CHAPTER 5

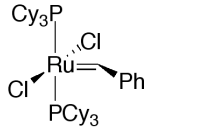
Water-Soluble Phosphine-Free Olefin Metathesis Catalysts Containing an *N*-Heterocyclic Carbene Ligand

Abstract

Two water-soluble, ruthenium-based olefin metathesis catalysts containing an *N*-heterocyclic carbene ligand are described. Both catalysts are phosphine-free and utilize ammonium salts to achieve solubility in water. The ability of these catalysts to mediate ring-opening metathesis polymerization, ring-closing metathesis and cross metathesis as homogenous reactions in water is examined. Both catalysts competently mediate ring-opening polymerization and ring-closing metathesis reactions in water, though their ability to enable aqueous cross metathesis is limited.

Introduction

Olefin metathesis, the metal-mediated exchange of double-bond substituents, has become a prominent reaction of contemporary chemistry.[1] Ruthenium catalysts **1**–**6** allow for the metathesis-mediated synthesis of small molecules,[1-3] macromolecules,[1,4,5] and even supramolecular complexes (Chapter 1).[6-8] While already a powerful tool in synthetic chemistry, the potential of olefin metathesis has yet to be fully realized. The desire to expand the utility of this reaction has served and still serves as motivation to develop transition metal catalysts that better enable this transformation. This chapter describes the synthesis and activity of two water-soluble metathesis catalysts that contain an *N*-heterocyclic carbene (NHC) ligand.



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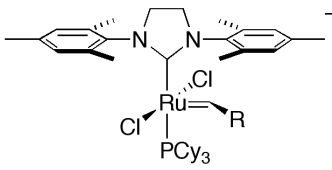

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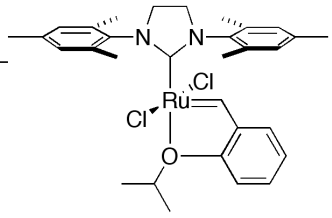

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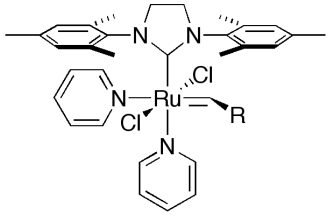

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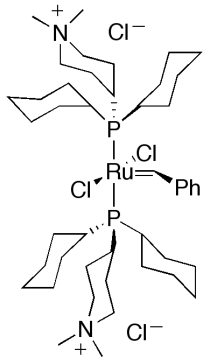

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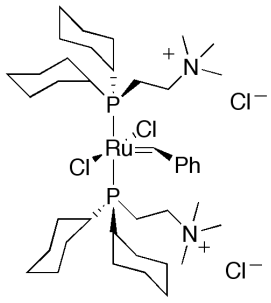

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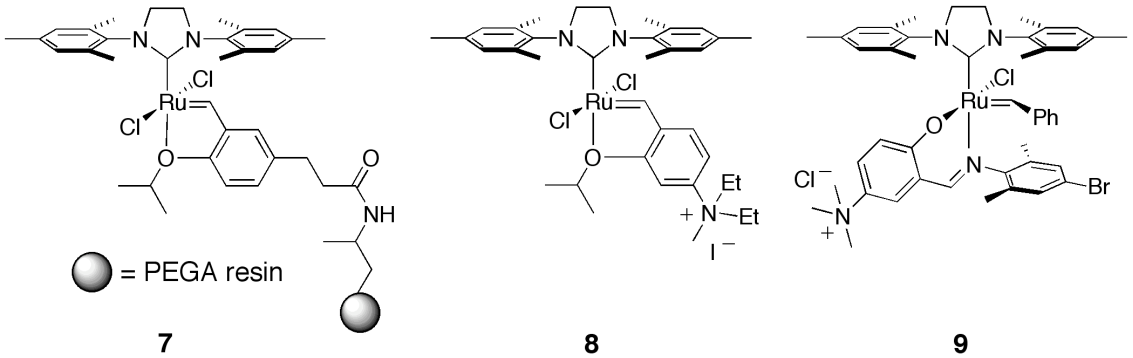
Earlier research by Lynn, Mohr, and Grubbs produced electron-rich phosphine ligands displaying water-soluble ammonium functional groups.[9] Incorporation of these

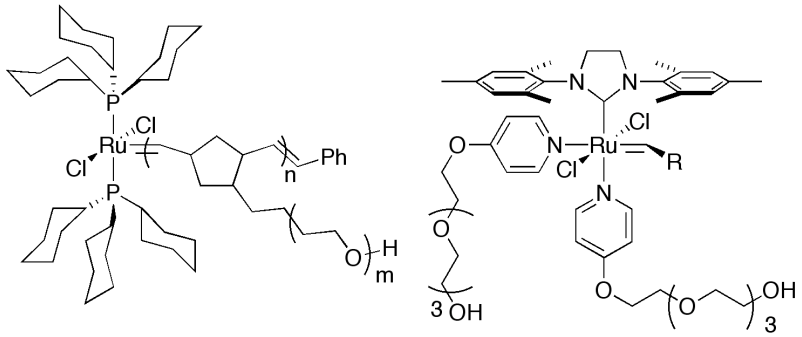
ligands onto ruthenium gave water-soluble catalysts **5** and **6**.[9-11] These catalysts were capable ROMP initiators and would polymerize water-soluble norbornene monomers in a living manner.[10,11] Moreover, these complexes were also capable of catalyzing ring-closing metathesis (RCM) in protic solvents, including water, with substrates that avoid the formation of intermediate ruthenium methylidene complexes, [Ru]=CH_2.[12] Unfortunately catalysts **5** and **6**, particularly their methylidene derivatives, were unstable in water, which limited their utility in aqueous environments.[11-13] Even so, these complexes were the first well-defined, active water-soluble metathesis catalysts, and they demonstrated the potential for ruthenium-based metathesis catalysts to mediate the metathesis of acyclic substrates in water.

A variety of methods and catalysts targeting metathesis in water have been produced since the introduction of the water-soluble bis(phosphine) catalysts.[14-25] A few reports have demonstrated that surfactants can be used to perform metathesis in water.[14-16] Catalysts **1** and **2** can also be occluded within a polydimethylsiloxane membrane to be used in methanol/water mixtures.[17] Furthermore, derivatives of catalyst **3** were anchored to a solid support to give catalysts such as complex **7**, a catalyst active in methanol and water though catalysis was believed to occur within the pores of the gel.[18,19] Also, Grela and co-workers synthesized analogs of **3** that displayed a single ammonium salt such as a pyridinium salt[20] or a tetraalkyl ammonium salt (**8**),[21] which showed ring-closing activity in methanol/water mixtures. Similarly, Blechert and co-workers have examined the ability of catalyst **3** and a couple of derivatives of **3** to perform metathesis in DMF/water and methanol/water mixtures.[22] A different approach was taken by Raines and co-workers who incorporated an ammonium-salt-containing salicylaldimine ligand onto a

ruthenium complex supported by an NHC ligand to produce catalyst **9**, which was active in methanol/water mixtures.[23] Finally, catalysts explicitly designed to be used in neat water include two macroinitiators that incorporate poly(ethylene glycol) (PEG) chains to form water-soluble analogs of catalyst **1** (**10**) and **4** (**11**) for ROMP in an aqueous environment.[24,25] Unfortunately, none of these systems effectively catalyzed the metathesis of hydrophilic acyclic substrates in neat water.



7 **8** **9**

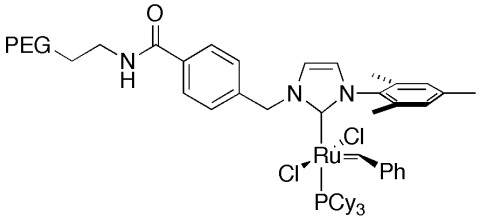


10 **11**

Desiring a water-soluble olefin metathesis catalyst with improved stability and activity relative to catalysts **5** and **6**, we synthesized catalyst **12**, which displays a PEG chain from a nitrogen substituent of an unsaturated NHC ligand (Chapter 2).[26] The hypothesis was that NHC ligands would impart the same increase in stability and activity onto water-soluble metathesis catalysts as observed with catalysts **2** and **3**.[27-29] Indeed, catalyst **12** did show increased ROMP activity over bis(phosphine) catalyst **6**. However,

12 was not sufficiently stable for the efficient mediation of ring-closing and cross-metathesis reactions in water (Chapter 2).[26]

A careful consideration of catalyst **12** revealed structural weaknesses that could be addressed to produce catalysts with greater stability and activity in water (Chapter 3). This analysis inspired the ruthenium-complex templates shown in Figure 5.1 as promising targets for the production of the desired catalyst. However, an examination of the decomposition of the methylidene derivative of catalyst **2** showed that nucleophilic attack at the carbon double-bonded to the ruthenium center by free tricyclohexylphosphine (PCy_3) is a major path of complex decomposition.[27,28] Moreover, examining the effect of water on the decomposition of the methylidene derivative of **2** indicated that pathways involving the nucleophilic attack by PCy_3 at this carbon also dominated its decomposition in aqueous environments (Chapter 4).[30] Therefore, the targeted catalysts should be phosphine-free (templates **B**–**D**, Figure 5.1). Because of the greater stability of catalysts containing isopropoxybenzylidene ligands,[31,32] complexes modeled from template **B** (Figure 5.1) are particularly attractive as potentially stable and active water-soluble catalysts.



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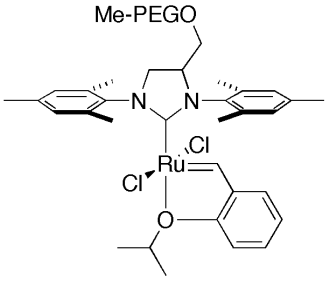

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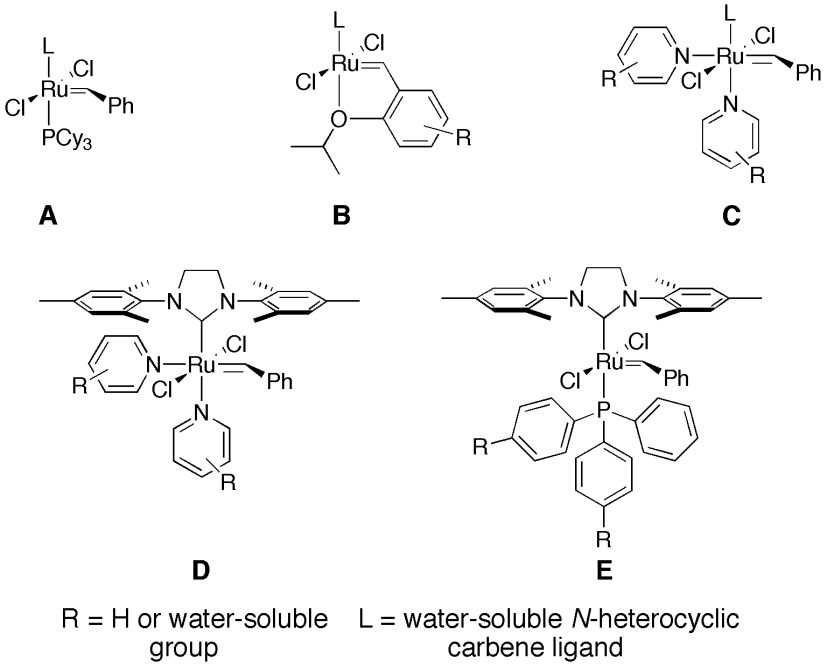


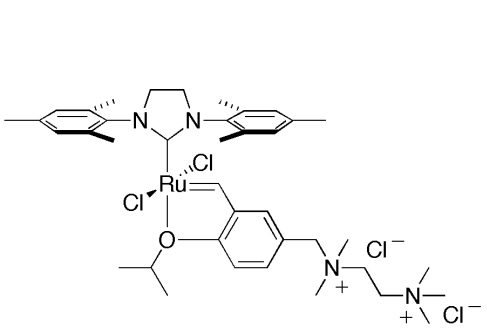
Figure 5.1. Water-soluble groups can be incorporated onto NHC ligands and/or ligands that dissociate during metathesis reactions to produce NHC-containing olefin metathesis catalysts that are soluble in water.

