Expanding the Scope of Ruthenium-Based Olefin Metathesis Catalysts

Thesis by

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For my family

"Nothing in the world can take the place of persistence.
Talent will not; nothing is more common than unsuccessful men with talent.
Genius will not; unrewarded genius is almost a proverb.
Education will not; the world is full of educated failures.
Persistence and determination alone are omnipotent."

-- Calvin Coolidge

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Abstract

The development of well-defined ruthenium alkylidene $(PCy_3)_2Cl_2Ru{=}CHPh$ brought about a revolution in the area of olefin metathesis. The objective of the work presented here is to expand the scope of ruthenium-based olefin metathesis catalysts such as $(PCy_3)_2Cl_2Ru{=}CHPh$ through the development of novel synthetic organic methods for ring-closing metathesis as well as through modification of the ligand sphere of the ruthenium complexes.

Chapter 2 describes the application of ruthenium alkylidenes to the catalysis of polycyclization reactions. Several acyclic precursors have been synthesized and reacted with $(PCy_3)_2Cl_2Ru{=}CHPh$. These precursors vary in topology and contain acetylenic and/or cycloolefinic metathesis relays. The cyclization reactions proceed in good yields to produce polycyclic polyenes.

Chapter 3 focuses on the synthesis of racemic and enantiopure targets containing the 6,8-dioxabicyclo [3.2.1]octane skeleton using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step. The natural product frontalin is synthesized in racemic and enantiopure forms and in excellent yields using this methodology.

Chapter 4 outlines the preparation of a novel imidazolylidene-substituted ruthenium-based complex starting from $(PCy_3)_2RuCl_2(=CHPh)$. The N-heterocyclic carbene-substituted olefin metathesis initiator exhibits increased ring-closing metathesis activity at elevated temperature compared to that of the parent complex $(PCy_3)_2Cl_2Ru(=CHPh)$. Di-, tri-, and tetra-substituted cycloolefins are successfully prepared from corresponding diene precursors in moderate to excellent yields.

Chapter 5 describes the preparation of a new family of 1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene-substituted ruthenium-based complexes. These air and water tolerant systems exhibit an increased ring-closing metathesis activity at elevated temperature when compared to that of the parent complex $(PCy_3)_2Cl_2Ru(=CHPh)$ as well as to the complexes disclosed previously in Chapter 4. In many instances the activity of these new complexes also rivals or exceeds that of the alkoxy-imido molybdenum-based olefin metathesis catalysts. Applications of chiral N-heterocyclic carbene ruthenium complexes to asymmetric ring-closing metathesis are also briefly discussed.

Finally, the synthesis of the Schiff base-substituted ruthenium carbene complexes on a solid support is described in Chapter 6. The activities of the supported complexes are compared to those of their unsupported counterparts. The newly prepared systems are found to be highly stable to air, moisture, and temperature, and exhibit increased catalytic activity in acidic media.

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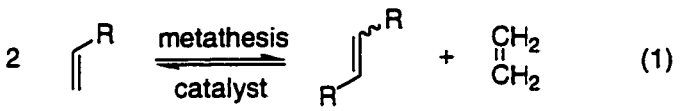
Chapter 1

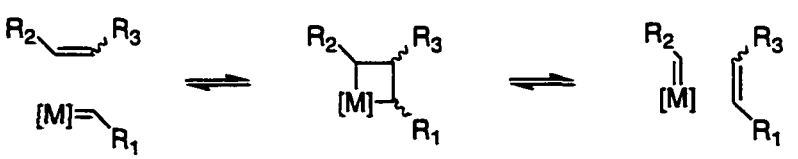
General Introduction to Olefin Metathesis and to Olefin Metathesis Catalysts

The olefin metathesis reaction is a unique rearrangement of unsaturated carbon-carbon bonds involving the exchange of alkylidene moieties of two olefins (Eq. 1). Although Eleuterio at Du Pont observed the olefin metathesis reaction as early as in 1957,[1] the term "olefin metathesis" was first used only in 1967 by Calderon.[2]



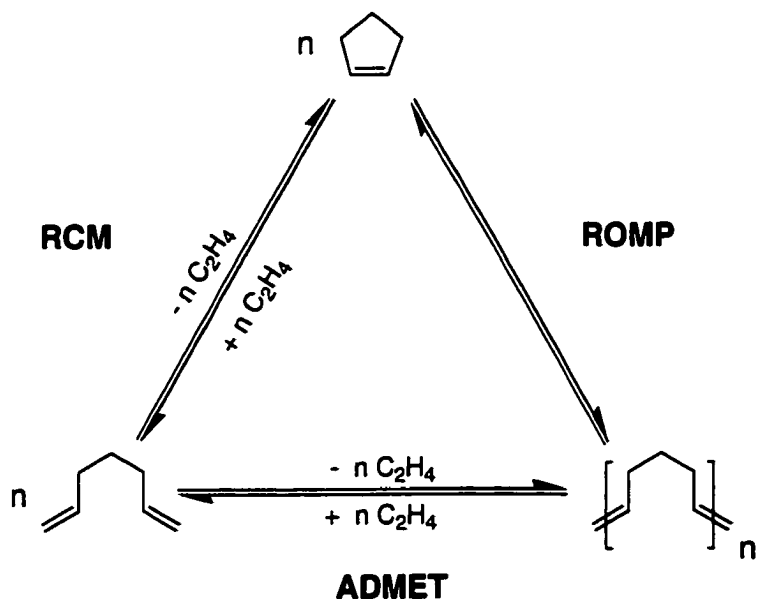
(1)

In 1971 Chauvin and coworkers[3] proposed what is now a generally accepted mechanism of the olefin metathesis reaction (Scheme 1): (a) formation of a metallacyclobutane, formally a [2+2] cycloaddition between an olefin and an alkylidene, and (b) subsequent non-degenerate retrocycloaddition to produce a new olefin and a new metallacarbene species. Since all steps of this mechanism are generally reversible, the reaction is typically under thermodynamic control. Also of particular significance is the fact that the olefin metathesis reaction utilizes no additional reagents beyond a catalytic amount of metal carbene and that the byproduct of the reaction is generally a volatile olefin such as ethylene.



Scheme 1. Chauvin mechanism of the olefin metathesis reaction

The olefin metathesis reaction can be divided into three closely related types of reactions (Scheme 2): (1) ring-closing metathesis (RCM); (2) acyclic cross-metathesis for alkenes, acyclic diene metathesis polymerization (ADMET) for dienes; and (3) ring-opening metathesis polymerization (ROMP). The competition among these three reversible processes is affected by the reaction conditions: olefin concentration, reaction pressure (ethylene) and temperature, as well as by the thermodynamic properties of the reactants such as ring strain.



Scheme 2. Olefin metathesis reaction pathways

The olefin metathesis reaction is catalyzed by transition metal carbenes. The classical transition metal-based olefin metathesis catalysts, with the exception of the Tebbe reagent, were ill-defined, multiple-component mixtures, which suffered from

instability and lack of functional group tolerance.[1c,4] More recently, well-defined single-component catalyst systems have been developed (Figure 1).

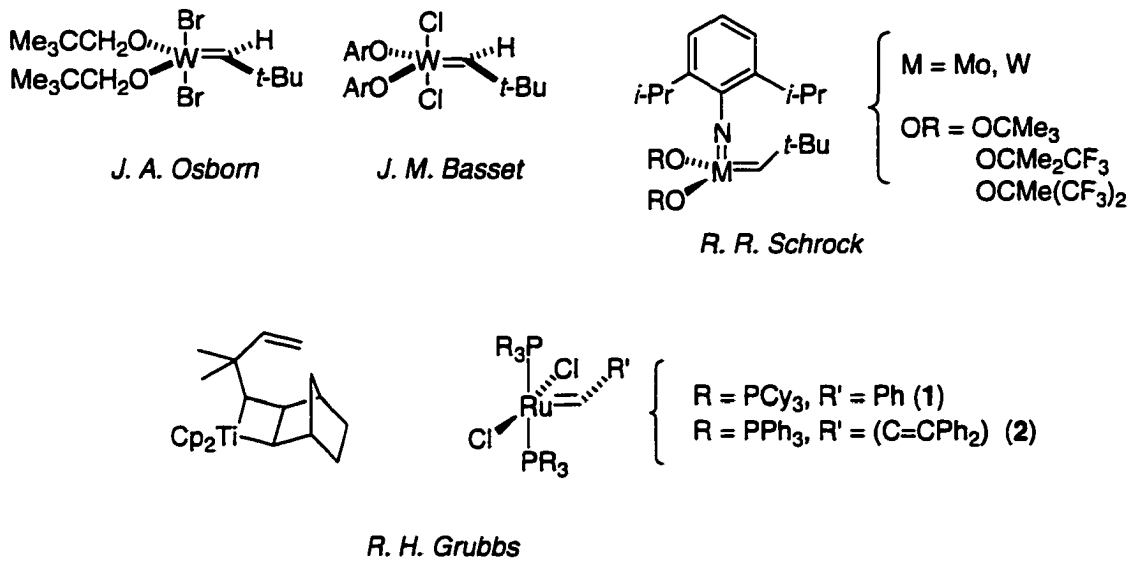
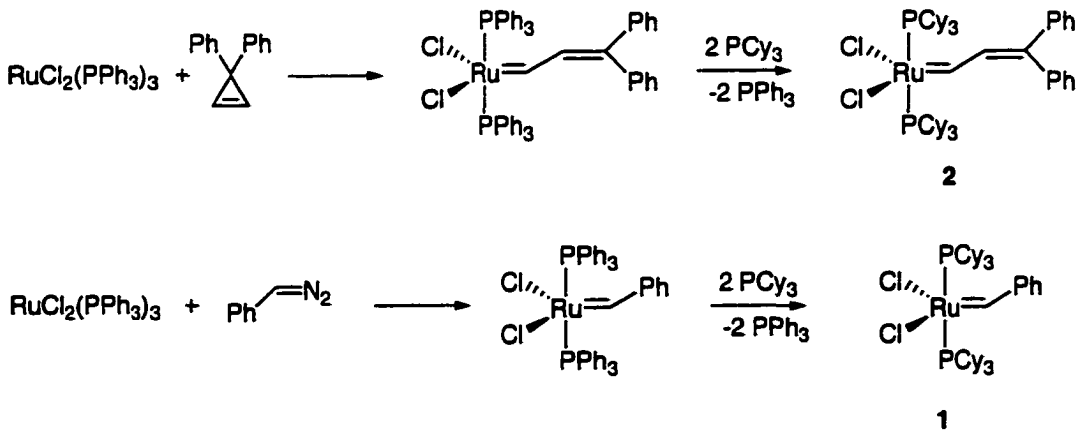


Figure 1. Select group of single component olefin metathesis catalysts

While these catalysts are well-defined and exhibit high metathesis activity, the problems with stability and functional group tolerance have not been fully addressed in most of these systems. In addition, the wide spread use of many of these catalysts has been limited because of their difficult syntheses. A significant advance in the area of olefin metathesis catalysts was the development and the commercial availability of Schrock's molybdenum systems.[5] These catalysts are highly reactive toward a broad range of substrates with various steric and electronic properties. However, they also lack the tolerance to a variety of functional groups and require rigorous exclusion of water and oxygen from the reaction mixtures.

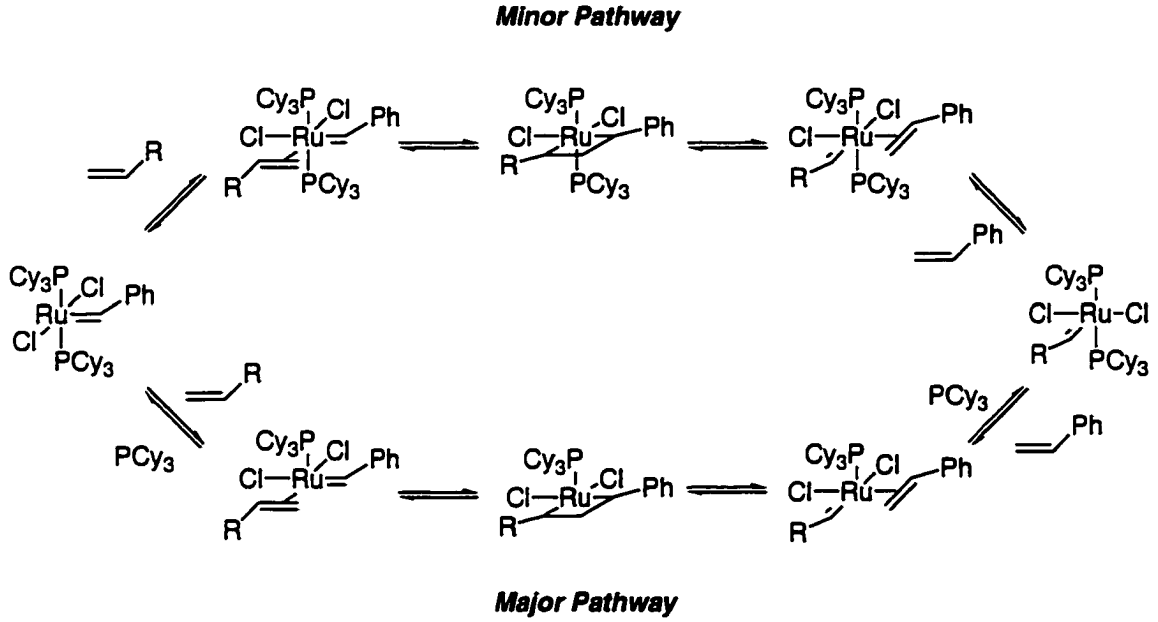
The development of the ruthenium alkylidene system $(PR'_3)_2Cl_2Ru{=}CHR$ by Grubbs and coworkers,[6] was a major breakthrough since it alleviated most of the previously encountered difficulties. This well-defined, single-component system exhibits substantial metathesis activity even in the presence of air, water, and strong acids, although it is not as potent as the early transition metal catalysts. It is also tolerant of many functional groups including aldehydes, alcohols, amides, and carboxylic acids due to its increased affinity for olefins with respect to Lewis basic or protic functionalities. It can be stored at room temperature for prolonged periods of time without decomposition.

In addition, there exist several relatively inexpensive and straightforward preparations of the ruthenium alkylidene catalysts including reactions of ruthenium precursors with cyclopropenes, diazo compounds, *gem*-dihalo compounds and propargyl and vinyl chlorides (Scheme 3).[7] The ruthenium alkylidene complex **1** is commercially available, and is seeing increased use in synthetic organic and polymer chemistry.[8]



Scheme 3. Representative syntheses of selected ruthenium-based olefin metathesis catalysts

The effect of the ligand sphere of the ruthenium-based catalysts was studied in this laboratory.[9] Specifically, it was shown that phosphine dissociation is vital for the major pathway of the catalytic cycle (Scheme 4). As a result, larger phosphine ligands

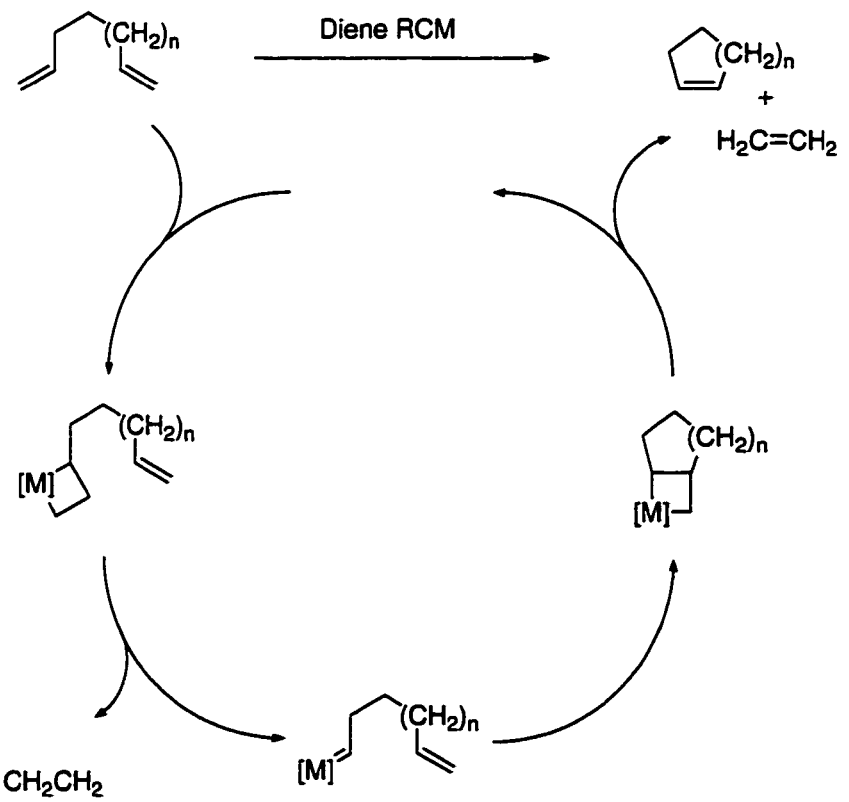


Scheme 4. Major and minor pathways in the mechanism for olefin metathesis

make better catalysts because they are easier to dissociate. In addition, the more basic the phosphines, the stronger the *trans*-influence they exhibit and the easier the dissociation of phosphines in the *trans* orientation. Based on these observations and in order to increase the utility of the ruthenium-based complexes by increasing their activity and/or selectivity, several novel olefin metathesis catalysts have been prepared, including bidentate salicylaldimine ruthenium complexes[10] and binuclear ruthenium complexes.[11] Chapters 4 and 5 of this thesis are a continuation of the effort to tinker with the ligand

sphere of the ruthenium-based olefin metathesis catalysts and describe the substitution of one of the phosphines in alkylidene complexes such as **1** and **2** by the more basic N-heterocyclic carbene ligands.

The ruthenium alkylidene catalyst **1** has found numerous applications in the diene RCM for the synthesis of cyclic olefins (Scheme 5).[8] The mechanism of diene RCM involves the initial formation of a metal alkylidene, which then undergoes intramolecular olefin metathesis involving a metallacyclobutane intermediate. The reaction is



Scheme 5. Mechanism of diene RCM

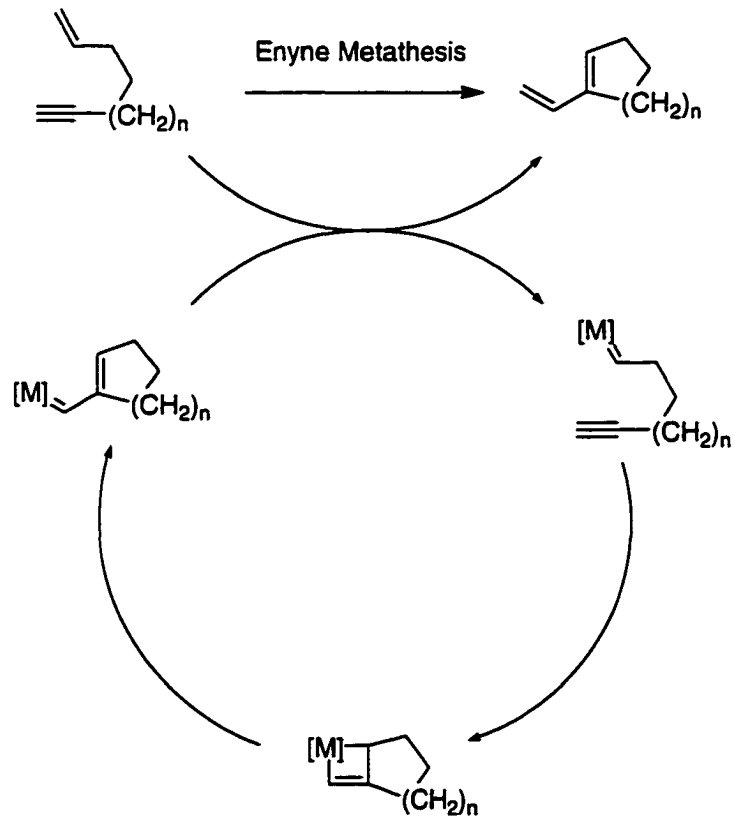
entropically favored: two molecules (of which one is usually a gas) are formed from one. However, ring strain is created, which involves loss of enthalpy. As a result, ring sizes of five to seven (small rings) and larger than eleven (macrocycles) are relatively easy to access by RCM,[8d] while medium size rings (8 to 11-membered) constitute a particular challenge.[12] These results are consistent with the relatively low ring strain values for 5- to 7-membered rings (2.5 - 7.2 kcal/mol, Table 1).[13]

Table 1. Ring strain values for common cycloolefins

Cycloolefin	Ring Strain (kcal mol^{-1})
Cyclopropene	54-56
Cyclobutene	31-34
Cyclopentene	6.8-6.9
Cyclohexene	2.5-2.6
cis-Cycloheptene	6.7-7.2
cis-Cyclooctene	7.4-8.8
cis-Cyclononene	11.5
cis-Cyclodecene	11.6

Enyne RCM, a related reaction to diene RCM, has recently been reported (Scheme 5).[14] The mechanism of the enyne RCM metathesis begins analogously to the diene RCM initially forming a metal alkylidene which then undergoes intramolecular acetylene (rather than olefin) metathesis involving a metallabicyclic intermediate to yield a cycloolefin and a vinyl carbene. In the last step, the vinyl carbene undergoes olefin

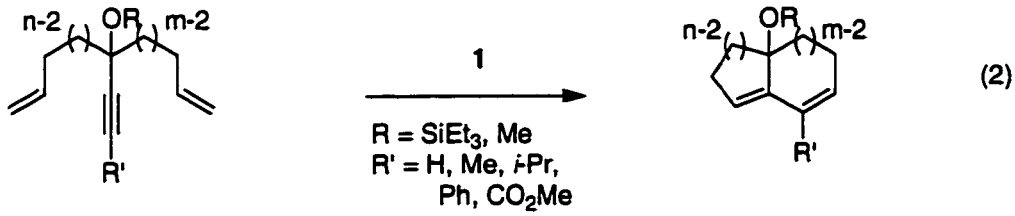
metathesis with a new substrate molecule to yield the final reaction product and start the cycle anew. It is important to note that unlike diene RCM, enyne RCM is not entropically driven but proceeds mainly based on enthalpic factors. One substrate molecule is converted exactly into one product molecule. The cyclic diene product, however, is energetically more stable than the acyclic enyne starting material by about 11 to 18 kcal/mol.



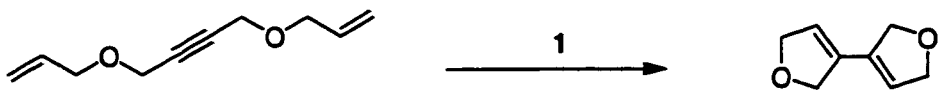
Scheme 6. Mechanism of Enyne Metathesis

Diene and enyne RCM, have been combined successfully in the synthesis of bicyclic molecules. This combination, or dienyne metathesis, has been observed when

stoichiometric amounts of electrophilic (Fisher) carbenes were used.[15] Based on this methodology, the catalytic synthesis of fused bicyclic [*n, m, 0*] ring systems has been developed. It has been established that ruthenium alkylidene **1** catalyzes the double metathesis of acyclic dienynes, in which the acetylene positioned between the two olefins acts as an "olefin metathesis relay" (Eq. 2).[16] The reaction begins at the terminal olefin group. The intermediate metallaolefin undergoes RCM with the alkyne (as opposed to the other olefin because formation of a 6-membered vs. an 8-membered ring is preferred) generating a new vinylcarbene complex. This new complex is then capable of undergoing RCM again with the second olefin. If two olefinic groups are placed one at each end of an alkyne (Eq. 3), formation of two independent (non-fused) rings is observed.[16a]



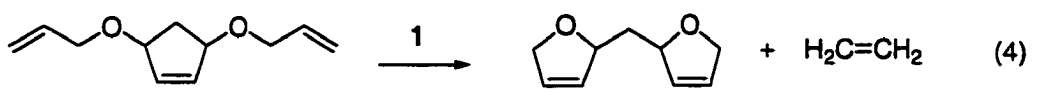
(2)



(3)

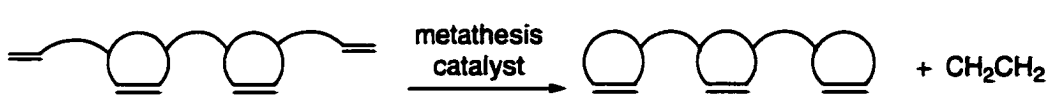
RCM and its formal reverse, the ring-opening metathesis reaction (ROM), have been used in succession in the so-called tandem ring-closing/ring-opening metathesis (RORCM, Eq. 4).[17] In this type of reaction, a cycloolefin rather than an acetylene is used

as the "olefin metathesis relay." In accord with the mechanism of dienyne metathesis, this reaction begins at one of the terminal olefins. The intermediate metallaolefin then undergoes ROM with the cycloolefin generating a new metallaolefin, which then undergoes a RCM with the second terminal olefin. This combination of ring-opening/ring-closing metatheses is enthalpically disfavored based on additional ring strain in the products and is again entropically driven: two molecules (one of which is a gas) are generated from one.



