# Olefin Metathesis

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Olefin metathesis consists of a unique metal-catalyzed carbon skeleton redistribution in which a mutual exchange of unsaturated carbon-carbon bonds takes place, as shown in the reaction between propene, ethylene, and 2-butene:



In other words, **olefin metathesis constitutes a catalytic method for both cleaving and forming C=C double bonds**. The reaction is generally reversible and limited to an equilibrium. The reacting alkenes need not be identical. Thus, while the forward reaction in the equation above constitutes an example of self-metathesis, its reverse is accomplished by allowing ethylene and 2-butene to react with each other.

Olefin metathesis is a child of industry and –as with many catalytic processes– it was discovered by accident. The reaction came to light as a serendipitous outgrowth in the systematic study of Ziegler polymerization catalysts with alternate transition metal-based systems. The first catalyzed metathesis reactions were observed in the late1950's when chemists at DuPont, Standard Oil, and Phillips Petroleum reported the metathesis of propene with catalysts based on molybdenum and tungsten. It was soon established that olefin metathesis could take place in the presence of various homogeneous and heterogeneous catalysts. Cyclic olefin monomers were also tested under similar experimental conditions and found to produce low yields of amorphous, rubbery polymers with unexpected structures. It took some more years to recognize that the disproportionation of acyclic olefins and the ring-opening polymerization reactions were two sides of the same coin, and even a longer period of time to establish the true nature of the reaction.

# Scope of The Reaction

Many olefinic substrates can undergo metathesis to afford an extensive range of new unsaturated products. Suitable substrates include substituted alkenes, terminal and internal alkenes, cycloalkenes, dienes, polyenes, and even alkynes or alkanes.

Through skeletal rearrangement, unsaturated products that can be acyclic compounds, small- or medium-size carbo- and hetero­cycles, macrocycles, or polymer chains are obtained. Depending on the types of substrate and transformation, several categories of metathesis have been defined.



Two or more basic operations can be combined in a one-pot procedure. In the so-called tandem, domino, or cascade metathesis processes, reactions occur in sequence. In other words, a subsequent reaction always takes place at the functionality formed in the previous step. In the shortest general tandem metathesis between an endocylic olefin and an exocyclic C=C double bond, the initial ring is opened by ROM and a new one is formed by RCM. In a slightly more elaborated sequence, an excess of acyclic olefin is added to the reaction mixture to enable a further CM. In both cases, the overall process is usually referred to as ring rearrangement metathesis (RRM), since it affords products with a rearranged ring system.



Alternatively, various metathesis reactions can proceed simultaneously and independently if suitable polyolefin substrates are employed. For example, several examples of double or even triple RCM reactions of tetraenes and hexaenes, respectively, have been described.



Whether the reactions occur in sequence or in parallel, the accumulation of multiple metathesis events allows to build up complex structural scaffolds very efficiently and rapidly in a single operation.

Although olefin metathesis does not generate stereogenic centers *per se*, the reaction may be employed for the desymmetrization of prochiral polyolefins or for the kinetic resolution of racemates. So far, the asymmetric ring-closing metathesis (ARCM) and the asymmetric ring-opening cross-metathesis (AROCM) reactions have been the most investigated variations for inducing chirality in organic substrates.



Whereas ring-opening processes are enthalpically driven due to the relief of ring strain, RCM is entropically driven because the reaction cuts one substrate into two compounds. In both cases, high selectivities toward products can usually be achieved. On the other hand, the metathesis of acyclic olefins is essentially a thermoneutral process that eventually results in a statistical distribution of reactants and products. Therefore, it is necessary to shift the equilibrium in one direction in order to make the process suitable for preparative applications. Metathesis of an -olefin yields ethylene and a symmetrical internal olefin. In such a case, the reaction can usually be driven to completion by removal of volatile ethylene.



The metathesis of alkadienes and polyenes may follow intra- or intermolecular pathways. The intramolecular metathesis of an -diene yields ethylene and an unsaturated carbocycle (or heterocycle) via RCM, whereas the intermolecular reaction results in the formation of ethylene and an oligomer or a polymer via ADMET. Whether the intra- or intermolecular pathway dominates depends on the relative stabilities of the linear and cyclic products, strained cycloolefins being prone to undergo ROMP. In a manner analogous to step-growth polycondensation of polyesters, polyenes are formed by step-growth metathesis of the double bonds in a diene if the reaction is run under sufficient vacuum to remove the ethylene as it is formed, thereby shifting the equilibrium toward high molecular weight species. Yet, because the ADMET process is equilibrium-driven, addition of excess ethylene to a macromolecular chain will shift the reaction in the reverse direction to give depolymerization. This procedure constitutes a possible method for recycling rubber and other unsaturated polymers.

