# Grubbs' Ruthenium-Carbenes Beyond the Metathesis Reaction: Less Conventional Non-Metathetic Utility

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## 1. Introduction

Metal-catalyzed olefin metathesis has become one of the most widely used organometallic transformations for carbon−carbon formation in organic synthesis. For this reason, the Royal Swedish Academy of Sciences decided to award the Nobel Prize in chemistry for 2005 to Yves Chauvin, Robert H. Grubbs, and Richard Schrock "For the development of the metathesis method in organic synthesis". In particular, Grubbs has developed powerful new catalysts, stable in air, for metathesis that enabled custom synthesis of many new molecules, such as pharmaceuticals and new polymers with novel properties. Metathesis has developed to industrial and pharmaceutical methods that are more efficient and less polluting. The recognition of this chemistry suggests a big step in the development of new green methods for the synthesis of essential chemicals. Metathesis is an example of how chemistry has been applied for the benefit of man, society, and the environment.

During the past decade, olefin chemistry has seen explosive growth as a synthetic tool; this growth can be attributed by the large number of articles appearing on this subject but also by the development of new catalysts such as ruthenium-based carbenes **1**−**4** (Figure 1), which combine high reactivity with very good tolerance to a wide range of functional groups.[1]

The large number of successful metathesis reactions (CM, ROM, RCM, RRM, and RCEYM) has been intensively investigated (Scheme 1).[2] Besides, nonmetathetic applications promoted by ruthenium−carbene complexes have been observed,[3] often as side reactions due to special reaction conditions or to decomposition of ruthenium catalysts. These

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Benito Alcaide was born in Aldea del Rey, Ciudad Real, Spain, in 1950. He received his B.S. degree (1972) and his Ph.D. (1978) from the Universidad Complutense de Madrid (UCM) under the supervision of Prof. Franco Fernández. His thesis work included synthesis and chiroptical properties of model steroid ketones. After a four-year period working on the chemistry of α-iminoketones and related compounds with Prof. Joaquín Plumet, he began working on β-lactam chemistry. In 1984 he assumed a position of Associate Professor of Organic Chemistry and in 1990 was promoted to Full Professor at the UCM. His current recent interests includes β-lactam chemistry, asymmetric synthesis of compounds of biological interest, free radicals, cycloaddition reactions, allenes, carbenes, metal-promoted cyclizations, C−C coupling reactions, and organocatalysis.

Pedro Almendros was born in Albacete, Spain, in 1966. He received his B.S. degree (1989) and his Ph.D. degree (1994) from the Universidad de Murcia under the supervision of Prof. Pedro Molina and Dr. Pilar M. Fresneda. After three years postdoctoral work for Prof. Eric J. Thomas at the University of Manchester, England, with a Spanish MEC Postdoctoral Fellowship (1995−1997) and an European Marie Curie Postdoctoral Grant (1997−1998), he joined the research group of Prof. Benito Alcaide (UCM, Madrid) in 1998 as Associate Researcher (Contrato de Reincorporación de Doctores y Tecnólogos). Subsequent appointments have included Assistant Professor at the UCM (2000−2002) and Científico Titular (Tenured Scientist) at the Instituto de Química Orgánica General, CSIC, Madrid. In 2007 he was promoted to Investigador Científico (Researcher Scientist) at the IQOG, CSIC, Madrid. His research interest includes β-lactam chemistry, allene chemistry, asymmetric synthesis, carbenes, metal-promoted heterocyclizations, and C−C coupling reactions.



complexes have been shown to catalyze Kharasch addition,[4] oxidation processes,[5] activation reactions (hydrosilylations of terminal alkynes and hydrosilylations of carbonyls),[6] hydrogenation of olefins,[7] cyclopropanation sequences,[8] cycloaddition reactions,[9] and olefin isomerizations,[10] among others. Although the mechanisms of these reactions have not been fully elucidated, they represent an interesting synthetic development.

Some of these nonmetathetic reactions have been optimized and show utility in organic synthesis. Indeed, the

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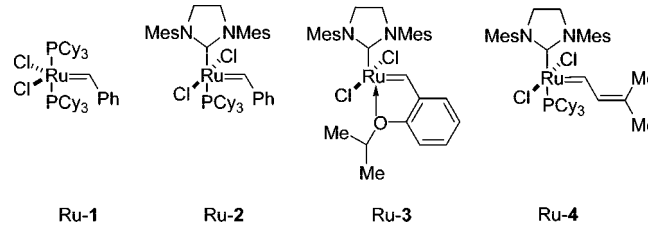
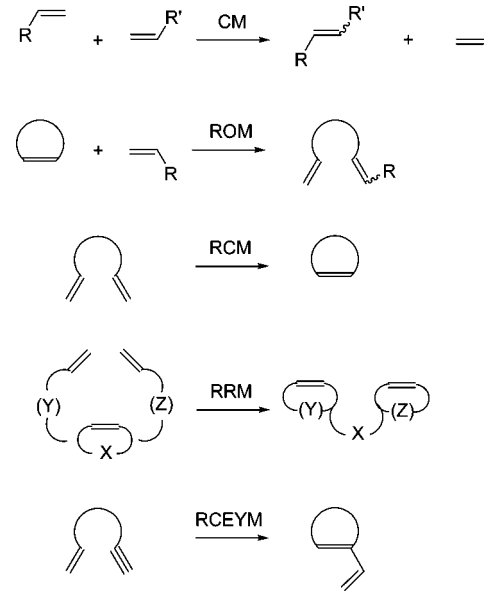


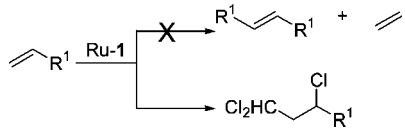

**Figure 1.**

**Scheme 1. Successful Metathesis Reactions: CM, ROM, RCM, RRM, and RCEYM**

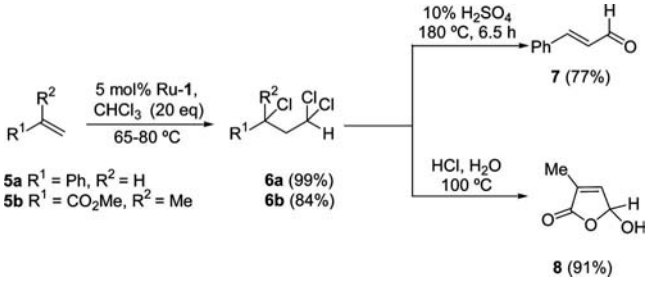



usefulness of the Grubbs' carbenes in deallylation of amines, amides, lactams, imides, pyrazolidinones, hydantoins, and oxazolidinones has been demonstrated.[11] The aim of this review is to provide an overview of the field, concentrating on recent advances in the nonmetathetic behavior of Grubbs' carbenes.

**Scheme 2. New Reactivity of Ru-1 in Kharasch Addition**




**Scheme 3. Kharasch Addition Catalyzed by Ru-1 Followed by Hydrolysis Reaction**




## 2. Kharasch Additions

The widely used Grubbs' ruthenium carbene Ru-**1,** well-known for its ability to promote olefin metathesis, is also an effective catalyst in radical atom transfer reactions such as Kharasch addition. In 1999, Snapper et al. isolated a product derived not from olefin metathesis but from a metal-catalyzed addition of $CHCl_3$ across an alkene (Scheme 2).[12] This chemistry led to the discovery that Ru-**1** is an efficient and mild catalyst for the Kharasch addition of $CHCl_3$ to olefins.[13]

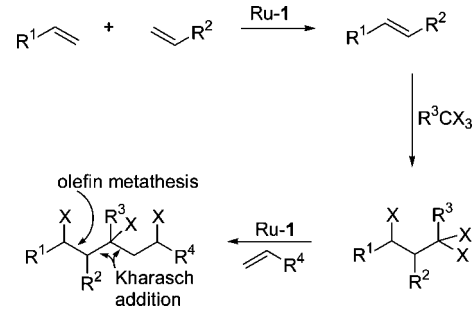
For this reason, they expanded this methodology to several trichloroalkyls groups across a variety of olefins, offering the hydrolysis of the corresponding polyhalogenated adducts a novel access to $\alpha,\beta$-unsaturated ketones, aldehydes, or $\gamma$-hydroxybutenolides.[14] The reaction was carried out using 5−10 mol % of Ru-**1** in the presence of excess trichloroalkanes at 65−80 °C. Alkenes less prone to undergo an olefin metathesis, such as styrenes and acrylates, serve as excellent substrates for Kharasch addition, especially with chloroform or 1,1,1-trichloroethane as their reaction partner. Adduct **6a** can be converted into aldehyde **7** in 77% yield by heating with 10% $H_2SO_4$ in a sealed reaction vessel for 6.5 h (Scheme 3). In comparison to the styrenyl substrates, hydrolysis of the acrylate-derived addition products offered an alternative carbonylation product. Acidic hydrolysis of trichlorinated ester **6b** provided $\gamma$-hydroxybutenolide **8** in 91% yield (Scheme 3).

The two-step sequence represents a convenient method for the attachment of the carbonyl functionality to olefins.

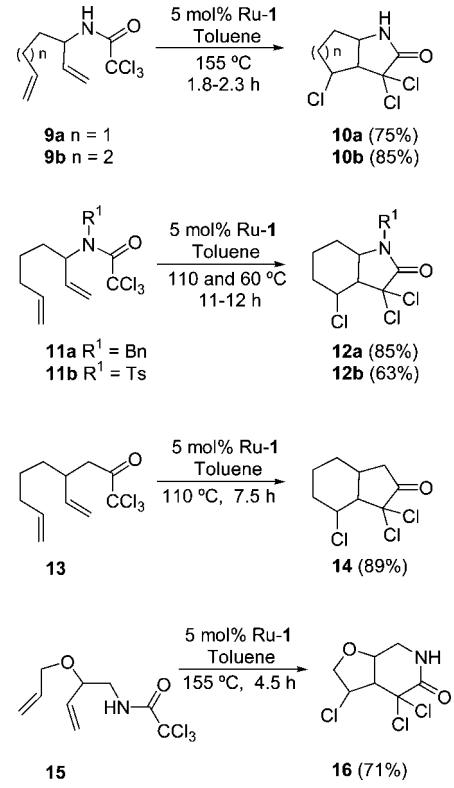
Tandem catalysis can involve multiple chemical transformations in a single reaction vessel, effecting multiple bond changes in a single operation.[15] As synthetic application of these catalytic reactions, a tandem ruthenium-catalyzed olefin metathesis/Kharasch addition, using complex Ru-**1**, was developed to convert acyclic halogenated diene precursors into highly functionalized systems. In this process, a single metal precursor, Ru-**1**, catalyzes the formation of up to three new carbon−carbon and two carbon−halogen bonds in one operation through two mechanistically unique pathways (Scheme 4).[4b]

Bicyclic ring systems [3.3.0], [4.3.0], and [5.3.0] can be prepared from acyclic dienes through a tandem RCM−intramolecular Kharasch addition reaction sequence. The metathesis reaction forms the 5,6-membered rings, at room temperature, followed by a Kharasch addition that generates the 5-membered lactam under more forcing conditions. The

**Scheme 4. Generation of Five New Bonds in a Single Reaction Sequence by Olefin Metathesis−Double Kharasch Addition Catalyzed by Ru-1**



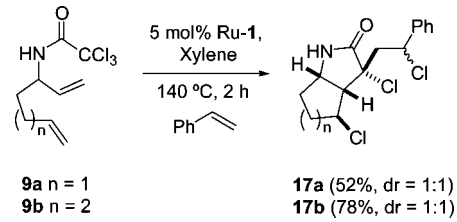

**Scheme 5. Tandem RCM−Kharasch Addition Promoted by Grubbs' Catalyst Ru-1**



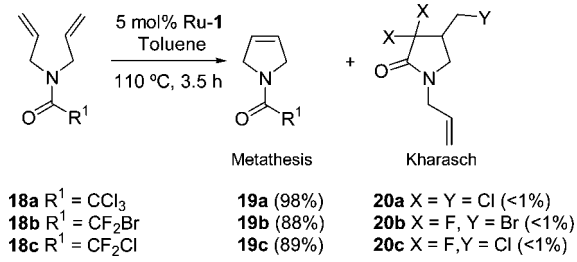

stereochemical outcome of the reaction supports an atom transfer radical mechanism compared to a ruthenium-mediated oxidative addition/reductive elimination pathway. The high temperature required for this intramolecular Kharasch addition is attributed to the unfavorable amide bond rotamer required for ring closure in the radical cyclization. However, the reactions proceed at lower temperatures in substrates **11a** and **11b** although requiring longer reaction times when benzyl or tosyl groups are added to the amide functionality. The aliphatic substrate **13** provides the highest yield of a tandem cycloadduct **14**. Evidently, the conformational freedom offered by removing the amide linkage more than compensates for the reduced Kharasch activity of the trichloroalkyl functionality. An alternative route to the 5,6-ring system is shown with substrate **15**. In this case, a RCM is used to prepare the furanyl ring, followed by a Kharasch addition that installs the 6-membered lactam **16** (Scheme 5).

An efficient example of tandem processes have been obtained when dienes **9a** and **9b** are heated in the presence of styrene, generating compounds **17a** and **17b** selectively in 52% and 78% yields, respectively, as a 1:1 mixture of

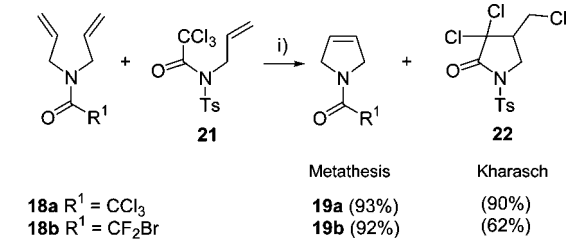
**Scheme 6. Tandem RCM−Intramolecular Kharasch Reaction Followed by an Intermolecular Kharasch Addition Catalyzed by Ru-1**




**Scheme 7. Intramolecular Competition Experiments (Metathesis Versus Kharasch Reactions)**




**Scheme 8. Sequential Metathesis−Kharasch Reactions[a]**

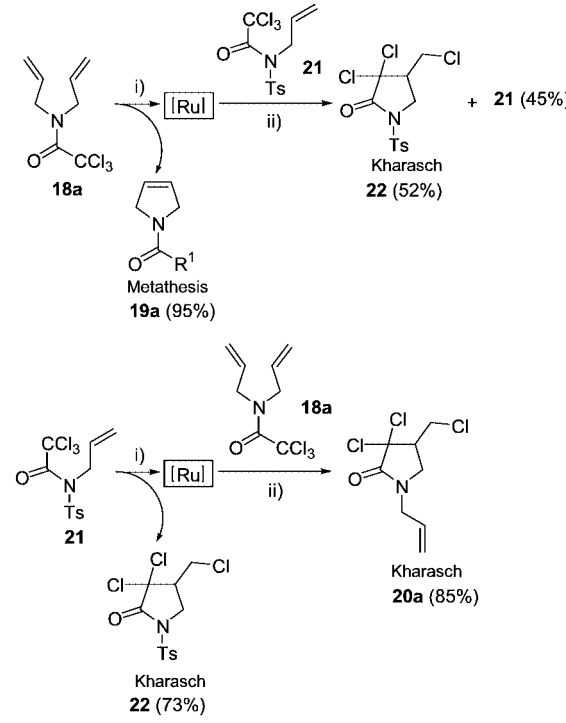



[a]Key: (i) 5 mol% Ru-1, toluene, 110 °C, 3.5 h.

benzyl chlorides. In these reactions, Grubbs' catalyst Ru-**1** first effects the RCM and then, upon heating, promotes an intramolecular Kharasch addition, before carrying out an intermolecular Kharasch on **9a** or **9b** with the addition of styrene. The result is the formation of three new contiguous carbon−carbon bonds, two carbon−halogen bonds, and four new stereogenic centers in a single reaction flask (Scheme 6).

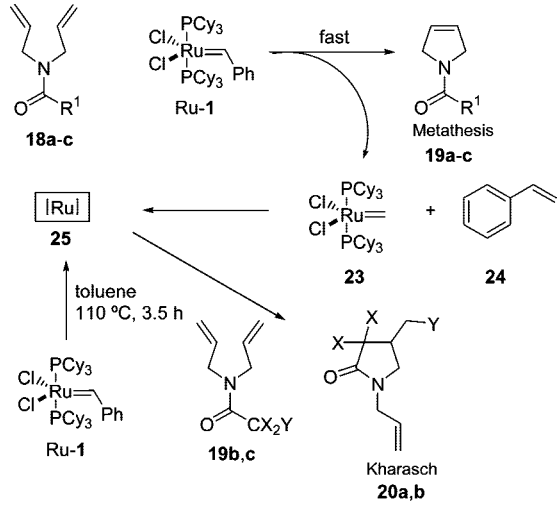
Studies in the group of Quayle have revealed that there is an important rate difference between olefin metathesis and Kharasch reactions in substrates exposed to both reactions conditions.[16] Amides **18** under thermolysis with Ru-**1** afforded the $\Delta^2$-pyrrolines **19** in excellent yields and only trace amounts (<5%) of the alternate Kharasch products **20** (Scheme 7). Taking into account these results, a 1:1 mixture of the amide **18a** and tosamide **21** was subjected to the standard reactions conditions using Ru-**1**. Again, the $\Delta^2$-pyrroline **19a** (metathesis) and the $\gamma$-lactam **22** (Kharasch) products were isolated in excellent yields (93 and 90%, respectively) and the alternate Kharasch product **20a** was not detected (Scheme 8). $^1$H NMR studies suggest that, for the substrate combination of **18a** (or **18b**) and **21**, the metathesis reaction initiates at a much faster rate than the Kharasch reaction (by a factor ~100 at 110 °C) and there is a byproduct generated in the breakdown of the catalyst Ru-**1** that is responsible for the Kharasch activity in these reactions. The sequential addition of the amide **18a** followed by the tosamide **21** to a solution of the catalyst Ru-**1** in refluxing toluene again afforded the $\Delta^2$-pyrrolines **19a** and the lactam **22**. However, upon reversing the order of addition of the

**Scheme 9. Sequential Addition of Substrates to Catalyst Ru-1[a]**




[a]Key: (i) 5 mol% Ru-1, toluene, 110 °C, 3.5 h; (ii) toluene, 110 °C, 3.5 h.

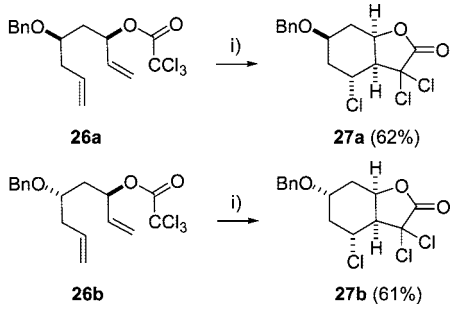
**Scheme 10. Metathesis Is Faster than the Alternative Kharasch Reaction Catalyzed by Ruthenium Carbene**




substrates to the catalyst, that is, when tosamide **21** was added first to a solution of the catalyst in toluene at 110 °C followed by the amide **18a**, then the Karasch product **20a** and **22** became the only isolable products of the reaction, with none of the alternate metathesis product **19a** (Scheme 9).

This group suggested that the process requires either direct denaturation of complex Ru-**1** (Scheme 10), which is itself formed as a byproduct of the initial metathesis cycle, or generation of a new ruthenium complex (or complexes **25**). Presumably there is a fine balance between the rate of decomposition of **23** into **25** and its participation in subsequent metathesis reactions.[17] However, once **23** has decomposed into **25**, metathetical reactivity is lost while "Kharasch" activity is retained. Support of this hypothesis can be found

**Scheme 11. Tandem Ring-Closing Metathesis−ATRC Reaction Sequence Catalyzed by Carbene Ru-2**[a]




[a]Key: (i) 5 mol% Ru-**2**, toluene, 20-110 °C.

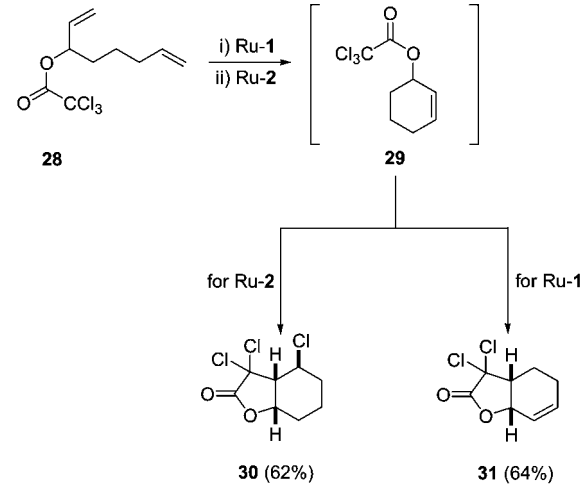
in Grubbs' work, where it has been shown that **23** is considerably less stable than Ru-**1** and is known to undergo thermolysis to a ruthenium complex of unknown constitution.[18]

Schmidt et al.[19] demonstrated that tandem ring-closing metathesis−atom transfer radical cyclization reaction (Kharasch-type reaction) sequence was possible. The second-generation Grubbs' catalyst, which had previously been reported by several groups to be less reactive in ATRC reactions than the first-generation catalyst, turned out to mediate both steps of these sequences in preparatively useful yields and rates of conversion. The diene **26a** was treated with 5 mol % of Ru-**1** in toluene at ambient temperature. Unfortunately, under these conditions, the reaction stops at ~30% conversion after 2 h. Even after 20 h at ambient temperature, no improvement could be observed. The experiment was repeated using 5 mol % of second-generation Grubbs' catalyst Ru-**2**. This led to a rapid consumption of the metathesis precursor within 30 min and clean formation of the primary metathesis product. Heating the mixture to reflux induced the formation of a bicyclic product via ATRC. The trichlorinated compound **27a** was obtained as the sole product in high diastereoselectivity, and no elimination products could be detected. Conversion of the diastereomeric precursor **26b** into **27b** proceeds equally efficiently, indicating that the different orientation of the benzyloxy group does not influence the efficiency of either cyclization step (Scheme 11).

The second-generation catalyst Ru-**2** can promote metathesis and ATRC reactions (Kharasch-type reaction) for obtaining bicyclic lactones[4a] in a similar manner as for the complex Ru-**1**[20] (Scheme 12). The cyclization of the readily available trichloroacetate **28** to ester **29** could be effected using Ru-**2** in $ClCH_2CH_2Cl$ (98% yield), and **29** could be further cyclized to trichlorolactone **30** under copper catalysis in 79% isolated yield. A combination of these two processes has been described, when compound **28** was treated with first-generation Grubbs' catalyst Ru-**1** (5 mol %) first at ambient temperature for 3 h and later under mild thermolysis to afford directly the unsaturated lactone **31** (in 64% yield) with a trace amount (<5%) of trichlorolactone **30**. When this reaction was repeated with the second-generation catalyst Ru-**2**, the trichlorolactone **30** was isolated as the major product (62% yield), together with a minor amount of the unsaturated lactone **31** (5%). In both instances, the sequential RCM−Kharasch sequences proceeded without requirement of a copper cocatalyst, while the product distribution is obviously dependent upon the catalyst system employed.

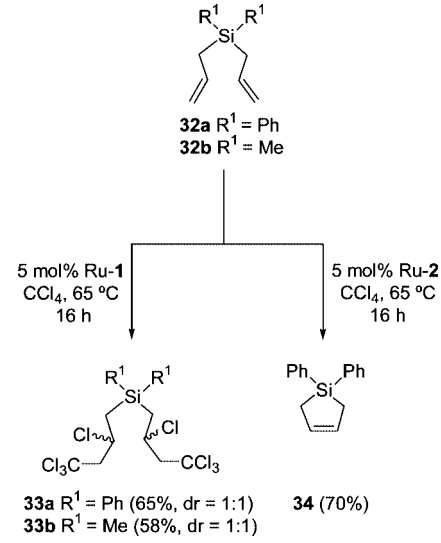
The application of first-generation ruthenium catalyst to the synthesis of silacycloalkenes was described in 2001 by

**Scheme 12. Sequential RCM/Kharasch Reaction Sequences Catalyzed by Grubbs' Carbenes**[a]




[a]Key: (i) (a) 5 mol% Ru-**1**, toluene, 20 °C, 3 h; (b) 110 °C, 16 h; or (ii) (a) 5 mol% Ru-**2**, 5 mol% CuCl, 5 mol% dHbipy, $DCCl_3$, 20 °C, 2 h rt, then 3 h at reflux

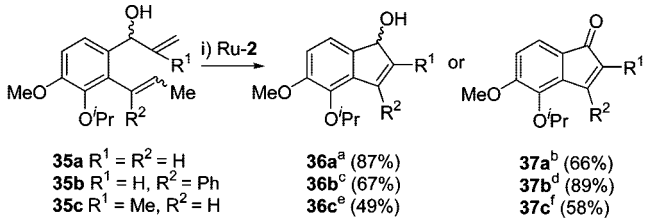
**Scheme 13. Divergent Reactivity of Diallylsilanes Catalyzed by Grubbs' Carbenes: Radical Addition Versus RCM**




Undheim.[21] Although RCM products were obtained in good yields, rather high catalyst loading and elevated temperatures were required to achieve complete conversion. In this context, Schmidt[22] decided to study the reactivity of diallylphenylsilanes with Grubbs' ruthenium catalysts in the atom transfer radical addition (ATRA, Kharasch-type reaction).

Starting from diallyldiphenylsilane **32a** the linear product **33a** was prepared through a double addition of $CCl_4$ with 5 mol % of Ru-**1** at 65 °C during 16 h. It should be noted that any type of cyclization was shown. The larger silicon atom in combination with the two sterically demanding phenyl substituents leads to a transition state geometry that is unfavorable for cyclization reactions, due to a larger distance between the reacting centers. The same result was observed for the dimethyl analogue **32b**. Application of Ru-**2** in the same reaction conditions to **32a** gives silacyclopentene **34** in good yield without noticeable formation of any radical addition product (Scheme 13). The reduced RCM activity of first-generation catalyst Ru-**1** toward diallylsilanes can be understood if the larger atomic radius of silicon is taken into

**Scheme 14. RCM−Dehydrogenative Oxidation Sequence Catalyzed by Carbene Ru-2[a]**




[a]Key: (i) (a) 5 mol% Ru-**2**, $CH_2Cl_2$, r.t., 2 h; or (b) 8 mol% Ru-**2**, toluene, 80 °C, 2 h; (c) 5 mol% Ru-**2**, $CH_2Cl_2$, r.t., 1 h; or (d) 8 mol%, Ru-**2**, xylene, 110 °C, 18 h; (e) 10 mol% Ru-**2**, toluene, 60 °C, 24 h; or (f) 10 mol%Ru-**2**, toluene, 60 °C, 48 h.

account. This methodology described that, for RCM substrates that are difficult to cyclize, a cyclization mode involving atom radical transfer addition can efficiently compete with the metathesis pathway. The diastereoselectivity observed is obviously the result of kinetic control. First- and second-generation Grubbs' ruthenium catalysts gave qualitatively different results, with less active metathesis catalyst selectively promoting a nonmetathesis reactivity pattern.

## 3. Oxidation Processes

### 3.1. Dehydrogenation Reactions

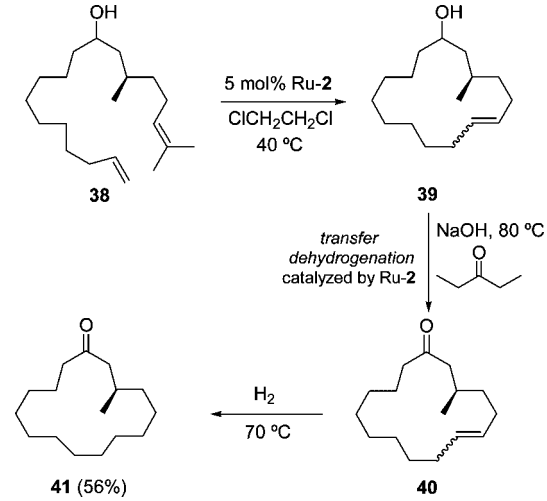
The oxidation reaction is considered an excellent strategy for constructing aromatic compounds as indenols or pyrroles due to the importance of these compounds in organic chemistry.[23] The potential of the dehydrogenation reaction was observed using Ru-**2** for providing (*R*)-(−)-muscone, an interesting natural product.

The indene skeleton[24] is a fairly common benzannulated motif in natural products. The formation of indenones or substituted indenols, with reasonable selectivity, from the corresponding acyclic precursors can be achieved by tandem RCM−dehydrogenative oxidation reaction mediated by Grubbs second-generation catalyst.[5c] Standard RCM experimental procedures (moderate temperatures), including the rigorous exclusion of oxygen from the reaction mixtures, allowed the isolation of indenols **36a**−**c**. These kinds of compounds under harsher reaction conditions (80−110 °C) also can be converted into their corresponding indenone substrates **37a**−**c** in situ by way of a novel tandem dehydrogenative oxidation reaction (Scheme 14). The structural skeletons that result from these tandem strategies mediated by Ru-**2** have the potential of being applied to the synthesis of interesting natural products and their analogues.

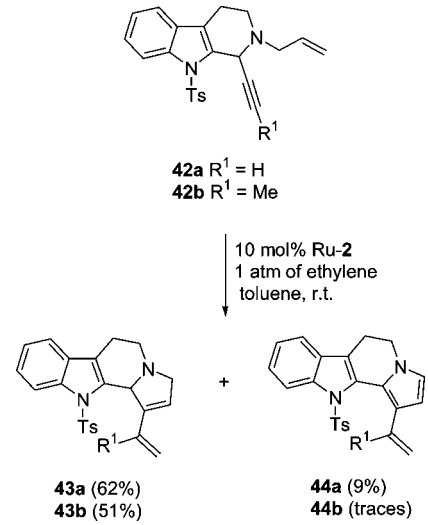
Synthesis of the valuable natural product (*R*)-(−)-muscone **41** was carried out by a "one-pot" reaction catalyzed by Ru-**2**.[25] Thus, initially substrate **38** was cyclized by RCM to the product **39**. The addition of 3-pentanone and NaOH initiated the (Ru catalyzed) transfer dehydrogenation of the resulting alcohol **39** and afforded the macrocyclic ketone **40** (Scheme 15). Finally, the chemoselective hydrogenation at the olefinic double bond gave the ketone **41** in 56% overall yield.

The metathesis reaction of enynes **42** in toluene with the ruthenium alkylidene complex Ru-**2**, under an ethylene atmosphere, achieved the corresponding dienes **43** in good yield along with small amounts of oxidized pyrroles **44**. This ability to oxidize the reaction product is a nonmetathetic

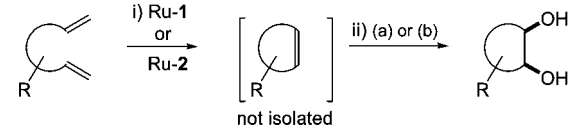
**Scheme 15. One-Pot/Three-Step Synthesis of (*R*)-(−)-Muscone Catalyzed by Ru-2**




**Scheme 16. Reactivity of Enynes 42 under Ru-2 Complex Catalysis**




**Scheme 17. One-Pot Ring-Closing Metathesis/ Dihydroxylation Sequence Catalyzed by Grubbs' Carbenes[a]**




[a]Key: (i) Ru-**1** or Ru-**2**; (ii) crude containing the catalyst and (a) $NaIO_4$, $YbCl_3 \cdot 6H_2O$ or (b) $CeCl_3$, $NaIO_4$.