(4)

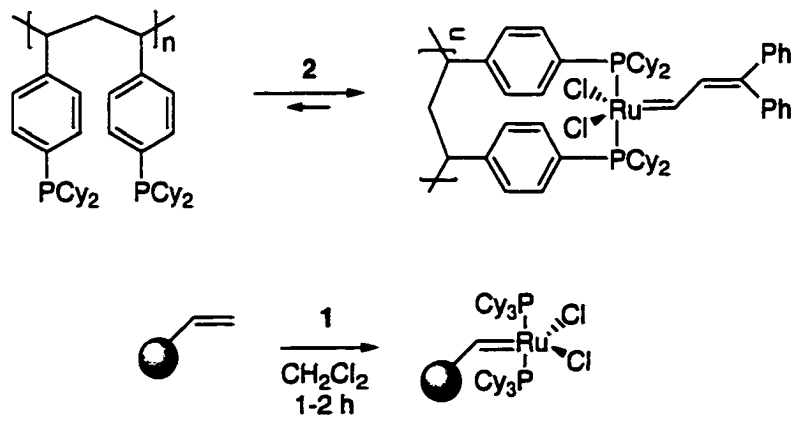
The objective of the work described in the next of this thesis has been directed at extending and applying the relay-metathesis methodology (dienyne and diene-cycloolefin metathesis reactions) to the formation of polycyclic molecules. This appears possible considering the fact that in the final stages of both dienyne (Eqs. 2 and 3) and diene-cycloolefin metathesis reactions (Eq. 4) a reactive metallaolefin intermediate is generated, which undergoes a final RCM with an end-olefin. Substitution of additional "olefin metathesis relays" (alkynes and/or cycloolefins) in place of the end-olefin should promote the formation of additional rings in a cascade fashion (Scheme 7).[18]



Scheme 7. Cartoon illustrating cascade ring-opening ring-closing metathesis

Chapter 3 of this thesis extends the applications of the relay-metathesis methodology to the construction of oxygen containing bridged bicyclic structures. This is a direct extension of work done in this group on carbocyclic bridged bicyclic structures.[19] Specifically, the natural product frontalin is prepared from cycloolefin containing diene precursors in both racemic and enantioselective fashion using tandem ring-opening ring-closing metathesis.

Despite all the profound accomplishments in the area of olefin metathesis catalysts, some acknowledged drawbacks, especially from the industrial standpoint, still remain associated with currently used metathesis catalysts such as **1** and **2**. Specifically, the catalysts are non-recyclable, they are destroyed upon workup, and frequently lead to highly colored ruthenium-based residues in the product mixture that are hard to remove by chromatography.[20] A successful immobilization of the metathesis catalysts on a solid support should alleviate some of these problems. Previous work in this group resulted in



Scheme 8. Examples of supported ruthenium olefin metathesis catalysts

the development of immobilized ruthenium vinyl carbene complex **2** on a polystyrene support (Scheme 8).[21] More recently, the immobilization of ruthenium alkylidene complex **1** was accomplished by Barrett and coworkers.[22] However, because the supported complexes were found to be either much less active than their homogeneous counterparts and/or were short-lived, improvements are desired. Hereto, findings for immobilization of the salicylaldimine ruthenium system onto a polystyrene support are presented in Chapter 6 of this thesis.

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Chapter 2

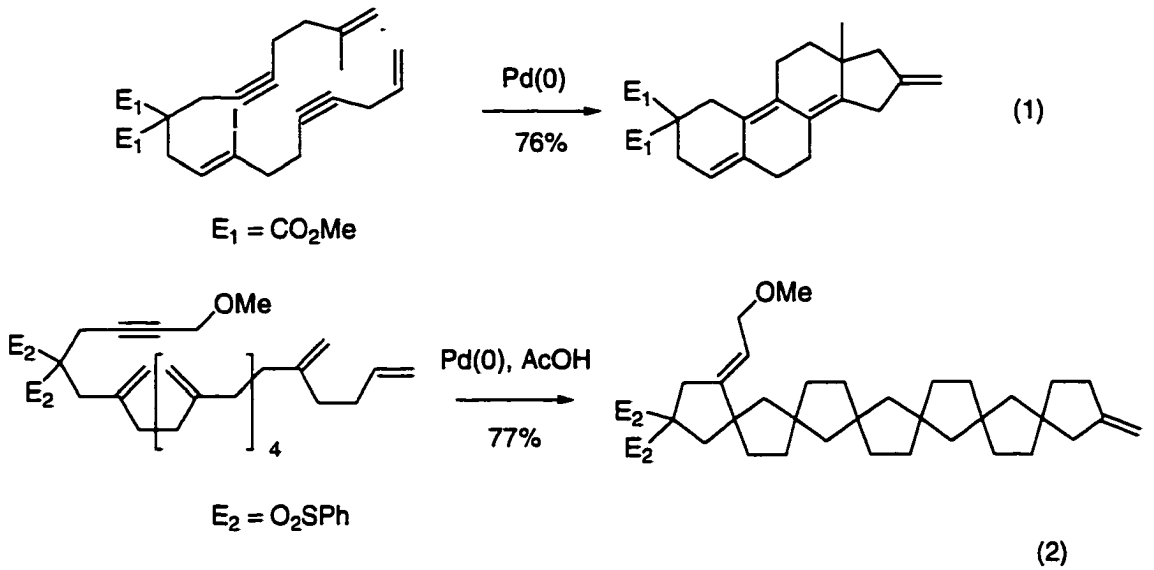
Ruthenium-Catalyzed Polycyclization Reactions[§]

Abstract

The application of ruthenium alkylidenes such as **1** to the catalysis of polycyclization reactions is reported. Several acyclic precursors have been synthesized and reacted with **1**. These precursors vary in topology and contain acetylenic and/or cycloolefinic metathesis relays. The cyclization reactions proceed in moderate to good yields to produce polycyclic polyenes when the precursors are subjected to catalytic amounts of **1**. In general, precursors bearing *n* relay units generate polycycles containing (*n* + 1) rings.

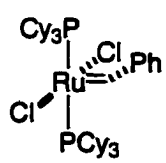
Introduction

Cascade reactions have proven effective in the assembly of complex polycyclic systems from simple acyclic precursors.[1] These cascade cyclizations are characterized by the formation of a reactive intermediate which undergoes a series ring-forming steps before termination. Examples have been reported for cationic,[2] anionic,[3] radical,[4] and transition-metal mediated cascade processes.[1] The application of homogeneous transition metal catalysts to cascade cyclizations of polyenes and polyynes appears very promising for the synthesis of polycyclic structures. For example, the groups of Negishi (Eq. 1)[5] and Trost (Eq. 2)[6] have utilized cyclic carbopalladation cascades in the one-step, catalytic assembly of systems containing up to seven rings (Scheme 1). Despite tremendous progress in this area, the development of efficient methods for the construction of polycyclic systems remains an important goal of synthetic chemistry.

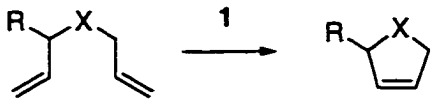


Scheme 1. Examples of tandem ring-forming processes

Previous reports from this laboratory[7] demonstrate the possibility of extending catalytic diene ring-closing metathesis[8] (RCM, Eq. 3) to the formation of polycyclic structures by a cascade of ring-opening olefin metathesis or carbene-acetylene metathesis reactions.[9] For example when a precursor diene containing an acetylene or a cycloolefin is exposed to ruthenium alkylidene **1**,[10] bicyclics are produced (Eqs. 4-5). Extending this reaction to analogous precursors bearing two or more of these olefin metathesis relays should lead to the production of polycyclic molecules. Herein we report the synthesis of such precursors and their cascade cyclization reactions catalyzed by **1.**



1



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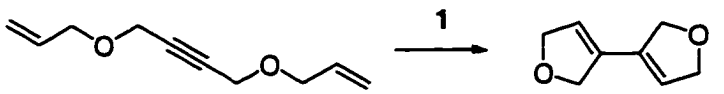

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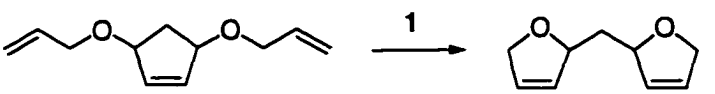
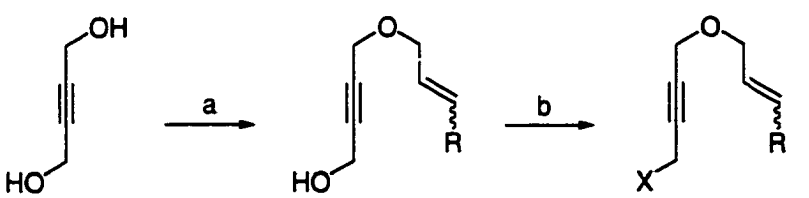


(5)

Results and Discussion

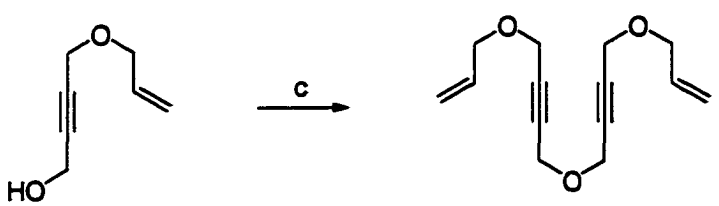
Precursor Synthesis

Several dienes containing two or more olefin metathesis relay units were prepared in order to study the possibility of ruthenium-catalyzed polycyclizations (Scheme 2). The



2a: R = H
2b: R = Me

3a: X = Cl, R = H
3b: X = Cl, R = Me
3c: X = OMs, R = H



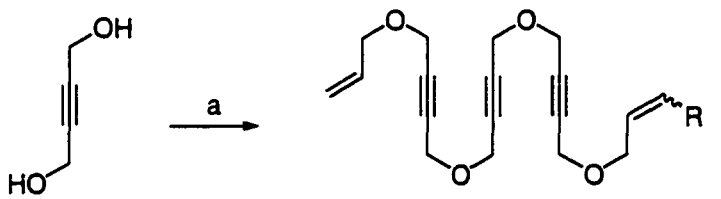
2a **4**

(a) NaH, Allyl (**2a**) or Crotyl Bromide (**2b**), DMF, 70%. (b) **3a**: **2a**, TsCl, NEt_3, DMAP, CH_2Cl_2; **3b**: **2b**, TsCl, Et_3N, DMAP, CH_2Cl_2; **3c**: **2a**, MsCl, Et_3N, DMAP, CH_2Cl_2 (c) NaH, DMF, **3a**, 60-82%.

Scheme 2. Synthesis of triether **4**

linear precursor **4** was prepared by alkylation of the anion of 2-butyne-1,4-diol monoallyl ether **2a** with propargyl chloride **3a**.[11]

The linear tetraether-triyne **5a** containing two unsubstituted terminal olefins was made by double alkylation of the dianion of 2-butyne-1,4-diol with propargyl chloride **3a** (Scheme 3). The corresponding tetraether-triyne **5b** containing one methyl substituted olefin was prepared by monoalkylation of the anion of 2-bytyne-1,4-diol with propargyl chloride **3b**, followed by another monoalkylation of the resultant isolated product with the propargyl mesolate **3c**.



5a: H
5b: CH_3

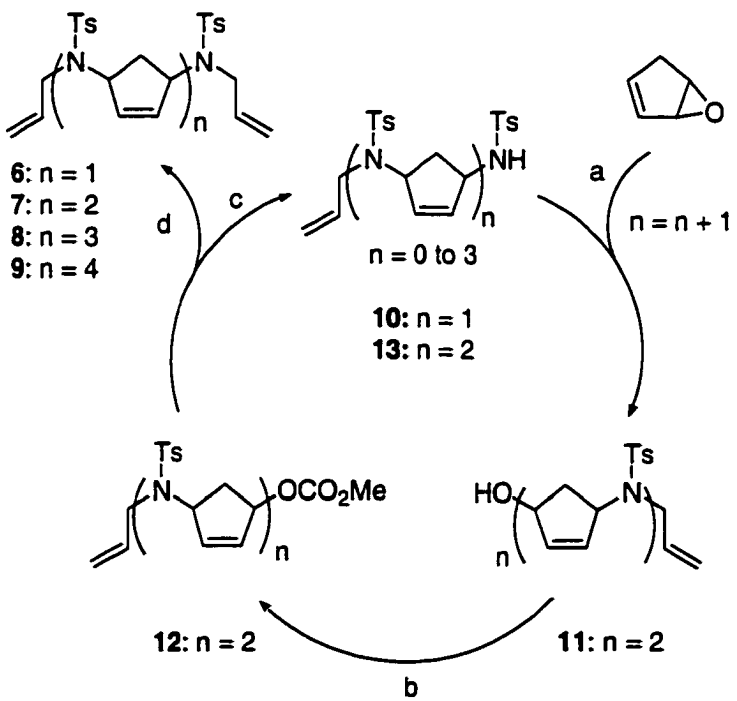
(a) **5a**: NaH, DMF, **3a** (2eq.), 64%; **5b**: NaH, DMF, **3b**, then NaH, DMF, **3c**.

Scheme 3. Synthesis of tetraethers **5a-b**

Four *N*-protected polyamines (**6-9**) bearing one to four cycloolefinic relay linkages, respectively, were prepared to study the possibility of a cascade ring-opening/ring-closing metathesis in such systems. The strategy for the synthesis of **6-9** (Scheme 4) was comprised by four reactions: (a) palladium-catalyzed ring opening[6] of cyclopentadiene monoepoxide; (b) treatment of the resulting amino alcohol with methyl

chloroformate to form an amino carbonate; and (c) or (d) palladium-catalyzed amination[6] reactions with either sodium *p*-toluenesulfonamide or *N*-allyl-*p*-toluenesulfonamide.

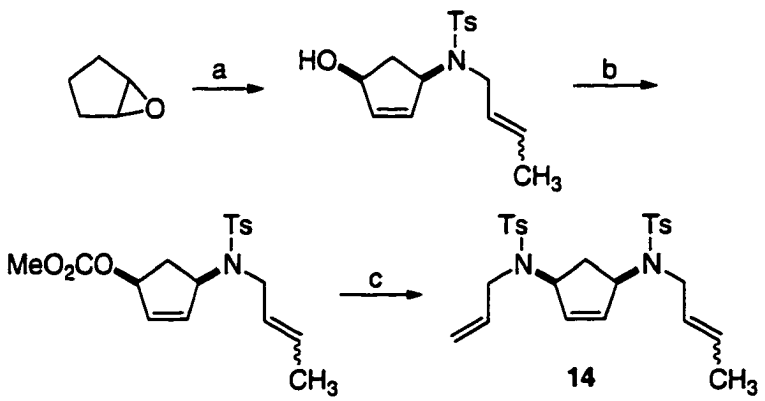
Steps a-c were repeated one to four times, respectively, and terminated with step d, which yielded the desired protected polyamines **6-9**. Because palladium-catalyzed ring-opening of cyclopentadiene monoxide is stereoselective and yields only the *syn*-isomer, the total number of stereoisomers in **6-9** was equal to the number of relay linkages *n*.



(a) $Pd_2dba_3{\cdot}CHCl_3$, dppe, BSA, THF, 40-100%. (b) CH_3OCOCl, C_5H_5N, CH_2Cl_2, 80-100%. (c) Ts-NHNa, $Pd(PPH_3)_4$, dppe, THF, 60-80%. (d) Allyl-NHTs, $Pd_2dba_3{\cdot}CHCl_3$, PPh_3, BSA, THF, 40-88% or Allyl-NTsNa, $Pd(PPH_3)_4$, dppe, THF, 72%.

Scheme 4. Synthesis of N-protected polyamines **6-9**

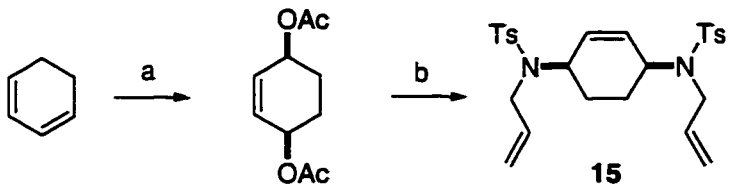
In order to study the effect of olefin substitution on the yield of the metathesis product, the analog of N-protected polyamine **7** bearing one methyl-substituted olefin was synthesized (**14**) (Scheme 5). The synthesis began with palladium-catalyzed ring opening of cyclopentadiene monoepoxide with *N*-crotyl-*p*-toluenesulfonamide, followed by treatment of the resulting amino alcohol with methyl chloroformate to form an amino carbonate. The amino carbonate was converted to **14** by palladium-catalyzed amination[6,12] with sodium *N*-allyl-*p*-toluenesulfonamide.



(a) Crotyl-NTsH, Pd_2dba_3•$CHCl_3$, dppe, BSA, THF, 61%.
(b) CH3OCOCl, pyridine, CH2Cl2, 70%. (c) Allyl-NTsNa,
Pd(PPh3)4, dppe, THF, 68%.

Scheme 5. Synthesis of precursor **14**

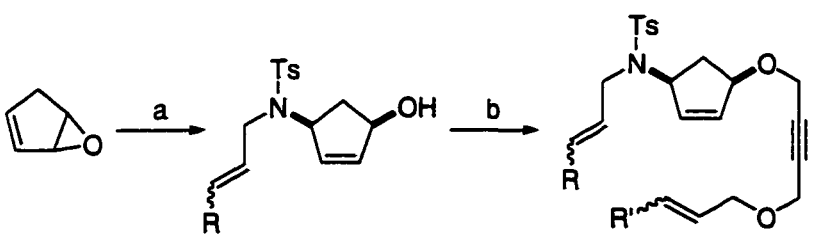
In order to explore the possibility of utilizing cyclohexenes as relays for polyamines in ring-opening/ring-closing metathesis reactions, **15** was prepared by palladium-catalyzed 1,4-diacetoxylation[12] of 1,3-cyclohexadiene followed by palladium-catalyzed amination of the resulting diacetate (Scheme 6).



(a) MnO_2, benzoquinone, $LiOAc{\bullet}2H_2O$, LiCl, $Pd(OAc)_2$, CH_3COOH/pentane, 80%. (b) Allyl-NTsNa, $Pd(PPh_3)_4$, dppe, THF:DMSO 4:1

Scheme 6. Synthesis of precursor **15**

A family of precursors (**17a-c**) containing both acetylenic and cycloolefinic metathesis relays was synthesized (Scheme 7). Palladium-catalyzed ring-opening of cyclopentadiene monoepoxide with *N*-allyl-*p*-toluenesulfonamide and *N*-crotyl-*p*-toluenesulfonamide[13] gave amino alcohols **16a** and **16b**, respectively. The *O*-alkylation of **16a** and **16b** with propargyl chloride **3a** produced **17a** and **17b**, respectively. Analogous, the *O*-alkylation of **16a** with propargyl chloride **3b** produced the precursor **17c**.



16a: R = H
16b: R = Me

17a: R = H, R' = H
17b: R = Me, R' = H
17c: R = H, R' = Me

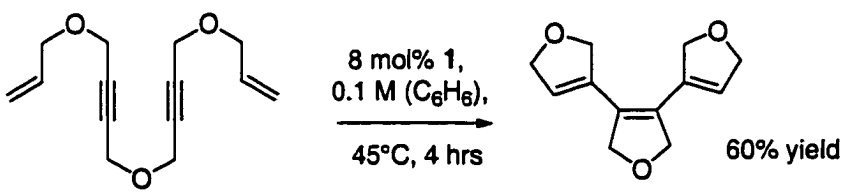
(a) **16a**: Allyl-NHTs, $Pd_2dba_3{\bullet}CHCl_3$, dppe, BSA, THF, 40-100%. **16b**: Crotyl-NHTs, $Pd_2dba_3{\bullet}CHCl_3$, dppe, BSA, THF, 61%. (b) **17a**: **16a**, NaH, DMF, than **3a**; **17b**: **16b**, NaH, DMF, than **3a**; **17c**: **16a**, NaH, DMF, than **3b**, 60-82%.

Scheme 7. Synthesis of precursors **17a-c**

Polycyclization Reactions

Acetylenic Relays

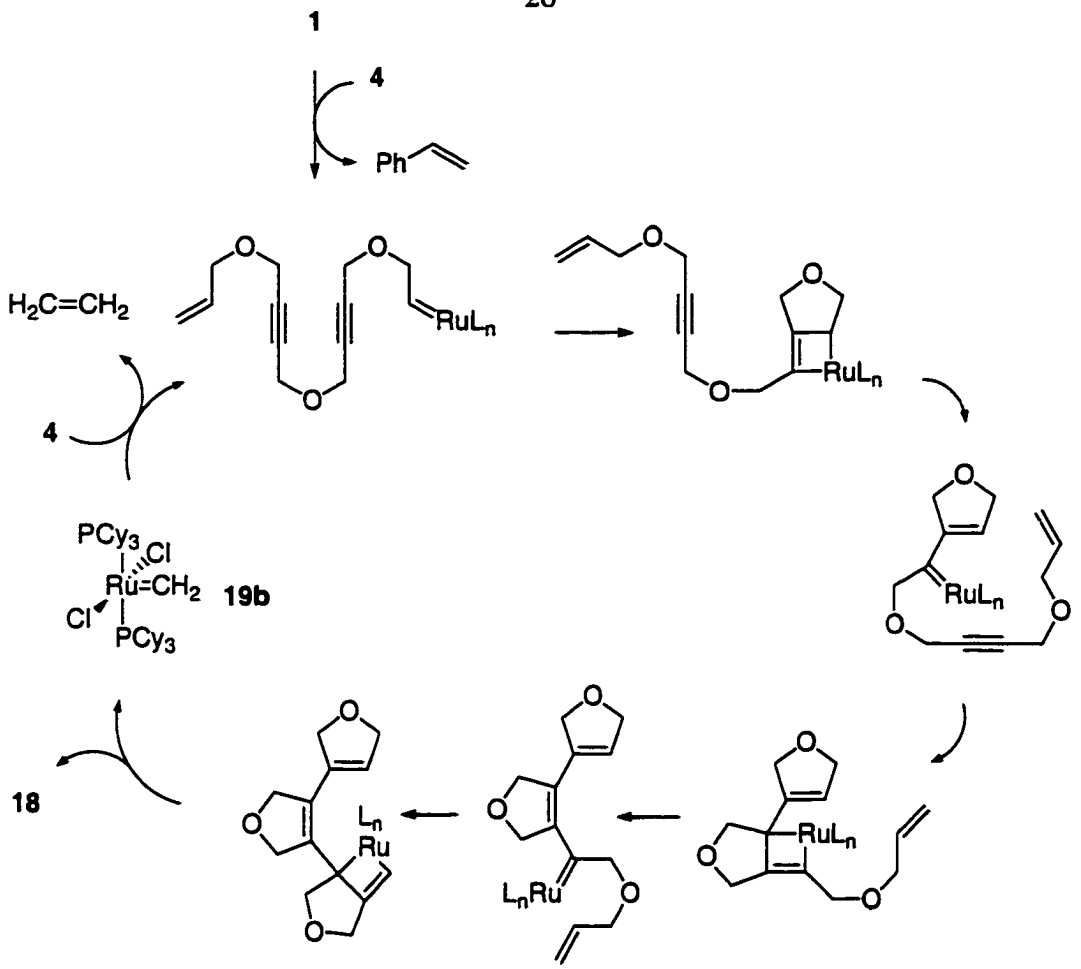
Treatment of the acyclic precursor **4** containing acetylenic relay units with a catalytic amount of **1** at ambient or slightly elevated temperatures results in the formation of non-fused heterocyclic product **18** in moderate yield (Scheme 8).[14] The products contain a conjugated triene system.



4 **18**

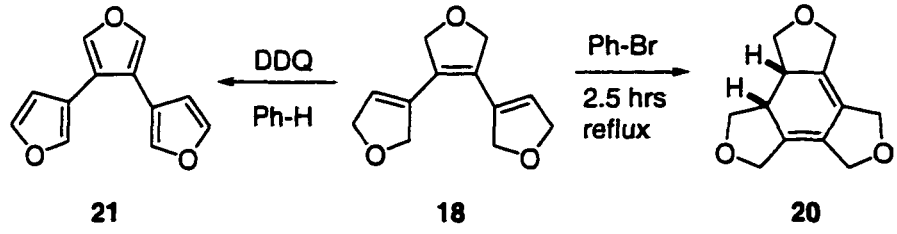
Scheme 8. Results of ring-opening ring-closing metathesis of **4**

The mechanism of the polycyclization of the precursor **4** involves the initial formation of a ruthenium alkylidene, which undergoes a series of intramolecular metatheses with the relay units prior to termination by a final ring closure. The conversion of **4** to **18** (Scheme 9) presumably begins with metathesis of **1** with either monosubstituted olefin of **4**. The newly formed carbene subsequently undergoes two intramolecular carbene-acetylene metatheses[15] involving respective metallacyclobutene intermediates. Cyclization is completed by intramolecular metathesis of the vinylcarbene with the remaining terminal olefin to yield product **18** and propagating, primary catalytic species the ruthenium methylidene **19b**.



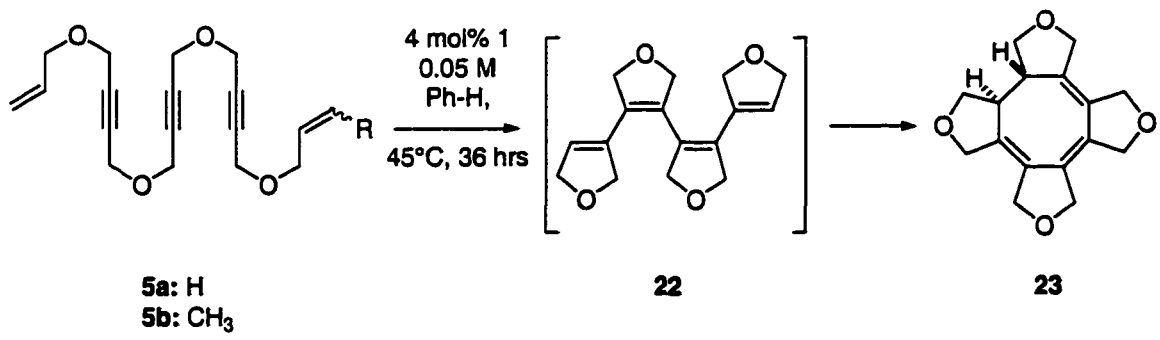
Scheme 9. Mechanism of the polycyclization of precursor **4**

Product **18** is a substituted hexatriene, and can in principle undergo a pericyclic 6π-electron electrocyclic closure[16] to yield **20** (Scheme 10). Indeed refluxing the precursor **18** in bromobenzene for 2.5 hrs yields a single product, which is consistent with the structure of **20** by ^{1}H NMR and LRMS. However, the NMR spectrum is not entirely clean, presumably due to high reactivity of **20** and the presence of an inseparable decomposition product. Attempts to isolate **20** in its more stable form as the oxidized aromatic species failed, but **18** was successfully oxidized to and isolated as the fully aromatic tri-furan **21**.



