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# Olefin metathesis—recent applications in synthesis*

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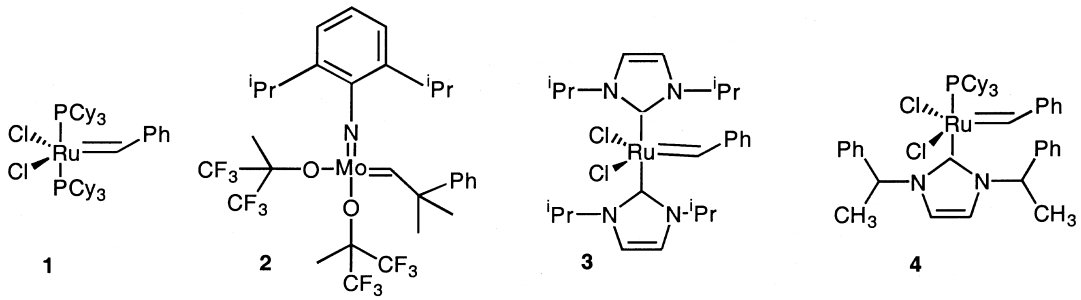
*Abstract:* Olefin methathesis allows for the catalytic cleavage and formation of C,C multiple bonds under mild conditions in the presence of various functional groups. Whereas ring closing metathesis has been widely used in the synthesis of cyclic olefins, less applications have been described for other metathesis types, namely cross and ring opening metathesis. The combination of these two reactions in domino processes and their application to the synthesis of complex natural products is described.

## INTRODUCTION

During the last years, olefin metathesis has gained significant importance due to the development of well-defined catalysts with a remarkable tolerance of functional groups [1]. The popularity of this C,C-bond forming and cleaving reaction can be attributed to the catalytic conversion of double bonds, which normally would have to be considered rather inert, in the presence of various functional groups. Among the common catalysts, Grubbs' complex **1** has found the widest application [2]. Schrock's carbene complex **2** is especially useful for the conversion of sterically hindered olefins [3]. Both catalysts are commercially available. However, catalyst development is going on. Recently, Herrmann *et al*. introduced imidazolinylidene complexes such as **3** [4], which can serve as a basis for the development of chiral metathesis catalysts. The use of mixed ligands results in complexes like **4** exhibiting exceptionally higher reactivities as demonstrated by the formation of tetrasubstituted double bonds [5]. Compounds **1**–**4** (Scheme 1) have to be regarded as precatalysts. The catalytically active species are the corresponding methylidene complexes. Apart from polymerization reactions olefin metathesis can be classified into three categories as shown in Scheme 2. Ring closing metathesis (RCM) is meanwhile considered as a standard method for the synthesis of rings of different size. Ring opening metathesis (ROM) has been applied to a lesser extent. Selective cross metathesis (CM) still presents a major challenge. The synthesis of multiply substituted double bonds, accompanied by the formation of ethylene as the exclusive by-product, appears especially attractive.




**Scheme 1**

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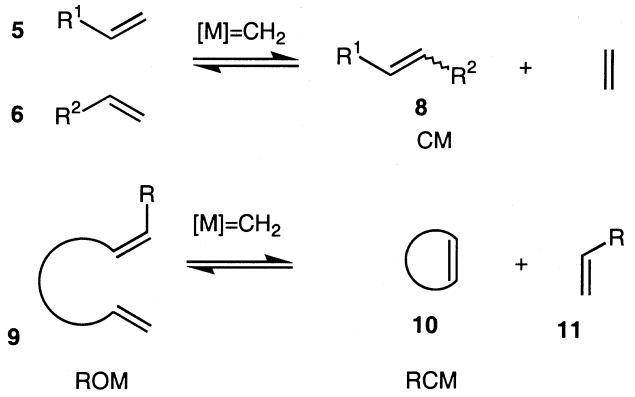
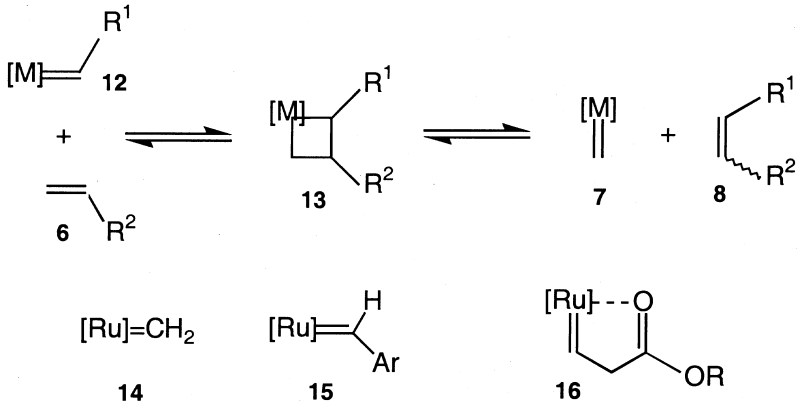



