient resolution of a wide range of chiral oxygenated 1,6- and 1,7-dienes can be achieved once the appropriate catalyst, from a small set of two to four possibilities, is identified.



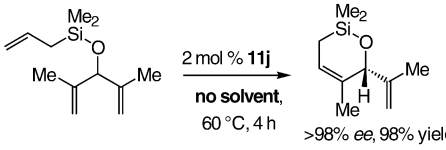
Scheme 34. Small structural changes within the substrate structure can alter the identity of the optimum chiral Mo catalyst.

5.2.6. Enantioselective Synthesis of Small Rings without use of Solvents: Molybdenum-Catalyzed Enantioselective Desymmetrization

The arena in which catalytic asymmetric olefin metathesis can have a significant impact on organic synthesis is the desymmetrization of achiral molecules. Formation of the unsaturated furan in Equation (15) is promoted with 5 mol% **11a** in 99% *ee* and 93% yield;[185] the reaction is complete within five minutes at 22 °C and can be carried out without solvent. As the example in Equation (16) illustrates, enantioselective synthesis of unsaturated six-membered-ring heterocycles is catalyzed by **11j** with exceptional efficiency and selectivity and, again, without need for solvents.[186] Moreover, although 5 mol% catalyst is typically used, 1–2 mol% loading often delivers equally efficient and selective transformations. It must be noted that the ARCM reaction in Equation (15) is less efficient with **11j** (< 5% conversion in 18 h). With **11a** as the catalyst, the transformation in Equation (16) proceeds only to 50% conversion in 24 h to afford the desired siloxane in only 65% *ee*. In the latter transformation, even in a 0.1 M solution, the major product is that formed through homometathesis of the terminal alkenes. The lack of homodimer generation when **11j** is used as the catalyst, particularly in the absence of solvent, bears testimony to the remarkable degree of catalyst–substrate specificity in these asymmetric transformations. Finally, it has been reported recently that chiral tungsten-based catalysts **1h** and **2h** (see Figure 1) promote the reactions shown in Equations (15) and (16) with yields and enantioselectivities similar to the analogous molybdenum-based catalysts.[9]

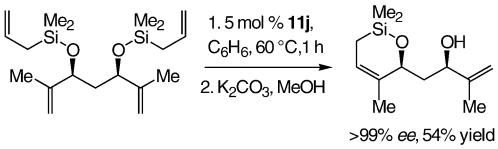


(15)



(16)

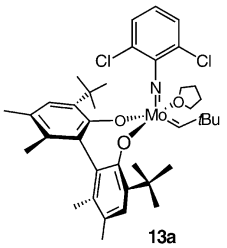
The catalytic desymmetrization depicted in Equation (17) involves ARCM of a *meso*-tetraene.[24] The unaffected siloxy

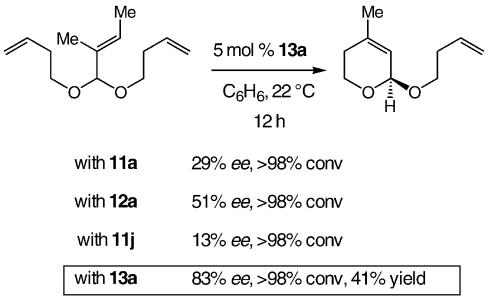


(17)

ether moiety can be subsequently removed to deliver the derived carbinol. In this enantioselective desymmetrization, alkylidenes of both enantiotopic terminal alkenes are likely to be generated. Since alkylidene formation is reversible, the major product arises from the rapid RCM of the "matched" segment of the tetraene. If any of the "mismatched" RCM takes place, a subsequent and more facile matched RCM leads to the formation of the *meso*-bicyclized product. Such a byproduct is absent from the unpurified mixture, which highlights the exceptionally high degree of stereodifferentiation induced by the chiral catalyst. As before, in contrast to **11j**, Mo complex **11a** is ineffective in facilitating the ARCM depicted in Equation (17).

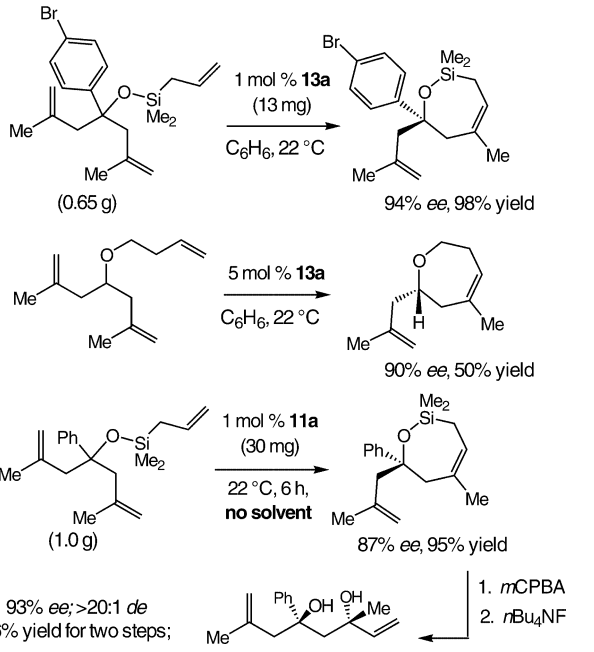
Incorporation of electron-withdrawing groups within either the imido or diolate moieties of a chiral Mo complex can result in enhanced Lewis acidity of the metal center and higher catalyst activity. As the examples in Scheme 35 outline,





Scheme 35. Chiral complex **13a** is the catalyst of choice for asymmetric synthesis of acetals.

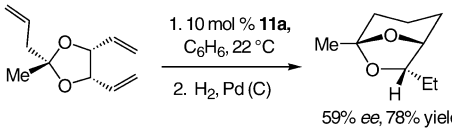
such structural modifications can have an effect on enantioselectivity as well. In the desymmetrization of the acetal substrate in Scheme 36, dichlorophenylimido complex **13a** provides higher asymmetric induction than the biphen- or binol-based catalysts that carry 2,6-dialkylphenylimido ligands (e.g., **11a** and **11j**). Note that cyclic unsaturated



Scheme 36. Molybdenum-catalyzed tandem ARCM can be used to synthesize enantioenriched seven-membered heterocycles in a practical and efficient manner; *m*CPBA = *m*-chloro peroxybenzoic acid.

acetals of this type retain their stereochemical integrity through various laboratory operations (such as chromatography on silica gel) and can be functionalized to deliver a range of chiral nonracemic functionalized heterocycles.

Molybdenum-catalyzed ARCM has been utilized by Burke et al. in a brief and enantioselective total synthesis of *endo*-brevicomin [Eq. (18)]; the key step is a catalytic



(18)

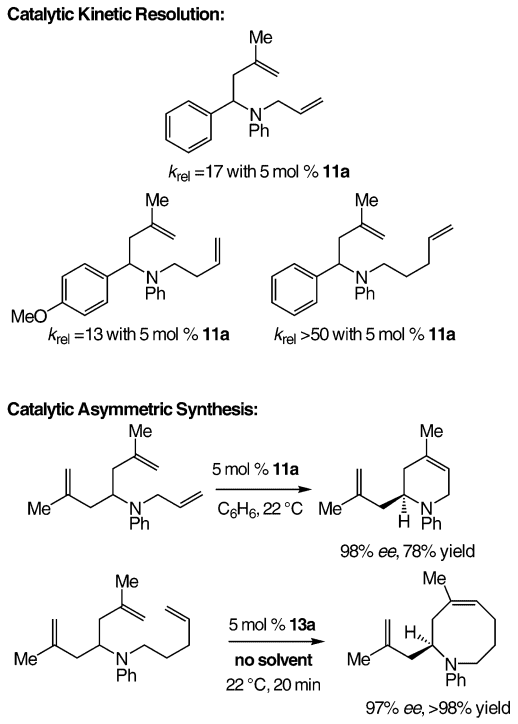
enantioselective desymmetrization of a triene.[187] It is possible that screening of additional molybdenum-based catalysts, unavailable at the time of this study, could lead to significantly higher asymmetric induction.

5.2.7. *Enantioselective Synthesis of Medium-Ring Ethers; Use of Solvent not Required*

As the examples in Scheme 36 (see also Scheme 37) indicate, molybdenum-catalyzed ARCM has been applied to the enantioselective synthesis of medium ring heterocycles.[188] These processes are effected efficiently in preparative scale, at low catalyst loading and without use of solvent. Moreover, as the last example in Scheme 36 illustrates, the optically enriched siloxanes obtained by molybdenum-catalyzed ARCM can be stereoselectively functionalized to afford compounds that are otherwise difficult to synthesize.

5.2.8. Enantioselective Synthesis of Acyclic and Small- and Medium-Ring Amines; Use of Solvent not Required

The functional group tolerance of chiral molybdenum-based catalysts is underlined in ARCM reactions illustrated in Scheme 37. Acyclic and cyclic tertiary amines are synthesized with high enantiopurity through catalytic kinetic resolution or asymmetric synthesis.[189] The facility and selectivity with which medium-ring unsaturated amines are obtained is noteworthy. Catalytic enantioselective synthesis of the eight-membered-ring amine (Scheme 37) proceeds efficiently, with excellent enantioselectivity and in the absence of solvent.



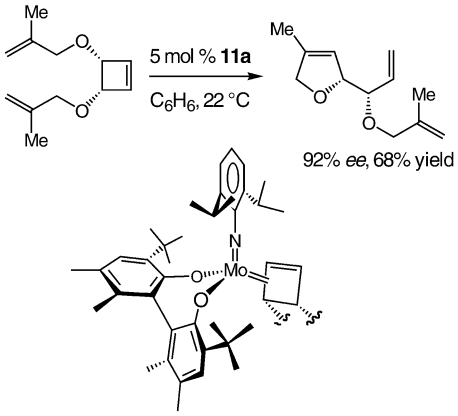
Scheme 37. Enantioselective synthesis of amines through molybdenum-catalyzed ARCM.