Scheme 10. Reactions of the tricyclic ether **18**

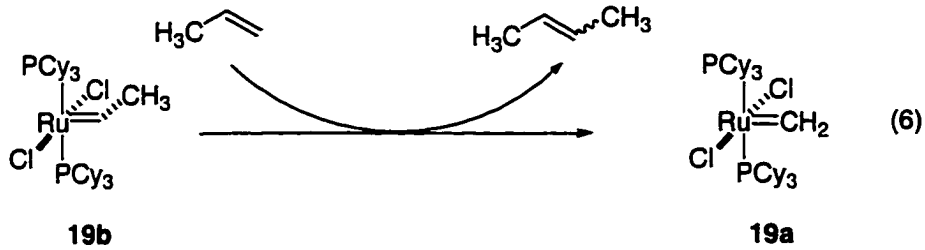
An attempt has been made to cyclize the precursor **5a** bearing three acetylenic metathesis relay units (Scheme 11). The expected product from this reaction would be a tetracyclic non-fused tetraether **22**. At the end of the reaction a single product is isolated. However, the spectral data of that product (^{1}H and ^{13}C NMR) is not consistent with the structure of **22**. Further considerations lead to the conclusion that a spontaneous 8-electron pericyclic closure to **23** (analogously to the pericyclic closure of **18** to **20**) may have occurred.



Scheme 11. Spontaneous perycyclic closure of tetraether **22**

While the ^{13}C NMR spectrum of **23** is clean and consistent with the product, the ^{1}H NMR indicates again the presence of either an inseparable impurity or a decomposition product. The exact identity of the impurity is unknown but spectroscopic data indicates that it might have formed *via* an intermolecular metathesis of acyclic olefins. This type of side reaction has been observed previously in cycloolefin-relay metathesis relay reactions.[7c] In order to slow down the oligomerization pathway by means of deactivating the terminal olefins relative to acetylene relay units for acyclic olefin metathesis, precursor **5b** has been synthesized. There is ample precedent that increasing substitution on an olefin decreases the rate of olefin metathesis.[7,17] However, in this case the substitution turns out not to have any significant effects on the formation of the product and **23** along with previously observed impurities is produced in a comparable yield. In addition, attempts to cleanly isolate derivatized **23** in the form of the fully hydrogenated analog have failed and multiple products were obtained.

The initiation and subsequent reactions of **1** are followed by observing the ^{1}H NMR signal of the α-proton of the ruthenium alkylidene. As the benzylidene (singlet 20.02 ppm in CD_2Cl_2) is consumed, a signal for the propagating alkylidene **19b** appears. In the reaction of **5b** this species is expected to be the ethylidene and is observed initially as a multiplet (quartet at 19.26 ppm in CD_2Cl_2). However, as the reaction progresses, a singlet corresponding to the ruthenium methylidene **19a** (18.94 ppm in CD_2Cl_2) grows as the alkylidene signal decays. Additionally, the formation of ethylene (singlet, 5.35 ppm in CD_2Cl_2) and 2-butene is observed in the reaction mixture. These observations indicate a secondary metathesis with the α-olefin byproduct of the cyclization reaction (Eq. 6) and are consistent with the reported reactivity of **1** with α-olefins.[10a]

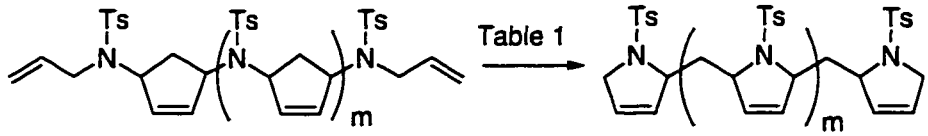


19b **19a** (6)

Cyloolefinic Relays

Multiple cycloolefinic relays can be used to promote cascades of ring-opening ring-closing metathesis reactions. Treatment of *N*-protected polyamines **6-9**, bearing one to four cycloolefinic relays, respectively, with catalytic amounts of **1** at ambient or slightly elevated temperatures results in the formation of *N*-protected polycyclic amines **24-27** in moderate to good yields (Scheme 12; Table 1).

The mechanism of these polycyclizations is thought to be similar to the previously described mechanism for the polycyclization of polyenes bearing acetylenic relays (Scheme 9) and involves an initial formation of a ruthenium alkylidene which undergoes a series of intramolecular metatheses with the cyclopentene relay units prior to termination by a final ring closure. For example, the conversion of **7** to **25** (Scheme 13) presumably begins with metathesis of **1** with the monosubstituted olefin of **7**. The newly-formed carbene subsequently undergoes two intramolecular ring-opening/ring-closing metathesis reactions, involving the respective metallacyclobutene intermediates. The cyclization is completed by metathesis of the ruthenium carbene with the monosubstituted olefin to yield product **25** and a propagating methylidene **19a**.



6: m = 0
7: m = 1
8: m = 2
9: m = 3

24: m = 0
25: m = 1
26: m = 2
27: m = 3

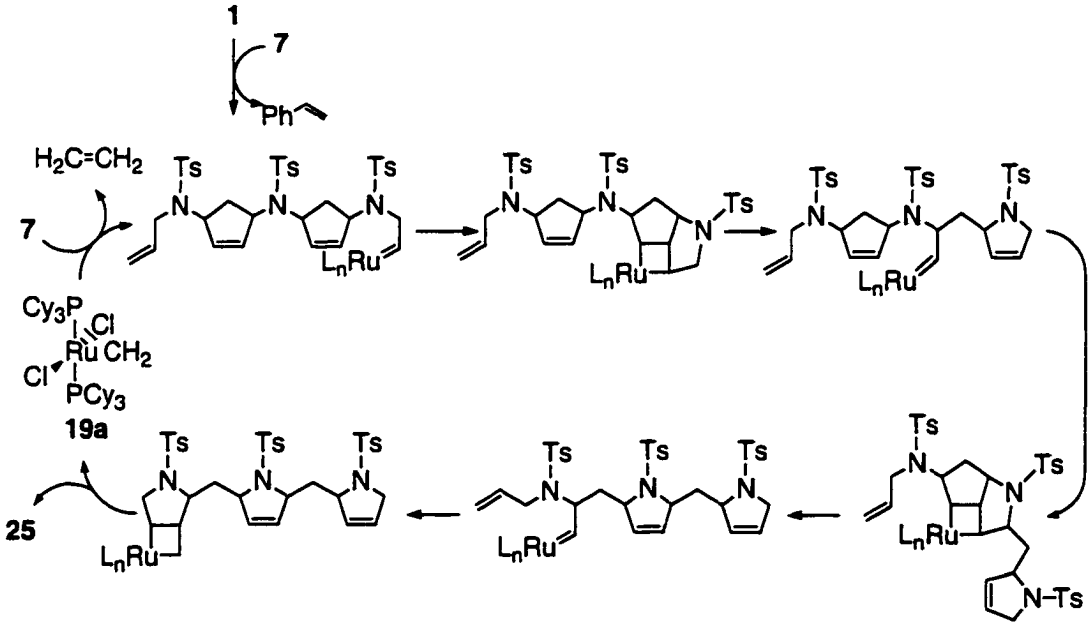
Scheme 12. Tandem ring-opening ring-closing metathesis of *N*-protected polyamines **6-9**

Table 1. Results of polycyclizations (Scheme 12) upon treatment with 5 mol% of **1**

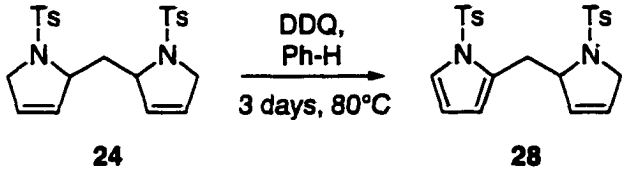
Entry	m	Catalyst	Time (h)	Solvent	Concentration (M)	Temp (°C)	Yield (%)
1	0	**1**	1	C_6H_6	0.05	RT	76
2	1	**1**	3	C_6H_6	0.05	45	70
3	2	**1**	8	C_6H_6	0.06	45	20
4	2	**1**	8	CH_2Cl_2	0.003	RT	50
5	2	**29**	24	CH_2Cl_2	0.003	40	60
6	2	**30**	4	CH_2Cl_2	0.003	RT	70
7	3	**1**	48	CH_2Cl_2	0.003	RT	51
8	3	**29**	48	CH_2Cl_2	0.003	40	59

While the polycyclization reactions of polyamines containing one to two cyclopentene metathesis relays proceed in good yields (Table 1, Entries 1-2), significant impurities were found initially in the reaction mixtures. These impurities proved inseparable by normal-phase flash chromatography and were attributed to either inter- or intramolecular acyclic olefin metathesis. Although product **24** could be isolated cleanly as its derivatized (aromatic) analog **28** (Scheme 14), this procedure did not seem ideal

due to long reaction times (3 days) needed for aromatization. Significant breakthrough in the isolation of the products **24** and **25** was made, when it was discovered, that upon treatment of the products containing inseparable impurities with concentrated sulfuric acid the impurities were degraded and products **24** and **25** could be isolated cleanly.

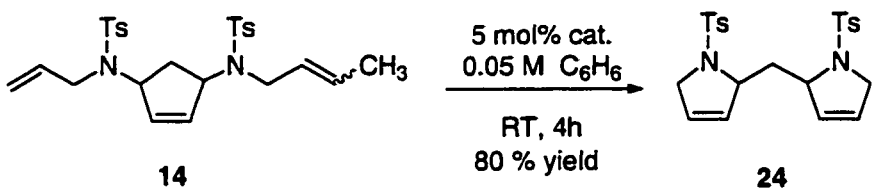


Scheme 13. Mechanism of tandem ring-opening ring-closing metathesis of precursor **7**



Scheme 14. Aromatization of the product **24**

The problem of inseparable impurities was also ameliorated by introduction of olefin substitution (Scheme 15). As discussed earlier in this section, acyclic olefin metathesis reactions are greatly slowed down with olefin substitution. When **14**, the methyl substituted analog of **6**, is treated with a 5 mol% of **1**, the initially observed inseparable impurities are no longer detected and the product **24** is isolated directly without additional acid work-up in an increased 80% yield.[68]



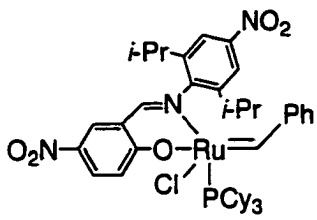
14 **24**

Scheme 15. Metathesis of precursor **29**

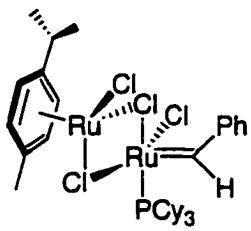
The diene-cycloolefin relay metathesis of substrates bearing increasingly greater number of cyclopentene relays is more challenging (Table 1, Entry 3). Greater variety of intermolecular side reactions can be expected and the yields drop off sharply under the same conditions. This problem is effectively solved by decreasing reaction concentration and temperature (Entries 4-8); this decreases the relative rate of intermolecular side reactions with respect to intramolecular metathesis cyclizations and lowers the rate of catalyst decomposition.[18]

Ruthenium alkylidenes with salen ligands such as **29** have exhibited greater stability than **1** in the RCM of diallyl malonates.[19] Although the cyclizations of precursors **8** and **9** catalyzed by **29** are generally slower, increased yields of an additional 8-10% (Table 1, Entries 5 and 8) are observed. Treatment of the tricyclic N-protected

polyamine **8** with the bimetallic ruthenium complex **30**[20] resulted in further increase of the yield and the product **26** was isolated in a 70% yield! (Table 1, Entry 6).

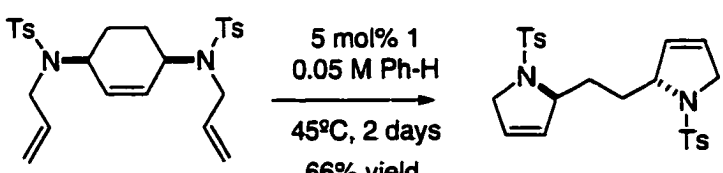


29



30

In addition to cyclopentenes, cyclohexenes are also effective as metathesis relays in the polycyclizations of *N*-protected polyamines. Precursor **31** is converted to product **32** in 66% yield upon treatment with a catalytic amount of **1** (Scheme 16). As expected, the rate of reaction is much slower than in the case of similar substrate bearing a cyclopentene relay (2 days at 45°C vs. 1 hr at RT) due to lower ring strain energy released upon ring-opening metathesis. Nevertheless, it is anticipated that treatment of acyclic *N*-protected polyamines bearing multiple cyclohexene relays with olefin metathesis catalysts will lead to polycyclic *N*-protected amines.

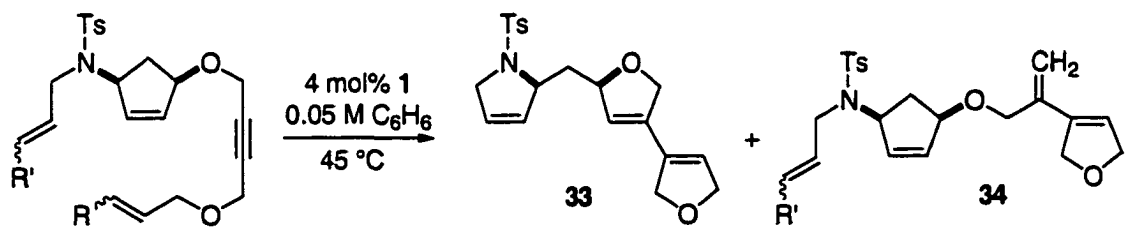


31 **32**

Scheme 16. Use of cyclohexene as metathesis relay

Mixed Acetylenic and Cycloolefinic Relays

Cycloolefins as well as acetylenes are effective relays in the polycyclization reactions (Scheme 17). When precursor **17a** is exposed to 4 mol% of **1**, tricycle **33** is recovered but only in a 40% yield. The mass balance is found in an uncharacterized side product which appears to be oligomerized starting material. This type of side reaction has been observed previously in cycloolefins metathesis relay reactions, and the problem was ameliorated through alkyl substitution of one of the terminal olefins, thereby slowing the relative rate of the competing oligomerization reactions.[7] This strategy works in the present study as well: when **17b** is exposed to 4 mol% of **1**, cyclization proceeds cleanly over a period of 4 hrs to a single product, and the tricycle **33** is isolated in 76% yield.



		yield:
17a:	R = H, R' = H	40%
17b:	R = CH_3, R' = H	76%
17c:	R = H, R' = CH_3	25%

Scheme 17. Utility of a combination of acetylenic and cycloolefinic metathesis relays

Interestingly, alkyl substitution of the other terminal olefin as in the case of precursor **14** does not produce the same result. Treatment of the precursor **17c** with 4 mol% of **1** yields the product **33**, but in a rather low yield (25%). The result is elucidated by isolation of the other (major) product of this reaction, which by ^{1}H NMR and HRMS

appears to be **34**. Since **17** is not symmetric, methyl substitution of the olefin on the nitrogen-side forces initiation of the metathesis reaction to occur on the allyl ether olefin. The initially formed alkylidene reacts in this case with an acetylene rather than with the cycloolefin. The vinyl carbene formed in the next step reacts preferably with another substrate molecule yielding **34** rather than undergoes ring opening metathesis reaction with the cycloolefin. This is presumably the rate determining step. An intermolecular pathway is also accessible to **17b**, but ring opening could still be rate determining. Intermolecular reactions prior to ring opening would result in the formation of dimers and after ring opening the rate of intramolecular processes dominates.

Conclusions

We have presented an efficient, catalytic method for the production of polycyclic molecules from acyclic precursors. The reaction proceeds through a cascade of metathesis steps with either acetylenic or cycloalkenyl relay units. A variety of structural types are accessible depending on the topology of the precursor and relay unit employed. The use of more and varied metathesis relays as well as the further functionalization of the resulting cyclolefin systems are currently under investigation.

Acknowledgments

The authors wish to thank Dr. Soong-Hoon Kim for helpful discussions. This work was supported by the National Institutes of Health.

Experimental Section

General Considerations

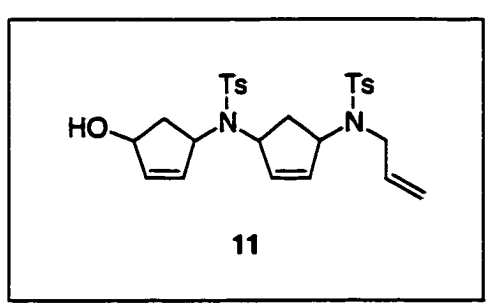
High resolution mass spectra were provided by the Southern California Mass Spectrometry Facility (University of California at Riverside). Analytical thin-layer chromatography (tlc) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with one or more of the following: UV light, $KMnO_4$, phosphomolybdic acid (PMA), cerric ammonium nitrate (CAN), or *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[21]

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise specified. Catalyst **1** was prepared according to published procedure and is commercially available.[10a] Catalyst **29** and **30** were prepared according to published procedures[19,20] and were generously provided by Drs. Sukbok Chang and Eric Dias, respectively. Solvents were purified by passage through a column containing A-5 alumina (all solvents) followed by a column containing Q-5 reactant (non-ethereal solvents). Argon was purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4Å molecular sieves (Linde). Allyl bromide was purchased from ARCOS. All other reagents were purchased from the Aldrich Chemical Company. Cyclopentadiene monoepoxide was prepared following published procedure.[22]

General and Specific Procedures

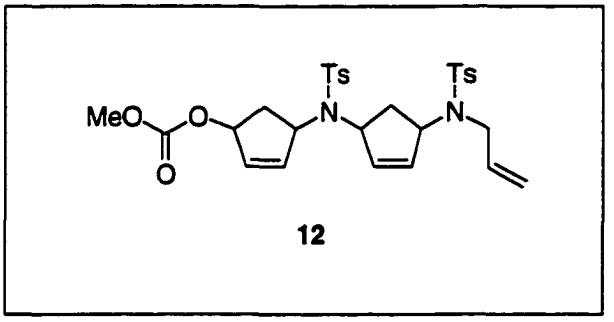
General procedure for the formation of aminocyclopentenyl alcohols (Scheme 4, a). To a stirring solution of palladium dibenzylidene acetone adduct (21 mg,

0.02 mmol, 0.02 equiv.) in THF (1 mL, 0.02 M) is added diphenylphosphinoethane (32 mg, 0.08 mmol, 0.08 equiv.) The resulting deep violet mixture is stirred for several minutes at RT until its color changed to yellow. To this reaction mixture is added **10** (447 mg, 1.0 mmol, 1 equiv.) in THF (1 mL, 1M). The resulting mixture is cooled to 0°C and treated with *N,O*-bis(trimethylsilyl)acetamide (305 mg, 1.5 mmol, 1.5 equiv.) The reaction mixture is allowed to stir for 20 minutes, after which cyclopentadiene monoxide (123 mg, 1.5 mmol, 1.5 equiv.) is added dropwise over a period of 1 hr. The temperature is kept at 0°C for an additional hour, after which it was allowed to warm up to RT and stirred overnight. The solvent was removed under reduced pressure. The remaining, dark brown residue is redissolved in Et_2O (10 mL) and hydrolyzed with 4N aqueous HCl (5 mL) until a complete disappearance of the initial reaction product, TMS-protected alcohol, is observed by tlc (R_f = 0.6, 30% EtOAc in hexanes). The organic phase is separated and the aqueous phase is extracted twice with Et_2O (10 mL). The organic phases are combined, dried over $MgSO_4$, and the solvent is removed under reduced pressure. The free alcohol **11** (400 mg, 76%) is isolated by flash chromatography as a clear colorless oil.



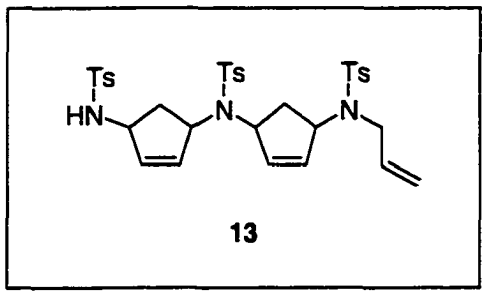
11

General procedure for the formation of aminocyclopentenyl carbonates (Scheme 4, b). To a stirring solution of **11** (11.0 g, 37.5 mmol) in CH_2Cl_2 (300 ml, 0.125 M), is slowly added at 0°C methyl chloroformate (17.8 g, 188 mmol, 5 equiv.) and pyridine (5.93 g, 75 mmol, 2 equiv.) The reaction mixture is stirred at rt until complete consumption of starting material is observed by tlc (product *Rf* = 0.4, 30% EtOAc in hexanes). The reaction mixture is washed twice with water (100 mL), dried over $MgSO_4$, filtered and the solvent is removed under reduced pressure. Flash chromatography affords **12**, as a yellow oil (13.4 g, 100%).



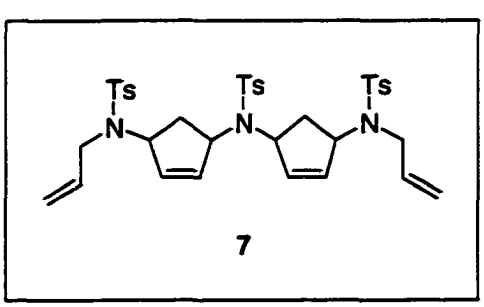
12

General procedure for the formation of aminocyclopentenyl *p*-toluenesulfonamides (Scheme 4, c). To a stirring solution of **12** (8.5 g, 24.4 mmol, 1.0 equiv.) in THF (120 mL, 0.2M) is added sodium *p*-toluenesulfonamide (4.17 g, 24.4 mmol, 1 equiv.), $Pd(PPh_3)_4$ (2.26 g, 1.95 mmol, 0.08 equiv.) and diphenyl–phosphinoethane (777 mg, 1.95 mmol, 0.08 equiv). The resulting reaction mixture is stirred overnight. The solvent is removed under reduced pressure and the remaining dark residue is purified by flash chromatography to afford **13**, as a yellow solid (8.6 g, 79%).



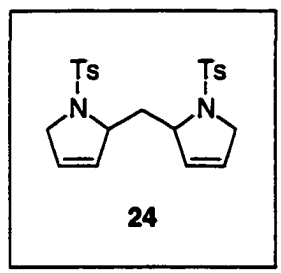
13

General procedure for the formation of aminocyclopentenyl N-allyl-*p*-toluenesulfonyl amides (Scheme 4, d). To a stirring solution of palladium dibenzylidene acetone adduct (43 mg, 42 μmol, 0.08 equiv.) in THF (2 mL, 0.02 M) is added triphenylphosphine (27 mg, 104 μmol, 0.2 equiv.) The resulting yellow-brown mixture is stirred at RT for 20 minutes. To this reaction mixture is added *N*-allyl *p*-toluenesulfonamide (115 mg, 546 μmol, 1.05 equiv.) The resulting mixture is cooled down to 0°C and treated with *N,O*-bis(trimethylsilyl)acetamide (212 mg, 1.04 mmol, 2 equiv.) for 20 min, after which **12** (300 mg, 520 μmol, 1.0 equiv.) in THF (2.5 mL, 0.21 M) is added dropwise over a period of 1 hr. The temperature is kept at 0°C for an additional hour, after which the reaction mixture is allowed to warm to RT and stirred overnight. The solvent was removed under reduced pressure. Compound **7** (300 mg, 80%) is isolated by flash chromatography as a yellow solid.



7

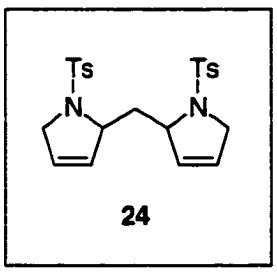
Typical procedure for the metathesis reaction of 6 (Scheme 12). To a stirring solution of **6** (200 mg, 0.41 mol) in benzene (8 ml, 0.05M) is added **1** (17 mg, 21 μm, 0.05 equiv.) The reaction mixture is stirred at 45°C for 1 hr, at which time complete consumption of the starting material is observed by tlc (product Rf = 0.3; 30% EtOAc in hexanes). The solvent is removed under reduced pressure. The remaining dark oil is redissolved in 1 mL of benzene and treated with concentrated H_2SO_4 (1 mL) and 0.1 mL of H_2O (0.1 ml) until tlc of the organic phase indicates disappearance of the product. The reaction mixture is diluted with H_2O (10 mL) and benzene (10 mL), cooled to 0°C and carefully made basic with KOH. The liquid phases are separated and the aqueous phase is extracted twice with CH_2Cl_2 (10 mL). All organic phases are combined, dried over $MgSO_4$, filtered, and the solvent is removed under reduced pressure. The resulting oil is purified by flash chromatography (20% EtOAc in hexanes) to yield **24** as a white solid (135 mg, 72%).



24

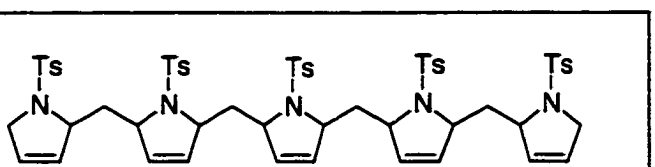
Typical procedure for the metathesis reaction of 29 (Scheme 14). To a stirring solution of **29** (500 mg, 1.0 mmol) in C_6H_6 (20 ml, 0.05 M) is added **1** (41 mg, 0.05 mmol, 0.05 equiv.) The reaction mixture is stirred at RT for 4 hrs, at which time complete consumption of the starting material is observed by tlc. The reaction mixture is

purified by flash chromatography (20% EtOAc in hexanes) to yield **24** as a white solid (365 mg, 80%).



24

General procedure for the metathesis reactions of 7-9 (Scheme 12). To a stirring solution of **9** (45 mg, 38 μmol) in CH_2Cl_2 (12.5 ml, 0.003 M) is added **29** (1.7 mg, 1.89 μmol, 0.05 equiv.) The reaction mixture is stirred at 40°C for 24 hrs, at which time complete consumption of the starting material is observed by tlc (product Rf = 0.4; 40% EtOAc in hexanes). The solvent is removed under reduced pressure. The remaining residue is purified by flash chromatography (20% EtOAc in hexanes) to yield **27** as a white solid (26 mg, 59%).