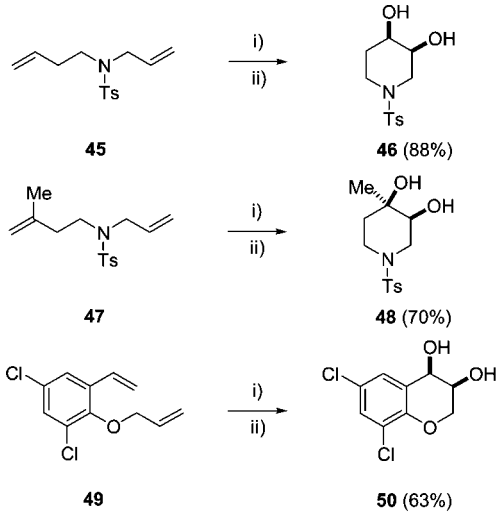
behavior of ruthenium catalyst, and it was particularly observed with complex of type Ru-**2** (Scheme 16).[26]

### 3.2. Dihydroxylation Reactions

In this section is described a ruthenium-catalyzed olefin metathesis−oxidation sequence for the preparation of *cis*-diols from simple olefinic precursors (Scheme 17).

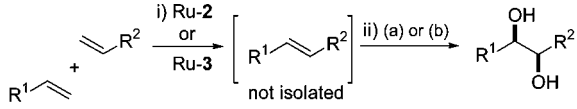
Blechert et al.[5a] have developed a new process combining a metathesis step (RCM or CM) followed by *cis*-dihydroxylation step using Ru-**1**. Dienes bearing a variety of functional groups, **45**, **47**, and **49**, were treated with 1 mol % of Ru-**1** in dichloromethane under reflux conditions (Scheme 18). Some studies revealed that the presence of small quantities of dichloromethane resulted in low yields in the dihydroxy-

**Scheme 18. RCM−Dihydroxylation Sequence Catalyzed by Carbene Ru-1[a]**



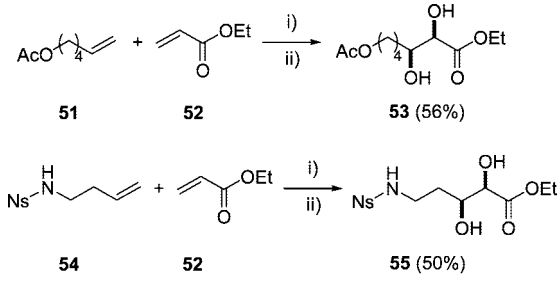

[a]Key: (i) 1 mol% Ru-**1**, $CH_2Cl_2$, Δ; (ii) then MeCN/EtOAc/$H_2O$, 0 °C, $NaIO_4$, $YbCl_3·6H_2O$.

**Scheme 19. One-Pot Cross-Metathesis−Dihydroxylation[a]**




[a]Key: (i) Ru-**1** or Ru-**3**; (ii) crude containing the catalyst and (a) $NaIO_4$, $YbCl_3·6H_2O$ or (b) $CeCl_3·7H_2O$, $NaIO_4$.

**Scheme 20. CM−Dihydroxylation Sequence Catalyzed by Carbene Ru-3[a]**



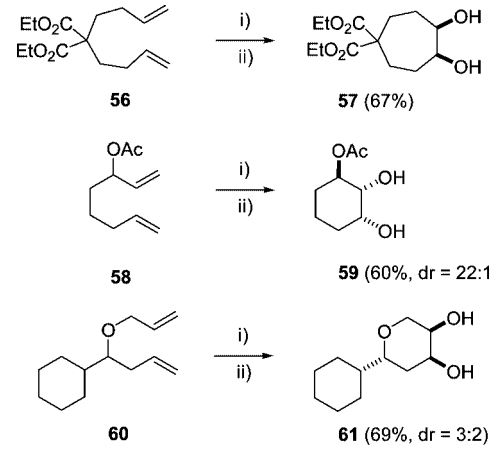

[a]Key: (i) 2.5-3 mol% Ru-**3**, $CH_2Cl_2$, Δ; (ii) then MeCN/EtOAc/$H_2O$, 0 °C, $NaIO_4$, $YbCl_3·6H_2O$.

lation step. Therefore, the solvent was removed after completion of the RCM step. The crude ring-closed product containing Ru-**1** was treated with 10 mol % of $YbCl_3·6H_2O$ and 1.2−1.6 equiv of $NaIO_4$. The overall yield was increased with shorter reaction times. For compound **49**, the electron density of the double bond appears to influence this dihydroxylation step, with electron-poor double bonds leading to higher yields.

In the process of the one-pot CM−dihydroxylation, likely partners were chosen in order to give good selectivity and good yield (Scheme 19).

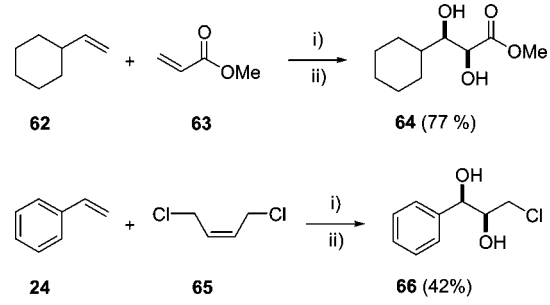
On the other hand, the protocol for CM−dihydroxylation was changed and the Hoveyda−Grubbs catalyst Ru-**3** (2.5−3 mol %) was used (Scheme 20) because it has been previously shown to be very efficient for CM with electron-deficient olefins.[27] A 1:1 mixture of coupling partners was used for the reactions. The dihydroxylated products were successfully obtained, but the yields were lower than for the RCM−dihydroxylation.

**Scheme 21. RCM−Dihydroxylation Sequence Catalyzed by Ru-2[a]**




[a]Key: (i) 5 mol% Ru-**2**, [0.1-0.2 M in EtOAc], r.t.; (ii) then MeCN/$H_2O$, $NaIO_4$, $CeCl_3·7H_2O$.

**Scheme 22. CM−Dihydroxylation Sequence Catalyzed by Ru-2[a]**




[a]Key: (i) 5 mol% Ru-**2**, [0.1-0.2 M in $CH_2Cl_2$], r.t.; (ii) then EtOAc/MeCN/$H_2O$, $NaIO_4$, $CeCl_3·7H_2O$.

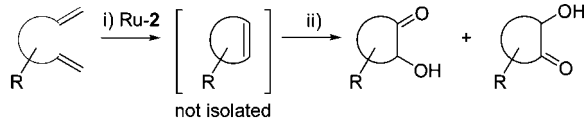
This is presumably because the Hoveyda catalyst Ru-**3** promotes the dihydroxylation less effectively and the diols required more time of reaction.

A similar methodology was developed by Snapper,[5b] but in this case the dihydroxylation reaction was performed with alkylidene Ru-**2**. After completion of the RCM, the EtOAc solution containing the metathesis products was added to a stirred suspension of the preformed Ce(IV)−periodate complex in a mixture of MeCN/$H_2O$. This complex was formed by the treatment of 1.5 equiv of $NaIO_4$ with 10 mol % of $CeCl_3·7H_2O$. The reaction was rapid, and the *cis*-dihydroxylated products **57**, **59**, and **61** were obtained in 60−69% yields (Scheme 21). The oxidation does not proceed in the absence of the ruthenium complex. Again, a variety of functional groups can be tolerated in the tandem sequence (RCM or CM). Scheme 22 demonstrates that aliphatic and aromatic olefins are viable substrates for the tandem CM/dihydroxylation reaction sequence. In this methodology, the CM step can be performed in different solvents. For example, diol **64** is isolated in 49% yield in EtOAc and 77% yield in $CH_2Cl_2$, and when the reaction is run in the absence of solvent, the diol is isolated in 19% yield.

## 3.3. Ketohydroxylation Reactions

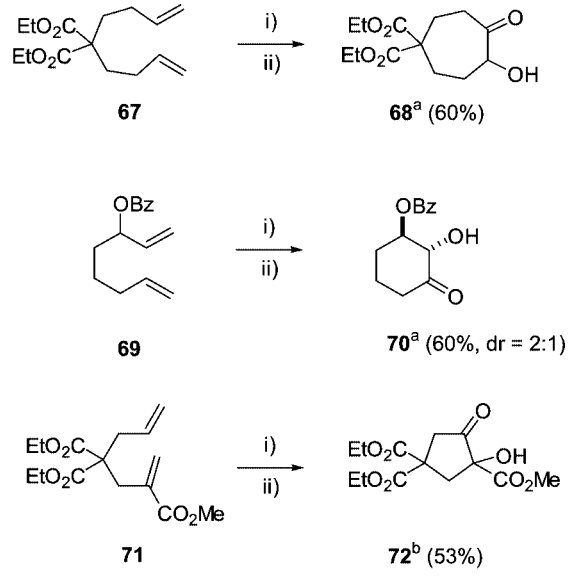
It has been described in the literature that $RuCl_3$-catalyzed oxidations of olefins to generate *cis*-diols or α-hydroxy ketones show dependence on the reaction conditions used.

**Scheme 23. One-Pot Ring-Closing Metathesis/ α-Ketohydroxylation Catalyzed by Carbene Ru-2[a]**




[a]Key: (i) Ru-**2**; (ii) crude containing the catalyst and oxone, $NaHCO_3$, EtOAc/MeCN/$H_2O$.

**Scheme 24. RCM/α-Ketohydroxylation Sequence Catalyzed by Carbene Ru-2[a]**




[a]Key: (i) (a) 5 mol% Ru-**2**, [0.1 - 0.2 M in EtOAc], r.t.; or (b) 10 mol% Ru-**2**, [0.1 - 0.2 M in EtOAc], r.t.; (ii) then MeCN/$H_2O$, $NaHCO_3$, oxone.

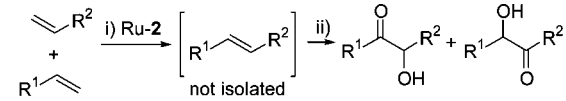
In situ formation of the oxidative species, $RuO_4$, or $NaIO_4$ in the presence of a Lewis[28] or Brønsted[29] acid afforded diols in high yields, whereas treatment with oxone and $NaHCO_3$ provided α-hydroxy ketones.[30] In light of these transformations, Snapper and colleagues modified a ruthenium alkylidene in situ to effect similar oxidations after completing a metathesis reaction (Scheme 23).[5b]

The RCM/α-ketohydroxylation of different olefinic substrates was studied with the Grubbs' second−generation catalyst Ru-**2** in ethyl acetate (Scheme 24). After 1 h, the reaction was diluted with MeCN/$H_2O$ and treated with $NaHCO_3$ and oxone. The oxidation of unsymmetrical substrates (for example **69**) led to a mixture of regioisomers (the regioselectivity was 2:1 and only the major product is shown). Oxidations of trisubstituted olefins like **71** led to the tertiary alcohol-containing product **72** in moderate yield. Taking these results into account, the strategy was expanded to include cross-metathesis (CM). Initial olefinic reaction partners were chosen to afford the CM products in good yield and *E*/*Z* selectivity (Scheme 25). The metathesis in $CH_2Cl_2$ with a 1:2 mixture of olefins gave the desired compounds in excellent yields. For the ketohydroxylation step, the excess of both cross-metathesis partner and solvent were removed in vacuo prior to addition of the oxidants (Scheme 26).

### *3.3.1. Preparation of α-Methyl Ketones*

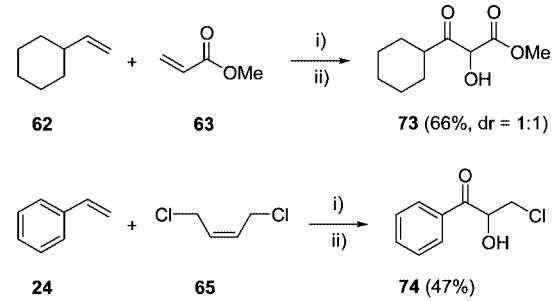
In different studies it has been shown that the terminal vinyl group proximal to tertiary allylic hydroxyl groups is much more reactive toward the Grubbs' initiator than its methyl ester analogue. For this reason, this hypothesis was tested in route to the synthesis of the C1−C14-containing fragment of the marine natural product callipeltoside A. However, the desired RCM reaction did not occur. Indeed, the starting substrate remained intact throughout. Then, the reaction was examined using a simpler secondary alkenol with Ru-**1**, and the formation of the methyl ketone **76** was observed (Scheme 27).[31]

**Scheme 25. Cross-Metathesis/α-Ketohydroxylation Catalyzed by Carbene Ru-2[a]**



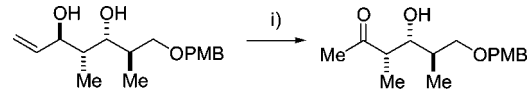

[a]Key: (i) Ru-**2**; (ii) crude containing the catalyst, EtOAc, $H_2O$, $NaHCO_3$, and oxone.

**Scheme 26. CM/α-Ketohydroxylation Sequence Catalyzed by Carbene Ru-2[a]**




[a]Key: (i) 10 mol% Ru-**2**, [0.1-0.2 M in $CH_2Cl_2$], r.t.; (ii) then EtOAc/MeCN /$H_2O$, $NaHCO_3$, oxone.

**Scheme 27. Preparation of α-Methyl Ketone 76 Catalyzed by Carbene Ru-1[a]**



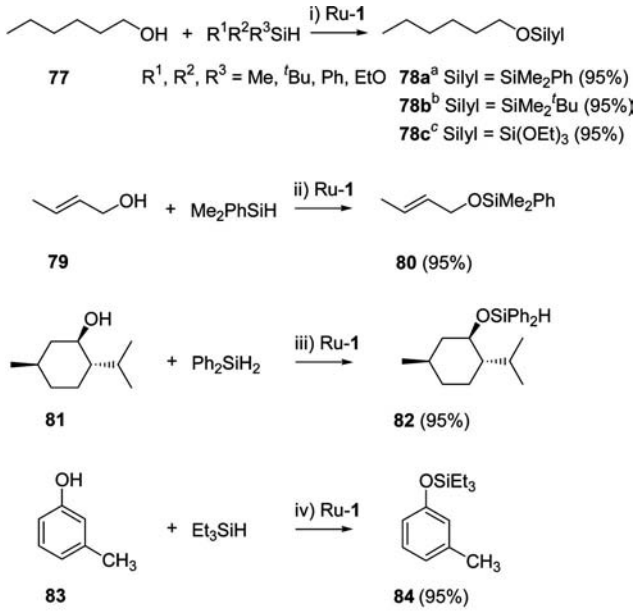

[a]Key: (i) 50 mol% Ru-**1**, $CDCl_3$, r.t.

## *4. Activation Reactions*

## 4.1. Activation of Silanes By Grubbs' Carbenes

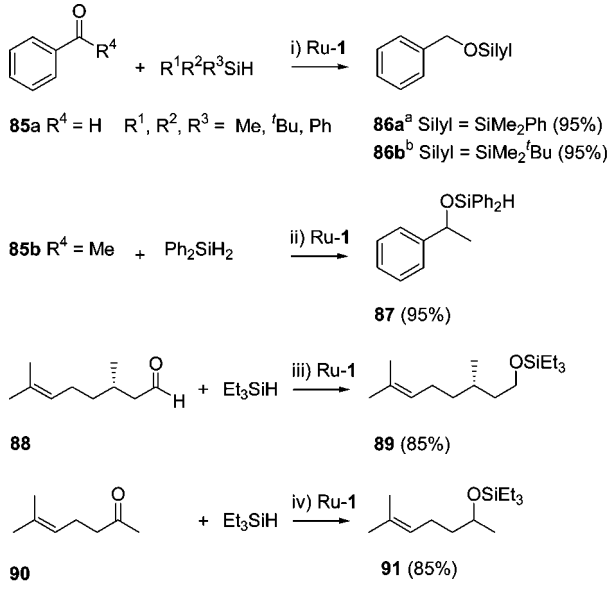
Silyl ethers comprise one of the most widely used classes of protecting groups in synthetic chemistry due to their ease of formation and selective removal in the presence of other protecting groups.[32] Although the conventional silylation procedure is straightforward and dependable, its reliance on environmentally undesirable organic solvents as well as excess amine bases makes the synthesis of silyl ethers an excellent target for greener methodology. Lee et al. found that ruthenium−carbene complex Ru-**1** is an effective catalyst for the condensation of alcohols and silanes, showing no indication of competing olefin metathesis even with a terminal alkene.[33] In the presence of 0.5 mol % of Ru-**1**, these reactions efficiently give complete conversion of the substrate alcohols to the corresponding silyl ethers in nearly quantitative yield. Generally, dialkyl aryl ($Me_2PhSiH$) and alkyl diaryl ($Ph_2MeSiH$) silanes react more efficiently than

**Scheme 28. Dehydrogenative Condensation of Alcohols and Silanes Catalyzed by Carbene Ru-1[a]**




[a]Key: (i) 0.5 mol% Ru-**1**, [(a) 25 °C, 0.25 h; or (b) 45 °C, 6 h; or (c) 35 °C, 5.5 h]; (ii) 0.5 mol% Ru-**1**, 25 °C, 2 h; (iii) 0.5 mol% Ru-**1**, 25 °C, 0.25 h; (iv) 0.5 mol% Ru-**1**, 55 °C, 8h.

**Scheme 29. Hydrosilylation of Aldehydes and Ketones Catalyzed by Carbene Ru-1[a]**

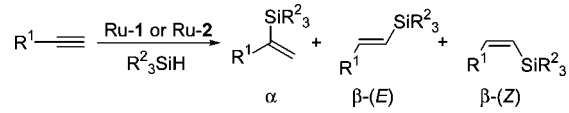



[a]Key: (i) 1 mol% Ru-**1**, [(a) 50 °C, 3 h; or (b) 80 °C, 0.5 h]; (ii) 1 mol% Ru-**1**, 50 °C, 2 h; (iii) 1 mol% Ru-**1**, 80 °C, 1 h; (iv) 1 mol% Ru-**1**, 80 °C, 6 h.

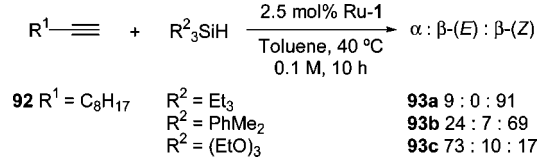
either trialkyl ($Et_3SiH$, $^tBuMe_2SiH$) or trialkoxy silanes [$(EtO)_3PhSiH$] (Scheme 28).

After demonstrating the generality of Ru-**1** for alcohols, the same research group extended this methodology for the hydrosilylation of aldehydes and ketones.[33] In this case, 1 mol % of Ru-**1** promoted the hydrosilylation of aldehydes and ketones with a variety of silanes (Scheme 29). In contrast to dehydrogenative condensation between alcohols and silanes, carbonyl−hydrosilylation reactions required higher temperatures (>50 °C), which generated a slightly increased amount of silyl byproducts. In general, these two types of reactions showed similar reactivity.

**Scheme 30. Hydrosilylation of Terminal Alkynes Providing Three Isomeric Vinylsilane Products**




**Scheme 31. Hydrosilylation of Terminal Alkyne 92 Catalyzed by Carbene Ru-1**



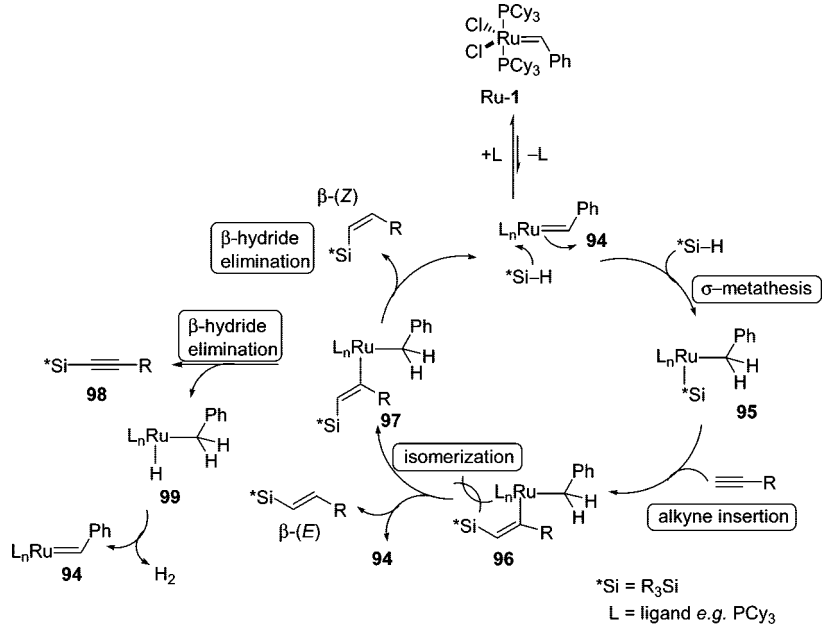

## 4.2. Hydrosilylation of Terminal Alkynes

Vinylsilanes have emerged as powerful intermediates in organic synthesis, and further advances continue to enhance their synthetic utility. Although vinylsilanes can be prepared in a number of ways, the transition metal-catalyzed hydrosilylation of alkynes offers a simple and direct means of producing these compounds.[34] Hydrosilylation of a terminal alkyne can provide a mixture of three isomeric vinylsilane products, including the α-isomer as well as the (*E*)-*β* and (*Z*)-*β* vinylsilanes resulting from respective *cis*- and *trans*-addition across the alkyne (Scheme 30).

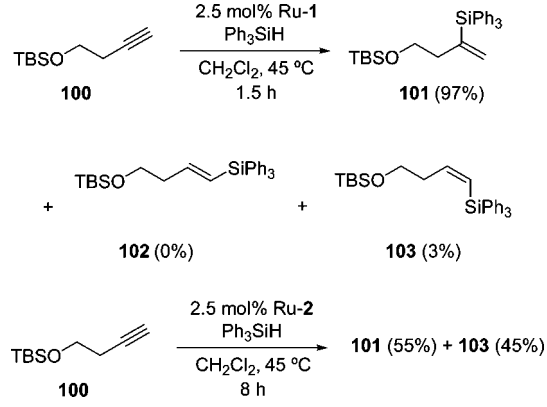
The group of Cox[35] has shown that a variety of factors including the choice of substrate, solvent, and temperature affect the regio- and stereoselectivity of alkyne hydrosilylation. In no case was the presence of cross-metathesis products observed. A range of alkynes and silanes were investigated using optimized reaction conditions of toluene as solvent, at 40 °C, concentration of 0.1 M and 2.5 mol % of Ru-**1** (Scheme 31).

It was interesting to speculate both on the nature of the active catalyst in the hydrosilylation reaction as well as a mechanism of reaction that rationalizes the selectivity differences involving various substrates and silanes. When $^{31}P$ NMR spectroscopy was used to monitor the hydrosilylation reaction between 1-hexyne and $Et_3SiH$ in the presence of 5 mol % of Ru-**1**, the only major resonance observed throughout the experiment was that for the $PCy_3$ ligands in the ruthenium alkylidene complex. This might suggest that Ru-**1** provides the resting state in the catalytic cycle and coordinatively unsaturated ruthenium alkylidene complex **94**, generated by loss of a phosphine ligand, for example, is the active catalyst. If this is the case, reaction might therefore commence with the formation of the ruthenium silyl intermediate **95** through *σ*-metathesis between the silane and the ruthenium alkylidene **94**, in analogy with the classical Chauvin mechanism involving olefins (Scheme 32).[36] Subsequent insertion of the alkyne into the Ru−Si bond would be expected to proceed in a *syn* fashion to provide a vinyl complex **96**. *β*-Hydride elimination would then provide the *β*-(*Z*)-stereoisomer vinylsilane product and regenerate the ruthenium alkylidene complex **94**, thereby completing the catalytic cycle. If the rate of isomerization of **96** to **97** is slow, the direct *β*-hydride elimination from the *syn* metallametalation intermediate **96** would nicely account for the formation of the *β*-(*E*)-stereoisomer for this class of alkyne substrates. Then, the formation of the intermediate **97** comes from the identification of a silylacetylene byproduct **98**. The formation of this byproduct can be rationalized by invoking competing *β*-hydride elimination on the vinyl ruthenium

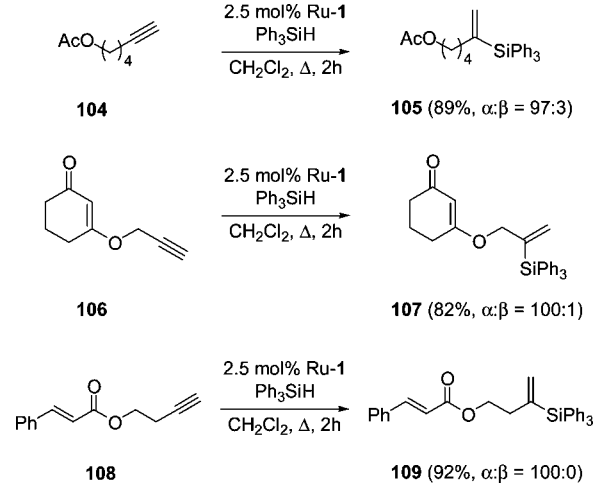
**Scheme 32. Possible Mechanism (Pathway I) of Alkyne−Hydrosilylation Involving Carbene Ru-1 Catalysis**




**Scheme 33. Hydrosilylation Reaction of Alkyne 100 Catalyzed by Carbenes Ru-1 or Ru-2**




**Scheme 34. Hydrosilylation Reactions of Alkynes Catalyzed by Ru-1 Affording Almost Exclusively α-Products**



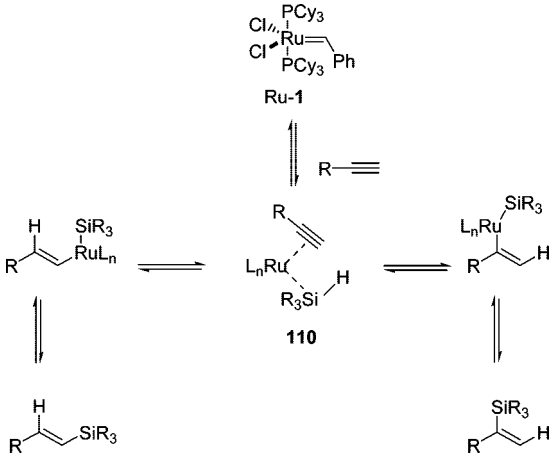

isomerization product **97**, forming the silylacetylene **98** and hydrido ruthenium complex **99**, which itself may also be catalytically active. This NMR experiment does not discount the possibility that very small concentrations of another class of ruthenium complex, which were not detectable by NMR, were mediating the reaction.

The butyn-3-ol derivative **100** was selected as a suitable substrate, in which the bulky *t*-butyldimethylsilyl protecting group suppresses efficiently the directing effect of the polar hydroxyl group (Scheme 33).[6] The effect of the hydrosilylating agent on the regiochemistry of the addition was examined under 2.5 mol % of Ru-**1** and triphenylsilane in refluxing $CH_2Cl_2$. A clear preference for α-selective addition was observed. Triphenylsilane produced almost quantitatively the desired α-vinylsilane **101** (yield = 98%, ratio **101**/**102**/**103** = 97:0:3). It was interesting to compare the selectivity of the hydrosilylation of the alkyne **100** in the presence of Ru-**2**. Contrary to reactions with Ru-**1**, Ru-**2** catalyst afforded a roughly 1:1 mixture of α- and *β*-isomers **101** and **103** in a slow reaction process when $Ph_3SiH$ was used.

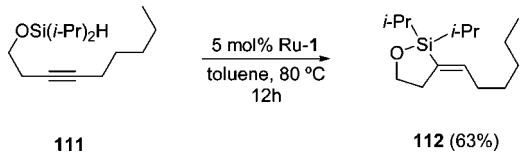
Under the same reaction conditions as those described for substrate **100**, terminal akynes **104**, **106**, and **108** were investigated. Under these conditions, the reaction afforded almost exclusively the desired α-products **105**, **107**, and **109**. The reaction was chemoselective and can be performed in the presence of enones without reducing either the olefin or the carbonyl function. In addition, it is compatible with the presence of esters (Scheme 34).

Again, the mechanism of the hydrosilylation of alkynes catalyzed by ruthenium alkylidene complexes is the subject of conjectures. In the same manner that Cox et al. postulated a possible mechanism, Cossy proposed another chance. The next mechanism only speculates on the plausible intermediates involved in the process. The catalyst can mediate the hydrosilylation of alkynes by a modified Harrod−Chalk mechanism[37] or by an analogous process described by Markó et al. for carbene−Pt complexes.[38] The departure of the $P(Cy)_3$ ligand from the Ru−alkylidene complex can generate a transient 16-electron metal complex ($RuL_n$), which may react simultaneously with the alkyne and with the silane to produce intermediate **110** (Scheme 35). The addition of Ru−H bond to the alkyne followed by reductive elimination of the metal are probably the elementary steps involved in the catalytic cycle. The pronounced α-selectivity can be the result of stereoelectronic factors when the reaction is run under kinetic conditions. When the mixture is allowed to equilibrate, steric

**Scheme 35. Possible Mechanism (Pathway II) of Alkyne−Hydrosilylation Involving Carbene Ru-1 Catalysis**




**Scheme 36. Intramolecular Hydrosilylation of a Homopropargylic Silyl Ether Catalyzed by Carbene Ru-1**



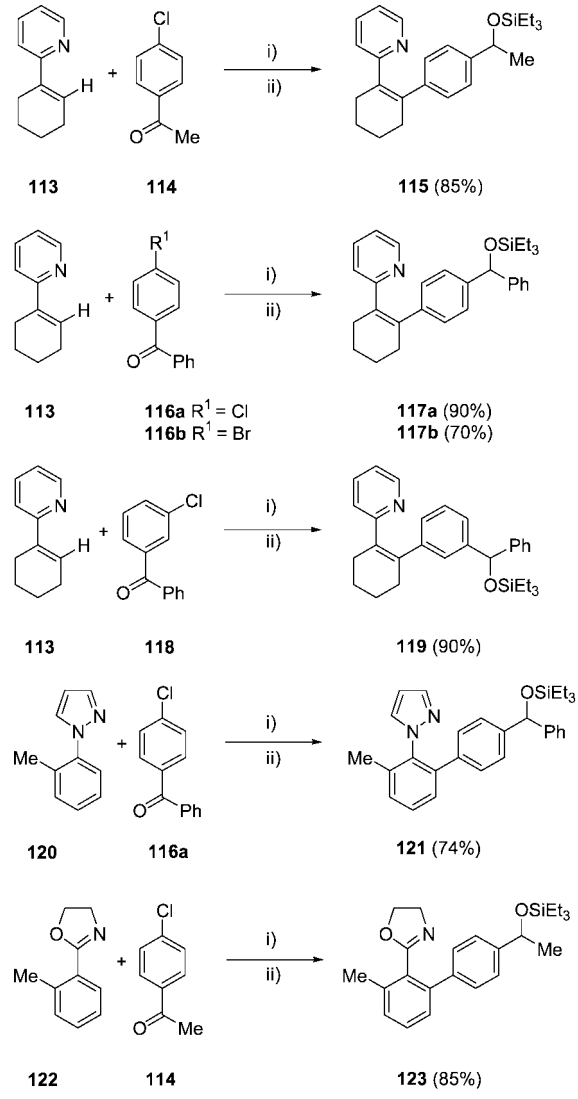

factors may compensate for the stereoelectronic factors, thus increasing the amount of the $\beta$-products.

Intramolecular hydrosilylation of triple bonds has been shown to be a useful tool in organic synthesis to control both regio- and stereochemistry of the resulting double bond.[39] The intramolecular hydrosilylation of homopropargylic silyl ether **111** required a solvent to prevent dehydrogenative condensation between the hydride-bearing silyl ether. Although the use of toluene as a solvent (0.025 M) slowed reaction rates and required higher temperatures, the siloxacycle **112** was isolated in 63% yield under Ru-**1** catalysis (Scheme 36).[40] Previously studied transition metal-catalyzed hydrosilylation reactions suggest that the present hydrosilylation likely proceeds by initial oxidative addition of the silane to the metal center; however, characterization of this initial metal hydride complex by $^1$H NMR has been elusive.

