MULTIPLE METAL-CARBON BONDS FOR CATALYTIC METATHESIS REACTIONS

Nobel Lecture, December 8, 2005

by

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It's my great priviledge to be here today, in a position I never thought possible. I hope the story that I will tell you will give you some idea what I have contributed to the area for which the Nobel Prize in Chemistry was awarded this year.

The story begins thirty two years ago in 1973, the year the Nobel Prize was shared by G. Wilkinson and E. O. Fischer. Wilkinson's Nobel Lecture[1] concerned the nature of a single bond between a transition metal and a carbon atom in an alkyl group, and emphasized the fact that the metal-carbon bond is not inherently weak. E. O. Fischer in his Nobel Lecture[2] summarized the extensive chemistry of transition metal "carbene" complexes[3,4] that contain a metal-carbon double bond discovered by him and his group in 1964 (Fig 1).[5] He also reported new "carbyne" complexes that contain a metal-carbon triple bond.[6] It was clear that metal-carbon single bonds were of great importance in the emerging area of homogeneous catalysis. However, no catalytic reactions involving species that contain metal-carbon double or triple bonds were known. When I went to the Central Research Department of E. I. DuPont de Nemours and Company in 1972, transition metal organometallic chemistry and homogeneous catalysis were of great interest as a consequence of their huge potential in organic chemistry and therefore in industry.

In the early 1970's inorganic chemists knew that many transition metal species containing a metal-carbon bond are subject to various modes of decomposition that are much more rapid than in a non-transition metal species such as $Zn(CH_2CH_3)_2$ or $Al(CH_2CH_3)_3$. The most common of these involves transfer of a β hydrogen, from an ethyl group (MCH_2CH_3) for example, to the metal to

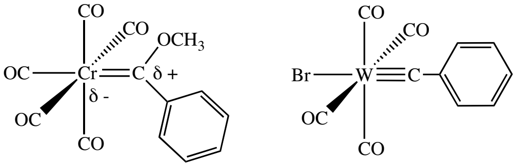


Figure 1. "Low oxidation state" carbene (left) and carbyne complexes (right).

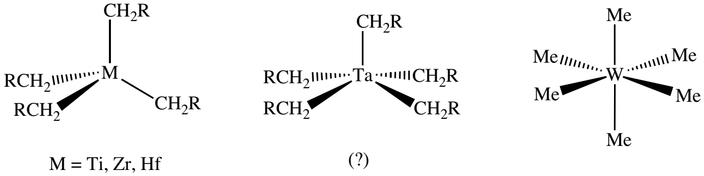
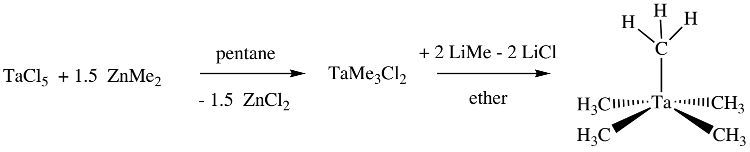


Figure 2. “Peralkyl” complexes of Group 4, 5, and 6, metals in their highest possible oxidaton states.

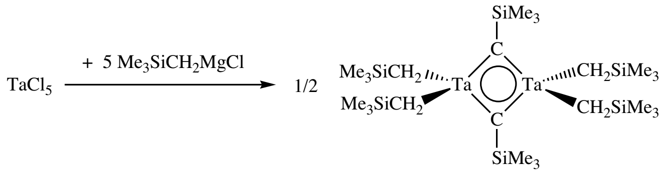
yield a metal-hydride and an alkene. The relative stabilities of high oxidation state “homoleptic” or “peralkyl” compounds such as $M[CH_2Si(CH_3)_3]_4$, $M(CH_2C_6H_5)_4$, and $M[CH_2C(CH_3)_3]_4$ (M = Ti, Zr, or Hf; Fig 2), were rationalized on the basis of the fact that unlike a compound having an ethyl ligand, the alkyl ligands in these species lack β hydrogens and so of course cannot undergo decomposition processes that involve β hydrogens.[7] In 1973 Wilkinson published the synthesis of $W(CH_3)_6$.[8] Unlike $M(CH_3)_4$ species (where M = Ti, Zr, or Hf) $W(CH_3)_6$ is stable at 22°C. The methyl carbon is α with respect to the metal; there is no β carbon and so no β hydrogens. However, methyl species *are not sterically protected* against bimolecular reactions that involve *α hydrogens.* As you can see from the note added in the proof of Wilkinson’s Nobel address,[9] I was intrigued by high oxidation state peralkyl complexes and had chosen to explore the organometallic chemistry of tantalum soon after my arrival at DuPont. Little alkyl chemistry was known of the metals in group 5 (V, Nb, Ta) at that time; I chose tantalum because it is next to tungsten in group 6 (Cr, Mo, W), and like tungsten, tantalum is relatively stable in its highest possible oxidation state, Ta(5+). Peralkyl tantalum complexes therefore must be pentaalkyls.

My starting point for tantalum alkyl chemistry was a paper by G. L. Juvinall[10] in which he described the low yield synthesis of niobium and tantalum trimethyl dichloride species through addition of dimethylzinc to the metal pentachlorides. I found that crystalline $TaMe_3Cl_2$ not only could be prepared quantitatively in pentane on a large scale (Eq 1), but it could be stored for

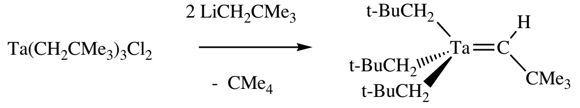


(1)

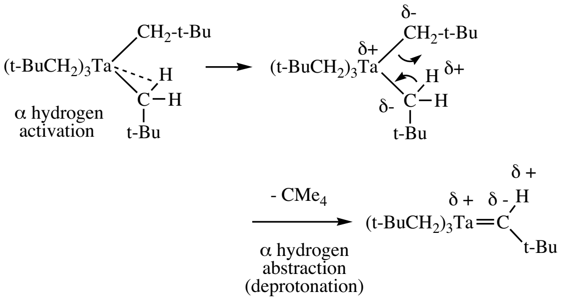
long periods at −40 °C in the solid state. Moreover, it reacted with two equivalents of LiMe to generate volatile, yellow, crystalline $TaMe_5$.[11] This species is much less stable than $W(CH_3)_6$, but much more stable than $Hf(CH_3)_4$. Pentamethyltantalum decomposes above 0 °C to yield ~3.7 equivalents of methane, and it does so in a bimolecular fashion. Pentamethyltantalum has 15 sterically unprotected α C-H bonds and the metal is highly electron-deficient (10 electrons, 8 shy of the preferred 18 electron count). Interactions between one metal center and CH bonds in another metal complex thereby are encouraged, and are easier in $TaMe_5$ than in WMe_6 for simple steric reasons.


(2)

Wilkinson had just published a reaction that yielded an unusual dimeric species containing what he called "carbene bridge," μ-$CSiMe_3$ (actually a carbyne bridge; Eq 2). With respect to $Ta(CH_2SiMe_3)_5$ he said "It is assumed that a penta-alkyl complex cannot exist for steric reasons."[12] Therefore, I turned to experiments involving the neopentyl (CH_2CMe_3) ligand in order to probe the limit of steric crowding in homoleptic d^0 tantalum pentaalkyls and the nature of the decomposition pathways that might be observable in such circumstances. The crucial experiment (Eq 3) consisted of an attempt to prepare


(3)

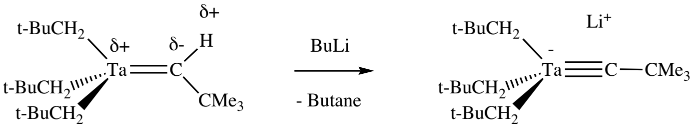
$Ta(CH_2CMe_3)_5$ through addition of two equivalents of $LiCH_2CMe_3$ to $Ta(CH_2CMe_3)_3Cl_2$. Instead of $Ta(CH_2CMe_3)_5$, orange, crystalline, and thermally stable $(Me_3CCH_2)_3Ta{=}CHCMe_3$ was formed in quantitative yield.[13] The exact mechanism is still not known, but it is likely that an α hydrogen is activated by the metal and subsequently removed as a proton by a neopentyl group, possibly in an *intramolecular* manner in pentaneopentyltantalum itself (Eq 4).


