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Development of O,N-bidentate Ruthenium Catalysts for Isomerization and Kinetic Studies of Ruthenium Carbenes for C=C Coupling Reactions

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Proefschrift ingediend tot het behalen van de graad van
Doctor in de Wetenschappen: Scheikunde

Zi Han: There four things from which the Master(Confucius)
were entirely free. He had no foregone conclusions,
no arbitrary predeterminations, no obstinacy,
and no egoism.

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This research was funded by the University of Ghent

Acknowledgments

When I started to write the last part of my dissertation---the acknowledgments, all the memories about my life as PhD student in Gent came back to my mind as a slide show. As my dissertation is the final product of an educative and fascinating journey, it could not be done without help of financers, colleagues, friends and family.

First of all, I'd like to express my eternal gratitude to my promoter Prof. Dr. Francis Verpoort who gave me the opportunity to join his group, for his guidance and knowledge of the subject, his understanding and willingness to help me through the stressful time, also for these years' of support during this project.

I would like to thank Ghent University especially BOF (Bijzonder Onderzoeks Fonds) for financing this research project and the Vakgroep Anorganische en Fysische Chemie for hosting it. Furthermore, I would like to thank all the members of the jury for making the necessary time to judge this document and their valuable feedback.

I am indebted to Dr. Renata Drozdzak for the introduction of Schlenk equipment, the helpful and supportive advice, and the friendly words.

I feel extremely lucky to work with so many nice colleagues. They help me to overcome so many small and big difficulties on working and living. These special thanks I address to, Jeroen, Nele, Siegfried, Bart, Hans, Stijn, Carl for the assistance in the lab, the insightful discussions and the pleasant working atmosphere. Of course, my acknowledgments also go to the other colleagues: Ana, David, Steven, Agatha for their never-ending kindness.

Moreover, I would like to show gratitude to the ATP-personnel, thanks Danny for your patient and regarding GC, thanks Claudine and Pierre for your kind help to arrange all kinds of administration, thanks Pat for your friendly help to solve computer problems, and Ilse, Philp, Els, Cindy for your warm-hearted help and kindness.

Furthermore, I can not forget other researchers: Thuy, Ilke, Matthias, Els, Sofie, Veerle, Klaartje, Zeki, Frederik for good times during these years.

Within the Building of S3, many more members deserve to be mentioned here.

Moreover, I would like to thank my friends from OBSG, the warm-hearted arrangement and friendly help from the management staff conveniences my life a lot; I've enjoyed the friendship from Peng Shengjing, Teng Jie, Han Guohua and Liu Ting, they accompanied me during difficult times and give mental support. I will remember them with pleasure. I am also indebted to all friends that I know in Belgium for their caring and improving of my life during the past years.

The last but not the least, my mom, my parents-in-law, my husband and my son are gratefully acknowledged for their unconditional love and support.

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Preface

The fountainhead to develop the chemical science is the demand of various compounds by human being. While most of the requirement concerns organic molecules e.g. the formation and transformation of carbon-carbon bonds, they are of crucial importance in chemistry.

The major aim to use catalyst in a chemical reaction is:

- Lowering the activation energy by providing an alternative reaction pathway
- increasing the reaction rate
- accelerating the desired reaction, while retarding unwanted side reactions

Homogeneous catalysis is the success story of organometallic chemistry and catalytic applications have paved the way of organometallic compounds in producing the bulk, fine chemicals, and even natural products. During the last decade, ruthenium catalysts have provided new indispensable synthetic methods that cannot be promoted by other catalysts, and they now constitute an emerging field for the selective preparation of chemicals. Ruthenium catalyst are applied in wide range of chemical reaction such as metathesis, atom transfer radical polymerization, Kharasch addition, transfer hydrogenation, hydroamination, enol ester synthesis, cyclopropanation and isomerization.

Herein, the basic issue of this dissertation is to develop O,N-bidentate ruthenium homogeneous catalysts for isomerization and execute kinetic studies of ruthenium carbenes for C=C coupling reactions.

Specifically designed ligands is the key in optimizing the efficiency of catalyts, Schiff bases are known to strongly enhance the thermal and moisture stability of the corresponding complexes and isomerization reaction is an important chemical process. The above reasons promote the first part of my work to concentrate on the synthesis of a novel class of homogeneous ru-complexes containing Schiff bases as O,N-bidentate ligands to catalyze the isomerization reaction. By a proper choice of the Schiff base, the new ru-complexes showed improved reactivity, selectivity and stability toward air and moisture in the isomerization reaction. The temperature and solvent tolerance was likewise substantially improved.

The formation of carbon-carbon bonds is one of the most fundamental chemical processes. In this context, C=C coupling reactions (metathesis, cyclopropanation and etc.) makes a significant contribution. Despite the recent advances, the search for commercially relevant catalyst systems remains challenging. The kinetic studies of ruthenium carbenes should be a useful fundamental research to design new catalysts or to improve existing catalytic systems. The second part of my work established a pre-research for the future outlook.

Outline

Chapter 1 describes to a general introduction on the olefin isomerization reactions, mechanism, catalysts, and applications.

Chapter 2 consists of a second introductory part. Since the catalysts developed in the first part of this project all contain a Schiff base ligand or a Schiff base analog, some general properties of these ligands in organometallic complexes were described. The bidentate Schiff base ligand exerts, due to its ”dangling” character, a pronounced effect on both the activity and stability of the resulting complex.

Chapter 3 provide the synthesis and catalytic performance of a ruthenium hydride complexes catalyst bearing a Schiff base ligand $[Ru(PPh_3)_2(CO)H(L^n)]$ (n=1-8). Furthermore, the beneficial properties of Schiff base ligands in ruthenium based olefin isomerization catalysts were explained by thoughtful consideration of the reaction mechanism. Meanwhile, the scouting for the isomerization activity of ruthenium indenylidene Schiff base complexes also is initiated for the first time.

Chapter 4 encloses a contribute to the synthesis of a ruthenium complexes [(η^6-*p*-Cymene)RuCl(L)] (L incorporate an arylazo group [azonaphthol groups (**1-4**) and azophenyl group (**5-7**)]). The air and moisture stable, easy to synthesize, ruthenium dimer [(p-cymene)$RuCl_2]_2$ as a catalyst precursor. The catalytic performance investigation of these compounds for isomerization is the first time reported.

Chapter 5 gives a general introduction on olefin metathesis reactions, mechanism, catalysts, and applications. In particular, the transition metal-catalyzed olefin ring-opening metathesis polymerization that was studied in this dissertation is highlighted.

Chapter 6 deal with the kinetics of ring-opening metathesis polymerization (ROMP) of *exo,exo*-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, promoted by the Grubbs’ 1st

generation precatalyst. Since the Grubbs' 1st generation catalyst is commonly used as catalyst not only for metathesis, but also for some catalytic tandem reactions. Nowadays, many of the development of new catalysts are based on tuning of the ligand environment. The kinetic study could clarify the pathway of the catalytic process and achieve the aim easily.

It was described in chapter 5 that the metathesis reaction has been effectively monitored by FT-Raman and NMR spectroscopy. Both techniques evidenced similar monomer conversions to be attained under the same reaction conditions. The present FT-Raman study provided information on the polymer steric configuration, the Raman bands at 1670 cm-1 and 1677 cm-1 being specifically assigned to stretching vibrations of double bonds from the *cis*- and *trans*- polymer, respectively. The *trans/cis* ratio observed by FT-Raman parallels the corresponding result from 1H-NMR. For the first time, a comparison was made on application of these complementary methods on the same ROMP reaction, evidencing their assets and disadvantages and reliability of FT Raman.

Chapter 7 provides a general introduction on olefin cyclopropanation reactions, mechanism and catalysts. The applications of cyclopropanation reaction are described, along with several methods of synthesis. Especially, the transition metal-catalyzed method that was studied in this work is specified.

Chapter 8 addresses the evaluation of Grubbs 1st generation catalyst in relation to the cyclopropanation of olefins using ethyl diazoacetate. From a fundamental study of the reaction by means of FT-IR, GC and NMR, some elementary kinetic parameters are calculated and based on these findings, a mechanism is proposed. It is found that the catalyst shows good activity for the cyclopropanation of styrene. An effort is made to suppress the most common side reactions by modifying the ligand sphere and the nature of the carbene.

Chapter 9 briefly summarizes the conclusions made in the thesis, and a short future outlook is given.

List of Abbreviations

General

^{13}C NMR Carbon-13 nuclear magnetic resonance

GC Gas Chromatogram

^{1}H NMR Proton Nuclear Magnetic Resonance

IR Infrared Spectroscopy

L Ligand

M Metal, e.g. in complexes: [M]

PMP Primary metathesis products

RCM Ring-closing metathesis

ROM Ring Open Metathesis

ROMP Ring Open Metathesis Polymerization

RT Rome Temprature

SMP Secondary metathesis products

Chemical and ligands

Ar Aryl

Bz Benzyl

Cp Cyclopentadienyl

Cy Cyclohexyl

H2IMes 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene

IMes 1,3-dimesityl-4,5-imidazol-2-ylidene

Mes Mesityl = 2,4,6-trimethylphenyl

NHC N-Heterocyclic carbene

Ph Phenyl

PCy_3 Tricyclohexylphenyl

PPh_3 Triphenylphosphine

TEA Triethylamine

THF Tetrahydrofuran

Chapter 1
Olefin Isomerization

1.1 Introduction

Since the discovery of homogeneous catalysis in 1938, it is among the most important areas of contemporary chemistry and chemical technology. The new applications of transition metals as central atoms of ligand-modified complexes open novel routes to new compounds, together with new possibilities for reaction control.[1] The catalytic applications catalyzed by organometallic compounds have been developed in many fields, such as hydrogenation, metathesis, hydroformylation, oligomerization, etc. in both bulk and fine chemicals. Isomerization occurs in many cases as a side reaction in the above reactions,[2] while it is also one of the important transformations used in a number of transition-metal-catalyzed reactions,[3] such as hydrozirconation,[4] [5-9] hydroformylation, [10-14] hydrosilylation, [15-21] and hydrocyanation. [22-26]. Furthermore, it is an essential intermediate step during industrial processes, e.g. in the SHOP and Dow's 1-Octene process.

Generally, isomerization is the process by which one molecule is transformed into another molecule having exactly the same atoms, however the atoms are rearranged (these related molecules are known as isomers). The energy difference between two isomers is called isomerization energy. The equal or roughly equal bond energy provides preconditions for interconversion of relatively freely olefins and the reaction involves either movement of the position of the double bond or skeletal alteration. A reorientation of the group around the double bond to bring about *trans-cis* isomerization [5] and the aldose-ketose isomerism in biochemistry should also be included. Even the isomerization between conformational isomers and fluxional

molecules displaying a rapid interconversion of isomers are also mentioned as isomerization reactions.

The following observations generally apply to alkene isomerization reaction:[1, 3]

1. *Trans* alkenes are more stable than *cis* alkenes.
2. Internal alkenes are more stable than terminal alkenes.
3. Conjugated di- and oligoalkenes are favored over isolated double bonds.
4. Substituted (internal) alkenes with the highest degree of branching are thermodynamically favored.
5. Polar solvents accelerate the isomerization reaction.

Many transition metal complexes, such as Cr, Fe, Ni, Ru, Rh, Pd, Ir, and Pt, have been reported as the isomerization catalysts and the extent of isomerization depends on the property of the complexes i.e. the metal, the ligands surrounding the metal and the structure of the complex. This property is little altered by the support in case of heterogeneous catalysts. [6] A decreasing order of metals for double bond isomerization is: Pd>Ni>>Rh>>Ru~Os>Ir>Pt. Furthermore, there seems to be a general agreement that heterogeneous catalysts are favored by a low hydrogen concentration on the catalyst surface ("hydrogen poor catalysts") [7]

The following figure depicts the statistic data of the number of articles about olefin isomerization and the data specially catalyzed by all kinds of transition metals (source: web of science).

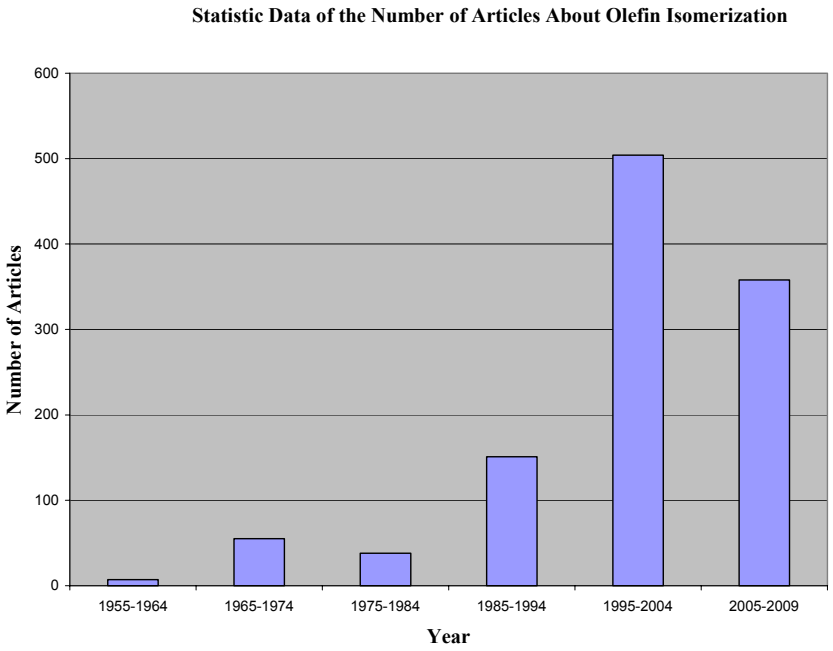
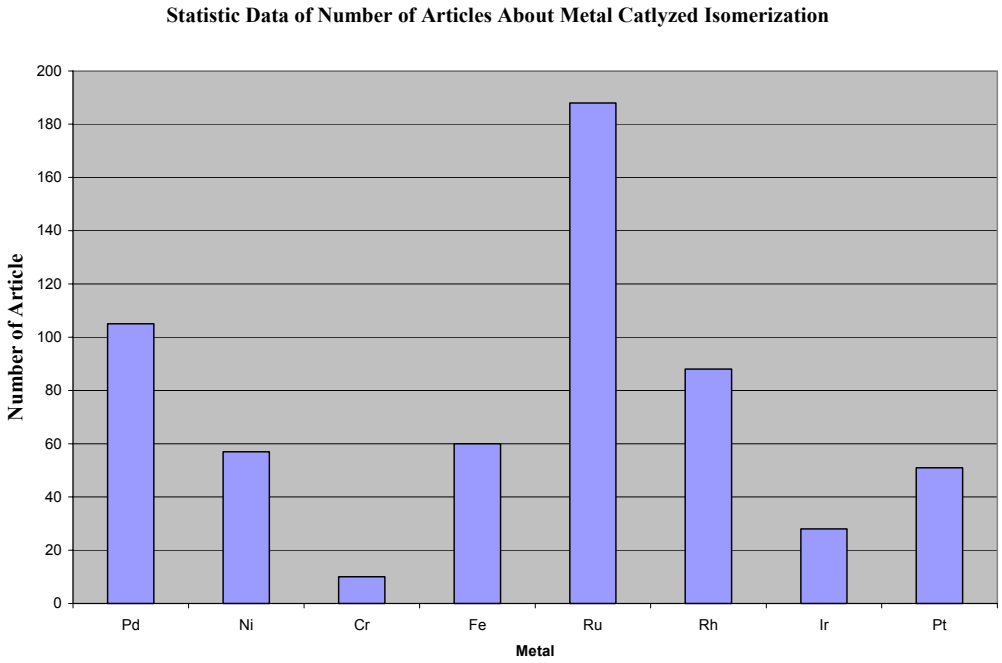


Figure 1.1 Statistic dada of the number of articles about olefin isomerization.

From the figure 1.1 and 1.2, we can easily see that the isomerization reaction has developed into a popular hot topic after 1995 and ruthenium is the most attractive metal.

Generally, as a normal side reaction of other catalyzed alkenes reactions, most isomerization reactions occur from terminal to internal alkenes. Only a few “contra-thermodynamic” examples of internal to terminal double bond isomerization are reported in literature.



Figuer 1.2 Statistical data of the number of articles regarding metal catalyzed olefin isomerization.

In this dissertation, based on the systematically and extensively literature review on the isomerization of alkenes by organometallic catalysis, a serial of novel ruthenium hydride complexes incorporating a Schiff base ligand has been developed and investigated as catalysts for the isomerization of alkenes. To identify and optimize the reaction conditions, allylbenzene and 1-Octene have been used as model substrates. The different factors that influence the isomerization reaction and selectivity of the catalyst such as, temperature, solvents and catalyst/substrate mol ratio have been taken into account to optimize the isomerization conditions.

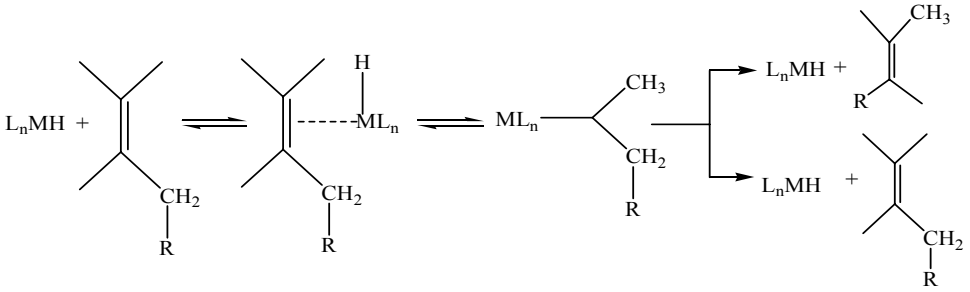
1.2 Mechanism

The mechanism of olefin isomerization catalyzed by organometallic complexes has been assumed as many hypotheses of different catalytic systems have been studied. The most popular interpretations involves the reaction of metal hydride with an olefin, oxidative addition of a transition metal complex to an allylic carbon-hydrogen bond of the olefin, the mechanism

involving the intermediacy of *α,β*-unsaturated carbonyl species and the radical abstraction of hydrogen from allylic sites.

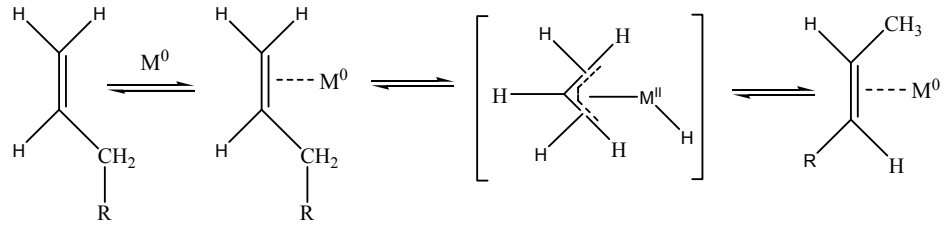
Among the above mentioned mechanisms, the radical abstraction of hydrogen from allylic sites might be the significant mechanism, less well characterization thwarted further investigation. While on the basis of deuterium-labeled studies, the other two major mechanisms were explored largely especially on the difference between them.

When a metal hydride reacts with an olefin, a π-alkene metal complex will be generated and then followed by a subsequent addition or elimination to achieve the olefin isomerization. This mechanism involves the formation and decomposition of an alkyl metal complex.[8]



Scheme1.1 Isomerization via transition metal hydride catalyst in hydrometalation-dehydrometalation mechanism.[9]

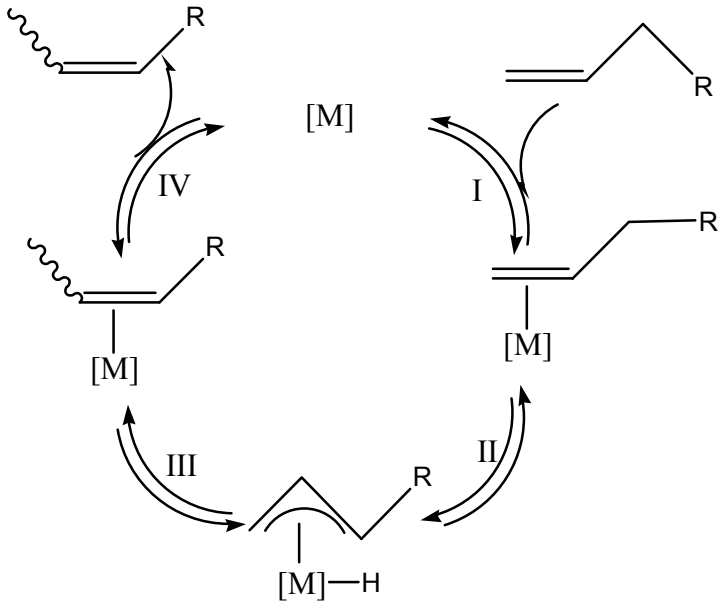
While under the non-hydride conditions, two kinds of mechanisms have been widely accepted. In the first the key step in the isomerization of alkenes is supposed to be the oxidative addition of an allylic carbon-hydrogen bond of alkene substrate to a transition metal complex with formation of a π-alkene hydride intermediate. By reductive elimination of the alkene from this intermediate, the isomerization can be obtained if the hydrogen moves to C_1 instead of returning to C_3 (in the case of terminal alkene).[2, 20, 21] The second mechanism happen when the starting catalyst is not a metal hydride or no hydride can be formed in the preliminary step of the reaction. The formation of a π-alkene metal complex followed by the formation of a π-alkene system coordinated to a metal hydride complex occurs.



Scheme 1.2 Isomerization via transition metal catalyst in the π-allyl mechanism.[9]

1.2.1 The π–allyl mechanism

As one of the two prevalent pathways for transition metal catalyzed isomerization of alkenes, the π–allyl metal mechanism (1,3-hydrogen shift) is a less common mechanism. [10] (Scheme 1.3) First of all, a free alkene coordinates with the metal fragment that does not have a hydride ligand. Oxidative addition of the activated allylic C-H bond to the metal yields a π–allyl metal hydride. This aliphatic β-C-H activation is the key feature of this mechanism and this step includes the three-carbon arrangement in π–bonding to the metal. The hydride attached to the metal has two possibilities to be transferred, α and γ, until the thermodynamic equilibrium is established. Transfer of the coordinated hydride to the opposite end of the allyl group yields the isomerized olefin. If all steps are truly reversible, eventual a thermodynamic equilibrium is observed.

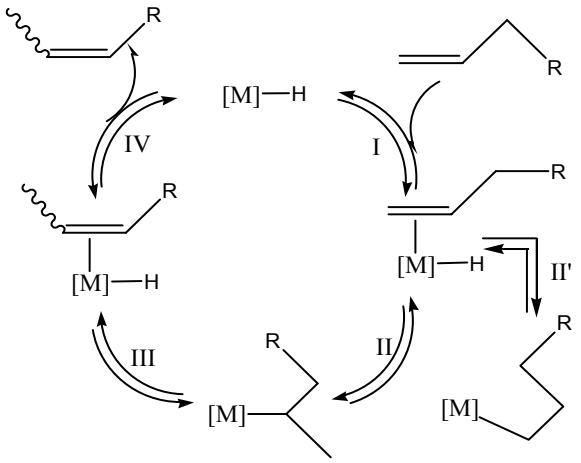


Scheme 1.3 The π–allyl mechanism.

The investigation on the mechanism has proved that ruthenium catalyzed isomerization take place via an intermolecular 1,3-migration of the allylic-C-H, which is analogous to π–allyl metal mechanism. Some other transition metal such as Fe, Ni, Rh and Pd assisted π–allyl complex formation and are normally very active in alkene isomerization. [3, 11]

1.2.2 The alkyl mechanism

The other established pathway for transition-metal-catalyzed olefin isomerization is the metal hydride addition-elimination mechanism (alkyl mechanism, 1, 2-hydrogen shift) and it is favored when the catalytic species are metal hydrides.



Scheme 1.4 The alkyl mechanism.

In this mechanism, free olefin coordinates to a kinetically long-lived metal hydride species. Subsequent insertion into the metal-hydride bond yields a metal alkyl. Formation of a secondary metal alkyl followed by β-elimination yields isomerized olefins and regenerates the initial metal hydride. During the reaction, the pathways (Markovnikov or an anti-Markovnikov) of hydride migration or insertion step depend on the nature of the metal and the ligands, especially the steric bulk is of importance.

Various catalyst systems based on cobalt, [17-20] rhodium, [12-18] iridium, [33-36] platinum[49-51] and nickel[19-21] have been reported to isomerizes olefins through this mechanism. Although some of these catalyst systems consists of stable, isolable metal hydrids (e.g. $HCo(CO)_4$, $RhH(CO)(PPh_3)_3$, $IrH(CO)(PPh_3)_3$, $RuHCl(PPH_3)_3$), many are not (e.g. $RhCl_3$, $RhCl(PPh_3)_3$, $Ni[P(OEt)_3]_4$). These systems require co-catalysts, such as acids[21, 22, 28, 12, 13] and hydrogen, [14, 15] which are responsible for the generation of the initial metal hydride. A number of pathways are known for the generation of the initial metal hydrides with the latter catalysts.[14]

McGrath and Grubbs[10] has modified the generic metal hydride addition-elimination mechanism as shown in Scheme 1.4 step II',to fit with the observed data for certain individual systems. Deuterium incorporation or lack thereof, into the substrate from deuterated solvents or co-catalyst can give some idea of the relative rates of the individual steps in the catalytic cycle. The ratio of nonproductive (step II') or productive (step II) insertion is indicative of the relative rates of Markovnikov versus anti-Markovnikov addition of the metal hydride across the olefin bond and is determined by examining the position of deuterium incorporation in the products after isomerization.

