PERSPECTIVE

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Ru complexes bearing bidentate carbenes: from innocent curiosity to uniquely effective catalysts for olefin metathesis

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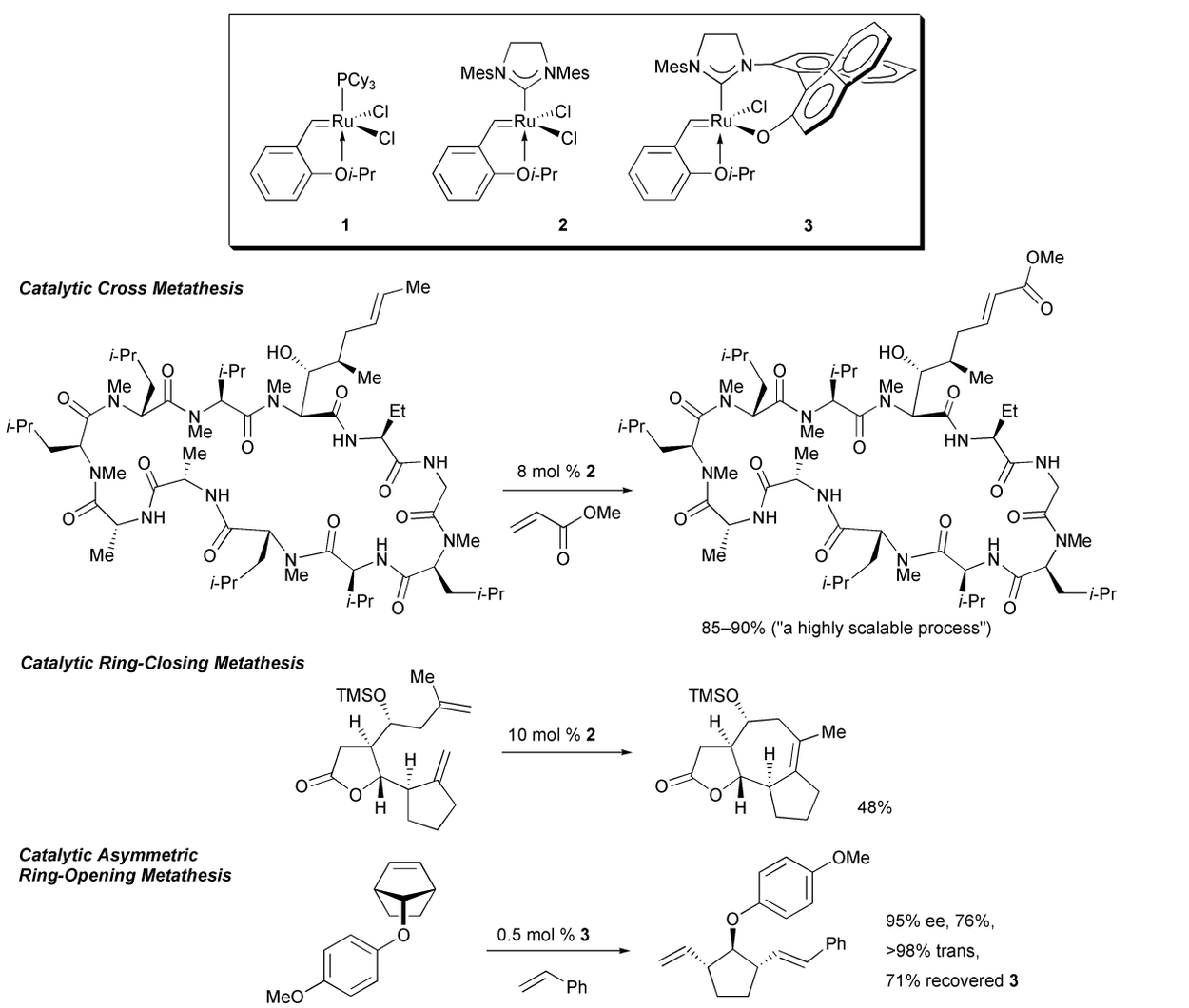
The discovery and development of a new class of Ru-based catalysts for olefin metathesis is described. These catalysts, particularly those that do not bear a phosphine ligand, have been demonstrated to promote unique levels of reactivity in a variety of olefin metathesis reactions. The design and development of supported and chiral optically pure variants of this class of Ru catalysts for use in enantioselective metathesis are discussed as well. All catalysts are air stable, reusable, and can be employed with unpurified solvents.

1 Introduction

Since the early nineties and the discovery of structurally well-defined catalysts for alkene metathesis by Schrock and Grubbs, the field of organic synthesis has undergone an exciting transformation.[1] Through catalytic olefin metathesis, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and tedious routes. The primary reason for the success of olefin metathesis is the development of increasingly efficient and selective catalysts.

In this perspective article, we outline the development of a class of Ru carbenes represented by **1**–**3**, that are emerging as increasingly popular metathesis catalysts as a result of their unique properties; three representative transformations that are most effectively promoted by this class of Ru complexes are depicted in Scheme 1 (see below for additional details). The story begins with the serendipitous discovery of Ru-based complex **1** through a set of experiments intended to shed light



Scheme 1 Ru-based complexes bearing a bidentate styrene ether ligand serve as effective and practical olefin metathesis catalysts. The reactions shown can only be catalyzed or promoted with high efficiency by this class of Ru complexes. Mes = 2,4,6-$Me_3C_6H_2$.

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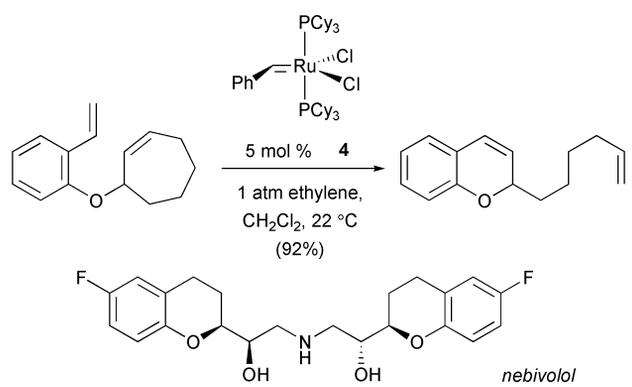
on the mechanism of various metal-catalyzed ring-opening/ring-closing metathesis (ROM/RCM) reactions.[2] Subsequent studies resulted in the availability of non-phosphine Ru carbene **2** and its chiral analogue **3** as catalysts that are recyclable, stable to air or moisture, and operate in the presence of a wide range of common organic functionalities.

2 Styrenyl ether Ru complexes: discovery, synthesis and characterization

2.1 Serendipitous discovery of Ru complex 1

In the mid-nineties, one program of research in our laboratories focused on the development of a metal-catalyzed process for efficient conversion of styrenyl cycloalkenyl ethers to 2-substituted chromenes (Scheme 2);[2,3] these reactions are promoted by 4–10 mol% $(PCy_3)_2Cl_2Ru{=}C(H)Ph$[4] (**4**) or the more active $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3)(OCMe(CF_3)_2)_2$.[5] The catalytic metathesis rearrangement, which proceeds through a tandem ROM–RCM, was later used, together with a Zr-catalyzed kinetic resolution, to synthesize optically pure 2-substituted chromenes and the antihypertensive agent (*S*,*R*,*R*,*R*)-nebivolol (Scheme 1).[6]

While studying the mechanism of catalytic conversion of styrenyl ethers to chromenes, we found that various metathesis



Scheme 2 Ru-catalyzed metathesis rearrangement of styrenyl ethers carried out under ethylene and the antihypertensive agent nebivolol, synthesized enantioselectively through the use of this method.

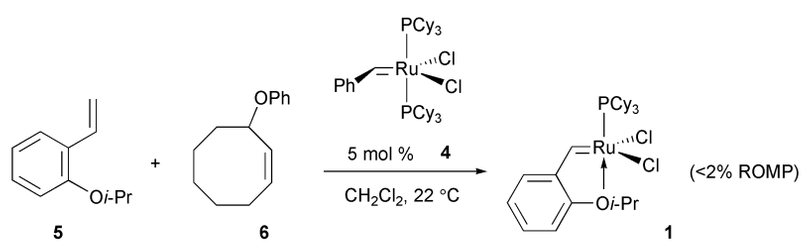
reactions, such as ring-opening metathesis polymerization (ROMP) of **6**, are promoted less effectively by **4** when styrene ether **5** is present in solution (Scheme 3). To explain these observations, we proposed that Ru-chelate **1** is formed *in situ*, and that this complex is catalytically less active (relative to **4**) when in the presence of excess styrenyl terminal olefin (*e.g.*, **5**).[7] We suggested that following the formation of **1** (through metathesis involving styrene **5**), the adjacent ether oxygen may associate with the transition metal, to reduce the rate of subsequent propagation steps.

2.2 Synthesis and characterization of Ru complex 1

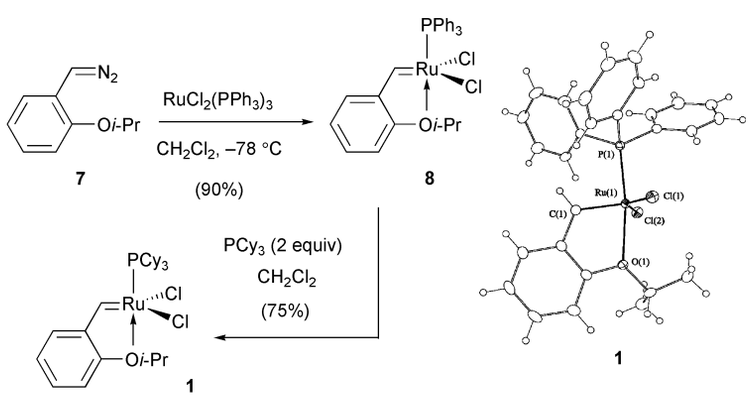
To gain support for our proposal and the intermediacy of **1** in reactions such as that in Scheme 3, we synthesized, isolated and characterized this metal carbene.[8] We showed that when 2-isopropoxystyrene **5** is treated with one equiv. of **4** (24 h), Ru carbene **1** is formed in 67% yield after silica gel chromatography (Scheme 3). As the method of purification suggests, **1** proved to be exceptionally robust.

To avoid the use of stoichiometric amounts of **4** in preparing **1**, we developed a two step single-vessel alternative procedure (Scheme 4).[8] We established that exposure of $Cl_2Ru(PPh_3)_3$ to aryldiazomethane **7** results in the formation of a monophosphine **8** without generation of the derived bisphosphine; it is worthy of note that efficient synthesis of complex **8** later proved critical in our ability to synthesize related chiral Ru complexes (*cf.* Scheme 18). Large, needle-like crystals of **8** were obtained by recrystallization (X-ray structure in Scheme 4). Intermediate **8** need not be isolated; Ru-carbene **1** can be accessed in similar yield when PCy_3 is added shortly after exposure of **7** to $Cl_2Ru(PPh_3)_3$.

A range of data support the proposed structure for Ru carbene **1**.[8] Internal Ru–oxygen chelation is evident in its ^{1}H NMR and ^{13}C NMR spectra. Shielding of the carbene proton (δH_α = 17.44 ppm) results in an upfield shift of ~2.5 ppm relative to the parent complex (**4**). The carbene carbon atom resonates upfield (δC_α = 280.63 ppm) in comparison to that of **4** (δC_α = 294.72 ppm). Whereas coupling between the phosphorus nucleus and the carbene proton is absent in **4** (P–Ru–C_α–H_α dihedral angle = 90°), J_{PH} = 4.4 Hz in the case of **1**, suggesting that formation of the five-membered chelate is coincident with a 90° rotation about the carbon–metal double bond. The proposed structure

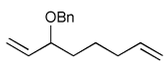
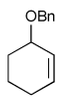
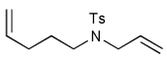
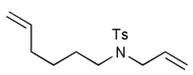
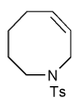


Scheme 3 Studies in connection to the mechanism of Ru-catalyzed styrene ethers led to the synthesis and isolation of complex **1**.



Scheme 4 One-vessel synthesis of Ru-based metathesis catalyst **1**.

Table 1 RCM of acyclic dienes catalyzed by Ru catalyst **1** [a]

Entry	Substrate	Product	Time/h	Product [b] yield (%)	Rec. catalyst [b] yield (%)
1			2.0	95	89
2 [c]			1.0	99	88
3 [c]			1.0	72	95

[a] Conditions: 5 mol% **1**, CH_2Cl_2, 22 °C, Ar or N_2 atm. [b] Isolated yields after silica gel chromatography. [c] Reaction performed in refluxing CH_2Cl_2.

for **1** was further confirmed by single crystal X-ray analysis of naphthyl derivative **9** (Fig. 1). Consistent with the ^{1}H NMR analysis, the C_α–H_α bond of the distorted square pyramidal structure lies in plane with the Ru–P and Ru–O bonds. The Ru–O distance (2.257(7) Å) in **9** is typical for related O⟶Ru chelate complexes and suggests that the chelate linkage is reasonably strong.