(4)

$(Me_3SiCH_2)_3Ta{=}CHSiMe_3$ may be an intermediate in the reaction shown in equation 2, but it must decompose intermolecularly to give tetramethylsilane and the observed dimeric species; $(Me_3CCH_2)_3Ta{=}CHCMe_3$ does not.

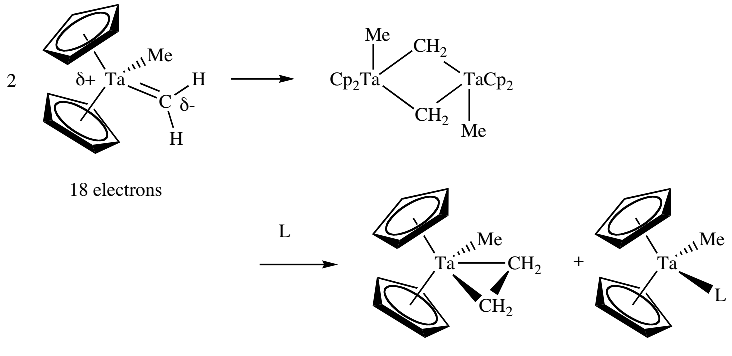
The tantalum neopentylidene complex, $(Me_3CCH_2)_3Ta{=}CHCMe_3$, was new in several respects. It was the first example of a stable transition metal M=CHR species. Second, the terminal alkylidene was formed through a new type of reaction, an intramolecular α hydrogen abstraction from an alkyl. Third, unlike "carbene" complexes discovered by Fischer and his group, $(Me_3CCH_2)_3Ta{=}CHCMe_3$ was highly electron-deficient (10 electrons in metal-based bonding orbitals). Fourth, $(Me_3CCH_2)_3Ta{=}CHCMe_3$ appeared to behave as if the metal were in its highest possible oxidation state with the Ta=C bond being polarized so that the metal is relatively positive and the carbon relatively negative, opposite to what is found in Fischer-type carbene complexes. Fifth, the high thermal stability and resistance of $(Me_3CCH_2)_3Ta{=}CHCMe_3$ toward intermolecular decomposition reactions, *as well as toward further intramolecular reactions,* suggested that other high oxidation state, four-coordinate species that contain four sterically demanding covalently bound ligands might be viable. This simple but important principle pervaded much of the high oxidation state chemistry that was developed over the next 30 years in my group.

"Deprotonation" of a neopentyl ligand to give a neopentylidene ligand suggested that a neopentylidene ligand might be deprotonated further by an external base. Indeed, addition of *n*-butyllithium to $(Me_3CCH_2)_3Ta{=}CHCMe_3$ led to formation of the related high oxidation state, anionic, *neopentylidyne* species, $\{(Me_3CCH_2)_3Ta{\equiv}CCMe_3\}Li$[14] (Eq 5).



(5)

Finally, it was demonstrated that even a methylene ($Ta{=}CH_2$) species could be prepared through deprotonation of $[TaCp_2(CH_3)_2]^+$.[15,16] Even though $TaCp_2(CH_3)(CH_2)$ contains 18 electrons in metal-based orbitals, it is unstable toward bimolecular decomposition to yield an ethylene complex in 50% yield, plus related species that are formed in the presence of some ligand L (Eq 6). Bimolecular decomposition of alkylidenes, especially methylenes, is a battle that continues to be fought today. The main point is that between 1973 and 1975 *high oxidation state* tantalum-carbon double and triple bonds had been prepared, and they appeared to be significantly different in several important respects from the *low oxidation state* species prepared by Fischer.

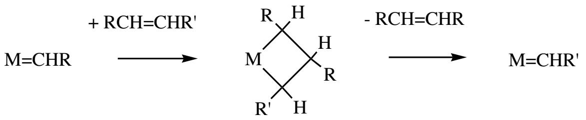


L = CO, C_2H_4, PR_3

(6)

At some point in the early 1970's I became aware of the "olefin metathesis" reaction (Eq 7), a startling and mysterious reaction catalyzed by homogeneous Mo and W catalysts (and heterogeneous Re catalysts), the identities of which were not known.[17-20] Physical organic experiments by (*inter alia*) R. H.

$$2\,\mathrm{RCH{=}CHR'} \rightleftharpoons \mathrm{RCH{=}CHR} + \mathrm{R'CH{=}CHR'} \qquad (7)$$

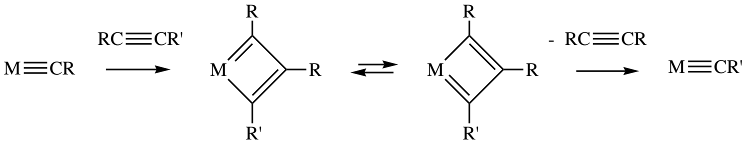


(8)

$$2\,\mathrm{RC{\equiv}CR'} \rightleftharpoons \mathrm{R'C{\equiv}CR'} + \mathrm{RC{\equiv}CR} \qquad (9)$$

Grubbs,[21-23] T. J. Katz,[24,25] C. P. Casey,[26] and Y. Chauvin[27] were designed to determine whether the reaction proceeded by a "pair-wise" or "non-pair-wise" mechanism.[20] It was shown that the reaction proceeded in a "non-pair-wise" fashion, and Chauvin was the first to propose the correct "carbene/metalacyclobutane" mechanism (Eq 8) that would account for all observations.[27] However, at that time no "carbene" complexes were known that would react efficiently with ordinary olefins as proposed by Chauvin.

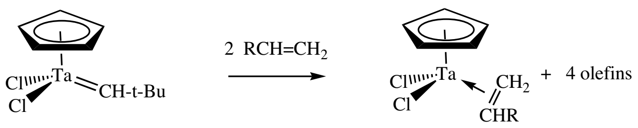
Alkyne metathesis (Eq 9), both heterogeous[28,29] and homogeneous,[30] catalyzed by Mo and W compounds of unknown type, also had been discovered. T. J. Katz[24] proposed a mechanism of alkyne metathesis analogous to that for olefin metathesis (Eq 10), i.e., one that involves formation of *metalacyclobutadiene* intermediates. Yet no "carbyne" complexes were known that would catalyze alkyne metathesis.



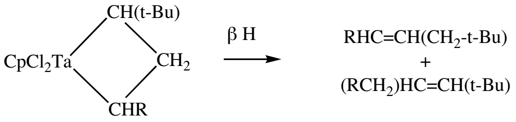
(10)

I asked myself whether the new types of tantalum "alkylidene" and "alkylidyne" complexes might not be at least the type of species that metathesize olefins and acetylenes, respectively, even though tantalum was not known to be a catalyst for either of these reactions at that time.

After my move to MIT in 1975, I began to explore reactions between various tantalum alkylidene complexes and olefins in some detail. It became clear (Eq 11) that electron deficient tantalum and niobium alkylidenes would react with olefins readily to give metalacyclobutane intermediates, but these species would rearrange via a β hydride process to give as many as four of the possible rearrangement products instead of losing an olefin to reform a new alkylidene (Eqs 12 and 13); the alkylidene chain reaction never started and



(11)



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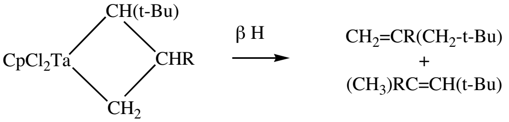
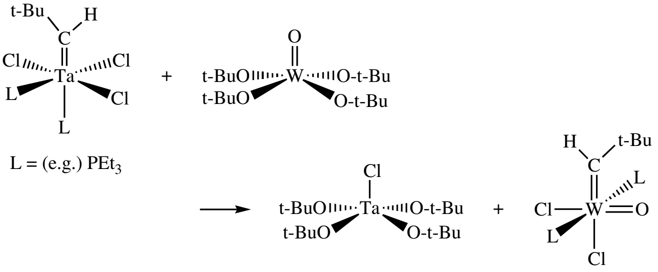