1.2.3 Other possible mechanisms

Except the mechanisms proposed above, a mechanism involving the intermediacy of *α,β*-unsaturated carbonyl species has been reported by Trost and Kulawiec[15, 16] for the selective isomerization of allylic alcohols by (η^5-Cp)(PPh_3)RuCl. This "internal redox" mechanism involves the coordination of the allylic alcohol as a bidentate ligand. *β*-Hydride elimination from the coordinated alkoxide[17] leads to an enone hydride complex (Fig. 1.3) which rearranges to an oxa-allyl species, presumably through exclusive Markovnikov addition of the metal hydride to the coordinated olefin moiety. Protonation liberates the product. This system demonstrates selectivity only for allylic alcohols, leaving other alcohol and isolated olefin functionalities untouched. Evidence for this pathway includes an observed intra-molecular 1, 3-hydride shift as well as the detection of small amounts of enone in the reaction mixture. A similar mechanism has been proposed by Inoue et al. for the asymmetric isomerization of allylamines by $[Rh(binap)S_2]^+$. [18-20]

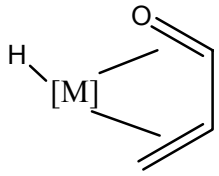


Figure 1.3 Enone hydride complex.

1.3 Catalyst systems for olefin isomerization

Many organometallic complexes have been reported to catalyze isomerization reactions, but most of them are multi-functional. Industrially, soluble catalysts are used to isomerize alkenes that are involved as intermediates in other homogeneous catalytic processes.[2] For instance, the ruthenium alkylidene developed by Grubbs and the molybdenum alkylidene developed by Schrock are the most widely used, well-defined metathesis catalysts. While together with the very selective activity for alkene metathesis, these metathesis initiators also have been reported to isomerize. [18] Grubbs type catalysts have been paid attention since their moderately sensitivity to air and moisture and the significant tolerance towards functional group. The Schrock's molybdenum catalyst gained interests because in RCM and in the metathesis of simple alkenes, alkene isomerization was observed.

1.3.1 Metal complex catalysts for olefin isomerization

Olefin isomerization with transition-metal catalysts is well established in organic chemistry.[3] Various transition metals, such as Cr, Fe, Ir, Ni, Pd, Ru, Rh and Pt have been involved in the catalysis for isomerization and some transition metal complexes have been reported as very effective isomerization catalysts. [5, 19]

1.3.1.1 Olefin isomerization with Ni, Pd and Pt complexes

The isomerization catalyzed by a nickel complex can be traced back to the reaction of 1-butene using a mixture of $NiCl_2Py_2$ and $AlEt_3$. Cramer [20] reported a very fast isomerization of this olefin in an acidic solution of $Ni[P(OEt)_3]_4$. The final result of 2-butene has a 1:3 *trans-cis* ratio in favor of the *trans*-isomer. The isomerization with $Ni[P(OEt)_3]_4$ in acid solution has been studied also in detail by Tolman. [21] It was found that when the acid was absence, no isomerization of 1-butene occurred, while in the presence of acids, both 2-butene and butane were generated. To prove the assumption that olefin isomerization and π-allyl formation can potentially occur in the same system, the reaction of $NiH[P(OMe)_3]_4^+$ 1-penta-4-diene was also investigated. The results implied that double bond isomerization occurred initially and was followed by the formation of allylic complexes because dimethyl-1,3- π-allylic products were formed along with 1-penta-3-diene.[21]

Bingham has reported the isomerization of 1-pentene catalyzed by Ni[bis(diphenylphosphino)butane]$_2$ and HCN, and by $Ni[P(OEt)_3]_4$ and CF_3CO_2H. [22] The later isomerization was carried over 24h and the products were 1-pentene (3%), *cis*-2-pentene (23%), and *trans*-2-pentene (74%). Comparing the result of 1-pentene with those of 1-butene as substrate, the deuterium redistribution rate is greater than the rate of isomerization.

Later, the acidic solutions of $Ni[P(OEt)_3]_4$ has also been reported to effectively catalyze the stereoselective isomerization of C=C double bonds in olefinic esters. With acidic solutions of $Ni[P(OEt)_3]_4$, only 4-pentenoate was produced from 3-pentenoate at early times. However, in the presence of excess phosphite, 2-pentenoate was the only positional isomer produced (61% yield). In the absence of excess phosphite, a kinetically controlled process is proposed to explain the initial formation of 4-pentenoate. [23]

By combining a group of Ni-base catalysts and co-catalysts, extremely active olefin isomerization catalysts were developed that could be generated from $[Ni(CH_3C(S)CHC(S)CH_3)(PBu_3)Cl]$ and appropriate co-catalysts. [24]

The systems based on $Ni(acac)_2$, combined with co-catalyst $AlEt_2Cl$ showed catalytic activity for the isomerization of 1-butene, 1-hexene and 1-octene. Precursors such as $Ni(ste)_2$, and $Ni(oct)_2$, combined with $AlEt_3$, $AlEt_2OEt$ or $AlEt_2Cl$, also showed high catalytic isomerization activity towards these substrates. In the case of $Ni(acac)_2$, a direct relationship between selectivity and the Lewis acidity of the aluminum co-catalysts was observed, suggesting the formation of bimetallic Al-X-Ni active species. [25]

By cleavage of the allyloxycarbonyl protecting group from oxygen and nitrogen under mild conditions by a nickel carbonyl frequently employed in the isomerization of allylic ethers.[26]

Isomerization of 2-methyl-3-butenenitrile to 3-pentenenitrile is a relevant step in the industrially important hydrocyanation of butadiene (the DuPont adiponitrile process). Chaudret[27] and Vogt [28] reported that this isomerization can be catalyzed by a nickel π-allyl cyanide complex. The mechanism was supported by *in situ* NMR monitoring and DFT studies[27] This isomerization reaction could also be catalyzed by the corresponding complex [(P-P)Ni(eta(2)-C,C-cyano-olefin)] produced by the nickel(0) fragment [(P-P)Ni], (P-P=dcype (1,2-bis(dicyclohexylphosphino)ethane) or dtbpe (1,2-bis(di-tert-butylphosphino)ethane)) reacted with the cyano-olefins. [29] By suing a triptycene-based diphosphine ligand catalyst tript-PPh_2Ni(cod), the exceptionally high selectivity for the linear product 3-pentenenitrile, combined with the high activity for both hydrocyanation and isomerization would be achieved. This one-step procedure could be the key toward process intensification.[30]

Some platinum hydride complexes have been studied as isomerization catalysts, such as $PtHClOP(Ph_3)_2$, $PtH(NO_3)(PPhMe)_2$, $[PtH(PPh_3)_3(acetone)]BF_4$ and $PtH(SnCl_3)(PPh_3)_2$ are readily catalyst for isomerization of allyl methyl- and allyl phenyl ether. [31] A mechanism involving the addition of Pt-H across the terminal C=C bond before double bond migration occurs was also favored, which led to the catalytic formation of *cis*-propenyl alkyl ethers. A similar mechanism was considered for the reaction of 1-butene, where both Markovnikov and anti-Markovnikov addition occurred.[32] Platinum hydrides also play a role in the hydrosilylation reaction[33] and it was suggested that the mechanism in the hydrosilylation reaction accounts for alkene isomerization via the reversible formation of the metal alkyl.[34]

The platinum complexes activated by methyl fluorosulfonate and the platinum complexes of thiacyclooct-4-enes are reported to catalyze the olefin isomerization.[35, 36]

Reactions of $PtCl_4^{2-}$ with *cis*-thiacyclooct-4-ene, *cis*-2-methylthiacyclooct-4-ene and *cis*-2-phenylthiacyclooct-4-ene (*cis*-*S*-4-oct) give chelate complexes of general formula MCl_2(*cis*-*S*-4-oct). X-ray structure determination indicates that coordination to the metal occurs through both the olefinic double bond and the sulfur atom. Reaction of CN^- with the adduct obtained from $PtCl_4^{2-}$ and a mixture of *cis*- and *trans*-2-methylthiacyclooct-4-ene liberates the *cis* ligand, and GLC analysis excludes the presence of free *trans* olefin. It is suggested that platinum complexes induce extensive *trans* to *cis* olefin isomerization.[36]

The stoichiometric isomerization of 1-pentene coordinated to palladium(II) chloride has been investigated in aprotic solvents. The action of basic cocatalysts has been discovered. The observed selective formation of *cis*-2-pentene in the stoichiometric process may explain some aspects of the stereoselectivity observed in the first stages of catalytic isomerization. [37]

Casey and Cyr[11] have presented $Fe(CO)_{12}$-catalyzed isomerization of 3-ethyl-1-pentene-3-d_1. In this study they found clear evidence in favor of the π–allyl hydride mechanism and concluded that the equilibria leading to isomerization (stept II and III in Scheme 1.3) are fast relative to the decomplexation of the coordinataed olefin (step IV in Scheme 1.3).

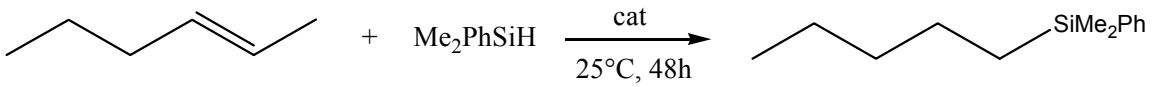
Isomerization of 1-pentene to *cis/trans* 2-pentene was catalyzed at 50°C and above by a $Fe(CO)_{12}$ or $PdCl_2(C_6H_5CN)_2$ solution in benzene. In both cases the preferential formation of *trans*-2-pentene occurred. Isomerization of 1-pentene revealed that each reaction proceeded by intramolecular transfer of hydrogen and deuterium atoms. The reaction mechanisms involved the π-allylic mechanism. [38]

Coordinated with different ligands, the palladium complexes perform the isomerization in a different way. The mechanism on isomerization catalyzed by a serial of Pd complexes was carried out by Francis[39, 40] By studying the isomerization of 2-(methyl-d^3)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol into an equilibrium mixture of itself and 2-methyl-4-(methyl-d^3)-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in aqueous solution catalyzed by $[PdCl_4]^{2-}$ $[H^+][Cl^-]_2$, the result required that isomerization and exchange occur by a hydroxypalladation route, rather than through palladium (IV)-π-allyl intermediates. While further mechanistic studies on the $PdCl_3(pyridine)^-$ catalytic system in similar conditions strongly suggested that the hydroxypalladation by $PdCl^3(Py)^-$ at low $[Cl^-]$ is a *trans*-process as opposed to a *cis*-process with $PdCl_4^{2-}$.

The Group 10 complex *trans*-$Pd(C_6H_5CN)_2Cl_2$ is also reported as an effective catalyst for the stereoselective isomerization of C=C double bonds in olefinic esters. For example, *trans*-$Pd(C_6H_5CN)_2Cl_2$ selectively produces 2-pentenoate from 3-pentenoate (58%). [23]

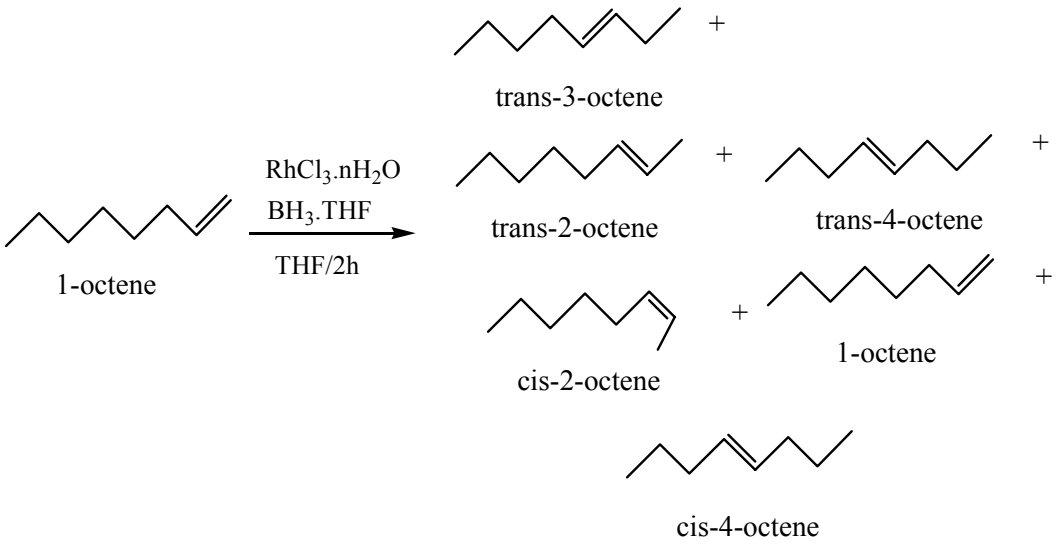
1.3.1.2 Olefin isomerization with Fe, Co and Rh complexes

The Wilkinson catalyst $(Ph_3P)RhCl$ is a well-know catalyst for hydrogenation and give inter alia terminal alkenes when an internal alkene is subjected to typical hydrogenation conditions. [41] During the hydrosilylation of internal alkenes at moderate reaction condition, the Wilkinson catalyst gives only terminal adducts by a series of isomerization suggesting an internal-to-terminal migration during the reaction.[42] Furthermore, the Wilkinson catalyst is also frequently employed in the isomerization of allylic ethers.[43]



Scheme 1.5 The hydrosilylation catalyzed by Wilkinson catalyst.

In the metal hydride analogue of the Wilkinson catalyst, one of the phosphine ligand of $(Ph_3P)_3RhH$ can be replaced with borane.[44, 45] Under high pressures or even less severe hydrogenation condition, these complexes isomerize internal alkenes . Later, it was reported that alkenes isomerizes rapidly in the presence of a catalytic amount of a hydroborating reagent and a rhodium compound. Apparently the hydroborating reagent is responsible for the *in situ* generation of a metal hydride species, which has been implicated to account for the stepwise isomerization. In order to make a clear picture of the isomerization process, Morrill et al. [46]carried out a hydroboration/oxidation of 1-octene using less than the stoichiometric amount of the hydroborating reagents, see Scheme 1.6. Analysis of the reaction mixture revealed the presence of 1-octene(0.6%) and isomeric internal olefins (87%), along with octane and octanol.



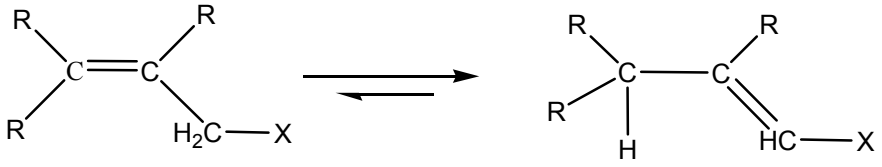
Scheme 1.6 Isomerization of 1-octene catalyzed by $RhCl_3{\cdot}nH_2O/BH_3{\cdot}THF$ in THF.

The above scheme depicts the isomerization of 1-octene catalyzed by the combination of catalytic amounts of $RhCl_3{\cdot}nH_2O/BH_3{\cdot}THF$. This catalytic system performs in an excellent way the olefin isomerization. Morrill proposed that the rapid reversibility of the olefin insertion/β-hydride elimination step in the mechanism is the key to olefin isomerization.[46]

It could be also noticed that during the isomerization of 1-octene, trans-4-octene was not the major product, and when 4-octene was subjected to similar experimental conditions, the product ratio resembled that obtained with 1-octene. This phenomenon agrees with the theory that typically equilibration favors structures with the double bond farther from the end of the carbon chain. We can deduce that no matter what isomeric olefin starts with, the final product composition was virtually a thermodynamic mixture of isomeric alkenes.

The asymmetric isomerization of allylic compounds with chiral catalysts can also be of importance to the internal-terminal double bond migration of simple alkenes. Chiral Rh complexes containing a BINAP ligand give terminal alkenes in high yields with allylic compounds:[47]

Some of rhodium catalysts present their activities in a special mechanism. Tani has reported a series of reaction involving $[Rh(binap)S_2]^+$ [18-20] via the mechanism that intermediacy of *α,β*-unsaturated carbonyl species for the asymmetric isomerization of allylamines. This "nitrogen triggered" system exhibits selectivity for allylic amines over isolated olefins. Convincing evidence for the necessity of the amine functionality for isomerization activity is the displacement of solvent from $[Rh(binap)S_2]^+$ by triethylamine, to form $[Rh(binap)S(triethylamine)]^+$, but not by 2-methyl-2-butene. More importantly, the rate of isomerization of diethylgeranylamine is inhibited by addition of triethylamine but not affected by the presence of a large excess of 2-methyl-2-butene.



X=OH, OR, NH_2, NR_2

Scheme 1.7 Asymmetric isomerization catalyzed by chiral Rh complexes.

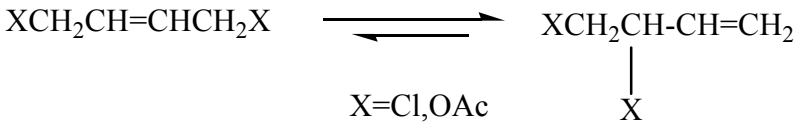
The effect of ligand donor-acceptor properties on selectivity of catalytic olefin isomerization reaction has been studied by using 1-hexene, 1,5-hexadiene and 1,7-octadiene as substrates applying $HRh(CO)(PPh_3)_3$, and $HRh(PPh_3)_4$ at 40°C.[48] 1-Hexene underwent total conversion to 2-hexene at the presence of both catalysts in 100 min, whereas isomerization of dienes is catalyzed only by the $HRh(CO)(PPh_3)_3$ complex. The observed differences in catalyst activity elucidated that the isomerization reaction course depends on the electron density distribution in the rhodium-olefin complex as well as on the way how the olefin coordinates to the rhodium. By adding H_2, the catalytic activity of both catalysts can be improved.

Based on theoretical calculations for model structures $[HRh(CO)_3(hexadiene)]$ (**I**) and $[HRh(PPh_3)_3(hexadiene)]$ (**II**) using the Fenske-Hall method and experimental data, the following general conclusions regarding the formation of the active rhodium catalyst for olefin isomerization can be drawn:[48]

- Electron density on rhodium and the coordinated hydride ligand depend on the donor-acceptor properties of the remaining coordinated ligands.

- Distribution of electron density on the olefinic carbon atoms of the coordinated olefin depends on the way it is coordinated to the Rh-atom.
- The branched alkyl rhodium complexes are formed only for some modes of rhodium olefin species and are determined by the electron density distribution.
- Steric factors, i.e. size of coordinated ligands and shape of the carbon chain are decisive for which isomer of the olefinic complex will be formed.

The isomerization of allylbenzene by $HCo(CO)_4$ and $DCo(CO)_4$ at ambient temperature and pressure was examined by Orchin and Roos,[49] . They found that both catalysts could isomerizes the substrate to propenyl benzene at the same rate. In the hydroesterification reaction of internal alkene, Co-complexes are known to rapidly isomerize the double bond to the 1-position to give a linear ester as a major product.[50]



Scheme 1.8 Olefin isomerization catalyzed by Co complexes.

In order to investigate the relationship between the ratio of nonproductive or productive insertion and the relative rates of Markovnikov versus anti-Markovnikov addition of the metal hydride across the olefin bond, Cramer has estimated that this can be determined by examining the position of the deuterium incorporation in the products after isomerization. From the ratio of $CH_2DCH=CHCH_3$ versus other deuterated butenes in the isomerization of 1-butene by DCl-activated rhodium catalysts, Cramer gave the rates of Markovnikov : anti-Markovnikov addition to be approximately 1:15. [51] This ratio seems to be consistent with the thermodynamics of metal alkyls, although contradicting results have been reported for other systems. For example, both Hendrix and Rosenberg[52] and Taylor and Orchin[53] reported isomerization product composition from the $HCo(CO)_4$-catalyzed isomerization of deuterated olefins to be consistent with a 65-70% preference for Markovnikov metal hydride addition.

Another very effective isomerization catalyst was prepared by treatment of $Co_2(CO)_8$ with a silicon hydride in sufficient quantity, slightly exceeding the Co carbonyl concentration. The behavior of 1-heptene and 1-pentene in the presence of this catalyst was very similar to that observed with $RhCl_3$-$3H_2O$ as catalyst, the isomerization occurred in stepwise fashion. Co-isomerization of 1-pentene and 1-heptene results in an exchange of 0.5 deuterium atoms per molecule of isomerized 1-hepene. The exchanged deuterium has being distributed between all the carbon atoms of the allylic system of the 2-pentene.

From the comparison of the results obtained with the Co carbonyl/silane catalysts, it was found that they were so closely to the results obtained with the rhodium complex catalyst. Knowing that the latter operate through a metal alkyl intermediate a similar mechanism operating in the former catalyst was assumed.

A relatively recent metal carbene system, based on Rh (Fig 1.4) and used in hydroformylation, catalyses the stereo-specific isomerization of 1-alkenes to *cis*-2-alkenens under appropriate conditions. [54] These are heterocyclic carbenes derived from inidazole and related N-heterocyclic compounds that form stable metal complexes with a large number of metals e.g.

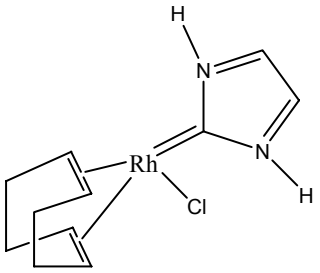
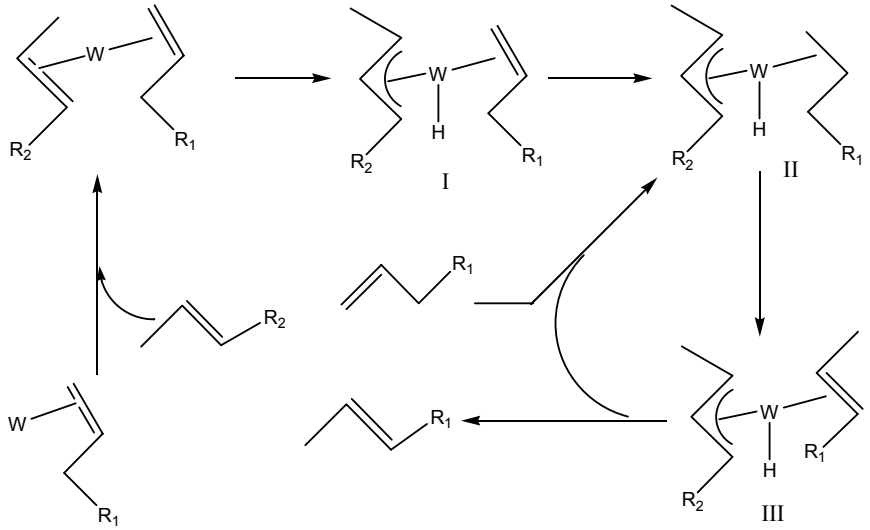


Figure 1.4 Rhodium carbene catalyst.

1.3.1.3 Olefin isomerization with W complexes

It had already been reported in 1970th that the olefin isomerization of 1-alkenes could be catalyzed by WCl_6/Et_3Al and this reaction was enhanced by the addition of the internal alkenes including cyclooctene [55] A mechanism in which a metal hydride formed by the abstraction of a hydrogen atom from internal olefin was proposed. (Scheme 1.9)



Scheme 1.9 Isomerization of olefins catalyzed by a tungsten system.

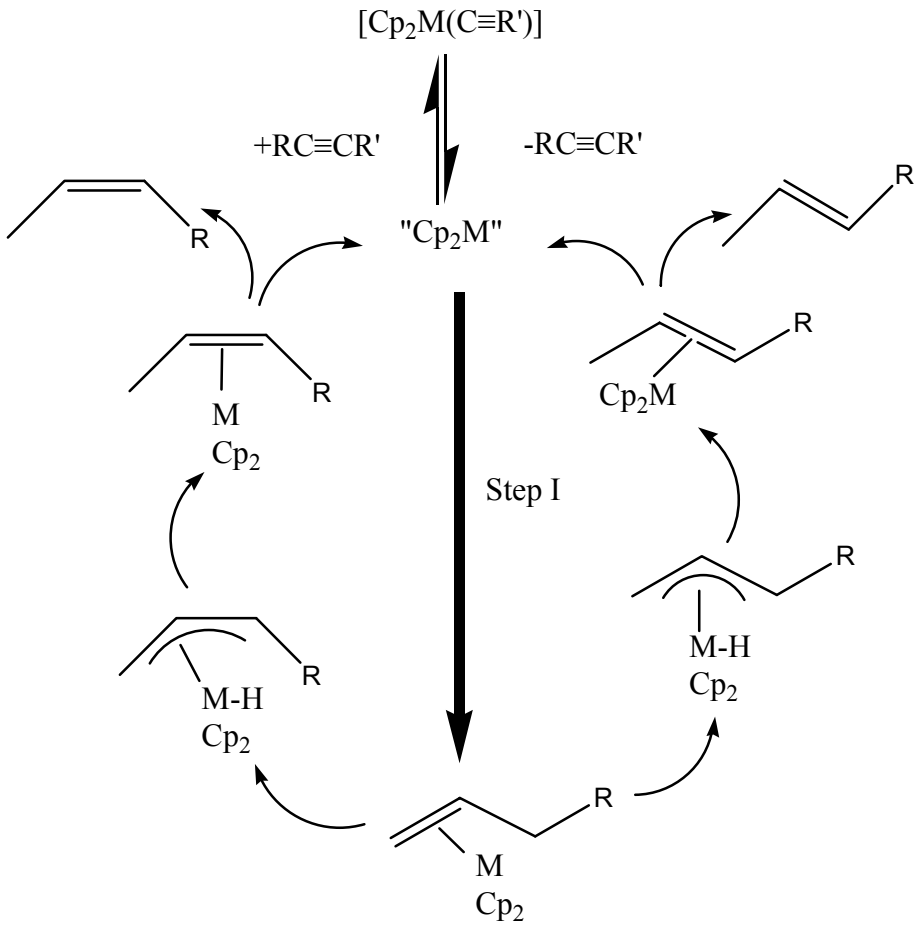
In the above scheme, since the double bond of internal olefin has higher electron density than the double bond of terminal alkenes, they prefer the formation of hydride complex such as (I) which transfers to a σ-alkyl complex (II) to give a thermodynamically more stable internal olefin.

