Alkyne metathesis

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This review discusses the emergence of alkyne metathesis as a valuable synthetic tool applicable in the synthesis of complex molecules and polymer science.

Introduction

A striking success in the catalytic arena is alkene metathesis which has been rapidly incorporated into the synthetic lexicon, now existing as one of the primary tools considered in both organic synthesis and polymer chemistry. This is due to the extraordinary generality, chemoselectivity, functional group tolerance and predictability associated with the method. These factors, coupled with the ready availability of the catalysts, have fuelled the widespread use of alkene metathesis in many synthetic routes.[1]

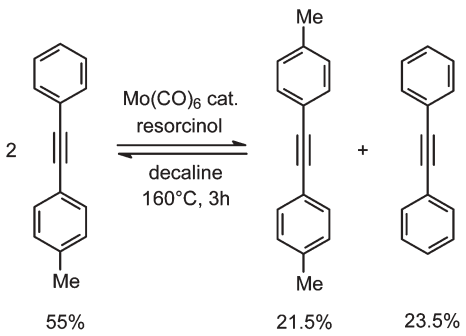
In comparison, the related metathesis of alkynes is in its infancy.[2] Only recently has it been shown that this transformation holds great synthetic promise. This feature article is intended as an entry point charting the recent developments in this emerging field rather than as a comprehensive review.

Classical catalyst systems for alkyne metathesis

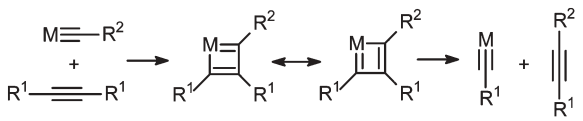
Alkyne metathesis refers to the mutual exchange of the alkylidyne units between a pair of (non-terminal) acetylene derivatives. The first effective catalyst described in the literature consists of a heterogeneous mixture of tungsten oxides and silica that operates only at a very high temperature (*ca.* 200–450 °C) and is therefore hardly relevant for preparative purposes.[3] This disclosure was followed by the work of Mortreux *et al.* showing that such a scrambling process is effected by a homogeneous mixture of $Mo(CO)_6$ (or related molybdenum sources) and simple phenol additives heated in high boiling solvents (Scheme 1).[4]

Whilst the nature of the catalytically active species formed *in situ* from these precursors remained elusive, Katz *et al.* proposed as early as 1975 that metal carbynes likely account for the catalytic turnover[5] in a sequence of formal [2+2] cycloaddition and cycloreversion steps as depicted in Scheme 2. Even though at the time of this proposal the known metal carbyne complexes were unable to induce alkyne metathesis reactions,[6] this mechanism was later experimentally established by Schrock using high valent metal alkylidynes.[7] Several metallacyclobutadiene complexes formed by the [2+2] cycloaddition of alkylidynes and alkynes were isolated and characterised[8] and proven to be catalytically competent intermediates.

The "Mortreux systems" have gained relatively widespread use due to their ease of application; cheap, commercially



Scheme 1 Mortreux's discovery.



Scheme 2 Accepted mechanism of alkyne metathesis.

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Alois Fürstner (1962) studied chemistry at the Technical University of Graz, Austria, where he got his PhD in 1987 (Professor H. Weidmann). After postdoctoral studies with the late Professor W. Oppolzer in Geneva, he finished his Habilitation in Graz (1992) before joining the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany, in 1993 as a group leader. Since 1998, he has been Director at that Institute and is also affiliated with the University of Dortmund. He has received several awards for his work on organometallic chemistry, homogeneous catalysis, and natural product synthesis including the prestigious Leibniz award from the German Science Foundation (1999), the IUPAC-Thieme Prize in Synthetic Organic Chemistry (2000), the Arthur C. Cope Scholar Award of the ACS (2002), the Centenary Lectureship of the RSC (2003), the Tetrahedron Chair (2004), as well as industrial awards from Merck and AstraZeneca.

Paul Davies (1977) studied chemistry at the University of Sheffield, UK, receiving his MChem degree in 1999. He was awarded his PhD in 2003 from the University of Bristol where he worked with Professor Varinder K. Aggarwal in the area of palladium catalysis. Since 2003 he has been a post-doctoral co-worker with Professor Fürstner in Mülheim exploring the development of new catalysts for metathesis processes whilst continuing to pursue his interests in the development of new transition metal-catalysed transformations.

available and stable "off the shelf" reagents can be used without the requirement for rigorously purified solvents and inert atmosphere. Whilst these factors make this an attractive protocol from a practical point of view, with growing applications in polymer chemistry (*vide infra*), the rather harsh conditions required and the low activity preclude its use with sensitive moieties.

To address these issues approaches such as purging the reaction mixture with dinitrogen to remove the released by-product,[9] temperature adjustment and the addition of chelating 1,2-diphenyloxyethane[10] have resulted in somewhat higher yields and reaction rates. System pre-activation by heating the phenol and molybdenum species either with[11] or without[10] sacrificial 3-hexyne prior to addition of the desired reaction partners resulted in extension of the scope and the use of lower temperatures, respectively.

Recent reports by Grela *et al.* emphasise the beneficial effects of certain phenols and integrate their use with the approaches mentioned above. Building on Mori's[12] and later Bunz's[9,13] advances, Grela identified 2-fluorophenol and 2-fluoro-5-methylphenol as the optimal additives in various alkyne metatheses.[14]

Well-defined precatalysts for alkyne metathesis

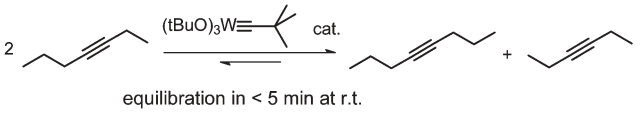
Although no "Fischer-type" carbyne has been found that allows alkyne metathesis to proceed to any sustained degree, Schrock *et al.* have demonstrated in a series of elegant investigations that the corresponding high valent metal alkylidyne complexes are catalytically competent and remarkably active (Scheme 3).[15]

Strikingly, they were found to be unreactive towards alkenes[16] suggesting that metal alkylidyne complexes allow orthogonal activation of unsaturated C–C bonds despite the obvious mechanistic ties between alkene and alkyne metathesis.[17]

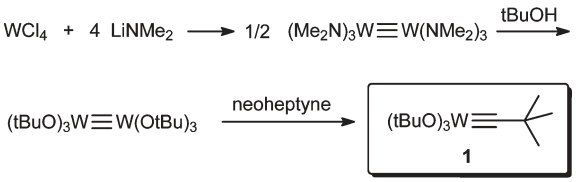
Most applications involving Schrock alkylidyne complexes utilise $(t\mathrm{BuO})_3\mathrm{W}{\equiv}\mathrm{CCMe}_3$ **1**[18] and related species which operate under fairly mild conditions, sometimes ambient temperature, effecting up to several hundred catalytic turnovers per minute. Preparation of **1** *via* the metathetic event between $(t\mathrm{BuO})_3\mathrm{W}{\equiv}\mathrm{W}(\mathrm{O}t\mathrm{Bu})_3$[19] and neoheptyne (Scheme 4) is the most convenient approach amenable to be carried out on a fairly large scale;[15] importantly, complex **1** has recently been made commercially available.[20] As there have been several recent reviews on the preparation and properties of metal alkylidynes, their background will not be discussed here any further.[6b,15,21]

Ring closing alkyne metathesis (RCAM)

Evolving from our interest in Ring Closing Metathesis (RCM) for macrocycle formation[22] we investigated the potential for alkyne metathesis to realise the ring closing of acyclic diynes to



Scheme 3 Early demonstration of the exceptional activity of defined alkylidyne complexes as catalysts for alkyne metathesis.

