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A resourceful new strategy in organic synthesis: Tandem and stepwise metathesis/non-metathesis catalytic processes

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Abstract

Highlighting the impressive potential of tandem and stepwise metathesis/non-metathesis reactions in synthesis, the present review extends the scope of the newly gained renown of metathesis as a progressive policy for advanced, elegant and economical organic synthesis. Background is provided for the most encountered to date applications where fundamental non-metathetical synthetic transformations (hydrogenation, oxidation, isomerization, allylation, cyclopropanation, etc.) and a variety of name reactions (Diels–Alder, Claisen, Heck, Ugi, Pauson–Khand, Kharasch addition, etc.) are occurring in tandem, as concurrent or sequential processes, with every known type of metathetical reactions catalyzed by ruthenium or molybdenum complexes.

Keywords: Tandem; Catalysis; Metathesis; Metal-alkylidenes; Transition metals; Non-metathetical processes

1. Introduction

With increasing demand for rapid and economical synthesis, organometallic catalysts, customarily engineered to promote a single catalytic process, are nowadays often required to catalyze mechanistically distinct reactions either as such or through minimal chemical modifications [1]. Sustained efforts are therefore being made to create multifunctional catalytic systems applied in tandem and domino/cascade reactions [2,3]. The advantageous tandem methodology [2a] provides excellent tactics to combine different concurrent or sequential processes in productive single operation employing one or several catalysts [2c–e]. Therefore tandem protocols are considered to be superior to stepwise procedures as they significantly shorten the synthesis scheme [3].

In the area of metathesis chemistry, the recently developed tandem catalysis links metathesis steps (cross-metathesis, ring-opening metathesis, ring-closing-metathesis, enyne metathesis, ring-opening metathesis polymerization) with one another [4] or with various non-metathetical transformations [5] aiming at constructing a diversity of structural motifs in a one-pot procedure and in the presence of only one metathesis catalyst. When in the tandem process the metathesis catalyst cannot be switched in situ to a non-metathesis activity (e.g. through conversion into a metal-hydride active in hydrogenation or isomerization), another compatible metal-catalyst has to be added into the reacting system. To reach high performance in all the pathways of the tandem sequence, conditions have to be found that allow for controlling reactivity and selectivity in each step. A usual strategy is to create catalytic systems able to catalyze distinct reactions by just simple introduction of adjuvants [1] or to devise reactions making use of catalysts that are compatible and perform specific reactions with different rates [6].

The exceptional achievements in olefin metathesis during the last decade [7], following the substantial advance

Abbreviations: ADMET, acyclic diene metathesis; ATRA, atom transfer radical addition; ATRP, atom transfer radical polymerization; D.-A., Diels–Alder; P.K., Pauson–Khand; RAFT, reversible addition fragmentation chain transfer; RCEYM, ring-closing enyne metathesis; RCM, ring-closing metathesis; ROM, ring-opening metathesis; ROMP, ring-opening metathesis polymerization; TCQ, tetrachloro-1,4-benzoquinone.

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on metal carbenes [8,9], have been accompanied by the disclosure of unexpected non-metathetical catalytic activity patterns for metathesis catalysts [10]. Ruthenium carbene-catalyzed non-metathetical reactions, including hydrogenation [11], isomerization [12], cycloisomerization [13], hydrosilylation [14], atom-transfer radical addition [15], atom-transfer radical polymerization [16], open broad perspectives towards diversity oriented synthesis [17] and the rapid and economical preparation of intricate organic molecules and supramolecular assemblies [18]. In this context, the tandem metathesis/non-metathesis approach puts forward great challenges for the synthetic chemist in maximizing efficiency by conversion of simple building blocks into complex targeted units [19].

With the advent of well-defined alkylidene complexes of molybdenum [20] and ruthenium [21], olefin metathesis turned into a most powerful synthetic method for carbon–carbon bond formation [22]. Molybdenum-based complexes, e.g. **1** [23], are generally more reactive towards highly substituted olefins and electron-rich double bonds but also more sensitive to air and moisture. On the other hand, ruthenium carbene complexes, e.g. **2** [24], are more stable and tolerant of polar functional groups and, although their activity is lower, can be applied on a broad range of substrates. A substantial increase in the metathesis activity and stability of the metathesis precatalysts was gradually achieved by appropriate ligand manipulations in the coordination sphere of the metal. Along these lines, Ru complexes containing N-heterocyclic carbenes (**3**–**5**) [25], as well as various monodentate (**6**) [26] or bidentate donor ligands (**7** and **8**) [27], have been designed and screened in metathesis reactions.

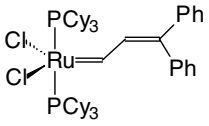
It has been established that in some tandem metathesis/non-metathesis transformations, such as metathesis/hydrogenation and metathesis/isomerization, the Ru complex induces both the metathesis and non-metathesis processes, being active in non-metathesis as result of a simple conversion of the Ru-alkylidene into Ru-hydride species. In a large number of tandem sequences, however, a catalyst suitable for the non-metathesis transformation and compatible with the metathesis catalyst, is to be used additionally.

Highlighting the impressive potential of tandem metathesis/non-metathesis reactions in synthesis, the present review provides background for the most encountered to date applications in different name reactions.

2. Tandem and sequential metathesis/hydrogenation

Traditionally, the double bond formed through metathesis was hydrogenated, if needed, in a next step with help from of a second catalyst, conventional for hydrogenations. In the last few years, however, it was discovered that well-defined ruthenium catalysts can promote both reactions in a just one-step operation as will be outlined below. Even more, Fogg and co-workers proved that repeated catalyst cycling between metathesis and hydrogenation is possible and can be achieved in a one-pot procedure [11a].

Association of metathesis with hydrogenation in the same operation was first reported by McLain et al. [28] in synthesis by ROMP (with catalyst **9**) of an ethylene/methylacrylate copolymer, subsequently hydrogenated under hydrogen pressure (400 psi) at 135 °C; the hydrogenation catalytic species was assumed to be $RuHCl(PCy_3)_2$ formed in situ from the initial ROMP catalyst. A similar procedure, implying this time ROMP of 1,5-cyclooctadiene and homogeneous in situ hydrogenation, was applied by Dias and Grubbs [29] using a bimetallic, bridged-chloride ruthenium carbene precatalyst **10**, under mild conditions.



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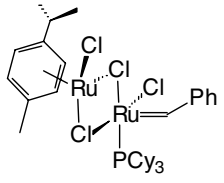

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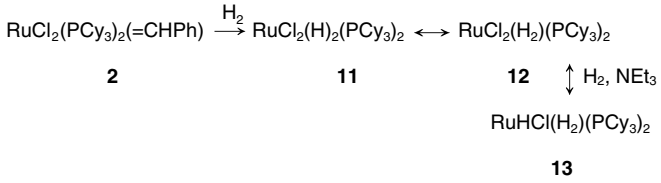
It was supposed that in the presence of hydrogen, at elevated temperatures, the residual ruthenium carbene complex is converted by selective hydrogenolysis into $[Ru(H_2)HCl(PCy_3)_2]$ which is the actual hydrogenation catalyst [30]. Indeed, H_2 hydrogenolysis of complex **2** to form toluene and the Ru tautomers **11** and **12** (Scheme 1) has been reported by Fogg et al. [31a] to readily occur under certain conditions (neat THF).



Scheme 1. Hydrogenolysis of $RuCl_2(PCy_3)_2(=CHPh)$ complex.

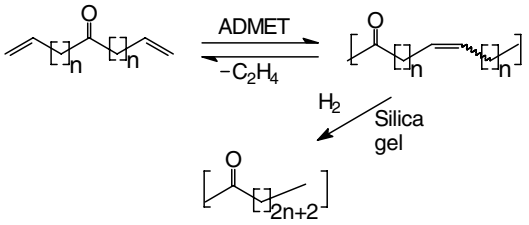
Transformation of **11** and **12** into **13** by addition of NEt_3 in CH_2Cl_2 dramatically increased the hydrogenation accompanying ROMP of cyclooctene. On treatment with 3-chloro-3-methyl-1-butyne, the alkylidene functionality was reinstalled in **11**–**13** to form Ru vinyl methylidene complex **14**, active in ROMP (Scheme 2).

Starting from these results, Fogg et al. [11a] prepared a blend of unsaturated polymers via sequential ROMP of 5-methoxymethylene-norbornene/hydrogenolysis (1 atm H_2, NEt_3)/restoration of metathesis activity of the residual Ru complex/ROMP of newly added monomer. A saturated polymer was obtained starting from the same monomer by a ROMP/hydrogenation (H_2, 250 psi)/ROMP sequence. Repeated catalyst cycling between metathesis and hydrogenation activity has been effected in one-pot procedures. Methanol addition resulted in a dramatic increase in the hydrogenation activity, with an upper limit of 20% imposed by the solubility of polyethylene.

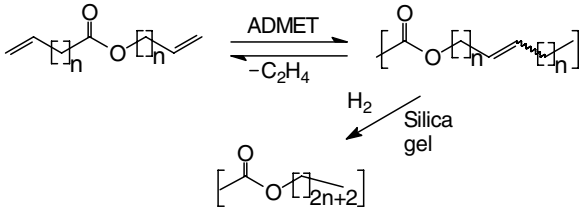
Complex $OsHCl(CO)(P\textit{i}\text{-}Pr_3)_2$ is a performant precatalyst in tandem ROMP-hydrogenation of norbornene and 2,5-norbornadiene [31b]. Esteruelas and co-workers have shown that poly(norbornene) is fully hydrogenated in 48 h at 40 °C and 3 atm of H_2, while poly(norbornadiene) necessitates 75 °C for complete hydrogenation. They also found the complex $RuHCl(CO)(P\textit{i}\text{-}Pr_3)_2$ to be active in ROMP and tandem ROMP-hydrogenation of norbornene, leading to *trans*-poly(norbornene) and hydrogenated poly(norbornene), respectively.

