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Aqueous Olefin Metathesis

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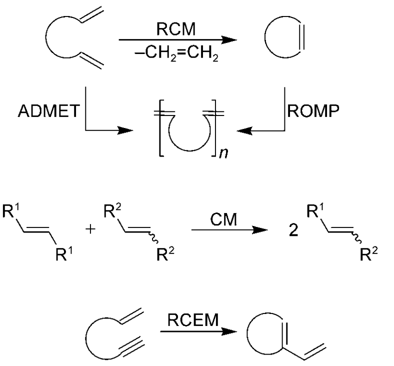
aqueous media · homogeneous catalysis ·
olefin metathesis · ruthenium · sustainable chemistry

According to popular belief, oxygen and water are the natural enemies of organometallic reactions and therefore must be excluded rigorously from the reaction vessel. This belief is founded in the case of the highly reactive nucleophilic metal alkylidene complexes that were used in early catalytic olefin metathesis. However, owing to the high stability of the ruthenium carbene complexes introduced by Grubbs, metathesis in water has become reality.

1. Introduction

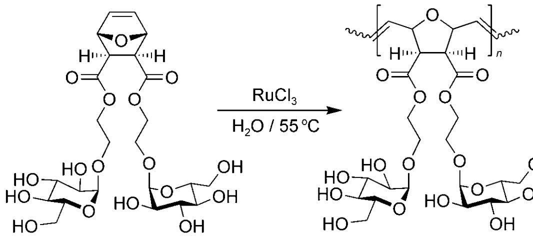
Olefin metathesis is a powerful transformation that is widely used in organic synthesis for the formation of carbon–carbon double bonds (Scheme 1).[1] Like many other organometallic reactions, olefin metathesis is usually carried out in dry, degassed organic solvents to avoid catalyst deactivation by oxygen and moisture.[1] However, owing to environmental concerns, there is increasing interest in the use of water as a solvent.[2,3] Furthermore, for some biological applications, it is critical that metathesis reactions be carried out in water.



Scheme 1. Selected variants of olefin metathesis. ADMET = acyclic diene metathesis, CM = cross-metathesis, RCEM = ring-closing enyne metathesis, RCM = ring-closing metathesis, ROMP = ring-opening metathesis polymerization.

2. Early Aqueous Systems

Early attempts at metathesis in water were made during the evaluation of the ring-opening metathesis polymerization (ROMP) of 7-oxanorbornene derivatives with salts of Group VII metals, such as $RuCl_3$(hydrate) or $OsCl_3$(hydrate).[4] These reactions proceeded with long initiation times in organic solvents. During their efforts to decrease the initiation time, Novak and Grubbs observed that the rigorous exclusion of water had the opposite effect to that expected: Water acted as a cocatalyst and decreased the initiation period dramatically. In further studies, they found that when water was used as the only solvent, the molecular weight of the polymerization product increased by a factor of four, and the PDI value (polydispersity index) dropped to 1.2.[5] The same trends were observed when $Ru(OTs)_2(H_2O)_6$ (Ts = *p*-toluenesulfonyl) was used as the catalyst, and it was found that carboximide-functionalized 7-oxanorbornene derivatives could also be used as monomers.[6] The power of this simple method was demonstrated by Kiessling and co-workers, who prepared a number of neoglycopolymers, such as **1** (Scheme 2), by using $RuCl_3$(hydrate) in aqueous solution. These polyvalent carbohydrates act as ligands for the mannose/glucose-binding protein concanavalin A.[7]



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Scheme 2. Synthesis of a neoglycopolymer in water.

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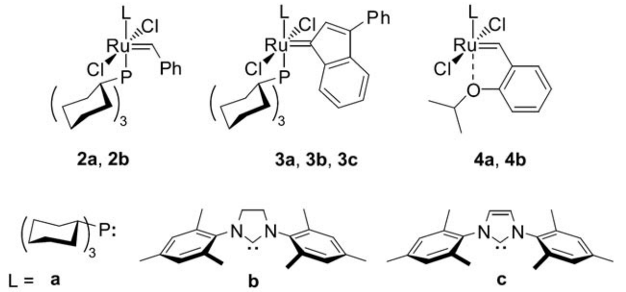
3. Application of Water-Insoluble Catalysts in Aqueous Media

The development of well-defined ruthenium catalysts,[8] such as **2**–**4** (Scheme 3),[9] has popularized metathesis chemistry in organic synthesis.[1] As outlined in Section 2, olefin metathesis in water can be useful for the preparation of polar polymers and biomolecules. The use of water as a solvent offers several general advantages, such as safety, economy, and environmental compatibility. Unfortunately, the low water solubility of the commercially available ruthenium catalysts **2**–**4** and the hydrophobicity of the majority of alkenes and dienes used in metathesis constitute serious limitations of this approach. The development of aqueous reaction conditions suitable for water-insoluble substrates and catalysts can be viewed as the simplest solution to this problem.



2a, 2b **3a, 3b, 3c** **4a, 4b**

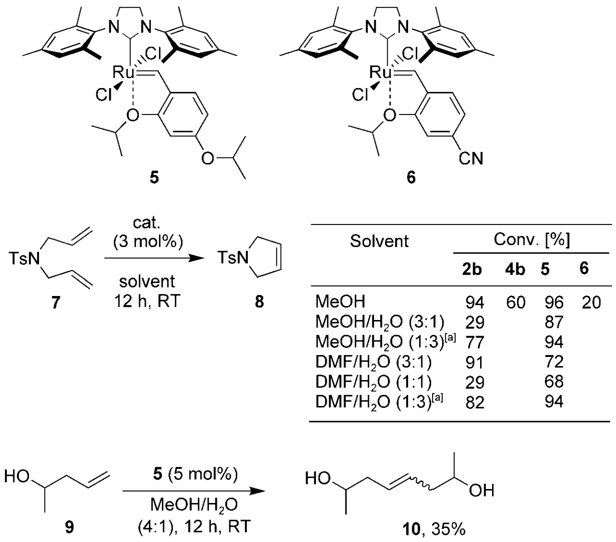
L = **a** **b** **c**

Scheme 3. Selected commercially available ruthenium olefin-metathesis catalysts.

3.1. Metathesis in Homogeneous Aqueous Solutions

Metathesis reactions in homogeneous mixtures of water and water-miscible organic cosolvents added in sufficient amount to make the catalyst and substrate(s) soluble would appear to be technically simpler than those in heterogeneous systems. However, reports on the use of common water-insoluble metathesis catalysts under homogeneous aqueous conditions are limited.

The utility of the Hoveyda–Grubbs catalyst **4b** for olefin metathesis in neat methanol was identified initially by Connon and Blechert.[10] This complex was found to be insoluble in water and only slightly soluble in aqueous methanol, and was therefore not used in these media. The same research group later compared the effectiveness of two substituted analogues of the Hoveyda–Grubbs catalyst, **5** and **6**, in aqueous media (Scheme 4).[11] Whereas catalyst **6**, activated with an electron-withdrawing group, was not very active in methanol, the isopropoxy-substituted complex **5** was found to be an excellent catalyst for the ring-closing metathesis (RCM) of alkenes, not only in neat methanol or DMF, but also in mixtures of these solvents with water. In contrast, low conversion was observed in the homo-cross-metathesis (homo-CM) reaction of the simple homoallylic alcohol **9** with **5** in aqueous methanol.[11]



Solvent	Conv. [%]			
	2b	4b	5	6
MeOH	94	60	96	20
MeOH/H_2O (3:1)	29		87	
MeOH/H_2O (1:3)[a]	77		94	
DMF/H_2O (3:1)	91		72	
DMF/H_2O (1:1)	29		68	
DMF/H_2O (1:3)[a]	82		94	

Scheme 4. Metathesis under homogeneous and heterogeneous conditions. [a] The substrate is not miscible with the solvent. DMF = *N*,*N*-dimethylformamide.