Similar to the Grubbs ruthenium catalysts, the commercial Schrock catalyst based on tungsten(Tris(t-butoxy)(2,2-dimethylpropylidyne)(VI)tungsten) is also a widely used metathesis catalyst. A model study was conducted to compare the extent to which olefin isomerization occurs during olefin metathesis of simple olefins with Grubbs' ruthenium catalysts and Schrock's molybdenum catalyst. It was found that the NHC-ligated ruthenium complex promotes extensive isomerization of both internal and terminal olefins at temperatures of 50-60 °C, whereas the Schrock's molybdenum complex did not.[56]

1.3.1.4 Olefin isomerization with metallocene complexes

With the success of the metallocenes in the polymerization of alkenes and the recent application of these systems in the isomerization of terminal alkenes, it will be worthwhile to investigate these systems for the isomerization of internal alkenes. $CpTiCl_2$ combined with various activating reagents, such as Grignard reagent, Li-organoyls, $LiAlH_4$ or Na-napthalide, has been employed to convert 1-alkenes into 2-alkenes with preferred *trans* geometry using the immobilized catalyst and t-butylmagnesium bromide and showed high isomerization activities and selectivities. [21-24]
The catalyst systems which consist of $TiCl_2(C_5R_5)_2$(R=H, CH_3)/$NaC_{10}H_8$, *i*-C_3H_7MgBr, *n*-C_4H_9Li or $LiAlH_4$ in 1 : 2 ratio were highly effective for the stereoselective isomerization of mono-substituted 1-alkenes to (*E*)-2-alkenes. The catalyst with the bulky C_5Me_5 ligand showed extremely high activities and resulted in the complete isomerization of 1-alkenes in >99% stereoselectivity within a short period. The catalysis of the corresponding zirconium systems, in contrast to titanium, was very poor irrespective of the reducing agents and substrates and only allows coupling reactions. The larger atomic radius of zirconium could explain the difference in the activity between titanocene and zirconocene.[57]

An efficient isomerization of aliphatic and cyclic olefins has been achieved by using well-defined metallocene alkyne complexes as catalysts.[58] (Scheme 1.10) Titanocene complexes (Table 1.1) isomerize 1-alkenes to internal alkenes under mild conditions. Cyclic olefins-cyclohexadienes also undergo isomerization, but a competing intermolecular hydrogen transfer reaction takes place as well. Whereas zirconocene complexes were found to be mainly inactive in isomerization reactions of aliphatic alkenes



Scheme 1.10 Proposed π-allyl mechanism for the isomerization of aliphatic alkenes by metallocene alkyne complexes. [58]

Table 1.1 Isomerization of alkenes catalyzed by (η^5-$C_5Me_5)_2TiCl_2$/Na naphthalide at 20 °C in 60-120 min (alkene/catalyst ratio 100:1). [57, 59]

Substrate	End Product	Yield(%)	*Trans* isomer (%)
1-Butene	2-Butene	>99	99
3-Phenyl-1-propene	1-Phenyl-1-propene	>99	99
4-methyl-1-pentene	4-Methyl-2-pentene	25	99
1,4-pentadiene	1,3-Pentadiene	99	>99

Base on the investigation of the chemo- and regio-selectivities of the obtained alkyne complexes, it was conclude the activity of the titanocene complexes depend on different substituents. A decreasing catalytic activity of the alkyne complexes is in the order: [$Cp_2Ti(Me_3SiC{\equiv}CSiMe_3)$]> [$Cp_2Ti(Me_3SiC{\equiv}CtBu)$]> [$Cp_2Ti(Me_3SiC{\equiv}CPh)$].[60] These isomerization were exclusive transformations of 1-alkenes to 2-alkenes producing preferentially the *E*-isomers, which is in accordance with the factors influencing thermodynamic stability of alkenes. [61]

1.3.1.5 Olefin isomerization by metal chlorides

The isomerization of functionalized internal alkenes to terminal alkenes using Cu(I) complexes like (PhCN)CuCl and $R_4N^+CuCl_2$ and Pt chloride complexes as catalyst are well known. [2, 3]

As one of the starting materials in the synthesis of the Grubbs catalyst, in the 1960s, $RuCl_3$ hydrate has already been reported to be an effective catalyst for ring opening metathesis of highly stained cyclic alkenes such as norbornene, but did not catalyze metathesis of acyclic alkenes. [54]

Later, metathesis of 1-octene was carried the by combining the olefin with $RuCl_3 \cdot 3H_2O/RuBr_3$ dissolved in alcohol, phosphine and an alkyne at 60-90°C. As a side reaction, isomerization of 1-octene to internal octenes was observed in small amounts. When little or no alkyne was present, the dominant reaction would be isomerization of 1-octene to internal octenes. In the presence of an alkyne, isomerization tended to increase relative to metathesis with increasing reaction time and with increasing reaction temperature.[62]

$RuCl_3$ also was reported to catalyze the isomerization of 1-hexene in ethanol. Since the reduction of Ru(III) to Ru(II),to provide active species for olefin isomerization, was slow process, an 1h induction period was observed. [63]

1.3.2 Olefin isomerization with Ru complexes

Through the years, a great number of Ru(II) complexes have been studied as isomerization catalysts and ruthenium complexes are well known because they promote alkene isomerization reaction. [64] (see Table 1.2)

Table 1.2 Some ruthenium(II) catalyst for isomerization reaction.

Catalyst Precursor	Substrate	Products
$[RuCl_2(PPh_3)_3]$	Allylbenzene	*cis / trans*-β-styrene
	4-phenylbutene	1-phenylbutenes
$[RuCl_2(PPh_3)_3]$	4-vinylcyclohexene	3- and 4- ethylidenecyclohexenes
$[RuCl_2(PPh_3)_3]$	1, 4-diarylbut-2-ene	1,4 – diarylbut-1-enes
$[RuCl_2(\eta\text{-}C_6H_6)]_2$	1-hexene	2-hexene
$[Ru(PPh_3)_4(\eta\text{-MeCN})]\cdot MeCN$	Allylbenzene	*cis / trans*-β-methylstyrene

The isomerization mechanism catalyzed by ruthenium catalyst is not restricted to the above described mechanisms, e.g. the $Ru(H_2O)$(*p*-toluenesulfonate) catalyst has been reported to isomerizes allylic ethers and alcohols and other alkenes in a metal hydride mechanism by Grubbs, although the catalyst is not a ruthenium hydride [10]

1.3.2.1 Ruthenium metal carbene for olefin isomerization

Catalysts derived from carbenes have also been found to promote the isomerization of terminal alkenes to internal alkenes.[65-67] As an important side reaction in olefin metathesis reaction, normally, double bond isomerization gives rise to a spectrum of products formed due to *inter alia* cross metathesis between the original olefin and the isomer olefin. A metal carbene and in some cases a metal carbene hydride mechanism was suggested to account for this observation with some evidence that such species may exist. [54, 68, 69] The features of the metal carbene mechanism are characteristic of the π-allyl mechanism.[54] Double bond isomerization via a metal carbene may take place via a series of equilibrium transformations and whether these equilibriums do indeed take place need to be investigated.

Although the carbene complexes were evidently prepared in 1915, they were not recognized until the synthesis of $(OC)_5W=C(OMe)Ph$, the first carbene complex to be formulated. [70] Cardin defined the term carbene complexes as the following general type in which a carbene, =CXY, is coordinated to a transition metal atom M and L_n refer to various other coordinated ligands.[70]

In most of case, the carbene ligand is terminal bound, while sometimes also as a bridging moiety. When the metal is in a low oxidation state, the carbene may be considered as a “soft” ligand.

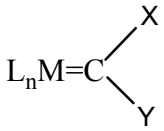


Figure 1.5 General type of metal carbene.

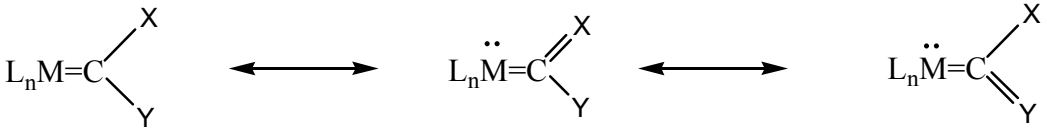
For carbene complexes, there are two types of isomerizations. The first one involves rearrangement of the ligands in the coordination sphere of the metal, and two rotamers are interconverted by rearrangement within the aminocarbene ligand. [70] It has been shown that the *cis* isomers are more thermodynamically stable in the square planar Pd(II) and Pt(II) carbene complexes. The second method of isomerization involves heating in refluxing alcohol, the reactivity sequence with respect to the ease of isomerization of such *trans* complexes are Pd>Pt. The *trans* complexes owe their preparation to kinetic rather than thermodynamic factors. [70]

The discovery of the carbene complexes was a breakthrough in organometallic chemistry. These carbene complexes are involved in many crucial processes, such as olefin metathesis and polymerization. Transition metal carbene complexes can be divided into the Fischer type and the Schrock type named after their discoverers. [71]

1) Fisher carbenes

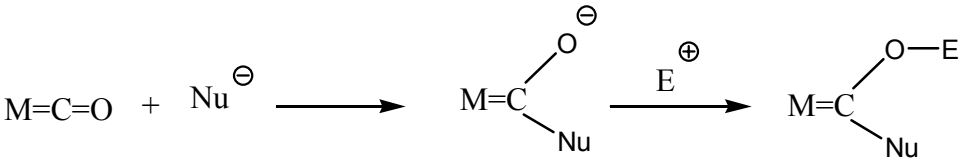
In 1964, E.O Fischer reported the first example of electrophilic carbenes which are called Fisher carbenes in honour of him and later he received the Nobel Prize for his pioneering work on ferrocene with Wilkinson. [72]

Fisher type compounds contain a metal from Groups VI to VIII and are typical electron-rich, low oxidation state metal complexes. The low oxidation state is stabilized by a series of other ligands with π-acceptor properties. The carbene carbon in this compound is considered to be sp^2-hybridised; the bonding is therefore described by the three resonance structure:



Scheme 1.11 Three resonance structure of the Fisher type carbene.

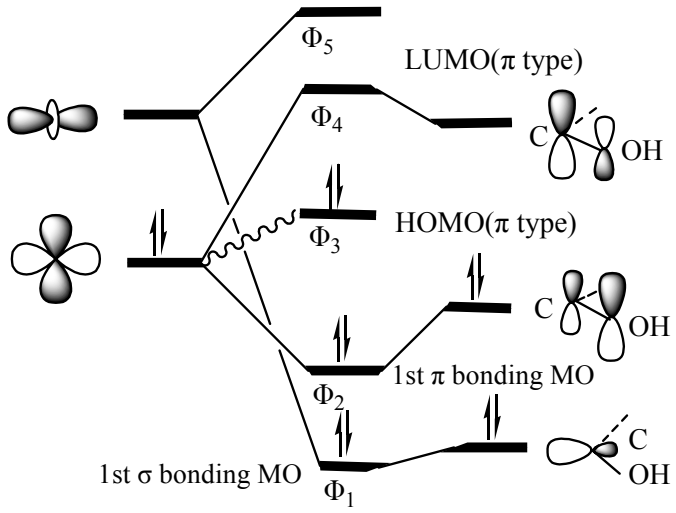
The presence of the heteroatom on the α-carbon allows to draw a resonance structure that is not possible for an unsubstituted (Schrock type) alkylidene:



Scheme 1.12 Resonance structure of Fisher type carbene with heteroatom.

Analyzing the above resonance structure applying a molecular orbital perspective (Scheme 1.13), one lone pair is donated from the singlet carbene to an empty d-orbital on the metal, and a lone pair is back donated from a filled metal orbital into a vacant p_z-orbital on carbon. There is competition for this vacant orbital by the lone pair(s) on the heteroatom, consistent with the second resonance structure. Generally, the bonding closely resembles to that of carbon monoxide. Therefore, carbene ligands are usually thought of as neutral species, unlike dianionic Schrock alkylidenes (which usually lack electrons for back-donation). [72]

As below, the σ-type MO's give a pattern typical of classical single bond. However, the π-system is comprised of three MO's in an allyl-like arrangement: one bonding (Φ_2), one non-bonding (Φ_3), and one antibonding (Φ_4). The antibonding LUMO of the carbonic system is localized on the carbon, whilst the HOMO resides mainly on the metal.

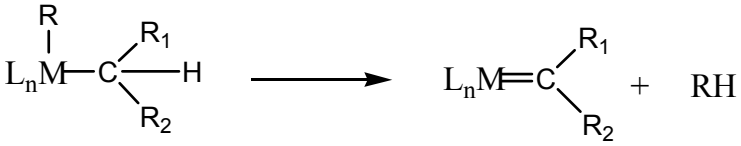


Scheme 1.13 Molecular orbital diagram which shows the metal orbitals which are involved in bonding to the carbene. [72]

The general synthesis methods of Fisher carbenes include nucleophilic attack of metal carbonyls, alkylation of an acyl complex, tautomerization of terminal alkyne complexes to acetylides followed by the transfer of the hydride to the *β*-carbon and form activated alkenes.

2) Schrock carbenes

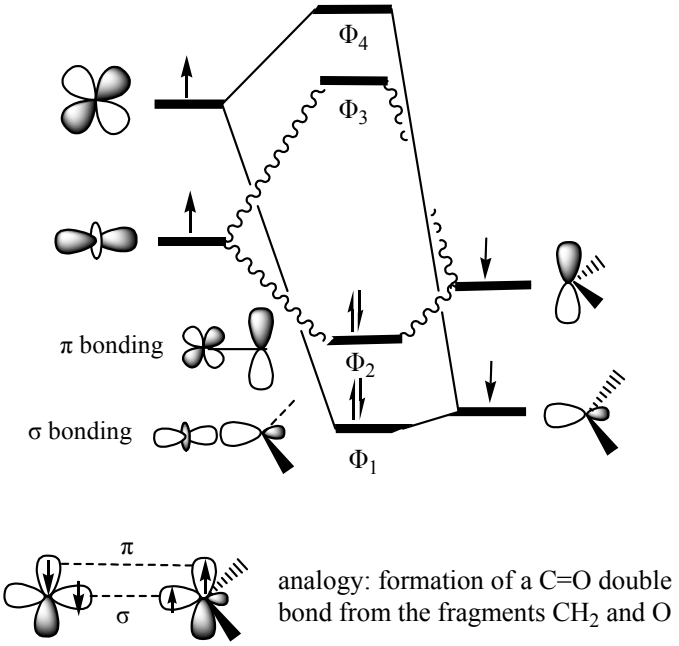
After the Fischer carbenes were discovered 10 years later, the Schrock carbenes complexes were discovered. They confer nucleophilic properties and complexes of the Schrock-type are characterized by an early transition metal:



Scheme 1.14 Schrock type carbene.

Their bonding may be interpreted as the interaction of a triplet carbene and a triplet ML_n fragment, as for the case of ethylene.[72]

It is demonstrated in the below scheme that two MO's are formed. The highest –HOMO– is mainly localized upon the carbon; accordingly the LUMO is localized on the metal. During investigations of intermolecular metathesis polymer degradation using a stable molybdenum Schrock carbene complex, $Mo(=CHMe_2Ph)(=NAr^iPr_2)[OCMe(CF_3)_2]_2$, olefin isomerization was found as a side reaction. [73]



Scheme 1.15 Molecular orbital diagram which shows the metal orbitals which are involved in bonding to carbene. [72]

3) Ruthenium carbenes

Olefin metathesis has revolutionized organic chemistry over the past decade. As one of the most valuable metathesis catalysts, the Grubbs metathesis catalysts $RuCl_2(=CHPh)(PCy_3)_2$ and $RuCl_2(=CHPh)(H_2IMes)(PCy_3)$ has become an increasingly useful tool for organic transformation since their significant tolerance towards functional group. [74] Not only they expanded our options regarding C-C bond formation, but also for isomerization. Single component tandem catalysis in the presence of the above catalysts has so far included metathesis followed by hydrogenation, dehydrogenation, and most recently isomerization. [75]

The 1st generation Grubbs catalyst, the ruthenium carbene complex, $RuCl_2(=CHPh)(PCy_3)_2$ is moderately sensitive to air and moisture and show significant tolerance to functional groups. [76] These significant high performance and the excellent tolerance of these complexes toward an array of functional groups is attributed to the well balanced electronic and coordinative unsaturation of the Ru(II) center.[77] Compared with the early systems (i.e. $RuCl_2(=CHCH=CPh_2)(PPh_3)_2$), the early one was only effective in the ROMP of highly strained alkenes and showed a lower thermal stability. [78]

The catalyst $RuCl_2(=CHPh)(PCy_3)_2$ is active in wide range of RCM, CM and ROMP applications, however they are limited to alkene substrates that are not sterically hindered. [68]

The influence of the changing phosphine ligands also demonstrate the change of initiation since the catalytic activity of the complex originates from the liberation of one phosphine followed by coordination of an alkene substrate. [79] The nature of the carbene moiety has been shown to influence not only the initiation but also the propagation of the catalytic reaction. [76] Sterically demanding and highly donating phosphine ligand (PCy_3) stabilize the intermediate catalytic species. Despite its versatility, this catalyst displays a low thermal stability as a result of easily accessible bimolecular decomposition pathways. [80]

The heterocyclic carbenes deriving from imidazole and the related N-heterocyclic compounds are similar to electron rich phosphines in many respects. They form stable metal complexes with metals across the periodic table and they form efficient catalysts for C-C bond forming reactions.[3, 81] A fateful advanced development in the ruthenium catalysts is the introduction of N-Heterocyclic carbene (NHC) ligands to obtain the 2nd generation of Grubbs catalyst:

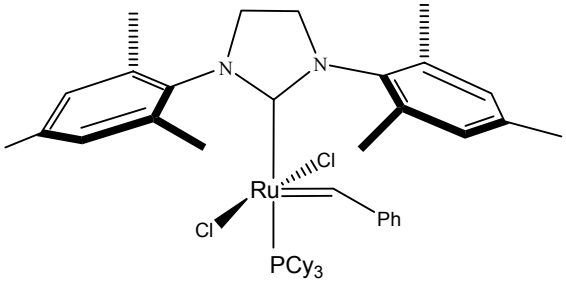


Figure 1.6 Grubbs 2nd generation catalyst.

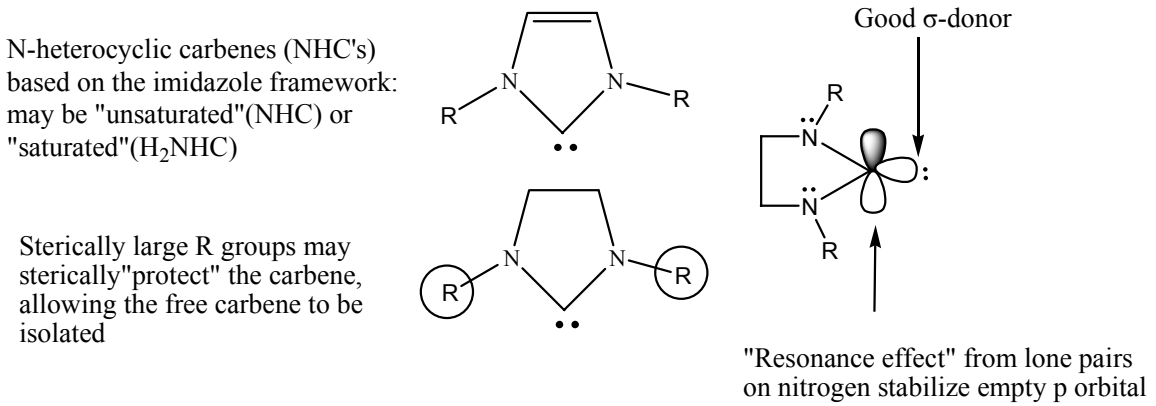
Comparing with the corresponding alkyl phosphine ligands, N-Heterocyclic carbene (NHC) ligands are much more basic and increases the reactivity of the catalyst by making it easier to decoordinate the *trans*-PR_3 ligand of the metal. This correlates well with a dissociative mechanism.

NHC's are more comparable to P-, N- or O-donating ligands rather than to classical Fischer or Schrock carbenes (Scheme 2.7) since they are σ-donating ligands. In contrast to the "conventional" carbene ligands, the metal-carbon bond is much longer and is chemically and thermally more inert towards cleavage. A remarkable difference with many other heteroatom donating ligands NHC's show very high dissociation energy. [82] Since they are very poor π-acceptor ligands, little tendency to dissociate from the metal center was shown. In addition because they can be easily endowed with sterically demanding substituent on their N-atoms, they are able to stabilize the catalytically relevant intermediates by electronic and steric ways. [83]

Since air and water sensitivity is the well-known character of free NHC's, the development of NHC-coordinated catalysts have to solve the initial problem. [84] The isomerization may occur

analogously to that of the related $16e^-$ Ru complexes, by hydrometallation followed by a β-elimination. The active catalyst is probably the corresponding hydrido derivative formed *in situ*.

The nucleophilic carbene ligands, imidazol-2-ylidenes, are neutral, two electron donor ligands with negligible π-back-bonding tendency. Grubbs and co-workers [85] have presented an extensive *in situ* NMR study in which it was concluded that the origin of increased activity in the 2nd generation catalyst $RuCl_2(=CHPh)(PCy_3)(NHC)$ derived from its improved selectivity for binding π-acid olefinic substrates in the presence of σ-donating free phosphine instead of its ability to promote phosphine dissociation . [86-88]



Scheme 1.16 N-heterocyclic Grubb metal carbenes.

4) Isomerization of olefin using Grubbs metal carbenes

$Ru(=CHPh)Cl_2(PCy_3)_2$, known as a catalyst for metathesis, is also a catalyst for isomerization, but the reaction usually affords a mixture of alkene isomers. The Grubbs carbene complex and its second generation counterpart have demonstrated a remarkable efficiency in metathesizing alkenes. Furthermore, the ready availability of these stable ruthenium-based catalyst, combined with their tolerance toward a wide variety of common functional groups, make the Grubbs catalysts very convenient synthetic tools. Isomerization occurred as a side reaction in the metathesis reaction using the Grubbs' metal carbene as the catalyst.

Olefin isomerization of substrates with allylic oxygen or nitrogen functionality catalyzed by the 1st generation Grubbs catalyst [89] have been reported, moreover Grubbs et al. also studied the isomerization of *cis*-2-pentene and terminal alkenes as substrates. [68]

A detailed study on double-bond isomerization activity of 1st and 2nd generation Grubbs catalyst and the comparison with Mo-based Schrock metathesis catalyst has been made by Wagener. By studying the catalytic activity and selectivity of $Ru(=CHPh)Cl_2(PCy_3)_2$ in the metathesis of linear

alkenes, it can be concluded that if a catalyst is also active for olefin isomerization, additional products can be formed by cross-metathesis reactions. This would result in a complex product mixture and in a decrease in yield of the desired compounds.[90]

A serial of Grubbs type (benzylidene and vinyl-alkylidene) catalysts have been monitored in toluene by NMR. When subjected to elevated temperatures, signs of decomposition afforded a straightforward gauge of the thermal stability of the carbene complexes. So it was presumed that the initial step of the thermal decomposition is the decoordination of one phosphine ligand form the metal center. Because the IMes-ligand is stronger bonded to the metal center and provides better steric protection compared to phosphine ligands, the lifetime of the resulting 14-electron intermediate and therefore the thermal stability of the mixed phosphine/carbene compounds of 2nd generation Grubbs catalyst should be enhanced compared to that of the 1st generation. Ruthenium alkylidenes of the type $RuCl_2(=CHPh)(PCy_3)L$ display characteristic chemical shift in their NMR spectra that provide valuable information for elucidating solution state geometries of the complexes(Table 1.3). [91]

Table 1.3 Selected ^1H, ^{13}C, and ^{31}P δ values of $RuCl_2(=CHPh)(PCy_3)L$.