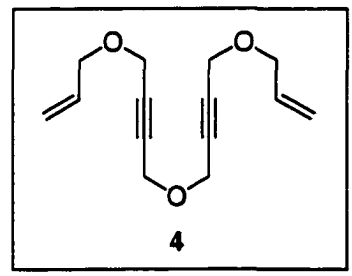


27

Synthesis and Characterization Data

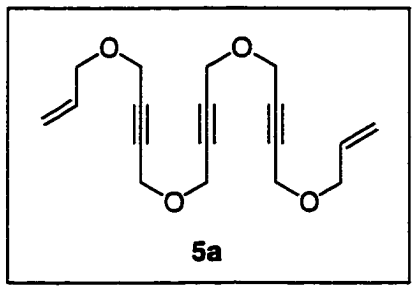
All new precursors and metathesis products were characterized by 1H-NMR, 13C-NMR, IR and HRMS, whenever possible. Characterizations and experimental details are followed by each structural formula.

1-Allyloxy-4-(4-allyloxy-but-2-ynyloxy)-but-2-yne (4). ^{1}H NMR (C_6D_6, 300 MHz) δ 5.74-5.63 (m, 1H), 5.18-5.10 (m, 1H), 4.96-4.91 (m, 1H), 4.04 (t, J = 1.8 Hz, 2H), 3.86 (t, J = 1.8 Hz, 2H), 3.81-3.78 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ 134.7, 116.8, 83.1, 81.6, 70.0, 56.8, 56.1; IR (neat, cm^{-1}) 3080, 3015, 2982, 2943, 2854, 1074; HRMS calcd for $C_{14}H_{18}O_3$ (MNH_4^+) 252.1600, found 252.1599.



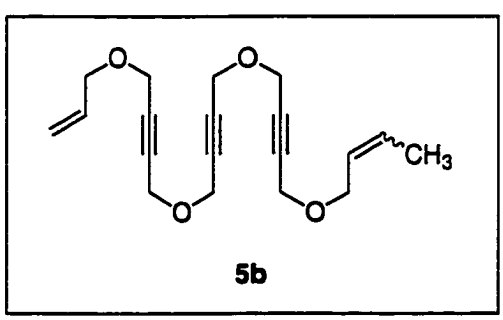
4

1-Allyloxy-4-[4-(4-allyloxy-but-2-ynyloxy)-but-2-ynyloxy]-but-2-yne (5a). ^{1}H NMR (C_6D_6, 300 MHz) δ 5.95-5.82 (m, 2H), 5.33-5.19 (m, 4H), 4.28-4.27 (m, 8H), 4.18 (t, J = 1.8 Hz, 4H), 4.04 (dt, J = 5.8, 1.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 117.4, 82.7, 81.8, 81.1, 70.3, 57.0, 56.5, 56.4; IR (neat, cm^{-1}) 3080, 3014, 2980, 2944, 2896, 2853, 1730, 1646, 1442, 1344, 1264, 1247, 1120, 1074; HRMS calcd for $C_{18}H_{23}O_4$ (MH^+) 303.1596, found 303.1588.



5a

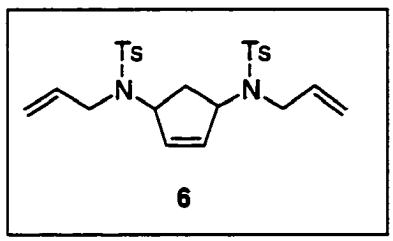
1-{4-[4-(4-Allyloxy-but-2-ynyloxy)-but-2-ynyloxy]-but-2-ynyloxy}-but-2-ene (5b), trans isomer (major). ^{1}H NMR (C_6D_6, 300 MHz) δ 5.95-5.81 (m, 1H), 5.78-5.67 (m, 1H), 5.60-5.49 (m, 1H), 5.33-5.18 (m, 2H), 4.30-4.26 (m, 8H), 4.15 (dt, *J* = 10.3, 1.7 Hz, 4H), 4.04 (dt, *J* = 5.8, 1.4, 2H), 3.98-3.94 (m, 2H), 1.72-1.69 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.7, 131.4, 127.4, 118.6, 83.7, 83.5, 82.7, 82.6, 81.9, 81.7, 71.1, 70.9, 57.7, 57.4, 57.2, 57.2, 57.1, 57.1, 17.9; IR (neat, cm^{-1}) 2854, 1442, 1344, 1140, 1119, 1070; HRMS calcd for $C_{19}H_{28}NO_4$ (MNH_4^+) 334.2025, found 334.2025.



5b

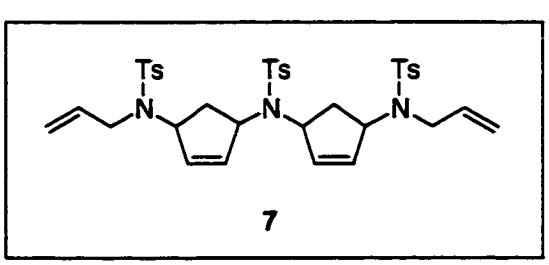
Compound (6). ^{1}H NMR (C_6D_6, 300 MHz) δ 7.65 (d, *J* = 8.2 Hz, 4H), 6.74 (d, *J* = 8.2 Hz, 4H), 5.80-5.67 (m, 2H), 5.19 (s, 2H), 5.10 (dd, *J* = 17.2, 1.4 Hz, 2H), 4.84 (dd, *J*= 10.2, 1.4 Hz, 2H), 4.78 (app t, *J* = 8.1 Hz, 2H), 3.56-3.52 (m, 4H), 2.19 (app dt, *J*= 13.4, 8.1 Hz, 1H), 1.88 (s, 6H), 1.44 (app dt, *J*= 13.4, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 143.5, 137.6, 135.8, 133.9, 129.8, 127.2, 117.1, 61.6, 46.6, 34.4, 21.5; IR (neat, cm^{-1}) 2921, 1598, 1335, 1158, 1091; HRMS calcd for $C_{25}H_{31}N_2O_4S_2$ (MH^+) 487.1725, found 487.1730.



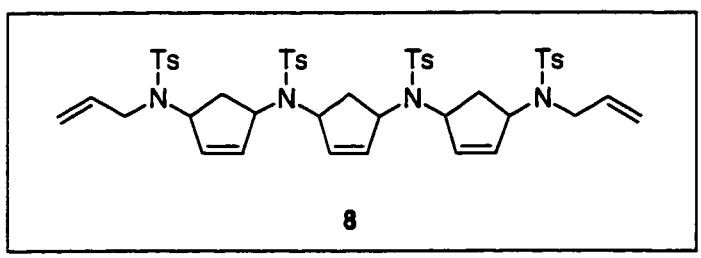
6

Compound (7), 2 isomers. ^1H NMR (C_6D_6, 300 MHz) δ 7.71-7.55 (m, 6H), 7.33-7.22 (m, 6H), 5.92-5.74 (m, 2H), 5.63-5.44 (m, 4H), 5.24-5.03 (m, 4H), 4.87-4.74 (m, 2H), 4.38-4.22 (m, 2H), 3.90-3.66 (m, 4H), 2.41-2.31 (m, 11H), 1.88-1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 143.4, 138.9, 137.7, 136.2, 134.6, 134.1, 133.1, 132.7, 129.8, 129.8, 127.2, 127.2, 127.1, 117.0, 116.9, 61.9, 61.8, 60.9, 60.7, 46.6, 46.6, 36.5, 36.1, 21.5; IR (neat, cm^{-1}) 3065, 2954, 1598, 1340, 1158, 1091; HRMS calcd for $C_{37}H_{43}N_3O_6S_3Na$ (MNa^+) 744.2212, found 744.2245.



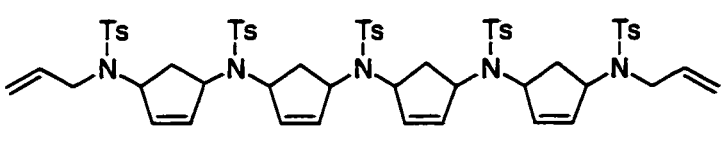
7

Compound (8), 3 isomers. ^{1}H NMR (C_6D_6, 400 MHz) δ 7.67-7.56 (m, 8H), 7.36-7.18 (m, 8H), 5.89-5.74 (m, 2H), 5.72-5.60 (m, 2H), 5.58-5.48 (m, 2H), 5.45-5.38 (m, 2H), 5.23-5.00 (m, 4H) 4.88-4.76 (m, 2H), 4.47-4.31 (m, 4H), 3.89-3.71 (m, 4H), 2.55-2.34 (m, 15H), 2.00-1.83 (m, 3H); IR (neat, cm^{-1}) 2923, 1597, 1331, 1155, 1085; HRMS calcd for $C_{49}H_{56}N_4O_8S_4Na$ (MNa^+) 979.2879, found 979.2915.



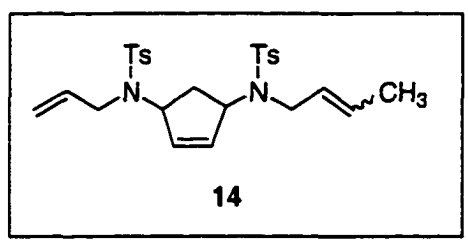
8

Compound (9), 4 isomers. ^{1}H NMR (C_6D_6, 400 MHz) δ 7.68-7.58 (m, 10H), 7.31-7.23 (m, 10H), 5.92-5.53 (m, 8H), 5.45-5.40 (m, 2H), 5.25-5.04 (m, 4H), 4.88-4.78 (m, 2H), 4.51-4.37 (m, 6H), 3.90-3.72 (m, 4H), 2.58-2.43 (m, 19H), 2.12-1.84 (m, 4H); IR (neat, cm^{-1}) 3063, 2955, 1598, 1332, 1157, 1092; LRMS calcd for $C_{61}H_{70}N_5O_{10}S_5$ (MH^+) 1192, found 1192.



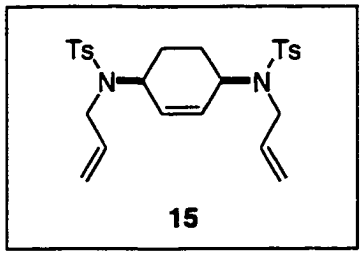
9

Compound (14), trans isomer (major). ^{1}H NMR (C_6D_6, 400 MHz) δ 7.62 (app t, J = 6.6 Hz, 4H), 7.26 (d, *J* = 6.6 Hz, 2H), 7.24 (d, *J* = 6.6 Hz, 2H), 5.78-5.71 (m, 1H), 5.52-5.28 (m, 4H), 5.14-5.04 (m, 2H), 4.76-4.72 (m, 1H), 3.70-3.51 (m, 4H), 2.39 (s, 3H), 2.38 (s, 3H), 2.29 (dt, *J* = 10.0, 6.2 Hz, 1H), 1.57 (dd, *J* = 4.9, 1.1 Hz, 3H), 1.46 (dt, *J* = 10.0, 6.2, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 143.3, 137.8, 137.5, 135.8, 134.2, 133.5, 129.8, 129.7, 128.5, 128.4, 127.2, 127.1, 117.1, 61.5, 61.5, 46.5,46.4, 34.5, 21.6, 21.5, 17.6; IR (neat, cm^{-1}) 2922, 1594, 1440, 1379, 1331, 1156, 1085; HRMS calcd for $C_{26}H_{36}N_3O_4S_2$ (MNH_4^+) 518.7145, found 518.7145.



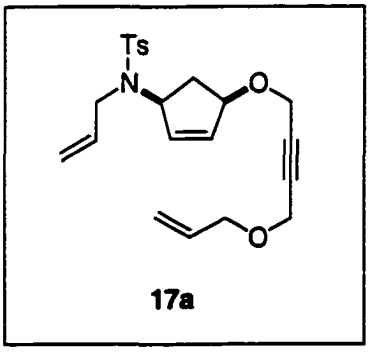
14

Compound (15). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 8.1 Hz, 4H), 7.26 (d, *J* = 8.1, 4H), 5.85-5.72 (m, 2H), 5.35 (s, 2H), 5.20-5.06 (m, 4H), 4.29 (s, 2H), 3.90-3.83 (dd, *J* = 16.9, 5.4 Hz, 2H), 3.69-3.61 (dd, *J* = 16.9, 5.8 Hz, 2H), 2.40 (s, 6H), 1.73-1.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 138.1, 136.0, 131.9, 129.8, 127.1, 116.9, 52.3, 47.5, 25.8, 21.5; IR (neat, cm^{-1}) 3028, 2923, 1598, 1337, 1163, 1090; HRMS calcd for $C_{26}H_{33}N_2O_4S_2$ (MH^+) 501.1882, found 501.1889.



15

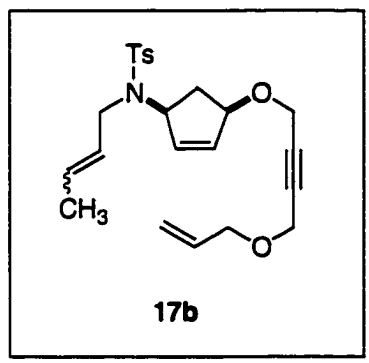
N-Allyl-N-[4-(4-allyloxy-but-2-ynyloxy)-cyclopent-2-enyl]-4-methylbenzene-sulfonamide (17a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.99-5.76 (m, 3H), 5.62-5.59 (m, 1H), 5.32-5.07 (m, 4H), 4.97-4.93 (m, 1H), 4.46-4.42 (m, 1H), 4.15-4.12 (m, 4H), 4.03-4.00 (m, 2H), 3.72-3.54 (m, 2H), 2.43 (dt, J = 14.7, 8.0 Hz, 1H), 2.41 (s, 3H), 1.38 (dt, J = 14.4, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 137.3, 135.9, 134.3, 134.2, 133.8, 129.6, 127.2, 117, 9, 116.9, 82.2, 80.9, 70.6, 61.7, 57.3, 56.6, 45.6, 34.9, 21.5; IR (neat, cm^{-1}) 3078, 3020, 2980, 2922, 2854, 1645, 1088; HRMS calcd for $C_{22}H_{31}N_2O_4S$ (MNH_4^+) 419.2004, found 419.2004.



17a

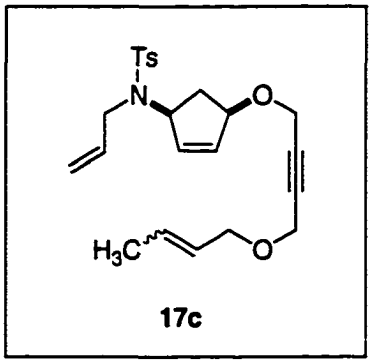
N-[4-(4-Allyloxy-but-2-ynyloxy)-cyclopent-2-enyl]-N-but-2-enyl-4-methyl-benzenesulfonamide (17b), trans isomer (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 6.0 Hz, 2H), 7.28 (d, J = 6.0 Hz, 2H), 5.97 (dt, J= 5.5, 2.2 Hz, 1H), 5.93-5.83 (m,

1H), 5.67-5.52 (m, 2H), 5.45-5.38 (m, 1H), 5.31-5.18 (m, 2H), 4.95-4.91 (m, 1H), 4.46-4.42 (m, 1H), 4.15-4.13 (m, 4H), 4.02 (dt, J = 4.4, 1.1 Hz, 2H), 3.71-3.48 (m, 2H), 2.40 (s, 3H), 1.64-1.60 (m, 4H), 1.42 (dt, J = 11.0, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 136.7, 134.5, 134.1, 130.7, 129.7, 129.6, 127.3, 127.3, 117.9, 82.4, 81.1, 70.8, 61.7, 61.7, 57.5, 56.7, 45.4, 35.2, 21.6, 17.7; IR (neat, cm^{-1}) 2853, 2369, 1718, 1340, 1159, 1089; HRMS calcd for $C_{23}H_{33}N_2O_4S$ (MNH_4^+) 433.2164, found 433.2164.



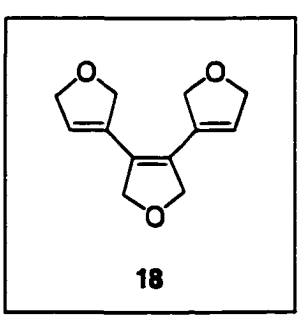
17b

N-Allyl-N-[4-(4-but-2-enyloxy-but-2-ynyloxy)-cyclopent-2-enyl]-4-methyl-benzenesulfonamide (17c), trans isomer (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.97 (dt, J= 5.5, 2.2 Hz, 1H), 5.87-5.50 (m, 3H), 5.22-5.07 (m, 4H), 4.96-4.93 (m, 1H), 4.46-4.43 (m, 1H), 4.16-4.07 (m, 4H), 3.95-3.93 (m, 2H), 3.73-3.56 (m, 2H), 2.40 (s, 3H), 1.71-1.64 (m, 3H), 1.39 (dt, J = 14.3, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 137.6, 136.1, 134.5, 134.3, 130.7, 129.7, 127.3, 126.8, 117.1, 82.2, 81.0, 70.5, 65.0, 61.9, 57.1, 56.7, 45.7, 35.2, 21.6, 17.8; IR (neat, cm^{-1}) 2939, 2854, 2359, 1340, 1160, 1091; HRMS calcd for $C_{23}H_{30}NO_4S$ (MH^+) 416.1912, found 416.1905.



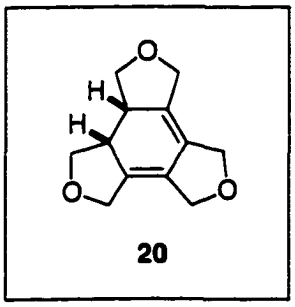
17c

2,5,2',5',2'',5''-Hexahydro-[3,3';4',3'']terfuran (18). To a stirring solution of **4** (234 mg, 1.0 mmol) in C_6H_6 (20 ml, 0.05 M) was added **1** (41 mg, 0.05 mmol, 0.05 equiv.) After stirring for 12 hrs at 45°C was added additional **1** (25 mg, 0.03 mmol, 0.03 equiv.) After stirring for another 12 hrs at 45°C, **4** was not detectable by tlc (product R_f = 0.3; 30% EtOAc in hexanes) and the reaction mixture was purified by flash chromatography (30% EtOAc in hexanes containing 2% NEt_3 elution). The product **18** was isolated as a white solid: 140 mg, 68%; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 5.78 (s, 2H), 4.74 (s, 4H), 4.65 (s, 8H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 132.2 (s), 128.1 (s), 125.9 (d, J = 179 Hz), 78.2 (t, J = 147 Hz), 75.6 (t, J = 147 Hz), 75.5 (t, J = 147 Hz); IR (neat, cm^{-1}) 3076, 2846, 1078, 1064; HRMS calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0937.



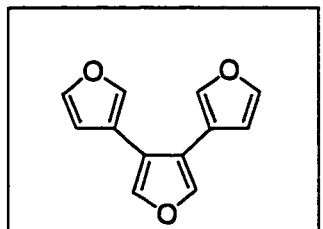
18

1,3,3a,3b,4,6,7,9-Octahydro-2,5,8-trioxa-trindene (20). A solution of **18** (24 mg, 0.12 mmol) in bromobenzene (0.5 ml, 0.05 M, b.p. 157°C) was stirred for 2.5 hrs at reflux. The reaction mixture was purified by flash chromatography (30% EtOAc in hexanes elution). The product **20** was isolated (R_f = 0.8; 30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.07 (s, 2H), 4.72-4.62 (m, 6H), 4.30-4.26 (m, 2H), 3.56-3.50 (m, 2H), 3.13-3.08 (m, 2H).



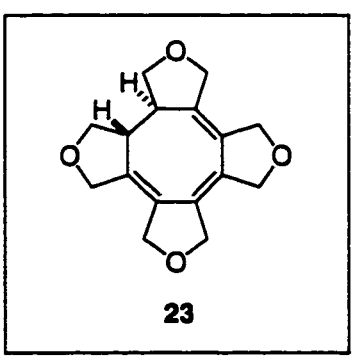
20

[3,3';4',3'']-Terfuran (21). To a solution of **18** (5 mg, 24 μmol) in C_6D_6 (0.5 ml, 0.05 M) was added DDQ (26 mg, 0.117 mmol, 4.9 equiv.) After stirring for 18 hrs at RT, **18** was not detectable by NMR or tlc (product R_f = 0.8; 30% EtOAc in hexanes), and the reaction mixture was purified by flash chromatography (30% EtOAc in hexanes elution). The product **21** was isolated. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.55 (s, 2H), 7.48-7.45 (m, 4H), 6.48-6.49 (m, 2H); LRMS (GC-MS) calcd for $C_{12}H_8O_3$ (M^+) 200, found 200.



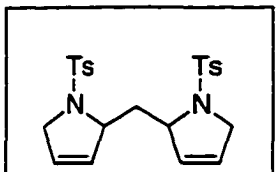
21

1,3,3a,3b,4,6,7,9,10,12-Decahydro-2,5,8,11-tetraoxa-tetracyclopenta[a,c,e,g]-cyclooctene (23). To a stirring solution of **5a** (302 mg, 1.0 mmol) in C_6H_6 (10 ml, 0.1 M) was added **1** (33 mg, 0.04 mmol, 0.04 equiv.) After stirring for 36 hrs at 45 °C, **5a** was not detectable by tlc (product $R_f = 0.1$; 30% EtOAc in hexanes), and the reaction mixture was purified by flash chromatography (25% EtOAc in CH_2Cl_2 elution). The product **23** was isolated as a white solid: 96 mg, 33%. ^1H NMR (CD_2Cl_2, 300 MHz) δ 4.10 (s, 4H), 4.02 (s, 4H), 3.89 (s, 4H), 3.71-3.68 (m, 2H), 3.15-3.10 (m, 2H), 2.39-2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 127.9, 126.7, 73.3, 72.5, 72.0, 71.9, 48.3; LRMS calcd for $C_{16}H_{18}O_4$ (M^+) 274, found 274.



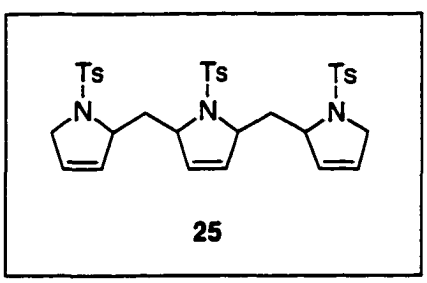
23

Compound (24). To a stirring solution of **6** (200 mg, 0.41 mol) in benzene (8 ml, 0.05M) is added **1** (17 mg, 21 μm, 0.05 equiv.) The reaction mixture is stirred at 45°C for 1 hr, at which time complete consumption of the starting material is observed by tlc (product R_f = 0.3; 30% EtOAc in hexanes). The solvent is removed under reduced pressure. The remaining dark oil is redissolved in 1 mL of benzene and treated with concentrated H_2SO_4 (1 mL) and 0.1 mL of H_2O (0.1 ml) until tlc of the organic phase indicates disappearance of the product. The reaction mixture is diluted with H_2O (10 mL) and benzene (10 mL), cooled to 0°C and carefully made basic with KOH. The liquid phases are separated and the aqueous phase is extracted twice with CH_2Cl_2 (10 mL). All organic phases are combined, dried over $MgSO_4$ filtered, and the solvent is removed under reduced pressure. The resulting oil is purified by flash chromatography (20% EtOAc in hexanes) to yield **24** as a white solid (135 mg, 72%). Alternatively, to a stirring solution of **6** (500 mg, 1.0 mmol) in C_6H_6 (20 ml, 0.05 M) is added **1** (41 mg, 0.05 mmol, 0.05 equiv.) The reaction mixture is stirred at RT for 4 hrs, at which time complete consumption of the starting material is observed by tlc. The reaction mixture is purified by flash chromatography (20% EtOAc in hexanes) to yield **24** as a white solid (365 mg, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 8.3 Hz, 4H), 7.31 (d, J = 8.3 Hz, 4H), 5.86-5.81 (m, 2H), 5.64-5.61 (m, 2H), 4.61-4.54 (m, 2H), 4.19-4.04 (m, 4H), 2.47-2.40 (m, 7H), 2.17-2.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 134.3, 130.5, 129.8, 127.6, 24.6, 64.7, 55.4, 42.6, 21.5; IR (neat, cm^{-1}) 3066, 2918, 2861, 1596, 1340, 1163, 1095; HRMS calcd for $C_{23}H_{27}N_2O_4S_2$ (MH^+) 459.1412, found 459.1404.



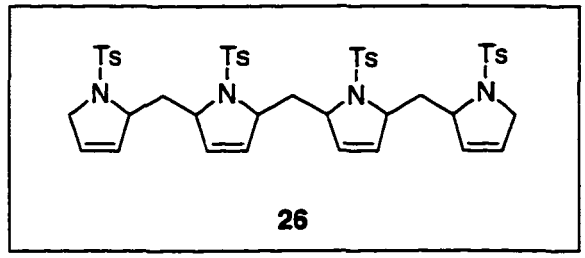
24

Compound (25), 2 isomers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70-7.65 (m, 6H), 7.29-7.27 (m, 6H), 6.09 (s, 2H), 5.62-5.56 (m, 4H), 4.72 (d, J = 8.8 Hz, 2H), 4.56-4.48 (m, 2H), 4.14-4.02 (m, 4H), 2.69-2.64 (m, 2H), 2.40-2.37 (m, 9H), 1.95-1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7, 142.9, 139.4, 134.4, 130.5, 129.8, 129.7, 129.6, 127.6, 126.8, 125.0, 65.0, 64.7, 55.4, 40.1, 21.6, 21.5; IR (neat, cm^{-1}) 2923, 1597, 1340, 1161, 1093; HRMS calcd for $C_{35}H_{40}N_3O_6S_3$ (MH^+) 694.2079, found 694.2068.