Two strategies can be employed to render analogs of catalyst **3** soluble in water. Like catalyst **12**, the first strategy utilizes PEG to achieve solubility in water. Indeed, Grubbs and Hong followed this strategy to produce catalyst **13**, which showed greater activity for ROMP, ring-closing, and cross-metathesis reactions in water than earlier catalysts.[32] However, catalysts that incorporate PEG are inherently polydisperse and are amenable to limited structural characterization. Furthermore, a long PEG chain may interact with substrate molecules or with the catalyst itself in manners affecting catalyst structure and activity. For example, catalyst **13** forms aggregates resembling micelles in water.[32] Therefore, the strategy employed by the research presented in this chapter pursues the synthesis of small-molecule catalysts. Such complexes are amenable to full

characterization by both X-ray and spectroscopic techniques and avoid any potential complications arising from a large pendant group.

Results and Discussion

Catalyst synthesis and characterization. The ammonium functional group was used to produce discrete, water-soluble catalysts. This functionality was chosen based both on its ease of synthesis and the prior use of ammonium salts to successfully generate water-soluble analogs of catalyst **1**.[9,11] Earlier research has shown that at least two ionic functional groups must be incorporated to yield water-soluble metathesis catalysts containing an NHC ligand.[33] Therefore, catalysts **14** and **15**, which each contain two ammonium functional groups, were synthesized. While catalyst **14** displays both ammonium groups from its 2-isopropoxybenzylidene ligand, catalyst **15** includes only one ammonium salt on its benzylidene ligand. A second ammonium group is attached to this complex through its NHC ligand.



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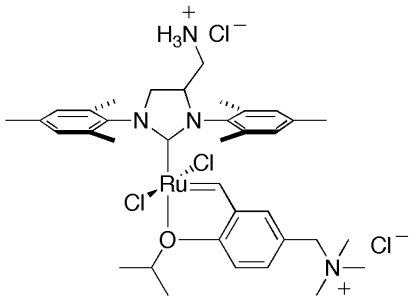

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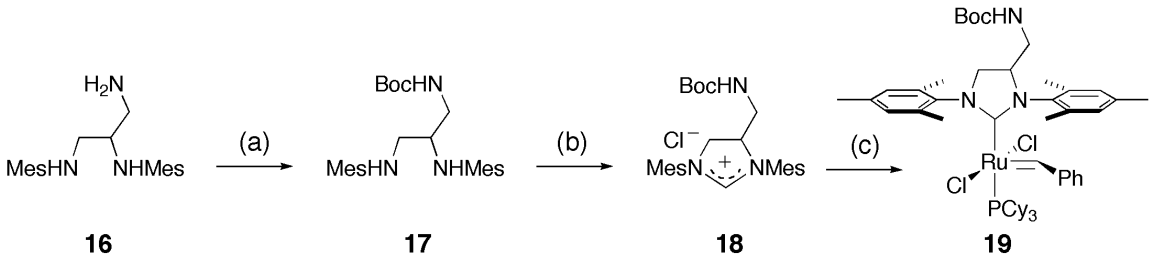
The syntheses of the ruthenium starting material and the 2-isopropoxystyrenes used to construct catalysts **14** and **15** are shown in Schemes 5.1 and 5.2. The synthesis of ruthenium complex **19** is straightforward and is described in more detail in Chapter 3

(Scheme 5.1). Also, the syntheses of the 2-isopropoxystyrenes are chromatography free and readily allow for the rapid production of multiple grams of both styrenes **23** and **25**.

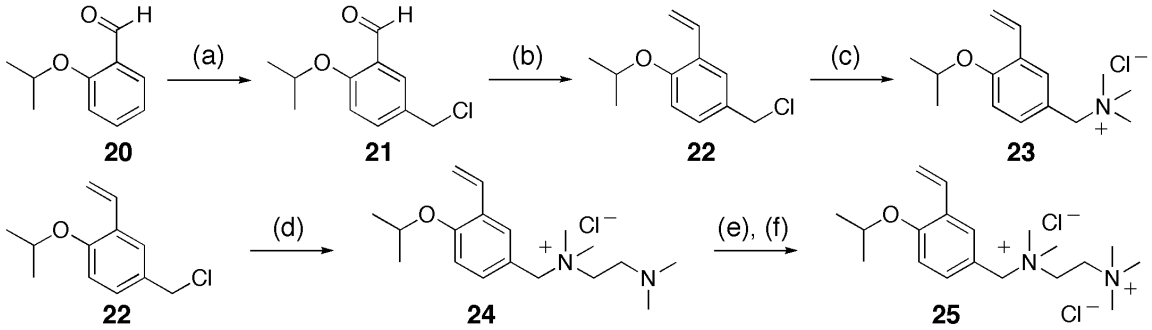
Scheme 5.1.



Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, rt, 2 h (86%), (b) $(EtO)_3CH$, NH_4Cl, 120 °C, 16 h (90%), (c) ^tBuOK, **1**, THF, rt, 17 h (61%). Boc: *tert*-butoxycarbonyl

The syntheses of styrenes **23** and **25** used to produce catalysts **14** and **15** are shown in Scheme 5.2. Chloromethylation followed by Wittig olefination of readily synthesized benzaldehyde **20** provides benzyl chloride **22** in moderate yield. Amination with trimethylamine then yields isopropoxystyrene **23**. Amination of **22** with N,N,N',N'-tetramethylethylenediamine followed by methylation and ion exchange gives isopropoxystyrene **25**.

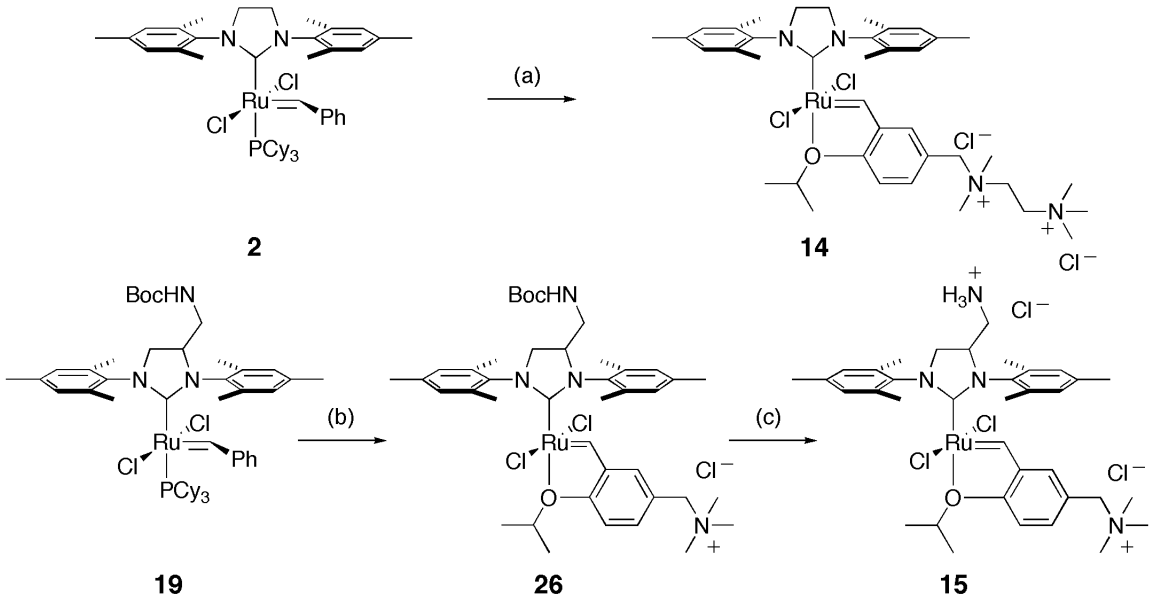
Scheme 5.2.



Reagents and conditions: (a) CH_2O, HCl(aq), HCl(g), 50 °C, 3h (66%), (b) $BrCH_3PPh_3$, KO^tBu, THF, –60 – 15 °C, 2 h (78%), (c) NMe_3, MeCN, 0 °C – rt, 12 h (81%), (d) $MeN(CH_2)_2NMe_2$, MeCN, rt, 24 h (90%), (e) MeI, CH_2Cl_2, rt, 7 h, (f) Amberlite IRA-400(Cl), H_2O, 12 h (performed 3 times) (81%, 3 steps).

Catalyst **14** and ruthenium complex **26** can be readily assembled by mixing ruthenium complexes **2** and **19** with 2-isopropoxystyrenes **25** and **23** in the presence of copper(I)chloride (Scheme 5.3). The deprotection of **26**'s primary amine with a freshly prepared solution of hydrogen chloride in benzene then yields catalyst **15**. Interestingly, catalyst **14** is also produced by mixing styrene **25** with ruthenium bis(pyridine) complex **4** in dry, degassed DMF at 30 °C. However, because the reactions in DMF gave lower conversions to product **14**, this route was abandoned..

Scheme 5.3.



Reagents and conditions: (a) **25**, CuCl, CH_2Cl_2, 45 °C, 1 h (46%), (b) **19**, CuCl, CH_2Cl_2, 40 °C, 1 h, (c) HCl, C_6H_6, rt, 1 h (67%, 2 steps).

The isolation of catalysts **14** and **15** was challenging as both the desired catalysts and the impurities were highly polar. As neither catalyst ran on silica gel and recrystallizations of crude material were ineffective, chromatography on alumina was explored. The anaerobic passage through two neutral Brockman grade V alumina

columns followed by a single neutral Brockman grade III alumina column provided **14** in sufficient purity that its recrystallization from methanol with diethyl ether yielded pure catalyst. To obtain catalyst **15**, ruthenium complex **26** was passed through a single neutral Brockman grade III alumina column prior to its deprotection with hydrogen chloride in benzene. After this deprotection, trituration with dichloromethane followed by recrystallization from methanol with diethyl ether gave pure catalyst **15**.