(13)

no metathesis products therefore were observed.[31] At an international symposium on olefin metathesis (ISOM III) in 1979 in Lyon I reported that niobium and tantalum complexes that contain *t-butoxide* ligands in place of chloride ligands, such as $M(CH\text{-}t\text{-}Bu)(O\text{-}t\text{-}Bu)_2Cl(PMe_3)$, could be coaxed into metathesizing olefins. Several dozen catalytic metathesis cycles could be observed for an olefin such as cis-2-pentene.[32] It was proposed that the t-butoxide ligands "prevent reduction" of the metal and "promote metathesis." At that same conference I reported that an attempt to carry out a "Wittig-like" reaction between a tantalum alkylidene and a tungsten oxo complex to yield $W(CH\text{-}t\text{-}Bu)(O\text{-}t\text{-}Bu)_4$ and $Ta(O)L_2Cl_3$, instead produced an unanticipated 18 electron oxo neopentylidene complex of tungsten (Eq 14).[33] This oxo



(14)

neopentylidene complex would react with olefins to yield metathesis products and new alkylidenes that one would expect from the metathesis reaction, including a methylene complex, and especially rapidly in the presence of a trace of $AlCl_3$. This was a convincing demonstration that the oxo alkylidene species react with olefins readily and reform an alkylidene complex of the same type from half an olefin that was present. The role of $AlCl_3$, it was proposed, was to remove either chloride or phosphine (reversibly) and thereby create an empty coordination site at the electronically saturated metal center.

A four-coordinate neopentylidene species containing large, covalently bound ligands was believed to be the most likely isolable, but reactive, electron deficient species. A neopentylidene ligand clearly was required. We also knew that alkoxides were desirable, but what should the fourth, and necessarily dianionic, ligand X (Fig 3) be? An oxo ligand was unsuitable because it almost certainly would encourage bimolecular decomposition reactions. We focussed on an imido ($[NR]^{2-}$) ligand, an isoelectronic analog of an oxo ligand, since the imido ligand could be sterically protected by a large R group. After consid-

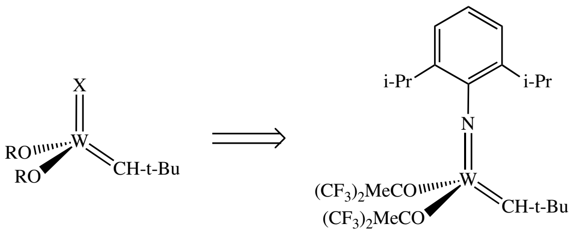
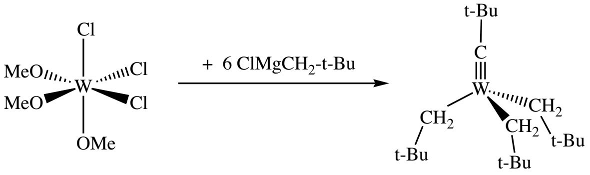


Figure 3. Design of a stable tungsten imido alkylidene bisalkoxide complex.

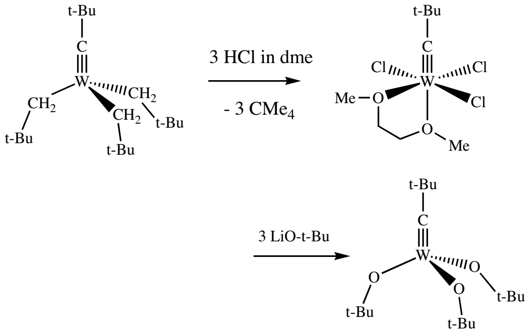
ering the likely synthetic difficulties associated with R being a 2,6-di-t-butylphenyl group, we settled on the 2,6-diisopropylphenyl group, a choice that in part was in response to a comment by K. B. Sharpless concerning the value of isopropyl groups in general versus t-butyl groups. (The 2,6-diisopropylphenyl group is found in many nitrogen-based ligands in a large variety of catalysts today.) Several large and sterically demanding tertiary alcohols and phenols were available, including fluorinated t-butanols such as $(CF_3)_2MeCOH$ whose pKa in water (~9) is significantly less than that of t-butanol itself (~19). We felt that the electron withdrawing ability of the hexafluoro-t-butoxide ligand should increase the electrophilicity of the metal dramatically and therefore also increase the rate of the reaction of an alkylidene complex with an olefin. Therefore, we aimed to prepare $W(NAr)(CHCMe_3)[OCMe(CF_3)_2]_2$ (Fig 3) with the expectation that this 14 electron species not only could be isolated, but that it would metathesize olefins readily.

Being aware of the almost magical properties of the neopentyl ligand (as well as neopentylidene and neopentylidyne ligands), we also were curious about simple reactions between W(VI) compounds (initially WCl_6) and neopentyllithium or neopentylmagnesium chloride, and had begun exploring such reactions in 1977. We discovered that a volatile, yellow, crystalline alkylidyne complex could be isolated from such reactions,[34] and that the reaction between $W(OMe)_3Cl_3$ and six equivalents of Me_3CCH_2MgCl in diethyl ether produced that species in a yield of ~50% (Eq 15).[35] $(Me_3CCH_2)_3W{\equiv}CCMe_3$ is



(15)

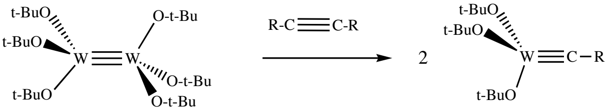
closely related to $(Me_3CCH_2)_3Ta{=}CHCMe_3$ in having four neopentyl or neopentyl-derived ligands around the metal. As we became aware of the benefits of alkoxides for efficient olefin metathesis, we became curious whether a trialkoxide species such as $(Me_3CO)_3W{\equiv}CCMe_3$ could be prepared and whether it would be an efficient *alkyne metathesis* initiator. We were pleased to find that $(Me_3CO)_3W{\equiv}CCMe_3$ in fact could be prepared readily (Eq 16), and especially pleased to find that alkynes *are* metathesized at room temperature



(16)

with $(Me_3CO)_3W{\equiv}CCMe_3$ as the initiator[36] at rates thousands of times faster than "black box" catalysts known in the literature. This finding proved to us that sterically bulky alkoxides were indeed highly beneficial for metathesis activity. In contrast to $(Me_3CO)_3W{\equiv}CCMe_3$, $(dme)Cl_3W{\equiv}CCMe_3$ does not metathesize alkynes, even though a tungstenacyclobutadiene intermediate necessary for that transformation, e.g., $Cl_3W[C(t\text{-}Bu)C(CH_3)C(CH_3)]$, could be isolated and crystallographically characterized![37] Other reactions took precedence.[38-40] $(Me_3CCH_2)_3W{\equiv}CCMe_3$ also did not metathesize internal alkynes; it was simply too unreactive. When the OR group in $(RO)_3W{\equiv}CCMe_3$ was a more electron withdrawing alkoxide or phenoxide, we could isolate and crystallographically characterize intermediate tungstenacyclobutadiene complexes in alkyne metathesis reactions and study them in detail.[41,42]

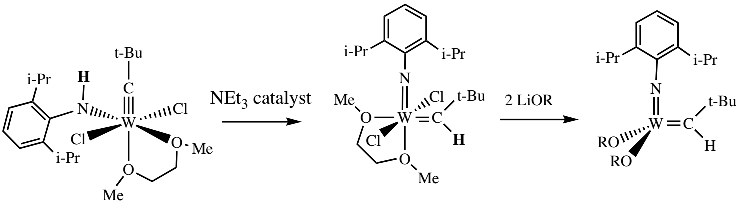
A large variety of species that contain tungsten-tungsten or molybdenum-molybdenum triple bonds, $X_3M{\equiv}MX_3$ species, were known at that time,[43,44] and in particular hexa-t-butoxide ditungsten, $(Me_3CO)_3W{\equiv}W(OCMe_3)_3$. An interesting question, therefore, was whether $(Me_3CO)_3W{\equiv}W(OCMe_3)_3$ would



(17)