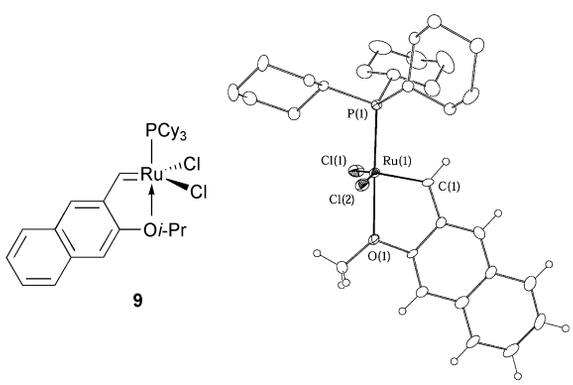
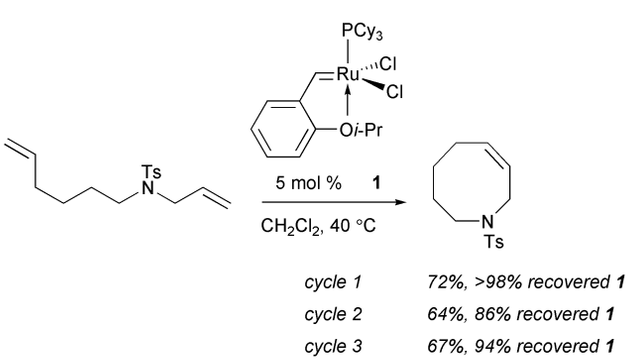


Fig. 1 ORTEP diagram of $PCy_3Cl_2Ru(=CH\text{-}o\text{-}OMeC_{10}H_6)$ (**9**).

2.3 Synthetic utility of Ru complex 1

Monophosphine Ru carbene **1** promotes ring-closing metathesis (RCM) of five-, six-, seven-, and eight-membered carbo- and heterocycles (Table 1). In each case, the catalyst is recovered chromatographically in high yield as a homogeneous solid residue and maintains its catalytic activity in subsequent reactions.[8] As illustrated by the example in Scheme 5, recycled **1** may be carried through at least three additional rounds of RCM. The data presented constitute typical results obtained when recovered residue **1** is transferred to a new reaction vessel followed by the addition of substrate and solvent.

It merits mention that all product isolation work for reactions shown in Table 1 and Scheme 5, including solvent removal following silica gel chromatography, was performed in air with undistilled, reagent-grade solvents; an inert atmosphere is not required to prevent catalyst decomposition. In the solid state, **1** is stable indefinitely in air; in undistilled organic solvents in the presence of water, alcohol, and/or dilute acid (0.01 M HCl), no signs of decomposition (<2%) are evident, according to ^{1}H NMR analysis, after up to one week.[8]



Scheme 5 Ru-based metathesis catalyst **1** can be recycled efficiently.

2.4 Nature of styrene ether and stability of first generation Ru complexes

Ru carbene **10**, bearing a methyl ether *vs*. an *i*-Pr ether, initially presented itself as an attractive alternative, since the requisite styrene ether can be prepared from an inexpensive and commercially available aldehyde. However, **10** proved to be a less effective catalyst (see example in Fig. 2), and its preparation led to several complications. In a solution of undistilled chloroform in air, **10** slowly decomposes over a period of several weeks to produce *o*-anisaldehyde (through oxidation of the metal carbene). In the case of **1**, after two weeks under identical conditions, there is <2% decomposition. Moreover, unlike **1**, complex **10** cannot be recovered in high yield after silica gel chromatography.

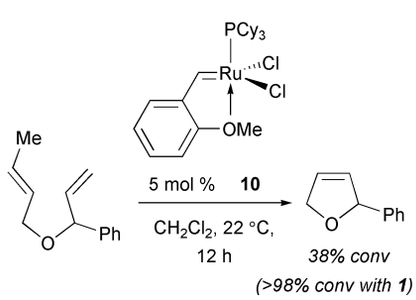
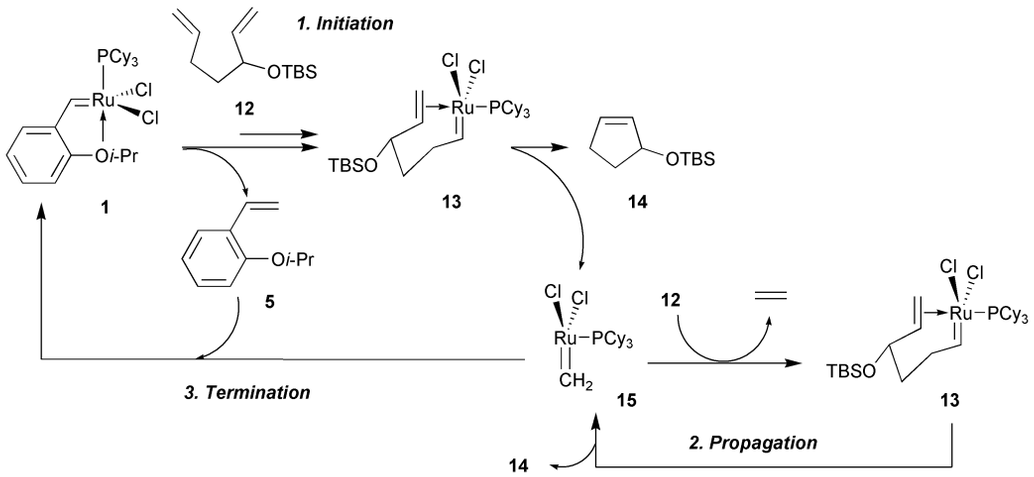


Fig. 2 Substitution of the O*i*-Pr (catalyst 1) group with an OMe group (catalyst **10**) significantly reduces the stability and metathesis activity of the Ru complex.

The difference in catalytic activity of **10** and **1** indicated that the nature of the ether chelate is critical to the stability, as well as activity, of a styrene ether Ru complex.[8] We suspected that the differences in activity and stability of the methoxy- (**10**) *vs*. isopropoxy (**1**) Ru-carbene complexes arise from the relative steric bulk of these two substituents. Since catalytic metathesis likely proceeds through a dissociative mechanism (see Scheme 6), we argued that the larger *i*-Pr group may facilitate dissociation of the oxygen atom from Ru during catalyst initiation. It is also tenable that the isopropoxy group is a more robust ligating unit due to its higher Lewis basicity, offering more effective electronic stability to **1**. As will be discussed later, such considerations proved useful in the development of subsequent generations of this class of Ru catalysts (*cf*. **2c** in Fig. 8 and **3d** and **3f** in Scheme 20).



Scheme 6 Proposed route for the release, catalytic activity and return of Ru complex **1**.

The stability of **1** implies that increased sterics might allow for more effective protection of the metal center from undesirable side reactions (*e.g.*, carbene oxidation). In this context, it has been reported that the stability of bridged-chloride Ru-carbene complexes can be critically dependent on steric requirements of the ligand environment surrounding the metal center.[9] Indeed, as illustrated in Fig. 3, Ru complex **11** bearing the smaller OMe group, an intermediate synthesized *en route* to **10**, crystallizes as a dimeric entity containing bridging anionic chloride ligands.

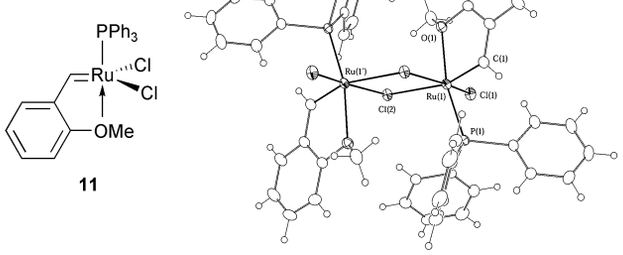


Fig. 3 Ru complex **10** bearing styrene methyl ether (*vs.* O*i*-Pr) is less stable and not as catalytically active. The derived PPh_3 complex **11** crystallizes as a dimer, underlining the reduced sterics at the metal center.

2.5 Mechanistic considerations regarding catalytic activity of complex 1

A plausible mechanistic scenario can be proposed that accounts for RCM activity and recyclability of Ru complex **1** (Scheme 6). Formation of carbene **13** results in the release of styrene ether **5**. Subsequent conversion of **13** to RCM product **14** through the derived metallacyclobutane intermediate releases monophosphine Ru-methylene **15** to complete the initiation stage. With an excess of the diene substrate present, the highly reactive **15** enters the propagation cycle to promote additional product formation (concomitant with the release of ethylene). Complex **15** may encounter **5**, leading to regeneration of **1**; as the concentration of **12** decreases, initiation of **1** is also reduced to cause efficient catalyst recovery.[10]

The influence of internal chelation on the initiation and propagation rates of **1** relative to benzylidene **4** was probed by monitoring the ROMP of cyclooctene (Fig. 4).[7] Pseudo first-order rate constants for initiation (consumption of **1**) and propagation (formation of **16**) were measured by integration of the H_α resonances of carbenes **1** and **16** and the olefinic proton signals of cyclooctene and **16**, respectively (^{1}H NMR). These

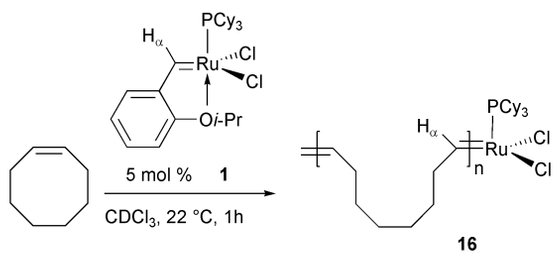


Fig. 4 Polymerization of cyclooctene was used to measure initiation and propagation rates of Ru catalyst **1** *vs.* **4**.

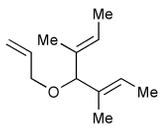
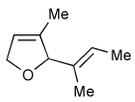
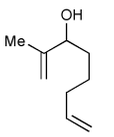
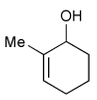
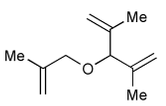
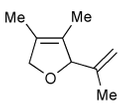
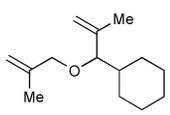
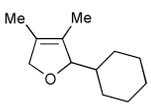
experiments indicated that **1** initiates approximately 30 times slower and propagates nearly four times faster than **4**. The slower initiation (**1** *vs.* **4**) may be due to the less facile dissociation of the smaller isopropyl aryl ether ligand (relative to PCy_3) from the sterically congested metal center (see also Scheme 14). In addition, in the case of **1**, generation of the active complex (*e.g.*, **13**) requires dissociation of the aryl ether ligand as well as a metathesis step (activation of **4** only requires phosphine dissociation). Re-association of the alkoxy unit to the transition metal center should be rate-inhibiting and more favored on entropic grounds (alkoxy styrene is bound to the transition metal at two sites). The enhanced propagation of **1** is consistent with the intermediacy of monophosphine **15** (Scheme 6) and the rate-retarding effects of excess phosphine in Ru-catalyzed metathesis reactions; it is likely that PCy_3 is more effective at re-associating with a Ru carbene (slowing rate of metathesis) than ether **5**.[11]

3 Second generation non-phosphine Ru-based olefin metathesis catalyst

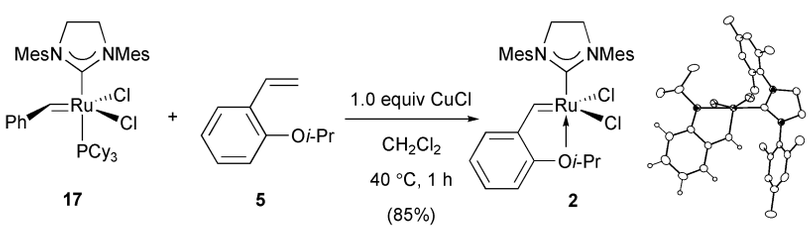
3.1 Synthesis and characterization of Ru complex 2

Despite the attractive attributes of **1**, this catalyst for the most part proved to be an efficient metathesis catalyst only with substrates that contain terminal alkenes. To address the question of reactivity without altering the structural features that allow the catalyst to be recyclable, in 1999 we synthesized, characterized and examined the catalytic activity of Ru complex **2**.[12] Our adopted strategy was based on the accelerating effect of a variety of saturated imidazolin-2-ylidene[13] and unsaturated[14] imidazol-2-ylidene carbene ligands[15] on the activity of Ru-based metathesis catalysts. We established that, as depicted in Scheme 7, treatment of Grubbs's second generation catalyst **17**[12a] with 1.0 equiv. CuCl and 0.97 equiv. **5** in CH_2Cl_2 at 40 °C leads to the formation of **2** within 1 h. Ru complex **2** can be isolated in air as a bright green solid in 85% yield after silica gel chromatography (mp = 178–181 °C dec.). Single crystal X-ray analysis of **2** (Scheme 7) confirmed the structural assignment (see Scheme 2).

