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Olefin metathesis and isomerization: From undesired side reactions to useful synthetic methodology

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Abstract

Conversion of ruthenium carbene complexes to ruthenium hydride complexes by organometallic transformations in situ opens up interesting synthetic perspectives. In this account the use of Grubbs' catalyst to synthesize pent-4-enals selectively from diallyl- and allyl homoallyl ethers and scope and limitations of a Tandem RCM-isomerization sequence for the synthesis of cyclic enol ethers are discussed.

Keywords: Metathesis; Ruthenium; Isomerization; Tandem reaction

1. Introduction

The development of modern molybdenum [1] and ruthenium precatalysts [2–4] for olefin metathesis [5–7] made novel and hitherto unforeseen strategies for target molecule synthesis available [8,9]. However, with increasing popularity of these metathesis precatalysts more and more examples were reported in the literature that describe the occasional occurence of olefin isomerization reactions [10,11] in small molecule [12] as well as polymer synthesis [13,14].

We first came across this problem during the investigation of a group-selective double ring closing metathesis. In an attempt to cyclize the tetraene **1** under conditions that were assumed to be thermodynamic control, we were surprised to obtain aldehyde **4** as the only low molecular weight product, albeit in extremely low yield. The expected product of a double ring closing metathesis reaction, spirocycle **2** [15], was not observed [16]. Formation of **4** can be understood by assuming the following scenario (Scheme 1): first, ring closing metathesis occurs to give the dihydropyran, followed by isomerization of the remaining allyl ether to enol ether **3**, which undergoes Claisen-rearrangement to **4**.

The conversion of **1** to **4** can be described as a Tandem sequence [17,18] with at least two of the three steps catalyzed by ruthenium. Although this sequence, conducted under the original conditions, is synthetically useless due to the low yield and the unexplored scope, some lessons might be learned from this unexpected observation, that eventually lead to the development of useful synthetic methods. However, it is important to consider first some possibilities concerning the nature of the actual isomerization catalyst: in the example described above, the isomerization might be catalyzed by the unaltered Ru-carbene complex, by an impurity formed during the synthesis of the precatalyst, or by a degradation product of the metathesis catalyst. In the case of olefin isomerization it has early been suspected that Ru-carbene complexes decompose to Ru-hydrides [19], which catalyze the observed isomerization side reaction via a hydrometallation-β-hydride elimination pathway [20]. Consequently, research in this area has focused on finding reaction conditions that would lead to a reduced amount of isomerization byproducts [21,22] and on the elucidation of decomposition pathways leading to Ru-hydrides [23–28]. The benefit obtained from the development of isomerization-free reaction conditions for olefin metathesis is obvious, however, we thought that interesting synthetic perspectives might also arise if it is possible to switch selectively from metathesis to isomerization activity. In this account we will highlight two synthetic methods recently developed in our laboratory that are located at the interface of olefin metathesis and olefin isomerization and place these in a more general context.

2. Selective metathesis versus non-metathesis conversion using Ru-carbene complexes

If it is possible to change the reactivity of commercially available standard metathesis catalysts such as $[Cl_2(PCy_3)_2$ Ru=CHPh] (**A**) [29] or its second generation congeners

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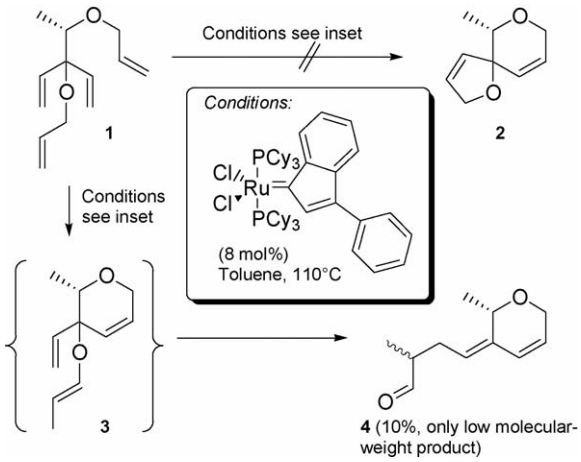
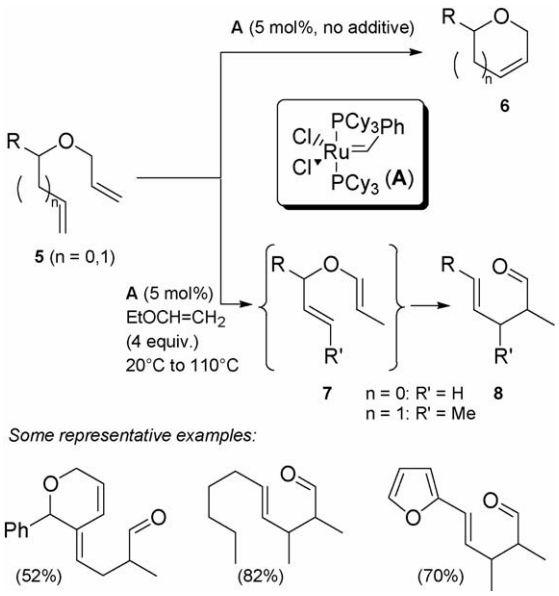