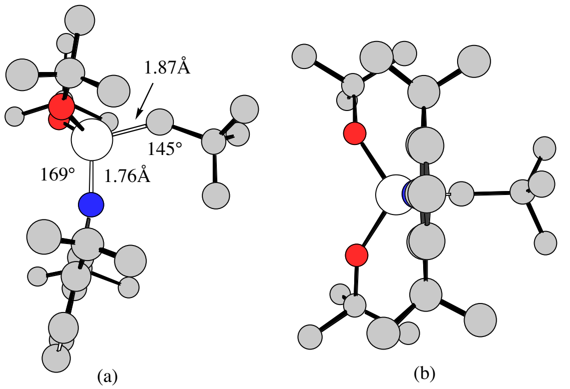
react with internal alkynes to yield $(Me_3CO)_3W{\equiv}CR$ complexes (Eq 17), which is effectively a metathesis-like reaction? The answer turned out to be yes, and it did so amazingly readily.[45] Although this is not a general reaction for all $X_3M{\equiv}MX_3$ species (M = Mo or W), the fact that it is facile only when X is a relatively sterically bulky alkoxide, had to be more than a coincidence. This discovery opened up a route to $(Me_3CO)_3W{\equiv}CR$ species that did not rely on α hydrogen abstraction reactions,[46] and cemented the relationship between, and interconvertibility of, strong triple bonds between metals, between carbons (in alkynes), and between a metal and a carbon in an alkylidyne complex. It is interesting to note that the C≡N bond in nitriles is also cleaved readily, although the N≡N bond in dinitrogen is not. That spectacular reaction, which requires a (three-coordinate) triamido species, would not be reported until 1995.[47]

But tungsten alkylidynes were important for an additional reason. If a neopentylidyne species could be prepared by removing an α proton from a neopentylidene ligand, could not that reaction be run in the reverse direction, i.e., could not a proton be added to a neopentylidyne species to yield a neopentylidene species? Moreover, could that not be accomplished in a manner that would produce the other desired metal-ligand multiple bond, namely the imido ligand, at the same time? An amido/alkylidyne complex could in fact be prepared readily and the proton then moved from **N** to **C** by a base (Eq 18). A large variety of W(NAr)(CH-t-Bu)(OR)$_2$ complexes then could be prepared readily from the dichloride species, as long as OR was large enough to prevent complications that resulted from bimolecular reactions. X-ray structures such as that in Figure 4 showed how the t-butyl group of the neopentylidene ligand points toward the imido ligand (a *syn* orientation), and how the diisopropylphenyl group on nitrogen protects the imido nitrogen and the alkylidene carbon atom against bimolecular reactions.



(18)

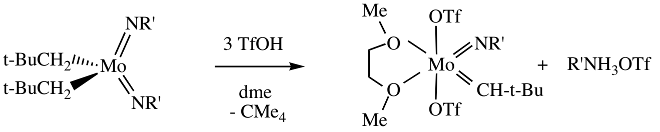
It soon became clear that W(NAr)(CH-t-Bu)(OR)$_2$ species would metathesize olefins in the expected manner with an activity that correlated roughly with the electron withdrawing power of the OR ligand. Catalysts that contain hexafluoro-t-butoxide ligands appeared to have the highest activities. We found that tungstenacyclobutane intermediates, the very intermediates proposed by Chauvin in the metathesis reaction, actually could be isolated and crystallographically characterized.[48] However, tungstenacyclobutane stabilities proved to be a problem is some circumstances; loss of an olefin from an un-



(a)

(b)

Figure 4. The structure of W(NAr)(CH-t-Bu)(O-t-Bu)$_2$; (a) top view; (b) side view.

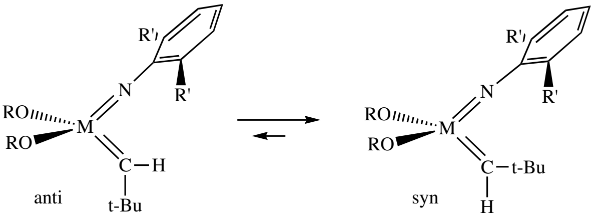


(19)

substituted tungstenacyclobutane intermediate, in particular, could be relatively slow. The metal therefore would remain sequestered in the form of a tungstenacyclobutane. Since Mo-ligand bonds are generally weaker than W-ligand bonds, we felt that a molybdacyclobutane complex might lose an olefin more readily. Therefore, we aimed to synthesize analogous Mo(NAr)(CH-t-Bu)$(OR)_2$ catalysts. A synthesis of bisalkoxides was devised, the key feature of which is the use of an imido "protecting group" that is then removed upon addition of triflic acid (Eq 19), thereby forming in the process a neopentylidene ligand from two neopentyl ligands through an α hydrogen abstraction reaction in a hypothetical Mo(NR')$(CH_2$-t-Bu$)_2$(Triflate$)_2$ intermediate.[49] The imido (NR') and alkoxide groups could be varied widely and a large number of molybdenum catalysts therefore became accessible.

The molybdenum bisalkoxide catalysts are also remarkably active for a wide range of metathesis reactions, again especially when the alkoxide is the highly electron withdrawing OCMe$(CF_3)_2$ group, and molybdacyclobutane intermediates *are* less stable than tungstacyclobutane intermediates toward loss of olefin. The steric bulk of the OCMe$(CF_3)_2$ and Ar (2,6-diisopropylphenyl) groups are also of considerable importance in preventing bimolecular reactions between the intermediate Mo(NAr)(CHR')$(OR)_2$ species in any given reaction. We slowly began to understand the extent to which the metathesis reaction could be *controlled* through systematic variation of the size and the electronic characteristics of the alkoxide and imido groups.

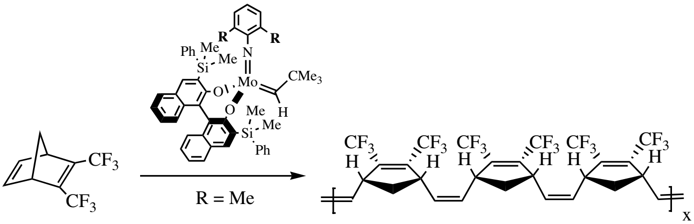
We also discovered that two isomers of any M=CHR catalyst are possible (Eq 20). In the isomer that is usually observed the alkylidene's substituent



(20)

points toward the imido group (*syn*), while in the other it points away from the imido group (*anti*). *Syn* and *anti* species can be formed during the course of a metathesis reaction, but *syn* and *anti* isomers of any given alkylidene also can interconvert simply through rotation about the Mo=C bond. The rate of rotation of a neopentylidene or neophylidene was found to vary by a factor of at least 10^6, and to depend (largely) on the nature of the alkoxide,[50,51] with rotation being relatively fast in the presence of alkoxide ligands such as t-butoxide and relatively slow in the presence of hexafluoro-t-butoxide ligands. In ring-opening metathesis polymerization (ROMP) studies, one of many variations of the basic olefin metathesis reaction, we proved (for one type of polymerizeable monomer) that the *anti* isomer was the more reactive by a factor of ~10^4. Therefore one, or the other, or both *syn* and *anti* intermediates in a catalytic reaction might be involved, with the outcome depending upon the nature of the imido and alkoxide groups, *and* the reactivity of the olefin involved in the reaction with *syn* and *anti* intermediates, and also the temperature and other variables. This circumstance complicates to a considerable degree a detailed understanding of the metathesis reaction by such catalysts, but at the same time dramatically increases the flexibility of the catalysts and the possibility that a metathesis reaction will proceed efficiently.