Convincing demonstration of the potentiality of the tandem metathesis/hydrogenation approach, as first encountered in an ADMET reaction, is the relevant study of Watson and Wagener [32] on α,ω-dienes taking advantage of the Ru complex **2** as a homogeneous catalyst. After completion of ADMET, addition of chromatographic grade silica gel converted in situ catalyst **2** into an active heterogenous hydrogenation catalyst, likely a ruthenium hydride species. Gratifyingly, this silica supported active species catalyzed olefin hydrogenation rapidly and quantitatively, under mild conditions (room temperature, moderate pressure) and without the need for highly specialized equipment. Furthermore, the procedure allowed easy removal of the catalyst and isolation of the hydrogenated products by simple filtration. A variety of polyethylene-based materials, such as sequence ordered ethylene/CO (Scheme 3) and ethylene/CO_2 copolymers (Scheme 4), as well as telechelic polyethylene, were made accessible by this ingenious methodology.

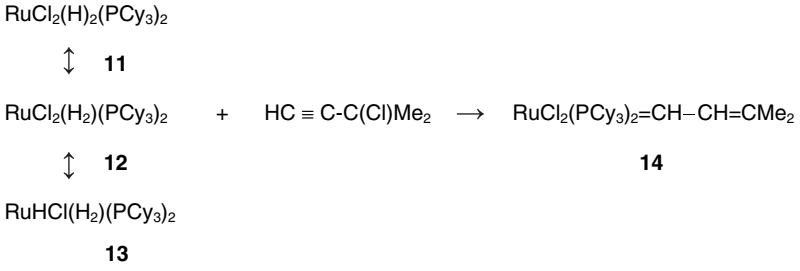
Another early example of a tandem metathesis/hydrogenation comes from Bielawski and Grubbs [33] who achieved hydrogenation of the ROMP product of a sterically hindered cyclic alkene, 1,5-dimethyl-1,5-cyclooctadiene, through sequential processes catalyzed by the prototypical catalyst **4** and using *p*-toluenehydrazide as hydrogen source; the final product is an ethylene-propylene copolymer. Further work from the same group focused on a set of assisted tandem RCM- or CM-hydrogenation reactions involving regiospecific ketone and olefin reduction, transfer hydrogenation of ketones and dehydrogenative oxidation of alcohols, all of which mediated by the above highly active NHC–Ru catalyst **4** leading to good to



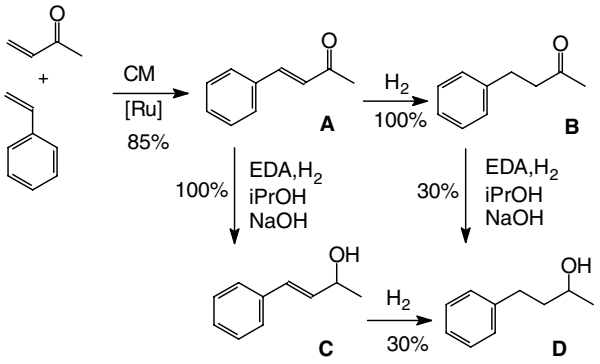
Scheme 3. Tandem ADMET/hydrogenation of CO-containing dienes.



Scheme 4. Tandem ADMET/hydrogenation of CO_2-containing dienes.



Scheme 2. Generation of Ru vinyl methylidene complex **14**.

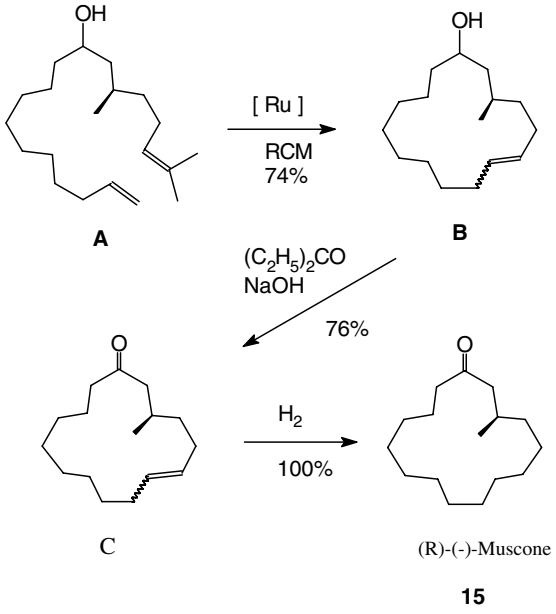


Scheme 5. Tandem CM/hydrogenation/hydrogen transfer using NHC–Ru catalysts.

excellent overall yields [33]; the broad spectrum of catalytic activity of **4** is evidenced hereinafter for the tandem CM-hydrogenation and -transfer hydrogenation (Scheme 5).

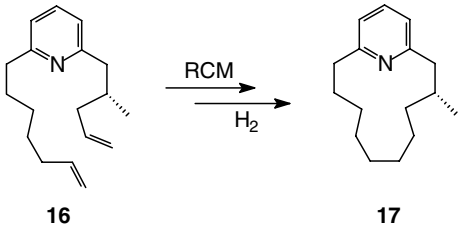
The A → B → D sequence in Scheme 5, consists of cross-metathesis (CM) between styrene and methyl vinyl ketone to give the unsaturated ketone **A**, followed by hydrogenation to **B** (likely promoted by a Ru-hydride species generated from **4** and H_2) and transfer hydrogenation to **D** (ethylenediamine/NaOH/*i*-PrOH and H_2), and was suggested to occur under the action of a Noyori-type catalyst, RuHCl(EDA)(PCy_3)(H_2IMes). In the second cascade (A → C → D) the allyl alcohol **C**, obtained quantitatively by transfer hydrogenation with no trace of C=C reduction, was hydrogenated to the saturated final product, the alcohol **D**.

An illustrative cascade catalysis, also with catalyst **4**, is the "one-pot" enantioselective, short synthesis of (*R*)-(−)-muscone (**15**), a valuable natural fragrance (Scheme 6) [34]. Thus, the diene substrate A, bearing an unprotected secondary hydroxyl group, was cyclized (RCM) to a macrocyclic alkenol B (mixture of geometrical isomers), followed by dehydrogenative oxidation to **C** (via hydrogen transfer to 3-pentanone in the presence of NaOH), and chemoselective hydrogenation (H_2 gas) at the olefinic double bond of the suitable stereoisomer in C, to give the targeted saturated macrocyclic ketone **15** in the desired stereoconfiguration (56% overall yield).

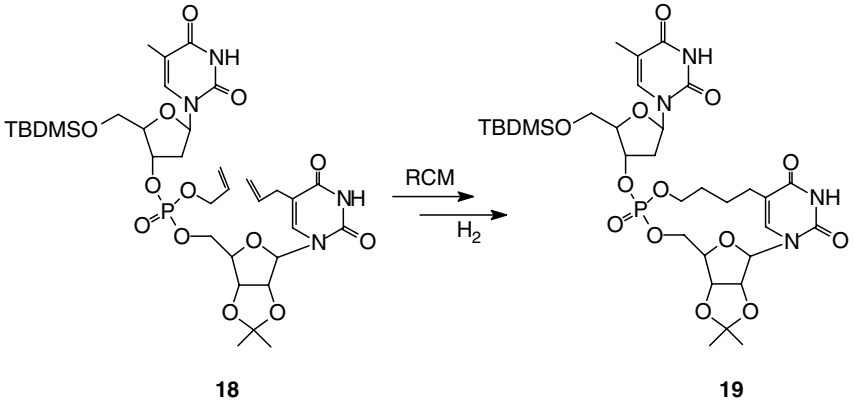


Scheme 6. Stepwise RCM/hydrogen transfer/hydrogenation in synthesis of (*R*)-(−)-muscone.

Interesting applications of the sequential metathesis/hydrogenation methodology in synthesis of the natural product (*R*)-(+)-muscopyridine **17** from diene **16** and the cyclic dinucleotide **19** from diene **18** have been provided by Fürstner and Leitner [35] and Børsting and Nielsen [36], respectively (Schemes 7 and 8).



Scheme 7. Synthesis of (*R*)-(+)-muscopyridine by sequential RCM/hydrogenation.



Scheme 8. Synthesis of cyclic dinucleotide **19** by RCM/hydrogenation.

In an alternative approach, activation of the metathesis catalyst for hydrogenation has been achieved by using inorganic hydrides as additives in a RCM/hydrogenation sequence [37]. For instance, sodium hydride effectively activates ruthenium carbene complexes to catalyze hydrogenation reactions subsequent to ring closing olefin metathesis. Under these conditions, hydrogenation of cyclopentenols proceeds smoothly at ambient temperature and under 1 atm of hydrogen in toluene. A variation of this procedure was also developed and involved formation of hydrogen in situ by reaction of excess sodium hydride with protic functional groups and water (Scheme 9).

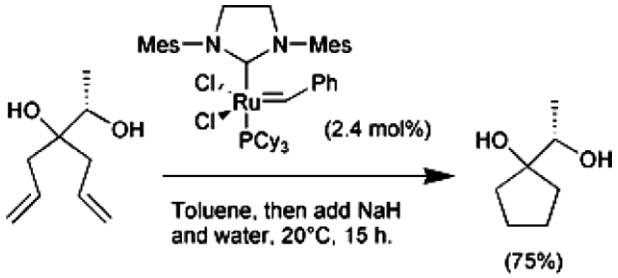
A highly efficient sequential metathesis/hydrogenation protocol to dicarba analogues of the cyclic peptide octreotide has been reported by Robinson et al. [38] using a combination of the Ru benzylidene complex **2** with the Wilkinson catalyst $Rh(PPh_3)_3Cl$. Treatment of a fully protected peptide deposited on a solid phase resin with the Ru benzylidene complex **2** led to quantitative formation of the *cis* isomer of the carbocycle **20** (see Scheme 10).

No oligomerization or dimerization product via acyclic diene metathesis or cross-metathesis was observed. Subsequent hydrogenation of **20** with the Rh (I) catalyst in 10% MeOH–CH_2Cl_2, at room temperature and under mild hydrogen pressure (60 psi), gave quantitatively the reduced resin-attached product. Finally, after cleavage from the resin and deprotection, pure compound **21** was obtained in 23% overall yield.