5.3. Molybdenum-Catalyzed Asymmetric Ring-Opening Metathesis (AROM)

Catalytic ROM transformations—although less explored than RCM processes—offer unique and powerful approaches to selective organic synthesis.[190] Moreover, chiral Mo alkylidene complexes that are products of AROM may be trapped either intramolecularly (by RCM) or intermolecularly (by CM) to generate an assortment of versatile optically enriched compounds.

5.3.1. Molybdenum-Catalyzed Tandem Ring-Opening/Ring-Closing Metathesis Reactions (AROM/RCM)

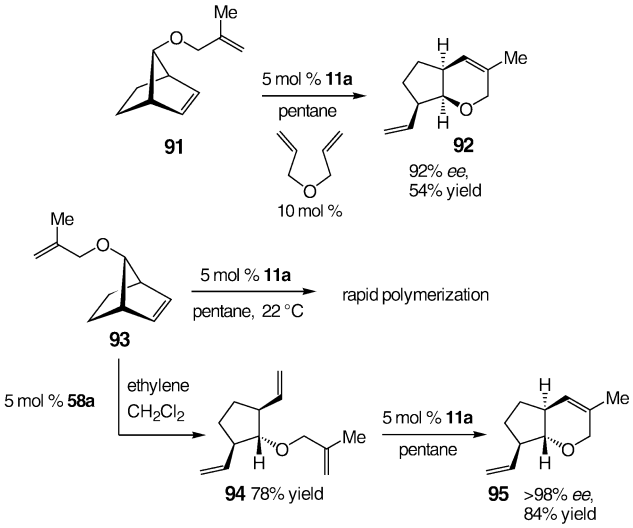
Transformations described in this section are the first reported examples of catalytic asymmetric ring-opening (AROM). In 2000, it was disclosed that *meso*-triene substrate in Equation (19) can be converted into a chiral heterocyclic triene in 92% *ee* and 68% yield in the presence of 5 mol% **11a**.[191] It has been proposed that, as illustrated, stereo-



(19)

selective approach of the more reactive cyclobutenyl alkene leads to the enantioselective formation of the observed dihydrofuran enantiomer.

Another early example of AROM, shown in Scheme 38, involves the net rearrangement of *meso*-bicycle **91** to **92** in 92% *ee*. The reaction is promoted by 5 mol% **11a** and



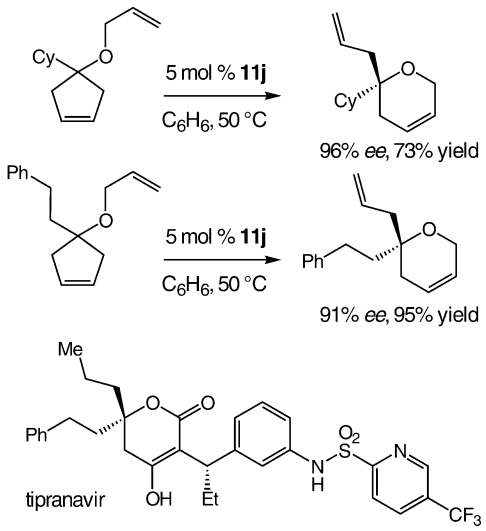
Scheme 38. Efficiency of catalytic AROM processes can depend on the stereochemical identity of the substrate.

requires the addition of diallyl ether.[127g] As mentioned previously (see Scheme 28), initial reaction of diallyl ether with neophylidene **11a** most likely leads to the formation of the substantially more reactive chiral Mo=CH_2 complex, which can react with the sterically hindered norbornyl alkene to initiate the catalytic cycle.

In contrast to **91**, diastereomer **93** undergoes rapid polymerization in the presence of **11a** (Scheme 38), presumably because of its more exposed strained olefin. The less-reactive Ru catalyst **58a** (Figure 11) can, however, be used

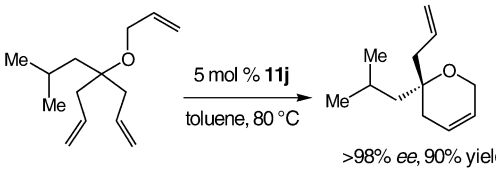
under an atmosphere of ethylene to effect a tandem ROM/CM to generate *meso*-**94**. The resulting triene may be subsequently induced to undergo molybdenum-catalyzed ARCM to afford optically pure **95**, the AROM/RCM product that would be directly obtained from **93**.

The molybdenum-catalyzed transformations shown in Scheme 39 might be viewed as examples of tandem AROM/RCM.[192] It is however possible that initiation occurs at the terminal olefin, followed by an ARCM involving the cyclic alkene. The enantioselective rearrangements shown in Scheme 39, catalyzed by binaphtholate-based catalyst **11j**, deliver unsaturated pyrans bearing a tertiary ether site with excellent enantioselectivity. Biphenolate Mo catalysts, such as **11a**, deliver significantly lower *ee* values. This class of heterocycles would not be accessible by an asymmetric synthesis of the precursor diene, followed by RCM promoted by an achiral catalyst. The enantioselective synthesis of the pyran portion of the anti-HIV agent tipranavir (Scheme 39) demonstrates the potential of the method in asymmetric synthesis of biomedically important agents.[193]



Scheme 39. Molybdenum-catalyzed enantioselective rearrangement of cyclopentenes to unsaturated pyrans. Cy = cyclohexyl.

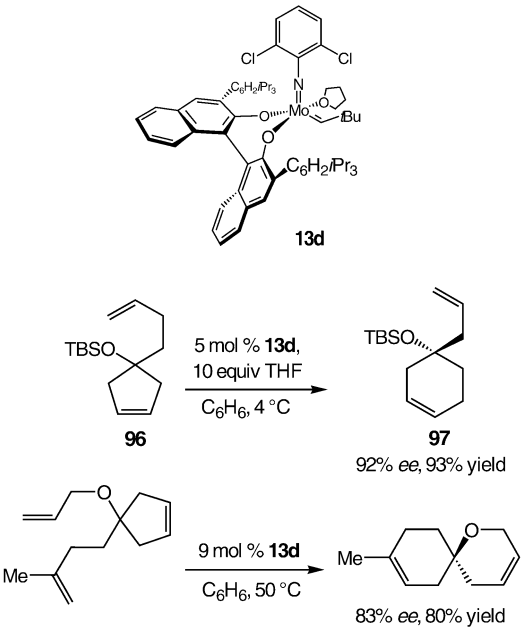
The nonracemic pyrans shown in Scheme 39 can be obtained by molybdenum-catalyzed ARCM of trienes as well. The example shown in Equation (20) is illustrative.



(20)

Elevated temperatures are required for high enantioselectivity; under conditions shown in Scheme 39, (50 °C) the triene substrates are converted into the desired pyrans in significantly lower *ee* values.

A related process to those discussed above is the asymmetric molybdenum-catalyzed synthesis of cyclohexenyl ethers (**96**→**97**, Scheme 40).[194] An unusual attribute of this class of reactions is that higher levels of enantioselectivity are obtained when substrate THF is added to the reaction mixture. As an example, **97** is formed in only 58% *ee* in the absence of THF (< 5% conversion when THF is used as solvent). As also shown in Scheme 40, enantioenriched spirocycles are accessed easily by a similar approach; in this case, additive effects are not observed.[195]

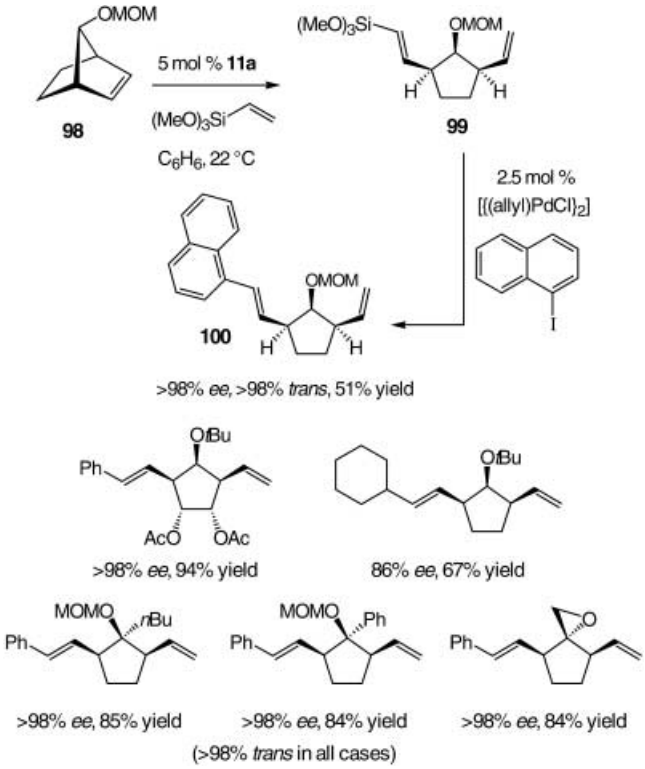


Scheme 40. Enantioselective synthesis of carbocyclic tertiary ethers and spirocycles through molybdenum-catalyzed asymmetric olefin metathesis.

5.3.2. Molybdenum-Catalyzed Tandem Asymmetric Ring-Opening/Cross Metathesis Reactions (AROM/CM)

The chiral molybdenum alkylidene complex derived from AROM of a cyclic olefin may participate in an intermolecular cross metathesis. As depicted in Scheme 41, treatment of **98** with a solution of 5 mol% **11a** and two equivalents of vinylsiloxane leads to the formation of optically pure **99**.[196] Subsequent palladium-catalyzed cross-coupling delivers optically pure **100** in 51% yield (> 98% *trans*).[197]

As the representative products illustrated in Scheme 41 indicate, the molybdenum-catalyzed AROM/CM may be performed on functionalized norbornenes and aryl or aliphatic terminal alkenes. These are optically pure and easily functionalizable organic molecules that cannot be easily prepared by other methods. It should be noted that the relative orientation of the heteroatom substituent versus the reacting olefin has a significant influence on reaction efficiency (see Sections 5.6 and for a discussion of complementarity of Mo and Ru catalysts).