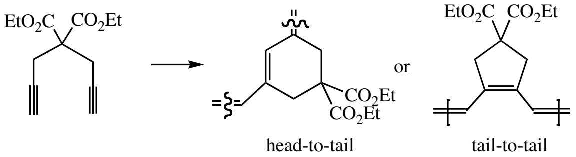
Ring-opening metathesis polymerization of cyclic olefins had been studied for many years before well-defined catalysts were developed.[17,18] We naturally asked whether well-defined catalysts behaved as polymerization catalysts for cyclic olefins, and if so, what advantages did they offer? In our only publication together, one that resulted from my sabbatical at Caltech as a Fairchild scholar in 1986, Grubbs and I showed that these new well-defined catalysts did behave in the expected manner, and that the process could be "living" in the right circumstances, i.e., intermediate alkylidenes that contain the growing polymer chain would not decompose.[52] In my laboratory we went on to show that the polymerization process could be controlled in a dramatic fashion to yield polymers with a highly regular repeating structure. Generally polymers with highly regular structures have the most interesting properties and therefore are the most desirable. In many cases we found that the entire polymer structure can be controlled through minute, but critical, changes in the catalyst structure. For example (Eq 21) a highly regular *cis,isotactic* polymer is formed if the catalyst contains a specific binaphtholate ligand and a *dimethyl*phenylimido group (R = CH_3 in the 2,6-disubstituted phenyl group).[53,54] In contrast, if the R group in the imido ligand is *isopropyl*, then the polymer has a *relatively random structure*. The smaller *dimethyl*phenylimido group is believed to allow polymerization to proceed solely via *syn* isomers to give *cis* linkages. Control of the "tacticity," or the way the five-membered rings point in this polymer, is greatest in the presence of a chiral (racemic) binaphtholate ligand, which is a consequence of "enantiomorphic site control" over the polymerization process. In a series of experiments with related monomers that contain two esters made from enantiomerically pure alcohols, we could distinguish between *isotactic* and *syndiotactic* polymers, and therefore could



(21)

prove the *cis,isotactic* structure, which is formed through enantiomorphic site control, and the *trans,syndiotactic* structure, which is formed through chain-end control, for the first time in ROMP polymers.[55] The degree to which one can control the polymer structure through systematic, tiny variations of the catalyst is of great importance for many ROMP polymers that are made today with high oxidation state alkylidene catalyst initiators.

For some time it had been known that "classical" Mo and W catalysts that would metathesize olefins would also polymerize alkynes. This suggested that metal alkylidenes were responsible.[56-58] We showed that well-defined species do indeed polymerize alkynes[59] or cyclopolymerize 1,6-heptadiynes[60] (Eq 22)



(22)

to yield polymers analogous to those described in the literature. In the case of a cyclopolymerization of 1,6-heptadiynes such as diethyldipropargylmalonate, a six-membered or a five-membered ring can form, depending upon the regiochemistry of the addition of the first alkyne to the alkylidene. Since the optical properties of such polyenes vary with the polymer's structure and chain length,[61] it is highly desirable to make a polymer with a single structure and to control the molecular weight of that polymer through a polymerization with a well-defined catalyst. Although work is still ongoing in this area, it now appears possible to do so.[62,63]

In 1992 G. C. Fu and R. H. Grubbs published two papers in which they demonstrated how $Mo(NAr)(CHCMe_2Ph)[OCMe(CF_3)_2]_2$ could be employed to make cyclic olefins quickly and efficiently that contain functionalities other than a C=C bond,[64,65] with the only other product being a volatile olefin such as ethylene, propylene, or butene (Fig 5). Rings of many sizes, and even rings that contain tetrasubstituted olefinic bonds, could be prepared. These papers helped awaken organic chemists to the possibility that olefin metathesis by well-defined catalysts had significant potential in organic chemistry. The fact that the Mo and W catalysts in this general class are sen-

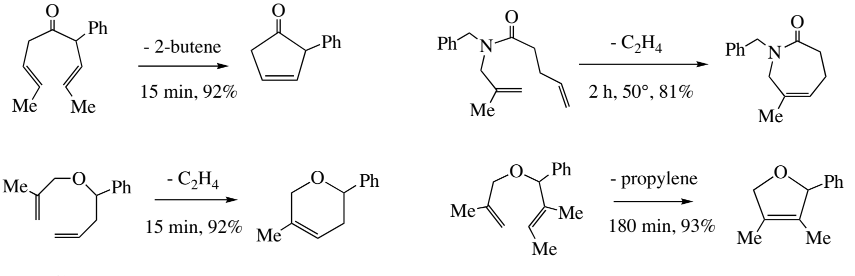
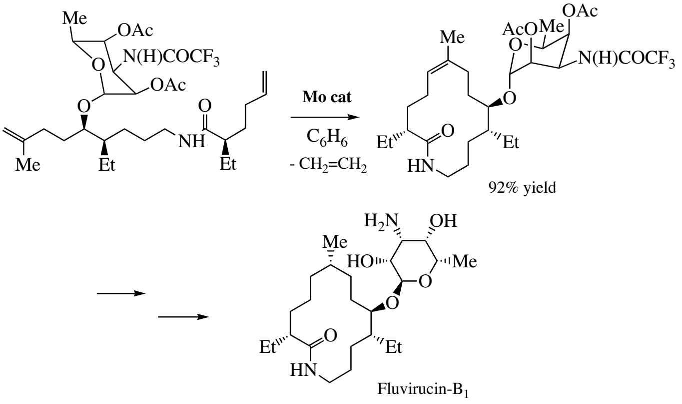


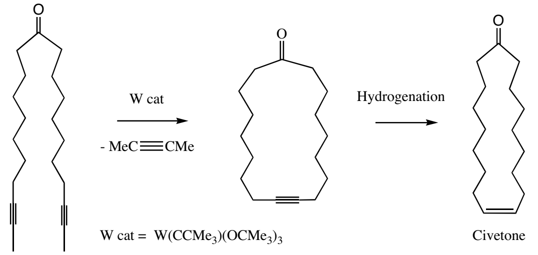
Figure 5. Some ring closing metatheses initiated by $Mo(NAr)(CHCMe_2Ph)[OCMe(CF_3)_2]_2$.

sitive to air, moisture, and some functionalities did not prohibit their use in organic reactions. In 1995 A. H. Hoveyda and his group reported a synthesis of a cyclic natural product, Fluvirucin-B_1, in which one of the steps consisted of a ring closing metathesis (RCM) reaction (Eq 23).[66] This paper demonstrated that relatively complex molecules could be prepared via metathesis. These and other applications of metathesis technology, along with the commercial availability of $Mo(NAr)(CHCMe_2Ph)[OCMe(CF_3)_2]_2$, helped fuel applications of Mo metathesis technology to organic chemistry.[67] The possibility that metathesis could be employed routinely in organic chemistry I believe was a significant factor that drove Grubbs to develop ruthenium catalysts in the early 1990's.[20,68,69]



(23)

The use of alkyne metathesis catalysts for organic chemistry also was realized in the 1990's, primarily through work by A. Fürstner, who showed that large rings could be prepared through alkyne metathesis with the $(Me_3CO)_3W{\equiv}CCMe_3$ initiator.[70] A cyclic alkyne then could be hydrogenated selectively to yield a *cis* olefin (Lindlar reduction). This alternative to alkene metathesis circumvented a still unsolved problem, formation of largely (~75%) thermodynamically more favored *trans* double bonds in alkene metathesis, instead of *cis* double bonds. An example is the stereoselective synthesis of civetone (Eq 24).[71] Many other reactions that involve formation of a carbon-carbon triple bond through alkyne metathesis as part of a synthetic organic procedure began to appear, such as syntheses of the cytotoxic marine alkaloid motuporamine C,[72] prostaglandin E_2-1,15-lactone,[73] and epothilone



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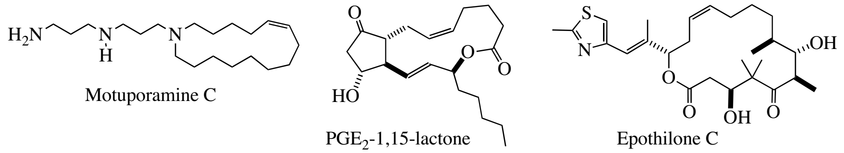
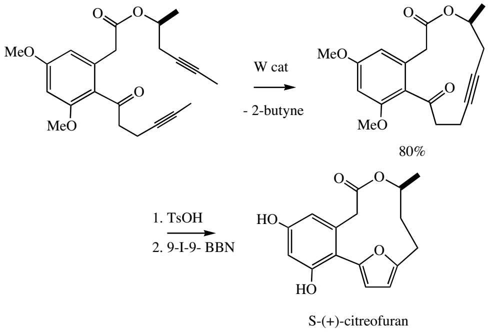


Figure 6. Some molecules whose syntheses involve alkyne metathesis to create the *cis* double bond.