Table 2 Ring-closing metathesis of acyclic dienes by Ru Complex **2**[a]

Entry	Substrate	Product	Time	Conv (%)	Product yield (%)[b]	Catalyst recovery (%)[b]
1			20 min	>98	87	98
2			2 h	>98	75	95
3			44 h	38	81	
4			30 min	70	65	60

[a] Conditions: 1 mol% **2** for entry 1, 5 mol% **2** for entries 2–4; 22 °C, CH_2Cl_2 for entries 1–2, 24 h at 22 °C and 20 h at 40 °C, CH_2Cl_2 for entry 3; toluene, 80 °C for entry 4. [b] Isolated yields.



Scheme 7 First generation synthesis and X-ray structure of non-phosphine Ru-based complex **2**. Mes = 2,4,6-$Me_3C_6H_2$.

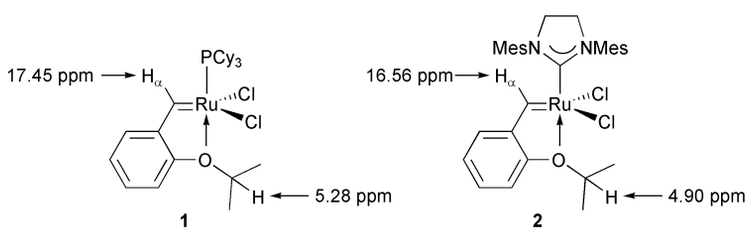


Fig. 5 Selected spectroscopic differences between Ru complexes **1** and **2**.

Comparison of the ^{1}H NMR spectra of **1** and **2** points to their subtle structural characteristics. As illustrated in Fig. 5, there are two distinct chemical shift changes in the ^{1}H NMR spectra of **1** and **2**; one variation is observed at the *i*-Pr methine proton and another at the carbene CH (H_α). In both instances, the protons for the imidazolin-2-ylidene system **2** are more shielded. These differences are likely due to higher electron density at the transition metal center of **2**, caused by the stronger electron donation by the heterocyclic ligand (relative to PCy_3).[12] The weaker electron donation by the oxygen ligand to the Ru center in **2** is manifested by the more upfield appearance of the isopropyl methine proton (4.90 *vs*. 5.28 ppm). However, the difference in the chemical shifts of H_α may be partially due to an anisotropic effect caused by the aryl units of the heterocyclic ligand in **2**.

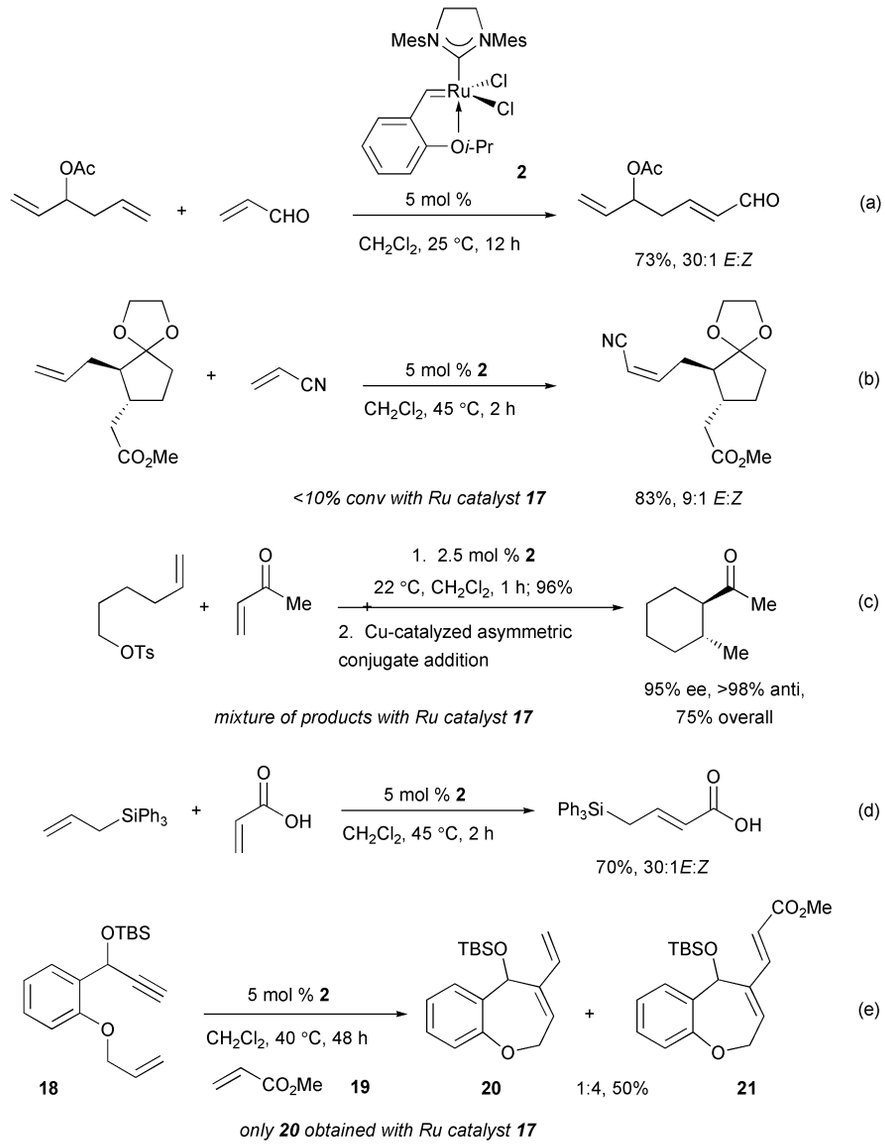
3.2 Ru-based complex 2: a recyclable and highly active metathesis catalyst

As the representative data in Table 2 illustrate, Ru complex **2** is a highly effective catalyst for RCM of dienes; trisubstituted (entry 1) and 1,1-disubstituted (entry 2) olefins can be utilized in the synthesis of trisubstituted cyclic alkenes. As indicated by the catalytic RCM in entry 3, trisubstituted allylic alcohols can be accessed in the presence of 5 mol% **2**.[16] Catalyst loadings lower than 5 mol% are sufficient; as exemplified by the reaction in entry 1, catalytic RCM can readily proceed to completion with only 1 mol% **2**. Tetrasubstituted olefins are obtained through catalytic RCM promoted by **5**, albeit less efficiently (entries 3–4, Table 2). The lower levels of efficiency observed in the synthesis of tetrasubstituted alkenes may be because the released styrenyl ether effectively competes with 1,1-disubstituted olefins to re-form the initial Ru carbene, thereby diminishing formation of the requisite Ru-carbene derived from the triene substrate. In addition, the catalyst (or the released Ru-methylene) may undergo partial decomposition under metathesis conditions at the required 80 °C for more than a few minutes.

As was the case with complex **1**, catalyst **2** can be recovered with high efficiency after silica gel chromatography (recrystallization not needed) and used in subsequent reactions with equal efficiency. It merits mention that monophosphine Ru catalyst **1** is significantly less efficient in promoting the transformations shown in Table 2. As an example, treatment of the alcohol in entry 2 of Table 2 with 5 mol% **1** (22 °C) leads to only 15% conversion after 2 h.

3.3 Synthetic utility of Ru complex 2: more than just a recyclable alternative

A number of reports from various laboratories have appeared indicating that *Ru catalyst **2** is not only a recyclable metathesis*

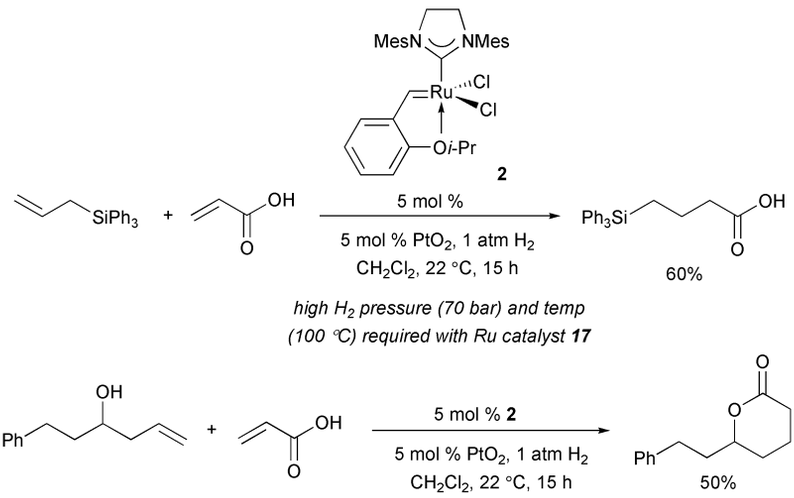


Scheme 8 Non-phosphine Ru complex **2** offers reactivity levels in effecting CM reactions that are not available by related systems such as catalyst **17**.

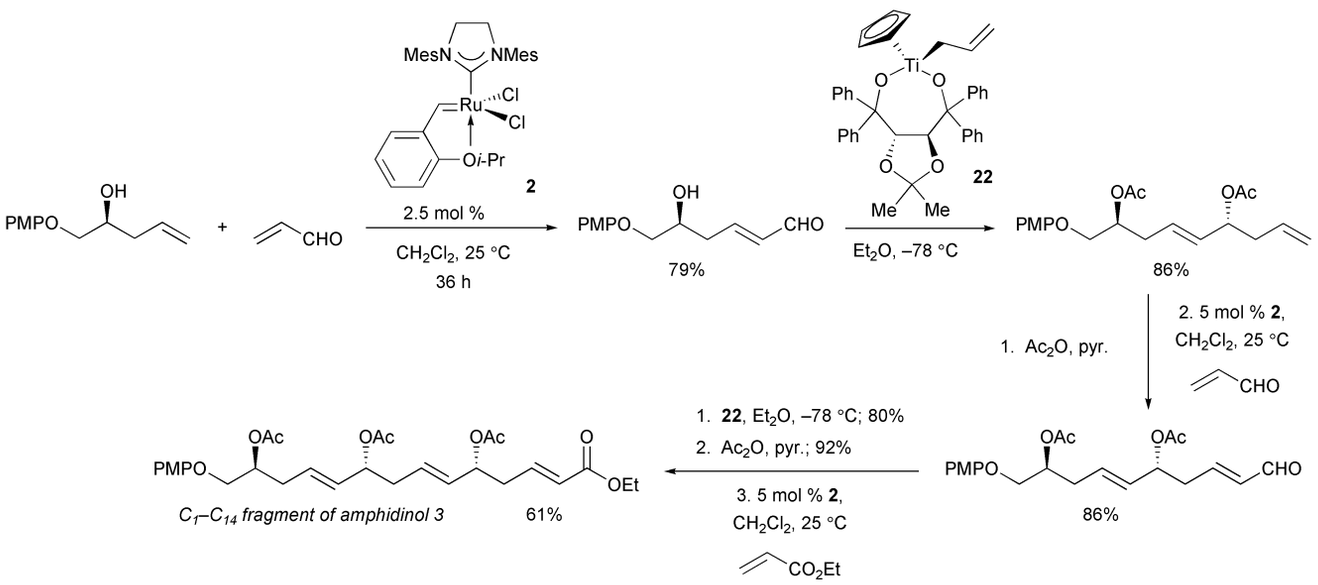
*catalyst, but also offers reactivity levels unavailable by the corresponding phosphine-bearing complex **17***. Complex **2** thus expands the scope of metal-catalyzed olefin metathesis. Representative examples are reviewed below. It must be noted that the point of the discussion below is not to suggest that **2** is superior to **17**, but to alert the reader of the advantages that can be offered by Ru complex **2**. It should also be noted that **2** and **17** are commercially available (Aldrich).[17]

3.3.1 Utility in catalytic cross metathesis (CM) reactions. The earliest examples suggesting that Ru complex **2** may have unique properties as a metathesis catalyst appeared in the context of cross metathesis (CM) reactions involving electron deficient olefin partners. Several examples are shown in Scheme 8 (see Scheme 10 for an application to target-oriented synthesis). The catalytic CM shown in Scheme 8a has been reported by Cossy to occur site-selectively at the more electron-rich homoallylic olefinic site to deliver the α,β-unsaturated aldehyde in 73% isolated yield.[18] The reaction of acrylonitrile with a variety of terminal alkenes, such as that illustrated in Scheme 8b, cannot be effected in the presence of phosphine-bearing Ru complex **17**.[11,19] In contrast, Blechert *et al*. have disclosed that with 5 mol% **2**, CM proceeds readily to afford the desired products, predominantly as their *Z* isomer, in high yields.[20] In the course of investigations in our laboratories in connection to the development of new methods for catalytic asymmetric conjugate additions of alkylzincs to enones, we observed that many of the requisite α,β-unsaturated enones can be easily accessed in >90% isolated yield through effective catalysis by 1–5 mol% **2** (Scheme 8c).[21] However, in most such cases, use of catalyst **17** led to the generation of a number of undesired products. The reaction in Scheme 8d is one of several examples reported by Cossy *et al*. in their report outlining the ability of Ru complex **2** to effect CM of various allylsilanes and unsaturated aldehydes, ketones, esters and carboxylic acids.[22] The example depicted in Scheme 8e was recently disclosed by Grimaud and coworkers. Attempted tandem enyne RCM–CM involving **18** and unsaturated ester **19** with 5 mol% **17** leads to the formation of **20** as the major product in 50% yield, the transformation does not venture beyond the initial RCM stage (exclusive generation of **20**).[23]

Since Ru-based complexes are capable of carrying out transformations other than olefin metathesis,[24] an emerging area of investigation involves the development of tandem catalytic protocols.[25] In this context, as illustrated in Scheme 9, Cossy and coworkers have shown that Ru catalyst **2** can be used to effect efficient tandem Ru-catalyzed CM–catalytic hydrogenation to access organic molecules which would otherwise have to be prepared by less efficient routes.[26] It should be noted



Scheme 9 Tandem CM–hydrogenation reactions promoted by Ru complex **2** under mild conditions.