# Important Milestones in Olefin Metathesis

|  |  |
| --- | --- |
| Late 1950's | Industrial chemists discover accidentally olefin disproportionation during the systematic study of Ziegler-Natta polymerizations. |
| 1964 | E. O. Fischer and A. Maasböl isolate and characterize the first stable metal carbene complex. |
| 1967 | N. Calderon coins the term "olefin metathesis" to designate the exchange of carbon atoms between C=C double bonds. |
| 1971 | J.-L. Hérisson and Y. Chauvin postulate the intermediacy of metal-alkylidene and metalla­cyclo­butane species in olefin metathesis. |
| 1976 | T. J. Katz demonstrates that Fischer-type carbene complexes of tungsten initiate olefin metathesis. |
| 1980 | R. R. Schrock designs a metathetically active tantalum-alkylidene complex that provides experimental support to the Chauvin mechanism. |
| 1992 | R. H. Grubbs introduces a series of well-defined ruthenium-alkylidene olefin metathesis catalysts. |
| 1999 | Work by W. A. Herrmann, R. H. Grubbs, and S. P. Nolan leads to a second generation of well-defined ruthenium-based olefin metathesis catalysts. |
| 2001 | A. H. Hoveyda and R. R. Schrock achieve high enantioselectivities in asymmetric ring-closing metathesis with a chiral molybdenum catalyst. |
| 2005 | Y. Chauvin, R. H. Grubbs, and R. R. Schrock receive the Nobel prize in chemistry for the development of the metathesis method in organic synthesis. |

# Mechanism of Olefin Metathesis

Though many researchers put forward proposals to explain how metathesis could take place, the breakthrough came in 1970 from Yves Chauvin at the Institut Français du Pétrole. In a publication with his student Jean-Louis Hérrison, he proposed that the catalyst was a metal carbene (a compound in which the metal is bound to the carbon with a double bond, also referred to as a metal alkylidene).



In the Chauvin catalytic cycle for cross metathesis (CM), the metal carbene (or alkylidene) reacts with the olefin, forming a metallacyclobutane intermediate. This intermediate then cleaves, yielding ethylene and a new metal alkylidene, which reacts with a new alkene substrate molecule to yield another metalla­cyclobutane intermediate. On decomposition in the forward direction, this second intermediate yields the internal alkene product and regenerates the initial metal carbene who is now ready to enter another catalytic cycle. Thus, each step in the catalytic cycle involves exchange of alkylidenes leading to metathesis.

The ring-opening metathesis polymerization (ROMP) of cycloalkenes proceeds according to a similar reaction mechanism:



The ability of a cycloalkene to undergo ROMP is primarily related to the difference in free energy between the ring and the corresponding open-chain structure. Thermodynamic calculations indicate that amongst cycloalkenes comprising 4 to 8 ring carbon atoms, the 6-membered cycle is the only one with a positive ΔG value associated to its ring opening. Hence, it does not undergo ROMP unless there is ring strain in the molecule due to bridging, as in norbornene. Steric factors such as substituents close to the double bond are also important in determining the reactivity of a cyclic monomer.

|  |  |
| --- | --- |
| Monomer | G° (kJ/mol) |
|  | -105 |
|  | -2.6 |
|  | 7.3 |
|  | -7 |
|  | -13 |
|  | -24 |
|  | -47 |

# Early Transition Metal Initiators

Katz was one of the first chemists to recognize the significance of the Hérisson and Chauvin mechanism and to demonstrate that stable metal-carbene complexes were able to initiate olefin metathesis reactions. Using the most reactive metal-carbene species known at that time, pentacarbonyl(diphenyl­methylene)tungsten, he successfully polymerized strained and low-strain cycloolefins with remarkably high stereoselectivities.

Another important milestone on the path to modern metathesis initiators was reached with the synthesis of well-defined, high oxidation state imido alkylidene complexes of tantalum first, soon followed by tungsten and molybdenum, in the Schrock Laboratory at M.I.T. The successful development of such species owes a lot to the use of the neopentyl ligand (CH2C(CH3)3, Np) in which no mode of decomposition involving  hydrogen atoms is possible. Indeed, a neopentyl group is sterically protected and tends to block intermolecular decomposition processes. At the same time, it promotes an intramolecular reaction through the activation of an  hydrogen atom, thereby yielding an alkylidene moiety that is most stable toward bimolecular decomposition. Trineopentyl­neopentylidene tantalum was the first stable compound possessing a terminal alkylidene ligand isolated along these lines.



