Chemoselective olefin metathesis transformations mediated by ruthenium complexes

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Chemoselective Olefin Metathesis Transformations Mediated by Ruthenium Complexes

Steven P. Nolan*[a] and Hervé Clavier*[b]

Over the past decade, ruthenium-mediated metathesis transformations, including polymerization reactions, cross-metathesis, ring-closing metathesis, enyne metathesis, ring-rearrangement metathesis, and also tandem processes, represent one of the most 10 studied families of organic reactions. This has translated into the development of a large number of structurally diverse catalysts. Whereas, most of these investigations are focused on determining catalytic performance, only rare examples of studies dealing with chemoselectivity have been reported to date. Usually, variations are observed in product conversions but rarely in product distributions. Herein, we provide an overview of the 15 stereochemistry of newly formed C=C bond either in ring-closing or cross-metathesis as a function of the catalyst structure. A discussion of disparities encountered in macrocyclisation reactions leading (or not) to the formation of dimeric products is also presented. Since distinctive metathesis products could be isolated as a function of the ligand borne by the ruthenium centre – phosphine or N-heterocyclic carbene - in the 20 dissymetrization of trienes, enyne metathesis and ring rearrangements, these topics are also discussed.

1. Introduction

Olefin metathesis represents one of the most powerful and attractive tools in polymer science and organic synthesis for 25 the formation of carbon-carbon double bonds.[1] The spectacular improvements in this reaction achieved over the last two decades are quite familiar to most chemists since a number of these catalysts, able to perform a plethora of olefin metathesis reactions, are commercially available.[2] The 30 popularity of the method is also due to the numerous types of metathesis transformations that have been developed, for example, ring-closing metathesis (RCM),[3] enyne RCM,[4] cross metathesis (CM),[5] ring-rearrangement metathesis (RRM),[6] or ring-opening polymerization metathesis (ROMP).[7] Thus, with 35 the same metal-carbene complex, several reactions can be achieved depending on the substrates and reaction conditions. For these reasons, the development of catalytic systems, ever more active in metathesis transformations, is still a field of intensive research.[8] The rapid progresses in this area have 40 been punctuated by groundbreaking developments particularly focusing on well-defined ruthenium-carbene complexes, such as the highly tolerant to functional group ruthenium-benzylidene **Cat-1A** by Grubbs in 1995 (Figure 1).[9] In 1999, other ruthenium-alkylidene complexes were discovered: Ru-45 indenylidene[10] and Ru-isoproxybenzylidene,[11] namely the Hoveyda catalyst. At the same time, substitution of a tertiary phosphine by an *N*-heterocyclic carbene (NHC) ligand led to the emergence of second generation complexes displaying enhanced catalytic performances, catalysts such as **Cat-1B**[12] 50 and **Cat-1C**.[13] Since then, systematic derivatisation has been carried out on benzylidene-,[14] indenylidene-[15] and isopropoxybenzylidene-catalysts[16] playing on phosphine,[17]

NHC,[18] pyridine adducts,[19] or anionic ligands,[20] as well as the development of supported catalysts.[21] This has translated into 55 a large number of ruthenium-based complexes, which are occasionally compared to each other mainly in terms of efficiency.[22] Nonetheless, several reports have demonstrated that catalyst structure could also influence the distribution of metathesis products, i.e. the chemoselectivity.
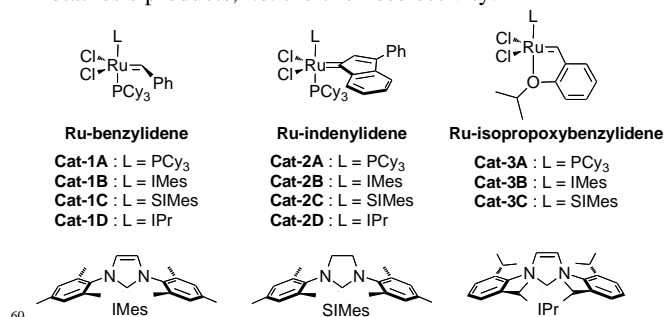

Figure 1 Most frequently encountered ruthenium complexes for metathesis transformations

Here, we propose to provide a critical overview of chemoselectivity in ring-closing metathesis of dienes and 65 enynes, ring-rearrangement metathesis and cross metathesis as a function of the catalyst employed. Even if reactivity differences are usually reported between 1st and 2nd generation complexes, several other parameters have proven to affect chemoselectivity. Of note, this review focuses on commonly 70 employed ruthenium-mediated olefin metathesis since tungsten- or molybdenum-based complexes are scarcely investigated. For the Reader's convenience, the structures of the most frequently encountered ruthenium catalysts are presented in Figure 1.

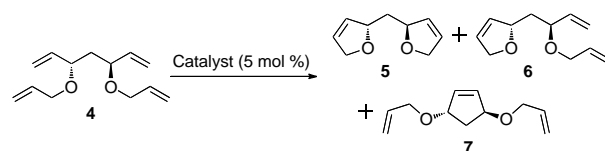## 2. Ring-Closing Metathesis of Alkenes

2.1. RCM of compounds with multiple C-C double bonds

Over the past few years, it has been demonstrated that RCM reactions involving more than two C-C multiple bonds presented interesting opportunities for the construction of functionalized heterocycles.[23] In 2000, Schmidt reported a rare example of comparison between benzylidene- and indenylidene-based catalysts for RCM of polyalkene substrate **1**.[24] Mediated by pre-catalyst **Cat-1A**, metathesis reaction led to the formation of the spiro product **2** in low yield due to the competition with intermolecular metathesis (Scheme 1). On the other hand, the 1st generation indenylidene complex **Cat-2A** was also evaluated; the double RCM sequence did not occur and only the dihydropyran **3** was isolated in poor yield. The formation of **3** can be explained by a succession of RCM reaction, sequential double bond isomerization, and then Claisen rearrangement. Unfortunately considering the low yields of **2** and **3**, this example is not entirely pertinent. Moreover, the reactivity of **1** was not investigated further and no details were given as to the cause of this difference in reaction behavior: the nature of the ruthenium complex or reaction conditions (temperature or solvent).
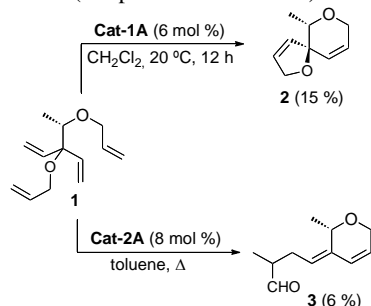
Scheme 1 Ring-closing metathesis of polyalkene **1** with indenylidene ruthenium-based catalysts

As a part of a reaction scope investigating novel polymer-supported ruthenium olefin metathesis catalysts, Nolan and co-workers have examined acyclic tetraenes such as **4** for the preparation of bicyclic compounds.[25] In addition to polymers, several products were obtained, resulting from competition between a single RCM affording cycloalkane **7** and two RCM steps leading to bis-heterocycle **5**; **6** coming from a mono RCM involving an O-allyl moiety (Scheme 2). Due to the reversibility of olefin metathesis, cycloalkene **7** can be converted into the more thermodynamically stable bicyclic compound **5**. Several complexes were used to carry out this study: **Cat-1A**, **Cat-1B**, **Cat-1C**, as well as their immobilized polymer-supported analogues. Unfortunately, these catalysts were tested under different reaction conditions (solvent and temperature), thus the differences observed in product distribution cannot be unambiguously attributed to the complex itself. Moreover, in the case of recycling, some chemodivergence has been noted between two consecutive runs, and could be explained by the loss of activity during the recycling process.