**Scheme 2** Olefin metathesis types.

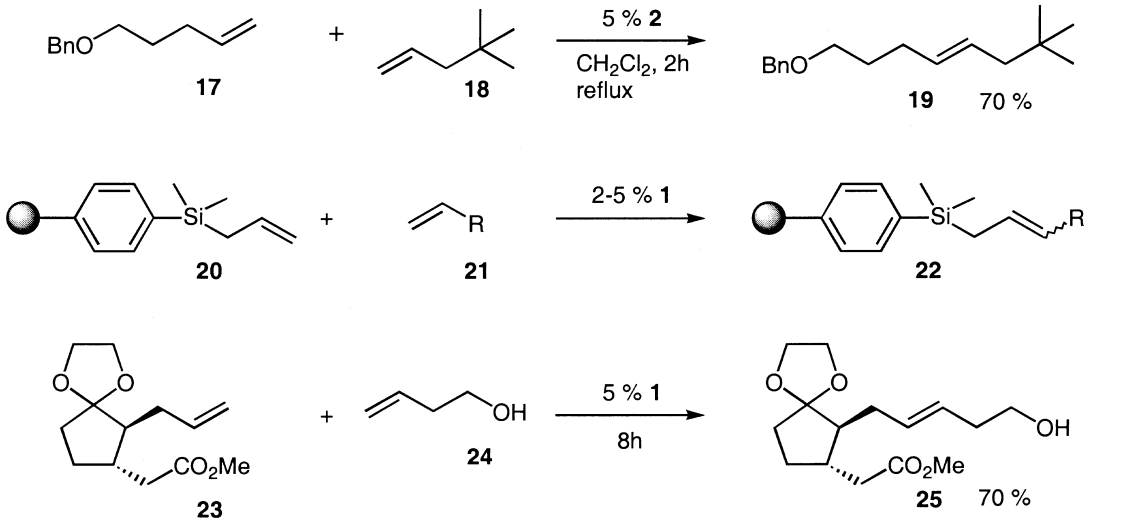
## SELECTIVE CROSS METATHESIS

The reactivity of monosubstituted double bonds in the presence of metathesis catalysts of type 7 strongly depends on steric factors as well as on neighboring group effects. In case of a very rapid reaction of **5** carbene complex **12** would result via cycloaddition and -reversion. The reactivity of metal-carbene complexes is strongly influenced by substituents. For instance, it is well-known, that **14** is much more reactive than **15**. Despite steric and electronic properties neighboring group effects have to be considered as well. For example, the reactivity of **16** is strongly influenced by a complexing carbonyl group (Scheme 3). Like the reactivity, the selectivity of metal-carbene complexes should also strongly depend on substituents. If a suitable substituent $R^1$ is chosen, **12** could selectively react with **6** to afford cross product **8**. Indeed, several selective cross metatheses have been reported. In dichloromethane **17** or **18** are both cleanly dimerized in the presence of **2**. However, a 1:1 mixture of both compounds preferably gives cross product **19** with an *E*:*Z* ratio of 10:1.