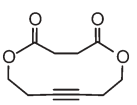
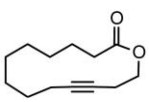
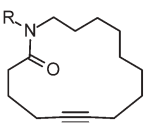
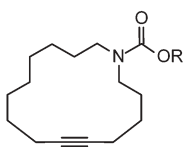
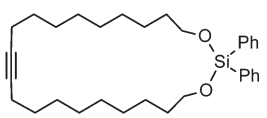


Scheme 4 Scaleable preparation of the tungsten alkylidyne complex **1**.

afford cyclic alkynes. While early reports of alkyne metathesis dealt only with the dimerisation or cross metathesis of simple acetylene derivatives[7,12a,16,23] and specialty polymers[24] (*vide infra*), we were able to show the efficient syntheses of functionalised macrocycles by ring closing alkyne metathesis (RCAM).[25] This report utilised tungsten alkylidyne **1** under high dilution in either trichlorobenzene, chlorobenzene, toluene or THF. The removal of butyne or hexyne side products under vacuum was found to be beneficial for conversion in some cases. Whilst terminal alkynes were known to be incompatible with the catalyst[6b,21b–c] end-capped substrates with R = Me or Et were successfully transformed. This initial report highlighted the lack of any formation of unwanted allenic by-products associated with preparation of cycloalkynes *via* conventional methods and demonstrated that cyclic products with ring sizes 12 or greater can be obtained in good to excellent yields.[25]

Ether, ester, enoate, amide, silyl ether, sulfonamide, carbamate and sulfone functionalities were accommodated in the RCAM process catalysed by complex **1** (Table 1).[26]

Table 1 Formation of cycloalkynes by RCAM: comparison of the performance of the tungsten alkylidyne catalyst **1** with the Mortreux catalyst system ('instant' activation of $\mathrm{Mo(CO)_6}$ with $p\text{-ClC}_6\mathrm{H}_4\mathrm{OH}$)

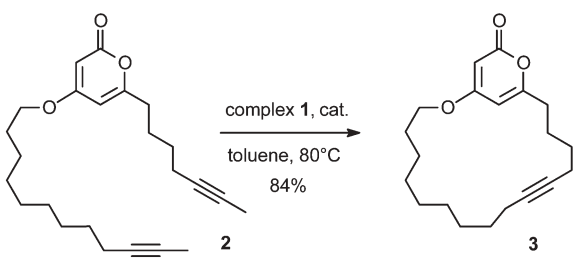
Product	Yield (%)	
	Complex **1**	'Instant'
	73	64
	52	
	62 (R = H) 72 (R = Me)	0 (R = H) 64 (R = Me)
 R = 9-fluorenylmethyl	62	68
	55	decomp.

Similarly cycloalkyne **3** containing a *meta*-pyronophane skeleton could be prepared in high yields using this procedure during a model study towards bioactive pyrone derivatives (Scheme 5).[27] Limitations were encountered with functional groups evincing high affinity to the Lewis acidic tungsten centre of complex **1** such as thioether or basic nitrogen groups which were recovered unchanged. Likewise, a butynoate failed to afford the desired product. Comparison of different tungsten alkylidyne complexes showed there to be no major improvement in terms of yield or reaction rate by choosing either different alkylidyne substituents or by replacing the *tert*-butoxy ligands in **1** with more electron withdrawing hexafluoro-2-propoxy groups, leading to the use of complex **1** in all subsequent applications. In comparison with RCM, which often requires prolonged reaction times when applied to macrocyclic series,[1] cyclisations effected by **1** were usually complete within 30–60 minutes demonstrating the high activity of this precatalyst.

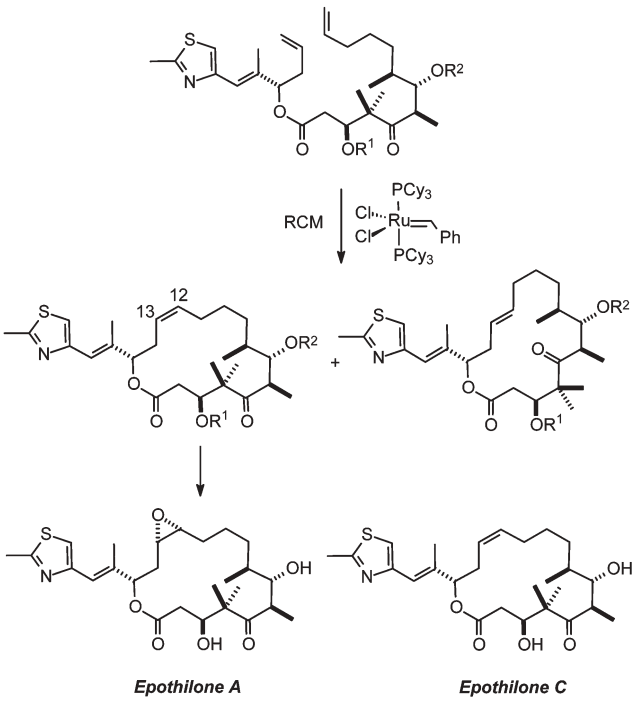
Using the best conditions known at the time for the 'instant procedure' [$Mo(CO)_6$ (5–10 mol%), *p*-chlorophenol or 4-trifluoromethylphenol (50–150 mol%), chlorobenzene or 1,2-dichlorobenzene][9b,12a,23] showed that these systems also apply to the formation of cycloalkynes but display a narrower scope with regard to structure and functional group tolerance as evident from the results compiled in Table 1.

The dual alkyne metathesis/Lindlar manifold approach to stereoselective synthesis

RCM of dienes provides ready access to carbo- and heterocycles of almost any size including medium and macrocyclic rings.[1g–i] In the latter series, however, the cycloalkenes are usually provided as mixtures of the (*E*)- and (*Z*)-isomers, the ratio of which can neither be controlled nor properly predicted at present. This problem was strongly represented in the first three syntheses of epothilone A which utilised RCM to form the 16-membered ring (Scheme 6).[28] Whilst demonstrating the enormous potential for RCM in advanced organic synthesis, they inevitably suffered from the fact that there was little, if any, selectivity in favour of the required (*Z*)-alkene, coupled with the fact that the isomeric alkenes could not be readily separated. This raises a very serious issue at a late stage in what are laborious sequences and might be one of the reasons why subsequent syntheses were largely based on alternative strategies that ensure better control over all structural elements of this target.[29]



Scheme 5 Prototype example of a ring closing alkyne metathesis reaction.

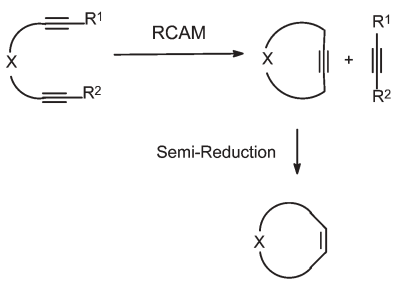


Scheme 6 Early RCM approaches to epothilone A and C plagued by the lack of control over the stereochemistry of the newly formed cycloalkene.

Whilst in the long term this fundamental problem calls for the development of stereoselective RCM catalysts, we considered that a RCAM/semireduction manifold should also constitute a viable solution.[25] Although inherently less attractive than a one-step strategy, the possibility of exerting rigorous *stereocontrol* in the preparation of cyclic alkenes overrode this concern. The combination of RCAM and Lindlar hydrogenation constitutes a stereoselective route to (*Z*)-configured cycloalkenes (Scheme 7). The nature of the process allows for similar retrosynthetic logic as with RCM to be applied whilst having the additional benefit of introducing a predictable component for stereocontrol.

Olfactory molecules: ambrettolide, yuzu lactone and civetone

The first tests for the RCAM/semireduction manifold were some naturally occurring musks incorporating (*Z*)-configured alkene entities. As the olfactory nuances of the macrocyclic



Scheme 7 Stereoselective synthesis of macrocyclic (*Z*)-alkenes by RCAM followed by Lindlar hydrogenation or an equivalent semi-reduction.