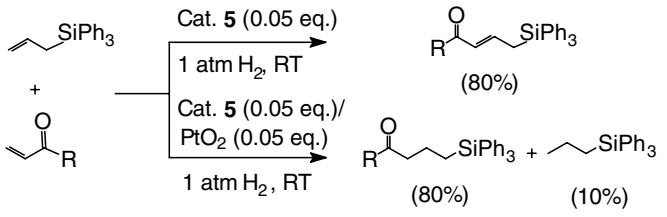
The issue of compatibility of two catalysts in tandem metathesis/hydrogenation was raised again by Cossy et al. [39] in a relevant example of orthogonal catalysis, a one-pot CM-hydrogenation employing a Ru–NHC metathesis catalyst resistant to hydrogenolysis, the Hoveyda–Grubbs catalyst (**5**). With **5** alone, under hydrogen and at room temperature, cross-metathesis of allyltriphenyl silane and an α,β-unsaturated carbonyl compound gave the metathesis product (80% yield) and only traces of the corresponding saturated derivative. Nevertheless, when a hydrogenation catalyst (PtO_2) was used in conjunction with the metathesis precatalyst **5**, the reaction tandem shifted towards the saturated derivative which now became the major product (80%). With Pd/C, instead of PtO_2, the hydrogenation products prevailed, hence hydrogenation was faster than metathesis. Results clearly show that by astute interplay between two compatible catalysts the reaction rates can be manipulated to give the desired product. The high yield in the metathesis (over hydrogenation) product obtained in the presence of **5** suggests that, in contrast to the traditional NHC–Ru **4**, the Hoveyda–Grubbs catalyst **5** is not converted to a Ru–H species able to promote hydrogenation of the double bond of the CM product. This is not surprising if we take into consideration that in **5** the O,C-bidentate ligand prevents formation of a Ru-hydride species (Scheme 11).

The sequence, RCM/hydrogenation (with the catalyst couple **4**/Pd–C), is at the basis of a convenient synthesis of saturated, unsubstituted medium-sized lactams (Scheme 12) [40].

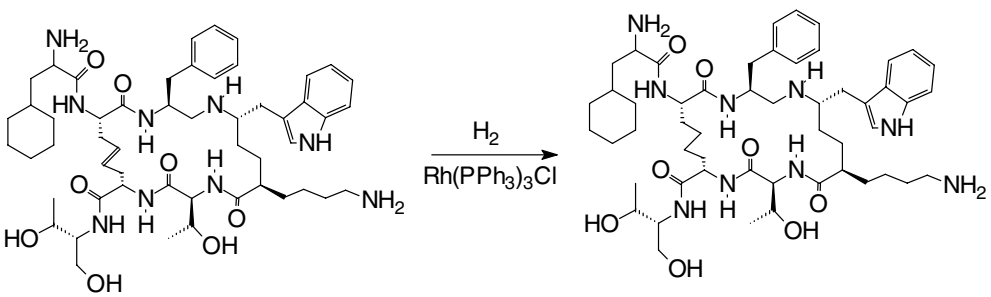
The starting oxyoxazolidinones, prepared from secondary *O*-acylmandelamides by treatment with TBSOTf,



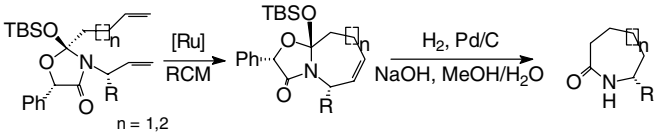
Scheme 9. Synthesis of cyclopentanols by RCM/hydrogenation.



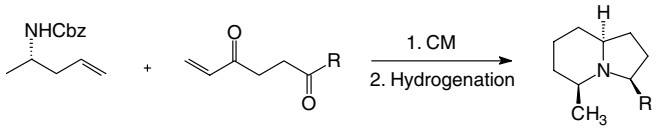
Scheme 11. Tandem cross-metathesis/hydrogenation using the **5**/PtO_2 system.



Scheme 10. Synthesis of ocreotide by the RCM/hydrogenation sequence.



Scheme 12. Sequential RCM/hydrogenation in synthesis of saturated lactams.



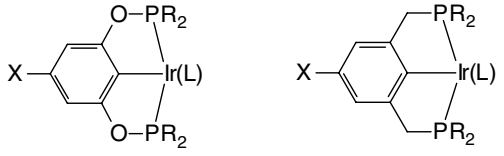
Scheme 13. Synthesis of 3,5-dialkyl-substituted indolizidine alkaloids by metathesis/double-reductive cyclization.

underwent RCM in the presence of the Grubbs catalyst **4** to give either oxazoloazepines or oxazoloazecines.

Highly stereoselective cross-metathesis is the key step in the synthesis of a natural product from the class of 3,5-dialkyl-substituted indolizidine alkaloids by metathesis/double-reductive cyclization [41]. Cross-metathesis of an α,β-unsaturated ketone and a chiral homoallylic amine is followed by a domino reaction involving hydrogenation, N-deprotection, and two diastereoselective reductive aminations leading in an enantioselective mode to the indolizidine (see Scheme 13).

3. Tandem dehydrogenation/metathesis

Alkane metathesis is a selective disproportionation of alkanes, a common process known since decades to occur during the catalytic cracking of petroleum hydrocarbons. Initially, this process has been studied by Burnett and Hughes using Pt on alumina (dehydrogenation catalyst) associated with tungsten oxide (metathesis catalyst) [42a] and then by Basset with Ta and W hydrides as the catalysts [42b] but the product yield and selectivity were generally low. More recently, Brookhart and co-workers [43] reported two types of catalytic systems by which metathesis of linear alkanes was achieved efficiently and selectively, at moderate temperatures. A combination of two compatible catalysts, the Ir-based pincer complexes **22** or **23a**,**b**, active for dehydrogenation, and either the Schrock-type catalyst **1** or Re_2O_7/Al_2O_3, active for metathesis, was used.



22 **23**

R= *t*-Bu, X = H
L = C_2H_4, H_2

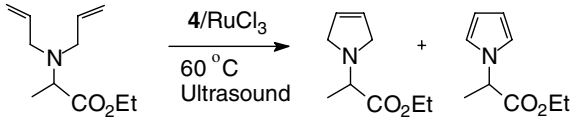
a. R= *t*-Bu, X = H
b. R = *i*-Pr, X = OMe
L = H_2 and/or C_2H_4

With the catalyst pair **22** (dehydrogenation) and **1** (metathesis), in tandem reactions of *n*-hexane, at 125 °C, the product distribution ranged from C_2 to C_5 and C_7 to C_{10}. A wide distribution of products was also recorded in tandem dehydrogenation/cross-metathesis of *n*-hexane with eicosane under similar conditions. These results were rationalized by assuming that a substantial degree of olefin isomerization took place before olefin metathesis. This assumption is, however, questionable taking into account that the molybdenum complex **1** has a high activity in metathesis reactions. Quite interesting data were obtained using a more robust metathesis catalyst, Re_2O_7/Al_2O_3, as a partner to the Ir complexes **22** and **23a**,**b** in tandem reactions of *n*-decane; after 9 days, at 175 °C, the *n*-decane starting material was converted to comparable molar amounts of *n*-nonane and *n*-undecane products (C_9:C_{10}:C_{11} molar ratios of 0.6:1:0.6). This indicated a total suppression of isomerization reactions during the tandem processes.

4. Tandem RCM/oxidation

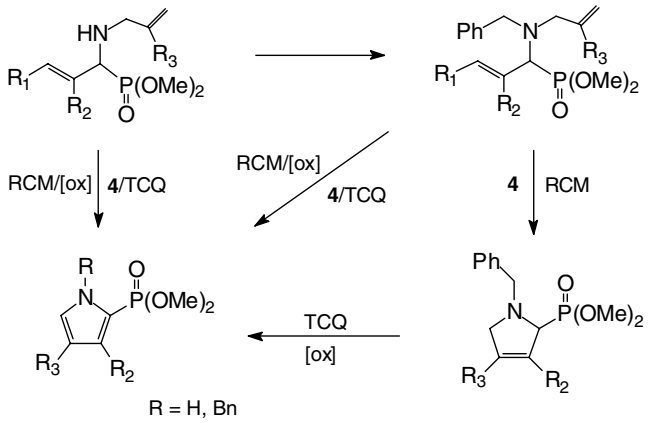
A tandem RCM/oxidation strategy proved productive in the straightforward one-pot synthesis of valuable carbocyclic and heterocyclic compounds based on orthogonal catalysis with Grubbs' second generation catalyst (**4**) associated with a dehydrogenation agent [44–46]. Thus, diallylamines (e.g. **24**) were converted to the corresponding pyrroles (e.g. **26**) in more than 90% yield on using catalyst **4** (10% mol) with 2% $RuCl_3 \cdot H_2O$, in 1,2-dichloroethane at 60 °C and under ultrasonic irradiation (to form a fine dispersion of the $RuCl_3 \cdot H_2O$ in the reaction mixture) (Scheme 14) [44].

To establish if the role of the catalyst **4** in the two mechanistically different yet simultaneously occurring reactions is limited to just RCM, a comparative study at 60 °C was performed with or without addition of $RuCl_3 \cdot H_2O$. In both cases the formation of the corresponding pyrroline **25** and pyrrole **26** was observed, but pyrrole formation was greatly favoured in the presence of 2% $RuCl_3 \cdot H_2O$. When only catalyst **4** is employed at lower temperatures, no pyrrole was observed. This might suggest that at higher temperatures, due to the decomposition of the catalyst, some other Ru-species are formed catalyzing dehydrogenation. The general applicability of these tandem reactions was demonstrated on a number of substrates producing a variety of pyrroles in good to excellent yields. Taking



24 **25** **26**

Scheme 14. Conversion of N-substituted diallylamines by tandem RCM/oxidation using **4**/$RuCl_3$ system.



Scheme 15. Reaction pathways in tandem RCM/oxidation processes.

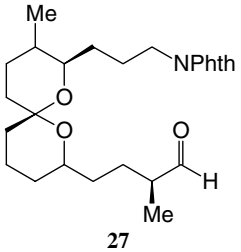
advantage of a somewhat modified technique (dehydrogenating agent: TCQ), the same authors succeeded synthesis of 2-phosphonopyrroles starting from the suitable aldehydes, under mild conditions (Scheme 15) [45].

The key step involves a one-pot ring-closing metathesis/oxidation sequence of a functionalized α-aminoalkenyl phosphonate using catalyst **4** (5% mol)/TCQ. A synergism was observed between the RCM catalyst and the oxidizing agent, causing higher oxidation rates and allowing reaction for substrates that fail to ring close under standard RCM conditions.

A novel tandem strategy making use of ring-closing metathesis of 1-(2-propenylphenyl)prop-2-en-1-ols followed by a dehydrogenative oxidation in situ to afford substituted indenones has also been described by van Otterlo et al. [46]. The structural motifs resulted from this tandem catalysis have a large potential of being applied to the synthesis of natural products and their derivatives.