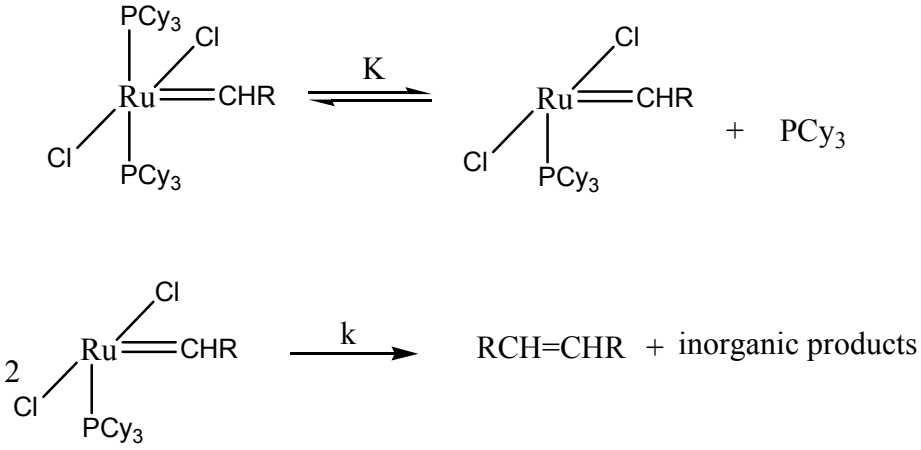
Complex	^1H NMR Ru=CH	^{13}C NMR RU=C	^{31}P NMR
$RuCl_2(=CHPh)(PCy_3)_2$ [b]	20.02 [b]	294.72 [b]	36.6 [b]
$RuCl_2(=CHEt)(PCy_3)_2$ [b]	19.12 [b]	322.59 [b]	36.4 [b]
$RuCl_2(=CHOEt)(PCy_3)_2$	14.39	276.86	37.4
$RuCl_2(=CHSEt)(PCy_3)_2$	17.67	281.60	32.9
$RuCl_2(=CHPh)(PCy_3)(IMes)$	19.91	295.26	34.9
$RuCl_2(=CHOEt)(PCy_3)(IMes)$	13.81	277.50	35.0
$RuCl_2(=CHPh)(PCy_3)(H_2IMes)$ [b]	19.16 [b]	294.24 [b]	31.4 [b]

[a] Unless otherwise noted, CD_2Cl_2 was used as solvent. [b] Solvent C_6D_6. [c] Complex was only slightly soluble in C_6D_6

Ulman reported the study on thermodynamic decomposition pathways for several ruthenium carbene-based alkene metathesis catalysts. [80] Although the benzylidene complex $RuCl_2(=CHPh)(PCy_3)_2$ is used to initiate most metathesis reactions, the propagating species in RCM, [76] is usually either an alkylidene, $RuCl_2(=CHR)(PCy_3)_2$ with R from the alkene substrate, or the methylidene, $RuCl_2(=CHCH_2)(PCy_3)_2$ since the phenyl of the starting carbene is lost in the first turnover. To gain insight in the decomposition pathway the NMR spectra of these reaction mixtures were studied.

^1H NMR spectrum of the decomposition of propylidene showed the presence of minute signals at -7 ppm suggesting the presence of some ruthenium hydrides. Combining other ^1H NMR information, a possible explanation for the formation of new olefin and the new carbene can be provided. The ^{31}P NMR spectrum of the propylidene decomposition reaction mixture showed that

the predominant product was free PCy_3, but a number of other small unidentifiable phosphine signals also grew in over the course of the decomposition. [80] The above observations are consistent with a decomposition mechanism involving dissociation of a phosphine followed by coupling of the two monophosphine species (Scheme 1.17). The build-up of the free phosphine as the decomposition progresses is expected to inhibit the formation of monophosphine species and retard the rate of decomposition.



Scheme 1.17 Proposed pathway for alkylidene decomposition.

Assuming a pre-equilibrium in the first step and the formation of n moles of free phosphine for every mole of $RuCl_2(=CHPh)(PCy_3)_2$, the following rate equation was deduced for alkylidene decomposition:

$$\frac{d[conc]_t}{dt} = \frac{Kk}{n^2} \frac{[conc]_t}{([conc]_0-[conc]_t)^2}$$

$$f(conc)=2([conc]_0 Ln)\frac{[conc]_n}{[conc]_t} + \frac{([conc]_t-([conc]_t+[conc]_0)}{[conc]_0)} \frac{}{[conc]_t}$$

$$=\left(\frac{Kk}{n^2}\right) t$$

Where $[conc]_t$ is the concentration of the alkylidene at time t, $[conc]_0$ is the initial alkylidene concentration, K is the equilibrium constant for the first step and k is the rate constant for the second step (Scheme 2.8). Integration of the first equation produced the second equation.

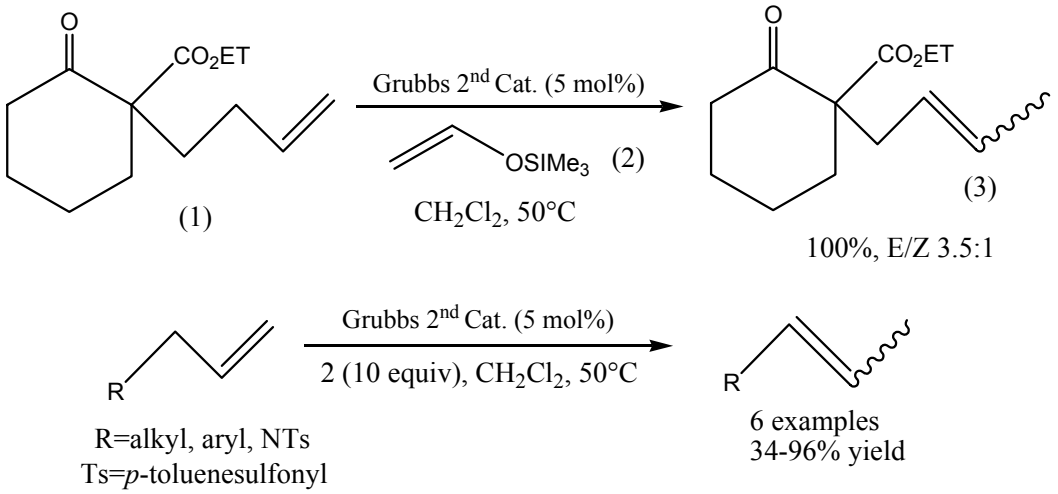
The ruthenium 2nd generation Grubbs catalyst could efficiently mediates the isomerization of β,γ-unsaturated ethers and amines to the corresponding vinyl ethers and enamines. [67] This complex is the most efficient ruthenium metathesis catalyst to date, displaying substantial enhancements

in both activity and versatility when compared to its predecessors. [74, 92-95] It exhibits the ability to metathesize olefins that are essentially unreactive when using either Grubbs' 1st generation or Schrock's molybdenum catalysts. [76, 96]

Taylor has investigated ruthenium-mediated diene metathesis applied to the synthesis of a range of oxocenes in CH_2Cl_2 and found the occurrence of alkene isomerization during the procedure. He explained this phenomenon with the residual acidity of the solvent and suggest to replace C_2H_2 by diethyl ether to prevent isomerization. [97]

Later, Nolan reported their investigation on the RCM of substrates requiring high temperature and extended reaction time. They noticed significant isomerization of one of the double bonds in the starting diene with the 2nd generation of Grubbs and point out that the ruthenium catalyst coordinated to the less sterically crowded alkene. [96]

The use of the Grubbs 2nd generation catalyst for general olefin isomerization was reported by Nishida and co-workers in 2002. [65] During the attempted cross-metathesis of alkene (1) with silyl enol ether (2), an unexpected reaction occurred, which resulted in the selective isomerization of the terminal olefin to give the corresponding propenyl species (3). (Scheme 1.18) Recently, Donohoe and Rosa applied this method in synthesis (-)-allosamizoline.[98] The discovery that ruthenium metathesis catalysts can be used in the isomerization of terminal olefins is potentially very useful in synthesis, especially in cases where the introduction of a vinyl or propenyl substituent is problematic.



Scheme 1.18 Isomerization of terminal olefins by a Grubbs 2nd generation catalyst.

Both Grubbs' 2nd generation and Hoveyda-Grubbs' ruthenium alkylidenes are shown to be effective catalysts for cross-metatheses of allylic alcohols with cyclic and acyclic olefins, as well as isomerization of the resulting allylic alcohols to alkyl ketones. The net result of this tandem methodology is a one-pot process that provides highly functionalized, ketone-containing products from simple allylic alcohol precursors.[99]

It was found that the N-heterocyclic carbenes (NHC) ligated and the ruthenium complex promotes extensively isomerization for both internal and terminal alkenes at 50-60°C.[56] Lehmann et al. [56] reported that 1-octene catalyzed by 2nd generation Grubbs catalyst resulted in a mixture of products. Whether the catalyst had been purified by column chromatography or not a similar mixture was always obtained. It suggested that alkene isomerization is promoted by the catalyst itself or a species formed *in situ* during the metathesis reaction. Simultaneous alkene isomerization and metathesis easily describe the formation of such a product mixture of 1-octene.

When 2-octene was taken as substrate, the reaction proceeded in an analogous manner as using 1-octene to produce a complex mixture of isomerization and metathesis products, although the rate of isomerization for 2-octene is slower than for 1-octene. This suggests that the methylidene complex is not solely responsible for the isomerization. However, just one isomerization step in the reaction of 2-octene using Grubbs 2nd generation catalyst could provide 1-octene, which could finally generate a methylidene complex via metathesis.

From several experimental observations, Lehman et al. conducted a study to determine that isomerization occurs as a side reaction during ADMET polymerization applying Grubbs 2nd generation catalyst. In the context of ADMET, isomerization of a terminal to an internal olefin followed by productive metathesis step with a terminal olefin would liberate an α-olefin such as propene or 1-butene. Isomerization occurs concurrently with metathesis to produce a mixture of linear olefins of consecutive carbon numbers. In case of linear internal olefin, if the metathesis products remain in the reaction mixture, a statistical distribution of reactant and product molecules is eventually the result.

Recently, a RCM-double bond isomerization-cyclopropanation triple tandem process has been discovered in which simple acyclic substrates can be transformed into bicyclic compounds. This process is catalyzed by Grubb's 2nd generation catalyst without the requirement of other reactives or additives. In addition, a one-pot RCM-isomerization reaction followed by a cyclopropanation using $CHCl_3$/NaOH allows the synthesis of products related to NOS (nitric oxide synthase) inhibitors, which are currently under clinical evaluation.[100]

1.3.2.2 Olefin isomerization with Ru carbonyl/carboxylates

After years of development, a great number of Ru(II) carbonyl complexes have been studied as isomerization catalysts. [64] (see Table 1.4)

Table 1.4 Part of summary of Ruthenium(II) carbonyl catalyst for isomerization reaction.

Catalyst Precursor	Substrate	Products
$[RuCl_2(CO)_2(PPh_3)_2]$	*trans*-cyclodecene	*cis / trans* – cyclodecene
	1, 5 – cyclooctadiene	1, 3 – cyclooctadiene
$[RuCl_2(CO)_2(PPh_3)_2]$	1-octene	Mainly 2-octene
$[RuCl(CO)_3(\eta\text{-}C_3H_5)]$	1-hexene	*cis / trans* 2-hexene
	1-butene	*cis / trans* 2-butene
	N-allylamides	N-(1-propenyl)amides
$[Ru_4(CO)_8(MeCO_2)_4(PBu_3)_2]$	1-hexene	2-hexene
$[Ru_2(CO)_4(MeCO_2)_2(PBu_3)_2]$	1-hexene	2-hexene

Frequently, phosphine-substituted ruthenium carbonyls have often been used as catalytic precursors in reactions such as the hydrogenation or the hydroformylation of olefins. The behavior of a series of phosphine substituted ruthenium carbonyl carboxylates $Ru(CO)_2(MeCO_2)_2(PBu_3)_2$, $Ru_2(CO)_4(MeCO_2)_2(PBu_3)_2$ and $Ru_4(CO)_8(MeCO_2)_4(PBu_3)_2$ in the presence of 1-hexene has been investigated by Salvini. [101] The complexes $Ru_2(CO)_4(MeCO_2)_2(PBu_3)_2$ and $Ru_4(CO)_8(MeCO_2)_4(PBu_3)_2$ react at room temperature with a large excess of 1-hexene giving the $Ru_2(CO)_4(MeCO_2)_2(PBu_3)$(hex-1-ene) compound at 80 °C, while mononuclear $Ru(CO)_2(MeCO_2)_2(PBu_3)_2$ is not transformed under these conditions, even after an extended reaction time (6 days) at 80°C.

Catalytic tests performed at 80°C in the presence of $Ru_4(CO)_8(MeCO_2)_4(PBu_3)_2$ or $Ru_2(CO)_4(MeCO_2)_2(PBu_3)_2$ indicate that these complexes display almost the same catalytic activity in the isomerization of 1-hexene which is in agreement with the formation of the same intermediate. In the presence of $Ru_4(CO)_8(MeCO_2)_4(PBu_3)_2$, after 70h at 80°C, a conversion of 85% was obtained. In case of *cis*-3-Hexene, after 6 h, the conversion did not exceed 1% ! This behavior was ascribed to the kinetic and thermodynamic control of the reaction. The *cis*-isomer initially formed by elimination from the Ru complex is subsequently isomerized to the thermodynamically more stable *trans*-isomer. A reaction scheme has been suggested to rationalize the behavior of these complexes.

From the activity of the ruthenium carbonyl carboxylates in the catalytic isomerization of 1-hexene, an indication of the coordinating ability of these complexes was provided toward linear olefins.

When using a terminal olefin as substrate, a π-olefin metal complex could be obtained in the first reaction step. By activation of a hydrogen atom on the carbon atom in α-position with respect to the double bond resulted in the formation of an π-allylic system. Addition of the M-H bond to one of the carbon atoms of the allylic systems gives rise to either the initial π-metal complex or to another π-metal complex containing the isomerized olefin. The internal olefin formed is thereafter replaced in the complex by the terminal one minimizing the steric hindrance, thus producing a stable complex.

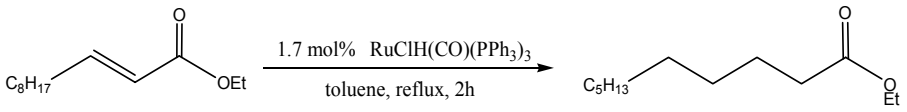
In order to collect evidence on the coordination of the olefin as a preliminary step for these reactions Salvini have investigated the isomerization of 1-hexene in a hydrocarbon solvent applying the phosphine-substituted ruthenium carbonyls $Ru(CO)_3(PR_3)_2$, $Ru_3(CO)_9(PR_3)_3$ and $Ru(CO)_2(OAc)_2(PR_3)_2$ (R = Bu, Ph) as catalysts. [102]

When using $Ru(CO)_3(PPh_3)_2$, the reaction rate shows a partial first order with respect to the concentration of the catalyst and substrate. The reaction rate significantly changes if an alcohol is used as solvent and this behavior is attributed to a modification of the catalytic precursor with formation of a ruthenium hydride. The isomerization was retarded by the presence of an 'additional gas' such as nitrogen gas. This influence is more evident than the analogous one reported in the hydroformylation reaction. Salvini et al. also observed that these Ru(0) complexes are catalytic active for the isomerization of 1-hexene to 2-hexene and 3-hexenes whereas the Ru(II) complexes $Ru(CO)_2(OAc)_2(PnBu_3)_2$ and $Ru(CO)_2(OAc)_2(PPh_3)_2$ showed little or no isomerization activity.

It has been reported that the three component system $Ru_3(CO)_{12}$/1,3-bis(2,6-diisopropylphenyl) imidazolinium chloride/Cs_2CO_3 (molar ratio 1:3:6) successively promotes both allyl to vinyl isomerization and Claisen rearrangement (tandem reactions) from allyl, homoallyl and diallyl ethers to afford γ, δ-unsaturated aldehydes in a selective manner.[103] An unexpected catalyst $Ru(methallyl)_2(COD)$ was found to perform the above reaction without additional ligands or reagents. [104]

1.3.2.3 Olefin isomerization with Ru hydride complexes.

In 1970, James reported that in the absence of H_2, the complexes $RuLH(PPh)_3$ (L=Cl or $OCOCF_3$) could very slowly isomerizes 1-hexene to 2-hexene in solution,[105] Ruthenium hydride compounds have been developed as a large group of complexes who have well-known isomerization capacity. The complex $RuHCl(CO)(PPh_3)_3$, [106] although it has seldom been used as an isomerization catalyst in organic synthesis, usually affords a mixture of alkene isomers. [107] Recently it has been employed in an isomerization-RCM approach to heterocycles. [108-110]



Scheme 1.19 Isomerization reaction catalyzed $RuClH(CO)(PPh_3)_3$.

1) *In situ* generated ruthenium hydride species

It was proposed that the ruthenium species responsible for the isomerization was a ruthenium hydride generated *in situ*. Actually conversion of ruthenium complexes to ruthenium hydride complexes by organometallic transformations *in situ* opens up interesting synthetic perspectives. The use of a this kind of ruthenium hydride provides especially mild and effective conditions that ensure that the olefin is not hydrogenated and that the terminal olefin is only isomerized to the adjacent position.[111]

Previously, it has been noted that the alkene isomerization reaction may interfere with alkene metathesis reactions as an undesired side reaction. [112, 113] It was discovered that Grubbs catalyst can catalyze the hydrogenation of the C=C formed in the metathesis under hydrogen pressure after metathesis reaction. [114] The hydrogenation reactivity of the ruthenium carbene in the reaction originates from a hydrogenolysis of the carbene complex to a ruthenium hydride species. By investigating the conversion of allyl ethers to cyclic enol ethers using a tandem metathesis/ isomerization reaction, the assumed mechanism has been described.[115, 116]

For years, the goal was to develop catalysts that were highly selective for a single transformation. However, a promising current area of research is the use of a single catalyst to mediate more than one transformation in a selective manner. That means the double-bond isomerization might even change from undesired side reaction to a preferred or exclusive pathway. [67] By treatment of the ruthenium metathesis catalysts with hydrogen, [75] inorganic hydrides, [85, 86] and sodium hydroxide-2-propanol, the decomposition of these catalysts to form a ruthenium hydride for use in olefin-isomerization occurred. [117] The tandem metathesis-isomerization reactions are the way to beat two birds with one metallic stone. It is also clear that when the metathesis ring closure event is relatively slow due to large ring size or conformational issues, RCM-isomerization reaction occurs. [83]

The synthetically useful tandem RCM-isomerization reactions have been developed independently by Snapper et al. and by Schmidt.

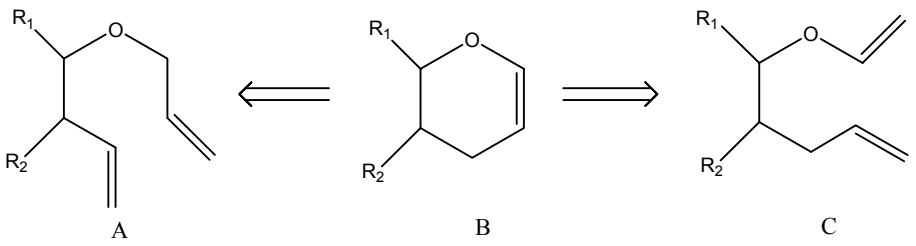
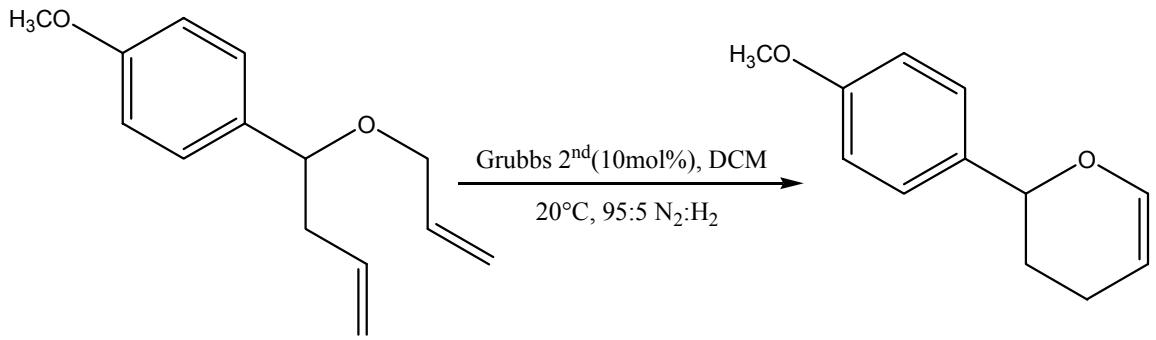


Figure 1.7 Tandem approach (A to B) and enol ether metathesis approach (B to C) for cyclic enol ether.

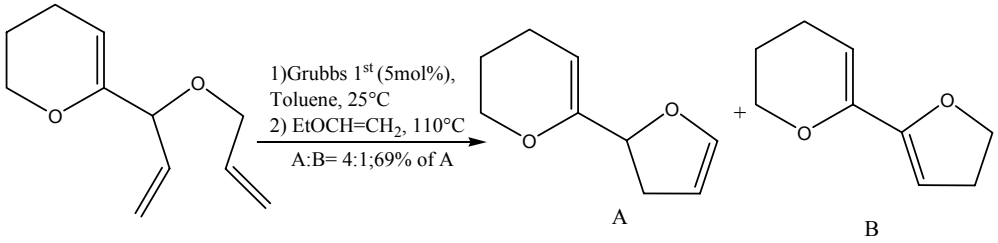
Snapper has reported the metathesis-isomerization reaction for the synthesis of cyclic enol ethers in which the metathesis catalyst was converted by hydrogen after metathesis has ceased, into an uncharacterized isomerization catalyst.[75] The study revealed that treatment of the ruthenium alkylidene in CH_2Cl_2 with small amount of H_2 leads in a reproducible way to an alkene isomerization-active catalyst. They used a 95:5 mixture of nitrogen and hydrogen to replace the inert gas atmosphere to permit isomerization of the primary metathesis products . (Scheme 1.19)



Scheme 1.20 Snapper's protocol for a tandem RCM-isomerization sequence.

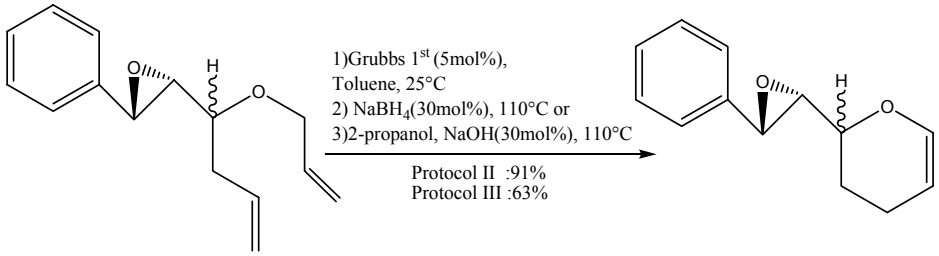
Schmidt's approach to overcome the difficulty was to avoid the addition of molecular hydrogen using other "chemical triggers" to promote the conversion of Ru-carbenes to Ru-Hydrides *in situ*. In 2004, Schmidt demonstrated the efficient syntheses of five-, six-, and seven-membered cyclic enol ethers by a tandem reaction which relies on the conversion of a metathesis-active ruthenium carbene species to an isomerization-active ruthenium-hydride species *in situ* [118] Four different additives or additive combinations (protocols I-IV) have been identified. [119] (Scheme 1.21-1.23)

Protocol I[119] is the addition of ethyl vinyl ether to a completed metathesis reaction in toluene with subsequent heating to reflux induces isomerization of the primary metathesis products to cyclic enol ethers. However, this protocol is limited to five-membered ring systems as exemplified in Scheme 1.21.



Scheme 1.21 Schmidt's protocol I for a tandem RCM-isomerization sequence.

In protocol II, [88, 89] ruthenium carbene complexes were activated to catalyze the double bond migration step by addition sub-stoichiometric amount of inorganic hydride sources, such as NaH or $NaBH_4$.[120] Under these conditions, the direct conversion of allyl ethers to five-, six-, and seven-membered cyclic enol ethers using an olefin metathesis/double bond migration sequence was achieved in preparatively way with useful yields and selectivities. (Scheme 1.22) Protocol III [83, 86]uses 2-propanol as a co-solvent in combination with NaOH in sub-stoichiometric amount. Compared to protocol II, the reaction times are significantly reduced and a broader tolerance toward functional groups is observed. This protocol is also highly regioselective for the less-substituted isomers. (Scheme 1.22) Later, this method has been developed to access side chain by starting from glyceraldehyde, structurally and stereochemically diverse dihydrofurans and dihydropyrans with a 1,2-dihydroxyethylene. [121]

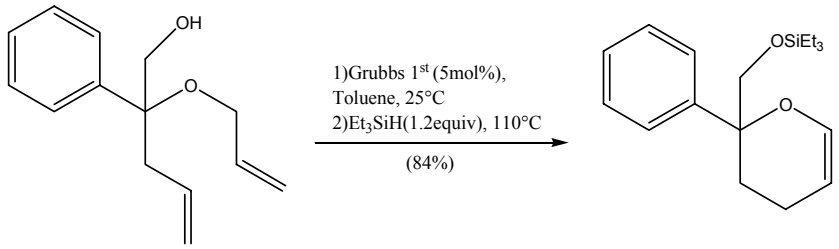


Scheme 1.22 Schmidt's protocol II and III for a tandem RCM-isomerization sequence.

