

## Das Reagenz • The Reagent

**(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Ru=CHR: An Efficient and Selective Reagent for the Formation of C=C-Double Bonds by Non-Polymerizing Metathesis Reactions**

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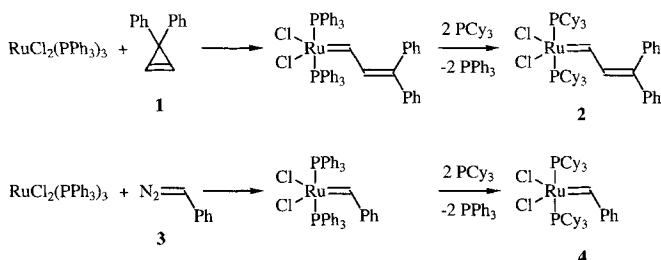
Received December 10th, 1996

Numerous research efforts have focused on the development of catalysts for metathesis reactions since the discovery of this type of C=C-double bond formation in 1955 [1, 2]. Besides the utilization in important technical processes like the Philipps-Triolefin-Process and the Shell-Higher-Olefin-Process [2c] the domain of these catalysts was the Ring-Opening-Metathesis-Polymerization (ROMP) [3]. For a long time the catalyst were highly air-sensitive (they had to be handled in a glove box in purified solvents) and did not tolerate polar functionalities in the substrate. In order to overcome these difficulties, instead of early transition metals ruthenium was used in a new generation of metathesis catalysts developed by Grubbs *et al.* in 1992 [4,5]. Since besides ROMP these ruthenium complexes also catalyzed Ring-Closing-Metathesis (RCM), they initiated a rapid development of applications in total synthesis which recently have been crowned with Danishefsky's synthesis of (–)-epothilon A [6].

The following sections will describe the preparation and properties of the catalysts, explain the mechanism and important principles of the reactions and give examples of the functional group tolerance and the different rings that can be formed.

**1 The Catalysts**

The ruthenium–vinylcarbene complex **2** [7] was used in most of the examples below for “historic” reasons and can easily be prepared from RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> and 3,3-diphenylcyclopropene (**1**). Subsequent ligand exchange with PCy<sub>3</sub> (Cy = Cyclohexyl)



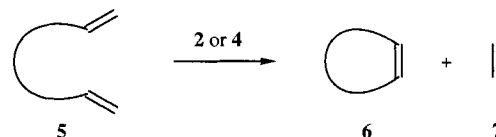
generates the vinylcarbene complex **2** which shows a higher activity than the complex with PPh<sub>3</sub>. As far as its reactivity is concerned the compound shows moderate stability to air, free NH (amines have to be protected as hydrochlorides), OH and even COOH groups. Reagent grade solvents can be used and ROMP is even possible in aqueous solution [8]. Stoichiometric reactions with olefins have also been investigated [9].

The major drawback of **2** was the low rate of initiation that leads to long reaction times in RCM and to a broad molecular weight distribution in ROMP. Since after initiation the propagation was fast, a possible solution was to use a catalyst which is more closely related to the propagating species (see next section), i.e. a carben complex rather than a vinylcarbene complex. These considerations lead to the preparation of catalyst **4** in 1995 [10]. For its preparation phenyldiazomethane (**3**) instead of a cyclopropene is treated with the RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> complex. Then once again the PPh<sub>3</sub> ligand is exchanged for PCy<sub>3</sub>.

Polymer-supported [11] and water soluble versions [12] of **2** have also been described. Catalyst **4** is commercially available from only one supplier, but presumably this will change within the next months.