The fundamental work of Schrock helped gain a better understanding of the parameters that affect the activity of the catalysts based on early transition metals. The strategy elaborated to obtain highly efficient, well-defined, four-coordinate high oxidation state alkylidene complexes implied the selection of bulky alkoxide ligands, which lower the LUMO of the metal and favor reactions with olefins while blocking bimolecular decompositions. The design of tetrahedral Mo(VI) and W(VI) complexes that contain a neopentylidene and two alkoxide ligands also required that a sterically bulky dianionic ligand be the fourth substituent. In this respect, the 2,6-dimethyl- or 2,6-diisopropyl­phenyl imido ligands were found to maximize steric bulk while limiting the possibility of side reactions. All together, the sterically bulky nature of all four ligands in (RO)2M(NR')(CH-*t*-Bu) complexes prevented coupling of the neopentylidene ligands and allowed many such species to be isolated and characterized.

The rate of olefin metathesis is especially high for molybdenum complexes. The relatively high stability of tungstenacyclobutane intermediates is possibly the reason why metathesis with a tungsten catalyst is often slower than with its molybdenum counterpart, even though the reaction of a W=C bond with a C=C bond is believed to proceed faster than the reaction of the analogous Mo=C unit with the same C=C bond.

Prominent among these initiators are Schrock's four-coordinate alkoxy imido complexes of molybdenum with a bulky aryl substituent on the imido group and bulky, electron withdrawing alkoxide ligands which, as already pointed out, provide steric shield and contribute to increase the electrophilicity of the metal center. The two complexes on the left are commercially available and constitute very active catalyst precursors. They are, however, very sensitive towards oxygen and moisture and must be handled under rigorously inert atmosphere in dry solvents using Schlenk techniques or a glove box.

Chiral alkoxides may also serve as ligands for high oxidation state imido alkylidene complexes of molybdenum and tungsten. For example, molybdenum-based compounds associated with enantiomeri­cally pure biphenolate or binaphtolate derivatives have been used in a variety of metathesis reactions to induce asymmetry. High enantiomeric excesses could be achieved for kinetic resolutions, asymmetric ring-closing metathesis (ARCM), or in the enantioselective synthesis of medium-size cyclic ethers and amines via tandem AROM/CM.

# Late Transition Metal Initiators

Among the many carbene complexes based on late transition metals from groups 8–10 that were tested as potential metathesis catalysts, **ruthenium** derivatives stand out for their versatility and efficiency. Carbene precursors associated with Fe, Co, and Rh react stoichiometrically with olefins to generate cyclopropanes. With Ru and Os, a low coordination number of the metal usually results in catalytic metathesis activity, whereas high coordination number complexes lead to stoichiometric cyclopropanation. Ir tends to act only as a metathesis initiator in ill-defined systems. However, both Os and Ir complexes are generally less active than their Ru counterparts. They are also much more expensive, therefore they have not been widely studied.

The complex on the left was the first well-defined olefin metathesis Ru-based catalyst synthesized in the Grubbs' Laboratory at Caltech. Poorly active, it only polymerized highly strained cycloolefins, such as norbornene. In sharp contrast with the Mo-based systems developed by Schrock where the more electron-withdrawing the ancillary ligands, the higher the catalytic activity, Ru(II) complexes need to be associated with powerful electron-donating ligands in order to display high catalytic activities. Thus, a second initiator containing the strongly basic tricylohexylphosphine ligand (PCy3) proved to be a much more efficient metathesis promoter than its predecessor. Tailoring phosphine bulkiness is also crucial for achieving high catalytic efficiencies. Indeed, PCy3 –or to a somewhat lesser extent P*i*Pr3– yielded active catalytic systems, whereas no or little activity was observed with the more sterically demanding P*t*Bu3 and tricyclooctylphosphine ligands, a likely consequence of the excessive steric crowding imparted by the phosphine moiety.