**Scheme 3** Mechanisms of cross metathesis.

Selective cross metatheses are often observed, when two sterically comparable olefins are combined and when one of them contains a complexing heteroatom like O or N. Allyl silanes react similarily as **18** [6]. This functionality offers many opportunities for subsequent reactions. It can also be used to attach organic molecules to a polystyrene resin. Polystyrene is easily converted into allylsilane **20** by deprotonation and silylation. Various substrates **21** can be immobilized by selective cross metathesis [7]. The cleavage by protodesilylation corresponds to a traceless linker. Moreover, cleavage can be combined with a bond-forming step. In the course of detailed studies into cross methathesis we found, that sterically not comparable olefins can be selectively cross-coupled, too. Selective coupling between slightly sterically hindered olefins and unhindered olefins are often observed, when both partners contain complexing heteroatoms as in the case of **23** and **24** (Scheme 4). Steric crowding prevents dimerization of




**Scheme 4** Selective cross metathesis reactions.

**23**. The *E*:*Z* selectivity observed for **25** was 6:1. Jasmonate **23** was successfully cross-coupled with numerous terminal olefins. The yields were usually higher than those of the respective Wittig olefinations.

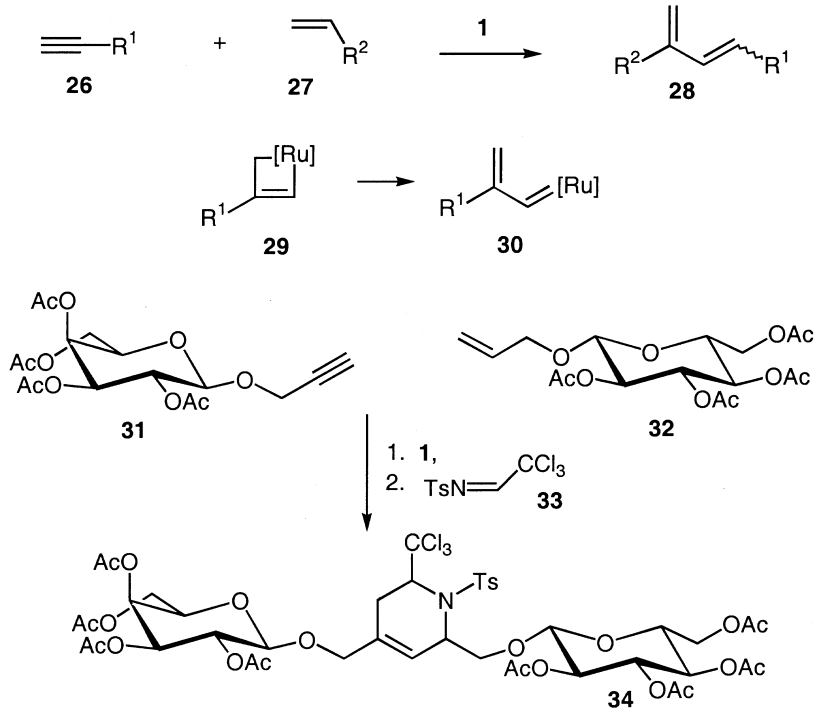
## CROSS METATHESIS INVOLVING TRIPLE BONDS

Triple bonds are also subject to CM. The reaction of monosubstituted acetylenes with metathesis catalysts often affords polymers. However, a mixture of **26** and **27** is converted to disubstituted butadienes **28** in an atomeconomic fashion by Grubbs' complex **1** [8] The reaction starts at the triple bond. A cycloaddition should yield **29** and subsequent cycloreversion should give rise to vinylidene complex **30**. A subsequent selective cross metathesis with the olefin affords the butadiene. The reaction can be adapted to solid phase. Butadienes are useful building blocks, as illustrated by the synthesis of pseudooligosaccharide **34** (Scheme 5). The approach shown is very flexible and allows different sugars to be coupled at different positions. The dienophile is variable as well. Non-natural amino acids are thus also available.

