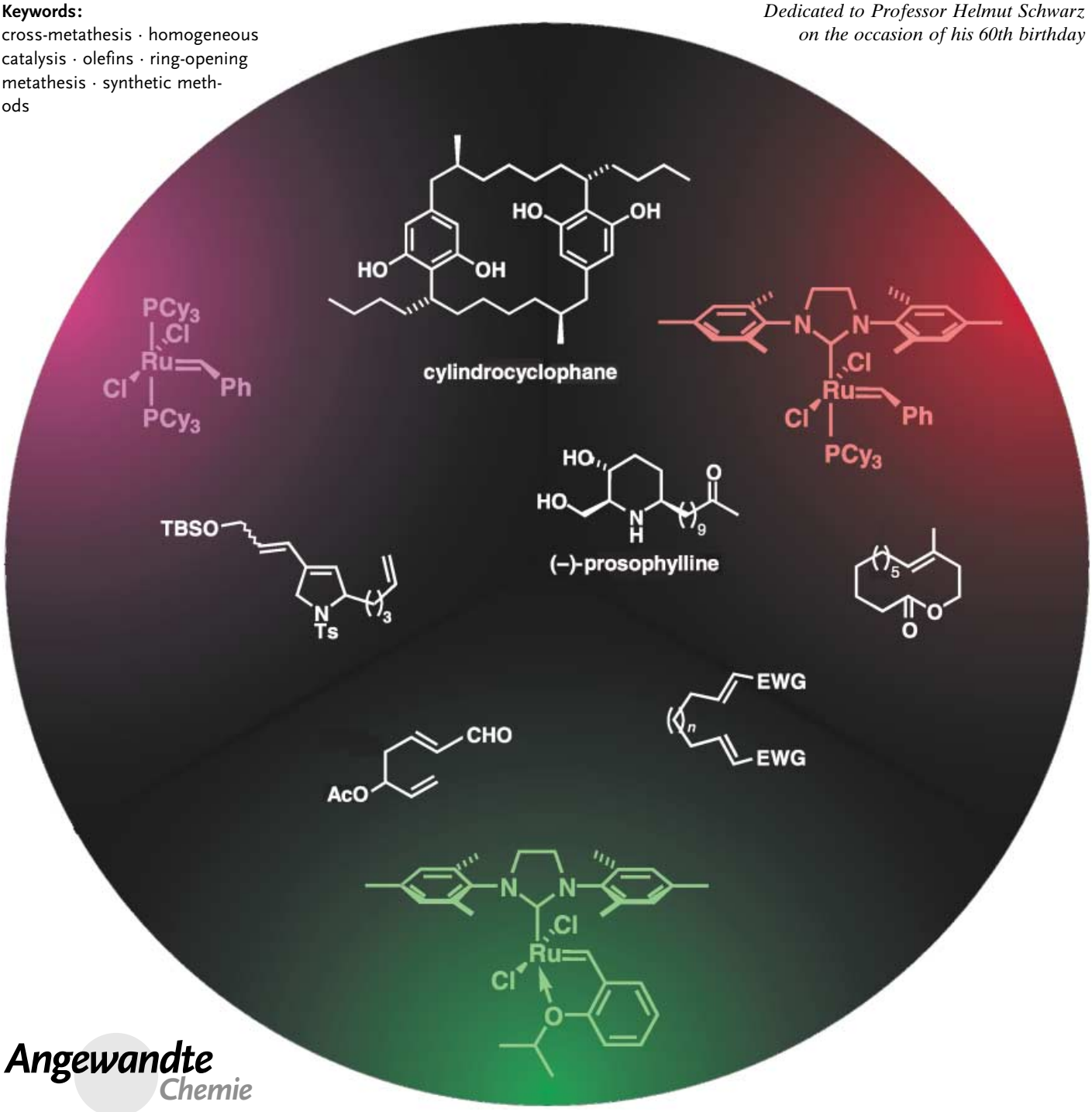
Cross-Metathesis of Olefins

Recent Developments in Olefin Cross-Metathesis

*Stephen J. Connon and Siegfried Blechert**

Keywords:
cross-metathesis · homogeneous catalysis · olefins · ring-opening metathesis · synthetic methods

Dedicated to Professor Helmut Schwarz on the occasion of his 60th birthday



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Among the many types of transition-metal-catalyzed C–C bond-forming reactions, olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago. These advances, together with a better understanding of the mechanism and catalyst–substrate interactions, have brought us to a stage where more and more researchers are employing cross-metathesis reactions in multistep procedures and in the synthesis of natural products. The recent inclusion of alkynes and hindered bicyclic olefins as viable substrates for bimolecular metathesis coupling, the discovery of enantioselective cross-metathesis and cross-metathesis in water, and the successful marriage of metathesis and solid-phase organic synthesis has further widened the scope of this versatile reaction.

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1. Introduction

Olefin cross-metathesis[1] can be formally described as the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes. There are three main variations on this theme (Figure 1): a) cross-metathesis, b) ring-opening cross-metathesis, and c) intermolecular enyne metathesis (C).[2]

As an acyclic carbon–carbon bond-forming tool, cross-metathesis has numerous advantages typical of modern olefin-metathesis reactions:

1) The process is catalytic—typically 1–5 mol% of catalyst required.
2) High yields can be obtained under mild conditions in relatively short reaction times.
3) A wide range of functional groups are tolerated, with minimal substrate protection necessary.
4) The reaction is reversible, relatively atom-economic, and gaseous ethylene is usually the only by-product, which is an important consideration in industrial applications.
5) The olefin substrates are generally easier and less expensive to prepare than those associated with other common catalytic C–C bond-forming reactions (e.g. unsaturated boranes, stannanes, halides, triflates).
6) The olefinic products are suitable for further structural elaboration (e.g. hydrogenation, epoxidation, halogenation, cycloaddition).
7) High levels of chemo-, regio-, and stereoselectivity can be attained.

Cross-metathesis (CM) has found numerous industrial uses, including the well-known Shell Higher Olefin Process (SHOP),[3] the Further Exploitation of Advanced Shell Technology (FEAST) Process, and the Phillips Triolefin Process.[4] CM is not yet in such widespread laboratory use as the more entropically favorable ring-closing metathesis (RCM) reaction. However, the development of a second generation of active and robust ruthenium catalysts such as **1**–**4** (Figure 2), which combine the high activity previously only associated with molybdenum-based catalysts with an impressive functional-group tolerance, has recently allowed many groups to breathe new life into what were previously in many cases little more than unselective mechanistic curiosities. This Review will for the most part consist of an in-depth overview of these achievements, with particular emphasis placed on substrate/functional-group compatibility and the factors that influence selectivity. It is hoped that clearly defining the current scope and capabilities of these reactions will help to draw attention to these processes, which are rapidly gaining in significance.

The literature on CM, ring-opening metathesis (ROM), and enyne metathesis up to 1997 has been individually reviewed by Fürstner,[1h] Gibson, and Keen[5] and by Mori,[6] and hence this report concentrates on an overview of the

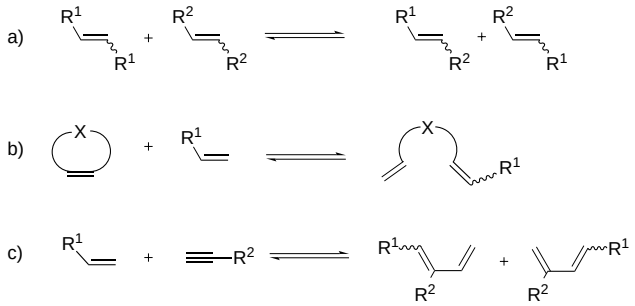

Figure 1. Variations of cross-metathesis.

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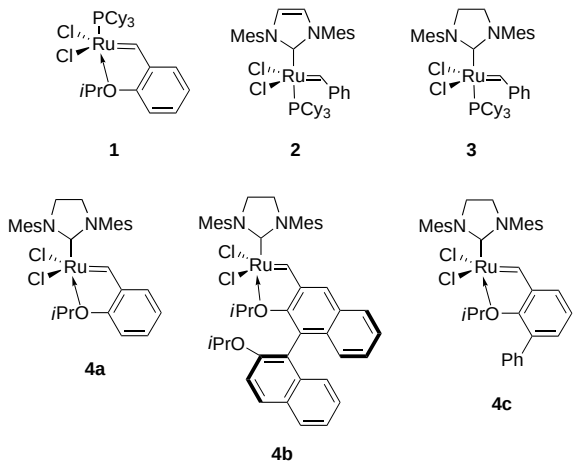


Figure 2. Recently developed, highly efficient, ruthenium-based metathesis catalysts (Mes = 2,4,6-trimethylphenyl, Cy = cyclohexyl).

material since then—a period of unprecedented activity and success in this field.

1.1. Mechanism

A general mechanistic scheme[2] for the CM of two symmetrically substituted olefins (in practice, this is quite difficult) is presented in Figure 3. The first step in the catalytic cycle (after the first catalyst turnover to produce **A**) is a [2+2] cycloaddition reaction between olefin **B** and a transition-metal carbene **A** to give a metallacyclobutane **C**. The latter undergoes subsequent collapse in a productive fashion to afford a new olefin product **D** and a new metal carbene (alkylidene) **E**, which carries the alkylidene fragment R^1. Similarly, **E** can react with a molecule of **F** via **G** to yield **D** and **A**, which then re-enters the catalytic cycle. The net result is that **D** is formed from **B** and **F** with **A** and **E** as catalytic intermediates.

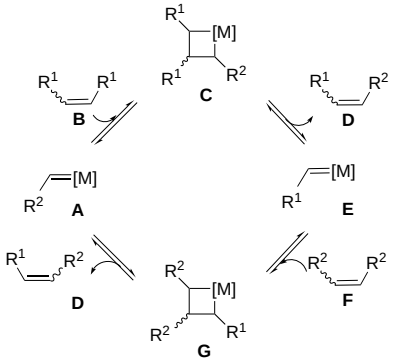


Figure 3. Mechanism of olefin metathesis.

2. Cross-Metathesis

2.1. Selectivity: A Historical Perspective

As is the case with most transformations, the two most important questions concerning any CM reaction are those of efficiency and selectivity. The goal is to achieve high yields of the cross-product with minimal amounts of competing dimerization (self-metathesis) products. In the majority of CM reactions (particularly when the produced olefin is required for a further stereoselective transformation such as epoxidation) *E*/*Z* selectivity is also a critical issue. Early reports described a variety of strategies to tackle selectivity problems. With the active molybdenum catalyst [Mo(=CHCMe$_2$Ph)(=NAr)(OCH(CF$_3$)$_2$Me)] (**5**) Crowe et al. have demonstrated selective CM between terminal alkenes and either acrylonitrile, styrene, or allyltrimethylsilane.[7–9] It was proposed that both acrylonitrile and styrene were capable of stabilizing the intermediate electron-rich molybdenum–carbon bond, leading to selective metathesis. We have shown that selective cross-metathesis with allyltrimethylsilane is mostly due to steric and not electronic factors, as originally proposed.[10]

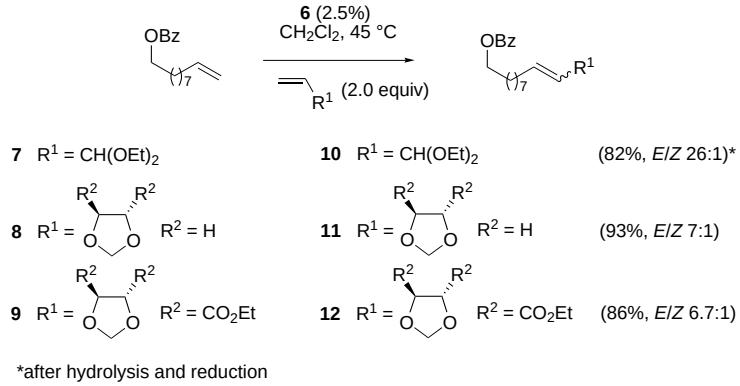
Another important strategy for preventing self-metathesis by-products was the attachment of one of the substrates to a solid support. Provided that an excess of a relatively hindered soluble olefin was used, good yields of CM product could be obtained after cleavage from the resin.[11,12] Selective CM was also possible with hindered substrates such as protected olefinic amino acids[13–15] and protected jasmonates[10] in the presence of the Grubbs ruthenium catalyst [Cl$_2$(PCy$_3$)$_2$Ru=CHPh] (**6**).

Siegfried Blechert was born in Aalborg, Denmark, in 1946. He studied chemistry at the University of Hannover, Germany, and completed his PhD under the supervision of Prof. E. Winterfeldt in 1974. After a research stay with Prof. P. Potier at Gif-sur-Yvette, France, he completed his habilitation at the University of Hannover in 1986 before taking up a professorship at Bonn University in 1986. In 1990 he accepted the Chair of the Organic Chemistry Department at the Technical University of Berlin. His research interests include the development of new catalysts for olefin metathesis, novel synthetic methods, and the stereoselective synthesis of natural products.

Stephen J. Connon was born in Dublin, Ireland, in 1976. After graduating from Dublin City University he moved to University College Dublin in 1997, where he studied pyridyne reactive intermediates under the supervision of Prof. A. F. Hegarty, completing his PhD in 2000. In 2001 he took up a postdoctoral position with Prof. Blechert, where he held an Alexander von Humboldt Fellowship, working on the development and application of new homo- and heterogeneous olefin-metathesis catalysts. In January 2003 he became a lecturer at the chemistry department at the University of Dublin, Trinity College.