5. Metathesis/hydrogenation/Dess–Martin oxidation

Association of metathetical with non-metathetical reactions gets sometimes really complicated. Thus, in the atom economical ring-opening/cross-metathesis cascade, followed by hydrogenation and Dess–Martin oxidation, Kozmin et al. [47] prepared the key spiroketal fragment **27** (Phth = phthalimido). With **27** in hand, they were able to productively complete the enantioselective total synthesis of (+)-bistramide A, a protein kinase C activator.



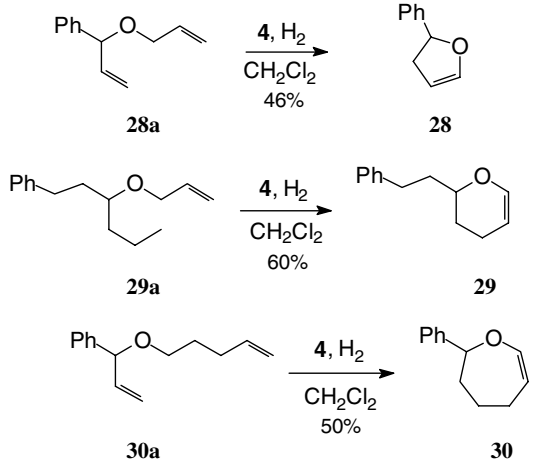
27

6. Tandem RCM/isomerization

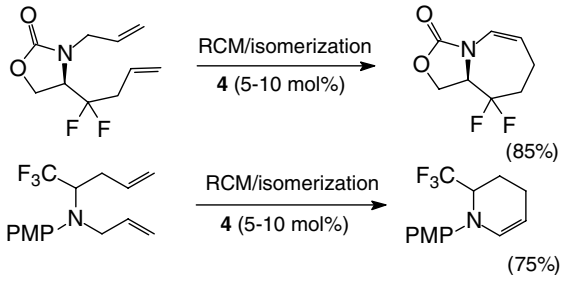
An ingeniously simple tandem protocol implying double-bond isomerization/RCM, communicated by Snapper et al. opened a rapid access to medium-sized O-heterocycles, starting from oxygen-containing dienes such as **28a**–**30a** (Scheme 16) [48]. The reaction products (e.g. **28**–**30**) are cyclic enol ethers, versatile subunits of bioactive compounds such as glycals, polyether or nucleoside antibiotics and other natural products.

Importantly, treatment of the NHC–Ru complex **4** in CH_2Cl_2 with small amounts of H_2 (95:5 of mixture N_2:H_2) led reproducibly to an isomerization Ru-catalyst, while keeping down the competitive olefin hydrogenation (<10%). In the total absence of hydrogen, however, isomerization is suppressed, thus indisputably evidencing the involvement of a Ru-hydride species. Screening of the isomerization activity in different solvents showed methylene chloride to lead to best results. In all examined cases the less substituted enol ether was favoured. When enantiomerically enriched dienes were used as the substrates, cyclic enol ethers were generated without loss of enantiomeric purity, indicating that the isomerization does not proceed via achiral enol ethers. In a related synthesis of cyclic enol ethers through tandem metathesis-isomerization of allyl ethers, Schmidt activated the Ru carbene complex **4** for promoting double bond isomerization by addition of conventional hydride sources (NaH or $NaBH_4$) [49]. In situ formation of Ru–H species during isomerization of allyl ethers with Grubbs' catalyst has been evidenced spectroscopically also by Schmidt [49c]. Hydride transfer from $NaBH_4$ was exploited in research performed on a pincer $PC^{NHC}P$–Ru complex to generate *mer*-RuHCl(CO) $PC^{NHC}P$ [50].

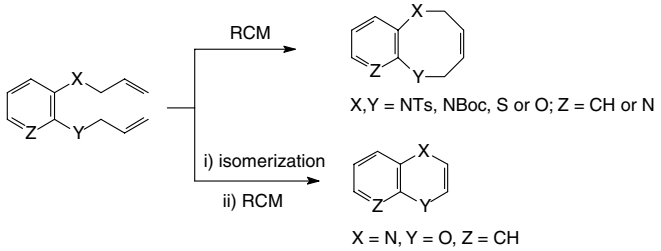
Tandem RCM/isomerization also enabled regioselective synthesis of fluorinated or nonfluorinated unsaturated lactams starting from the corresponding amides (Scheme 17) [51].



Scheme 16. Isomerization/RCM sequences induced by the Ru complex **4**.



Scheme 17. Synthesis of unsaturated fluorinated lactams and tetrahydropyridines by tandem RCM/isomerization.



Scheme 19. Synthesis of benzo-fused rings by tandem isomerization/RCM.

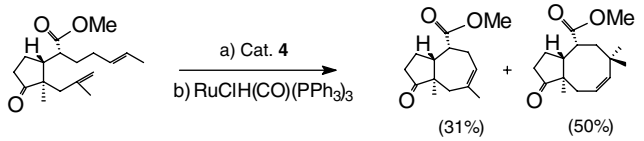
The authors demonstrated that regioselectivity of the overall tandem process is due to the presence of the *gem*-difluoro moiety of the precursor, crucially important for a controlled isomerization, and also to the heteroatom. As expected, the process is most productive for synthesis of five- to eight-membered lactams for which the RCM step is very fast and surpasses isomerization; nevertheless, the reverse is true for the nine-membered ring lactam in which case isomerization takes place first resulting in formation of several lactams with different ring-sizes. The same tandem process afforded CF_3-substituted tetrahydropyridines in good yield.

Another suggestive tandem isomerization-RCM sequence applied on sterically congested 1,9-dienes as substrates, takes advantage of a binary system consisting of two compatible catalysts, the first or second generation Grubbs catalyst and $HRuCl(CO)(PPh_3)_3$ (Scheme 18) [52].

van Otterlo et al. applied successfully isomerization/RCM to prepare a variety of benzo-fused heterocycles with the catalyst couple $RuClH(CO)(PPh_3)_3$ and **4** [53]. The authors demonstrate the in situ isomerization of aryl allyl ethers or arylallyl groups into aryl 1-propenyl ethers or 1-propenylbenzenes, respectively, prior to RCM. This strategy, circumventing the difficult direct synthesis of aryl vinyl ethers or styrenes, resulted in several products including two substituted benzo[1,4]dioxins, naphtho[2,3-*b*][1,4]dioxin, 2*H*-chromene and benzo[*b*]furan [53a]. In a related research, the isomerization/ring-closing metathesis methodology conveniently afforded *N*-substituted 4*H*-1,4-benzoxazines from the protected *N*-allyl-2-(allyloxy)anilines. Synthesis of a seven-membered ring system, 2,5-dihydro-1,5-benzothiazepine 1,1-dioxide, from the protected *N*-allyl-2-(allylsulfonyl)aniline, was also achieved (Scheme 19) [53b].

At the same time, RCM alone was applied to synthesize the *N*-substituted, eight-membered benzo-fused heterocycles from the respective diallyl compounds: 1,2,5,6-tetrahydro-1,6-benzodiazocine, 5,6-dihydro-2*H*-1,6-benzoxazocine, 5,6,9,10-tetrahydropyrido[2,3-*b*][1,4]diazocine and 5,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide [53c].

Numerous other examples of tandem isomerization/ring-closing metathesis for production of diverse organic compounds, using isomerization mediating transition metal catalysts, associated with the ruthenium precatalysts **2** or **4**, can be found in recently published work [54].



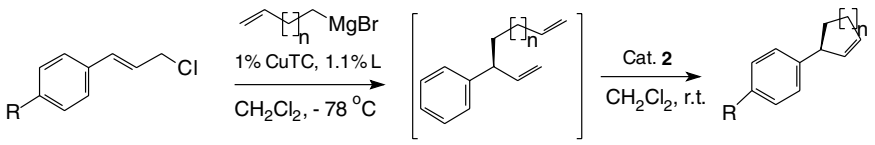
Scheme 18. Tandem isomerization/RCM using the catalyst system **4**/$HRuCl(CO)(PPh_3)_3$.

7. Allylation/RCM

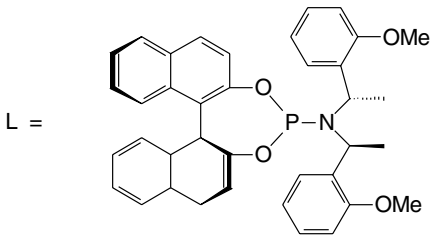
Allylic substitution, a fundamental transformation in organic synthesis mediated by transition metal complexes (Pd, Mo, Ir, Cu, etc.), exhibits in case of chiral ligands a high degree of stereoselectivity. In the introduction of hard nucleophiles, such as alkyl groups, copper showed to be highly efficient. Of particular interest is allylic substitution with Grignard reagents bearing a remote double bond in the alkyl group, in the presence of Cu. When coupled with the ruthenium catalyzed ring-closing metathesis (catalyst **2**), this sequence led to cyclized products in good yield and high enatioselectivity [55] (Scheme 20).

Whereas stereoselectivty in the substitution reaction could be adjusted through the chiral ligand, the diene reactivity in RCM was shown to be influenced by the nature of the substrate and the relative position of the two double bonds. In practice, it is desirable to run both the allylic substitution and metathesis in one-pot, provided that the Ru catalyst is compatible with the excess of Grignard reagent, the Cu salt and the ligand L (i.e. phosphoramidite).

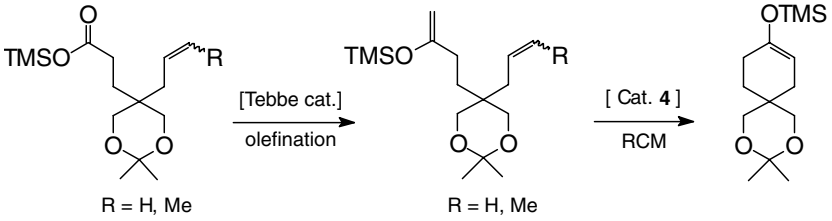
The tandem allylation/RCM enabled synthesis of substituted quinoline derivatives in excellent yield, by a sequence involving first allylation (allyl bromide, K_2CO_3) of anthranilic acid-derived enol ethers, followed by RCM with catalyst **4** [56]. This is the first report on synthesis of a heterocyclic enol silyl ether (4-TBDMSO-1-Ts-quinoline) via enol silyl ether–ene metathesis highlighting the utility of enol TBDMS ethers as substrates in RCM. Almost at the same time, a highly regioselective cascade leading to carbocyclic enol ethers, starting from acyclic alkenyl ketones or acyclic alkenyl silyl esters was reported to necessitate first carbonyl olefination (Tebbe reagent) and secondly RCM (catalyst **4**) (Scheme 21); utility of OTMS ethers as RCM substrates was this time evidenced [57].