## RING REARRANGEMENTS

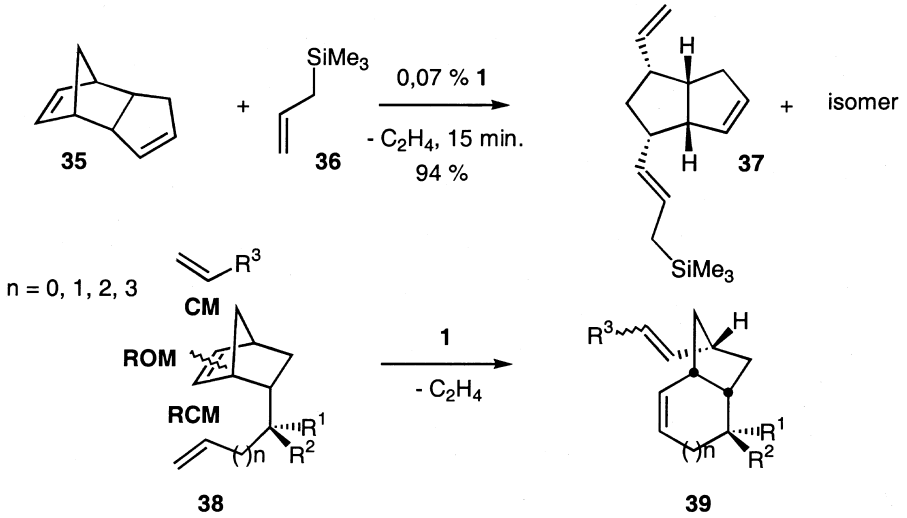
Comparably little is known about ring opening metathesis. Strained olefins like norbornene or the dimeric cyclopentadiene **35** are cleanly polymerized by **1**. In the presence of a monosubstituted olefin, however, a sequence of ring opening and cross metathesis occurs [9]. A regioselective C,C-bond formation takes place in the case of unsymmetrically substituted cycloolefins. Thus, even **37** is formed as the dominating product starting from **35**. The functional group tolerance of **1** enables a broad application of such ring opening reactions of norbornene derivatives and their heteroanalogs. The reaction sequence can be extended by a further ring closing metathesis. In the presence of a monosubstituted olefin, bicycles like **38**, which are easily accessible by Diels–Alder reactions, are cleanly converted to **39** in a domino process (Scheme 6) [10].

Depending on the size of the new ring the sequence can start with ROM-CM (eight-membered ring) or ROM-RCM (five- to seven-membered ring). Olefin metathesis is an equilibrium reaction. Applying a driving force, the equilibrium can be shifted in favor of the product. Practically, this can be achieved by removal of the by-product ethylene or by release of ring strain as in opening of norbornene derivatives. However, other effects may also be employed to influence the equilibrium. Cycloolefins considered nonstrained like five- and six-membered rings can be converted in a ROM-RCM sequence. Such a concept represents an approach towards ring rearrangements. The variation of the side chain enables the flexible construction of carbo- or heterocycles, whereas the opened ring results in a new side chain. Here, the reaction equilibrium is neither influenced by ethylene removal nor by release of ring strain. Since the stereochemistry in ring systems is easily controlled, interesting applications in stereoselective synthesis

