Angewandte
Reviews

DOI: 10.1002/anie.201204513

Catalysis for Synthesis

Alkyne Metathesis on the Rise

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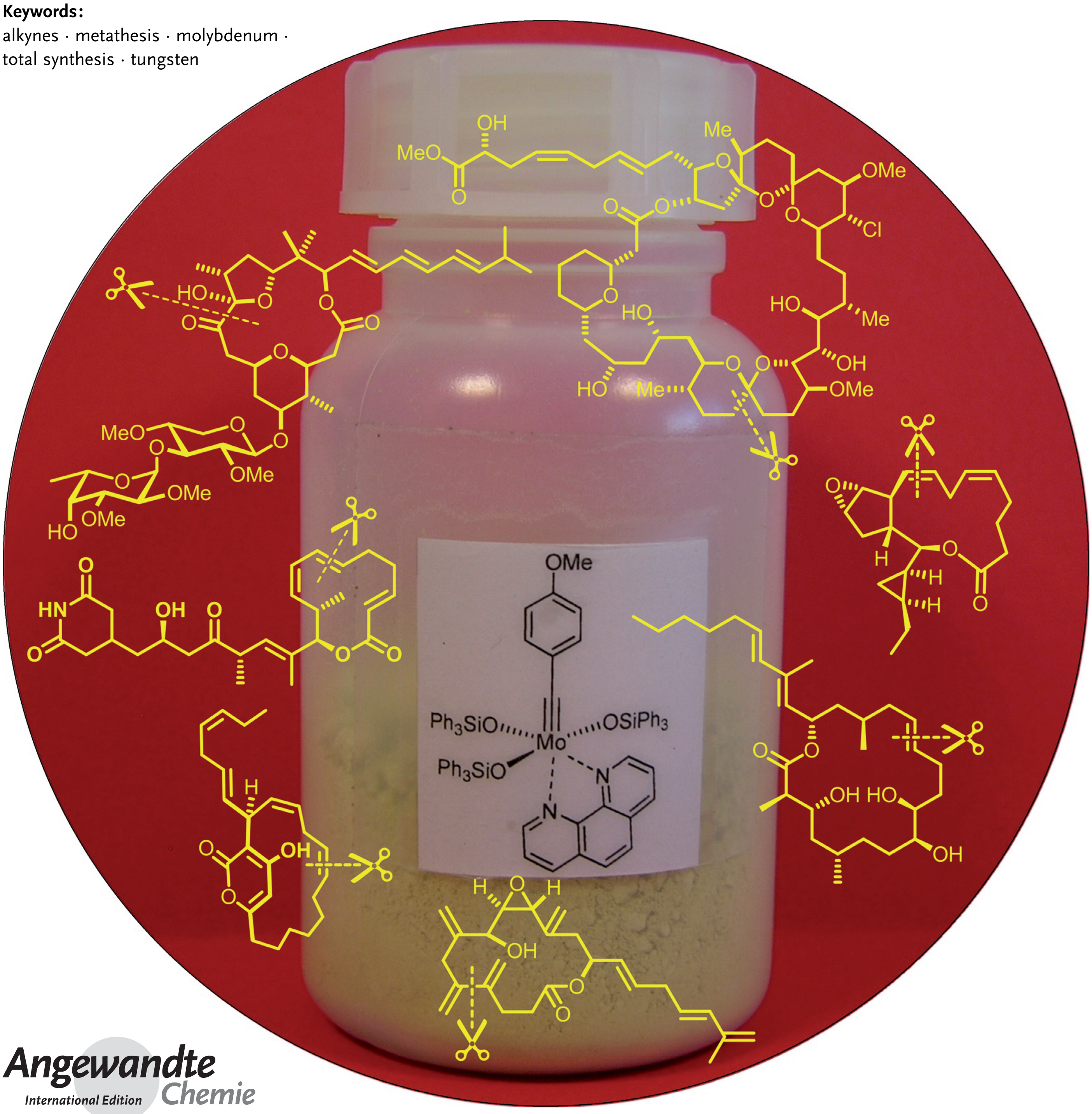
Keywords:
alkynes · metathesis · molybdenum · total synthesis · tungsten



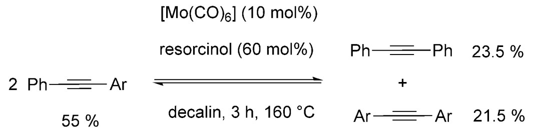
Angewandte
International Edition Chemie

The early years of alkyne metathesis were marked by a somewhat ironic state of affairs: the proposed mechanism was swiftly validated and more than one effective catalyst became available shortly after the discovery of this transformation; surprisingly, however, the impact on synthesis remained very limited for a long period of time. Recent advances, however, suggest that this situation is about to change: the remarkable activity, functional-group tolerance, and reliability of the latest generation of catalysts open the door for highly advanced applications. The resulting (cyclo)alkynes are amenable to numerous postmetathetic transformations, which diversify the product portfolio and bring many different structural motifs into reach. Since the catalysts have also evolved from the glovebox to the benchtop, there should be little barrier left for a wider use of this reaction in organic synthesis.

From the Contents

1. Introduction

Alkyne metathesis originates from heterogeneous catalysis. It was Penella et al. who showed as early as 1968 that WO_3 on silica (6.8% w/w) is able to scramble 2-pentyne into a mixture of 2-butyne and 3-hexyne.[1,2] The impact of this initial discovery, however, was limited, because of the competing polymerization of the substrate under the forcing reaction conditions (200–450 °C). Homogeneous catalysis followed shortly, when Mortreux and Blanchard found that a mixture of $[Mo(CO)_6]$ and resorcinol becomes catalytically competent when heated in inert solvents to 160 °C (Scheme 1).[3] The operational simplicity of this recipe is attractive and explains the numerous attempts at an empirical optimization. To this end, various molybdenum sources, substituted phenols, and solvents were screened in the presence or absence of further additives.[4–11] Some improvements notwithstanding, elevated reaction temperatures are still necessary in most cases and the exact nature of the active species generated in situ remains elusive, even though there is little doubt that it must be some kind of molybdenum alkylidyne with one or more phenolates in the ligand sphere. The low concentration of this species in solution likely explains why the reaction rates are usually rather slow when working with such catalyst preparations.[3–11]



Scheme 1. Original discovery of alkyne metathesis in a homogeneous phase by Mortreux and Blanchard; the numbers show the relative amounts of the three alkynes in the equilibrated mixture.

The arguably most serious limitation of Mortreux-type mixtures, however, is the narrow functional-group tolerance. Resorcinol or other substituted phenols are normally used in excess, and even ≥ 1 equivalents relative to the substrate is not uncommon. However, at elevated temperatures (substituted) phenols are by no means innocent and may endanger many polar substituents. This aspect is evident from the examples displayed in Scheme 2. Compound **3** bearing no functional groups other than aromatic ethers was cyclized in respectable yield with the aid of $[Mo(CO)_6]$ (10 mol%)/$F_3CC_6H_4OH$ (100 mol%) in chlorobenzene at 135 °C to cycloalkyne **4** as an immediate precursor of the cyclophanic natural product turriane.[12] In contrast, the attempted formation of the prostaglandin derivative **6** with a similar Mortreux catalyst mixture met with failure, as the substrate **5** was decomposed under the harsh conditions; this particular cyclization, however, posed no problem for the Schrock tungsten alkylidyne **1** or the two component system **2**/CH_2Cl_2 (see Section 2.2).[13]

Only one year after Mortreux's seminal discovery,[3] Katz and McGinnis proposed a mechanism which follows the logic of the Chauvin cycle of olefin metathesis (Scheme 3).[14] According to this proposal, a reactive species **A** with a metal–carbon triple bond as the operative unit combines with the alkyne in a formal [2+2] cycloaddition to give a metallacyclobutadiene **B**. Cycloreversion of this intermediate from the resonance extreme **B′** releases the product and regenerates a competent catalyst entity, which then undergoes the same steps to complete the turnover.

Although other mechanistic scenarios invoking metallacyclopentadienes and/or cyclobutadiene complexes were occasionally considered in the literature, there is little physical evidence in their favor.[7c,15–17] In contrast, the mechanism proposed by Katz and McGinnis soon found experimental confirmation in a series of classical papers from the Schrock research group.[18,19] Specifically, certain high-valent alkylidyne complexes of molybdenum, tungsten, and rhenium were found to exhibit remarkable catalytic activity, and the derived metallacyclobutadienes were shown to be intermediates rather than transition states. Actually, they

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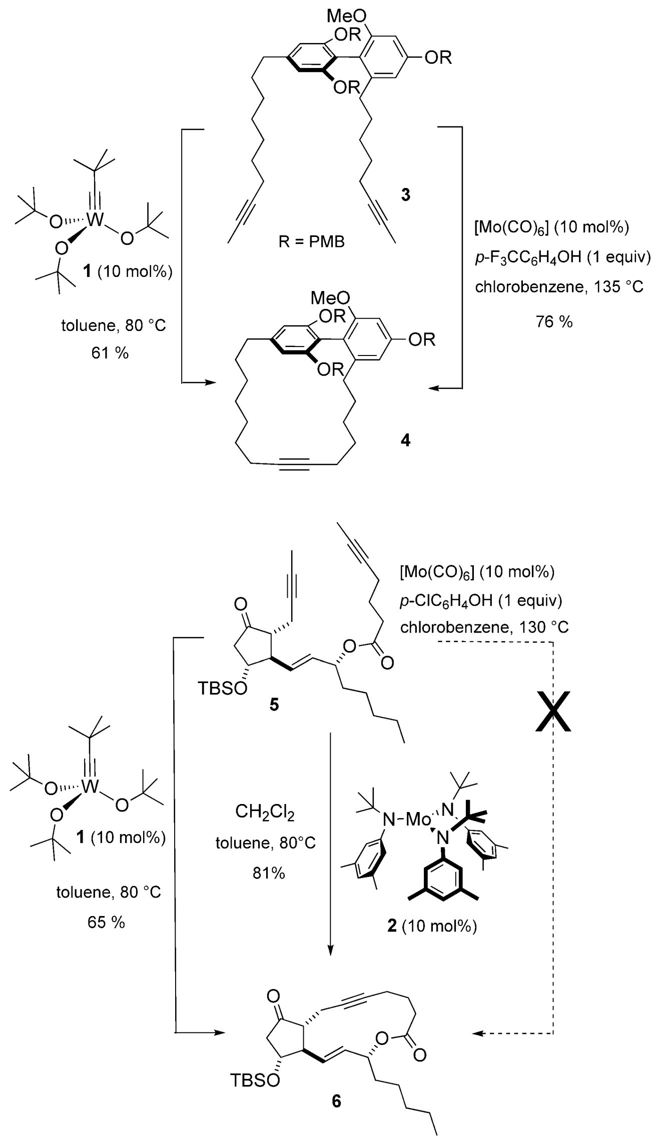
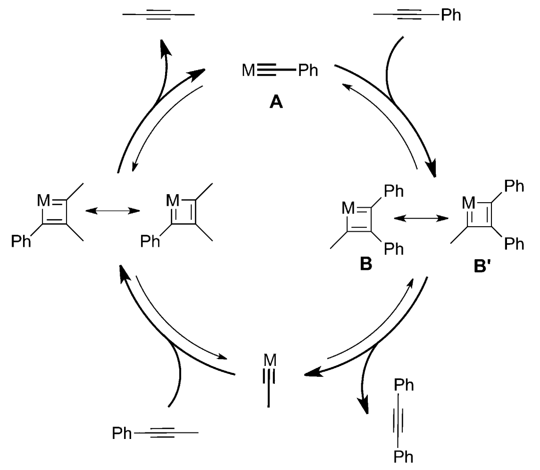


Scheme 2. Direct comparison of Mortreux-type catalysts generated in situ from [Mo(CO)$_6$] and substituted phenols with the structurally defined catalysts **1** and **2**. PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

likely represent the catalyst resting state, at least in the then most popular tungsten series.

Alois Fürstner (1962) obtained his PhD in 1987 at the Technical University of Graz, Austria (Prof. H. Weidmann). After postdoctoral research with Prof. W. Oppolzer in Geneva, Switzerland, and a Habilitation in Graz (1992), he joined the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany, where he became Director in 1998. His work focuses on organometallic chemistry and homogeneous catalysis, including applications to the total synthesis of structurally complex natural products of biological significance. His work in these fields has been recognized with many awards.



Scheme 3. Generally accepted mechanism of alkyne metathesis shown for the reaction of 1-phenyl-1-propyne to form tolane and 2-butyne; the latter needs to be removed from the mixture to drive the reaction to completion.

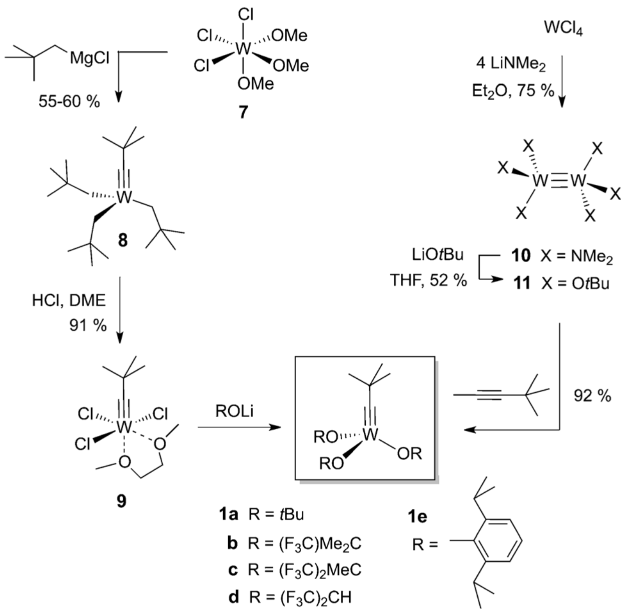
In view of these early breakthrough discoveries, one may diagnose—in retrospect—a somewhat paradoxical situation. The mechanism of alkyne metathesis was validated and several competent catalysts or catalyst systems were known by the early 1980s. Moreover, detailed insights into the comportment of Schrock-type alkylidyne complexes as the key players were gained as ever more variants became available.[20,21] However, the impact of this transformation on organic and polymer chemistry remained limited, with most applications being fairly simple in structural terms.[3–11,22] It was only much later that alkyne metathesis caught the attention of the synthetic community, with the advent of ring-closing alkyne metathesis (RCAM) shortly before the turn of the millennium marking a significant step forward.[23,24] This Review intends to summarize this development.[25–27] To fully appreciate the recent advances, however, it is necessary to describe the organometallic background in more detail.

2. Well-Defined Catalysts for Alkyne Metathesis

2.1. Lessons from the Organometallic Chemistry of Schrock-Type Tungsten Alkylidynes

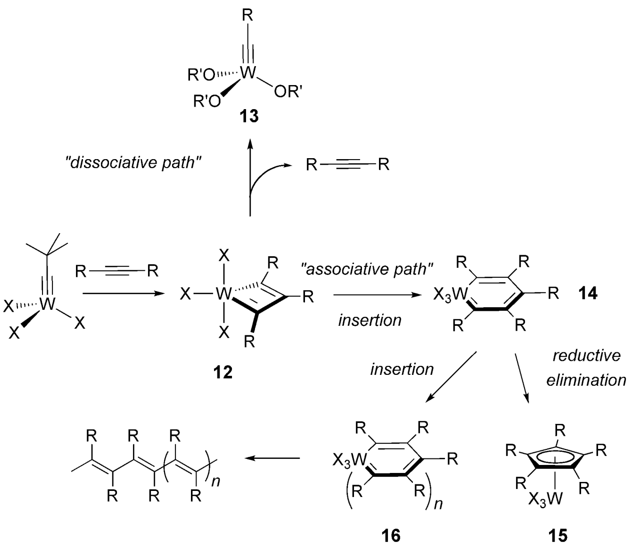
Although the mechanism proposed by Katz and McGinnis[14] suggested that complexes containing metal–carbon triple bonds should be competent catalysts, the Fischer carbyne complexes known at the time were totally inactive. Following the conventions of organometallic chemistry, a species such as [Br(CO)$_4$W$\equiv$CPh][28] is generally regarded as "low valent" and the carbyne ligand as monoanionic.[29] These characteristics allow Fischer complexes to be distinguished from Schrock alkylidynes, in which the metal center is usually in its highest possible oxidation state and the alkylidyne unit is considered to be trianionic.[19–21,30] It should be noted, however, that this formalism is somewhat arbitrary; in any case, the M$\equiv$C bond of a prototype Schrock alkylidyne is not as highly polarized as this way of electron counting may suggest, even though the alkylidyne carbon atom does show nucleophilic character. Several authoritative reviews provide in-depth treatises of the preparation, structure, bonding, and reactivity of metal alkylidynes.[19–21] The following section is, therefore, limited to the information that is most relevant for catalyst design.