The structures of catalysts **14** and **15** are readily confirmed by spectroscopic analysis. The ^{1}H NMR spectra of **14** and **15** each display a resonance at 16.8 ppm, which is consistent with phosphine-free benzylidene complexes containing an NHC ligand.[31,34] Similarly the ^{13}C NMR spectra of **14** and **15** contain the expected resonances corresponding to their two carbene carbons, 295.3 and 209.4 ppm for **14** and 306.1 and 210.8 ppm for catalyst **15**.[31,34] Finally, the composition of catalysts **14** and **15** was further confirmed by high resolution mass spectrometry.

Additionally, the diffusion of diethyl ether into a relatively dilute solution of **14** in methanol yields crystals suitable for X-ray analysis. The crystal structure reaffirms the assigned structure of **14** (Figure 5.2). X-ray quality crystals of catalyst **15** have not been obtained at this time.

Interestingly, the water-solubility properties of catalysts **14** and **15** are quite different. Catalysts **15** readily dissolves in water to form homogenous solutions. In contrast, complex **14** is only moderately soluble in water. Full dissolution of catalyst **14** only occurs under highly dilute conditions though it is sufficiently soluble to be observed in deuterium oxide by ^{1}H NMR spectroscopy. For reactions run with five mol% catalyst

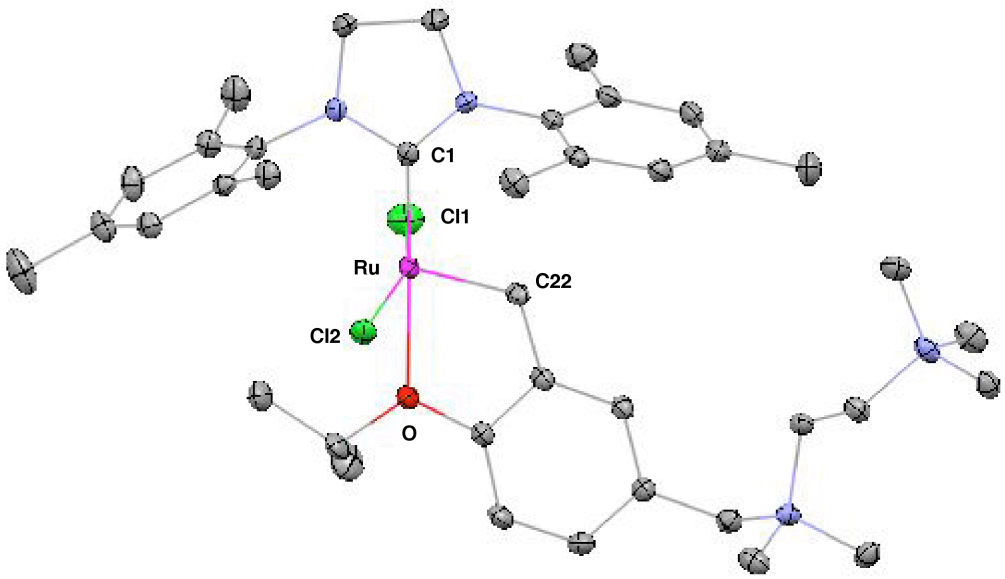


Figure 5.2. The structure of catalyst **14** has been confirmed by X-ray crystallographic analysis. Solvent molecules and the chloride counter-ions are omitted for clarity. Selected bond lengths (Å) and angles (°) for catalyst **14**: Ru-C22 1.8266(16), Ru-C1 1.9683(17), Ru-O 2.2601(12), Ru-Cl1 2.3378(4), Ru-Cl2 2.3459(5), C22-Ru-C1 101.68(7), C22-Ru-O 79.64(6), C1-Ru-O 178.65(5), C22-Ru-Cl2 97.14(5), C1-Ru-Cl2 96.62 (5), O-Ru-Cl2 82.94(3), Cl1-Ru-Cl2 158.086(18).

and 0.2 M substrate, the standard conditions for most reactions described in this chapter, catalyst **15** will form a homogenous solution while catalyst **14** does not fully dissolve. Many of the differences in the activity of catalysts **14** and **15** are likely related to these differences in their solubility properties.

Both catalysts are quite stable in water in the absence of substrate. For example, catalyst **15** has a decomposition half-life of over one week under inert conditions in deuterium oxide. Interestingly, the benzylidene hydrogen of these compounds does not appear to participate in deuterium exchange with deuterium oxide. Such an exchange process is rapid for water-soluble bis(phosphine) catalysts **5** and **6**.[13,35]

ROMP in water with catalysts 14 and 15. The ability to ROMP challenging, water-soluble *endo*-norbornene monomer **27** has been used to compare the activity of PEG-

catalyst **11** with water-soluble bis(phosphine) catalyst **6**.[26] Therefore, as an initial screen of their aqueous metathesis activity, the ability of catalysts **14** and **15** to polymerize **27** in water was examined. As shown in Figure 5.3, both **14** and **15** successfully polymerize monomer **27** in less than three hours. The ability of parent catalysts **2** and **3** to polymerize **27** in water was also examined to determine whether either catalyst would show activity in water. Neither catalyst **2** nor **3** demonstrated any ROMP activity in water, neither showing any visible reaction when mixed with monomer **27**.

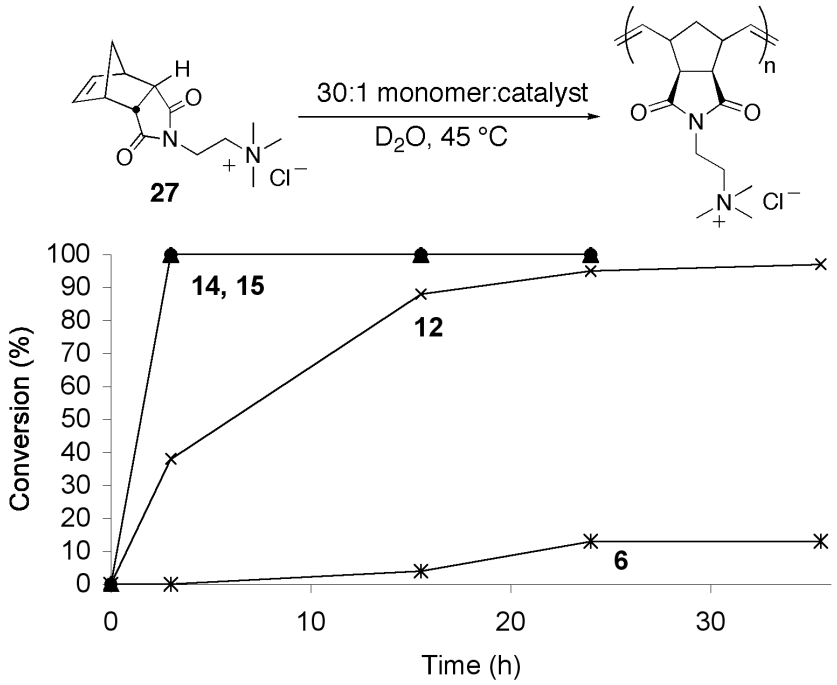
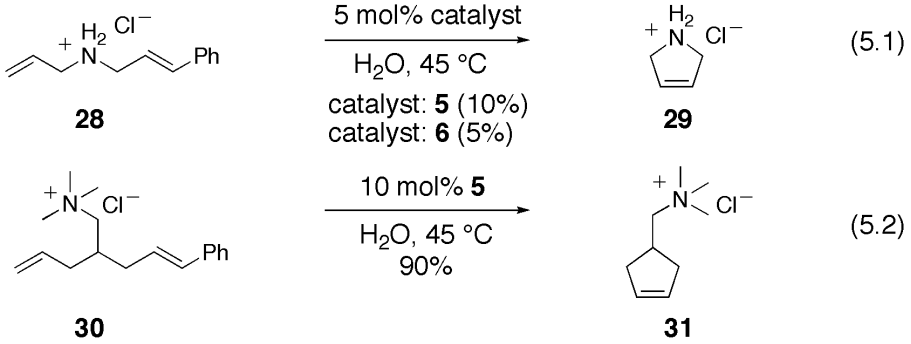


Figure 5.3. Following the ROMP of monomer **27** by ^{1}H NMR spectroscopy provided a measure of the relative activities of catalysts **6**, **12**, **14**, and **15** in water. For catalysts **5** and **11** the polymerization was run in the presence of one equivalent of deuterium chloride (versus catalyst) for increased activity. (The data for catalysts **14** and **15** overlap.)

The ROMP of monomer **27** does indicate increased activity for catalysts **14** and **15** in water relative to earlier water-soluble catalysts. Even so, the ROMP of norbornene monomers in water is one of the oldest reactions for ruthenium-based metathesis

catalysts.[36-38] Of greater interest is the ability of these catalysts to mediate metathesis reactions in water involving acyclic substrates, such as ring-closing or cross-metathesis reactions. Most prior research in ring-closing and cross-metathesis reactions in water with catalysts containing an NHC ligand either involved mixed solvent systems[20-23] or heterogenous systems where catalysis was believed to occur in organic pores.[17,24,25] Therefore, the ability of catalysts **14** and **15** to enable aqueous ring-closing metathesis and cross metathesis as homogenous reactions in water is of particular interest.

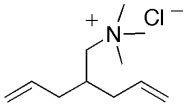
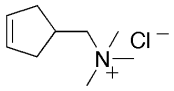
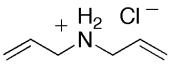
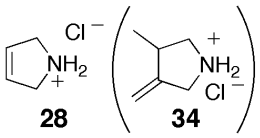
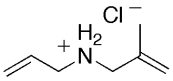
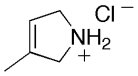
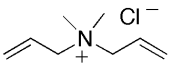
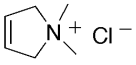
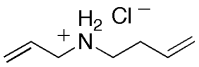
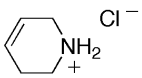
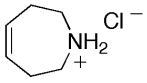
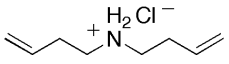
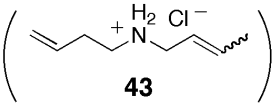
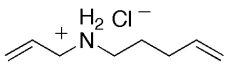
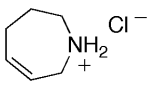
Ring-closing metathesis in water with catalysts 14 and 15. Prior to PEG-catalyst **13**, there are only three examples of homogenous ring-closing metathesis reactions in neat water. Water-soluble catalysts **5** and **6** mediate the ring-closing metathesis of substrate **28** (eq 5.1). Additionally catalyst **6** also ring-closes substrate **30** (eq 5.2).[12] Note that both substrates contain one terminal olefin and one internal olefin with a terminal phenyl group. This substrate composition is required to inhibit the formation of the highly unstable bis(phosphine) ruthenium methylidene derivative for these reactions to be successful.[12,39,40] However, as the substrates are more synthetically accessible and the reactions more atom efficient, the ring-closing of α,ω-dienes is preferred. Currently, catalysts **13** through **15** are the only catalysts capable of performing homogenous, RCM reactions of α,ω-dienes in neat water.