Protocol IV[119] relies on the addition of triethylsilane to the reaction mixture after completion of the metathesis step. This leads not only to an isomerization catalyst, but allows the extension of the sequence by an additional Ru-catalyzed step, which is followed by a dehydrogenative silylation of the primary alcohol [122] and finally a double-bond isomerization to yield the silylated cyclic enol ether. (Scheme 1.23)

The group discussed the synthesis of pent-4-enals selectively from diallyl- and allyl homoallyl ethers and the scope and limitations of tandem RCM-isomerization sequence for the synthesis of cyclic enol ethers using Grubbs' catalyst.[123] Recently, the tandem RCM-isomerization reaction

has been used as the key step to synthesize 3,6-dideoxyglycals de novo as single isomers starting from ethyl lactate [124] and deoxy glycals from a mannitol-derived C-2-symmetric diene diol. In the later synthesis, incorporation of a ruthenium-catalyzed dehydrogenative silylation step into the reaction sequence is possible. Thus, an orthogonally protected 3-deoxy glycal results via a tandem RCM/hydrosilylation/isomerization sequence. [125]



Scheme 1.23 Schmidt's protocol IV for a tandem RCM-isomerization sequence.

Bressy also reported that starting from readily available substrates, a tandem RCM-isomerization procedure has been devised to prepare polycyclic lactams and sultams. Isomerization was promoted by ruthenium hydride complexes. [126]

Isomerization-claisen transformation reaction is another type of double bond isomerization tandem reaction. [103, 127]

Some efforts have been made to identify the active species responsible for the isomerization reactions since various hydride species are thought to be involved. In 2003 Dinger et al. has described an initial study of degradation of 1st and 2nd Grubbs generation metathesis catalyst to generate hydrides. [97, 98] (Scheme 1.25(B))

When the catalyst $RuCl_2(=CHPh)(PCy_3)_2$ was reacted with an excess of methanol in toluene at 70 °C for 2 days, the initially purple red solution gradually became clear dark orange. The progress of the reaction was monitored by ^{31}P NMR which showed the slow disappearance of the signal at δ 37.3 ppm from $RuCl_2(=CHPh)(PCy_3)_2$ concomitant with the emergence of a new peak at δ 47.4 ppm. Similarly, in the ^1H NMR, the benzylidene resonance from $RuCl_2(=CHPh)(PCy_3)_2$ at δ 20.6 ppm was gradually replaced with a hydride signal at δ -24.3 ppm. Whereas ethanol and propanol were found to readily generate the hydride, 2-propanol and water were found to be ineffective. [128]

$RuH(PCy_3)_2Cl(CO)$ as decomposition product of 1st Grubbs catalyst is a highly efficient double bond isomerization catalyst of 1-octene at various temperatures. The catalyst showed a high degree of selectivity to form 2-octene, even when a high conversion was attained. A reaction of 88000 mol equivalent of 1-octene with this catalyst at 100 °C gave 97% conversion together 92% selectivity for 2-octene after 3 hour. At 120 °C, selectivity was compromised, decreasing to 50%

after 3 hours. The *cis:trans* ratio of 2-octene was independent of the reaction temperature. At higher temperature more isomerization occurred. The yield of 3-octene was relatively high which imply that 2-octene did not decompose the catalyst. The decomposition of the active catalyst largely attribute to the decrease in selectivity over time.[128]

Catalyst $RuH(PCy_3)Cl(CO)(IMes)$ obtained from the decomposition of 2nd Grubbs by the treatment with methanol in the presence of triethylamine [129] has been characterized by ^1H and ^{31}P NMR.[130] It was found that the 2nd generation system was more active and the reaction proceeded readily at lower temperature. NHC ligands in ruthenium systems generally show stronger covalent bonds than phosphines, and so the latter tend to dissociate.[13]

Hanessian et al. reported an efficient method for the isomerization of terminal olefins with minimal self-dimerization or cross-metathesis by employing methanol to generate the same hydride *in situ*. The reaction was successful for the isomerization of a variety of allylic compounds and produces the corresponding propenyl species as *E/Z* mixtures of isomers. Even substrates that had proven to be difficult to isomerize by other methods could be transformed into the desired products under these conditions. For instance, the electron-deficient aryl compound pentafluoroallylbenzene was isomerized to pentafluoro(*trans*-methylstyrene) in 80% yield.[131] Recently, this procedure was employed by Willis and co-worker in total sythesis of clavosolide D.[132]

The isomerization of terminal olefins has proven to be a versatile approach to the synthesis of natural products. In 2005, Wipf and Spencer reported the first total synthesis of (1)-tuberostemonine.[133] The isomerization of the terminal olefin helps the achievement of end product. In 2006, Bohrsch and Blechert also employed a terminal-olefin isomerization in the synthesis of (-)-centrolobine.[134] The ruthenium hydride generated by converting the metathesis catalyst with sodium borohydride generated a hydride that exclusively isomerized the terminal olefin to the desired end product.

In 2008, Trost reported that readily available indenylbis(triphenylphosphine)ruthenium chloride in conjunction with an indium co-catalyst (indium triflate) and Bronsted acid (camphorsulfonic acid) isomerized primary and secondary propargylic alcohols in good yields to provide *trans* enals and enones exclusively. Deuterium labeling experiments suggest that the process occurs through hydride intermediate.[135]

2) Olefin isomerization with ruthenium hydrido complexes

In the very early period, $RuHCl(PPh_3)_3$ has been reported to isomerize pent-1-ene to *cis*-pent-2-ene (60%) and *trans*-pent-2-ene (40%) at 50° in benzene in 1972. Isomerization of deuterium-labeled pent-1-ene has revealed (i) that equilibrium is established between uncoordinated and

coordinated pent-1-ene, (ii) that redistribution of deuterium in pent-1-ene accompanies its isomerization, (iii) that normally isomerization involves the movement of the double bond to the adjacent position only, (iv) that *cis*-and *trans*-pent-2-ene are each formed by a mechanism involving a pentyl intermediate,(Scheme 1.24) (v) that a mechanism involving a π-allylic intermediate also contributes to the formation of the *trans*-isomer, and (vi) that some processes require the formation of transient species having two hydrogen atoms as ligands of ruthenium and in which two phosphine ligands have been lost by dissociation. [136]

Scheme 1.24 Pentyl intermediate.

Bingham has reported that a higher catalyst concentration favored the formation of the *cis*-olefin, while a lower concentration of catalyst resulted in more *trans*-isomer. The change in selectivity is not a result of a changment of the mechanism, but of a progressive decongestion of the catalytic site by a gradual increase of the dissociation degree of the catalyst by loss of PPh_3 ligands.[38]

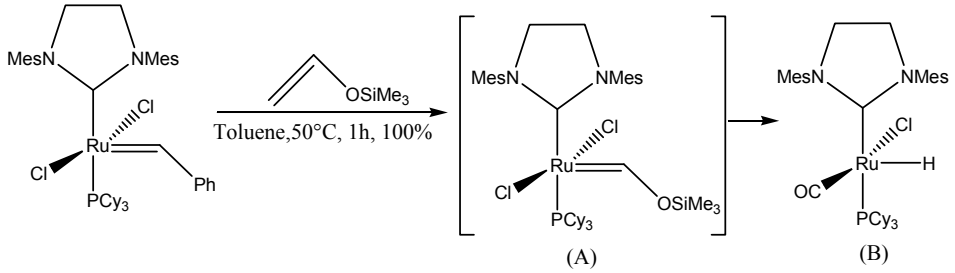
$RuH_4(PPh_3)_3$ and $RuH_2(N_2)(PPh_3)_3$ were taken as the catalysts for isomerization of 1-pentene at 25 °C in toluene solution. The reaction could be divided into two steps: initially, it proceeds very fast and then the rate quickly declines. Both of the reaction rates inhibited by N_2 since the N_2 competed with the olefin to coordinate on the ruthenium. [137]

Furstner et al. has isolated a ruthenium dihydride complex, $RuCl_2(H)_2(PCy_3)_2$ which may be responsible for olefin isomerization, presumably through a hydride mechanism.[83]

From $RuHCl(CO)(PPh_3)_3$, the hydrido-ruthenium complexes $RuHCl(CO)(NHC)(PPh_3)$ (NHC = IMes, H_2IMes) was accessed conveniently and exhibited high activity for hydrogenation of unactivated internal olefins and isomerization of terminal olefins. [138] While the precursor $RuClH(CO)(PPh_3)_3$ used simultaneously with Grubbs catalyst the isomerization-metathesis tandem reactions were facilitated when sterically congested 1,9-dienes were applied. Compared with this, for the same substrate, efficient double bond isomerization-RCM reaction was observed when only Grubbs ruthenium catalyst was used. [139, 140]

Nolan, [130] Grubbs [141] and their co-worker have isolated a ruthenium hydride (Scheme 1.25(B)), but its full potential as an isomerization catalyst was not exploited. [142] In 2006, Nishida and co-workers reported that in the presence of a silyl enol ether, the Grubbs 2nd generation catalyst forms a Fischer carbene complex (Scheme 1.25(A)), which decomposes to afford a ruthenium

hydride complex (Scheme 1.25(A)). [143] This active hydride adds reversibly to the olefin and promotes the isomerization of the terminal olefin by one atom. [144] Presumably, the reaction stops with the double bond at this position due to steric reasons.



Scheme 1.25 Conversion of Grubbs 2nd generation catalyst into ruthenium hydride

Recently, the activity of $RuHClH_2(PCy_3)(L)$ 2a/b and $RuHCl(CO)(PCy_3)(L)$ 3a/b (a: L = PCy_3; b: L = 1,3-dimesitylimidazol-2-ylidene) was assessed in isomerization of allylbenzene. Under these conditions, 3a/b outperform their dihydrogen analogues in both total productivity and turnover frequencies, despite theoretical and experimental evidence that the π-acid CO ligand should be deactivating. A thermolysis study reveals that the CO complexes are much less susceptible to deactivation under conditions relevant to catalysis (also, the IMes derivative 2b has a shorter life time than 2a).[145]

1.4 Factors influencing the isomerization reaction

Recently, the state-of-the-art ruthenium olefin metathesis catalysts have attracted widespread attention not only as highly active catalysts but also due to the compatibility with most functional groups and ease of use. Many new applications have become possible because of major advances in catalyst design. Since these catalysts are also reported to isomerizes olefin, here we particular emphasis on $(PCy_3)_2Cl_2Ru{=}CHPh$ and its derivatives ($RuX_2(=CHPh)L_2$) to discus the factors influencing the isomerization reaction.

1.4.1 Catalytic activity and selectivity

The identity of X- and L-type ligands is one of the most important factors influencing the activity of $RuX_2(=CHPh)L_2$. It was found that more sterical and more electron-donating phosphines resulted in higher catalyst activity, contrariwise, the larger and more electron-donating halides the lower the catalyst activity. One of the contributions of the phosphine ligand is σ–donation to the metal center, which promotes formation of the mono phosphine alkene complex by facilitating phosphine dissociation and stabilizing the vacant *trans* site in the $16e^-$ intermediate. σ–Donation also helps to stabilize the $14e^-$ metallacyclobutane intermediate. [146]

1.4.2 Relative steric effects

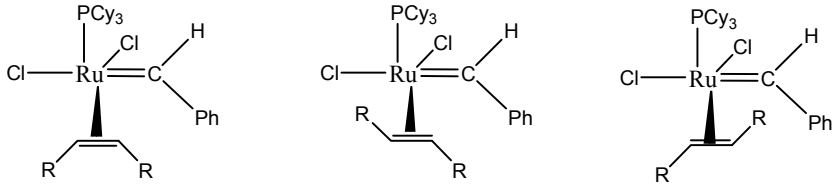
Considering the steric effects, the phosphine ligands are easily to control . This ability to control the bulk of the ligand permits the fine-tuning of the reactivity of the metal complex. The steric bulk of the ligands may stimulate to phosphine dissociation by de-stabilizing the crowded bis(phosphine) alkene complex. PCy_3, is a more basic and bulkier phosphine (Table 1.5) resulting in an easier phosphine decoordination.[146]

Table 1.5 Cone angles for some common phosphine ligands.[147]

Phosphine Ligand	Cone Angle
PH_3	87°
PF_3	104°
$PF(OMe)_3$	107°
PMe_3	118°
PMePh	122°
PEt_3	132°
PPh_3	145°
PCy_3	170°
$P(t\text{-}Bu)_3$	182°
$P(mesityl)_3$	212°

From the investigation of Ulman and Grubbs, it can be declare the most active carbenes are the alkylidenes. The experimental data about the relative activity of the carbenes was supported by the function of their electronic and steric properties. Their electron-donating properties and their relative size help to dissociated the phosphine and speed up reaction. The least active carbene-methylidene lacks both the size and the electron-donating ability. The benzylidene is an intermediate case where the resonance of the phenyl ring is somewhat electron-withdrawing while the size of the ring helps to dissociate a phosphine. [148]

After examining the relative rates of *cis*- and *trans*-alkenes, it was found that the benzylidene reacted approximately twice as fast with *cis*-3-hexene as with *trans*-3-hexene. This can be explained by considering the binding of the alkene to the complex (Scheme 1.26). When the *cis*-alkene binds to the metal, the substituents can push away the bulky phosphine. The *trans*-alkene can bind either as 2 or 3; in either case there is an adverse steric interaction with the phosphine.[148]



Scheme 1.26 Olefin complex formation affecting the rates of metathesis of *cis*- and *trans*-alkenes.

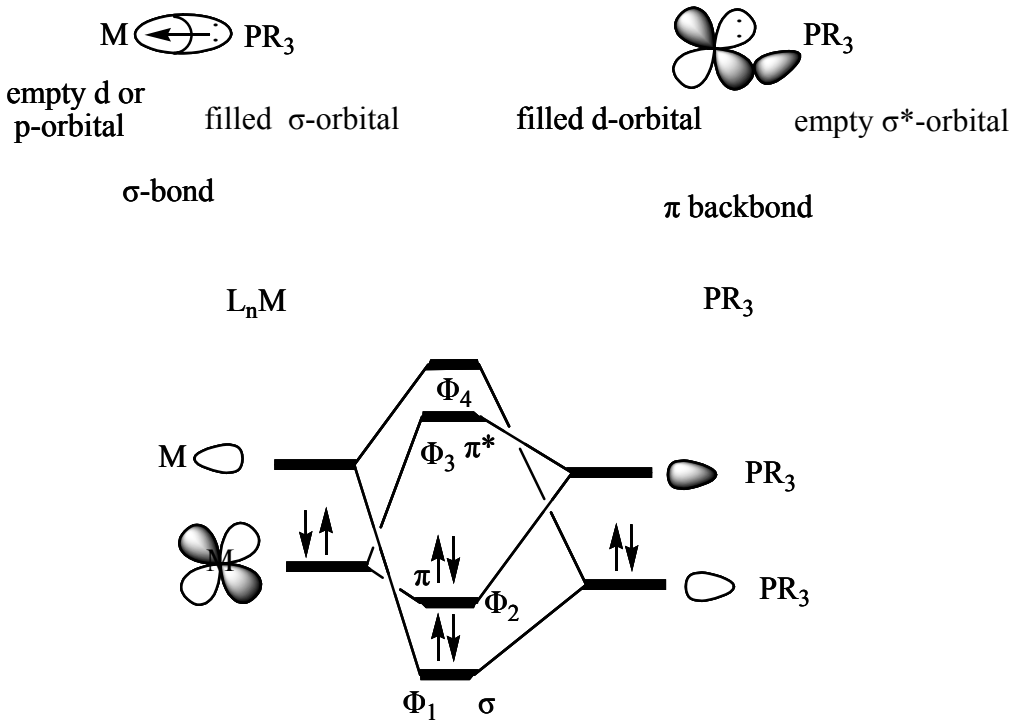
1.4.3 Electronic effects

There are two bonding mode for phosphine ligands. σ-Donation of the phosphine lone pair to an empty orbital on the metal is the primary component. The second component is back-donation from a filled metal orbital to an empty orbital on the phosphine ligands (Scheme 1.27). The empty phosphorus orbital has been described as being either a d-orbital or an antibonding σ-orbital.[147]

When there are electronegative groups on the phosphorus atom, the σ-donating capacity of the phosphine ligand tends to decrease. Meanwhile, the energy of the π-acceptor on phosphorus is lowered in energy, providing an increase in backbonding ability. For that reason, phosphine ligands can show a range of σ-donor and π-acceptor capabilities, and the electronic properties of a metal center can be tuned by the substitution of electronically but different isomeric phosphines.[147]

Comparing with phosphines, a contrast trend of the halide ligands was found. The halide ligands correlate with the decreasing activity as they become larger and more strongly electron-donating, in the order Cl, Br>>I. Because the coordination olefin may initially bind *trans* to a halide, a more electron-donating halide should weaken the ruthenium-alkene bond and disfavor olefin coordination. These small changes in the steric and electronic character of the ligands combined with the influence of olefin binding, phosphine dissociation, and the stability of the intermediates, results in large variations of catalyst activity. [146]

Furstner, Werner and Grubbs et al. have reported these systematic investigations on the factors governing the catalytic activity of ruthenium carbenes. It can be deduced for phosphine ligands, that the electron-donating one with large cone angles lead to particularly active catalysts, such as PPh_3<<$P(^iPr)_2Ph$ <PCy_2Ph<$P(^iPr)_3$<PCy_3. While for halide ligands, an opposite order was obtained that an increasing activity determined by the anionic ligand I<Br<Cl. i.e., the smaller and more electron-withdrawing chloride leads to the most active species. [77, 149]



Scheme 1.27 Molecular orbital diagram showing the bonding and antibonding tendency between the metal and the phosphine ligand.

In general, the activity also depends on catalyst initiation and on the nature of the alkylidene moiety. Commonly, compared with methylidene complex, alkyl-substituted alkylidenes display more efficient initiation. The benzylidene seems to be the intermediate case, the phenyl group is somewhat electron withdrawing, but its size may assist phosphine dissociation. [146]

Under certain catalytic conditions, the various catalysts show different lifetimes which is also an important factor in the overall activity. By comparing the kinetics of the thermal decomposition of various catalysts, it was revealed that substituted alkylidene complexes decompose by a different mechanism than the methylidene complex. For substituted alkylidenes, the observations are consistent with a bimolecular decomposition mechanism involving phosphine dissociation followed by coupling of monophosphine species, while the methylidene complex decomposes through a uni-molecular pathway that is independent of concentrations. So, the relative stabilities of the initiating and propagating species can directly influence the catalyst activity. [146]

Solvent is also a factor that can influence the isomerization behavior of the catalysts. For instance, optimum conditions for the metathesis of internal alkenes in the presence of $RuCl_2(=CHPh)(PCy_3)_2$ were found in dichloromethane and dichloroethane solutions. The reaction proceeded with high selectivity to primary metathesis products, while the final *trans/cis* ratios were the thermodynamic equilibrium values, regardless of the configuration of the substrate.[90]

1.4.4 Relative reaction rates

The relative reaction rates of olefin substrates with ruthenium(II) carbene metathesis initiators were studied by Ulman and Grubbs.[148] The metathesis of terminal alkenes have a different stericity and different geometries as well as electronically different *para*-substituted styrene with the ruthenium based initiator $RuCl_2(=CHPh)(PCy_3)_2$. Bulkier alkenes were found to react slower, and *trans*-internal alkenes were slower than their *cis* counterparts. The kinetic product of all reactions was found to be the alkylidene rather than the methylidene.

1.4.5 Side Reaction (Metathesis)

It is well known that the isomerization reaction produce a thermodynamic stable product via a catalytic process and it has also been recognized as a side reaction in hydrogenation, polymerization, hydroformylation and other reactions catalyzed by organometallic complexes.[54] Herein, the isomerization reaction was discussed as a side reaction in alkene metathesis.

Double bond isomerization has been considered as a major limitation of alkene metathesis since it is the primary cause of secondary metathesis products in metathesis chemistry. (see Table 1.7)

If the produced ethylene is allowed to escape, the metathesis of 1-octene is rendered essentially irreversible otherwise it can be a fully reversible reaction.

During the metathesis reaction, some important figures are impossible to analyze. For instance, since the metathesis events cannot be monitored, the total turnover number for a given catalyst for the metathesis of 1-octene cannot be calculated at any degree of certainty; in addition, the active metathesis catalyst is the phosphine dissociated species, [150] and the concentration of this species at any given time cannot be accurately determined; also the actual number of substrate molecules that have been involved in metathesis by a particular ruthenium center can not be determined. The only figure that can be calculated with any degree of certainty is the effective TON. It is the total number of 1-octene molecules that have converted to metathesis products per molecule of the catalyst precursor. To ensure the highest possible TON, an excess of the substrate should be added [151] what will increase the possibility of isomerization.

Each catalyst has its own decomposition temperature, such as the Grubbs 1st generation catalyst showed a steady increase in TON at elevated temperatures but at 80°C, a sharp drop-off activity was noted and this presumably represents the decomposition temperature of the catalyst. While for the Grubbs 2nd generation catalyst the thermal degradation was induced over 100°C and decrease in TON was observed at 122°C. Since temperature is also a condition for the isomerization, the decomposition temperature of catalyst affected the initiation of the side reaction and its selectivity.

Yield is dependent on not only temperature, but also on reaction time and concentration. For instance, in the case of Grubbs 1st generation catalyst, when all metathesis activity has ceased, the remaining unreacted 1-octene was slowly isomerized to produce almost equal parts of 1-, 2-, 3-octene. It could be presumed that the decomposed metathesis initiator becomes a quite efficient double bond isomerization catalyst which has been proved later by Mol. [128]

Table 1.6 Different metathesis products produced during the metathesis of 1-octene.

Reaction	Substrate	Products
Primary metathesis		
Homo-metathesis	$CH_3(CH_2)_6=CH_2$	$CH_3(CH_2)_6=(CH_2)_6CH_3$ + $CH_2=CH_2$
Isomerization	$CH_3(CH_2)_6=CH_2$	$CH_3(CH_2)_5=CH_2CH_3$
Secondary metathesis		
Cross metathesis	$CH_3(CH_2)_6=CH_2$ + $CH_3(CH_2)_5=CH_2CH_3$	$CH_3(CH_2)_6=(CH_2)_6CH_3$ + $CH_3CH_2=CH_2$ $CH_3(CH_2)_6=CH_2CH_3$ + $CH_3(CH_2)_5=CH_2$
Homo-metathesis	$CH_3(CH_2)_5=CH_2CH_3$	$CH_3(CH_2)_5=(CH_2)_5CH_3$ + $CH_3CH_2=CH_2CH_3$
Isomerization	$CH_3(CH_2)_5=CH_2$	$CH_3(CH_2)_4=CH_2CH_3$
Secondary metathesis		
Cross metathesis	$CH_3(CH_2)_5=CH_2$ + $CH_3(CH_2)_4=CH_2CH_3$	$CH_3(CH_2)_5=(CH_2)_4CH_3$ + $CH_3CH_2=CH_2$ $CH_3(CH_2)_4=CH_2$ + $CH_3(CH_2)_5=CH_2CH_3$
Homo-metathesis	$CH_3(CH_2)_5=CH_2$	$CH_3(CH_2)_5=(CH_2)_5CH_3$ + $CH_2=CH_2$
Homo-metathesis	$CH_3(CH_2)_4=CH_2CH_3$	$CH_3(CH_2)_5=(CH_2)_5CH_3$ + $CH_3CH_2=CH_2CH_3$

1.5 Industrial Application

Since the normal linear 1-alkenes' derivatives have a wide range of special applications, for instance, as polyethylene comonomers, plasticizer, synthetic motor oils, lubricants, automotive additives, surfactants, paper size, etc. and featuring highly accessible terminal double bonds they

become the ideal materials for manufacturing numerous products. As major petrochemical building blocks, it has been extensively use in the development of new chemical products and has unlimited prospect.

Double bond isomerization occurs in many cases as an unwanted side reaction in organometallic catalyzed reactions of alkenes, while it is also found in number of important industrial processes, such as the SHOP (Shell Higher Olefin Process) process as an intermediate step. In the SHOP process, the conversion of terminal alkenes to a near-equilibrium mixture of internal alkenes is carried out on massive scale as one step.

The Shell Higher Olefin Process is a chemical process for the production of linear alpha olefins via ethene oligomerization and olefin metathesis invented and exploited by Royal Dutch Shell. [152] Both linear alkenes and linear detergent alcohol can be produced in the SHOP process. The process and its mechanism were intensively studied by the group of Professor Wilhelm Keim at the RWTH Aachen, who is also regarded as one of the key figures in the development of the process. The process was commercialized in 1977 and in 1993 global annual production capacity was ten million tons.

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Chapter 2
Ruthenium Complexes Containing Bidentate Schiff Base Ligands as Homogeneous and Immobilized Catalysts

2.1. Introduction

Schiff base ligands are easily synthesize and generate complexes with almost all metal ions.[1] Many metal Schiff base complexes are potential catalysts that can influence the yield and selectivity in chemical transformations. They have already shown excellent catalytic activity at high temperature and in the presence of moisture.