## 4.3. Direct Arylation−Hydrosilylation Sequence

The application of a single catalyst for more than one chemical transformation in one-pot reaction is an important goal in synthesis. Because ruthenium carbene complexes are known to catalyze a variety of important transformations, the direct arylation-based sequential catalysis was probed. A one-pot reaction sequence consisting of a direct arylation and a hydrosilylation catalyzed by Ru-**1** was studied (Scheme 37).[41] A variety of differently substituted phenones proved applicable to the one-pot protocol. Importantly, the C−H bond functionalization catalyzed by the ruthenium carbene Ru-**1** was not restricted to alkenes but also proved viable using arenes as pronucleophiles. The use of 2-pyridyl substituents was not a stringent requirement for the direct arylation. Thus, both pyrazolyl-**120** and oxazolinyl-substituted **122** pronucleophiles could be employed. It is important to note that change or removal of solvent was not required for the sequential catalysis to proceed with high yields of isolated product.

**Scheme 37. Direct Arylation−Hydrosilylation Sequence Catalyzed by Carbene Ru-1**[a]



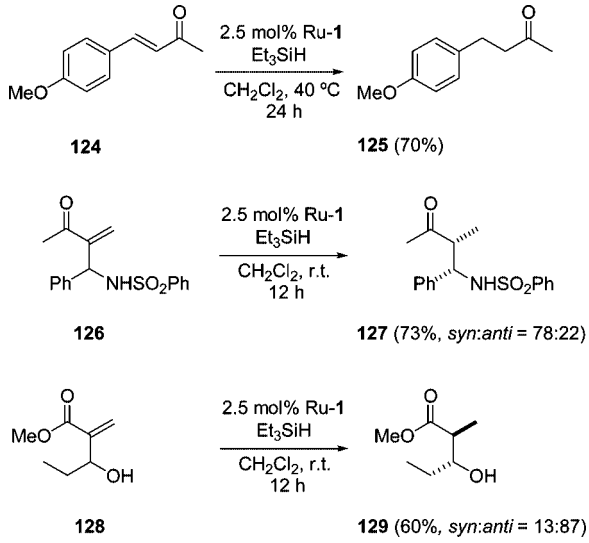

[a]Key: (i) 5 mol% Ru-1, $K_2CO_3$, NMP, 120 °C, 22 h; (ii) then $Et_3SiH$, 60 °C, 22 h.

# 5. Hydrogenation Reactions

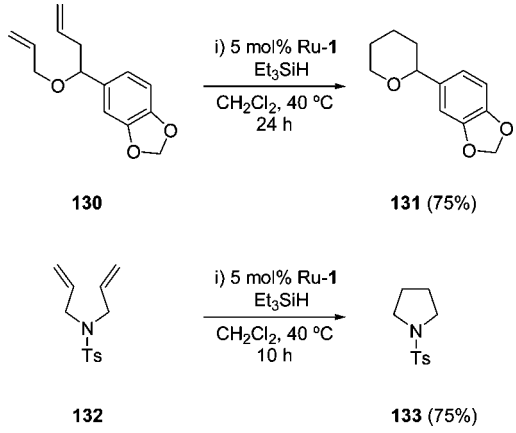
## 5.1. Reduction of Olefins Using Ru-1 and Silanes

The selective reduction of olefins using ruthenium carbene complex Ru-**1** in the presence of silanes was described by Cossy et al.[7] The selective transformation of $\alpha,\beta$-unsaturated carbonyl compounds to the corresponding saturated products was made by Ru-**1** and triethylsilane in refluxing $CH_2Cl_2$ or at room temperature (Scheme 38). After 24 h, compound **124** was transformed to ketone **125** in 70% yield. The reduction of the ketone moiety under the reaction conditions was not observed. The diastereoselectivity of the transformation was studied in the reduction of acyclic enone **126** and $\alpha,\beta$-unsaturated ester **128**. Furthermore, the ability in mediating tandem metathesis reaction−reduction under the reaction conditions was tested (Scheme 39). Even in the presence of trialkylsilanes, the metathetic activity of ruthenium carbene Ru-**1** was retained, as **130** was transformed to tetrahydropyran **131** in one cyclization−reduction sequence. Likewise, *N*-tosyl-*N*,*N*-diallylamine **132** was converted to the pyrrolidine derivative **133** in one-pot sequence. This method described the selective reduction of nonactivated and acti-

**Scheme 38. Selective Hydrogenation of Olefins in the Presence of Silanes Catalyzed by Carbene Ru-1**



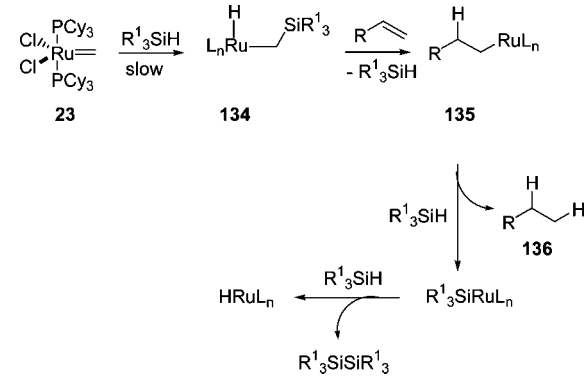

**Scheme 39. Tandem RCM−Reduction Catalyzed by Carbene Ru-1 in the Presence of Silanes**



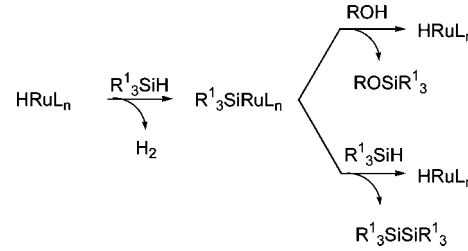

vated olefins in the presence of Ru-**1** and silanes. The hydrogenation occurred by the metathesis-inactive catalyst after the RCM reaction was completed, because the RCM was much faster than the modification of carbene catalyst by silanes or hydrogen, generated from dimerization of silanes.

The mechanism of the transformation is the subject of supposition. It was difficult to account all the observed events to a single organometallic complex, and they were probably the consequence of competing processes. Unfortunately, it was not possible to characterize any of these complexes by $^1$H NMR techniques, and only plausible intermediates involved in the process are present in Scheme 40. The first step of the mechanism can be the addition of the silane to the metal−carbene, which produces **134**. The methylidene complex **23** derived from Ru-**1** probably reacts slowly with silanes under the reaction conditions, which would explain the sustained metathetic activity of the mixture even after extended reaction time. The addition of the ruthenium hydride $L_nRuH$ to olefins can then follow a classical oxidative addition−reductive elimination pathway. Accordingly, the addition will provide **135**, which is reduced in the presence of Si−H, and gives rise to the corresponding alkane **136** and $L_nRuSiR^1_3$. The starting RuH is regenerated by further reduction with silane, forming disilane as a byproduct.

**Scheme 40. Mechanism of the Reduction of Olefins Using Silanes Catalyzed by Carbene Ru-1**




**Scheme 41. Dimerization of Silanes Forming Disilanes or Disiloxanes in Presence of Ru-1**



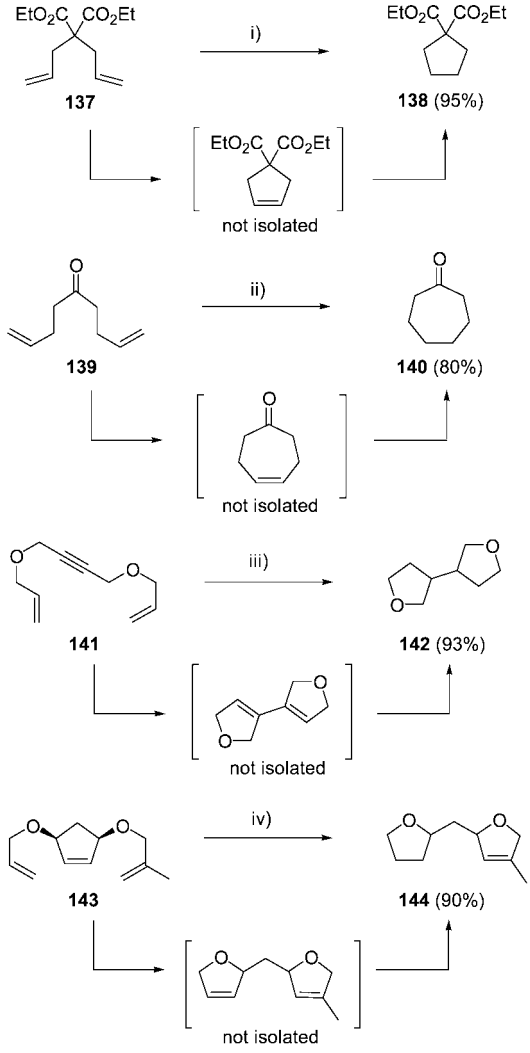

A secondary reaction is the dimerization of silanes forming disilanes or disiloxanes and molecular $H_2$, when alcohol is present (Scheme 41). In fact, in all the reactions, the corresponding silyl ether was the major secondary product. Because of this competing reaction, an excess of silane is necessary for completing the desired reaction.

## 5.2. One-Pot RCM and CM−Hydrogenation Using Ru-1 and Ru-2

Different saturated compounds were obtained by using a convenient one-pot catalysis protocol,[25] because the Grubbs' carbenes Ru-**1** or Ru-**2** have shown to be effective precatalysts in hydrogenation reactions. The addition of $H_2$ to complex Ru-**1** quantitatively afforded the hydride complex $RuHCl(H_2)(PCy_3)_2$, an effective hydrogenation catalyst. The same hydride complex was observed upon the introduction of $H_2$, following a RCM or CM reaction. In some cases, higher pressures were employed to achieve acceptable reaction rates under the relatively dilute conditions necessary for the olefin metathesis reaction (Scheme 42). Interestingly, the catalyst Ru-**1** did not facilitate the hydrodehalogenation of aryl halides such as **148** (Scheme 43), which is a common drawback of many hydrogenation procedures where Pd/C or Rh hydrogenation catalysts were used.[42]

Cyclic dinucleotide containing a butylene nucleobase-phosphotriester connection **150** was synthesized from diene **149** by one-pot RCM−hydrogenation sequence catalyzed by second-generation Grubbs' carbene (Scheme 44).[43] When diene **149** was subjected to standard hydrogenation conditions, i.e., atmospheric pressure of hydrogen and a palladium catalyst, this led not only to the hydrogenation of the double bond but also to the reduction of the phosphotriester linkage. A good solution for this problem was given by a catalytic RCM and subsequent hydrogenation in the presence of Ru-**2** in refluxing DCE and $H_2$ (1000 psi and 50 °C).

**Scheme 42. One-Pot RCM−Hydrogenation Reaction Catalyzed by Carbenes Ru-1 and Ru-2**[a]



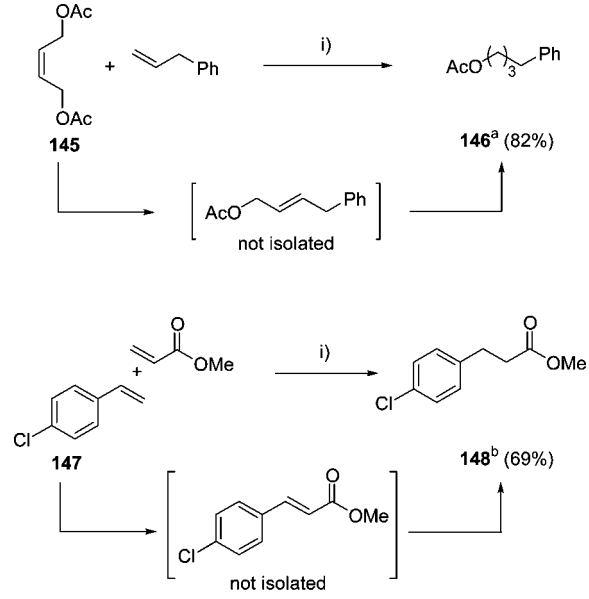

[a]Key: (i) 5 mol% Ru-**1**, DCE, 40 °C, then $H_2$ (1 atm, 70 °C); (ii) 3 mol% Ru-**2**, DCE, 40 °C, then $H_2$ (100 psi, 70 °C); (iii) 3 mol% Ru-**1**, DCE, 40 °C, then $H_2$ (1000 psi, 100 °C); (iv) 3 mol% Ru-**2**, DCE, 40 °C, then $H_2$ (1 atm, 70 °C).

## 5.3. Transfer Reductions of Ketones With Alcohols

In contrast to conventional reduction routes, which frequently require a high hydrogen pressure and hazardous reducing reagents, the transfer hydrogenation has some unique advantages in its simplicity and avoidance of cumbersome reducing agents. Of various hydrogen donors used, primary or secondary alcohols were the most used. In conventional transfer hydrogenation, the alcohol is oxidized to the corresponding ketone (or aldehyde) depending on the nature of the alcohol (Scheme 45, route a). Taking the diverse reactivities of the Grubbs' carbene Ru-**1** into account, the group of Shim and Cho directed the transfer hydrogenation of ketones by alcohols, and they discovered only the formation of unconventional transfer hydrogenation products (Scheme 45, route b).[44]

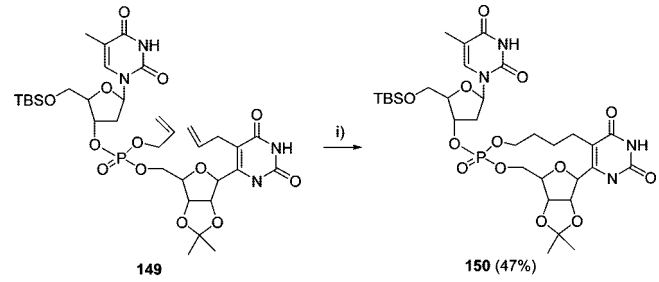
The transfer hydrogenation of acetophenone **151a** with butanol **152** catalyzed by Ru-**1** produced unconventional alkylated products, namely, 1-phenyl-hexan-1-ol **153** and 1-phenylhexan-1-one **154**, rather than the expected direct transfer hydrogenation product, 1-phenylethanol, the yield

**Scheme 43. One-Pot CM−Hydrogenation Reactions Catalyzed by Carbene Ru-2**[a]



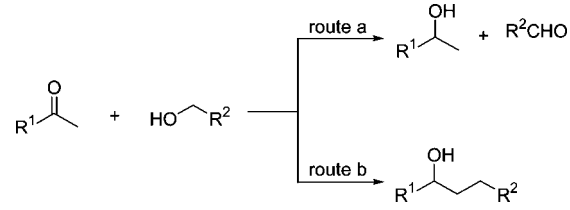

[a]Key: (i) 3 mol% Ru-**2**, DCE, 40 °C, then $H_2$ (100 psi, 70 °C).

**Scheme 44. Synthesis of Cyclic Dinucleotide 150 through RCM−Hydrogenation Reaction Catalyzed by Carbene Ru-2**[a]

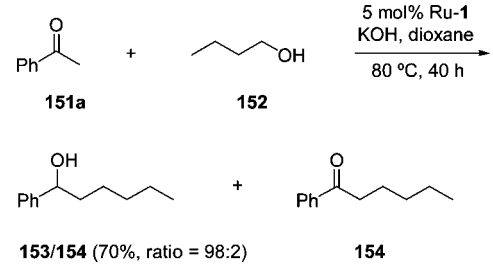



[a]Key: (i) 5 mol% Ru-**2**, $CH_2Cl_2$, 40 °C, then $H_2$ (1000 psi, 50 °C).

**Scheme 45. Transfer Hydrogenation of Ketones with Alcohols**

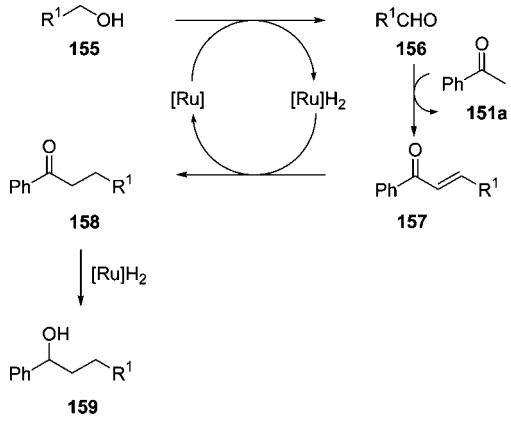



**Scheme 46. Transfer Hydrogenation of Ketones with Alcohols Catalyzed by Carbene Ru-1**




of which remains less than 5% (Scheme 46). This result is an unusual example of ruthenium-catalyzed transfer hydrogenation between ketones and primary alcohols involving carbon−carbon bond formation.

**Scheme 47. Possible Reaction Pathway for the Transfer Hydrogenation of Ketones with Alcohols Catalyzed by Grubbs' Carbene Ru-1**



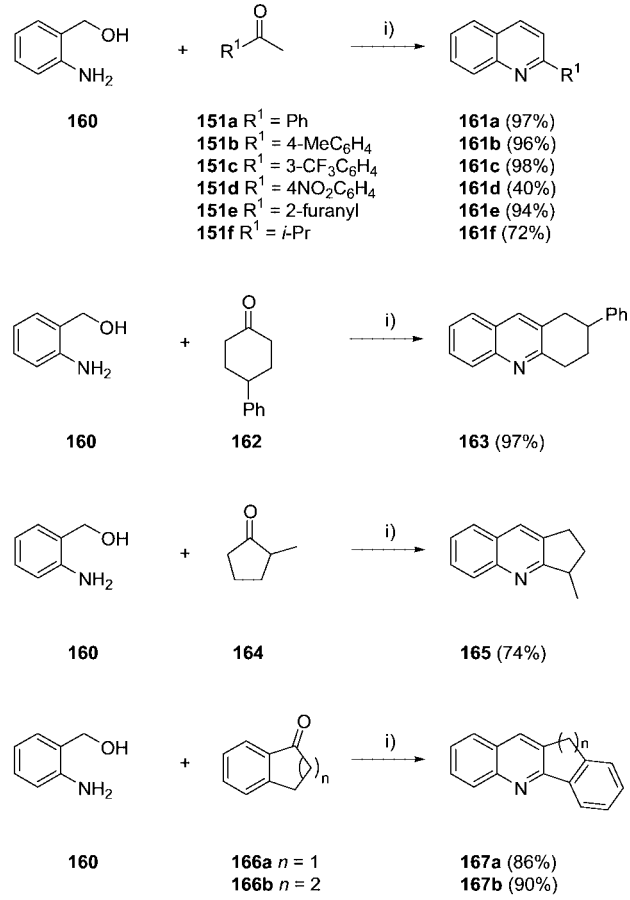

A possible reaction pathway was proposed (Scheme 47) on the basis of the work of Bäckvall.[45] The key step involves the cross-aldol condensation reaction of aldehyde **156** with the substrate ketone **151a** to form α,β-unsaturated ketone **157**, which is subsequently hydrogenated to **158** or **159** by dihydridoruthenium species generated in the initial oxidation stage of the alcohol **155**. With regard to the initial oxidation of alcohol to aldehyde, it is well-documented that the reaction proceeds via oxidative addition of the O−H bond to low-valent ruthenium and subsequent β-hydrogen elimination.

A similar strategy was applied to the synthesis of different *N*-heterocycles.[46] A modified Friedlaender quinoline synthesis via a ruthenium-catalyzed oxidative cyclization of 2-aminobenzyl alcohol **160** with different ketones was achieved in the presence of Ru-**1** (Scheme 48). Alkyl aryl ketones were cyclized irrespective of the examined functional groups on the aromatic ring, affording the corresponding 2-arylquinolines. The good yield of this reaction was not affected by the position of the substituent on the aromatic ring of ketones. With alkyl heteroaryl ketones, the products were formed in high yields, but lower reaction rate and yields were observed with acetophenones having nitro, hydroxyl, and cyano functional groups on the aromatic ring. The oxidative cyclization with alkyl, aryl, cyclic, and benzo-fused cyclic ketones having only the methylene reaction site was carried out in good yields.

The same group disclosed a ruthenium-catalyzed coupling between secondary alcohols and primary alcohols, which led to β-alkylation of the former product (Scheme 49).[47] These findings allowed the cyclization of 2-aminobenzyl alcohol with a secondary alcohol for affording a quinoline in moderate yield.[48] When 2-aminobenzyl alcohol **160** and 1-phenylethanol **168** reacted in the presence of Ru-**1** (1 mol %) along with KOH, 2-phenylquinoline **161a** was produced in only 10% yield. However, the addition of 1-dodecene as hydrogen acceptor increased the yield of **161a** to 52% (Scheme 50).

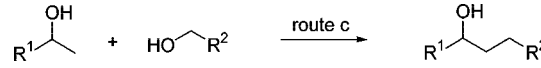
The reaction proceeded via a sequence involving initial oxidations of both substrates to carbonyl compounds **169** and **151**, cross-aldol condensation under KOH promotion to afford α,β-unsaturated ketone **170**, and a final cyclodehydration to **161a** (Scheme 51). The initial oxidation of alcohols to carbonyl compounds, which proceeded via oxidative addition of ruthenium to O−H bond and subsequent β-hydrogen elimination, is well-documented in transition metal-catalyzed transfer hydrogenations.[49] In this protocol, 1-dodecene

**Scheme 48. Oxidative Cyclization of 2-Aminobenzyl Alcohol 160 with Ketones in Presence of Ru-1[a]**

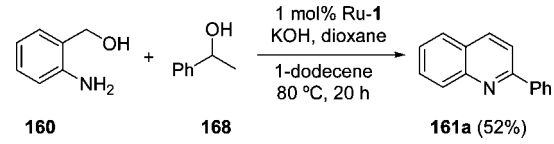



[a]Key: (i) 1 mol% Ru-**1**, dioxane, KOH, 80 °C, 1 h.

**Scheme 49. β-Alkylation of Secondary Alcohols with Primary Alcohols**




**Scheme 50. Synthesis of Quinoline 161a Catalyzed by Carbene Ru-1**



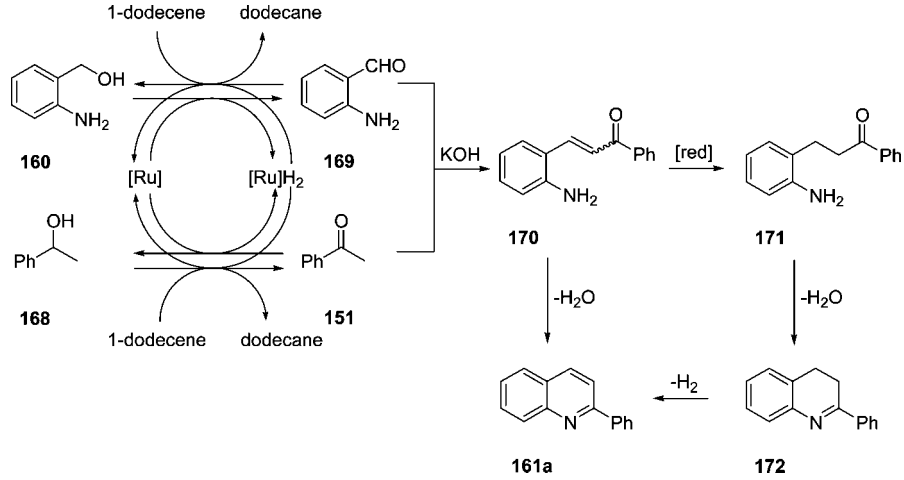

acted as a sacrificial hydrogen acceptor oxidizing [Ru]$H_2$ generated in the initial oxidation stage to [Ru]. An alternative route for **161a** involves a sequence such as reduction of **170** to saturated ketone **171**, cyclodehydration to form 3,4-dihydroquinoline **172**, and dehydrogenation.[50]

## 6. Cyclopropanation Reactions

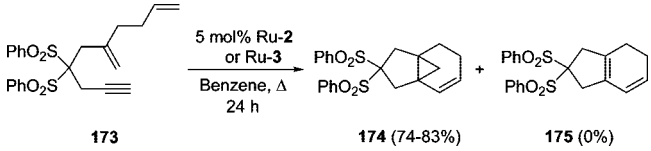
### 6.1. Tandem Cyclopropanation−RCM of Dienynes

The variety of reactions catalyzed by ruthenium suggested that numerous tandem processes might also be possible. In particular, the ability of ruthenium alkylidenes to cyclopropanate olefins,[51] combined with similarities between the olefin metathesis and cyclopropanation mechanisms, indicated that a tandem cyclopropanation−metathesis reaction sequence could be achievable. A tandem cyclopropanation−RCM

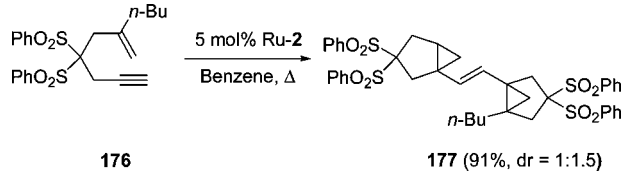
**Scheme 51. Possible Reaction Pathway for the Transfer Hydrogenation of Ketones with Alcohols Catalyzed by Ruthenium-Based Carbenes**



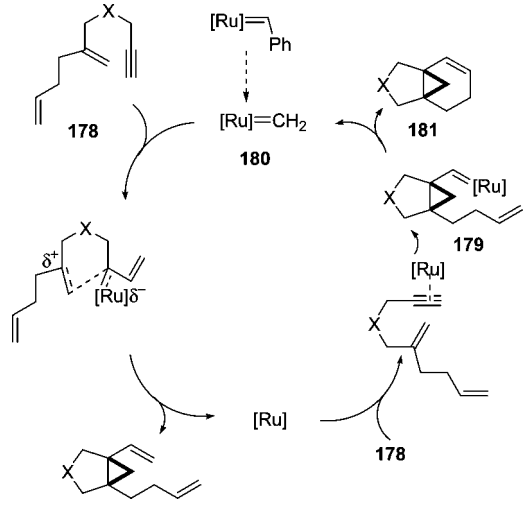

**Scheme 52. Tandem Cyclopropanation−RCM Reaction Catalyzed by Carbenes Ru-2 or Ru-3**




**Scheme 53. Cyclopropanation−CM Sequence Catalyzed by Carbene Ru-2**



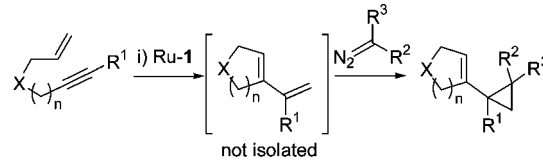

**Scheme 54. Mechanism of the Cyclopropanation−RCM Reaction Catalyzed by Carbenes Ru-1 or Ru-2**




process was developed by Diver et al.[52] Different enynes in the presence of Grubbs' carbenes ruthenium Ru-**2** and Ru-**3** gave the tandem RCEM−RCM products like **175** and trace amounts of cyclopropane derivatives. However, using the **173** bis-sulfone as substrate with Ru-**2** and Ru-**3** in benzene at reflux gave only the cyclopropane compound **174** in 83% and 74% yields, respectively (Scheme 52). Thus, the intermediate cyclopropyl carbene may evolve through cyclopropanation reaction, which is competing with enyne metathesis. To test the predilection of bis-sulfone **176** for cyclopropanation and to determine whether the exocyclic cyclopropyl carbene might be interconverted into an endocyclic carbene, the pendant alkene was removed. In this case, Ru-**2** promoted a tandem cyclopropanation−CM reaction, giving **177** as a 1:1.5 mixture of *syn*- and *anti*-diastereomers (Scheme 53). Most likely, this process occurred via an intermediate cyclopropyl carbene.

The ring-closing enyne metathesis step is especially critical to this catalytic process since it allows metal activation to result in metal carbene production (**179** to **180** and **181**). It is clear that either noncarbenic metal complexes or metal carbenes may catalyze the tandem cyclopropanation−ring-closing metathesis (Scheme 54).

**Scheme 55. One-Pot RCEYM−Cyclopropanation Reaction by Addition of a Diazo Ester Catalyzed by Carbene Ru-1[a]**



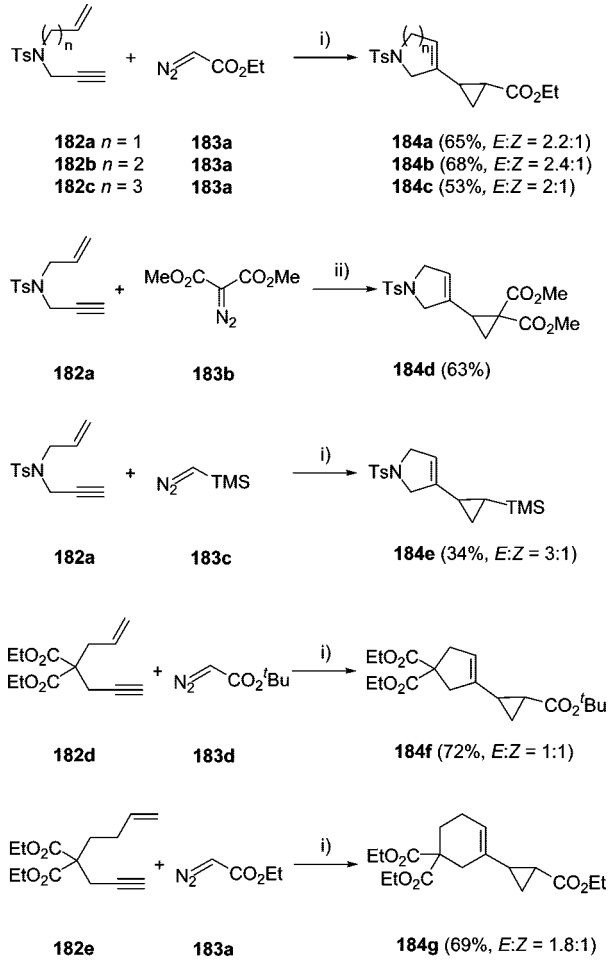

[a] Key: (i) Ru-**1**, ethylene, benzene, 75 °C.

## 6.2. One-Pot Enyne Metathesis−Cyclopropanation in the Presence of Diazoacetates

A one-pot ring-closing enyne metathesis (RCEYM)−cyclopropanation reaction has been developed by the group of Snapper,[8] when Grubbs' ruthenium carbene Ru-**1** catalyzed the reaction of enynes with a variety of diazo compounds at elevated temperatures. The one-pot process appeared to be specific to catalyst Ru-**1**, because the Ru-**2** complex provided only the triene dimer without any evidence of cyclopropanation. The cyclopropanation occurred almost exclusively on the less-hindered olefin with moderate *E*/*Z* stereoselectivity (Scheme 55).

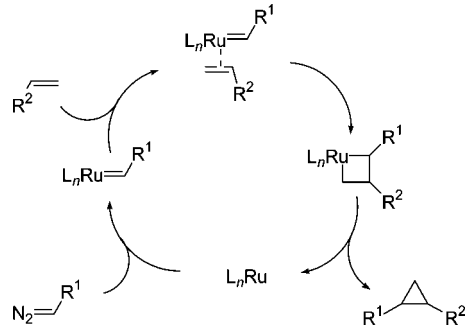
Scheme 56 shows the synthesis of a series of vinyl cyclopropane compounds prepared in a single reaction vessel from readily available enynes. Five-, six-, and seven-membered cyclopropyl cycloalkenes were generated through a tandem process accompanied by only trace amounts of the regioisomeric cyclopropane (<5%). An increase of the bulkiness of diazoester group from ethyl **183a** to *t*-butyl **183d**

**Scheme 56. RCEYM−Cyclopropanation Reaction Catalyzed by Carbene Ru-1**[a]



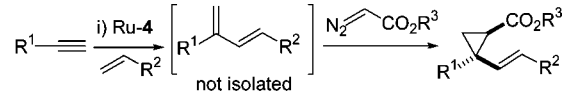

[a]Key: (i) 10 mol% Ru-**1**, 75 °C, [0.05-0.10 M in benzene]; RCEYM was conducted under ethylene atm and cyclopropanation under $N_2$ atm; (ii) 20 mol% Ru-**1**, 100 °C, [0.05-0.10 M in toluene].