With the L2X2Ru=CHR structure identified as a promising target for designing well-defined, highly efficient metathesis initiators, considerable synthetic efforts were thrown into the preparation of readily accessible and active species. In 1995, Grubbs reported the the synthesis of RuCl2(=CHPh)(PCy3)2 in high yield and purity. This complex is obtained as a purple microcrystalline powder. It is commercially available and often referred to as the ***(first generation) Grubbs catalyst***. Because of its relative ease of synthesis, high catalytic activity, and broad functional group tolerance, it constitutes the most frequently used well-defined, ruthenium-based olefin metathesis catalyst in research laboratories.



Extensive mechanistic studies suggest that diphosphino complexes of the first generation form a highly active monophosphine intermediate (formally a 14 e- complex) during the catalytic cycle:



According to this mechanism, the overall catalytic activity of a generic species is dictated by the relative rates of three processes:

1. phosphine dissociation (initiation, *k*1)
2. phosphine re-coordination (*k*-1)
3. olefin binding (*k*2)

The re-coordination of free PR3 is competitive with substrate binding and the balance between the two processes determines the propagation rate, provided that the subsequent formation of the metallacyclobutane intermediate is fast. High catalytic activities are therefore anticipated when initiation occurs readily (i.e., *k*1 is large) and when the coordinatively unsaturated intermediate reacts preferentially with an olefinic substrate instead of free phosphine (i.e., *k*2/*k*-1 is large).

This rational analysis led to the synthesis of mixed complexes where one phosphine is replaced by a *N*-heterocyclic carbene ligand (NHC). Compared to phosphines, NHCs are better -donors and form stronger bonds to metal centers. Indeed, the Ru–NHC bond strengths were calculated to be 20–40 kcal/mol stronger than Ru–PR3 bond strengths. Although the substitution of one PCy3 ligand in RuCl2(PCy3)2(=CHPh) with a NHC decreases the phosphine dissociation rate (*k*1) of about 2 orders of magnitude, the selectivity for binding olefinic substrates over free phosphine (*k*2/*k*-1) increases simultaneously by 4 orders of magnitude. In other words, once the phosphine comes off, coordination of olefin is highly favored compared to re-binding of PCy3. As a consequence, the NHC complexes can perform multiple olefin metathesis events before they re-coordinate phosphine and return to their resting state.

It follows that mixed phosphine/NHC complexes are dramatically superior to the bis(phosphine) or bis(NHC) species when considering overall metathesis activities. In a number of cases, these second generation ruthenium catalysts could rival with the molybdenum initiators in terms of activity, while maintaining a superior stability and a broader functional group compatibility.

Regarding the nature of the *N*-heterocyclic ring, the imidazole system has been the most extensively investigated so far. Thanks to its aromaticity and the presence of electron-pair donating atoms next to the divalent carbon, it stabilizes the nucleophilic carbene center. Thus, the first stable singlet carbenes isolated by Arduengo in the 1990's were unsaturated imidazol-2-ylidene species, later complemented by their saturated imidazolidin-2-ylidene analogues. Accordingly, two NHCs bearing mesityl groups on a five-membered ring are available, an unsaturated one (abbreviated IMes) and its saturated dihydro derivative (abbreviated SIMes or H2IMes). Highly active and stable ruthenium alkylidene complexes are obtained with both ligands, although the SIMes catalyst is somewhat superior in certain cases, but the trend is not general. This latter complex is commercially available and is nicknamed the ***Super Grubbs* or *second generation Grubbs catalyst***.



The scope of Ru-catalyzed olefin metathesis was further expanded by the introduction of Grubbs-type catalysts containing monodentate and/or chelating N-, O-, P- and Cl-donor ligands. Among them, styrenyl ether complexes stand out for their high stability toward air and moisture. Hence, they are conveniently purified and recycled by column chromatography without any special precautions. Compounds bearing a PCy3 or a SIMes ligand are both commercially available, although expensive. They are known, respectively, as the ***first and second generation Hoveya-Grubbs catalysts***.



The internal chelation of the ether influences the initiation and propagation rates defined for the corresponding non-chelated initiators. The Hoveyda-Grubbs complex initiates approximately 30 times slower but propagates nearly four times faster than the original Grubbs catalyst, while the Hoveyda-Grubbs complex, an air stable bright green solid is a fast initiating catalyst which proved particularly efficient in cross metathesis of electron-deficient olefins, offering reactivity levels and selectivities surpassing those displayed by RuCl2(=CHPh)(PCy3)(SIMes).