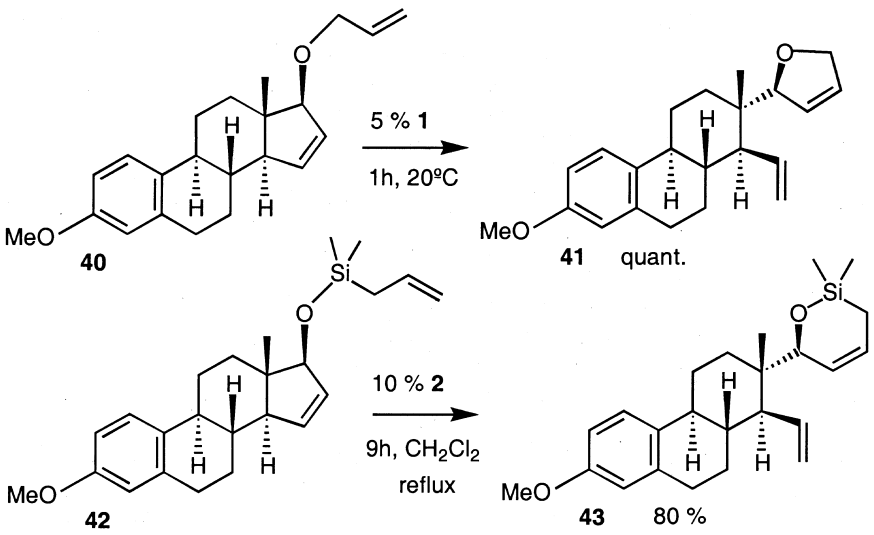


**Scheme 5** Selective yne-ene cross metathesis and application to the synthesis of pseudooligosaccharides.

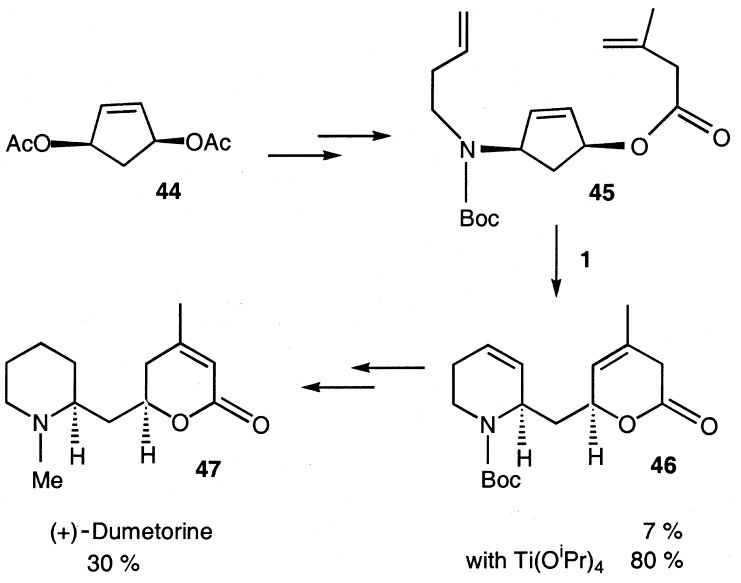
can be envisioned. The ring opening of the D-ring of a steroid is shown as a representative example for this new type of rearrangement. In a special case it was even possible to perform the rearrangement using **2** (see synthesis of **43**; Scheme 7), however, this process is less general compared to the (Ru)-catalyzed reaction. The rearrangement can be combined with further metathesis steps as illustrated by the first total synthesis of (+)-dumetorine. **47** was isolated from tubers of *Discorea dumetorum Pax* (Scheme 8) [11]. Yam extracts were used for treatment of diabetes, as topical anestetic and as arrow poison. The concept of rearrangement by metathesis also offers a flexible approach towards substituted heterocycles with defined stereochemistry. This is best demonstrated by the synthesis of tetraponerines. It has been reported, that the venom of pseudomyrmecine ants *Tetraponera* sp. contains eight toxic alkaloids **T-1** to **T-8** (Scheme 9)



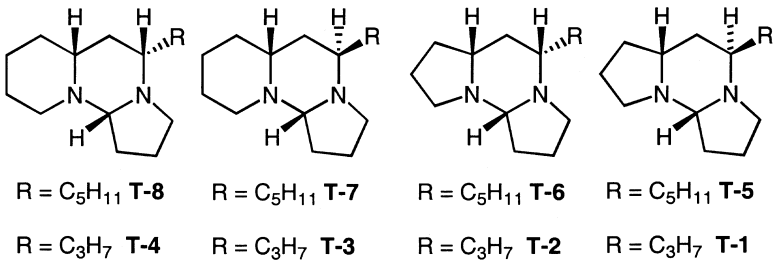
**Scheme 6** Ring opening metathesis of strained rings.