Scheme 1. Unexpected result of an attempted double RCM under thermodynamic conditions.

$[Cl_2(PCy_3)(H_2IMes)Ru{=}CHPh]$ (**B**) [30] and $[Cl_2(PCy_3)(IMes)Ru{=}CHPh]$ (**C**) [31] at the beginning of a reaction by very simple measures, a given substrate can be converted to structurally diverse products using only one precatalyst. The obvious advantage would be that the number of expensive or less conveniently available precatalysts required in an organic synthesis laboratory could be significantly reduced, a principle that has recently been described as "catalyst economy" by Quayle and co-workers [32]. Starting point and inspiration of our investigation on this field was the unexpected result described in Scheme 1. The ring closing metathesis of diallyl ethers (**5**, $n = 0$) and allyl homoallyl ethers (**5**, $n = 1$) to oxacycles **6** is normally an extraordinarily facile process where undesired olefin isomerization does not play a role [33]. If the alternative pathway, selective isomerization to **7** followed by Claisen-rearrangement to pent-4-enals **8**, is desired, conditions are needed that will (1) suppress ring closing metathesis and (2) induce the in situ conversion of precatalyst **A** to an isomerization catalyst. As mentioned above, the decomposition of Ru-carbenes under various conditions has been thoroughly investigated by several groups. When planning this project we became particularly attracted by a study recently published by Louie and Grubbs, who reported that the metathesis initiator **A** undergoes a fast reaction with ethyl vinyl ether, and that the resulting Fischer-type carbene complex eliminates chloroethane upon heating to give a Ru-hydride complex $[Cl(CO)(PCy_3)_2Ru{-}H]$ (**D**) [24]. In Scheme 2 is described how this organometallic transformation can be applied to the synthetic problem in question: addition of the metathesis catalyst to a solution of ethyl vinyl ether and the substrate in toluene does not give noticeable amounts of RCM-products, but – after heating the mixture to reflux – results in the formation of Claisen-rearrangement products **8** in good to excellent yields [34]. In a number of contributions from Dixneuf and co-workers it has been demonstrated that other Ru-catalysts without alkylidene ligand can be used to promote the same isomerization-Claisen-rearrangement sequence with good results [35–37].

This result can be placed in a more general context when considering other types of metal-catalyzed transformations of α,ω-dienes. For instance, apart from RCM and isomerization-

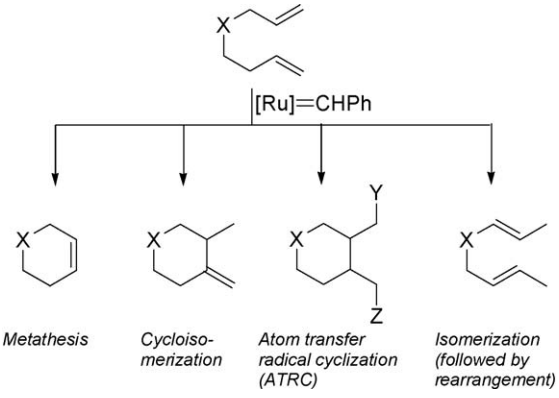


Scheme 2. Isomerization-Claisen-rearrangement vs. olefin metathesis.