**Scheme 57. Mechanism of Ruthenium Alkylidene-Catalyzed Cyclopropanation Reaction**



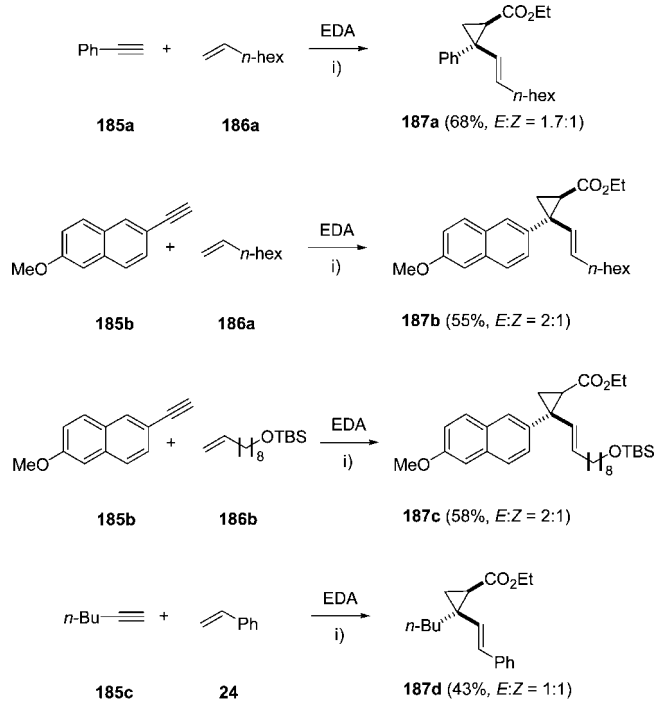

does not influence the diastereoselectivity observed in the reaction; trimethylsilyl diazomethane **183c** was also suitable for cyclopropanation, but the reaction was less efficient than other diazo transfer reactions. Overall, these results suggested that, even though the ruthenium carbene complex was generally electrophilic,[53] the steric hindrance of the enyne appeared to override any electronic bias in determining the regioselectivity of the cyclopropanation reaction. The stereoselectivity of the cyclopropanation reaction with Ru-**1** was moderate at best, with *E*:*Z* ratios ranging 1:1 to 3:1. A

**Scheme 58. Tandem Three-Component Coupling between an Olefin, An Alkyne, And a Diazoester Catalyzed by Carbene Ru-4**[a]




[a]Key: (i) Ru-**4**, ethylene.

**Scheme 59. Tandem Enyne Cross-Metathesis/ Cyclopropanation Reaction Catalyzed by Carbene Ru-4**[a]




[a]Key: (i) 10 mol% Ru-**4**, r.t., RCEM was conducted under ethylene atm and cyclopropanation under $N_2$ atm.

tentative mechanistic proposal for the ruthenium alkylidene-catalyzed cyclopropanation is depicted in Scheme 57.

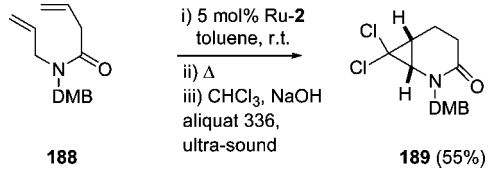
Recently, substituted vinylcyclopropanes have been prepared through a ruthenium-catalyzed, tandem three-component coupling between olefins, alkynes, and diazoesters (Scheme 58).[54]

Grubbs' second-generation ruthenium carbene Ru-**4** in the presence of ethylene achieved a stereoselective enyne−cross-metathesis between alkynes and olefins in order to generate 1,3-substituted dienes. The slow introduction of diazoacetates to this reaction mixture then allows for the regioselective cyclopropanation of the resulting diene (Scheme 59).

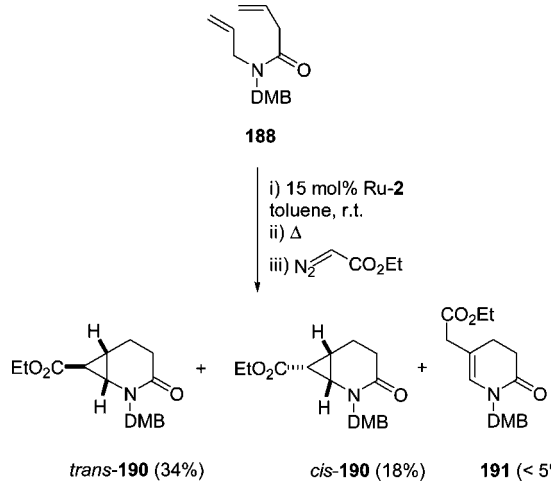
## 6.3. One-Pot RCM/ Isomerization−Cyclopropanation Reaction

Recently, a new triple one-pot process in which simple acyclic substrates can be transformed into bicyclic compounds via RCM−double-bond isomerization−cyclopropanation has been discovered.[55] The tandem process combined a RCM−isomerization sequence with a cyclopropanation reaction with dichlorocarbene, which was catalyzed by second-generation Grubbs' carbene Ru-**2**. The reaction was achieved by adding a 50% solution of NaOH in water, $CHCl_3$, and Aliquat 336 to the reaction mixture once the RCM−isomerization

**Scheme 60. RCM/Isomerization−Cyclopropanation Sequence Catalyzed by Carbene Ru-2**




**Scheme 61. RCM/Isomerization−Cyclopropanation Reactions of Dienamide 188 Catalyzed by Carbene Ru-2**




reaction had been completed. After sonication for achieving the cyclopropanation step, the product **189** was isolated in 55% yield (Scheme 60). This compound is structurally related to a recently disclosed selective inhibitor of the human inducible isoform of *nitric oxide synthase* (iNOS).

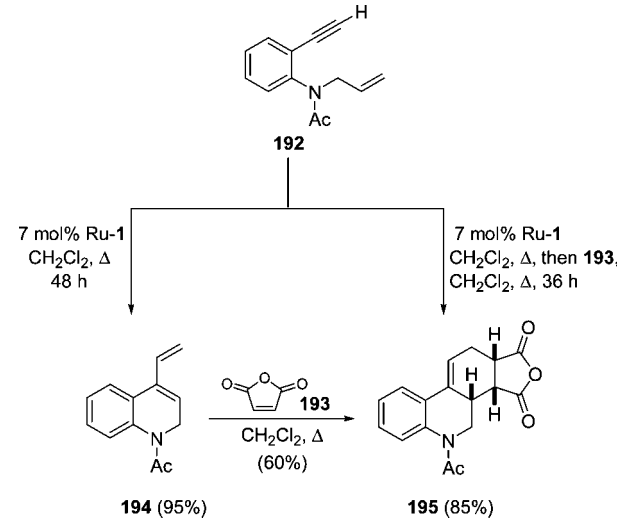
A triple one-pot process involving a cyclopropanation step with diazocompounds was carried out using ethyl diazoacetate (EDA). Three reactions were performed from **188** in one-pot sequence. After the RCM−isomerization (12 h), EDA was slowly added to the reaction mixture and yielded 52% of the two isomeric cyclopropanes **190** and traces (<5%) of the insertion product **191** (Scheme 61). The second-generation Grubbs' carbene was able to catalyze the three processes without requiring other reagents. The authors suggested that the identity of the catalytic species and the mechanism of this transformation need study, but they assume that the complex mediating in the isomerization step is a ruthenium hydride formed by thermal modification of the initial carbene.

## *7. Cycloaddition Reactions*

### 7.1. RCEYM/Diels−Alder Reaction Sequence

RCEYM−Diels-Alder reaction sequence is a key pathway in a synthesis of the skeleton of aza- or oxa-steroids.[56] This methodology is based on stepwise or one-pot Diels-Alder reactions. The first step was the construction of aromatic enynes **192** (obtained by the Sonogashira coupling reaction) and subsequent RCEYM with Ru-**1**. The resulting diene **194** and maleic anhydride **193** were used in the next step in order to develop a thermal Diels-Alder reaction (Scheme 62). After 48 h, the tetracyclic structure **195** was obtained in 60% yield and a minor isomer of this compound was detected in less than 10% in the $^1$H NMR spectrum of the crude. However, more interesting results were obtained when the reaction was carried out in one-pot sequence from the corresponding enyne

**Scheme 62. Comparison between RCEYM/Diels−Alder Sequence by Stepwise Procedure or One-Pot Reaction Catalyzed by Ru-1**



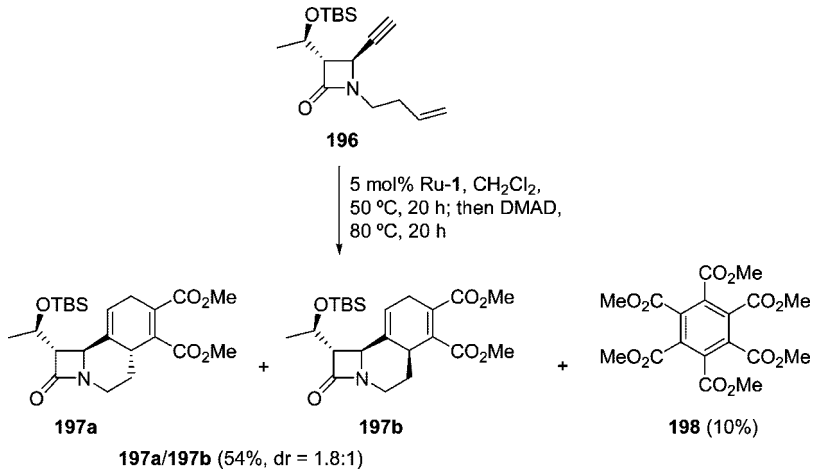

**192** and the dienophile in the metathesis reaction mixture, once total conversion of the enyne was verified. Regarding compound **195**, the yield of the two-step, one-pot process was 85%, after 36 h of reaction in refluxing dichloromethane. This result showed a possible beneficial action of the ruthenium complex in the Diels−Alder reaction. This course would imply a nonmetathetic behavior of the ruthenium complex.

### 7.2. [2 + 2 + 2]-Cycloaddition Reactions

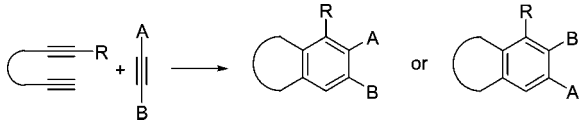
The synthesis of polycyclic $\beta$-lactams based on RCEYM and Diels−Alder reaction was developed by Savignac and Genêt.[57] For comparison, metathesis and cycloaddition were first accomplished in separate steps. The stepwise procedure gave better yield (80%) of the 4:6:6 cycloadduct **197** than "one-pot" metathesis−cycloaddition (54% yield) with dimethyl acetylenedicarboxylate (DMAD). This result was due to the formation of side-products resulting from the side-reactions of the Grubbs' catalyst Ru-**1** with the cycloadducts or the dienophile. For example, one-pot sequence with DMAD afforded byproduct **198** in approximately 10% yield (Scheme 63). Formation of hexamethyl mellitate **198** might involve the [2 + 2 + 2]-cyclotrimerization of DMAD catalyzed by the ruthenium complex.

Deiters and colleagues[58] have demonstrated the application of ruthenium-catalyzed (Ru-**1**) solid-supported [2 + 2 + 2]-cycloaddition reactions in combinatorial chemistry, enabling their use in the assembly of complex compound libraries (Scheme 64). The formation of phtalans **201** was investigated using the cycloaddition precursor **199** (Scheme 65). Because of the presence of an internal triple bond, high reaction temperature (80 °C) in 1,2-dichloroethane (DCE) was required to achieve complete conversion of the starting material. Cycloadditions of the unsymmetrical diyne **199** with substituted alkynes **200** led to the formation of the corresponding regioisomers, but low (1:3) or no regioselectivity was obtained using Wilkinson's catalyst [$RhCl(PPh_3)_3$]. In order to obtain a high degree of control over the regioisomeric ratio, Grubbs' carbene Ru-**1** was used in the [2 + 2 + 2]-cycloaddition. A high degree of regioselectivity (1:9) was observed, independently of the nature of the alkyne.

**Scheme 63. RCEYM/Diels−Alder One-Pot Sequence Catalyzed by Ru-1 with Concomitant Formation of a Cyclotrimerization Adduct**




**Scheme 64. Metal-Catalyzed [2 + 2 + 2]-Cycloaddition Reaction**




## 7.3. [3 + 2]-Cycloaddition Reactions Catalyzed By Grubbs' Carbene Complexes

A novel, nonmetathetic application of Grubbs' carbenes was discovered by Mascareñas et al., during a study of the intramolecular [3 + 2]-cycloaddition of ynylidenecyclopropanes[9] (Scheme 66). The treatment of enyne **202a** with Grubbs' carbene Ru-**2** gave not only the expected product from ring-closing enyne metathesis **204a** (32% yield) but also considerable amounts (8%) of the cyclopentene adduct **203a**. The novelty of this nonmetathetic behavior of Ru-**2** led to the change of the catalyst to Ru-**1**, owing to its lower enyne metathesis activity. Indeed, better yields of [3 + 2]-cycloaddition product were obtained. Then, under Ru-**1** catalysis (20 mol %) in dichloromethane at 40 °C, **202a** gave the cycloadduct **203a** in 36% yield; most of the remaining reaction mass was unreacted starting material and small amounts of the product due to intramolecular enyne metathesis, diene **204a** (<5% yield) and the cross-metathesis enyne **205a** (<10% yield). Increasing the substrate concentration and using 10 mol % of Ru-**1** provided the desired cycloadduct **203a** in 78% yield. In these conditions, the consumption of starting enyne **202a** was completed. However, the reaction was quite sensitive to the steric bulk of the substituent, because the complete consumption of enynes **202c** and **202d** required the use of a slightly higher catalyst loading. In all cases, traces of cross-metathesis enynes **205** were detected (Scheme 67).

With regard to the reaction mechanism, it was confirmed that diene **204a** is not an intermediate in the process because prolonged heating of this compound in toluene, either in the presence or absence of Ru-**1**, did not led to adduct **203a** (**204a** remains mostly unchanged). A particularly relevant issue concerns the specific ruthenium species responsible for initiating the cycloaddition reaction. Preliminary results may point to the possibility of promotion of the cycloaddition by a noncarbene ruthenium species generated under the reaction conditions.

# 8. Olefin Isomerizations

## 8.1. Isomerization in Diversely Functionalized Compounds

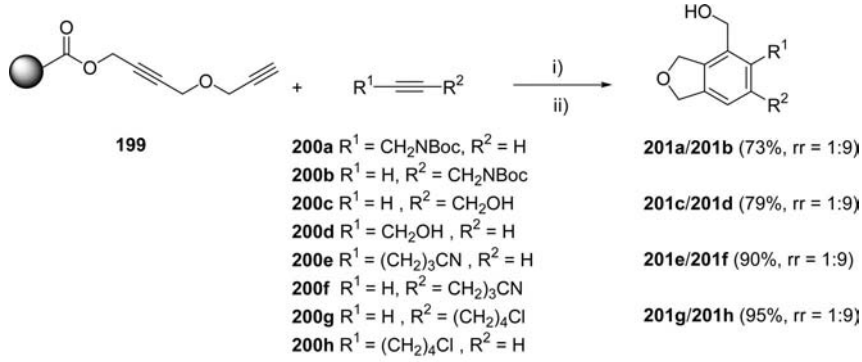
When the substrate **206** containing a methyl substituent on the allene side was subjected to ruthenium catalyst Ru-**2** at 84 °C, instead of cyclization, an interesting and unprecedented ruthenium-catalyzed isomerization to dienamide **207** in quantitative yield was observed (Scheme 68).[59]

Secondary allylic alcohols **208a−d** in the presence of a catalytic amount (10 mol %) of Ru-**1** in refluxing toluene or 1,2-dichloroethane provided the isomerized products (ethyl ketones) **209a−d** (Scheme 69).[60] It seems that, at higher temperatures, the process of hydrogen transfer precedes the cycloreversion reaction of metallocyclobutane leading to isomerization. Final $\beta$-elimination from metallo intermediates **210** and **211**, which proceeds via C−C cleavage, followed by hydride transfer from ruthenium species led to the ethyl ketone product and regeneration of catalyst Ru-**1** (Scheme 70).

Analogously, the exposure of allylic alcohol **208e** to Ru-**1** in refluxing toluene under an atmosphere of argon resulted in clean conversion to ketone **209e** in 85% yield, together with the $\alpha,\beta$-unsaturated ketone **212** and benzaldehyde **213** (in trace amounts). In addition, Grubbs' carbene-catalyzed reaction of *trans*-cinnamyl alcohol **214** resulted in the isolation of *trans*-cinnamaldehyde **215** (33% yield), 3-phenylpropanal **216** (33% yield), and benzaldehyde **213** (<5%) (Scheme 71).[61] It is suggested that, in the case of the reaction of *trans*-cinnamyl alcohol **214**, initial oxidation to **215** followed by conjugate reduction by hydride (delivered either from **214** or a ruthenium hydride complex) can generate **216**, thereby providing a viable, alternative mechanism to the pathway suggested by Gurjar in Scheme 70.

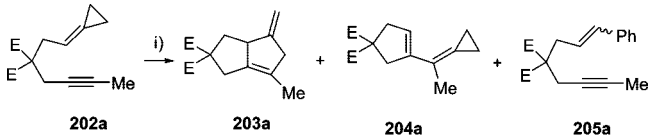
Metathesis of [D]-**208e** initially generates an unstable methylidene complex **217**, which suffers decomposition to a new, and as yet uncharacterized, complex **218**. Interaction of **218** with more starting material leads to formation of $\alpha,\beta$-unsaturated ketone **212** together with the hydride complex **219**. This hydride complex was then responsible for the generation of [D]-**209e** via a number of well-documented processes. Isomerization of internal double bonds presumably proceeds via initial $\pi$-complexation followed by allylic C−H activation as adumbrated by Nolan (Scheme 72).[62]

**Scheme 65. Synthesis of Phtalans Catalyzed by Grubbs' Carbene Complex Ru-1**[a]



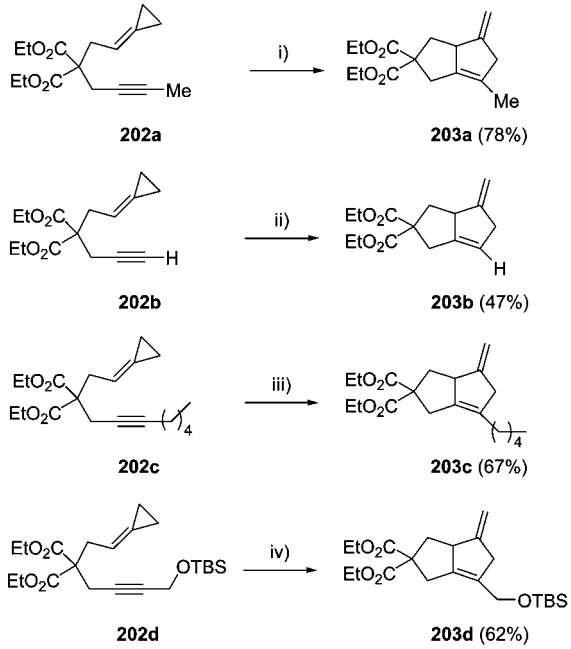

[a]Key: (i) 10 mol% Ru-**1**, DCE, 80 °C, 48 h; (ii) $K_2CO_3$, THF-MeOH (4:1), r.t., 12 h.

**Scheme 66. Alkylidene−Cyclopropane/Alkyne Cycloaddition Catalyzed by Grubbs' Carbenes**[a]




[a]Key: (i) 20 mol% Ru-**1** or 10 mol% Ru-**2**, $CH_2Cl_2$, 40 °C.

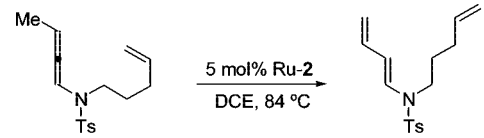
**Scheme 67. Intramolecular [3 + 2]-Cycloaddition of Alk-5-ynylidenecyclopropanes 202 Catalyzed by Carbene Ru-1**[a]



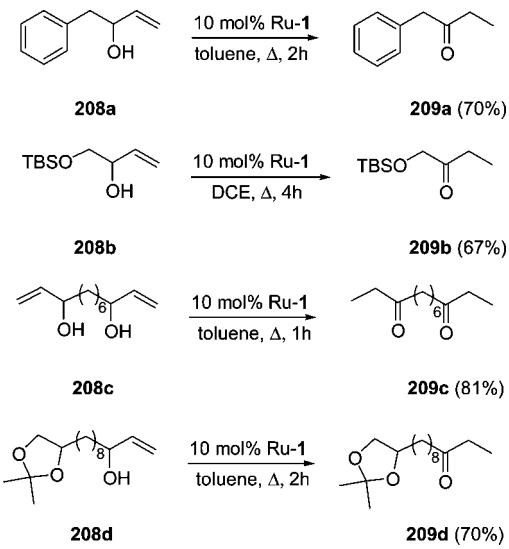

[a]Key: (i) 10 mol% Ru-**1**, toluene, Δ, 0.8 h; (ii) 10 mol% Ru-**1**, DCE, Δ, 4 h; (iii) 15 mol% Ru-**1**, toluene, Δ, 2 h; (iv) 15 mol% Ru-**1**, toluene, Δ, 3.5 h.

A series of allyl derivatives of Boc-protected amino acid derivatives **220a**−**d** in the presence of 10 mol % of Ru-**1** in anhydrous dichloromethane provided the isomerization compounds **221a**−**d** and **222a**−**d**, along with the isomerized metathesis products (although in low yield) (Scheme 73).[63] These isomerized metathesis products presumably derive from the symmetrical metathesis products (not isolated in the reaction). The same experiment was repeated using Grubbs' catalyst Ru-**2** for the allyl amide **220a**, and the isomerization product was obtained in similar yield (44%) (*E* and *Z* products in roughly 1:1 ratio), but no metathesis product was obtained.[64]

**Scheme 68. Isomerization of Allenamide 206 Catalyzed by Grubbs' Ruthenium Carbene Ru-2**

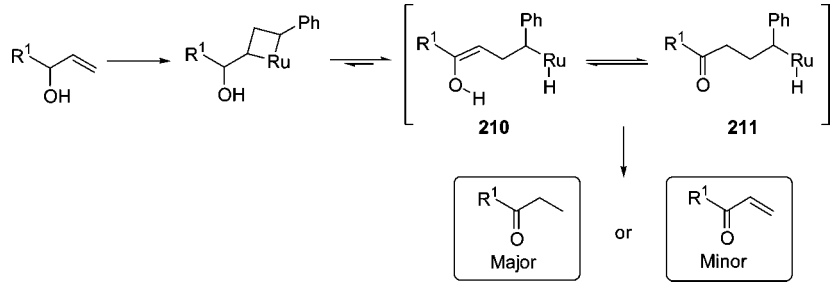



**Scheme 69. Ru-1 Catalyzed Isomerization of Secondary Allylic Alcohols 240 to Ethyl Ketones 241**

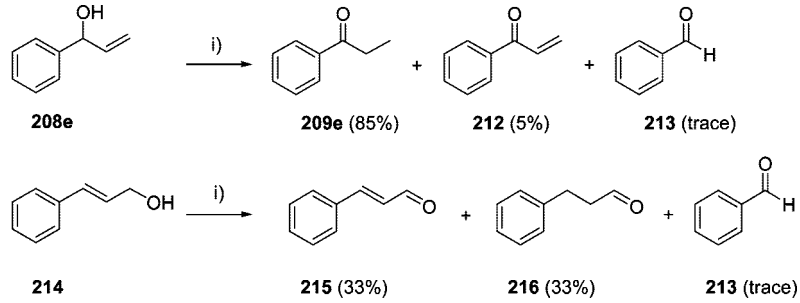



Hanessian et al.[10c] have developed a simple, mild, and efficient method for the isomerization of terminal unsubstituted olefins into their 2-alkenyl counterparts, with minimal if any self-dimerization or cross-metathesis products. The study was started with simple allyl aromatics **223**, **225**, **227**, and **229** with 10 mol % of Ru-**2** in MeOH at 60 °C, with a high tolerance observed for a variety of aromatic substituents (Scheme 74). The same good results were obtained for substituted amino ester **231**, lactam **233**, ketone **235**, ester **237**, and lactone **239**, where the *C*-allyl groups were smoothly isomerized to the corresponding 2-propenyl olefins in high yields, without further conjugation (Scheme 75). Although these functionalized olefins with multiple coordination sites were isomerized at lower rates than the aromatic-containing olefins, their reactions were complete after 12 h

**Scheme 70. Proposed Mechanism to Explain the Isomerization of Secondary Allylic Alcohols to Ethyl Ketones Catalyzed by Carbene Ru-1**

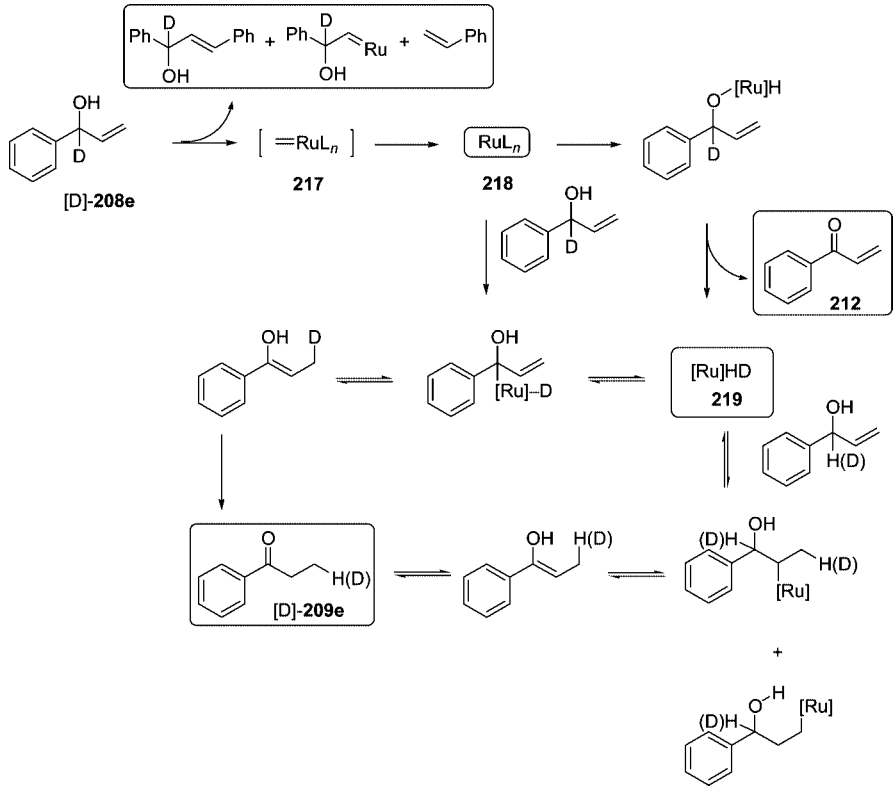



**Scheme 71. Ru-1 Catalyzed Reaction of Secondary Allylic Alcohol 208e and Primary Allylic Alcohol 214[a]**




[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ.

**Scheme 72. Alternative Mechanism for Explaining the Isomerization of Secondary Allylic Alcohol 208e Catalyzed by Carbene Ru-1**

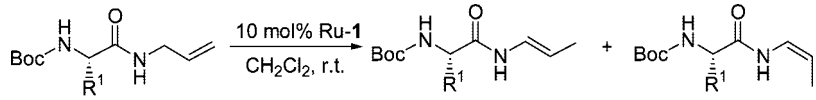



at 60 °C, giving the *trans*-isomers as major or exclusive products. Finally, the isomerization of 1-butenyl benzylic acetate **241**, *O*-TBS ether **243**, or *N*-allylindole derivative **245** produced the corresponding 2-butenyl isomers **242**, **244**, and **246**, respectively, in good yields without methanolysis or hydrolysis under these conditions (Scheme 76).

It was found that terminal alkenes can be isomerized to internal alkenes using Grubbs' second-generation catalyst and an excess of vinyloxytrimethylsilane. In 2007, Donohoe and colleagues also used this strategy for the synthesis of the pyrrolidinone core of the polyene β-lactone antibiotic KSM-2690B.[65] Thus, the intermediate single diastereoisomer homoallylic alcohol **247** was isomerized in the presence of Ru-**2** to the corresponding allyl alcohol **248** (Scheme 77).

In the same context, the group of Rutjes has described a RCM of dehydroamino esters **249a**−**c** with 10 mol % of

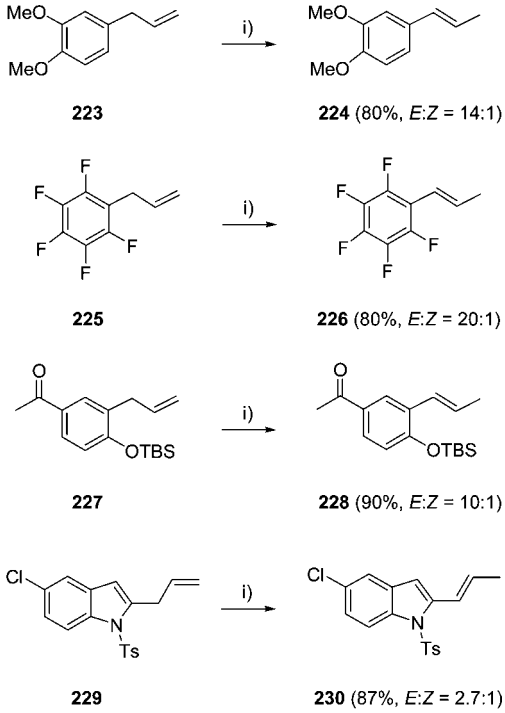
**Scheme 73. Isomerization of Boc-Protected Amino Acid Derivatives 220a−d Catalyzed by Carbene Ru-1**




**220a** $R^1$ = glycine
**220b** $R^1$ = phenylalanine
**220c** $R^1$ = ($N^{Im}$-tos)histidine
**220d** $R^1$ = tryptophan

**221a** (28%) **222a** (20%)
**221b** (20%) **222b** (30%)
**221c** (32%) **222c** (24%)
**221d** (22%) **222d** (28%)

**Scheme 74. Isomerization of Simple *C*-Allyl Aromatic Derivatives Catalyzed by Carbene Ru-2[a]**




**223** **224** (80%, *E*:*Z* = 14:1)

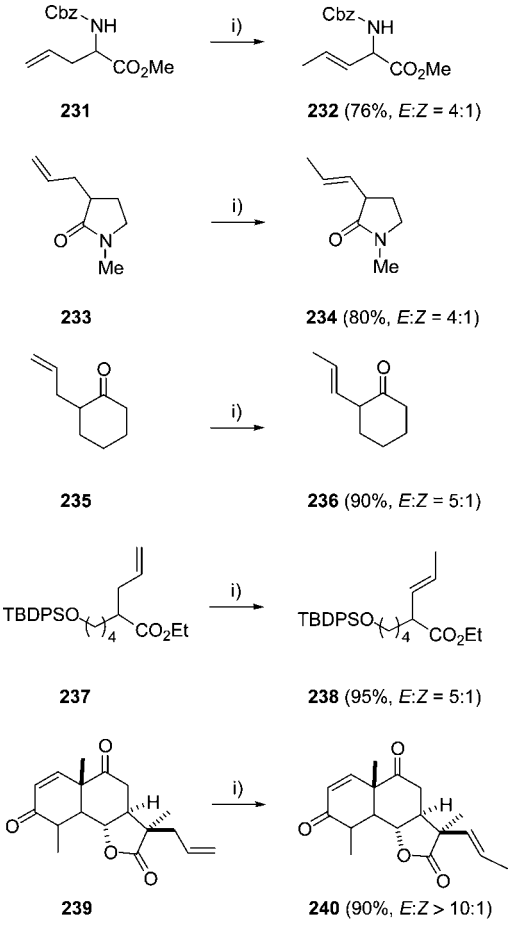
**225** **226** (80%, *E*:*Z* = 20:1)

**227** **228** (90%, *E*:*Z* = 10:1)

**229** **230** (87%, *E*:*Z* = 2.7:1)

[a]Key: 10 mol% Ru-**2**, MeOH, 60 °C, [0.075 M], 3 h.