A and C, all of which contain a *cis* olefin within a ring (Fig 6).[74] Alkyne metathesis can be useful in other ways, as shown in the synthesis of S-(+)-citreofuran (Eq 25).[75] Although molybdenum-based alkyne metathesis catalysts were known,[76,77] work by Cummins,[78] Fürstner,[79] and Moore,[80] recently have demonstrated how these relatively inaccessible Mo catalysts can be prepared *in situ* from trisamidoalkylidyne precursors.



(25)

With the knowledge that certain sterically protected biphenolates and binaphtholates can be attached to Mo to yield stable neopentylidene or neophylidene ROMP initiators, we turned to the development of enantiomerically pure catalysts for asymmetric metathesis reactions in the mid 1990's. Some preliminary results were obtained with an enantiomerically pure biphenolate catalyst (Fig 7) in 1997. We then began a collaboration with A. H. Hoveyda

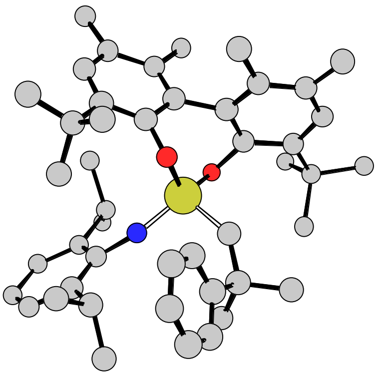


Figure 7. The structure of Mo(NAr)(CHCMe$_2$Ph)(3,3'-di-t-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diolate).

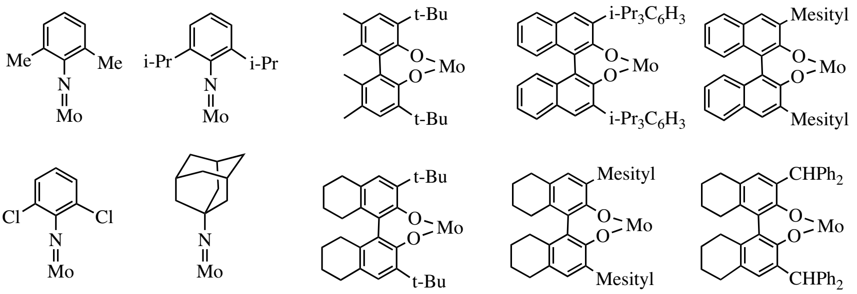
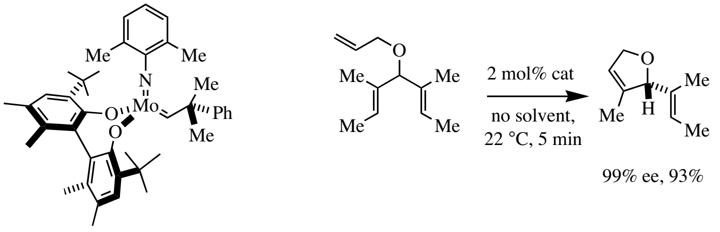


Figure 8. Imido groups and enantiomerically pure diolates (shown in racemic form) that are employed to make asymmetric catalysts..

that was aimed at the application of *asymmetric* metathesis reactions to organic synthesis.[67,81,82] The modularity of the catalysts allowed us to prepare many enantiomerically pure variations that contain one of several different imido ligands and several different diolates (Fig 8). It soon became apparent that with the right catalyst, asymmetric reactions could be efficient in terms of both yield and enantioselectivity, in many cases producing a single enantiomerically pure product in virtually quantitative yield relatively quickly (Eqs 26 and 27).[83] Again, byproducts usually consist of simple olefins such as ethyl-



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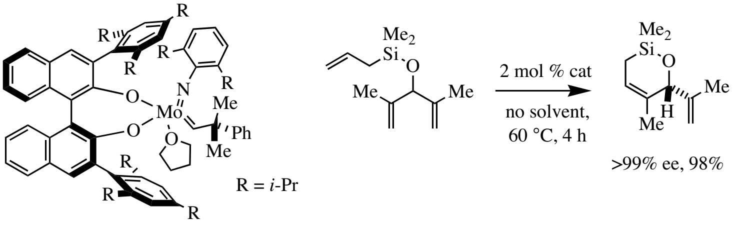

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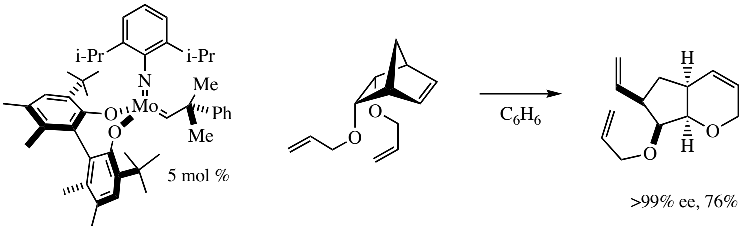

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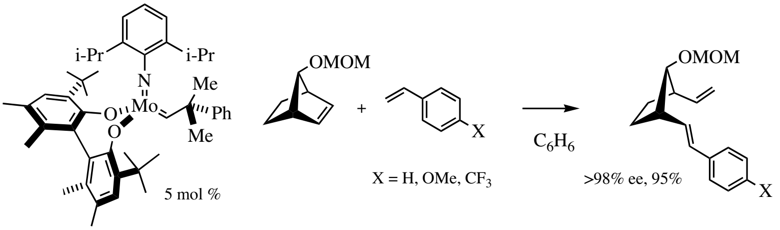

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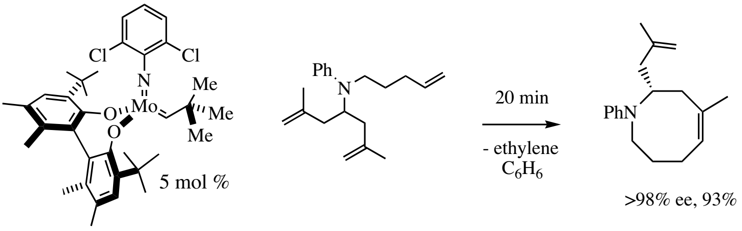

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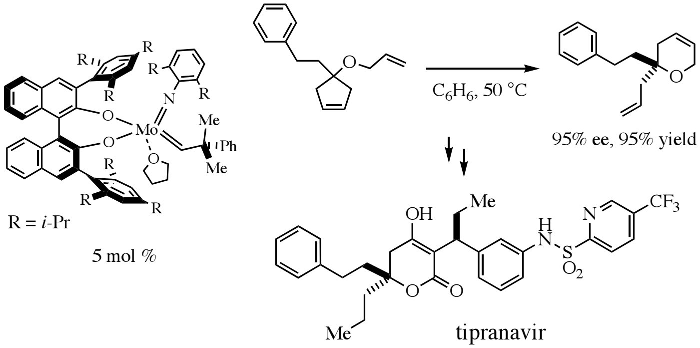

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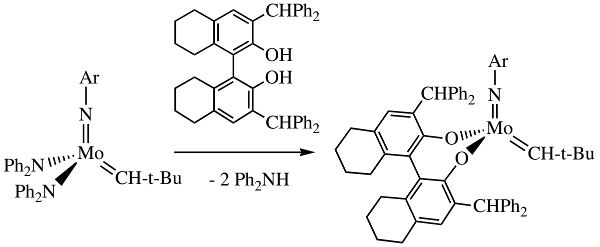
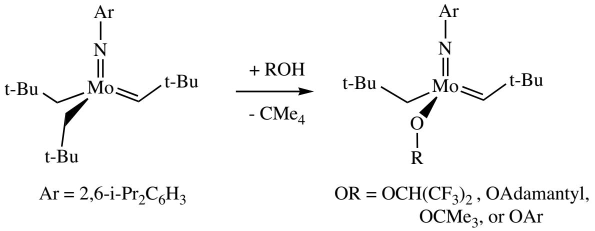


(32)

ene, propylene, or butene. A wide variety of other asymmetric reactions were developed, among them ring-opening/ring-closing metathesis (Eq 28),[84] ring-opening/cross metathesis (Eq 29),[85] and the ring closing of tertiary amines to yield products resembling substructures of various drugs and other natural products (Eq 30).[86] It also was shown that the synthesis of drugs such as tipranavir, an HIV protease inhibitor, could be shortened dramatically through the use of an asymmetric metathesis step to synthesize the problematic enantiomerically pure tertiary ether (Eq 31).[87,88] These are but a few examples of what has been accomplished in the last several years.