All effective alkyne metathesis catalysts known to date fall into the "high-valent" Schrock category, but this condition alone is not sufficient. This is best illustrated by complexes of the general type [$X_3W{\equiv}CR$]. The substituent R on the alkylidyne unit has little bearing on the inherent activity, as it is lost in the first turnover of the catalytic cycle. It does, however, affect the stability and ease of preparation of a given complex, as well as the rate of initiation. In contrast, the anionic ancillary ligands X play a decisive role (Scheme 4).



Scheme 4. Two complementary routes to tungsten neopentylidyne complexes of type **1**. DME = 1,2-dimethoxyethane.

Specifically, the tris(neopentyl)neopentylidyne complex **8**[31] as well as the trichloroneopentylidyne complex **9** fail to metathesize internal alkynes.[32–34] Complex **9** will react with two equivalents of the substrate to form cyclopentadienyl complexes of type **15** (X = Cl) with a formally reduced tungsten center (Scheme 5). This outcome may represent a possible decomposition pathway that limits the lifetime of alkyne metathesis catalysts, although this notion needs further scrutiny. In contrast, the tris(*tert*-butoxy) derivative **1a** is not only historically the first well-defined catalyst for alkyne metathesis but still continues to serve as the benchmark three decades later.[18] It can be prepared by different routes: the classical Schrock method relies on the exhaustive alkylation of a W^{VI} precursor, preferably [$(MeO)_3WCl_3$] (**7**), to give a reactive intermediate which undergoes two consecutive α eliminations to form the alkylidyne **8**, which is then readily elaborated.[31,35] Alternatively, the metathetic cleavage of the metal–metal triple bond of the ditungsten complex **11**,[36] derived from WCl_4 and $LiNMe_2$, with neoheptyne is recommended (Scheme 4).[37,38] Complex **1a** is now also commercially available.



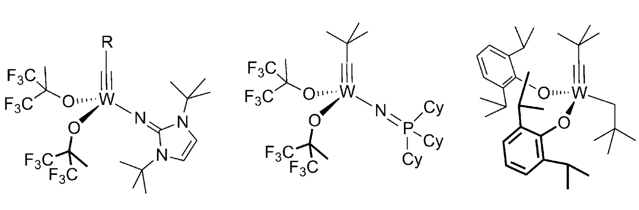
Scheme 5. Dissociative versus associative reaction pathways of tungsten alkylidyne complexes.

The bulk of the *tert*-butoxy groups is important to shield the tungsten center, prevent dimerization of the complexes through oxygen bridges,[39] and disfavor bimolecular decomposition of the catalyst.[40] Bulk alone, however, is not the only relevant parameter. Neither the tris(neopentyl) complex **8** nor complexes bearing sterically hindered -NR_2, -SR, or carboxylate groups as ancillary ligands give any sustained metathesis.[32,34,41,42] In contrast, the use of bulky phenolates leads to active catalysts, which may be unsurprising in view of Mortreux's results. Complex **1e**, for example, with 2,6-diisopropylphenolate ligands, even allowed the corresponding metallacyclobutadiene **12e** to be isolated from reactions with excess 3-hexyne.[43,44] The metallacyclobutadienes **12** feature a trigonal bipyramidal coordination geometry; the tungstacyclobutadiene ring is equatorially positioned and essentially planar. **12e** was also used in various kinetic investigations, which showed that the release of the product from the metallacycle is rate-limiting, at least for the particular case investigated. In line with the general characteristics of Schrock alkylidynes, complex **1e** was found to be sufficiently nucleophilic to engage in Wittig reactions with various carbonyl compounds, including benzaldehyde, acetone, ethyl formate, and even DMF.[45] This propensity is undesirable from an application point of view, and other catalysts of more tempered character are needed for use in advanced organic synthesis. As one might expect, alkylidynes of type **1** also react irreversibly with water to give tungsten oxo alkyl species, which are inactive in metathesis reactions.[46]

Attempts to tune the Lewis acidity of the tungsten center through replacement of the *tert*-butoxide ligands by branched fluorinated alkoxides also deserve comment.[34,47] Tungsten alkylidynes **1b–d** (Scheme 4) show good catalytic activity;

once again, the corresponding tungstacyclobutadiene intermediates of type **12** could be isolated and characterized. Whereas complex **12c** reacts further through the usual dissociative Katz-type mechanism, the slightly smaller $(F_3C)_2CHO$ groups in **12d** allow an associative channel to compete (Scheme 5). Specifically, the insertion of an additional substrate molecule leads to ring expansion with formation of a tungstacyclohexatriene intermediate **14**, which may evolve to a cyclopentadienyl complex **15**, as already mentioned above for the case that X = Cl. Alternatively, further insertion steps may follow, which eventually result in the polymerization of the substrate. Although the resulting polyacetylenes are interesting materials in their own right, substrate polymerization is detrimental for the use of alkyne metathesis in organic synthesis. Appropriate ligand tuning is, therefore, absolutely critical, and steric as well as electronic factors have to be carefully balanced in catalyst design. In this context, one should also note that 2-butyne, as the smallest internal alkyne, has the highest chance to undergo an associative mechanism and hence to get polymerized. Since 2-butyne is formed as the generic by-product in all metathesis reactions of methyl-capped alkyne substrates, it is important to effectively remove this compound from the mixtures (see Section 2.7).[48]

The formal 12-electron count (disregarding π donation) of the W^{VI} center in $[(t\mathrm{BuO})_3\mathrm{W}\equiv\mathrm{CCMe}_3]$ (**1a**) allows the appreciable Lewis acidity of this complex to be rationalized (although the actual electron density at the metal center is certainly different). This property surfaced in many reactions and seriously limits the preparative scope of **1a**. For example, this complex is unable to metathesize substrates containing donor sites such as amines, thio ethers, or crown ether segments.[24,60] Moreover, **1a** can deprotect acetal groups or even destroy acid-sensitive materials (for a representative example, see Sections 2.4 and 3.3). Replacement of the *tert*-butoxide ligands by fluorinated alkoxides further up-regulates the inherent Lewis acidic character. To reach an appropriate balance, it was proposed to craft a heteroleptic push/pull environment around the tungsten center. This is borne out in complexes such as **17**–**19** (Figure 1).[49–51] Complex **17** is highly active, with loadings of 1–2 mol% being sufficient in several applications. It is compatible with esters, ethers, thioethers, aryl chloride, and nitro groups, and was used for the preparation of ether-bridged *meta*-cyclophane structures by RCAM or cyclodimerization.[49,52] Therefore, a more comprehensive investigation into the scope and functional group tolerance of this heteroleptic complex seems warranted.



17 R = Ph, *t*Bu **18** **19**

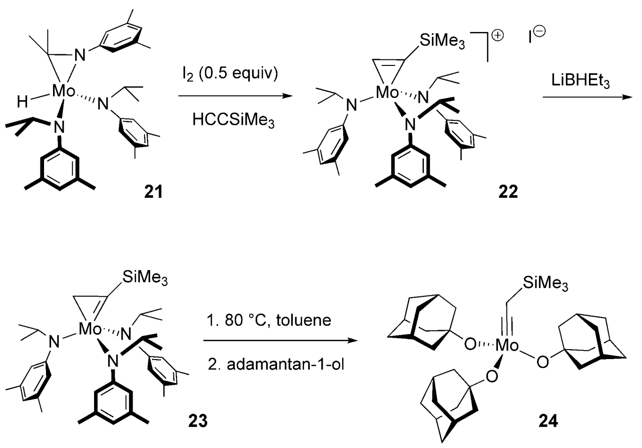
Figure 1. Tungsten alkylidyne complexes with heteroleptic ligand spheres. Cy = cyclohexyl.

2.2. Molybdenum-Based Catalysts

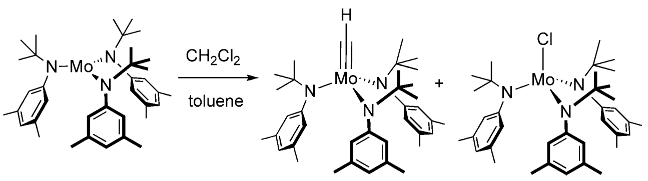
Schrock swiftly extended his pioneering studies on tungsten alkylidynes to similarly thorough investigations into their rhenium- and molybdenum-based cousins. Although rhenium alkylidynes—a priori—qualify as catalysts for alkyne metathesis, their lower performance may explain why they found little resonance.[53] In comparison, the impact of molybdenum alkylidynes is significant, even though the original synthesis of complexes of the type $[X_3\mathrm{Mo}\equiv\mathrm{CR}]$ was plagued by low yields and problems with scale-up.[54]

In striking contrast to the tungsten series, the parent *tert*-butoxide complex $[(t\mathrm{BuO})_3\mathrm{Mo}\equiv\mathrm{CCMe}_3]$ (**20**) performs poorly;[54] carboxylates or thiolates as ancillary ligands were also found to be inadequate. On the other hand, molybdenum neopentylidyne complexes endowed with sterically demanding phenolates or branched fluorinated alkoxides showed appreciable activity, with the reaction rate once again correlating with the size and electron-withdrawing character of the chosen ligands.[54,55]

Despite the promising characteristics, the somewhat problematic preparation of the required molybdenum alkylidyne complexes by the standard Schrock procedures represented a serious setback.[54] The cleavage of $[(t\mathrm{BuO})_3\mathrm{Mo}\equiv\mathrm{Mo}(\mathrm{O}t\mathrm{Bu})_3]$ with alkynes is not a real alternative either, because it is not as clean as in the tungsten series.[56] An interesting and potentially general alternative was disclosed by Cummins and co-workers, who showed that the successive treatment of the metallaaziridine hydride species **21** with iodine and trimethylsilylacetylene afforded complex **22** (Scheme 6).[57] Subsequent reduction with LiBHEt_3 furnished the unusual η^2 derivative **23**, which rearranges upon heating to its alkylidyne counterpart. A final alcoholysis with 1-adamantanol gave the trisalkoxide species **24** in high overall yield. This compound showed appreciable metathesis activity even at 25 °C in the small set of model reactions investigated. A systematic screening, however, is missing.



Scheme 6. Preparation of a metathesis-active molybdenum alkylidyne starting from a metallaaziridine hydride precursor.



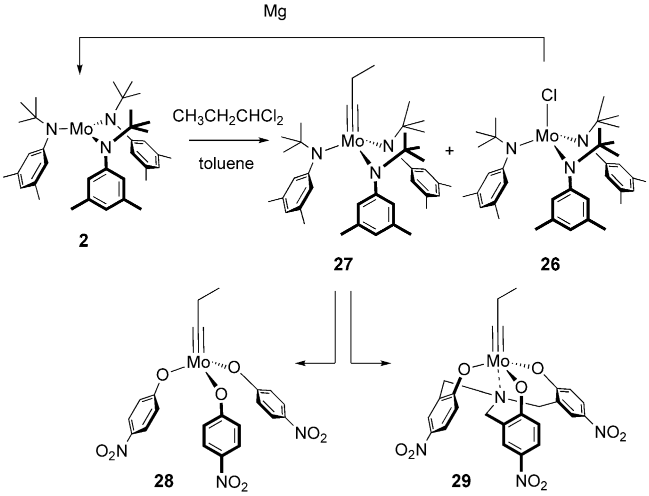
2 **25** **26**

Scheme 7. Activation of **2** with dichloromethane generates complexes **25** and **26** as the major products. Whereas the terminal alkylidyne **25** leads to roughly one turnover only, the chloride (**26**) is presumed to react with the substrate to form a new complex responsible for the observed sustained catalysis.

The related precursor complex **2** provides even greater opportunities. Originally designed for the stoichiometric cleavage of molecular nitrogen,[58] **2** was found to react with CH_2Cl_2 in toluene (Scheme 7).[59,60] The resulting mixture is capable of catalyzing numerous alkyne metathesis reactions at slightly elevated temperature. The major species formed under these conditions are the methylidyne complex **25**[61] and the monochloride **26**. Whereas the terminal alkylidyne **25** effects only one turnover of an alkyne substrate,[62] **26** is likely responsible for the sustained metathesis activity of the combination **2**/CH_2Cl_2.[60] It is not entirely clear by which mechanism chloride **26** converts into a competent alkylidyne that is responsible for the catalytic turnover. It is, however, not unreasonable to think that a route similar to the one shown in Scheme 6 might be followed, in which oxidation of **21** with iodine to the corresponding monoiodo derivative precedes alkylidyne formation in the presence of an alkyne substrate.[57]

In any case, the combination **2**/CH_2Cl_2 tolerates numerous polar groups, including moderately basic amines and even divalent sulfur substituents, which deactivate the more Lewis acidic complex $[(t\mathrm{BuO})_3\mathrm{W{\equiv}CMe_3}]$ (**1a**).[59,60] As a consequence of this excellent profile, **2**/CH_2Cl_2 was our catalyst system of choice for almost a decade and was also used to great effect in several challenging total synthesis projects. A few representative cases are discussed in Section 3.

Following the initial discovery that **2** converts into active catalysts when treated with CH_2Cl_2,[59,60] higher *gem*-dichlorides $RCHCl_2$ were used as the activating agents as they provide substituted alkylidynes right away. The preparation of the propylidyne complex **27** is representative (Scheme 8).[63,64] This route can be combined with a reductive recycle strategy, which allows the chloride by-product **26** to be reconverted into the starting complex **2**. As a result, all of the molybdenum eventually ends up in the valuable alkylidyne product. After ligand exchange, preferably with *para*-nitrophenol, this method gives access to very active catalysts such as **28**, which was effective in many applications, in particular in polymer chemistry and material science.[63a,103a] Immobilized variants have also been described.[65,66] Moreover, alcoholysis of **27** with an electron-poor triphenolamine derivative allowed a tridentate ligand to be attached to the molybdenum alkylidyne core, with the aim of increasing the catalyst lifetime and the substrate scope.[67] The resulting complex **29** showed high metathesis activity and even tolerated aldehyde and nitro groups, which are endangered with other catalysts.