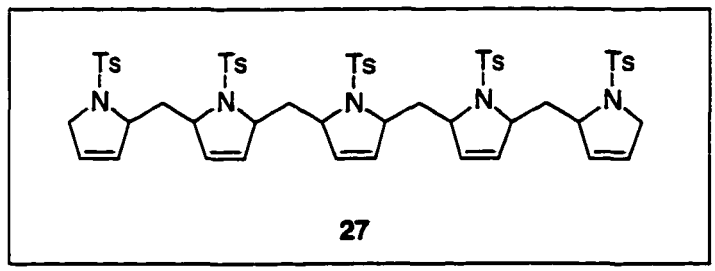
25

Compound (26), 3 isomers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73-7.64 (m, 8H), 7.30-7.26 (m, 8H), 6.15-6.03 (m, 2H), 5.84-5.71 (m, 2H), 5.62-5.57 (m, 4H), 4.82-4.37 (m, 6H), 4.17-4.04 (m, 4H), 2.95-2.91, 2.72-2.54 (m, 3H), 2.44-2.28 (m, 12H), 2.11-1.85 (m, 3H); IR (neat, cm^{-1}) 3066, 2923, 2869, 1598, 1339, 1162, 1099; HRMS calcd for $C_{47}H_{53}N_4O_8S_4$ (MH^+) 929.2746, found 929.2747.



26

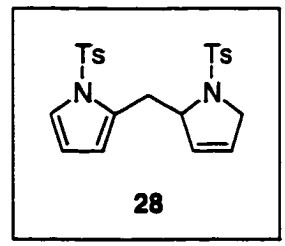
Compound (27), 4 isomers. To a stirring solution of **9** (45 mg, 38 μmol) in CH_2Cl_2 (12.5 ml, 0.003 M) is added **30** (1.7 mg, 1.89 μmol, 0.05 equiv.) The reaction mixture is stirred at 40 °C for 24 hrs, at which time complete consumption of the starting material is observed by tlc (product R_f = 0.4; 40% EtOAc in hexanes). The solvent is removed under reduced pressure. The remaining residue is purified by flash chromatography (20% EtOAc in hexanes) to yield **27** as a white solid (26 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77-7.62 (m, 10H), 7.34-7.26 (m, 10H), 6.18-6.12 (m, 2H), 5.92-5.55 (m, 8H), 4.85-4.36 (m, 8H), 4.17-4.03 (m, 4H), 2.96-2.92, 2.71-2.51, 2.40-2.63 (m, 19H), 2.12-1.81 (m, 4H); IR (neat, cm^{-1}) 2922, 1598, 1338, 1162, 1092; HRMS calcd for $C_{59}H_{66}N_5O_{10}S_5$ (MH^+) 1164.3413, found 1164.3467.



27

Compound (28). To a stirring solution of **24** (150 mg, 0.33 mol, 75% pure) in benzene (20 ml, 0.01M) is added DDQ (363 mg, 1.64 mmol, 5 equiv.) The reaction

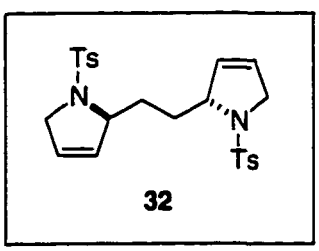
mixture is stirred at 80 °C for 72 hrs, at which time tlc indicates roughly 80% consumption of the starting material (product R_f = 0.2; 30% EtOAc in hexanes). The reaction mixture is purified by flash chromatography (20% EtOAc in hexanes) to yield **28**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 6.8 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 6.8 Hz, 2H), 7.29 (d, *J* = 8.3, 2H), 6.18 (app t, *J* = 3.3 Hz, 1H), 6.05-6.04 (m, 2H), 5.55-5.47 (m, 2H), 4.82-4.76 (m, 1H), 4.18-4.00 (m, 2H), 3.52 (dd, *J* = 14.6, 4.4 Hz, 1H), 2.85 (dd, *J* = 14.6, 9.2 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.5, 136.2, 134.3, 130.7, 130.1, 129.8, 129.4, 127.8, 127.1, 124.9, 122.9, 115.3, 111.7, 66.6, 56.1, 35.1, 21.7, 21.6; HRMS calcd for $C_{23}H_{25}N_2O_4S_2$ (MH^+) 457.1256, found 457.1257.



28

Compound (32). To a stirring solution of **31** (200 mg, 0.40 mol) in benzene (8.0 ml, 0.05M) is added **1** (17 mg, 20 μm, 0.05 equiv.) The reaction mixture is stirred at 45 °C for 48 hrs, at which time complete consumption of the starting material is observed by tlc (product R_f = 0.4; 30% EtOAc in hexanes). The reaction mixture is purified by flash chromatography (30% EtOAc in hexanes). The obtained white solid is dissolved in 1 mL of benzene and treated with concentrated H_2SO_4 (1 mL) and 0.1 mL of H_2O (0.1 ml) for 10 hrs. The reaction mixture is diluted with H_2O (10 mL) and benzene (10 mL), cooled to

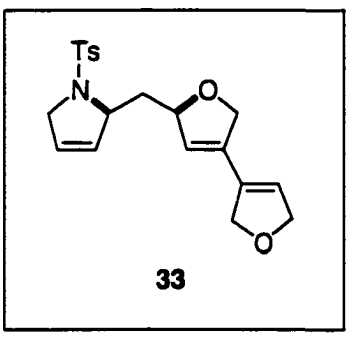
0°C and carefully made basic with KOH. The liquid phases are separated and the aqueous phase is extracted twice with CH_2Cl_2 (10 mL). All organic phases are combined, dried over $MgSO_4$, filtered, and the solvent is removed under reduced pressure. The resulting solid is purified by flash chromatography (30% EtOAc in hexanes) to yield **32** as a white solid (125 mg, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, J = 8.3 Hz, 4H), 7.29 (d, J = 8.3, 4H), 5.63-5.54 (m, 4H), 4.54 (s, 2H), 4.18-4.03 (m, 4H), 2.40 (s, 6H), 1.83-1.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 134.7, 129.8, 129.7, 127.5, 125.0, 67.1, 56.0, 30.0, 21.5; IR (neat, cm^{-1}) 2911, 2859, 1592, 1330, 1157, 1089, 1047; HRMS calcd for $C_{24}H_{29}N_2O_4S_2$ (MH^+) 473.1569, found 473.1570.



32

2-(2,5,2',5'-Tetrahydro-[3,3']bifuranyl-5-ylmethyl)-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrole (33). To a stirring solution of **17b** (180 mg, 0.43 mol) in benzene (8.6 mL, 0.05M) is added **1** (14.3 mg, 17 μm, 0.04 equiv.) The reaction mixture is stirred at 45°C for 4 hrs, at which time complete consumption of the starting material is observed by tlc (product R_f = 0.2; 30% EtOAc in hexanes). The reaction mixture is purified by flash chromatography (20% EtOAc in hexanes) to yield **33** as a clear, colorless oil (123 mg, 76%). ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.66 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 5.73-5.57 (m, 4H), 5.03-4.93 (m, 1H), 4.82-4.67 (m, 6H), 4.52-

4.46 (m, 1H), 4.16-4.01 (m, 2H), 2.41 (s, 3H), 2.21-2.13 (m, 1H), 2.00-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7, 132.2, 132.0, 130.1, 129.8, 127.4, 126.4, 124.2, 123.4, 84.0, 76.2, 75.0, 74.5, 64.7, 55.5, 42.3, 21.2; IR (neat, cm^{-1}) 2847, 1597, 1470, 1162, 1088; HRMS calcd for $C_{20}H_{24}NO_4S$ (MH^+) 374.1426, found 374.1423.



33

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(§) The majority of this chapter was previously reported in a separate publication. See: Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291-4298.

(1) (a) Teitze, L. F. *Chem. Rev.* **1996**, *96*, 115-136. (b) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3-30. (c) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Wiley-Interscience: New York, 1992. (d) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103-13159.

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(10) (a) Synthesis: Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. (b) Mechanism and activity: Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.

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Chapter 3

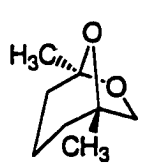
Total Synthesis of (–)- and (±)-Frontalin *via* Ring-Closing Metathesis[§]

Abstract

Racemic and enantiopure targets containing the 6,8-dioxabicyclo[3.2.1]octane skeleton, can be conveniently synthesized from monocyclic diene precursors using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step. The natural product frontalin was synthesized in racemic and enantiopure forms and in excellent yields using this methodology.

Introduction

Ring-closing metathesis (RCM), catalyzed by transition metal carbenes, has recently become a popular tool for the conversion of acyclic dienes to cycloolefins.[1] While a large number of mono- and polycyclic compounds has been prepared by this method, not much effort has been directed toward application of RCM to the construction of bridged systems, so ubiquitous in natural products. A recent report from this laboratory described the first application of RCM to the formation of small ring bridged bicycloalkenes from monocyclic dienes.[2] We now report the first synthesis of small ring bridged oxygen heterocycles using RCM as demonstrated by the synthesis of **1**.

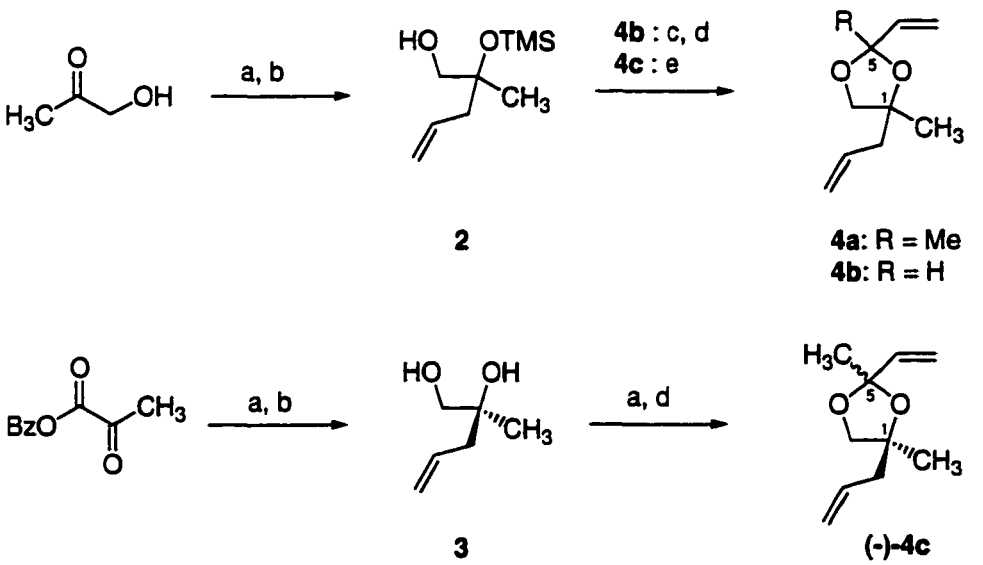


1

(+)-Frontalin

Results and Discussion

The 6,8-dioxabicyclo[3.2.1]octane ring system defines the skeleton of frontalin (**1**), the aggregation pheromone of the southern bark beetle *Dendroctonus frontalis*.[3] Although the biologically active enantiomer of frontalin (1*S*,5*R*)[4] contains two chiral centers, only one of them needs to be considered since the correct configuration of the second center is dictated by the formation of the bicyclic structure. The 1*S* center can be set in the 1,2-diol **2** with a high degree of enantiocontrol, utilizing either the recently developed Mukiyama asymmetric allylation[5] or the Sharpless asymmetric dihydroxylation[6] reaction (Scheme 1).[7]



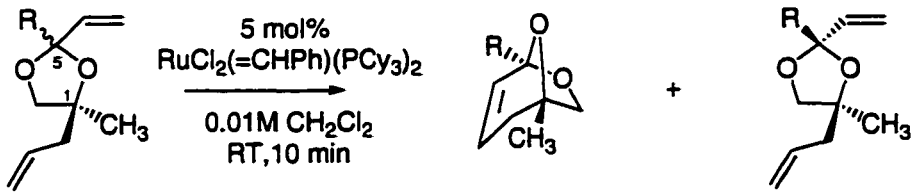
a: Sn(II)-catecholate, (+)-DIPT, DBU, CuI, Allyl-Br, CH_2Cl_2, -78°C, 81%; b: $LiAlH_4$, Et_2O, 0°C, then 25°C, 89%; a: TMS-Cl, Et_3N, CH_2Cl_2, 0°C, then 25°C, 83%; d: MVK, cat. TMS-OTf, CH_2Cl_2, -78°C, then -20°C, 85%; b: $H_2C{=}CHCH_2MgCl$, THF, 0°C, 67%; e: $H_2C{=}CHCH(OCH_3)_2$, cat. CH_3COCl, CH_2Cl_2, 0°C, 74%.

Scheme 1. Synthesis of precursors **4a-c**

Alternatively, the racemic mono-TMS-protected 1,2-diol **3** can be conveniently prepared *via* Grygnard addition of allyl magnesium chloride to the TMS-protected hydroxyacetone.

To utilize RCM for the formation of the bicyclic structures, the monocyclic dienes **4a** and **4b-c** are prepared starting from enantiopure[8] (**2**) and racemic (**3**) diols, respectively. The ketals **4a** and **4b** are synthesized under mild conditions using Noyori TMS-OTf assisted ketal formation[9] and the acetal **4c** is prepared via acetyl chloride-catalyzed condensation of **3** with acrolein dimethyl acetal.

Formation of bicyclo[3.2.1]alkenes by closure of the six membered ring is extremely facile.[2] The ring closed products **5a-c** can be obtained within minutes at room temperature by treatment of **4a-c** with a catalytic amount of ruthenium benzylidene[10] (Scheme 2). Since the precursors **4a-c** are most conveniently prepared as a mixture of the *syn*- and *anti*-isomers and only the *syn*-isomer can undergo cyclization, the unreacted *anti*-isomers **4a'-c'** can be recovered[11] and are easily equilibrated to a mixture of the two isomers.[12]



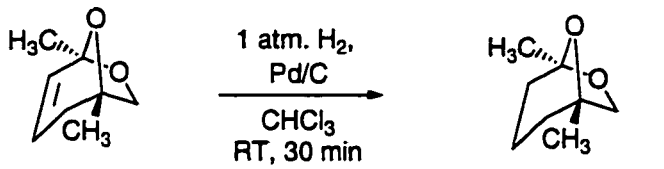
(-)-4a : (1-*S*), R = Me
4b : R = Me
4c : R = H

(-)-5a : (1-*S*) (5-*R*), R = Me (89%)
5b : R = Me (89%)
5c : R = H (90%)

(+)-4a' : (1-*S*) (5-*S*), R = Me (89%)
4b' : R = Me (89%)
4c' : R = H (90%)

Scheme 2. Ring-closing metathesis of precursors **4a-c** utlilizing 5 mol% of catalyst

Finally, the 1,5-dimethyl-6,8-dioxabicylo[3.2.1]oct-3-enes **5a** and **5b** are hydrogenated to yield racemic and enantiopure frontalin **1a** and **1b**, respectively, in excellent yields[13] (Scheme 3). Synthetic **1a** shows nearly identical optical rotation to that reported for the authentic (-)-isomer ($[\alpha]_D$ -50.0 vs. lit.[4] $[\alpha]_D$ –52.0).



(-)-5a
(±)-5b

(-)-1a : (89%)
(±)-1b : (89%)

Scheme 3. Hydrogenation of **5a-b** to yield frontalin (**1a-b**)

Conclusions

In conclusion, enantiopure and racemic products, such as frontalin, containing the 6,8-dioxabicyclo[3.2.1]octane skeleton can be prepared in 4 steps from 2-methyl-4-pentene-1,2-diols **2** and **3**, respectively. Current investigations are directed at *in situ* epimerization[14] of the C5 center of the monocyclic acetals and ketals **4a-c** leading to a theoretically quantitative conversion of **4a-c** to the corresponding bicycles **5a-c**. In addition, the synthesis of other small ring bridged natural products *via* RCM is in progress.

Acknowledgements

Support has been generously provided by the National Institutes of Health. MS thanks Pharmacia and Upjohn for a Graduate Fellowship in Synthetic Organic Chemistry. The authors thank Dr. Andrew Morehead, Jr., for useful discussions.

Experimental Section

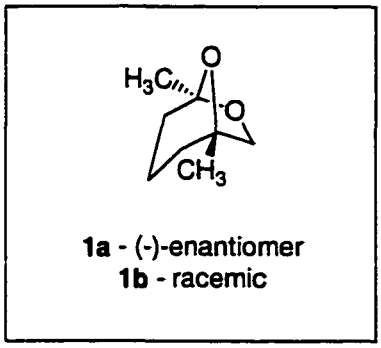
General Considerations

High resolution mass spectra were provided by the Southern California Mass Spectrometry Facility (University of California at Riverside). Analytical thin-layer chromatography (tlc) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with one or more of the following: UV light, $KMnO_4$, phosphomolybdic acid (PMA), cerric ammonium nitrate (CAN), or *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[15]

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise specified. Catalyst **1** was prepared according to published procedure and is commercially available.[10a] Solvents were purified by passage through a column containing A-5 alumina (all solvents) followed by a column containing Q-5 reactant (non-ethereal solvents). Argon was purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4Å molecular sieves (Linde). Allyl bromide was purchased from ARCOS. All other reagents were purchased from the Aldrich Chemical Company.

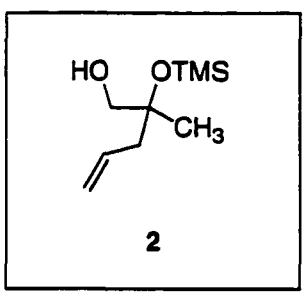
Synthetic Procedures and Characterization Data

1,5-Dimethyl-6,8-dioxa-bicyclo[3.2.1]octane (1a) and (1b). Match literature, see: Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443-5445.; **1a**: $[\alpha]_D$ -50.0°.



1a - (-)-enantiomer
1b - racemic

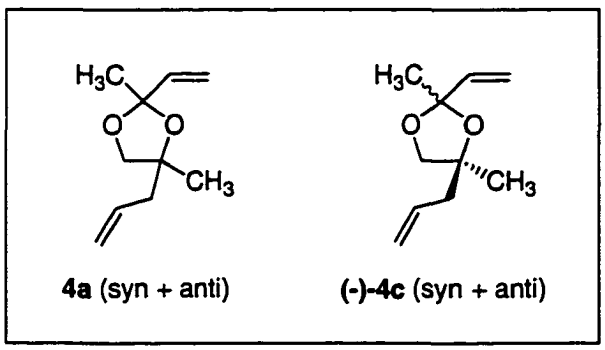
2-Methyl-2-trimethylsilanyloxy-pent-4-en-1-ol (2). NMR and IR match lit.: Barluenga, J.; Florez, J.; Yus, M. *J. Chem. Soc. - Perkin Trans. I* **1983**, 3019-3026.; HRMS calcd for $C_6H_{16}NO_2$ (MNH_4^+) 134.1181, found 134.1188.



2

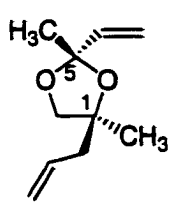
4-Allyl-2,4-dimethyl-2-vinyl-[1,3]dioxolane (4a) and (4c). (each ~1:1 mixture of *syn*- and *anti*-diastereomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86-5.71 (m, 4H), 5.38-5.32 (m, 2H), 5.10-5.02 (m, 6H), 3.80 (d, J = 8.4 Hz, 1H), 3.72 (d, J = 8 Hz, 1H), 3.69 (d, J = 8.0 Hz, 1H), 3.53 (d, J = 8.4 Hz, 1H), 2.39-2.23 (m, 4H), 1.45 (s, 6H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 140.0, 133.9, 133.8, 118.3, 118.2, 114.4, 114.3, 108.2, 108.1, 81.2, 81.2, 73.9, 73.2, 45.0, 44.0, 26.2, 26.2, 25.0, 23.9; IR

(neat, cm^{-1}) 2968, 1630, 1426, 1374, 1218, 1166, 1047; HRMS calcd for $C_{10}H_{17}O_2$ (MH^+) 169.1229, found 169.1228.



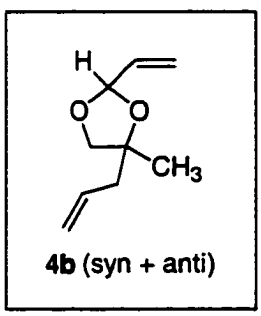
4a (syn + anti) **(-)-4c** (syn + anti)

4-Allyl-2,4-dimethyl-2-vinyl-[1,3]dioxolane (4a') and (4b'). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.89-5.79 (m, 2H), 5.38-5.32 (m, 1H), 5.12-5.09 (m, 3H), 3.80 (d, J = 8.4 Hz, 1H), 3.53 (d, J = 8.4 Hz, 1H), 2.35-2.26 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 134.0, 118.3, 114.4, 108.2, 81.3, 73.3, 45.0, 26.2, 23.9; IR (neat, cm^{-1}) 2931, 1641, 1372, 1217, 1170, 1050; HRMS calcd for $C_{10}H_{17}O_2$ (MH^+) 169.1229, found 169.1228.



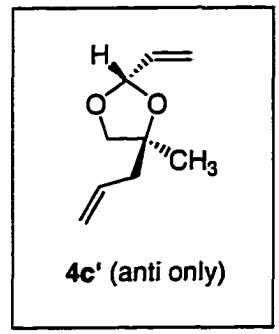
(+)-4a' - enantiopure (1-*S*) (5-*S*) (*anti* only)
4b' - racemate (*anti* only)

4-Allyl-4-methyl-2-vinyl-[1,3]dioxolane (4b). (~1:1 mixture of *syn*- and *anti*-diastereomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86-5.75 (m, 4H), 5.50-5.43 (m, 2H), 5.35-5.29 (m, 4H), 5.14-5.07 (m, 4H), 3.85 (d, J = 7.6 Hz, 1H), 3.74 (d, J = 7.6 Hz, 1H), 3.66 (d, J = 7.6 Hz, 1H), 3.55 (d, J = 7.6 Hz, 1H), 2.42-2.30 (m, 4H), 1.29 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 135.1, 133.6, 133.4, 120.1, 119.9, 118.5, 118.4, 104.0, 103.5, 80.8, 80.7, 74.4, 44.5, 43.1, 30.4, 24.7, 23.3; IR (neat, cm^{-1}) 2978, 1642, 1436, 1377, 1097; HRMS calcd for $C_9H_{15}O_2$ (MH^+) 155.1072, found 155.1070.



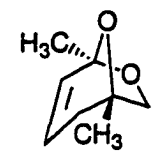
4b (syn + anti)

4-Allyl-4-methyl-2-vinyl-[1,3]dioxolane (4c'). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84-5.72 (m, 2H), 5.41 (d, J = 17.2 Hz, 1H), 5.31-5.26 (m, 2H), 5.09-5.04 (m, 2H), 3.70 (d, J = 8.0 Hz, 1H), 3.62 (d, J = 8.0 Hz, 1H), 2.39-2.25 (m, 2H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 133.4, 119.9, 118.5, 104.0, 80.8, 74.4, 43.1, 24.7; IR (neat, cm^{-1}) 2979, 1728, 1642, 1436, 1378, 1097; HRMS calcd for $C_9H_{15}O_2$ (MH^+) 155.1072, found 155.1070.



4c' (anti only)

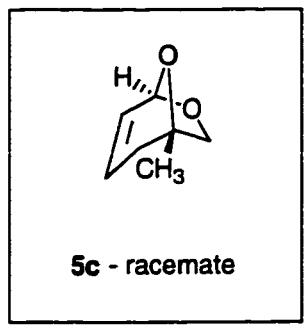
1,5-Dimethyl-6,8-dioxa-bicyclo[3.2.1]oct-3-ene (5a) and (5b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80-5.66 (m, 2H), 3.72 (d, J = 7.3 Hz, 1H), 3.53-3.50 (m, 1H), 2.40 (dd, J = 17.9, 7.3, 1H), 1.99-1.93 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.0, 125.3, 103.3, 78.9, 74.6, 38.6, 24.1, 22.1; IR (neat, cm^{-1}) 2932, 1711, 1374, 1260, 1062, 1020; HRMS calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0846.



(-)-5a - enantiopure (1-*S*) (5-*R*)
5b - racemate

1-Methyl-6,8-dioxa-bicyclo[3.2.1]oct-3-ene (5c). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.85-5.81 (m, 1H), 5.72-5.67 (m, 1H), 5.44 (d, J = 3.3 Hz, 1H), 3.72 (d, J = 7.3 Hz, 1H), 3.42 (dd, J = 7.3, 3.3 Hz, 1H), 2.48-2.41 (m, 1H), 2.00-1.94 (m, 1H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.0, 126.1, 97.3, 77.8, 73.5, 39.3, 23.8; IR (neat, cm^{-1})

2973, 1686, 1638, 1384, 1169, 1073; HRMS calcd for $C_7H_{10}O_2$ (M^+) 126.0681, found 126.0689.



5c - racemate

References and Notes

(§) The majority of this chapter was previously reported in a separate publication. See: Scholl, M.; Grubbs, R. H. *Tet. Lett.* **1999**, *40*, 1425-1428.

(1) For recent reviews of RCM see: (a) Armstrong, S. K. *J. Chem. Soc. - Perkin Trans. 1* **1998**, 371-388.; (b) Randall, M. L.; Snapper, M. L. *J. Mol. Cat. A-Chem.* **1998**, *133*, 29-40.; (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037-2056.; (d) Ivin, K. J. *J. Mol. Cat. A-Chem.* **1998**, *133*, 1-16.

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(7) For a similar approach to define the 1*S* stereocenter see: Turpin, J. A.; Weigel, L. O. *Tet. Lett.* **1992**, *33*, 6563-6564.

(8) The enantiopurity of the 2-hydroxy-2-methyl-pent-4-enoic acid benzyl ester derived from the Mukaiyama allylation reaction is assessed to be 99+% as determined by its optical rotation ($[\alpha]_D$ 6.5 vs. lit.[5] $[\alpha]_D$ 5.8) and the ^{1}H NMR

analysis of its Mosher's ester. The absolute configuration of the 2-hydroxy-2-methyl-pent-4-enoic acid benzyl ester was determined to be (*S*) by the conversion to (*S*)-(+)-dimethyl citramalate.[5]

(9) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tet. Lett.* **1980**, *21*, 1357-1358.

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

(11) No dimerization of the non-cyclizable isomer of (+)-4a was observed at 0.01M; the reaction was not run at any other concentrations.

(12) Treatment of the *anti*-isomer with a cat. amount of Amberlyst® 15 acidic ion exchange resin results in a rapid equilibration to a mixture of the *syn*- and *anti*-isomers.