# Applications of Alkene Metathesis

Olefin metathesis has opened up new routes to important petrochemicals, oleochemicals, polymers, and specialty chemicals. The transformation often gives access with remarkable atom economy to structures that are not available by any other means, or only via multi-step painstaking procedures. Currently, there is still a marked dichotomy between major industrial processes, which rely on inexpensive, ill-defined, multicomponent catalytic systems, and research laboratory applications, where the use of well-defined metal-alkylidene complexes is often favored to guarantee high activities under reproducible conditions, albeit at the price of a much higher cost.

The manufacture of neohexene (3,3-dimethyl-1-butene) is accomplished by cross-metathesis of technical grade diisobutene with ethylene (ethenolysis). The isomer that goes through metathesis is 2,4,4-trimethyl-2-pentene, the internal double bond of which reacts readily with ethylene. A catalyst is added to isomerize other diisobutenes with terminal double bonds into the desired internal olefin.



In the industrial process, the dimers of isobutene are first fractionated to remove an oxidation inhibitor that would otherwise poison the dual catalytic system. The purified diisobutene feed enters the top of the reactor containing the catalysts along with an ethylene stream compressed to the required pressure. The separation of reactants and products is achieved by stripping and fractionation. With a heterogeneous catalyst mixture of WO3/SiO2 and MgO, the selectivity to neohexene is about 85% at 370 °C and 30 bar for an average 60–70% diisobutene conversion. The isobutene co-product is recycled by dimerization in a separate reactor. A neohexene unit built in 1980 with an initial capacity of 1,600 tons per year (but expanded several times) is operating at Chevron Phillips Houston petrochemical complex in Pasadena, Texas.

##### *Diisobutene (DIB)*

Ethene

Ethene

recycle

Isobutene

# Neohexene

*Compressor*

Gas



DIB

recycle

Liquid

Heavies

##### Reactor &

*separator*

##### DIB

*column*

*Stripper*

###### Fractionation

Cross-metathesis (CM) and ring-closing metathesis (RCM) are particularly suited for the construction of small open-chain molecules and macrocycles, respectively. These reactions served, *inter alia*, as key steps in the synthesis of various agrochemicals and pharmaceuticals such as macrocyclic peptides, cyclic sulfonamides, novel macrolides, or insect pheromones.

When targeting this last category of molecules, ruthenium-alkylidene complexes proved especially efficient catalysts. For example, the cross-metathesis of 11-eicosenyl acetate and 3-hexene (4 equivalents) catalyzed by the second generation Grubbs catalyst RuCl2(=CHPh)(PCy3)(SIMes) afforded 11-tetradecenyl acetate in 84% yield.



This product acts as a sex pheromone for the omnivorous leafroller, a common pest of apples, grapes, peaches, pears, and nectarines. Recourse to traps filled with this synthetic equivalent of the sex attractant emitted by the females confuses the males and disrupt the mating cycle. Thus, the use of pheromones is an effective and environmentally-friendly method for controlling insect populations. The *E*/*Z* distribution of internal double bonds in 11-tetradecenyl acetate obtained by ruthenium-catalyzed metathesis matches the one observed in the natural pheromone (*E*/*Z* = 82/18) and the two starting materials, 11-eicosenyl acetate and 3-hexene, are easily prepared from commodity chemicals (jojoba oil and 1-butene, respectively).



The synthesis of epothilones has also benefited from the superior catalytic activity and high functional group tolerance of the second generation Grubbs catalyst. For instance, Danishefsky has selected this complex to close the macrocyle of epothilone 490. Selective reduction of this key intermediate with diimide then affords 12,13-desoxyepothilone B (dEpoB) in 55% overall yield for the two steps.



Epothilones have stirred much excitement in the scientific community and have stimulated the creativity of synthetic organic chemists because of their promising anticancer properties. These cytotoxic macrolides exhibit the same mode of action than paclitaxel, which is sold as Taxol® by Bristol-Myers Squibb. They all bind to [microtubules](http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=tubule) and inhibit their depolymerization (molecular disassembly) into [tubulin](http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=tubulin). In contrast to paclitaxel, epothilones seem, however, to retain potency against multiple drug resistant tumors.

# Ene-Yne Metathesis

Enyne metathesis is a powerful method for the synthesis of 1,3-dienes. It involves bond reorganization between an alkene and an alkyne to produce a butadiene. The procedure can occur intra- or intermolecularly and is commonly used in organic synthesis. Contrasting with the RCM or CM of two alkene moieties, however, no ethylene or any other by-product is released during enyne metathesis. Thus, C–C bond formation occurs with complete atom economy.