28 **29** (5.1)

30 **31** (5.2)

Table 5.1. Ring-closing metathesis of α,ω-dienes in water with catalysts **13**–**15**[a]

Entry (Catalyst)	Substrate	Time (h)	Product	Conversion (%)
1 (**13**)[b]		12		>95%
2 (**14**)		24		>95%
3 (**15**)	**32**	0.5	**31**	>95%
4 (**13**)[b]		36		67 (+28)
5 (**14**)		24		>95
6 (**15**)	**33**	4	**28** **34**	36 (+59)
7 (**13**)[b]		24		42
8 (**14**)		24		70
9 (**15**)	**35**	6	**36**	26
10 (**13**)[b]		24		<5
11 (**14**)		24		<5
12 (**15**)	**37**	24	**38**	<5
13 (**13**)[b]		24		>95
14 (**14**)		24		>95
15 (**15**)	**39**	4	**40**	84
16 (**13**)[b]		24		68 (+14)
17 (**14**)		24	**42**	77
18 (**15**)	**41**	4	 **43**	36 (+30)
19 (**13**)[c]		24		39
20 (**14**)		24		45
21 (**15**)	**44**	4	**45**	9

[a]Reactions were performed at 30 °C with 5 mol% of catalyst and an initial substrate concentration of 0.2 M in deuterium oxide. Reaction times were not optimized, and the conversions represent the maximum conversion for the reaction. All conversions were measured by ^{1}H NMR and are the average of two trials. [b]Reactions were performed at room temperature. These data are from reference 41. [c]These data are from reference 41.

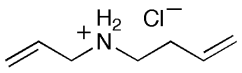
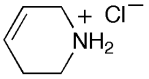
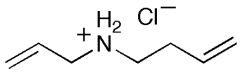
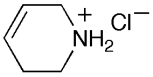
Table 5.1 lists the results of the RCM of several α,ω-dienes in water with catalysts **14** and **15**. The reported results for the RCM of these substrates with catalyst **13** are also provided for comparison.[32,41] As shown, all three catalysts are capable of ring-closing α,ω-diene substrates to form five-membered ring (entries 1–9), six-membered ring (entries 13–15), and seven-membered ring (entries 16–21) products in good to moderate yields. Moreover, like catalyst **13**, catalysts **14** and **15** show sufficient activity to ring-close substrate **35** to yield **36**, which contains a trisubstituted olefin (entries 7–9). Finally, ring-closing the fully symmetric substrate **46** to form seven-membered ring **47** occurs far more readily with all three catalysts than the cyclization of the analogous unsymmetrical substrate **49** (entries 16–21).

Both catalysts **13** and **15** produce a significant amount of isomerized product **34** when ring-closing substrate **33** (entries 4–6). Significant isomerization is also observed during the ring-closing metathesis of substrate **41** with catalyst **15** (entry 18). These isomerized products are believed to be the results of reactions with ruthenium hydrides formed upon catalyst decomposition.[24,32,27,42-46]

Table 5.1 clearly indicates that catalyst **14** has a greater aqueous ring-closing activity than catalyst **15**. To gain a better insight into this apparent difference in activity, the aqueous ring-closing metathesis of substrate **39** with both catalysts was examined after short reaction times. As shown in Table 5.2, after 30 minutes, catalyst **14** has cyclized 53% of **39** while **15** has ring-closed 78% of the substrate. However, allowing the reactions to proceed for an additional 30 minutes allows catalyst **14** to ring-close an additional 23% of **39** to give a conversion of 76%. In contrast, in that same period of time, catalyst **15** is only able to ring-close an additional 4% of **39** yielding an 82%

conversion. Finally, as listed in Table 5.1, after extended reaction times, catalysts **14** will fully cyclize **39** while catalyst **15** gives a maximum conversion of 88%.

Table 5.2. The ring-closing metathesis of substrate **39** with catalysts **14** and **15**[a]

Catalyst	Substrate	Time (h)	Product	Conversion (%)
14		0.5		53
15	**39**	0.5	**40**	78
14		1		76
15	**39**	1	**40**	82

[a]Reactions were performed at 30 °C with a 5 mol% catalyst loading and an initial substrate concentration of 0.2 M in deuterium oxide. Conversions were determined by ^{1}H NMR spectroscopy and represent the average of two trials.

The data in Table 5.2 suggest that catalyst **15** is the more kinetically reactive and less stable than catalyst **14**. While slower than **15**, the increased stability of catalyst **14** allows it to ring-close more substrate prior to decomposition. The increased stability of catalyst **14** over **15** is also reflected in the aqueous ring-closing of substrates **38** and **46** where catalyst **15** yields a greater amount of isomerized product (Table 5.1, entries 5, 6, 17, and 18).

The differences in their water-solubility are believed to dominate the kinetic reactivity and stability of catalysts **14** and **15**. Catalyst **15** dissolves in water to form a homogenous solution. This allows catalyst **15** to be more accessible to substrate molecules and, therefore, the more kinetically reactive catalyst. For the same reason, catalyst **15** is the least stable catalyst as it is the most accessible to water, which is a solvent known to be harmful to the stability of ruthenium metathesis catalysts.[30,47,48]

Under the shown reaction conditions, catalyst **14** only partially dissolves in water, leaving a solid reservoir of catalyst. The low concentration of dissolved catalyst is likely responsible for **14**'s lower kinetic reactivity relative to catalyst **15**. However, the low solubility of **14** is probably also responsible for its increased stability, as catalyst consumed during the reaction can be replenished from the solid reservoir. This may serve to minimize the amount of **14** that decomposes prior to performing any productive metathesis. The low concentration of catalyst **14** in water may also increase its stability by decreasing the rate of decomposition pathways involving two metal centers. Such pathways are known to play a role in the decomposition of metathesis-active ruthenium alkylidene complexes.[49]

At this point it is important to note the likelihood for microphase behavior with these catalysts during metathesis reactions. Solubility changes during the course of metathesis reactions may cause catalysts **14** and **15** to form microphases. Ruthenium metathesis catalysts containing an NHC ligand require at least two ionic groups to dissolve in water.[33] With catalyst **14**, both groups are displayed by its isopropoxybenzylidene ligand while catalyst **15** contains only one ionic group on its isopropoxybenzylidene ligand. However, this ligand is freed from the ruthenium center during productive metathesis.[31,50] Hence, the only water-soluble group on catalyst **14**'s alkylidene derivative is that provided by the water-soluble substrate while **14**'s methylidene derivative lacks a water-soluble functional group (Figure 5.4). Catalyst **15**'s alkylidene derivative will display two water-soluble groups, one from its NHC ligand and that provided by the water-soluble substrate and is likely fully soluble in water. However, **15**'s methylidene derivative relies entirely on the ionic NHC ligand for dissolution in

water (Figure 5.4). Therefore, the formation of microphases by catalysts **14** and **15** during metathesis reactions is plausible.

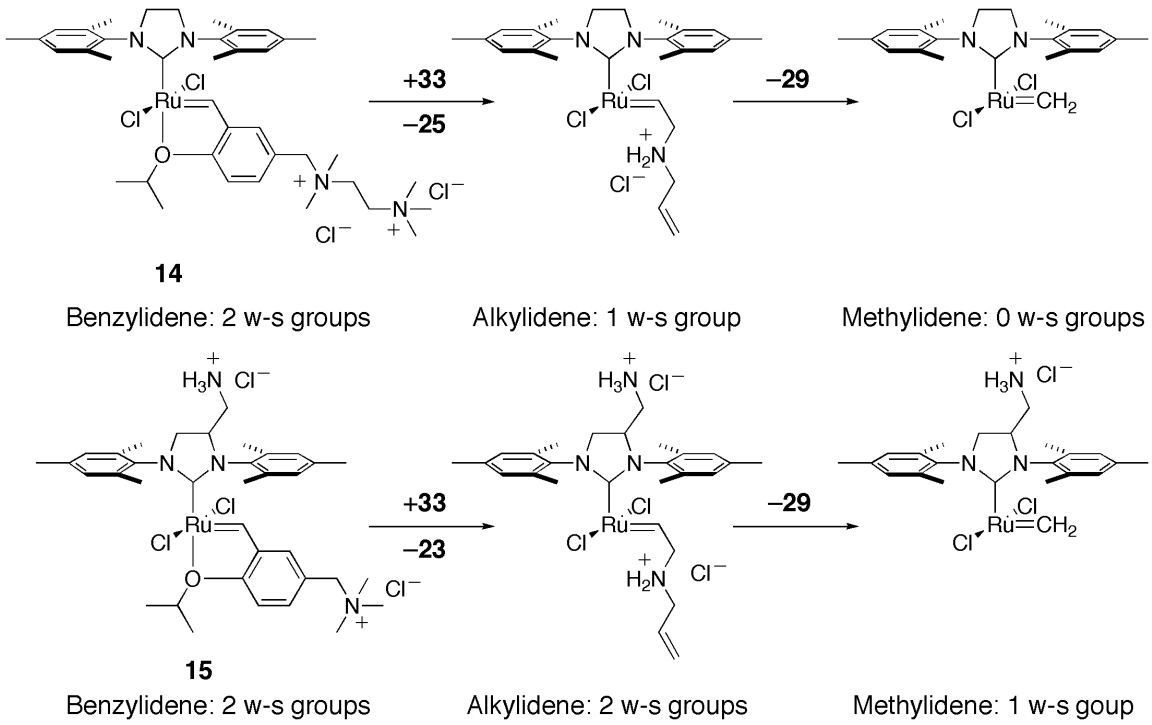


Figure 5.4. The alkylidene and methylidene derivatives formed during the ring-closing metathesis of substrate **33** with catalysts **14** and **15** are shown. Provided below each structure is the number of water-soluble (w-s) functional group(s) that each complex contains.

Tolerance of water-soluble functional groups. There exist a variety of functional groups commonly encountered in water and not in organic media. Such groups include the sulfate, sulfonate, carboxylate, phosphate and guanidinium functional groups. The ability of ruthenium-based metathesis catalysts to tolerate these groups is of interest as this tolerance is required for substrates containing such functionality.

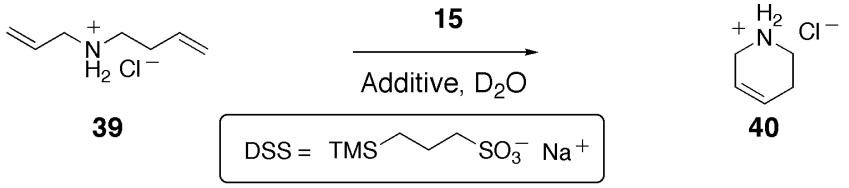
The RCM of substrate **39** with catalyst **15** was utilized to examine the tolerance of ruthenium-based metathesis catalysts for the listed functional groups. This reaction was chosen because catalyst **15** is fully soluble in water, which removes many concerns

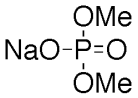
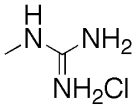
regarding mass transfer. Furthermore, **15** does not isomerize nor fully cyclize **39** making RCM reactions with this substrate an excellent platform for comparing the effect of various additives on catalyst **15**. The chosen additives each display a functional group of interest. These reactions provide a good method for judging the effect of various functional groups on ruthenium-based metathesis catalysts.