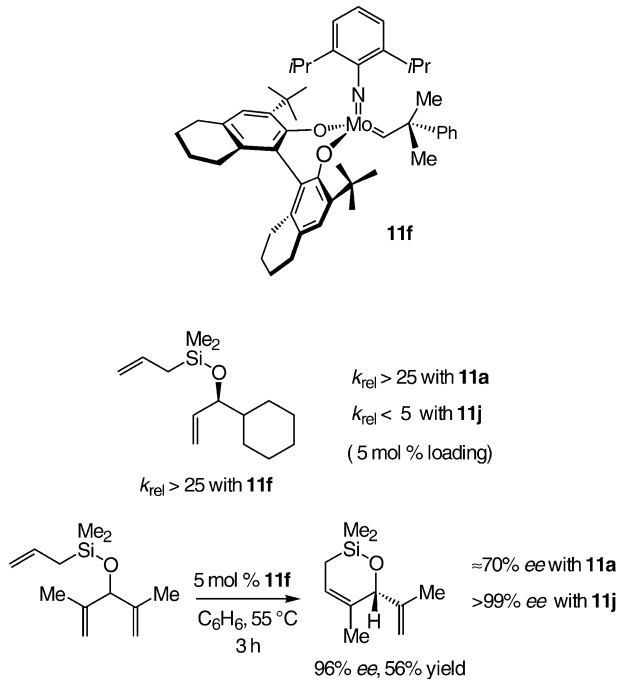
Scheme 41. Molybdenum-catalyzed tandem AROM/CM proceeds with high enantioselectivity and olefin stereocontrol; MOM = methoxymethyl.

5.4. Towards more User-Friendly and Practical Chiral Molybdenum-Based Catalysts for Olefin Metathesis

The issue of practicality is a critical aspect of research regarding the development of practical molybdenum-based metathesis catalysts. Two related key advances have recently been reported. One is in connection to the in situ preparation of commercially available Mo catalysts from commercially available compounds, and the other is related to the development of a recyclable polymer-supported chiral Mo catalyst.

5.4.1. Chiral Molybdenum Catalysts Prepared In Situ: Catalyst Isolation not Required

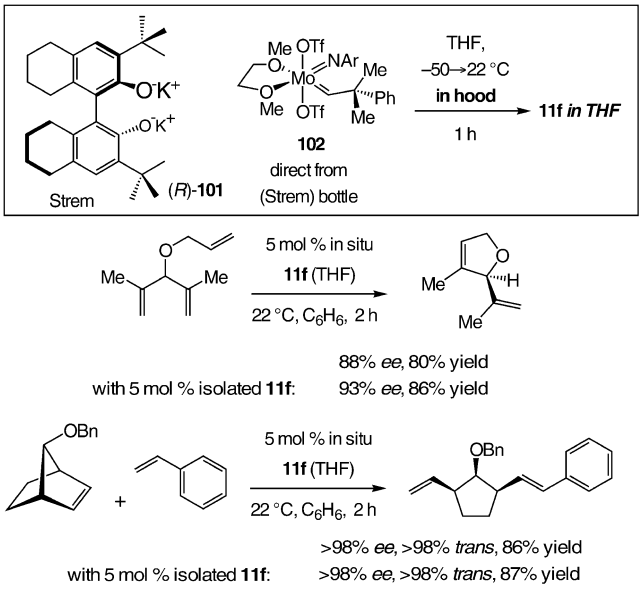
From a practical point of view, binaphthol-based catalysts such as **11j** have an advantage over the biphenol complexes represented by **11a**. The synthesis of the optically pure diolate begins from the inexpensive and commercially available (*R*)- or (*S*)-binaphthol. Access to the optically pure biphenol ligand in **11a** and its derivatives requires resolution of the racemic material by fractional crystallization of phosphorus(v) mentholates.[14] Enantiomerically pure **11f**,[22] shown in Scheme 42, is a catalyst that bears a "biphenol-type" ligand but is synthesized from the readily available optically pure binaphthol. Complex **11f** shares structural features with both the biphen- and binol-based catalysts and represents an intriguing possibility regarding the range of reactions for which it can serve as a suitable catalyst.[22] Two examples are depicted in Scheme 42. Note that in many, but not all,



Scheme 42. Chiral complex **11f** represents a hybrid between biphen- and binol-based catalysts and provides a unique selectivity profile.

instances, **11f** delivers compounds of high optical purity where either biphen- or binol-based catalysts are ineffective.

Not only is Mo complex **11f** easier to prepare than biphenolate **11a**, it is also simpler to use. As outlined in Scheme 43, a solution of **11f**, obtained by the reaction of bis(potassium salt) **101** (commercially available from Strem) and Mo triflate **102** (commercially available from Strem), can be used directly to promote enantioselective metathesis.[22] Similar reactivity and selectivity is observed with in situ **11f** as with isolated and purified **11a** or **11f**. Moreover, asymmetric

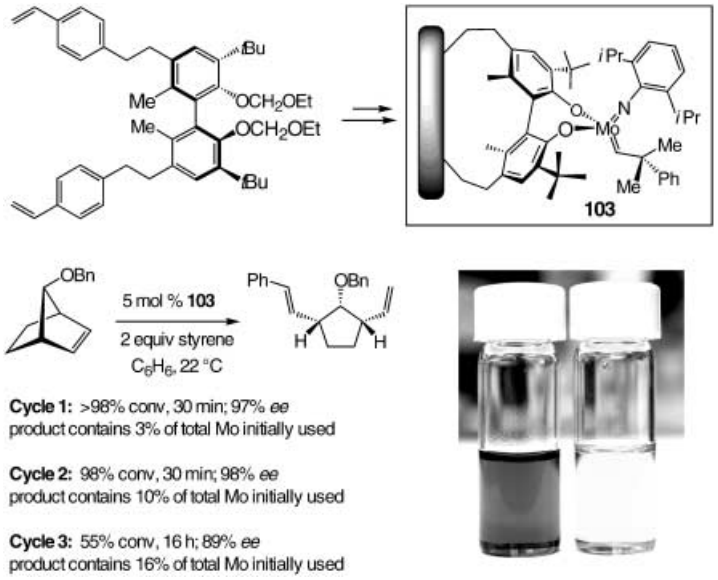


Scheme 43. In situ preparation and utility of chiral metathesis catalyst **11f**.

olefin metatheses proceed with equal efficiency and enantioselectivity with the same stock solutions of (*R*)-**101** and **102** after two weeks, which makes the use of glovebox, Schlenk equipment, or vacuum lines no longer mandatory. It has subsequently been demonstrated that the in situ catalyst preparation procedure can be readily applied to other chiral Mo complexes as well.[194]

5.4.2. The First Enantiomerically Pure Solid-Supported Catalyst for Olefin Metathesis

Synthesis and catalytic activity of the first supported chiral catalyst for olefin metathesis was disclosed in 2002.[198] As illustrated in Scheme 44, supported catalyst **103** efficiently promotes a range of ARCM and AROM processes. Reactions are slower than with the corresponding monomeric complex **11a**, but often similar enantioselectivity is observed. Although **103** must be kept under dry and oxygen-free conditions, it can be recycled. Moreover, the unpurified product solution, after simple filtration, contains significantly lower levels of metal impurity than detected when using the monomeric catalysts, where >90% of the Mo used is found in the unpurified product (ICP-MS analysis). The lower levels of activity exhibited by **103** might be due to inefficient diffusion of substrate molecules into the polymer. On the other hand, the supported catalyst is also expected to be less susceptible to bimolecular decomposition of methylidene intermediates (see Scheme 14).[114]



Scheme 44. The first recyclable and supported chiral catalyst for olefin metathesis delivers reaction products that contain significantly less metal impurity. The two dram vials show unpurified product from a reaction catalyzed by **11a** (left) and **103** (right).

5.5. The First Enantiomerically Pure Alkyl Imido Molybdenum Catalyst

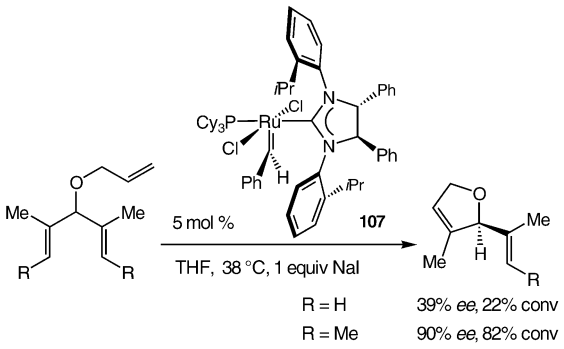
In spite of the advances discussed above regarding chiral molybdenum-based complexes, a large number of problems in selectivity and reactivity cannot be addressed by the available chiral catalysts. Accordingly, recent efforts have been directed towards the development of structurally distinct chiral catalysts. Such initiatives have resulted in the synthesis, characterization, and study of the catalytic activity of the first enantiomerically pure molybdenum-based alkyl imido complex (Scheme 45).[25] Enantiomerically pure alkylidene complex **17** exists almost exclusively in its *syn* form (≈0.5% *anti* alkylidene at 22 °C) and can be easily prepared on multigram scale. Importantly, the adamantylimido complex exhibits unique reactivity and selectivity profiles not available through the use of aryl imido systems. One representative example, where **17** promotes an AROM/CM substantially more efficiently than any molybdenum-based catalysts, is presented in Scheme 45.