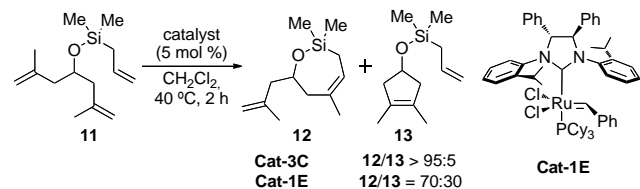**Scheme 2** Ring-closing metathesis of acyclic tetraene **4**

Taking advantage of the activity difference between catalysts, it has been possible to perform chemoselective metathesis transformation. Wallace investigated diastereoselective double RCM reaction exploiting the unique characteristics of the catalyst.[26] Treatment of tetraene **8** with Hoveyda-Grubbs catalyst **Cat-3C** led to ca. 50 % of the spirocyclic product **9** with only poor diastereoselectivity (Scheme 3). In spite of the use of ethylene, formation of significant amounts of by-products was observed due the high catalytic activity of **Cat-3C**. Conversely, the less active Ru-indenylidene complex **Cat-2A** gave cleanly and quantitatively the monocyclised product **10** with good diastereoselectivity (86% dr). The second RCM leading to the spiro compound **9** was achieved with the more active complex **Cat-3C**. Wallace reported as well an analogue example but involving a quadruple RCM for which the stereoselectivity depends of the catalyst used.[27]
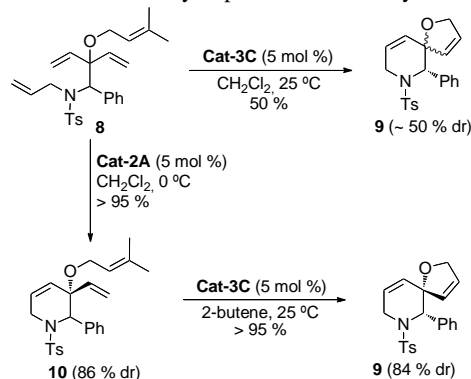
Scheme 3 Diastereoselective double ring-closing metathesis reaction

Dissymetrization of prochiral trienes is the most frequently encountered enantioselective metathesis reaction.[1e,28] During the course of a study aimed at designing and synthesizing new chiral NHC ligands for asymmetric ring-closing metathesis,[29] Grubbs and co-workers observed that RCM product distribution could be related to the structure of the NHC ligand (Scheme 4).[30] Usually, metathesis catalysts enable RCM between the most activated olefins, i.e. for which the steric hindrance is least important. Therefore, in the case of substrate **11**, catalysts such as **Cat-3C** formed only 7-membered ring **12**. The strategy for the chiral induction developed by Grubbs is based on a transfer of stereochemistry from the chirality of the backbone to the N-substituents of the NHC that are dissymmetric and sterically less bulky. **Cat-1E** bearing a less sterically hindered NHC catalyzed the RCM of **11**, however with this complex significant amount of the unfavored 5-membered ring **13** was observed. Less bulky NHC containing complexes are more reactive towards hindered C-C double bonds. From this observation, several catalysts have been developed for the formation of tetrasubstituted olefins by RCM[30,31] and tetrasubstituted C-C

double bond by CM.[32] This example clearly showed that the NHC congestion can influence the outcome of a metathesis transformation.

Scheme 4 Ring-closing metathesis: dissymetrisation of triene

2.2. Cyclisation versus dimerisation and oligomerisation

As often is the case in cyclisation processes, metathesis by-products such as dimers, oligomers and polymers are observed in significant amounts when the size of the targeted ring increases. Thermodynamically, the formation of 5- and 6-membered rings is greatly favored, however, for rings larger than 8, problems are encountered. Reaction mixtures in high dilution are generally used to circumvent the formation of these by-products. Although barely exploited, structure of the catalyst used can play a significant role. Recently, Percy surveyed the synthesis of difluorinated pentopyranose analogues involving the formation of 8-membered ring **15** by RCM.[33] Diene **14** was cyclised into **15** in good yield using 2nd generation Grubbs catalyst **Cat-1C** and Ti(O*i*Pr)$_4$ as co-catalyst (Scheme 5). On the other hand, when the indenylidene catalyst **Cat-2A** was used only traces of the expected product **15** (4%) were observed, mass balance accounting for noticeable quantities of dimer **16**. Unfortunately, in this case the reactivity difference between **Cat-1C** and **Cat-2A** is not clear as the role of the co-catalyst Ti(O*i*Pr)$_4$ has not been established.
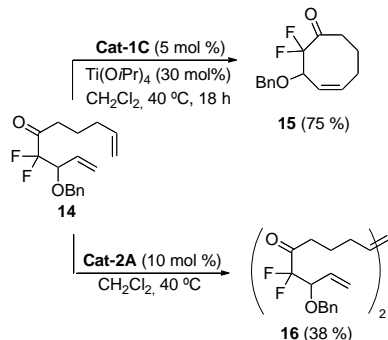

Scheme 5 Formation of 8-membered ring by RCM

A different example showed that 1st generation catalysts are more favourable to dimerisation than those bearing a NHC ligand. The macrocyclisation of trisubstituted diene **17** led to the formation of dimer **19** in the presence of catalyst **Cat-1A** (Table 1).[34] Thus the activity of (PCy$_3$)$_2$-containing complexes is related to the steric bulk of the substrate; whereas for RCM giving rise to small rings, trisubstituted dienes are tolerated and only RCM of disubstituted diene is possible for larger rings. Second generation complexes **Cat-1B**-**D** displayed superior reactivity and the 14-membered ring **18** was isolated in acceptable yields for all catalysts. Nonetheless, a study of the reaction profile demonstrated that **18** is not only obtained by direct RCM of **17** but **19** is also a reaction intermediate.

Table 1 Comparison of catalyst activity in macrocyclisation

Entry	Catalyst	Loading	18(%)	19 (%)
1	**Cat-1A**	10 mol %	-	79
2	**Cat-1B**	10 mol %	65	-
3	**Cat-1C**	6 mol %	57	-
4	**Cat-1D**	6 mol %	57	-

Subsequent to the development of 2nd generation catalyst **Cat-1C**, Grubbs investigated the performance of this catalyst in the formation of macrocyles and compared it to the 1st generation analogue **Cat-1A**.[35] Since **Cat-1A** is inactive toward α,β-unsaturated carbonyl compounds, treatment of ester **20** with **Cat-1A** gave only the homodimer **22** in 62 % isolated yield (Scheme 6). The formation of the expected 7-membered ring did not occur either with the NHC-containing catalyst **Cat-1C**. The higher activity of this complex allowed the formation of the "head-to-tail" dimer, which was further converted into the macrocycle **21** by RCM. It appears that the catalyst governs the macrocycle formation but also solvent and concentration have an effect. For example, with **Cat-1C**, at higher concentrations, the trimeric "head-to-tail" ring-closed product can be obtained. A similar example has been reported by Eustache.[36]
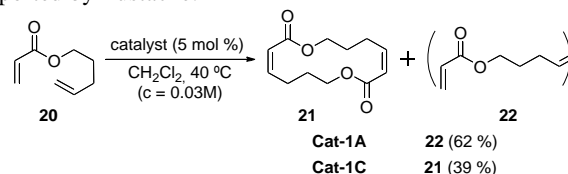