Raines and co-workers recently reexamined the performance of conventional catalysts **2** and **4** in homogeneous mixtures of water and organic solvents. The second-generation Hoveyda–Grubbs catalyst **4b** exhibited excellent efficiency in the RCM of a variety of dienes in aqueous dimethoxyethane (DME) and acetone (Scheme 5).[12] Interestingly, the use of aqueous THF and aqueous 1,4-dioxane as reaction media led to much lower conversion. Charged dienes, such as **13**, also underwent cyclization; however, a

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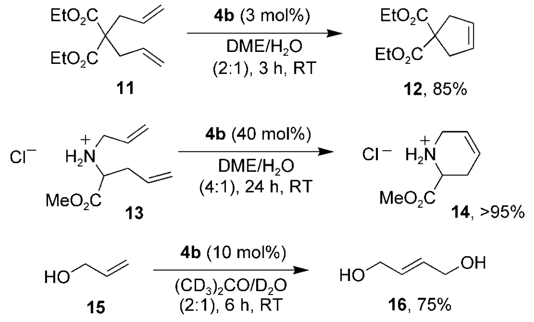
Karol Grela received his PhD degree from the Institute of Organic Chemistry of the Polish Academy of Sciences (IChO PAN) under the supervision of Mieczysław Makosza. After postdoctoral research with Alois Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, he returned in 2000 to IChO PAN, where he was promoted to full professor in 2008. He also holds a part-time position at Warsaw University. His research interests include catalysis and new synthetic methodologies.



Scheme 5. Metathesis in homogeneous aqueous solutions with **4b** as the catalyst.

higher catalyst loading was required for good conversion. Furthermore, the Hoveyda catalyst **4b** also promoted the homodimerization of allyl alcohol (**15**) in acetone/water (Scheme 5).[12]

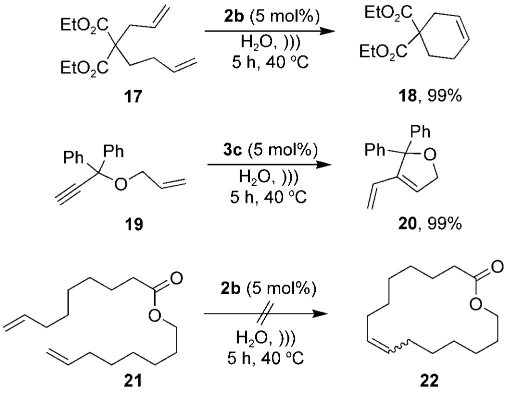
3.2. Metathesis in Heterogeneous Mixtures Containing Water

The results of the research groups of Blechert and Raines show that conventional catalysts, such as **2b** and **4b**, are active in homogeneous aqueous solutions and catalyze the metathesis of both neutral and ionic substrates. On the other hand, it is well established that the performance of organic reactions in water under heterogeneous conditions can lead to notable effects on the reaction rate and selectivity.[13] Therefore, it is reasonable to expect that olefin metathesis of water-insoluble substrates in heterogeneous mixtures of water and organic solvents could be advantageous in some cases.

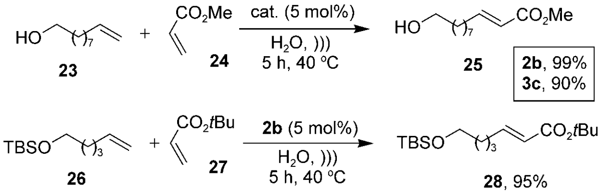
3.2.1. Metathesis "on Water"

Blechert and co-workers[11] observed that the efficiency of the RCM of **7** in aqueous DMF (Scheme 4) falls sharply as the proportion of water in the solvent mixture increases, until enough water is present that the substrate is no longer miscible (> 50% H_2O), whereupon the conversion improves again. This important observation is consistent with homogeneous catalysis that occurs in the liquid substrate and not the aqueous phase. The reaction would then be one of the few examples[14,15] of the olefin metathesis of water-insoluble substrates in aqueous media without surfactants.

Recently, Grela and co-workers described the performance of commercially available olefin-metathesis catalysts in water in the absence of surfactants.[16] The ultrasonication of water-insoluble reactants floating on water[17] led to the formation of an emulsion in which smooth catalytic CM, RCM, and enyne metathesis took place in up to quantitative yield after the addition of a water-insoluble catalyst, **2b** or **3c** (Scheme 6). Although it is possible to form five- and six-membered rings by metathesis in water by using acoustic emulsification, attempts to close larger rings by this method failed. Thus, RCM of diene **21** did not give the expected exaltolide precursor **22** with a 16-membered ring,[18a] but instead led to the formation of a complex mixture of oligomers through acyclic diene metathesis (ADMET; Scheme 6).[18b] Interestingly, under these conditions, it was possible to conduct more challenging olefin cross-metathesis reactions with electron-deficient reaction partners.[19] Such transformations are extremely rare under aqueous conditions[10] and usually proceed with poor conversion and low selectivity. These studies revealed that the cross-metathesis of electron-poor substrates is possible in water, and that the reactions provide the desired products in very good yields and with high selectivities (Scheme 7).[16] We speculate that under such conditions, the "protection" of sensitive ruthenium intermediates inside the water-insoluble organic droplets leads to higher turnovers. Products of the small-scale screening reactions were isolated by extraction from the aqueous solution. In experiments on a larger scale, the crude products deposited as an oil on the water surface or precipitated from the water mixture as solids and could be separated by simple decantation or filtration.[16]



Scheme 6. RCM in ultrasonicated aqueous emulsions.))) = ultrasound.

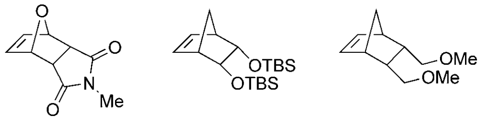


Scheme 7. CM of electron-deficient substrates in ultrasonicated aqueous emulsions. TBS = *tert*-butyldimethylsilyl.

3.2.2. Metathesis in Aqueous Emulsions

Emulsion polymerization is a well-known and established technique for the production of a variety of polymers under mild, practical, and environmentally friendly conditions.[20] Logically, the drive to develop environmentally benign production methods for specialty polymers has resulted in the widespread development and implementation of olefin-metathesis polymerization processes in aqueous emulsions. Since the mid-1990s, many metathesis reactions have been carried out successfully in water through the use of Grubbs catalysts **2a**,**b** with the aid of various surfactants.

The ruthenium alkylidene **2a** efficiently catalyzes the living ring-opening polymerization of hydrophilic and hydrophobic monomers (Scheme 8) in the presence of water.[21] As **2a** is insoluble in water, the catalyst was dissolved in a small amount of an organic solvent before addition to the aqueous solution of the monomer. Complex **2a** was found to be an effective catalyst for emulsion ROMP with dodecyltrimethylammonium bromide (DTAB) as the emulsifying agent. Interestingly, the molecular weight of the product was lower when the polymerization was carried out in an emulsion than when it was carried out in solution (or in a suspension), whereas the PDI was the same in both cases. The polymerization of **30** in an emulsion was not a living process; in contrast, a living process was observed in solution.