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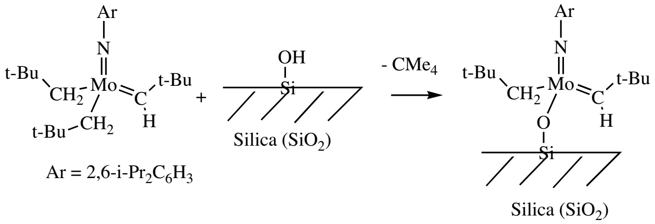


(34)

The isolation and testing of many catalyst variations side by side for one specific asymmetric reaction revealed that the efficiency of the asymmetric catalysts in terms of yield and enantioselectivity can vary dramatically, and that in the long run one could be relatively confident of finding an efficient catalyst. However, dozens of catalysts have to be prepared, isolated, and tested. Therefore, we have begun to explore the possibility of preparing catalysts *in situ* that we know exist as relatively stable species, either through addition of the biphenolate or binaphtholate to the bistriflate precursor (Eq 19), or through addition of the parent biphenol or binaphthol to a bisamido precursor (Eq 32). We have shown that catalysts prepared *in situ* for asymmetric metathesis reactions behave as well as catalysts that have been isolated and purified.[89] Surprisingly, similar approaches using dineopentyl species led to formation of *monoalkoxide* species (Eq 33).[90] Initially we thought these would be relatively poor metathesis catalysts, since dineopentyl species are essentially inactive for metathesis. The presence of one neopentyl and one alkoxide instead of two alkoxides therefore should be detrimental. However, preliminary results suggest that monoalkoxides are highly active catalysts. Recent theoretical calculations in related isoelectronic rhenium systems have suggested why this might be the case.[91] Formation of only monoalkoxides from dineopentyl species recently has allowed the synthesis of "well-defined" and highly active molybdenum-based (and tungsten-based) metathesis catalysts on silica surfaces (Eq 34) that are relatively long-lived because intermediate alkylidenes cannot decompose bimolecularly.[92] A variety of relatively well-defined catalysts now can be prepared on silica surfaces using other Ta(V), Mo(VI), W(VI), and Re(VII) neopentyl precursors (Fig 9).[93] In some cases entirely new reactions can be observed such as "alkane metathesis" by tantalum catalysts.[94] This reaction has now been shown to involve *alkene* metathesis steps.[95]

Rhenium forms metathesis catalysts of the "classical" type. Therefore we

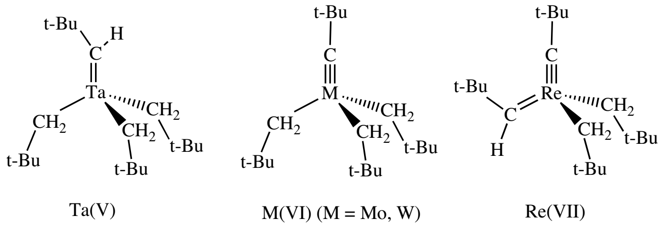
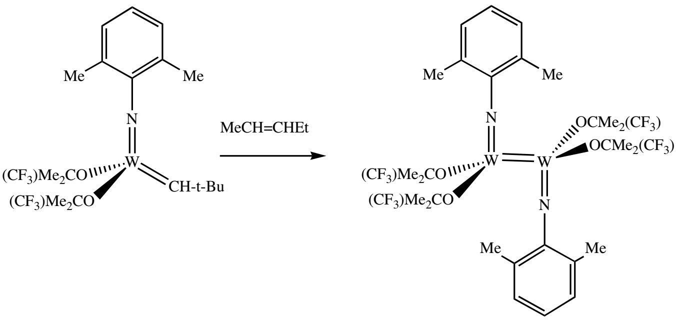


Figure 9. "Clean" sources of catalysts formed upon addition of them to silica surfaces.

felt that we should be able to prepare well-defined catalysts. In order to maintain the four-coordinate geometry around a neutral Re center, a sterically demanding ligand that is triply bound to the metal is required. The only logical choice is a neopentylidyne ligand. In fact, well-defined Re(VII) bisalkoxide catalysts for alkene metathesis can be prepared following the principles learned in W and Mo chemistry,[96,97] since the neopentylidyne ligand does not react with olefins readily (Fig 10). Monoalkoxide mononeopentyl analogs are believed to be even more reactive than bisalkoxides, especially on silica surfaces.[91]

Finally, we have found that M=M double bonds can form where M = Mo,[98] W,[99] or Re[100] as a consequence of decomposition of alkylidene species (Eq 35). Metal-metal double bonds are unusual, especially when the double bond is not bridged by potentially bridging ligands such as an alkoxide or an imido. The fact that these species themselves will metathesize certain olefins[98] (slowly) raises the possibility that alkylidenes are being reformed from M=M bonds. If this turns out to be the case, it would constitute strong evidence that interconversion of metal-metal, carbon-carbon, and metal-carbon bonds is possible for double bonds, as we know it to be for triple bonds (Eq 17).



(35)

We have come an enormous distance in the last 30 years, from "ill-defined" metathesis catalysts to those whose structure and reactivity in solution (and perhaps now on surfaces) we can control with pinpoint precision. Fundamental problems with known catalysts remain, the most important being how to prevent catalyst decomposition and/or how to regenerate catalysts from "clean" decomposition products. I expect these challenges to be met and hope that the consequences of the synthesis and fundamental study of

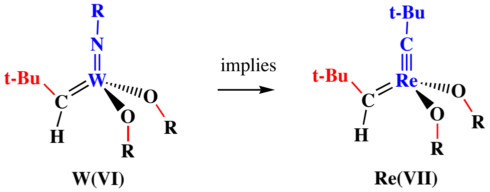


Figure 10. Rhenium neopentylidyne bisalkoxide complexes are olefin metathesis catalysts.

new types of catalysts, and the application of them to a wide variety of problems, will continue to be felt in the coming years.

ACKNOWLEDGEMENT

I am grateful for the freedom given to me in early years at the Central Research Department at duPont, for the opportunity to broaden my efforts and my interests at MIT, and for the support provided by various funding agencies (the National Science Foundation, the National Institutes of Health, the Navy, the Army, and the Department of Energy) over the years for high oxidation state organometallic chemistry and other projects. I am forever indebted to my graduate and postdoctoral students, each of whom in his or her own way has contributed to the massive effort required to turn a few observations and new compounds into chemistry that has had a significant impact on fields outside of inorganic chemistry. Finally, I want to thank my wife Nancy and my family for their love and support.

REFERENCES

1. G. Wilkinson, Nobel Lecture, December 11, 1973.
2. E. O. Fischer, Nobel Lecture, December 11, 1973.
3. Fischer, E. O. *Pure Appl. Chem.* **1970**, *24*, 407.
4. Fischer, E. O. *Pure Appl. Chem.* **1972**, *30*, 353.
5. Fischer, E. O.; Maasbol, A. *Angew. Chem. Int. Ed.* **1964**, *3*, 580.
6. Fischer, E. O.; Kreis, G.; Kreiter, C. G.; Müller, J.; Huttner, G.; Lorenz, H. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 564.
7. Schrock, R. R.; Parshall, G. W. *Chem. Rev.* **1976**, *76*, 243.
8. Shortland, A. J.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1973**, 872.
9. *"Note added in proof.* Hexamethylrhenium (K. Mertis and G. Wilkinson) and pentamethyl[t]antalum (R. Schrock, DuPont, Wilmington, private communication) have recently been synthesized;" Geoffrey Wilkinson, Nobel Lecture, December 11, 1973.
10. Juvinall, G. L. *J. Am. Chem. Soc.* **1964**, *86*, 4202.
11. Schrock, R. R.; Meakin, P. *J. Am. Chem. Soc.* **1974**, *96*, 5288.
12. Mowat, W.; Wilkinson, G. *J. Chem. Soc, Dalton Trans.* **1973**, *10*, 1120.
13. Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.
14. Guggenberger, L. J.; Schrock, R. R. *J. Am. Chem. Soc.* **1975**, *97*, 2935.
15. Schrock, R. R. *J. Am. Chem. Soc.* **1975**, *97*, 6577.
16. Schrock, R. R.; Guggenberger, L. J. *J. Am. Chem. Soc.* **1975**, *97*, 6578.
17. Ivin, K. J. *Olefin Metathesis*; Academic Press: New York, 1983.
18. Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997.