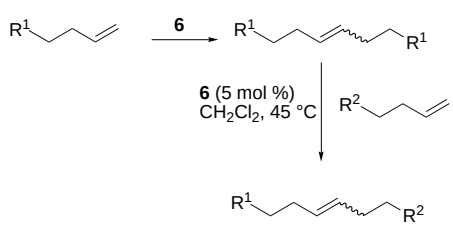
2.2. Selectivity—New developments with $[Cl_2(PCy_3)_2Ru{=}CHPh]$

Although molybdenum-catalyzed selective (with respect to cross-product/dimer ratio) CM with acrylonitrile was possible, **5** was found to be incompatible with enones and enoic esters.[8] Furthermore, Grubbs and co-workers found that the more practical and robust ruthenium catalyst **6** was incompatible with conjugated olefins, including acrolein. This apparent shortcoming could be partially circumvented by using an excess of acrolein acetals such as **7**–**9**. In the presence of 9-decen-1-yl benzoate, CM products **10**–**12** were formed in good yields and with good *E*/*Z* selectivity (Scheme 1).[16,17] Unfortunately, this method did not prove generally applicable: orthoesters, ketals, and homologues of **7** all proved unsuitable.



Scheme 1. Acrolein equivalents in CM.

However, Grubbs and co-workers also reported an innovative and promising new method for avoiding undesired self-metathesis products. In a two-step procedure, a terminal olefin was first homodimerized in a CM reaction, and the internal olefin product (in excess) was then treated with a second terminal olefin in the presence of **6** to give cross-coupled products (Scheme 2).[18] Although again not always applicable, it was shown that in many cases this strategy was preferable to straightforward CM coupling of two terminal olefins (Table 1). Both *E* and *Z* homodimers were found to be



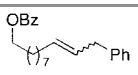
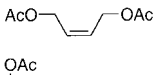
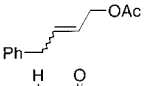
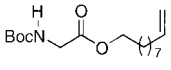
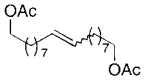
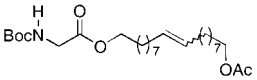
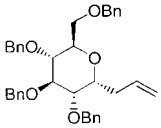
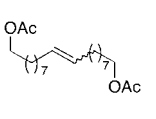
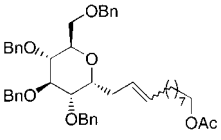
Scheme 2. Two-step selective CM with olefin dimers.

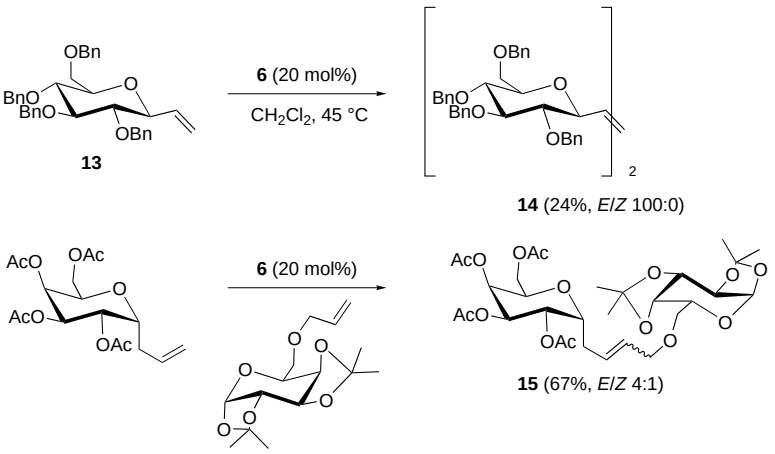
reactive, and high yields and selectivities were possible in the presence of various functional groups.[19] Unreacted homodimer could also be recovered for further use. The authors convincingly argued that these results could be explained in terms of the preferential formation (due to the presence of excess homodimer) of a more stable, substituted ruthenium alkylidene (rather than methylidene) intermediate.[20]

The compatibility of **6** with conjugated electron-deficient olefins is a matter of current debate. The lack of material on this potentially important reaction would seem to point towards incompatibility; however, two reports have appeared which cast doubt on this conjecture, at least in the case of certain substrates. Castedo and Blanco[21] found that allylbenzene could efficiently react with a range of CM partners (2 equiv), including acrylonitrile or acrolein, in the presence of **6** (5 mol %). This report also detailed the first example of CM with allyl bromide catalyzed by **6**. (Roy and co-workers have also been able to demonstrate the compatibility of both **6** and **3** with allyl halides in CM couplings.[22]) Lovely and Seshadri[23] were able to effect CM reactions between olefinic ferrocene derivatives[24] and methyl acrylate, albeit with a very high catalyst loading (20 %). It is clear that more reports are needed before this contentious issue can be resolved.

Roy et al.[25] found that CM dimerization of *O*-allylglycosides in the presence of catalyst **6** could be reasonably *E*-selective (*E*/*Z* = 5:1), whereas the corresponding *C*-glycosides gave 1:1 mixtures of *E*/*Z* isomers. Dimerization of tetrabenzyl *C*-vinylglycoside **13** gave the dimer **14** as a single *E* isomer but in low yield (Scheme 3). It can be reasonably assumed that

Table 1: Selective CM with olefin dimers.

Olefin	Dimer	Product	Yield [%]	*E*/*Z*
			68	3.7:1
			80	3:1
			72	3.5:1
			73	2.8:1



Scheme 3. Selective CM with carbohydrates.

increased steric hindrance and greater Ru–O chelation possibilities associated with having the reacting olefin in close proximity to the bulky carbohydrate is responsible for both the selective formation of the more stable *E* product and the low yield. The ability of *O*-allylglycosides to undergo relatively *E*-selective CM was also exploited in the preparation of mixed *O*- and *C*-pseudosaccharide **15** (Scheme 3).

2.3. Selectivity with Electron-Withdrawing Alkenes : IMes-Based Catalysts

The advent of catalysts **3**[26] and **4a** (Figure 2)[27,28] has had a tremendous impact on the CM reaction. These ruthenium alkylidenes contain nonlabile, sterically hindered NHC (N-heterocyclic carbene) ligands with strong σ-donor and poor π-acceptor properties, which help to stabilize the 14-electron ruthenium intermediates during metathesis. Catalyst **3** displays a functional-group tolerance akin to that of bisphosphane-based catalyst **6**, but has a reactivity closer to that of the highly active yet oxophilic molybdenum catalyst **5,** and thus is far superior to **6** in terms of reactivity. This reactivity increase is demonstrated by the traditionally difficult formation of trisubstituted alkenes (a common structural subunit in natural products) in a CM reaction between the *gem*-disubstituted olefin 2-methyl-1-undecene and terminal olefins in moderate to good yields and moderate *E* selectivity (Figure 4).[29]

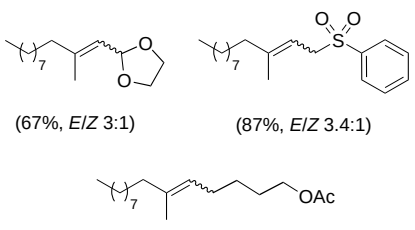


Figure 4. Trisubstituted olefins by CM using **3**.

This method was recently expanded by Grubbs and co-workers to include solvent-free CM reactions with symmetrical *gem*-disubstituted olefins.[30] Along similar lines, Stoltz and Spessard[31] demonstrated the viability of 2-methyl-2-butene as an efficacious CM partner in the synthesis of the bicyclo[3.3.1]nonane core of garsubellin A catalyzed by **3** (10 mol%).

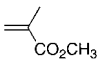
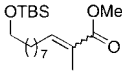
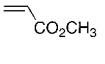
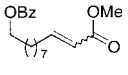
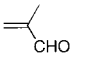
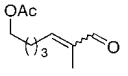
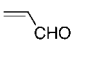
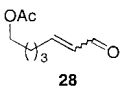
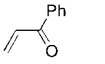
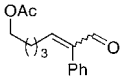
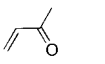
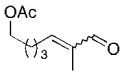
However, it is the unprecedented activity of **3** and **4a** in the presence of conjugated electron-deficient olefins that has revolutionized the CM reaction. Metathesis transformations involving these substrates often give high cross-product/dimer ratios and excellent *E*/*Z* selectivity. The main reason for the high CM selectivity is the slow rate of dimerization of α,β-unsaturated carbonyl compounds. If one sees a typical CM reaction as a competition between three reaction pathways, that is, selective CM or dimerization of either starting material, then if one partner dimerizes relatively slowly, the selectivity naturally increases. The first such report came from Grubbs and co-workers at Caltech,[32] who observed that CM between α,β-unsaturated compounds (esters, aldehydes,[33] and ketones **19**–**24**) and simple terminal olefins **16**–**18** in the presence of **3** (5 mol%) in CH_2Cl_2 at 45 °C proceeded in good to excellent yields with impressive *E* selectivity (Table 2). In most cases, an excess of one olefin component is used to improve selectivity. However, Grubbs and Chatterjee recently showed that high-yielding and selective CM reactions are possible in the presence of equimolar amounts of olefin partners.[34] Thus CM can be used as a mild method for formal C–H activation or allylic oxidation,[34] depending on whether terminal or internal olefin substrates, respectively, are employed. Significantly, vinylic halides, phthalimides, sulfones, silanes, acetates, ethers, alkyl stannanes and acrylonitriles were initially found to be unreactive.

Catalyst **3** can also be generated in situ and used to effect selective CM reactions with electron-withdrawing alkenes.[35] After metathesis reactions, **3** (and also **6**) can be used to hydrogenate the products under high H_2 pressure (average 100 psi).[36] The CM of α,β-unsaturated amides[37] has also been demonstrated using catalyst **3**. Yields using these relatively electron-rich substrates were generally not as high as those found with **19**–**24**. This was attributed to the ability of amides to chelate to ruthenium during metathesis, thus siphoning off the catalyst in an unreactive form. This premise was supported by the observation that sterically hindered or electron-deficient amides **31b** and **31c**, respectively, gave higher yields of CM product than the electron-rich and unhindered analogue **31a** (Scheme 4).

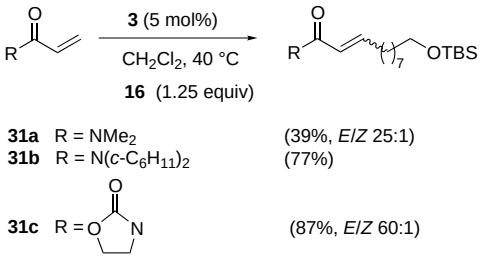
We have found that the 2-isopropoxystyrene-derived catalyst **4a** was also active in CM reactions of challenging substrates.[28] A twofold excess of electron-deficient olefins **20**, **22**, **24**, and **31a** (**4a** (5 mol%), CH_2Cl_2, 40 °C) gave good to excellent yields of products **32**–**35** with pent-1-enylbenzoate; *E*/*Z* selectivity was also generally high (Table 3).

Catalyst **4a** was also found to be active in the CM of acrylonitrile derivatives. These electron-deficient substrates, which were incompatible with catalyst **3**, could be coupled smoothly with a variety of terminal olefins in high yields and

Table 2: CM using **3** and electron-deficient alkenes.[a]

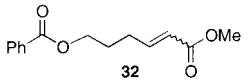
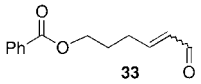
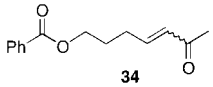
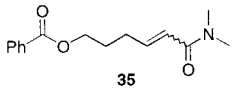
Terminal olefin	α,β-unsaturated olefin (equiv)	Product	Yield [%] (*E*/*Z*)
 **16**	 (0.5) **19**	 **25**	62 (>20:1)
 **17**	 (2.0) **20**	 **26**	91 (4.5:1)
 **18**	 (0.5) **21**	 **27**	92 (>20:1)
 **18**	 (2.0) **22**	 **28**	62 (>20:1)[33]
 **18**	 (2.0) **23**	 **29**	99 (>20:1)
 **18**	 (2.0) **24**	 **30**	95 (>20:1)

[a] TBS = *tert*-butyldimethylsilyl.



Scheme 4. CM with α,β-unsaturated amides.

Table 3: CM using **4a** and electron-deficient alkenes.

α,β-unsaturated olefin	Product	Yield [%] (*E*/*Z*)
20	 **32**	87 (>20:1)
22	 **33**	93 (>20:1)[33]
24	 **34**	85 (>20:1)
31a	 **35**	98 (>20:1)

E-selectivity.[38] More recently, Cossy et al.[39] demonstrated efficient and selective CM between chiral homoallylic alcohol derivatives and a range of electron-deficient alkenes (including acrylonitrile) with only 2.5 mol% of **4a** at 25 °C.

In the course of our studies on the CM of fluorinated molecules as electron-deficient olefin partners, we discovered a markedly improved CM efficiency of **4a** over that of **3**. Across a range of fluorinated alkenes, **4a** gave consistently higher yields of CM products. Although yields using **3** were still acceptable, an increased propensity for dimerization of the electron-rich terminal alkene substrate with this catalyst was apparent.[40] Given the current interest in fluorinated phases,[41] this new efficient method for forming fluorinated alkenes is of some synthetic utility. Itoh et al. prepared bis- and oligo-*gem*-difluorocyclopropanes through CM dimerization promoted by **3**. However, relatively high catalyst loadings (15 mol%) were required to achieve moderate to good yields.[42]

Interestingly, vinyl- and allylphosphonates **36** and **37** are viable CM partners in metathesis reactions catalyzed by **3**.[43] High yields were obtained on coupling with simple terminal olefins to give products of synthetic interest (Figure 5).

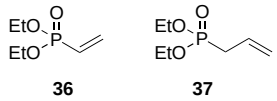
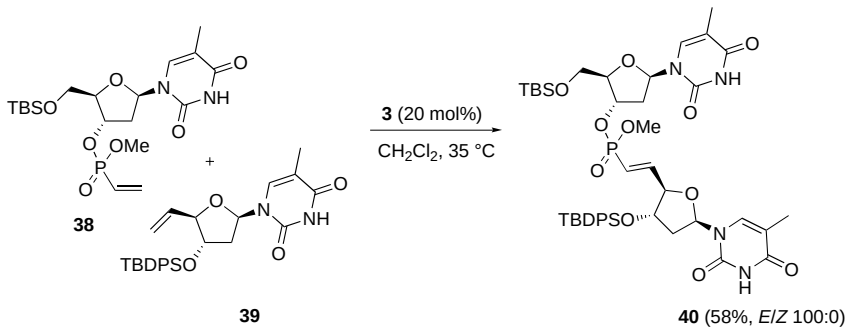


Figure 5. Vinyl- and allylphosphonates for CM.