The catalytic activity of Schiff base complexes boomed the interest in polymerization of olefins [2-6] and allowed the controlled molecular weight polymer obtained from the ring opening polymerization of cycloalkenes at low temperature without any side reaction. [2] For instance, Schiff base complexes of cobalt(II) [3] and chromium(III) [4] were reported to be effective in these reactions with significant enantioselectivity. The complexes of iron(II) with pyridyl bis(imide) and pyridine bis(imine) ligand have been used as catalysts in the polymerization of ethylene and propylene. The phenoxy-imine complexes of zirconium, titanium and vanadium and Schiff base complexes of nickel(II) and palladium(II) were also reported to catalyze the polymerization of ethylene. [1]

Phosphine substitution by *N*-heterocyclic carbene Schiff base ligand has enhanced ring closing metathesis reaction to synthesize functionalized olefins. [5] The phosphine Schiff base complexes also showed improved enantioselectivity in hydrosilylation reactions. [6]

Schiff base complexes showed significant applications in reduction of ketones to alcohols [7] and alkylation of allylic substrates [8] and in carbonylation of alcohols and alkenes at low pressure to produce α-arylpropionic acid and their esters. [9-11] The Heck reaction was successfully catalyzed to synthesize fine chemicals and pharmaceutical by using Schiff base complexes.[17-20] The optically active cyanohydrins were synthesized successfully in the presence of Schiff base complexes of transition metals. [12-14]

Chiral Schiff base complexes are found to be more selective in various reactions such as oxidation, hydroxylation, aldol condensation and epoxidation. The chiral Schiff base complexes of salen [15] and binaphthyl were used as efficient catalysts in the Michael addition reaction. In the presence of Schiff base complexes of copper(II) and manganese(III), the enantiomeric synthesis of aziridines and amides with chiral metalolloporphyrins was improved. [16] The homogeneous chiral lanthanum(III) Schiff base complexes showed catalytic activity in asymmetric Diels–Alder reactions [17] furthermore, the product yield and enantioselectivity were influenced by the nature of the catalysts.[18]

Schiff base complexes played a significant role in desymmetrization of *meso* compounds with significant yield and enantiomeric excess. [19] The enantioselectivity in the cyclopropanation reactions could be also improved by using Schiff base complexes as catalysts. [20-22] The complexes of nickel(II) and copper(II) have increased enantioselectivity in the alkylation of enolates. [23-26]

The isomerization of norbornadiene has been reported by using diimine complexes of rhodium. [27, 28] A serial of ruthenium (III) Schiff base complexes $RuCl(PPh_3)$ $[ONNO]\cdot xH_2O$ ([ONNO] = symmetrical and unsymmetrical Schiff base derivatives) have been studied for the isomerization reaction of selected O-allyl systems, i.e., 1,4-diallyloxybutane and 4-allyloxybutan-1-ol. Some of the complexes showed high efficiency and E-stereoselectivity in double bond migration of the allyl group to 1-propenyl and also in the isomerization of allyloxyalcohol to cyclic acetal high selectivities were obtained.[29] The ruthenium Schiff base complexes $(H_6\text{-acen})Ru(PPh_3)_2$ could serve as a catalyst precursors for the isomerization of 1-hexene.[30] A group of diastereomeric Ru and Os complexes were synthesized and tested as catalysts in the enantioselective isomerization of 2-*n*-butyl-4,7-dihydro-1,3-dioxepin to give 2-*n*-butyl-4,5-dihydro-1,3-dioxepin. Enantioselectivities up to 64% ee were achieved. [31]

In addition to monometallic complexes, the bimetallic Schiff base complexes also showed catalytic activity in carbonylation reactions.[32]

In general, Schiff base complexes not only could catalyze a ring opening polymerization at low temperature but also showed significant activities

in the oxidation of sulfides, thioanisoles, aldehydes, phenol and styrene;
in allylic alkylations;
in hydrosilation;
in the decomposition of hydrogen peroxide;
in the isomerization; and
in the carbonylation reactions.

According to our work, herein, an overview of ruthenium Schiff base complexes focusing on their synthesis and certain application in homogeneous and heterogeneous catalysis is presented.

Over the past few year ruthenium complexes have opened up enormous possibilities for a variety of catalytic organic processes, [33],[34-82]due to great advances in the design and synthesis of efficient and selective catalysts based thereupon. [34-53] Mainly responsible for this progress are recently introduced ligands such as N-hetero- cyclic carbenes. [54-62] Schiff bases, [101-109] other N- or N, S, P, bi- or multidentate donor ligands, [63-65]O-donor ligands etc. [66],[67] When astutely combined with traditional ligands [64, 68] they confer targeted catalytic properties to the resulting ruthenium systems. Some ligands induce unprecedented catalyst tolerance towards organic functional groups, air, moisture and impurities, thus largely expanding the scope of utilization of the corresponding metal complexes. [69-72]Furthermore, examination of the catalytic performance of the structure formed showed that replacement of the ubiquitous phosphine by a Schiff base result in considerable improvement in the activity and thermal stability of the complex.

As one of the most relevant synthetic ligand systems with importance in catalysis, Schiff bases are easily accessible, usually through a one-step procedure *via* condensation of aldehydes with amines, often in quantitative yields. Including the oldest classes of the salen and benzylidene derivatives, Schiff bases have been used extensively in coordination chemistry to build complexes with transition and main group metals. During the last decade a new surge in the field occurred in connection with the disclosure of a multitude of pharmacological applications of Schiff bases in their own right but mostly of their transition metal complexes which are biologically active as antibacterial agents, radiopharmaceuticals for cancer targeting or as anticancer agents, as model systems for biomacromolecules, and as dioxygen carriers. [73]

The proper choice of ligands is key in manipulating the activity and selectivity of catalysts, and Schiff base building blocks, owing to their structural and stereoelectronic diversity, are playing a significant role in ligand optimization strategies. Steric and electronic effects around the Ru centre can be finely adjusted through an appropriate selection of the substituents on the Schiff base unit. Experimental data suggests that the steric bulk of the Schiff base has a greater impact on catalytic performance compared to the electronic influence of the Schiff base substituents. [74] The two donor atoms, N and O, in the ligated Schiff base exert opposite electronic effects: the

phenolate oxygen is a hard donor known to stabilize the higher oxidation state of the ruthenium atom whereas the imine nitrogen is a softer donor and, accordingly, will better stabilize the lower oxidation state of the ruthenium; thus, a flexible interplay between these two binding sites can be achieved. The Schiff base ”dangling” ligand stabilizes the resting state of the catalyst while one coordination site becomes available at elevated temperature or upon addition of an acid co-catalyst which promotes substrate coordination and triggers catalytic activity.

Capitalizing on the highly desirable attributes of this ligand class, several families of Schiff base containing ruthenium complexes, of wide applicability as promoters in diverse organic reactions, have been ingeniously designed and prepared. Some of them, *e.g.* Ru-salen[52, 75] and Ru-porphyrin[76-81] complexes, exhibit good to excellent activity and remarkably high stereoselectivity in organic catalysis.[82, 83]

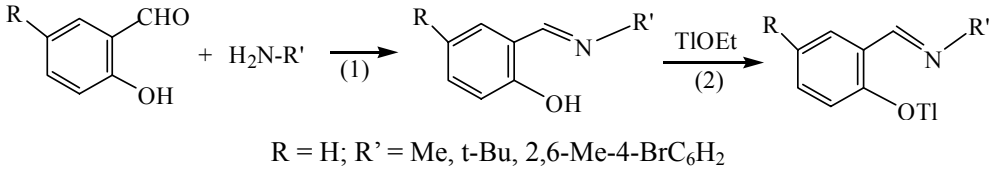
Recently, a wide array of Schiff base ruthenium complexes containing arene, alkylidene, indenylidene, vinylidene and diene ligands have been prepared and characterized in our laboratory. [84-86]The Schiff base approach afforded quite active and stable ruthenium catalysts successfully initiating a variety of organic transformations spanning carbon-carbon, carbon-hydrogen and carbon-heteroatom bond formation. [36, 87] As not long ago only relatively few metathesis catalyst systems based on the Schiff base-Ru concept had been developed, the present paper focuses on the synthetic methodology devised in our group for producing homogeneous and immobilized Ru precatalysts bearing Schiff bases as specific O,N-bidentate ligands. Research in our laboratory was first to systematically explore the field, varying successively each structural element (O,N substituents, ancillary or spectator ligands) on all types of Ru carbenes (alkylidene, vinylidene, allenylidene, indenylidene) creating a large library of structures and placing information about the physical and catalytic properties of these complexes at the disposal of the scientific community. Gratifyingly, our precatalysts exhibited a broad application profile in metathesis and C-C coupling reactions, [87] radical mediated reactions (ATRA, ATRP), enol-ester synthesis, as well as in one-step procedures to access simple heterocycles (furan, pyrrole, thiophene) from diallyl compounds and quinolines *via* modified Friedlander synthesis. [88, 89]

2.2. Arene Schiff base Ru complexes

Schiff bases, providing important diversification of the coordinating sites, are of particular interest in the synthesis of arene ruthenium(II) complexes. Our group first introduced the arene ruthenium complexes **1–3** bearing the bidentate Schiff base O,N bonding system, associated with the η^6-coordinated *p*-cymene moiety. Synthesis succeeded through the well-established two-step procedure employing the commercially available Ru-dimer $[(p\text{-cymene})RuCl_2]_2$ from which one of

the *p*-cymene Ru-units was cleaved by addition of the Tl-salt of an aliphatic or aromatic salicylaldimine. [84, 85] (Scheme **1**)

In the first step the Schiff bases were prepared and purified using conventional methods.[90] In our protocol condensation of salicylaldehydes with aliphatic amines was carried out in THF (at reflux; 2 hr). The resulted crude products (yellow, viscous oils) were purified by column chromatography (silica gel; eluent: 5:1 benzene-THF) affording the salicylaldimines in excellent yields (90-99%). Condensation of salicylaldehydes with aromatic amines was conduted in ethanol (80 °C; 2 hr.) and the products isolated as yellow solids (at 0 °C), which were further purified by washing with cold ethanol and drying *in vacuo* to afford salicylaldimines in quantitative yields. The spectroscopic properties[84, 85] of the Schiff bases in Scheme **1** are in accord with data published earlier.[90]



R = H; R' = Me, t-Bu, 2,6-Me-4-BrC_6H_2

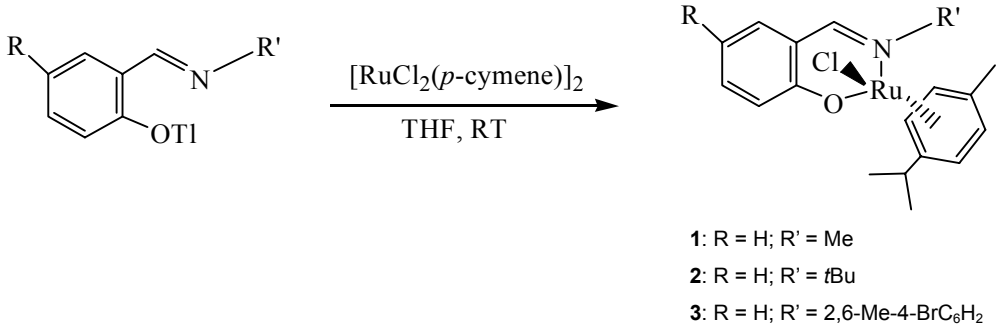
Scheme 2.1. Synthesis of Schiff base thallium salts.

To access the arene ruthenium complexes **1-3**, the above set of Schiff bases were converted into the corresponding thallium salts (yellow solids; quantitative yields) by treatment with thallium ethoxide (in THF, at room temperature, 2 hr., under nitrogen). The salts were filtered under N_2 and then used, without further purification, in the second reaction step with $[RuCl_2(p\text{-cymene})]_2$ in THF, at room temperature for 6 hr. After filtration of thallium chloride and concentration of the filtrate, Schiff base ruthenium arene complexes crystallized as red-brown crystals upon addition of a minimal amount of toluene at 0 °C, and were purified by washing with cold toluene and drying *in vacuo* (Scheme **2**).

The structures of these complexes were unambiguously determined by IR, Raman, H and C-NMR spectroscopy, corroborated by elemental analyses.[84, 85] The most striking structural feature of complexes **1**-**3**, beneficial for their catalytic ability, is that the stronger chelated Schiff base, a non-transferable ligand, is present along with the coordinatively labile *p*-cymene group; easy release of the latter allows formation of the transient carbene species responsible for the metathesis activity. Substituents attached to the N atom in the Schiff base exert an obvious influence on the RCM capacity of catalysts **1**-**3** (Table **1**).

The same substituent-dependant variation of the reactivity profiles holds true in Kharasch addition of polyhalogenated alkanes to methyl methacrylate and styrene promoted by **1**-**3** [84, 85] and also

polymerization reactions, namely ATRP of acrylates, methacrylates and styrene and ROMP of norbornene. [86]

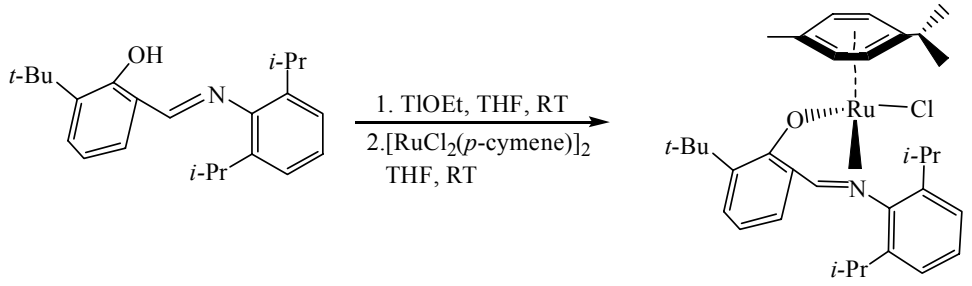


1: R = H; R' = Me
2: R = H; R' = *t*Bu
3: R = H; R' = 2,6-Me-4-BrC_6H_2

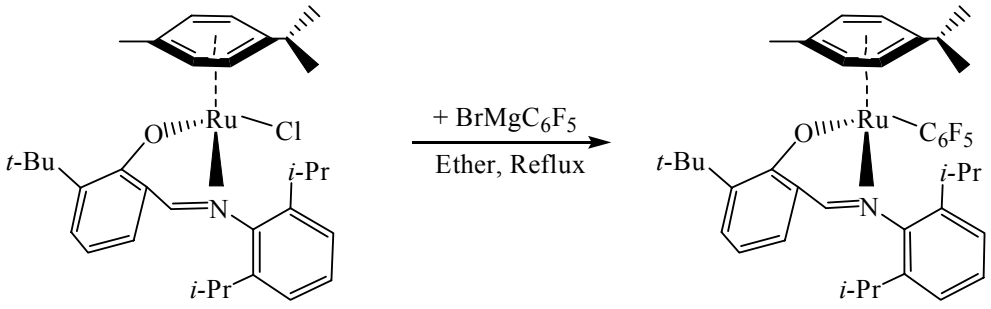
Scheme 2.2. Synthesis of Schiff base ruthenium arene complexes.

After having established the optimum reaction conditions for the Schiff-base/arene synthetic procedure, preparation of further new arene ruthenium complexes became accessible, as are complexes **4** and **5**, ortho-substituted with respect to the O coordination site. Our two-step protocol afforded compound **4** (yield: 84%), which led to **5** (yield: 68%) upon treatment with the Grignard derivative BrMgC6H5 (Scheme **3-4**). [91]

The strong electron-withdrawing properties of the pentafluorophenyl group have proven helpful in ring-opening metathesis polymerization of norbornene (e.g. the polymer yield is 73% with catalyst **5** *vs*. 5% with catalyst **4**, under the same reaction conditions).[91]

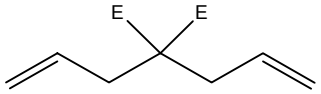
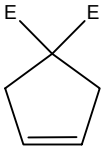
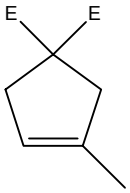
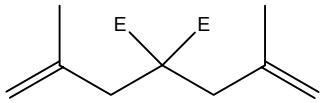
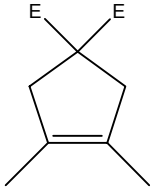
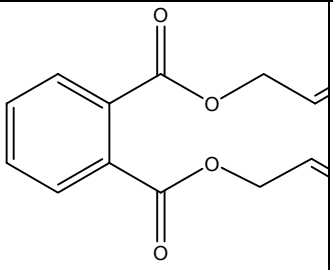
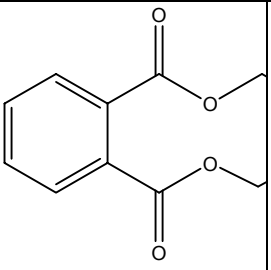
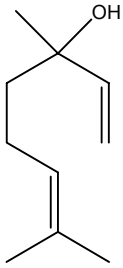
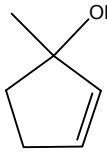


Scheme 2.3 Synthesis of alkylated Schiff base ruthenium arene complex **4.**



Scheme 2.4 Synthesis of alkylated Schiff base ruthenium arene complex **5**.

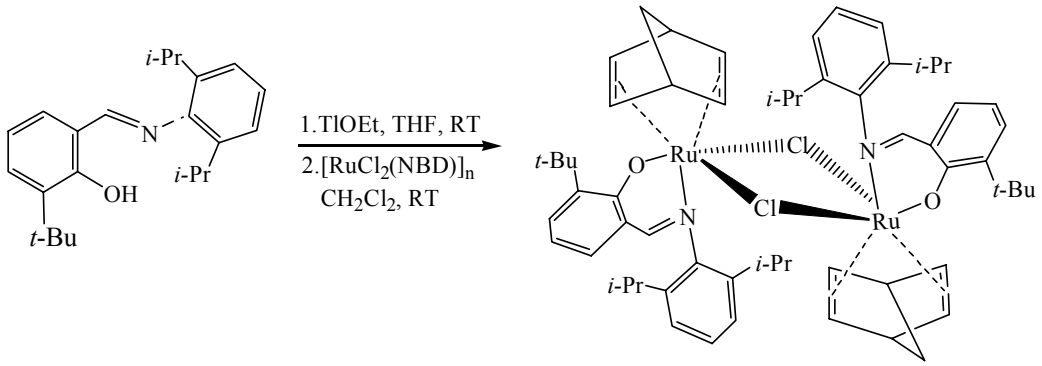
Table 2.1 Influence of N-Substituents on Yields in RCM of Diene Substrates with Catalysts 1-3a.

Entry	Substrate	Product	Yield (%) in RCM[b,d,e]		
			1	2	3
1			100	100	100
2			22	26	32
3			<5	<5	<5
4			48	55	60
5			16	21	28

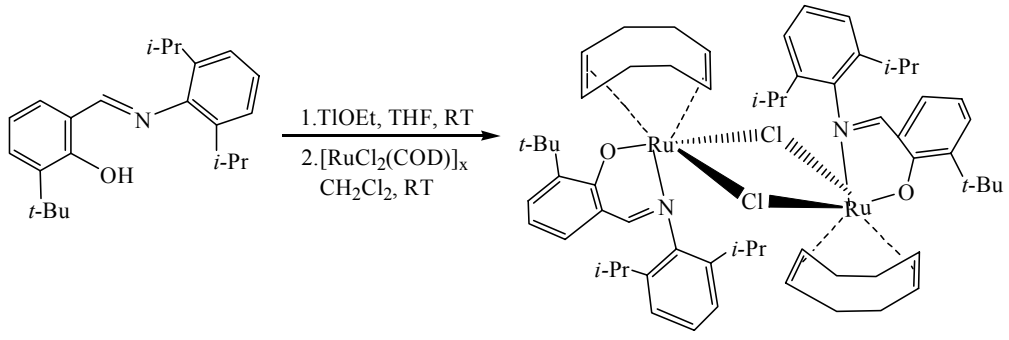
[a]Data from Ref. [70]. [b]Yield after 60 min. reaction time as determined by H-NMR and confirmed by GC. [c]E=COOEt. [d]Reaction conditions:70 [o]C; 5 mol% catalyst in toluene; 2.2 equiv. of trimethylsilyldiazomethane (added to generate the metal-carbene). [e]Higher yields were attained for the three catalysts under more drastic conditions.

2.3. Cyclodiene Schiff base Ru complexes

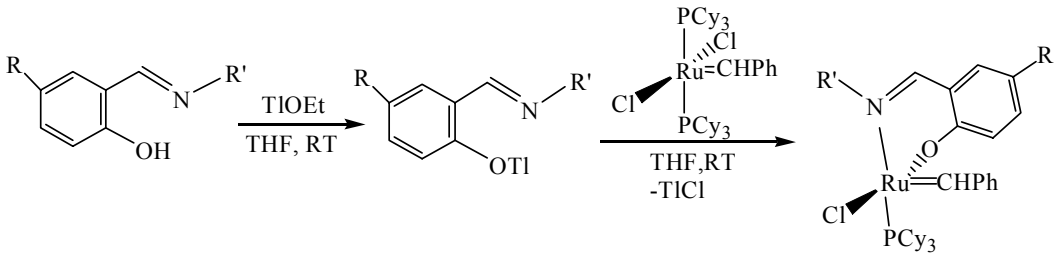
Subsequent extension of our methodology for Schiff base Ru complexes allowed us to create the interesting homobimetallic complexes **6** and **7**, coordinating cyclic dienes (norbornadiene and cyclooctadiene) as additional bidentate ligands (Schemes **5-6**).[91] Introduction of such bulky ligands (also endowed with electron-donating propensity) into a dinuclear arrangement, along with the Schiff base, confers new catalytic properties on the targeted bimetallic structures. Synthesis of the neutral 18-electron complexes **6** and **7** comprised the two usual reaction steps involving the Tl-salt of salicylaldimine, further reacted with the appropriate ruthenium precursor, $[RuCl_2(NBD)]_n$ or $[RuCl_2(COD)]_x$, (in dichloromethane, at room temperature; yield 63%). The Raman spectra of **7** and **8** evidence strong bands at 259 and 253 cm, assignable to the two ν(RuCl) modes of bridging Cl atoms, in agreement with the high tendency of arene, COD and NBD complexes to form $(\mu\text{-Cl})_n$ (n = 2,3) structures.



Scheme 2.5 Synthesis of homobimetallic norbornadiene Ru complex **6**.



Scheme 2.6 Synthesis of homobimetallic cyclooctadiene Ru complex **7**.



8: R = H; R' = Me

9: R = NO_2; R' = Me

10: R = H; R' = 2,6-Me-4-BrC_6H_2

11: R = NO_2; R' = 2,6-Me-4-BrC_6H_2

12: R = H, R' = 2,6-*i*PrC_6H_2

13: R = NO_2; R' = 2,6-*i*PrC_6H_2

Scheme 2.7 Synthesis of Schiff base ruthenium benzylidene complexes **8**-**13.**

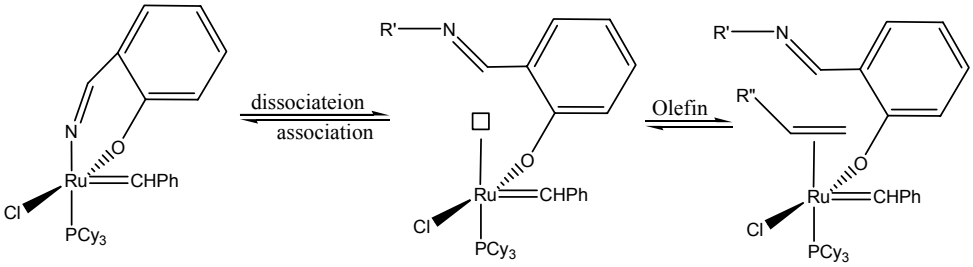
2.4. Benzylidene Schiff base Ru complexes

A large body of work was invested in the synthesis of diversified Schiff base Ru benzylidene complexes **8**-**13** employing the first generation Grubbs catalyst $RuCl_2(PCy_3)_2(CHPh)$ as the ruthenium source. Reaction of this latter compound with the Tl salt of an aliphatic or aromatic salicylaldimine readily led to the corresponding bidentate Schiff base complex. Structure determination by FTIR and NMR spectroscopy unequivocally demonstrated that one of the initial phosphane ligands has been displaced by the N-donor fragment of the Schiff base creating an N-Ru coordination mode in the Ru atom environment. As compared with the starting diphosphane congener, the bidentate N,O-bonding conferred an increased stability on the resulted complexes **8**-**13**, in conjunction with a broad palette of reactivity (Scheme **7**).[84, 85, 92]

Relative to phosphines, Schiff base fragments are stronger σ donors and are much less labile. A distinctive property of monometallic complexes from this class is de-coordination of the imine, under certain circumstances, occurring in competition with the phosphane ligand, and yielding a “one arm” Schiff base unit. Dissociation of the N-bonded arm of the chelated salicylaldimine, rationalized by σ, π interactions, was considered to be the key step in the dissociative mechanism that we have proposed for metathesis reactions induced by the monometallic precatalysts **8-13** (Scheme **8**).[74]

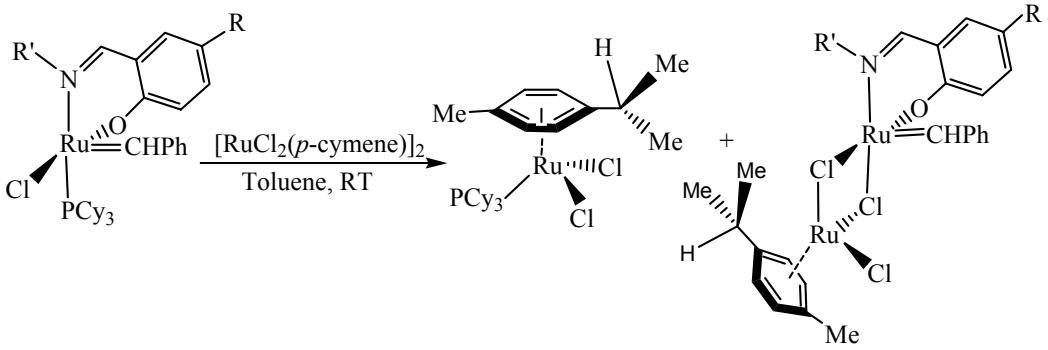
An O-bonded arm dissociation is ruled out since Ru-O bonds are much stronger than Ru-N bonds. Further, replacement of the second phosphane in the Ru-benzylidene complexes **8-13**,

this time by a Ru(*p*-cymene) fragment stemming from the Ru dimer $[RuCl_2(p\text{-cymene})]_2$, conveniently led to a new range of bridgehead bimetallic Ru complexes **14 -19** (Scheme 2.**9**).