2 **27** **26** **28** **29**

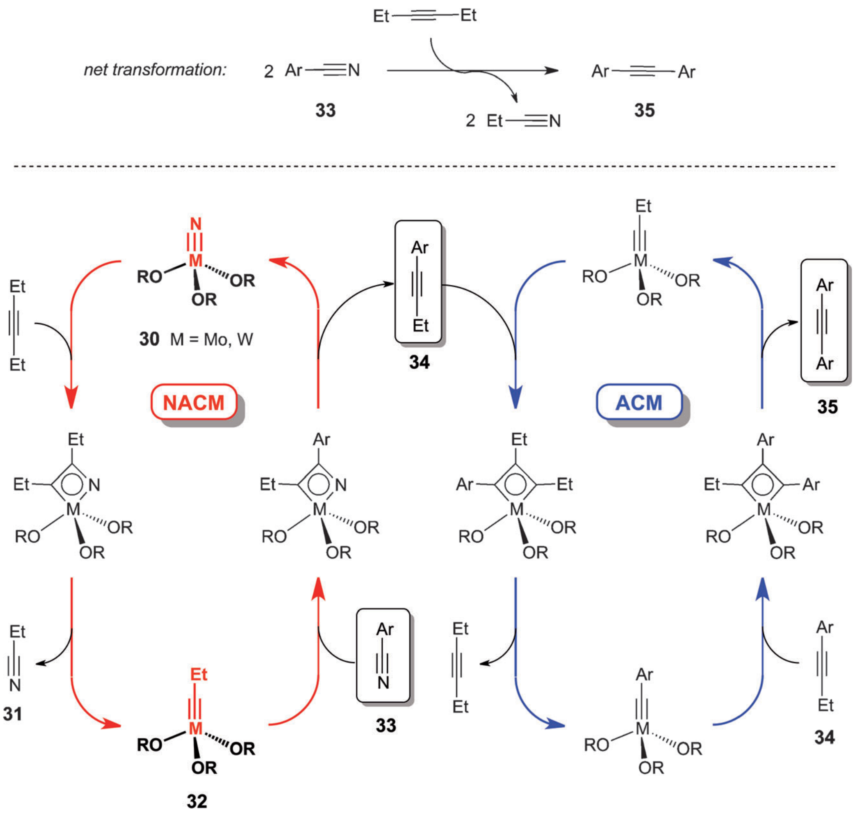
Scheme 8. "Second-generation" mode of activation of **2**, combined with a reductive recycling strategy.

Despite the favorable characteristics of such catalysts, it should be noted that complex **2** must be handled with great care. This compound is not only very sensitive to oxidation and hydrolysis, but even reactive enough to cleave molecular nitrogen.[58] Working under argon with strict Schlenk techniques is, therefore, mandatory. As a consequence of this handicap, we were eager to develop more robust and hence more user-friendly alternatives. To this end, the molybdenum alkylidynes endowed with triarylsilanolate ligands discussed in Section 2.4 are recommended, because they are highly active, exquisitely selective, readily prepared, and can even be rendered bench-stable.[68,69] We trust that such complexes can replace the combination **2**/CH_2Cl_2 or complex **28** in most cases (except, maybe, for very hindered substrates).

2.3. Metal Nitrides: From Nitrile/Alkyne Cross-Metathesis to Improved Catalyst Design

It is the thermodynamic stability of the nitride complex $\{[(\mathrm{Ar})(t\mathrm{Bu})\mathrm{N}]_3\mathrm{Mo{\equiv}N}\}$ (Ar = 3,5-dimethylphenyl) that provides the driving force for the smooth cleavage of N_2 by **2** mentioned above.[58] For the very same reason, $[(t\mathrm{BuO})_3\mathrm{W{\equiv}W}(\mathrm{O}t\mathrm{Bu})_3]$ (**11**)[37,38] as well as tungsten alkylidynes such as $[(t\mathrm{BuO})_3\mathrm{W{\equiv}CPr}]$ are able to cleave the triple bond of nitriles with formation of $[(t\mathrm{BuO})_3\mathrm{W{\equiv}N}]_n$.[45,70]

With this background in mind, it was captivating to learn that the course of the reaction can also be reversed.[71,72] For a given set of ligands, the positive charge density at the metal center is higher in a nitride than in an alkylidyne complex, because of the more polarized M≡N bond. Poorly donating ancillary ligands should, therefore, destabilize the nitride relative to the alkylidyne ligand. This rationale most likely explains why molybdenum and tungsten nitrides such as **30** bearing fluorinated alkoxides slowly convert into the corresponding propylidyne complexes **32** when heated in the



Scheme 9. An intertwined nitrile/alkyne cross-metathesis (NACM) and alkyne cross-metathesis (ACM) sequence based on the reversible interconversion of metal nitrides and metal alkylidynes. R = hexafluoro-*tert*-butyl.

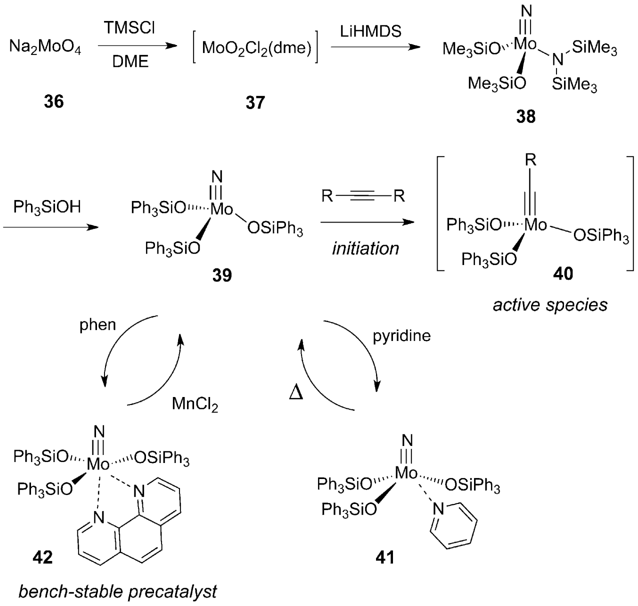
presence of 3-hexyne. This discovery opened the intriguing possibility of performing nitrile/alkyne cross-metathesis (NACM) reactions (Scheme 9).[71] In essence, two interconnected cycles allow an aromatic nitrile **33** in combination with 3-hexyne to be transformed into the corresponding tolane derivative **35** and propionitrile. Although the preparative scope of this method is still fairly limited, it does open interesting perspectives for future research into metathesis.

Two fundamental lessons can be learnt from the pathway shown in Scheme 9. First, it is of note that the primary product **34** generated in the actual NACM cycle (colored in red) does not accumulate, but rapidly reacts further to give the symmetrical tolane derivative **35**. This means that the second cycle, consisting of a pure alkyne cross-metathesis (ACM, colored in blue), is more effective than the nitrile/alkyne crossing. Secondly and more fundamentally, the results demonstrate that molybdenum or tungsten nitrides qualify as precatalysts for alkyne metathesis per se.

Complexes **30** originally used for such purposes were prepared by azide decomposition and incorporate highly fluorinated, and hence expensive, alkoxide ligands.[71] In a quest for more practical alternatives, my research group showed that complex **38** constitutes a favorable choice.[73] No azide decomposition is involved in its synthesis, and the route depicted in Scheme 10 is therefore safe, cheap, and scalable. Although **38** itself is metathesis-inactive, alcoholysis with Ph_3SiOH provides complex $[(Ph_3SiO)_3Mo{\equiv}N]$ (**39**), which is a competent precatalyst for alkyne metathesis reactions of all kinds.[73,74] It is presumed to convert into an active alkylidyne **40** on reaction with a given substrate (see Section 2.4).

Furthermore, **39** can be stabilized by complexation with appropriate nitrogen donor ligands. Originally, pyridine was used for this purpose.[73] The corresponding adduct **41** is sufficiently stable to be weighed in air, although it will eventually hydrolyze on storage in air. Gratifyingly though, the analogous 2,2′-bipyridine or 1,10-phenanthroline complexes are much more robust. Complex **42**, for example, is indefinitely air stable in crystalline form (> 2 years) and is, therefore, easy to work with.[68,69,75]

Whereas the pyridine dissociates from **41** upon heating to 80 °C in toluene, and thereby releases the active principle, the phenantroline complex **42** is inert under these conditions. However, the catalytic activity is restored when **42** is in the presence of metal salts that bind phenanthroline more tightly than the Mo^{VI} center does ($MnCl_2$, $ZnCl_2$, $CuCl_2$ etc.). $MnCl_2$ is recommended, because it is cheap, benign, nontoxic, readily available, hardly Lewis acidic, and nonhygroscopic; hence, this salt can be used as purchased without any pretreatment or drying. The activation of **42** with $MnCl_2$ can either be performed prior to the addition of the substrate or in its presence. In terms of functional-group compatibility, the combination **42**/$MnCl_2$ shows the same selectivity profile as



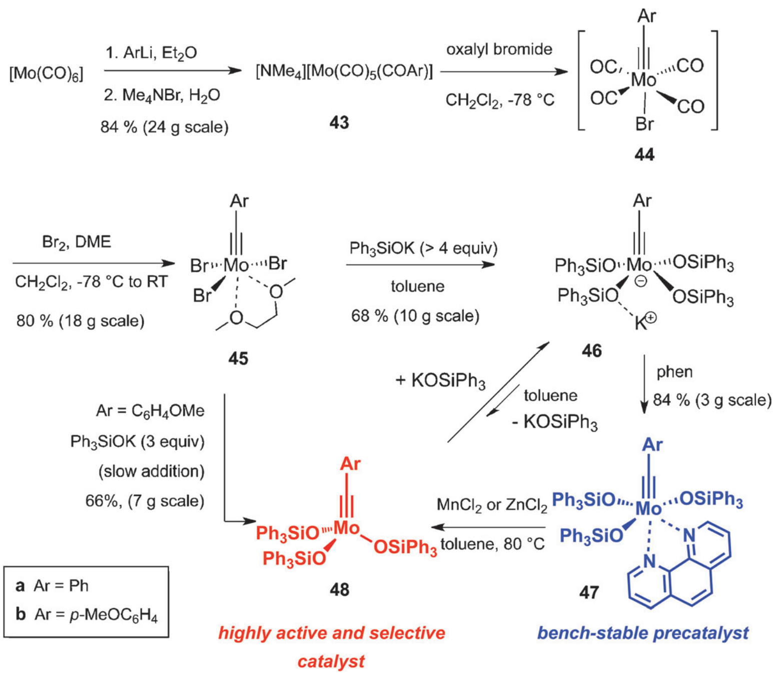
Scheme 10. Scalable synthesis of a bench-stable molybdenum nitride complex for alkyne metathesis. TMS = trimethylsilyl.

the pyridine complex **41**, with both systems thought to release—via **39**—the identical active principle **40**.[68,69,76]

Overall, precatalysts **39**–**42** exhibit a favorable application profile and have already stood the test of natural product synthesis; specific examples are discussed in Section 3. These precatalysts tolerate numerous functional groups, except for aldehydes and acid chlorides, which convert into the corresponding nitriles. This observation is interesting in its own right, since such nitride complexes can also serve as nitrogen-transfer agents in organic synthesis.[73]

2.4. From the Glovebox to the Benchtop: Catalysts with Improved Activity and Stability

The next step in catalyst design was initiated by the surprising discovery that only tiny amounts of nitride **39** actually convert into an alkylidyne of type **40** when treated with an alkyne substrate, as evidenced by NMR spectroscopy and mass spectrometry. In view of the gratifying preparative results obtained with **39** as a precatalyst, however, this finding implied that molybdenum alkylidynes **40** endowed with triphenylsilanolate ligands must be very active. Therefore, complexes of this type were prepared by an independent route, and were found to exhibit a unique application profile. Similar to their nitride counterparts, they can also be rendered air stable upon complexation with 1,10-phenanthroline or 2,2′-bipyridine. The resulting adducts serve as convenient and bench-stable precatalysts, which are easy to activate in solution with $MnCl_2$ or $ZnCl_2$. This procedure allows alkyne metathesis reactions of elaborate, sensitive, and highly functionalized substrates to be performed with excellent results with the help of user-friendly precursor complexes.[68,69]



Scheme 11. Scaleable synthesis of molybdenum benzylidyne complexes endowed with triarylsilanolate ligands. phen = 1,10-phenanthroline.

To fully exploit the potential of such catalysts, it was necessary to develop a practical and scalable synthesis route. The sequence depicted in Scheme 11 is an adaptation of a versatile literature procedure which links the classical Fischer carbyne chemistry with the Schrock alkylidyne domain by bromine oxidation of the low-valent complex **44** to its high-valent tribromo congener **45**.[77] Since multigram amounts of **45** can be prepared with ease, this compound served as an expedient starting material for the preparation of numerous highly metathesis-active molybdenum alkylidynes. The route allows for systematic variations of the residue Ar on the alkylidyne, the ancillary silanolate belt, and the stabilizing N donor ligand. The results of a systematic molecular editing exercise along these lines can be summarized as follows:[68,69,78]

1) Except for a few cases, ate complexes are the preferred products formed upon addition of Ar_3SiOK to a solution of **45** in toluene. To satisfy this bias and avoid the formation of product mixtures, the use of ≥ 4 equivalents of Ar_3SiOK is recommended for preparative purposes. This allows prototype ate complexes such as **46** to be obtained in high yields in either solvate-free or solvated form.[69] When treated with 1,10-phenanthroline or related chelate ligands, the fourth silanolate ligand is lost and the corresponding neutral adducts

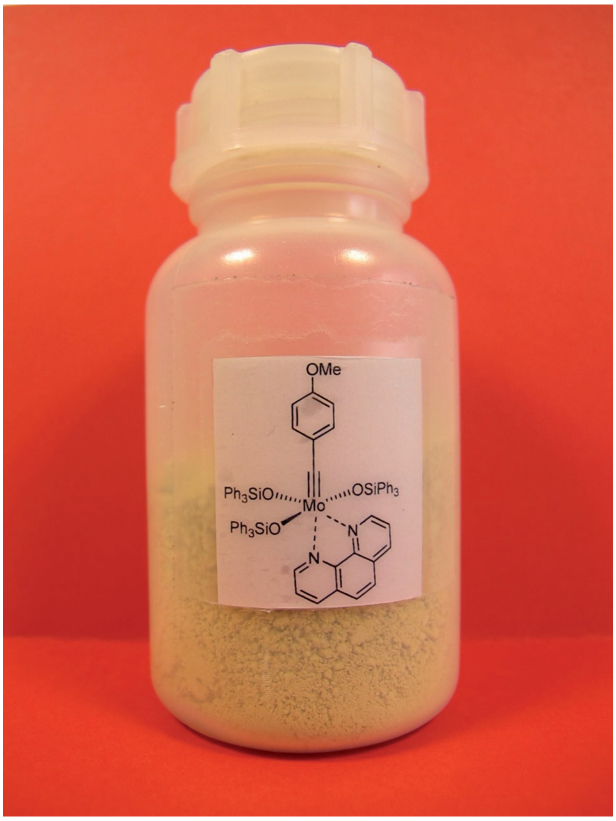
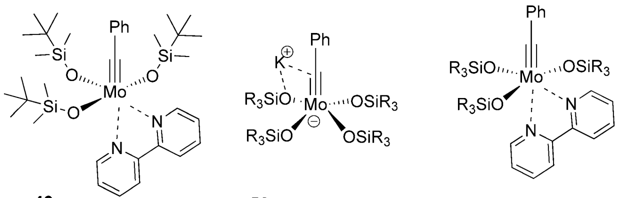


Figure 2. Shelf-stable phenanthroline adduct **47 b**, which serves as a privileged precatalyst for many alkyne metathesis reactions.

47 are formed as air-stable crystalline materials (Figure 2). In solution, the ate complexes seem to be in equilibrium with small amounts of the corresponding neutral alkylidynes (e.g. **48**), which are thought to be the actual catalysts for alkyne metathesis. As a result, the ate complexes **46** themselves can be used as highly effective and selective catalysts for inter- and intramolecular alkyne metathesis reactions of all sorts.