Scheme 6 Formation of macrocycle *via* dimerisation and RCM

2.3. *E/Z* Ratio in Macrocyclisation

Macrocycles are particularly common in antitumoral, antibiotic and antifungal compounds. Traditional strategies for their synthesis allowing for structure confirmation and pharmacomodulation involve intramolecular macrolactonisations, macrolactamisations or macroaldolisations. Alternatively, some approaches have employed RCM as a key step.[1d] As illustrated in Scheme 7, Fürstner and co-workers carried out the synthesis of Herbarumin I using a macro RCM as a key step.[37] The RCM of substrate **23** was achieved using benzylidene catalyst **Cat-1B** and the ruthenium-indenylidene **Cat-2A**. A catalytic amount of **Cat-2A** in refluxing DCM afforded the desired (*E*)-lactone **24** as the major product, only 9% of the (*Z*)-isomer was detected. The *E:Z* ratio being constant during the course of the reaction indicating that the formation of the thermodynamically less stable (*E*)-isomer results from kinetic control. On the other hand, the treatment of diene **23** with catalyst **Cat-1B**, bearing a NHC, leads to the selective formation of the *Z* isomer in excellent yield. In order to explain such a difference, the authors suggested that the (PCy$_3$)$_2$-containing catalysts afforded mainly the (*E*)-isomer

macrocycle, resulting from a kinetic control. However, the reversibility of the reaction and the superior activity of complexes bearing NHC led to the formation of the thermodynamically stable (*Z*)-macrocycle with the 2nd generation catalyst. To reach the end-game in this total synthesis, cleavage of acetal groups was performed by treatment with diluted aqueous HCl providing Herbarumin I (*E*)-**25**.
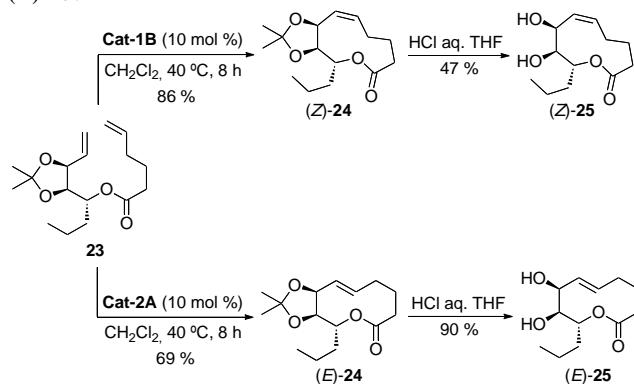
Scheme 7 Metathesis key-step for the synthesis of Herbarumin I **25**

For the synthesis of the 12-membered Salicylihalamide A, a macrocyclisation strategy has been employed using **Cat-1A** and **Cat-1C**.[38] In this case, the selectivity was significantly poorer, since both isomers were obtained with a *E*/*Z* ratio of ≈ 9:1 for 1st generation catalyst and ≈ 2:1 for 2nd generation. Recently, Matsuya and Nemoto investigated the formation of 12-membered Salicyclic macrolides *via* macro-RCM mediated by complexes **Cat-1A**, **Cat-1C**, and **Cat-3C**.[39] Unprotected diene **26** and protected-phenol such as the tert-butyldimetylsilyl ether **27** were used as substrates; results are summarized in Table 2. On both dienes, **Cat-1A** promoted the formation of the *E* isomer exclusively, respectively (*E*)-**28** and (*E*)-**29**. In contrast, when using 2nd generation catalysts **Cat-1C** and **Cat-3C**, both enantiomers were obtained with *E*/*Z* ratio ≈ 1:1 for product **28** and ≈ 5:1 for **29**, respectively. The authors also investigated the origin of the controlled RCM and suggested a slightly different explanation. Indeed, ^{1}H NMR spectroscopy studies revealed that the *E*/*Z* ratio was constant all along the course of the reaction with all catalysts used. More importantly, the interconversion between the *E* and *Z* isomers cannot occur since treatments of isolated isomers (*E*)-**28** and (*Z*)-**28** with catalysts **Cat-1A** and **Cat-1C** did not result in any product redistribution. Therefore, it has been proposed that this macro-RCM takes place purely under kinetic control and the relative stabilities of *E* and *Z* isomers are not involved. However, the stereochemical results would depend on the stabilities of the ruthenacycle intermediates and the difference of rate-determining steps between 1st and 2nd generation catalysts. The formation of the ruthenacycle would be the rate-determining step for phosphine-containing catalysts whereas for those bearing an NHC, it is likely its cleavage. Moreover, as the *trans*-ruthenacycle is more stable that its *cis*-counterpart, 1st generation catalyst give only the more stable intermediate providing the *E*-macrocycle. On the other hand, with 2nd generation complex both intermediates are in an equilibrium that is displaced as a function of relative

facility of ruthenacycle cleavage leading to the *E*/*Z* ratio.

Table 2 Products and yields of RCM for the synthesis of 12-membered Salicylic macrolides

| | | | 26 (R = H) | (*Z*)-28 (R = H) | (*E*)-28 (R = H) |
| | | | 27 (R = TBS) | (*Z*)-29 (R = TBS) | (*E*)-29 (R = TBS) |

Entry	Substrate	Catalyst	Yield of (*Z*) (%)	Yield of (*E*) (%)
1	**26**	**Cat-1A**	0	64
2	**26**	**Cat-1C**	16	21
3	**26**	**Cat-3C**	11	10
4	**27**	**Cat-1A**	0	47
5	**27**	**Cat-1C**	6	35
6	**27**	**Cat-3C**	6	30

2.4. The effect of the alkylidene moiety

Recently, Fürstner reported the synthesis of 11-membered biaryl lactones of the aspercyclide family.[40] One of the approaches leading to the structural core made use of a metathesis step. Nonetheless, the ring-closure was found difficult and stoichiometric amounts of ruthenium catalysts were required. **Cat-1B** and **Cat-3C** afforded **32** as major product by cross metathesis between the less hindered alkene in **30** with the benzylidene unit of the ruthenium complex while leading to only small quantities of the cyclised compound **31** (Scheme 8). In order to avoid this alkylidene transfer, indenylidene-based catalyst **Cat-2A** was used leading exclusively to the formation of **31** in moderate yield. Compared to the benzylidene, the indenylidene with a α,α-disubstitution is sterically more hindered which disallows the cross metathesis process. Of note, it would have been interesting to test 2nd generation indenylidene catalysts that have been proven to be more tolerant of harsher reaction conditions.[15b]

|	
Cat-1B	**31** (4 %) - **32** (72 %)
Cat-3C	**31** (14 %) - **32** (33 %)
Cat-2A	**31** (43 %)
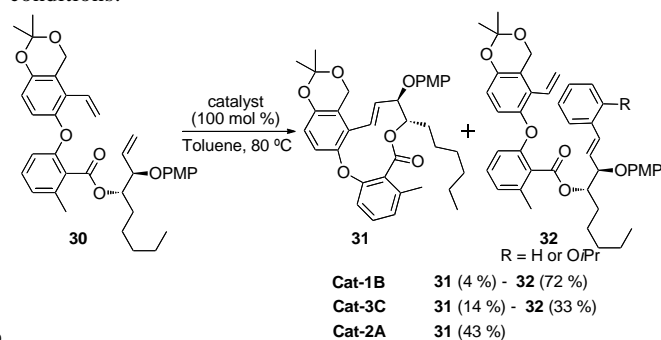
**Scheme 8** Synthesis of aspercyclides by metathesis