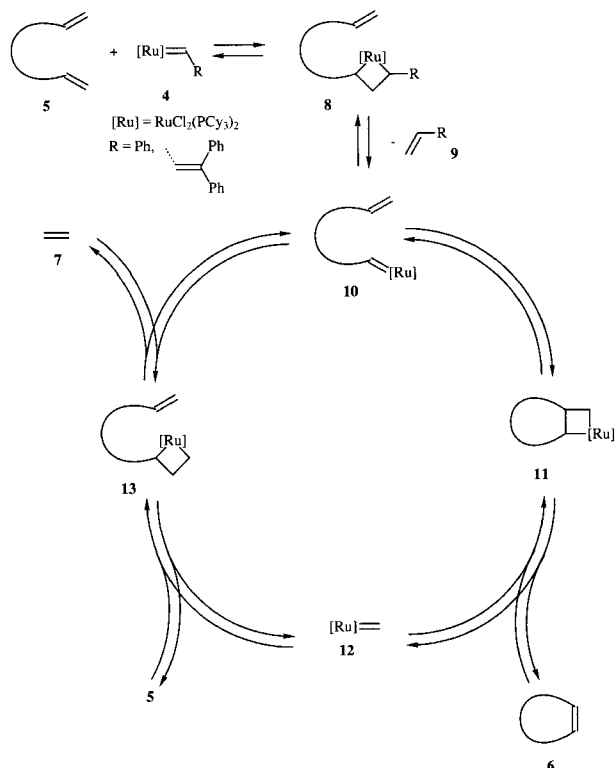
**2 The Mechanism**

As far as the mechanism of metathesis reactions is concerned, today the Chauvin mechanism is well accepted [2]. The RCM of a 1,*n*-diolefin shall serve as an example for a description of the steps involved. The net reaction is shown below.



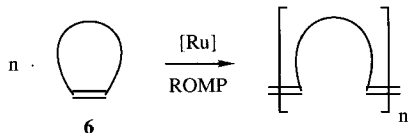
In the initiation step the catalyst (actually the pre-catalyst) and the substrate **5** form the ruthenacyclobutane **8** by a [2+2] cycloaddition. A cycloreversion of this intermediate produces

the side-product **9** and the new carbene complex **10** and thus enters the catalytic cycle. Now **10** can form a new ruthenacyclobutane **11** by another, intramolecular [2+2] cycloaddition. Again cycloreversion sets a carbene complex (**12**, the actual catalyst) free and the product (**6**) is formed. Finally, **12** and the substrate undergo one more [2+2] cycloaddition to form the ruthenacyclobutane **13**, the cycloreversion of **13** closes the catalytic cycle and releases ethylene (**7**) as the stoichiometric by-product.



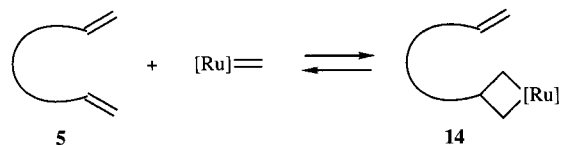
All steps are reversible, but over all these equilibria the formation of two product molecules from one substrate (see net reaction) favors product formation for entropic reasons. In the case of ethylene or other volatile by-products the equilibria are additionally shifted towards the products. The net reaction suggests that the ethylene is formed from the two methylene-ends of one substrate molecule, but as shown above, it is always formed from the methylene-ends of two different substrate molecules.

Since the product **6** is a cyclic olefin, one could fear the destruction of the product by ROMP.



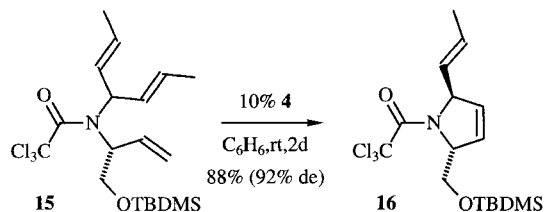
But usually only activated (i.e. strained) olefins undergo fast ROMP [13]. Furthermore the 1,2-disubstituted double bonds of the product don't react as readily as the terminal double bonds usually found in the substrates for RCM [14]. Generally the substrates are chosen in a way that the product double bond is higher substituted than the substrate double bonds, the application of this principle made the synthesis of even tetrasubstituted double bonds possible [2d].

The regiochemistry of the [2+2] cycloadditions mentioned above is not crucial, since the other regioisomer **14** is non-productive, any cycloreversion of it forms identical molecules. Over all a selective RCM depends on a delicate interplay of kinetic and thermodynamic factors.