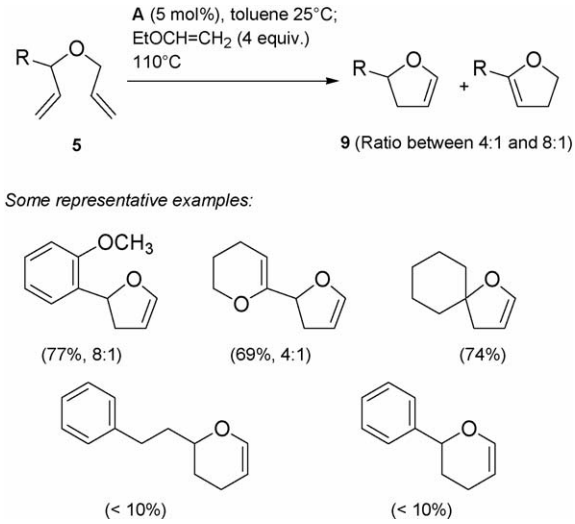
Claisen-rearrangement, these substrates can undergo cycloisomerization reactions [38] or atom transfer radical cyclizations (ATRC) [39]. Both reactivity patterns have indeed been realized using typical metathesis initiators: we were able to show that substrates with reduced reactivity towards first generation catalyst **A** undergo radical cyclization with addition of CCl_4 selectively using the same precatalyst [40]. Arisawa et al. have recently demonstrated that addition of a silyl enol ether to precatalyst **B** changes the reactivity from metathesis to isomerization [41] and for certain substrates to cycloisomerization [42]. The different opportunities resulting for selective organic synthesis are summarized in Scheme 3.

3. Tandem reactions with one metathesis step followed by a non-metathesis step

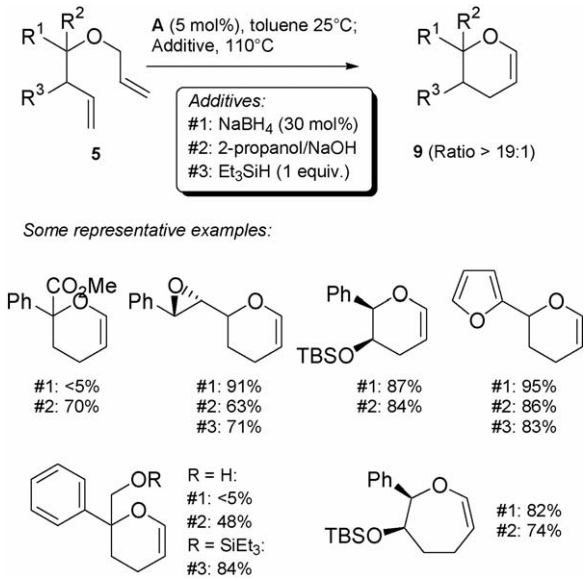
Equally attractive from a synthetic point of view are Tandem sequences where an olefin metathesis reaction is followed by a non-metathesis transformation of the newly formed C–C-double bond. In contrast to the synthetic methodology discussed in the



Scheme 3. Examples for metathesis and non-metathesis transformations of α,ω-dienes using Ru-carbene complexes as precatalysts.



Scheme 4. Tandem RCM-isomerization: ethyl vinyl ether as "chemical trigger".



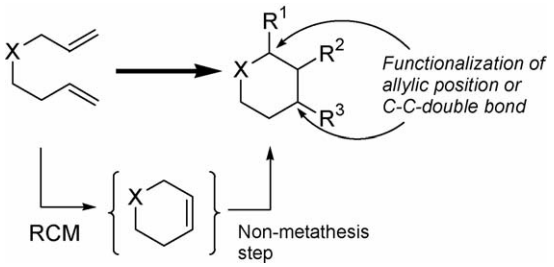
Scheme 5. Tandem RCM-isomerization: $NaBH_4$, 2-propanol/NaOH, and Et_3SiH as "chemical triggers".

previous section, the development of such Tandem reactions requires a switch from metathesis to non-metathesis activity after completion of the metathesis step. Again, we want to achieve this switch in reactivity by using a "chemical trigger" which induces the required organometallic transformation in situ. Referring to the taxonomy recently devised by Fogg and dos Santos, the Tandem sequences in question can be classified as "assisted Tandem catalysis" [17].