3. Ring-Closing Metathesis of Enynes

Enyne metathesis involves the bond reorganization of an alkyne and an alkene to afford a 1,3-diene.[4] Enyne metathesis is an atom-economical process driven by the formation of thermodynamically stable conjugated diene that has demonstrated its utility in the context of biologically relevant

compounds. However the main problem associated with this transformation is the possible formation of *endo* and *exo* products.[41] *Exo* products are generally exclusively obtained, nevertheless in some cases *endo* analogues are formed. Mori *et al.* were the first to report the formation of *endo*-cyclized rings.[42] Whereas no reaction occurred using 1st generation catalyst **Cat-1A** on the hindered enyne **33**, both 5- and 6-membered rings **34** and **35** were isolated in approximately similar amounts with 2nd generation complex **Cat-1C** (Scheme 9). Mori observed that *endo* product formation takes place uniquely when the C-C double bond is sterically hindered. Mechanistically, Ru-alkenylidene active species react on the more reactive C-C double bond affording *exo* products through *α,β*-metallacyclobutene **IV**,[43] however when it is not possible due the steric hindrance, approach of the alkyne can be *cis* or *trans* leading to respectively *α*– and *β*-metallacyclobutene yielding to *endo* and *exo* isomers (Scheme 10).[41] Moreover Mori noticed small amounts of cyclopropane-containing compounds resulting from a reductive elimination of the ruthenacyclobutane intermediates.
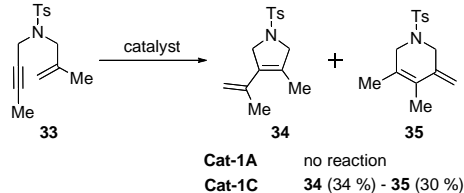
**Scheme 9** Ring-closing metathesis of enyne
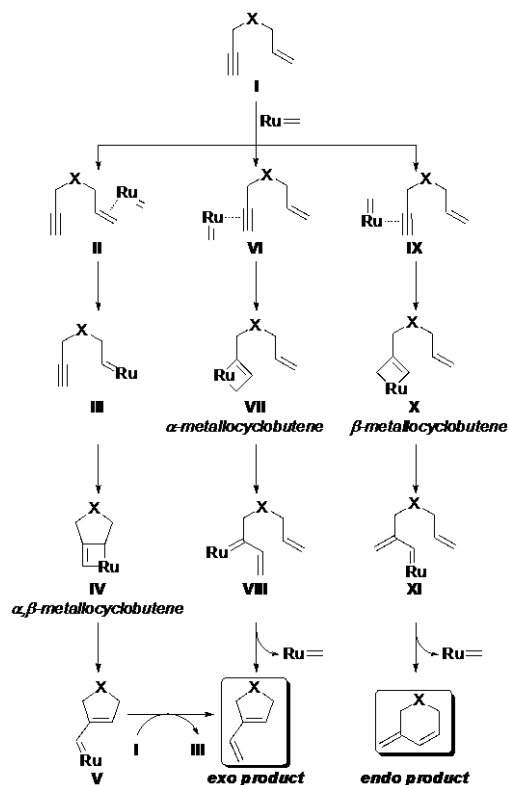
**Scheme 10** Reaction pathways in Ring-closing metathesis of enyne

In the course of a study involving a latter generation catalyst, Grela observed the formation of unexpected products in enyne

RCM as a function of the Ru-complex used.[44] As a consequence, the pioneering work of Mori was further elaborated in order to examine the influence of the catalyst.[45] It was already reported that RCM of enyne **36** mediated by 1st generation catalyst **Cat-1A** gave only the 5-membered ring **37**,[42] this was also the case with 1st generation Hoveyda and Grela catalysts, respectively **Cat-3A** and **Cat-4A** (entries 1 and 2, Table 3). On the other hand, using their congeners bearing a NHC ligand, small but significant amounts of *endo* cyclized product **38** were isolated, particularly with **Cat-4C** (entries 3-5). Of note, minor quantities of cyclopropane derivative **39** were equally detected when 2nd generation catalysts were employed.

Table 3 Products distribution for RCM of enyne **36**
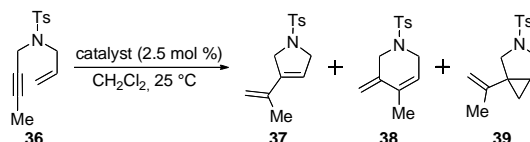
Entry	Catalyst	Yield (%)	Products ratio (%)		
			37	**38**	**39**
1	**Cat-3A**	89	100	-	-
2	**Cat-4A**	92	100	-	-
3	**Cat-1C**	72	94	5	1
4	**Cat-3C**	59	87	7	4
5	**Cat-4C**	87	83	14	3
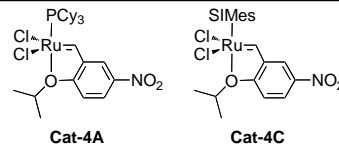
A similar example has been described for the synthesis of carbohydrate derivatives using an enyne RCM methodology.[46] As depicted in Scheme 11, treatment of enyne **40** with 1st generation catalyst **Cat-1A** afforded the 5-membered diene **41** in moderate yield with traces of its dimer **43**. When **Cat-1C** was employed in the same reaction, **41** was still the major product with also traces of **43**, but 25 % of 6-membered ring *endo* product **42** was also isolated. In this case, the C-C double is not directly hindered, but the benzyloxy function in the allyl position should contribute to its lower reactivity.

Cat-1A (30 mol %, 96 h)   **41** (38 %) - **43** (5 %)
Cat-1C (15 mol %, 30 h)   **41** (40 %) - **42** (25 %) - **43** (5 %)
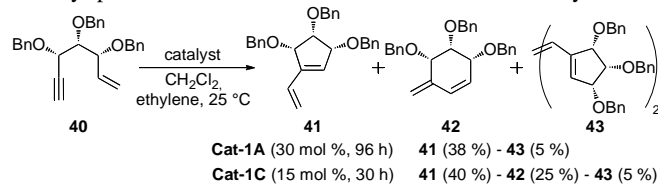
Scheme 11 Carbohydrate derivatives synthesis by enyne RCM

Of note, these issues of chemoselectivity have also been pointed out with molybdenum-type catalysts. Recently, Hoveyda reported the synthesis of a new molybdenum-based catalyst **Cat-Mo** that gave selectively the *endo* cyclised product even when no steric congestion is present on the alkene moiety.[47] More interestingly, in the case of competition between thermodynamically favored 6- and unfavoured 7-membered rings, the 7-membered ring *endo* isomer was exclusively obtained.
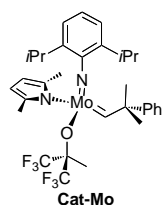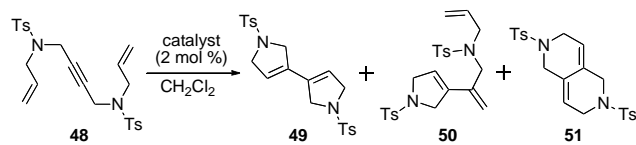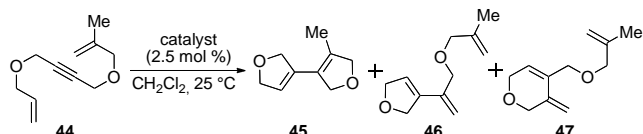
Cat-Mo

To confirm results obtained with enyne **36**, Grela and Sashuk studied the cascade enyne RCM of linear dienyne (Table 4).[45] With complexes **Cat-3A** and **Cat-4A**, the dihydrofuran derivative **46** was isolated as the main product together with small amounts of bisdihydrofuran **45** (entries 1 and 2). The presence of a methyl group on one of the alkenes hindered the second RCM with less active phosphine-containing catalysts. This did not occur with **Cat-3C** and **Cat-4C**, since no dihydrofuran **46** was obtained; but quantities of bicyclic compound **45** were still low (entries 3 and 4). The 6-membered heterocycle **47**, issue from *endo* cyclisation, was also observed in low yields. According to results presented in tables 3 and 4, the nitro-activated version of Hoveyda-Grubbs catalyst **Cat-4C** shows a better performance in the formation of *endo* cyclised products.
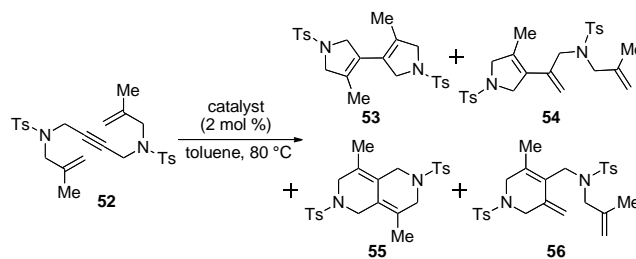
Table 4 Cascade enyne RCM of dienyne **44**