Scheme 8. Selected hydrophilic (compound **29**) and hydrophobic monomers (compounds **30** and **31**) that have been polymerized in water.

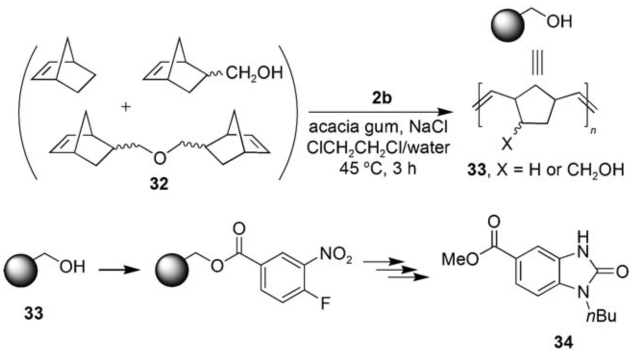
After the initial success in the polymerization of sugar-functionalized norbornene derivatives,[7] the investigation was continued by Kiessling and co-workers with well-defined catalysts, such as **2a**.[22] When sulfated sugar-functionalized norbornene derivatives were subjected to polymerization in a mixture of CH_2Cl_2 and MeOH, incomplete conversion and precipitation of the growing polymer chain were observed. Under aqueous emulsion conditions with DTAB as a surfactant, the polymerization proceeded with complete and rapid consumption of the monomer, and no precipitation was observed.[23] In a short period, several other successful polymerizations of sugar-functionalized norbornene derivatives in water–emulsion systems were reported.[24]

Claverie et al. used the water-insoluble catalyst **2a** in the synthesis of solid norbornene latices by emulsion polymerization. It was found that **2a** can be used conveniently if encapsulated in toluene microemulsion droplets; sodium dodecyl sulfate (SDS) was used as the surfactant. Cyclooctadiene (COD) and cyclooctene (COE) can also be polymerized by this method.[25]

Gnanou and co-workers synthesized norbornene latices by using **2a** in miniemulsion systems with SDS or poly(styrene-*b*-ethylene oxide) (PS-*b*-PEO) as the surfactant. In one approach, the catalyst was added to the miniemulsion of norbornene, either as a solid, as a solution in toluene, or as a dispersion in an aqueous medium. Although monomer consumption was almost quantitative in all cases, coagulation was observed within minutes. In a second approach, the monomer was added to a miniemulsion of **2a**, and in this case, stable latices were obtained.[26]

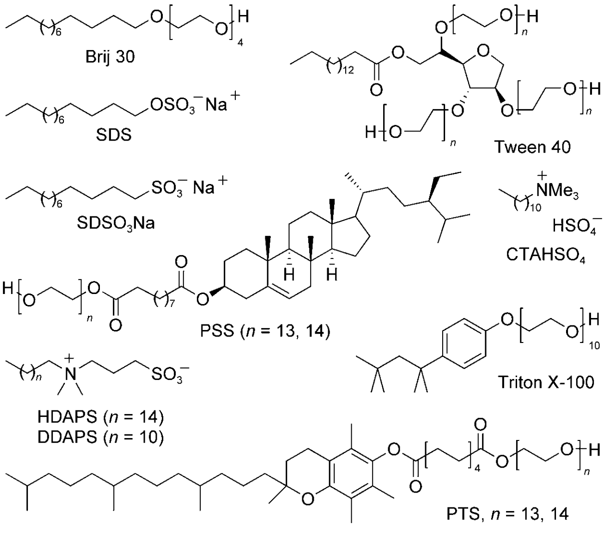
Mecking and co-workers also described the synthesis of polymer latices with catalyst **2a**.[27] Stable latices were obtained when a microemulsion of the catalyst was added to a microemulsion of a monomer in the presence of the surfactant SDS. Less-strained monomers, such as COD and COE, were also used.

Clapham, Janda, and co-workers[28] prepared a set of norbornene-based resin beads by ROMP in aqueous suspension. These beads were used as polymeric supports for solid-phase organic synthesis (SPOS).[29] The resins were prepared from norbornene, norbornene-5-methanol, and various cross-linkers, such as **32**. Catalysts **2a** and **2b** were used for suspension polymerization with acacia gum as the surfactant. Although **2a** was not very effective under these aqueous conditions, insoluble resins were obtained in good yield with **2b**.[28] As an example of the use of such resins, Scheme 9 shows the solid-phase synthesis of a benzimidazolone derivative with **33**.



Scheme 9. Preparation of a norbornene-based resin, and its application in SPOS by Clapham, Janda, and co-workers.[28]

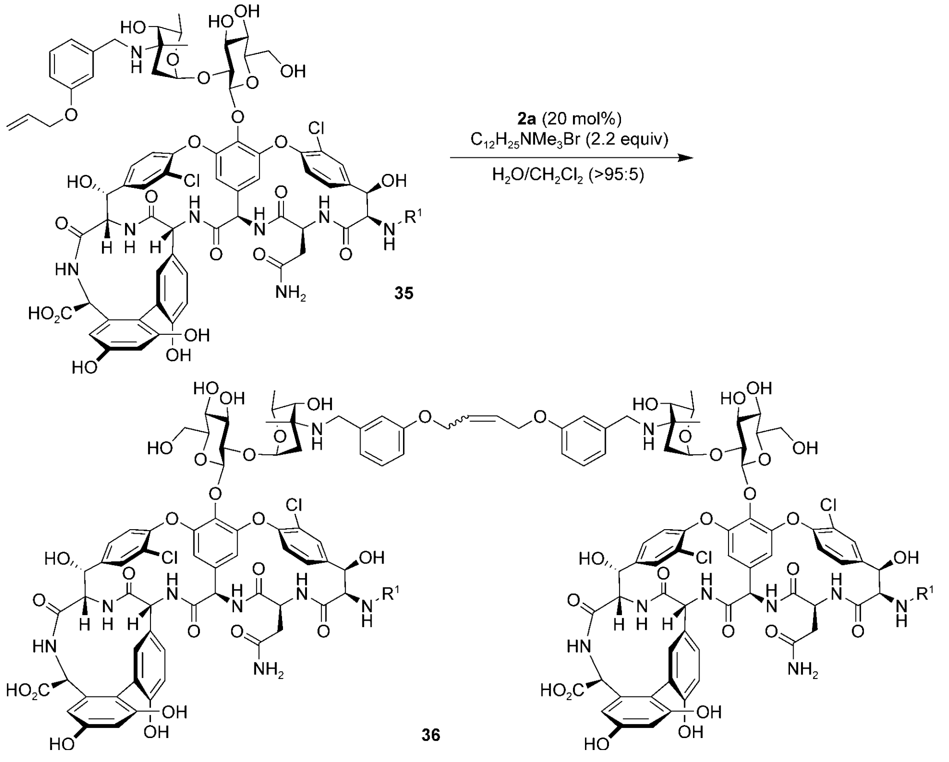
Following the success of metathesis polymerization in emulsions, the first examples of RCM and CM under heterogeneous aqueous conditions were described. Davis and Sinou studied the activity of **2a** and related complexes towards RCM in water in the presence of surfactants, such as SDS, $SDSO_3Na$, $CTAHSO_4$, Brij 30, Tween 40, HDAPS, and DDAPS (Scheme 10).[30] Although the RCM of diethyl