Scheme 2.8 The dissociative mechanism for metathesis reactions with monometallic precatalysts **8-13**.

An important characteristic of these binuclear Ru complexes is that the labile *p*-cymene ligand located in a sterically congested environment can be readily replaced by another coordinating ligand, which accounts for the high activity displayed by **14-19** in a variety of metathesis and related reactions. [74] The easy release of *p*-cymene, creating first a vacant site and thus enabling subsequent olefin coordination at ruthenium is crucial in the dissociative mechanism postulated for metathesis reactions promoted by these bimetallic catalysts (Scheme **10**),[74] in agreement with previous reports by Herrmann for the parent NHC-Ru bimetallic complexes.[62]



14-**19**

14: R = H; R' = Me

15: R = NO_2; R' = Me

16: R = H; R' = 2,6-Me-4-BrC_6H_2

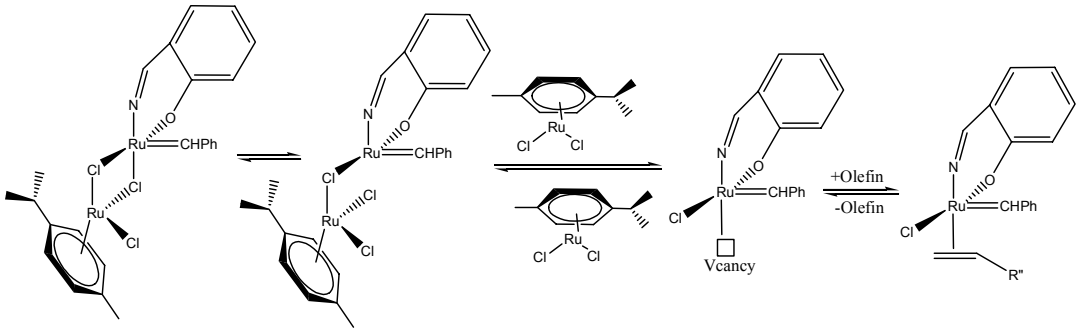
17: R = NO_2; R' = 2,6-Me-4-BrC_6H_2

18: R = H, R' = 2,6-*i*PrC_6H_2

19: R = NO_2; R' = 2,6-*i*PrC_6H_2

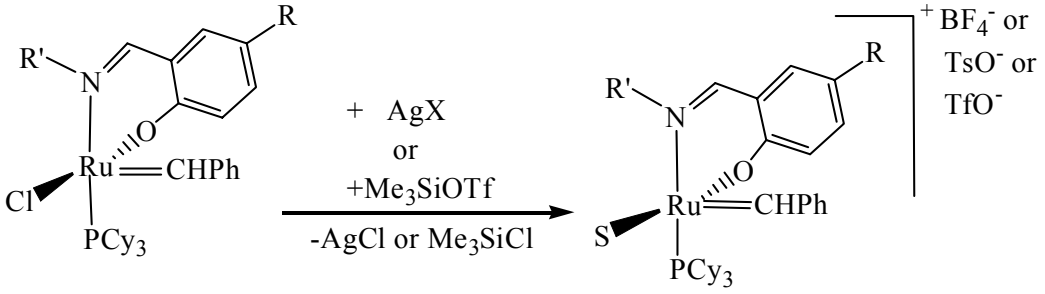
Scheme 2.9 Formation of bridgehead bimetallic Ru complexes **14 -19.**

It must be pointed out that the synergy between Schiff base ligands and the coordinatively labile ligands is responsible for the very high activity, combined with an excellent stability, observed for the above bimetallic catalytic systems.



Scheme 2.10. The dissociative mechanism for metathesis promoted by bimetallic catalysts

A divergent development offers a practical route to the cationic Ru-benzylidene complexes **20-25** generated *in situ* by treatment complexes **8-13** with one equiv. of silver salts or trimethylsilyl triflate (Scheme **11**). [84, 85, 93]



20-**25**

20: R = H; R' = Me

21: R = NO_2; R' = Me

22: R = H; R' = 2,6-Me-4-BrC_6H_2

23: R = NO_2; R' = 2,6-Me-4-BrC_6H_2

24: R = H, R' = 2,6-*i*PrC_6H_2

25: R = NO_2; R' = 2,6-*i*PrC_6H_2

Scheme 2.11. Synthesis of the cationic Ru-benzylidene complexes **20-25.**

Rewardingly, complexes **20-25** showed outstandingly high activity in a number of metathesis and radical controlled reactions. In this respect, both the counterion and the solvent exert dramatic effects. These cationic ruthenium benzylidene complexes were the first Ru-alkylidene catalysts reported to perform the precisely controlled radical suspension polymerization of methyl methacrylate, methyl acrylate and styrene in water affording high polymer yields.

2.5. NHC Schiff base Ru complexes

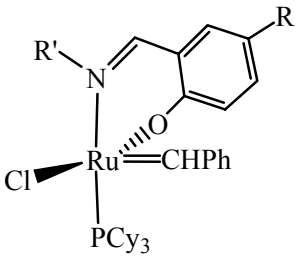
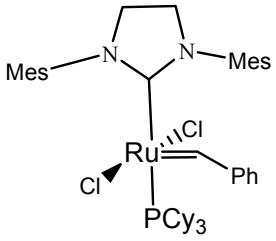
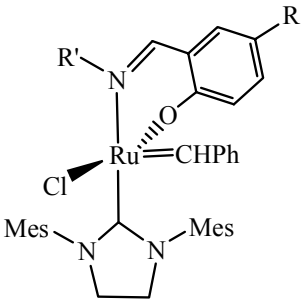
Overwhelming progress in the chemistry of Ru-alkylidene complexes was achieved following the introduction of Ru-benzylidene complexes containing N-heterocyclic carbene (NHC) ligands.[8-18] Abundant evidence has since demonstrated that these nucleophilic ligands are excellent σ-donors, form rather strong metal-carbon bonds, are stronger Lewis bases than phosphines and allow fine-tuning of the catalyst reactivity through a systematic variation of substituents in the heterocyclic moiety. In addition, this class of ligands is easily accessible and complexes bearing NHCs generally have better air and thermal stability in comparison with the corresponding phosphane counterparts. Moreover, the higher dissociation energy of NHC ligands make them suitable candidates for chiral modification and catalyst immobilization.

Consequently, taking advantage of our expertise in the synthesis of Schiff base Ru complexes we developed a synthetic approach based on the NHC structural motif and conveniently prepared a range of Ru-benzylidene complexes, **26-31,** incorporating both NHC and Schiff base ligands (Scheme **12**).[94-97] Introducing the 1,3-bis(2,4,6-trimethylphenyl)-4,5 dihydroimidazol-2-ylidene (SIMES) ligand in the phosphine bearing complexes **8**-**13**, by *in situ* formation of the free carbene from its stable adduct, was not an appropriate route to **26**-**31**. Instead, the synthesis succeeded by attaching salicylaldimine ligands to a complex already bearing SIMES, such as is the di-pyridine NHC Ru benzylidene complex where the two chloride ligands are more labile than those from **8**-**13** and can be easily displaced by the Schiff base Tl salts (Scheme **12**).[96-98]

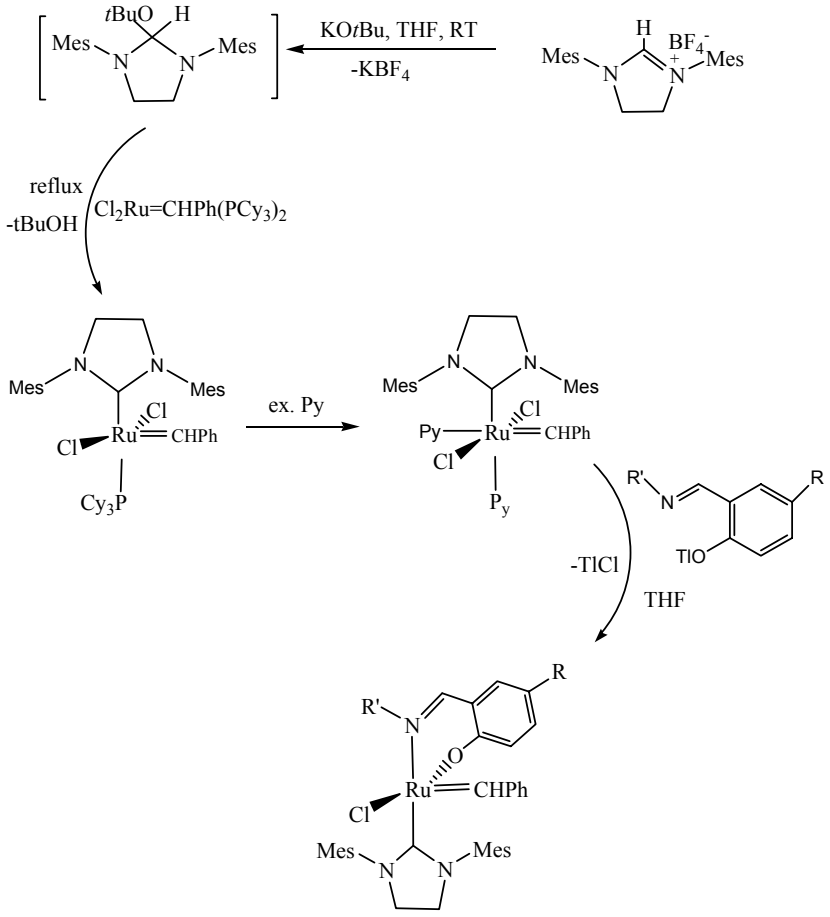
Association of both bidentate Schiff base and NHC ligands in Ru-benzylidene complexes resulted in air and moisture compatible and unusually stable catalysts, albeit of rather low activity. To achieve activation of these ”latent” catalysts specific protocols, e.g. heating or introduction of acidic cocatalysts (Brönsted (HCl) and Lewis acids (BF_3, $SiCl_4$, $HSiCl_3$) were put forward. [90, 97] They led to catalyst systems with advantageous extra features such as the possibility for storage of the catalyst in the monomer without initiating the polymerization reaction, an asset of utmost significance for some industrial processes (e.g. the Reaction Injection Molding RIM process where there are two monomer streams, one containing the dormant catalyst and the other the acidic activator).

There are obvious structural changes when passing from catalysts **8-13** to **26-31** by incorporating an NHC ligand in place of the PCy_3. Thus, the Ru-N bond in **31** (2.125 (2) Å) is somewhat longer than in **13** (2.106 (4) Å), this result being ascribed to the enhanced *trans* influence of the NHC ligand in the latter (Table **2**, Fig. **1**). Additionally, the Ru-C(NN) bond in **31** (2.035 (3) Å) is shorter than in the second generation Grubbs catalysts (2.085 (2) Å), due to a decreased *trans* influence of the N atom in **31** *vs.* **13**.

Table 2.2 Representative Bond Lengths (Å) and Angles (°) in Ru Complexes[a]

	 **13** **(R=NO_2, R´=2,6-iPr-C_6H_3)**	 **2nd Generation Grubbs**	 **31** **(R=NO_2, R´=2,6-iPr-C_6H_3)**
Ru-N	2.106 (4)	2.125 (2)	
Ru-C(NN)		2.085 (2)	2.035 (3)
L(2)-Ru=C	103.5 (2)	95.98 (6)	106.3 (1)

[a]Data from Ref. [96]



Scheme 2.12 Synthetic route to NHC Ru-benzylidene complexes, **26-31.**

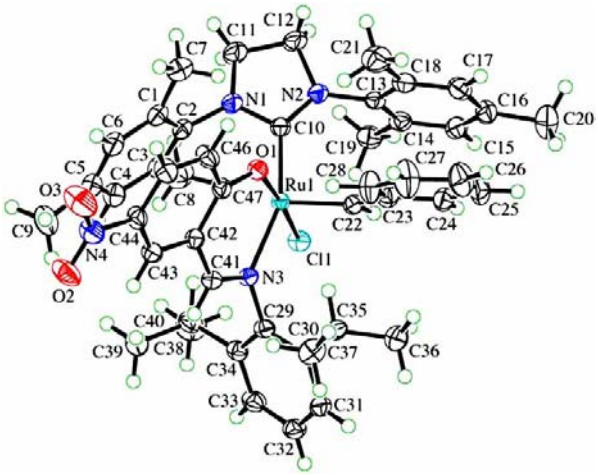
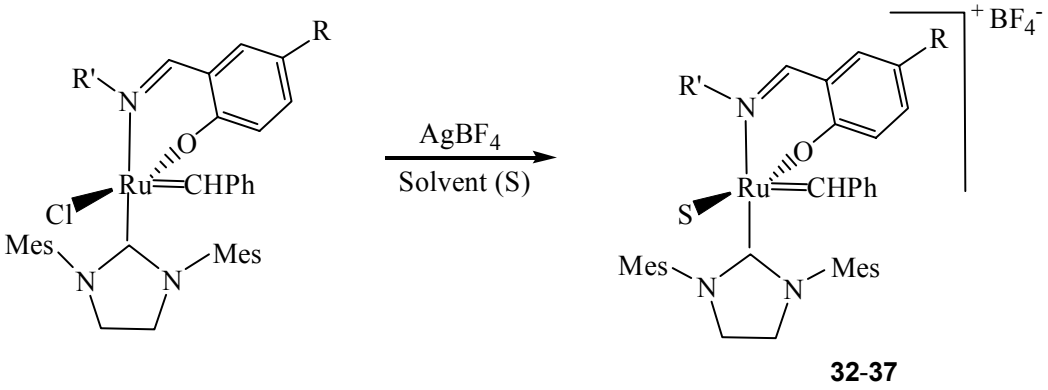


Figure 2.1 ORTEP plot of the ruthenium complex **31**.

Furthermore, the corresponding cationic Ru-benzylidene complexes **32-37 (**Scheme **13**) became available from **26-31** and AgBF4 and were tested as precatalysts in ATRP of vinyl monomers. [95]



32-37

32: R = H; R' = Me

33: R = NO_2; R' = Me

34: R = H; R' = 2,6-Me-4-BrC_6H_2

35: R = NO_2; R' = 2,6-Me-4-BrC_6H_2

36: R = H, R' = 2,6-*i*PrC_6H_2

37: R = NO_2; R' = 2,6-*i*PrC_6H_2

Scheme 2.13 Generation of the cationic Ru-benzylidene complexes **32-37.**

2.6. Vinylidene and allenylidene Schiff base Ru coplexes

Our strategy for the preparation of Schiff base Ru complexes works nicely in the synthesis of a range of new Ru vinylidene complexes, **38-43**, containing various O,N-chelated Schiff bases.

The target complexes are efficiently prepared from the parent Ru vinylidene complexes, $RuCl_2(PCy_3)_2$[=C=CHR'], and the Tl salts of the aromatic salicylaldimines **38a**-**43a** (Scheme **14**).[99]

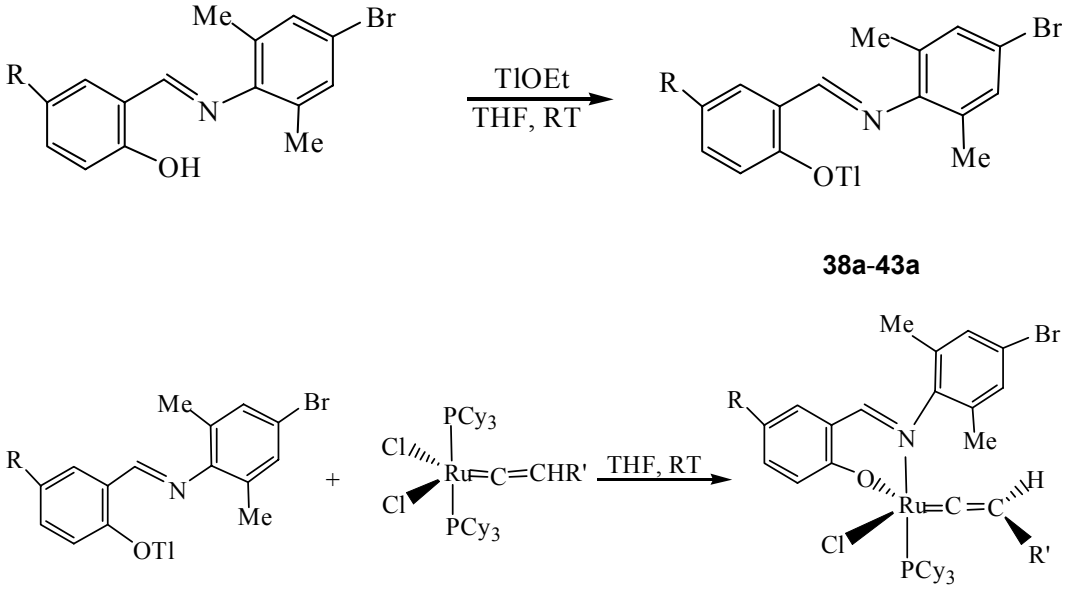
In comparison with other metathesis-active alkylidene systems, these precursors possess extremely high stability toward air, heat and moisture; no significant catalyst decomposition was found after several days at elevated temperatures. It should be mentioned that complexes **38**-**43** displayed superior activity in enol-ester synthesis *via* nucleophilic addition of carboxylic acids to terminal alkynes, while activity of these complexes in metathesis reactions remained substantially lower, especially in the case of more difficult diolefin substrates. Rationalization of this behavior is a challenging issue for further research efforts in our group.

Application of our Schiff base approach in the allenylidene series led to interesting results. Coordination of a Schiff base ligand to a 3rd generation ruthenium allenylidene complex **43b** conducted to three isomers of the targeted product (**43c-e**). The major isomer **43c** was successfully isolated, and tested in olefin metathesis test reactions. Acids such as HCl and $HSiCl_3$ were found to boost metathesis rates but the obtained turnover numbers did not meet the results achieved with the corresponding benzylidene complex because *in situ* formation of a neutral Ru carbyne species suppressed the catalytic capacity. Using the $PhSiCl_3$ as activator, generation of this carbyne was circumvented and turnover numbers up to 30 000 were reached in ROMP of cycloocta-1,5-diene.[100]

2.7. Indenylidene Schiff Base Ru Complexes

When translated into the indenylidene series our Schiff base methodology provided the Ru indenylidene complex **44**, accessible from the aromatic salicylaldimine **44a** (as the Tl salt) and the corresponding bisphosphane Ru-indenylidene complex, $RuCl_2(PCy_3)_2$ (Ind) (**44b**) (Scheme **16**).[101]

Noteworthy, the indenylidene complex **44** is rather stable and could be fully characterized by ^{1}H-^{13}C- and ^{31}P-NMR spectroscopy and elemental analysis. In spite of the large steric encumbrance of the bulky ligands in **44**, its activity in enol-ester synthesis surpasses that of the bisphosphane Ru cogener **44b** (Table **3**). In addition, this Schiff base containing complex exhibited an extraordinary high level of activity in ring-closing metathesis of α, ω-dienes and enol-ester syntheses. [101]



38: R = H; R' = Ph

39: R = NO_2; R' = Ph

40: R = H; R' = *t*Bu

41: R = NO_2; R' = *t*Bu

42: R = H, R' = $SiMe_3$

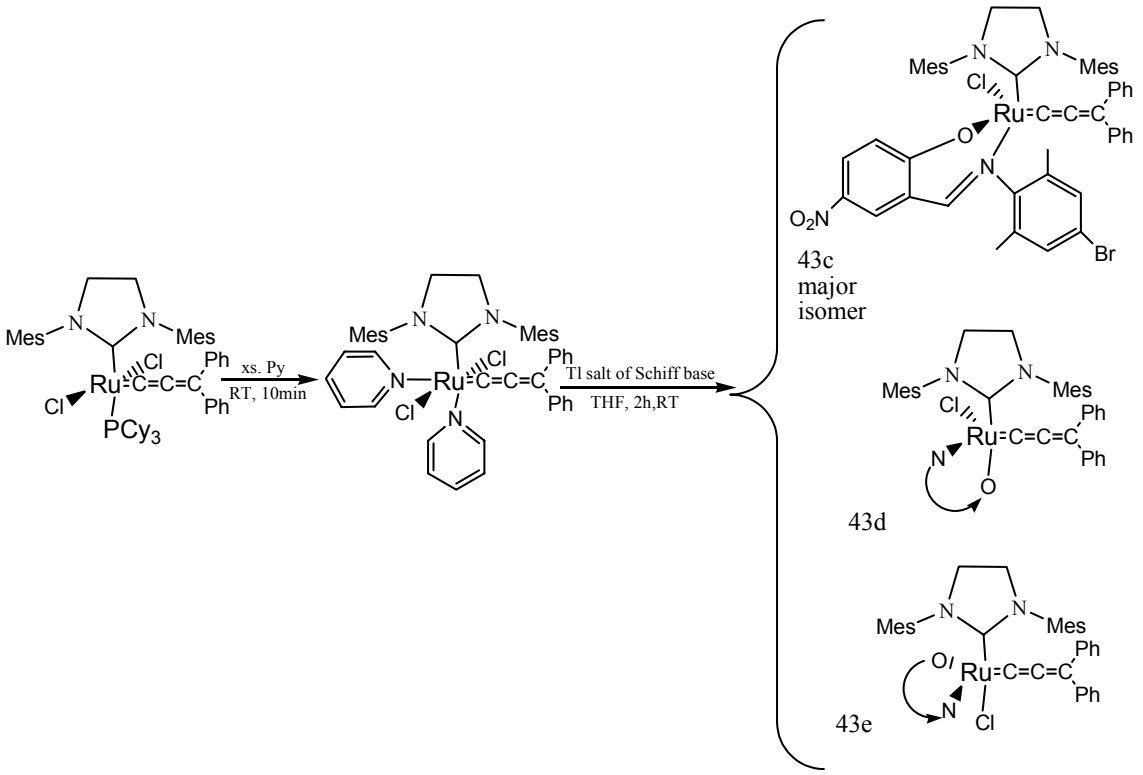
43: R = NO_2; R' = $SiMe_3$

Scheme 2.14 Synthetic strategy for Schiff base Ru vinylidene complexes **38-43.**

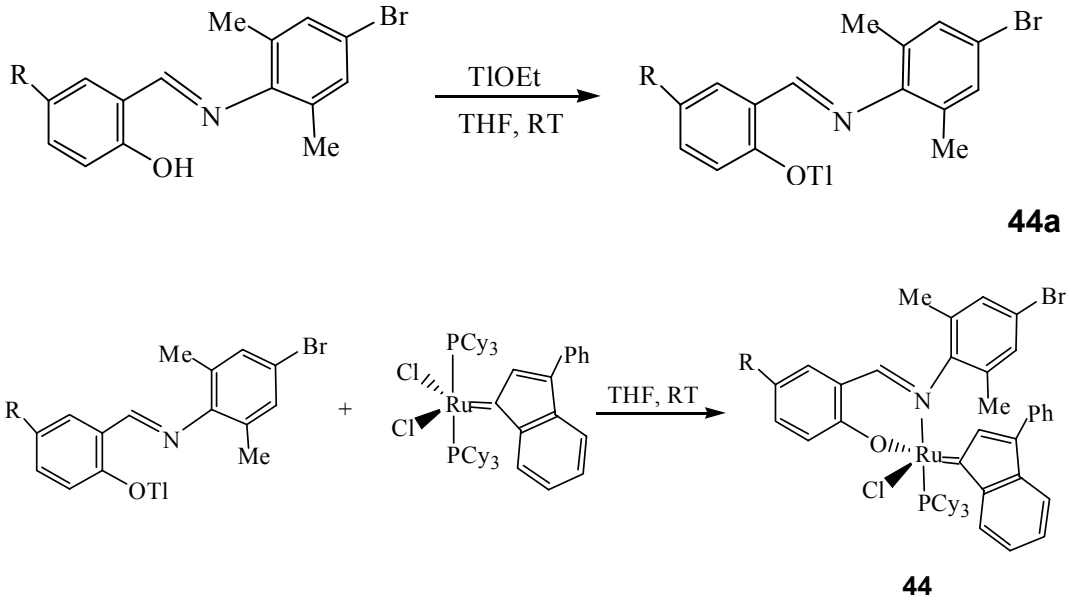
Table 2.3 Yields in Enol-Ester synthesis promoted by the Schiff base indenylidene complex 44 *vs*. the related biphosphane Complex 44b