Entry	Catalyst	45 (%)	46 (%)	47 (%)
1	**Cat-3A**	3	64	-
2	**Cat-4A**	12	29	-
3	**Cat-3C**	23	-	14
4	**Cat-4C**	14	-	25

During the investigation of the reaction scope of Ru-indenylidene complexes,[15b] Clavier and Nolan observed also the formation of *endo* products, which were investigated as a function of the L ligand borne on the active catalytic species.[48] Dienyne **48** was selected as the model substrate (Table 5). The 1st generation indenylidene catalyst **Cat-2A** gave cleanly the bisheterocycle **49** (entry 1). With IMes-containing complex **Cat-2B, 49** was found to be the only product formed, but when the reaction conversion was improved, a small amount of dihydropyrrole **50** was observed as was the case for **Cat-2D** bearing the more sterically demanding IPr (entries 2 and 4). Using a different NHC: SIMes in **Cat-2C**, the by-product was found to be hexahydro-2,6-naphthyridine **51**. Unexpectedly, a minute variation of the NHC ligand, as in the saturation of its backbone, allowed for the formation of an *endo* 6-membered ring. Of note, another product was obtained with a phosphabicyclononane-containing indenylidene complex but could not be identified.[49]

Table 5 RCM of tosylamine-containing dienyne **48**

Entry	Catalyst	Conditions	49 (%)	50 (%)	51 (%)
1	**Cat-2A**	25 °C, 0.5 h	88	-	-
2	**Cat-2B**	40 °C, 5 h	51	-	-
3	**Cat-2C**	40 °C, 2 h	75	-	19
4	**Cat-2D**	40 °C, 2 h	81	13	-

When the more hindered dienyne **52** was employed in order to obtain single-crystal for X-ray analysis allowing for structure confirmation of products **53**-**56**, **Cat-2A** was found inefficient (Table 6, entry 1). **Cat-2B** and **Cat-2D** led to the formation products **53** and **54** with a 5-membered ring core (entries 2 and 4). In sharp contrast, catalyst **Cat-2C** gave compounds **55** and **56** issue from *endo* cyclization (entry 3). Through experimental and DFT calculations, information on the mechanism supports the co-existence of ene-then-yne and yne-then-ene reaction pathways. The 1st generation catalysts react according to the ene-then-yne pathway giving rise to exclusively *exo* cyclized products. Complexes bearing an NHC can follow both pathways as a function of the steric hindrance of C-C double and triple bonds. When the alkene is accessible and the alkyne congested, the ene-then-yne pathway is dominant. In the opposite case, the yne-then-ene pathway seems to prevail but all products can be formed. DFT calculations showed that for NHC = SIMes, the *endo* cyclization is favorable, whereas for IPr *exo* cyclizations is slightly privileged. In all the previous examples, the formation of *endo* occurs only when SIMes-complexes are employed, this seems to be a general trend.

**Table 6** Cascade dienyne RCM of **52**

Entry	Catalyst	53 (%)	54 (%)	55 (%)	56 (%)
1	**Cat-2A**	-	-	-	-
2	**Cat-2B**	67	13	-	-
3	**Cat-2C**	-	-	19	78
4	**Cat-2D**	19	45	-	-

The reactivity of other types of dienynes has also been investigated. For example, Hanna *et al.* were interested in the construction of polyoxygenated bicyclic moieties through dienyne RCM.[50] While the more active 2nd generation catalyst **Cat-1C** was able to complete the metathesis sequence affording the bicyclic compound **59** in quantitative yield, treatment of dienyne **57** with **Cat-1A** under these reaction conditions gave rise to the monocyclic product **58** (Scheme 12). This is a representative example of the difference in RCM

activity of complexes **Cat-1A** and **Cat-1C**.
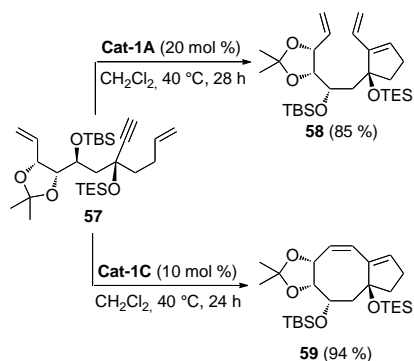
Scheme 12 Construction of polyoxygenated bicyclic compounds via dienyne metathesis

Lui and co-workers have also investigated the dienyne ring-closing metathesis as a methodology leading to the formation of oxygen-containing bicyclic systems.[51] Among the substrates examined, dienyne **60** is of interest since numerous products are formed as a function of the catalyst used (Scheme 13). Both complexes **Cat-1A** and **Cat-1C** displayed a good activity leading to the formation of dioxabicyclo[4.4.0]decane **61** as major product, resulting from an *endo* cyclization. Nonetheless, 5-membered ring-based compounds were obtained as byproducts. **63** was isolated with the less competent **Cat-1A**, while **Cat-1C** was efficient in performing the second RCM affording dioxabicyclo[5.3.0]decane **62**.
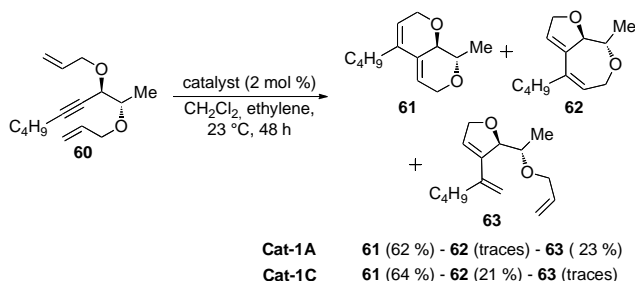
Scheme 13 Dienyne RCM for the synthesis of oxygen-containing bicyclic products

For the total synthesis of (+)-β-Erythroidine, a strategy involving a RCM step of ene-yne was put into action.[52] During the course of this study, an intriguing example of chemoselectivity was illustrated (Scheme 14). As a function of the catalyst employed and/or the configuration of the chiral centre in position 12 of the substrate **64**, the outcome of the dienyne RCM was completely different. Treatment of (*S*)-**64** with **Cat-1A** gave only bicyclic compound **65** coming from the RCM with the C-C double bonds and no involvement of the alkyne. On the other hand, **Cat-1C** catalyzed the metathesis of (*R*)-**64** with participation of all unsaturated bonds affording the tricycle **66** in good yield with no traces of **65**. Unfortunately, no crossover experiments have been reported so far to determine if the complex used or the 12C configuration was responsible for such dissimilarity in reactivity. The configuration of carbon 12 seems to be far

enough to not influence dienyne RCM transformation, but it cannot be unequivocally discounted.
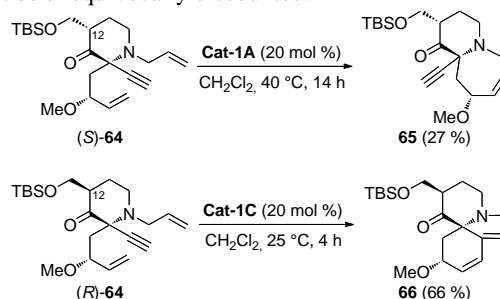
**Scheme 14** Synthesis of (+)-β-Erythroidine analogues via enyne RCM