R = H, Me; CuTC = copper thiophene-2-carboxylate; n = 1,2
Yield = 69-79%; ee = 93-96%



Scheme 20. Application of tandem allylation/RCM in synthesis of cyclic compounds.



Scheme 21. Synthesis of carbocyclic enol ethers by tandem olefination/RCM reactions.

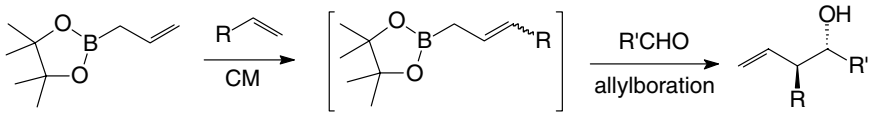
Allyl transfer associated with CM, in the highly enantioselective synthesis of linear homoallylic alcohols with terminal ester functionality, conducted in a single reaction vessel, has been achieved by Lee and Loh [58]; the homoallyl reaction partner was prior obtained by enantioselective allyl transfer to phenylpropenal (or other aldehydes) using a camphor-derived homoallylic alcohol, and then cross-metathesized (catalyst **4**) with acrylic or methacrylic esters. Asymmetric allyl transfer followed by olefin cross-metathesis provided easy access to a wide variety of linear enantiomerically enriched and geometrically defined homoallylic alcohols. Ordered addition of reagents and catalysts enabled a controlled reaction ensuring complete consumption of the starting aldehyde.

8. Sequential metathesis/allylboration

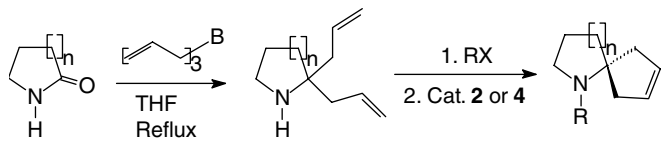
An excellent alternative for stereoselective access to homoallylic alcohols, widely used in organic synthesis, consists of allylation of aldehydes with allyl boron reagents [59]. The availability of functionalized allyl boron reagents, however, has remained limited for decades. With the advent of ruthenium catalyzed metathesis reactions, a new route for construction of allyl boronates was opened. In this context, Goldberg and Grubbs [60] reported a one-pot cross-metathesis/allylboration sequence that affords densely functionalized homoallylic alcohols (Scheme 22).

The three-component coupling protocol combines two orthogonal, mild and chemoselective, carbon–carbon bond-forming reactions and eloquently illustrates the ability of metathesis in mediating production of novel and highly reactive organic reagents.

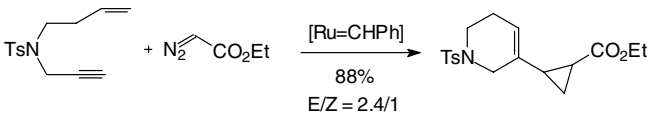
The scenario allylboration/RCM is taken advantage of by Mol et al. [61] in building the most challenging fragment (6-azaspiro[4.*n*]alk-2-ene) of a class of alkaloids, starting from lactams (Scheme 23). Allylboration at the carbonyl carbon gave an amino-diallyl compound that was protected ($COCF_3$) at the amino group in order to spare the metathesis Ru catalyst; under the action of either the catalyst **2** or **4**, the N-protected diallyl compound ring-closed to



Scheme 22. Synthesis of homoallylic alcohols by metathesis/allylboration.



Scheme 23. Synthesis of N-containing spiro compounds by the allylboration/RCM sequence.



Scheme 25. Synthesis of cyclopropyl derivatives by tandem enyne metathesis/cyclopropanation reactions.

the azaspiro compound in good yield (58–99%, depending on the size of the nitrogen-containing cycle).

9. Tandem metathesis/dihydroxylation

The metathesis/dihydroxylation sequence, applied on a variety of dienes and utilizing the same ruthenium source, was reported to efficiently afford vicinal diols under mild conditions [62]. The innovative concept was to promote metathesis (RCM or CM) with a NHC–Ru precatalyst and then oxidize this Ru source to perform *cis*-dihydroxylation on the newly formed disubstituted olefin, in a single operation. This seems to be the first reference for an NHC–Ru catalyst as activator in dihydroxylation of olefins (Scheme 24).

As it was observed that even small amounts of dichloromethane resulted in low yields in the dihydroxylation step, after completion of RCM the methylene chloride was totally removed and replaced with a solvent mixture (Scheme 24). Dihydroxylation proceeded rapidly at 0 °C for the optimal order of addition of reagents ($YbCl_3 \cdot 6H_2O$ before $NaIO_4$) to the solution of crude ring-closed product and when stirring of the heterogeneous reaction mixture was vigorous. Of a series of catalysts tested, the Grubbs II and Hoveyda–Grubbs gave lower yields, even at longer reaction times (ca. 50% for **5** in CM/dihydroxylation sequences), because the strong binding between the NHC ligand and Ru in these complexes slows down formation of the oxidating species [63].

Tandem dihydroxylation/metathesis, has been explored by White and co-workers [64] in asymmetric synthesis of enantiopure *trans*-cyclooctene isomers. Regioselective Sharpless asymmetric dihydroxylation at the central double bond of (*E*)-1,5,9-decatriene (using methanesulfonamide to promote selectivity at this non-terminal double-bond), followed by RCM gave enantiomerically pure *cis*-cyclooctene. By epoxidation, ring-opening (with lithium diphenylphosphide) and oxidation, two diastereomeric hydroxyphosphine oxides were obtained; separate *syn*-elimination in these diastereomers led to the enantiomerically pure chair and twist *trans*-cyclooctenes.

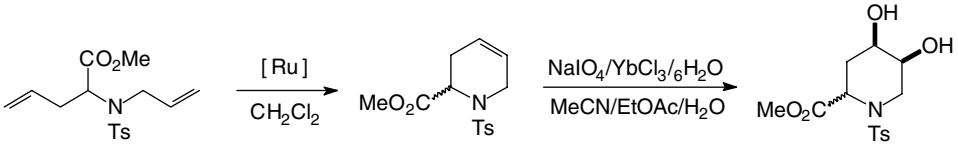
10. Enyne metathesis/cyclopropanation

Tandem enyne metathesis-cyclopropanation was carried out successfully in the presence of the bisphosphane-Ru catalyst **2** to yield alkenyl cyclopropanes (Scheme 25) [65]. Cyclopropanation took place almost exclusively at the less hindered double bond with moderate *E*/*Z* stereoselectivity. Attempts to use in the process the NHC–Ru catalyst **4**, instead of **2**, failed; in this case the sole product was a triene dimer resulting from an enyne metathesis–cross-metathesis sequence.

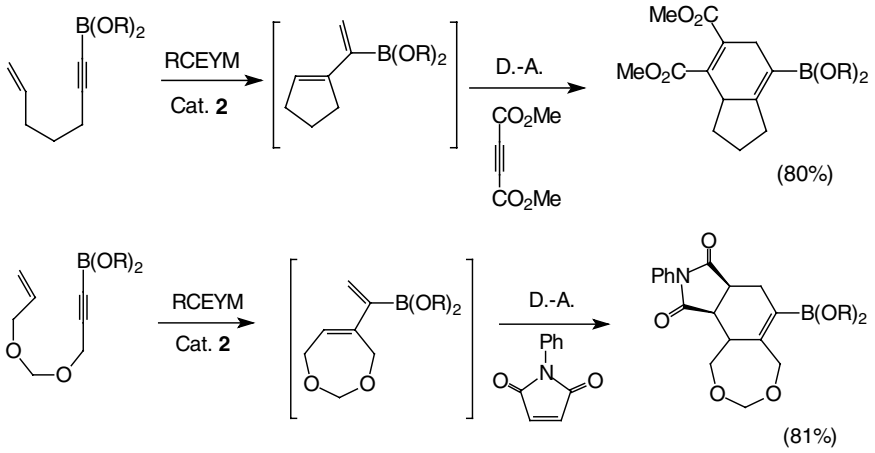
11. Sequential or tandem metathesis/Diels–Alder

Ring-closing enyne metathesis (RCEYM) readily provides exocyclic 1,3-dienes which can be further converted to complex polycyclic molecules by a Diels–Alder reaction with an appropriate dienophile [66]. This protocol has been recently explored for obtaining numerous cyclic and polycyclic systems like perhydroindenes [67], tetrahydropyridines [68a], hexahydroisoindoles [68b], aza- and oxa-steroids [69], tricyclic and tetracyclic benzoxepin derivatives [70] or polycyclic-β-lactams [71]. Two main techniques have been most frequently applied in sequential or tandem metathesis/Diels–Alder: (i) the dienophile is added to the reaction mixture after the enyne metathesis has gone to completion to further convert the intermediate compound into the targeted product, and (ii) the enyne, dienophile and metathesis catalyst are introduced in the reaction mixture from the beginning.

The first technique proved to be quite productive even when the intermediate metathesis products are unstable. Thus, Renaud and co-workers [72], reported high yields in tandem reactions of enyne boronates with dienophiles in the presence of $RuCl_2(PCy_3)_2(=CHPh)$ as the metathesis catalyst. The Diels–Alder adducts were obtained in 81–86% yield just by trapping the initially formed 1,3-dialkenylbor-



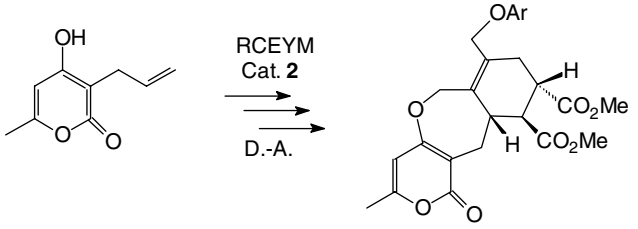
Scheme 24. Synthesis of dihydroxy compounds by tandem metathesis/dihydroxylation.