(13) Yields determined by ^{1}H NMR are quantitative; isolated yields are slightly lower due to high volatility of products.

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Chapter 4

Increased Ring-Closing Metathesis Activity of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with Imidazol-2-ylidene Ligands[§]

Abstract

The novel air and water tolerant, imidazolinylidene-substituted ruthenium-based complex **3**, has been prepared starting from $RuCl_2(=CHPh)(PCy_3)_2$ **2** and shown to exhibit increased ring-closing metathesis activity at elevated temperature compared to that of the parent complex **2**. Di-, tri-, and even tetra-substituted cycloolefins were successfully prepared from corresponding diene precursors using catalytic amounts of **3** in moderate to excellent yields.

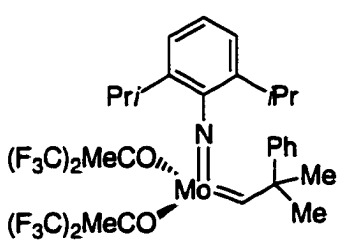
Introduction

With the advent of efficient catalysts, the olefin metathesis reaction has emerged as a powerful tool for the formation of C-C bonds.[1] Widely used well-defined alkylidene-metal complexes for this transformation include the alkoxy imido molybdenum complex **1**[2] and the benzylidene ruthenium complex **2**.[3] The molybdenum complex **1** exhibits the higher reactivity of the two towards a broad range of substrates with many steric or electronic variations;[4] however, it also suffers from high sensitivity to air and moisture and decomposition upon storage. To increase the utility of the ruthenium family of complexes by increasing the activity and/or selectivity, a number of derivatives of **2** have been prepared. These derivatives of **2** include bidentate salicylaldimine ruthenium complexes[5] and binuclear ruthenium complexes.[6] The recent reports from the Herrmann group on the derivatization of **2** with imidazolinylidene ligands[7] prompted us to explore this family of complexes for use in organic applications. Herein, we report a ruthenium-based imidazolinylidene complex **3**, showing a ring closing metathesis activity

comparable to that of the molybdenum complex **1**, yet exhibiting a remarkable air and water stability similar to that of the parent benzylidene ruthenium complex **2**.

Results and Discussion

Herrmann *et al.* prepared a novel class of ruthenium complexes **4** by substituting both of the phosphine with imidazolinylidene ligands.[7] Although these complexes showed little if any improvements in applications to ROMP and RCM, their potential activity expected from the ligand's basicity and steric bulk[8] led us to explore some of the other members of the Arduengo imidazolinylidene ligand family.[9] Of the number of 1,3-diaryl-imidazolin-2-ylidene ligands that were tried, only the 2,6-disubstituted aryl systems including the 1,3-dimesityl-imidazolin-2-ylidene ligand gave clean substitution products. In contrast to the Herrmann systems, this ligand displaced only one of the two phosphines to produce **3**.[10] This new derivative of **2** allows many of the desirable RCM reactions to be carried out with ruthenium complexes.



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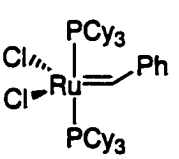

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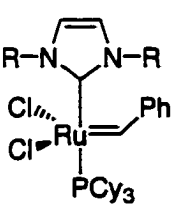
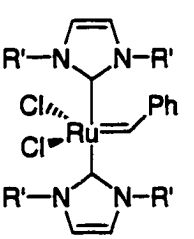


R = C_6H_2-2,4,6-$(CH_3)_3$

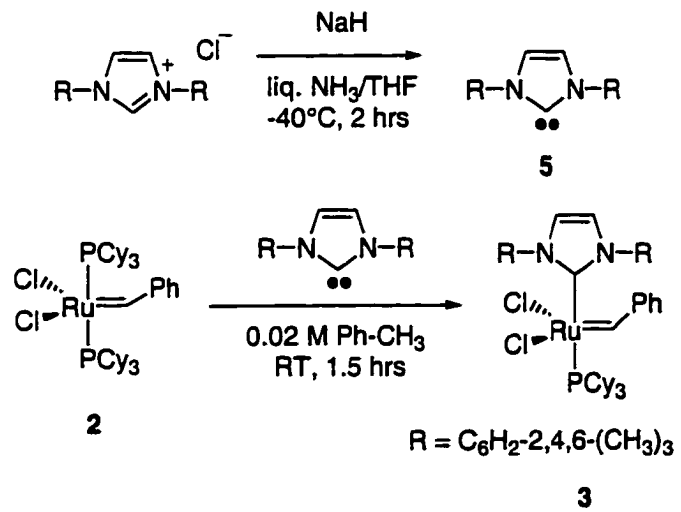
3



R' = C_6H_{11}, C_3H_7

4

The monosubstituted imidazolinylidene complexes can be prepared using Herrmann's procedure,[7] provided that the substituents on the imidazole ring are sufficiently bulky to prevent disubstitution (Scheme 1). The imidazolinylidene ligand **5**[9] is conveniently synthesized from the corresponding salt with sodium hydride in liquid ammonia/THF[11] and can be isolated or used without purification in the subsequent step. The ligand exchange reaction in toluene[12] is rapid at room temperature and the product **3** is isolated as a pinkish-brown microcrystalline solid that can be purified by recrystallization from pentane at –78°C.

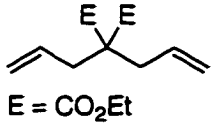
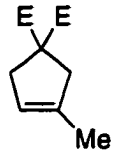
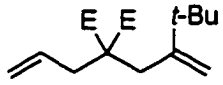
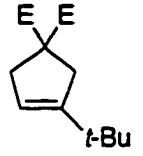
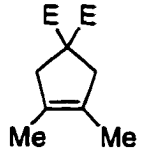
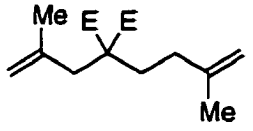
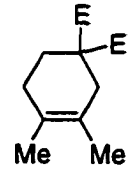
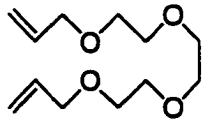
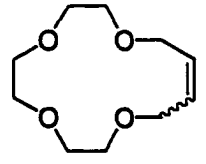


Scheme 1. Synthesis of imidazolinylidene ligand **5** and catalyst **3**

The activity of the complex **3** has been briefly explored as shown in Table 1. Although the new species is less reactive than the parent **2** at room temperature for ring closing metathesis reactions, the reactivity increases dramatically at slightly higher temperatures. For instance, although the ring closure of diethyl diallylmalonate ester

(Entry 1) takes hours at room temperature with complex **3**, the reaction is completed within 30 minutes at 40°C with the same carbene catalyst.

Table 1. Results of the RCM with 5 mol% **2** or **3** in 0.05M CD_2Cl_2 at reflux

Entry	Substrate	Product	Time (min)	Yield with **2** (%)[a]	Yield with **3** (%)[a]
1	 E = CO_2Et		30	100	100
2			30	82	100
3			60	N.R.	100
4			90	N.R.	40
5			90	N.R.	95
6			60	39[b]	55 (45)[c]

[a] Yields represent the conversion to product as determined by ^1H NMR. [b] E:Z = ~1.6:1
[c] Isolated yield in parentheses; E:Z~2:1.

In addition, the complex **3** exhibits increased ring closing activity towards sterically demanding olefins. For example, 2-*t*-butyl diethyl diallyl malonate ester (Entry 3) can be cyclized with 5 mol% of **3** in 1 hr, while the corresponding reaction with 5 mol% of **2** does not yield any significant amount of cyclized product.[4] Similarly, tetra-substituted olefins (Entries 4 and 5) can be prepared in moderate to excellent yields using the complex **3**.

Ring closing metathesis of macrocyclic ethers with complex **3** is comparable to that with complex **2**. For instance, triethylene glycol diallyl ether (Entry 6) is cyclized at 40°C to a 45% isolated yield with complex **3** and to a 39% yield with complex **2**.[13] The stereoselectivities of both complexes are similar and the product is obtained as a ~2:1 and a ~1.6:1 mixtures of trans:cis isomers, respectively.

Conclusions

In conclusion, complex **3** exhibits high olefin metathesis activity in RCM reactions and extends the potential of the ruthenium family of complexes. Di-, tri-, and tetra-substituted olefins can be prepared in moderate to excellent yields. Further detailed studies regarding the mechanistic description, the scope and limitations, and the steric/electronic tuning of on the complex are under investigation.

Acknowledgements

Support has been generously provided by the National Institutes of Health. MS thanks Pharmacia and Upjohn for a Graduate Fellowship in Synthetic Organic Chemistry,

TMT thanks the DOD for a NDSEG graduate fellowship and JPM thanks Caltech for an Institute graduate Fellowship. The authors thank Michael Ulman for useful discussions. Thomas A. Kirkland and Heather D. Maynard are acknowledged for the generous supply of substrates in entries 2-5 and entry 6, respectively.

Experimental Section

General Considerations

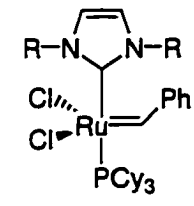
High resolution mass spectra were provided by the Southern California Mass Spectrometry Facility (University of California at Riverside). Analytical thin-layer chromatography (tlc) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with one or more of the following: UV light, $KMnO_4$, phosphomolybdic acid (PMA), cerric ammonium nitrate (CAN), or *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[14]

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise specified. Solvents were purified by passage through a column containing A-5 alumina (all solvents) followed by a column containing Q-5 reactant (non-ethereal solvents). Argon was purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4Å molecular sieves (Linde).

Representative Procedures and Characterization Data

Representative procedure for the preparation of 3: To a solution of imidazolin-2-ylidene ligand **5** (304 mg, 1.0 mmol) in toluene (40 mL) was added a solution of Ru complex **2** (823 mg, 1.0 mmol) in toluene (10 mL) under N_2 atmosphere. The reaction mixture immediately turned from purple to dark red and it was allowed to stir at RT for 1.5 hrs. The reaction mixture was filtered, toluene was evaporated in vacuo and the remaining solid residue was recrystallized from pentane at -78°C thrice to give

the desired complex **3** (700 mg, 85%) as a pinkish-brown microcrystalline solid: ^{1}H NMR (C_6D_6, 400 MHz) δ 19.93 (s, 1H), 7.15 (m, 5H), 7.03-6.93 (m, 2H), 6.91(s, 2H), 6.20-6.17 (m, 2H), 2.78-2.45, 2.40-2.00, 1.84, 1.80-1.48, 1.36-0.98 (all m, 51H); ^{31}P NMR (C_6D_6, 161.9 MHz) δ 32.43; HRMS (FAB) $C_{46}H_{63}Cl_2N_2PRu$ [M^+] 846.3143, found 846.3116.



R = C_6H_2-2,4,6-$(CH_3)_3$

3

References and Notes

(§) The majority of this chapter was previously reported in a separate publication. See: Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tet. Lett.* **1999**, *40*, 2247-2250.

(1) For recent reviews on olefin metathesis see: (a) Ivin, K. J. *J. Mol. Cat. A-Chem.* **1998**, *133*, 1-16.; (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.; (c) Randall, M. L.; Snapper, M. L. *J. Mol. Cat. A-Chem.* **1998**, *133*, 29-40.

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(11) Herrmann, W. A.; Köcher, C.; Goossen, L. J.; Artus, G. R. J. *Chem.- Eur. J.* **1996**, *2*, 1627-1636.

(12) The same reaction in THF leads to formation of a ~ 1:1 mixture of two ruthenium carbene complexes which are inseparable by recrystallization. One of the two complexes is the monosubstituted product; the other is thought to be the disubstituted complex but no characterization beyond ^{1}H and ^{31}P NMR of the mixture has been attempted.

(13) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101-1103.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Chapter 5

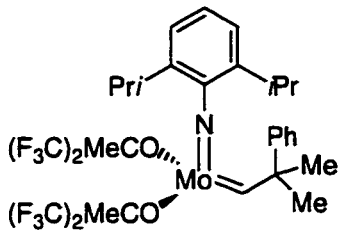
Synthesis and Activity of a New Generation of Ruthenium-based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydro-imidazol-2-ylidene Ligands[§]

Abstract

A new family of 1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene-substituted ruthenium-based complexes **9a-f** has been prepared starting from $RuCl_2(=CHPh)(PCy_3)_2$ **2** or $Cl_2(PCp_3)_2Ru(=CH\text{-}CH=C(CH_3)_2)$ **10**. These air and water tolerant complexes exhibit an increased ring-closing metathesis activity when compared to that of the parent complex **2** and the previously developed complex **3**. In many instances the activity of these complexes also rivaled or exceeded that of the alkoxy-imido molybdenum complex **1**. Catalyst loadings of as low as 0.05 mol% could be used. In addition, applications of the chiral complexes **9c-f** to asymmetric ring-closing metathesis are discussed.

Introduction

With the advent of efficient catalysts, the olefin metathesis reaction has emerged as a powerful tool for the formation of C-C bonds.[1] Well-defined alkylidene-metal complexes, which are widely used for this transformation, include the alkoxy-imido molybdenum complex **1**[2] and the benzylidene ruthenium complex **2**.[3] The molybdenum complex **1** exhibits the higher reactivity of the two towards a broad range of substrates with many steric or electronic variations;[4] however, it also suffers from extreme sensitivity to air and moisture as well as decomposition upon storage. To increase the utility of the ruthenium family of complexes by increasing their activity, we recently prepared ruthenium-based complexes coordinated with 1,3-dimesityl-imidazol-2-ylidene ligands **3**.[5] These complexes exhibited a high ring-closing metathesis activity similar to that of the molybdenum complex **1**, yet have also retained the remarkable air and water stability characteristic of the parent benzylidene ruthenium complex **2**.



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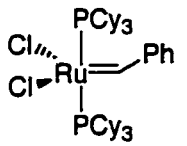

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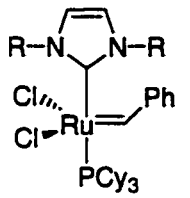
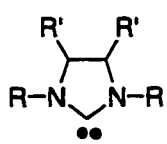


R = C_6H_2-2,4,6-$(CH_3)_3$
C_6H_2-2,4-$(CH_3)_2$-4-(OCH_3)

3

In search for even more efficient ligands for our ruthenium olefin metathesis catalysts, we have focused on the related 4,5-dihydro-imidazol-2-ylidenes **4**.[6,7,8] We reasoned that due to the lack of carbene stabilization provided by the absence of π-interactions, these saturated imidazole ligands might be more basic then their unsaturated analogues.[9] The higher basicity of these ligands should in turn translate into an increased activity of the desired catalysts.[10]



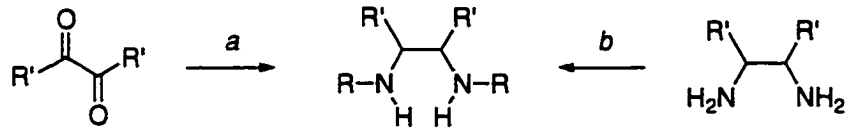
4

Results and Discussion

Catalyst Synthesis

We began the synthesis of ligands **4** with the preparation of ethane-1,2-diamines **5** (R'=H) and 1,2-disubstituted ethane-1,2-diamines **6** (R'=Ph, alkyl). The diamines **5a-d** were easily made *via* the condensation of a variety of aromatic and aliphatic amines with

glyoxal, followed by a reduction of the resulting Schiff-bases with either $NaCNBH_3$, $NaBH_4$, or with H_2 and Pd/C (Scheme 1).[11] The diamines **6a-e** were obtained in one step *via* the palladium-catalyzed amination reaction of various aryl bromides with 1,2-disubstituted ethane-1,2-diamines.[12]



Method *a*

- **5a**: R' = H, R = Mesityl
- **5b**: R' = H, R = Isopinocampheyl
- **5c**: R' = H, R = 2,6-Diisopropylphenyl
- **5d**: R' = H, R = 1-Adamantyl

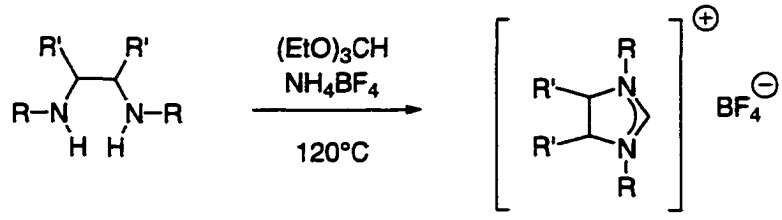
Method *b*

- **6a** : R' = $-(CH_2)_4-$, R = Mesityl
- **6b** : R' = $-(CH_2)_4-$, R = 2-isopropylphenyl
- **6c** : R' = $-(CH_2)_4-$, R = 9-Anthracenyl
- **6d** : R' = Ph, R = Mesityl
- **6e** : R' = Binaphthyl, R = Mesityl

Method *a*: (i) R-NH_2, acetone/water; (ii) $NaCNBH_3$, HCl, MeOH, or $NaBH_4$, MeOH, or H_2, Pd/C; Method *b*: R-Br, Pd_2dba_3, (±)-BINAP, NaO^tBu, Ph-CH_3, 100°C.

Scheme 1. Synthesis of ethane-1,2-diamines **5** and **6**

The diamines **5** and **6** were subsequently converted to the corresponding imidazolium salts through treatment with triethyl orthoformate in the presence of one equivalent of ammonium tetrafluoroborate at 120°C (Scheme 2).[13] The resultant imidazolium tetrafluoroborate salts **7** were obtained quantitatively and could be purified further by recrystallization from ethanol/hexanes.



5, 6

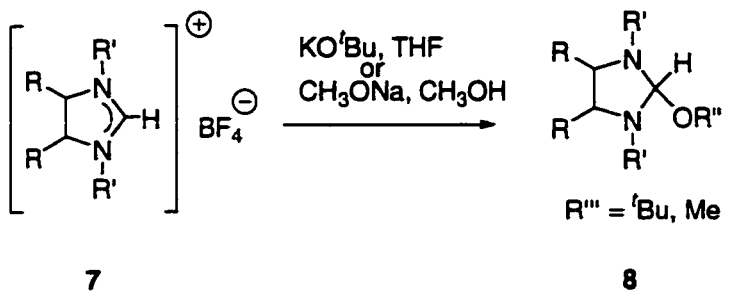
7a : R' = H R = Mesityl
7c : R' = -$(CH_2)_4$-, R = Mesityl
7d : R' = Ph R = Mesityl
7e : R' = -$(CH_2)_4$-, R = 2-isopropylphenyl
7f : R' = H R = Isopinocampheyl

Scheme 2. Formation of 4,5-dihydroimidazoyl tetrafluoroborate salts

We had hoped that these precursors (**7**) could be readily deprotonated with metal hydrides to yield the desired ligands **4** directly,[7] especially since similar procedures have worked well for many unsaturated imidazolium salts.[14] Unfortunately, we were unsuccessful at extending the published procedures[7,14] to our saturated systems. Parallel work in our group, however, revealed the possibility of using protected carbenes as precursors to generate the free carbene ligands *in situ*. Specifically, it was found that 5-methoxy-triazoles could be reacted directly with metal complexes at elevated temperatures *via* the *in situ* conversion to the free triazol-5-ylidenes.[15]

Correspondingly, we prepared the similar 2-alkoxy-4,5-dihydro-imidazoles **8** by treatment of the tetrafluoroborate salts **7** with sodium methoxide in methanol or potassium tert-butoxide in THF at ambient temperature (Scheme 3). Interestingly, the tert-butoxide/THF route worked much better than the methoxide/methanol route.[16] Although compounds **8** were too unstable to be isolated by common experimental techniques, presumably due to facile alcohol elimination and conversion to the desired

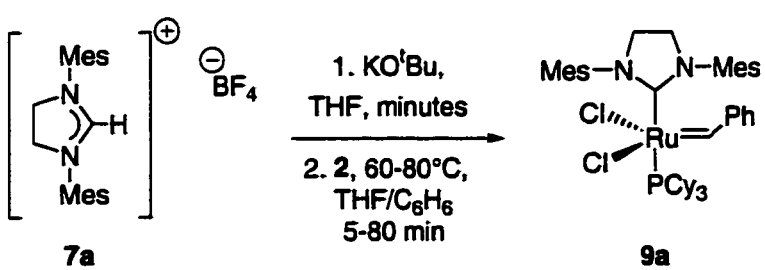
ligands **4** upon workup, HRMS investigations revealed the presence of compounds **8** in the reaction mixtures.



7 **8**

Scheme 3. Formation of 2-alkoxy-4,5-dihydroimidazoles **8**

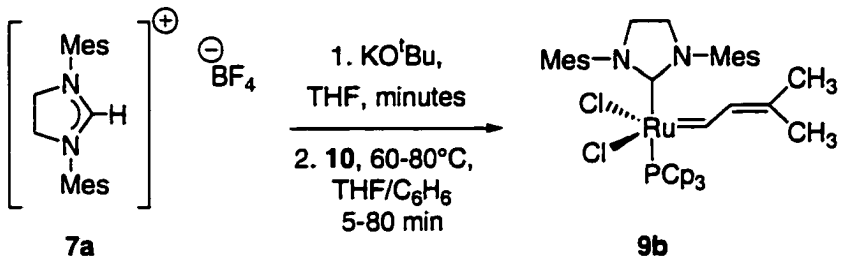
The alkoxy-protected species **8** did not react with the benzylidene ruthenium complex **2** in benzene at ambient temperature. However, they readily reacted with the complex **2** when deprotected *in situ* by heating to 60-80°C. Specifically, when the alkoxy-protected ligand **8a** was heated in the presence of complex **2** at 60-80°C, the desired ruthenium complex **9a** coordinated with 1,3-dimesityl-4,5-dihydro-imidazol-2-ylidenes was readily obtained as a pinkish-brown microcrystalline solid in good yield (Scheme 4). This complex could be purified further by recrystallizing from methanol.



7a **9a**

Scheme 4. Formation of the ruthenium complex **9a**

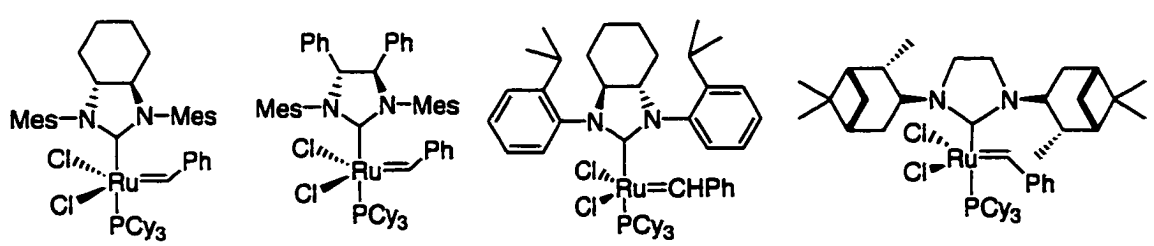
In addition, ruthenium sources other than the parent ruthenium benzylidene **2** could be utilized. For instance, the treatment of tetrafluoroborate salt **7a** with *tert*-butoxide in THF and then the exposure of the resultant adduct to vinyl carbene ruthenium species $Cl_2(PCp_3)_2Ru(=CH\text{-}CH=C(CH_3)_2)$ **10** at 80°C, leads to the formation of 1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene substituted ruthenium vinyl carbene **9b** in good yields (Scheme 5).



7a **9b**

Scheme 5. Formation of the ruthenium complex **9b**

As a variety of chiral N-heterocyclic carbene substituted ruthenium olefin metathesis catalysts were desired for our project, they could be obtained in a similar manner, starting with the other tetrafluoroborate salts **7c-f** (Figure 1).



9c **9d** **9e** **9f**

Figure 1. Selected N-heterocyclic carbene substituted ruthenium olefin metathesis catalysts

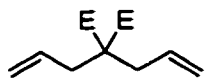
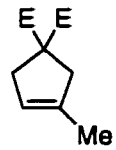
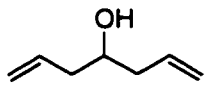
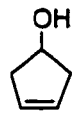
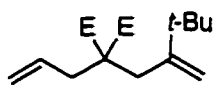
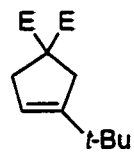
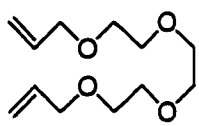
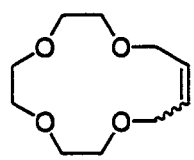
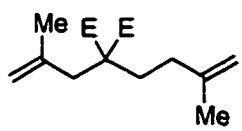
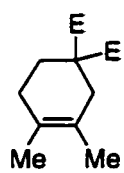
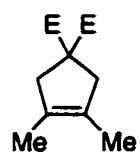
Ring-Closing Activity of Complexes 9a-c

The RCM activity of complexes **9a** and **9c** was briefly explored and compared to that of complexes **1** and **2** as illustrated in Table 1. All complexes catalyzed the ring closure of diethyl diallylmalonate to form the corresponding di-substituted cycloolefin within minutes at 45°C (Entry 1). In the case of 2-substituted α,ω-dienes, however, the increased ring-closing metathesis activity of the complexes **9a** and **9c** was readily evident.[17] For example, compound **11** was converted within minutes to the corresponding tri-substituted cycloolefin using complexes **9a**, **9c** and complex **1**. In the same time duration the previously developed complex **3** facilitated a conversion of 85% and the parent ruthenium complex **2** a conversion of only 20% (Entry 2). For comparison, the same reaction at room temperature was completed within 1 hour with complex **9a**, while little (< 5%) or no conversion was achieved with complexes **2** and **3**.

A more dramatic illustration of the ring-closing metathesis activity of complexes **9a** and **9c** was observed during cyclization of compound **12** at 45°C (Entry 4). This compound was readily converted to the corresponding tri-substituted cycloolefin with catalytic amounts of complexes **9a** and **9c**. But in the same time duration the molybdenum complex **1** resulted in a conversion of only 37%, and the parent ruthenium complex **2** completely failed to promote the cyclization.