A similar example described the construction of taxosteroids by dieyne RCM methodology.[53] Recently Movassaghi noticed some differences in product distribution of a dienyne RCM key step in the synthesis of an antitumor Illudins core.[54]

Olefin metathesis was also investigated to accomplish simultaneous or sequential processes known as tandem reactions.[55] In this context, Snapper *et al.* reported the tandem enyne metathesis - cyclopropanation sequences.[56] Successfully, in the presence of the bisphosphine catalyst **Cat-1A**, alkenyl cyclopropane **68** was obtained from enyne **67** and diazoester (Scheme 15). Cyclopropanation took place mostly exclusively at the less hindered double bond. Attempts to use the SIMes–Ru complex **Cat-1C**, in the same process failed; in this case the superior activity of the catalyst led to a second cross metathesis step after the enyne metathesis yielding to triene **69**. Of note, this is one of the rare examples of additional cross metathesis in enyne metathesis.
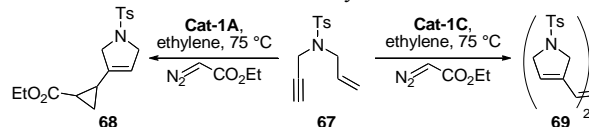
Scheme 15 Tandem enyne metathesis - cyclopropanation

During the course of a study aiming to synthesise functionalized fused oxazepine frameworks via a enyne RCM step, the formation of an expected product was observed.[57] As depicted in Scheme 16, the treatment of enyne **70** with NHC-containing ruthenium catalyst **Cat-1C** gave rise to dihydropyridine **72**, resulting from elimination of propargyl alcohol as the unique product. Surprisingly, in spite of much reaction conditions optimisation, **Cat-1C** was not able to promote the ring-closure. Alternatively, under the same reaction conditions, first-generation complex **Cat-1A** reacted with **70** to yield the desired pyrido[2,1-*b*]- [1,3]oxazepine **71**. Variation of reaction conditions affected the **71**/**72** ratio and the RCM carried out at room temperature and under ethylene atmosphere using 10 mol % of **Cat-1A** led to the formation of **71** as single product (90 % yield).
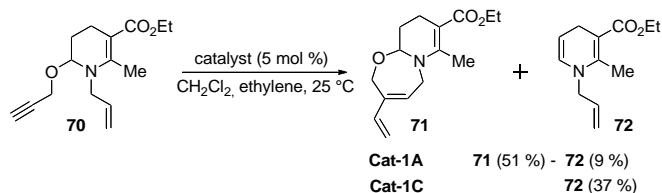
Scheme 16 Synthesis of fused oxazepine analogues by enyne RCM

4. Ring-Rearrangement Metathesis

Ring-Rearrangement metathesis is defined as a combination of metathesis reactions carried out in one pot – domino reactions - which involve generally ring-opening metathesis (ROM), RCM and/or cross metathesis.[6] Combinations of several metathesis steps involving C-C double or triple bonds allow for the straightforward construction of complex scaffolds.

4.1. Ring-rearrangement metathesis involving C-C double bonds

One of the most interesting chemoselective RRM was described in 2004 by Holtsclaw and Koreeda and deals with the synthesis of cyclopenta- and cyclohexa[*c*]indenes.[58] As depicted in Scheme 17, treatment of the homoallyl-tethered enone **73** with (PCy₃)₂-containing catalyst **Cat-1A** gave smoothly and quantitatively the tricyclic enone **74**. When the same reaction was conducted with 2nd generation catalysts **Cat-1C** and **Cat-3C**, a significant amount of spirocycloheptenone **75** was obtained (ca. 20 %). Interestingly, whereas the conversion of **74** into **75** was found to be impossible, reaction of **75** with **Cat-1C** gave cleanly the cyclohexa[*c*]indene system **74** and showed the higher thermodynamic stability of **74**. This raises the question of why usually superior performing complexes, (bearing a NHC ligand) were not able to reach reaction completion where Grubbs I **Cat-1A** could. Surprisingly, the same metathesis transformation performed on **76**, the methylated counterpart of **73**, led to the formation of tricyclic enone **74** with **Cat-1A**, but with **Cat-1C** the spiro compound **75** was now the major product (Scheme 18). RRM of allyl-tethered enone leading to cyclopenta[*c*]indene derivatives also exhibited some chemoselectivity but parameters governing this reactivity remain unclear.
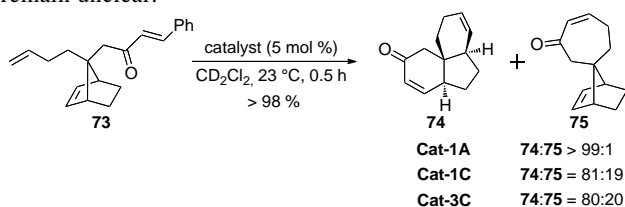

**Scheme 17** RRM of norbornene derivative
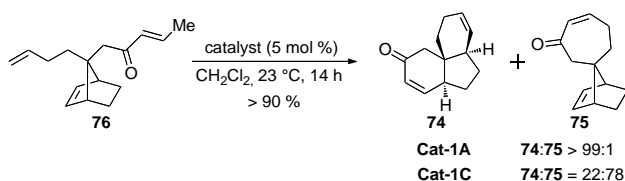
Scheme 18 RRM of norbornene derivative

When treated with 1st or 2nd generation Grubbs catalysts, cyclopentene **77** afforded **78** and **79** with very differents ratios (Scheme 19).[59] The authors suggested that the RRM leading to the fused bicyclic product **78** takes place under thermodynamic control whereas **79** results from the simple RCM reaction affording the kinetically controlled product **79**.
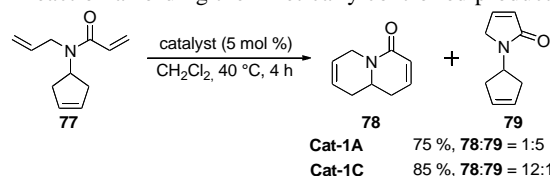
Scheme 19 RRM of cyclopentene derivative

Metathesis reaction of the *N*,*N*'-diallyl-*N*,*N*'-bis-tosyl cis-diamine **80** in the presence of catalyst **Cat-1A** bearing tricyclohexylphosphine formed exclusively the 6,8-fused bicycle **81** by simple RCM reaction (Scheme 20).[60] The same reaction carried out under ethylene atmosphere also gave **81** as the single product. Alternatively, when 2nd generation catalyst **Cat-1C** was employed, a second product was formed in significant amounts and was identified as the bis-dihydropyrrolidine **82**. Compound **82** results formally from a ring-opening metathesis followed by RCM. Under ethylene atmosphere, the reaction proceeded much more slowly but the **81**/**82** ratio was found to be the same. Regrettably, the transformation of **81** into bis-dihydropyrrolidine **82** was not attempted. This would had provided mechanistic information as to whether RCM yielding **81** and ROM leading to **82** were competing or if the higher activity of 2nd generation catalysts allows for the formation of the presumably more stable compound **82** from **81**. In the last case, the RRM mechanism would be different than the expected tandem ROM/RCM.
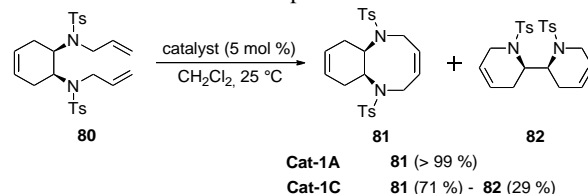
Scheme 20 RRM of cyclohexene derivative

4.2. Ring-rearrangement metathesis involving C-C triple bonds

Metathesis transformations involving a C-C triple bond are generally conducted under ethylene atmosphere, due to a improved stability of the active species in the presence of ethylene gas.[61] However, ethylene can also be a reagent and as shown in Scheme 21 react with C-C triple bonds.[62] When cyclohexen-yne **83** and catalyst **Cat-1A** were stirred at room temperature in dichloromethane under an atmosphere of ethylene only 1,3-diene **84** was isolated as product of ethylene cross enyne metathesis. This example illustrates the lack of activity of 1st generation catalyst toward cyclic C-C double bonds, as previously mentioned (Scheme 21). When **83** was treated with **Cat-1C** under the same conditions, **84** was not observed and 3 other products were isolated. The 16-membered ring compound **87** resulting from RRM/dimerization process was found to be the major product.