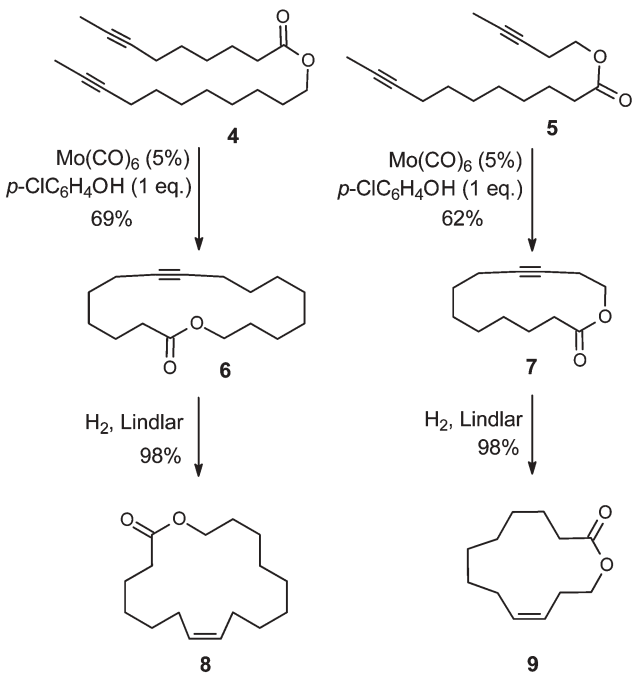
products depend on the double bond configuration, a stereoselective entry into these series was called for. RCM approaches to macrocyclic musks and other economically important perfume ingredients were shown to be unprecedently short and amenable to scale-up yet further demonstrated the unpredictability of *E*/*Z* ratios in the alkene products.[22c,d,f] In contrast, the RCAM based syntheses of ambrettolide **8** and yuzu lactone **9** (Scheme 8) afforded stereoselectively the required (*Z*)-alkenes in high overall yield.[26]

In a similar vein, a stereoselective synthesis of the valuable fragrance civetone **12** was achieved (Scheme 9). RCAM of the acyclic diyne **10** at 80 °C with the Schrock complex **1** as the catalyst afforded the desired cycloalkyne **11** in good yield with only minor amounts of the cyclodimeric side-product.[30] Of particular interest was the demonstration that the carbonyl functions of the starting material and product are kinetically inert toward the tungsten alkylidyne.[30,31] Furthermore the RCAM with the user friendly low-tech approach of *in situ* generated catalysts from a $Mo(CO)_6$–phenol mixture afforded **11** in 59% yield after 7 h, highlighting the lower activity of this mixture compared to the well defined precatalyst **1** whilst demonstrating the potential applicability of this easy to use system.

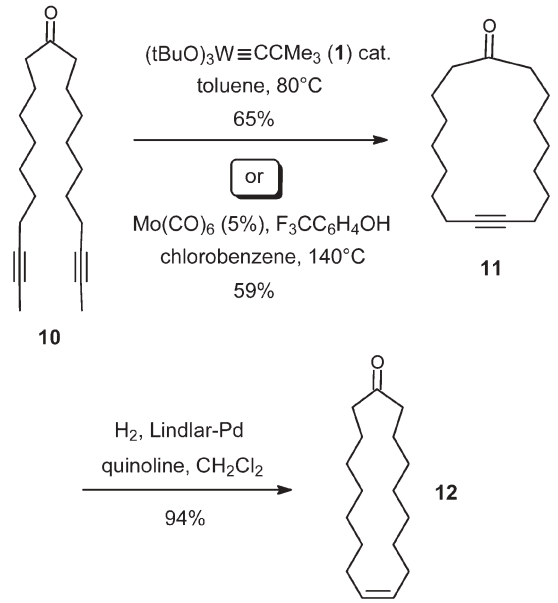
The completion of the synthesis by Lindlar hydrogenation of **11** afforded stereoselectively the (*Z*)-alkene **12** and underscored the complementary nature of the RCAM/semi-reduction manifold relative to RCM with regard to stereoselectivity (a RCM approach to **12** led to mainly the undesired (*E*)-isomer).[22c]

Epilachnene and motuporamine C

Comparable results were seen in the syntheses of the insect repellent alkaloids epilachnene and homologues (Scheme 10),[26] and the cytotoxic sponge extract motuporamine C



Scheme 8 Stereoselective syntheses of ambrettolide **8** and yuzu lactone **9**.

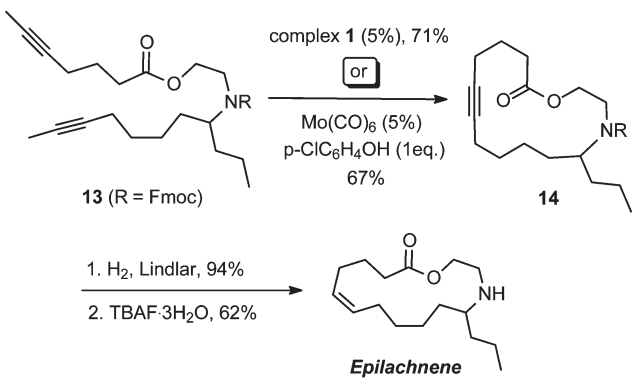


Scheme 9 Stereoselective synthesis of civetone.

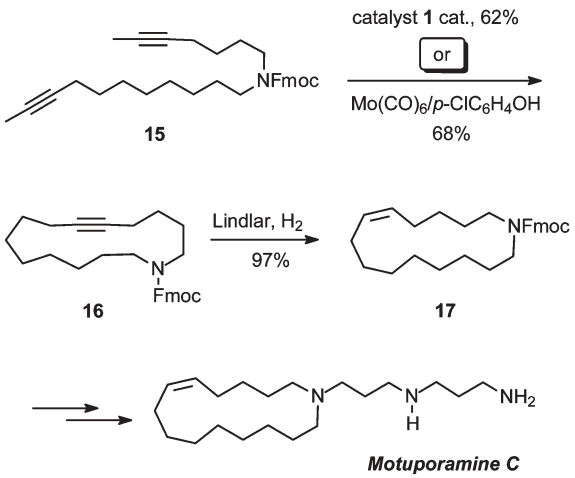
(Scheme 11),[32] where RCAM could be achieved using either **1** or the '*in situ*' system. The RCAM/Lindlar hydrogenation approach resulted in the high yielding formation of the macrocyclic (*Z*)-alkenes in a fully stereoselective manner, compared to related RCM approaches to each of these molecules which gave mixtures with the undesired (*E*)-isomers prevailing.

Macrocyclic perimeter of nakadomarin A

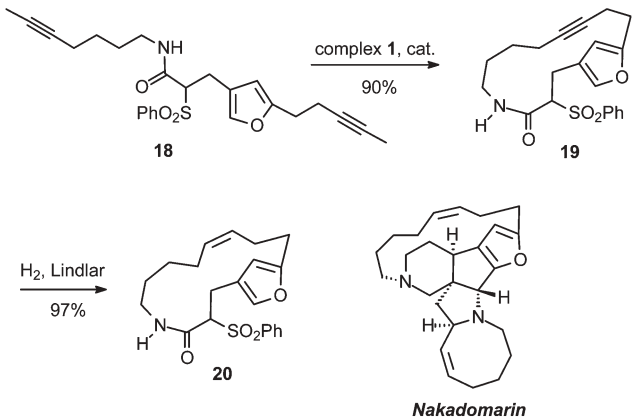
In what was then the most elaborate species subjected to the RCAM conditions with subsequent reduction, the (*Z*)-cycloalkene **20** could be formed in 87% yield on gram scale using catalyst **1**, constituting a fully functionalised building block for an envisaged synthesis of nakadomarin A (Scheme 12).[26] As well as demonstrating that the rather labile furan moiety could be tolerated along with the sulfone and amide group under the reaction conditions, this approach is worth comparing to a recently completed total synthesis of nakadomarin A in which a late stage RCM results in the



Scheme 10 Stereoselective synthesis of the insect repellent alkaloid epilachnene.



Scheme 11 Stereoselective synthesis of the cytotoxic alkaloid motuporamine C.



Scheme 12 RCAM-approach to the macrocyclic perimeter of nakadomarin A.

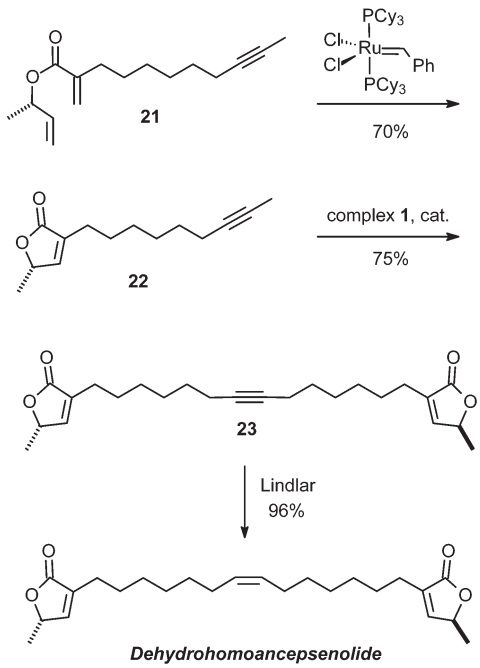
formation of a $Z/E = 1 : 1.8$ ratio, where the desired product is the minor one and is thus isolated in low yield (26%).[33]

(*S,S*)-(+)-Dehydrohomoancepsenolide

Whilst all previous examples of the metathesis/semi-reduction approach involved ring closure, a total synthesis to a member of the acetogenin family of natural products occasioned the application of a homodimerisation strategy.[34] Incorporating both alkene metathesis and alkyne homodimerisation, this example demonstrated that the two procedures could be combined into the same synthetic approach with no contamination between the two routes (Scheme 13). RCM of diene **21** affords the butenolide **22** without touching the alkyne unit which, on treatment with the Schrock tungsten alkylidyne catalyst **1**, afforded the C_2-symmetrical product **23** with inversed chemoselectivity.