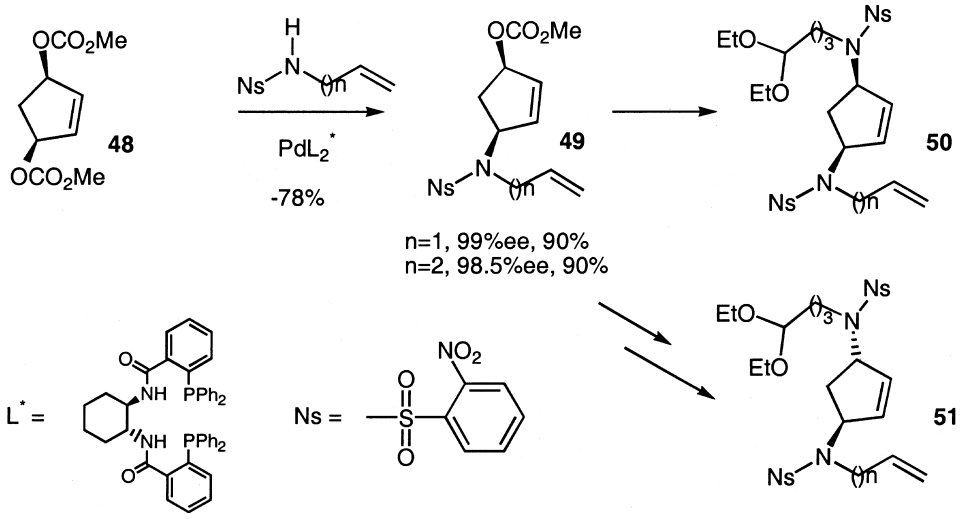

**Scheme 7** Ring rearrangement of steroids.




**Scheme 8** Total synthesis of (+)-dumetorine via domino metathesis.




**Scheme 9** Tetraponerines **T-1**–**T-8**.

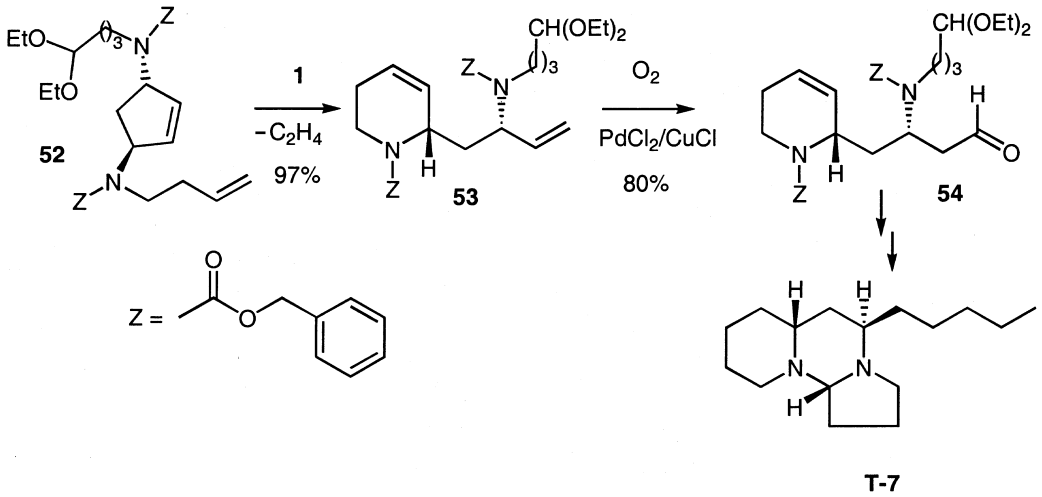



**Scheme 10** Pd-catalyzed synthesis of metathesis rearrangement precursors **50** and **51**.

[12]. They are distinguished by the size of ring A, by their stereochemistry and by the length of their side chains. The metathesis ring rearrangement allows to vary all three parameters. Starting from meso-dicarbonate **48** the product **49** is available in enantiomerically pure form by enantioselective Pd-catalysis.

Alternatively, the cis-disubstituted product **50** can be obtained in one-pot. **49** is transformed into the *trans*-product **51** by a Mitsunobu reaction (Scheme 10). The length of the side chain determines the ring size established during the rearrangement (five- or six-membered ring). A second variation is offered by choosing *cis*- or *trans*-stereochemistry. The equilibrium of the rearrangement itself was found to strongly depend on the protective groups. For example, an exchange of the protective group from **51** to **52** was accompanied by a significantly higher conversion (from starting material:product = 1:2 to complete conversion). Subsequent Wacker oxidation and olefination enable the variation of the side chain length and, thus, finally open the access to all tetraponerines **T-1** to **T-8** (Scheme 11).

We are currently exploring further metathesis reactions and domino metatheses and their application to natural product synthesis.




**Scheme 11** Synthesis of tetraponerine **T-7** by metathesis ring rearrangement.

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