Table 5.3 lists the results of ring-closing 0.2 M of substrate **39** with 5 mol% of catalyst **15** in deuterium oxide in the presence of 0.2 M of an additive of interest. While the sulfonate group dramatically reduces the ability of **15** to ring-close **39**, the sulfate group only has a moderate effect on conversion though it appears to cause complex decomposition over time (entries 2 and 3). Neither phosphate nor guanidinium groups have much of an effect on this reaction though the guanidinium-containing additive significantly retards the rate of **15**'s dissolution in water (entries 4 and 5). Interestingly, while the carboxylate group completely shuts down the reaction to give an orange solution, the corresponding acid does not significantly effect catalyst **15** though it promotes the formation of a minor, unidentified side-product (entries 6 and 7).

The additives that had the largest impact on the shown reaction, sodium acetate and 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS)**,** both contain functional groups that are known to displace the chloride ligands of ruthenium-based metathesis catalysts.[51-54] Therefore, these additives likely displace one or more of **15**'s chloride ligands to yield a complex that is less stable and/or active than catalyst **15**. As would be expected from this theory, when DSS is the additive, an insoluble green precipitate is formed. This is consistent with replacing **15**'s chloride ligand(s) with a greasy trimethysilylpropyl group of DSS to yield a water-insoluble complex(es).

Table 5.3. The effect of various functional groups on the ring-closing of substrate **39** with catalyst **15**[a]



Entry	Additive	Conversion (%)	Comments
1	None	88	--
2	DSS	18	MOST of **15** rapidly forms a water-insoluble complex.
3	Na_2SO_4	72	Dissolution of **15** is noticeably retarded. Decomposition to an orange complex and a precipitate are observed.
4		83	Only a minor effect on catalysis is observed.
5		90	Dissolution of **15** is noticeably retarded.
6	NaOAc	< 5	**15** rapidly decomposes to an orange complex.
7	AcOH	94	A minor side-product is observed.

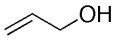
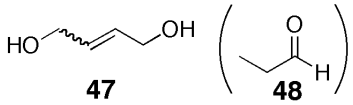
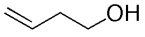
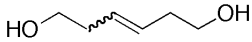
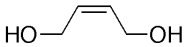
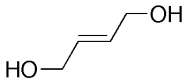
[a]Reactions were performed at 30 °C with a 5 mol% catalyst loading and initial substrate and additive concentrations of 0.2 M in deuterium oxide. Conversions were determined after 4 h by ^{1}H NMR spectroscopy and represent the average of two trials.

Catalyst cross-metathesis activity in water. As shown, catalysts **14** and **15** are able to mediate ROMP in water and are competent catalysts for RCM in an aqueous environment. Another prominent metathesis transformation is the cross-metathesis reaction. This is a challenging reaction in water that earlier water-soluble catalysts failed to catalyze.[11,26]

The homodimerization of various substrates was used as an initial examination of the ability of catalysts **14** and **15** to perform cross-metathesis in water. As shown in Table 5.4, both catalysts successfully homodimerized allyl and homoallyl alcohol. The catalysts

were also able to isomerizes *cis*-2-butene-1,4-diol. Again, the reported results for catalyst **13** with these substrates are also provided for comparison.[32,41]

Table 5.4. Homodimerization in water with catalysts **13**–**15**[a]

Entry (Catalyst)	Substrate	Time (h)	Product	Conversion (%)	E:Z
1 (**13**)[b]	 **46**	12	 **47** **48**	>95	15:1
2 (**14**)		24		82 (+4)	13:1
3 (**15**)		6		69 (+12)	19:1
4 (**13**)[c]	 **49**	12	 **50**	83	8:1
5 (**14**)		24		81	9:1
6 (**15**)		6		70	4:1
7 (**13**)[b]	 **51**	12	 **52**	94	--
8 (**14**)[d]		24		92	--
9 (**15**)[d]		2		94	--

[a]Reactions were performed at 45 °C with 5 mol% of catalyst and an initial substrate concentration of 0.2 M in deuterium oxide. Conversions were determined by ^{1}H NMR spectroscopy and represent the average of two trials. Reactions times were not optimized. [b]These data are from reference 41. [c]Reaction was performed at room temperature. These data are from reference 41. [d]Reaction was performed at 30 °C.

That catalysts **14** and **15** homodimerize allyl alcohol and homoallyl alcohol raises an interesting possibility. Both allyl and homoallyl alcohol can coordinate to the ruthenium center through their oxygen atoms to form a four- and five-membered chelate respectively (Figure 5.5). In contrast, such substrates as *O*-allyl tyrosine hydrochloride, allyl amine hydrochloride and (4-vinylbenzyl)trimethyl ammonium chloride, which lack a well-placed coordinating group, do not show any noticeable reaction with these catalysts. This inspires the hypothesis that productive cross metathesis in water requires a coordinating group that can chelate to the ruthenium center and stabilize the ruthenium alkylidene formed during the reaction. To test this hypothesis, we examined the homodimerization of 2-*O*-allyl-*β*-glucopyranoside, 3-butenoic acid, 4-pentenoic acid, 3-

butenamide and 4-pentenamide, which all contain reasonably well-placed coordinating groups. Unfortunately, these substrates also fail to homodimerize, though some isomerization was observed during attempts to homodimerize the olefins displaying sugar or carboxylic acid functionalities. Therefore, while a well-placed coordinating group may be required for successful cross metathesis in water, the mere presence of such functionality is not sufficient for successful aqueous cross metathesis.

Figure 5.5. Four- and five-membered ring chelate complexes might be formed during the homodimerization of allyl alcohol (**A**) and homoallyl alcohol (**B**) respectively.

Admittedly, the cross-metathesis activity of catalysts **14** and **15** is limited. Even so, the reactions shown in Table 5.4 represent the first examples of successful cross metathesis in water. Moreover, Kuo and Grubbs have used catalyst **14** to mediate cross-metathesis reactions between olefin-displaying ruthenium dyes and a few different cross partners.[41] Two examples of these reactions are provided in Figure 5.6. While the yields are low to moderate, the cross-metathesis reactions of Kuo and Grubbs are the only examples of successful cross metathesis between two different substrates in water.

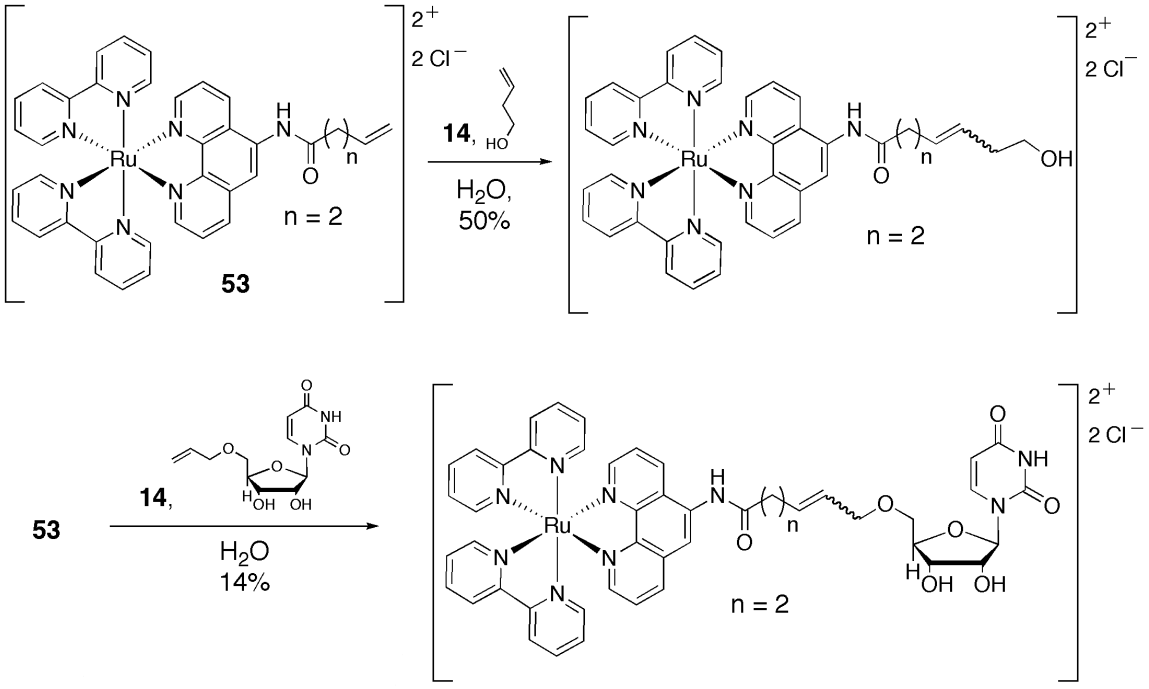


Figure 5.6. Catalyst **14** is able to cross terminal olefins onto ruthenium dye complex **53**.[41]

Summary

Water-soluble catalysts **14** and **15**, containing an NHC ligand, were synthesized. Both catalysts are phosphine-free and utilize ammonium salts to achieve solubility in water. While **14** is only moderately soluble, catalyst **15** readily dissolves in water. Both catalysts show superior ROMP activity over earlier water-soluble bis(phosphine) catalysts. Also, catalysts **14** and **15** are able to ring-close α,ω-dienes in water to form five-, six-, and seven-membered ring products in good to moderate conversions. Furthermore, though their aqueous cross-metathesis activity is limited, these catalysts are able to homodimerize allyl and homoallyl alcohol in good conversion.

Acknowledgements

The author is grateful to Dr. Soon Hyeok Hong and Professor Louis Kuo for their collaboration in developing aqueous metathesis catalysts. Also, Dr. Soon Hyeok Hong generously provided substrates **35** and **39**. Dr. Ian Stewart and Professor Tobias Ritter are acknowledged for helpful conversations. Dr. Mona Shahgholi generously assisted with mass spectometry, and Drs. Larry M Henling and Michael W. Day are thanked for their assistance with X-ray crystallography. Finally, the National Institute of Health (5R01GM068647) is acknowledged for funding.

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under dry, degassed conditions were performed using standard Schlenk techniques under an atmosphere of dry argon using flame or oven-dried glassware. All NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, d = doublet, ψd = pseudo-doublet, ψt = pseudo-triplet, dd = doublet of doublets, sept = septet, m = multiplet, and br = broad. All thin-layer chromatography (TLC) of organic compounds was accomplished on silica-gel 60 F254 percoated plates with a fluorescent indicator and visualized by UV light and/or by standard potassium permanganate stains. All flash chromatography of organic compounds was performed with silica-gel 60 (230–400 mesh). Neutral Brockman grade III alumina was generated by mixing 6% water (by mass) with neutral Brockman grade I

alumina (~150 mesh). For anaerobic chromatography, columns are first purged with argon, and all eluant is degassed with a generous argon sparge (at least 30 minutes). Product is then eluted under argon and collected in a round-bottom flask already purged with argon and equipped with a magnetic stir bar while under a stream of argon. Eluant is then removed *in vacuo*, not by rotary evaporation.