2) Despite this bias for the formation of ate complexes, neutral alkylidyne complexes could be isolated in analytically pure form in certain cases. The *para*-methoxybenzylidyne species **48b** (Ar = *p*-MeOC$_6$H$_4$) is representative; it is one of the most active and selective alkyne metathesis catalysts known to date, since no preactivation or ligand loss is necessary.[69]

3) Triarylsilanolates are better ancillary ligands than trialkylsilanolates, although complex **49** still shows appreciable activity (Figure 3). A favorable match between the characteristics of the high-valent molybdenum center and the electronic and steric features of the triarylsilanolates imparts a well-balanced character on the central metal center: it is sufficiently Lewis acidic to ensure excellent catalytic activity, yet sufficiently tempered to leave polar and even fairly acid-sensitive substituents uncompromised. The parent triphenylsilanolate itself represents an excellent choice, since Ph$_3$SiOH is cheap and commercially available. Complexes such as **46**–**48** are highly active and nicely crystalline.[68,69] Another preferred catalyst is complex **50** or its stabilized variant **51** (Figure 3). Their use is recommended when working with fairly lipophilic substrates; the MeO substituents on the silanolate ligands render the silicon-containing by-products derived from this catalyst upon work up quite polar and hence readily separable from the desired products.[69]



49   **50** R = *p*-MeOC$_6$H$_4$ **51** R = *p*-MeOC$_6$H$_4$

Figure 3. Additional important catalyst variants.

4) The fact that 1,10-phenanthroline can be pulled off adduct **47** even with moderately Lewis acidic salts such as MnCl$_2$ or ZnCl$_2$ can be rationalized on the basis of its structural features. As evident from Figure 4, this complex shows a strongly distorted coordination geometry about the metal center.[68,69] Whereas the equatorially oriented N atom of the donor binds tightly (2.244(2) Å), the second N···Mo contact is much looser (2.408(2) Å), thus reflecting the strong *trans* influence of the alkylidyne group. Moreover, the rigid phenanthroline backbone does not allow this second N atom to reach the best geometrical position for binding. When **47a** is treated with MnCl$_2$ or ZnCl$_2$ in toluene for about 30 min at 80 °C, a sufficient amount of the active principle is released to allow even demanding intramolecular alkyne metathesis reactions to proceed with generally high rates and good yields. A quantitative removal of the phenanthroline ligand from **47**, however, takes considerably longer (ca. 3 h with ZnCl$_2$ as the additive).[69]

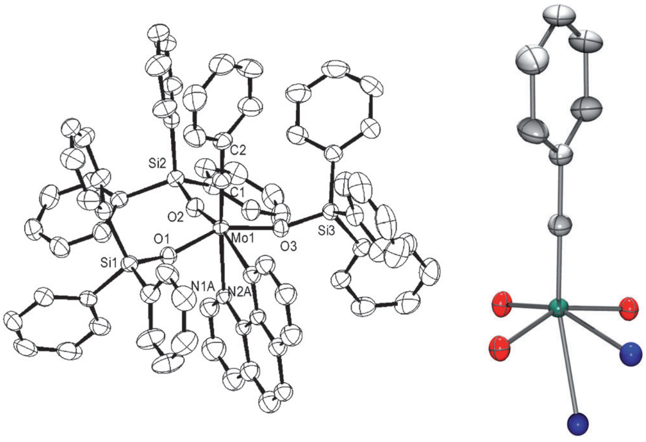


Figure 4. Left: Structure of complex **47a** (Ar = Ph) in the solid state. Right: the distortion of the first coordination sphere about the Mo center and the uneven Mo···N distances (2.244(2) versus 2.408(2) Å). Mo: green, O: red, N: blue.

5) At the current stage of development, molybdenum alkylidynes endowed with triarylsilanolate ligands are usually preferred over their tungsten counterparts, which can be prepared analogously from [ArC≡WBr$_3$]·(DME) (Ar = aryl, DME = 1,2-dimethoxyethane) by ligand exchange. However, the higher Lewis acidity of W^{VI} renders the corresponding ate complexes more stable,[68] whereas some neutral variants are prone to rearrange to tungsten alkylidenes. However, it is possible to obtain useful catalysts by fine-tuning the silanolate belt. Thus, a recently disclosed tungsten alkylidyne endowed with siloxane-based ligands effected several model reactions at ambient temperature and was found to be compatible with ester, ether, thioether, and chloride substituents, and this complex even promoted metathesis reactions of 1,3-diyne substrates (see Section 3.3.1).[79]

The outstanding activity of the new complexes is manifest in the direct comparison of **46a** with [(tBuO)$_3$W≡CMe$_3$] (**1a**) (Figure 5). At a catalyst loading of 1 mol %, the reaction of 1-

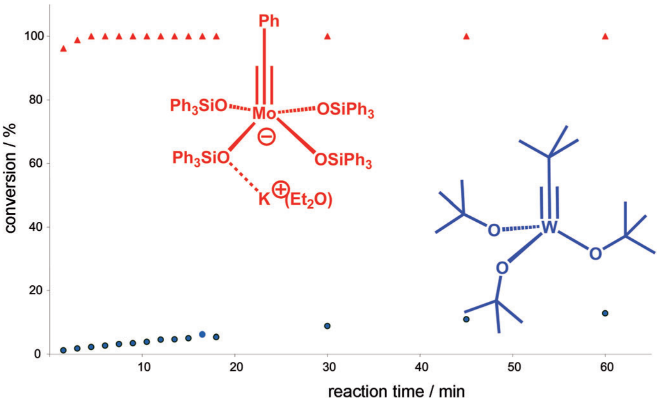
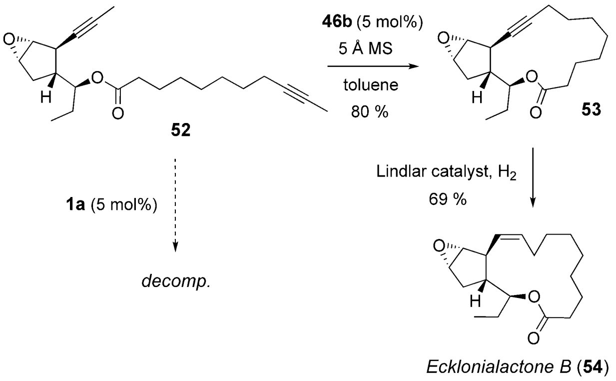


Figure 5. Comparison of the performance of the Mo alkylidyne ate complex **46a**·Et$_2$O with the classical tungsten alkylidyne **1a** in the conversion of 1-phenyl-1-propyne into tolane. The reaction was performed at ambient temperature with 1 mol % catalyst loading in the presence of 5 Å MS to trap the released 2-butyne (see Section 2.7).



Scheme 12. The tempered Lewis acidity of **46b** (Ar = p-MeOC$_6$H$_4$) was instrumental for the total synthesis of ecklonialactone B, whereas the tungsten alkylidyne **1a** destroyed the labile substrate. MS = molecular sieves.

phenyl-1-propyne catalyzed by **46a** is quantitative after ≤5 min at ambient temperature,[69,80] whereas **1a** does not even reach 20% conversion after 1 h under otherwise identical conditions. Another instructive case relates to a recent total synthesis of the ecklonialactones (Scheme 12).[81] Whereas **1a** destroyed the acid-sensitive epoxide **52**, the molybdenum ate complexes of type **46** allowed this fragile compound to be converted into product **53** in excellent yield. Moreover, **1** is inactivated by basic nitrogen or divalent sulfur groups, whereas **46** remains fully operative in the presence of pyridine, thiazole, thiophene, and MeS groups. Only aromatic aldehydes are endangered, while nitriles are kinetically inert. Additional groups that pose no problem include esters, ethers, silyl ethers, tosylates, ketones, amides, carbamates, aldols, acetals, spiroketals, epoxides, vinyl epoxides, aryl-X groups (X = F, Cl, Br), aldols, alkyl chlorides, propargyl acetates, carbazoles, pyrones, as well as trifluoromethyl and nitro groups, to mention but the most important ones.[68,69] Likewise, the catalyst rigorously distinguishes between alkynes (reactive) and alkenes, which are tolerated irrespective of whether they are terminal, internal, or conjugated to a carbonyl group; 1,3-dienes as well as skipped alkenes are also inert. We hence conclude that alkyne metathesis is strictly orthogonal to alkene metathesis, a fact that provides valuable opportunities for synthesis.[82] The selected applications discussed in Section 3 feature the excellent application profile of such silanolate-bearing molybdenum alkylidynes. Their ready availability, remarkable activity, outstanding functional-group tolerance, and user-friendliness, when handled as the air-stable phenanthroline adducts, should form a sound basis for further applications in organic and polymer chemistry.

2.5. Structural Considerations and Adaptable Electronic Features

Numerous X-ray structures of molybdenum alkylidynes endowed with silanolates ligands, both from the neutral and the ate series, allowed their advantageous profile to be correlated with distinct structural characteristics.[69] As mentioned above, there is a strong bias for the uptake of four Ar$_3$SiO ligands by a single Mo center with formation of ate complexes such as **46**. The neutral variants **48** readily coordinate additional donor ligands, which can be bound either *trans* or *cis* to the alkylidyne.[69] Although one may perceive, at first sight, Ph$_3$SiO groups as being very bulky, these data suggest that the silanolates do not provide any serious impediment for substrate binding (except for, maybe, very bulky ones). However, they seem to be large enough to disfavor an associative mechanism, which explains why substrate polymerization did not interfere to any noticeable extent in any of the alkyne metathesis catalyzed by any such molybdenum alkylidynes studied so far.[69,83]

In electronic terms, siloxides are weaker net donors than alkoxides because $p_\pi \rightarrow d$ donation has to compete with backbonding from the oxygen atom into the low-lying Si–C σ^* orbitals.[84] Furthermore, the donor capacity of silanolates is angle-dependent (Figure 6): when the Mo–O–Si bond angle Θ is close to 180 °C, both orthogonal electron pairs on the oxygen atom can engage in O→Mo bonding, which down-regulates the Lewis acidity of the central atom. In contrast, bending gives only one lone pair of electrons on the oxygen atom the chance to overlap with a metal d orbital and should, therefore, increase the acidic character of the Mo center.

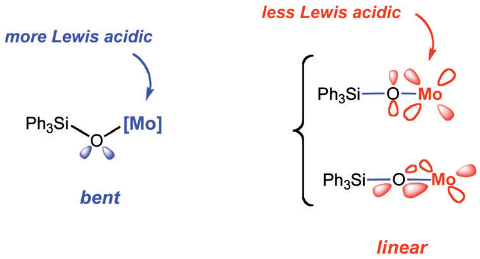


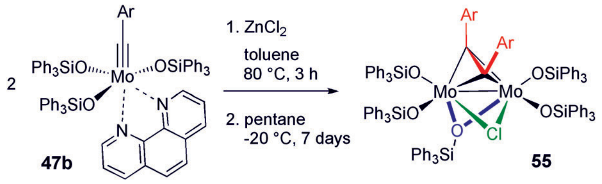
Figure 6. Bending of the Mo-O-Si hinge gently reduces $p_\pi \rightarrow d$ electron donation, thereby increasing the Lewis acidity of the metal center and hence favoring substrate binding; stretching has the opposite effects and thus facilitates the release of the product.

The many X-ray structures now available of alkylidynes with silanolate ligands advocate the notion that stretching and bending of the Mo–O–Si hinges is very facile.[69] This floppiness of the silanolate belt may actually help the catalyst meet the opposing electronic demands of the catalytic cycle: note that a Lewis acidic metal center is advantageous for substrate uptake and formation of a metallacycle (Scheme 3, **A**→**B**), whereas the cycloreversion step and release of the product will benefit from a higher electron density at the metal center. It is tempting to speculate that the constant thermal motion of the silanolates, which results in stretching and bending of the Mo-O-Si joints, engenders a nonstatic electronic influence and allows the active species to meet the disparate electronic demands while passing through the catalytic cycle. This aspect needs further investigations and could also be relevant for other types of catalytic transformations.

2.6. Factors Influencing the Catalyst Lifetime

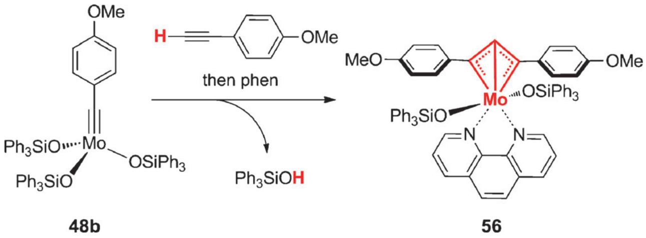
The available data suggest that triarylsilanolates also exert a positive effect on the catalyst lifetime.[69] Whereas $R_3C{-}O$ bonds, when ligated to a Lewis acidic metal center, are endangered by the facile generation of a tertiary carbocation, $R_3Si{-}O$ bonds are unlikely to break in a similar fashion; this may explain the good thermal stability of catalysts of type **46**–**48**.[69] Hydrolysis is the most serious threat, and working in anhydrous solvents remains imperative. Even the stabilized phenanthroline adducts eventually decompose (**47a** has a half-lifetime of ca. 5 days in CD_2Cl_2 containing 10 ppm water); some of the resulting hydrolysis products have been structurally characterized by X-ray diffraction.[69]

Under anhydrous conditions, bimolecular decomposition pathways seem to prevail, which are disfavored by the bulky silanolate periphery about the operative alkylidyne unit; this translates into appreciable catalyst lifetimes ($t_{1/2}$ of **46a**·Et_2O in anhydrous toluene ca. 30 h).[69] However, dimerization of the alkylidyne units remains possible, as can be seen from complex **55**, which was isolated in small amounts when a mixture of **47b** and $ZnCl_2$ was heated for 3 h to 80 °C and the resulting solution then kept at −20 °C for several days (Scheme 13).[69] The dimetallatetrahedrane frame of **55** derives from two alkylidyne units and can be interpreted as a μ-bridging alkyne complex.[85,86] Therefore, the isolation of compound **55** lends credence to the notion that the collision of two active catalyst entities engenders coupling of their benzylidyne units with formation of a (substituted) tolane and, in this particular case, concomitant replacement of one silanolate by a bridging chloride ligand.



Scheme 13. Bimolecular decomposition under forcing conditions. Ar = *p*-$MeOC_6H_4$.

In addition to the decomposition pathways by bimolecular collision or hydrolysis, Schrock alkylidyne complexes are known to degrade upon attempted metathesis of terminal (rather than internal) alkynes. The critical step occurs after formation of the metallacycle and consists of a transannular C−H activation with formation of a deprotio-metallacyclobutadiene and concomitant loss of one alkoxide ligand.[54a,87] This reaction course remains viable for the new alkylidynes with silanolate ligands. Specifically, when complex **48b** was treated with *p*-$MeOC_6H_4C{\equiv}CH$, the deprotio-molybdacyclobutadiene **56** could be isolated upon addition of 1,10-phenanthroline (Scheme 14).[69] Thus, we are not yet able to metathesize terminal alkynes with similar efficiency.[88,170]



Scheme 14. Deactivation pathway operative when working with terminal alkyne substrates.

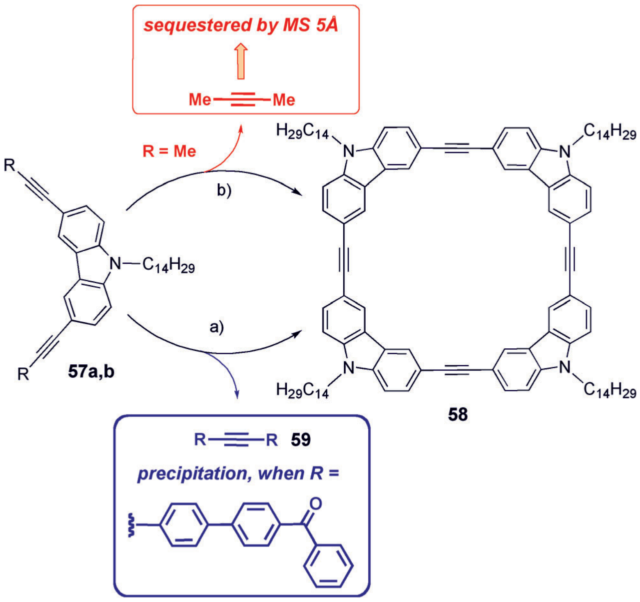
2.7. Molecular Sieves As Butyne Scavengers

Any alkyne metathesis leads to an equilibrium between the two substrate and the two product molecules (Scheme 3). To render the reaction preparatively meaningful, it is necessary to shift the equilibrium to one side. When starting from methyl-capped alkynes, this can be reached by removing the 2-butyne (b.p. = 27 °C) formed as the generic by-product from the mixture by either performing the reactions at higher temperatures and/or by applying a gentle vacuum. Since the solvent will also (partly) distill off under reduced pressure, however, the concentration of the mixture may change as the reaction proceeds; therefore, this set-up is not preferred. Accumulating 2-butyne, on the other hand, either stops the conversion or may lead to polymerization if the chosen catalyst can engage in an associate mechanism (see Scheme 5).[48]

Precipitation-driven alkyne metathesis constitutes an alternative set-up.[89] Rather than relying on methyl-capped alkynes, tailor-made substrates such as **57a** with 4-benzoylbiphenyl groups on the termini are used. Metathesis produces the shape-persistent macrocycle **58** in good yield (61–81 %) together with compound **59**, which precipitates from 1,2,4-trichlorobenzene or CCl_4 solution and, in so doing, propels the conversion.