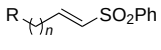
Along the same lines, Lera and Hayes[44] coupled nucleotides through a CM coupling of vinylphosphonate **38** with terminal olefin **39** catalyzed by **3** (20 mol%). Under similar conditions, catalyst **6** gave none of the desired nucleotide dimer **40**, thus highlighting the superiority in terms of both activity and functional-group tolerance of **3**, and its potential for CM modification of biologically important molecules (Scheme 5). Interestingly, the authors cite intramolecular chelation of the nucleotides to ruthenium as the reason why such large amounts of catalyst are required to achieve acceptable CM yields.

Krausz and co-workers were able to dimerize various nonphosphorylated 3′-allyl nucleosides through CM promoted by the bisphosphane catalyst **6** (10–20 mol%). Yields were moderate (≤45%) and the reaction was largely unselective with regard to olefin geometry.[45]

As noted earlier, Grubbs and co-workers[32] reported that vinyl sulfones are not successful substrates in CM reactions catalyzed by **3**. However, Grela and Bieniek subsequently found that phenyl vinyl sulfone gave good yields of products of general type **41** with a variety of terminal olefins in the presence of **3** (Figure 6).[46] In our hands, CM of similar CM



Scheme 5. Coupling of nucleotides by CM (TBDPS = *tert*-butyldiphenylsilyl).



41

R = OTBS, n = 4	(85%)
R = $CH(CO_2Et)_2$, n = 1	(74%)
R = CO_2Me, n = 8	(76%)

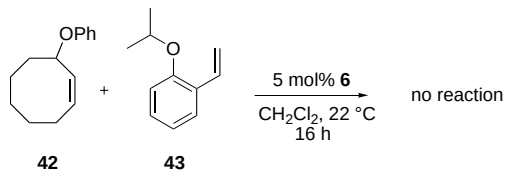
Figure 6. Products from CM with phenyl vinyl sulfone.

partners with phenyl vinyl sulfone was much less efficient with catalyst **3** than one would expect from analysis of the literature data;[46] however, good conversions were possible with the phosphane-free catalyst **4a**.[47] Given the synthetic potential of sulfones as both Michael acceptors and cycloaddition-reaction substrates these findings are of some value and interest in organic synthesis.

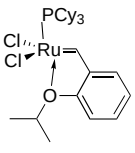
2.4. CM Selectivity Derived from Chelation

That the chelation of oxygen functionalities to ruthenium during metathesis is possible and plays an important role in the course of the reaction is beyond doubt.[48] One particularly instructive example is a report by Hoveyda and co-workers concerning the serendipitous discovery of a stable, catalytically active species **1** from the attempted ROM–CM of 2-isopropoxystyrene (**43**) with octadiene **42** in the presence of **6** (Scheme 6).[49]

The complex **1** was active in metathesis reactions (although not tested in CM) and was of sufficient stability to be recovered efficiently by chromatography after reaction,

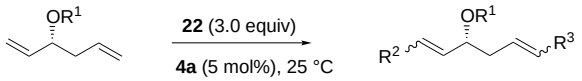


Scheme 6. Serendipitous discovery of **1** from an attempted ROM–CM reaction.



1

thus allowing the catalyst to be recycled. This clearly demonstrates the potential of intramolecular chelating effects to interfere dramatically with a metathesis reaction. This same chelation principle has been utilized to prepare the chromatographically stable catalyst **4a** from **3**,[27,28] and as we have seen, the effect of the chelating isopropoxystyrene moiety on CM catalyst activity can be advantageous under certain circumstances.[28,38,40] Two recent reports cast some light on the potential role of chelated intermediates in both chemo- and *E*/*Z* selectivity in CM reactions. Cossy and BouzBouz[50] discovered that in the case of CM of hydroxy- and acetoxyolefins **44** and **45**, respectively, with acrolein (**22**) promoted by **4a** under identical conditions, **44** is functionalized twice (to give **46**), whereas acetoxyolefin **45** affords the product of a single cross-coupling reaction, **47** (Scheme 7).



44 R^1 = H
45 R^1 = Ac

46 R^1 = H, R^2 = CHO, R^3 = CHO (70%, *E*/*Z* 30:1)
47 R^1 = Ac, R^2 = H, R^3 = CHO (73%, *E*/*Z* 30:1)

Scheme 7. Chelation effects in chemoselective CM.

These results were rationalized in terms of catalyst deactivation by chelation of the acetoxy group to the metal center during the catalytic cycle (Figure 7). It was proposed that selectivity could arise through either deactivation of one of the C–C double bonds by the electron-withdrawing acetoxy group, or as would seem more plausible to us, through the formation of an unreactive six-membered chelate ring **H′**, which results in selective CM of the homoallylic unit. The corresponding chelate derived from **I′** would require

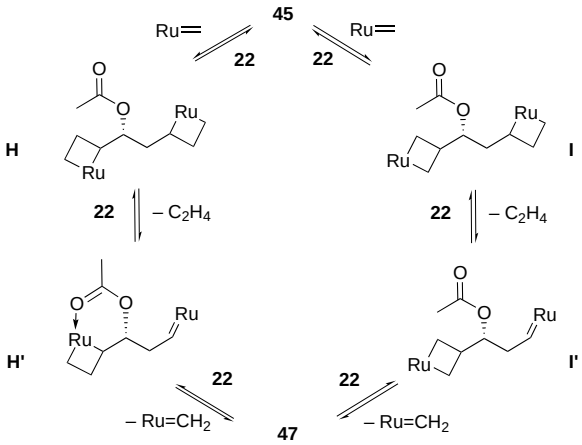
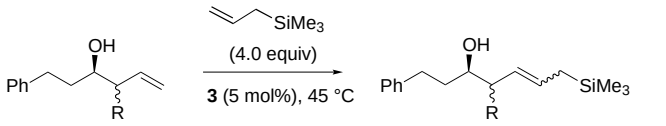


Figure 7. Proposed catalytic cycle for chemoselective CM.

seven-membered ring formation and as such would be expected to be much less stable. In the case of hydroxy substrate **44** no such stable ring chelates are possible, and thus unselective CM is observed.

At approximately the same time Taylor and co-workers demonstrated the contribution that chelates can make to the *E*/*Z* selectivity of CM reactions between homoallylic alcohols with *syn*- and *anti*-allylic substituents and allyltrimethylsilane (Scheme 8).[51] Both diastereomers led to higher *E*/*Z* ratios than the unsubstituted case **48**, and *anti*-substituted substrates **49** and **51** resulted in the highest stereoselectivity. What is most striking is that the same *E*/*Z* ratios were obtained in both *syn* products and in both *anti* products (**55**, **57** and **54**, **56**, respectively) regardless of the nature of the *syn* or *anti* group.



48	R = H	**53** R = H	(84%, *E*/*Z* 70:30)
49	R = *anti*-CH_3	**54** R = *anti*-CH_3	(86%, *E*/*Z* 92:8)
50	R = *syn*-CH_3	**55** R = *syn*-CH_3	(81%, *E*/*Z* 80:20)
51	R = *anti*-CO_2Et	**56** R = *anti*-CO_2Et	(67%, *E*/*Z* 92:8)
52	R = *syn*-CO_2Et	**57** R = *syn*-CO_2Et	(74%, *E*/*Z* 80:20)

Scheme 8. *E*-selective CM of substituted homoallylic alcohols.

Again the postulation of intramolecular chelates provided the most satisfactory explanation for the unexpected stereoselectivity observed. Assuming that chelation of the hydroxy group to ruthenium occurs, and taking **49** and **50** as examples, examination of the chelated metallacyclobutane intermediates clearly shows that the formation of a *Z* intermediate from the *anti* diastereomer **49** is particularly disfavored on steric grounds as a result of an interaction with the trimethylsilyl group, thus explaining the observed increased *E* selectivity with this substrate relative to *syn*-**50** (Figure 8). Similar arguments can be used to explain the isomer ratios in products **56** and **57**.

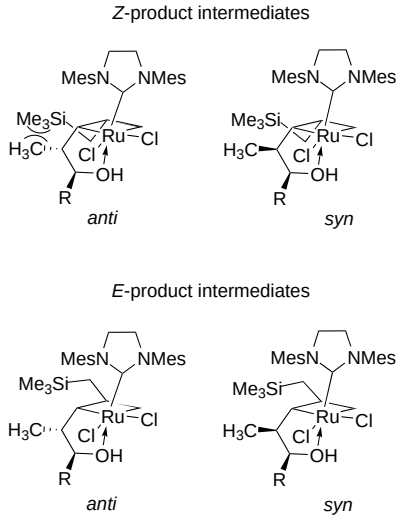


Figure 8. Intermediates in *E*-selective CM of homoallylic alcohols.

2.5. Reversibility in Selective CM

The reversible nature of the CM reaction is of synthetic importance because it generally ensures the preferential formation of the most thermodynamically stable product. As we have seen, this results in the transformation of terminal olefins into internal olefins through CM, with *E*/*Z* ratios higher than 1:1 in most cases.

A highly impressive demonstration of how the reversible nature of the CM reaction can be exploited to give highly selective transformations is the total synthesis of (−)-cylindrocyclophanes A and F (Figure 9) reported by Smith and coworkers.[52] The key step in this remarkable synthesis is a

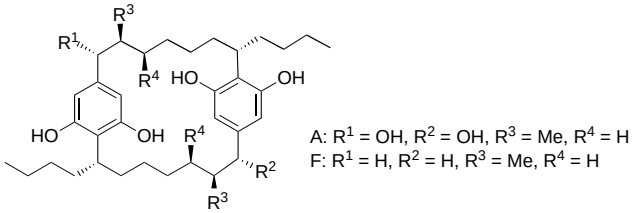
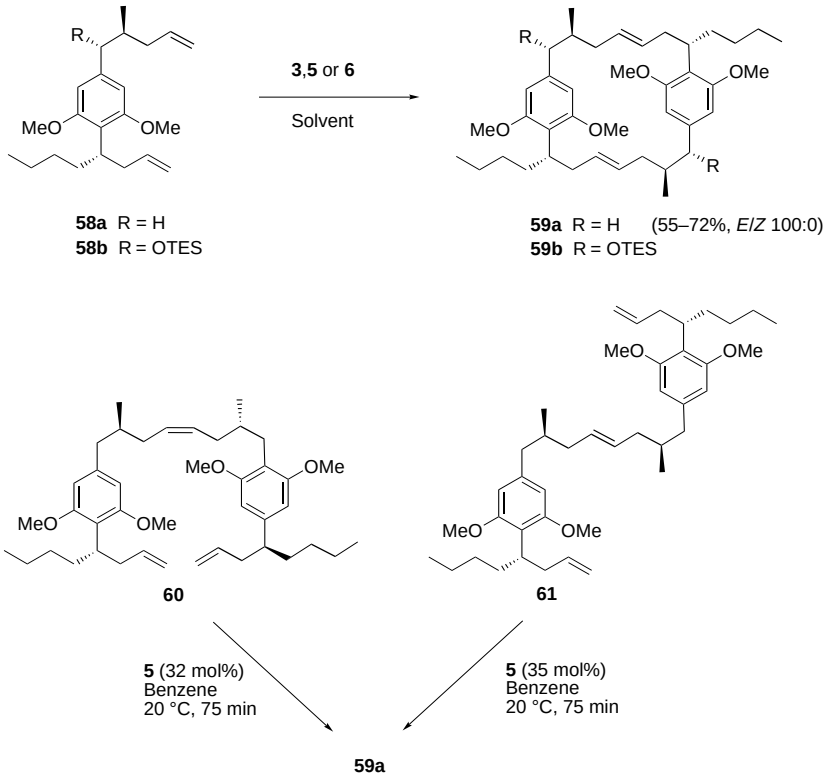


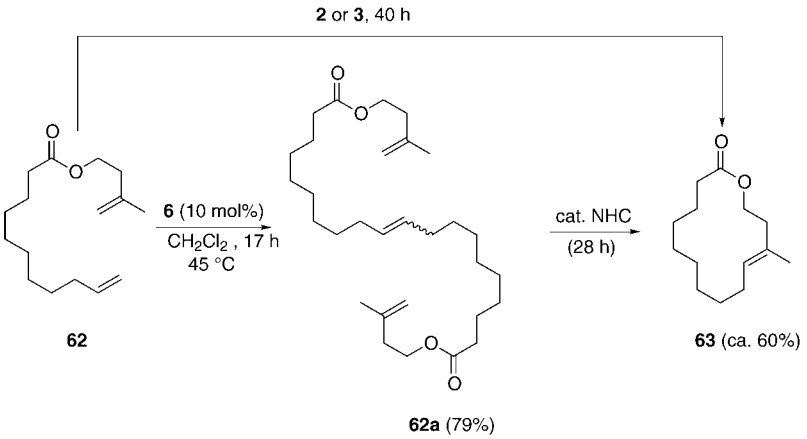
Figure 9. Cylindrocyclophanes A and F.

head-to-tail CM dimerization reaction of terminal olefins **58a**,**b** catalyzed by either **3**, **5**, or **6** (Scheme 9) to give macrocyclic products **59a**,**b**, which could be readily converted into cylindrocyclophanes A and F by standard functional-group manipulations. The level of selectivity in these reactions was both surprising and outstanding: Neither "head-to-head" dimerization nor *Z*-olefin products were observed. Of the seven possible dimeric products (head-to-head, head-to-tail, and *E*/*Z* isomers) only **59a**,**b** were formed.

This led the authors to investigate this reaction further, particularly with a view to discovering the root cause of this extraordinary regio- and stereoselectivity. The most likely explanation is that the reversible nature of CM resulted in a cascade of reactions to form a single dimer product as long as the catalyst remained sufficiently active. This theory was supported by Monte Carlo methods (MM2 force field), which showed that for the dimerization of **58a**, the (*E*,*E*)-[7,7]-paracyclophane product **59a** was the most stable of the possible dimer structures by approximately 2.6–4.7 kcal mol^{-1}. More convincing still was the discovery that RCM of **60** or **61** with the Schrock catalyst **5** gave only **59a** in good yields (75 and 81%, respectively), despite the fact that these substrates should be inclined to furnish [8,6]-paracyclophane instead of [7,7]-paracyclophane products (Scheme 9). It is also noteworthy that catalyst **5** consistently outperformed **6** and **3** in these reversible CM processes. This efficient synthesis of cylindrocyclophanes A and F demonstrates the potential of CM for target-oriented synthesis, in addition to highlighting the advantages in terms of selectivity that can be obtained by exploiting the reversibility of the CM reaction.