At the beginning of the project, we wanted to exploit Louie and Grubbs' method for the conversion of first generation catalyst **A** to Ru-hydride [Cl(CO)$(PCy_3)_2$Ru–H] (**D**) [24] a second time. To this end, ethyl vinyl ether was added to a metathesis reaction of dienes **5** after completion of the RCM step, followed by heating to reflux. Gratifyingly, isomerization of the primary RCM-products **6** (dihydrofurans for $n=0$, dihydropyrans for $n=1$) to the desired cyclic enol ethers **9** occurred. Unfortunately, this protocol gives good results only for five-membered ring systems as the isomerization step is to slow for six- and seven-membered rings and stops at approximately 10% conversion. The regioselectivity of the isomerization step is in the range of 4:1 to 8:1 in favor of the less substituted isomer (Scheme 4) [43].

The limited scope made the further evaluation of other additives necessary. One reagent that has already been used in the 1970s to synthesize Ru-hydrides from Ru-chloro complexes is $NaBH_4$ [44–46]. We thought that a nucleophilic displacement of Ru-bound chloride by hydride might also be possible for Ru-metathesis initiators and eventually lead to the formation of an isomerization catalyst. Although we do not know yet whether our mechanistic assumption is true, the addition of $NaBH_4$ (or NaH) to a metathesis reaction activates the ruthenium catalyst for isomerization. The scope of this protocol is much broader than that of the first one, as a wide range of dihydropyrans and oxepins is also isomerized. The regioselectivity observed for dihydrofurans is in the same range as for the first protocol, but for six- and seven-membered oxacycles it is generally better than 19:1 [43,47]. A limitation of this protocol is a reduced tolerance to functional groups. Alcohols, esters and unsaturated side chains interfere with the isomerization conditions, which prompted us to test other additives. Recent investigations by Mol and co-workers revealed that Ru metathesis catalysts react with primary alcohols to Ru-hydride complexes [25–27]. We tested a number of alcohols as co-solvents and bases as additives in the olefin metathesis reaction, however, results remained unsatisfactory for primary alcohols. Finally, the breakthrough came with the use of 2-propanol and NaOH in sub-stoichiometric amounts as additives. Under these conditions, a wide range of six- and seven-membered cyclic enol ethers was obtained via Tandem RCM-isomerization in high regioselectivity. Typical reaction times for the isomerization are in the range of two to three hours, which is approximately one third of the time required for the $NaBH_4$-protocol. Interestingly, these conditions cannot be used for the dihydrofurans, because partial hydrogen transfer to the C–C-double bond of the cyclic enol ethers occurs, resulting in the formation of tetrahydrofurans [43,48]. The fourth protocol developed in our group relies on the reaction of the metathesis catalyst with silanes. The activity of Grubbs' catalyst for the silylation of alcohols [49] and alkynes [50,51] has previously been established, but these steps have not been implemented in metathesis Tandem reactions. Addition of Et_3SiH to a completed metathesis reaction, followed by heating to reflux, induces isomerization to the enol ethers. Regioselectivity and reaction times are comparable to those observed for the $NaBH_4$-protocol, however, the absence of nucleophilic reducing agents might be beneficial for some synthetic applications [43]. Scheme 5 summarizes the four protocols from our laboratory and lists some representative examples.

Parallel to our work, other conditions for a metathesis-isomerization sequence have been developed by Snapper and co-workers. These authors exploit the observation that Ru-carbene complexes are converted to Ru-hydrides in the presence of molecular hydrogen [23]. However, the use of hydrogen as a "chemical trigger" requires that the competing hydrogenation is suppressed. Snapper et al. achieved this goal by applying



Scheme 6. General principle of catalytic Tandem RCM non-metathesis reaction sequence.

a highly diluted hydrogen atmosphere (95:5 N_2/H_2 mixture), which reduces the amount of hydrogenation products to less than 10% [52].

We think that this Tandem sequence is particularly valuable, because it makes cyclic enol ethers easily accessible from conveniently available starting materials and avoids enolether metathesis steps. First applications of our method have recently been published by us [53] and others [54].