Turrianes

A remarkable rate acceleration of microwave heating with the 'instant' Mortreux system allowed the overall reaction time of the RCAM of **24** to macrocycle **25** to be reduced from 6 h to

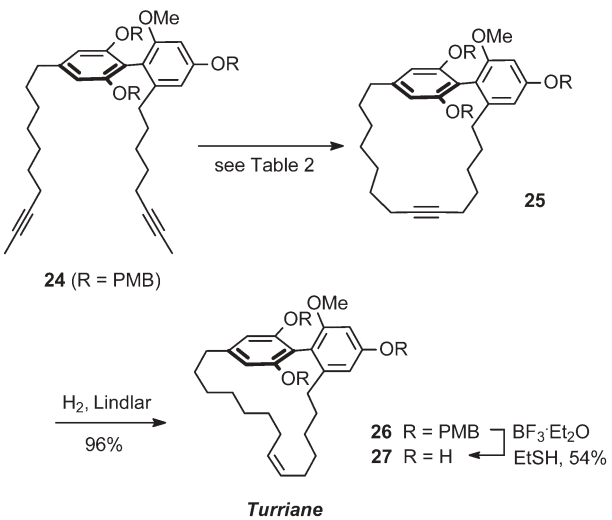


Scheme 13 Key steps of a total synthesis of dehydrohomoancepsenolide.

5 min, highlighting the importance of the Mortreux system when substrates are robust enough to be compatible with the harsher conditions (Scheme 14, Table 2). The overall synthesis *via* oxazoline biaryl coupling and subsequent RCAM/Lindlar hydrogenation affords rapid entry into these naturally occurring cyclophane derivatives. Again specific comparison with a RCM strategy of the analogous acyclic dienes highlighted the superiority of the two step process for predictable synthesis of the (*Z*)-alkene.[35]

An alternative post-metathesis transformation: citreofuran

Whilst most of the applications for RCAM from these labs have involved the two-step metathesis/Lindlar hydrogenation



Scheme 14 End game of a total synthesis of a member of the turriane family of natural products.

Table 2 RCAM in the turriane series: formation of compound **25** from diyne **24** using different catalyst systems

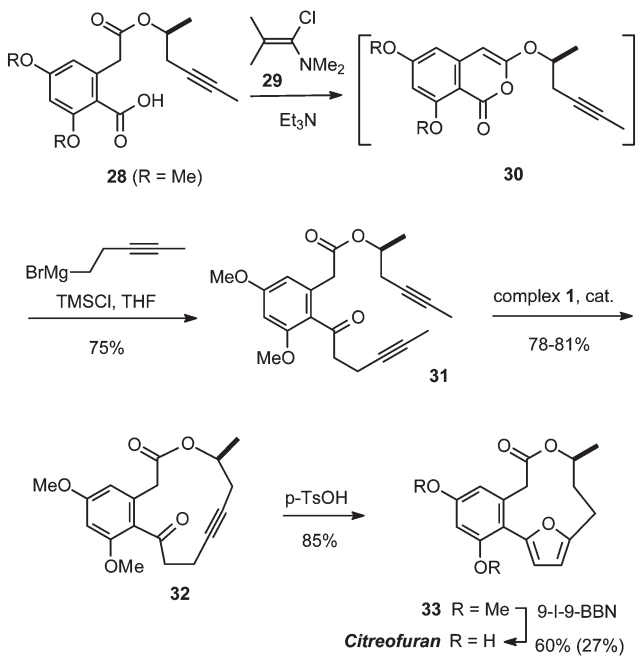
Catalyst	Conditions	Time	Yield (%)
Complex **1**	Toluene, 80 °C	16 h	61
$Mo(CO)_6$, $F_3CC_6H_4OH$	Chlorobenzene, 135 °C	6 h	76
$Mo(CO)_6$, $F_3CC_6H_4OH$	Chlorobenzene, microwave, 150 °C	5 min	71

strategy to stereoselectively form (*Z*)-alkenes, there are many other post-metathetic transformations of the cycloalkynes to be explored. Illustrating this, the synthesis of citreofuran, a member of the curvularin family of natural products, was performed.[36]

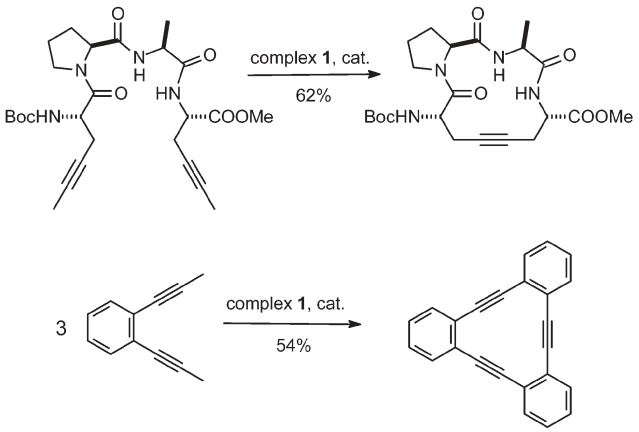
The retrosynthetic analysis suggested that recourse to the established logic with disconnections at the biaryl axis was unnecessary and instead encodes the furan ring as a macrocyclic yne–one derived from RCAM. Schrock's tungsten alkylidyne complex **1** worked well, as long as substrate **31** was free of impurities that can act as catalyst poisons (Scheme 15). As expected the ketone withstood the cyclisation conditions with no recourse to protecting groups required. The yield of this step is highly dependent on the chosen dilution, most probably reflecting the strain in the benzo-annellated oxacyclododecyne ring of the yne–one product **32**. Treatment of **32** under acidic conditions afforded the furan **33** in good yield as the immediate precursor of the natural product.[36]

Miscellaneous applications

Further to the work in the area of natural product synthesis a variety of applications of RCAM have been carried out. These demonstrations of the efficacy of this transformation with the Schrock alkylidyne **1** include cyclic β-turn mimics (Scheme 16),[37] acetylene containing amino acids[38] and



Scheme 15 Total synthesis of citreofuran.



Scheme 16 Miscellaneous applications of alkyne metathesis.

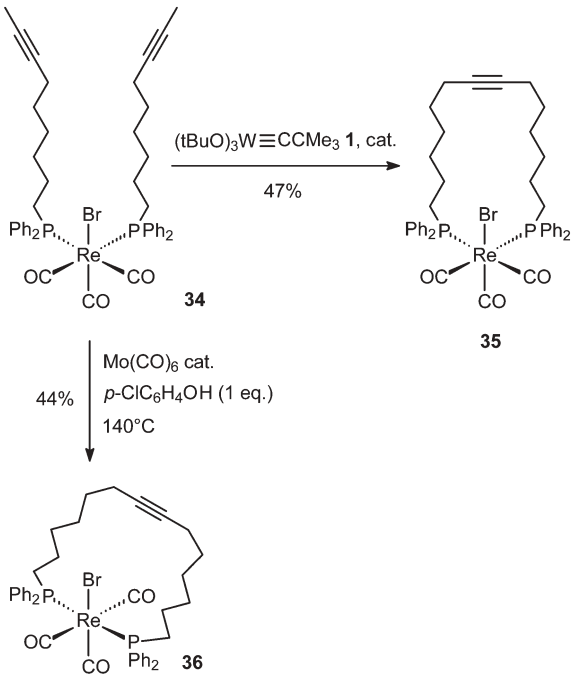
diaminosuberic acid derivatives, prepared using a transient tether approach.[39] Various authors have demonstrated the cyclo*di*- and cyclo*tri*merisation of acyclic diynes using either catalyst **1** or the Mortreux system.[40] The use of the latter in a modified form by Bunz and Štěpnička led to the preparation of twisted diphenylacetylenes[41] and diferrocenylethyne[42] respectively.