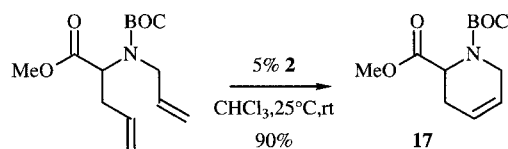


### 3 Formation of One New Ring

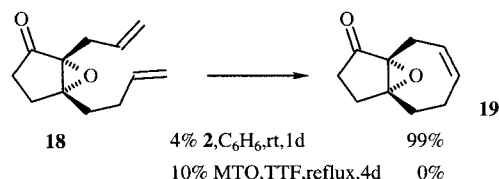
Five- to eight-membered carbo- and heterocycles have been formed by RCM [15, 16, 17], solid phase RCM has also been tested [17e,g]. In the product the double bond geometry is (*Z*) [18], otherwise highly strained rings would result. First stereoselective applications have been reported recently. The diastereoselective formation of the five-membered heterocycle **16** from a precursor with a prochiral diene unit (**15**) is one example [17f].



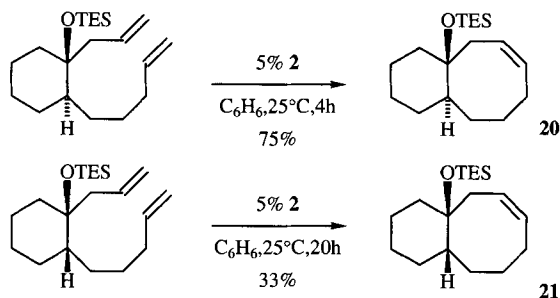
Grubbs used this methodology for the synthesis of conformationally restricted amino acids like **17** [17b].



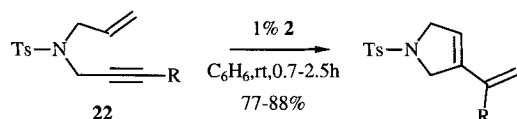
Blechert studied the synthesis of hydroazulenes **19** from precursors **18** [15a]. Here the ruthenium catalyst proved to be superior to the methyltrioxorhenium catalyst (MTO, [5]) and even an  $\alpha$ -epoxyketone was tolerated.



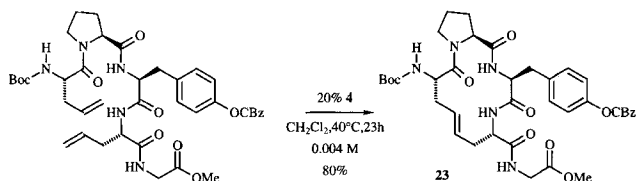
For the formation of eight-membered rings a conformational constraint was essential for good yields [15b], otherwise much of the substrate polymerized (compare the formation of **20** and **21**).



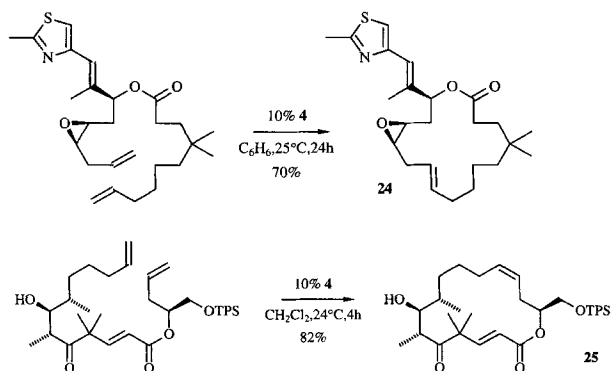
1,*n*-Enynes **22** were used by Mori for the formation of heterocyclic olefins carrying vinyl substituents [17a,h]. Conjugated dienes don't react well in ROMP [13], this reduced reactivity might explain why the vinyl group of the product remains untouched. But still an additional substituent R is necessary for good yields.



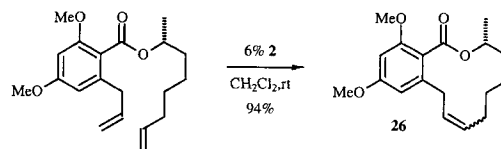
In macrocycles the (*E*) and/or (*Z*) olefin geometry [18] can be observed [19]. Since polymerization is a real threat here, high dilution is necessary (about 0.005M). Fürstner demonstrated that conformationally predisposed systems are not necessary and the site of ring closure rather than the ring size is pivotal for a successful macrocyclization [19c]. Grubbs synthesized rigidified carbon–carbon bond analogs of tetrapeptide disulfides ( $\beta$ -turn inductors) like **23** [15d].