Scheme 10 Sequential CM–enantioselective allylation involving Ru catalyst **2** used by Cossy in an efficient synthesis of a segment of amphidinol **3**. PMP = *p*-methoxyphenyl.

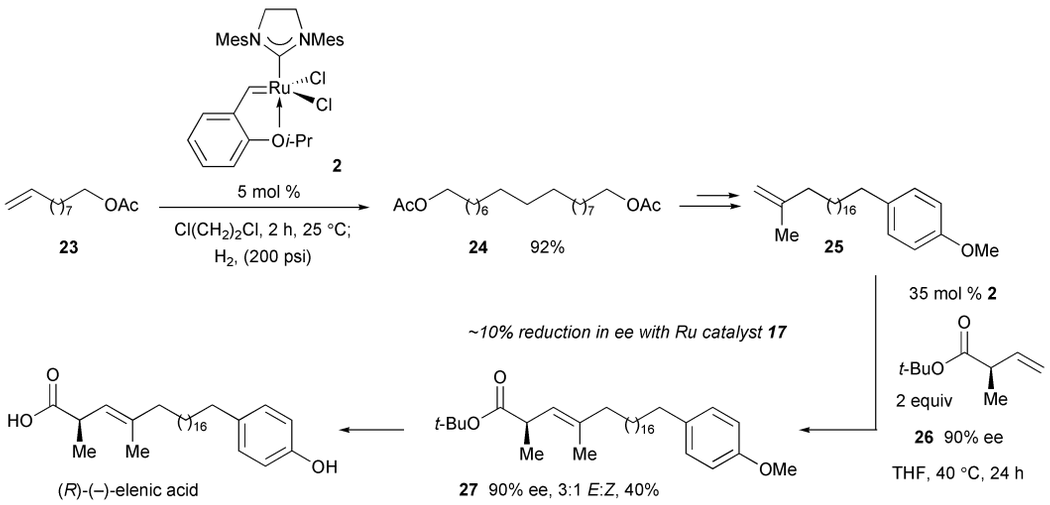
that similar tandem transformations in the presence of Ru complex **17** require more forcing conditions.

3.3.2 Utility of Ru complex 2 in synthesis of biologically active molecules. The unique ability of Ru carbene **2** as an olefin metathesis catalyst has been exploited in a number of studies directed towards syntheses of biologically active molecules. As illustrated in Scheme 10, Cossy *et al*. have utilized complex **2**, in conjunction with Ti-allyl reagent **22**, to effect two catalytic CM–allyltitanation sequences and another catalytic CM to develop a stereoselective and efficient synthesis of the C_1–C_{14} segment of amphidinol 3.[27]

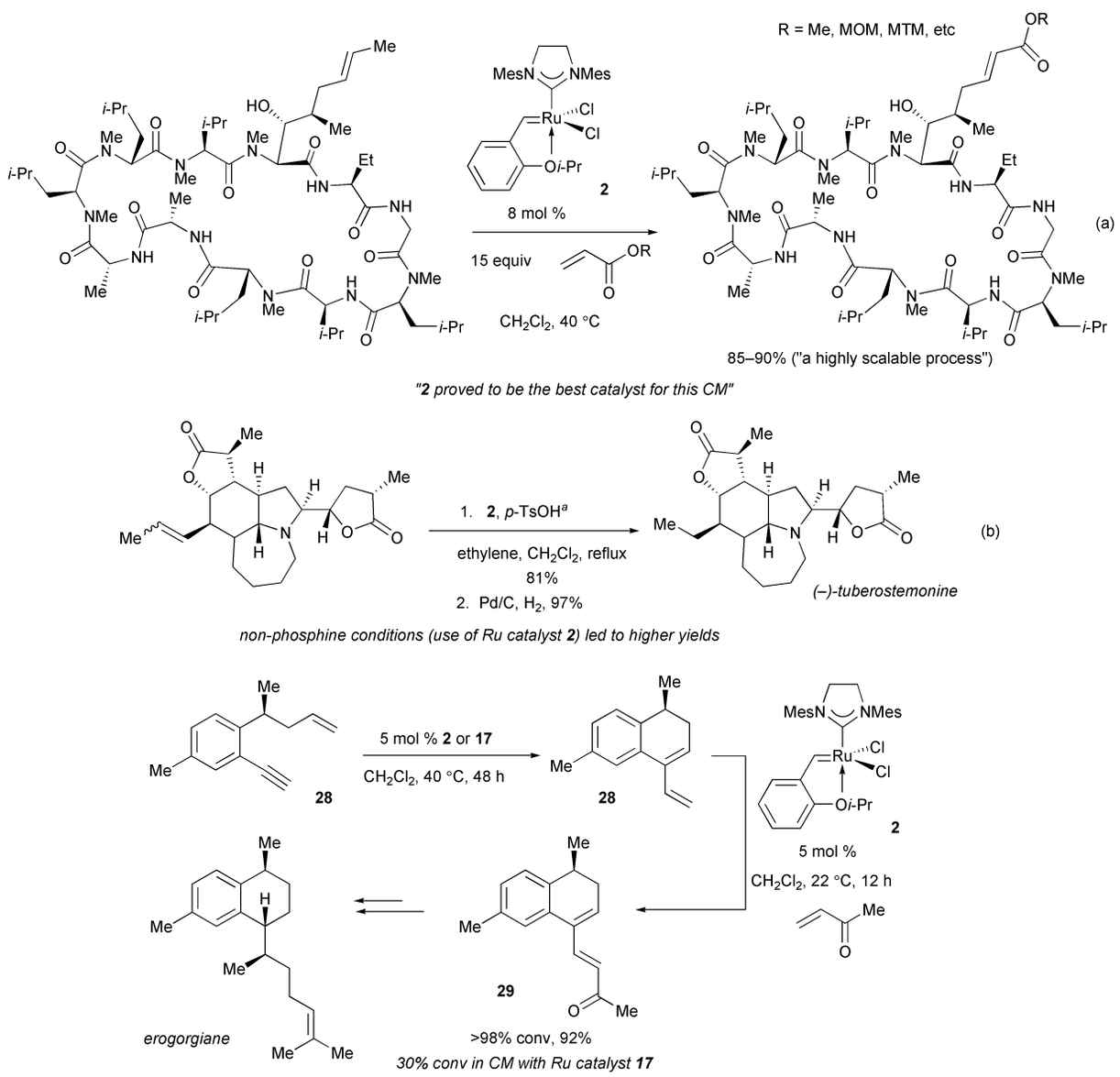
In a recent enantio- and stereoselective total synthesis of topoisomerase II inhibitor (*R*)-(−)-elenic acid, we utilized a sequential Ru-catalyzed homodimerization–hydrogenation in the presence of 5 mol% **2** to convert unsaturated acetate **23** to saturated bis(acetate) **24** (Scheme 11).[28] At a later point, CM of 1,1-disubstituted olefin **25** with optically enriched chiral terminal olefin **26** was effected with 35 mol% **2** to afford trisubstituted alkene **27** in 40% isolated yield as a 3 : 1 mixture of *E* : *Z* olefin stereoisomers. Related studies indicated that use of Ru complex **17** to effect CM with chiral terminal alkenes such as **26** can lead to ~10% reduction in optical purity. The high catalyst loading required in the synthesis of **27**, as well as the moderate stereoselectivity observed, point to the need for the development of more effective catalysts for this important class of CM reactions.[29]

Another instance where the unique catalytic activity of Ru carbene **2** is underlined is in the preparation of cyclosporin A analogues obtained through catalytic CM of the immunosuppressant with a range of other α,β-unsaturated esters (Scheme 12a). Lazarova *et al*. report that **2** "proved to be the best catalyst for this cross metathesis" reaction and that the catalytic coupling is a "highly scalable process" and delivers 85–90% yields of >95% pure products.[30] Conversion of a crotyl side chain to a desired vinyl group was reported by Wipf and coworkers to be effected in the presence of **2**, *p*-TsOH and ethylene in the context of a total synthesis of the alkaloid (−)-tuberostemonine (Scheme 12b).[31] These researchers point out that "phosphine-free conditions were important to avoid extensive chromatographic purification that led to decomposition." Interestingly, the Ru-catalyzed CM is followed by a catalytic hydrogenation. Assuming that the presence of sulfonic acid does not bear detrimental consequences, it would be intriguing to consider whether a one-pot process involving Ru-catalyzed CM–hydrogenation would be successful in this case.

The final example shown in Scheme 12 involves a sequential Ru-catalyzed enyne RCM–CM that was recently encountered in these laboratories *en route* to the total synthesis of erogorgiaene.[32] Whereas both Ru complexes **2** and **17**



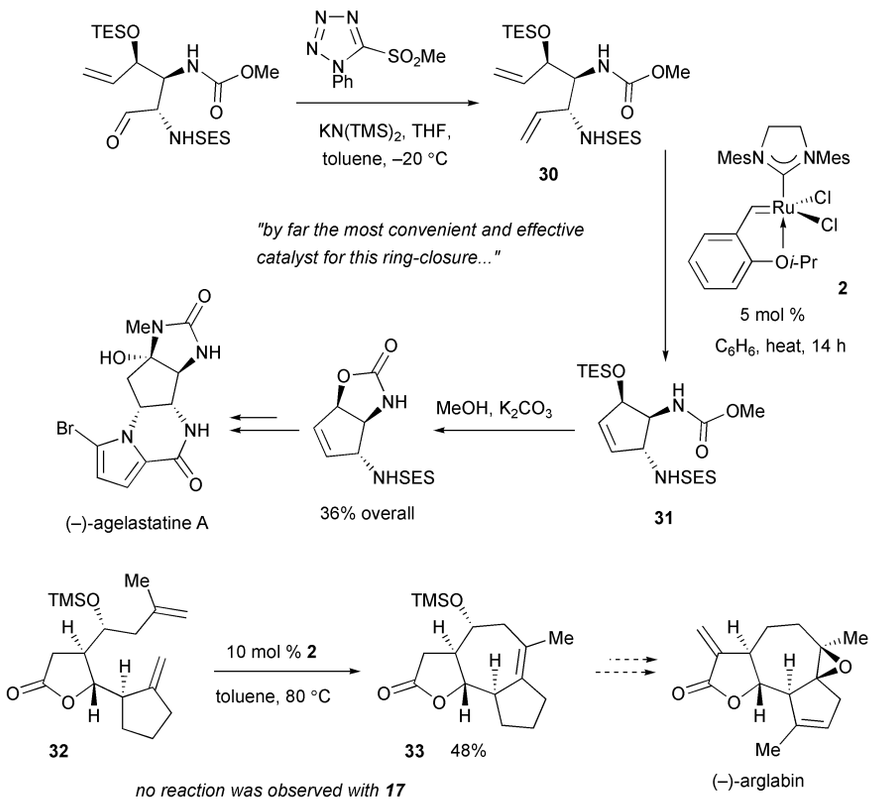
Scheme 11 Use of sequential CM–hydrogenation and another stereoselective CM catalyzed by Ru complex **2** in the enantioselective total synthesis of (*R*)-(−)-elenic acid.



Scheme 12 Additional examples of Ru catalyst **2** serving a unique role in syntheses of biologically active molecules; *a*: mol% not reported.

efficiently promote the formation of cyclic 1,3-diene **28**, it is the non-phosphine complex (**2**) that promotes the subsequent catalytic CM with methyl vinyl ketone to afford **29** (>98% conv. *vs*. 30% conv. with **17** after 12 h).