Scheme 10. Selected surfactants used in aqueous olefin metathesis.

diallylmalonate (**11**; 25 °C, 15–60 min) occurred in degassed water even in the absence of the surfactant, the addition of SDS (5 mol %) improved conversion. The increase in the reaction rate is probably due to the formation of micelles. Interestingly, no influence of cationic ($CTAHSO_4$) and zwitterionic surfactants (HDAPS and DDAPS) on the activity of the catalyst in this reaction was observed. Similarly, the use of nonionic surfactants, such as Brij or Tween 40, led to almost the same conversion as that observed in water alone. Unfortunately, no insight was gained into the mechanism of substrate and product transfer during the reaction.[30]

A convincing example of the synthetic utility of heterogeneous aqueous metathesis was provided by Nicolaou et al., who used CM as a ligation method to generate libraries of vancomycin dimers (Scheme 11).[31] After some experimentation, it was found that the homodimerization of vancomycin derivatives proceeded smoothly at 23 °C in a heterogeneous mixture composed of water and CH_2Cl_2 (> 95:5) in the presence of the phase-transfer catalyst $[C_{12}H_{25}NMe_3]^+Br^-$. For example, dimer **36** was obtained cleanly as the only product under these conditions.[31] The fact that metathesis of such an advanced polyfunctional substrate proceeds so well in water with the standard Grubbs catalyst **2a** is a testament to the robust nature of this biphasic system, which is comparable to systems used for micellar catalysis. The water-soluble ruthenium-based catalysts **51** and **52** (see Section 4.1) were found to be less suitable for the preparation of vancomycin dimers.[31]



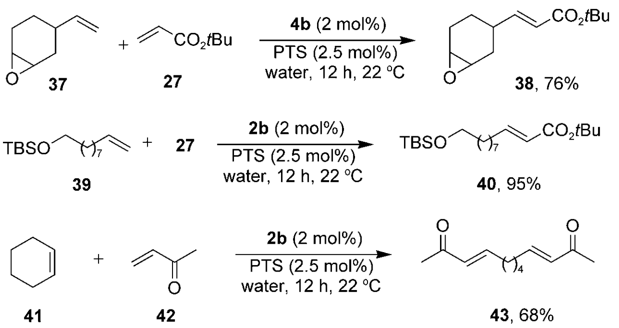
Scheme 11. Dimerization of a vancomycin analogue (R^1 = D-NMeLeu).

Arimoto et al.[32] previously reported the application of ROMP for the preparation of vancomycin-based oligomers. In this study, vancomycin was linked through regioselective reductive amination to the norbornene unit, which was later subjected to ROMP in methanol.

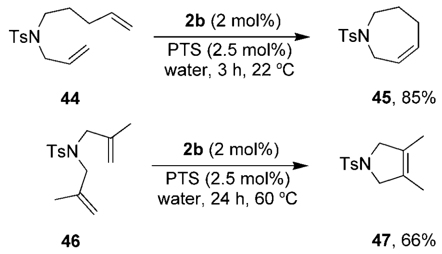
An impressive number of challenging olefin cross-metathesis reactions in water in the presence of the commercially available catalysts **2b** and **4b** were reported recently by Lipshutz et al.[33] The key to success was the use of the nonionic amphiphile PTS (Scheme 10) derived from vitamin E as the surfactant. Other additives, such as Triton X-100, Brij 30, PEG-600 (PEG = poly(ethylene glycol)), SDS, and PSS, were less effective. With a combination of the Grubbs catalyst **2b** (2 mol %) and PTS (2.5 mol %), a series of difficult CM and ROM-CM reactions involving water-insoluble alkenes and electron-deficient substrates proceeded at room temperature in air with high efficiency and very high selectivity (Scheme 12). The crude products were isolated from the reaction mixture by filtration of the emulsion through a bed of silica gel layered over celite and subsequent washing with ethyl acetate.[33]

This powerful methodology was also used to effect the ring-closing metathesis in air of lipophilic substrates in the presence of **2b** in water.[34] Water containing only 0.8–2.5 mol % of PTS served admirably as a reaction medium for the preparation of five- to seven-membered cyclic products (Scheme 13). The formation of product **47**, which contains a tetrasubstituted C–C double bond, is particularly noteworthy; this reaction is considered to be very challenging even in organic solvents.[35] The formation of larger rings was not attempted.[34]

A completely different strategy was chosen by Bowden and co-workers, who reported a new method for the heterogenization of the Grubbs first- and second-generation catalysts.[36] They occluded **2a** and **2b** in a slab of polydimethylsiloxane (PDMS) and used this material in various metathesis reactions in aqueous media. Reagents dissolved in an aqueous solvent

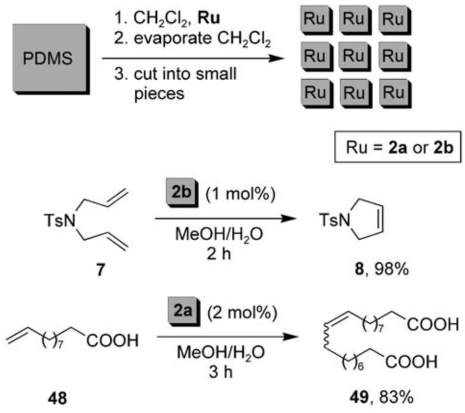


Scheme 12. CM and ROM–CM reactions of alkenes in the presence of the nonionic amphiphile PTS.



Scheme 13. RCM in the presence of the nonionic amphiphile PTS.

can diffuse into the PDMS slab to react with the occluded catalyst, which is itself insoluble in the aqueous solvent and therefore does not diffuse out of the PDMS slab. This interesting idea offers the possibility of combining homogeneous and heterogeneous catalysis without modifying the catalysts. The PDMS slab can function as an "active membrane" to exclude polar media, which would alter the reactivity of the occluded catalysts. The occluded Grubbs catalysts **2a** and **2b** efficiently catalyze both CM and RCM reactions in aqueous methanol (Scheme 14).[36]



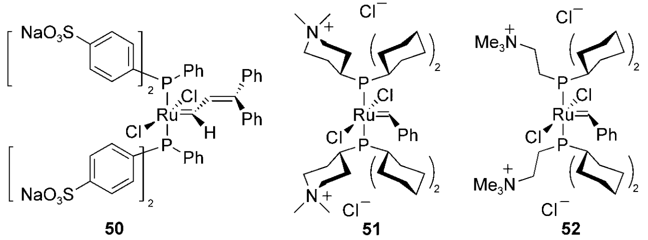
Scheme 14. Occlusion of **2a** and **2b** in a slab of PDMS.

4. Design and Application of Tagged Catalysts

During the past ten years, many "tagged" ruthenium catalysts have been synthesized to facilitate the removal of the catalyst during workup.[3] Catalyst tags can include ionic groups, such as groups derived from ionic liquids, or perfluorinated ponytails. This strategy makes use of the high affinity of these tags for given reaction media, such as ionic liquids (ILs) or perfluorinated solvents.[3] The use of polar tags appears to be a suitable method for making ruthenium complexes compatible with aqueous media.