**Scheme 75. Isomerization of *C*-Allyl Carbonyl Derivatives Catalyzed by Ru-2[a]**




**231** **232** (76%, *E*:*Z* = 4:1)

**233** **234** (80%, *E*:*Z* = 4:1)

**235** **236** (90%, *E*:*Z* = 5:1)

**237** **238** (95%, *E*:*Z* = 5:1)

**239** **240** (90%, *E*:*Z* > 10:1)

[a]Key: 10 mol% Ru-**2**, MeOH, 60 °C, [0.075 M], 12 h.

Ru-**2** in toluene.[66] In all cases, the expected cyclic products **250a−c** were formed in 27−59% yields. Nevertheless, significant amounts of noncyclic isomerized **251a−c** starting materials were recovered (Scheme 78).

## 8.2. Deprotection of *N*-Allyl Amines, *N*-Allyl Ethers, and *N*-Propargyl Amines

### *8.2.1. Deprotection of N-Allyl Amines*

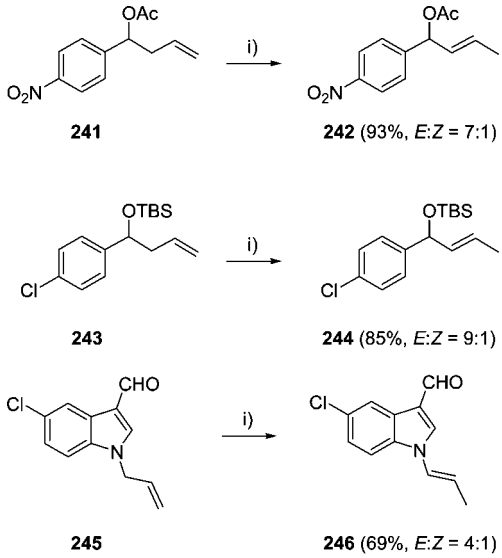
Grubbs' carbenes Ru-**1** and Ru-**2** are metal complexes that act as efficient catalysts for the isomerization of unsaturated oxygen- and nitrogen-containing compounds. In particular, our group has described the first examples accounting for the catalytic cleavage of allylic amines by using reagents different from palladium catalyst.[67] A chemoselective deprotection of allylic amines (secondary as well as tertiary) in the presence of allylic ethers was also achieved.[11b,68] Exposure of the tertiary allylic amines to the ruthenium catalyst Ru-**1** in toluene at 110 °C resulted in clean formation of the secondary amines in good yields. Tertiary allylic amines, many of which bear pendant functionalities, were efficiently and catalytically deallylated by the Grubbs' carbene. Aromatic as well as aliphatic amines were amenable to this deallylation reaction (Scheme 79).

The ability of the Grubbs' carbene Ru-**1** to selectively deprotect allylic amines in the presence of allylic ether **254** deserves special mention, as it competes favorably with the $\pi$-allyl palladium deallylation methodology. Conjugation of the new double bond with the lone pair of the nitrogen atom is believed to promote the enamine intermediate formation in allyl amines, with this ability being minimized in allyl ethers.

The same chemistry was also carried out but with the second-generation ruthenium-based catalyst Ru-**2**, which led to essentially identical results to those observed with the Grubbs' carbene Ru-**1**. Because replacement of the first-generation Grubbs' catalyst with its second-generation analogue neither accelerated the reaction rate nor improved the yield of *N*-deallylated amines, the less expensive first-generation Grubbs' carbene was chosen in this study.

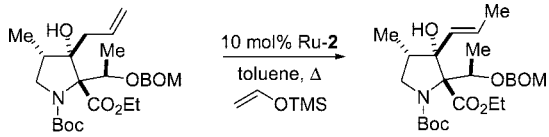
Several of the above examples provided interesting and useful structural motifs. For example, piperidinone **258** could

**Scheme 76. Isomerization of Functionalized C- and N-allyl Compounds Catalyzed by Carbene Ru-2**[a]

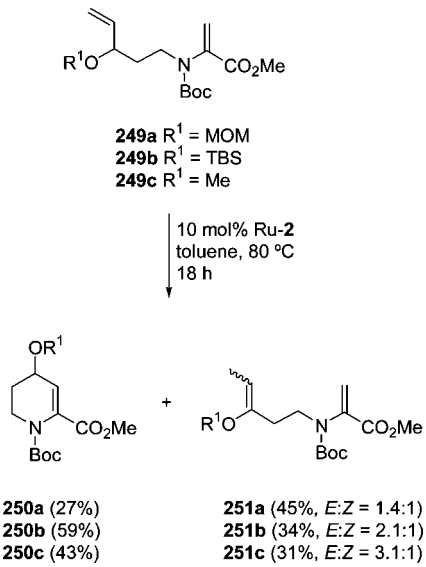



[a]Key: 10 mol% Ru-**2**, MeOH, 60 °C, [0.075 M], 12 h.

**Scheme 77. Isomerization Step Induced by the Grubbs' Carbene Ru-2 during the Synthesis of KSM-2690B**

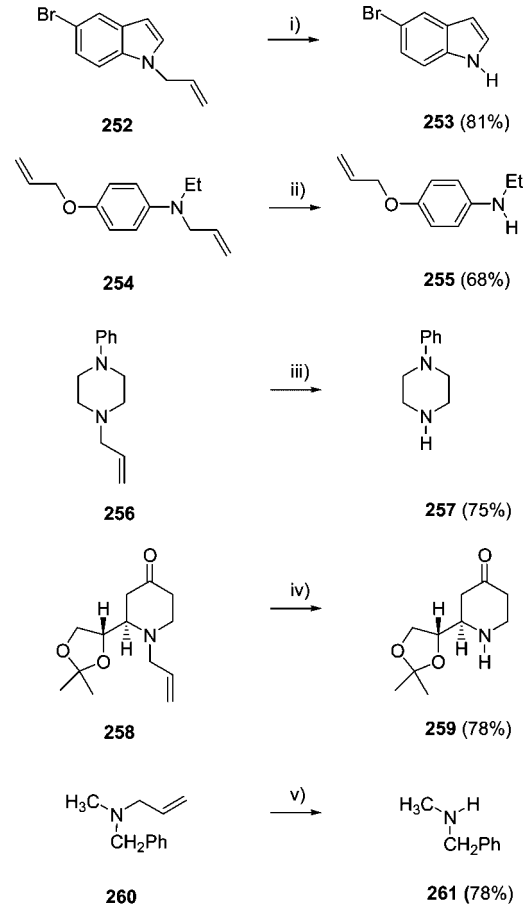



**Scheme 78. Competence between RCM and Isomerization for Dehydroamino Esters 249a−c Catalyzed by Carbene Ru-2**




be converted into a pipecolic acid derivative, a nonproteinogenic amino acid present in several natural products, some of which are of important pharmaceutical interest.[69] A further synthetic application of this reaction was presented in the synthesis of indolizidinones. In principle, piperidine $\beta$-lactams can be convenient precursors for the construction of indolizidine alkaloids, natural products with diverse and potent biological activities.[70] However, the removal of nitrogen protecting groups on *N*-protected piperidine-$\beta$-

**Scheme 79. Grubbs' Carbene Ru-1 Catalyzed Deprotection of Tertiary Allylic Amines**[a]



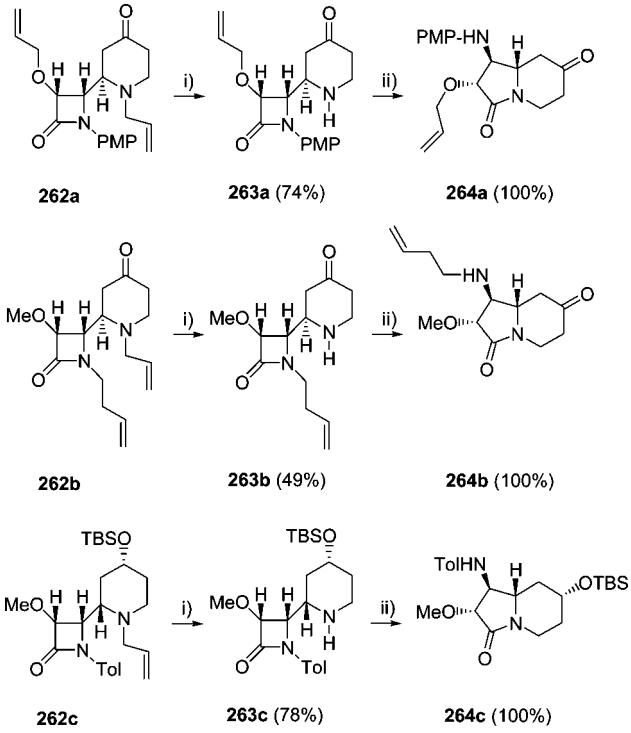

[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ, 5 h; (ii) 5 mol% Ru-**1**, toluene, Δ, 1 h; (iii) 5 mol% Ru-**1**, toluene, Δ, 4.5 h; (iv) 5 mol% Ru-**1**, toluene, Δ, 4.5 h; (v) 5 mol% Ru-**1**, toluene, Δ, 1.5 h.

lactams presented some difficulties. For this reason, the Grubbs' carbene Ru-**1** was tested in *N*-deallylation processes and the deprotection reactions showed excellent chemoselectivities (Scheme 80). For example, in compound **262a**, the $\beta,\gamma$-unsaturated ether remained unreacted and the sustrate **262b** showed that a selective *N*-deallylation can be achieved in the presence of $\gamma,\delta$-unsaturated amines. In this case, the reaction with Grubbs' carbene Ru-**1** afforded the *N*-deallylated product **263b** (49% yield) and the corresponding RCM product as a minor product (~30% yield).

Extrapolation of the deprotection of tertiary allylic amines to secondary allylic amines was not obvious, since free bases are claimed to be ineffective for RCM mediated by the Grubbs catalyst because of poisoning of the catalyst by the amine functionality due to coordination of the amine group to the ruthenium.[71] Scheme 81 shows two examples of deprotection of nitrogen on secondary allylic amines **265a** and **265b**. All substrates reacted efficiently to afford high yields of the corresponding primary amines **266a** and **266b**. Because of the yield of the deprotection reaction, apparently the primary and secondary amine products have no inhibiting effect.

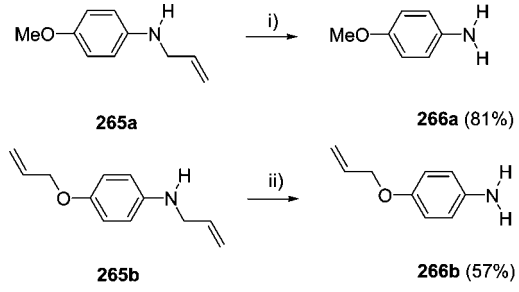
It has been postulated that a nitrogen-assisted ruthenium-catalyzed isomerization to a more stable olefin took place, followed by hydrolysis under chromatographic workup of the enamine intermediate to the free amine. One piece of

**Scheme 80. Grubbs' Carbene Ru-1 Catalyzed Deprotection of *N*-Allyl Piperidines**[a]




[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) MeONa, MeOH, r.t.

**Scheme 81. Grubbs' Carbene Ru-1 Catalyzed Deprotection of Secondary Allylic Amines**[a]

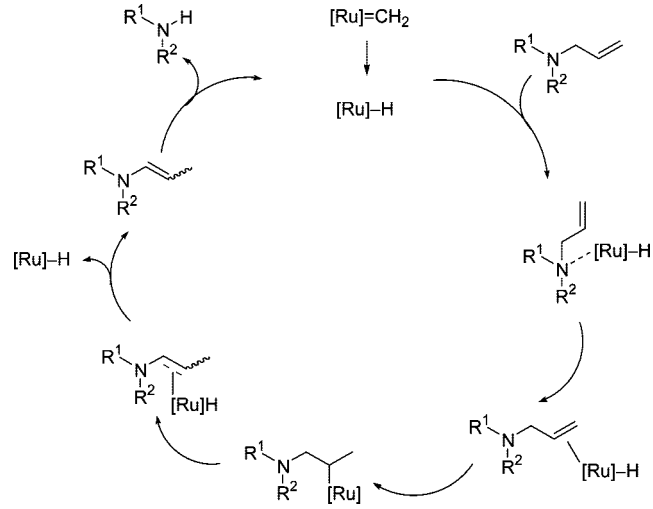



[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ, 5 h; (ii) 5 mol% Ru-**1**, toluene, Δ, 1 h.

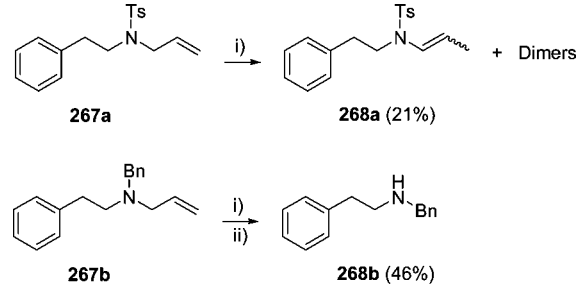
hypothesis that should be taken into account is that, because of the reaction conditions, it may be possible that there is not much catalyst left and the active species might well be a decomposition product derived from the Grubbs catalyst. The active catalyst was probably the corresponding hydrido derivative formed in situ under the reactions conditions. Thus, the isomerization may occur according to the hydride mechanism, by hydrometalation followed by $\beta$-elimination (Scheme 82). Precoordination of the substrate nitrogen atom directs subsequent coordination of the olefin to the metal center, with the metal hydride addition to the olefin occurring in a Markovnikov fashion to afford a secondary metal alkyl. Subsequent $\beta$-hydride elimination gives the enamine, which decomplexes and hydrolyzes to the deallylated amine. The formation of the ruthenium hydride may arise from traces of impurities present in the commercial Grubbs carbene as well as the basic amine media under the reaction conditions.

Cossy et al.[72] reported that the second-generation Grubbs' carbene Ru-**2** was able to mediate isomerization of the *N*-allyl group to produce the corresponding enamine. The resulting

**Scheme 82. Mechanistic Explanation for the Ruthenium-Catalyzed Deprotection of *N*-Allyl Amines**




**Scheme 83. Deprotection of *N*-allylamines Catalyzed by Ru-2**[a]




[a]Key: (i) 3 mol% Ru-**2**; (ii) HCl (aq.).

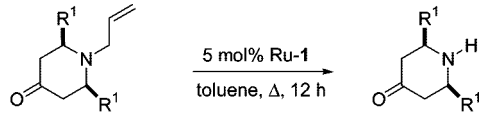
enamine can be transformed to the corresponding amine by acidic workup (Scheme 83). When tosyl allylamine **267a** was treated with Ru-**2**, without acidic treatment, the dimer was formed, which corresponds to the cross-metathesis product in 41% yield and the enamine **268a** in 21% yield. In the case of the benzylallylamine **267b**, the only product observed and isolated was the amine **268b** in 46% yield.

Again, the isomerization may occur analogously to that of related 16-electron Ru complexes, by hydrometalation followed by $\beta$-elimination. The active catalyst is probably not complex Ru-**2** but rather the corresponding hydrido derivatives formed in situ under the reaction conditions.

The piperidine ring is an important framework present in a large variety of natural products.[73] In particular, piperidin-4-ones are versatile building blocks because of the easy manipulation of the carbonyl group for the introduction of different substituents into the six-membered ring. Isomerization of the *N*-allylic moiety has been exploited for the synthesis of *meso*-2,6-diarylpiperidin-4-ones.[74] In this case, the deprotection of *N*-allyl substituted piperidinones **269** was achieved using the first-generation Grubbs catalyst Ru-**1**, with *N*-unsubstituted *meso*-2,6-diarylpiperidin-4-ones **270** being obtained in good yields (Scheme 84).

The higher stability of enamides comparing with enamines favors the Grubbs' carbene double-bond isomerization, preventing (CO)−*N*-allyl cleavage.[11a,75] On the basis of these principles, it was to be expected that successful catalytic C−N deprotection in *N*-allyl lactams would require an additional step. Ruthenium(III) chloride was chosen because

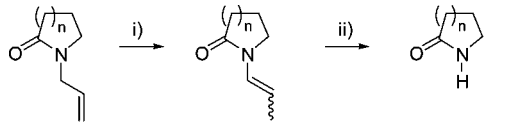
**Scheme 84. Deprotection of *N*-Allyl-4-piperidones Catalyzed by Ru-1**




**269a** $R^1$ = Ph
**269b** $R^1$ = PMP
**269c** $R^1$ = 4-F-$C_6H_4$
**269d** $R^1$ = 2-I-$C_6H_4$

**270a** (67%)
**270b** (68%)
**270c** (70%)
**270d** (63%)

**Scheme 85. Deprotection of Allylic *γ*-, *δ*-, and *ε*-Lactams Catalyzed by Carbene Ru-1[a]**




**271a** n = 1
**271b** n = 2
**271c** n = 3

**272a** (90%, dr = 55:45)
**272b** (90%, dr = 53:47)
**272c** (90%, dr = 0:100)

**273a** (87%)
**273b** (70%)
**273c** (65%)

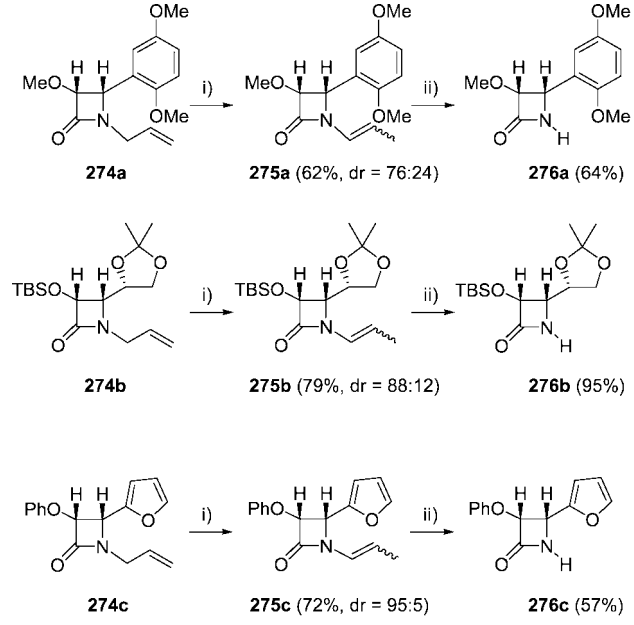
[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$).

it has been probed as an excellent catalyst for the oxidative cleavage of olefins to aldehydes.[76] Besides, it has been reported that *N*-formyl lactams smoothly lose CO under slightly basic conditions to give the corresponding *NH*-amides.[77] The deprotection of *N*-allyl *γ*-butyrolactam **271a** with first-generation Grubbs' carbene Ru-**1** (5 mol %) resulted in clean formation of the corresponding enamide **272a** as an isomeric *E*/*Z* mixture (1.2:1) in good isolated yield (90%) after chromatographic purification. The catalytic scission of the internal C═C was attained by using the system $RuCl_3$−$NaIO_4$ in 1,2-dichloroethane−$H_2O$ (1:1), followed by an aqueous workup in slightly basic conditions (sat. aq. $NaHCO_3$ containing a catalytic amount of $Na_2CO_3$). In this way, the *N*-unsubstituted 2-pyrrolidone **273a** was obtained in 87% yield. Exposure of *N*-allyl *δ*-valerolactam **271b** and *N*-allyl *ε*-caprolactam **271c** to the above sequential catalytic conditions smoothly afforded the *NH*-lactams **273b** and **273c** (Scheme 85). Under the reaction conditions, the intermediate *N*-formyl lactams accumulated in the reaction mixture immediately after the $RuCl_3$−$NaIO_4$ system was added over the enamide and could be isolated under a neutral workup.

In a similar way, the *N*-allyl cleavage protocol in the strained four-membered lactam series was tested. Racemic as well as enantiopure allylic *β*-lactams **274a**−**c** were conveniently deprotected to the corresponding *NH*-*β*-lactams by using both ruthenium catalysts. This transformation tolerates different substituents at the lactam ring, such as aryl, heteroaryl, alkoxy, silyloxy, dioxolanyl, and carboxyalkyl moieties. Of special interest are the furan and electron-rich arene moieties, both of them sensitive to oxidative deprotection conditions, as well as the acid-labile silyl ether and acetonide groups. Importantly, the stereochemical integrity of the stereogenic centers at the lactam rings, when applicable, remained unaltered during the transformation of *N*-allyl compounds **274a**−**c** into *NH*-products **276a**−**c** (Scheme 86).

In order to show that the above ruthenium-catalyzed *N*-deallylation protocol could be considered in a complex synthetic planning, it was successfully used for the cleavage of highly functionalized *N*-allyl bis-*β*-lactams. Bis-*β*-lactam **277** was conveniently deallylated via ruthenium catalysis for

**Scheme 86. Deprotection of *N*-Allyl *β*-Lactams Catalyzed by Carbene Ru-1[a]**




**274a**
**275a** (62%, dr = 76:24)
**276a** (64%)

**274b**
**275b** (79%, dr = 88:12)
**276b** (95%)

**274c**
**275c** (72%, dr = 95:5)
**276c** (57%)

[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$).

affording the *NH*-bis-*β*-lactam **278**. Thus, *N*-allyl bis-*γ*-lactam **280** was achieved from compound **277** by a two-step route through sequential sodium methoxide rearrangement to give the homopyroglutamic derivative **279** followed by acid-promoted cyclization. The *NH*-bis-*γ*-lactam **281** was obtained in 64% yield by using ruthenium-catalyzed allyl breakage (Scheme 87).

The *N*-allyl cleavage protocol was used in the alicyclic series. Aromatic and aliphatic amides **282** were conveniently deprotected to the corresponding free amides **284**, which could be smoothly obtained via the corresponding enamides **283** through ruthenium catalysis (Scheme 88).

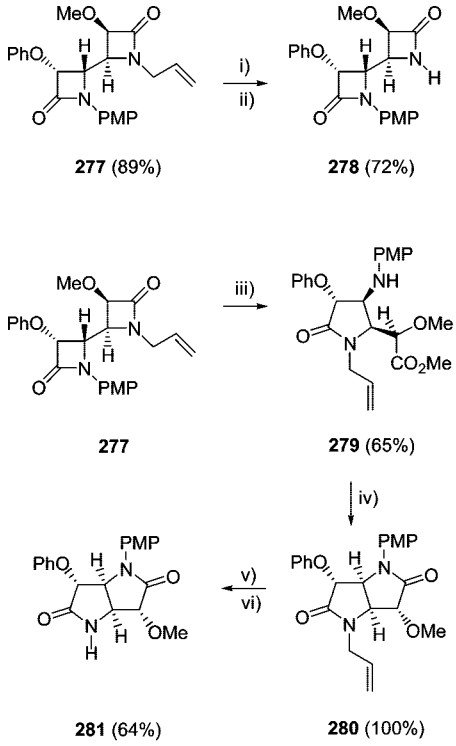
The extension of the above methodology to related systems bearing extra heteroatoms was studied next. The ruthenium-catalyzed allyl cleavage worked nicely for imides, pyrazolidinones, hydantoins, and oxazolidinones **285a**−**d** (Scheme 89).

The isomerization process from *N*-allyl lactams, imides, and analogous to enamide-like moieties is catalyzed either by a hydride decomposition compound or, alternatively, by impurities remaining from catalyst synthesis. The isomerization may occur according to the hydride mechanism, by hydrometalation followed by *β*-elimination, analogously to the double-bond migration of allyl ethers promoted by related ruthenium complexes. This metal hydride mechanism, which requires the presence of a coordinatively unsaturated ruthenium hydride species, is shown in Scheme 90. Coordination of the olefin to the metal center gives a *π*-allyl complex **288**, making the metal hydride addition to the olefin occur in a Markovnikov fashion to afford a *σ*-alkyl complex **289**. Subsequent *β*-hydride elimination gives the enamide *π* complex **290**, which decomplexes to the free enamide, regenerating the catalytically active species.

### 8.2.2. Deprotection of N-Allyl Ethers

Ruthenium catalysts such as Grubbs' carbene complex Ru-**2** efficiently mediated isomerization of *β*,*γ*-unsaturated

**Scheme 87. Deprotection of *N*-Allyl bis-$\beta$-Lactams Catalyzed by Carbene Ru-1**[a]



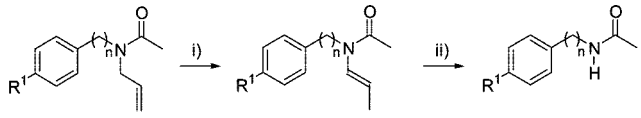

**277** (89%) **278** (72%)

**277** **279** (65%)

**281** (64%) **280** (100%)

[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$); (iii) MeONa, MeOH, r.t.; (iv) PTSA cat., Dean-Stark apparatus, toluene, Δ; (v) 5 mol% Ru-**1**, toluene, 110 °C; (vi) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$).

**Scheme 88. Deprotection of Allylic Amides Catalyzed by Carbene Ru-1**[a]




**282a** *n* = 0, $R^1$ = OMe
**282b** *n* = 1, $R^1$ = H

**283a** (71%, dr = 100:0)
**283b** (78%, dr = 100:0)

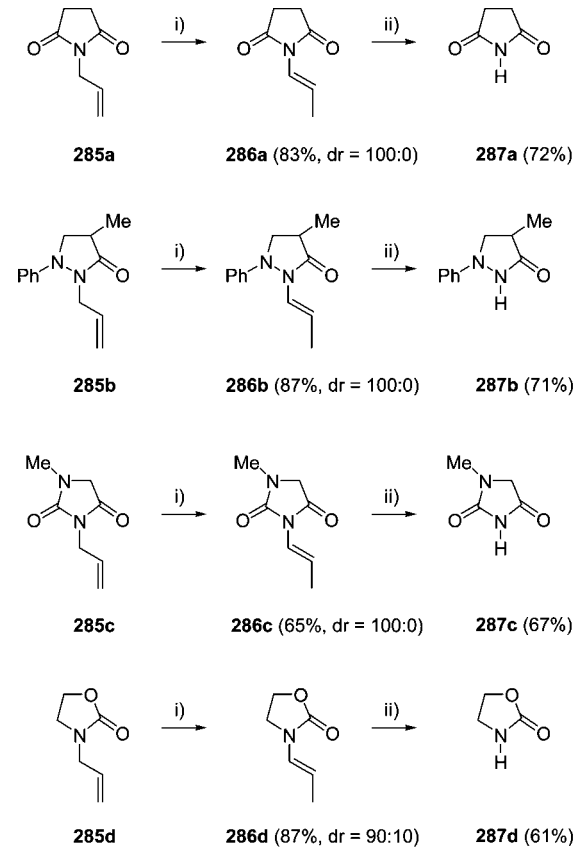
**284a** (97%)
**284b** (69%)

[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$).

ethers to the corresponding vinyl ethers.[72] The resulting enol ethers can be transformed into the corresponding alcohols by acidic workup (Scheme 91). When allylic ethers were treated with Ru-**2** (3 mol %) in dichloromethane at room temperature and subsequently acidic treatment (HCl, 2N), the corresponding alcohols were isolated in a range of 75−95% yield. The isomerization reaction also took place when the allyl group was substituted at the external or internal positions as in compounds **299** and **302**, which were transformed to indanol **301**. For these compounds, the corresponding enol products were isolated in 30 and 78% yield, respectively, when the acidic treatment was omitted (Scheme 92).

The isomerization of olefins was not limited to allylic substrates. When the homoallylic derivative **304** was treated with Ru-**2**, a 1:1 mixture of *E*/*Z* isomers of vinyl ethers **305** was recovered and subsequently transformed under acidic conditions to the corresponding alcohol **306** (Scheme 93).

**Scheme 89. Deprotection of Imides, Pyrazolidinones, Hydantoins, and Oxazolidinones Catalyzed by Ru-1**[a]




**285a** **286a** (83%, dr = 100:0) **287a** (72%)

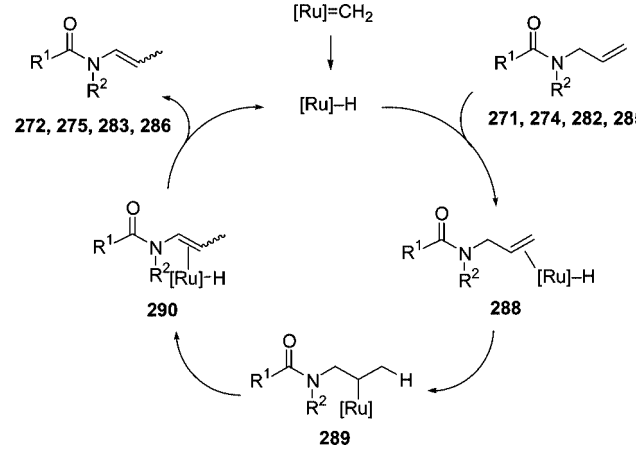
**285b** **286b** (87%, dr = 100:0) **287b** (71%)

**285c** **286c** (65%, dr = 100:0) **287c** (67%)

**285d** **286d** (87%, dr = 90:10) **287d** (61%)

[a]Key: (i) 5 mol% Ru-**1**, toluene, Δ; (ii) $RuCl_3$-$NaIO_4$, DCE-$H_2O$ (1:1), aqueous workup (sat. aq. $NaHCO_3$ + $Na_2CO_3$).