Scheme 26. Synthesis of cyclic dialkyl boronates by sequential RCEYM/Diels–Alder.

onates with the dienophile, without removing the catalyst (Scheme 26).

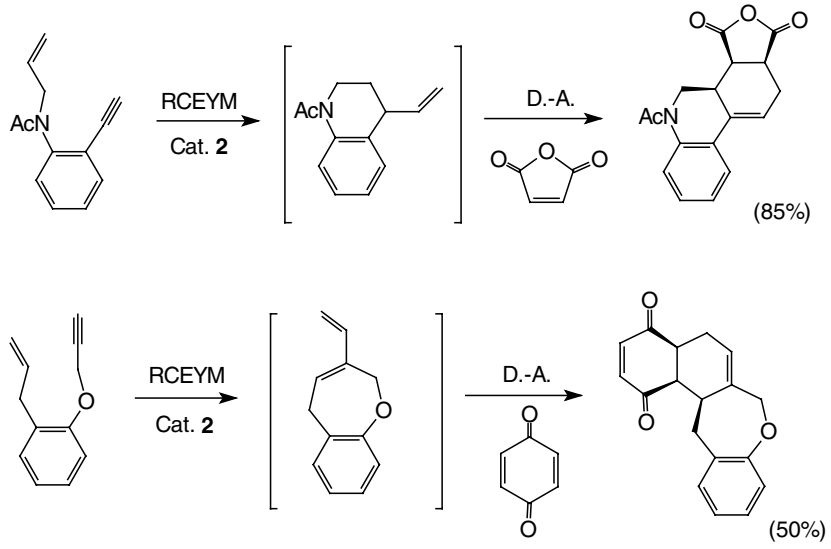
Sequential RECYM/Diels–Alder is also the key pathway in the synthesis of tricyclic pyranoxepin derivatives [73]. The dienophile was added after the ring-closing enyne metathesis induced by catalyst **2** (Scheme 27). Both reactions, partners in the process, afforded excellent yields.



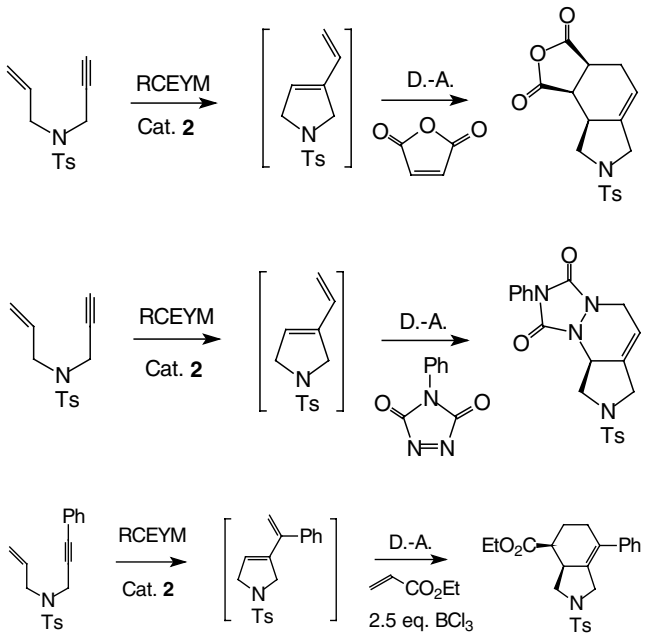
Scheme 27. Synthesis of tricyclic pyranoxepin derivatives by sequential RECYM/Diels–Alder reaction.

A new entry to the steroid ring-system and aza- or oxa-steroids has been introduced by Pérez-Castells and co-workers [69a], based on stepwise enyne metathesis/Diels–Alder reactions. The tetracyclic structures were readily constructed from aromatic enynes (obtained by the Sonogashira coupling) by a one-pot metathesis/Diels–Alder cascade using $RuCl_2(PCy_3)_2(=CHPh)$ as the catalyst for metathesis. RCEYM was carried out in CH_2Cl_2, followed by addition of the dienophile and heating to reflux for several hours (Scheme 28).

Interesting results have been obtained in tandem reactions also by the alternative technique, where the enyne, dienophile and the metathesis catalyst are added from the start. RCEYM is immediately followed by cycloaddition, without adding further reagents or isolating the intermediate products. The approach was utilized by Bentz and Laschat [67] in the one-pot synthesis of polycyclic compounds from N-tosyl enynes and several dienophiles catalyzed by **2** (in CH_2Cl_2 at room temperature) (Scheme 29).



Scheme 28. Synthesis of aza- and oxa-steroids synthons by enyne metathesis/Diels–Alder.



Scheme 29. One-pot synthesis of bi- and tricyclic compounds by the RCEYM/Diels–Alder tandem.

As expected, the Diels–Alder reaction favoured formation of the *endo*-isomer. Due to its lower activity in the cycloaddition, ethyl acrylate needed the presence of a Lewis acid (e.g. BCl_3) that did not affect the catalytic activity of the metathesis catalyst. It should be noted that the yields of the sequence were significantly higher (60–75%) than those obtained by the stepwise procedure.

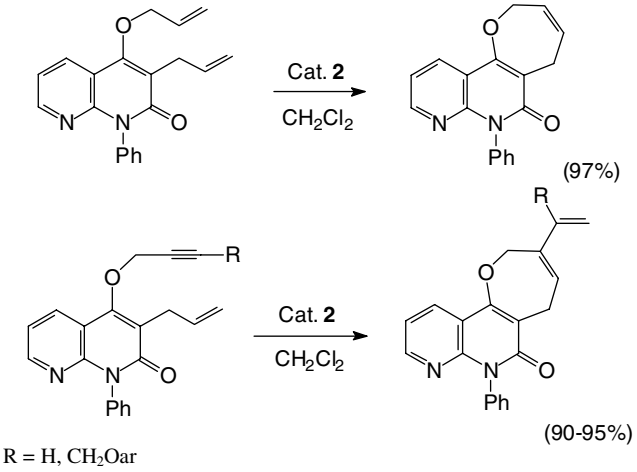
Combination of two enyne metathesis and Diels–Alder reactions has been achieved by Banti and North [74] in synthesis of heptacyclic compound **32** from the norbornene derivative **31** (Scheme 30).

The enyne metathesis was performed with Ru catalyst **2** and under ethylene atmosphere in order to avoid ring-opening polymerization of **31**. The most appropriate solvent proved to be ethyl acetate, unusual for metathesis reactions. Maleic anhydride was added immediately after the complete conversion of **31** has been achieved. The isolated yield in the final product (34%) was also in this case slightly higher than that from the step-wise procedure. Remarkably, by this method only one stereoisomer was obtained although compound **32** contains 10 consecutive stereogenic centers.

12. Sequential Claisen rearrangement/metathesis

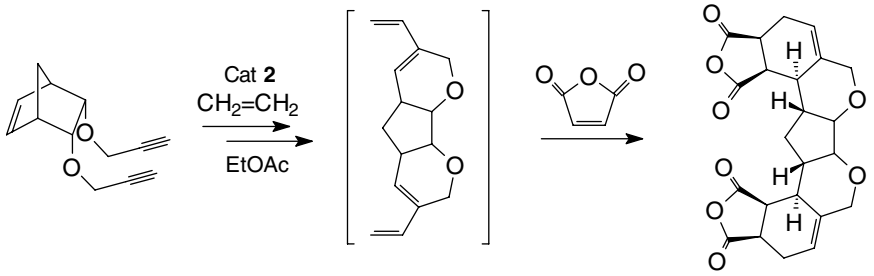
Claisen rearrangement of allyl aryl ethers to *o*-allylphenols and its further extension to the corresponding aza- and thia-analogues are versatile means for synthesis of numerous five- and six-membered oxygen, nitrogen and sulphur heterocycles, through synthetic transformations of the initial rearrangement products. Combination of a Claisen rearrangement with metathesis provides simpler access to various medium sized carbocyclic and heterocyclic systems of interest.

Along these lines a procedure for the synthesis of substituted 1,8-naphthyridinones via a sequence implying Claisen rearrangement and either ring-closing metathesis or ring-closing enyne metathesis has been reported quite recently [75] (Scheme 31). The approach could be an opening toward a more general synthesis of naphthyridines, an important class of biologically active compounds, and in particular of 1,8-naphthyridines, known to possess remarkable therapeutic effects. A similar methodology is encountered in the successful design and synthesis of oxepin- and oxocin-annulated coumarin derivatives [76].

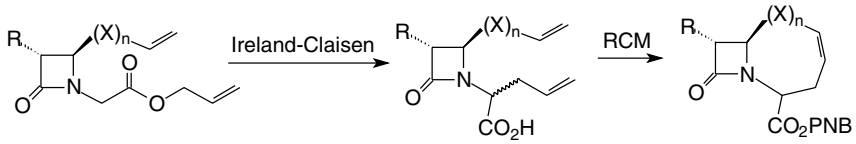


R = H, CH_2Oar

Scheme 31. Synthesis of substituted 1,8-naphthyridinones by Claisen rearrangement/RCM sequence.



Scheme 30. Polycyclic compounds by sequential enyne metathesis/Diels–Alder.



X=O, S, N-SO_2-*p*-C_6H_4-CH_3 R= H, TBDMSO-CH_2CH_2 n=1,2

Scheme 32. Sequential Ireland ester Claisen rearrangement/RCM to bicyclic lactams.

The related sequence, Ireland ester Claisen rearrangement/RCM, has been exploited in the construction of bicyclic β-lactam carboxylic esters containing the 2-azetidinone ring system [77]. Thus, an array of 4-alkenyl-2-azetidinones were converted into β-lactam dienes via sequential *N*-alkylation, Ireland-Claisen ester enolate rearrangement and esterification. Ring-closing metathesis of the resulting dienes using the alkylidene Schrock (**1**) or Grubbs (**2**) catalysts gave a series of [5.2.0] and [6.2.0] bicyclic compounds (Scheme 32).

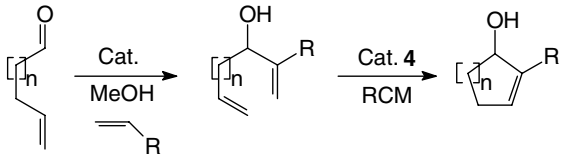
The same scenario also furnishes a useful entry into spiro[5.5]undecanes containing a quaternary carbon atom adjacent to a spirocentre [78]. Starting from cyclohexanecarboxylic acid, a combination of an Ireland ester Claisen rearrangement and RCM reactions led to spiro[5.5]undecanes, with extension to total syntheses of three chamigrenes.