Despite their respectable efficiency, such precipitation-driven metathesis reactions are poorly atom economical (the precipitated product **59** has a molecular weight of 538 (!)), the required substrates need to be prepared in separate steps, and the high boiling point of 1,2,4-trichlorobenzene renders product isolation tedious. The use of CCl_4 as an alternative medium is worrisome because of its carcinogenicity.

These inconveniencies are avoided altogether by a new set-up which relies on the use of powdered molecular sieves, preferably 5 Å MS, as an additive.[68] Its pore size is large enough to sequester 2-butyne but small enough not to entrap the substrate, product, catalyst, or toluene solvent. As a consequence, methylated alkynes are suitable substrates. In the presence of 5 Å MS, the reactions can be carried out at ambient temperature and quantitative conversion still be reached, even though the generated 2-butyne does not evaporate (see Figure 5). As an illustrative example, the formation of the same cyclotetramer **58** is quoted, which was formed under these conditions in consistently high yield from the methyl-capped alkyne **57b** (R = Me) by using either the nitride complex **42** (83 %), the ate complex **46a** (82 %) or the phenanthroline adduct **47a** (81 %) as (pre)catalysts



Scheme 15. Two different ways to drive alkyne metathesis reactions to completion, exemplified by the formation of a shape-persistent cyclo-oligomer: Sequestration of 2-butyne with the aid of molecular sieves versus a "precipitation-driven" route: a) **27** (33 mol%), *p*-nitrophenol, CCl_4, 50°C, 61%; b) toluene, 5 Å MS, **46a** (2 mol%), 82%, or: **42** (10 mol%)/$MnCl_2$ (10 mol%), 83%; or: **47a** (5 mol%)/$MnCl_2$ (5 mol%), 81%.

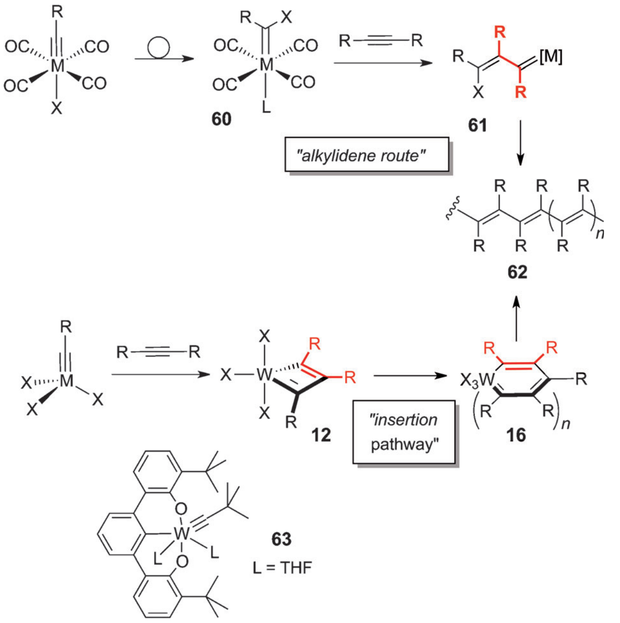
(Scheme 15). The addition of 5 Å MS is, therefore, recommended as a simple measure to improve the efficiency and convenience of alkyne metathesis reactions of all types, irrespective of the chosen catalyst.[68] Several examples outlined in Section 3 corroborate this aspect. As an additional bonus, 5 Å MS helps to keep the medium water free, which retards eventual hydrolytic deactivation of the catalyst and, therefore, has a positive impact on the total turnover number.

3. Selected Applications

3.1. Highlights from Material Science

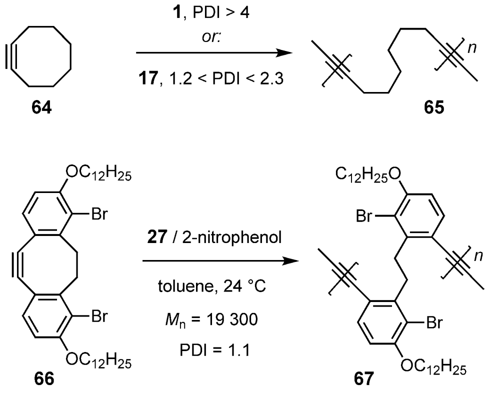
Alkynes can participate in two distinctly different ways in metathetic transformations:[90,91] on the one hand, they can undergo "true" alkyne metathesis in which the triple bond is broken and reformed, as discussed in this Review. Alternatively, alkynes can engage only the two π bonds and retain their σ framework. The latter behavior underlies enyne metathesis[92] as well as many alkyne polymerization reactions catalyzed by appropriate metal alkylidenes (preformed or generated in situ).[93] This latter process ("alkylidene path") is more like olefin metathesis and will not be covered herein, although the resulting polyacetylene derivatives **62** have fascinating material properties.

Alkylidyne complexes may also trigger such an "alkylidene path" to polymers upon in situ protonation or rearrangement to a competent metal alkylidene (Scheme 16).[93,94] Alternatively, alkylidynes may produce polyacetylenes **62** by an associative pathway. In this case, the metallacyclobutadiene **12** initially formed fails to cyclorevert but instead keeps inserting additional monomer. This will grow into a macrocyclic metallacycle **16**, which eventually disintegrates with release of the polymeric material.[95] As the product microstructures generated by the alkylidene route and the insertion pathway are identical, the operative mechanism usually remains unknown. In any case, several highly effective alkylidyne initiators for polyacetylene synthesis have been described in the literature, amongst which the tungsten complex **63** with a trianionic pincer ligand is particularly noteworthy.[96]



Scheme 16. Two conceivable pathways by which metal alkylidynes may effect alkyne polymerization with formation of substituted polyacetylene derivatives. Structure of the trianionic pincer alkylidyne complex **63** for alkyne polymerization.

The first example of a "true" alkyne metathesis polymerization, during which the triple bond is fully scrambled, relied on the ring opening of cyclooctyne **64** as the substrate (Scheme 17). Treatment of **64** with either tungsten- or



Scheme 17. Ring-opening alkyne polymerization. PDI = polydispersity index.

molybdenum-based catalysts resulted in the formation of an elastomer **65** with a wide molecular weight distribution ($M_w/M_n>4$).[97,98] This high polydispersity index (PDI) reflects a sluggish initiation and/or a partial degradation by backbiting of the catalyst into the acetylene units embedded into the growing polymer chain. More recently, the outcome could be improved by using the tungsten-imidazoline-2-iminato complex **17**, which gave PDI values between 1.2 and 2.3, depending on the reaction conditions.[99] To ensure good polymer yields, however, it was necessary to work in neat cyclooctyne.

It is the ability of the new rapidly initiating catalysts to discriminate between the cycloalkyne substrate and the unstrained acetylene units in the polymer backbone that determines the polydispersity. Based on such differential reactivity, it was possible to polymerize the dibenzo[*a*,*e*]-[8]-annulene **66**, a highly angle-strained monomer, without any significant degree of undesirable chain-transfer processes interfering by using **27**/2-nitrophenol. This example is the first documented case of a "living" ring-opening alkyne metathesis polymerization.[100] Neither the PDI (ca. 1.1) nor M_n value eroded with time, and the catalytic head groups terminating the growing chains remained active after the initial monomer had been consumed.

An alternative way to polymerize alkyne substrates is acyclic diyne metathesis polymerization (ADIMET).[101] This step-growth process was extensively used for the preparation of poly(aryleneethynylene)s (PAEs), which are of interest for their electronic and optical properties. Although the original Schrock tungsten alkylidyne **1a** works well, the use of either modified Mortreux-type catalyst mixtures or the combination **27**/nitrophenol are more popular. The repeat units of a few representative PAEs produced in this way are shown in Figure 7. ADIMET usually gives products with higher molecular weights and fewer defects than palladium-catalyzed polycondensation processes of the Sonogashira-type.[102] As expected, the degree of polymerization (P_n) strongly depends on the nature of the side chains attached to the monomers, which largely determine the solubility of the growing chains. It is remarkable that the molybdenum-based catalyst derived from **27**/nitrophenol even allowed poly(thienyleneethynylene)s to be prepared, whereas sulfur-containing heterocycles completely block the more traditional catalysts.[103a]

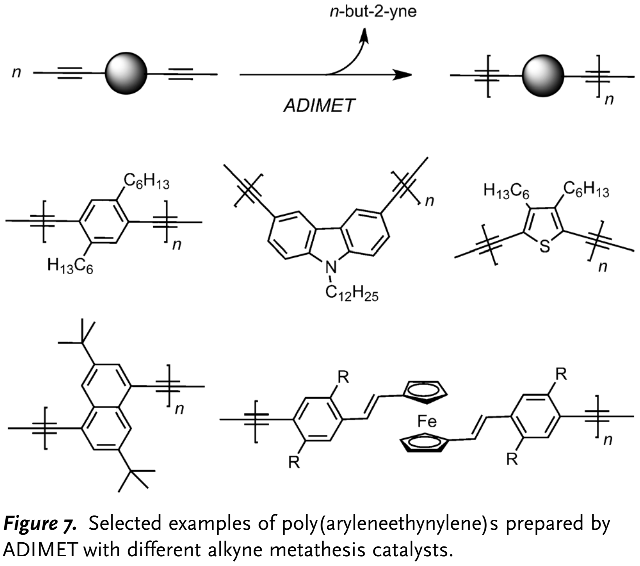


Figure 7. Selected examples of poly(aryleneethynylene)s prepared by ADIMET with different alkyne metathesis catalysts.

Alkyne metathesis also enabled cyclooligomerization reactions of dipropynylated arenes, thereby affording shape-persistent macrocycles often in remarkably good yields.[103–105] A prototype case has already been presented in Scheme 15; additional examples are shown in Figure 8. The most significant advantage of this method over more conventional approaches lies in its dynamic covalent character, which results from the inherent reversibility of the alkyne metathesis reaction. Reversibility ensures that the product mixture initially formed from a given substrate is able to equilibrate; as a result, the thermodynamically most stable product(s) will accumulate in solution. Reversibility is also the key for the productive depolymerization of poly(aryleneethynylene) derivatives recently reported in the literature.[106]

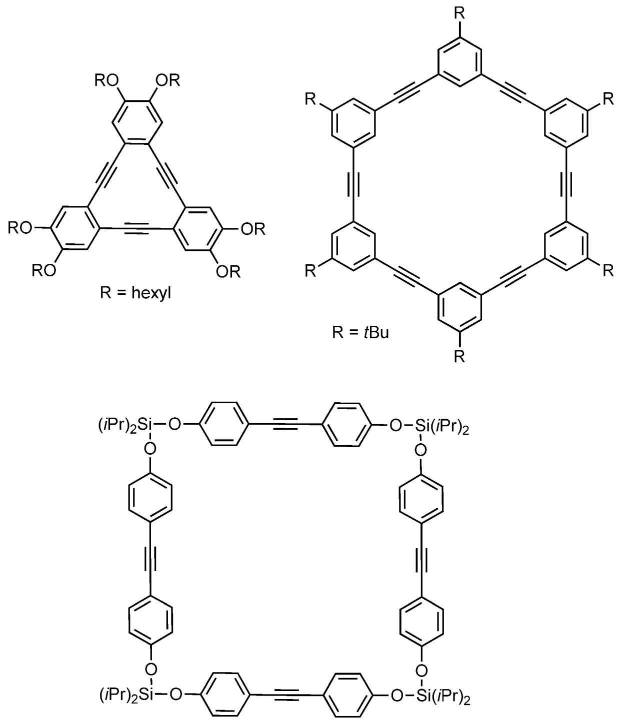


Figure 8. Additional examples of shape-persistent cyclooligomers.

3.2. Alkyne Cross-Metathesis

Nonterminal alkynes may either react with themselves ("self-metathesis") or with an appropriate second alkyne (alkyne cross-metathesis, ACM). Aliphatic substrates are particularly reactive, but numerous substituted 1,2-diarylacetylene derivatives have been prepared by this route from readily available propynylated (hetero)arene substrates.[107] The new catalysts, in particular the molybdenum alkylidynes endowed with silanolate ligands, are exquisitely selective,

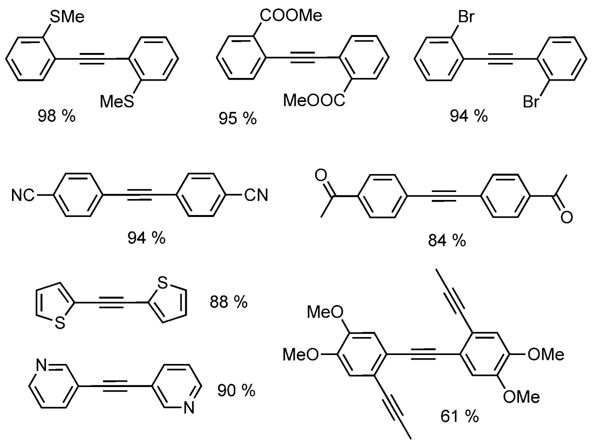
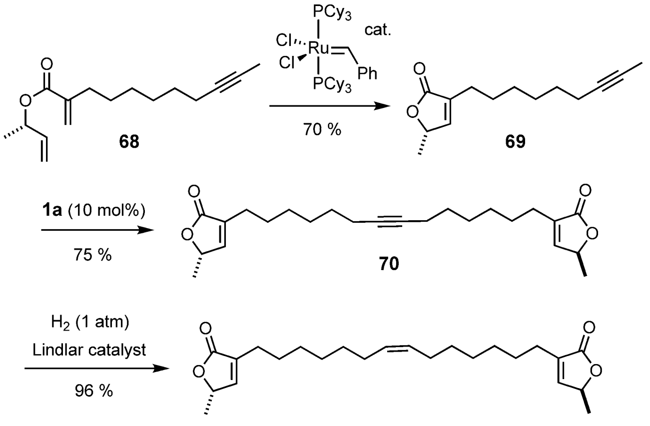
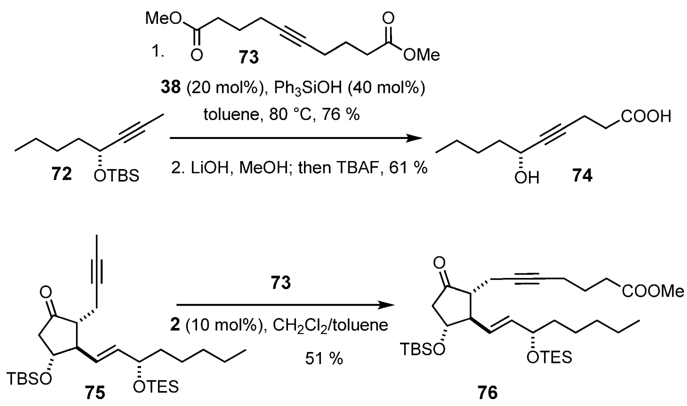


Figure 9. Symmetrical alkynes prepared by self-metathesis reactions of propynylated arenes by using complexes **46** or **47** as catalysts in the presence of 5 Å MS.