Scheme 9. Synthesis of cylindrocyclophane precursors by reversible CM (TES = triethylsilyl).



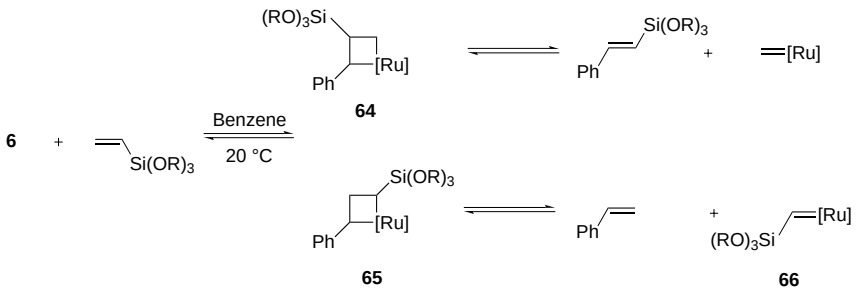
Scheme 10. Reversible-CM-based macrocycle formation.

Fürstner et al.[53] have utilized a similar concept to prepare the 14-membered macrolide **63** from acyclic diene **62** (Scheme 10). The reaction (40 h) of **62** in the presence of NHC catalysts **2** (10 mol%) or **3** (6 mol%) afforded macrocycle **63** in approximately 60% yield. The less active Grubbs catalyst **6** gave only CM dimer **62a** after 17 h at 45 °C. A slightly modified NHC catalyst then transformed **62a** into lactone **63**, which demonstrates that macrocyclic RCM can be preceeded by a reversible CM dimerization. This reversible CM–RCM strategy was subsequently used in the total synthesis of the antibiotic (*R,R*)-(−)-pyrenophorin.

2.6. CM with Vinylsilanes

Silylated olefins are an important class of compounds that have found wide application in organic synthesis. Of particular interest are vinyl siloxane derivatives, which can participate in palladium(0)-catalyzed C–C-coupling reactions with aryl iodides.[54] Thus the functionalization of vinyl silanes and siloxanes by CM is an attractive prospect. Fischer and co-workers[55] have shown that the reactivity of vinylsilanes towards CM with styrene increases with increasing oxygen substitution at silicon: $CH_2{=}CHSi(OR)_3 > CH_2{=}CHSiMe(OR)_2 > CH_2{=}CHSiMe_2OR > CH_2{=}CHSiMe_3$.[56] Vinyltrimethoxy- and vinyltriethoxysilanes gave good CM conversions (76–100%) in the presence of only 1 equivalent of styrene (2 mol% **6**) and only the *E* isomer of the cross-product was detected by ^{1}H NMR spectroscopic analysis. A gentle stream of argon was required to remove the ethylene by-product during the reaction; in closed systems substrate conversions were unsurprisingly lower. In test reactions between vinyltrialkoxysilanes and stoichiometric amounts of **6**, Fischer and co-workers[56] observed high selectivity in the formation of $PhCH{=}CHSi(OR)_3$ over $PhCH{=}CH_2$. This result indicates that in the first step of the metathesis reaction ([2+2] cycloaddition), metallacyclobutane **64** is generated in preference to **65** (Scheme 11). The ruthenium silylalkylidene **66** was also not detected. As this intermediate is required for dimerization of vinyltrialkoxysilane, its absence in these stoichiometric studies is possibly significant in explaining why high CM selectivities are possible with only a 1:1 ratio of siloxane and styrene.

The discovery that vinyltrialkoxysilanes are inactive in CM dimerizations was significant as it allows the use of these reagents in excess to drive selective CM reactions with more challenging partners than styrene.[32,57] *E*-Selectiv le CM reactions with 1-hexene, 1-decene, allylbenzene, and allyl phenyl ether (amongst others) were possible in the presence of a fivefold excess of siloxane and 5 mol% of **6**. In all cases, yields were between 70 and 100%, with *E*/*Z* ratios between 5:1 and 15:1.[56,57] In another interesting application, vinylsilanes were found to couple with alkyl vinyl ethers ($ROCH{=}CH_2$) in the presence



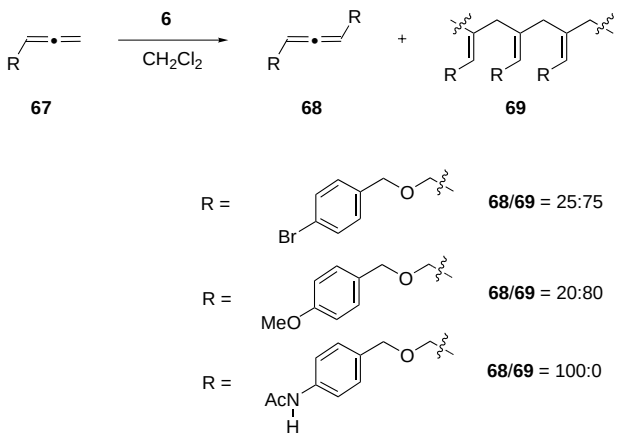
Scheme 11. Reaction of **6** and vinyltrialkoxysilanes.

of **6** (5 mol%) to give CM products of general type ROCH=$CHSiR_3$ in high yields, although deuterium-labeling studies have shown that this reaction almost certainly does not proceed through a metathesis-type mechanism.[58] Similar reactions with allyl alkyl ethers (through a ruthenacycle-based mechanism) have also been reported.[59]

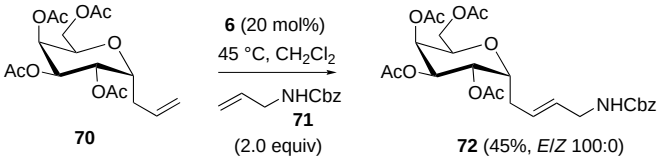
2.7. Cross-Metathesis of Allenes

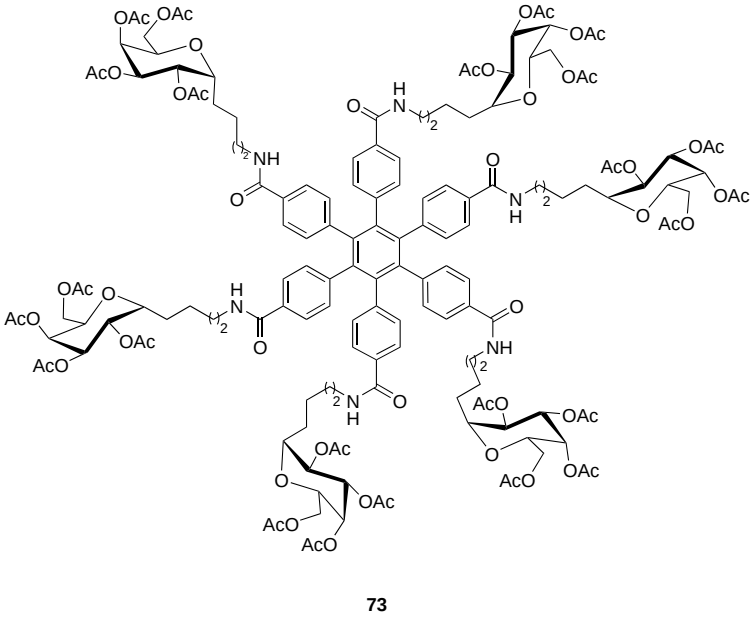
To the best of our knowledge, only one example of a CM reaction involving well-defined ruthenium complexes and allenes has been reported.[60] Barrett and co-workers treated a variety of monosubstituted allenes of general type **67** with **6** (5 mol%) at 20°C. Under these conditions, self-metathesis 1,3-disubstituted allene products **68** along with polymeric material **69** were obtained (Scheme 12). The ratio of **68**/**69** varied considerably with the steric and electronic properties of **67** with no clear general trends emerging, although it was determined that simple phenyl-substituted allenes (R = Ph and *o*-, *m*-, and *p*-tolyl, for example) were poor substrates and afforded **69** exclusively. Catalysts **3** and **5** were less active than the first-generation Grubbs catalyst **6** in these reactions.

The absence of theoretically possible cumulene products from the reaction was rationalized in terms of the likely relative instability of the bis(exo-methylene)metallacyclobutane intermediates (required to form cumulenes) compared to the mono(exo-methylene)metallocyclobutane that forms **68**.



Scheme 12. Self-metathesis of allenes.





Scheme 13. Synthesis of "molecular asterisks" by CM (Cbz = benzyloxycarbonyl).

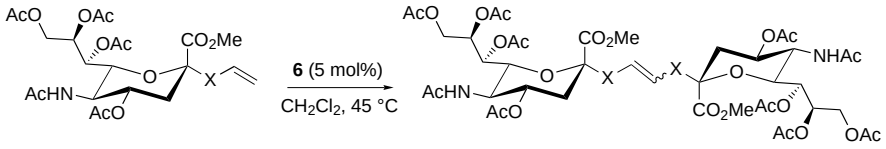
2.8. Synthesis of Biologically Important Molecules

From humble beginnings,[1j] the evolution of CM into a flexible and powerful methodology for synthesis of biomolecules (and their analogues) and of natural products is steadily gaining momentum. Quite recently the volume of material published in this area has increased as more and more chemists are turning to CM to achieve smooth high-yielding transformations as key components of multistep selective syntheses.

2.8.1. Carbohydrates

The application of olefin metathesis to carbohydrate chemistry has been the subject of two reviews published in 2000.[1c,61] As this particular area of the field has been well-documented, this section will concentrate on developments in this area since.

Roy and co-workers have used a selective CM reaction as a key C–C bond-forming step in the preparation of so-called "molecular asterisks".[62] An initial CM reaction between peracetylated α-D-allylgalactopyranoside **70** with protected amine **71** catalyzed by **6** afforded cross-product **72** in moderate yield with complete *E* selectivity (Scheme 13). The predominance of the *E* isomer in this CM reaction remains to be explained; CM reactions involving various other sugar derivatives under identical conditions gave selectivity no better than 4:1 in favor of the *E* form. Glycoside **72** then served as the template on which to build the necessary functionality to give the aryl glycoside cluster **73** after (double) Sonogashira coupling and cyclotrimerization reactions. This class of compounds is anticipated to be important in elucidating the binding specificity of multiple carbohydrate–protein interactions. It was also possible to use a protected amino acid instead of **71** to give a novel C-linked glycopeptidomimetic product after CM. However the *E*/*Z* selectivity was modest.



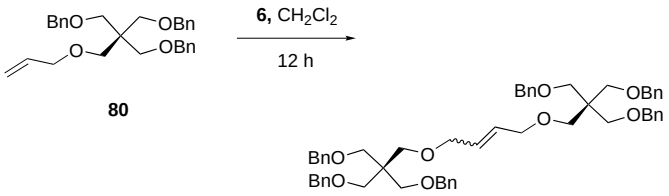
74 X = OCH_2
75 X = $O(CH_2)_3$
76 X = SCH_2 (10 mol% **6**)

77 X = OCH_2 (82%, *E*/*Z* 7:1)
78 X = $O(CH_2)_3$ (88%, *E*/*Z* 3:1)
79 X = SCH_2 (26%, *E*/*Z* 2.5:1)

Scheme 14. Sialoside dimers.

Roy and Gan prepared divalent sialoside derivatives based on a CM reaction.[63] For example, the dimerization of sialosides **74**–**76** promoted by **6** allowed the isolation of dimers **77**–**79** (Scheme 14). Yields were good using *O*-α-sialosides, however thiosialoside **76** was a considerably less efficacious CM partner as a result of the coordinating (and hence catalyst-poisoning) proclivities of sulfides. Even so, to the best of our knowledge, the formation of **79** in low yield is the first example of a sulfide participating in a straightforward CM reaction catalyzed by well-defined ruthenium initiators such as **6**.

A CM strategy has also been employed to construct a hexameric cluster, which can be further elaborated to bear saccharide-based xenotransplantation antagonists such as the Galili antigen.[64] CM dimerization of monoallyl ether functionalized pentaerythritol derivative **80** in the presence of **6** afforded hexameric cluster **81** in excellent yield with high *E*/*Z* selectivity (Scheme 15). Dendrimer template **81** was then hydrogenated/deprotected and functionalized with the appropriate saccharides by standard techniques.



80

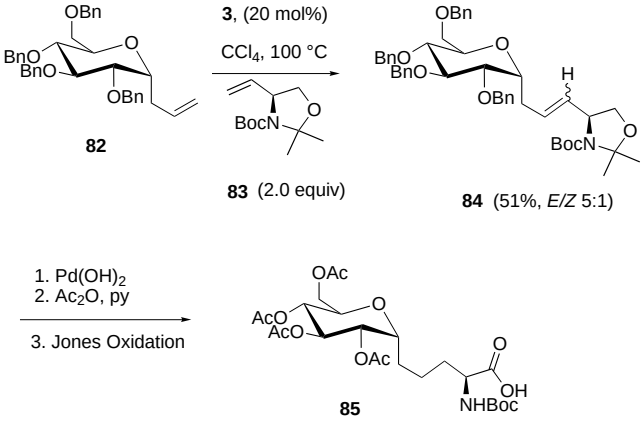
81 (85%, *E*/*Z* 10:1)

Scheme 15. Formation of saccharide dendrimer template by CM.

Dondoni et al.[65] reported a successful CM between olefinated carbohydrates such as **82** and vinyloxazolidenes such as **83** catalyzed by the second-generation Grubbs catalyst **3** (20 mol%). After CM, the vinyloxazolidene protecting group can be cleaved with Jones reagent to unmask *C*-glycosyl amino acids such as **85** (Scheme 16). This methodology has also been extended to prepare a potential glycopeptide nephritogenoside mimetic.