Materials. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane was dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Deuterated methanol and deuterated dichloromethane were degassed by three freeze, pump, and thaw cycles while deuterium oxide was degassed by a generous argon sparge. Anhydrous methanol was purchased from Aldrich and degassed with a generous argon sparge. Anhydrous DMF was purchased from Acros Organics and degassed with a generous argon sparge. Acetonitrile was purchased from Aldrich. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained. Ruthenium complexes **1**, **2**, and **3** were gifts from Materia. The syntheses of compounds **16**–**18** and ruthenium complex **19** was described in Chapter 3. Benzaldehyde starting material, **20**,[55] homoallyl amine,[56] and *N*-(*tert*-butoxycarbonyl)allylamine[57] were made following literature procedures. Substrates and products **27**,[26] **28**,[58] **29**,[59] **30**,[11] **31**,[60] **32**,[32] **34**,[24] **35**,[32] **36**,[59] **39**,[32] **40**,[61] **50**,[62,63] **52**,[64] *O*-allyl tyrosine hydrochloride,[65] 2-*O*-allyl-*β*-glucopyranoside,[66] 3-butenamide,[67] 4-pentenamide,[67] (4-vinylbenzyl)trimethyl ammonium chloride,[68] and 5-hexenoyl chloride[69] have already been reported. Substrate

33 was purchased from TCI America. Compounds **37**, **46**, **49**, **50**, triphenyl(methyl)phosphonium bromide, di-*tert*-butyl dicarbonate, homoallyl bromide, 60% sodium hydride, sodium hydride, 5-bromo-1-pentene, 3-butenoic acid, 4-pentenoic acid, 4 M HCl in dioxane, *N*,*N*,*N*',*N*'-tetramethylethylenediamine, trimethylamine gas, Amberlite IRA-400(Cl) ion-exchange resin were purchased from Aldrich. Sulfuric acid was purchased from Fischer Scientific. Ammonium chloride, hydrochloric acid, sodium hydroxide, sodium chloride, sodium bicarbonate, and magnesium sulfate were purchased from Malinkrodt. Sodium sulfate was purchased from EMS.

5-(Chloromethyl)-2-isopropoxybenzaldehyde (21). A two-neck round-bottom flask, equipped with a stir bar, was charged with compound **20** (10.0 g, 61 mmol), aqueous formaldehyde (37%, 13.6 mL, 180 mmol, 3.0 equiv), and concentrated hydrochloric acid (40 mL). The reaction mixture was heated to 50 °C prior to sparging with hydrogen chloride. (Hydrogen chloride was generated by slowly dripping 10 equivalents of sulfuric acid onto 10 equivalents of ammonium chloride.) The reaction was allowed to continue for 3 hours with a constant hydrogen chloride sparge at 50 °C. The produced dark-red, biphasic reaction mixture is cooled to 0 °C and diluted with diethyl ether. This mixture is made basic by the slow addition of 15% aqueous sodium hydroxide, and the resulting precipitate was removed by vacuum filtration. The filtrate is transferred to a separatory funnel and rinsed with water (2×) and brine (2×). The organic layer is dried over magnesium sulfate and evaporated to give a yellow solid. Recrystalization from petroleum ether yields 8.50 g (66%) of a white, crystalline product. ^{1}H NMR ($CDCl_3$, ppm): δ 10.46 (s, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.99 (d,

J = 8.1 Hz, 1H), 4.70 (sept, *J* = 6.0 Hz, 1H), 4.55 (s, 2H), 1.41 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 189.8, 160.7, 136.2, 129.8, 128.6, 125.6, 114.5, 71.5, 45.6, 22.1. HRMS (EI+) *m*/*z* calc for $C_{11}H_{13}O_2Cl$: 212.0604, found 212.0600.

4-(Chloromethyl)-1-isopropoxy-2-vinylbenzene (22). A flame-dried, three-neck round-bottom flask, equipped with a stir bar and an addition funnel and purged with argon, was charged with triphenyl(methyl)phosphonium bromide (8.23 g, 23 mmol, 1.2 equiv), dry, degassed THF (157 mL), and potassium *tert*-butoxide (3.11 g, 28 mmol, 1.5 equiv) to give a bright-yellow solution. This solution was allowed to stir at room temperature under a positive argon pressure for 2 hours prior to cooling to ~ –60 °C. A solution of compound **21** (4.00 g, 19 mmol) in dry, degassed THF (78 mL) was slowly added over a period of 30 minutes while maintaining the temperature at ~ –60 °C. The reaction was then allowed to continue under a positive argon pressure while slowly warming to ~15 °C (~2 hours). Upon reaction completion, this mixture was diluted with diethyl ether, transferred to a separatory funnel and rinsed with a saturated aqueous solution of sodium bicarbonate (2×) and with brine (2×). The organic layer was dried over sodium sulfate and evaporated. The product was then passed through a plug of neutral alumina with 5% ethyl acetate in hexanes to obtain 3.07 g (78%) of clear, colorless liquid product of sufficient purity for use (~90% pure). For improved purity, the product can be eluted from a short flash column with 5% ethyl acetate in hexanes. However, the yield is significantly lowered (~50% yield) by the instability of **22** on silica-gel 60. The characterization data are of pure material. ^{1}H NMR ($CDCl_3$, ppm): δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.2 Hz, 2.2Hz, 1H), 7.02 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.84 (d, *J* = 8.7

Hz, 1H), 5.74 (dd, *J* = 18 Hz, 1.8 Hz, 1H), 5.25 (dd, *J* = 11 Hz, 1.5 Hz, 1H), 4.55 (s, 2H), 4.53 (sept, *J* = 6.0 Hz, 1H), 1.34 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 155.4, 131.7, 129.6, 129.3, 128.2, 127.3, 114.8, 114.2, 71.1, 46.6, 22.3. HRMS (EI+) *m*/*z* calc for $C_{12}H_{15}OCl$: 210.0811, found 210.0814.

1-(4-Isopropoxy-3-vinylphenyl)-*N*,*N*,*N*-trimethylmethanaminium chloride (23). A round-bottom flask was equipped with a stir bar and a cold-finger filled with a dry-ice/acetone bath. The flask was charged with compound **22** (501 mg, 2.4 mmol) and acetonitrile (12.0 mL) and cooled to 0 °C prior to a 5 minute sparge with trimethylamine gas. The reaction was allowed to continue overnight (~12 hours) while slowly warming to room temperature. Upon reaction completion, the reaction mixture was sparged generously with air to remove excess trimethylamine. The acetonitrile was removed by rotary evaporation and the acquired solid dissolved in dichloromethane. Precipitation from diethyl ether followed by isolation by vacuum filtration yielded 520 mg (81%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm): δ 7.60 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.88 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.73 (dd, *J* = 18 Hz, 1.2 Hz, 1H), 5.19 (dd, *J* = 11 Hz, 1.2 Hz, 1H), 4.88 (s, 2H), 4.50 (sept, *J* = 6.0 Hz, 1H), 3.32 (s, 9H), 1.28 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 156.8, 133.7, 131.3, 130.9, 128.1, 119.2, 115.9, 113.6, 70.7, 68.8, 52.4, 22.1. HRMS (FAB+) *m*/*z* calc for $C_{15}H_{24}NO$: 234.1858, found 234.1854.

2-(Dimethylamino)-N-(4-isopropoxy-3-vinylbenzyl)-*N*,*N*-dimethylethanaminium chloride (24). A round-bottom flask equipped with a stir bar was charged with compound

22 (3.04 g, 14 mmol), *N*,*N*,*N*',*N*'-tetramethylethylenediamine (15.2 mL, 100 mmol, 7.1 equiv), and acetonitrile (72.0 mL). This reaction mixture was allowed to stir at room temperature for 14 hours. Upon reaction completion, the acetonitrile was removed by rotary evaporation, and the product was dissolved in dichloromethane. Precipitation from –78 °C diethyl ether followed by vacuum filtration yields 4.26 g (90%) of product as a white powder that rapidly forms an oil in the presence of moisture (extremely hygroscopic). A solid is obtained by extensive drying under high vacuum. The sample for NMR spectroscopy was prepared in a N_2-filled glove box with dry, degassed deuterated dichloromethane. ^{1}H NMR (CD_2Cl_2, ppm): δ 7.74 (d, *J* = 3.0 Hz, 1H), 7.54 (dd, *J* = 9.0 Hz, 2.7 Hz, 1H), 6.96 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.88 (d, *J* = 9.3 Hz, 1H), 5.80 (dd, *J* = 18 Hz, 1.8 Hz, 1H), 5.24 (dd, *J* = 12 Hz, 1.8 Hz, 1H), 5.03 (s, 2H), 4.57 (sept, *J* = 6.0 Hz, 1H), 3.81 (t, *J* = 5.4 Hz, 2H), 3.27 (s, 6H), 2.73 (t, *J* = 5.4 Hz, 2H), 2.23 (s, 6H), 1.31 (d, 6.6 Hz, 6H). ^{13}C NMR (CD_2Cl_2, ppm): δ 157.0, 134.4, 132.0, 131.5, 128.2, 120.0, 115.7, 113.9, 71.1, 68.4, 60.6, 54.3, 49.7, 45.6, 22.2. HRMS (FAB+) *m*/*z* calc for $C_{18}H_{31}N_2O$: 291.2436, found 291.2424.

***N*-(4-Isopropoxy-3-vinylbenzyl)-*N*,*N*,*N'*,*N'*,*N'*-pentamethylethane-1,2-diaminium chloride (25).** A round-bottom flask equipped with a stir bar was charged with compound **24** (4.26 g, 13 mmol), dichloromethane (65.0 mL), and iodomethane (7.00 mL, 110 mmol, 8.6 equiv). The reaction was allowed to stir at room temperature for 7 hours. Precipitation of the reaction mixture from diethyl ether yields an ivory solid. This solid was allowed to stir in diethyl ether overnight prior to isolation by vacuum filtration to yield a white solid, which rapidly forms an oil in the presence of moisture (highly

hygroscopic). The material was dissolved in water (433 mL) followed by the addition of 65 g of Amberlite IRA-400(Cl) resin. This mixture was allowed to stir for 12 hours prior to removing the resin by vacuum filtration. 65 g of fresh resin was then added to the filtrate and the mixture was stirred for 12 hours prior to the resin's removal by vacuum filtration. This process was repeated one more time. Water was removed by rotary evaporation at elevated temperature, and the product was triturated 3 times with benzene. Drying under high vacuum for an extended period of time (~16 h) at 50 °C yields 3.97 g (81%) of product as a white powder (highly hygroscopic). ^{1}H NMR (DMSO-d_6, ppm) δ 7.87 (d, J = 1.8 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 1.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.93 (dd, J = 11 Hz, 18 Hz, 1H), 5.88 (dd, J = 18 Hz, 1.5 Hz, 1H), 5.30 (dd, J = 11 Hz, 1.5 Hz, 1H), 4.76 (s, 2H), 4.70 (sept, J = 6.0 Hz, 1H), 4.41 (br s, 2H), 4.24 (br s, 2H), 3.31 (s, 9H), 3.14 (s, 6H), 1.29 (d, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, ppm): δ 155.9, 134.0, 131.5, 130.9, 126.7, 119.3, 115.7, 113.7, 70.1, 66.1, 56.8, 55.4, 52.6, 49.1, 21.8. HRMS (FAB+) m/z calc for $C_{19}H_{34}N_2OCl$: 341.2360, found 341.2361.