Its monomer **86** and RRM/isomerization/RCM product **85** were obtained is small quantities.
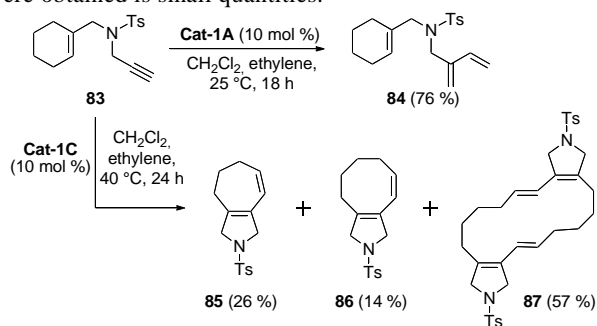
Scheme 21 ROM-RCM sequence of cyclohexen-yne

Having established that treatment of norbornene derivative **88** by **Cat-1C** yielded a complex mixture of products, Spring tested the less reactive 1st generation complex **Cat-1A** (Scheme 22).[63] This catalyst permitted the formation of the ring-opened compound **89**, in a reaction with ethylene, in moderate isolated yield but with only traces of by-products – only **90** was observed. Then a second step, a metathesis mediated by 2nd generation catalyst **Cat-1C** afforded the bicycle compounds **91** with again **90** as by-product but in small amounts. This strategy exploits the activity difference between both catalyst generations in order to minimize formation of unwanted by-products; nevertheless the development of task specific catalysts would be beneficial for sustainable chemistry. Of note is a related example of diversity-oriented synthesis in metathesis that was reported by North and co-workers.[64]
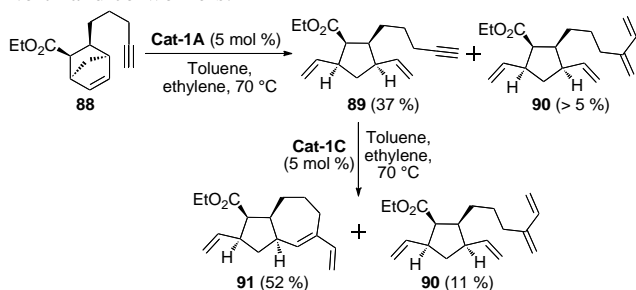

Scheme 22 ROM-RCM sequence of cyclohexen-yne

5. Cross Metathesis

Despite a clearly important potential, the intermolecular variant of metathesis, namely cross metathesis, was neglected in the 90's. However, with the development of new ruthenium-based complexes exhibiting improved efficiency and tolerance to functional groups, the interest in this transformation has tremendously increased. Perfect reaction selectivity using this methodology, such as the control of the E/Z selectivity, remains a goal yet unreached.[5] For instance, the self metathesis of oleochemicals is of considerable interest for the conversion of low value feedstock into useful chemicals in petrochemistry and polymerization.[65]

Recently, Stockman and co-workers investigated the simultaneous elongation of a symmetrical substrate in two directions by cross-metathesis.[66] For example, CM between diene **92** and 6 equivalents of ethyl acrylate was performed

using **Cat-1B** and **Cat-3B**[67] (Scheme 23). Whereas Hoveyda-type catalyst **Cat-3B** displayed good activity and gave in excellent yield the dihomologated product **94**, **Cat-1B** failed reach completion and mono CM product **93** was obtained as the major product. Considering the long reaction time required for this reaction, the superior stability of **Cat-3B** is a significant advantage.
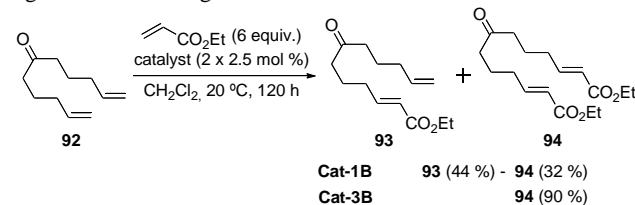
Scheme 23 Two-directional cross metathesis

In spite of the relevance of the E/Z control in CM, newly synthesized catalysts are not systematically tested and only a few reports present a thorough comparison of E/Z ratio as a function of the catalyst used. Nevertheless, it has been shown that the active sites in metathesis could be characterized through the reaction stereoselectivity at low conversion.[68] In 2009, Thieuleux reported, using several complexes, the self-metathesis of ethyl oleate **95** affording 9-octadecene **96** and diethyl 1,18-octadec-9-enedioate **97**, which may be valuable for materials applications (Table 7).[69] Conversions only reach 50 % due to the presence of a thermodynamic equilibrium; the reversible reaction or unproductive metathesis leads to the formation of the E-isomer of the ethyl oleate, i.e. ethyl aleidate. Therefore, E/Z ratio must be determined at an early stage of the transformation and then can be extrapolated for the equilibrium as presented in the Table 7. Results showed a clear difference between 1st- (**Cat-1A**, **Cat-2A**, and **Cat-3A**) and 2nd-generation catalysts (**Cat-1B**, **Cat-1C**, and **Cat-3C**) with respective E/Z ratios ≈ 3.5:1 and 2.5:1 for both products **96** and **97**. It seems that the saturation or unsaturation of NHC backbone does not play a role in the selectivity (entries 4 and 5). These results are in line of those for macrocyclisation, which, in a way, can be linked to cross metathesis. The better performance of NHC-containing catalysts allows for olefin approach to the ruthenium-alkylidene in *syn* or *anti* manner and consequently displays a lower E/Z stereoselectivity.

Table 7 E/Z selectivity in cross metathesis of ethyl oleate

Entry	Catalyst	E/Z **96**[a]	E/Z **97**[a]
1	**Cat-1A**	2.7 (3.6)	3.0 (3.4)
2	**Cat-2A**	3.2 (3.5)	2.7 (3.4)
3	**Cat-3A**	3.2 (3.5)	3.2 (3.5)
4	**Cat-1B**	1.7 (2.6)	2.6 (2.6)
5	**Cat-1C**	1.5 (2.5)	1.7 (2.7)
6	**Cat-3C**	1.6 (2.3)	2.0 (2.5)

[a] Ratio determined at an early stage of the reaction; values in parantheses are extrapoled for the equilibrium.

Another representative example was reported by Grubbs.[70] The CM reaction between allylbenzene **98** and **99** afforded the CM product **100** in good yield but a moderate to good stereoselectivity as a function of the catalyst used (Scheme

24). With **Cat-1C**, the selectivity is largely in favor of the thermodynamically more stable *trans* isomer due to the higher activity of this complex which facilitates the *cis/trans* isomerization by a secondary metathesis process.