3.3.3 Utility in catalytic ring-closing metathesis (RCM) and applications to syntheses of biologically significant molecules. The unique attributes of Ru complex **2** have been demonstrated in the context of RCM processes as well. Hale and coworkers



Scheme 13 Examples of RCM reactions where Ru complex **2** uniquely provides an effective solution.

report that conversion of highly functionalized diene **30** to cyclopentenyl adduct **31**, which is an intermediate in the total synthesis of anticancer (−)-agelastatin A, is best effected in the presence of **2** (Scheme 13).[33] In another example, Reiser *et al.* have recently disclosed that the challenging catalytic RCM of diene **32** to afford polycyclic **33** can only be promoted in the presence of Ru catalyst **2**. When phosphine complex **17** was used, no reaction was observed.[34]

3.3.4 The mechanistic origin of unique catalytic activity of non-phosphine Ru catalyst 2. The origin of unique activity of Ru complex **2** may be due to the fact that it does not bear a phosphine ligand and thus, in the course of catalytic metathesis, there is no free phosphine in solution. It has been demonstrated that phosphine ligands might suppress catalyst activity in Ru-catalyzed olefin metathesis through competition for open ligation sites in the catalytically active 14-electron intermediate (**b** in Scheme 14).[19] That is, free phosphine in solution can inhibit coordination of olefins to the transition metal center by re-association with the active Ru complex (**c**⟶**b** in Scheme 14). In a similar fashion, with *non-phosphine* Ru complex **2** activation occurs through loss of O⟶Ru chelation (**2**⟶**d**, Scheme 14); however, in this case, the styrenyl ether ligand is less efficient at re-binding the active transition metal complex (**c** in Scheme 14) and, therefore, competes less effectively with olefin substrates for Ru chelation. With Ru complex **2**, efficient turnover can occur without sequestration of the active complex **b** (see Scheme 14). Such effects are likely to be pronounced in catalytic CM involving electron-deficient alkenes. With electron-withdrawing carbenes (*e.g.*, R = CN in **b** in Scheme 14), chelation of the Lewis basic PCy_3 should be more favored and catalytic activity with **17** can suffer significantly. As validated by experimental data (*cf.* Schemes 8, 11 and 12), for metathesis reactions involving potential formation of an electron-deficient carbene, a phosphine-free catalyst (*e.g.*, **2**) is best suited.[35]

Such a mechanistic proposal is supported by previous studies disclosed by Grubbs and coworkers in connection to catalytic metathesis reactions involving difluoroethylene.[36] In the above study, it is demonstrated that once an electron deficient difluoromethylidene is formed, it rapidly associates with a phosphine ligand to afford a complex that is reluctant towards reinitiation; only higher temperatures or additives (such as CuCl or HCl to promote phosphine dissociation) re-establish the activity of the difluoromethylene Ru complex.

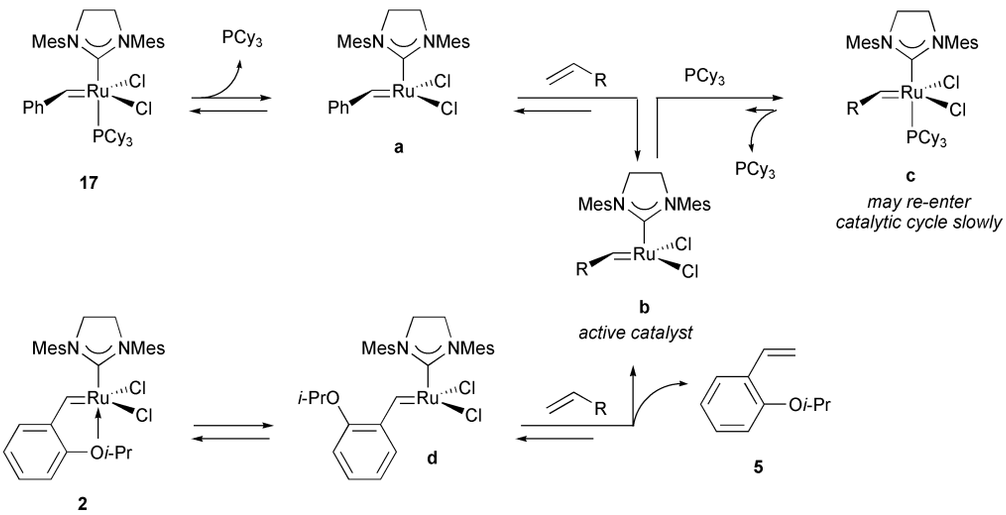
4 Supported variants of Ru-based metathesis catalysts 1 and 2

4.1 Dendritic complexes

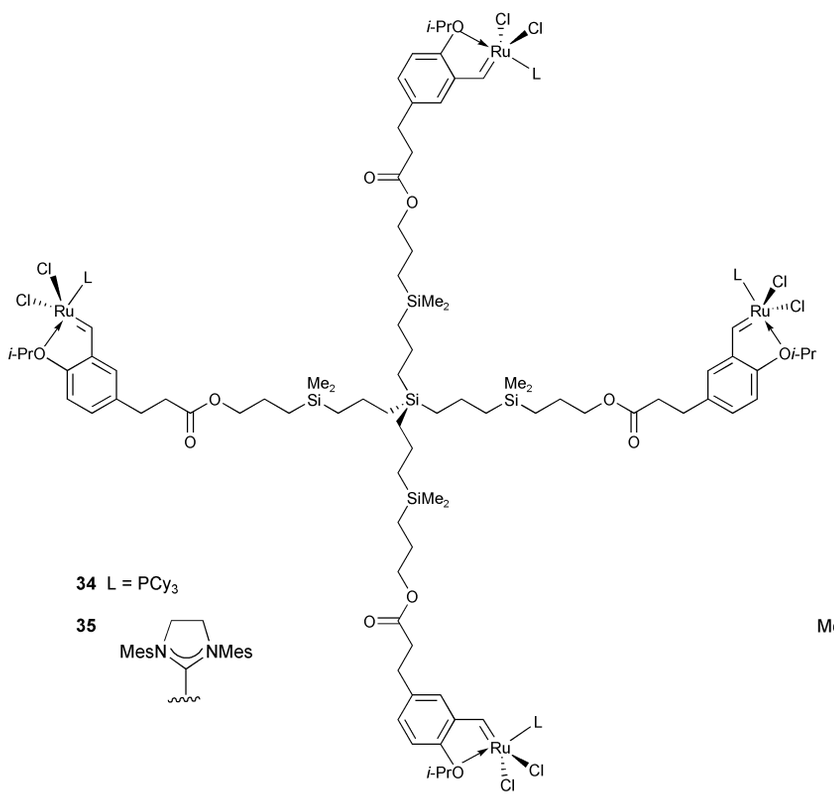
The structural robustness and synthetic utility of Ru complexes **1** and **2** suggest that their supported variants should also be of significant utility.[37] With the availability of easy-to-handle, efficient and recyclable supported Ru complexes, catalytic metathesis could be extended to preparative synthetic and combinatorial chemistry.

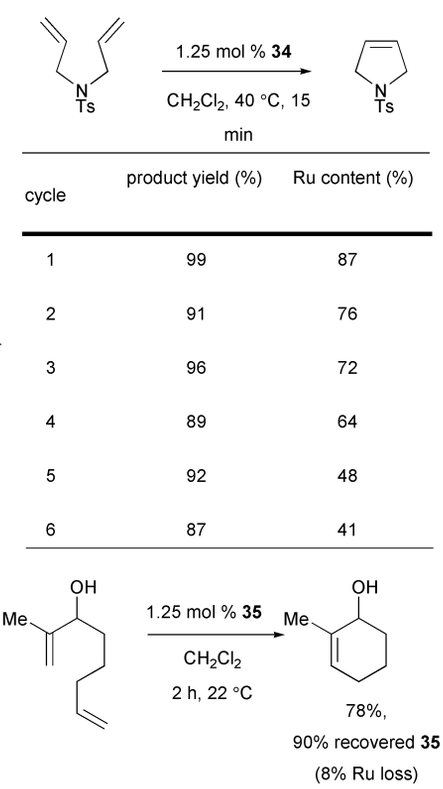
In 2000, we reported the synthesis and catalytic activity of Ru-based dendrimers **34** and **35**.[12] We initiated our studies of supported metathesis catalysts with dendritic systems because of their ease of characterization and the high level of certainty with which metal-containing sites can be introduced at their periphery. With a catalyst based on these small branching polymers, it would be possible to gauge rigorously the efficiency with which the active metal carbene leaves the ligation site and returns to the macromolecule (*cf.* Scheme 6).

The high solubility of dendrimers **34** and **35** in organic solvents permitted full analysis by NMR spectroscopy and high-resolution mass spectrometry. Multi-component catalyst **34** exhibits activity similar to monomeric **1**. Furthermore, product isolation is simple: the reaction mixture is passed through a short silica gel column. Subsequent washing of silica gel led to quantitative recovery of the dendritic catalyst. Our studies indicate that, after one representative Ru-catalyzed RCM (see Scheme 15), 13% of the styrene ligands on the dendrimer become vacant – presumably due to Ru complex decomposition (^{1}H NMR analysis). Repeated use of recycled **34**, in spite of this steady Ru loss per reaction, promoted facile RCM and the desired product was isolated in >86% yield. The dendritic



Scheme 14 The absence of a phosphine ligand in Ru catalyst **2** avoids formation of complexes such as **c** (formed when **17** is used) which may not be able to re-enter the catalytic cycle readily.





cycle	product yield (%)	Ru content (%)
1	99	87
2	91	76
3	96	72
4	89	64
5	92	48
6	87	41

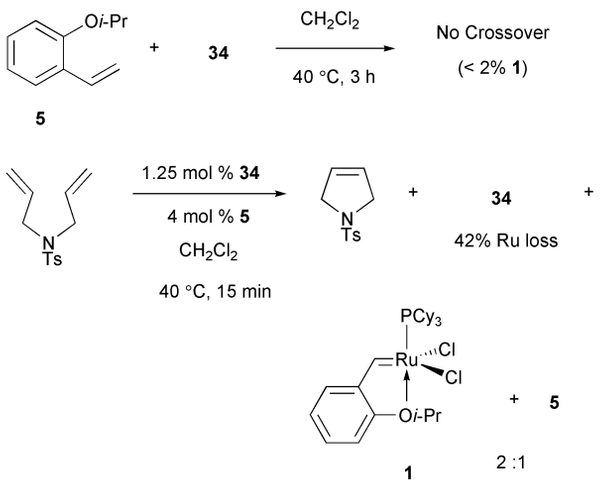
Scheme 15 Dendritic variants of Ru complexes **1** and **2** and their activity as olefin metathesis catalysts.

complex remained active even after 50% of its sites were depleted of Ru (see cycle 6, Scheme 15). This high level of reactivity suggests the intermediacy of a coordinatively unsaturated, monophosphine carbene (**15**, Scheme 6). As expected, non-phosphine dendrimer **35** exhibited higher levels of activity (see Scheme 14); as an example, the formation of the cyclohexenyl allylic alcohol proved significantly slower in the presence of **34**. Attempts to avoid chromatography and recycle the dendrimers **34** and **35** by precipitation in the presence of a variety of solvents proved unsuccessful.

The recycling experiments shown in Scheme 15 indicate that substantial turnover can accompany minor amounts of Ru release. At this point, the question arises as to whether any of the released Ru carbene ever returns to the styrene ether site. Our efforts to address this issue were facilitated by a minor chemical shift difference for the carbene proton signals of **1** and **34**; this allowed us to determine the amount of Ru bound to dendritic *versus* monomeric styrene ligands by integration of the appropriate downfield signals in the ^{1}H NMR spectrum of a mixture.[12] In a control reaction, as illustrated in Scheme 16, we established that prolonged treatment of **34** with 2-isopropoxystyrene (**5**) results in <2% metal crossover. However, repetition in the presence of an olefin substrate results in RCM and statistically-driven scrambling of the transition metal between monomeric and dendritic ligation sites within 15 minutes. These results imply that the Ru center, after reacting with a substrate alkene and leaving the dendrimer, can be trapped again by a styrene ether. These findings further suggest that a significant portion of the available metal initiates the moment a metathesis reaction begins, providing direct evidence for the 'release/return' mode of action (Scheme 6).

4.2 Polymer-supported variants of Ru complex 1

Two polymer-supported versions of monophosphine Ru complex **1** have been prepared. PEG-supported catalyst **36** has been



Scheme 16 Experiments regarding return of Ru carbenes to dendrimer surface.

reported by Yao.[38] The choice of PEG as the carrier is noteworthy in Yao's system, as it permits catalysis under standard homogeneous conditions and enables easy recovery of the catalyst by precipitation and filtration. Supported catalyst **36** effectively promotes RCM of terminal olefins, including medium ring structures. Precipitation, filtration, and re-use of the recovered catalyst gives high conversion in a second round of metathesis. In fact, there was little or no loss in activity after eight runs of recycling. All operations, including concentration of the reaction mixture, precipitation, filtration, and washing with reagent-grade diethyl ether can be carried out in air.

Dowden and Savovic[39] have disclosed a complementary strategy based on a subtle change in the site of polymer attachment. With Ru complex **1** again serving as a model, these workers manipulated the isopropyl portion of the styrene ether as a covalent linker unit to prepare **37**. Polymer-supported catalyst **37** readily promoted RCM reactions of monosubstituted olefins; general laboratory-grade methylene chloride was used without degassing in air. Catalytic metatheses were performed by addition of substrate solutions to the resin in a solid plastic tube fitted with a glass frit which was then sealed and subjected to 360° rotation. Filtration and washing with methylene chloride directly afforded the product and recovered catalyst. Good yields were reported in certain cases when the catalyst was recycled over five runs; however, a decreased catalyst loading of 1.5 mol% resulted in less effective recycling.