Ruthenium complex 14. In a N_2-filled glove box, a flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **2** (200 mg, 0.24 mmol), compound **21** (133 mg, 0.35 mmol, 1.5 equiv), and copper(I)chloride (47 mg, 0.48 mmol, 2.0 equiv) and capped with a septum. The flask was brought out of the glove box, and its seal was reinforced with Teflon tape. Dry, degassed dichloromethane (6 mL) was added, and the reaction was heated to 45 °C. The reaction was stirred at 45 °C for 1 hour. Upon reaction completion, the product mixture was passed through a plug of celite, and the dichloromethane was removed by rotary evaporation. Purification was accomplished by

running 2 anaerobic (as previously described in the general considerations section), long, approximately gravimetric neutral Brockman grade V alumina columns with 20% methanol in dichloromethane. (The material was loaded with dichloromethane, and the green band is product.) These columns are followed by a single anaerobic, long ~gravimetric neutral Brockman grade III alumina column with 20% methanol in dichloromethane. (The material was loaded with CH_2Cl_2.) The product is then dissolved in dry, degassed methanol (~0.02 M solutuion) and layered with 5–6 volume equivalents of dry, degassed diethyl ether and allowed to crystallize overnight. The brown supernatant is decanted from the dark green crystals, which are then rinsed with diethyl ether (3×). The product is dried under high vacuum at ~45 °C for ~20 hours to yield 90 mg (46%) of a green, crystalline product. The sample for NMR spectroscopy was prepared in a N_2-filled glove box with dry, degassed deuterated methanol. The NMR spectra for this complex are provided in Appendix 1. The X-ray crystal data for this complex are provided in Appendix 2. ^{1}H NMR (CD_3OD, ppm): δ 16.81 (s, 1H), 7.91 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.09 (s, 4H), 5.01 (sept, J = 6.2 Hz, 1H), 4.78 (s, 2H), 4.20 (s, 4H), 4.20–4.05 (br, 4H), 3.32 (s, 9H), 3.14 (s, 6H), 2.44 (s, 18H), 1.24 (d, J = 6.3 Hz, 6H). ^{13}C NMR (CD_3OD, ppm): δ 295.3, 209.4, 155.5, 147.1, 140.5, 135.7, 130.6, 127.0, 122.3, 115.5, 78.1, 69.4, 59.1, 57.8, 54.7, 52.9, 50.5, 50.0, 21.8, 21.6, 20.0. HRMS (FAB+) *m*/*z* calc for $C_{39}H_{58}N_4OCl_3Ru$: 807.2731, found 807.2747.

Ruthenium complex 15. In a N_2-filled glove box, a flame-dried round-bottom flask, equipped with a stir bar, was charged with copper(I)chloride (62 mg, 0.63 mmol, 2.4

equiv), compound **19** (90 mg, 0.33 mmol, 1.3 equiv), and ruthenium complex **25** (253 mg, 0.26 mmol) and capped with a septum. This flask was removed from the glove box, and its seal was reinforced with Teflon tape. Dry, degassed dichloromethane (7.7 mL) was added, and the reaction was heated to 45 °C. The reaction was allowed to continue for 1 hour at 45 °C. Upon reaction completion, the reaction was allowed to cool, and the dichloromethane was removed by rotary evaporation. The dark-green material was passed through a plug of celite with benzene and precipitated from diethyl ether. The green solid was isolated from diethyl ether by centrifugation (rinsing with diethyl ether (2x)), and eluted from a long, neutral Brockman grade III alumina column with 7% methanol in dichloromethane to obtain ruthenium complex **26** as a dark-green solid. A flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **26** and purged with argon. Freshly prepared hydrogen chloride/benzene solution (13 mL) was added to give a green suspension. (The hydrogen chloride/benzene solution was generated by sparging dry, degassed benzene (~20 mL) with hydrogen chloride gas for 1 hour. The hydrogen chloride gas was produced by slowly dripping sulfuric acid onto an equivalent (versus sulfuric acid) of ammonium chloride.) The reaction was allowed to stir for 45 minutes at room temperature. The product was isolated from benzene by centrifugation, rinsing with dichloromethane (2×). This green solid is dispersed in ~500 mL of degassed, reagent-grade dichloromethane in a round-bottom flask and allowed to stir overnight (~16 hours) under a positive argon pressure. The fine, green powder was isolated by vacuum filtration through a medium frit. The product was dissolved in dry, degassed methanol (~0.2 M solution) in a 20 mL vial. This vial was brought into a N_2-filled glove box and placed in a reservoir of dry, degassed diethyl ether

to recrystalize by liquid/vapor diffusion. The light-green supernatant was decanted from the green crystals, which were rinsed with diethyl ether (3x). The product was dried under high vacuum at 45 °C for ~20 hours to obtain 138 mg (67%, 2 steps) of green, crystalline material. The NMR sample was prepared under an inert atmosphere using degassed deuterium oxide (generous argon sparge). Dry, degassed methanol was used as an internal standard for the ^{13}C-NMR spectrum. The NMR spectra for this complex are provided in Appendix 1. ^{1}H NMR (D_2O, ppm): δ 16.83 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.31–7.15 (m, 4H), 7.05 (s, 1H), 5.09–4.86 (m, 2H), 4.58 (ψt, J = 11.1 Hz, 1H), 4.47 (s, 2H), 4.19 (ψt, J = 10.0 Hz, 1H), 3.48 (ψt, J = 11.2 Hz, 1), 3.39–3.31 (m, 1H), 3.03 (s, 9H), 2.51 – 2.20 (m, 18H), 1.16 (ψt, J = 6.4 Hz, 6H). ^{13}C NMR (D_2O, ppm): δ 306.1, 210.8, 154.4, 146.1, 141.3, 141.0, 139.7, 136.6, 130.8, 130.5, 130.2, 130.1, 126.5, 122.5, 115.2, 77.9, 68.9, 61.7, 52.6, 42.4, 21.2, 20.9, 20.8, 19.0. HRMS (FAB+) *m*/*z* calc for $C_{36}H_{51}N_4OCl_2Ru$: 727.2484, found 727.2490.

Dibut-3-enylammonium chloride (41). A flame-dried round-bottom flask, equipped with a condenser, was charged with homoallyl amine (551 mg, 7.7 mmol, 2 equiv), dry, degassed THF (4 mL), and homoallyl bromide (0.4 mL, 3.82 mmol). The reaction mixture was heated to reflux and allowed to continue at reflux for 20 hours under a positive argon pressure. Upon reaction completion, the reaction was allowed to cool, and the THF was removed by rotary evaporation. The product was dissolved in water, and the mixture was made acidic with 3 M hydrochloric acid prior to transferring the solution to a separatory funnel. The water layer was rinsed with diethyl ether (3×) and made basic with solid potassium hydroxide. The basic solution was extracted with diethyl ether (4×), and

the combined ether layers were rinsed with water (6×) and with brine (1×). The organic fraction was dried over magnesium sulfate, and the volatiles were removed by rotary evaporation. To purify, the crude material was protected by stirring in the presence of di-*tert*-butyl dicarbonate (834 mg, 3.8 mmol, 1 equiv) in dichloromethane (19 mL) overnight (~16 hours) at room temperature. The volatiles were removed by rotary evaporation, and the product was eluted from a flash column using 10% ethyl acetate in hexanes. The product was stirred in a solution of hydrochloric acid in methanol (3 M, 19 mL) overnight (~16 h). The volatiles were removed by rotary evaporation and the product was dried under high vacuum to obtain 171 mg (52%) of white, solid product **41**. ^{1}H NMR (CD_2Cl_2, ppm): δ 9.70 (s, 2H), 5.89–5.75 (m, 2H), 5.21–5.10 (m, 4H), 3.03–2.98 (m, 4H), 2.69–2.62 (m, 4H). ^{13}C NMR (CD_2Cl_2, ppm) δ 133.5, 118.4, 47.3, 30.5. HRMS (ES+) *m*/*z* calc for $C_8H_{16}N$: 126.1283, found 126.1291.

***N*-allylpent-4-en-1-aminium chloride (44).** A flame-dried round-bottom flask was charged with *N*-(*tert*-butoxycarbonyl)allylamine (1.21 g, 7.7 mmol), anhydrous DMF (15 mL), and 60% sodium hydride (619 mg, 16 mmol, 2.1 equiv). After stirring for 20 minutes at room temperature under a positive argon pressure, 5-bromo-1-pentene (2.3 mL, 18.5 mmol, 2.4 equiv) was added, and the reaction mixture was heated to 80 °C. The reaction was allowed to continue at 80 °C under a positive argon pressure for 16 hours. After being allowed to cool to room temperature, the product mixture was diluted with diethyl ether and rinsed with water (6×) and with brine (1×). The organic fraction was dried over magnesium sulfate, and the volatiles were removed by rotary evaporation. Flash chromatography with 10% ethyl acetate in hexanes yielded 1.25 g (72%) of a clear,

colorless liquid product. Substrate **44** was obtained by stirring this liquid (1.05 g, 4.65 mmol) in a solution of hydrochloric acid in methanol (3 M, 8 mL) for 8 hours. The volatiles were removed by rotary evaporation, and the crude material was dissolved in water made acidic with hydrochloric acid. This aqueous solution was rinsed with diethyl ether (3×), made basic with solid potassium hydroxide and extracted with diethyl ether (4×). The combined dietyl ether extracts of the basic solution were dried over magnesium sulfate, and the diethyl ether was removed by rotary evaporation. A solution of this material in diethyl ether was cooled to -78 °C prior to the drop-wise addition of 4 M hydrogen chloride in dioxane to yield an acidic solution. The white precipitate produced was isolated by vacuum filtration and dried under high vacuum to obtain 367 mg (49%, 35% over the 2 steps) of compound **44** as a hygroscopic white solid. ^{1}H NMR ($CDCl_3$, ppm): δ 9.66 (s, 2H), 6.14–6.00 (m, 1H), 5.79–5.66 (m, 1H), 5.50–5.42 (m, 2H), 5.09–4.97 (m, 2H), 3.57 (d, J = 6.9 Hz, 2H), 2.90–2.85 (m, 2H), 2.18–2.11 (m, 2H), 2.02–1.92 (m, 2H). ^{13}C NMR ($CDCl_3$, ppm): δ 136.4, 128.0, 124.1, 116.5, 49.7, 46.0, 30.8, 25.0. HRMS (ES+) m/z calc for $C_8H_{16}N$: 126.1283, found 126.1284.