**Scheme 90. Mechanistic Explanation for the Ruthenium-Catalyzed Isomerization of Amides to Enamides**




**272, 275, 283, 286** **271, 274, 282, 285**

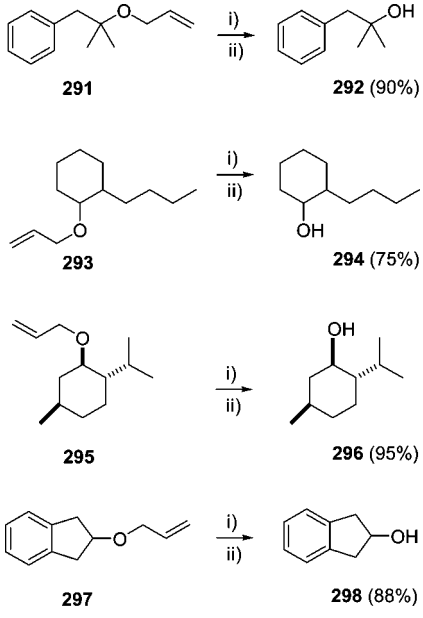
**290** **288**

**289**

### *8.2.3. Deprotection of N-Propargyl Ethers*

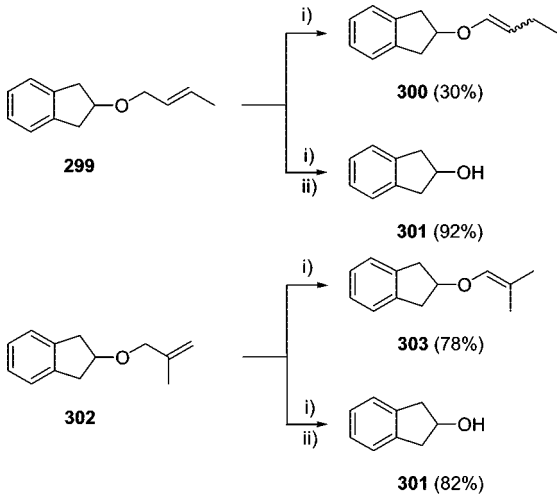
Recently, the propargyl group was selectively removed without any metathesis reactions.[78] The isomerization of a triple bond was studied with ruthenium carbene complexes Ru-**1** and Ru-**2** in dichloromethane at 45 °C. In these conditions, the best result was obtained with Ru-**2**. Taking this result into account, the scope of the deprotection of the propargyl group was investigated by examining different solvent systems and reaction temperatures [($CH_2Cl_2$, 45 °C), (benzene, 100 °C), and (toluene, 125 °C)] with Grubbs' carbene Ru-**2**. Aryl propargyl ether **307a** bearing electron-

**Scheme 91. Deprotection of Allylic Ethers Catalyzed by Carbene Ru-2**[a]



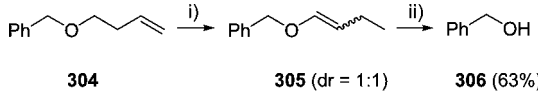

[a]Key: (i) 3 mol% Ru-**2**, $CH_2Cl_2$, r.t; (ii) HCl (aq.).

**Scheme 92. Reaction of Allylic Ethers Catalyzed by Carbene Ru-2 Followed or Not by Acidic Treatment**[a]




[a]Key: (i) 3 mol% Ru-**2**, $CH_2Cl_2$, r.t.; (ii) HCl (aq.).

**Scheme 93. Deprotection of Homoallylic Ether 304 Catalyzed by Carbene Ru-2**[a]

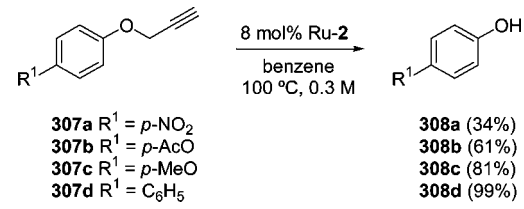



[a]Key: (i) 3 mol% Ru-**2**, $CH_2Cl_2$, r.t.; (ii) HCl (aq.).

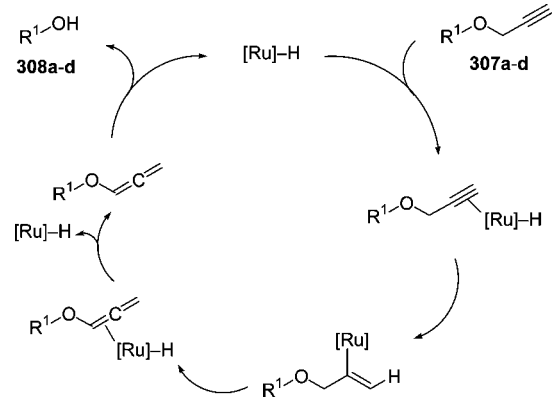
withdrawing groups at the *para*-position of the aromatic ring gave a poor 34% yield of the corresponding phenol **308a**, while compounds **307b** and **307c** having electron-donating groups proved to be good substrates (61−81% yield). The deprotection of phenyl propargyl ether **307d** was completed in quantitative yield to give the corresponding phenol **308d** (Scheme 94).

The detailed mechanism for the deprotection of propargylic ethers by carbene ruthenium complexes is unclear. However,

**Scheme 94. Deprotection of Propargylic Ethers Catalyzed by Carbene Ru-2**




**Scheme 95. Mechanistic Explanation for the Deprotection of Propargylic Ethers**




the ruthenium hydride mechanism, which is typically used to explain the deprotection of allyl groups, may also apply in this case. The allenyl ethers generated by isomerization of the corresponding propargyl ethers may hydrolyze to the corresponding alcohols **308a**−**d** (Scheme 95).

## 8.3. Ring-Closing Metathesis Followed By Isomerization

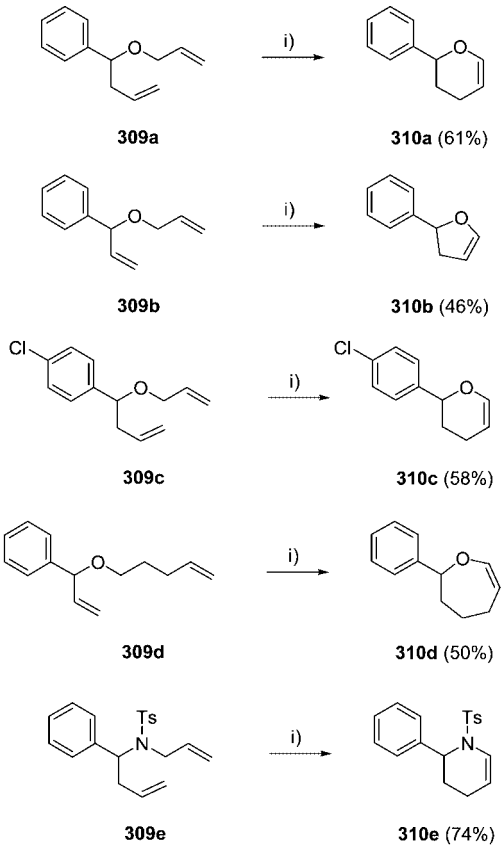
Olefin isomerization (considered to be an undesired side reaction in olefin metathesis) may be converted into a valuable reaction if conditions are found that allow one to distinguish strictly between metathesis and isomerization activity.

In this context, Snapper et al.[79] have described a process that generates cyclic enol ethers through a ruthenium alkylidene-catalyzed ring-closing metathesis (RCM) of acyclic dienes followed by ruthenium hydride-catalyzed olefin isomerization of the resulting RCM products. Enol ethers **310a**−**e** were generated in 46−74% yields in a single reaction vessel from readily prepared dienes **309a**−**e** by treatment with Ru-**2** in $CH_2Cl_2$ (Scheme 96). The authors suggested that the isomerization is sensitive to steric factors because, under these conditions, the generation of trisubstituted enol ethers was not possible.

A methodology for the synthesis of five-, six-, and seven-membered cyclic enol ethers was developed by Schmidt.[10d,80] In this sequence, metathesis−nonmetathesis tandem reactions require a change in the nature of the catalytically active species, which is induced by the addition of appropriate reagents to the reaction mixture after the completion of the metathesis step. In this context, four different additives were investigated in order to activate the metathesis catalyst in the isomerization step (Scheme 97).

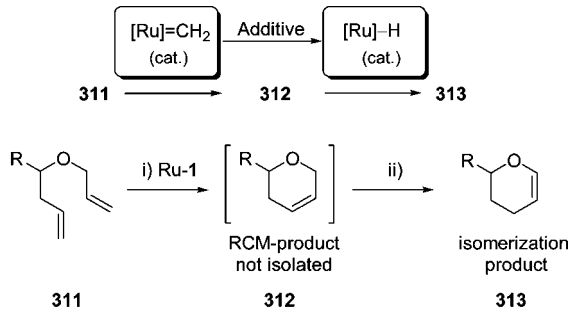
Grubbs described the formation of "Fischer-type" carbene complexes derived from Ru-**1** by treatment of this complex with electron-rich alkenes, such as ethyl vinyl ether.[81] In this case, metathetic exchange of the benzylidene ligand occurs

**Scheme 96. Preparation of Cyclic Enol Ethers and Enamides through a Tandem RCM−Olefin Isomerization Sequence Catalyzed by Grubbs' Carbene Ru-2**[a]




[a]Key: (i) 10-15 mol% Ru-**2**, $CH_2Cl_2$ [0.03-0.05 M], (95:5 $N_2$:$H_2$), 45-70 °C.

**Scheme 97. Tandem RCM−Isomerization: Activation of Carbene Ru-1 with Additives**[a]

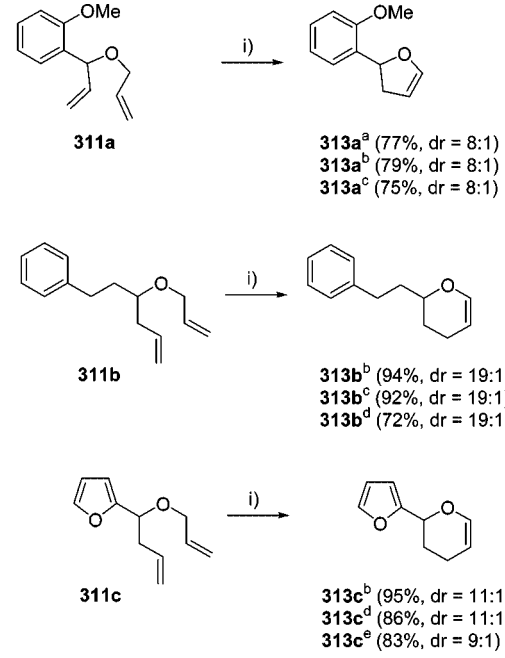



[a]Key: (i) Ru-**1**; (ii) crude containing the catalyst Ru-**1** and the corresponding additive.

with the formation of the new carbene complex $[Cl_2(PCy_3)_2Ru{=}CHOEt]$, which, when heated, decomposes to the hydride complex $[Cl(CO)(PCy_3)_2Ru{-}H]$. Taking these results into account, it was assumed that the propagating species during the RCM of dienes **311a−c** promoted by $[Cl_2(PCy_3)_2Ru{=}CH_2]$ would also undergo metathetical exchange with ethyl vinyl ether to give complex $[Cl_2(PCy_3)_2Ru{=}CHOEt]$ (Scheme 98).

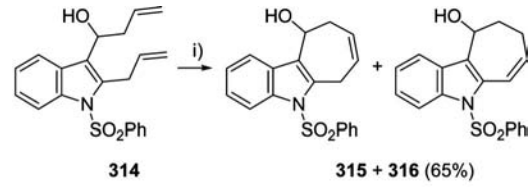
When Grubbs' catalyst Ru-**1** is used in the presence of $NaBH_4$ or a strong base like NaH, a nucleophilic attack by hydride takes place that gives an isomerization-active Ru−H species. Similarly, addition of 2-propanol and solid NaOH to the reaction mixture turned out to be very effective because, under these conditions, the intermediate RCM

**Scheme 98. RCM−Olefin Isomerization Catalyzed by Carbene Ru-1 in Presence of Additives**[a]




[a]Key: (i) (a) 5 mol% Ru-**1**, toluene, 25 °C, add $EtOCH{=}CH_2$ after completion of the metathesis reaction, 25 °C for 10 min, and then 110 °C; or (b) 5 mol% Ru-**1**, toluene, 25 °C, and then add 50 mol % NaH, 5-8 h; or (c) 5 mol% Ru-**1**, toluene, 25 °C, and then add 50 mol % $NaBH_4$, 5-8 h; or (d) 5 mol% Ru-**1**, toluene, 25 °C, and then add 2-propanol (25% v/v) and 50 mol % NaOH, 110 °C, 1-2 h; or (e) 5 mol% Ru-**1**, toluene, 25 °C, and then add $Et_3SiH$ (1.1 eq).

**Scheme 99. Tandem RCM−Isomerization for the Preparation of Cyclohepta[*b*]indole Catalyzed by Carbene Ru-1**[a]

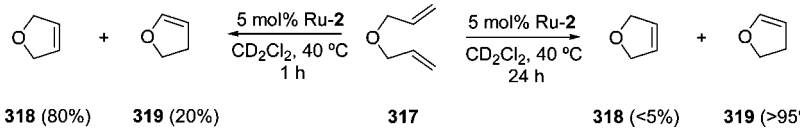



[a]Key: (i) 10 mol% Ru-**1**, $CH_2Cl_2$, Δ, overnight.

product was converted quantitatively to the isomerized product.[82] Finally, the use of silanes to convert the propagating species of olefin metathesis $[Cl_2(PCy_3)_2Ru{=}CH_2]$ to an isomerization catalyst was developed by Ru-**1**. Because the activation of the Si−H bond occurs by oxidative addition of the silane to the metal complex, a metal−hydride complex, which is the active species, is postulated to be formed.[83]

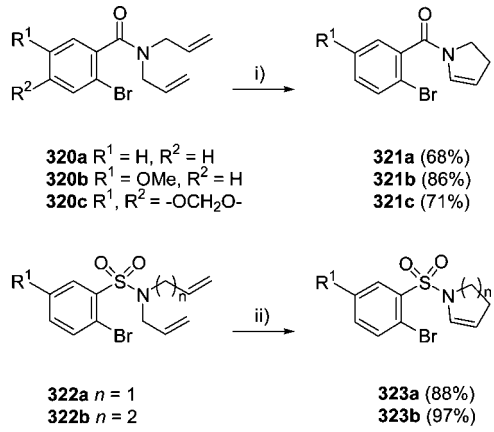
A seven-membered carbocycle fused to the 2,3-position of the indole ring, representing tricyclic substructures of indole alkaloids, has been synthesized using Ru-**1** in refluxing dichloromethane.[84] Under these conditions, **314** gave a mixture of the expected cyclohepta[*b*]indole **315** and its isomer **316**, in which the double bond has moved to the indole α-position. The above isomerization to a 2-vinylindole system deserved comment as it might be mediated by the Grubbs' carbene or some species derived from this catalyst (Scheme 99).

**Scheme 100. RCM−Isomerization Sequence of Diallyl Ether 317 Catalyzed by Ru-2 without Additive**




**318** (80%) **319** (20%) **317** **318** (<5%) **319** (>95%)

**Scheme 101. Tandem RCM−Olefin Isomerization of bis(Allylamides) and bis(Allylsulfonamides) Catalyzed by Carbene Ru-1[a]**

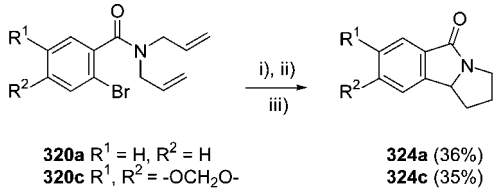


**320a** $R^1$ = H, $R^2$ = H — **321a** (68%)
**320b** $R^1$ = OMe, $R^2$ = H — **321b** (86%)
**320c** $R^1$, $R^2$ = -$OCH_2O$- — **321c** (71%)

**322a** *n* = 1 — **323a** (88%)
**322b** *n* = 2 — **323b** (97%)

[a]Key: (i) 4 x 2.5 mol% Ru-**1**, 120 mol% NaH, toluene, Δ; (ii) 5 x 2.5 mol% Ru-**1**, NaH (5 x 0.3 eq.), toluene, Δ.

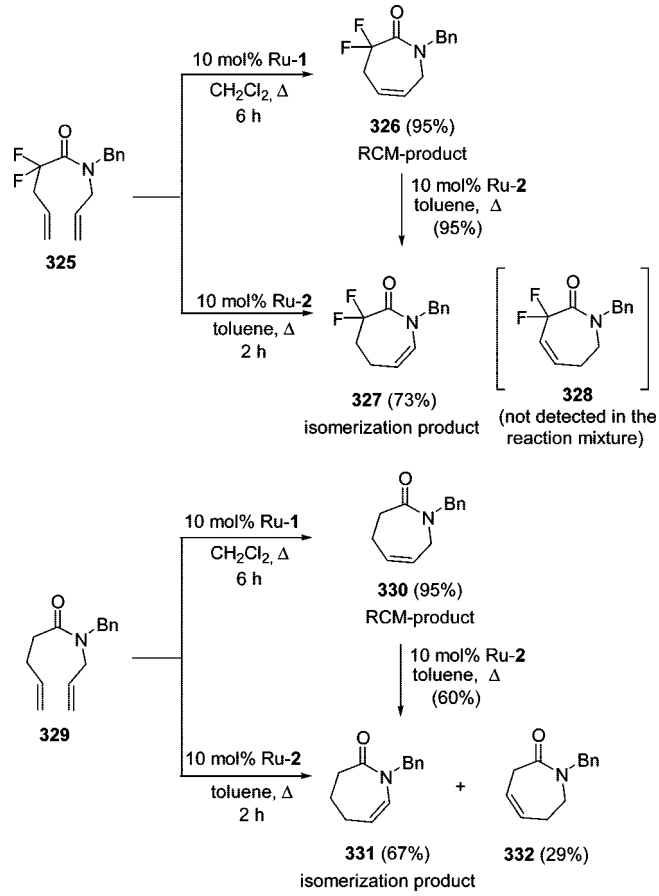
**Scheme 102. One-Pot RCM−Isomerization/Radical Cyclization Catalyzed by Ru-1[a]**



**320a** $R^1$ = H, $R^2$ = H — **324a** (36%)
**320c** $R^1$, $R^2$ = -$OCH_2O$- — **324c** (35%)

[a]Key: (i) 2.5 mol% Ru-**1**, toluene, r.t., 1 h; (ii) [5 x 2.5 mol% Ru-**1** + NaH (0.15 eq.)], toluene, 130 °C, 60 h; (iii) TTMS (2eq.), AIBN (0.10 eq.), toluene, 130 °C, 6 h.

**Scheme 103. Tandem RCM−Olefin Isomerization Sequence Catalyzed by Grubbs' Carbenes for the Preparation of Seven-Membered Lactams**

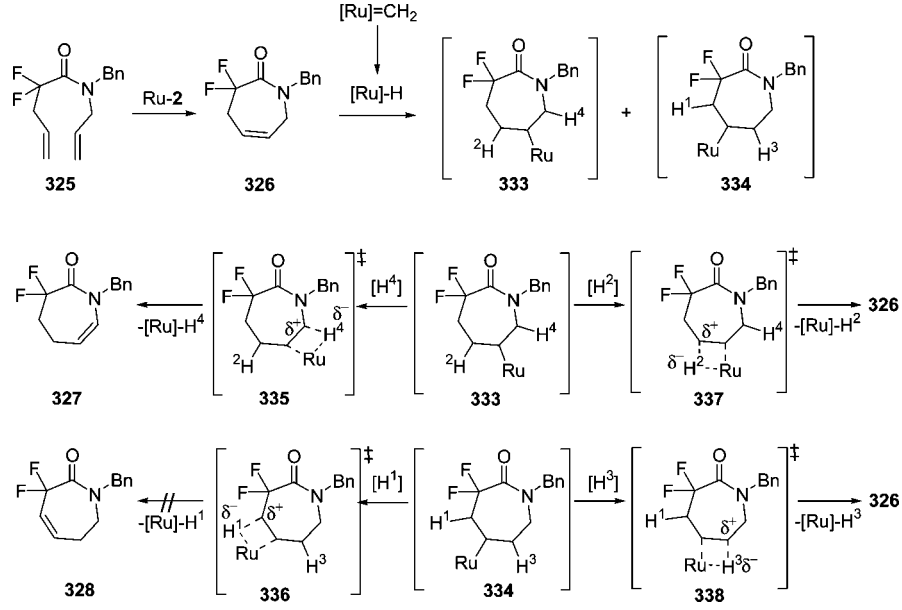



Grubbs' and colleagues[85] studied different types of additives for preventing olefin isomerization of a number of allylic ethers during olefin metathesis reaction with ruthenium catalyst Ru-**2**. For the RCM of diallyl ether **317**, the metathesis product 2,5-dihydrofuran **318** was observed as the major product after 1 h. After extended reaction times (24 h), it was isomerized to 2,3-dihydrofuran **319** (Scheme 100). This fact suggested that decomposition products from the catalyst were responsible for the isomerization. Both acetic acid and 1,4-benzoquinone as additives were effective to prevent the isomerization of **318** to **319**. In the presence of these additives and Ru-**2**, only product **318** (>95% yield) was recovered. By contrast, radical scavengers such as BHT, TEMPO, phenol, and 4-methoxyphenol were, in general, not effective in preventing isomerization.

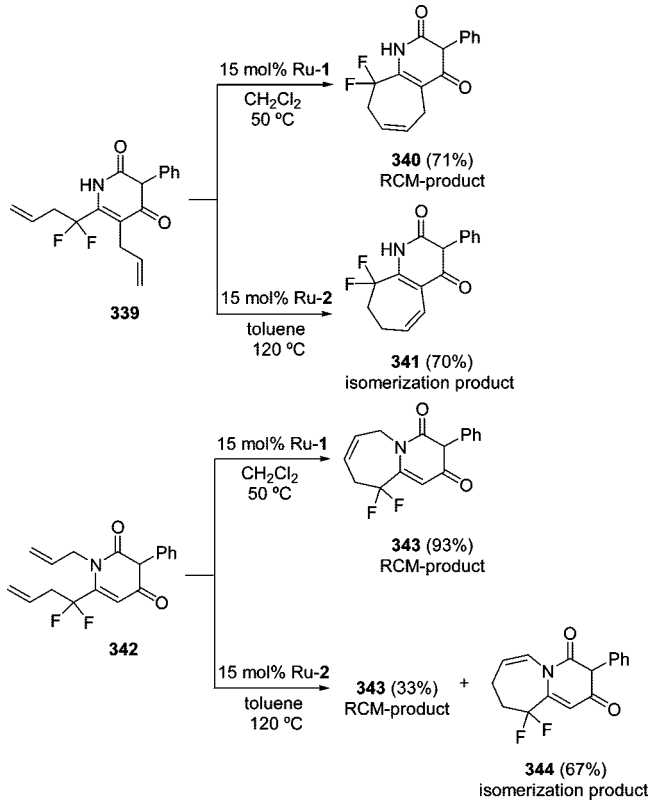
Bicyclic lactams and sultams have been prepared by RCM combined with a subsequent isomerization promoted by the Grubbs' carbene Ru-**1**.[86] 2-Pyrrolines **321a−c** were obtained from *N*,*N*-bis(allylamides) **320a−c** with good yields using Ru-**1** and sodium hydride in refluxing toluene. This overall sequence was applied to sulfonamides **322a** and **322b**, with the isomerization being totally regioselective (Scheme 101). Finally, under the same cyclization−isomerization conditions but incorporating a further radical cyclization, amides **320a** and **320c** were converted into tricyclic lactams **324a** and **324c** in moderate yields (Scheme 102).

Fustero and colleagues have reported a tandem RCM−isomerization reaction that allows preparation of fluorinated and nonfluorinated, unsaturated lactam derivatives of various ring sizes.[10b,87] In this case, the RCM−isomerization sequence does not require the use of any additives to generate ruthenium hydride species, which are believed to be responsible for the regioselective isomerization reaction. Starting from acyclic diene **325**, the formation of ε-lactams **326** was carried out in the presence of Ru-**1** in refluxing dichloromethane. By contrast, the corresponding seven-membered enamide **327** was exclusively formed by tandem RCM−isomerization sequence catalyzed by Ru-**2** in hot toluene. This overall process also could be carried out in two steps, because when lactam **326** was heated in toluene with Ru-**2**, an isomerization reaction took place smoothly, affording lactam **327** in 95% yield. When this protocol was applied to the corresponding nonfluorinated lactam **329**, the formation of expected lactam **331** in 67% yield along with another isomeric lactam **332** (29%) was observed. This latter compound arises from the double bond isomerization toward the opposite side. Using the two-step sequence, the exposure of nonisomerized RCM product **330** to Ru-**2** in refluxing

**Scheme 104. Possible Mechanism for the Isomerization of ε-Lactams Catalyzed by Ru-2**



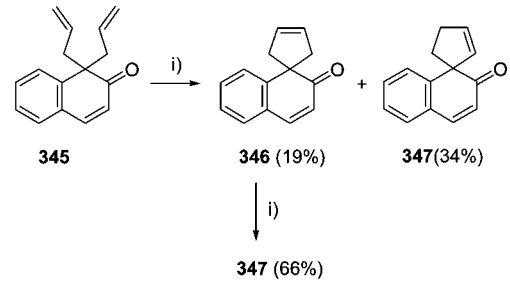

**Scheme 105. Tandem RCM−Olefin Isomerization Catalyzed by Carbene Ru-2 for the Preparation of Fluorinated Uracils**




toluene afforded a mixture of lactams **331** and **332** in a 2:1 ratio (Scheme 103).

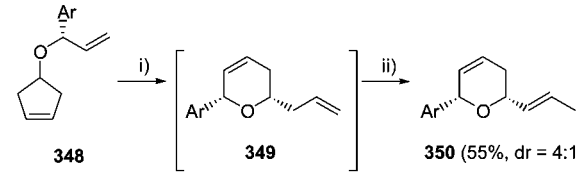
When amide **325** was heated in a NMR tube in deuterated toluene in the presence of Ru-**2**, after 10 min at 80 °C, a 1:1 mixture of amides **326** and **327** was the only product observed in the $^1$H NMR spectrum, indicating that the cyclization of dienic amide **325** occurs rapidly, with lactam **326** being formed first. The ruthenium hydride generated in the reaction conditions could then add to the olefinic moiety of lactam **326**, giving rise to the isomeric intermediates **333** and **334** (Scheme 104). β-Elimination of the appropriate hydride would lead to the final isomerized amides. Intermediates **333** and **334** each contain two different kinds of suitable hydrogen atoms that can undergo the elimination process ($H^2$ and $H^4$ for **333**; $H^1$ and $H^3$ for **334**). The elimination of hydrogen $H^2$ or $H^3$ on intermediates **333** and **334** would cause the formation of transition states (TSs) **337** and **338**, respectively, which in turn would again revert to the starting lactam **326**. In contrast, the elimination of hydrogen $H^4$ on intermediate **333** would lead to TS **335**, the formation of which is favored as a result of the stabilization of the positive partial charge in the α carbon to the nitrogen, which in turn is caused by the lone nitrogen electron pair. Finally, the elimination of hydrogen $H^1$ on intermediate **334** would cause the formation of TS **336**, wich would be destabilized due to the fact that the partial positive charge on the carbon atom contiguous to the *gem*-difluoro moiety

**Scheme 106. Formation of Spirocyclopentene 347 through a Tandem RCM−Isomerization Induced by Carbene Ru-1[a]**



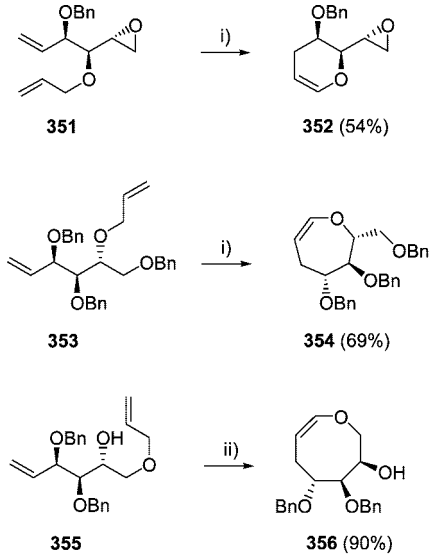

[a]Key: (i) 10 mol% Ru-**1**, toluene Δ.

**Scheme 107. dRRM Followed by Isomerization of the Terminal Double Bond during the Synthesis of (−)-Centrolobine[a]**



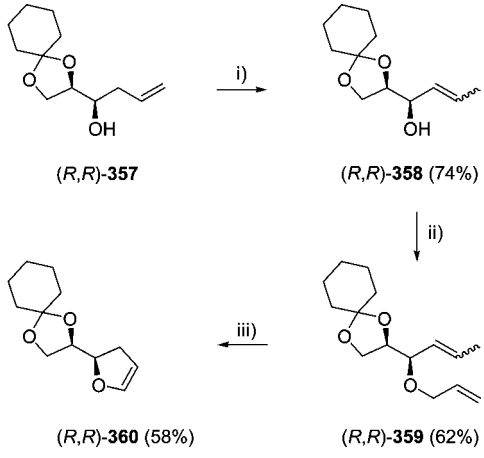

[a]Key: (i) 10 mol% Ru-**2**, benzene-ethylene, 50 °C, 6 h; (ii) then add $NaBH_4$, 100 °C, 30 h.

**Scheme 108. Preparation of Six- To Eight-Membered Oxacycles Catalyzed by Carbenes Ru-1 and Ru-2 through a RCM−Isomerization Sequence[a]**



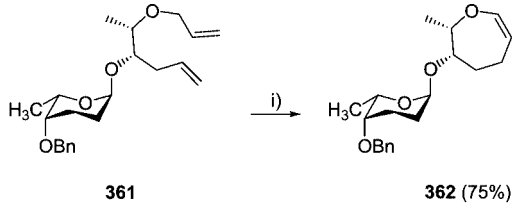

[a]Key: (i) 5 mol% Ru-**1**, toluene, 20 °C, then 2-propanol and NaOH, 110 °C; (ii) 5 mol% Ru-**2**, toluene, 110 °C, then $NaBH_4$, 110 °C.

**Scheme 109. Grubbs' Carbene-Catalyzed Preparation of Dihydrofuran 360 Using a RCM−Isomerization Sequence[a]**




[a]Key: (i) 5 mol% Ru-**1**, toluene, $EtOCH{=}CH_2$; (ii) $Br\text{-}CH_2CH{=}CH_2$, THF, 65 °C; (iii) 5 mol% Ru-**1**, toluene, 25 °C, then 2-propanol and NaOH, 110 °C.

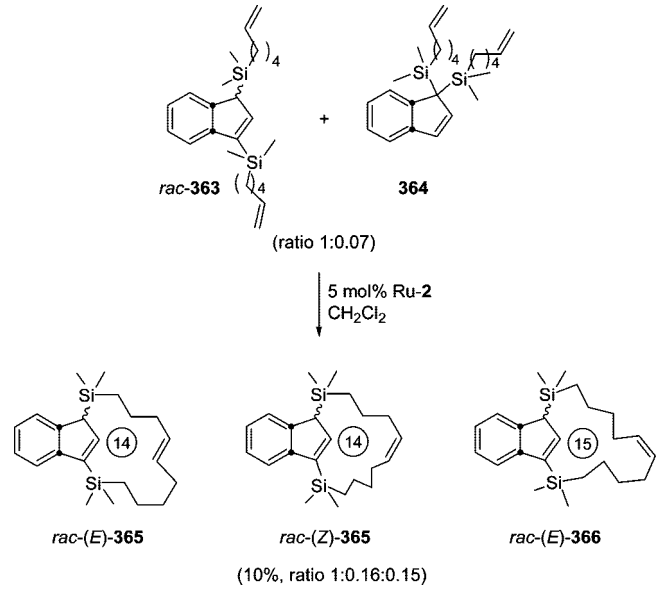
**Scheme 110. Synthesis of a Disaccharide Glycal of L-Rhodinose Using RCM−Isomerization Sequence Catalyzed by Carbene Ru-1[a]**



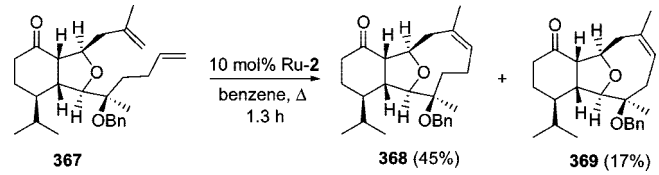

[a]Key: (i) 5 mol% Ru-**1**, toluene, 20 °C, then 2-propanol (20 vol%) and NaOH (30 mol%), 110 °C.

should be destabilized by its electron-withdrawing effect. Thus, the formation of TS **336** would be disfavored in comparison to that of TS **335**. Since TSs **335** and **336** would lead to the formation of lactams **327** and **328**, respectively, this mechanism, which takes into account the destabilizing influence of the *gem*-difluoro group on TS **336** as compared to the stabilizing effect of the N atom on TS **335**, would explain why lactam **328** is not observed as reaction product.