More recently, Yao and Zhang have reported a variant of Ru catalyst **1** that bears an ionic tag (**38**, Fig. 6).[40] Complex **38** promotes RCM of dienes in ionic liquid [Bmim]PF_6 and CH_2Cl_2 (1 : 9 v/v) to afford cyclic disubstituted cyclic alkenes. The catalyst can be recycled. In one instance, ten cycles of RCM required an equal length of time (3 h) to generate an unsaturated seven-membered ring amide. Nevertheless, in another case, reactivity is diminished significantly after two cycles. Reactions seem to require elevated temperatures (55 °C) and are run under Ar; moreover, multiple washes with Et_2O are used to obtain the product. Such factors detract from this interesting system, particularly when its use in a library synthesis and in large scale preparations are being considered.

4.3 Polymer-supported variants of Ru complex 2

We have reported a procedure for the surface derivatization of small glass (sol-gel)[41] pellets and applied this procedure to the synthesis of supported Ru catalysts (Scheme 17, **39**⟶**41**).[42] Accordingly, treatment of **39** with allylchlorodimethylsilane and a full equivalent of Ru complex **17** led to rapid ROM/CM and metallation of the styrenyl ether (⟶**40**). Pre-weighed monolithic (smallest dimension ≥ 1 mm) sol-gels were then

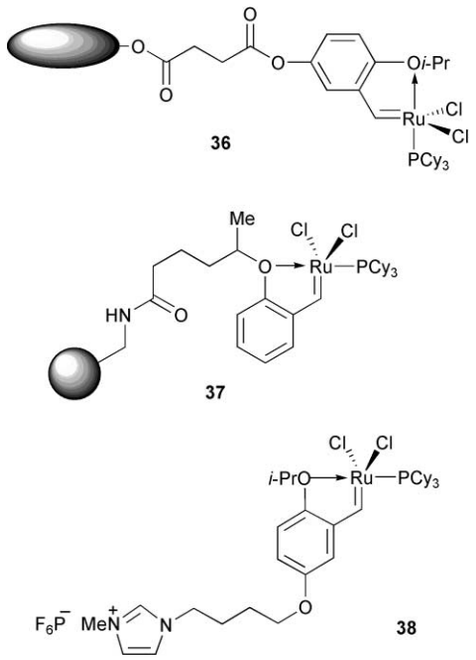
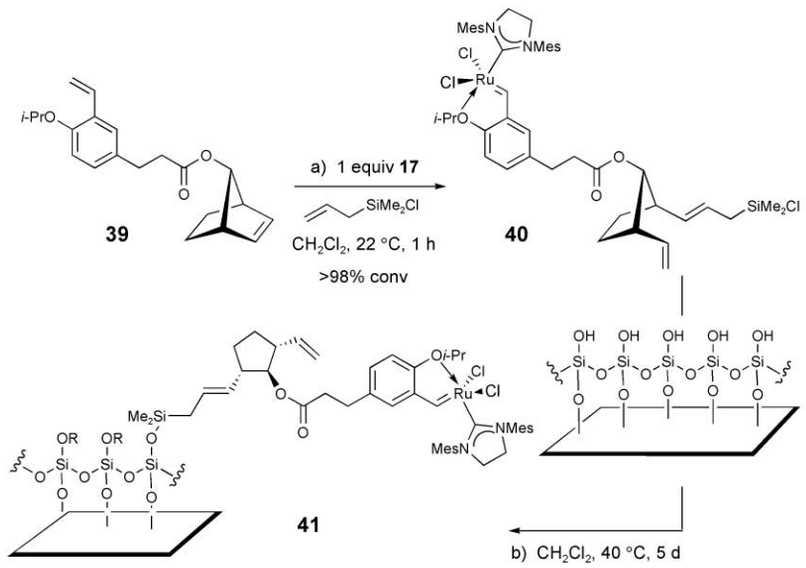


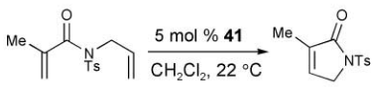
Fig. 6 Supported variants of Ru catalyst **1**.

added to the solution, and substitution of the labile Si–Cl bond in **40** with free hydroxyl groups on the glass surface anchored the catalyst to the support, affording dark green glass pellets (**41**). Sol-gel glass was selected for catalyst support for several reasons: (1) These porous glasses retain a rigid and exposed interfacial surface area (typically 300–1000 $m^2\ g^{-1}$), whereas organic polymer beads swell and shrink in different solvents, often with unpredictable effects on catalysis. (2) Functionalization of a monolithic (smallest dimension ≥ 1 mm) gel affords a bulk catalyst sample; this obviates the need for filtration to recover the catalyst – tweezers can be used instead. (3) Gelation occurs after a sol is cast into a mold. The glass pieces can therefore be tailored to a uniform size or shape.

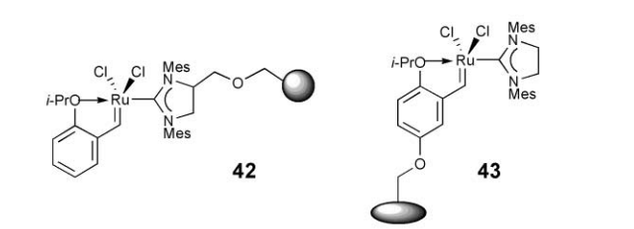
Sol-gel-supported Ru complex **41** proved to be a remarkably efficient and recyclable catalyst. With purified solvent under N_2, as illustrated in Scheme 17, catalyst **41** was used in the synthesis of a trisubstituted olefin for a total of twenty cycles. Moreover, the glass-bound Ru complexes were used to effect synthesis of two small libraries through catalytic RCM (6 hours at 22 °C under air with reagent-grade methylene chloride). For reactions that proceeded to completion and delivered a single product, representative elemental (C,H) and ICP-MS analyses showed that the products – without purification or workup – were of high (often analytical) purity and the level of Ru contamination was typically <1%.

Synthesis and catalytic activity of supported Ru catalysts **42** and **43**[43] (Scheme 17) have been reported by Blechert *et. al*. One significant difference between these two complexes is that with **42**, the Ru carbene remains bound to the support, whereas in the case of **43**, similar to glass-supported **41**, the metal carbene is likely released into solution. Both catalysts effect RCM reactions effectively; re-use up to four cycles is reported, although reaction times have not been provided in all cases. Studies regarding CM revealed notable differences in catalyst efficiencies. As the representative data in Scheme 17 illustrate, complex **43** displays enhanced activity in the reaction of a terminal olefin of a β,γ-unsaturated ester with a variety of electron-deficient partners. Although **42** and **43** are bound to distinct polymer supports, making a direct comparison difficult, the higher activity of **42** is likely a function of its ability to release the active complex. Since the propagating carbene from **43** remains bound to support, diffusion of reacting alkenes into the cavities of the polymer is rate-limiting – especially with the more challenging CM reactions.





cycle (time)	conv (%); yield (%)
cycle 1 (3 h)	>98; >98
cycle 2 (3 h)	>98; >98
cycle 3 (3 h)	>98; >98
cycle 4 (3 h)	>98; >98
cycle 5 (5 h)	>98; >98
cycle 6 (6 h)	>98; >98
cycle 7 (6 h)	>98; >98
cycle 8 (7 h)	>98; >98
cycle 9 (8 h)	>98; >98
cycle 10 (8 h)	>98; >98
cycle 11 (9 h)	>98; >98
cycle 12 (10 h)	>98; >98
cycle 13 (12 h)	>98; >98
cycle 14 (14 h)	>98; >98
cycle 15 (14 h)	>98; >98
cycle 16 (16 h)	>98; >98
cycle 17 (18 h)	>98; >98
cycle 18 (20 h)	>98; >98
cycle 19 (22 h)	>98; >98
cycle 20 (24 h)	>98; >98



entry	EWG	% conv with **42**	% conv with **43**
1	CN	15	98
2	$COCH_3$	68	97
3	CO_2CH_3	96	97
4	$CON(CH_3)_2$	42	40
5	CONH*i*Pr	–	96
6	CHO	–	86

Scheme 17 Several early examples of supported variants of Ru complex **2** and representative reactivity data.

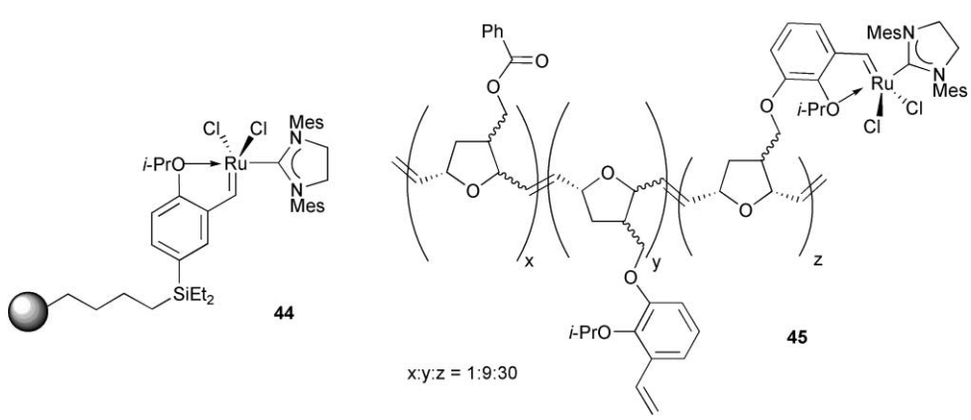
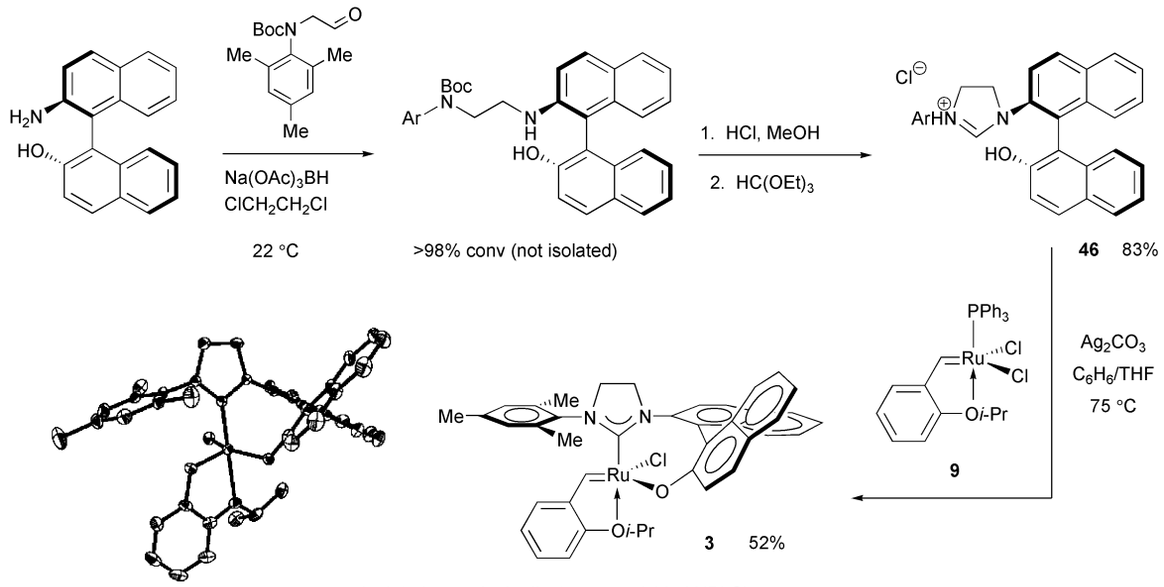


Fig. 7 More recent supported variants of Ru complex **2**.

Grela *et al*. have reported the synthesis and catalytic activity of the polystyrene-supported Ru complex **44** (Fig. 7).[44] The catalyst shows high activity, as it readily promotes RCM to afford trisubstituted olefins. Relevant examples involving syntheses of medium and large ring structures are provided; moreover, complex **44** can be recycled, although by the fifth cycle significantly longer reaction times seem to be required. Blechert and coworkers recently disclosed the synthesis and catalytic activity of polymeric Ru-based catalyst **45** (Fig. 7).[45] Attractive features of complex **45** include ease of synthesis and low levels of Ru impurity detected in product mixtures, suggesting that small amounts of highly active Ru carbenes are released upon exposure to substrate molecules. However, in spite of the presence of the imidazolinium ligand only reactions of terminal alkenes leading to disubstituted olefins are reported, and in one recycling study (involving formation of a disubstituted cyclic



Isolated as a single diastereomer (chiral HPLC)

Purified by silica gel chromatography

Scheme 18 Synthesis and X-ray structure of non-phosphine Ru-based chiral metathesis catalyst **3**.

amide), the catalyst loses significant activity after the seventh cycle.