Both types of catalyst systems have been shown by Gladysz and co-workers to be applicable to RCAM within transition metal coordination spheres. Ligated alkyne bearing species are metathesised to prepare chelated rhenium, ruthenium and platinum complexes.[43] In one case, the nature of the alkyne metathesis catalyst system used affects the main product of the reaction: whilst the Schrock catalyst **1** gives the *cis*-chelate **35**, the Mortreux system furnishes the isomeric *trans*-chelate product **36** (Scheme 17).

Development of a new catalyst system

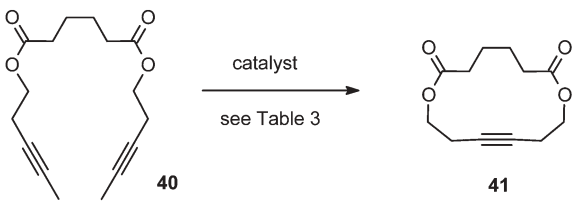
During our investigations it was clear that the development of a catalyst system with enhanced functional group tolerance would be particularly beneficial to this area. Inspired by the spectacular work of Cummins on molybdenum species of the general type $Mo[N(tBu)(Ar)]_3$ **37**[44] which activate the triple bond of dinitrogen in a *stoichiometric* fashion, the reactivity of such compounds towards alkynes was investigated. Whilst complex **37** (Ar = 3,5-dimethylbenzene) did not induce any catalysis event by itself, when mixed with CH_2Cl_2 an endothermic process occurred resulting in a mixture capable of efficiently *catalysing* the metathetic coupling of different aliphatic as well as aromatic alkynes. Equally effective as using CH_2Cl_2 as a solvent was the addition of >2 equivalents of CH_2Cl_2 to a solution of **37** in toluene. Similarly, activation of **37** with $CHCl_3$, CCl_4, CH_2Br_2, CH_2I_2, $C_6H_5CHCl_2$, $C_6H_5CH_2Cl$, Me_3SiCl also resulted in productive catalytic alkyne metathesis (Table 3).[45]

Analysis of the products formed during the reaction of $Mo[N(tBu)(Ar)]_3$ (**37**) and CH_2Cl_2 after removal of all the volatiles indicated the presence of several molybdenum species by NMR and MS (Scheme 18). The major components of this mixture, present in a ratio of about 1 : 2, were the terminal alkylidyne complex $[HC{\equiv}Mo\{(tBu)(Ar)N\}_3]$ (**39**)[46] and



Scheme 17 Representative example for RCAM within a transition metal coordination sphere.

Table 3 Screening of the catalytic performance of various molybdenum complexes (10 mol%) for the cyclization of diyne **40** to cycloalkyne **41**. All reactions were carried out at 80 °C



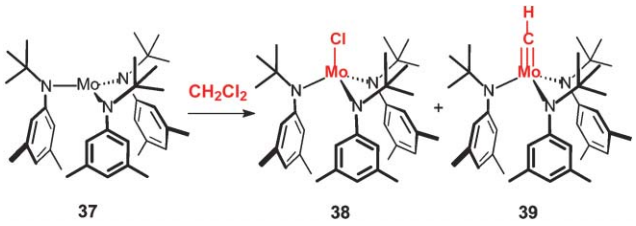
Conditions	Yield (%)
Complex **37**/CH_2Cl_2 (‘*in situ*’)	81
Complex **37**/CH_2Br_2 (‘*in situ*’)	84
Complex **37**/$PhCHCl_2$ (‘*in situ*’)	78
Complex **37**/TMSCl (‘*in situ*’)	75
Molybdenum methylidyne **39**[a]	38
Molybdenum chloride **38**	70
Molybdenum bromide **38a**[b]	79

[a] Using 35% of complex **39**. [b] Corresponds to the bromo analogue of complex **38**.

$[ClMo\{(tBu)(Ar)N\}_3]$ (**38**), both of which were independently prepared for comparison.[47]

The catalytic competence of all the molybdenum species formed in the course of this and related studies were investigated in a model reaction which showed that the *terminal* alkylidyne **39** effected essentially only one turnover, consistent with the known instability of such species (Table 3).[15]

In contrast, all the molybdenum halide species showed catalytic activity in the test reaction when performed at 80 °C. Whilst these intriguing results could not help summarise the actual nature of the propagating species, they illustrated that

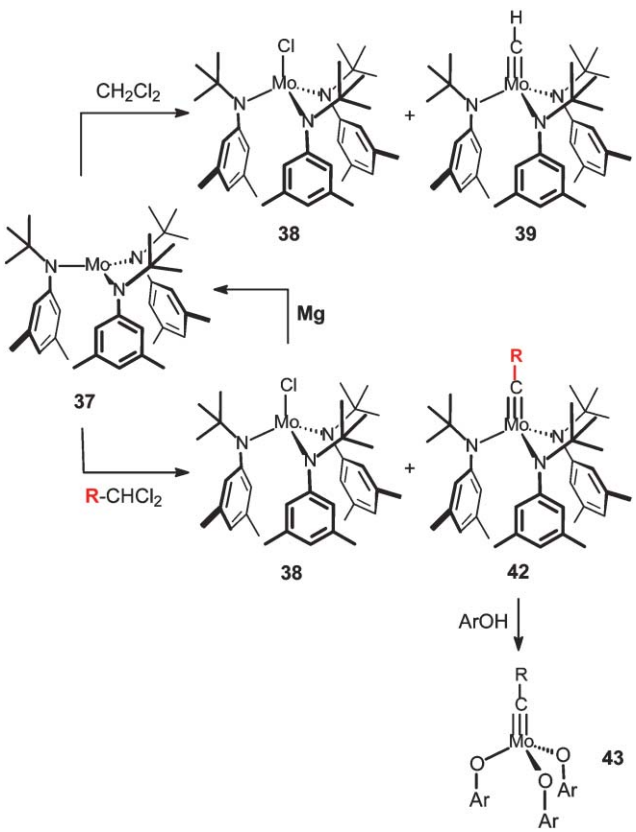


Scheme 18 Activation of the molybedum trisamido complex **37** to form metathesis active components.

(*i*) structurally quite diverse molybdenum complexes can serve as highly effective pre-catalysts for an alkyne metathesis manifold, and that (*ii*) molybdenum halides exhibit a rich yet hardly understood redox chemistry.

In 2003 Moore *et al.* further refined this process by introducing a “reductive-recycle” strategy (Scheme 19).[48] The use of *gem*-dihalides such as 1,1-dichloropropane to activate precatalyst **37** results in the formation of non-terminal molybdenum alkylidynes **42** and the molybdenum choride complex **38**, with the latter being recycled by reduction with Mg to regenerate the parent trisamido species **37**. This strategy allows for the preparation of various catalytically relevant molybdenum alkylidynes (**42**, **43**) and therefore creates a link to the work of Schrock[49] and Cummins[50] on high valent alkylidyne complexes of early transition metals.

Interestingly the terminating group has an effect on the catalytic efficacy of these systems, with R = Et superior to



Scheme 19 ‘Reductive recycle’ strategy for the preparation of molybdenum alkylidyne complexes.

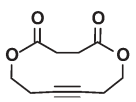
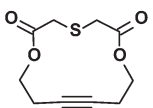
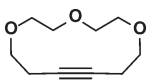
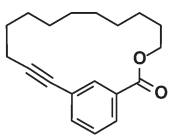
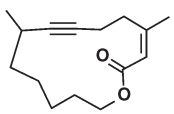
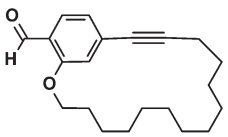
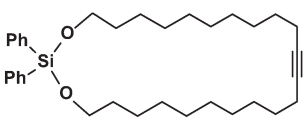
R = Me.[10,48a] A recent application of this system was shown in the preparation of arylene–ethynylene macrocycles in which a clever precipitation approach leads to high yields and clean multigram syntheses.[51]

Application of the new catalyst system to synthesis

Whilst the metathesis active component of the mixture obtained from the reaction between **37** and CH_2Cl_2 can be isolated, all applications used *in situ* generation of the catalyst. This system not only effects the formation of macrocyclic cycloalkynes of different ring sizes (Table 4) but also tolerates functional groups which completely shut down the catalytic activity of the tungsten alkylidyne catalyst **1**.[47] This is true for thioethers, basic nitrogen atoms and polyether chains. In contrast however, ''acidic'' protons such as those of secondary amides, which are tolerated by **1**, could not be endured by catalyst **37** whereas tertiary amides are fully compatible. As with **1**, **37** is immune to esters, isolated double bonds, silyl ethers, sulfones, aldehydes, nitro groups, ketones, alkyl chlorides, acetals and nitriles.