Similarly, while the parent ruthenium complex **2** was not active for the formation of tetra-substituted olefins, these compounds could be prepared in moderate to excellent yields using both complexes **9a** and **9c** as well as complex **1** (Entries 6 and 7). For example, in the formation of the 6-membered tetra-substituted cycloolefin a higher

Table 1. Results of ring-closing metathesis at 45 °C utilizing 5 mol% of catalysts 1, 2 and 9a and 9c

Entry	Substrate	Product	Time	Yield of product (%) using: 1	2	9a	9c
1.			10 min	quant.	quant.	quant.	quant.
2.	 **11**		10 min	quant.	20	quant.	quant.
3.			10 min	N.P.	N.P.	quant.	quant.
4.	 **12**		60 min	37	N.P.	quant.	quant.
5.			60 min	(15)[a]	(39)[a]	(35)[b]	(45)[b]
6.			90 min	52	N.P.	90	87
7.			24 hrs	93	N.P.	31	55

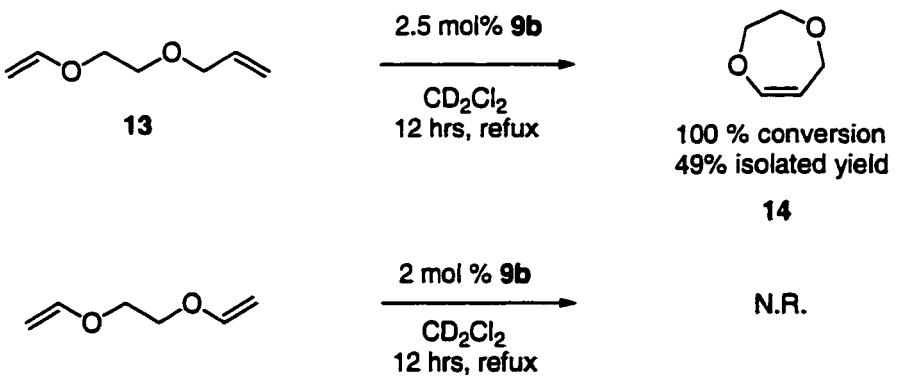
E = CO_2Et; quant. = quantitative conversion; N.P. = no product observed by ^1H NMR; yields in parentheses are isolated, all other yields are determined by ^1H NMR; [a] E:Z = 1.6:1; [b] E:Z = 2.0:1

conversion was achieved with catalysts **9a** and **9c** then with catalyst **1** (Entry 6). This trend was reversed in the formation of the tetra-substituted 5-membered cycloolefin (Entry 7).

Furthermore, the advantage of the ruthenium carbene complexes **9a** and **9c** over complexes **1** and **2** could be demonstrated in cases where the molybdenum complex **1** was inactive due to its incompatibility with functional groups,[2] while the parent ruthenium complex **2** also failed, presumably due to a formation of unreactive chelates. Specifically, the ring-closing metathesis of unprotected 1,6-heptadien-4-ol was quantitative with both **9a** and **9c** while no reaction was observed with either complex **1** or **2** (Entry 3).

Since the complexes **9a** and **9c** showed enhanced ring-closing metathesis activities and the propagating species of these complexes in RCM reactions were long-lived,[18] the use of lower catalysts loadings for RCM reactions was investigated. The ring closure of diethyl diallylmalonate in refluxing methylene chloride was conducted using 0.1, 0.05, and 0.01 mol% of catalysts **9a** and **9c** with respect to the substrate. In the first case (0.1 mol% catalyst) quantitative conversions within 1 hr were observed with both catalysts; in the second case (0.05 mol% catalyst) the conversions were quantitative with **9a** (1 hr) and nearly quantitative (94%) with **9c** (3 hrs). In the third case (0.01 mol% catalyst) the yields were nearly zero with both catalysts. These results indicated a lower limit for the catalyst loading of approximately 0.05 mol%, which is about two orders of magnitude lower than for the parent complex **2** in this reaction. This feature might be especially useful, since ruthenium-based compounds are generally expensive, highly colored and moderately toxic.[19]

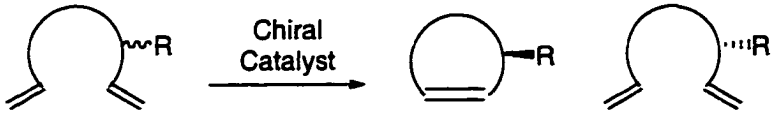
Since the catalysts **9a** and **9c** showed unique activity towards challenging substrates for presently known ruthenium-based olefin metathesis catalysts (Table 1, Entries 3-4, 6-7), we also decided to investigate the participation of α-functionalized olefins in the metathesis reaction using **9b**.[20] Specifically, the ring-closing metathesis reactions of substrates bearing vinyl functional groups were attempted (Scheme 5). The ring-closing reaction of vinyl ether **13** proceeded in good conversion to give the cyclic adduct **14**. Interestingly, substrates bearing both a vinyl ether and allylic ether were previously found to be inactive for ring-closing metathesis using **2**.[13] It is presumed that the allylic ether is initially reacting with the catalyst followed by a fast reaction with the vinyl ether minimizing the formation of a stabilized Fischer-type carbene. This proposed reaction mechanism is further evidenced by the inability of **9b** to ring close substrates where both alkenes are vinyl ethers (Scheme 6).



Scheme 6. Ring-closing metathesis of substrates containg vinyl ethers

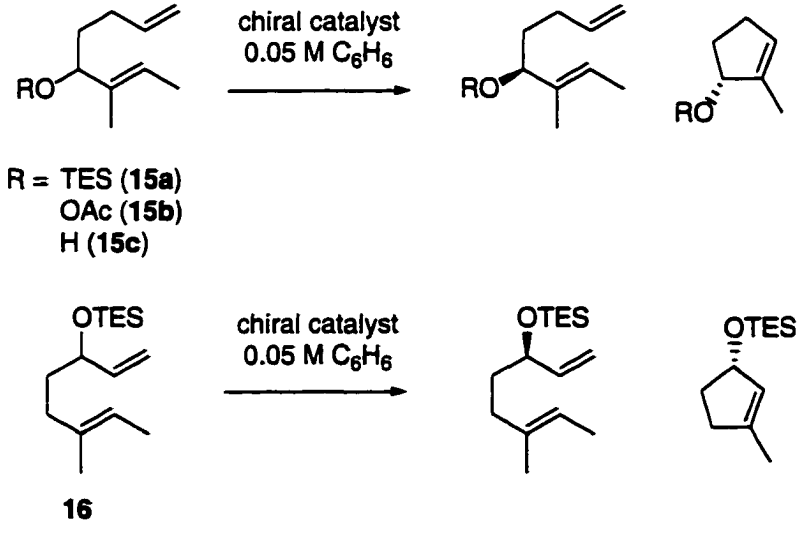
Asymmetric Ring-Closing Metathesis (ARCM)

The utility of chiral N-heterocyclic carbene complexes **9c-f** was tested briefly for the asymmetric ring-closing olefin metathesis reaction (Scheme 7).[21]



Scheme 7. Cartoon depicting asymmetric ring-closing metathesis

The acyclic diene precursors **15a-c** and **16** were exposed to catalytic amounts of chiral **9c-f**. The reactions were stopped at moderate conversions and the enantiopurities of the recovered starting materials were determined by chiral GC or by the preparation of Mosher's esters (Scheme 8, Table 2).



Scheme 8. Asymmetric kinetic resolution of alcohols **15a-c** and **16**

Table 2. Results of Kinetic Resolution of Prochiral Alcohols (Scheme 8)

Entry	Catalyst	Substrate	Catalyst loading (mol%)	Reaction time, Conversion	Enantiopurity of recovered starting material
1	**9c**	**15a**	5	23 min, 52%	18 ee%
2	**9c**	**15b**	5	40 min, 85%	40 ee%
3	**9c**	**16**	5	50 min, 50%	11 ee%
4	**9c**	**16**	5	160 min, 75%	20 ee%
5	**9d**	**15a**	6	60 min, 50%	26 ee%
6	**9e**	**15c**	0.1	40 min, 70%	31 ee%
7	**9f**	**15a**	5	30min, 75%	9 ee%
8	**9f**	**15b**	5	60 min, 50%	3 ee%

The cyclohexyl diamine based chiral catalyst **9c** was prepared initially and found to catalyze the ring-closing of precursors **15a-b** and **16** with low to moderate enantioselectivities ranging from 11 to 40ee%. In search for catalysts that would mediate the same reaction with a better control of enantioselectivity different chiral moieties were incorporated into catalyst design using a semi-combinatorial approach. For instance, the chiral cyclohexyl diamine moiety was replaced with chiral diphenyl ethylenediamine (**9d**) and with isopinocampheyl amine (**9f**). In addition, other structural changes were made which were geared at providing better chirality transfer from the far-lying chiral cyclohexyl diamine moiety to the metal center through the introduction of additional asymmetry of the N-substituents (**9e**) as well as a better interaction of the ligand sphere with the prochiral substrate through the introduction of substituents extending further into the metal sphere (**9f**). Disappointingly, these changes did not result in a better control of enantioselectivity.

Conclusions

The novel 4,5-dihydro-imidazol-2-ylidene substituted ruthenium-based complexes exhibit high olefin metathesis activity in RCM reactions and extend the potential of the ruthenium family of complexes. Di-, tri-, and tetra-substituted cycloolefins can be prepared in moderate to excellent yields through RCM. With certain substrates, similar yields may be obtained when catalyst loadings are reduced to as low as 0.05 mol%. In addition, the ring-closing metathesis of substrates containing vinyl ethers is reported using ruthenium alkylidene **9b**. Also, the application of chiral N-heterocyclic carbene-substituted systems **9c-f** to asymmetric ring-closing metathesis is discussed. Despite low to moderate enantioselectivities observed more systematic studies are warranted. Especially, the effect of solvent and temperature on enantioselectivity should be assessed. Further detailed studies regarding the mechanistic description, the scope and the steric/electronic tuning of these complexes are under investigation.

Acknowledgments

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Experimental Section

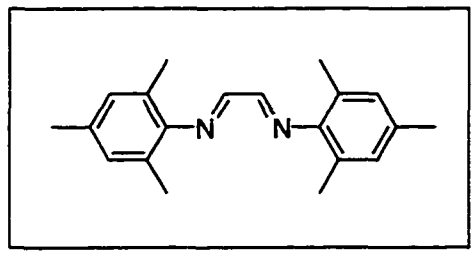
General Considerations

High resolution mass spectra were provided by the Southern California Mass Spectrometry Facility (University of California at Riverside). Analytical thin-layer chromatography (tlc) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with one or more of the following: UV light, $KMnO_4$, phosphomolybdic acid (PMA), cerric ammonium nitrate (CAN), or *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[22]

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise specified. Solvents were purified by passage through a column containing A-5 alumina (all solvents) followed by a column containing Q-5 reactant (non-ethereal solvents). Argon was purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4Å molecular sieves (Linde).

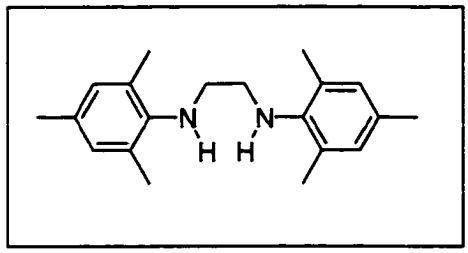
Representative Procedures and Characterization Data

Preparation of 1,2-dimesityl ethylene diimine: A 300 mL round bottom flask was charged with isopropanol (50 mL), water (100 mL) and mesityl amine (10.0 g, 74 mmol). The solution was cooled to 0°C and a solution of 40% glyoxal in water (5.38 g, 37 mmol) was added slowly. The reaction mixture was allowed to warm up to room temperature slowly and was stirred for additional 8 hours. The yellow precipitate formed was filtered off, briefly washed with cold acetone and air-dried to yield 1,2-dimesityl ethylene diimine.

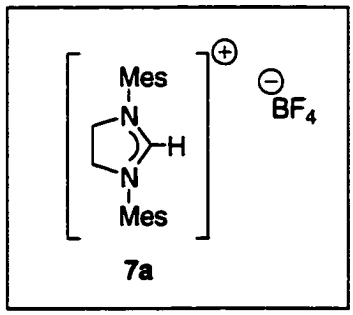


Preparation of 1,2-dimesityl ethylene diamine: (a) with $NaCNBH_3$: A 300 mL round bottom flask was charged with 1,2-dimesityl ethylene diimine (3.8 g, 13 mmol), methanol (100 mL) and $NaCNBH_3$ (4.92 g, 78 mmol). Concentrated HCl was added dropwise to maintain the pH below 4, and the reaction was stirred at room temperature for 20 hours (overnight). The solution was then diluted with 50 mL water, made basic with NaOH, and extracted thoroughly with CH_2Cl_2. The organic layer war dried over $MgSO_4$, filtered and the solvent was removed in vacuo to yield 1,2-dimesityl ethylene diamine (95% yield). **(b) with $NaBH_4$**: A 500 mL round bottom flask was charged with 1,2-dimesityl ethylene diimine (6.8 g, 23.3 mmol), THF (100 mL) and methanol (100 mL). $NaBH_4$ (6.40g, 230 mmol, 10 equiv.) was added portionwise over a period of several hours, until the initially deep yellow reaction mixture became colorless. Water (50 mL) and NaOH (1 M in H_2O, 50 mL) were added and the reaction mixture was concentrated in vacuo to 100 mL. The resultant aqueous phase was extracted with ether. The organic layer was separated dried over $MgSO_4$, filtered and concentrated in vacuo to give crude 1,2-dimesityl ethylene diamine 7g (quantitative yield). **(c) with H_2, Pd/C:** A 50 mL round bottom flask was charged with 1,2-dimesityl ethylene diimine (300 mg, 1.01 mmol) and ethanol (20 mL). 10% Pd/C (30 mg) was added and a hydrogen balloon was attached via a needle. TLC indicated complete spot-to-spot conversion within 4

hours. The Pd catalyst was filtered off and the volatiles were pumped off in vacuo to yield 1,2-dimesityl ethylene diamine.



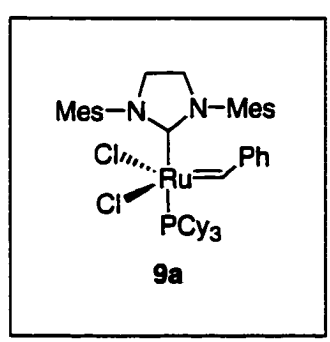
Preparation of 1,3-dimesityl-4,5-dihydro-imidazolium tetrafluoroborate 7a: A round bottom flask was charged with 1,2-dimesityl ethylene diamine (3.8 g, 12.8 mmol), triethyl orthoformate (15 mL) and ammonium tetrafluoroborate (1.35 g, 12.8 mmol). The reaction mixture was stirred at 120°C for 4 hrs at which time TLC indicated complete conversion. Volatiles were removed in vacuo and the product was used as prepared or it could be purified further by recrystallization from ethanol/hexanes.



7a

Representative procedure for the preparation of 9a-f: A 500-mL flame-dried Schlenk flask equipped with a magnetic stir bar was charged with 1,3-dimesityl-4,5-

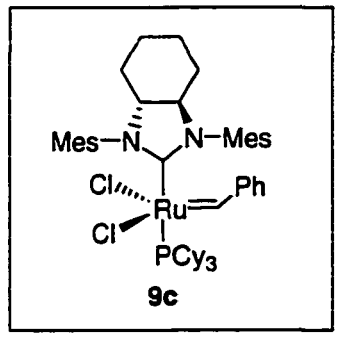
dihydro-imidazolium tetrafluoroborate **7a** (4.02 g, 10.2 mmol, 1.4 equiv.) and dry THF (100 mL) under nitrogen atmosphere. To this suspension, a solution of potassium *tert*-butoxide (1.25g, 10.2 mmol, 1.4 equiv.) in dry THF (200 mL) was slowly added at room temperature. The tetrafluoroborate salt dissolved immediately to give a cloudy yellow solution. The reaction mixture was allowed to stir at room temperature for one hour, followed by cannula transfer of the reaction mixture to another 1000-mL flame-dried Schlenk flask under argon. To this solution, dry benzene (400 mL) and $RuCl_2(=CHPh)(PCy_3)_2$ (6.00 g, 7.29 mmol, 1.0 equiv.) were added. The reaction mixture was heated at 80°C for 30 min, at which point the reaction was complete as indicated by ^1H NMR. The volatiles were removed under high vacuum and the residue was washed with anhydrous methanol (4x100 mL) to give **9a** as a pinkish-brown microcrystalline solid (4.64 g) in 75% yield: ^1H NMR (CD_2Cl_2, 400 MHz) δ 19.16 (s, 1H), 7.37-7.05 (m, 9H), 3.88 (s, 4H), 2.56-0.15 (m, 51H); ^{31}P NMR (CD_2Cl_2, 161.9 MHz) δ 31.41; HRMS (FAB) $C_{45}H_{65}Cl_2N_2PRu$ [M^+] 848.3306, found 848.3286.



9a

Compound **9c** was prepared in the same manner as above utilizing **7c**: ^1H NMR (C_6D_6, 400 MHz) δ 19.60 (s, 1H), 7.15 (m, 5H), 7.00 (s, 1H), 6.94 (s, 1H), 6.73 (s, 1H),

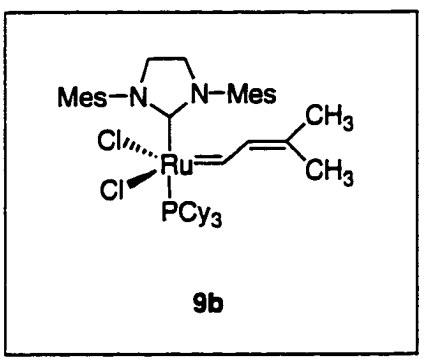
6.68 (s, 1H), 3.89-3.50 (m), 3.10-2.60 (m), 2.57-2.52 (m), 2.26 (m), 2.17 (s), 2.08 (s), 1.85 (s), 1.80-1.40 (m) 1.35-0.97 (m) (all resonances 3.89-0.97: 62H); ^{31}P NMR (C_6D_6, 161.9 MHz) δ 31.06; HRMS (FAB) $C_{50}H_{71}Cl_2N_2PRu$ [M$^+$] 902.3775, found 902.3766.



9c

Representative procedure for the preparation of 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene dichlorotricyclopentyl ruthenium dimethylvinyl carbene 9b: A 250-mL flame-dried round bottom flask equipped with a magnetic stirbar was charged with 1,3-dimesityl-4,5-dihydro-imidazolium tetrafluoroborate (3.08 g, 7.80 mmol, 1.6 equiv.) and dry THF (30 mL) under nitrogen atmosphere. A solution of potassium *tert*-butoxide (0.88 g, 7.80 mmol, 1.6 equiv.) in dry THF (30 mL) was slowly added at room temperature. The reaction mixture was allowed to stir for 1/2 hr and was then slowly transferred to a 500-mL flame-dried Schlenk flask containing a solution of $Cl_2(PCp_3)_2Ru(=CH=C(CH_3)_2)$ (3.50 g, 4.88 mmol, 1.0 equiv.) in dry toluene (200 mL). This mixture was stirred at 80°C for 15 min, at which point the reaction was complete as indicated by ^1H NMR. The reaction mixture was filtered through a glass frit under argon and all volatiles were removed under high vacuum. The residue was recrystallized thrice from anhydrous methanol (40 mL) at –78°C to give **9b** as a pinkish-brown micro-

crystalline solid (2.95 g) in 77% yield: ^{1}H NMR (C_6H_6, 400 MHz) δ 19.16 (d, J = 11 Hz, 1H), 7.72-7.69 (d, J = 11 Hz, 1H), 6.89 (s, 2H), 6.62 (s, 2H), 3.36-3.24 (m, 4H), 2.80 (s, 6H), 2.54 (s, 6H), 2.41-1.26 (br m, 27H), 2.20 (s, 3H), 2.02 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{31}P NMR (C_6H_6, 161.9 MHz) δ 26.50; HRMS (FAB) $C_{41}H_{61}Cl_2N_2PRu$ [M^+] 784.2993, found 784.2963.



9b

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(16) It is surprising that tert-butoxide leads to higher yields of compounds **9** compared to methoxide because the bulkiness of tert-butoxide should prevent its addition to the tetrafluoroborate salt and deprotonation should be preferred. This is, however, not the case as compounds **8** have been observed spectoscopically.

(17) For a study of the effects of olefin substitution on the ring-closing metathesis of dienes with complexes **1** and **2** see: Ref. 4.

(18) The decomposition half-life at 55°C in benzene of the (tricyclohexylphosphine)-(1,3-dimesityl-4,5-dihydo-imidazol-2-ylidene) methylidene ruthenium dichloride is approximately 6 hrs: Ulman, M. **1999**, unpublished results. This is significantly longer than the corresponding half-life for the decomposition of bis(tricyclohexylphosphine) methylidene ruthenium dichloride, which is only approximately 40 min: Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202-7207.

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(20) Catalyst **9d** is prepared analogously to catalysts **9a-c** except that the ruthenium source is $Cl_2(PCp_3)_2Ru{=}CHCH{=}(CH_3)_2$, which is more inexpensive and easier to prepare than $Cl_2(PCy_3)_2Ru{=}CHPh$. The activities of **9a-c** and **9d** in cross-metathesis reactions are quite similar: Chatterjee, A.; Grubbs, R. H. Personal Communication.

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Chapter 6

Olefin Metathesis Activity Study of Polymer-Supported Ruthenium Bidentate Schiff Base Catalysts

Abstract

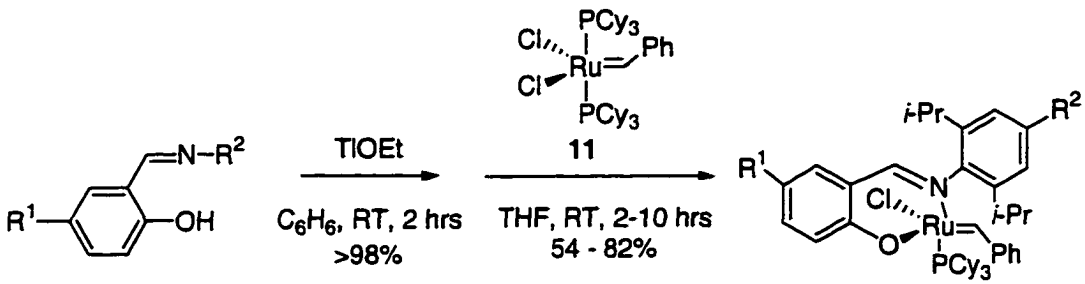
Synthesis of the Schiff base-substituted ruthenium carbene complexes was achieved on a solid support by the treatment of $RuCl_2(=CHPh)(PCy_3)_2$ with a Schiff base ligand attached to polystyrene support in the form of its thallium salt. The activities of the supported complex were compared to those of their unsupported counterparts. The newly prepared system was found to be highly stable to air, moisture, and temperature, and exhibited increased catalytic activity in acidic media.

Introduction

The development of more efficient well-defined single-component metal carbene complexes for use in olefin metathesis reactions has attracted the attention of the synthetic organometallic chemists.[1] Consequently with the advent of more efficient catalyst systems, olefin metathesis has emerged as a powerful tool for the formation of C-C bonds in chemistry.[2] However, the development of efficient, user-friendly olefin metathesis complexes for enantioselective and stereoselective applications remains to be accomplished.[3] To facilitate the progress in this area, catalysts which exhibit improved thermal stability as well as tolerance toward polar protic solvents need to be developed.

Recently, we disclosed the synthesis and characterization of new ruthenium-based catalysts **1a-i** coordinated with bidentate Schiff base ligands (Scheme 1).[4] These complexes showed high metathesis activity in polar protic solvents and in commonly used organic solvents such as dichloromethane or benzene. Because the complexes were found to initiate only to a small extent and were mostly found unchanged at the end of reactions, we decided to direct our efforts on recyclability and reusability of these

complexes. We now wish to report the synthesis and activity of solid supported versions of the homogeneous Schiff base substituted systems.



1a-i

a) R^1=H, R^2=H; b) R^1=NO_2, R^2=NO_2; c) R^1=NO_2, R^2=H; d) R^1=H, R^2=NO_2; e) R^1=NO_2, R^2=OMe; f) R^1=OMe, R^2=NO_2; g) R^1=OMe, R^2=NO_2; h) R^1=H, R^2=OMe; i) R^1=OMe, R^2=OMe

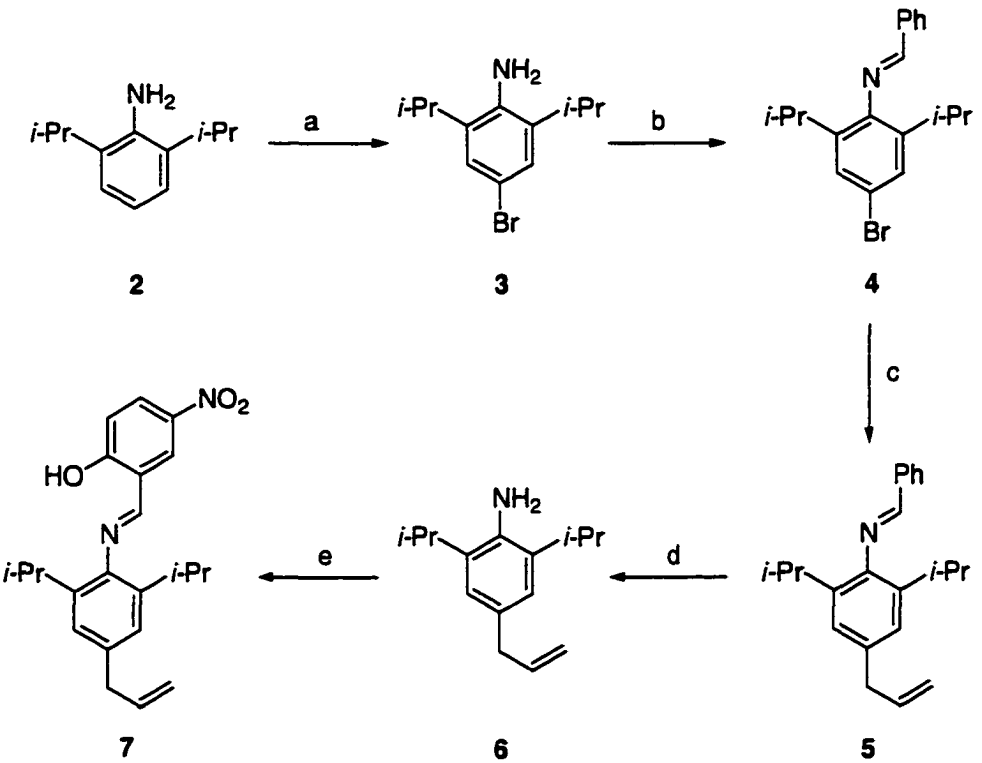
Scheme 1. Formation of salicylaldimine Ruthenium complexes **1a-i**

Results and Discussion

Synthesis of Heterogeneous Ruthenium Schiff Base Complexes

For the purpose of attachment of the Schiff base ligand to a solid support, an allyl moiety was introduced to the amine portion of the ligand (Scheme 2). The commercially available 2,6-diisopropyl aniline **2** was brominated with NBS to yield the 4-bromo-2,6-diisopropylaniline **3** in quantitative yield.[5] 4-Bromo-2,6-diisopropyl aniline **3** was then protected with benzaldehyde as the *N*-benzylideneamine[6] **4** and the desired allyl moiety was introduced via standard Stille cross-coupling with allyl tributyl tin.[7] Quantitative deprotection of the resultant allyl-substituted benzylideneamine derivative **5** was accomplished with Girard's T reagent to yield 4-allyl-2,6-diisopropylaniline **6**.[8] Finally,

the 4-allyl-2,6-diisopropylaniline **6** was condensed with 4-nitro-salicylaldehyde to yield the desired ligand **7**.