5 Chiral non-phosphine Ru-based catalysts for enantioselective olefin metathesis

A critical objective in the field of catalytic olefin metathesis relates to the design and development of *chiral* versions of this class of catalysts that can be utilized in *enantioselective* olefin metathesis.[46] With the availability of such chiral complexes, a variety of optically pure compounds become accessible in an efficient and practical manner. It was within this context that in 2002, we reported the synthesis, structure and reactivity of a chiral non-phosphine Ru carbene **3**.[47,48]

5.1 Synthesis of the first generation chiral Ru complex

Optically pure **3** was synthesized as shown in Scheme 18; all reactions were performed on gram scales. The critical step is the conversion of **46** to **3**. After extensive experimentation, we established that in the presence of silver carbonate and the catalytically inactive Ru complex **9**, the desired complex **3** is formed in 52% isolated yield. The optically pure non-phosphine complex **3**, bearing a stereogenic Ru center, was isolated as a single diastereomer.[49] Ru complex **3** is air-stable, can be purified by silica gel chromatography with undistilled solvents and its diastereo- and enantiomeric purity was established by HPLC analysis (isolated in >98% de and ee).

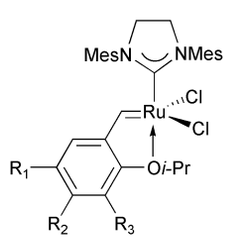
5.2 Utility in asymmetric ring-opening/cross metathesis (AROM/CM)

Chiral Ru catalyst **3** promotes asymmetric ring-opening/cross metathesis (AROM/CM)[50] in air, with undistilled solvents and with substrates that readily polymerize with chiral Mo catalysts (Scheme 19).[51] Complex **3** can be recovered after chromatography (86–71% yield) and can be re-used without significant loss of enantioselectivity and reactivity. The catalytic AROM/CM in Scheme 19 demonstrate the synthetic potential of chiral Ru catalysts. Enantioselective metatheses can be promoted efficiently and enantioselectively, with as low as 0.5 mol% catalyst loading, at room temperature, in air and with undistilled and non-degassed solvent. Even reactions run at 50 °C can be run in air without significant reduction in reactivity or selectivity.

5.3 Second generation chiral Ru complexes: higher reactivity and expanded scope

In spite of the promising levels of selectivity observed in catalytic reactions of **3**, this chiral catalyst proved to be less reactive than its achiral analogue **2**, probably as a result of steric (large chiral ligand) and electronic factors (an aryloxide *vs*. a Cl group).[52] To access more active catalysts, we have most recently prepared several new optically pure Ru carbenes **3a**–**3f** (Scheme 20) through modifications of the benzylidene and chiral ligands in **3**.[53] Chiral catalyst **3a**, bearing the electron-withdrawing NO_2 (*para* to the ligating O*i*-Pr) was investigated based on the expectation that the nitro substituent would weaken *i*-PrO⟶Ru chelation and facilitate initiation of the catalytic cycle. A similar influence was expected from the electron-releasing OMe (*para* to the Ru=C bond) in **3c**, where increased electron donation into the metal center would reduce its Lewis acidity. The above hypotheses were based on reports by Grela *et al*. regarding the catalytic activity of achiral **2a**[54] and **2b** (Fig. 8).[55] The validity of such proposals in relation to chiral Ru complexes would be further substantiated if **3b** proved to be significantly less active than **3**. Complex **3d** was investigated to establish whether a recent observation regarding higher activity of its corresponding achiral analogue **2c** (Fig. 8) pertains to the present class of chiral Ru catalysts.[56] Enantiomerically pure Ru carbenes **3e** and **3f** were prepared to determine the influence of reduced electron donation to the Ru center by the aryloxide oxygen on catalytic activity.[57]

Study of catalytic activity of the modified chiral Ru complexes shown in Scheme 20 led us to establish that catalysts **3d**

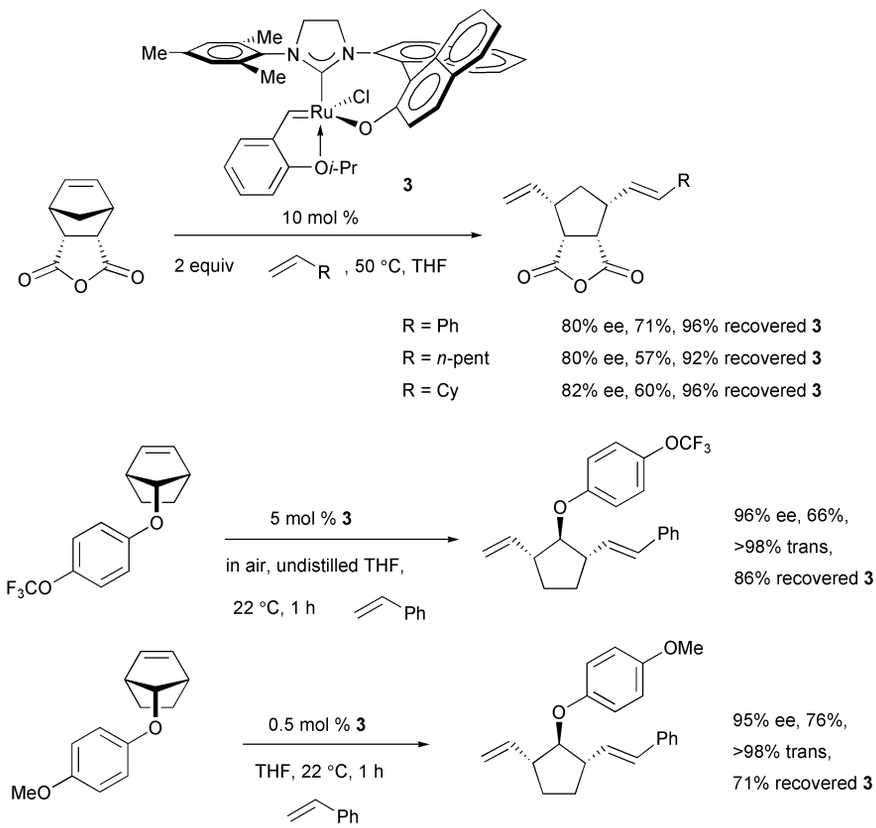


2a $R_1 = NO_2$, R_2, R_3 = H

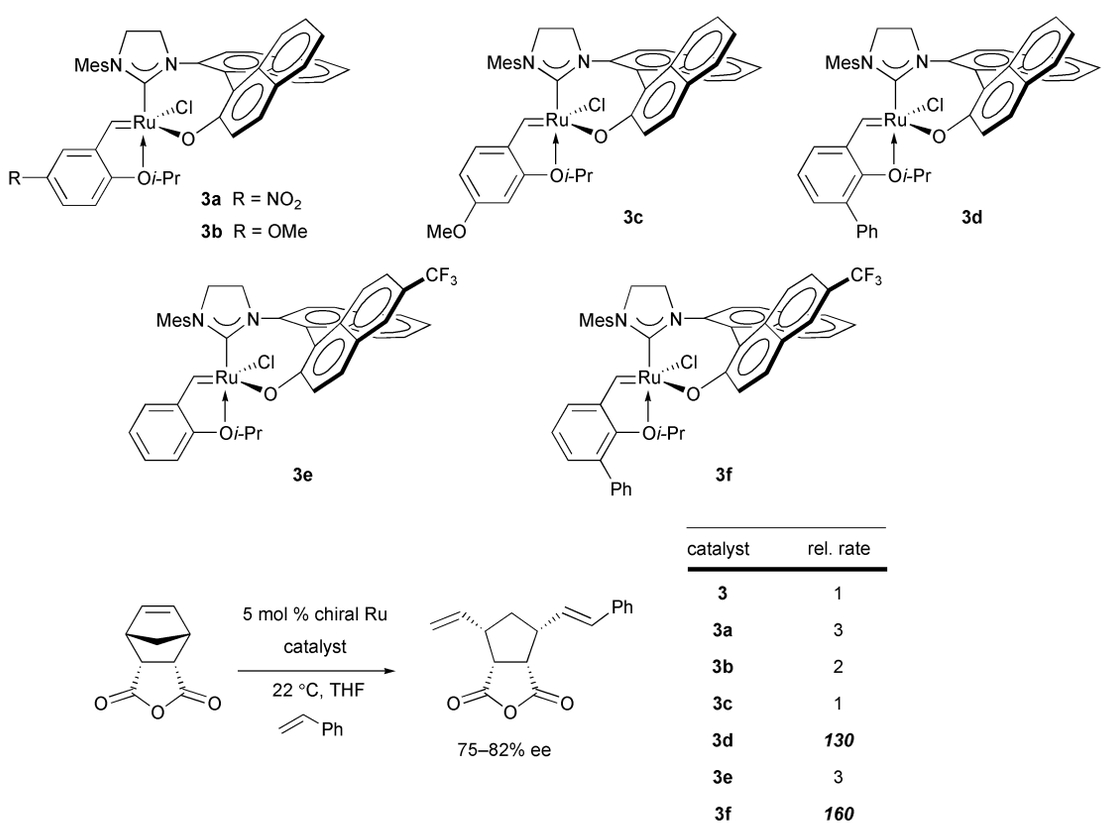
2b R_1, R_2 = OMe, R_3 = H

2c R_1, R_2 = H, R_3 = Ph

Fig. 8 Modified versions of Ru complex **2**.



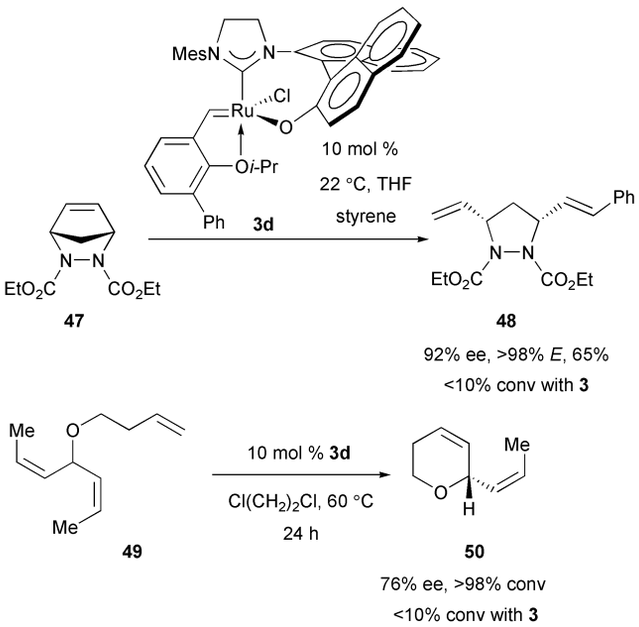
Scheme 19 AROM/CM promoted by Ru-based chiral metathesis catalyst **3**.



Scheme 20 Steric and electronic modifications of chiral Ru complex **3** leads to significantly more reactive catalysts **3d** and **3f**.

and **3f** exhibit reactivity levels that are *more than two orders of magnitude higher than 3*. The relative rate data shown in Scheme 20 are illustrative.

The availability of the more effective chiral complexes has led to new possibilities in catalytic asymmetric olefin metathesis. Two examples are shown in Scheme 21. Whereas Ru-catalyzed AROM/CM of **47** leads to <10% conversion with **3** (and likely results in rapid polymerization with chiral Mo catalysts),[58] in the presence of 10 mol% **3d**, diamide **48a** is generated in 92% ee and 65% isolated yield. Reaction of triene **49** cannot be promoted in the presence of chiral Ru complex **3**. However, in the presence of 10 mol% **3d**, asymmetric RCM



Scheme 21 Representative Ru-catalyzed enantioselective olefin metathesis reactions made possible by the more reactive complex **3d**.

proceeds to >98% conversion to afford **50** in 76% ee. It should be noted that, thus far, chiral Mo-based catalysts are able to promote enantioselective RCM more effectively than either available class of chiral Ru catalysts;[46,59] on the other hand, reactions with **3** or **3d** can be carried out in air and with undistilled solvents.

6 Conclusion and perspectives

The discovery of Ru complex **1** in 1996 and subsequent synthesis and investigation of the catalytic activity of non-phosphine catalyst **2** has yielded a class of user-friendly and practical olefin metathesis catalysts that offer unique levels of reactivity and selectivity. Of particular significance is the absence of a phosphine ligand in complex **2**, an attribute that is largely responsible for its signature reactivity profile. Another important chracteristic, shared by Ru catalysts represented by **1**–**3**, is the presence of an aryl ether ligating group which, not only provides a convenient handle for attachment of the transition metal complex to various solid supports but also allows for facile steric and electronic modifications of the catalyst structure. Increasingly effective achiral and chiral catalysts and their supported versions thus continue to be developed that are based on the structural platforms provided by complexes **1** and **2**. Representative examples provided in this article indicate that the community of synthetic chemists is becoming increasingly aware of the special activity of this class of Ru catalysts. Furthermore, indications are beginning to appear in the literature that the field of polymer chemistry may soon follow suit.[60]

A number of critical issues remain to be addressed, despite the advances made in the past several years. Design, synthesis and development of more effective chiral Ru-based catalysts that promote a wider range of ring-closing, ring-opening or cross metathesis reactions should probably be placed at the top of this priority list. Although significant strides have been taken in enhancing the catalytic activity of Ru-based complexes, 1–10 mol% loadings are still required for efficient catalysis. Such conditions may be acceptable in small scale laboratory experiments but present a notable economic challenge in large scale synthesis. Judging from the remarkable developments of the recent past, it is likely that many more exciting and important advances will be forthcoming in this important area.