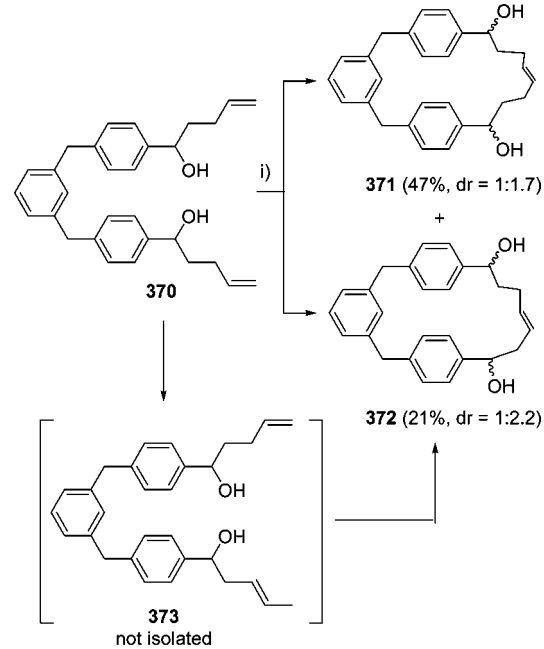
**Scheme 111. Preparation of Macrocyclic Bridged Indenes by Isomerization−RCM Strategy Catalyzed by Carbene Ru-2**




**Scheme 112. Reactivity of Diene 367 under Exposure to Grubbs' Carbene Ru-2 En Route to (+)-Vigulariol**

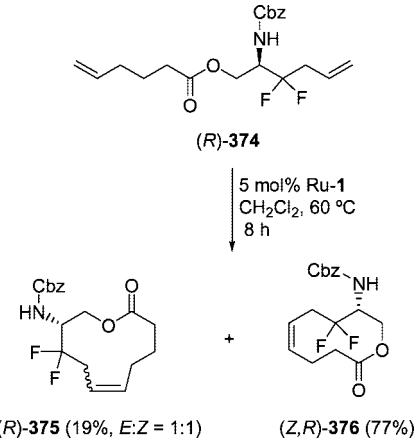



**Scheme 113. Isomerization−RCM Sequence on bis(Alkenol) 370 Catalyzed by Carbene Ru-2[a]**

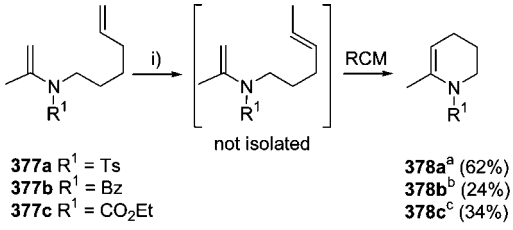



[a]Key: (i) Ru-**2**, $CH_2Cl_2$ [0.001M], r.t., 24 h.

**Scheme 114. Ten-Membered Macrolactone 376 Achieved by Isomerization−RCM Sequence Catalyzed by Carbene Ru-1**

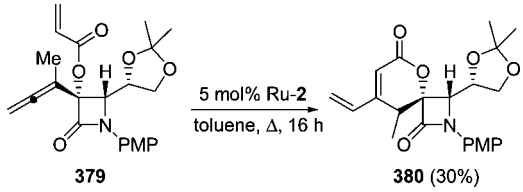



**Scheme 115. Grubbs' Carbene Ru-2 Catalyzed Synthesis of Tetrahydropyridines Using Isomerization−RCM of Enamides**[a]




[a]Key: (i) (a) 5 mol% Ru-**2**, DCE, 80 °C, 16h; or (b) 5 mol% Ru-**2**, DCE, 80 °C, 24h; or (c) 5 mol% Ru-**2**, DCE, 84 °C, 48h.

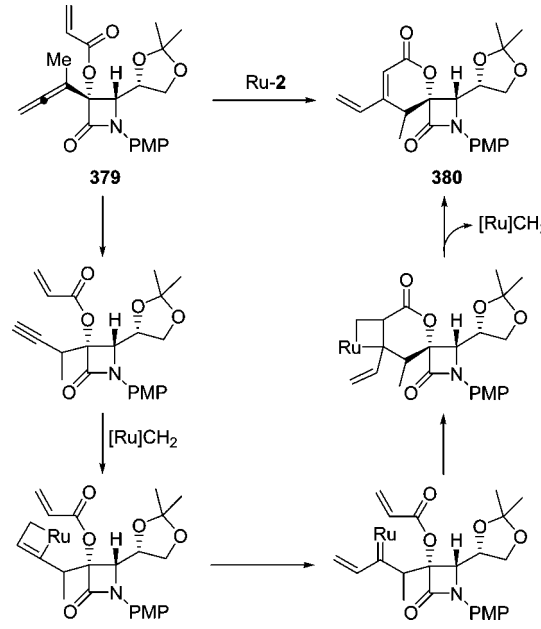
**Scheme 116. Preparation of Spirocyclic β-Lactam 380 through Enallene Isomerization−RCM Sequence Catalyzed by Carbene Ru-2**



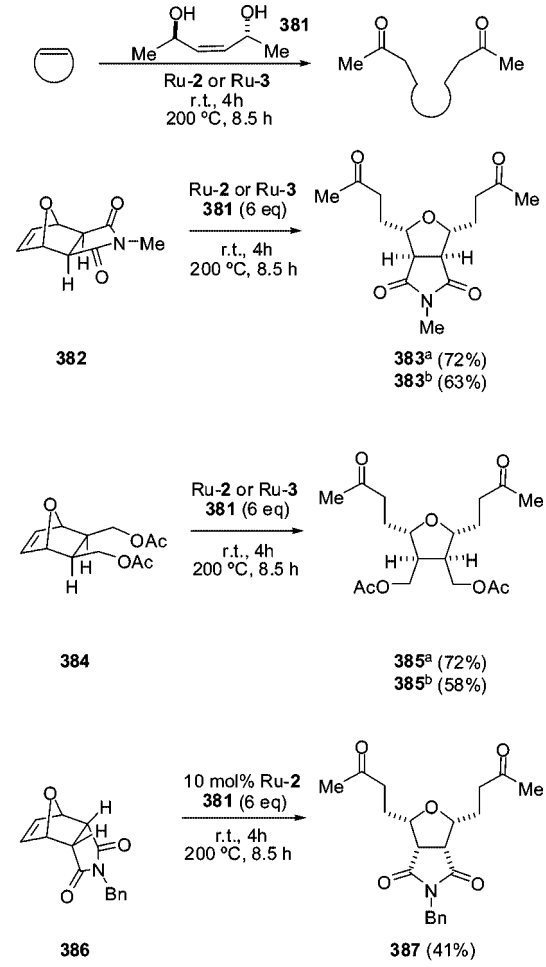

Finally, the amide **326** formed from TSs **337** and **338** would once again be subjected to the catalytic cycle, forming at the end of the process the most thermodynamically stable product **327**. The formation of this compound is therefore favored by the high temperature used in the reaction. This proposed mechanism would also explain why nonfluorinated amide **329** affords a mixture of isomerized lactams **331** and **332**.

The same group[88] has prepared two new families of fused bicyclic fluorinated uracils using RCM to form the new ring, which is fused to the uracil moiety. The selective formation of olefin regioisomers in the metathesis process can be controlled according to the reaction conditions (Scheme 105). When the RCM reaction of compound **339** was carried out in the presence of Ru-**2** and hot $CH_2Cl_2$ (50 °C), a mixture of the seven-membered isomeric uracils **340** and **341** was obtained (72:28 ratio), with the minor product coming from the isomerization of the double bond after the metathesis reaction. By contrast, the use of Grubbs' first-generation catalyst Ru-**1** in $CH_2Cl_2$ yielded only the isomer **340**. Interestingly, the use of Ru-**2** in toluene (120 °C) led to the isomerization product **341** as a single product. It should be noted that the other possible isomer (coming from the migration of the double bond toward the fluorine atoms) was not detected, apparently due to an unfavorable stereoelec-

**Scheme 117. Mechanistic Explanation for the Formation of Spirocyclic β-Lactam 380**

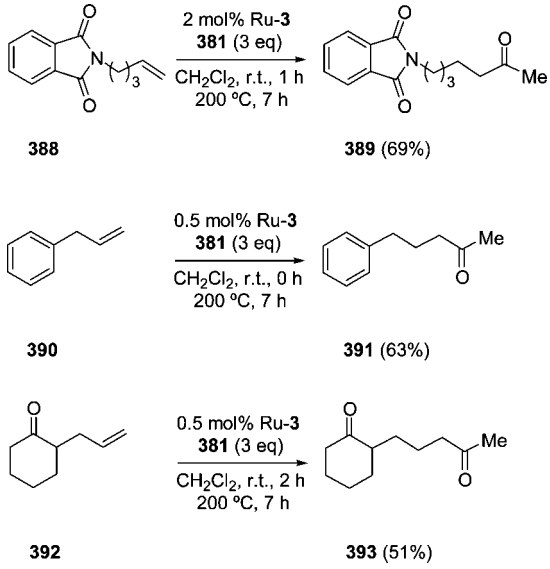



**Scheme 118. Synthesis of Diketones by Tandem Ring-Opening Cross-Metathesis−Isomerization Catalyzed by Carbenes Ru-2 or Ru-3**[a]

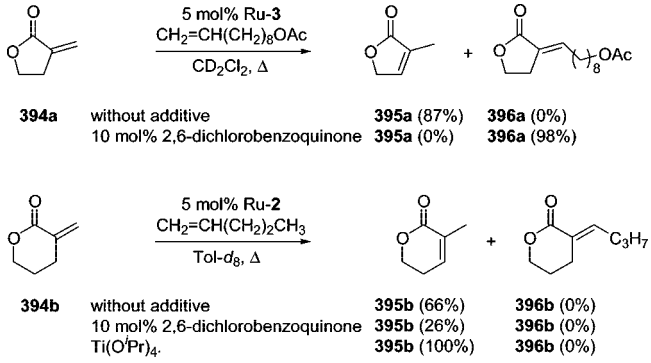



[a]Key: (a) 10 mol% Ru-**2**; (b) 1 mol% Ru-**3**.

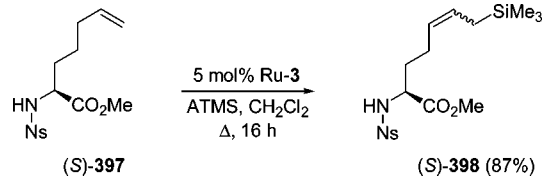
**Scheme 119. Synthesis of Ketones by Tandem Ring-Opening Cross-Metathesis−Isomerization**




**Scheme 120. Isomerization of α-Methylene-γ-butyrolactone 394a and α-Methylene-δ-lactone 394b Catalyzed by Carbenes Ru-2 and Ru-3**




**Scheme 121. Double-Bond Isomerization Followed by Cross-Metathesis Catalyzed by Ru-3**




tronic effect of the contiguous difluoromethylene moiety. The second family of bicyclic uracils was accessible from compound **342**. However, in contrast to uracil **339**, the double bond was only partially isomerized in the presence of Ru-**2** in toluene, resulting in a mixture of bicycles **343** and **344** (33:67 ratio).

The treatment of olefin **345** with the Grubbs' first-generation catalyst Ru-**1** for seven days gave the expected metathesis product **346** and the isomer **347**.[89] The thermal isomerization of **346** to **347** in the absence of Grubbs' carbene Ru-**1** was not viable, but in the presence of Ru-**1** under the above conditions, compound **346** gave the isomerized product **347** in 66% yield. The ruthenium-catalyzed isomerization of the double bond was feasible in the absence of alcohol, ether, or amide functional groups in the allylic or homoallylic positions. A possible mechanism for the isomerization reaction, through a 16-electron Ru complex, may involve intramolecular hydrogen transfer followed by β-elimination. It is believed that the ruthenium hydride species generated in situ by catalyst decomposition are responsible for the isomerization (Scheme 106).

The group of Blechert[90] described a selective isomerization of a terminal double bond in its synthesis of (−)-centrolobine. Diastereoselective ring-rearrangement metathesis (dRRM) of cyclopentene **348** gave the dihydropyran intermediate **349**. The reaction was carried out using Grubbs' carbene Ru-**2** in benzene, which had been saturated with ethylene, at 50 °C in a pressure vessel. After complete conversion, 40 mol % of $NaBH_4$ was added to convert the metathesis catalyst into a ruthenium hydride. Then, the vessel was flushed with nitrogen and subsequently heated to 100 °C for 30 h. The desired dihydropyran **350** was obtained in 60% yield with no isomerization of the endocyclic double bond (Scheme 107).

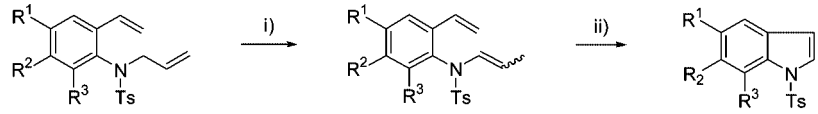
In the synthesis of glycals of 3-deoxyheptoses by Schmidt et al.,[91] the addition to the epoxide **351** of ruthenium catalyst Ru-**1**, toluene, and isopropanol/NaOH afforded the enol ether **352** as the only product of the reaction. Under these RCM−isomerization conditions, the seven-membered glycal **354** was obtained in comparable yield. By contrast, the cyclic enol ether **356** was not isolated in the presence of Ru-**1**, forming a dimer instead. The protocol was changed and Ru-**2** in the presence of 2-propanol/NaOH was tested, but isomerized product was not obtained. However, the use of $NaBH_4$ was successful, and the eight-membered oxacycle **356** was obtained in good yield as a single isomer (Scheme 108). Oxacyclic products with diverse relative stereochemistry, substitution patterns, and ring sizes can be prepared from just two diastereomeric precursors by using RCM−isomerization as key transformation.[92] Enol **358** was obtained as an *E*/*Z* mixture when the homoallylic alcohol **357** was isomerized under carefully controlled conditions, with ethyl vinyl ether being used as reagent to convert Ru−benzylidine complex Ru-**1** into the hydride species. The diastereomeric mixture of enols **358** was subsequently allylated to give the corresponding allyl ethers *E*-**359** and *Z*-**359**. Both products in the presence of Ru-**1** under RCM−isomerization conditions gave selectively the desired product **360** (Scheme 109).

Protected 3,6-dideoxyglycals have been synthesized as single isomers starting from ethyl lactate by using the one-pot RCM−isomerization sequence as the key step.[93] In this manner, glycoside **361** containing one septanose unit and one hexose unit (from L-rhodinal benzyl ether) was converted to the disaccharide glycal **362** by treatment with Ru-**1**, toluene, and isopropanol/NaOH (Scheme 110).

## 8.4. Isomerization Followed By Ring-Closing Metathesis

The ring-closure of the mixture of diene *rac*-**363** and **364** gave three different products, *rac*-(*E*)-**365**, *rac*-(*Z*)-**365** and *rac*-(*E*)-**366**, in a 1:0.16:0.15 ratio (Scheme 111).[94] Of these compounds, only the last mentioned has the expected 15-membered ring size. In the other two, a ring size of 14 was observed. Because of ruthenium-catalyzed isomerization reactions of terminal alkenes to more stable ones, prior to ring-closing, the RCM resulted in a decreased ring size as described by Rutjes and colleagues.[59] The precursor *rac*-**363** must be isomerized to form a more stable compound containing only one terminal alkene group. Then, the isomerized compound was exposed to the Grubbs' catalyst Ru-**2** suffering subsequent ring-closure, producing the 14-membered ring.

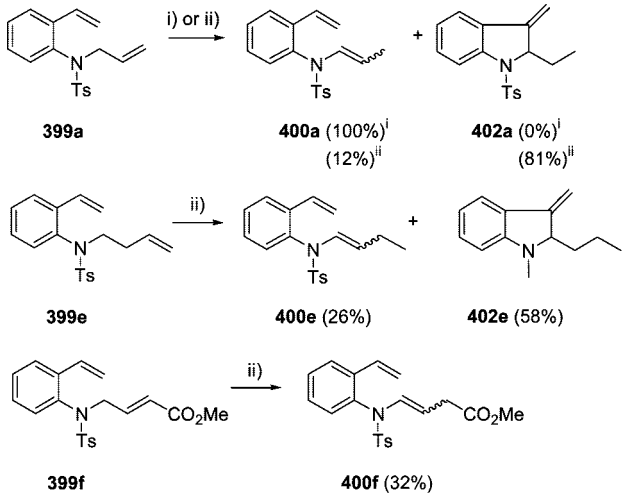
**Scheme 122. Selective Isomerization of Allyl Tosylamines Catalyzed by Grubbs' Carbene Ru-2[a]**



**399a** $R^1$ = H, $R^2$ = H, $R^3$ = H — **400a** (100%) — **401a**[a] (94%)
**399b** $R^1$ = OMe, $R^2$ = H, $R^3$ = H — **400b** (100%) — **401b**[b] (100%)
**399c** $R^1$ = OMe, $R^2$ = OMe, $R^3$ = OMe — **400c** (100%) — **401c**[c] (83%)
**399d** $R^1$ = H, $R^2$ = Cl, $R^3$ = H — **400d** (100%) — **401d**[d] (79%)

[a]Key: (i) 5 mol% Ru-**2**, $CH_2$=CHOTMS, $CH_2Cl_2$, 50 °C, 1.5 h; (ii) (a) 5 mol% Ru-**2**, benzene, 80 °C, 1 h; or (b) 5 mol% Ru-**2**, benzene, 80 °C, 3 h; or (c) 5 mol% Ru-**2**, toluene, 110 °C, 17 h; or (d) 5 mol% Ru-**2**, toluene, 110 °C, 13 h;

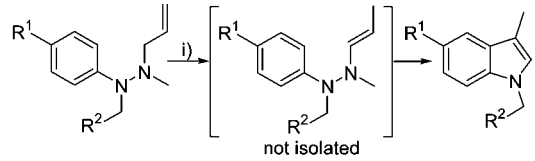
**Scheme 123. Isomerization and Isomerization/Cycloisomerization of Dienamines Catalyzed by Grubbs' Carbene Ru-2[a]**



**399a** — **400a** (100%)[i] (12%)[ii] — **402a** (0%)[i] (81%)[ii]
**399e** — **400e** (26%) — **402e** (58%)
**399f** — **400f** (32%)

[a]Key: (i) 5 mol% Ru-**2**, $CH_2$=CHOTMS, $CH_2Cl_2$, Δ, 1.5 h; or (ii) 10 mol% Ru-**2**, $CH_2$=CHOTMS, xylene, Δ, 2h.

**Scheme 124. Isomerization/Cyclization of Allyl Phenyl Hydrazines 403 to Indoles 405[a]**

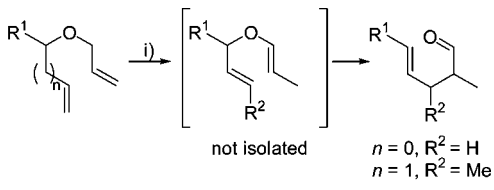


**403a** $R^1$ = H, $R^2$ = Me — **404a** — **405a** (56%)
**403b** $R^1$ = H, $R^2$ = Ph — **404b** — **405b** (62%)
**403c** $R^1$ = Me, $R^2$ = Me — **404c** — **405c** (62%)
**403d** $R^1$ = Me, $R^2$ = Ph — **404d** — **405d** (58%)

not isolated

[a]Key: (i) 5 mol% Ru-**1**, $LiBEt_3H$ (20 mol%), toluene, 100 °C, 12 h.

**Scheme 125. Tandem Isomerization/Claisen Rearrangement Catalyzed by Carbene Ru-1[a]**



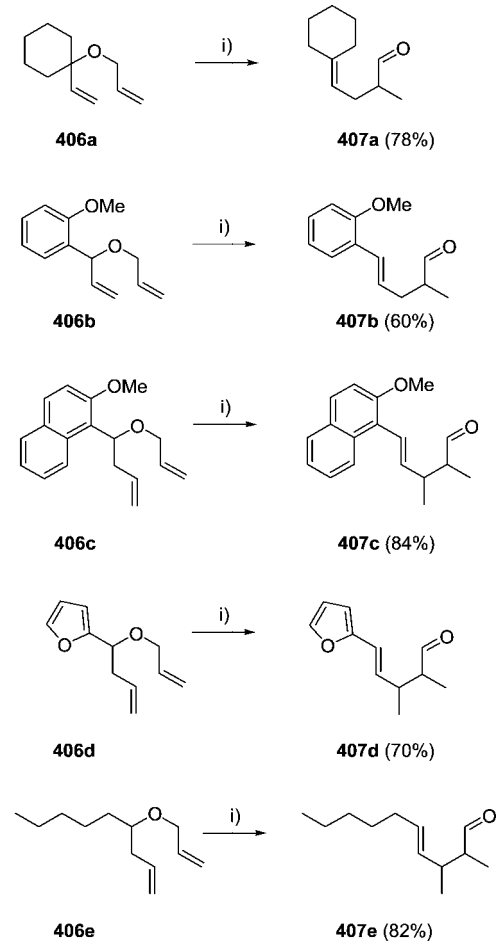
not isolated — $n$ = 0, $R^2$ = H; $n$ = 1, $R^2$ = Me

[a]Key: (i) 5 mol% Ru-**1**, $CH_2$=CHOEt (4 equiv.), toluene, Δ.

Recently, the group of Hoppe[95] developed a short synthetic route for obtaining (+)-vigulariol. Although, in principle, the oxacyclononene framework could be accessible by ring-closing metathesis, the cyclization of diene **367** under RCM conditions with Ru-**1** or Hoveyda's catalyst failed. However, the Grubbs' ruthenium carbene Ru-**2** in refluxing benzene afforded the oxacyclononene **368** along with its ring-contracted oxacyclooctene counterpart **369** (Scheme 112).

When the diolefinic compound **370** was exposed to the Grubbs' second-generation catalyst Ru-**2** in dichloromethane under high-dilution conditions (0.001 M) at room temperature, cyclophane derivative **371** (1:1.7 mixture of two diastereomers) was formed as a major component. A minor product **372** was isolated along with the target product as a mixture of two diastereomers (1:2.2 ratio) in significant

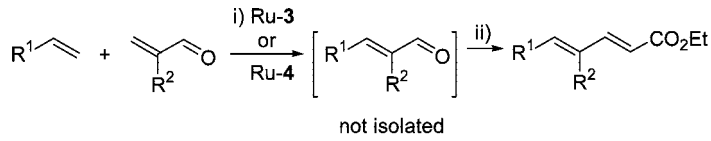
**Scheme 126. Synthesis of γ,δ-Unsaturated Aldehydes by Tandem Isomerization/Claisen Rearrangement Catalyzed by Grubbs' Carbene Ru-1[a]**



**406a** — **407a** (78%)
**406b** — **407b** (60%)
**406c** — **407c** (84%)
**406d** — **407d** (70%)
**406e** — **407e** (82%)

[a]Key: (i) 5 mol% Ru-**1**, $CH_2$=CHOEt (4 equiv.), toluene, Δ.

**Scheme 127. One-Pot CM/Wittig Olefination Catalyzed by Ruthenium Carbenes[a]**




[a]Key: (i) 5 mol% Ru-**3** or Ru-**4**, $CH_2Cl_2$, 60 °C, 10-12 h; (ii) then $PPh_3$, EDA, 60 °C, 4-8 h.

yield.[96] The unusual formation of compound **372** was explained in terms of a tandem isomerization induced by the Grubbs' catalyst, followed by a RCM sequence through the intermediacy **373** (Scheme 113).

During the preparation of macrolactones having 11-membered rings from diene **374**, the desired compound **375** was obtained in only 19% yield. The major reaction product was the 10-membered lactone **376**, which arises from an isomerization reaction previous to the RCM. The double-bond isomerization took place exclusively in the ester double bond and not in the amine moiety (Scheme 114).[97]

Rutjes and colleagues[59] found an interesting ruthenium-induced isomerization for obtaining six-membered cyclic enamides in good yield using Ru-**2** in 1,2-dichloroethane. These reaction conditions led to six- rather than seven-membered rings. Probably, ruthenium-catalyzed isomerization to the more stable olefins took place, followed by ring-closure of the isomerized intermediates to the six-membered enamides **378** (Scheme 115).

In 2007, our group described[98] the successful exposure of enallene **379** to second-generation Grubbs' catalyst. In this way, the spirocyclic diene-2-azetidinone **380** was generated (Scheme 116).

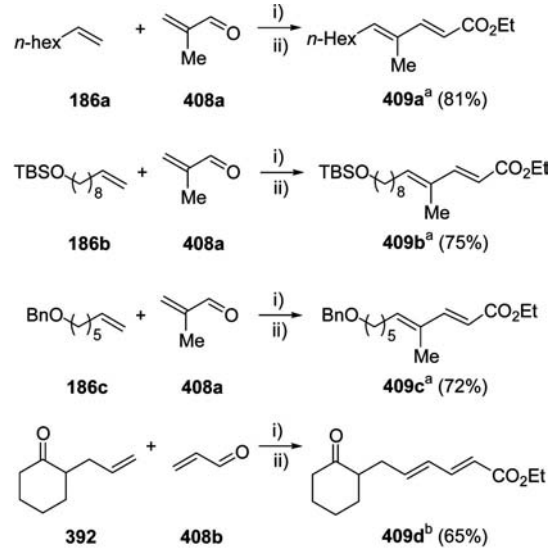
A plausible mechanism for the formation of **380** involves an initial allenyl−propargyl rearrangement promoted by Ru-**2**, followed by RCM of the resulting enyne (Scheme 117).

## 8.5. Cross-Metathesis Followed By Isomerization

Snapper[99] has described a tandem catalytic process in which a single ruthenium complex is used to achieve an olefin cross-metathesis and then is modified in situ to effect an olefin isomerization in the same reaction vessel. Using a secondary allylic alcohol, such as (*Z*)-hex-3-ene-2,5-diol **381**, the above sequence proved to be a good strategy for generating methyl ketones. To avoid oligomerization of the strained olefins during cross-metathesis with (*Z*)-hex-3-ene-2,5-diol **381**, slower addition of the cyclic olefin to the reaction was necessary. Moreover, the isomerization led to the desired diketones **383**, **385**, and **387** in higher yields with shorter reaction times when it was run at higher temperatures (200 °C). The optimized results for the tandem ROCM−isomerization were obtained with ruthenium complexes Ru-**2** and Ru-**3**. In general, the Hoveyda−Grubbs' alkylidene Ru-**3** proved more effective in these reactions, allowing for reduced catalyst loading with only minimal reduction in overall yields (Scheme 118). On the other hand, the cross-metathesis/isomerization of various aliphatic terminal olefins were achieved using Ru-**3** (0.5−2 mol %). Phthalimide **388** required a slightly higher catalyst loading to drive the olefin isomerization step to completion. The starting alkenone **392** demonstrated the chemoselectivity in the tandem process, because the pre-existing ketone functionality found in **392** does not interfere (Scheme 119).

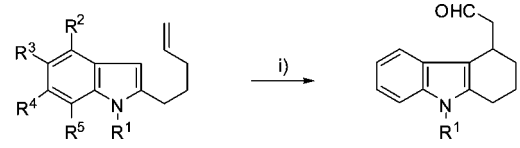
The cross-metathesis reactivities of α-methylene lactones have been investigated by Howeli and colleagues (Scheme

**Scheme 128. One-Pot CM/Wittig Olefination Catalyzed by Carbenes Ru-3 or Ru-4[a]**




[a]Key: (i) (a) 5 mol% Ru-**4**, $CH_2Cl_2$, 60 °C, 10-12 h; or (b) 5 mol% Ru-**3**; (ii) then $PPh_3$, EDA, 40 °C, 4-8 h.

**Scheme 129. Tandem CM/Intramolecular Hydroarylation Catalyzed by Ru-3[a]**

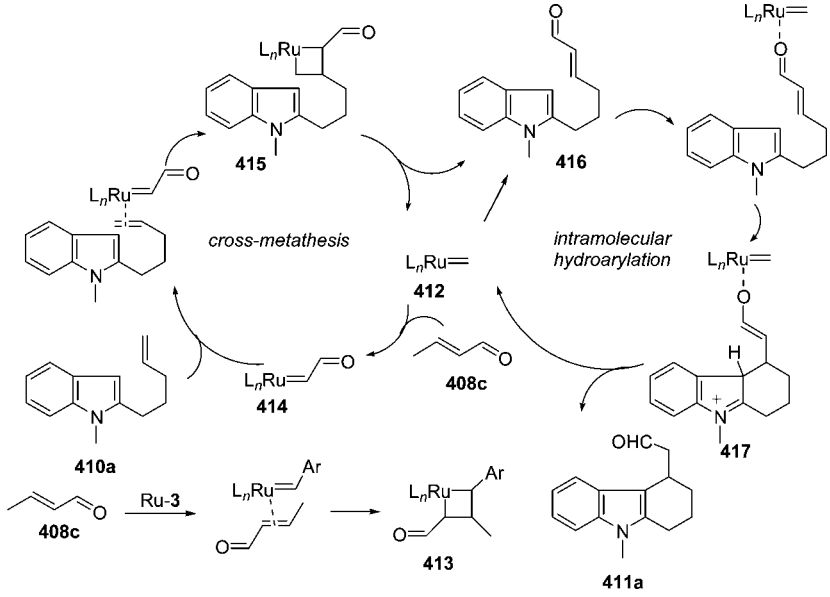



| | |
|---|---|
| **410a** $R^1$ = Me, $R^2$ = $R^3$= $R^4$ = $R^5$ = H | **411a**[a] (93%) |
| **410b** $R^1$ = $R^2$ = $R^3$= $R^4$ = $R^5$ = H | **411b**[b] (82%) |
| **410c** $R^1$ = $R^3$= $R^4$ = $R^5$ = H, $R^2$ = Me | **411c**[c] (82%) |
| **410d** $R^1$ = $R^3$ = Me, $R^2$ = $R^4$= $R^5$ = H | **411d**[d] (90%) |
| **410e** $R^1$ = Me, $R^2$ = $R^4$= $R^5$ = H, $R^3$ = F | **411e**[e] (95%) |
| **410f** $R^1$ = Me, $R^2$ = $R^3$ = $R^5$ = H, $R^4$ = Cl | **411f**[f] (81%) |
| **410g** $R^1$ = Me, $R^2$ = $R^3$ = $R^4$ = H, $R^5$ = Et | **411g**[g] (80%) |
| **410h** $R^1$ = $R^3$ = $R^5$ = Me, $R^2$ = $R^4$ = H | **411h**[h] (91%) |

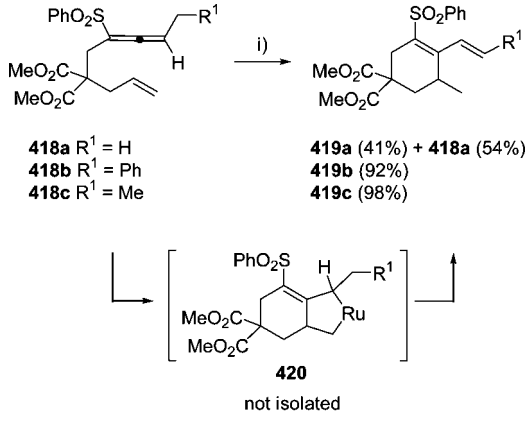
[a]Key: (i) 3 mol% Ru-**3**, crotonaldehyde (5 equiv.), DCE, Δ, [(a) 0.6 h; (b) 1 h; (c) 0.6 h; (d) 0.6 h; (e) 1.5 h; (f) 1 h; (g) 1 h; (h) 0.5 h.].