5.6. Comparison with Chiral Ruthenium Catalysts

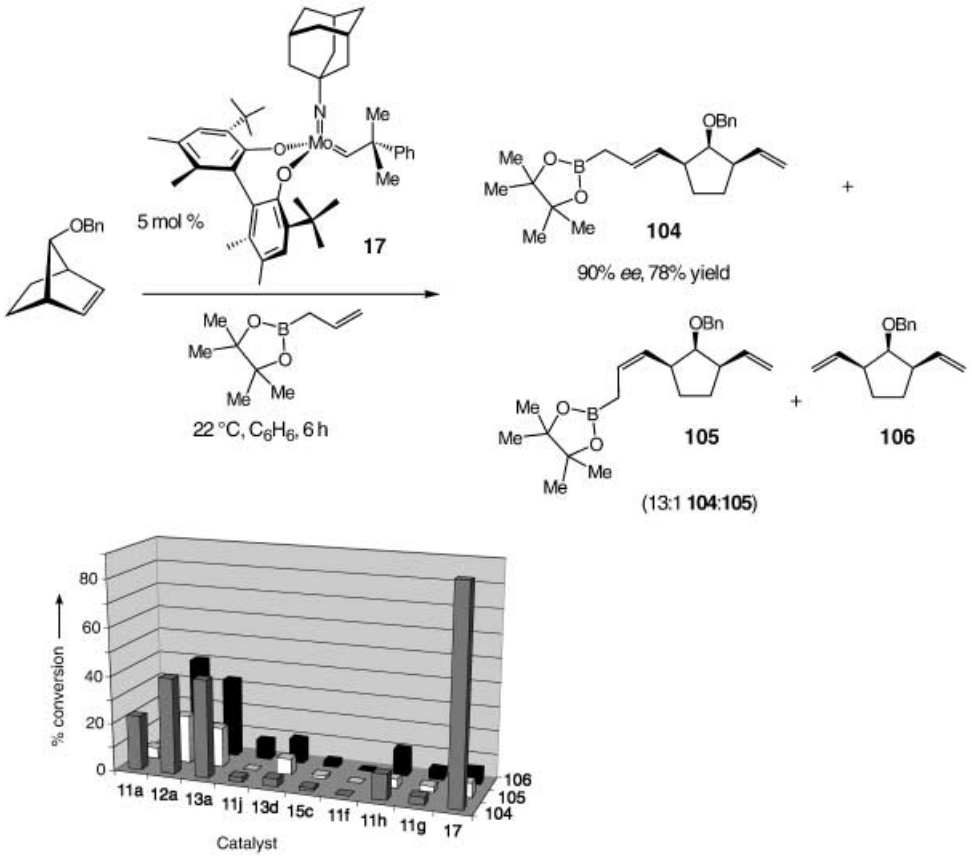
Two different types of chiral ruthenium-based catalysts have been disclosed. Although these Ru systems complement enantiomerically pure Mo catalysts, the latter class of catalysts have so far proven to be superior in scope.

In 2001, Grubbs and co-workers reported the first chiral Ru catalyst for olefin metathesis **107** [Eq. (21)].[199] The reactions illustrated in Equation (21) include the highest *ee* value reported in that study (13–90% *ee*). Asymmetric induction is lower than that obtained with molybdenum-based catalysts [see Eq. (15) for comparison] and is dependent on the degree of olefin substitution. As is the case with nearly all catalytic enantioselective reactions,[182] the identity of the optimal catalyst depends on the substrate being used. A number of chiral Ru catalysts were therefore synthesized and screened before **107** was identified as the most suitable.

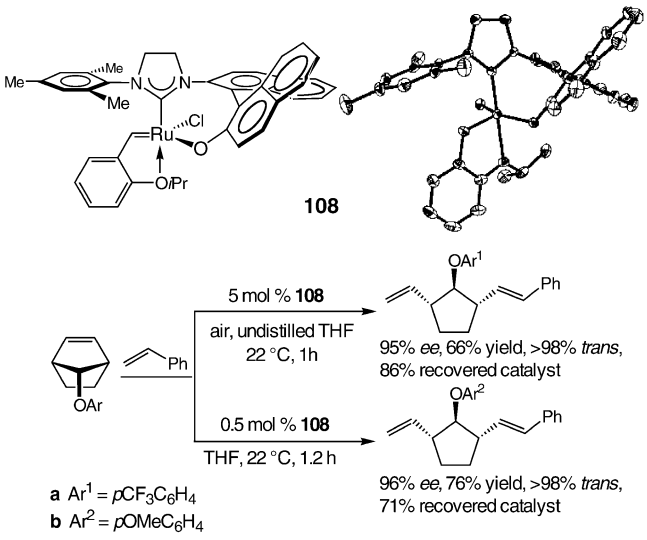
Early in 2002, the synthesis, characterization and catalytic activity of chiral ruthenium-based carbene **108** was disclosed (Scheme 46).[200] Catalyst **108** is stereogenic at the metal center, can be prepared in >98% diastereoselectivity and



(21)



Scheme 45. The adamantylimido chiral catalyst **17** can offer levels of reactivity and selectivity that are not available by the corresponding aryl imido catalysts.



Scheme 46. Air stable chiral ruthenium-based catalyst for olefin metathesis can be used to promote AROM/CM reactions.

purified by chromatography on silica gel with undistilled solvents. This styrene ether Ru complex, which is based on complexes represented by **58d,e** (Figure 11) which were first reported in 1997,[127f–i] catalyzes RCM and ROM reactions. Moreover, **108** is air stable and recyclable. As the representative cases in Scheme 46 illustrate, this chiral Ru catalyst is highly effective (0.5–10 mol % loading) in promoting AROM/CM. These enantioselective transformations can be effected in air and with unpurified solvents air (see Scheme 46). It should be noted that the substrates illustrated in Scheme 46 undergo rapid polymerization in the presence of chiral molybdenum-based catalysts.

6. A Few Notes Regarding Molybdenum- Versus Ruthenium-Based Metathesis Catalysts

6.1. Are Molybdenum Catalysts "Functional-Group Tolerant?"

Statements that simplify a complicated field of research often gain rapid popularity. One claim that is frequently stated by users of olefin metathesis is that "unlike ruthenium-based catalysts, high-oxidation-state complexes are not functional-group tolerant." Such a statement tends to marginalize important data and can lead to unwise decisions in experimental design.

In contrast to the ruthenium-based catalysts, such as those shown in Figure 11, Mo complexes are relatively sensitive to moisture and air, and should be handled under inert atmosphere and used in anhydrous solvents. The early-transition-metal complexes are incompatible with carboxylic acids, ketones, aldehydes, most alcohols and primary amines.

However, Mo catalysts are effective in the presence of phosphanes[201] and thioethers [see Eq. (10)],[202,203] functional groups that readily decompose Ru complexes. Molybdenum catalysts also have been shown to be active in the presence of nitriles[112] and a sterically protected free alcohol.[204] There are numerous reported examples, including several discussed above (see Scheme 37), where Mo catalysts not only show high catalytic activity in the presence of amines, they deliver unparalleled enantioselectivity.[205] Molybdenum catalyst **3d** (Figure 2, $G = CMe_2Ph$) is active in the presence of metal–carbonyl compounds.[206] Thus the response to a statement that a particular class of catalysts are "not functional-group tolerant" should be: exactly which functional groups are being discussed?

6.2. Do Molybdenum catalysts still Offer the Highest Levels of Reactivity?

Although recent generations of ruthenium-based catalysts, such as **58b,c** and **58e** (Figure 11), provide significantly improved activity compared to their precursors **58a** and **58d**, Mo catalysts can still offer unique levels of reactivity. As an example, the ROM/CM in Scheme 43, which occurs within minutes with 5 mol% **11a**, does not proceed, even at 70 °C, in the presence of catalytic or stoichiometric amounts of "second generation" Ru catalysts **58b** or **58e**.[207]

One important lesson that the field of catalysis has taught us is that simple generalizations, in spite of their lure, are best avoided. Blanket statements regarding reactivity or selectivity often carry as many (if not more) cases that are exceptions as agreements, particularly since higher activity of a catalyst is often claimed based on data collected regarding a narrow field of substrates (at times a single starting material is used).

As discussed above, molybdenum- and ruthenium-based catalysts offer complementary degrees of efficiency and stereoselectivity. Superior activity of a Mo catalyst in one case does not mean that such is true in all cases.

7. Conclusions and Outlook

The journey from a new high-oxidation-state Ta alkylidene to asymmetric Mo catalysts for the metathesis of olefins required twenty-five years. Investigations of high-oxidation-state Ta alkylidene chemistry led to the finding that bulky alkoxide ligands slow the rearrangement of tantalacyclobutane rings to olefins and promote olefin metathesis. Studies concerned with alkylidyne complexes of W and Mo confirmed that bulky alkoxide ligands are most desirable for efficient metathesis of alkynes and revealed that trigonal-bipyramidal metallacyclobutadienes are intermediates in alkyne metathesis reactions. Neopentylidene or neophylidene complexes of W or Mo can be isolated when sterically demanding aryl imido and alkoxide ligands are present and serve as effective olefin-metathesis catalysts, especially when the alkoxide is the relatively electron-withdrawing hexafluoro-*tert*-butoxide group. Moreover, several new alkylidenes derived from olefins and metallacyclobutane intermediates have been observed and isolated. Studies regarding ROMP have resulted in the realization that *syn* and *anti* isomers can be present in imido alkylidene complexes, and that their reactivities and rates of interconversion may vary dramatically with the nature of the alkoxide and imido ligands. Finally, the success at controlling ROMP structure with chiral biphenolates culminated with the synthesis of enantiomerically pure imido alkylidene catalysts which can be employed in asymmetric metathesis reactions.

The exciting results of the investigations described in the preceding sections clearly indicate that the modular construct of molybdenum- and tungsten-based imido alkylidene complexes can be exploited to generate a range of highly efficient and selective catalysts for olefin metathesis. A variety of ring-closing, ring-opening, and cross metathesis reactions can be promoted by high-oxidation-state complexes to obtain products that are typically unavailable by other methods or can only be accessed by significantly longer routes.

Molybdenum-based catalysts, although more sensitive to moisture and air than the related ruthenium-based systems, often provide complementary reactivity and selectivity patterns and offer the most effective chiral catalysts that can be used in asymmetric synthesis. Achiral catalyst **3d** and chiral complex **11a** (both antipodes and racemic) are commercially available from Strem, Inc. Molybdenum-based complexes can be handled on a large scale and in the significant number of cases, reactions proceed readily to completion in the presence of 1 mol% loading. In many cases, optically pure materials can be synthesized within minutes without the need for solvents.

The advent of protocols for in situ preparation of chiral Mo catalysts and the emergence of supported and new generations of easily recyclable complexes augur well for future developments towards truly practical molybdenum- and tungsten-based metathesis catalysts. The above attributes and ongoing research efforts will hopefully lead to the arrival of even more efficient catalysts that can be used in organic synthesis.