General procedure for ROMP, RCM, and cross-metathesis reactions with catalyst 14. In an N_2-filled glove box, catalyst **14** (5 mg, 5.9 μmol, 0.05 equiv) was weighed into a 1-dram vial. This vial was equipped with a stir bar, sealed with a septa-cap and removed from the glove box. The vial's seal was reinforced with Teflon tape, and the vial was charged with a 0.2 M solution of substrate in degassed deuterium oxide (0.6 mL). (The substrate stock solution was prepared under inert conditions with degassed deuterium oxide and stored under argon. A sufficient amount of the stock solution was

prepared to allow for at least 3 trials.) The vial was heated to the appropriate temperature and allowed to continue for 24 hours under a positive argon pressure. After 24 hours, the reaction mixture is transferred to an NMR tube and its conversion was determined by ^{1}H NMR spectroscopy.

For ROMP with **14**, in a N_2-filled glove box, catalyst **14** (1.9 mg, 2.3 μmol, 0.034 equiv) was weighed into a 1-dram vial which was equipped with a stir bar and sealed with a septa-cap. This vial was brought out of the box, and its seal was reinforced with Teflon tape. A 0.095 M stock solution of monomer **32** in degassed deuterium oxide (0.7 mL) was added, and the reaction was heated to 45 °C. (The monomer stock solution was prepared under inert conditions and stored under argon.) The reaction was monitored by the ^{1}H NMR spectroscopy of reaction-mixture aliquots.

General procedure for ROMP, RCM, and cross-metathesis with catalyst 15. In an N_2-filled glove box, catalyst **15** (4.8 mg, 6.0 μmol, 0.05 equiv) was weighed into a 1-dram vial. The vial was sealed with a septa-cap and removed from the glove box. A screw-cap NMR tube was also sealed with a septa-cap and removed from the glove box. The seals of both the vial and the NMR tube were reinforced with Teflon tape. A 0.2 M solution of substrate in degassed deuterium oxide (0.6 mL) was added to the vial, and full dissolution of **15** was accelerated with brief (~5–60 seconds) sonication. (The substrate solution was prepared under inert conditions with degassed deuterium oxide and stored under argon. A sufficient amount of substrate stock solution was prepared to allow for at least 3 trials.) The solution was transferred to the NMR tube by a air-tight syringe, and the reaction was heated to 30 °C. The reaction was monitored by ^{1}H NMR spectroscopy.

For ROMP, catalyst **15** (1.7 mg, 2.12 μmol, 0.032 equiv) was weighed into a 1-dram vial, which was sealed with a septa-cap. The vial and a septa-cap-sealed NMR tube were removed from the glove box, and their seals were reinforced with Teflon tape. A 0.095 M stock solution of monomer **27** in degassed deuterium oxide (0.7 mL) was added. (The monomer stock solution was prepared under inert conditions and stored under argon.) After brief sonication, the reaction mixture was transferred to the NMR tube using an air-tight syringe, and the reaction was heated to 45 °C. The reaction was monitored by ^{1}H NMR spectroscopy.

Newly Characterized Materials from RCM Reactions

(*Z*)-2,3,6,7-tetrahydro-1*H*-azepinium chloride (42). ^{1}H NMR (D_2O, ppm): δ 5.82 (t, *J* = 3.2 Hz, 2H), 3.19 (t, *J* = 5.2 Hz, 4H), 2.42 (ψd, *J* = 5.1 Hz, 4H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 130.0, 45.4, 24.8. HRMS (ES+) *m*/*z* calc for $C_6H_{12}N$: 98.0970, found 98.0973.

(*E*)-*N*-(but-3-enyl)but-2-en-1-aminium chloride (43). (Note: while both E and Z isomers were observed, the provided characterization is for the major isomer, the Z isomer.) ^{1}H NMR (D_2O, ppm): δ 6.03–5.95 (m, 1H), 5.83–5.72 (m, 1H), 5.57–5.50 (m, 1H), 5.26–5.16 (m, 2H), 3.58 (d, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H), 2.47–2.39 (m, 2H), 1.74–1.71 (m, 2H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 137.6, 133.5, 120.2, 119.5, 49.6, 46.0, 30.6, 17.9. HRMS (ES+) *m*/*z* calc for $C_8H_{16}N$: 126.1283, found 126.1290.

(*Z*)-2,3,4,7-tetrahydro-1*H*-azepinium chloride (45). ^{1}H NMR (D_2O, ppm): δ 6.25–6.17 (m, 1H), 5.81–5.73 (m, 1H), 3.77 (d, J = 5.7 Hz, 2H), 3.42 (t, J = 5.8 Hz, 2H), 2.43–2.36 (m, 2H), 1.96–1.88 (m, 2H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 138.7, 122.7, 50.1, 44.7, 27.2, 23.8. HRMS (ES+) m/z calc for $C_6H_{12}N$: 98.0970, found 98.0967.

References and Notes

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(1) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.

(2) Connon, S. J.; Blechert, S. Recent Advances in Alkene Metathesis. In *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C.; Dixneuf, P. H.; Eds.; Topics in Organometallics Chemistry 11, Springer-Verlag: Berlin, 2004; pp. 93–124.

(3) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

(4) Frenzel, U.; Nuyken, O. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2895–2916.

(5) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerizations*; Academic Press: San Diego, 1997.

(6) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3281–3285.

(7) Badjic, J. D.; Cantrill, S. J.; Grubbs, R. H. Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3273–3278.

(8) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F. *Org. Lett.* **2005**, *7*, 2129–2132.

(9) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317–4325.

(10) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627–1628.

(11) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601–6609.

(12) Kirkland, T. A.; Lynn, D. M., Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904–9909.

(13) Lynn, D. M. Ph.D. Thesis, California Institute Technology, 1999.

(14) Lynn, D. M., Kanaoka, S.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 784–790.

(15) Claverie, J. P.; Viala, S.; Maurel, V.; Novat, C. *Macromolecules* **2001**, *34*, 382–388.

(16) Davis, K. J.; Sinou, D. *J. Mol. Catal. A: Chem.* **2002**, *177*, 173–178.

(17) Mwangi, M. T.; Runge, M. B.; Bowden, N. B. *J. Am. Chem. Soc.* **2006**, *128*, 14434–14435.

(18) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873–1876.

(19) Zarka, M. T.; Nuyken, O.; Weberskirch, R. *Macromol. Rapid Commun.* **2004**, *25*, 858–862.

(20) Rix, D.; Clavier, H.; Coutard, Y.; Gulajski, L.; Grela, K.; Mauduit, M. *J. Organomet. Chem.* **2006**, *691*, 5397–5405.

(21) Michrowska, A.; Gulajski, L.; Kaczmarska, Z.; Mennecke, K.; Kirschning, A.; Grela, K. *Green Chem.* **2006**, *8*, 685–688.

(22) Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, *345*, 572–575.

(23) Binder, J. B.; Guzei, I. A.; Raines, R. T. *Adv. Synth. Catal.* **2007**, *349*, 395–404.

(24) Breitenkamp, K.; Emrick, T. *J. Polym. Sci. A: Polym. Chem.* **2005**, *43*, 5715–5721.

(25) Quémener, D.; Héroguez, V.; Gnanou, Y. *J. Polym. Sci. A: Polym. Chem.* **2006**, *44*, 2784–2793.

(26) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577–2580.

(27) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

(28) Hong, S. H. Ph. D. Thesis, California Institute of Technology, 2007.

(29) Bielawski, C., W.; Grubbs, R. H. *Angew Chem. Int. Ed.* **2000**, *39*, 2903–2906.

(30) Jordan, J. P.; Hong, S. H.; Grubbs, R. H. *Organometallics* submitted, 2007.

(31) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(32) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508–3509.

(33) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. unpublished results.

(34) Mirchrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.

(35) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 3187–3193.

(36) Novak, B. Ph.D. Thesis, California Institute of Technology, 1989.

(37) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542–7543.

(38) Hillmyer, M. A.; Lepetit, C.; McGrath, D. V.; Novak, B. M.; Grubbs, R. H. *Macromolecules* **1992**, *25*, 3345–3350.

(39) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.

(40) Ulman, M.; Grubbs, R. H. *Organomettalics* **1998**, *17*, 2484–2489.

(41) Jordan, J. P.; Kuo, L; Hong, S. H.; Grubbs, R. H. to be published, 2007.

(42) Terada, Y.; Arisawa, M.; Nishida, A. *Angew Chem. Int. Ed.* **2004**, *43*, 4063–4067.

(43) Hong, S. H.; Sanders, D. S.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127,* 17160–17161.

(44) Cetinkaya, B.; Demir, S.; Özdemir, I.; Toupet, L.; Sémeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem.—Eur. J.* **2003**, *9*, 2323–2330.

(45) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074–6086.

(46) While the isomerization of substrate **33** is not observed when it is ring-closed with five mol% of catalyst **14** in water, when **14**'s catalyst loading is lowered by half, a small amount of isomerization of substrate **33** to **34** is observed.

(47) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095.

(48) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827–2833.

(49) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.

(50) Kingsbury, J. S.; Hoveyda, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 4510–4517.

(51) Krause, J. O.; Lubbard, S.; Nuyken, O.; Buchmeiser, M. R. *Adv. Synth. Catal.* **2003**, *345*, 996–1004.

(52) Krause, J. O.; Nuyken, O.; Wurst, K.; Buchmeiser, M. R. *Chem.—Eur. J.* **2004**, *10*, 777–784.

(53) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687–4694.

(54) Vehlow, K.; Maechling, S.; Koehler, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 8617–8620.

(55) Leardini, R.; McNab, H.; Minozzi, M.; Nanni, D.; Reed, D.; Wright, A. G. *J. Chem. Soc. Perkin Trans. 1* **2001**, *20*, 2704–2710.

(56) Lavery, A.; Nelson, S. M. *J. Chem. Soc. Dalton Trans.* **1984**, 615–620.

(57) Bischofberger, N.; Waldmann, H.; Saito,m T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457–3465.

(58) Crozet, M. P.; Kaafaran, M.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1984**, 390–398.

(59) Gajda, T.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 992–1002.

(60) Tropsha, A. E.; Nizhinni, S. V.; Yaguzhinskii, L. S. *Bioorg. Khim.* **1985**, *11*, 1931–1941.

(61) *Beilstein* **20**, *IV*, 1912.

(62) Allan, R. D.; Dickenson, H. W.; Johnston, G. A. R.; Kazlauskas, R.; Tran, H. W. *Aust. J. Chem.* **1985**, *38*, 1651–1656.

(63) Gassman, P. G.; Bonser, S. T.; Mlinaric-Majerski, K. *J. Am. Chem. Soc.* **1989**, *111*, 2652–2662.

(64) Organ, M. G.; Cooper, M. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959–7970.

(65) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Royo, A. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2263–2276.

(66) Vic, G.; Crout, D. H. G. *Carbohydr. Res.* **1995**, *279*, 315–319.

(67) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006–4014.

(68) Gelman, M. A.; Weisblum, B.; Lynn, D. M.; Gellman, S. H. *Org. Lett.* **2004**, *6*, 557–560.

(69) Shaughnessyh, K. H.; Waymouth, R. M. *Organometallics* **1997**, *16*, 1001–1007.