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References

1 For reviews on catalytic olefin metathesis, see: (*a*) R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446–452; (*b*) H-G. Schmalz, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1833–1836; (*c*) M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036–2056; (*d*) *Alkene Metathesis in Organic Synthesis*, ed. A. Furstner, Springer, Berlin, 1998; (*e*) S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371–388; (*f*) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450; (*g*) A. J. Phillips and A. D. Abell, *Aldrichimica Acta*, 1999, **32**, 75–90; (*h*) A. Furstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012–3043; (*i*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29; (*j*) R. R. Schrock and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2003, **42**, 4592–4633.

2 J. P. A. Harrity, M. S. Visser, J. D. Gleason and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1997, **119**, 1488–1489.

3 J. P. A. Harrity, D. S. La, D. R. Cefalo, M. S. Visser and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1998, **120**, 2343–2351.

4 (*a*) P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039–2041; (*b*) P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100–110.

5 (*a*) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875–3886; (*b*) G. C. Bazan, R. R. Schrock, H-N. Cho and V. C. Gibson, *Macromolecules*, 1991, **24**, 4495–4502.

6 C. W. Johannes, M. S. Visser, G. S. Weatherhead and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1998, **120**, 8340–8347.

7 The first example of a catalytically active mono-phosphine Ru complex was reported by Snapper and coworkers: J. A. Tallarico, P. J. Bonitatebus and M. L. Snapper, *J. Am. Chem. Soc.*, 1997, **119**, 7157–7158.

8 J. S. Kingsbury, J. P. A. Harrity and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 791–799.

9 E. L. Dias and R. H. Grubbs, *Organometallics*, 1998, **17**, 2758–2767.

10 For application of the release/return mechanism to the design of a supported Ru catalyst. see: M. Ahmed, A. G. M. Barrett, D. C. Braddock, S. M. Cramp and P. A. Procopiou, *Tetrahedron Lett.*, 1999, **40**, 8657–8662.

11 E. L. Dias, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1997, **119**, 3887–3897.

12 S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168–8179.

13 (*a*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956; (*b*) A. K. Chatterjee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 1751–1753.

14 (*a*) T. Weskamp, W. C. Schattenmann, M. Spiegler and W. A. Hermann, *Angew. Chem., Int. Ed.*, 1998, **37**, 2490–2493; (*b*) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich and W. A. Hermmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 2416–2419; (*c*) M. Scholl, T. M. Trnka, J. P. Morgan and R. H. Grubbs, *Tetrahedron Lett.*, 1999, **40**, 2247–2250; (*d*) J. Huang, E. D. Stevens, S. P. Nolan and J. L. Petersen, *J. Am. Chem. Soc.*, 1999, **121**, 2647–2678; (*e*) L. Ackermann, A. Furstner, T. Weskamp, F. J. Kohl and W. A. Hermann, *Tetrahedron Lett.*, 1999, **40**, 4787–4790; (*f*) A. Furstner, O. R. Thiel, L. Ackermann, H-J. Schanz and S. P. Nolan, *J. Org. Chem.*, 2000, **65**, 2204–2207.

15 For reviews of nucleophilic carbenes, see: (*a*) M. Regitz, *Angew. Chem., Int. Ed.*, 1996, **35**, 725–728; (*b*) W. A. Herrmann and C. Kocher, *Angew. Chem., Int. Ed.*, 1997, **36**, 2162–2187; (*c*) A. J. Arduengo and R. Krafczyk, *Chem. Z.*, 1998, **32**, 6–14; (*d*) A. J. Arduengo, *Acc. Chem. Res.*, 1999, **32**, 913–921.

16 For a report on the accelerating effect of an α-hydroxyl group on Ru-catalyzed RCM reactions, see: T. R. Hoye and H. Zhao, *Org. Lett.*, 1999, **1**, 1123–1125.

17 For examples where **2** and **17** are reported to exhibit similar levels of efficiency (involving cross metathesis reactions), see: (*a*) A. J. Geissert, L. Snyder, J. Markham and S. T. Diver, *Org. Lett.*, 2003, **5**, 1793–1796; (*b*) O. M. Demchuk, K. M. Pietrusiewicz, A. Michrowska and K. Grela, *Org. Lett.*, 2003, **5**, 3217–3220.

18 (*a*) S. BouzBouz and J. Cossy, *Org. Lett.*, 2001, **3**, 1451–1454; (*b*) J. Cossy, S. BouzBouz and A. H. Hoveyda, *J. Organomet. Chem.*, 2001, **624**, 327–332.

19 M. S. Sanford, J. A. Love and R. H. Grubbs, *J. Am.Chem. Soc.*, 2001, **123**, 6543–6554.
20 (*a*) S. Imhof, S Randl and S. Blechert, *Chem. Commun.*, 2001, 1692–1693; (*b*) S. Randl, S. Gessler, H. Wakamatsu and S. Blechert, *Synlett*, 2001, 430–432; (*c*) S. Randl, S. J. Connon and S. Blechert, *Chem. Commun.*, 2001, 1796–1797; (*d*) S. Gessler, S. Randl and S. Blechert, *Tetrahedron Lett.*, 2000, **41**, 9973–9976.
21 H. Mizutani, S. J. Degrado and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2001, **123**, 779–780.
22 S. BouzBouz, E. De Lemos and J. Cossy, *Adv. Synth. Catal.*, 2002, **344**, 627–630.
23 F. Royer, C. Vilain, L. Ekraim and L. Grimaud, *Org. Lett.*, 2003, **5**, 2007–2009.
24 (*a*) T. Naota, H. Takaya and S-I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599–2660; (*b*) B. M. Trost, F. D. Toste and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067–2096.
25 For other Ru-catalyzed tandem protocols, where one of the transformations is an olefin metathesis, see: (*a*) C. W. Bielawski, J. Louie and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 12872–12873; (*b*) A. E. Sutton, B. A. Seigal, D. F. Finnegan and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 13390–13391; (*c*) C. Cadot, P. Dalko and J. Cossy, *Tetrahedron Lett.*, 2002, **43**, 1839–1841; (*d*) M. Arisawa, Y. Terada, M. Nakagawa and A. Nishida, *Angew. Chem., Int. Ed.*, 2002, **41**, 4732–4734.
26 (*a*) J. Cossy, F. C. Bargiggia and S. BouzBouz, *Tetrahedron Lett.*, 2002, **43**, 6715–6717; (*b*) J. Cossy, F. Bargiggia and S. BouzBouz, *Org. Lett.*, 2003, **5**, 459–462.
27 (*a*) S. BouzBouz and J. Cossy, *Org. Lett.*, 2001, **3**, 1451–1454; (*b*) J. Cossy, S. BouzBouz, F. Pradaux, C. Willis and V. Bellosta, *Synlett*, 2002, 1595–1606.
28 K. E. Murphy and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 4690–4691.
29 For recent key reports and reviews regarding catalytic CM reactions, see: (*a*) H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 58–71; (*b*) A. K. Chatterjee, T-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370; S. J. Cannon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900–1923.
30 T. Lazarova, J. S. Chen, B. Hamann, J. M. Kang, D. Homuth-Trombino, F. Han, E. Hoffmann, C. McClure, J. Eckstein and Y. S. Or, *J. Med. Chem.*, 2003, **46**, 674–676.
31 P. Wipf, S. R. Rector and H. Takahashi, *J. Am. Chem. Soc.*, 2002, **124**, 14848–14849.
32 R. R. Cesati, J. de Armas and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, in press.
33 K. J. Hale, M. M. Domostoj, D. A. Tocher, E. Irving and F. Scheinmann, *Org. Lett.*, 2003, **5**, 2927–2930.
34 B. Nosse, R. B. Chhor, W. B. Jeong, C. Bohm and O. Reiser, *Org. Lett.*, 2003, **5**, 941–944.
35 For a more recent non-phosphine Ru-based metathesis catalyst and discussion of related mechanistic issues, see: J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2002, **41**, 4035–4037.
36 T. M. Trnka, M. W. Day and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2001, **40**, 3441–3444.
37 For a comprehensive review of supported catalysts for olefin metathesis, see: J. S. Kingsbury, A. H. Hoveyda, in *Polymeric Materials in Organic Synthesis and Catalysis*, ed. M. R. Buchmeiser, Wiley-VCH, Weinheim, 2003, pp. 467–502.
38 Q. Yao, *Angew. Chem., Int. Ed.*, 2000, **39**, 3896–3898.
39 J. Dowden and J. Savovic, *Chem. Commun.*, 2001, 37–38.
40 Q. Yao and Y. Zhang, *Angew. Chem., Int. Ed.*, 2003, **42**, 3395–3398.
41 Sol-Gel Science: The Physics and Chemistry of Sol-Gel Processing, C. J. Brinkler and G. W. Scherer, Academic Press, San Diego, CA, 1990.
42 J. S. Kingsbury, S. B. Garber, J. M. Giftos, B. L. Gray, M. M. Okamoto, R. A. Farrer, J. T. Fourkas and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2001, **40**, 4251–4256.
43 S. Randl, N. Buschmann, S. J. Connon and S. Blechert, *Synlett*, 2001, 1547–1550.
44 K. Grela, M. Tryznowski and M. Bieniek, *Tetrahedron Lett.*, 2002, **43**, 9055–9059.
45 S. J. Connon, A. M. Dunne and S. Blechert, *Angew. Chem., Int. Ed.*, 2002, **41**, 3835–3838.
46 For reviews of Mo-catalyzed enantioselective olefin metathesis, see: (*a*) A. H. Hoveyda and R. R. Schrock, *Chem. Eur. J.*, 2001, **7**, 945–950; (*b*) R. R. Schrock and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2003, **42**, 4592–4633.
47 J. J. VanVeldhuizen, S. B. Garber, J. S. Kingsbury and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2002, **124**, 4954–4955.
48 For an alternative chiral Ru-based metathesis catalyst, see: T. J. Seiders, D. W. Ward and R. H. Grubbs, *Org. Lett.*, 2001, **3**, 3225–3228.
49 For a review of complexes chiral at the metal, see: H. Brunner, *Angew. Chem., Int. Ed.*, 1999, **38**, 1194–1208.
50 For an example regarding the utility of achiral non-phosphine complex **2** in ROM/CM, see: B. H. White and M. L. Snapper, *J. Am. Chem. Soc.*, 2003, **125**, in press.
51 (*a*) D. S. La, J. G. Ford, E. S. Sattely, J. P. Bonitatebus, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 11603–11604; (*b*) D. S. La, E. S. Sattely, J. G. Ford, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2001, **123**, 7767–7778.
52 For a related case, see: S. Chang, L. Jones, C. Wang, L. M. Henling and R. H. Grubbs, *Organometallics*, 1998, **17**, 3460–3465.
53 J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Kataoka and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 12502–12508.
54 K. Grela, S. Harutyunyan and A. Michrowska, *Angew. Chem., Int. Ed.*, 2002, **41**, 4038–4040.
55 K. Grela and M. Kim, *Eur. J. Org. Chem.*, 2003, 963–966.
56 H. Wakamatsu and S. Blechert, *Angew. Chem., Int. Ed.*, 2002, **41**, 2403–2405.
57 M. S. Sanford, L. M. Henling, M. W. Day and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2000, **39**, 3451–3453.
58 For representative reports on Mo-catalyzed AROM/CM, see: (*a*) G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 1828–1829; (*b*) Ref. 51b; (*c*) W. C. P. Tsang, J. A. Jernelius, G. A. Cortez, G. S. Weatherhead, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 2591–2596.
59 For examples of Mo-catalyzed ARCM, see: (*a*) J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda and R. R. Schrock, *J. Am. Chem. Soc.*, 1998, **120**, 4041–4042; (*b*) D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda and R. R. Schrock, *J. Am. Chem. Soc.*, 1998, **120**, 9720–9721; (*c*) S. S. Zhu, D. R. Cefalo, D. S. La, J. Y. Jamieson, W. M. Davis, A. H. Hoveyda and R. R. Schrock, *J. Am. Chem. Soc.*, 1999, **121**, 8251–8259; (*d*) D. R. Cefalo, A. F. Kiely, M. Wuchrer, J. Y. Jamieson, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2001, **123**, 3139–3140; (*e*) A. F. Keily, J. A. Jernelius, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2002, **124**, 2868–2869.
60 For a recent report where Ru catalyst **2** is reported to be an "especially effective" initiator in polymer synthesis, see: S. Demel, S. Riegler, K. Wewerka, W. Schoefberger, C. Slugovc and F. Selzer, *Inorg. Chim. Acta*, 2003, **345**, 363–366.