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[1] A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.
[2] M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056.
[3] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450.
[4] A. Fürstner, in *Topics in Organometallic Chemistry; Alkene Metathesis in Organic Synthesis, Vol. 1* (Ed.: A. Fürstner), Springer, Berlin, **1998**, pp. 37–72.
[5] A. J. Phillips, A. D. Abell, *Aldrichimica Acta* **1999**, *32*, 75–89.
[6] D. L. Wright, *Curr. Org. Chem.* **1999**, *3*, 211–240.

[7] R. R. Schrock, R. DePue, J. Feldman, C. J. Schaverien, J. C. Dewan, A. H. Liu, *J. Am. Chem. Soc.* **1988**, *110*, 1423 – 1435.
[8] R. R. Schrock, R. T. DePue, J. Feldman, K. B. Yap, D. C. Yang, W. M. Davis, L. Y. Park, M. DiMare, M. Schofield, J. Anhaus, E. Walborsky, E. Evitt, C. Krüger, P. Betz, *Organometallics* **1990**, *9*, 2262 – 2275.
[9] W. C. P. Tsang, K. C. Hultzsch, J. B. Alexander, P. J. Bonitatebus, Jr., R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 2591 – 2596.
[10] J. S. Murdzek, R. R. Schrock, *Organometallics* **1987**, *6*, 1373 – 1374.
[11] J. H. Oskam, H. H. Fox, K. B. Yap, D. H. McConville, R. O'Dell, B. J. Lichtenstein, R. R. Schrock, *J. Organomet. Chem.* **1993**, *459*, 185 – 198.
[12] R. R. Schrock, S. Luo, J. J. C. Lee, N. C. Zanetti, W. M. Davis, *J. Am. Chem. Soc.* **1996**, *118*, 3883 – 3895.
[13] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875 – 3886.
[14] J. B. Alexander, R. R. Schrock, W. M. Davis, K. C. Hultzsch, A. H. Hoveyda, J. H. Houser, *Organometallics* **2000**, *19*, 3700 – 3715.
[15] K. C. Hultzsch, P. J. Bonitatebus, Jr., J. Jernelius, R. R. Schrock, A. H. Hoveyda, *Organometallics* **2001**, *20*, 4705 – 4712.
[16] K. M. Totland, T. J. Boyd, G. G. Laovie, W. M. Davis, R. R. Schrock, *Macromolecules* **1996**, *29*, 6114 – 6125.
[17] R. R. Schrock, J. Y. Jamieson, S. J. Dolman, S. A. Miller, P. J. Bonitatebus, Jr., A. H. Hoveyda, *Organometallics* **2002**, *21*, 409 – 417.
[18] S. S. Zhu, D. R. Cefalo, D. S. La, J. Y. Jamieson, W. M. Davis, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1999**, *121*, 8251 – 8259.
[19] W. C. P. Tsang, R. R. Schrock, A. H. Hoveyda, *Organometallics* **2001**, *20*, 5658 – 5669.
[20] O. Fujimura, F. J. De la Mata, R. H. Grubbs, *Organometallics* **1996**, *15*, 1865 – 1871.
[21] D. H. McConville, J. R. Wolf, R. R. Schrock, *J. Am. Chem. Soc.* **1993**, *115*, 4413 – 4414.
[22] S. L. Aeilts, D. R. Cefalo, P. J. Bonitatebus, J. H. Houser, A. H. Hoveyda, R. R. Schrock, *Angew. Chem.* **2001**, *113*, 1500 – 1504; *Angew. Chem. Int. Ed.* **2001**, *40*, 1452 – 1456.
[23] J. Y. Jamieson, R. R. Schrock, W. M. Davis, P. J. Bonitatebus, S. S. Zhu, A. H. Hoveyda, *Organometallics* **2000**, *19*, 925 – 930.
[24] G. S. Weatherhead, J. H. Houser, J. G. Ford, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *Tetrahedron Lett.* **2000**, *41*, 9553 – 9559.
[25] W. C. P. Tsang, J. A. Jernelius, A. G. Cortez, G. S. Weatherhead, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 2652 – 2666.
[26] R. R. Schrock, in *Reactions of Coordinated Ligands* (Ed.: P. R. Braterman), Plenum, New York, **1986**, pp. 221 – 283.
[27] R. R. Schrock, *Pure Appl. Chem.* **1994**, *66*, 1447 – 1454.
[28] J. Feldman, R. R. Schrock, *Prog. Inorg. Chem.* **1991**, *39*, 1 – 74.
[29] R. R. Schrock, *Polyhedron* **1995**, *14*, 3177 – 3195.
[30] R. R. Schrock, *J. Chem. Soc. Dalton Trans.* **2001**, 2541 – 2550.
[31] R. R. Schrock, *Chem. Rev.* **2001**, *101*, 145 – 180.
[32] R. R. Schrock, in *Topics in Organometallic Chemistry. Alkene Metathesis in Organic Synthesis, Vol. 1* (Ed.: A. Fürstner), Springer, Berlin, **1998**, pp. 1 – 36.
[33] R. R. Schrock, *Tetrahedron* **1999**, *55*, 8141 – 8153.
[34] R. R. Schrock, in *Ring-Opening Polymerization* (Ed.: D. J. Brunelle), Hanser, Munich, **1993**, pp. 129 – 156.
[35] R. R. Schrock, in *Metathesis Polymerization of Olefins and Polymerization of Alkynes* (Ed.: Y. Imamoglu), Kluwer, Dordrecht, **1998**, pp. 1 – 27.
[36] R. R. Schrock, in *Metathesis Polymerization of Olefins and Polymerization of Alkynes* (Ed.: Y. Imamoglu), Kluwer, Dordrecht, **1998**, pp. 357 – 380.
[37] K. J. Ivin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, **1997**.
[38] K. J. Ivin, *Olefin Metathesis*, Academic, New York, **1983**.
[39] V. Dragutan, A. T. Balaban, M. Dimonie, *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, 2nd ed., Wiley, New York, **1985**.
[40] S. R. Wilson, D. E. Schalk, *J. Org. Chem.* **1976**, *41*, 3928 – 3929.
[41] D. Villemin, *Tetrahedron Lett.* **1980**, *21*, 175 – 178.
[42] J. Tsuji, S. Hashiguchi, *Tetrahedron Lett.* **1980**, *21*, 2955 – 2958.
[43] E. O. Fischer, A. Maasböl, *Angew. Chem.* **1964**, *76*, 645.
[44] a) E. O. Fischer, *Pure Appl. Chem.* **1970**, *42*, 407 – 423; b) E. O. Fischer, *Pure Appl. Chem.* **1972**, *44*, 353 – 372; c) E. O. Fischer, *Adv. Organomet. Chem.* **1976**, *14*, 1 – 32.
[45] D. J. Cardin, B. Cetinkaya, M. F. Lappert, *Chem. Rev.* **1972**, *72*, 545 – 574.
[46] F. A. Cotton, C. M. Lukehart, *Prog. Inorg. Chem.* **1972**, *16*, 487 – 613.
[47] D. J. Cardin, B. Cetinkaya, M. J. Doyle, M. F. Lappert, *Chem. Soc. Rev.* **1973**, *2*, 99 – 144.
[48] a) C. P. Casey, T. J. Burkhardt, *J. Am. Chem. Soc.* **1973**, *95*, 5833 – 5834; b) C. P. Casey, T. J. Burkhardt, *J. Am. Chem. Soc.* **1974**, *96*, 7808 – 7809; c) C. P. Casey, H. E. Tuinstra, M. C. Saemen, *J. Am. Chem. Soc.* **1976**, *98*, 608 – 609; d) C. P. Casey, T. J. Burkhardt, C. A. Bunnell, J. C. Calabrese, *J. Am. Chem. Soc.* **1977**, *99*, 2127 – 2134.
[49] J. L. Hérisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161 – 176.
[50] B. A. Dolgoplosk, K. L. Makovetsty, T. G. Golenko, Y. V. Korshak, E. I. Timyakova, *Eur. Polym. J.* **1974**, *10*, 901 – 904.
[51] R. H. Grubbs, D. D. Carr, C. Hoppin, P. L. Burk, *J. Am. Chem. Soc.* **1976**, *98*, 3478 – 3483.
[52] R. H. Grubbs, *Prog. Inorg. Chem.* **1978**, *24*, 1 – 50.
[53] T. J. Katz, J. McGinnis, *J. Am. Chem. Soc.* **1975**, *97*, 1592 – 1594.
[54] a) T. J. Katz, S. J. Lee, N. Acton, *Tetrahedron Lett.* **1976**, *17*, 4247 – 4250; b) T. J. Katz, R. Rothchild, *J. Am. Chem. Soc.* **1976**, *98*, 2519 – 2526; c) T. J. Katz, N. Acton, *Tetrahedron Lett.* **1976**, *17*, 4251 – 4254; d) T. J. Katz, J. McGinnis, C. Altus, *J. Am. Chem. Soc.* **1976**, *98*, 606 – 608; e) T. J. Katz, J. McGinnis, *J. Am. Chem. Soc.* **1977**, *99*, 1903 – 1912; f) T. J. Katz, W. H. Hersh, *Tetrahedron Lett.* **1977**, *18*, 585 – 588; g) J. McGinnis, T. J. Katz, S. Hurwitz, *J. Am. Chem. Soc.* **1976**, *98*, 605 – 606.
[55] T. J. Katz, *Adv. Organomet. Chem.* **1977**, *16*, 283 – 317.
[56] R. H. Grubbs, in *Comprehensive Organometallic Chemistry, Vol. 8* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, New York, **1982**, pp. 499 – 551.
[57] D. S. Breslow, *Prog. Polym. Sci.* **1993**, *18*, 1141 – 1195.
[58] N. Calderon, J. P. Lawrence, E. A. Ofstead, *Adv. Organomet. Chem.* **1979**, *17*, 449 – 492.
[59] This reference is often quoted as a 1970 paper, a consequence of a mistake in the running header in the volume 141, **1971** issue.
[60] C. P. Casey, S. W. Polichnowski, A. J. Shusterman, C. R. Jones, *J. Am. Chem. Soc.* **1979**, *101*, 7282.
[61] R. R. Schrock, P. Meakin, *J. Am. Chem. Soc.* **1974**, *96*, 5288 – 5290.
[62] R. R. Schrock, *J. Organomet. Chem.* **1976**, *122*, 209 – 225.
[63] R. R. Schrock, *J. Am. Chem. Soc.* **1974**, *96*, 6796 – 6797.
[64] R. R. Schrock, *J. Am. Chem. Soc.* **1976**, *98*, 5399 – 5400.
[65] H. Schmidbaur, *Adv. Organomet. Chem.* **1976**, *14*, 205 – 243.
[66] G. A. Rupprecht, L. W. Messerle, J. D. Fellmann, R. R. Schrock, *J. Am. Chem. Soc.* **1980**, *102*, 6236 – 6244.
[67] C. D. Wood, S. J. McLain, R. R. Schrock, *J. Am. Chem. Soc.* **1979**, *101*, 3210 – 3222.
[68] S. J. McLain, C. D. Wood, R. R. Schrock, *J. Am. Chem. Soc.* **1979**, *101*, 4558 – 4570.
[69] S. M. Rocklage, J. D. Fellmann, G. A. Rupprecht, L. W. Messerle, R. R. Schrock, *J. Am. Chem. Soc.* **1981**, *103*, 1440 – 1447.