This increased functional group tolerance can possibly be explained by the structure of the molecule. X-Ray analysis of

Table 4 RCAM reactions catalyzed by complex **37** activated *in situ* with CH_2Cl_2

Product	Yield (%)
	91
	84
	60
	83
	63
	75
	74

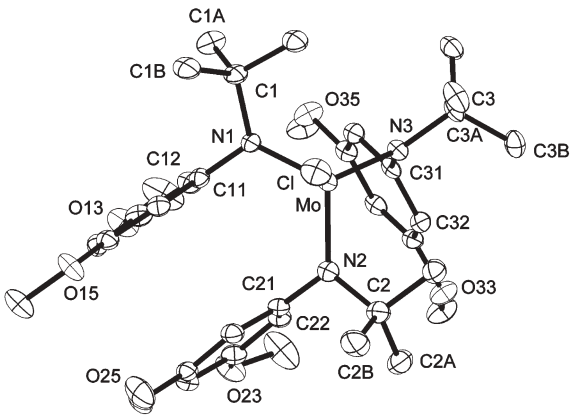


Fig. 1 Molecular structure of complex **38**. Anisotropic displacement parameters are drawn at 50% probability, hydrogen atoms are omitted for clarity.

38 shows the central metal to be efficiently shielded by the close packing amido ligands (Fig. 1). The steric hindrance thus attenuates the effective Lewis acidity of the metal by preventing coordination of potential donor substrates onto the catalytically active template.[47]

Homodimerisation and alkyne cross metathesis (ACM)

Furthermore this system allowed effective homodimerisation of propynylated arenes with superior scope to the classical Mortreux 'instant' system (Table 5).

The scope of this catalyst was further evidenced by application to alkyne cross metathesis (ACM),[52] a reaction manifold that had hardly been explored. Propynylated arenes afforded the desired products in respectable yields if exposed to a slight excess of an aliphatic alkyne as the reaction partner; the latter can be symmetrical or unsymmetrical bearing

Table 5 Comparision of alkyne metathesis of propynylated arenes in the presence of two different catalyst systems

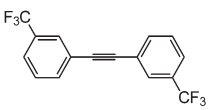
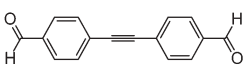
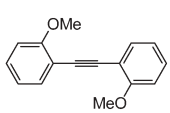
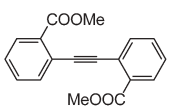
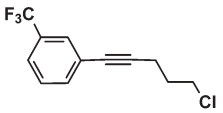
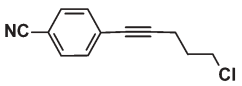
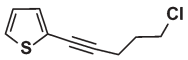
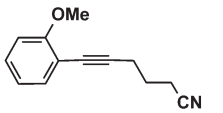
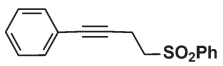
	Yield (%)	
Product	**37**/CH_2Cl_2	$Mo(CO)_6$/ClC_6H_4OH
	59	14
	58	15
	46	0
	68	0
	76	0

Table 6 Alkyne cross metathesis (ACM) of various propynylated arenes with functionalised aliphatic alkynes catalysed by complex **37** activated *in situ* with CH_2Cl_2

Product	Yield (%)
	70
	70
	55
	67
	71

electron withdrawing or electron-donating substituents (Table 6). It is particularly noteworthy that even C-*silylated* alkynes could be employed, despite such substrates being previously beyond the scope of alkyne metathesis.

Sophorolipid lactone

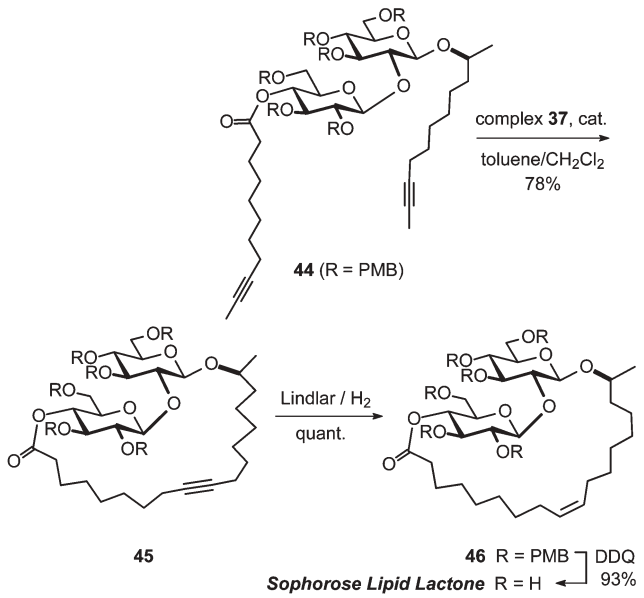
This enhanced functional group tolerance was exploited in the synthesis of sophorolipid lactone, a secondary metabolite produced by the yeast *Candida bombicola*. RCAM transformation of diyne **44** proceeded well using the catalyst prepared *in situ* from **37** and CH_2Cl_2, affording the desired product **45** in 78% yield. Neither the acid labile PMB ethers nor the glycosidic linkages were damaged by the Lewis acidic metal centre of the catalyst (Scheme 20).[53]

Prostaglandin E_2-1,15-lactone

The prostaglandin E_2-1,15-lactone is readily hydrolysed into parent prostaglandin E_2 (PGE_2) by various esterases and can be thus viewed as a naturally occurring prodrug. The intrinsic lability of the β-hydroxy ketone substructure towards acid and base rendered this remarkable natural product a formidable probe for the newly developed catalytic system.

The key RCAM transformation proceeded very well attesting to the general mildness of the system **37**/CH_2Cl_2 and illustrates the differentiation between triple bonds (reactive) and pre-existing double bonds (inert) (Scheme 21). The Schrock system also gave the desired cycloalkyne **49** with slightly lower conversion even on longer reaction times. In contrast, however, the '*in situ*' systems derived from $Mo(CO)_6$ afforded no products emphasising that the vigorous conditions required are completely unsuitable to elaborate and sensitive materials such as **48**.

Lindlar hydrogenation of cycloalkyne **49** proceeded stereoselectively either before or after deprotection of the -OTBS

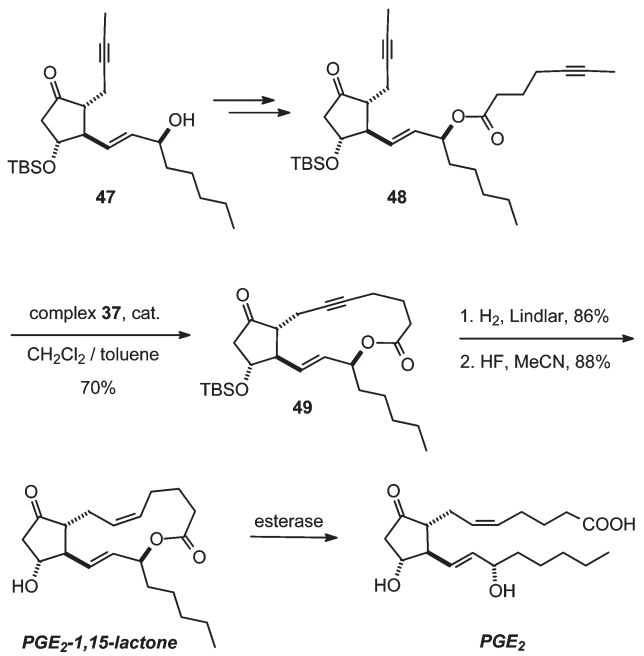


Scheme 20 Total synthesis of sophorolipid lactone.