13. Tandem Morita–Baylis–Hillman/metathesis

An inventive combination of Morita–Baylis–Hillman (MBH) reaction with RCM for synthesis of functionalized hetero- and carbocyclic alkenols has been recently described by Krafft et al. [79] (Scheme 33).

Methyl acrylate and alkenyl aldehydes, in the presence of quinuclidine as a base catalyst, in methanol at ambient temperature, afforded excellent yields of the MBH adduct which was subsequently ring-closed with the Grubbs second generation catalyst. Construction of furo[3,4-*c*]pyran skeleton, starting from Baylis–Hillman adducts, via ring-closing metathesis (RCM, catalyst **4**) of *exo*-methylene tetrahydrofuran has also been reported (Scheme 34) [80].

The synthesis of the B.-H. adducts was effected in several steps including propargyl alcohol introduction, radical cyclization, reduction and allylation.



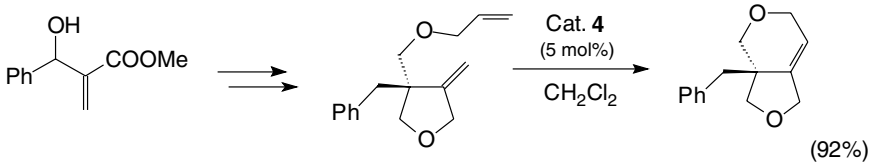
R = COOMe

Scheme 33. Synthesis of carbocyclic alkenols using the Morita–Baylis–Hillman/RCM protocol.

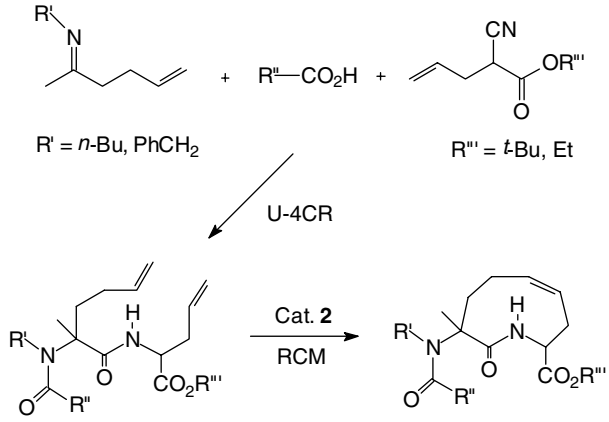
14. Stepwise Ugi/metathesis reactions

A straightforward strategy to unsaturated nine-membered lactams, potentially useful as external reverse turn inducers, has been developed by Banfi et al. [81a] by coupling the multicomponent Ugi reaction (Ugi-4CR) with ring-closing metathesis. By this approach, libraries of compounds of this class could be prepared in a few steps just manipulating three variables (R′, R″, R‴) existing in the starting materials employed in the Ugi reaction (Scheme 35).

It is worth noting that this is the first example of cyclization through RCM (with catalyst **2**) of secondary amides to nine-membered lactams. Overall yields ranged from moderate to good for both processes, Ugi-4CR (69–93%) and RCM (42–69%). Additionally, RCM reactions were found to be highly stereoselective (*Z*) with regard to the double bond configuration. Very recently, allylation/RCM on reaction products from a Ugi four-component coupling has been reported in a diversity-oriented synthetic approach toward cyclized peptidomimetics with various appendages [81b]. Related to the above Ugi couplings, a palladium-catalyzed four-component cascade process has been described [81c]; the latter involves carbon monoxide, allene and aryl/heteroaryl iodides generating (π-allyl) palladium species which are intercepted by alkene tethered nitrogen nucleophiles to afford 1,6- and 1,7-dienones. Subsequent RCM leads to five- and six-membered *N*-heterocyclic enones, active dipolarophiles in 1,3-dipolar cycloaddition reactions.



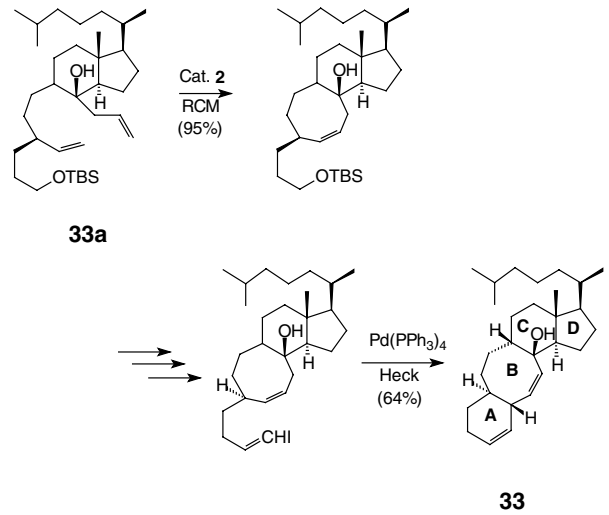
Scheme 34. RCM of Baylis–Hillman adducts.



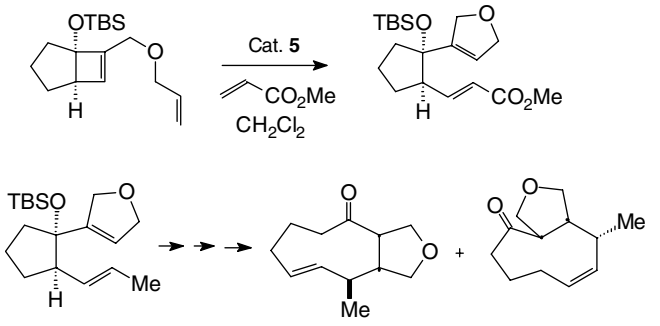
Scheme 35. Synthesis of lactams by stepwise Ugi-4CR/RCM.

15. Metathesis/Heck reaction

To access polycyclic systems containing eight-membered carbocycles, a large class of compounds of importance in organic chemistry, biology and medicine, a methodology has been devised for construction of steroid-like systems using a combination of RCM and Heck cyclizations. The stereoselective synthesis of the 6-8-6 fused carbocyclic system, that mimics the intermediate structure for the transition pre-vitamin $D_3 \rightarrow$ vitamin D_3, is exemplified below for compound **33** [82].



In the basic carbon framework, ring A was formed by Heck reaction in acetonitrile catalyzed by $Pd(PPh_3)_4$, and ring B by RCM catalyzed by the first generation Grubbs catalyst **2** (15%, in CH_2Cl_2). Of the three envisaged pathways, the successful route involved RCM and Heck as first and last key steps, respectively. It was shown that the essential factor for construction of a cyclooctene ring B is to achieve RCM on less-substituted, conformationally predisposed dienes (e.g. **33a**), whereas with more substituted diene substrates the ring-closing reaction (with either catalyst **2** or **4**) resulted instead in formation of a six-membered ring B. Of note is also the observation that all reactions in the sequence, including Heck and RCM, proceeded stereoselectively.



Scheme 36. Cascade reactions ROM/RCM/oxy-Cope rearrangement.

16. ROM/RCM/Cope rearrangement

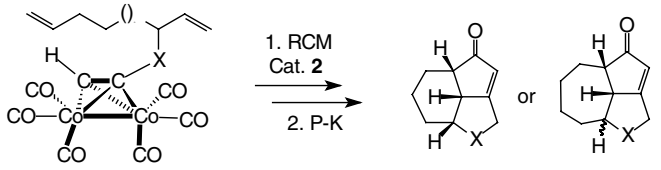
A tandem ring-opening metathesis/ring-closing metathesis/oxy-Cope rearrangement, developed by White and Snapper, enables flexible access to building blocks and various polycyclic units useful in synthesis of natural compounds (Scheme 36) [83]. The strategy benefits from the recognized high activity and selectivity displayed in metathesis reactions by the second generation Grubbs and Hoveyda–Grubbs catalysts. Since metathesis steps occur with high yields (82–95%) a good overall outcome of the tandem is attained (side reactions, such as dimerization of cyclobutene substrates or secondary metathesis intermediates, have not been detected).

By this reaction sequence, stereocontrolled preparation of a variety of medium ring-containing bicyclic systems became possible.

17. Cyclization reactions/RCM

In recent years an increasing number of synthetic applications use classical cyclization reactions in conjuction with metathesis-based transformations. An eloquent example is association of RCM with the presently trendy Pauson–Khand reaction in synthesis of important cyclic frameworks of natural compounds and analogues. Appropriate dienynes, complexed to Co, were subjected to the tandem RCM/intramolecular Pauson–Khand for gaining access to tricyclic compounds in one step [84]. The methodology allowed synthesis of the 6,5,5- and 7,5,5-systems (Scheme 37).

An interesting related methodology, making use of the Nicholas reaction/RCM tandem, has been recently envisaged for the stereoselective synthesis of eight-membered cyclic ethers and fruitfully applied in the short synthesis of (+)-*cis*-lauthisan [85]. The method is illustrated for *cis*-2,8-disubstituted oxocanes and the parent unsaturated precursors, prepared from the corresponding $Co_2(CO)_6$-cycloalkynic ethers (Scheme 38).



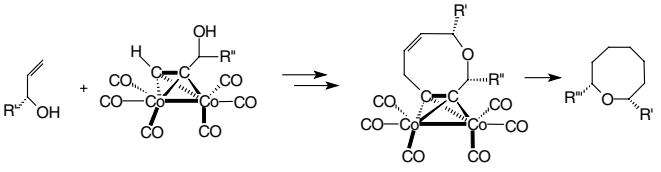
Scheme 37. Synthesis of tricyclic compounds by tandem RCM/Pauson–Khand.

Key steps to the latter compounds are ether linkage formation by intermolecular Nicholas reaction, RCM of the suitable acyclic dienyl ethers and montmorillonite K-10 induced isomerization of the complexed cycloalkynes.