Scheme 18. Total synthesis of the acetogenin dehydrohomoancepsenolide, showing the orthogonal character of alkene and alkyne metathesis.



Scheme 19. Two applications of ACM in natural product synthesis. TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl.

tolerating most of the common functional groups;[68,69] even thiophene units or thioether substituents posed no problem (Figure 9).

Modern alkyne metathesis catalysts leave olefins of all sorts untouched. As a result, alkene and alkyne metathesis are chemically orthogonal,[82] a fact that was instrumental for a concise total synthesis of the acetogenin (*S*,*S*)-dehydrohomoancepsenolide (**71**; Scheme 18).[108] Specifically, the first generation Grubbs ruthenium carbene catalyst allowed the butenolide head group to be closed without touching the tethered alkyne, which was then selectively activated by the tungsten alkylidyne **1a** in the presence of the enoate. A final Lindlar reduction furnished the desired natural product in good overall yield.

In analogy to alkene cross-metathesis,[109] alkyne cross-metathesis (ACM) gives good results if the two reaction partners differ in steric and/or electronic terms so as to avoid statistical scrambling.[7b,110] For example, neither electron-deficient alkynes nor propargyl alcohol derivatives undergo self-metathesis; thus, both types of substrates undergo cross-reactions with regular alkyne partners, as illustrated by the formation of gallicynoic acid I (**74**) shown in Scheme 19.[73] The successful synthesis of a small library of prostaglandin derivatives demonstrates that the different steric bulk of two substrates also allows for successful ACM.[13a,110,111]

3.3. Ring-Closing Alkyne Metathesis (RCAM)

Ring-closing alkyne metathesis (RCAM) originally helped to solve a stereochemical problem that could not be addressed directly by ring-closing alkene metathesis (RCM).[23,24] Although RCM provides efficient access to carbo- and heterocycles of virtually all ring sizes, it usually delivers mixtures of the corresponding *E* and *Z* isomers when applied to medium-sized or macrocyclic systems.[112,113] The product ratios are difficult to predict and depend on the chosen catalyst, the reaction time, and even on the nature of the substituents and protecting groups on a certain substrate. In most cases, the thermodynamically more stable isomer accumulates in solution, which is often (but not always) the *E* alkene.

Inherently *E*-selective alkene metathesis catalysts are currently unknown, and *Z*-selective catalysts have surfaced only very recently.[114,115] Although they have already led to a few spectacular applications, RCAM followed by a stereoselective semireduction represents a serious and reliable alternative, most notably when working with polyunsaturated compounds. This notion will become evident from some of the case studies presented below.

Furthermore, cycloalkynes provide ample opportunities for postmetathesis modifications other than semireduction. It is, therefore, reasonable to expect that substantial structural space can be covered by merging alkyne metathesis with creative follow-up reactions. A few illustrative studies along these lines will be outlined in Sections 3.3.4 and 3.3.5 and more will soon be published. The latest generation of alkyne metathesis catalysts should facilitate such investigations, as the handling has become easy, and polar substituents or fragile substrates no longer pose any serious limitations.[68,69]

Of course, cycloalkynes are also interesting in their own right. An example is the "alkynylogous" mimic of a peptidic loop of the lantibiotic nisin, in which the triple bond serves as a rigid and stable isostere for a disulfide bridge (Figure 10).[116,117] Another remarkable case is the chelate complex **77**, in which one organometallic catalyst served to tailor the coordination sphere of another organometallic entity.[118] Very recently, 1,3-diynes have also been successfully metathesized; for example, substrate **78** gave the corresponding macrocyclic product **79** in excellent yield (Scheme 20).[119] It is also of note that this interesting transformation features a tungsten alkylidyne endowed with silanolate ligands as the catalyst.[79]

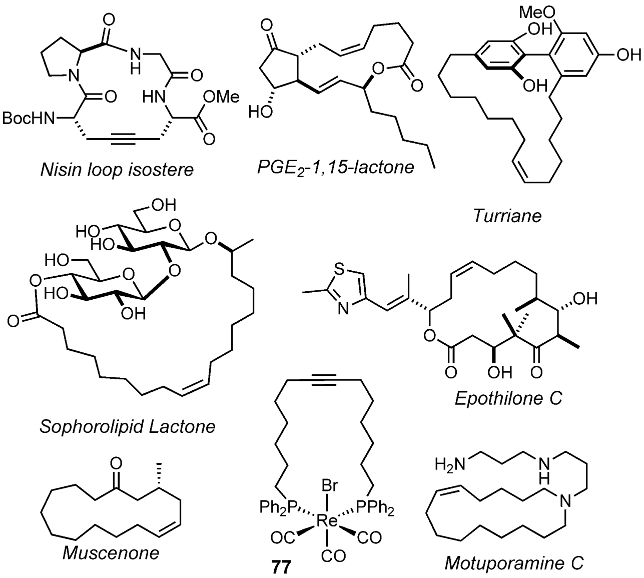
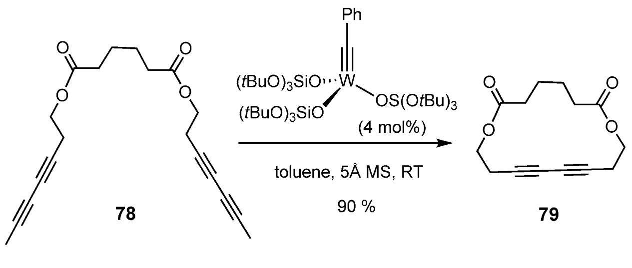


Figure 10. Early applications of RCAM, with or without subsequent semireduction of the newly formed cycloalkyne. Boc = *tert*-butyloxycarbonyl.

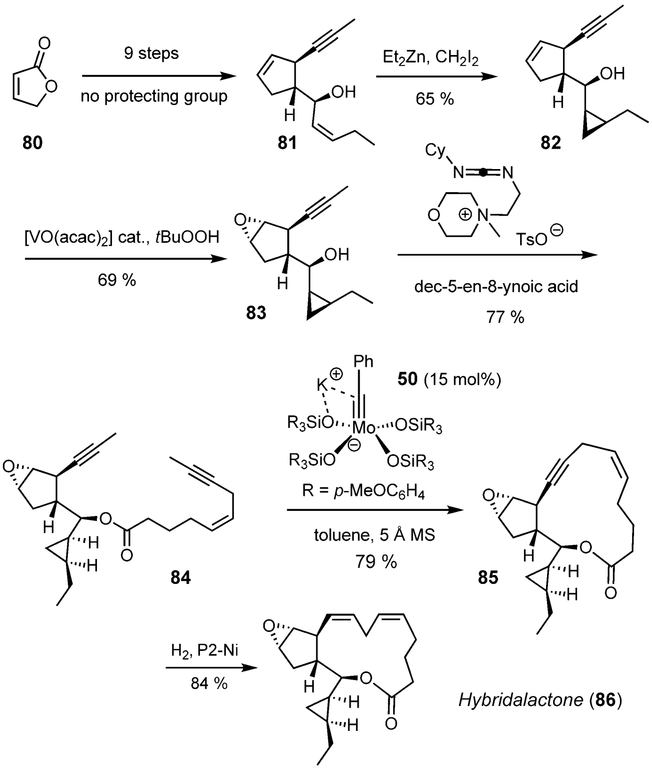
3.3.1. *RCAM for the Preparation of Z Alkenes*

RCAM followed by semireduction was used extensively for the formation of macrocyclic *Z* alkenes of various ring sizes and complexity. The scope ranges from rather simple ketones and lactones,[24,120,121] including the valuable perfume ingredients civetone[122] and (*R*,*Z*)-5-muscenone,[123] to structurally more challenging natural products of biological significance. The syntheses of epothilone C,[60,124] sophorolipid lactone,[125–127] motuporamine C,[128] the turrianes,[12] and prostaglandin E$_2$-1,15-lactone[13] are noteworthy early examples (Figure 10).



Scheme 20. First example of a ring-closing metathesis of 1,3-diyne substrates catalyzed by a tungsten alkylidyne endowed with tris(*tert*-butoxy)silanolate ligands.

A recent instructive case is the total synthesis of the unusual marine prostanoid hybridalactone (**86**) and the related oxylipins of the ecklonialactone family.[81,129] Without recourse to any protecting-group maneuver, butenolide **80** could be swiftly advanced to compound **81** in optically active form (Scheme 21). The unprotected hydroxy group then serves as relay substituent to direct the subsequent cyclopropanation to the β face of the flanking olefin, before guiding a vanadium-catalyzed epoxidation to the α face of the cyclopentene ring. Once all seven contiguous stereogenic centers were appropriately set, product **83** was esterified and the resulting diyne **84** subjected to ring closure. As one might expect, the cyclopropyl carbinol ester motif in **84** is highly acid sensitive. To complicate matters even further, the epoxide turned out to be unusually reactive and prone to intercept even weak nucleophiles. These challenges could only be met with the aid of the newly developed molybdenum alkylidyne **50** bearing triarylsilanolate groups, which delivered the desired cycloalkyne **85** in good yield. This outcome is best appreciated if one considers that the tungsten alkylidyne **1a** destroyed diyne **84** and related compounds instantaneously

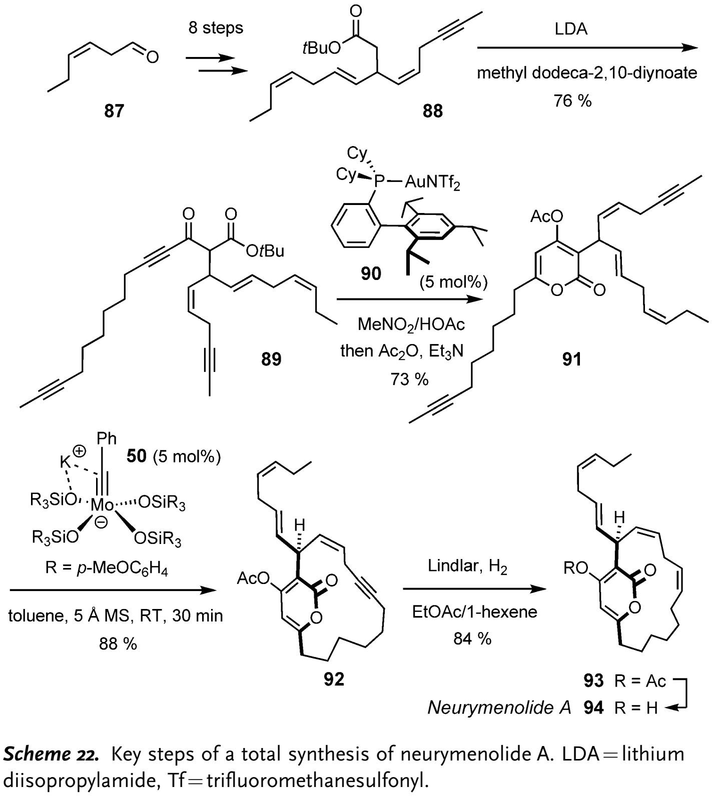


Scheme 21. Key steps of a total synthesis of hybridalactone. acac = acetylacetonate, P2-Ni = Ni(OAc)$_2$·4 H$_2$O/NaBH$_4$.

(see Scheme 12). The silanolate ligand sphere in **50** clearly imparts a well-balanced Lewis acidic character onto the molybdenum center, which is high enough to ensure excellent metathesis activity but sufficiently tempered to allow fragile groups to survive undamaged. Furthermore, the silanolate groups themselves are not sufficiently nucleophilic to open the oxirane ring. Semihydrogenation of **85** then furnished hybridalactone (**86**) in high yield.[129] The slightly less complex ecklonialactones A, B, and C have also be accessed by an analogous route (Scheme 12).

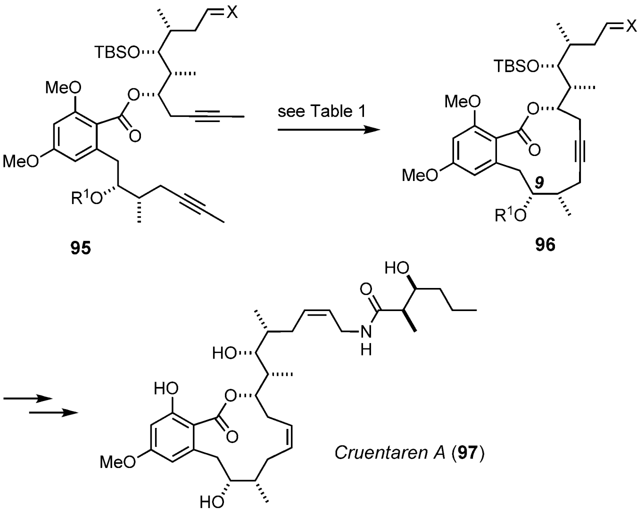
Although *Z*-selective olefin metathesis catalysts provide potentially more direct access to *Z*-configured cycloalkenes than RCAM/semireduction,[114,115] cases such as hybridalactone may remain beyond their reach. Catalysts able to form and activate *Z*-alkenes will address both olefinic sites of **86** and hence result in ring contraction. Since RCAM is orthogonal to any type of coexisting alkene substructure, however, it allows the site of ring closure to be unambiguously predetermined.

This aspect was absolutely critical for the total synthesis of the cyclophanic α-pyrone derivative neurymenolide A (**94**; Scheme 22).[130,131] This compound contains three *Z*-alkene units as well as one *E*-configured olefin in its lipidic chain and would hardly withstand any of the known alkene metathesis catalysts. Moreover, the skipped arrangement of the unsaturations renders this unusual natural product and all of its immediate precursors exceptionally sensitive. However, it could be formed in high yield by a sequence comprising a new gold-catalyzed hydroxy-pyrone synthesis and a subsequent alkyne metathesis as the key operations. The use of the new alkylidyne **50** was instrumental because it operates under very mild conditions and leaves the truly fragile olefinic array untouched. Cycloalkyne **92** formed in this remarkably clean and fast macrocyclization event was then converted into the highly sensitive target **94** without incident.[130]



Scheme 22. Key steps of a total synthesis of neurymenolide A. LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl.

Another instructive case concerns the highly potent F-ATPase inhibitor cruentaren A (**97**), which was prepared independently by three different research groups using RCAM as the strategic transformation. Specifically, Vintonyak and Maier forged the highly functionalized 12-membered ring **96a** in excellent yield with the aid of the Schrock tungsten alkylidyne catalyst **1a** (Scheme 23 and Table 1, entry 1).[132] The cycloalkyne was then carried through to the very end of the synthesis, because it held the OH group residing at C9 away from the transannular lactone and hence prevented undesirable ring contraction with formation of a δ-lactone from occurring. A final Lindlar reduction revealed the two *Z*-olefin moieties residing in the ring and the side chain of the target. This successful approach was nicely extended to the preparation of a set of cruentaren analogues for biological testing.[133]



Scheme 23. Key step of three independent total syntheses of cruentaren A.

An even more decorated substrate was used in the approach adopted by my research group, with the diyne **95b** already containing the *Z* alkene in the chain ($X = CHCH_2OTHP$).[134,135] It was imperative that the chosen catalyst rigorously distinguished between the two types of unsaturation present in this substrate. Although the tungsten alkylidyne **1a** should meet this condition, it turned out to be too Lewis acidic and only led to cleavage of the terminal THP-acetal (Table 1, entry 2). In contrast, the combination **2**/CH_2Cl_2 did an excellent job and furnished the desired product **96b** in 87 % yield. This transformation was revisited when the latest generation catalysts endowed with siloxide ligands became available. In line with our expectations, complex **46a** delivered **96b** with similar efficiency but required a significantly lower loading of only 2 mol %.