4.1. Early Results

Although older water-soluble initiators, such as $RuCl_3$(hydrate) and $Ru(OTs)_2(H_2O)_6$, are effective in some reactions, the lack of a preformed alkylidene moiety in these systems limits their practical usefulness. In an attempt to develop a water-soluble "well-defined" metal alkylidene, Grubbs and co-workers discovered the ruthenium alkylidene **50** with water-soluble triaryl phosphine ligands (Scheme 15).[37] This complex was synthesized by exchanging the triphenylphosphane ligand for the commercially available $PhP(p\text{-}C_6H_4SO_3Na)_2$ ligand. Although alkylidene **50** is soluble in water, it did not initiate ROMP in aqueous solution. In further studies, the same research group prepared the water-soluble complexes **51** and **52**,[38] which were active catalysts for olefin-metathesis polymerization in water and methanol. Although these catalysts initiated ROMP of the *endo*-norbornene **65** (see Scheme 18), the propagating species decomposed before polymerization was complete, and low conversions were observed. It was found that the addition of aqueous HCl enhanced the process, so that living polymerization occurred in water.[39] Unfortunately, these catalysts did not mediate RCM reactions of α,ω-dienes in water and showed limited stability towards oxygen.[40]



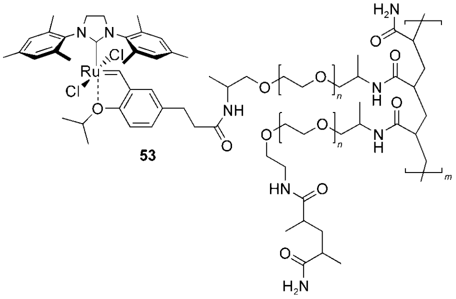
Scheme 15. Early water-soluble ruthenium catalysts developed by Grubbs and co-workers.

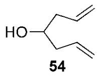
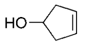
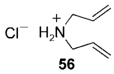
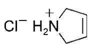
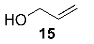
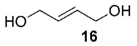
4.2. Ruthenium Complexes Bound to Hydrophilic Polymers

Many immobilized olefin-metathesis catalysts have been synthesized by using various anchoring strategies and solid supports.[3,41] Connon and Blechert synthesized the phosphine-free ruthenium alkylidene **53** bound to the hydrophilic solid support PEGA-NH_2 (PEGA = poly(ethylene glycol)-acrylamide copolymer). This heterogeneous catalyst was much less sensitive towards oxygen and promoted various RCM and CM reactions in nondegassed methanol and in water (Table 1).[10,42] The ammonium salt **56**, which was a problematic substrate with the second-generation catalyst **2c** in CH_2Cl_2,[43] underwent clean cyclization in moderate yield with **53** in methanol, and some reactivity was even observed in water. Although **53** was an active catalyst in the homo-cross-metathesis of allyl alcohol (**15**) and other alkenes, poor results were observed with electron-deficient alkenes as CM reaction partners. It was suggested that the electrophilic alkylidene intermediates formed in these reactions are of insufficient stability in nucleophilic solvents; thus, poor conversion and nonselective CM result.[10]

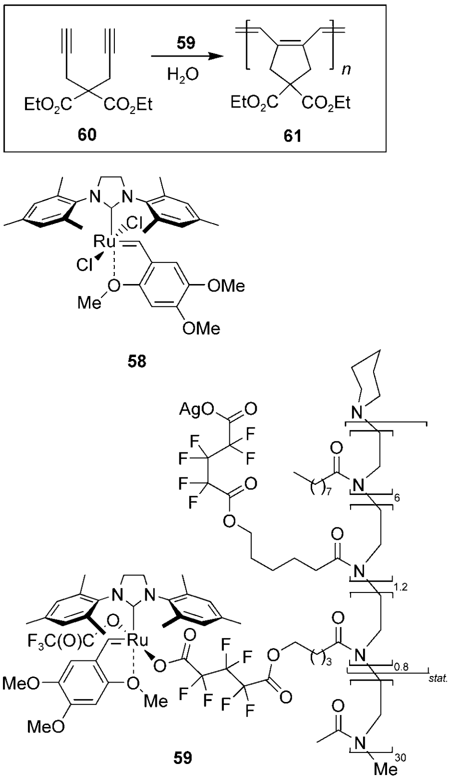
Buchmeiser and co-workers immobilized water-insoluble ruthenium catalysts, such as the asarone-derived complex **58** (Scheme 16),[44] on an amphiphilic poly(2-oxazoline)-derived block copolymer.[45] The resulting functionalized catalyst **59** was used in the polymerization of diethyl dipropargylmalo-

Table 1: RCM and CM reactions promoted by the polymer catalyst **53**.[a]



Entry	Substrate	Product	Solvent	Conv. [%]
1	 **54**	 **55**	MeOH D_2O	73 96
2	 **56**	 **57**	CH_2Cl_2 MeOH H_2O	33 57 11
3	 **15**	 **16**	MeOH D_2O	69 80

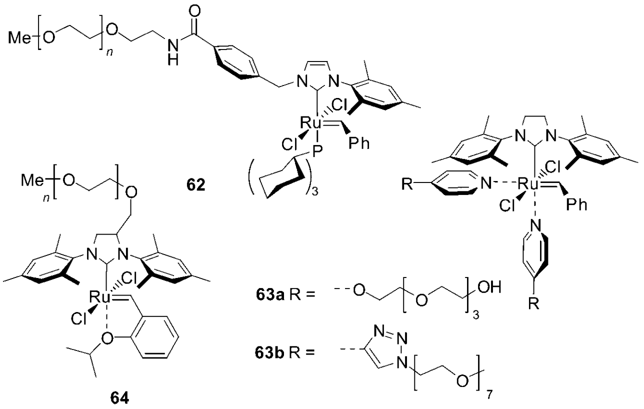
[a] Reaction conditions: **53** (5 mol%), 45 °C, 12 h.



Scheme 16. Cyclopolymerization of **60** under aqueous micellar conditions.

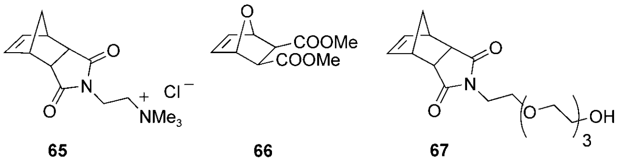
nate (**60**) under aqueous micellar conditions. The poly(acetylene) **61**, prepared with **59** in water as stable latex particles, was characterized by a lower polydispersity index (< 1.40) than that of **61** prepared with nonimmobilized catalysts in dichloromethane.[45]

Grubbs and co-workers developed the neutral, water-soluble catalyst **62** (Scheme 17), which contains a poly(ethylene glycol)-tagged N-heterocyclic carbene (NHC) ligand and shows good activity in aqueous ROMP reactions.[46]



Scheme 17. PEG-tagged ruthenium catalysts.

Although earlier reports demonstrated that *endo*-norbornenes are challenging substrates,[47] catalyst **62** promoted the almost quantitative polymerization of the sterically hindered cationic *endo*-norbornene **65** (Scheme 18) in acidified water. However, the presence of the PEG-substituted unsaturated NHC ligand limits the stability of this complex in acidic aqueous solution.[46]

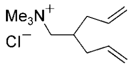
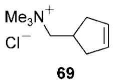
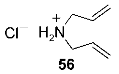
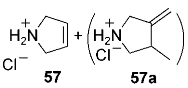
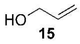
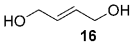
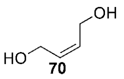
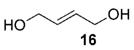


Scheme 18. Examples of monomers that have been used in aqueous ROMP.