19. Grubbs, R. H. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8.
20. Grubbs, R. H., Ed. *Handbook of Metathesis. Catalyst Development*; Wiley-VCH: Weinheim, 2003; Vol. 1.
21. Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, *97*, 3265.
22. Grubbs, R. H.; Carr, D. D.; Hoppin, C. R.; Burk, P. L. *J. Am. Chem. Soc.* **1976**, *98*, 3478.
23. Grubbs, R. H.; Hoppin, C. R. *J. Chem. Soc., Chem. Comm.* **1977**, 634.
24. Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, *97*, 1592.
25. McGinnis, J.; Katz, T. J.; Hurwitz, S. *J. Am. Chem. Soc.* **1976**, *98*, 605.
26. Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 7808.
27. Hérrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161.
28. Pannella, F.; Banks, R. L.; Bailey, G. C. *J. Chem. Soc., Chem. Commun.* **1968**, 1548.
29. Moulijn, J. A.; Reitsma, H. J.; Boelhouwer, C. *J. Catal.* **1972**, *25*, 434.
30. Mortreux, A.; Blanchard, M. *J. Chem. Soc. Chem. Commun.* **1974**, 786.
31. McLain, S. J.; Wood, C. D.; Schrock, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 4558.
32. Schrock, R. R.; Rocklage, S. M.; Wengrovius, J. H.; Rupprecht, G.; Fellmann, J. *J. Molec. Catal.* **1980**, *8*, 73.
33. Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515.
34. Clark, D. N.; Schrock, R. R. *J. Am. Chem. Soc.* **1978**, *100*, 6774.
35. Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645.
36. Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932.
37. Churchill, M. R.; Wasserman, H. J. *J. Organomet. Chem.* **1984**, *270*, 201.
38. Churchill, M. R.; Fettinger, J. C.; McCullough, L. G.; Schrock, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 3356.
39. Churchill, M. R.; Ziller, J. W.; Pedersen, S. F.; Schrock, R. R. *J. Chem. Soc., Chem. Commun.* **1984**, 485.
40. Schrock, R. R.; Pedersen, S. F.; Churchill, M. R.; Ziller, J. W. *Organometallics* **1984**, *3*, 1574.
41. Churchill, M. R.; Ziller, J. W.; Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1984**, *3*, 1554.
42. Freudenberger, J. H.; Schrock, R. R.; Churchill, M. R.; Rheingold, A. L.; Ziller, J. W. *Organometallics* **1984**, *3*, 1563.
43. Buhro, W. E.; Chisholm, M. H. *Adv. Organometal. Chem.* **1987**, *27*, 311.
44. Chisholm, M. H. *Acc. Chem. Res.* **1990**, *23*, 419.
45. Schrock, R. R.; Listemann, M. L.; Sturgeoff, L. G. *J. Am. Chem. Soc.* **1982**, *104*, 4291.
46. Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74.
47. Laplaza, C. E.; Cummins, C. C. *Science* **1995**, *268*, 861.
48. Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1.
49. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
50. Oskam, J. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 7588.
51. Oskam, J. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11831.
52. Schrock, R. R.; Feldman, J.; Cannizzo, L.; Grubbs, R. H. *Macromolecules* **1987**, *20*, 1169.
53. Totland, K. M.; Boyd, T. J.; Lavoie, G. G.; Davis, W. M.; Schrock, R. R. *Macromolecules* **1996**, *29*, 6114.
54. McConville, D. H.; Wolf, J. R.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413.
55. O'Dell, R.; McConville, D. H.; Hofmeister, G. E.; Schrock, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 3414.
56. Masuda, T.; Higashimura, T. *Adv. Polym. Sci.* **1987**, *81*, 122.
57. Masuda, T.; Higashimura, T. *Acc. Chem. Res.* **1984**, *17*, 51.
58. Choi, S.-K.; Gal, Y.-S.; Jin, H.-H.; Kim, H.-K. *Chem. Rev.* **2000**, *100*, 1645.
59. Schrock, R. R.; Luo, S.; Lee, J. C. J.; Zanetti, N. C.; Davis, W. M. *J. Am. Chem. Soc.* **1996**, *118*, 3883.

60. Fox, H. H.; Wolf, M. O.; O'Dell, R.; Lin, B. L.; Schrock, R. R.; Wrighton, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 2827.
61. Christensen, R. L.; Faksh, A.; Meyers, J. A.; Samuel, I. D. W.; Wood, P.; Schrock, R. R.; Hultzsch, K. C. *J. Phys. Chem. A* **2004**, *108*, 8229.
62. Schattenmann, F. J.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1996**, *118*, 3295.
63. Anders, U.; Nuyken, O.; Buchmeiser, M. R. *J. Mol. Catal. A* **2004**, *213*, 89.
64. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.
65. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
66. Houri, A. F.; Xu, Z. M.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.
67. Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592.
68. Grubbs, R. H., Ed. *Handbook of Metathesis. Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2003; Vol. 2.
69. Grubbs, R. H., Ed. *Handbook of Metathesis. Applications in Polymer Synthesis*; Wiley-VCH: Weinheim, 2003; Vol. 3.
70. Fürstner, A.; Seidel, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1734.
71. Fürstner, A.; Seidel, G. *J. Organomet. Chem.* **2000**, *606*, 75.
72. Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608.
73. Fürstner, A.; Grela, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 1234.
74. Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299.
75. Fürstner, A.; Castanet, A.-S.; Radkowski, K.; Lehmann, C. W. *J. Org. Chem.* **2003**, *68*, 1521.
76. McCullough, L. G.; Schrock, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 4067.
77. Murdzek, J. S.; Schrock, R. R. In *Carbyne Complexes*; VCH: New York, 1988.
78. Tsai, Y. C.; Diaconescu, P. L.; Cummins, C. C. *Organometallics* **2000**, *19*, 5260.
79. Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453.
80. Zhang, W.; Kraft, S.; Moore, J. S. *Chem. Commun.* **2003**, 832.
81. Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.
82. Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700.
83. La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720.
84. Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828.
85. La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11604.
86. Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991.
87. Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139.
88. Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868.
89. Sinha, A.; unpublished results.
90. Sinha, A.; Schrock, R. R. *Organometallics* **2004**, *23*, 1643.
91. Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2005**, 14015.
92. Blanc, F.; Copéret, C.; Thivolle-Cazat, J.; Basset, J.-M.; Sinha, A.; Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, 45, 1216.
93. Copéret, C.; Chabanas, M.; Saint-Arroman, R. P.; Basset, J.-M. *Angew. Chem. Int. Ed.* **2003**, *42*, 156.
94. Taoufik, M.; Schwab, E.; Schultz, M.; Vanoppen, D.; Walter, M.; Thivolle-Cazat, J.; Basset, J.-M. *Chem. Commun.* **2004**, 1434.
95. Soulivong, D.; Copéret, C.; Thivolle-Cazat, J.; Basset, J.-M.; Maunders, B. M.; Pardy, R. B. A.; Sunley, G. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 5366.
96. Toreki, R.; Schrock, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 3367.

97. Schrock, R. R.; Toreki, R.; Vaughan, G. A.; Farooq, A. In *Transition-Metal Carbyne Complexes*; Kreissl, F. R., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1992.
98. Schrock, R. R.; Lopez, L. P. H.; Hafer, J.; Singh, R.; Sinha, A.; Müller, P. *Organometallics* **2005**, *24*, 5211.
99. Lopez, L. P. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 9526.
100. Toreki, R.; Schrock, R. R.; Vale, M. G. *J. Am. Chem. Soc.* **1991**, *113*, 3610.

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