2.8.2. Natural Products

Although not nearly as successful as RCM in this area, CM is finding increasingly wide application in the synthesis of natural products as the chemo- and stereoselectivity of this process steadily improve. Some examples have already been noted: Cossy and BouzBouz[50] have used multiple selective CM/allyltitanations to prepare the C1–C14 fragment of the dinoflagellate amphidinol III, Smith et al.[52] reported the superb manipulation of the reversibility of CM to prepare cylindrocyclophanes A and F, and Stoltz and Spessard[31] have employed a CM step in the synthesis of the bicyclo[3.3.1]nonane core of garsubellin A.



82

83 (2.0 equiv)

84 (51%, *E*/*Z* 5:1)

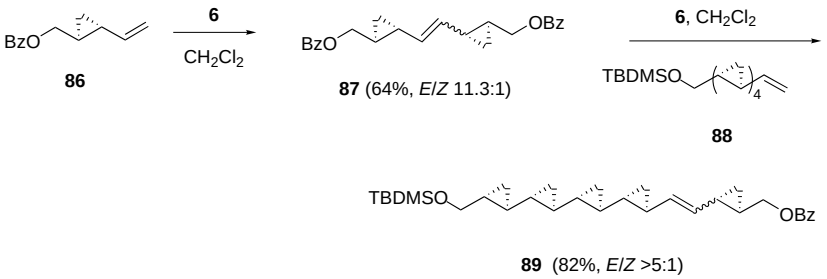
85

Scheme 16. *C*-glycosyl amino acid synthesis by CM (Boc = *tert*-butoxycarbonyl, py = pyridine).

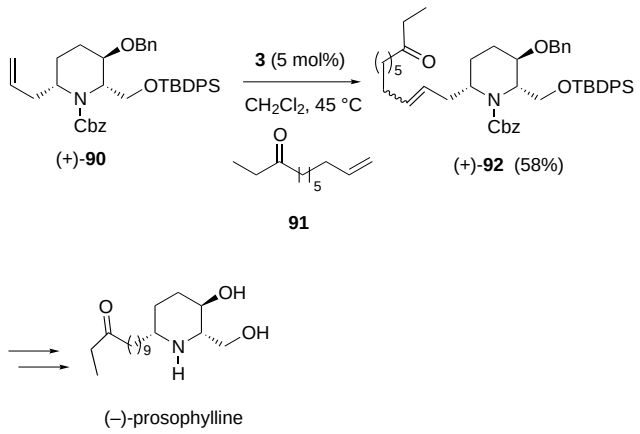
Verbicky and Zercher[66] have utilized a CM coupling strategy in the formal synthesis of the antifungal natural product (−)-FR-900848. Based on CM methodology initially proposed by Grubbs and co-workers[17,18] (i.e. selective CM by an initial self-metathesis of one olefin partner followed by CM coupling of the resulting dimer with a terminal olefin), self-metathesis of enantiopure cyclopropane **86** with **6** (5 mol%) gave dimer **87** in reasonable yield. CM coupling of **87** with tetracyclopropane **88** again promoted by **6** (5 mol%) furnished the key intermediate **89** (Scheme 17), which after selective cleavage of the benzoyl group is identical to an advanced intermediate in the synthesis of (−)-FR-900848 by Barrett and Kasdorf.[67]

Cossy et al. have also applied CM to the synthesis of the piperidine alkaloid (−)-prosophylline.[68] Metathesis coupling of alkene (+)-**90** with 2 equivalents of ketone **91** in the presence of **3** (5 mol%) resulted in the formation of advanced intermediate (+)-**92** in acceptable yield, which can be transformed into the natural product after a hydrogenation/deprotection sequence (Scheme 18).

One of the inherent limitations of the CM reaction is that it can fail in cases involving strained olefins, for which ROM–CM pathways are preferable. An impressive example is the synthesis of the AB fragment of ciguatoxin (CTX1B) by Hirama and co-workers.[69] A high-catalyst-loading CM reaction between seven-membered-ring substrate **93** (itself formed by RCM) and acetate **94** proceeded in poor yield and

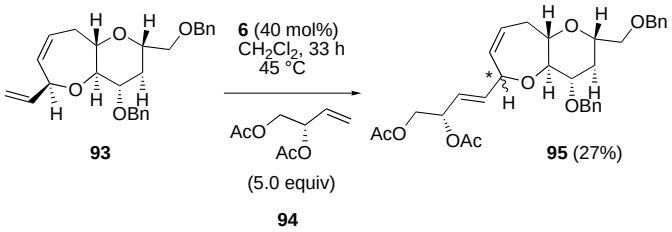


Scheme 17. Formal synthesis of (−)-FR-900848.

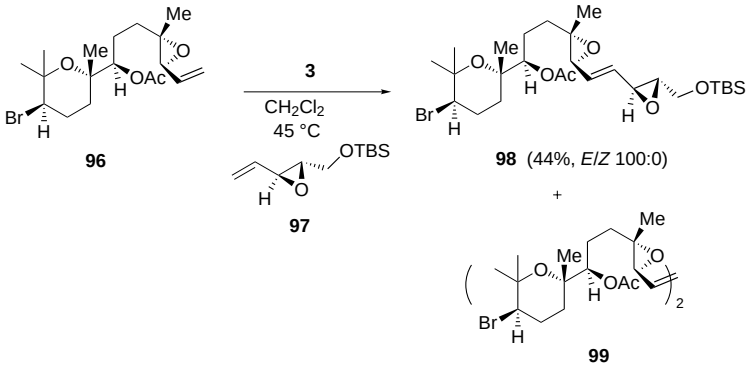


Scheme 18. CM in the synthesis of (−)-prosophylline.

also gave a mixture of diastereomers, epimeric at the indicated carbon center (Scheme 19). The authors cite ROM as the major fate of **93**.



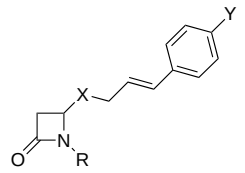
Scheme 19. Synthesis of AB-ring fragment of ciguatoxin by CM.



Scheme 20. Synthesis of ABC-ring fragment of thyrsiferol by CM.

Quite recently McDonald and Wei[70] reported the synthesis of the ABC tristetrahydropyran moiety common to the thyrsiferol and venustatriol natural products using a CM coupling step. Metathesis coupling of terminal olefin **96** with 3 equivalents of chiral epoxide **97** catalyzed by the second-generation Grubbs catalyst **3** (10 mol%) gave a mixture of CM product **98** (44%), homodimer **99**, and unreacted **97** (Scheme 20). Taking advantage of the fact that both **96** *and* **99** can participate in further CM couplings, the recovered starting material and dimer were subjected to a further charge of **3** in the presence of additional **97**, which led to another 20% yield of **98**.

Barrett et al. have utilized RCM, enyne metathesis, and CM to functionalize alkenylated β-lactam rings; in particular the CM of olefin lactam substrates and *p*-substituted styrenes allowed the preparation of coupled products in moderate to good yields (Figure 10).[71] In an interesting application, Diver and co-workers have recently demonstrated the applicability of CM to the modification of cyclosporin A derivatives for attachment to a solid support.[72]

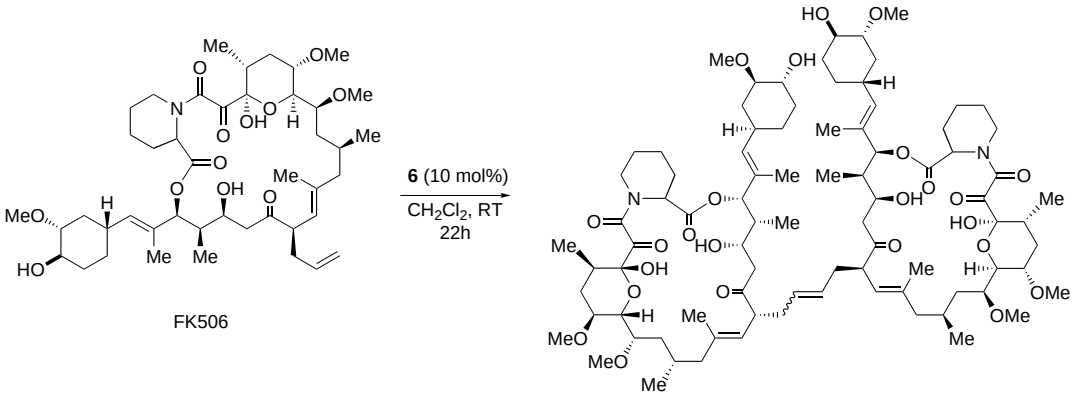


X = O, NTs
Y = H, Cl, Me, OMe
R = H, TBDMS, Bn, CH(OTBDMS)CO_2Et

Figure 10. Functionalized β-lactams from CM reactions.

CM has also been proposed as a concise method for the preparation of flavan-3-ol precursors. Gesson and co-workers[73] reported CM reactions between 2-allylphenol derivatives and styrenes promoted by **6** (typically 3 mol%), which give reasonable to good yields of cross-product (60–79%) with only the *E* isomer detected. The resulting 1,3-diaryl propenes are useful starting materials for the synthesis of flavan-3-ols, a class of natural product with wide-ranging biological activity. Recently Miller and Vasbinder demonstrated the superiority of CM over the Wittig reaction for the preparation of Pro-Gly dipeptide alkene isosteres.[74]

Schreiber and Diver[75] utilized CM to dimerize the immunosuppressant FK506. Treatment of the macrocycle with **6** (10 mol%) at room temperature furnished the corresponding dimer (FK1012) in moderate yield (Scheme 21). The high functional-group tolerance of **6** allows this reaction to be carried out on the unprotected substrate, despite the presence of several potential chelating groups



Scheme 21. Dimerization of FK506 by CM.

in the molecule. FK1012 was found to activate signal-transduction pathways and gene transcription in mammalian cells.

Nicolaou and co-workers employed a similar strategy to dimerize vancomycin derivatives through CM.[76] A small library of alkene-substituted vancomycin analogues were formed by self-metathesis in variable yields in the presence of **6** (20 mol%) in H_2O/CH_2Cl_2 (95:5; presumably the organic cosolvent is required for catalyst initiation) under phase-transfer conditions. In these processes, **6** exhibited unprecedented functional-group tolerance in the presence of amino, carboxy, hydroxy, and amide groups. These experiments led to the discovery of several highly potent antibiotics, some of which displayed high activity against vancomycin-resistant bacteria.

3. Ring-Opening Cross-Metathesis

The highly efficient and atom-economic ROM–CM reaction has been the subject of much recent investigation. The presumed catalytic cycle for this reaction is shown in Figure 11. The reaction of ruthenium methylidene and olefin substrate **100** furnishes metallacyclobutane intermediate **101**, which on collapse gives ring-opened alkylidene **102**. This step is most efficient for highly strained cyclic olefin substrates, in which relief from ring strain provides an energetic counterweight to the entropically favored reverse RCM reaction (**102**→**100**). It is hardly surprising, therefore, that norbornenes, oxanorbornenes,[77] and cyclobutenes[1i,78] are generally excellent substrates for ROM–CM reactions. CM between **102** and terminal olefin **103** (internal olefins may also serve as CM partners) then affords ROM–CM product **105** via intermediate **104** with loss of the ruthenium methylidene, which then reenters the catalytic cycle. An important condition for ROM–CM to be efficient is that CM between **102** and **103** must be faster than the reaction between **102** and **100** (a competing ROMP pathway), a factor which very much depends on the nature of the cyclic olefin **100** and the CM partner **103** used. However, in the majority of cases ROM–CM competes effectively with ROMP,[20,77,78] particularly under high dilution conditions. Another factor to be considered is the rate of homodimerization of the CM partner: Often the best CM partners are those that undergo self-metathesis relatively slowly, for example, styrenes and allytrimethylsilane.

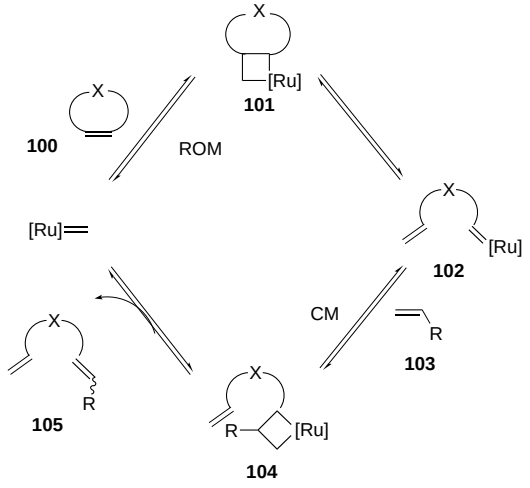


Figure 11. ROM–CM catalytic cycle.

One of the key issues to be tackled recently is the question of regioselectivity in ROM–CM. Although progress has been made, hard-and-fast rules regarding the factors that influence selectivity have not yet emerged. In the general example shown in Figure 11 only one product, **105**, is possible because **100** is symmetrical. However, if the starting cycloolefin is asymmetrically substituted, then different regioisomeric products are possible.