Breitenkamp and Emrick reported the synthesis of the poly(ethylene glycol)-tagged pyridine-based catalysts **63a** and **63b** (Scheme 17), which are soluble in organic solvents as well as in water.[48,49] Complex **63a** showed excellent reactivity and control over the polymerization of COE and **66** in CH_2Cl_2. Moreover, a linear relationship was observed between molecular weight and the monomer/catalyst ratio for these reactions, a result that serves as evidence for living polymerization. Although **63a** failed to polymerize the water-soluble monomer **67** in neutral aqueous solution, an efficient reaction occurred in aqueous solution at pH ≥ 2; however, no control over the molecular weight of the product was observed. Catalyst **63a** was obtained as a mixture with the unconverted PEG-tagged free pyridine ligand; nevertheless, NMR spectroscopy clearly supported the formation of **63a**.[48] Complex **63b** showed similar activity: In neutral aqueous solution only low conversion was observed; however, at pH 1.5, quantitative consumption of the monomer **67** occurred. The addition of a pyridine scavenger, such as $CuBr_2$ or $CuSO_4$, led to conversions of about 70 %.[49]

In early 2006, Hong and Grubbs described an improved, PEG-tagged Hoveyda-type catalyst, **64** (Scheme 17), which was active and stable in water (no decomposition was observed after one week in D_2O).[50] This macromolecular (MW ≈ 5000 $g\,mol^{-1}$) polydisperse catalyst, which forms aggregates in water, showed increased activity in the ROMP of **65** (Scheme 18). Furthermore, catalyst **64** showed unprecedented activity in RCM reactions of water-soluble dienes in water. The corresponding five- and six-membered-ring products were formed in good to excellent yields, although in the RCM of **56**, the cycloisomerized product **57a** was observed along with the major metathesis product **57** (Table 2). Catalyst **64** also showed reasonable activity in the homodimerization of allyl alcohol (**15**) and the self-metathesis of (*Z*)-2-butene-1,4-diol (**70**) in water (Table 2).[50]

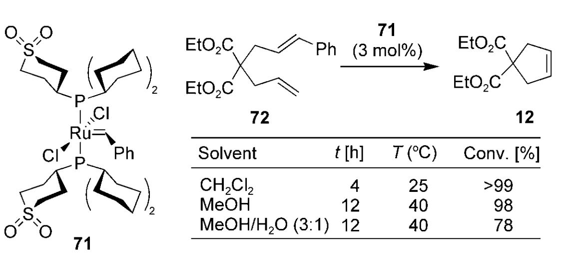
Table 2: RCM and CM reactions in water in the presence of the PEG-tagged catalyst **64** (5 mol %).

Entry	Substrate	Product	*t* [h]	*T* [°C]	Conv. [%]
1	 **68**	 **69**	12	RT	> 95
2	 **56**	 **57** **57a**	36	RT	67 (28)
3	 **15**	 **16**	12	45	> 95
4	 **70**	 **16**	12	45	> 94

4.3. Small-Molecule Polar Catalysts

4.3.1. Application in Homogeneous Solutions

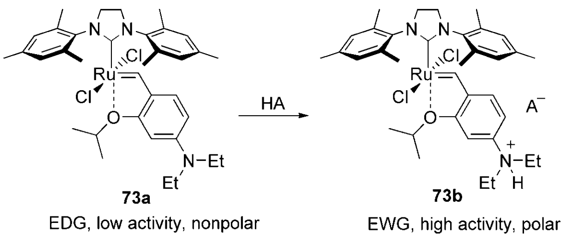
Following the studies with the charged, water-soluble catalysts **50–52** (Scheme 15),[37–40] Grubbs and Rölle prepared complex **71**, a neutral analogue of **2a** with polar phosphine ligands (Scheme 19).[51] Complex **71** is a universal catalyst: It promotes RCM in both aqueous methanol (at 40 °C) and "classical" nonpolar organic solvents, such as benzene or dichloromethane.[51] Peruzzini and co-workers prepared vinylidene and allenylidene analogues of **71** that promoted ring-opening cross-metathesis with electron-poor olefins.[52]



Solvent	*t* [h]	*T* (°C)	Conv. [%]
CH_2Cl_2	4	25	>99
MeOH	12	40	98
$MeOH/H_2O$ (3:1)	12	40	78

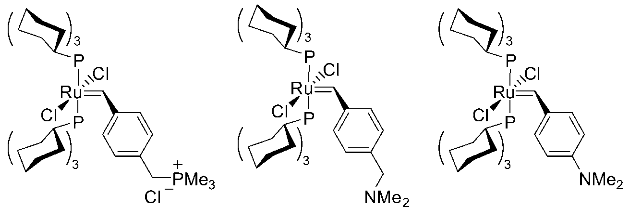
Scheme 19. A neutral polar catalyst prepared by Grubbs and Rölle.[51]

Grela and co-workers demonstrated that 5- and 4-nitro-substituted Hoveyda–Grubbs catalysts initiate olefin metathesis dramatically faster than the parent complex **4b**.[53] It was proposed that the electron-withdrawing nitro group decreases the electron density on the chelating oxygen atom of the isopropoxy group to weaken the O→Ru coordination and facilitate faster initiation of the metathesis catalytic cycle.[53,54] In accordance with this assumption, it was observed that complex **73a** (Scheme 20) with an electron-donating diethylamino group shows little or no activity in olefin metathesis.[55] In striking contrast, salts **73b** formed in situ by the treatment of the aniline **73a** with a Brønsted acid show high activity and surpass the parent Hoveyda–Grubbs complex **4b** in terms of initiation speed.[55] The formation of a polar salt not only activates the catalyst but also changes its physical properties, such as its solubility in polar media, and creates a site for noncovalent immobilization on a solid phase.[56]



Scheme 20. Switch in the activity of the pH-responsive catalyst **73**. EWG = electron-withdrawing group, EDG = electron-donating group, HA: Brønsted acid.

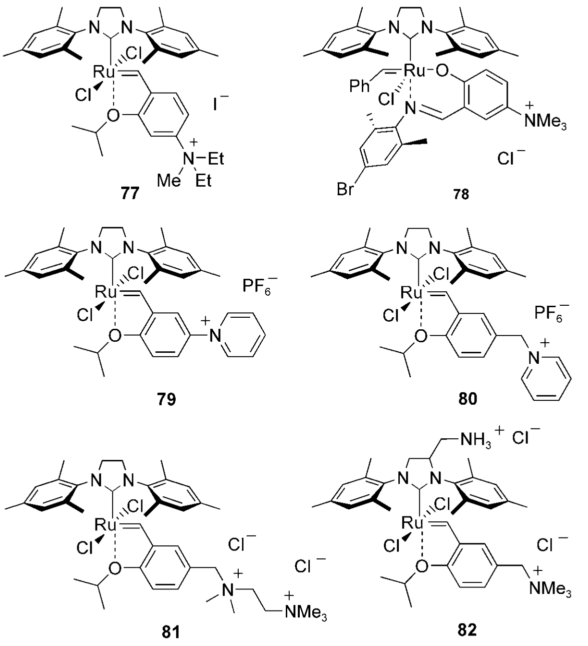
Another series of pH-responsive catalysts was reported recently by Schanz and co-workers (Scheme 21).[57] Complexes **74–76** were designed to promote ROMP in protic acidic media. Catalysts **74** and **75** are the first examples of complexes of the type $[(PCy_3)_2Cl_2Ru{=}CHR]$ (Cy = cyclohexyl) that can be used for the controlled ROMP of strained cyclic olefins in protic acidic media. Aqueous HCl was used in alcohol–water mixtures to protonate the NMe_2 group in **75** and **76** and enhance the dissociation of the PCy_3 ligand for the effective initiation of polymerization. Without the addition of HCl, no polymerization activity was observed for **74**. Whereas pseudo-first-order kinetics were observed with **74** and **75**, complex **76** showed slower initiation at first and accelerated polymerization over time.