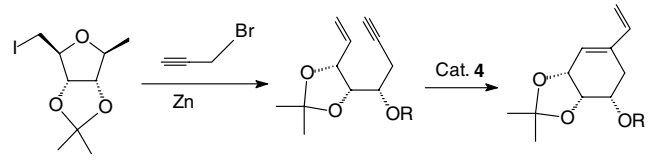
Carbohydrate carbocyclization by a tandem zinc-mediated reaction/RCM has been developed by Poulsen and Madsen [86]. According to this protocol, methyl 5-deoxy-5-iodo-pentofuranosides are reductively ring-opened and propargylated in a in the presence of zinc. The 1,7-enynes thus obtained are subjected to RCEYM with catalyst 4 to produce functionalized 1-vinyl cyclohexenes (Scheme 39).

Furthermore, by adding $C_6H_5CH_2NH_2$ into the tandem reaction, an amino group can be introduced in the 1,7-enyne intermediate product. Also, addition of 2-TMS-ethynylcerium(III) chloride, after the reductive ring-opening, produces the corresponding 1,6-enynes. The 1,3-dienes can be further annulated through a Diels–Alder reaction, with good control of stereochemistry. The approach constitutes an efficient route for rapid carbocyclization and annulation of carbohydrates to produce an array of functionalized five- and six-membered ring systems.

In a rather elaborate technique, RCM in conjunction with sequential conventional cyclizations enables essential steps in the highly efficient and enantioselective total synthesis of the alkaloid (−)-**205B** and of related alkaloids. The 3,5-disubstituted indolizidine ring, embedded in the 8b-azaacenaphthylene tricyclic scaffold of the alkaloid (−)-**205B**, was constructed prior to RCM through successive cyclizations proceeding in a single reaction vessel, in 70% yield [87]. The final RCM step leading the tricyclic framework gave nearly quantitative yield (Scheme 40).



Scheme 38. Formation of eight-membered cyclic ethers through tandem Nicholas reaction/RCM.

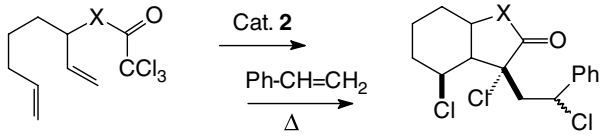


Scheme 39. Carbohydrate synthesis by tandem Zn-mediated addition/RCM reactions.

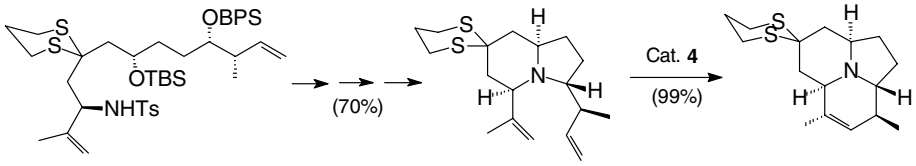
18. Tandem metathesis/Kharasch addition

There is ample evidence that a number of metathesis Ru complexes are efficient initiators in intramolecular and intermolecular Kharasch additions [30,88–93]. These two types of atom transfer radical reactions, ATRC (atom transfer radical cyclization) and ATRA (atom transfer radical addition), are excellent routes to produce highly functionalized cyclic and acyclic compounds of value in synthetic chemistry. The dual activity of the Ru alkylidene complexes, as metathesis and radical initiators, stimulated interesting applications of the two processes in a tandem mode for the synthesis of desirable products with catalyst economy, less waste and easy work-up handling.

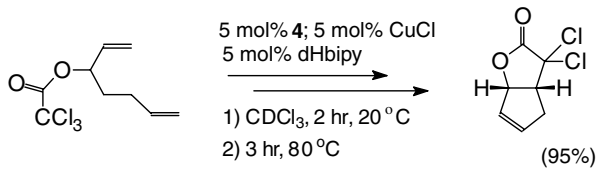
Synthesis of the bicyclic[3.3.0], [4.3.0] and [5.3.0] ring systems with the bisphosphane Grubbs catalyst, $RuCl_2(P\text{-}Cy_3)_2(=CHPh)$, in one step, from the appropriate acyclic precursors via Kharash addition and RCM has been reported by Snapper et al. [94]. Remarkably, these authors found that by combining both the intra- and intermolecular Kharasch reactions with RCM, three new contiguous C–C bonds with multiple stereocentres can be generated by the Ru-catalyst, in a controlled fashion, in one operation (Scheme 41).



Scheme 41. Synthesis of bicyclic ring systems by tandem RCM/Kharasch addition.



Scheme 40. Sequential steps in synthesis of the tricyclic framework of the alkaloid (−)-**205B**.



Scheme 42. Synthesis of bicyclic γ-butyrolactones by tandem RCM/Kharasch addition.

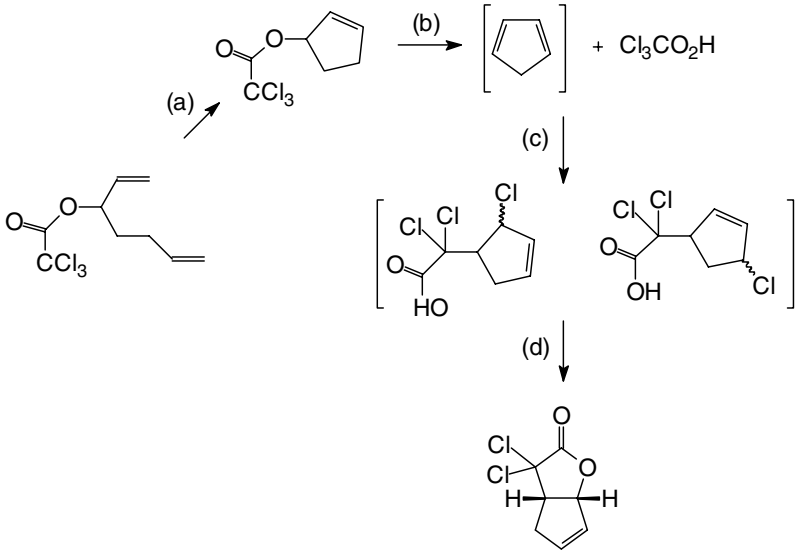
At the same time, Schmidt and Pohler evidenced that also the NHC–Ru Grubbs catalyst **4** is able to initiate both RCM and Kharasch addition reactions of α,ω-dienes, bearing a pendant trichloroacetoxy groups, to bicyclic γ-butyrolactones (Scheme 42) [95].

It is worth noting that the activity and selectivity were very high in both cyclization steps. Significantly, cycloaddition occurring in the second step also showed excellent diastereoselectivity indicating that the different orientations of the additional substituents do not influence either of the cyclizations. More recently, Quayle demonstrated that sequential RCM-ATRC reactions of halo-dienes proceed with either of the Grubbs metathesis catalysts **2** or **4** (bisphosphane- or NHC–Ru) to afford bicyclic lactones or lactams (Scheme 43) [96].

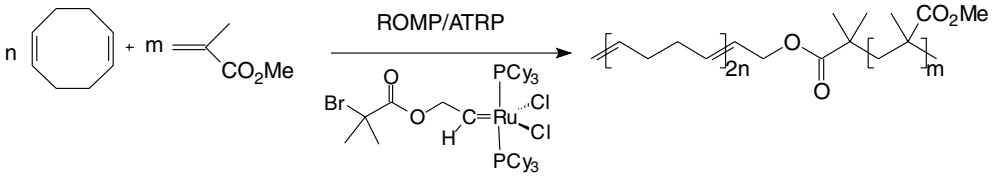
19. Tandem ROMP/ATRP

Synthesis of well-defined polymers with controlled topology and functionalization is presently a fully developed methodology for producing advanced materials with specific properties [97,98]. The dual propensity of ruthenium complexes of being active in metathesis and radical reactions stimulated extensive research on this class of catalytic systems in both ROMP and ATRP reactions. Early work by Grubbs and co-workers [30,99,100] reported on tandem ROMP/ATRP sequences to block copolymers, starting from cycloolefins and vinyl monomers, with the Ru complex **2**. More recently, Demonceau [101] described the concurrent tandem ROMP/ATRP of 1,5-cyclooctadiene (1,5-COD) and methyl methacrylate (MMA), induced by $RuCl_2(PCy_3)_2{=}CH(CH_2OCOCBr(CH_3)_2)$. It was established that both ROMP and ATRP occurred simultaneously, provided that an excess of PCy_3 is added to the reaction mixture (Scheme 44).

Kinetic investigations on the two processes involved in the tandem indicated that addition of PCy_3 slowed down the ROMP of 1,5-COD while the ATRP of MMA was accelerated. Important conclusions on the dual mechanism manifested by the Ru complex in the two reactions were drawn.



Scheme 43. Synthesis of bicyclic lactones by RCM/ATRC cascade reactions.



Scheme 44. Synthesis of diblock copolymers by ROMP/ATRP protocol.

20. Tandem ROMP/RAFT

Quite recently a new strategy for synthesis of ABA-type triblock copolymers based on tandem ROMP-RAFT polymerization has been delineated [102]. Thus, a symmetric, acyclic olefin possessing trithiocarbonate moieties, available in two synthetic steps from commercial starting materials, was selected to act as a chain transfer agent (CTA) in ring opening metathesis polymerizations (ROMP). The efficiency of the ruthenium-catalyzed ROMP of 1,5-cyclooctadiene in the presence of this new CTA was studied in view of producing telechelic polybutadienes bearing trithiocarbonate end groups. The synthesized telechelic polymers are macromolecular chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerization of styrene and acrylate monomers, useful in the synthesis of ABA-type triblock copolymers of varying compositions and possessing monomodal molecular weight distributions.

21. Conclusions

As a result of the constantly upward development of well-defined, highly active and robust molybdenum and ruthenium alkylidene complexes, metathesis became a powerful strategy in synthetic organic chemistry and, when used in conjuction with a variety of organic non-metathetical reactions, a shortcut to access intricate compounds. This review is eloquent demonstration that the artful plan of tandem metathesis/non-metathesis sequences, although conceived only a few years ago, has proved already very successful offering a practical route, sometimes in a single operation, for unprecedented synthetic achievements.

Acknowledgements

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[2] (a) Throughout the review the concept "Tandem" has been used according to the following wide acceptance: one behind another, alongside each other, and an association of events working towards the same goal. "Tandem reactions" = multiple reactions combined in one synthetic operation without isolating intermediates [2b]. "Tandem catalysis" = strategy involving sequential catalytic reactions with minimum change of conditions [2c]. Since this work reviews metathetical and non-metathetical processes, the described coupled reactions are a priori mechanistically distinct [2e];
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