Other "assisted Tandem catalysis" reactions incorporating metathesis steps have been published and the RCM-isomerization sequence discussed here can be considered as an example that illustrates a more general principle: The first and probably best explored Tandem catalysis in this context is the metathesis-hydrogenation sequence [17,22], which has already found application in target molecule syntheses [55–57]. Very recently, a Tandem RCM-dehydrogenative oxidation sequence has been developed by van Otterlo et al. as a tool for the synthesis of indanones from allylic alcohols [58]. As this sequence does not require any additives, it is not clear whether this is an assisted or an auto-Tandem catalysis. Clearly a case of assisted Tandem catalysis is the RCM-atom transfer radical cyclization (ATRC) sequence that has recently been communicated by us [59]. The "chemical trigger" in this reaction is the substrate itself [60]. As summarized in Scheme 6, Tandem sequences involving metathesis steps allow the synthesis of hetero- or carbocycles with a subsequent functionalization of the C–C-double bond or the allylic position.

4. Representative experimental procedures

*4.1. Synthesis of pent-4-enals (**8**)*

The appropriate diene **5** (2.0 mmol) and ethyl vinyl ether (8.0 mmol) are dissolved in toluene (10 mL) and first generation Grubbs' catalyst **A** (80 mg, 4.5 mol%) is added. Within 10 min a deep red solution is formed, which is then heated to reflux. The colour changes to yellow, indicating the formation of a hydride complex. TLC-control reveals consumption of the starting material **5** and formation of the isomerized intermediate **7** (staining of the TLC-plate with iodine is recommended for following the isomerization step). Prolonged heating leads to consumption of **7** and formation of the Claisen-rearrangement products **8**. After the reaction is completed, the solvent is evaporated, and the residue is purified by flash chromatography on silica or Kugelrohr distillation.

*4.2. Synthesis of cyclic enol ethers (**9**)*

4.2.1. Ethyl vinyl ether as additive

The appropriate diene **5** (2.0 mmol) and first generation Grubbs' catalyst **A** (80 mg, 4.5 mol%) are dissolved in toluene (10 mL). The reaction is run at ambient temperature or slightly elevated temperature (40 °C) until the starting material is fully consumed (TLC). Ethyl vinyl ether (8 mmol) is then added, and the reaction mixture is heated to reflux until the isomerization of the primary RCM-product is completed (TLC, staining with iodine is specific for enol ethers). The solvent is evaporated, and the residue is purified by flash chromatography on silica or by Kugelrohr distillation.

4.2.2. $NaBH_4$ as additive

The olefin metathesis step is conducted as before, but instead of ethyl vinyl ether, $NaBH_4$ (37 mg, 50 mol%) is added to the reaction mixture, which is then heated to reflux until complete consumption of the RCM-product is observed. The solution is cooled to ambient temperature and then diluted with ether (10 mL), washed with brine, dried with $MgSO_4$, filtered, and all volatiles are evaporated in vacuo. Purification is achieved by flash chromatography on silica or Kugelrohr distillation.

4.2.3. 2-Propanol and NaOH as additives

After completion of the metathesis step, 2-propanol (2.0 mL) is added, followed by solid NaOH (20 mg, 25 mol%). The mixture is heated to reflux until the RCM-product is isomerized to the enol ether (TLC). The same aqueous workup procedure is followed as for the $NaBH_4$-protocol (vide supra).

4.2.4. Triethyl silane as additive

After completion of the metathesis step, Et_3SiH (0.16 mL, 1.0 mmol) is added and the mixture is heated to reflux until the isomerization step is completed (TLC control). All volatiles are removed in vacuo, and the residue is purified by flash chromatography or Kugelrohr distillation.

5. Conclusions

Non-metathesis reactivities of established Ru-metathesis initiators, especially olefin isomerization, have so far mostly been recognized as undesired side reactions. However, recent studies demonstrate that novel synthetic methodologies may evolve from these unexpected reactivities of Ruthenium carbene complexes. In this contribution two synthetic methods are discussed that are located at the interface of Ru-carbene and Ru-hydride chemistry:

(1) Conditions are reported that allow the use of first generation Grubbs' catalyst to convert typical substrates for olefin metathesis reactions selectively following an isomerization-Claisen-rearrangement pathway.
(2) Combination of ring closing metathesis and isomerization to an assisted Tandem process is discussed. This method is useful for the selective synthesis of cyclic enol

ethers, extraordinarily valuable building blocks for organic synthesis.

Application of the methodology discussed herein to the synthesis of relevant target molecules and the development of novel synthetic methods along the line of this concept are currently in progress in our laboratory.

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