In both, Danishefsky's total synthesis of (–)-epothilon A [6] and Nicolaou's synthesis of the epothilone framework [19e], high yields of the macrocycles **24** and **25** were obtained as single diastereomers (the double bond geometries have not been proven yet).

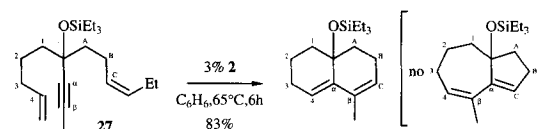


In Fürstner's (*R*)-(+)-lasiodiplodin synthesis the formation of a (*E*/*Z*) mixture (**26**) was no problem, since the olefin was hydrogenated in the next step [19d].



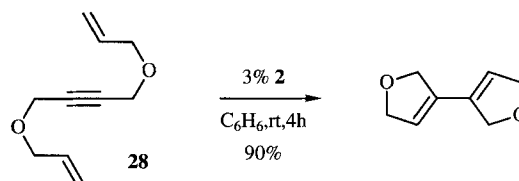
#### 4 Formation of Two Rings

Dienynes can be used for the construction of polycyclic ring systems [20]. In substrates like **27** the result can be explained by the principles mentioned in section 2.

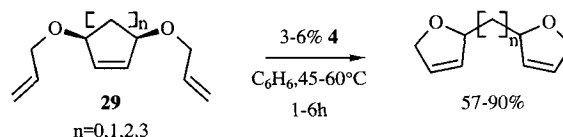


The reaction is initiated at the terminal, monosubstituted double bond. Then the intermediate ruthenium carbene complex undergoes an intramolecular [2+2] cycloaddition with the alkyne and not with the second olefin (six-membered ring versus eight-membered ring). Ring opening of the ruthenacyclobutene generates a new vinylcarben complex, which now is capable of reacting intramolecularly with the second, disubstituted olefin. If the second olefin is also terminal a product mixture is formed, since the reaction is also initiated from the other olefinic end of the substrate. Fortunately the directing, additional substituent ends up in the by-product.

If the two olefins and the alkyne are arranged in a different manner (**28**), two independent rings are formed.

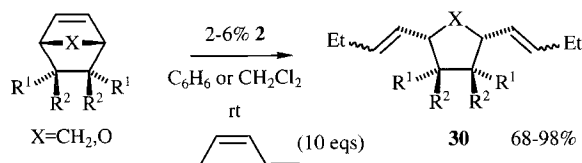


A combination of RCM and ROM (Ring-Opening Ring-Closing-Metathesis, RORCM) was also achieved [21]. In principle the reaction of dienynes mentioned above is a special case of this reaction if one regards the cyclic olefins used here (**29**) as alkynes where one  $\pi$  bond has been expanded to a ring.



#### 5 Ring-Opening Cross-Metathesis

This process is the reversal of RCM [22]. Here a second, acyclic olefin reacts with a cyclic substrate and forms a 1,*n*-diolefin. Blechert has used this principle for the formation of highly substituted tetrahydrofurans and cyclopentanes **30** [22b]. The starting materials are readily available from Diels-Alder reactions.



## 6 Miscellaneous

Besides ROMP also simple metathesis reactions catalyzed by **2** have been used for the synthesis of polymers [23]. As far as ruthenium carbene complexes are concerned there exists a whole family of related compounds, the vinylidene complexes [10, 24].

## 7 Future Prospects

One major problem of the macrocyclization reactions are the difficulties in predicting the geometry of the resulting double bond, here still remains a broad field for research. The second open question is the design of chiral catalysts for enantioselective reactions, e.g. for the reactions of the prochiral diolefins mentioned in section 3. Probably the reaction can be utilized not only for the formation of bi- but also of polycyclic compounds.

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