Arjona et al.[79] considered the ROM–CM between cycloolefin **106** and a terminal olefin and have put forward plausible arguments for the formation of products **107** and **108** (Figure 12): The reaction of cycloalkene **106** with the catalytically active methylidene gives rise to either **109** or **110**. It would seem reasonable to assume that cycloaddition would be preferable from the side opposite to the large group, and thus steric interaction between the metal–ligand moiety and the small group makes **109** more favorable than **110**. Cyclo-

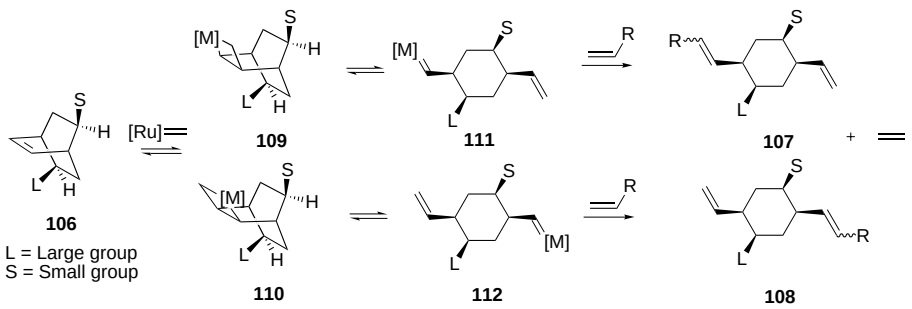
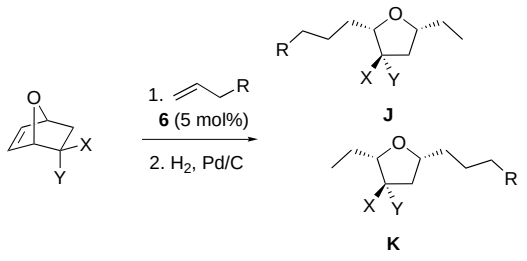


Figure 12. Rationale for the regioselectivity of ROM–CM.

reversion of **109** to **111** followed by CM then affords **107** as the major product, that is, the regioselectivity is derived from the initial cycloaddition reaction. Conversely, if the difference in steric bulk between the "small" and the "large" groups is considerable, then the difference in energy between **111** and the less-hindered **112** (which furnishes **108**) can dictate the outcome of the reaction, that is, the regioselectivity is largely derived from the CM reaction. It is also certain (although much more difficult to rationalize) that chelating and electronic effects are contributors to selectivity in certain substrates. What is clear is that regioselectivity is largely substrate-dependent.

Insight into the origins of regioselectivty of these processes was obtained from a ROM–CM study of various 2-substituted 7-oxanorbornenes (Scheme 22).[80] Variation of the substituents X,Y had a profound effect on selectivity. With small substituents Y no selectivity was found; however, even a small difference (Y = OH converted into Y = OAc) led to an impressive increase in selectivity. Also interesting is that the introduction of a substituent X (not H) does not improve the selectivity further, and that the major products all have the alkyl side chain on the same side of the ring as the Y substituent (i.e. *cis* products with respect to Y). This indicates that interaction between the Y substituent and the metal moiety in the putative metallated intermediates is critical. It is also known that these reactions are concentration-dependent. Increasing the concentration by 200% leads to dimerization of the resulting terminal olefin after initial ROM–CM.[81]

Cuny et al. [82] reported examples in which the nature of the terminal olefin CM partner can influence product ratios.

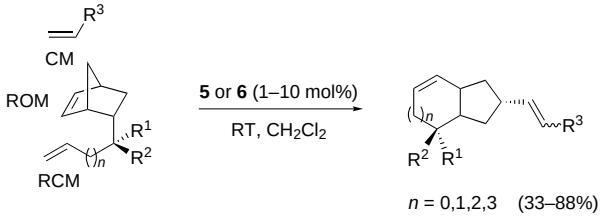


X, Y = C=O, R = OAc (75%, **J**/**K** 50:50)
X = H, Y = OH, R = OAc (80%, **J**/**K** 50:50)
X = H, Y = OAc, R = OAc (75%, **J**/**K** 19:81)
X = H, Y = $OCOCH{=}CH_2$, R = OAc (75%, **J**/**K** 23:77)
X, Y = OCH_2CH_2O, R = OAc (80%, **J**/**K** 21:79)
X, Y = OCH_2CH_2O, R = OBn (70%, **J**/**K** 23:77)

Scheme 22. ROM–CM with substituted oxanorbornenes.

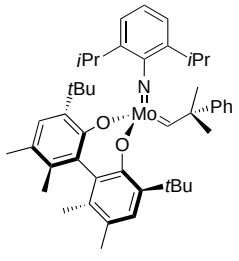
In ROM–CM reactions involving bicyclic *exo* norbornenes and *p*-substituted styrenes, use of 4-vinylanisole or 3-methoxy-4-vinylphenol gave a single *E* ROM–CM product, whereas *tert*-butyl 4-vinylphenylcarbonate gave a major *E* cross-product, along with significant amounts of the *Z* isomer and a bis-CM product (7 and 6%, respectively).

We have shown that tandem ROM-RCM–CM reactions are possible.[83] Exposure of norbornenes containing olefin side chains of various lengths to **5** or **6** (5–10%) in the presence of terminal olefins or ethylene gas gave rise to bicyclic products. Cyclopentane-fused five-, six-, seven-, and eight-membered rings could be constructed without difficulty in a practical domino process (Scheme 23).[84]



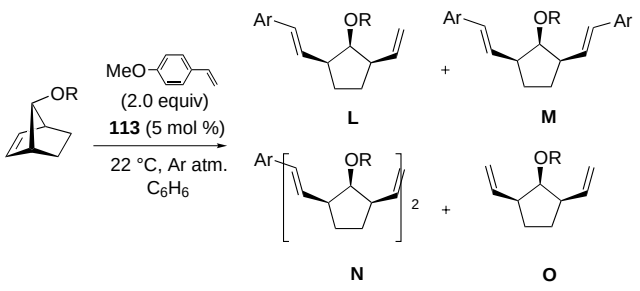
Scheme 23. Domino ROM–RCM–CM.

A very important development in this field came from Hoveyda, Schrock, and co-workers with the discovery of asymmetric ROM–CM.[85,86] Noting that the ROM–CM reaction can give rise to chiral products, they treated *meso* norbornenes with enantiopure molybdenum catalyst **113**[87] (Figure 13) in the presence of styrene derivatives (Scheme 24). 4-Methoxystyrene was the most efficient and selective coupling partner, giving the product as a single enantiomer in two cases with an accompanying high chemoselectivity (**L**/**M**/**N** ratio). The enantioselectivity was found to be largely independent of the ether R group and of the styrene; however, reactions involving styrene itself or 4-trifluoromethylstyrene tended to be less chemoselective, although results were still acceptable. Other terminal olefin



113

Figure 13. Chiral molybdenum catalyst for asymmetric ROM–CM.

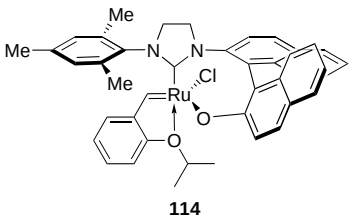


R = OTBS, conv (%) **L/M/N/O** 75:8:0:7, 91% *ee*, *E/Z* 100:0
R = OTMS, conv (%) **L/M/N/O** >98:0:0:0, >98% *ee*, *E/Z* 100:0
R = OMOM, conv (%) **L/M/N/O** 95:3:2:0, >98% *ee*, *E/Z* 100:0

Scheme 24. Enantioselective ROM–CM reactions (MOM = methoxymethyl).

CM partners were compatible with the reaction, including one example of a one-pot sequential asymmetric ROM–CM with vinyltriethoxysilane/Pd-catalyzed arylation to give a ring-opened and arylated product in 51% yield with >98% *ee*. These findings demonstrate the synthetic potential of asymmetric ROM–CM for the straightforward preparation of functionalized chiral cyclopentane building blocks.[88]

Hoveyda and co-workers recently also developed alkylidene **114**, a ruthenium-based enantiopure catalyst for asymmetric ROM-CM (Figure 14).[89] Due to the nature of the metal and the presence of an alkoxide ligand (which is expected not to be beneficial in ruthenium alkylidene catalysts because of their lower inductive electron withdrawing abilities relative to chloride ligands[90]), **114** exhibits lower reactivity in ROM reactions (10 mol% is required). However, it has an impressive stability akin to that of **4a**, and as such can be recovered chromatographically after the reaction and can be used exposed to air without difficulty. The levels of chemo- and enantioselectivity when using **114** were generally excellent.

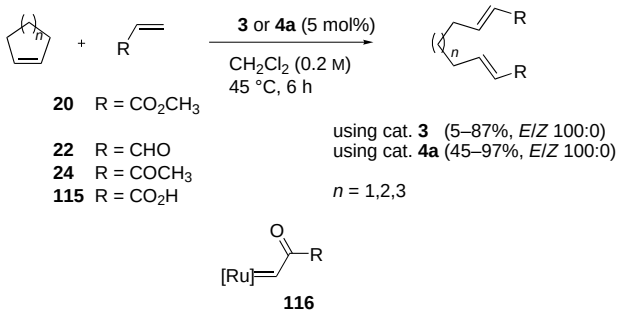


114

Figure 14. Chiral ruthenium catalyst for asymmetric ROM–CM.

Catalysts **4b**[91] and **4c**,[92] which incorporate steric bulk *ortho* to the chelating isopropoxy moiety, are powerful metathesis initiators. We found that the use of only trace amounts of these precatalysts (only 0.005 mol% in the case of **4c**) effects ROM–CM reactions between a range of norbornenes or oxanorbornenes and allyltrimethylsilane in near quantitative yields. In the modern era in which catalyst efficiency and trace-metal-contamination levels in reaction products can be critical issues, we envisage that stable yet active catalysts of these types may prove to be valuable.

In general, as noted previously, ROM–CM reactions are most successful when using highly strained substrates that are predisposed to ring opening. Furthermore, it is assumed that in these reactions, ring opening is the initial step, which is then followed by CM (see Figure 11). It is therefore not surprising that under standard conditions for norbornene ring opening, unstrained cycloalkenes such as cyclopentene and cyclohexene are unreactive. However, Grubbs and co-workers demonstrated that β-carbonyl ruthenium carbene species generated from diazoacetates are highly active and react in stoichiometric quantities with cyclohexene to afford new ruthenium carbene complexes.[93] This led both Grubbs's group and our group to speculate as to whether or not ROM–CM was possible with unstrained olefins in the presence of reactive metal carbenes. We found that it was possible to bisfunctionalize cyclopentene, cyclohexene, and cycloheptene in good yields using catalysts **3** or **4a** in the presence of either acrylic acid (**115**), **20**, **22**, or **24** (Scheme 25).[94]

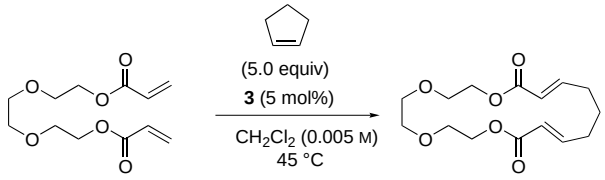


116

Scheme 25. ROM–CM of unstrained cycloalkenes.

Isopropoxy chelate catalyst **4a** gave higher yields of ring-opened products than did catalyst **3** in all cases tested. The order of reactivity of the cycloalkene substrates (cycloheptene ≥ cyclopentene > cyclohexene) presumably corresponds to ring strain, and the method was also applicable to heterocyclic substrates. It seems certain that the ring-opened species in these reactions are the highly electron-deficient carbenes of general type **116** (R = H, Me, OMe, OH). Unfortunately, vinyl sulfones, amides, and nitriles were unsuitable CM partners for the initial ROM reaction. Interestingly, a double-ROM–CM reaction with two different acceptor-substituted olefins was also demonstrated.

Grubbs and co-workers were able to use ROM–CM involving strained and unstrained olefins to effect ring-expansion reactions,[95] which seems like a promising method for the synthesis of macrocycles. For example, treatment of cyclopentene with bisacrylic ester **117** in the presence of **3** gave ring-expanded product **118** in a moderate yield through a ROM–CM process (Scheme 26). Grubbs and co-workers also demonstrated that reactive β-carbonyl ruthenium carbenes can be utilized in the selective ROM–CM of cyclooctadiene and trisubstituted cycloolefins to generate highly functionalized, long-chained olefins.[96] The latter class of substrates could be converted into products that are "end-differentiated" (i.e. one end of the chain contains an α-

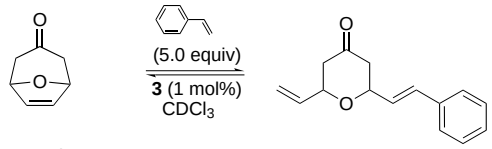


117 **118** (52%)

Scheme 26. Ring expansion of unstrained cycloalkenes through ROM–CM.

substituted terminal olefin and the other is end-capped with an α,β-unsaturated carbonyl moiety).[97,98]

Although in practice ROM–CM processes (particularly those involving highly strained substrates) are usually irreversible, an example of reversible ROM–CM has been reported (Scheme 27).[99] Wright et al. showed that the ROM–CM of oxabicyclo[3.2.1]octene derivatives are equilib-



119 **120** (83%, *E*/*Z* 100:0)

Scheme 27. Reversible ROM–CM.

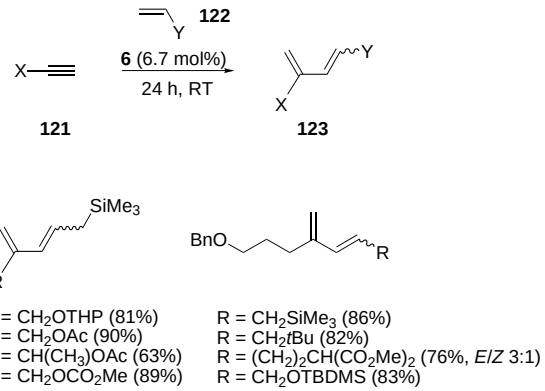
rium reactions. Reaction of ketone **119** with excess styrene promoted by **3** gave the ring-opened product **120** (*E* isomer) in good yield. However, after equilibrium had been reached (ca. 90% conversion by ^{1}H NMR spectroscopic analysis), addition of starting material had no effect on equilibrium ratios over time (isolated product **120** when exposed to **3** also gave **119** and styrene), indicating that the reverse RCM of **120** to give **119** and styrene was also occurring simultaneously. This reversibility could be circumvented by selective reduction of the keto group in **119** with L-Selectride followed by protection with the bulky TBS group. 1,3-Diaxial interactions then force both the olefin moieties in the product into equatorial positions, which are not conducive to ring closure, thus allowing irreversible ROM–CM.

4. Intermolecular Enyne Metathesis

Enyne metatheses are unique and interesting transformations involving the reaction of an alkene and an alkyne.[100] The products from these processes are synthetically useful butadiene derivatives, which lend themselves toward structural elaboration by Diels–Alder reactions and other cycloaddition processes.