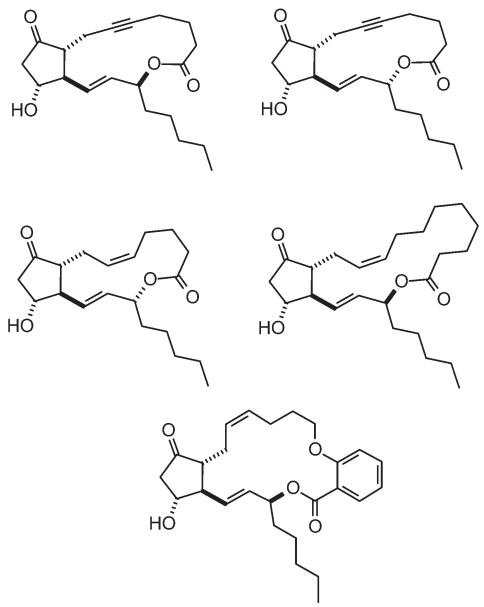
group, resulting in the PGE_2-1,15-lactone product in excellent overall yield.[54]

The metathesis approach bypasses the problems associated with installation of modified α-chains in classical prostaglandin syntheses[55] and therefore allowed for the preparation of several analogues. Representative examples are depicted in Scheme 22.

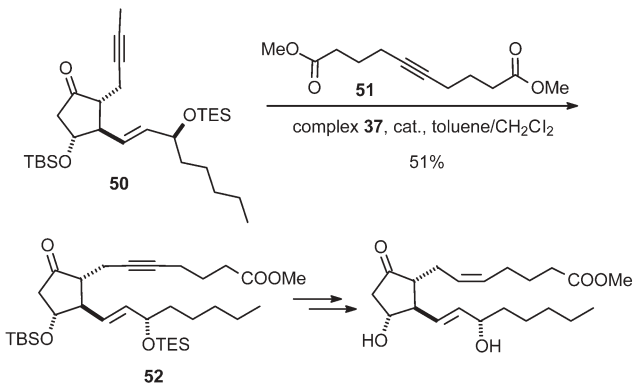
Alternatively, alkyne **50** could be directly derivatised to prostaglandins *via* ACM (Scheme 23). The first application of ACM to the synthesis of natural products[54b] resulted in formation of the desired product **52** in 51% yield with none of



Scheme 21 RCAM approach to prostaglandin E_2 and its naturally occurring 1,15-lactone.

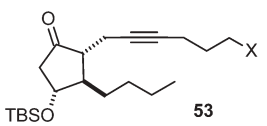


Scheme 22 Prostaglandin lactone analogues prepared by diverting from the route depicted in Scheme 21.



Scheme 23 ACM-route to PGE_2 methyl ester.

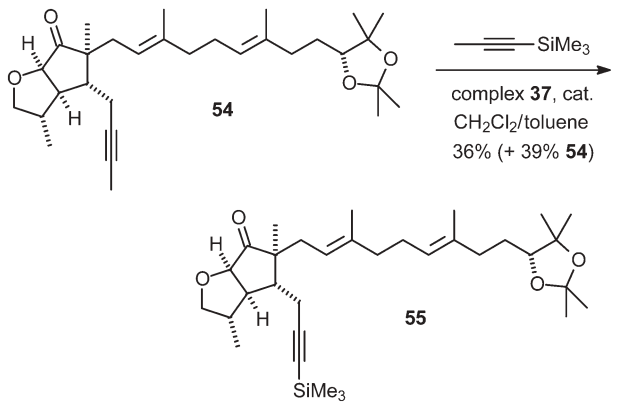
the homodimer of **50** seen when using symmetrical alkyne **51** as the reaction partner. Reduction and subsequent cleavage of the silyl group afforded the PGE_2-methyl ester in good yield. Similarly, a truncated precursor was shown to react with variously substituted internal alkynes to afford prostaglandin analogues **53** in respectable yields, further demonstrating the chemoselectivity of the catalysts.



X = Cl, CN, OTHP, COOMe

Studies towards terpestacin

Another application of ACM in complex molecule synthesis came during Jamison's studies on an intramolecular alkyne–aldehyde reductive coupling approach to terpestacin. Utilising



Scheme 24 Key step *en route* to terpestacin.

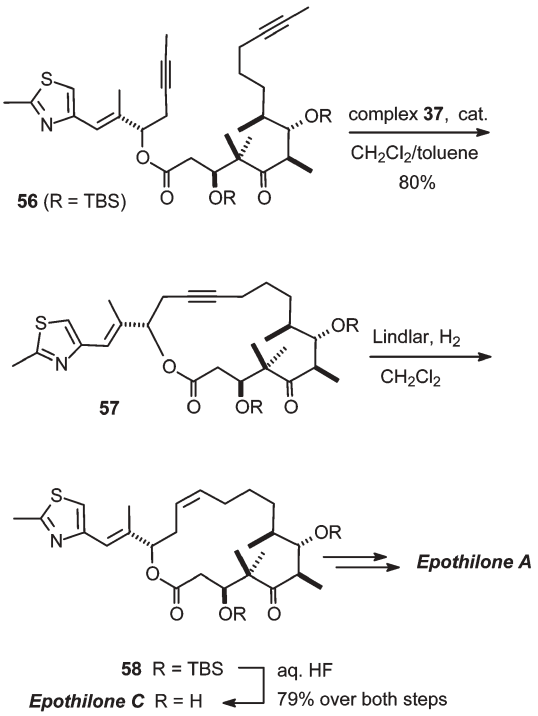
the *in situ* system **37**/CH_2Cl_2, successful alkyne cross metathesis of the highly functionalised molecule **54** with TMS–propyne afforded **55** in reasonable yield based on recovered starting materials (Scheme 24).[56]

Epothilone A and C

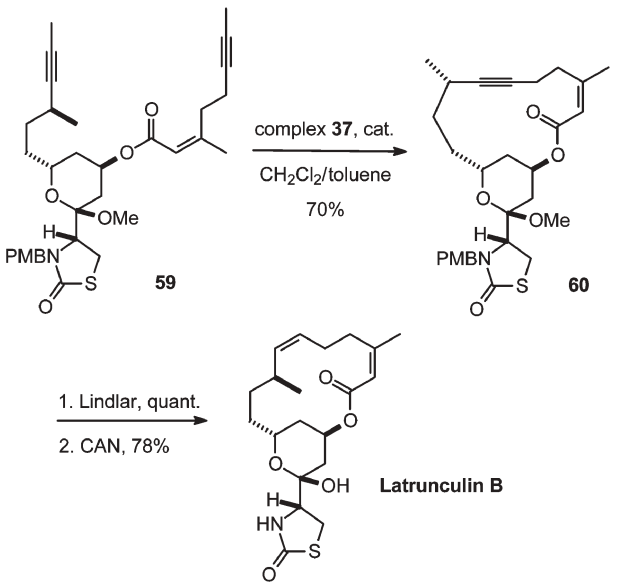
Encouraged by the previous successes we deemed RCAM to be ready for application in a more demanding context. As mentioned above, the synthesis of the epothilones had served to demonstrate the potential of RCM in advanced organic synthesis but had also highlighted the drawback of this method with regard to low selectivity for alkene isomers.[28] Gratifyingly the RCAM/Lindlar hydrogenation manifold afforded selectively the (*Z*)-alkene **58** in high yield (Scheme 25).[57] Furthermore it clearly attests to the benign nature and preparative relevance of the method since (i) neither the basic N-atom nor the sulfur of the thiazole ring in **56** interferes with the catalyst, (ii) the labile aldol substructure, the rather electrophilic ketone, as well as the ester and silyl ether groups are fully preserved, (iii) no racemisation of the chiral centre α to the carbonyl is encountered, and (iv) the rigorous chemoselectivity of the catalyst is confirmed, which reacts smoothly with alkynes but leaves pre-existing alkene moieties unaffected.

Latrunculins

The watershed synthesis of epothilones (Scheme 25) allowed the RCAM approach to be incorporated within a research program into the synthesis and biological assaying of the latrunculins, strikingly selective actin binding macrolides of marine origin. Searching towards a synthesis-driven mapping of the structural elements essential for activity, an approach was designed that would be flexible enough to allow substantial structural variations. The adopted route (Scheme 26) incorporated a late stage RCAM/Lindlar reduction manifold as the key step, reflecting the confidence we had gained in this procedure from our previous experiences. This faith was rewarded when treatment of diyne **59** with **37**/CH_2Cl_2 afforded the macrocyclic alkyne **60** in high yield, regardless of the dense array of functional groups nor the branching methyl substituent α to one of the alkyne units. Lindlar reduction gave the (*Z*)-alkene **60** that was deprotected



Scheme 25 Stereoselective total syntheses of epothilone A and C by an RCAM-based route.