Table 1: Preparation of **96** by RCAM.

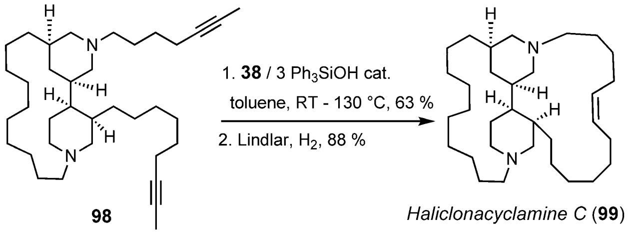
Entry		R	X	Catalyst (mol %)	T [°C]	Yield [%]	Ref.
1	**96a**	TIPS	H, ODMB	**1a** (10)	85	91	[132]
2	**96b**	TBDPS	$=CHCH_2OTHP$	**1a** (10)	80	–[a]	[134]
3	**96b**	TBDPS	$=CHCH_2OTHP$	**2** (10)[b]	80	87	[134]
4	**96b**	TBDPS	$=CHCH_2OTHP$	**46a** (2)	80	82	[68]
5	**96c**	TIPS	$=CHCH_2OPMB$	**41** (40)	110	75	[137]

[a] Only the THP group in the substrate was cleaved. [b] Activated with CH_2Cl_2. DMB = 3,4-dimethoxybenzyl; PMB = *p*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl; THP = tetrahydropyranyl; TIPS = triisopropylsilyl.

A few standard operations then allowed cruentaren A to be reached in high overall yield. By following the logic of "diverted total synthesis",[136] this approach could be reprogrammed to give access to a collection of designer analogues of this natural product with deep-seated structural point mutations.[135] Three of these fully synthetic compounds turned out to be as cytotoxic or even more so than cruentaren A itself against L-929 mouse fibroblast cells, with IC_{50} values reaching as low as 0.7 ng mL^{-1}.

Very recently, Barrett and co-workers reported yet another synthesis of cruentaren A through RCAM by using the pyridine adduct **41** to forge the macrocycle in good yield.[137] Since the initiation of this precatalyst by nitride-to-alkylidyne exchange is slow, a fairly high loading (40 %) was used to ensure a short reaction time and avoid thermal decomposition of the highly functionalized compound. Although this key step resembles the earlier syntheses of **97** outlined above, the preparation of the chosen substrate **95c** is distinguished by an innovative biomimetic de novo synthesis of the resorcyclide subunit.

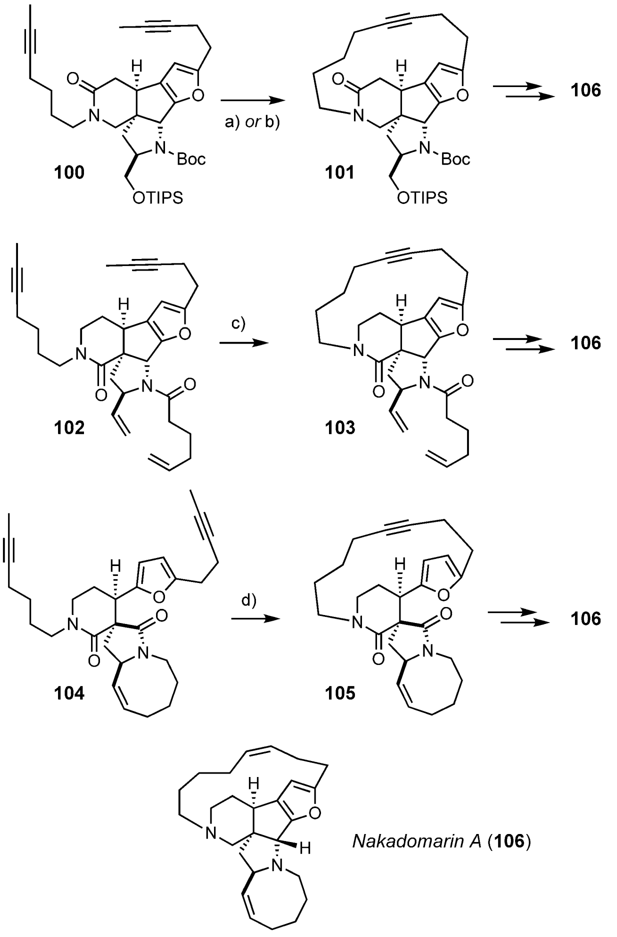
An elegant total synthesis of the tetracyclic alkylpiperidine alkaloid haliclonacyclamine C (**99**) illustrates another favorable characteristic of the new catalysts (Scheme 24).[138]



Scheme 24. Key step of a total synthesis of haliclonacyclamine C, featuring the compatibility of the new molybdenum silanolate catalysts with fairly basic amines.

In the penultimate step, substrate **98** containing two tertiary amines could be cyclized in appreciable yield to the corresponding cycloalkyne as the immediate precursor of the target compound. Of all the catalysts tested, only $[(Ph_3SiO)_3Mo{\equiv}N]$ (**39**) generated in situ from **38** and Ph_3SiOH was able to effect this transformation without getting blocked by the basic sites. Since **38**/Ph_3SiOH converts in situ into an alkylidyne **40** upon contact with the substrate (see above), it is reasonable to assume that the then not yet disclosed alkylidynes **46–51** would work at least equally well.

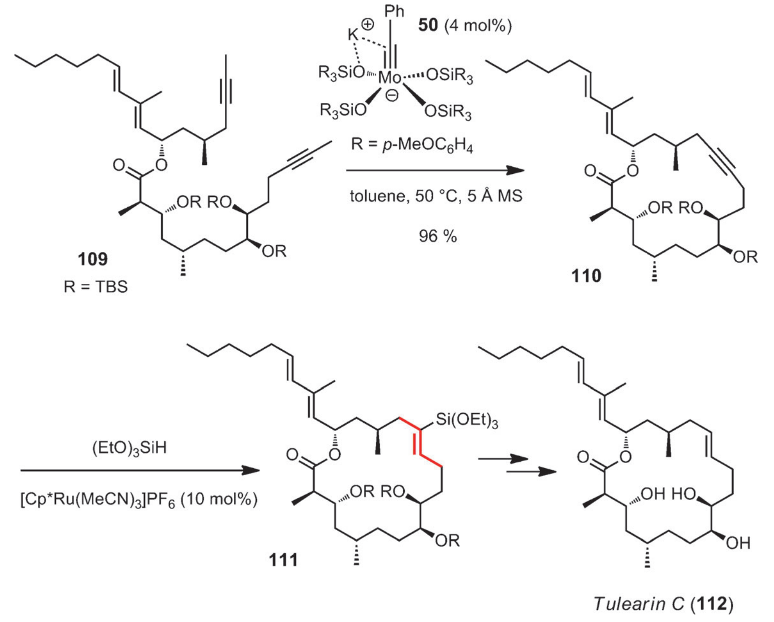
Following an early model study on the preparation of the macrocyclic perimeter of the polycyclic alkaloid nakadomarin A (**106**) through the aid of the tungsten alkylidyne **1a**,[24] three recent total syntheses beautifully used RCAM en route to this challenging target (Scheme 25). Specifically, Nilson and Funk forged cycloalkyne **101** with either the tungsten alkylidyne **1a** or the molybdenum nitride **41**.[139] Both catalysts systems gave similar yields (77 % and 80 %, respectively), which clearly surpassed the outcome obtained with a modified Mortreux catalyst under much harsher conditions. With product **101** in hand, nakadomarin A was reached after a short reaction sequence.



Scheme 25. RCAM-based total syntheses of nakadomarin A: a) **1a** (25 mol %), PhCl, 80 °C, 77 %; b) **41** (20 mol %), toluene, 80 °C, 80 %; c) **1a** (30 mol %), PhCl, 69 %; d) $[Mo(CO)_6]$ (100 mol %), 2-fluorophenol (5 equiv), PhCl, reflux, 36 %.

Complex **1a** was also used by Dixon and co-workers in their RCAM-based route to nakadomarin A reported shortly thereafter.[140] The elaborate substrate **102** was cyclized in 69 % yield and the resulting pentacyclic product **103** swiftly elaborated to the target by annulation of the still missing eight-membered E ring. In a slightly different setting, the

Dixon research group reported yet another approach involving the use of diyne **104** as the substrate, in which the E ring had already been set.[141] In this case, the macrocycle was closed with a modified Mortreux catalyst, but the yield of **105** remained low despite the high catalyst loading. While these three complementary routes to this architecturally intriguing marine natural product lend further credence to the notion that RCAM is a valuable tool for advanced synthesis, one must note that nakadomarin has recently also been reached with the aid of the new *Z*-selective RCM catalyst disclosed by Schrock, Hoveyda, and co-workers.[114a]

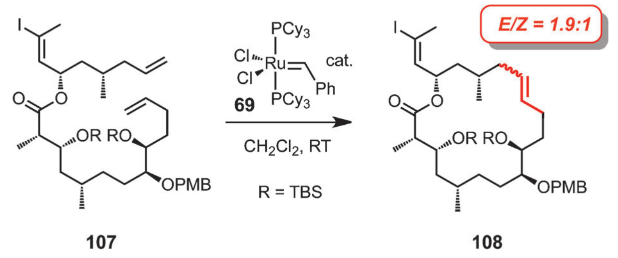


Scheme 27. Stereoselective total synthesis of tulearin C based on an RCAM/*trans*-hydrosilylation sequence. Cp* = C$_5$Me$_5$.

3.3.2. RCAM for the Preparation of E Alkenes

Cycloalkynes also open entry into the *E*-alkene series. However, since the traditional methods for *trans* reduction operate under strongly reducing conditions and are, therefore, of limited use for advanced organic synthesis, a ruthenium-catalyzed *trans*-hydrosilylation developed by Trost et al. is recommended.[142] The resulting alkenylsilanes are easily transformed into the corresponding *E* alkenes by protodesilylation.[143–145] Needless to say, they can also serve other preparative purposes, including oxidation and cross-coupling.

A sequence of RCAM and *trans* reduction was instrumental for the first total synthesis of tulearin C (**112**), an antiproliferative macrolide of marine origin.[146] Previous attempts to form the macrocyclic perimeter **108** by conventional RCM provided an unfavorable *E*/*Z* mixture of 1.9:1 (Scheme 26).[147] Attempts to improve on this result by changing the catalyst and varying the protecting groups were to no avail. This outcome shows that the lack of an inherently *E*-selective olefin metathesis catalyst can be a serious setback for target-oriented synthesis.



Scheme 26. The lack of an *E*-selective catalyst rendered an RCM approach to a tulearin isomer unsatisfactory, see Ref. [147].

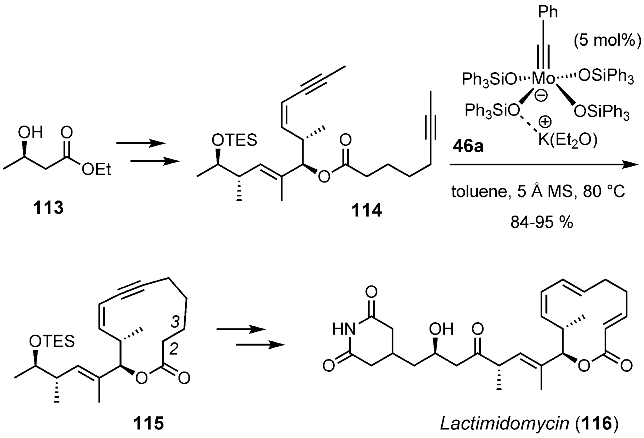
In contrast, RCAM of diyne **109** using the ate complex **50** as precatalyst and 5 Å MS as an additive gave the corresponding cycloalkyne **110** in almost quantitative yield, although the dienyl-alcohol motif as well as the aldol subunit are both fairly sensitive (Scheme 27).[146] A subsequent *trans*-hydrosilylation catalyzed by [Cp*Ru(MeCN)$_3$]PF$_6$ followed by global deprotection of **111** furnished tulearin C (**112**) with exquisite selectivity and good overall yield. It is worth mentioning that this particular project also spurred the development of a new synthesis of nonterminal alkynes from lactone precursors.[146]

3.3.3. Enyne-Yne Metathesis and the Preparation of Stereodefined 1,3-Dienes

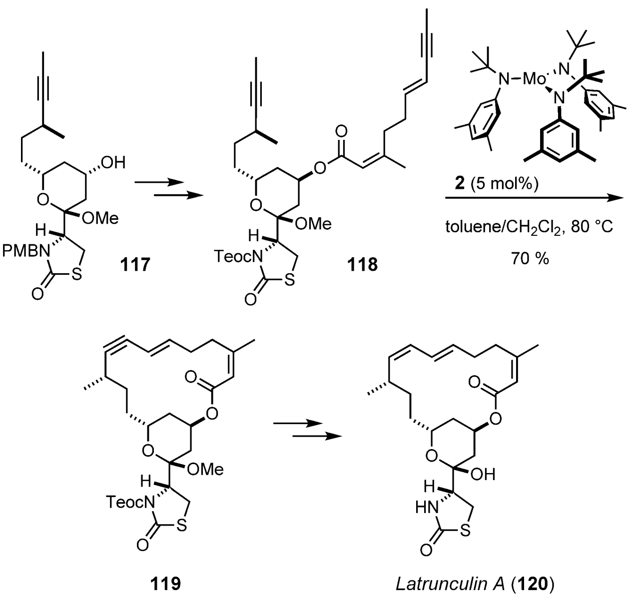
Applications of RCM to the synthesis of 1,3-dienes (or higher polyenes) are known to be problematic, because the standard olefin metathesis catalysts do not distinguish between the different double bonds of the substrates and provide no stereocontrol either. In many cases, the internal double bond of a given diene is preferentially activated, which leads to undesirable ring contraction. The resulting product mixtures are usually difficult or sometimes even impossible to separate. Only recently has progress been made by using substrates with strategically positioned C-silyl substituents on the inner double bond that serve as both protecting as well as stereodirecting groups.[148]

RCAM represents a reliable alternative for the preparation of stereodefined 1,3-dienes of all kinds. Early model studies showed that only the acetylenic bond of a 1,3-enyne substrate gets activated when exposed to an alkyne metathesis catalyst, whereas the conjugated double bond remains untouched.[144] This feature allows the regio- and stereochemistry to be dialed into a synthesis plan in a reliable and predictable manner, and hence enables the use of enyne-yne metathesis in the total synthesis of various challenging natural products of biological significance.[149]

An instructive example is lactimidomycin (**116**). This macrolide endowed with cell migration inhibitory properties might serve as a possible lead in the quest for drugs able to combat tumor metastasis. The high strain of the 12-membered head group of **116**, however, which incorporates no less than seven sp^2-hydridized C atoms, represents a serious challenge in any synthetic endeavor modeled around this compound. Yet, an RCAM-based approach brought this valuable natural product into reach (Scheme 28).[150] The chosen route turned out to be scalable as well as flexible enough for the preparation of several analogues for biological testing.[151]



Scheme 28. A stereoselective synthesis of the *Z*,*E*-diene subunit enabled the first total synthesis of lactimidomycin.



Scheme 29. RCAM-based total synthesis of the actin-binding macrolide latrunculin A. Teoc = 2-(trimethylsilyl)ethoxycarbonyl.