[70] R. R. Schrock, S. M. Rocklage, J. H. Wengrovius, G. Rupprecht, J. Fellmann, *J. Mol. Catal.* **1980**, *8*, 73 – 83.

[71] Tebbe et al. reported in 1979 that Ti complexes that contain a bridging methylene ligand would react with olefins to undergo methylene exchange, leading to a degenerate metathesis reaction. See: F. N. Tebbe, G. W. Parshall, D. W. Ovenall, *J. Am. Chem. Soc.* **1979**, *101*, 5074 – 5075.

[72] K. C. Wallace, J. C. Dewan, R. R. Schrock, *Organometallics* **1986**, *5*, 2162 – 2164.

[73] K. C. Wallace, R. R. Schrock, *Macromolecules* **1987**, *20*, 448 – 450.

[74] K. C. Wallace, A. H. Liu, J. C. Dewan, R. R. Schrock, *J. Am. Chem. Soc.* **1988**, *110*, 4964 – 4977.

[75] Although rare, tantalum alkylidene complexes that contain 18 electrons and do not contain ligands that can dissociate from the metal are stable when β protons are present. An example is $[(\eta^5\text{-}C_5H_5)_2MeTa{=}CHMe]$; see P. R. Sharp, R. R. Schrock, *J. Organomet. Chem.* **1979**, *171*, 43 – 51.

[76] R. R. Schrock, *Acc. Chem. Res.* **1986**, *19*, 342 – 348.

[77] J. H. Wengrovius, R. R. Schrock, M. R. Churchill, J. R. Missert, W. J. Youngs, *J. Am. Chem. Soc.* **1980**, *102*, 4515 – 4516.

[78] M. R. Churchill, A. L. Rheingold, W. J. Youngs, R. R. Schrock, *J. Organomet. Chem.* **1981**, *204*, C17 – C20.

[79] W. A. Nugent, J. M. Mayer, *Metal-Ligand Multiple Bonds*, Wiley, New York, **1988**.

[80] J. H. Wengrovius, R. R. Schrock, *Organometallics* **1982**, *1*, 148 – 155.

[81] R. R. Schrock, *J. Am. Chem. Soc.* **1975**, *97*, 6577 – 6578.

[82] R. R. Schrock, P. R. Sharp, *J. Am. Chem. Soc.* **1978**, *100*, 2389 – 2399.

[83] J. R. M. Kress, M. J. M. Russell, M. G. Wesolek, J. A. Osborn, *J. Chem. Soc. Chem. Commun.* **1980**, 431 – 432.

[84] J. Kress, M. Wesolek, J.-P. Le Ny, J. A. Osborn, *J. Chem. Soc. Chem. Commun.* **1981**, 1039 – 1040.

[85] J. Kress, M. Wesolek, J. A. Osborn, *J. Chem. Soc. Chem. Commun.* **1982**, 514 – 516.

[86] J. Kress, A. Aguero, J. A. Osborn, *J. Mol. Catal.* **1986**, *36*, 1 – 12.

[87] M. T. Youinou, J. Kress, J. Fischer, A. Aguero, J. A. Osborn, *J. Am. Chem. Soc.* **1988**, *110*, 1488 – 1493.

[88] F. Lefebvre, M. Leconte, S. Pagano, A. Mutch, J.-M. Basset, *Polyhedron* **1995**, *14*, 3209 – 3226.

[89] J. L. Couturier, C. Paillet, M. Leconte, J. M. Basset, K. Weiss, *Angew. Chem.* **1992**, *104*, 622 – 624; *.Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 628 – 631.

[90] A. Mortreux, J. C. Delgrange, M. Blanchard, B. Labochinsky, *.J. Mol. Catal.* **1977**, *2*, 73 – 82.

[91] A. Mortreux, M. Blanchard, *J. Chem. Soc. Chem. Commun.* **1974**, 786 – 787.

[92] See H. Fischer, P. Hofmann, F. R. Kreissl, R. R. Schrock, U. Schubert, K. Weiss, *Carbyne Complexes*, VCH, New York, **1988**.

[93] E. O. Fischer, G. Kreis, C. G. Kreiter, J. Müller, G. Huttner, H. Lorenz, *Angew. Chem.* **1973**, *85*, 618 – 620; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 564 – 565.

[94] D. N. Clark, R. R. Schrock, *J. Am. Chem. Soc.* **1978**, *100*, 6774 – 6776.

[95] J. S. Murdzek, R. R. Schrock, in *Carbyne Complexes*, VCH, New York, **1988**, pp. 148 – 203.

[96] J. H. Wengrovius, J. Sancho, R. R. Schrock, *J. Am. Chem. Soc.* **1981**, *103*, 3932 – 3934.

[97] M. R. Churchill, J. W. Ziller, J. H. Freudenberger, R. R. Schrock, *Organometallics* **1984**, *3*, 1554 – 1562.

[98] J. H. Freudenberger, R. R. Schrock, M. R. Churchill, A. L. Rheingold, J. W. Ziller, *Organometallics* **1984**, *3*, 1563 – 1573.

[99] S. F. Pedersen, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *J. Am. Chem. Soc.* **1982**, *104*, 6808 – 6809.

[100] a) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758 – 1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734 – 1736; b) A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453 – 9454; c) U. H. F. Bunz, L. Kloppenburg, *Angew. Chem.* **1999**, *111*, 503 – 505; *Angew. Chem. Int. Ed.* **1999**, *38*, 478 – 481; d) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108 – 11113; e) A. Fürstner, K. Grela, *Angew. Chem.* **2000**, *112*, 1292 – 1294; *Angew. Chem. Int. Ed.* **2000**, *39*, 1234 – 1236; f) A. Fürstner, G. Seidel, *J. Organomet. Chem.* **2000**, *606*, 75 – 78; g) N. G. Pschirer, W. Fu, R. D. Adams, U. H. F. Bunz, *Chem. Commun.* **2000**, 87 – 88; h) Y. C. Tsai, P. L. Diaconescu, C. C. Cummins, *Organometallics* **2000**, *19*, 5260 – 5262; i) G. Brizius, N. G. Pschirer, W. Steffen, K. Stitzer, H.-C. zur Loye, U. H. F. Bunz, *J. Am. Chem. Soc.* **2000**, *122*, 12435 – 12440; j) W. Zhang, S. Kraft, J. S. Moore *Chem. Commun.* **2003**, 832 – 833; k) B. Aguilera, L. B. Wolf, P. Nieczypor, F. Rutjes, H. S. Overkleeft, J. C. M. van Hest, H. E. Schoemaker, B. Wang, J. C. Mol, A. Fürstner, M. Overhand, G. A. van der Marel, J. H. van Boom, *J. Org. Chem.* **2001**, *66*, 3584 – 3589; l) K. Eder, E. Reichel, H. Schottenberger, C. G. Huber, M. R. Buchmeiser, *Macromolecules* **2001**, *34*, 4334 – 4341; m) A. Fürstner, A. Rumbo, *J. Org. Chem.* **2000**, *65*, 2608 – 2611; n) A. Fürstner, T. Dierkes, *Org. Lett.* **2000**, *2*, 2463 – 2465; o) A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799 – 11805; p) A. Fürstner, C. Mathes, K. Grela, *Chem. Commun.* **2001**, 1057 – 1059; q) A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* **2001**, *7*, 5299 – 5317; r) A. Fürstner, A. S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2002**, *67*, 1521 – 1528; s) K. Grela, J. Ignatowska, *Org. Lett.* **2002**, *4*, 3747 – 3749; t) T. Lindel, *Nachr. Chemie* **2000**, *48*, 1242 – 1244; u) O. S. Miljanic, K. P. C. Vollhardt, G. D. Whitener, *Synlett* **2003**, 29 – 34.

[101] S. M. Rocklage, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *Organometallics* **1982**, *1*, 1332 – 1338.

[102] R. R. Schrock; unpublished results. See also: R. R. Schrock, J. Y. Jamieson, J. P. Araujo, P. J. Bonitatebus, Jr., A. Sinha, P. H. J. Lopez, *J. Organomet. Chem*, in press.