98 (1 equiv.)   **99** (2 equiv.)   catalyst (3 mol %), CH₂Cl₂, 40 °C, 12 h   **100** (80 %)

Cat-1A *E/Z* = 3.2:1
Cat-1C *E/Z* = 7:1
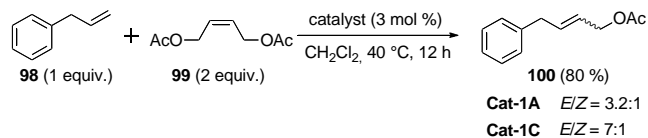
Scheme 24 Representative example of *E/Z* selectivity in CM

Cross metathesis involving acrylonitrile as reaction partner is one of the rare examples leading to mostly the *Z* isomer. Grubbs and co-workers evaluated several ruthenium-complexes in the reaction of acrylonitrile with allylbenzene **98**.[71] Tests were performed in dichloromethane at 40 °C for 12 h using 2.5 mol % of catalyst; yields and selectivities were found to vary as a function of the complex used (Table 6). Whereas Grubbs II **Cat-1C** gave **101** in poor yield with *E/Z* ratio = 1:1.7 (entry 1), its Hoveyda analogue **Cat-3C** and its 3-bromopyridine counterpart **Cat-5C** were found much more efficient but of equivalent stereoselectivity (entries 2 and 5). The 2nd generation catalyst bearing triphenylphenyl phosphine **Cat-5A** showed a better *E/Z* ratio = 1:4 (entry 3) and, in contrast, substitution of phosphine ligand by two pyridines **Cat-5B** gave a *E/Z* selectivity close to 1:1 (entry 4). These examples support the unexpected non-innocent role of released ancillary ligands on metathesis selectivity.

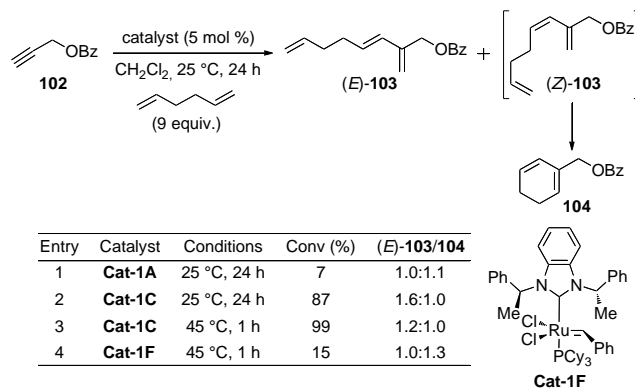**Table 8** Yields and *E/Z* ratios for CM between allylbenzene and acrylonitrile

98 (2.5 equiv.)   (1 equiv.)   catalyst (2.5 mol %), CH₂Cl₂, 40 °C, 12 h   **101**
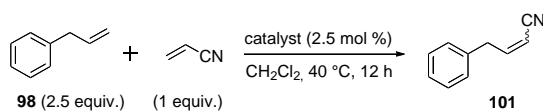
Entry	Catalyst	Yield (%)	*E/Z* **101**
1	**Cat-1C**	21	1:1.7
2	**Cat-3C**	68	1:1.9
3	**Cat-5A**	35	1:4
4	**Cat-5B**	26	1:1.2
5	**Cat-5C**	67	1:1.8

Cat-5A   **Cat-5B**   **Cat-5C**
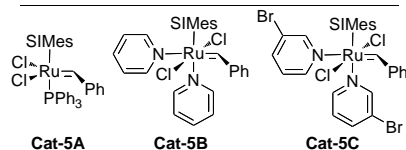
Cross metathesis between alkyne and alkene was also studied using several catalysts.[72] In the particular case depicted in Table 9, the *E* isomer (*E*)-**103** was easily isolated when (*Z*)-**103** further reacted to yield **104** by RCM. Thus, the *E/Z* ratio of the enyne cross metathesis can be determined in a straightforward manner by the (*E*)-**103**/**104** ratio. Usually the major product is the thermodynamically more stable *E* isomer, however the further RCM of the *Z* isomer favors its formation. The activity of **Cat-1A** was found very low with a *E/Z* ratio close to 1 (entry 1), whereas the more competent **Cat-1C** formed principally the *E* isomer at room temperature (entry 2); at higher temperature (*E*)-**103** was still the major product but the ratio varied slightly (entry 3). The chiral

benzimidazolylidene catalyst **Cat-1F** was also tested showing lower performance and an *E/Z* ratio slightly in favor of the Z isomer (entry 4). Similarly to common cross metathesis presented above, the nature of the catalyst can influence the selectivity of the reaction but differences reported to date are minute.

Table 9 *E/Z* ratios Enyne cross metathesis

102   catalyst (5 mol %), CH₂Cl₂, 25 °C, 24 h   (*E*)-**103**   (*Z*)-**103**

(9 equiv.)   **104**

Cat-1F

Entry	Catalyst	Conditions	Conv (%)	(*E*)-**103**/**104**
1	**Cat-1A**	25 °C, 24 h	7	1.0:1.1
2	**Cat-1C**	25 °C, 24 h	87	1.6:1.0
3	**Cat-1C**	45 °C, 1 h	99	1.2:1.0
4	**Cat-1F**	45 °C, 1 h	15	1.0:1.3

6. Concluding Remarks

Two decades after the first reports on ruthenium-mediated olefin metathesis transformations, this powerful reaction still attracts significant attention. Whereas efforts are still focused on the development of catalysts with ever increasing activity, the stereoselectivity questions arising in these uses has only been barely examined. Chemoselectivity issues are sometimes postulated, but only rarely investigated. Nonetheless, differences in complex reactivity leading to the formation structurally different compounds were reported for all metathesis transformations, including diene and enyne RCM, ring-rearrangement and cross metathesis.

Differences in metathesis chemoselectivity were observed mainly between first and second generation ruthenium catalysts as a result of activity difference between both generations showing the crucial role played by the phosphine and the NHC. However it has been reported that the architecture of the ancillary ligand, could also significantly influence the outcome of metathesis transformations. The steric bulk of NHCs was found determinant for the selective formation of expected products. In rare cases, the nature of the alkylidene moiety was found important.

Among the number of metathesis examples leading to the formation of different products, the usual trend is to optimize reaction conditions, such as solvent, temperature, ethylene atmosphere or not, etc, in order to favour the formation of the expected product. The influence of the catalyst used has barely been investigated and complexes employed are limited to commercially available catalysts (mainly 1st and 2nd generation Grubbs and Hoveyda catalysts). We believe there is a need for the commercialization of different catalysts as this will facilitate the development of chemoselective metathesis. Thus, the development of task-specific metathesis catalysts, using or not transition metals other than ruthenium, will certainly be of interest to the further development of olefin metathesis.

Acknowledgements

Notes and references

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TOC graphic
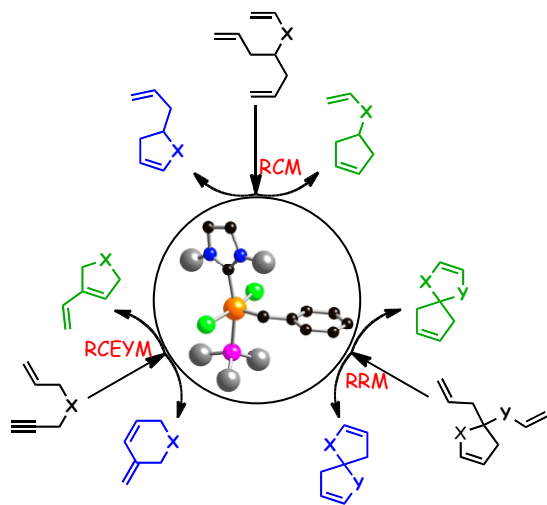
TOC text

This review provides an overview of studies dealing with chemoselectivity in olefin metathesis and intends to provide an explanation on how the structure of ruthenium-based catalysts can influence the distribution of metathesis products.