74 **75** **76**

Scheme 21. pH-responsive catalysts prepared by Schanz and co-workers.[57]

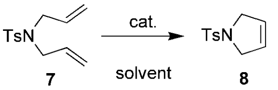
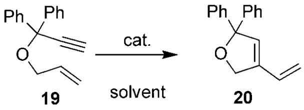
The concept of a switch in activity upon the conversion of electron-donating groups into electron-withdrawing groups[54] (Scheme 20) was later extended by Grela and co-workers to the preparation of complex **77** (Scheme 22) with a quaternary ammonium group.[58] Catalyst **77** not only initiates metathesis reactions in dichloromethane faster than the parent Hoveyda–Grubbs complex **4b**, but also promotes various metathesis reactions (RCM, CM, and enyne metathesis) in aqueous mixtures[58] and in neat water.[59] Other catalysts containing polar quaternary ammonium groups in the benzylidene fragment were later reported by Raines and co-workers (complex **78**),[60] Mauduit, Grela, and co-workers (complexes **79** and **80**),[61] and Jordan and Grubbs (complexes **81** and **82**; Scheme 22).[62]



Scheme 22. Ruthenium catalysts tagged with quaternary ammonium groups.

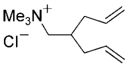
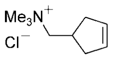
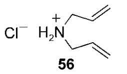
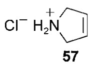
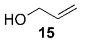
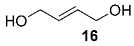
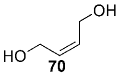
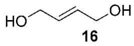
Comparison of the results of model RCM and CM reactions leads to the conclusion that, although the application profiles of these catalysts are in general quite similar, there are some interesting differences (Tables 3 and 4). Catalyst **77** is only slightly soluble in neat water (0.002M); however, a number of metathesis reactions of water-soluble substrates have been carried out with high efficiency in water.[58,63] Complex **78** is active in methanol and methanol–water mixtures at slightly higher temperatures. Catalysts **79** and **80** were initially designed for applications in ionic liquids[64] and are not soluble in neat water. Catalyst **82** dissolves readily in water, whereas **81** is soluble only in low concentrations (<0.01M). Both **81** and **82** are active catalysts in the ROMP of **65** (Scheme 18) in water. Moreover, **82** is relatively stable in water, with a decomposition half-life of more than a week at room temperature. Although **81** and **82** are very active in the RCM of charged dienes and the CM of allylic alcohols, the undesired isomerization product was sometimes found; this product was not observed with **77** (Table 4).

Table 3: Selected reactions mediated by catalysts **77**–**80** substituted with quaternary ammonium groups in aqueous media.

Catalyst (mol %)	Solvent	*t* [h]	*T* [°C]	Conv. [%]
 **7** → **8**				
77 (5)	EtOH/ H_2O (5:2)	24	25	83
78 (5)	CD_3OD	9	55	>95
79 (5)	EtOH/ H_2O (5:2)	24	25	50
80 (5)	EtOH/ H_2O (5:2)	24	25	75
 **19** → **20**				
77 (5)	EtOH/ H_2O (5:2)	0.5	25	99
78 (10)	CD_3OD/ D_2O	6	55	>95
79 (5)	EtOH/ H_2O (5:2)	0.5	25	99
80 (5)	EtOH/ H_2O (5:2)	0.25	25	97

In general, reactions with ionic catalysts in water are highly substrate dependent. The RCM of diene **56**, which contains a charged ammonium center in the allylic position,

Table 4: Selected reactions mediated by catalysts **77**, **81**, and **82** functionalized with quaternary ammonium groups in neat water.

Entry	Substrate	Product	Catalyst (mol%)	*t* [h]	*T* [°C]	Conv. [%]
1	 **68**	 **69**	**77** (5)	5	25	99
2			**81** (5)	24	30	>95
3			**82** (5)	0.5	30	>95
4	 **56**	 **57**	**77** (5)	0.12	110	44
5			**81** (5)	24	30	>95
6			**82** (5)	4	30	36 (59)[a]
7	 **15**	 **16**	**77** (2.5)	3.5	25	>99
8			**81** (5)	24	45	82 (4)[b]
9			**82** (5)	6	45	69 (12)[a]
10	 **70**	 **16**	**77** (2.5)	8	25	99
11			**81** (5)	24	45	92
12			**82** (5)	2	45	94

[a] The yield of the by-product **57a** (see Table 2) is given in parentheses. [b] The yield of the by-product propionaldehyde (C_2H_5CHO, **83**) is given in parentheses.

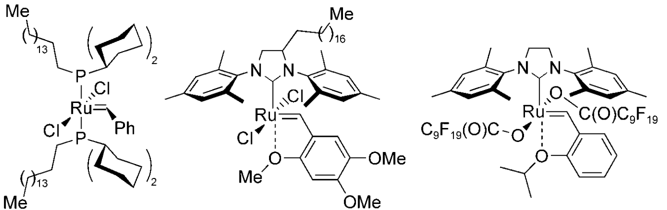
proceeds significantly more slowly with catalyst **77** than with **81** and **82** (Table 4). Despite the rather harsh conditions required to promote this transformation with **77** (110 °C, microwave oven), the formation of by-product **57a** was not observed, in contrast to the equivalent reaction with **81**. Diallylamine hydrochloride (**56**) also undergoes smooth cyclization in dichloromethane in the presence of **77**.[63]

Although catalysts **77**, **81**, and **82** could be used for many aqueous RCM and CM reactions, attempts to transform other substrates, including amino acids, carbohydrates, and ammonium salts, failed.[62,63]

4.3.2. Application in Heterogeneous Mixtures

Catalysts that are also surfactants are called inisurf molecules (for "initiator" and "surfactant"). Inisurfs have been used, for example, in radical polymerization, to minimize the quantity of surfactant needed for the stabilization of a latex.[65] To the best of our knowledge, only a few examples of the use of inisurf ruthenium complexes in olefin metathesis have been reported so far.