[103] a) D. S. Marynick, C. M. Kirkpatrick, *J. Am. Chem. Soc.* **1985**, *107*, 1993 – 1994; b) M. Sodupe, J. M. Lluch, A. Oliva, J. Bertran, *Organometallics* **1989**, *8*, 1837 – 1841; c) T. Upton, A. K. Rappe, *J. Am. Chem. Soc.* **1985**, *107*, 1206 – 1218; d) J. Ushio, H. Nakatsuji, T. Yonezawa, *J. Am. Chem. Soc.* **1984**, *106*, 5892 – 5901; e) M. Sodupe, J. M. Lluch, A. Oliva, J. Bertran, J. *Nouv. J. Chim.* **1991**, *15*, 321 – 325; f) Y.-D. Wu, Z.-H. Peng, *J. Am. Chem. Soc.* **1997**, *119*, 8043 – 8049; g) K. Monteyne, T. Ziegler, *Organometallics* **1998**, *17*, 5901 – 5907; h) S.-H. Choi, Z. Lin, Z. Xue, *Organometallics* **1999**, *18*, 5488 – 5495; i) E. Folga, T. Ziegler, *Organometallics* **1993**, *12*, 325 – 337; j) O. Eisenstein, R. Hoffmann, A. R. Rossi, *J. Am. Chem. Soc.* **1981**, *103*, 5582 – 5584; k) T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.* **1991**, *113*, 5231 – 5243; l) T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.* **1992**, *114*, 539 – 548; m) T. R. Cundari, M. S. Gordon, *Organometallics* **1992**, *11*, 55 – 63; n) H. H. Fox, M. H. Schofield, R. R. Schrock, *Organometallics* **1994**, *13*, 2804 – 2815; o) S. F. Vyboishchikov, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 1428 – 1438; p) S. F. Vyboishchikov, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 1439 – 1448; q) R. J. Goddard, R. Hoffmann, E. D. Jemmis, *J. Am. Chem. Soc.* **1980**, *102*, 7667 – 7676.

[104] J. H. Oskam, R. R. Schrock, *J. Am. Chem. Soc.* **1993**, *115*, 11831 – 11845.

[105] J. H. Oskam, R. R. Schrock, *J. Am. Chem. Soc.* **1992**, *114*, 7588 – 7589.

[106] M. Brookhart, M. L. H. Green, L. Wong, *Prog. Inorg. Chem.* **1988**, *36*, 1 – 124.

[107] R. R. Schrock, W. E. Crowe, G. C. Bazan, M. DiMare, M. B. O'Regan, M. H. Schofield, *Organometallics* **1991**, *10*, 1832 – 1843.
[108] J. Kress, J. A. Osborn, *Angew. Chem.* **1992**, *104*, 1660 – 1662; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1585 – 1587.
[109] R. R. Schrock, S. Luo, N. Zanetti, H. H. Fox, *Organometallics* **1994**, *13*, 3396.
[110] J. Feldman, W. M. Davis, J. K. Thomas, R. R. Schrock, *Organometallics* **1990**, *9*, 2535 – 2548.
[111] W. E. Crowe, Z. J. Zhang, *J. Am. Chem. Soc.* **1993**, *115*, 10998 – 10999.
[112] W. E. Crowe, D. R. Goldberg, *J. Am. Chem. Soc.* **1995**, *117*, 5162 – 5163.
[113] W. E. Crowe, D. R. Goldberg, Z. J. Zhang, *Tetrahedron Lett.* **1996**, *37*, 2117 – 2120.
[114] J. Robbins, G. C. Bazan, J. S. Murdzek, M. B. O' Regan, R. R. Schrock, *Organometallics* **1991**, *10*, 2902 – 2907.
[115] T. Masuda, H. Tachimori, *J. Macromol. Sci. Pure Appl. Chem. A* **1997**, *34*, 1977 – 1995.
[116] H. Shirakawa, T. Masuda, K. Takeda, in *The Chemistry of Triple-Bonded Functional Groups, Supplement C2*(Ed.: S. Patai), Wiley, **1994**, pp. 945 – 1016.
[117] a) J. Konzelman, K. B. Wagener, *Macromolecules* **1995**, *28*, 4686 – 4692; b) J. Konzelman, K. B. Wagener, *Macromolecules* **1996**, *29*, 7657 – 7660; c) K. B. Wagener, K. Brzezinska, J. D. Anderson, T. R. Younkin, K. Steppe, W. DeBoer, *Macromolecules* **1997**, *30*, 7363 – 7369.
[118] a) E. Thorn-Csanyi, K. P. Pflug, *Makromol. Chem. Rapid Commun.* **1993**, *14*, 619 – 624; b) E. Thorn-Csanyi, P. Kraxner, *Macromol. Rapid Commun.* **1995**, *16*, 147 – 153.
[119] S.-K. Choi, Y.-S. Gal, S.-H. Jin, H. K. Kim, *Chem. Rev.* **2000**, *100*, 1645 – 1682.
[120] H. H. Fox, M. O. Wolf, R. O' Dell, B. L. Lin, R. R. Schrock, M. S. Wrighton, *J. Am. Chem. Soc.* **1994**, *116*, 2827 – 2843.
[121] R. H. Grubbs, W. Tumas, *Science* **1989**, *243*, 907 – 915.
[122] M. R. Buchmeiser, *Chem. Rev.* **2000**, *100*, 1565 – 1604.
[123] W. J. Feast, V. C. Gibson, E. L. Marshall, *J. Chem. Soc. Chem. Commun.* **1992**, 1157 – 1158.
[124] G. Bazan, E. Khosravi, R. R. Schrock, W. J. Feast, V. C. Gibson, M. B. O'Regan, J. K. Thomas, W. M. Davis, *J. Am. Chem. Soc.* **1990**, *112*, 8378 – 8387.
[125] W. J. Feast, V. C. Gibson, K. J. Ivin, A. M. Kenwright, E. Khosravi, *J. Mol. Catal.* **1994**, *90*, 87 – 99.
[126] W. J. Feast, V. C. Gibson, K. J. Ivin, A. M. Kenwright, E. Khosravi, *J. Chem. Soc. Chem. Commun.* **1994**, 1399 – 1400.
[127] Ru-based complex **58a**: a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100 – 110; catalyst **58b**: b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, **1999**, *1*, 953 – 956; complex **58c**: c) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247 – 2250; d) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2647 – 2678; e) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787 – 4790; complex **58d**: f) J. P. A. Harrity, M. S. Visser, J. D. Gleason, A. H. Hoveyda *J. Am. Chem. Soc.* **1997**, *119*, 1488 – 1489; g) J. P. A. Harrity, D. S. La, D. R. Cefalo, M. S. Visser, A. H. Hoveyda *J. Am. Chem. Soc.* **1998**, *120*, 2343 – 2351; h) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791 – 799; complex **58e**: i) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.
[128] For a recent study of molybdenum-catalyzed CM, see: T. Yasuda, J. Abe, H. Yoshida, T. Iyoda, T. Kawai, *Adv. Synth. Catal.* **2002**, *344*, 705 – 711.
[129] A. G. M. Barrett, J. C. Beall, V. C. Gibson, M. R. Giles, G. L. P. Walker, *Chem. Commun.* **1996**, 2229 – 2230.
[130] M. Ahmed, T. Arnauld, A. G. M. Barrett, D. C. Braddock, K. Flack, P. A. Procopiou, *Org. Lett.* **2000**, *2*, 551 – 553.
[131] A. F. Houri, Z. M. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943 – 2944.
[132] Z. M. Xu, C. W. Johannes, S. S. Salman, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 10926 – 10927.
[133] Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofilena, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302 – 11016.
[134] For a study regarding the reversible nature of Ru-catalyzed olefin-metathesis reactions, see: N. J. Marsella, H. D. Maynard, R. H. Grubbs, *Angew. Chem.* **1997**, *109*, 1147 – 1150; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1101 – 1103.
[135] S. A. May, P. A. Grieco, *Chem. Commun.* **1998**, 1597 – 1598.
[136] A. B. Smith, S. A. Kozmin, C. M. Adams, D. V. Paone, *J. Am. Chem. Soc.* **2000**, *122*, 4984 – 4985.
[137] A. B. Smith, C. M. Adams, S. A. Kozmin, *J. Am. Chem. Soc.* **2001**, *123*, 990 – 991.
[138] A. B. Smith, C. M. Adams, S. A. Kozmin, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 5925 – 5937.
[139] K. C. Nicolaou, S. A. Snyder, K. B. Simonsen, A. E. Koumbis, *Angew. Chem.* **2000**, *112*, 3615 – 3620; *Angew. Chem. Int. Ed.* **2000**, *39*, 3473 – 3478.
[140] S. F. Martin, Y. S. Liao, Y. L. Wong, T. Rein, *Tetrahedron Lett.* **1994**, *35*, 691 – 694.
[141] a) I. M. Fellows, D. E. Kaelin, Jr., S. F. Martin, *J. Am. Chem. Soc.* **2000**, *122*, 10781 – 10787; b) S. F. Martin, H.-J. Chen, A. K. Courtney, Y. Liao, M. Patzel, M. N. Ramser, A. S. Wagman, *Tetrahedron* **1996**, *52*, 7251 – 7264; c) J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.-L. Wong, H.-J. Chen, A. K. Courtney, S. F. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 8584 – 8592; For Ru-catalyzed RCM reactions aimed towards the total synthesis of manzamine A, see: d) B. C. Borer, S. Deerenberg, H. Bieraugel, U. K. Pandit, *Tetrahedron Lett.* **1994**, *35*, 3191 – 3194.
[142] A. Fürstner, O. R. Thiel, *J. Org. Chem.* **2000**, *65*, 1738 – 1742.
[143] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746 – 8749.
[144] K. Nakashima, K. Inoue, M. Sono, M. Tori, *J. Org. Chem.* **2002**, *67*, 6034 – 6040.
[145] O. Fujimura, G. C. Fu, P. W. K. Rothemund, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2355 – 2356.
[146] A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130 – 9136.
[147] A. K. Ghosh, J. Cappielo, D. Shin, *Tetrahedron Lett.* **1998**, *39*, 4651 – 4654.
[148] A. G. M. Barrett, M. Ahmed, S. P. Baker, S. P. D. Baugh, D. C. Braddock, P. A. Procopiou, A. J. P. White, D. J. Williams, *J. Org. Chem.* **2000**, *65*, 3716 – 3721.
[149] D. Bourgeois, A. Pancrazi, L. Ricard, J. Prunet, *Angew. Chem.* **2000**, *112*, 741 – 744; *Angew. Chem. Int. Ed.* **2000**, *39*, 726 – 728.
[150] D. Bourgeois, J. Mahuteau, A. Pancrazi, S. P. Nolan, J. Prunet, *Synthesis* **2000**, 869 – 882.
[151] J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 123 – 126.
[152] J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127 – 130.
[153] J. S. Clark, J. G. Kettle, *Tetrahedron* **1999**, *55*, 8231 – 8248.
[154] For examples of adventitious olefin isomerization observed with molybdenum-catalyzed olefin-metathesis reactions, see: D. Joe, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8635 – 8638, and ref. [153].
[155] For representative studies on Ru-catalyzed olefin isomerization in conjunction with olefin metathesis, see: a) S. J. Miller, H. E. Blackwell, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 9606 – 9614; b) L. Ackermann, D. El Tom, A. Fürstner, *Tetrahedron* **2000**, *56*, 2195 – 2202; c) L. A. Paquette, I. Efremov, *J. Am. Chem. Soc.* **2001**, *123*, 4492 – 4501; d) M. Gurjar, P. Yakambram, *Tetrahedron Lett.* **2001**, *42*, 3633 – 3636; e) C. Cadot, P. Dalko, J. Cossy, *Tetrahedron Lett.* **2002**, *43*, 1839 – 1841; f) A. E. Sutton,

B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390 – 13391; g) M. Arisawa, Y. Terada, M. Nakagawa, A. Nishida, *Angew. Chem.* **2002**, *114*, 4926 – 4928; *Angew. Chem. Int. Ed.* **2002**, *41*, 4732 – 4734.