Until recently, intermolecular enyne metathesis reactions were thought of as unselective with regard to both *E*/*Z*- and chemoselectivity. Competing CM homodimerization of the alkene, alkyne metathesis, and polymerization hampered the development of the enyne-metathesis reaction. The intramolecular variant, in which side reactions are minimized as a result of entropic effects and the proximity of the reacting moieties, has received much more attention. The situation up to 1997 was summed up by Mori:[6] "Intermolecular diene metathesis produces many olefins, and it has usually been used as intramolecular diene metathesis".

In 1997 our group reported the first selective intermolecular enyne metathesis.[101] The reaction of terminal alkynes of general type **121** and alkenes **122** (in excess) in the presence of **6** gave 1,3-disubstituted butadienes **123** in a remarkably selective operation. Internal alkenes were unreactive, and catalyst **5** was found to be an unsuitable promoter as it resulted in polymerization of the starting materials in all cases. A simple protocol was used to prepare a variety of dienes in good yields (Scheme 28).



Scheme 28. Selective intermolecular enyne metathesis.

To explain the high regio- and chemoselectivity observed the mechanistic pathway outlined in Figure 15 was proposed. The key regioselective step is the initial formation of metallacyclobutene **124**, which arises from attack of the alkyne by ruthenium methylidene. Ring opening of **124** then affords vinyl carbene **125**. Interestingly, the corresponding α,α-disubstituted vinyl carbene, which would lead to 1,2-substituted butadienes (the major products of intramolecular enyne metathesis reactions), is disfavored, possibly because it is either too stable to undergo subsequent CM, or as a result of unfavorable steric interactions associated with its metallacyclobutene precursor. 1,2-Disubstituted butadiene products are not observed. CM between **125** and olefin **122** then yields

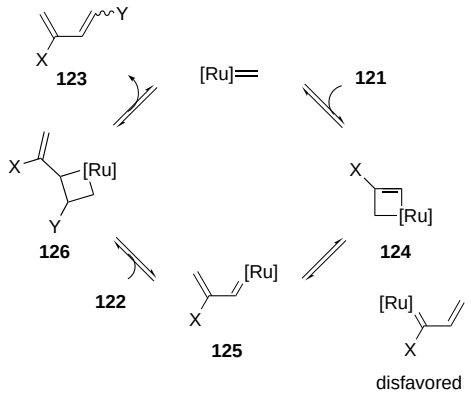
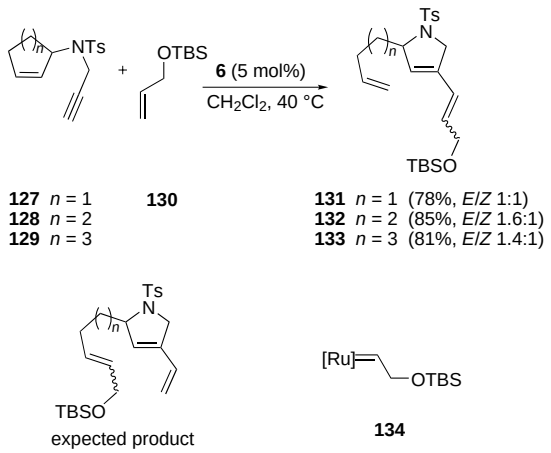


Figure 15. Intermolecular enyne-metathesis catalytic cycle.

126, which undergoes cycloreversion to afford **123** and the propagating species.

Although this rationale explains the results of our group and those of other groups in most cases, as always one must be cautious about mechanistic generalizations. An interesting example in which this scheme does not hold is the rearrangement of compounds **127**–**129** in the presence of olefin **130** and catalyst **6** (Scheme 29).[102] Instead of the expected product, which would be obtained after initial attack of the C–C triple bond by ruthenium methylidene followed by rearrangement and CM (and which is the main product in the reaction of O-



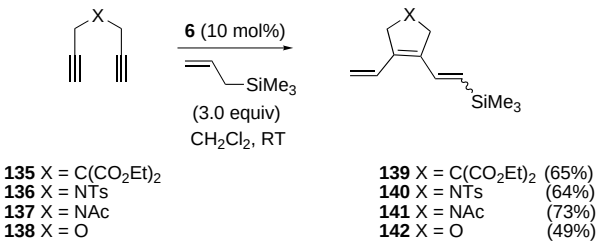
Scheme 29. Alternative mechanism for enyne metathesis.

analogues (**127, 128**: O in place of NTs) with ethylene[103]) we isolated the products **131**–**133**, in which the intermediate butadiene moiety appears to have undergone a CM reaction with **130**. We clearly demonstrated that CM between **130** and a 1,3-diene is not possible under the reaction conditions.[102] Control experiments using products from the rearrangement reaction in the presence of ethylene (i.e. containing a terminal butadiene and terminal olefin side chain) clearly demonstrated that CM between **130** and a terminal butadiene moiety is not possible under the reaction conditions, even in the presence of excess olefin CM partner. This points toward an initial CM reaction between **6** and **130**, and the resulting alkylidene **134** then participates in the enyne rearrangement reaction to afford **131**–**133**. This alternative mechanism highlights the inherent dangers of making assumptions regarding the general mechanism of this relatively young reaction.

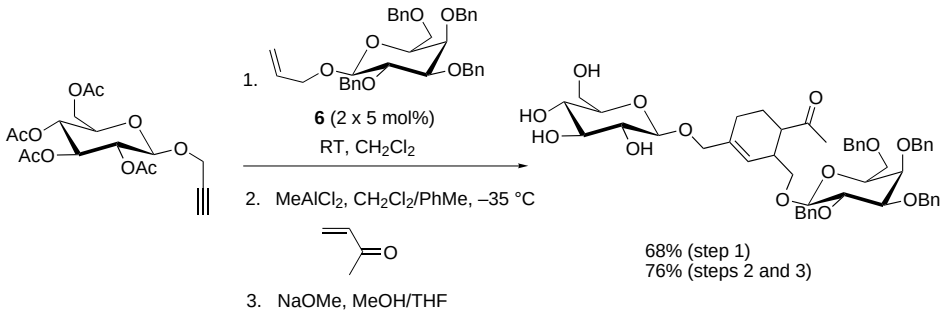
Mori and co-workers were the first to use ethylene gas (1 atm) successfully as a CM partner in enyne reactions.[104] In the presence of **6** (3–10%) as a catalyst, both terminal and internal alkenes were found to be active, furnishing butadiene adducts in moderate to good yields.[105] The presence of a heteroatom in the propargylic position was critical for high product yield. Substrates with ester or amide heterofunctions gave goods results, whereas ether or amine heteroatoms completely prevented any conversion, most likely via metathesis-inactive chelated intermediates.[106] Diver and Smulik later reported similar findings with terminal alkyne substrates, although a high pressure of ethylene gas (60 psi) was required to ensure smooth reactions.[107]

We have used enyne metathesis to prepare pseudooligosaccharides.[108] Alkene- and alkyne-functionalized carbohydrates were coupled in the presence of **6**, and then further elaborated by Diels–Alder protocols (Scheme 30).[109] Butadiene products of enyne reactions were also suitable substrates for aza-Diels–Alder reactions, allowing for rapid and simple preparation of tetrahydropyridine derivatives and azasugar analogues.[110] This methodology has been extended by Pandey and co-workers, who employed a similar strategy to couple alkenyl β-galactosides (and saccharides) to alkynyl purpurinimides (chlorin derivatives) through intermolecular enyne metathesis.[111] In a similar fashion, the same group attached chlorin and porphyrin analogues to fullerene (C_{60}), utilizing an enyne-metathesis/Diels–Alder sequence.[112] Kotha et al. have also used enyne metathesis to functionalize alkynated protected amino acids.[113]

Another interesting enyne metathesis application to have emerged is tandem-diyne-cycloisomerization–CM.[114] For example, the reaction of 1,6-heptadiynes **135**–**138** and allyltrimethylsilane promoted by **6** gives triene cycloadducts **139**–**142** in moderate to good yields (Scheme 31). Unfortunately,



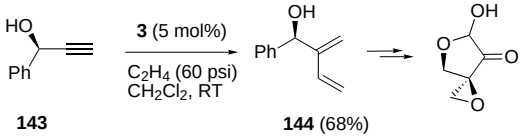
Scheme 31. Tandem diyne cycloisomerization-CM (Ts = *p*-toluenesulfonyl).



Scheme 30. Carbohydrate coupling by enyne metathesis.

the reaction has a limited scope: formation of six- or seven-membered rings was not possible, and internal alkynes were not reactive. Nevertheless this domino sequence demonstrates the power of enyne metathesis for impressive structural development from relatively simple starting materials.

There have been several reports of improved enyne metathesis efficiency using the second-generation Grubbs catalyst **3** instead of **6**.[115–117] Diver and Smulik[115] discovered that **3** could smoothly convert previously challenging substrates such as hindered alkynes, propargylic ethers, and even propargylic alcohols into the corresponding terminal butadienes under a high-pressure ethylene atmosphere. The high activity of **3** and its reduced tendency to form chelates with Lewis basic groups relative to **6** were cited as possible explanations for the improved properties. To show the potential utility of these reactions, enantiopure (99% *ee*) phenyl-substituted propargyl alcohol **143** was transformed into **144** in good isolated yield. Chiral diene **144** was then subjected to a series of oxidations to furnish enantiopure UCT4B side-chain analogues (Scheme 32).



143 **144** (68%)

Scheme 32. Efficient and functional-group-tolerant enyne metathesis.

Some of these findings were later confirmed by Mori and Tonogaki[116] and by our group.[117] It was discovered that enyne metathesis promoted by **3** was considerably more efficacious at lower ethylene pressures (1 atm) than identical reactions catalyzed by **6**. Another significant point was that when using catalyst **3**, the presence of a heteroatom in the propargylic position was not necessary for high-yielding metathesis to occur, thus overcoming a significant drawback associated with enyne reactions involving **6**, and considerably widening the scope of enyne metathesis with ethylene.[116,117] It was also found that internal alkynes underwent a reaction with terminal olefins for the first time, although the regioselectivity was poor.

The high activity of catalyst **3** also allows for the possibility of tandem enyne-CM–RCM reactions between terminal alkynes and 1,5-heptadiene.[118] The diene products from these reactions can be also used in [4+2] cycloadditions.

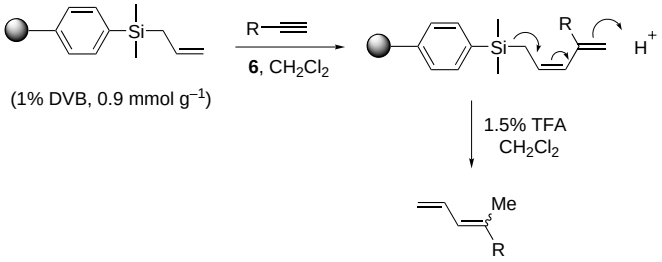
Another recent example highlighting the impact of **3** on enyne metathesis is the successful conversion of sulfur-containing alkynes.[119] Sulfides and thiols are known to be incompatible with **6** as a result of a presumed strong coordination of the soft sulfur atom to the ruthenium center, thus poisoning the catalyst. However catalysts **3** and **4a**, which contain strongly σ-donating NHC ligands, are less inclined to act as Lewis acids for chelation and were able to promote high-yielding enyne metathesis of propargyl thioesters in the presence of ethylene, whereas **6** proved relatively ineffective. The protection of the sulfur moiety as a less Lewis basic thioester was a key development, as sulfides (even those with large trityl protecting groups) gave minimal (ca. 10%) conversion even after a prolonged reaction time. Notably, self-metathesis of allylsulfides has been reported in the presence of catalyst **2**.[120] One interesting report has also appeared detailing the first examples of the use of selenocarbene NHC-containing complexes in ROM–CM.[121]

5. CM Applications in Solid-Phase Organic Synthesis

5.1. CM Reactions on a Solid Support

Since our initial reports[11,12] on the immobilization and CM reactions of olefins on solid supports, significant progress has been made. The main advantages associated with immobilizing an olefin substrate prior to CM, ROM–CM, or enyne metathesis are: 1) dimerization/oligomerization pathways are considerably less favorable, 2) the reaction can be driven to completion by using an excess of the other olefin substrates (the dimers of which can be removed by filtration), and 3) in many cases the required products can be cleaved from the resin after the reaction, and as such are available in relatively pure form for further use.

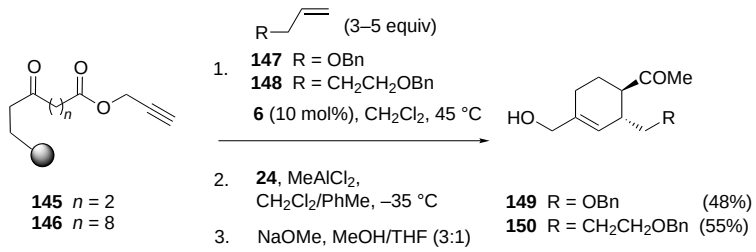
We found that enyne metathesis can be used to immobilize terminal alkynes on an allylsilylpolystyrene support.[122] Subsequent cleavage from the solid support through protodesilylation provided butadiene products (Scheme 33). Alkynated acetals, malonates, esters, acyrlates, protected amino acids, and carbohydrates are compatible with this methodology.



Scheme 33. Immobilization and functionalization by enyne metathesis (DVB = divinylbenzene, TFA = trifluoroacetic acid).