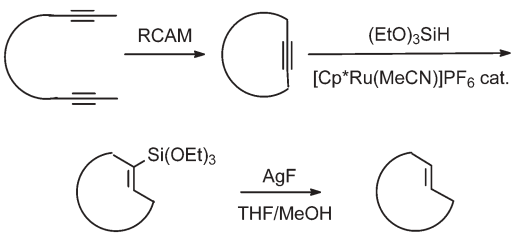
Scheme 26 Stereoselective total synthesis of the marine natural product latrunculin B.

to afford the natural product.[58] Similarly this strategy has been successfully applied in the synthesis of a variety of latrunculin analogues which will be discussed further elsewhere.

Preparation of (*E*)-configured cycloalkenes

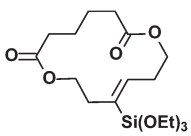
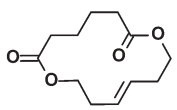
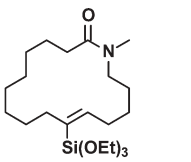
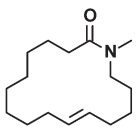
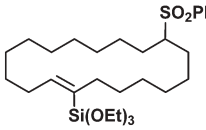
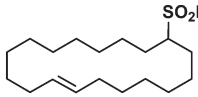
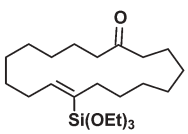
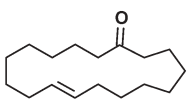
Whilst the semi-reduction of acetylenes to give (*Z*)-alkenes was well established and could be combined easily with RCAM, the complementary semi-reduction to give stereoselectively the (*E*)-isomer raises more issues. The methods for this transformation known in the literature at the time did not meet all of the criteria of selectivity and functional group tolerance required for application to advanced organic synthesis.[59] A general and mild procedure centring on a hydrosilylation/protodesilylation strategy was independently developed in both the Trost group, for acyclic substrates,[60] and this group with cyclic systems.[61] The use of the cationic ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ and $(EtO)_3SiH$ for hydrosilylation of the alkynes affords a highly chemo- and stereoselective *trans* addition[62] in decent to excellent yields with good compatibility with a host of functional groups (Scheme 27).

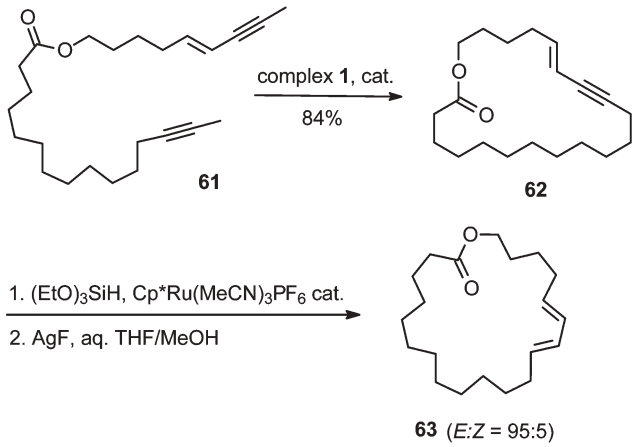
Standard methods for fluoride promoted desilylation of the resulting alkenyl silanes suffered from narrow functional group tolerance and damaged the configurational integrity of the double bond, whereas the use of AgF led to rapid, quantitative and selective desilylation under mild conditions (Table 7). AgF can also be used in sub-stoichiometric amounts (2–20 mol%) provided that TBAF is added to the medium as a stoichiometric



Scheme 27 Three-stage process for the stereoselective synthesis of macrocyclic (*E*)-alkenes *via* RCAM followed by *trans*-selective hydrosilylation and protodesilylation.

Table 7 Formation of (*E*)-cycloalkenes by *trans*-hydrosilylation of functionalised cycloalkynes (formed by RCAM) followed by AgF promoted protodesilylation

Vinylsilane	Yield	(*E*)-Alkene	Yield (*E*/*Z*)
	93%		92% (95/5)
	95%		82% (95/5)
	92%		88% (98/2)
	93%		70% (98/2)



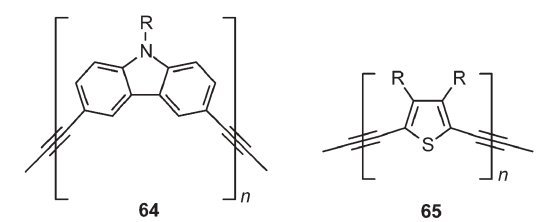
Scheme 28 Stereoselective entry into (*E,E*)-cycloalkadienes by RCAM/semi-reduction.

fluoride source. The overall set of conditions holds promise for the application of the three step RCAM/hydrosilylation/protodesilylation procedure to complex products.

Further demonstration of the scope of the 3-stage process was achieved in the synthesis of (*E,E*)-cycloalkadienes (Scheme 28), starting off with a novel RCAM of *enyne-yne* substrates.[61b] Subsequent *trans*-hydrosilylation proceeds chemoselectively at the alkyne site with no noticeable effect on the conjugated alkene moiety. This reaction proceeds best under neat conditions or with minimum CH_2Cl_2 as solvent. Scheme 28 shows a representative example giving regioisomeric vinyl silanes which converge to the same 1,3-diene product **63** upon protodesilylation. The use of this method as a highly stereoselective entry into macrocyclic dienes in the course of natural product synthesis is underway in these labs.

Polymerisations

The initial application of alkylidyne complexes in polymer science was demonstrated by Schrock and Krouse in the ring opening metathesis polymerisation of cyclooctyne using catalyst **1**.[24a] It took a number of years before significant interest arose; today, however, polymerisations by alkyne metathesis encompass a broad field utilising all the types of catalysts discussed above. Whilst the focus of our studies and hence this account is on the development and application of the alkyne metathesis for preparative organic chemistry, the pursuit of alkyne metathesis in polymerisation has led to significant advances that should be briefly mentioned. Polyarylene-ethynylenes (PAEs) are of particular interest in this context due to the desirable electronic and optical properties associated with these polymers.[63]



Recent examples of this include Moore and Zhangs synthesis of high molecular weight poly-2,5-thienyleneethynylenes **65** without structural defects using a trialkoxymolybdenum(VI) propylidyne catalyst **43** generated *in situ* as shown in Scheme 19.[64] Bunz and coworkers have contributed significantly to this field,[52,65] recently synthesizing carbazole polymers **64** with interesting fluorescence properties using modified Mortreux systems.[66]

Conclusions

Alkyne metathesis provides a widely applicable technology which is conceptually related to alkene metathesis yet rigorously controllable in its stereochemical consequences. From the early development of an *in situ* 'instant system' requiring harsh conditions applicable only to essentially unfunctionalised species, catalysts are now available that allow alkyne metathesis of highly functionalised substrates under mild conditions. Special mention of the striking chemoselectivity for alkynes with regards to alkenes is necessary. The rigorous distinction between different π-systems manifested by these catalysts is important from the conceptual standpoint and upgraded the impact of metathesis in general on the logic of retrosynthetic planning. Table 8 lists the behaviour of a variety of functional groups towards the available catalysts.

The combination of alkyne metathesis and subsequent semi-reduction elicits a stereoselective entry into either (*E*)- or (*Z*)-alkenes under mild conditions. Its use obviates the requirement for isomer separation and allows planned and diversionary synthesis to be incorporated. The preparative relevance of this procedure has been illustrated in a variety of flexible syntheses of natural products, often at a late stage in a manner that accommodates analogue synthesis. Elaboration of the resulting (cyclo)alkynes by other post-metathesis transformations is also promising and awaits further investigations. As has been

Table 8 Functional group compatibility profile of the most widely used catalyst systems for alkyne metathesis

Functional group	Alkylidyne **1**	**37**/CH_2Cl_2
Acetal	+	+
Aldehyde		+
Alkene	+	+
Alkyl chloride		+
Amide	+	−
tert-Amide	+	+
Enoate	+	+
Ester	+	+
Ether	+	+
Furan	+	
Glycoside		+
Ketone	+	+
Nitrile		+
Nitro		+
Pyridine	−	+
Silyl ether	+	+
Sulfonamide	+	+
Sulfone	+	+
Thiazole		+
Thiocarbamate	−/+	+
Thioether	−	+
Uretane	+	+

the case with alkene metathesis, the potential for this transformation is likely to increase further as the catalyst systems become better understood, more user-friendly and more readily accessible.

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