In this particular case, the *E*-alkene subunit of the (*E*,*Z*)-diene entity served as the strategic site for the macrocyclization. The strain of the resulting cycloalkyne **115** had to be counterbalanced by omitting the enoate double bond at this stage; this double bond was introduced only after the diene had been set. As shown in Scheme 28, these tactics met our expectations very well, since **115** could be formed in excellent yields by using the ate complex **46a** as the catalyst and 5 Å MS as an additive for the interception of the released 2-butyne. The ring strain of **115** likely explains why the cyclization had to be performed at 80 °C, although the catalysts are in general fully operative at much lower temperatures. The subsequent *trans*-hydrosilylation of **115** was also chemoselective and did not touch the residual double bonds. Simultaneous C and O desilylation of the resulting product and elaboration of the side chain completed the first total synthesis of lactimidomycin (**116**).[150]

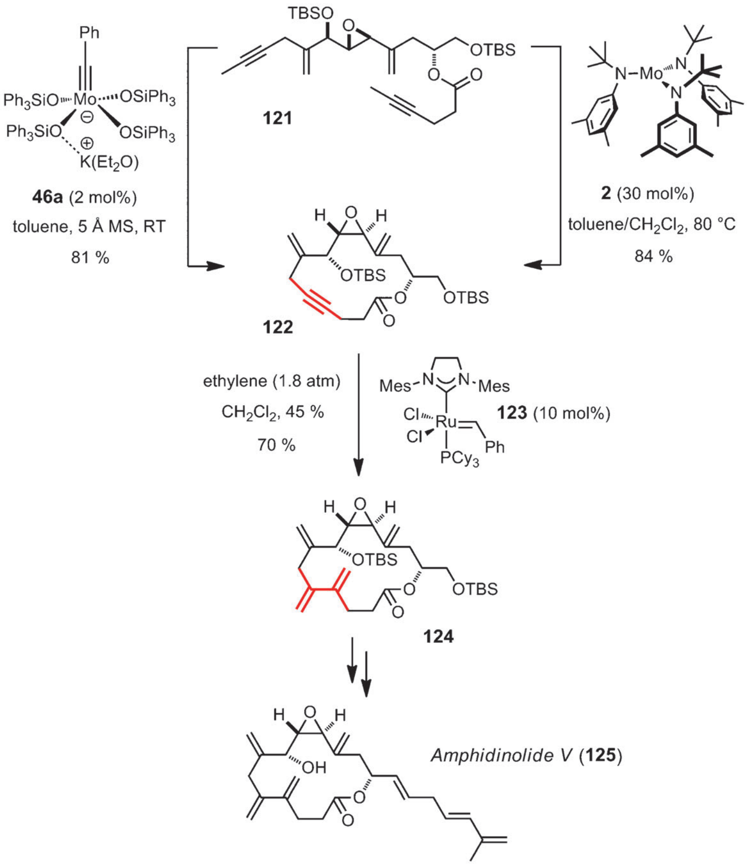
Considerations of ring strain had dictated the choice of the *E* alkene as the optimal assembly point for **116**.[150] If no such superordinate aspects need to be considered, a *Z*-configured alkene site can serve the very same purpose. This possibility is illustrated by a fairly comprehensive investigation into the potent actin-binding macrolides of the latrunculin family.[152–154] As exemplified in Scheme 29 for the parent compound latrunculin A (**120**), a convergent approach led to the elaborate enyne **118**, which displays a rare thiazolidinone unit; however, neither this unusual sulfur-containing heterocycle nor the elimination-prone tertiary glycoside posed any problem in the ring-closing step, which was catalyzed most effectively by the combination **2**/CH_2Cl_2 in toluene. A series of routine protecting-group manipulations and a Lindlar reduction allowed **119** to be transformed into the targeted natural product **120**. Its naturally occurring relatives latrunculin B, C, M, and S as well as 16-*epi*-latrunculin B were obtained analogously;[154] moreover, it was possible to prepare a collection of "designer analogues" with structurally deep-seated modifications, none of which could be attained by conventional derivatization of the natural products themselves.[155] This compound collection allowed us to demonstrate that the excision of two seemingly innocent peripheral methyl branches from the latrunculin backbone increases the potency of such actin-microfilament-disrupting agents while streamlining the synthesis.[155,156] This investigation is, therefore, a good example of the power of "diverted total synthesis" in general.[136]

The lactimidomycin and the latrunculin cases demonstrate that 1,3-dienes can be formed by RCAM/semireduction either at an *E*- or a *Z*-alkene subunit. Since any type of preexisting olefin is compatible with this method, it should also be possible to access all other kinds of 1,3-dienes of various substitution levels.[171] Of course, postmetathesis transformations other than semihydrogenation, when applied to the cyclic enynes initially formed, further enlarge the accessible structural space. Studies along these lines are currently underway in our laboratory.

3.3.4. *Cross-Talk between Alkyne and Enyne Metathesis*

As already mentioned in Section 3.1, alkynes engage only two of their three bonds in a metathetic transformation when exposed to a carbene catalyst. This reactivity mode forms the basis of the powerful ene-yne cross metathesis,[92] which has the potential to synergize with RCAM.

A synthesis campaign leading to the ultimate structure determination and first total synthesis of amphidinolide V (**125**) is currently the most convincing example (Scheme 30).[157,158] The chosen cyclization precursor **121**



Scheme 30. A sequence of alkyne and enyne metathesis allowed the core of amphidinolide V to be forged at the site of the *vic*-methylene branches. Mes = 2,4,6-trimethylphenyl.

exhibits a fragile vinyl epoxide, protected hydroxy-epoxide substructure, and a nonthermodynamic skipped 1,4-enyne motif in addition to an ester and a primary OTBS group. Despite this dense array of sensitive functionality, the ring closure worked exquisitely well. Originally, the combination **2**/CH_2Cl_2 in toluene was used, which delivered product **122** in 84 % yield.[157] After the advent of the new siloxide-bearing molybdenum alkylidynes, this transformation was revisited as a particularly stringent test reaction. As expected, the ate complex **46a** was not only similarly effective in terms of yield (81 %), but required a much lower loading (2 mol % versus 30 mol % of **2**).[159] Cycloalkyne **122** was then subjected to an ene-yne cross-metathesis with ethylene gas in the presence of the second-generation Grubbs catalyst **123**. The resulting product **124**, as the fully functional core of amphidinolide V (**125**), was easily elaborated into the challenging target compound.[157,160]

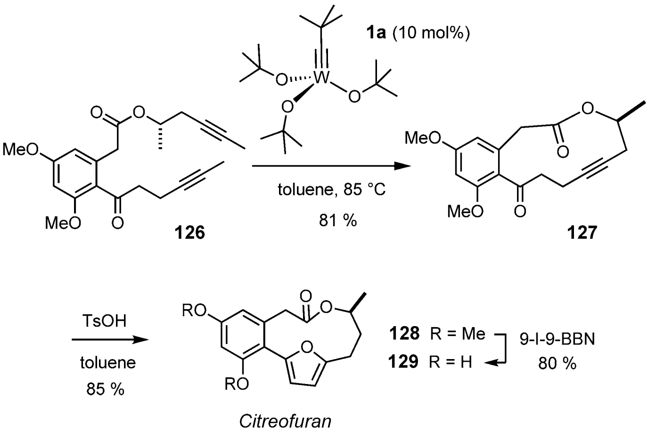
Since the structure originally assigned to amphidinolide V by the isolation team left some ambiguity, all conceivable stereomers of this compound were prepared following a similar synthetic approach.[157,160] In addition to solving a structural conundrum and providing precious materials for biological testing, the success of this campaign confirms the reliability of alkyne metathesis in general.

3.3.5. The Interface between Alkyne Metathesis and Heterocyclic Chemistry

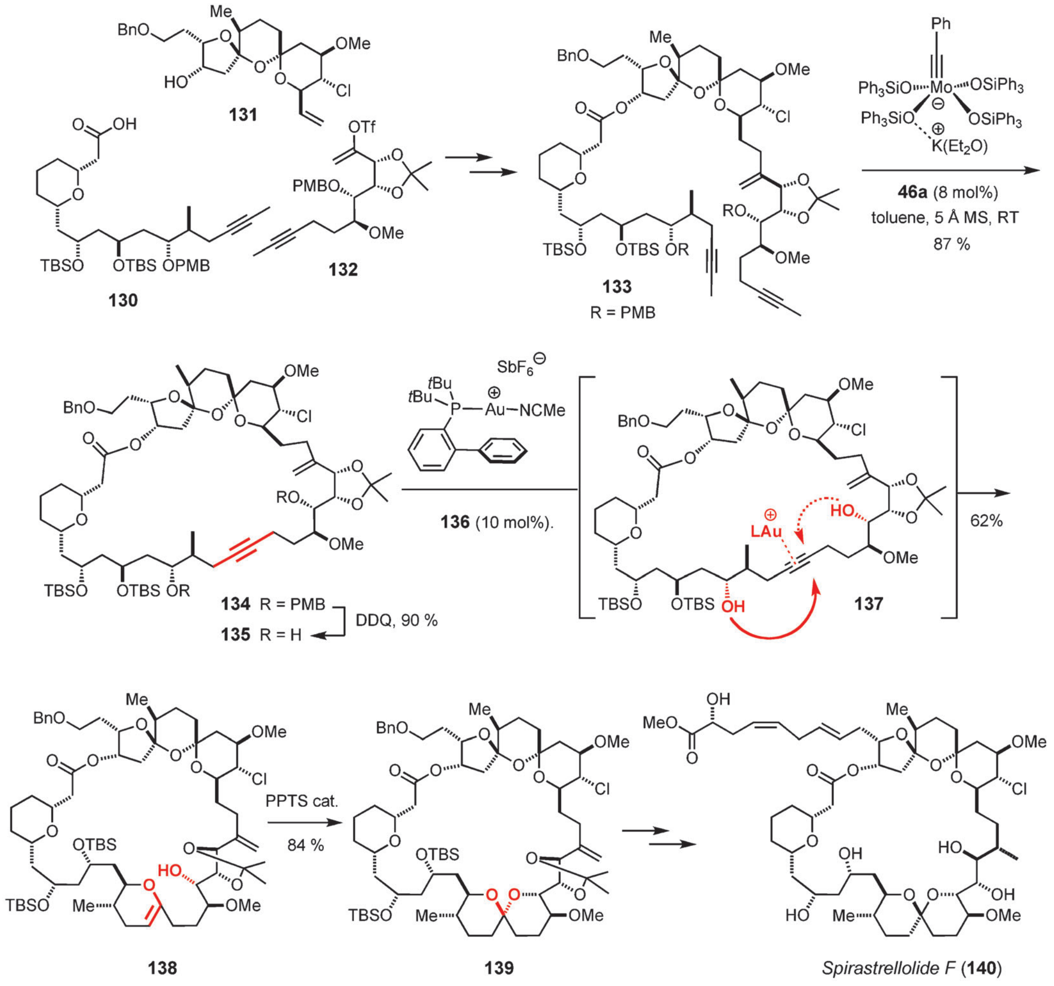
Acetylenes, as carbonyl equivalents, are excellent building blocks for the synthesis of heterocycles. Therefore, we expect alkyne metathesis to be very serviceable for this fertile field. Although many opportunities remain yet to be explored, the early synthesis of citreofuran (**129**) may serve as an appetizer (Scheme 31).[161] In this case, the readily accessible diyne **126** was ring closed in respectable yield with the aid of the tungsten alkylidyne **1a**. When the resulting cycloalkyne **127** was activated with *p*-toluenesulfonic acid, the heterocyclic skeleton was forged by a transannular 5-*exo*-dig attack of the ketone onto the acetylene moiety followed by aromatization of the resulting intermediate. A final deprotection of **128** unraveled citreofuran (**129**) in optically pure form.

Carbophilic Lewis acid catalysts allow alkynes to be activated under even milder conditions.[162,163] As a consequence, one may safely predict that alkynophilic catalysts based on platinum or gold may help transform the products of inter- or intramolecular alkyne metathesis into a multitude of valuable heterocyclic scaffolds.

A recent total synthesis of spirastrellolide F (**140**) illustrates this aspect (Scheme 32).[164] The molecular frame of this potent phosphatase inhibitor is decorated with no less than 21 stereogenic centers and features a labile skipped diene in the side chain. Its macrocyclic core incorporates a tetrahydropyran ring, a spiroketal unit, as well as a highly unusual chlorinated bis(spiroketal) motif.[165] Following earlier work from my research group,[166] a “second-generation” approach to this demanding target was pursued. Specifically, a sequence of RCAM coupled with a gold-catalyzed acetalization was meant to form the distinctive BC ring system of the “south-



Scheme 31. An RCAM/cyclization sequence as the key strategic maneuver en route to citreofuran. 9-I-9-BBN = 9-iodo-9-borabicyclo-[3.3.1]nonane, Ts = toluene-*p*-sulfonyl.



Scheme 32. End game of a "second-generation" total synthesis of spirastrellolide F. Bn = benzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PPTS = pyridinium toluene-*p*-sulfonate.

ern" hemisphere of spirastrellolide F at a late stage of the synthesis.[164]

To this end, the bis(spiroketal) building block **131** representing the "northern sector"[167] was subjected to hydroboration with 9-BBN and the resulting boron derivative cross-coupled with alkenyl triflate **132** under Suzuki conditions. The resulting product was esterified with the elaborate acid **130** to give diyne **133** as the substrate for the projected ring-closing alkyne metathesis reaction. It was gratifying to note that the molybdenum alkylidyne ate complex **46a** in the presence of 5 Å MS effected the macrocyclization with remarkable ease. Product **134** was formed in 87 % yield, which illustrates the performance of this latest generation of alkyne metathesis catalysts. After cleavage of the two *p*-methoxybenzyl (PMB) ether groups, a transannular ketalization was accomplished in two consecutive operations. In the event, treatment of **135** with the bulky cationic gold catalyst **136** enforced a regioselective 6-*endo*-dig attack of the C13-OH group onto the alkyne, which gave enol ether **138** in respectable yield. Exposure of this compound to mildly acidic conditions at higher temperature prompted the sterically more hindered hydroxy group at C21 to engage in the necessary second cyclization event. The integrity of ketal **139** thus formed was confirmed by X-ray diffraction before this product was elaborated into the target compound spirastrellolide F (**140**).[164]

4. Conclusions

Alkene metathesis rapidly turned into a quintessential tool of the preparative chemist once well-defined catalysts became available that were robust yet active and tolerant.[20,112,168,169] These catalysts offer a fabulous variety of applications, ranging from the inter- and intramolecular manipulation of small molecules to polymer chemistry. Since we will live in an "olefin age" as long as the chemical industry is based on crude oil, alkene metathesis also benefits from an excellent substrate basis.

Although the substrate basis of alkyne metathesis is, a priori, not as broad, this transformation also provides many opportunities. With a certain lag time, the necessary catalysts evolved from undefined in situ mixtures to fully characterized and mechanistically well understood entities. During this process, they increased in activity and acquired an outstanding compatibility with polar functional groups, which rivals that of the very best alkene metathesis catalysts known to date; some examples described in this Review bear witness of this fact. At the same time, the catalysts are practical, with bench-stable variants having recently been described. Therefore, this development is a noteworthy example of outstanding functional-group tolerance and user-friendliness not needing recourse to noble metals; it is reached with base-metal catalysts, which are cheap, benign, and more sustained.

Despite a close mechanistic relationship, alkyne metathesis is strictly orthogonal[82] to olefin chemistry and, therefore, ideally suited to the preparation and manipulation of compounds presenting more than one site of unsaturation. Although many of the published applications simply turned the alkyne products primarily formed into stereodefined alkenes by semireduction, it is fair to say that the structural coverage of alkyne metathesis is definitely much larger. Many other creative postmetathesis transformations can be envisaged, amongst which modern π-acid catalysis provides a particularly exciting outlook. It is expected that the recent advent of user-friendly alkyne metathesis catalysts will foster exploratory studies along these lines, and we will do our very best to contribute to this development.

Generous financial support from the MPG, the Fonds der Chemischen Industrie, and SusChemSys (Ziel 2 Programm NRW) is gratefully acknowledged. I am indebted to all my coworkers, who participated in our alkyne-metathesis project since 1998, for their intellectual and experimental contributions. Their names appear in the references.

Received: June 11, 2012
Published online: January 25, 2013

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