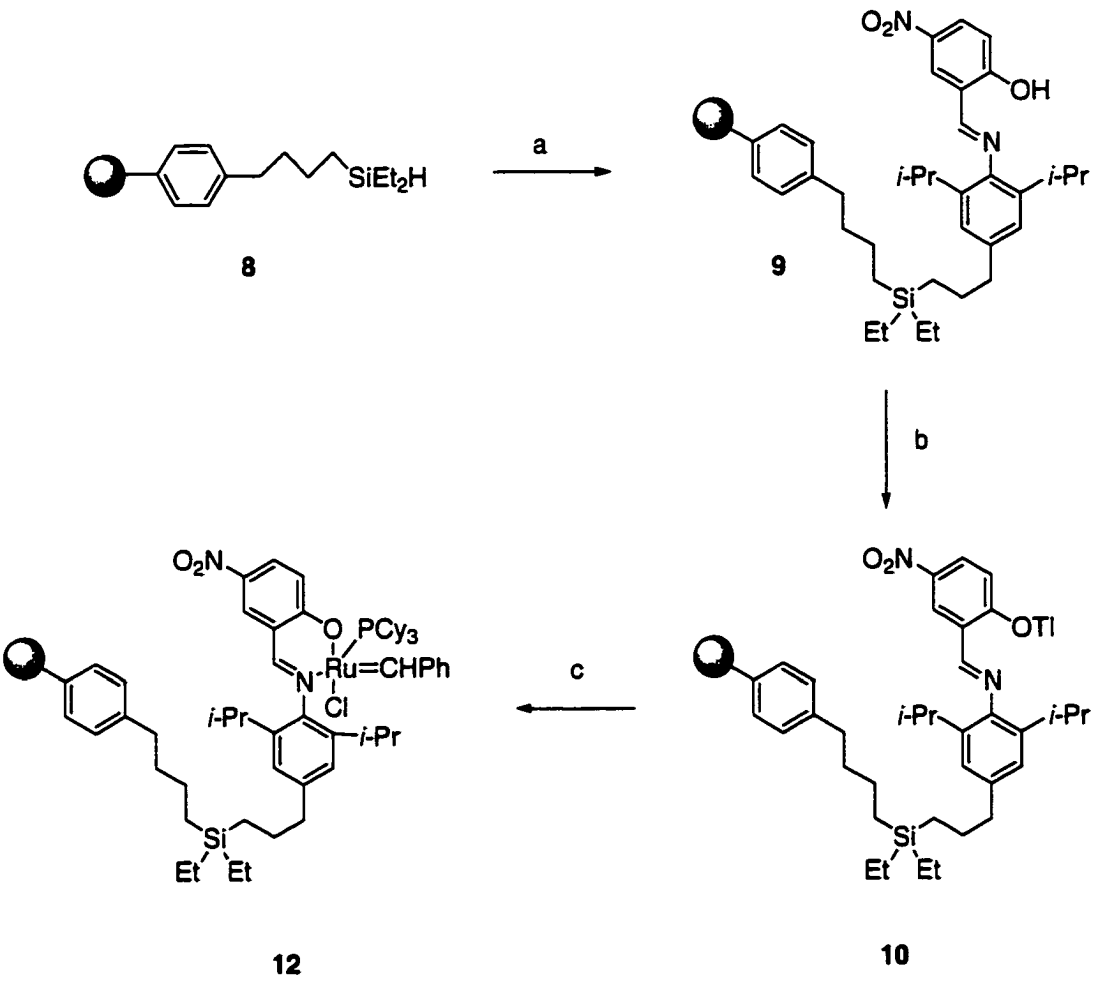


a: NBS, DMF, RT, 84%; b: PhCHO, cat. *p*-TsOH, 4Å mol. sieves, Ph-H, reflux, 78%; c: AllylBu $_3$Sn, cat. Pd(PPh $_3$) $_4$, Ph-H, 100°C, 100%; d: Girard's T Reagent, CH $_3$OI 92%; e: 5-NO_2-2-OH-PhCHO, cat. p-TsOH, 4Å mol. sieves, Ph-H, reflux, 65%.

Scheme 2. Preparation of ligand **7** bearing an allylic linker

The attachment of ligand **7** to solid support was envisioned via platinum catalyzed hydrosilylation reaction (Scheme 3).[9] Consequently, the commercially available polystyrene-diethylsilane linker (PS-DES) **8** was chosen as the solid support. The progress of the hydrosilylation reaction was monitored by the disappearance of the Si-H IR stretching resonance at ~2095 cm^{-1}. The extent of attachment of the ligand to the solid

support was also ascertained through elemental analysis and corresponded well with the initial amount of silane on the polymer support (0.5 mmol/g).



8 9 10 12

a: **7**, cat. Pt-DTD, THF, reflux; b: TlOEt, THF, RT; c: **11**, THF, RT.

Scheme 3. Attachment of the ligand to solid support and to the ruthenium metal

The subsequent steps for substituting the polystyrene supported Schiff base ligands on the ruthenium metal were identical to those of the unsupported ligands.[4,10]

Consequently, the intermediate **9** was treated with thallium ethoxide in THF at room temperature resulting in the thallium salt **10**. The intermediate **10** was then reacted with the catalyst precursor **11** to give the desired heterocyclic ruthenium complex **12**. The extent of ruthenium incorporation onto the solid support was again ascertained through elemental analysis and corresponded well with the initial amount of silane on the polymer support (0.5 mmol/g).

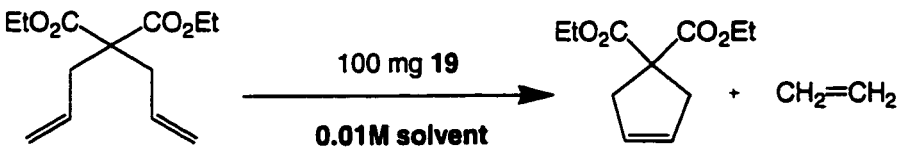
Metathesis Activity Studies of Heterogeneous Ruthenium Schiff Base Complexes

Based on NMR studies of ring-closing metathesis reactions of diethyldiallyl malonate esters with salen Ruthenium complexes **1a-i**, we have determined that only a small portion of the salen benzylidene complexes initiated in ring-closing metathesis reactions (i.e., was converted to alkylidene propagating species) and that majority of the catalyst remained uninitiated throughout the reaction. We decided to exploit this feature by designing salen Ruthenium complexes attached to a solid support. In doing so we would not only gain the advantage of a catalyst system that was easily separable from the reaction products,[11] but also give us the opportunity to exploit the uninitiated portion of the salen complexes through recycling. In addition, the difficulty of purification of some of the Schiff base complexes such as **1h** due to their high solubility in hydrocarbon solvents during crystallization would be alleviated since the purification of supported complexes would only require washing of the polymer bound complexes.

To test the supported salen systems, we exposed diethyl diallyl malonate to complex **12** in a variety of solvents for 24 hrs at room temperature (Table 1). The conversions achieved were low ranging from 0-31%. However, the significant rate

increase found for the homogeneous catalysts in acidic media[10] was again confirmed for the heterogeneous complex **12**. When the reactions were performed in chloroform containing traces of acid, the conversions increased to 83% under the same conditions. This rate increase is again most likely associated with the increased acidity of the media.[4,12] However, compared to the homogeneous catalyst, the supported systems are somewhat less active. For example, while with 8 mol% unsupported catalyst after 45 min at room temperature the reaction is completed, utilizing 5 mol% of the supported catalyst required 24 hrs to reach 83% conversion.

Table 1. Dependence of Solvent on Catalyst Activity

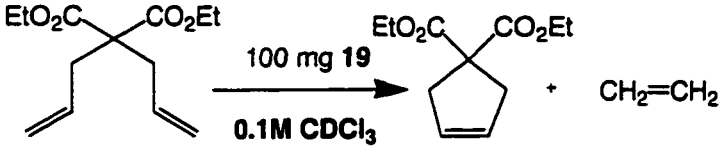


Solvent	% Conversion at RT[i]
THF-d_8	31
C_6D_6	28
CD_2Cl_2	16
Toluene-d8	14
MeOH	0
$CDCl_3$	83

[i] Percent conversion at 24 hrs unless otherwise noted.

To determine the longevity of the supported catalyst, diethyl diallyl malonate was exposed to complex **12** in chloroform at 65°C (Table 2). After the reaction was run for 24 hrs, the conversion was determined by ^{1}H NMR, the catalyst was recovered, washed with chloroform, and exposed to a new batch of diethyl diallylmalonate. This sequence was repeated until the catalyst lost its activity after 3 recovery cycles. This result demonstrates that although the acidic media increases the activity of catalyst **12**, it also leads to a faster decomposition of the catalyst.

Table 2. Supported Catalyst Activity/Longevity



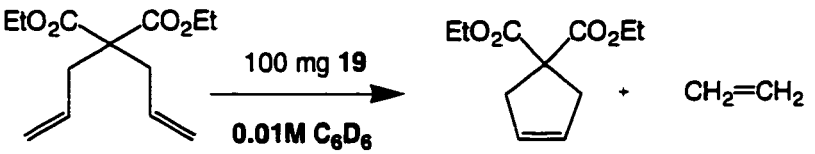
Times Recycled	% Conversion at 65°C [i]
0 (fresh)	83
1	72
2	27
3	0

[i] Percent conversion at 24 hrs unless otherwise noted.

To confirm the above results and also to provide further evidence for the acceleration of reaction rates in acidic media for the solid supported system, diethyl diallyl malonate was exposed to **12** in benzene containing a catalytic amount of DCl

(Table 3). While the ring closure of diethyl diallylmalonate at RT in C_6D_6 was completed in only 33% in 4 hrs, when catalytic amounts of DCl were added to the reaction mixture the conversion was increased to 90% under the same conditions and in the same time period.

Table 3. Acid Effect on the Catalyst Activity



Times Recycled	% Conversion at RT [i]
0 (fresh)	90
1	90
2	52
3	0

[i] Percent conversion at 4 hrs unless otherwise noted.

To test the longevity of the supported catalyst under the DCl conditions, after a 90% conversion was achieved (4 hrs), the catalyst was recovered, washed thoroughly with benzene and again exposed to diethyl diallylmalonate and a catalytic amount of DCl. The results were comparable to the ones obtained when $CDCl_3$ was used as a solvent without any additional acid added (unpurified): during the first two recycle runs 90%

conversions were achieved and during the third recycle run the catalyst lost its activity resulting in only 50% conversion after 4 hrs.

Conclusions

The object of this study was to disclose an efficient method of affixing ruthenium Schiff base-substituted catalysts to solid supports. The solid supported complexes were prepared efficiently, proved to be metathesis active and were easily recovered from reaction mixtures. However, the longevity of these systems leaves a lot of room for improvement. Current studies are directed at the exploration of other solid supports as well as other modes of attachment of the complexes to solid supports that may be able to slow down catalyst decomposition and extend the longevity of the supported complexes. In addition, the development of methods for support of other olefin metathesis catalysts such as the N-heterocyclic carbene-substituted olefin metathesis catalysts discussed in Chapters 4 and 5 is in progress.

Acknowledgments

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Experimental Section

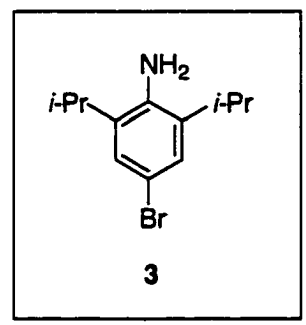
General Considerations

Unless otherwise noted, all operations were carried out using standard Schlenk techniques or dry-box procedures. Argon was purified by passage through a columns of BASF R3-11 catalyst (Chemalog) and 4 Å molecular sieves (Linde). Solid organometallic compounds were transferred and stored in a nitrogen-filled Vacuum Atmospheres dry-box. ^{1}H-NMR (300.1 MHz) and ^{13}C-NMR (75.49 MHz) spectra were recorded on a General Electric QE-300 spectrometer. ^{31}P-NMR (161.9 MHz) spectra were recorded on a JEOL GX-400 spectrometer. NMR chemical shifts are reported downfield from tetramethylsilane (TMS) (δ scale) with TMS employed as the internal solvent for proton spectra and phosphoric acid employed as the internal solvent for phosphorous spectra.

High resolution mass spectra were provided by the Southern California Mass Spectrometry Facility (University of California, Riverside. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All solvents were rigorously degassed in 18 L reservoirs and passed through two sequential purification columns.[13] Complex **11**[14] was prepared according to published procedures. Unless otherwise noted, all other compounds were purchased from Aldrich Chemical Company and used as received.

Specific Synthetic Procedures and Characterization Data

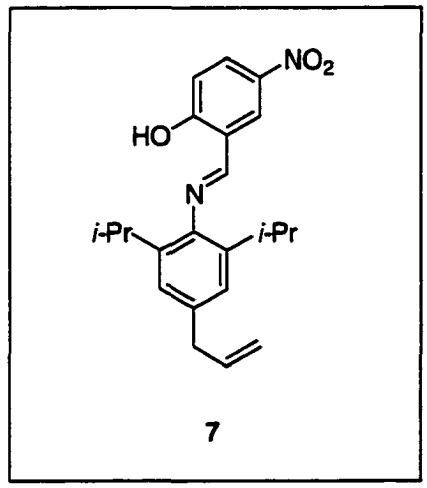
2,6-Diisopropyl-4-bromoaniline (3). To a solution of *N*-bromosuccinamide (0.36 g, 2 mmol) in dry DMF (20 mL) was added 2,6-diisopropylaniline (**1**) (0.38 mL, 2 mmol). The solution was stirred at room temperature overnight and poured into water. The organic layer was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* to afford 0.51 g (100%) of the title compound as a brown oil. R_f = 0.37 (9:1; hexane:ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ 7.11 (s, 2 H), 3.78 (br s, 2 H), 2.88 (septet, *J* = 6.9 Hz, 2 H), 1.24 (d, *J* = 7.0 Hz, 12 H).



3

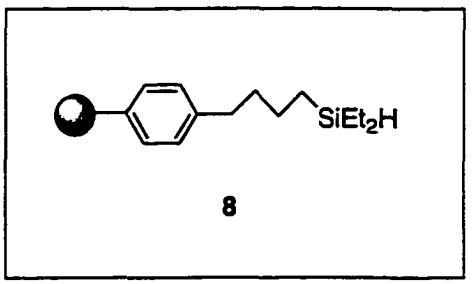
Specific Procedure for the Synthesis of 2-[(4-Allyl-2,6-diisopropyl-phenylimino)-methyl]-4-nitro-phenol (7). A solution of 2-hydroxy-5-nitrobenzaldehyde (0.67 g, 4.0 mmol), 4-allyl-2,6-diisopropylaniline **6** (0.87 g, 4.0 mmol) and *p*-toluenesulfonic acid (76 mg, 0.4 mol) in benzene (40 mL) containing 4 Å molecular sieves was stirred under reflux overnight. Upon cooling the reaction mixture to RT and addition of hexane, a yellow solid precipitated from the reaction mixture. The solid was filtered, washed with cold hexanes and dried to afford the title salicylaldimine ligand **7** (0.95 g, 65%) as a yellow solid: m.p. 120-121°C; ^{1}H-NMR ($CDCl_3$) δ 14.47 (s, 1 H), 8.38

(s, 1 H), 8.35 (d, J = 2.6 Hz, 1 H), 8.30 (dd, J = 9.2 Hz, 2.6 Hz, 1 H), 7.13 (d, J = 9.2 Hz, 1 H), 7.04 (s, 2 H), 6.05-5.95 (m, 1 H), 5.16-5.09 (m, 2 H), 3.41 (d, J = 6.6 Hz, 2 H), 2.92 (septet, J = 6.9 Hz, 2 H), 1.19 (d, J = 6.9 Hz, 12 H); ^{13}C-NMR ($CDCl_3$) δ 167.3, 165.5, 142.7, 140.0, 138.9, 138.1, 137.4, 128.6, 128.4, 123.8, 118.6, 117.6, 16.0, 40.3, 28.4, 23.6; IR (KBr, cm^{-1}) 3435, 2963, 1625, 1385, 1345, 1299, 1100, 916, 833; HRMS (EI) calcd for $C_{22}H_{26}N_2O_3$ (M^+) 366.1943, found 366.1941.



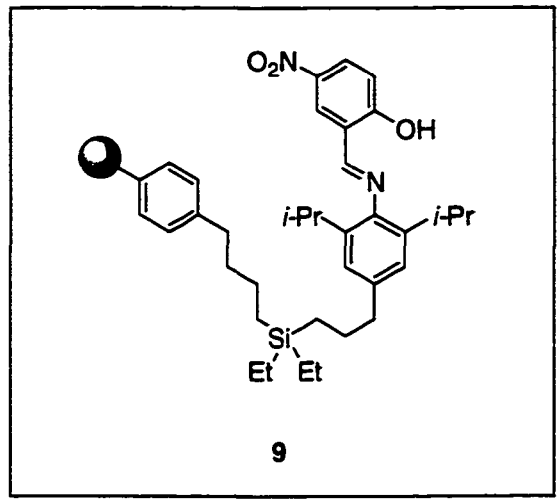
7

Polystyrene-Diethylsilane (PS-DES) Linker 8. This compound was obtained from Argonaut Technologies (San Carlos, CA): bead size = 100-200 mesh; loading = 0.69 mmol/g. IR and elemental analysis data was obtained for comparative purposes: IR (KBr, cm^{-1}) 3025, 2922, 2092, 1601, 1494, 1453, 754, 692; Anal. Found: C, 88.86%; H, 8.87%; Si, 2.1%.



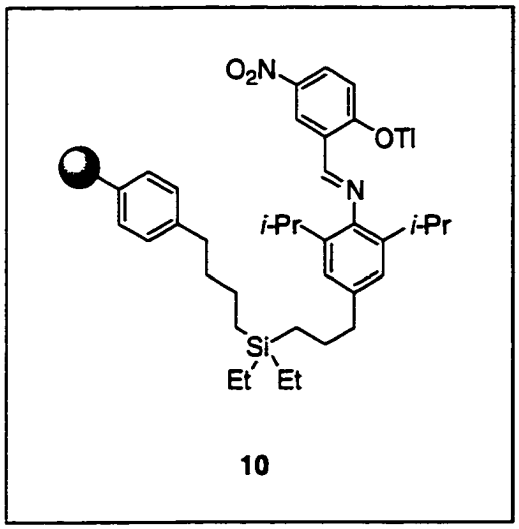
8

Specific Procedure for the Attachment of 2-[(4-Allyl-2,6-diisopropyl-phenylimino)-methyl]-4-nitro-phenol 7 to the polystyrene-diethylsilane (PS-DES) linker 8. To a 50 mL round bottom flask containing a stir bar and 15mL of dry THF was added 2-[(4-Allyl-2,6-diisopropyl-phenylimino)-methyl]-4-nitro-phenol **7** (0.41 g, 1.33 mmol) and platinum-divinyltetramethyl-disiloxane complex in xylene (2.1% Pt, 19.4mg, 1.33 μm). The reaction mixture was stirred under reflux for 0.5 hrs at which time polystyrene-diethylsilane (PS-DES) linker **8** was added. The initially yellow solution turned orange and the reaction mixture was allowed to stir under reflux for additional 24 hrs. The reaction mixture was then filtered through a 20-40μ filter frit funnel. The collected polymer beads were washed with copious amounts of THF and dried on high vacuum to give intermediate **9** (1.48 g, quant. yield) as yellow polymer beads: IR (KBr, cm^{-1}) 3449, 2989, 2886, 1773, 1633, 1379, 1104, 1016, 912, 746, 692; Anal. Found: C, 86.85%; H, 8.34%; Si, 2.53%.



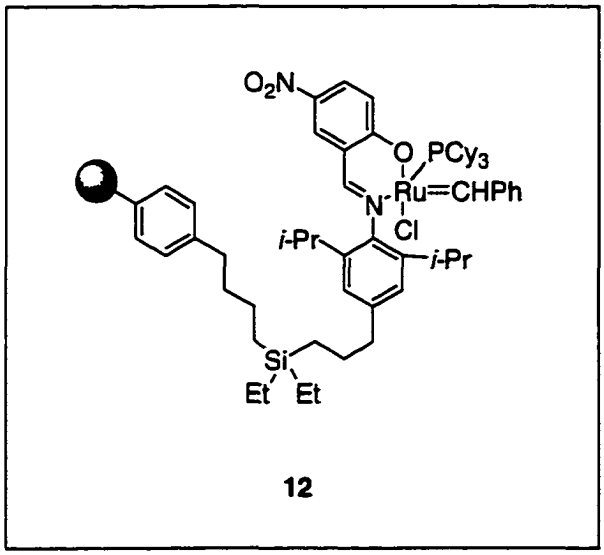
9

Specific Procedure for the Formation of the Thallium Salt of the Polymer Supported Schiff Base Ligand (10): To a 20 mL round bottom flask containing a stir bar and dry THF (7 mL) was added **9** (1.48 g) and TlOEt (110 mg, 0.44 mmol, highly toxic!). The initially yellow polymer beads immediately turned dark brown. The reaction mixture was allowed to stir at room temperature for 24 hrs at which time it was filtered through a 20-40 micron frit. The collected polymer beads were washed with copious amounts of THF and dried on high vacuum to give intermediate **10** (1.6 g, quant. yield) as dark brown polymer beads: IR (KBr, cm^{-1}) 3025, 2922, 1600, 1492, 1451, 1384, 1028, 751, 697; Anal. Found: C, 70.98%; H, 6.95%; O, 0.59%; Si, 4.45%; Tl, 10.39%.



10

Specific Procedure for the Formation of Polymer Supported Olefin Metathesis Catalyst (12): To a 20 mL round bottom flask containing a stir bar were added dry THF (5 mL), **10** (0.56 g) and the ruthenium precursor **11** (0.50 g, 0.6 mmol). The reaction mixture was allowed to stir at room temperature for 24 hrs at which time it was filtered through a 20-40 micron frit. The collected polymer beads were washed with copious amounts of THF and dried on high vacuum to give the desired product **12** (0.5 g, calculate yield) as dark brown polymer beads: IR (KBr, cm^{-1}) 3025, 2923, 1601, 1492, 1451, 1384, 1004, 904, 838, 753, 697; Anal. Found: C, 70.95%; H, 6.93%; Ru, 1.58%; Cl, 2.26%; P, 0.42%; Si, 5.77%.



12

General Procedure for the Ring-Closing Metathesis of Diethyl Diallylmalonate using the supported catalyst 12: All reactions were performed on the benchtop under an inert atmosphere of Argon. To a 50 mL round bottom flask containing the appropriate solvent (amount and identity given in Tables 1-3) were added catalyst **12** (100 mg, ~0.5 mmol) and diethyl diallylmalonate (240 mg, 1 mmol). In the experiments described in Table 3, also a solution of DCl in CD_3OD (0.32M, 10μL) was added. The studies were run at both ambient and higher temperatures (65°C) to access the activity and stability of the catalysts during the course of the reactions. The reaction mixtures were stirred for the indicated amounts of time (Tables 1-3). Product formation and diene disappearance were monitored by integrating the allylic methylene peaks.

Notes and References

(1) For representative examples, see: (a) Grubbs, R. H. and Pine, S. H. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: New York, 1991, Vol. 5, Chapter 9.3. (b) Ivin, K. J. and Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, 1997.

(2) For representative examples, see: (a) Novak, B. M.; Risse, W.; Grubbs, R. H. *Adv. Polymer. Sci.* **1992**, *102*, 47. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-552. (c) Hashimi, A. S. K. *J. Prakt. Chem.* **1997**, *339*, 195-199. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54(18)*, 4413-50.

(3) Although enantioselective molybdenum-based olefin metathesis catalysts have been developed, they are generally very air and water sensitive and require extensive substrate and solvent purifications. For examples of such systems, see: (a) Fujimura, O.; delaMata, F. J.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1865-1871. (b) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499-2500. (c) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824-832. (d) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251-8259.

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(5) For example see: a) Giumanini, A. G.; Verardo, G.; Polana, M. *J. Prakt. Chem.* **1988**, *330*, 161-174. (b) Mitchell, R.H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, *44(25)*, 4733-35.

(6) Bey, P.; Vevert, J.P. *Tetrahedron Lett.* **1977**, *17*, 1455-1458.

(7) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Toshihiko, M. *Chem Lett.* **1977**, 301-302.

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(11) For additional method of separation of ruthenium byproducts from reaction mixtures see: Maynard, H. D.; Grubbs R. H. *Tetrahedron Lett.* **1999**, *40*, 4137-4140.

(12) (a) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627-1628. (b) Diaz, E. L. Ph. D. Thesis, California Institute of Technology, 1998. (c) Sanford, M. S.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 5384-5389.

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