Of course the reverse mode of heterogeneous reactants is also feasible. For example, treatment of Merrifield-resin-bound alkyne **145** or **146** with alkenes **147** or **148** followed by Lewis acid catalyzed [4+2] cycloaddition with **24** gave **149** and **150**, respectively, in high purity after cleavage from the resin (Scheme 34).[123] An added advantage of this system is the isolation of a single diastereomer as a result of base-catalyzed equilibration of the Diels–Alder adduct during the cleavage step. A similar enyne-metathesis functionalization strategy led to a convenient modular synthesis of substituted octahydrobenzazapinones.[123]

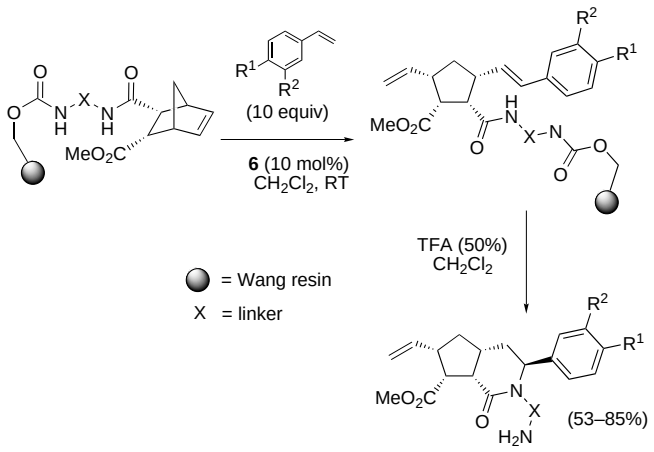
Barrett et al. have used ROM–CM to attach ROMP norbornene polymers to vinyl polystyrene. The resulting



Scheme 34. Enyne metathesis and Diels–Alder reaction on a Merrifield resin.

"ROMP-spheres" have distinct swelling properties, and functional diversity of the polymers is possible simply by varying the norbornene moiety.[124]

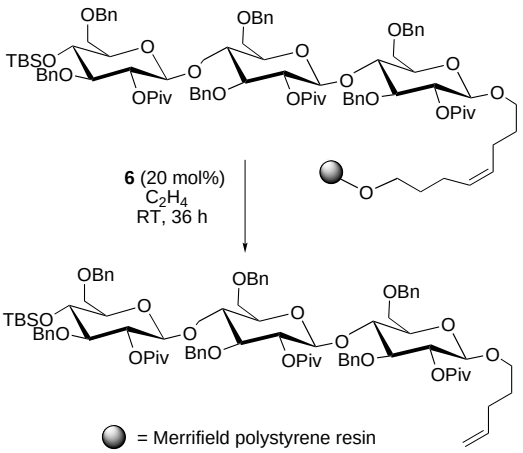
Cuny and co-workers have applied solid-phase ROM–CM of bicyclic alkenes with styrene derivatives to combinatorial library synthesis using resin-bound norbornenes.[125] In an interesting application, substituted norbornenes were subjected to ROM–CM conditions in the presence of substituted styrenes, followed by acid-induced cleavage from the resin with concurrent formation of a cyclopentene-fused piperidinone ring (Scheme 35).[126] The same group has also investigated the concept of resin capture, that is, attachment of the resin to the product of a ROM–CM reaction.[82]



Scheme 35. ROM–CM and cyclization on a solid support.

Seeberger and co-workers[127,128] developed a novel octenediol-based linker, which is cleaved by CM with ethylene gas promoted by **6**.[129] Successful application to the synthesis of saccharides was demonstrated, affording homoallylic polysaccharides (Scheme 36). In view of the mild metathesis conditions utilized for resin cleavage, this methodology should be useful in the solid-phase synthesis of biomolecules.[130]

Recently two reports have emerged detailing the exploitation of neighboring-group interactions on solid supports, allowing the synthesis of dimeric molecules by CM. In studies aimed toward the synthesis of macrocycles by RCM, Wareing and Tang[131] observed that the formation of oligomeric products from CM was dominant in the case of resin-bound large dienes, whereas only RCM was observed in analogous solution-phase chemistry. These counterintuitive results seemed to point towards intraresin CM reactions taking place between reactive groups that are not necessarily adjacent to one another on the resin but are nonetheless proximal as a result of nonlinearity and bending of the solid support. Setting out to achieve intersite CM, Schreiber and co-workers were able to generate dimeric pseudopeptides and a range of other symmetrical molecules by optimizing site–site interactions on highly loaded (1–2 $mmol\,g^{-1}$) lightly cross-linked (1% divinylbenzene) 500–600 μm polystyrene beads.[132]



Scheme 36. CM cleavage from a solid support (Piv = pivaloyl).

5.2. CM of Polymer-Supported Catalysts

As olefin metathesis quickly consolidates its position as a mild, practical, and versatile method for C–C bond formation, the demand for more efficient, more cost-effective, and more environmentally benign catalytic systems has increased. Given the wide scope of olefin metathesis for use in materials science, medicinal chemistry, and natural product synthesis, the development of catalysts that are both recyclable and capable of promoting efficient metathesis transformations without leaving behind significant levels of metal contaminants in the products is of particular importance.

In this regard, heterogeneous polymer-bound olefin-metathesis catalysts (Figure 16) have received considerable attention in recent years, the main reason being because they can be simply removed after reaction by filtration.

The first well-defined immobilized ruthenium alkylidene **151** was reported by Grubbs and Nguyen in 1995.[133] Although active and recyclable in metathesis reactions, this catalyst was considerably slower than its homogeneous analogue. Barrett and co-workers[134,135] devised a general CM-based immobilization strategy whereby the reaction between vinyl polystyrene (PS) and either **3** or **6** generates catalysts **152** or **153**, respectively. These catalysts (used at 2.5–5 mol% levels) were reasonably active in RCM reactions and could be recycled several times. As is unfortunately the case with most polymer-supported catalysts, no details of the activity of these catalysts in CM processes are known. Nolan

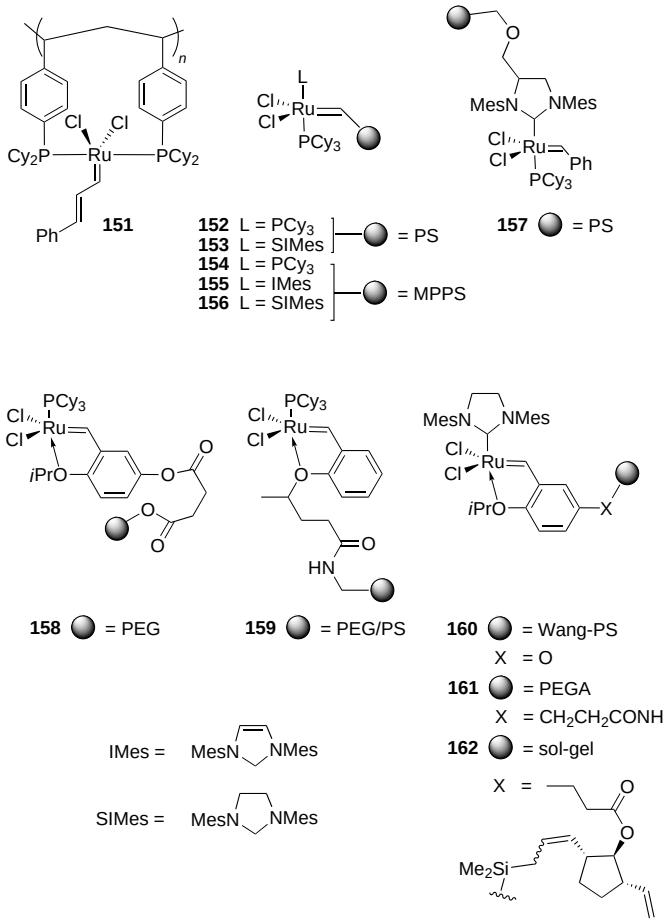


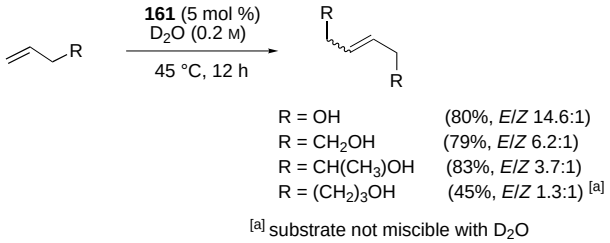
Figure 16. Immobilized olefin-metathesis catalysts.

and co-workers later prepared **154** and **155**, which were attached to macroporous polystyrene (MPPS) by the same CM methodology.[136,137] The advantage of this support (PS highly cross-linked with divinylbenzene) is that resin cavities are more spacious than those associated with PS, and so access to the substrate is easier and not as dependent on solvent swelling. Precatalysts **154** and **155** were suitable promoters for RCM, but performed poorly in the CM dimerization of styrene derivatives. The permanently immobilized recyclable catalyst **157**[138] has been shown to promote high-yielding enyne-metathesis reactions between terminal alkynes and allyltrimethylsilane.

Dowden and Savović[139] described the CM-based preparation of **159** (an immobilized analogue of **1**), which was the first immobilized catalyst to be active in nondegassed solvents under an air atmosphere. Again, RCM activity was reasonable and the catalyst recyclable, but the one CM reaction attempted gave poor results in a relatively unselective process.

To our knowledge, the only immobilized catalyst to have been both active and recyclable in CM reactions is **160**.[140] This polystyrene-bound analogue of **4a** catalyzed highly efficient and selective CM reactions with a range of electron-deficient alkenes. The cross-coupling of pent-1-enylbenzoate with **24** led to the formation of the CM product **34** (*E*/*Z* > 20:1) with quantitative conversion in each of five successive cycles.

In another exploitation of the high stability of NHC-based catalysts such as **4a**, catalyst **161**, which is bound to the highly hydrophilic polyacrylamide polyethylene glycol (PEGA) resin, catalyzed CM (self-metathesis) reactions in methanol or water.[141,142] Solvent degassing and reaction under an inert atmosphere are not required. Simple hydroxy-functionalized alkenes react well in D_2O (Scheme 37); however, acidic or



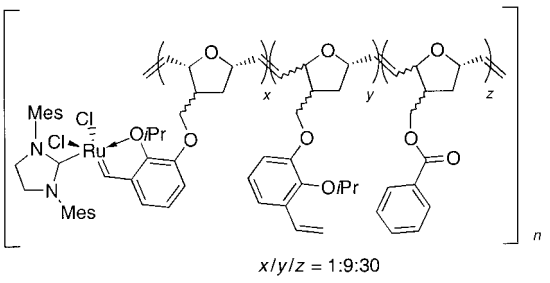
Scheme 37. CM dimerization in water.

electron-deficient substrates gave poorer results.[141] The use of the hydrophilic PEGA resin is critical. Control experiments demonstrated that a heterogeneous mixture of either **3** or **4a** in water gave no conversion of starting materials that undergo smooth reaction with **161**.[143] In our opinion, this indicates that the reactions between the hydrophobic methylidene propagating species and the metathesis substrates occur mostly in the resin pores (an area of relatively high precatalyst concentration), and not in the nucleophilic bulk solvent, where metathesis intermediates are quite unstable.[142]

Hoveyda and co-workers[144] reported that the immobilization of an appropriately substituted analogue of **4a** on porous monolithic[145] sol-gel glass affords a physically and chemically robust catalyst that is highly recyclable in RCM and ROM–CM reactions. In recyclability tests, catalyst **162** required extended reaction times to promote a RCM reaction to completion after four quantitative conversion cycles, which indicates the onset of significant catalyst decomposition. However, after the fourth cycle the same catalyst pellet was capable of catalyzing less-challenging ROM–CM reactions of norbornenes with various olefin partners with quantitative conversion for a further four cycles.[146] Furthermore, the products were often recovered in analytically pure form, and separation of the catalyst from the reaction mixture could be conveniently carried out with a Pasteur pipette. This novel and versatile catalyst was also shown to be highly effective in the synthesis of small libraries through various metathesis reactions.

Some of the major drawbacks associated with polymer-bound catalysts are that they often rely on commercially available resin supports, design of the linker and its attachment to the solid support can complicate catalyst synthesis, and most importantly, supported catalysts normally lag far behind their homogeneous counterparts in terms of activity. One promising way to circumvent the latter problem is to employ a catalyst-precipitation strategy, whereby one can aspire to prepare ruthenium alkylidenes with homogeneous reactivity profiles combined with a facile recovery method.

The first report involving this method detailed the preparation of homogeneous catalyst **158**, a version of **1** attached to a PEG chain, which could be precipitated with diethyl ether after metathesis.[147] Along the same lines we have recently developed catalyst **163** (Figure 17), which is prepared from simple starting materials in one pot through sequential ROMP and CM reactions.[148] This homogeneous catalyst is highly active (a maximum of 1 mol% is required) in a range of reactions, including ROM-CM, and displays unprecedented recyclability after precipitation from the reaction mixture by addition of either diethyl ether or hexane. The products from metathesis reactions involving these catalysts also contain unparalleled low ruthenium levels. Unfortunately, given the prevalence of internal olefin moieties in the polymer backbone, **163** is not highly active in CM reactions. Since **163** is assembled mostly by metathesis, it is not reliant on the commercial availability of resins, and polymer synthesis/resin loading are combined in a single operation. Further advantages of **163** are that it is also capable of a high degree of self-generation, it can be analyzed for alkylidene content by ^{1}H NMR spectroscopy, and it is suitable for structural modification of either the catalyst or the polymer backbone, thus providing scope for future fine tuning.



x/*y*/*z* = 1:9:30

163

Figure 17. ROMP-based catalyst **163**.

6. Summary and Outlook

Over the last 5 years, CM has begun to emerge from the shadow of RCM and ROMP to take its place as a powerful and mild method for the formation of C–C bonds. This is in no small part a consequence of the advent of highly active NHC-based ruthenium alkylidene catalysts, which allow the use of previously incompatible substrates with high chemo- and stereoselectivity. The realization that homodimers of one CM substrate can be used to induce selectivity in reactions in which an electronic or steric mismatch would otherwise make the reaction impossible is also very significant. As the volume of material published grows, we are beginning to understand more and more about the role that steric and electronic factors (and occasionally chelation) plays in the determination of both chemo- and particularly stereoselectivity on a case-by-case basis, although we clearly still have a lot more to learn and the scope for further research is considerable. What seems certain is that the era in which CM and related reactions were considered to be unselective and inefficient processes is at an end, and the tremendous increase in reports on the applicability of these reactions to all areas of organic chemistry research that we have recently witnessed looks set to continue.

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