[156] J. S. Clark, O. Hamelin, R. Hufton, *Tetrahedron Lett.* **1998**, *39*, 8321 – 8324.

[157] J. S. Clark, O. Hamelin, *Angew. Chem.* **2000**, *112*, 380 – 382; *Angew. Chem. Int. Ed.* **2000**, *39*, 372 – 374.

[158] J. P. Morken, M. T. Didiuk, M. S. Visser, A. H. Hoveyda, *J. Am. Chem. Soc.* **1994**, *116*, 3123 – 3124.

[159] M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 4291 – 4298.

[160] C. W. Johannes, M. S. Visser, G. S. Weatherhead, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 8340 – 8347.

[161] For example, see: a) J. A. Smulik, S. T. Diver, *Org. Lett.* **2000**, *2*, 2271 – 2274; b) M. J. Bassindale, P. Hamley, J. P. A. Harrity, *Tetrahedron Lett.* **2001**, *42*, 9055 – 9057; c) D. Banti, M. North, *Tetrahedron Lett.* **2002**, *43*, 1561 – 1564; d) M. Mori, Y. Kuzuba, T. Kitamura, Y. Sato, *Org. Lett.* **2002**, *4*, 3855 – 3858; e) D. Meng, D. L. Parker, Jr., *Tetrahedron Lett.* **2002**, *43*, 9035 – 9038.

[162] a) M. Seepersaud, Y. Al-Abed, *Org. Lett.* **1999**, *1*, 1463 – 1465; for a related example, see: b) O. Sellier, P. V. de Weghe, D. Le Nouen, C, Strehler, J. Eustache, *Tetrahedron Lett.* **1999**, *40*, 853 – 856.

[163] K. L. Lee, J. B. Goh, S. F. Martin, *Tetrahedron Lett.* **2001**, *42*, 1635 – 1638.

[164] S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1998**, *120*, 13523 – 13524.

[165] S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628 – 4641.

[166] S. G. Nelson, W. S. Cheung, A. J. Kassick, M. A. Hilfike, *J. Am. Chem. Soc.* **2002**, *124*, 13654 – 13655.

[167] S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2002**, *124*, 15196 – 15197.

[168] D. M. Hodgson, A. M. Foley, L. T. Boulton, P. J. Lovell, G. N. Maw, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2911 – 2922.

[169] O. Fujimura, G. C. Fu, R. H. Grubbs, *J. Org. Chem.* **1994**, *59*, 4029 – 4031.

[170] D. Calimente, M. H. D. Postema, *J. Org. Chem.* **1999**, *64*, 1770 – 1771.

[171] L. Liu, M. H. D. Postema, *J. Am. Chem. Soc.* **2001**, *123*, 8602 – 8603.

[172] M. H. D. Postema, D. Calimente, L. Liu, T. L. Behrmann, *J. Org. Chem.* **2000**, *65*, 6061 – 6068.

[173] J. D. Rainier, S. P. Allwein, J. M. Cox, *Org. Lett.* **2000**, *2*, 231 – 234.

[174] J. D. Rainier, J. M. Cox, S. P. Allwein, *Tetrahedron Lett.* **2001**, *42*, 179 – 181.

[175] J. D. Rainier, S. P. Allwein, J. M. Cox, *J. Org. Chem.* **2001**, *66*, 1380 – 1386.

[176] S. D. Burke, K. J. Quinn, V. J. Chen, *J. Org. Chem.* **1998**, *63*, 8626 – 8627.

[177] Throughout this article, the identity of the enantiomer formed is that which is obtained with the catalyst antipode illustrated. Transformations with binol-based complexes (e.g., **11**) were carried out with the opposite antipode of the catalyst versus that illustrated. Because (*S*)-biphen and (*R*)-binol complexes were employed in our studies, this adjustment has been made to facilitate comparison between biphen- and binol-based catalysts.

[178] O. Fujimura, R. H. Grubbs, *J. Org. Chem.* **1998**, *63*, 824 – 832.

[179] O. Fujimura, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 2499 – 2500.

[180] For a review of metal-catalyzed kinetic resolution, see: A. H. Hoveyda, M. T. Didiuk, *Curr. Org. Chem.* **1998**, *2*, 537 – 574.

[181] For an earlier overview of molybdenum-catalyzed asymmetric olefin metathesis, see: A. H. Hoveyda, R. R. Schrock, *Chem. Eur. J.* **2001**, *7*, 945 – 950.

[182] For discussions regarding combinatorial approaches to catalyst discovery and the issue of "catalyst generality," see: A. H. Hoveyda, *Handbook of Combinatorial Chemistry*, (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 991 – 1016.

[183] J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 4041 – 4042.

[184] The value for k_{rel} is calculated by the equation reported by Kagan and Fiaud: H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *53*, 708 – 710.

[185] D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 9720 – 9721.

[186] All transformations promoted by chiral Mo catalysts can be carried out in toluene (in addition to benzene) or alkanes (e.g., *n*-pentane) with equal efficiency. See text for specific examples.

[187] S. D. Burke, N. Muller, C. M. Beudry, *Org. Lett.* **1999**, *1*, 1827 – 1829.

[188] A. F. Kiely, J. A. Jernelius, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 2868 – 2869.

[189] S. J. Dolman, E. S. Sattely, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **2002**, *124*, 6991 – 6997.

[190] For representative studies regarding non-asymmetric ROM reactions, see: a) M. L. Randall, J. A. Tallarico, M. L. Snapper, *J. Am. Chem. Soc.* **1995**, *117*, 9610 – 9611; b) M. L. Snapper, J. A. Tallarico, M. L. Randall, *J. Am. Chem. Soc.* **1997**, *119*, 1478 – 1479; c) W. J. Zuercher, M. Hashimoto, R. H. Grubbs *J. Am. Chem. Soc.* **1996**, *118*, 6634 – 6640; d) see ref. [127f]; e) M. F. Schneider, N. Lucas, J. Velder, S. Blechert, *Angew. Chem.* **1997**, *109*, 257 – 259; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 257 – 259; f) F. D. Cuny, J. Cao, J. R. Hauske, *Tetrahedron Lett.* **1997**, *38*, 5237 – 5240; g) M. Michaut, J.-L. Parrain, M. Santelli, *Chem. Commun.* **1998**, 2567 – 2568; h) H. Katayama, H. Urushima, T. Nishioka, C. Wada, M. Nagao, F. Ozawa, *Angew. Chem.* **2000**, *112*, 4687 – 4689; *Angew. Chem. Int. Ed.* **2000**, *39*, 4513 – 4515.

[191] G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 1828 – 1829.

[192] D. R. Cefalo, A. F. Kiely, M. Wuchrer, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 3139 – 3140.

[193] For a subsequent catalytic enantioselective approach to tipranavir, see: B. M. Trost, N. G. Andersen, *J. Am. Chem. Soc.* **2002**, *124*, 14320 – 14321.

[194] X. Teng, D. R. Cefalo, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 10779 – 10784.

[195] For synthesis of spirocyclic structures through catalytic olefin metathesis, see: a) ref. [161b]; b) D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U.-H. Dolling, P. J. Reider, *Org. Lett.* **2001**, *3*, 671 – 674; c) D. J. Wallace, P. G. Bulger, D. J. Kennedy, M. S. Ashwood, I. F. Cottrell, U.-H. Dolling, *Synlett.* **2001**, 357 – 360.

[196] a) D. S. La, J. G. Ford, E. S. Sattely, J. P. J. Bonitatebus, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 11603 – 11604; b) D. S. La, E. S. Sattely, J. G. Ford, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 7767 – 7778.

[197] The chiral Mo alkylidene most likely approaches norbornyl alkenes from the exo face. For the X-ray structure of a related molybdacyclobutane, see: G. C. Bazan, J. H. Oskam, H. Cho, L. Y. Park, R. R. Schrock, *J. Am. Chem. Soc.* **1991**, *113*, 6899 – 6907.

[198] K. C. Hultzsch, J. A. Jernelius, A. H. Hoveyda, R. R. Schrock, *Angew. Chem.* **2002**, *114*, 609 – 613; *Angew. Chem. Int. Ed.* **2002**, *41,* 589 – 593.

[199] T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225 – 3228.
[200] a) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954 – 4955; b) J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Katoka, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, in press.
[201] Z. Wu, D. R. Wheeler, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 146 – 151.
[202] S. K. Armstrong, B. A. Christie, *Tetrahedron Lett.* **1996**, *37*, 9373 – 9376.
[203] Y. S. Shon, T. R. Lee, *Tetrahedron Lett.* **1997**, *38*, 1283.
[204] G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 3800 – 3801.
[205] See also: K. L. Lee, J. B. Goh, S. F. Martin, *Tetrahedron Lett.* **2001**, *42*, 1635 – 1638.
[206] J. A. Burlison, J. M. Gray, D. G. J. Young, *Tetrahedron Lett.* **2001**, *42*, 5363 – 5365.
[207] J. S. Kingsbury, A. H. Hoveyda; unpublished results.