120).[100] Unexpectedly, when α-methylene-γ-butyrolactone reacted with 1-acetoxy-9-decene under the conditions developed for CM of α-methylene-β-butyrolactone, the isomerization to enone **395a** was the sole reaction pathway observed. The authors reasoned that a ruthenium hydride complex was fueling the isomerization of **394a**. To address the possibility that the cross-partner might be responsible for the formation of a ruthenium hydride complex, **394a** was heated with either Ru-**2** or Ru-**3** in the absence of a cross-partner. Isomerization was sluggish using Ru-**3** (70% after 24 h) in comparison to Ru-**2** (98%, 20 min). These outcomes suggest that **394a** is a viable hydride donor, and this can be rationalized by a π-allyl or a σ-alkyl/π-allyl mechanism. On the basis of the CM−isomerization results with **394a**, the α-methylene-δ-lactone **394b** was submitted to the same

**Scheme 130. Mechanism for the CM/Intramolecular−Hydroarylation Sequence Catalyzed by Carbene Ru-3**




**Scheme 131. Cycloisomerization Reaction of Allenenes Catalyzed by the Grubbs' Carbene Ru-2**[a]




[a]Key: (i) 20 mol% Ru-**2**, $CH_2Cl_2$, Δ, 0.5-3.5 h.

reaction conditions, but the metathesis of **394b** failed. Addition of 2,6-dichlorobenzoquinone to the reaction suppressed isomerization somewhat (from 66 to 26%), but it did not promote CM. Puzzled by the lack of reactivity of **394b**, it was postulated that the catalyst might be forming a complex with the substrate.

Using Ru-**2** and adding Lewis acid Ti(O$^i$Pr)$_4$, the complete isomerization to afford **395b** occurred in toluene. It was reasonable to postulate that, as the ring size increases, a stable chelate may form, thus sequestering the active catalyst and inhibiting metathesis. This chelation was reduced at higher temperatures, but then only unwanted isomerization was observed. Lewis acid efficiently displaced the bound catalyst, but once again, isomerization was the only reaction observed (Scheme 120).

## 8.6. Isomerization Followed By Cross-Metathesis

Compound **398** (intermediate in the synthesis of 1-ethylquinolizidine) was obtained in 87% yield when the enantiopure protected 2-amino-6-heptanoic ester **397** was treated with the Hoveyda−Grubbs' catalyst Ru-**3** and allyltrimethylsilane, via an unusual double-bond isomerization followed by cross-metathesis (Scheme 121).[101]

# 9. Miscellaneous

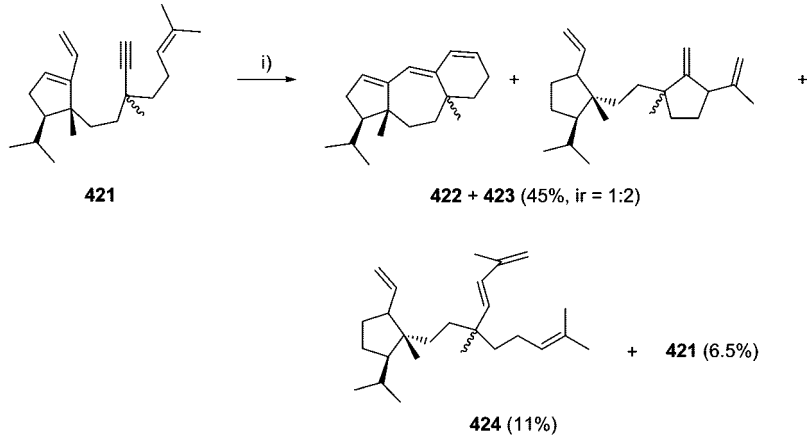
## 9.1. Isomerization/Cyclization

In 2002, Arisawa and colleagues reported a selective isomerization of a terminal olefin by combining a ruthenium-carbene catalyst Ru-**2** and vinyloxytrimethylsilane and its application to the synthesis of indoles from 2-(*N*-allyl-*N*-tosylamino)styrenes **399**.[102] The isomerization was carried out in competition with RCM. While the reaction of **399a** with Ru-**2** gave the 1,2-dihydroquinoline in excellent yield (6 h), the reaction of **399a** with Ru-**2** in the presence of vinyloxytrimethylsilane gave enamine **400a** (5 h) in quantitative yield, which was inaccessible by conventional methods. The utility of this reaction was demonstrated when the corresponding enamines were used in the preparation of four substituted indoles **401a**−**d** through a RCM reaction (Scheme 122).

On the other hand, an isomerization of terminal olefins and a highly selective cycloisomerization of 1,6-dienes were easily carried out with vinyloxytrimethylsilane in the presence of second-generation Grubbs' ruthenium catalyst Ru-**2**. Under these reaction conditions, the generation of RuH species was a key step. Isomerization is more favorable than metathesis in a competitive reaction; even in such a case, the substrates can easily give a metathesis product. This characteristic reaction was clearly demonstrated with *N*-allyl-*o*-vinylaniline **399a**. When the reaction was carried out in $CH_2Cl_2$ with 5 mol % of Ru-**2**, it afforded exclusively diene **400a**. In contrast to the reaction in $CH_2Cl_2$, the same reaction in refluxing xylene gave the domino isomerization/cycloisomerization indolidine **402a** as the major product (81%) together with **400a** (12%). As a further application, the cycloisomerization of a variety of *N*-functionalized alkenyl-*o*-vinylanilines was studied, and the results are summarized in Scheme 123.[103]

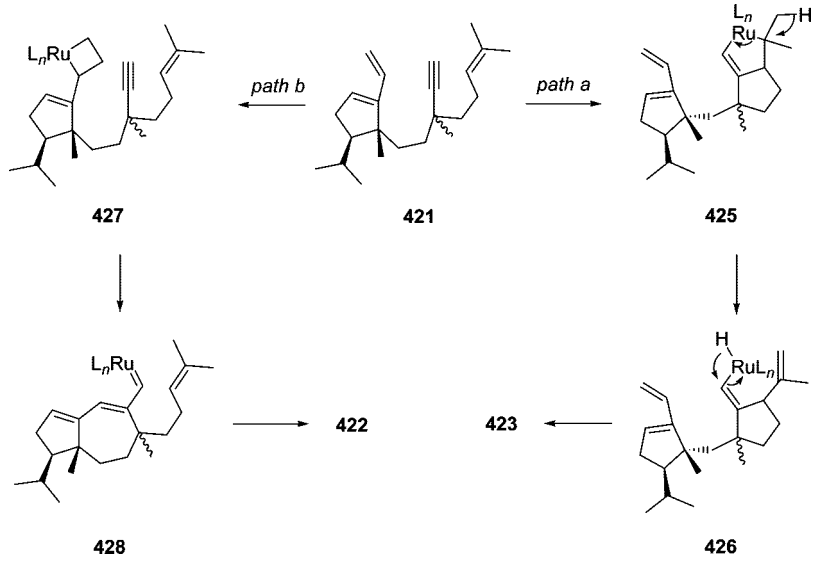
A combination of Grubbs' first-generation catalyst Ru-**1** and lithium triethylborohydride catalytically isomerized allyl phenyl hydrazines of type **403a**−**d** to phenyl enehydrazines **404a**−**d**. These intermediates **404a**−**d** were not isolated, but their formation was indirectly proven by the cyclization to the corresponding indoles **405a**−**d** in 56−62% yield. Heterocyclization was achieved using Ru-**1** (5 mol %) and

**Scheme 132. Cycloisomerization of Trienyne 421 Catalyzed by Grubbs' Carbene Ru-2[a]**

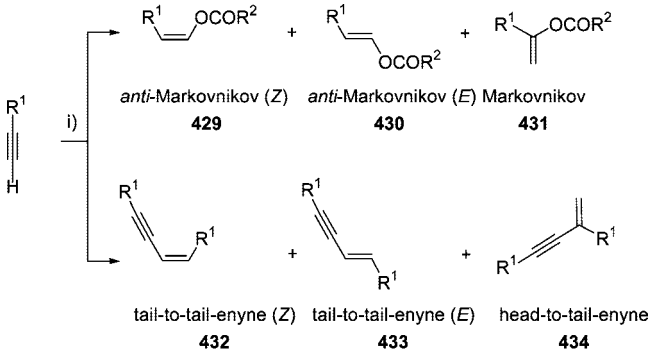



[a]Key: (i) 10 mol% Ru-**2**, $CH_2Cl_2$, Δ, 12 h.

**Scheme 133. Possible Pathways for Metathesis and Cycloisomerization Reactions of Trienyne 421 Catalyzed by Carbenes Ru-2 or Ru-3**

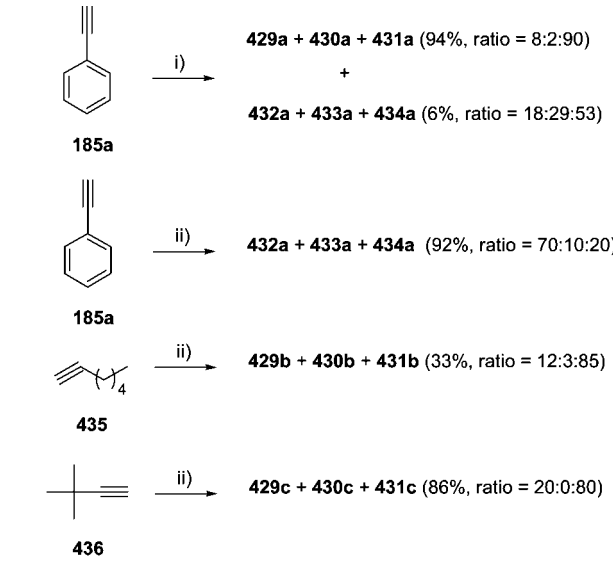



**Scheme 134. Synthesis of Enynes and Vinyl Esters from Terminal Alkynes in the Presence of Grubbs' Catalyst Ru-1[a]**




[a]Key: (i) Ru-**1**, $R^2COOH$.

**Scheme 135. Vinylation versus Dimerization of Alkynes Catalyzed by Ru-1[a]**



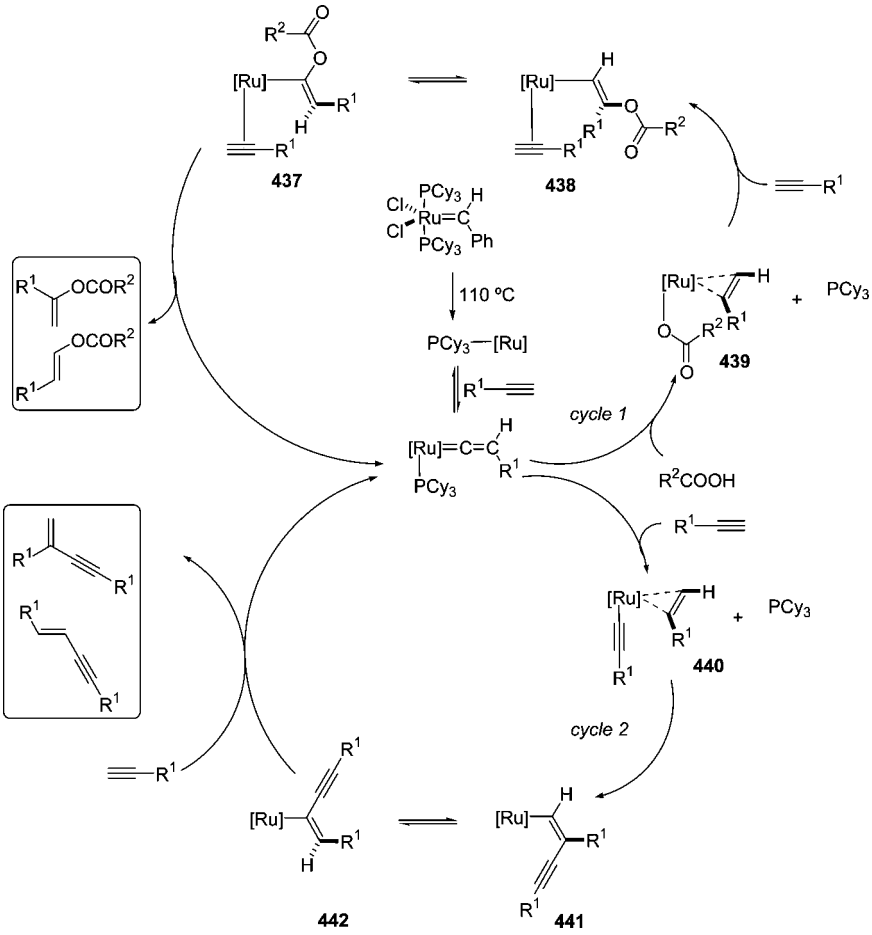

[a]Key: (i) 1 mol% Ru-**1**, trichloroacetic acid, 110 °C, 7 h; or (ii) 1 mol% Ru-**1**, acetic acid, 110 °C, 1 h.

lithium triethylborohydride (20 mol %) at 100 °C in toluene (Scheme 124).[104]

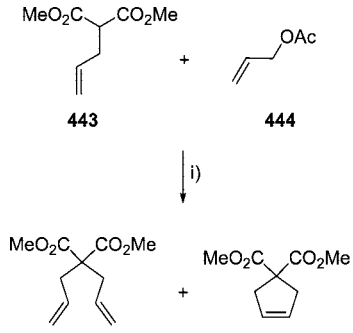
## 9.2. Isomerization/Claisen Rearrangement

Diallylethers and allyl homoallylethers, which cyclize to dihydrofurans or dihydropyrans under metathesis condition,

**Scheme 136. Mechanistic Explanation for the Synthesis of Enynes and Vinyl Esters Catalyzed by Grubbs' Carbene Ru-1**




**Scheme 137. Allylic Alkylation Catalyzed by Grubbs' Carbene Ru-2**[a]




**445** + **446** (100%, ratio = 43:57)[a]
**445** + **446** (55%, ratio = 100:0)[b]

[a]Key: (i) (a) 7.5 mol% Ru-**2**, $Pd(OAc)_2$, 5 mol% $PCy_3$, NaH, $CH_2Cl_2$, Δ; or (b) 7.5 mol% Ru-**2**, NaH, THF, Δ.

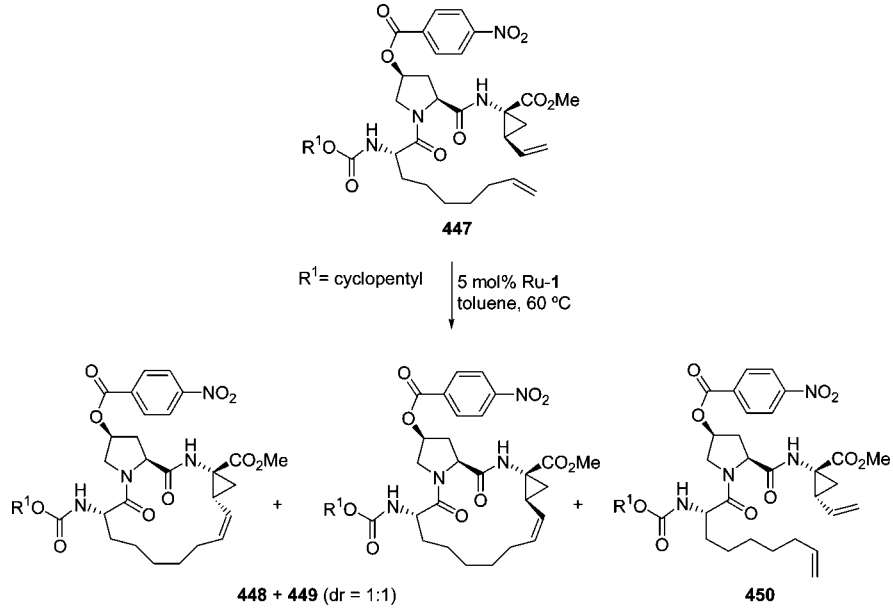
can also undergo a tandem isomerization/Claisen rearrangement sequence to pent-4-enals. If one wants to make use of Grubbs' carbene catalyst for the conversion of ethers into aldehydes, the olefin metathesis activity of Ru-**1** has to be reduced, while the isomerization activity has to be enhanced (Scheme 125).[105]

The experiments were carried out by using ruthenium complex Ru-**1** and 4 equiv of ethyl vinyl ether (2 equiv per double bond in the substrate) in boiling toluene. γ,δ-Unsaturated aldehydes were obtained in good yields (60−84%). The formation of aldehydes **407** was really clean, because no regioisomers resulting from a double-bond migration subsequent to the Claisen rearrangement step were observed (Scheme 126). Under the present conditions, olefin metathesis was inhibited, which can be attributed to the rapid formation of $[Cl_2(PCy_3)_2Ru{=}CHOEt]$ by metathetic exchange of the benzylidene ligand against the ethoxymethylidene ligand. The thus-generated carbene complex upon heating decomposes to the corresponding ruthenium−hydride complex. The starting diene was rapidly consumed once the hydride complex was formed, resulting in the formation of a less polar product (the primary isomerization product) and a more polar product, which was identified as the aldehyde. Over a period of a few hours, the enolether was fully converted to the Claisen rearrangement product.

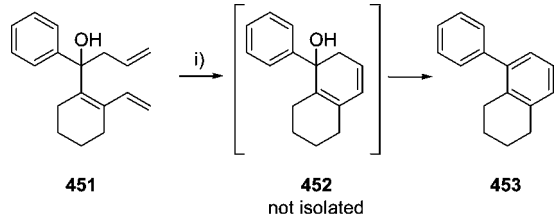
## 9.3. Cross-Metathesis/Wittig Olefination

Vinylidene complex Ru-**4** was an effective and selective catalyst for the CM of methacrolein **408a** with terminal olefins **186a**−**c** and **392**. Furthermore, this ruthenium complex served as a Wittig olefination catalyst when the resulting unsaturated aldehydes were treated in situ with $PPh_3$ and diazoesters (Scheme 127). The products from this ruthenium-catalyzed metathesis/olefination sequence were dienoic esters **409**, which were formed in 65−81% yields with >20:1 *E*,*E*-selectivity (Scheme 128). For enone **392**, acrolein was used in the tandem sequence.[106]

**Scheme 138. Vinylcyclopropane Epimerization Catalyzed by Carbene Ru-1**




**Scheme 139. Tandem RCM−Dehydration Catalyzed by Ru-1**[a]




[a]Key: (i) 6 mol% Ru-**1**, $CH_2Cl_2$, r.t., 12 h.

## 9.4. Tandem Cross-Metathesis/Intramolecular Hydroarylation

Xiao and colleagues[107] have developed a new process combining a cross-metathesis step and an intramolecular hydroarylation for the efficient synthesis of complex multiring heterocyclic compounds. The tandem catalytic strategy was examined by reacting $\omega$-indolyl alkenes **410** with an electron-deficient alkene **408c** (crotonaldehyde) in the presence of ruthenium complex Ru-**3** in 1,2-dichloroethane (Scheme 129). The reaction is amenable to significant structural variation in the $\omega$-indolyl alkene component, displaying an excellent generality and functional-group tolerance. Both free *N*−*H* and *N*-methyl substrates could be used without loss of yield. This tandem CM/intramolecular hydroarylation reaction was general with respect to the nature of the heteroatom in the alkenyl chain of the substrate. The corresponding polycyclic indoles **411** were obtained in good yields (80−95%).

In the presence of ruthenium catalyst Ru-**3**, cross-metathesis of **410a** and crotonaldehyde occurs. After a single turnover, the CM reaction generates intermediate **416** and methylidene complex **412**. It was envisioned that the ruthenium complex **412** (which can accept electrons owing to its empty orbital) acted as a Lewis acid and activated **416**. Subsequent intramolecular cyclization formed indolium **417**, which undergoes aromatization by loss of a proton, affording fused indole **411a** and regenerating catalyst **412** for the next catalytic cycle (Scheme 130).

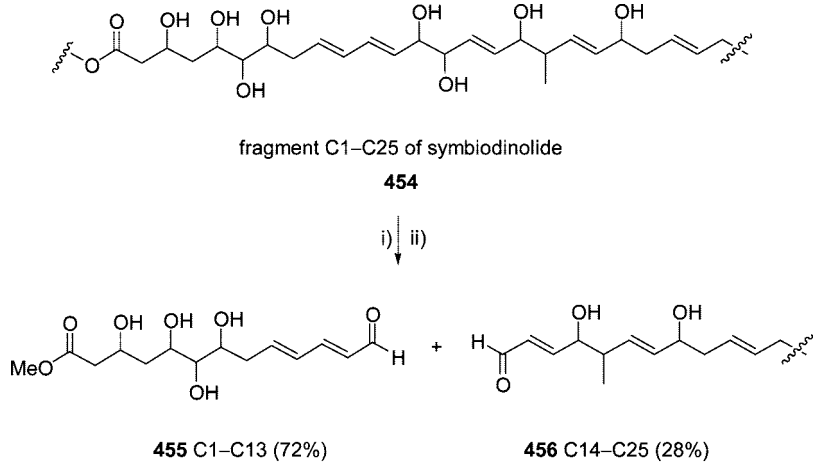
## 9.5. Cycloisomerization

When phenylsulfonylallenenes **418a**−**c** were reacted in the presence of 20 mol % of the ruthenium benzylidene complex Ru-**2** in $CH_2Cl_2$, cyclohexene derivatives **419a**−**c** were obtained in high yields (Scheme 131).[108] The unexpected formation of the cyclohexenes **419** might be tentatively rationalized in terms of the intermediacy of the ruthenacyclopentane intermediates **420**. The methyl (or methylene) hydrogen of the thus-formed metallacycle **420** would be abstracted via $\beta$-hydride elimination, collapsing into the 1,3-diene derivative **419**. Alternatively, the formation of this product might be interpreted as a result of the direct thermal ene-type reaction of allenenes **418**. To understand the latter process, compound **418b** was refluxed in $CH_2Cl_2$ without the catalyst Ru-**2** for a prolonged time, but no reaction took place. In addition, when heated at higher temperature (refluxing in toluene or xylene), the thermal [2 + 2]-cycloaddition between the terminal olefin and the distal double bond of the allenyl moiety furnished the corresponding cyclobutane derivative.

When trienyne **421** was subjected to ring-closing metathesis reaction conditions using the second-generation Grubbs' catalyst Ru-**2**, an unusual nonmetathetic activity was observed, with the cycloisomerization product being obtained as the major product. The main fraction of the reaction of trienyne **421** was found to be a mixture of the metathesis product **422** and the cycloisomerization adduct **423** (1:2 ratio) in 45% combined yield. Besides **422** and **423**, a minor product **424** was isolated (11%) along with starting material **421** (6.5%). When the Hoveyda−Grubbs' catalyst Ru-**3** was used, further cycloisomerization occurred and all that was isolated was a mixture of **422** and **423** in a 1:4 ratio (45% yield) and **421** (6.5%) (Scheme 132).[109]

This result suggested that the alkyne was more reactive toward the ruthenium−carbene complex than the terminal alkene for trienyne **421**. Therefore, initial coordination preferentially occurred at the alkyne to give the metallacyclopentene **425** (path *a*).

**Scheme 140. Cleavage of the (*E*)-Diallyl 13,14-Diol Moiety in Symbiodinolide Catalyzed by Ru-2**[a]




[a]Key: (i) MeOH, $Et_3N$; (ii) 100 mol% Ru-**2**, MeOH-Py (3:1), $CH_2=CH_2$, r.t., 2 h.



## 9.6. Reactivity of Alkynes in the Presence of Carboxylic Acids

The transformation of triple bonds of terminal alkynes by Grubbs' catalyst Ru-**1** in the presence of carboxylic acids was pH-dependent.[110] The acidity of the carboxylic acid plays a key role in the preference of terminal alkynes toward dimerization or toward vinylation of the triple bond (Scheme 134). The selectivity was strongly p*K*a dependent: vinylation was preferred at low p*K*a, but increasing p*K*a changed the selectivity toward the formation of dimeric products. The catalyst produced tail-to-tail dimeric adducts, except for phenylacetylene and trichloroacetic acid, in which proportional amounts of both tail-to-tail and head-to-tail adducts were formed.

Treatment of **185a**, **435**, and **436** with Ru-**1**, 96 equiv of the terminal alkyne, and 112 equiv of acetic acid during 1 h at 110 °C produced a total triple-bond conversion. The preference for dimerization or vinylation was strongly dependent on the nature of the terminal alkyne. Only phenylacetylene **185a** showed a 100% preference for dimerization and produced selectively *Z*-enynes. The other terminal alkynes preferred the nucleophilic addition of the carboxylic acid at the triple bond of the alkyne. Aliphatic alkynes **435** and **436** produced only vinylation products with high regioselectivity for Markovnikov addition. Increasing the steric hindrance of the alkyl group (from linear C-chain in **435** to bulky *tert*-butyl group in **436**) resulted in a higher degree of conversion of the triple bond (Scheme 135).

Nucleophilic addition of the carboxylic acid onto the alkyne (*cycle 1*) was preferred for aliphatic alkynes (Scheme 136). The Ru−vinylidene complex catalyzed the regioselective intermolecular attack of the acid at the internal C2 carbon atom of the terminal alkyne, generating the Markovnikov adduct **438**. Alternatively, the intermolecular addition may proceed by attack on the C1 carbon atom of the triple bond, forming the anti-Markovnikov compound **437**. For arylacetylene derivatives, vinylation (*cycle 1*) was preferred when strong acids were used (trichloroacetic acid), while dimerization (*cycle 2*) was favored when weak acids were added (acetic acid). The vinylation of arylacetylene compounds proceeded preferentially by attack of the acid on the internal C2 carbon atom of the alkyne **438**, forming the Markovnikov products. With acetic acid, the dimeric products were formed by attack of the incoming alkyne on the terminal C1 carbon atom of the coordinated alkyne **442**. For arylacetylene derivatives, the intermolecular attack proceeded preferentially on the terminal C2 carbon atom of the terminal alkyne, with a supplementary stereoselectivity for *trans*-addition **442**.

## 9.7. Allylic Alkylation

Recently, the group of Poli decided to study the feasibility of an allylic alkylation/ring-closing metathesis sequence concomitantly catalyzed by Pd and Ru.[111] It was found that Grubbs' catalyst Ru-**2** and $Pd(OAc)_2$ in the presence of a phosphine such as $PCy_3$ produced a mixture of the allylic alkylation product **445** and the domino product **446** in a ratio of 43:57. However, Ru-**1** bearing two $PCy_3$ and no *N*-heterocyclic carbene ligand did not allow the domino process, while the allylic alkylation step was quantitative due to the Pd catalyst. Furthermore, when both Ru and Pd catalysts were omitted, neither **445** nor **446** were observed. Surprisingly, when the reaction was run in the absence of both a Pd source and $PCy_3$, but in the presence of Ru-**2**, the formation of **445** was still observed. These two experiments clearly indicated that Ru-**2** was able to promote the allylic alkylation step. This is the first example of nonmetathetic behavior showing the activity of Grubbs' carbene in allylic alkylation (Scheme 137).

## 9.8. Vinylcyclopropane Epimerization

A ruthenium carbene-catalyzed epimerization of vinylcyclopropanes was reported by Wei and Farina.[112] When tripeptide diene **447** was subjected to RCM conditions with the first-generation Grubbs' catalyst Ru-**1** in toluene at 60 °C, side-product **448** was formed, together with the desired product **449**, in a ratio of 1:1. A pure sample of **448** was isolated by preparative HPLC, and its structure was assigned as the epimer of **449** at alkenyl-bearing cyclopropyl methine. In addition, an isomer of starting material **447** was observed, which was identified as **450**, because it was slowly converted to **448** on further treatment with Ru-**1**. In contrast, when Ru-**3** catalyst was used, little (<1%) or no epimerization was observed (Scheme 138).

### 9.9. Diol Cleavage

Han and Uemura have developed a new cleavage of the secondary (*E*)-allyl *vic*-diol moiety in the presence of the second-generation Grubbs' catalyst Ru-**2** in symbiodinolide (product that can be classified as supercarbon-chain compound with a molecular weight of 2 859) (Scheme 140).[114] The cleavage depended on the amount of Ru-**2** but no $O_2$, and the position of *vic*-diol adjacent to C=C played a crucial role in the cleavage reaction. A diallyl *vic*-diol structure gave a higher yield than monoallyl *vic*-diol structure at a low concentration of Ru-**2**.

### 9.10. Dehydration

When the tertiary alcohol **451** was treated with ruthenium alkylidene Ru-**1** at room temperature, not only ring-closing metathesis was achieved. The intermediate product **452** suffered spontaneous dehydration, affording directly a new aromatic compound **453** in 85% yield (Scheme 139).[113]

## 10. Conclusions

During the past decade, olefin chemistry has seen explosive growth as a synthetic tool; this growth can be attributed to the development of new catalysts such as Grubbs' ruthenium carbenes, which combine high reactivity with very good tolerance to a wide range of functional groups. However, nonmetathetic behavior patterns have appeared recently that deserve special attention. The reported formation of non-metathesis byproduct is catalyzed by the metathesis catalyst itself, by an impurity present in the precatalyst, or by a decomposition product of the catalyst. Carbenes Ru-**1**, Ru-**2**, Ru-**3**, and Ru-**4** have been shown to catalyze Kharasch addition, oxidation processes, activation reactions, hydrogenation of olefins, cyclopropanation sequences, cycloaddition reactions, and olefins isomerizations (deallylation of amines, amides, lactams, imides, pyrazolidinones, hydantoins, and oxazolidinones) among others. Therefore, this growing number of newly discovered catalytic processes mediated by Grubbs' carbene complexes broadens their synthetic utility beyond olefin metathesis. Tuning and new uses of this ruthenium-based catalyst are likely, and contribute to its relevance as a versatile and effective tool in organic and organometallic chemistry.

## 11. Abbreviations

| | |
|---|---|
| Ac | acetyl |
| Ar | aryl |
| AIBN | α−α′-azobisisobutyronitrile |
| ATMS | allyltrimethylsilane |
| ATRA | atom transfer radical addition |
| ATRC | atom transfer radical cyclization |
| BHT | butylated hydroxytoluene |
| Bn | benzyl |
| BOC | *tert*-butyloxycarbonyl |
| BOM | benzyloxymethyl |
| Bz | benzoyl |
| Cat | catalytic |
| Cbz | benzyloxycarbonyl |
| CM | cross-metathesis |
| DCE | 1,2-dichloroethane |
| DMAD | acetylenedicarboxylate |
| DMB | 2,4-dimethoxybenzyl |
| dr | diastereomeric ratio |
| dRRM | diastereoselective ring rearrangement metathesis |
| EDA | ethyl diazoacetate |
| HPLC | high-performance liquid chromatography |
| iNOS | nitric oxide synthase |
| ir | isomeric ratio |
| MOM | methoxymethyl |
| NMP | 1-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| PMB | *p*-methoxybenzyl |
| PMP | *p*-methoxyphenyl |
| PTSA | *p*-toluenesulfonic acid |
| RCEYM | ring-closing enyne metathesis |
| RCM | ring-closing metathesis |
| ROCM | ring-opening cross-metathesis |
| ROM | ring-opening metathesis |
| ROMP | ring-opening metathesis polymerization |
| rr | regioisomeric ratio |
| RRM | ring rearrangement reaction |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TEMPO | 2,2,6,6-tetramethylpiperidine-1-oxyl |
| TMS | trimethylsilyl |
| Tol | tolyl |
| Ts | tosyl |
| TSs | transition states |
| TTMS | tris(trimethylsilyl)silane |

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