Because the reaction bears an obvious kinship to alkene metathesis, the intermediacy of metallacycles was postulated in reactions catalyzed by transition metal-carbene complexes of chromium, tungsten, molybdenum, and ruthenium. With these initiators, the reaction formally proceeds via [2+2] cycloaddition between the triple bond of the alkyne partner and the carbene complex to give a metallacyclobutene intermediate. Ring opening of this complex via cycloreversion produces a new alkylidene fragment that can form a metallacyclobutane with the alkene partner and release the final product.



Most of the recent synthetic applications of enyne metathesis use ruthenium alkylidene catalysts because of their commercial availability, functional group tolerance, and constant development. In particular, first and second generation ruthenium carbene complexes developed by Grubbs were used to promote RCEYM reactions with high efficiencies. For instance, Barrett and coworkers synthesized bicyclic -lactams by RCM of enyne and obtained carbacephem in quantitative yield.



# Alkyne Metathesis

The pursuit of well-defined metal-alkylidene catalysts for alkene metathesis also led to the discovery of high oxidation state carbyne (or alkylidyne) complexes, first of tantalum and later of tungsten, molybdenum, and rhenium. Some of these species were found to metathesize alkynes with remarkable ease, principally those based on molybdenum and tungsten. Reasons underlying the rational design of alkylidene catalyst precursors also apply to their alkylidyne counterparts. Thus, steric protection is needed in order to prevent bimolecular decomposition and the use of bulky alkoxide ligands proved crucial for obtaining long-lived metathesis initiators. A large variety of (RO)3M≡CR' complexes was synthesized along these lines, primarily tungsten derivatives. Among them, the complex depicted on the left stands out for its remarkable activity under mild conditions and is the most widely used Schrock alkylidyne catalyst for alkyne metathesis.

Although the exact nature of the true catalytic species remains unknown, two possible mechanistic pathways are conceivable for alkyne metathesis: the alkylidyne mechanism and the metallacyclopentadiene mechanism.

In the alkylidyne mechanism, metallacyclobutadiene intermediates are initially formed from alkynes and carbyne complexes in much the same way that metallacyclobutanes are formed from olefins and metal alkylidene complexes. The reaction proceeds via a series of [2+2] cycloaddition and cycloreversion steps that lead to the split of internal alkynes. In several cases, metallacyclo­butadienes were isolated and characterized. They successfully promoted catalytic turnover when submitted to metathetical conditions.



In the metallacycle mechanism, a metallacyclopentadiene species is first formed through oxidative coupling of two alkyne partners with a metal catalyst. Reductive elimination then affords a cyclobutadiene complex, whose isomerization, followed by oxidative addition, gives a regioisomer of the first metallacyclobutadiene intermediate. Metathesis products are eventually released upon cycloreversion.



Despite the rather long history of alkyne metathesis and the availability of several efficient catalytic systems covering a wide range of substrates, the reaction has not received as much attention from the organic community than olefin metathesis. So far, only two kinds of alkylidyne unit exchanges were mainly investigated for the synthesis of small unsaturated molecules, viz., alkyne cross-metathesis (ACM) and ring-closing alkyne metathesis (RCAM).



These reactions are often accompanied by a post-metathesis reduction step to afford (cyclo)olefins with a controlled stereo­chemistry about the double bond. While alkene metathesis provides a more straightforward approach for exchanging substituents across double bonds, the geometrical isomer distribution that ensues is usually governed by steric and/or thermodynamic factors. Thus, mixtures of *E*- and *Z*-olefins (or only the most thermodynamically stable isomer) are obtained, and the stereochemical outcome of the reaction may be hard to predict. In sharp contrast with this situation, recourse to alkyne metathesis followed by a partial reduction of the triple bond using either Lindlar- or Birch-type procedures gives access to any given isomer at will.



This concept has been exploited by Fürstner in elegant syntheses of natural products using ACM or RCAM reactions. For instance, the total synthesis of prostaglandin E2-1,15-lactone (PGE2 lactone) was accomplished by ring-closing a diyne precursor in the presence of a molybdenum complex activated with CH2Cl2 in toluene at 80 °C. The catalytic system employed did not affect the C=C double bond present in the starting material and preserved all labile structural elements, including the chiral center  to the carbonyl group. Lindlar hydrogenation of the cycloalkyne adductfollowed by acidic cleavage of the protecting *tertio*-butyldimethylsilyloxy group (OTBDMS) afforded the desired target molecule in 53% overall yield.