Mingotaud, Sykes, and co-workers investigated the ROMP of norbornene-type monomers dissolved in the outer aqueous phase of liposomes with initiator **84** (Scheme 23).[66]



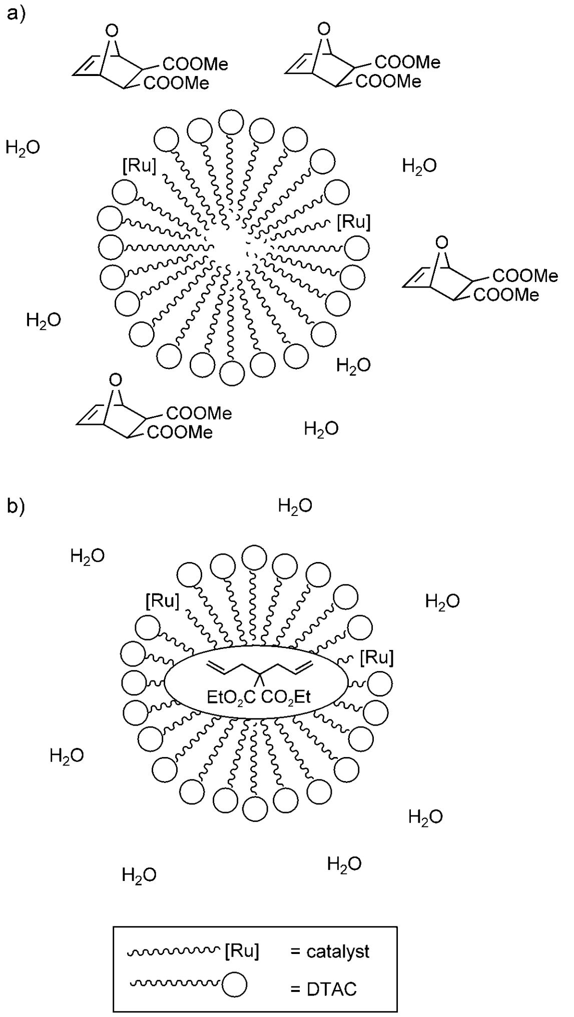
84 **85** **86**

Scheme 23. Catalytic surfactants for olefin metathesis in micellar solutions.

Polymer nodules (of up to 10 μm in diameter) were grown with a controlled shape at the surface of liposomes. The initiator **84** was designed to have a strong affinity for the hydrophobic part of the vesicles and to maintain the catalytic center along the bilayer during the polymerization, which occurred continuously at the surface of the liposome. The size of the liposomes was in the range of 1–4 μm. Polymerizations with 5-norbornene-2-carboxylic acid resulted in spherical-shaped nodules, whereas elongated nodules were observed predominantly for more hydrophilic 7-oxa-5-norbornene-2,3-dicarboxylic acid.[66]

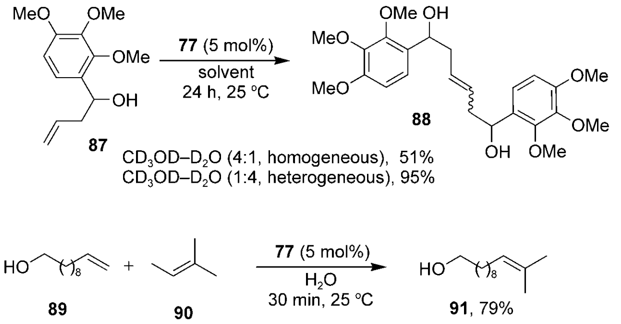
To improve the air stability of inisurf **84**, Mingotaud et al. synthesized complex **85**, an analogue of the asarone metathesis catalyst **58**[44] with a long alkyl chain in the NHC moiety, as well as the perfluorodecanoic acid derivative **86** of the parent Hoveyda catalyst **4b** (Scheme 23).[67] The surface activity of **85** and **86** was characterized by the formation of Langmuir films at the air–water interface. The formation of stable monolayers indicated without any doubt that these catalysts are surface active, which means that the ruthenium moiety is polar enough to be close to the water surface. These air-stable catalysts were used with success in the polymerization of the hydrophilic monomer **66** (Scheme 18) in water containing dodecyltrimethylammonium chloride (DTAC) as a cosurfactant. The ability of these catalysts to promote the RCM of diethyl diallylmalonate (**11**) in CH_2Cl_2 and in water was also evaluated. As expected, the Hoveyda catalyst **4b** exhibited the highest activity in CH_2Cl_2 (30 °C, 45 min, 89 %). It was closely followed in activity by **85** (30 °C, 55 min, 80 %); the pseudohalide catalyst **86** was the least active (30 °C, 210 min, 27 %).[68] Catalyst **85** was less active in the RCM of **11** in micellar solutions (room temperature, 137 min, 27 %), which indicates that the catalyst and reactant occupy unfavorable positions. It was proposed that the active site of catalyst **85** is in the hydrophilic part of the micelle, whereas the lipophilic diene is localized mostly in the core of the micelle (Scheme 24).[67] Interestingly, **86** was not stable under aqueous conditions, being converted back to parent **4b** in a ligand-exchange reaction with chloride ions from DTAC. These results are valuable for the rational design of improved Ru–inisurf structures.

During studies on metathesis reactions promoted by the activated catalyst **77** (see Section 4.3.1), it was found unexpectedly in a CM experiment in aqueous methanol that an



Scheme 24. Schematic illustration that shows the presumed localization of reagents for a) ROMP and b) RCM in micellar solutions.

increase in the water content of the water–alcohol mixture led to the formation of a quasiemulsion and resulted in much higher conversion than that observed under homogeneous conditions (Scheme 25).[63] The results of a number of CM and RCM reactions in heterogeneous MeOD–D$_2$O mixtures and in neat water demonstrated that **77** acts as an inisurf molecule with high catalytic activity in RCM and CM reactions.[63]



Scheme 25. CM reactions promoted by **77** in heterogeneous mixtures.

5. Conclusion and Outlook

The development of environmentally friendly processes for olefin-metathesis reactions is an important area that will continue to grow in the coming years. Furthermore, the use of water as a solvent has significance for biological applications. Aqueous olefin metathesis can be used in the absence of protecting groups as one of the final synthetic steps en route to complex polar target molecules. Aqueous ROMP and CM reactions have been applied successfully in the preparation of polar, biologically active compounds, such as oligopeptides, polymeric carbohydrates, anticancer agents, and antibiotics. RCM reactions have also been carried out with water-insoluble catalysts in aqueous emulsions and with "designer" water-soluble catalysts bearing polar tags.

Although many problems remain to be solved, such as the recycling of a catalyst-containing water phase and the insufficient control of *E*/*Z* selectivity, olefin metathesis in aqueous media has a promising future in view of the growing need for environmentally friendly catalytic processes.

This Minireview would not have been possible without the dedication of numerous collaborators, whose names can be found in the references. D.B. thanks the Österreichische Forschungsgemeinschaft for a postdoctoral fellowship, and K.G. thanks the Foundation for Polish Science for a Mistrz Professorship. We are grateful to Łukasz Gułajski for his helpful comments and discussion during the preparation of this manuscript.

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[2] For reviews, see: a) *Organic Reactions in Water* (Ed.: U. M. Lindström), Blackwell, Oxford, **2007**; b) *Aqueous-Phase Organometallic Catalysis: Concept and Applications*, 2nd ed. (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2004**; c) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie A&P, London, **1998**; d) C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023–2035; e) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82; f) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; g) K. H. Shaughnessy, R. B. DeVasher, *Curr. Org. Chem.* **2005**, *9*, 585–604; h) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751–2772; i) B. H. Lipshutz, S. Ghorai, *Aldrichimica Acta* **2008**, *41*, in press.

[3] For a review on sustainable olefin metathesis, see: H. Clavier, K. Grela, A. Kirschning, M. Maudit, S. Nolan, *Angew. Chem.* **2007**, *119*, 6906–6922; *Angew. Chem. Int. Ed.* **2007**, *46*, 6786–6801.

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