Entry	Cat.	Acid	Alkyne	Yield (%)
1	44b	formic acid	phenyl acetylene	68
2	44b	acetic acid	phenyl acetylene	58
3	44b	isovaleric acid	phenyl acetylene	62
4	44b	benzoic acid [b]	phenyl acetylene	95
5	44[a]	formic acid	phenyl acetylene	80
6	44[a]	acetic acid	phenyl acetylene	73
7	44[a]	isovaleric acid	phenyl acetylene	77
8	44[a]	benzoic acid [b]	phenyl acetylene	98

[a]Data from Ref. [101]; [b]solvent: chlorobenzene

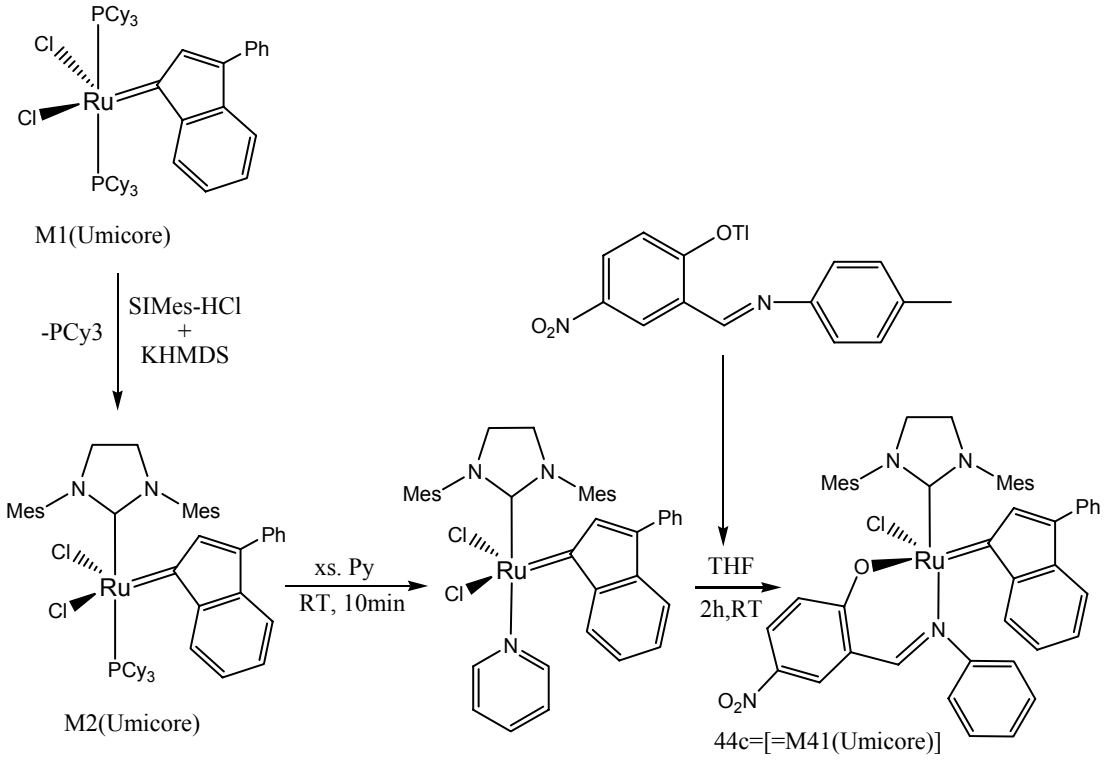


Scheme 2.15 Synthesis of Schiff base NHC-Ru allenylidene complex **43c.**



Scheme 2.16. Synthesis of Ru indenylidene complex **44.**

Quite recently we introduced, as effective metathesis catalysts, several ruthenium phenylindenylidene complexes bearing a bidentate Schiff base and a saturated NHC (SIMES) ligand, easily accessible from the respective pentacoordinated third-generation Ru indenylidene complexes and salicylaldimine salts. Activation of this group of catalysts by $PhSiCl_3$ resulted in a superior catalytic efficiency relative to that of the commercially available first and second-generation indenylidene complexes. This outcome was assigned to the higher stability of the precatalyst *vs.* that of its phosphine analogues.



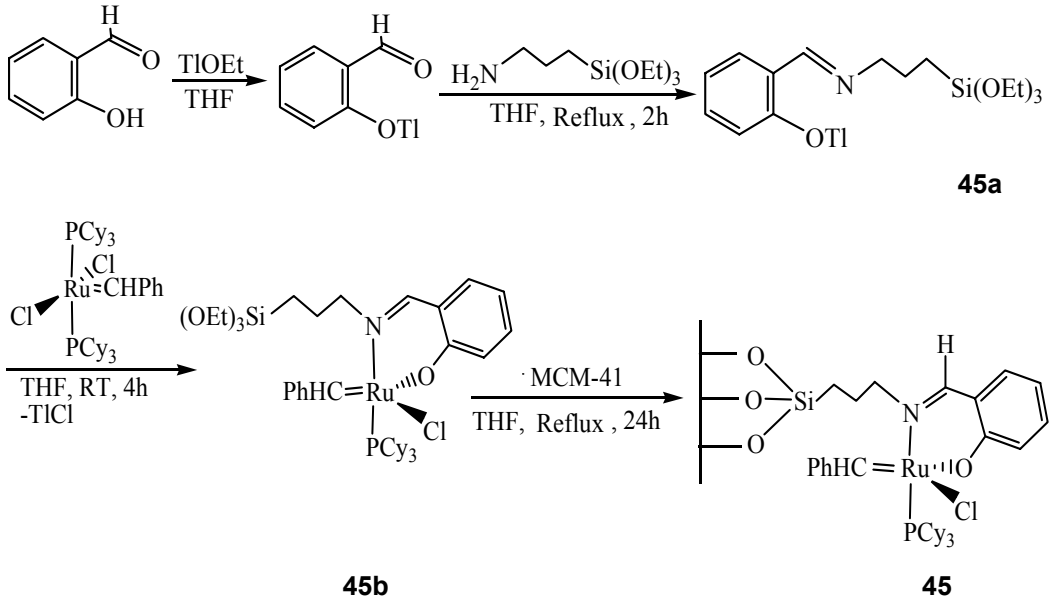
Scheme 2.17 Synthetic pathway for commercial Schiff-base Ru indenylidene complex **44c** [= M41 from Umicore].

Intensive, long-term research efforts of our group rewardingly converged into the creation of new Schiff base containing indenylidene complexes (**44c)**. Due to the fact that those new systems are very reliable catalysts, Umicore (a catalyst company) is commercializing those catalysts which can be used by the pharmaceutical industry and polymer industry.[102]

2.8. Immobilized Schiff base Ru complexes

Innovative research devoted to structurally robust and effective Ru catalysts led us to disclose new catalytic systems in which a previously homogeneous catalyst is immobilized on a solid carrier by a non-labile tether imposing little or no steric influence

at the reactive Ru-center. Immobilization allows simplification of the reaction procedure through better control of the process selectivity, easier separation of the catalyst from the reaction products, recyclability of expensive catalysts, good control of morphology of polymers, and high polymer bulk density.[154-158] For immobilization we selected inorganic mesoporous supports, e.g. MCM-41,[103] since they retain a rigid exposed surface area, as opposed to conventional polymer beads that typically swell and shrink differentially in different media, often resulting in unpredictable effects on catalyst activity. [104] Also, these supports are more robust than organic polymers, and essentially have a structured surface and a considerably larger area, and therefore an increased activity. In addition, the MCM-41 solid support consisting of an ordered array of hexagonal channels with a pore diameter in the mesoporous region permits a lower diffusion resistance (*vs.* nanoporous zeolite supports) to reactant molecules that access the metal active sites located within the channels. [105]

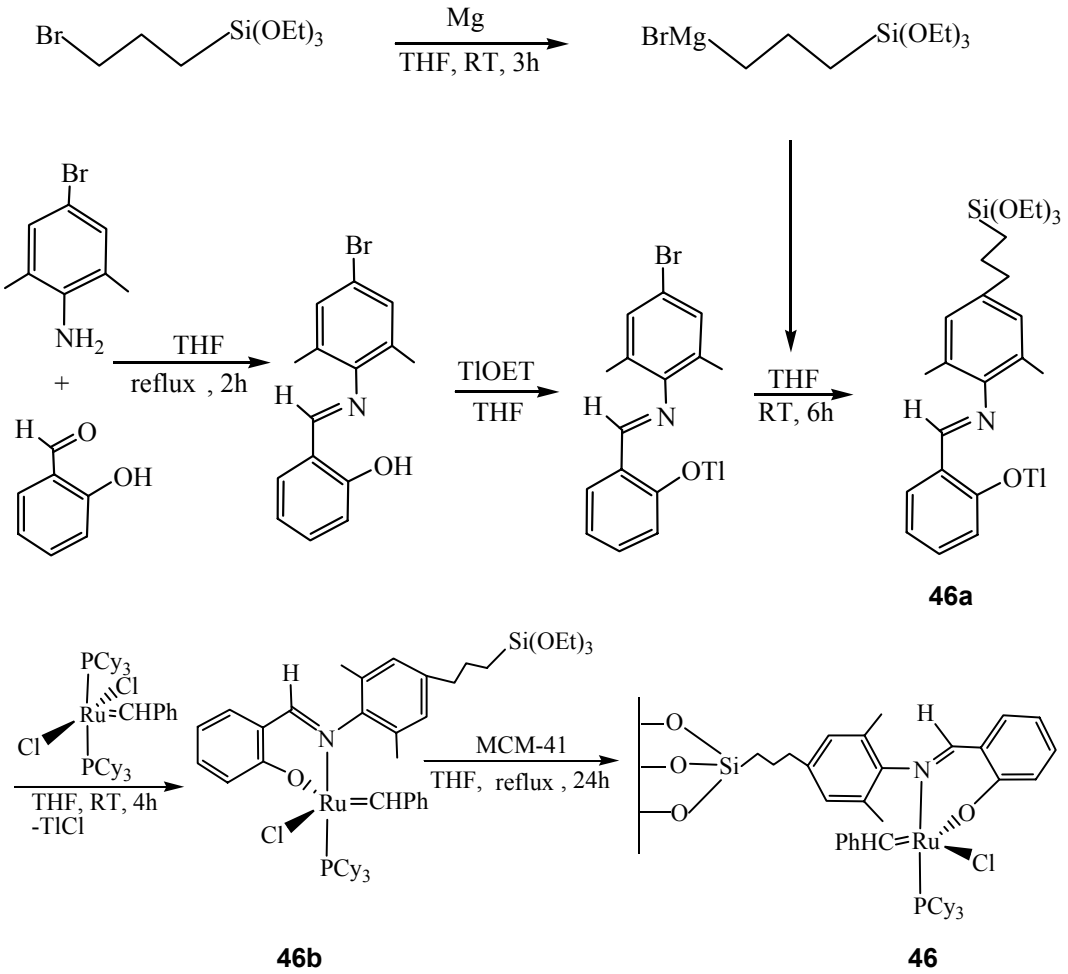


Scheme 2.18 1st Approach for immobilizing a Schiff base Ru-benzylidene complex on a MCM-41 support.

The immobilization studies have been mainly directed towards supported Schiff base ruthenium catalysts for versatile applications in ring-closing metathesis, ring-opening metathesis polymerizations, Kharasch addition, atom transfer radical polymerization and vinylation reactions. Aiming at improving the commercial potential of such chemical processes, we prepared two multifunctional Schiff base Ru carbene complexes supported on MCM-41, **45** and **46,** which are

recyclable and efficient solid catalysts. For each of these complexes the method we followed was to tether the organometallic compounds onto mesoporous silica surfaces by treating the inorganic support with a tris(alkoxy)silyl functionalized ruthenium complex, **45b** or **46b**. The synthetic pathway for the manufacture of the supported ruthenium complexes **45** and **46** is illustrated in the anchoring of the homogeneous catalyst onto MCM-41 *via* the Schemes **18** and **19.** [106-112]

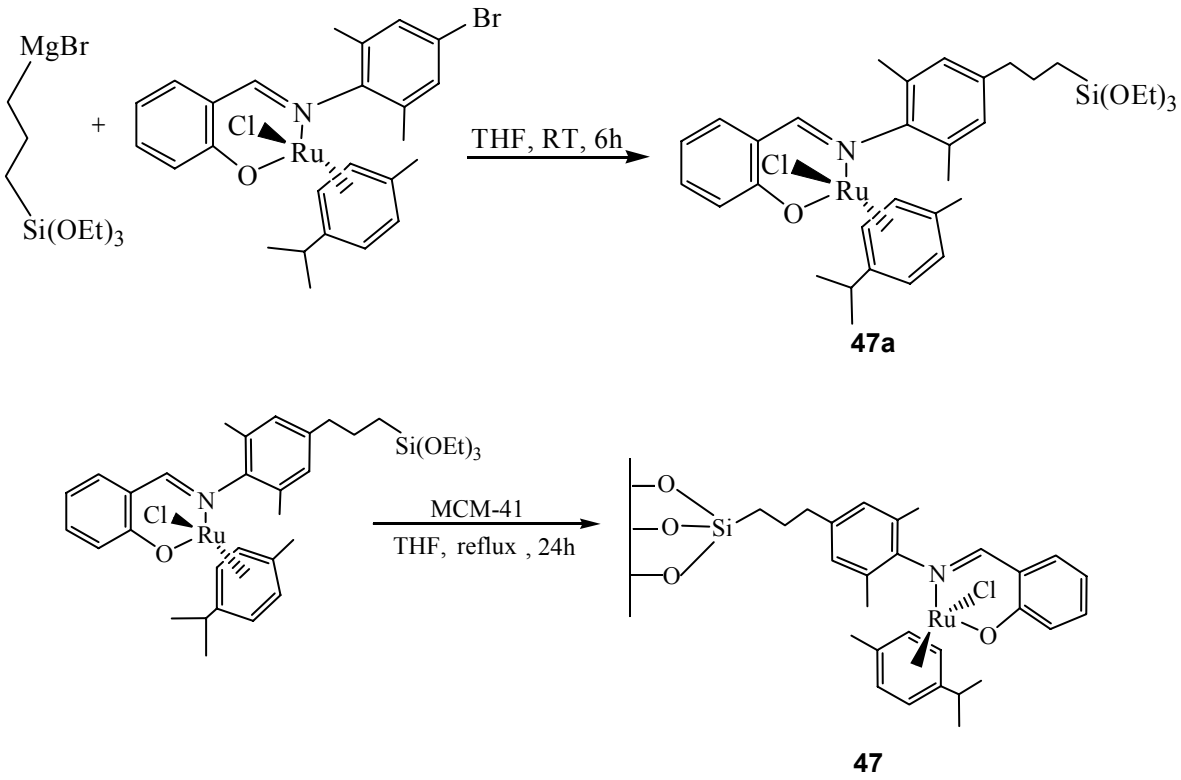
As can be easily observed from Schemes **18** and **19**, generation of the intermediate Tl salts **45a** and **45b** corresponding to the Schiff bases**,** was effected by two different approaches, the (alkoxy)silyl functionalization taking place either during or after Schiff base preparation. Examination by Raman spectroscopy, X-ray diffraction, X-ray fluorescence, solid state NMR, and N_2 adsorption analysis demonstrated that, in both cases, anchoring of the homogeneous catalyst onto MCM-41 *via* spacer molecule is achieved through two-three covalent bonds.



Scheme 2.19 2nd Approach for immobilizing a Schiff base Ru-benzylidene complex on a MCM-41 support.

Ruthenium complex **47** was prepared in an analogous way *via* the intermediate complex **47a,** Scheme **20.**[131, 132]

Detailed structural examination, based on Raman spectroscopy, X-ray diffraction, X-ray fluorescence, solid state NMR and N_2 adsorption analysis, of this immobilized complex clearly showed that the anchoring of the homogeneous catalyst onto MCM-41 *via* the spacer molecule is taking place by the intermediacy of the substituted phenyl tethered moiety, coupled to the support through three covalent bonds. To our delight, these new immobilized systems exhibited excellent stability, reusability and leaching properties in multiple catalytic applications. [103, 112]



Scheme 20. Immobilization of a Ru-arene complex on MCM-41 as a mesoporous support.

2.9. Conclusion

This chapter surveys the synthesis of a novel, broad class of homogeneous and immobilized ruthenium complexes containing a O,N-bidentate Schiff base as the principal ancillary ligand, in association with a variety of inorganic or organic ligands such as chloride, phosphane, arene, cyclodienes, NHCs, and different carbenes (alkylidene, vinylidene, allenylidene and indenylidene). The synergy of Schiff bases with appropriately selected ligands was exploited for the first time in design of catalysts of this type.

By manipulating both steric and electronic characteristics in the key Schiff base building block, the catalytic activity and stability of our ruthenium complexes were finely adjusted to obtain a library of robust and active precatalysts with excellent tolerance toward organic functional groups, air, moisture and impurities, while also ensuring considerable stability at the ambient temperature. Also prepared were latent Schiff base Ru catalysts which become active only under specific conditions (heat or acid activation) and are ideal for specific industrial applications, e.g. reaction injection molding processes. Application profiles range from metathesis and C-C coupling reactions, radical mediated reactions, enol-ester synthesis to convenient procedures for accessing heterocycles from diallyl compounds. Several of the new Ru catalysts moved further toward commercial products. Versatility of Schiff bases and our straightforward and flexible synthetic strategy open up opportunities for future developments in synthesis of valuable Ru complexes.

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Chapter 3
Isomerization Reactions Catalyzed by Ruthenium Hydrides Bearing Schiff Base Ligands

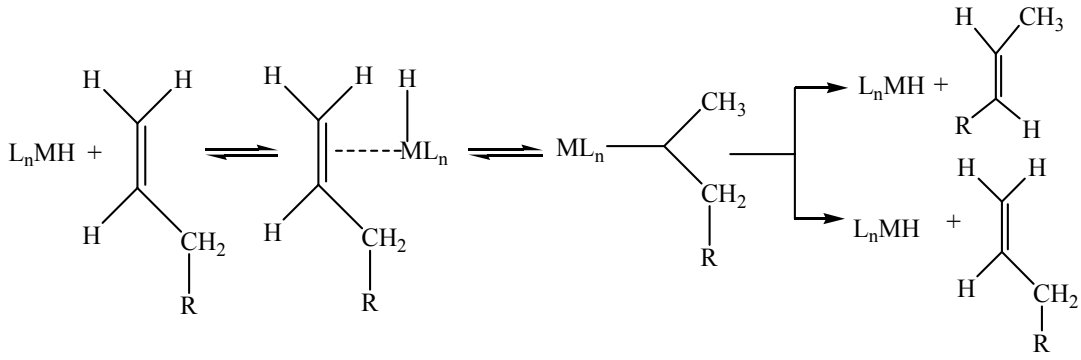
In this chapter, a series of Ruthenium hydride complexes $Ru(PPh_3)_2(CO)H(L^n)$ (n=a-h) incorporating a Schiff base ligand has been investigated as in situ catalysts for the isomerization reaction. ^{1}H-NMR was used to characterize the new hydride species in combination with ^{31}P-NMR. Allylbenzene and 1-Octene have been used as model substrates. Temperature, solvents and catalyst/substrate mol ratio have been taken into account as parameters to optimize the isomerization.

3.1 Introduction

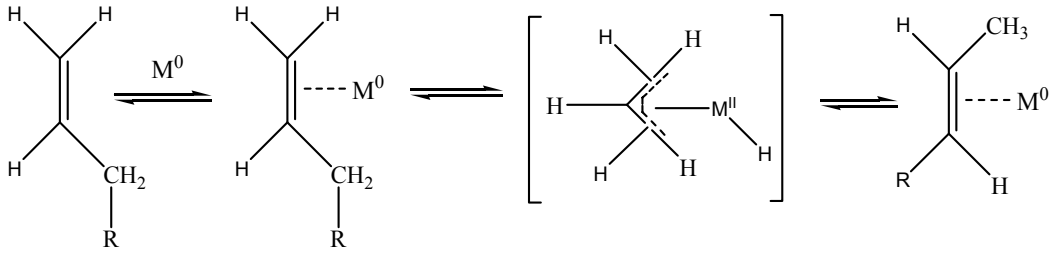
Since all kinds of unsaturated hydrocarbons play an important role in organic synthesis, the isomerization of double/triple bonds has been one of the highlights of transition-metal-catalyzed synthesis in terms of both academic curiosities and industrial interests.[1] Certain transition metal complexes based on Fe, [2-4] Pd, [2, 3] Rh, [4] Pt, [5] Ni, [3,6] Al, [7] Ir, [8] Ru, [9-11] and Cr[12, 13] are known as catalysts for isomerization. For instance, the Wilkinson catalyst $(PPh_3)_3RhCl$ is frequently employed in the isomerization of allylic ethers.[14] The common accepted transition metal-catalyzed alkene isomerization mechanisms are depicted in Scheme 3.1 and 3.2.

Ruthenium hydride has been employed as catalyst for the olefin isomerization for a long time [11,15-20] since Ewing et al. reported that a solution of $RuHCl(PPh_3)_3$ in benzene catalyze the double

bond migration of 1-pentene at 50℃ to give *cis*-2-pentene (60%) and *trans*-2-pentene (40%). [21]Although many elegant applications corroborate the notion that Ruthenium hydride complexes may outperform isomerization in a more conventional approach and an increased flexibility at the same time,[24-29] in most cases, it only exists as an intermediate species. Furthermore, the instability of the hydride retards the application of this kind of catalysts. In order to discover an effective catalyst applicable under mild conditions variation of the ligands at the metal is expected to tune the stability, reactivity, even selectivity of those compounds.



Scheme 3.1 Isomerization via transition metal hydride catalyst: the hydrometalation-dehydrometalation mechanism.



Scheme 3.2 Isomerization via transition metal catalyst: the π-allyl mechanism.

As all properties of the compounds are dictated primarily by the coordination environment around the metal centre, complexation of transition metal compounds by ligands of selected types is of significant importance for the catalytic activity. During many years in the past, Schiff base complexes of the transition metals offered a powerful synthetic methodology for organic transformations. Especially, they are playing a significant role in the ligand optimization strategies resulting in a novel class of robust and active ruthenium catalysts.[22-27] By a proper choice of the substituents on the Schiff base, the desired physical and chemical properties could be induced in the prepared complexes.

Although the Ruthenium hydride complexes bearing Schiff base ligands have been reported already several decades,[28, 29] the study of the isomerization activity remain relatively scarce. The

most investigated activity of ruthenium hydrides is their antibacterial activity and their oxidation of alcohols. [30-33] With the intention of developing long-lived, highly active Ruthenium isomerization catalysts, we undertook an exploration of the facile substitution of tertiary phosphines by Schiff Bases from Ruthenium hydride compounds to afford a very extensive range of ruthenium complexes that subsequently show improved catalytic activities and stabilities for isomerization compared to their parent compound, $RuH_2(CO)(PPh_3)_3$.

3.2 Experimental

3.2.1 General

Unless otherwise stated, all reactions were carried out under dry Argon atmosphere following conventional Schlenk techniques and all solvents were distilled from the appropriate drying agents and deoxygenated prior to use. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian 300 spectrometer in $CDCl_3$ (δ ppm). The salicylaldehydes and aromatic amines to synthesize the Schiff Base ligands and $RuCl_3 \cdot nH_2O$ to synthesize the precursor were all purchased from Aldrich and used as received. The precursor $RuH_2(CO)(PPh_3)_3$ was prepared according to the literature.[34] All other chemicals used were of analytical grade without further purified.

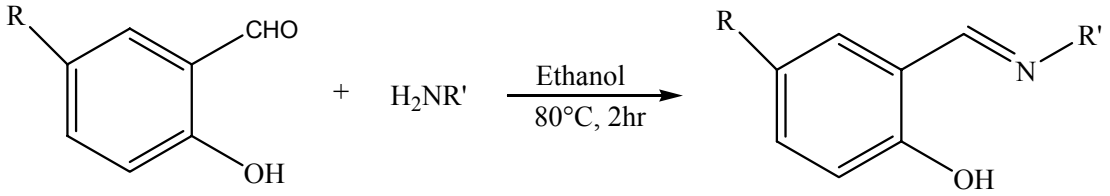
Yields and selectivity were obtained by using a Finnigan Trace GC Ultra with an Ultra Fast Column Module (PH-5 5% diphenyl/95% dimethyl poly-siloxane capillary, helium carrier gas, 1 ml/min) column (10 m x 0.10 mm, 0.40 μm) and a FID detection system. The temperature program starts at 50°C and heats at 20°C/min up to 255°C

Following operations were undertaken in a typical GC experiment. Pretreatment of the substrates was necessary before starting the isomerization reaction. 1-octene was passed through a column (20 cm x 1.5 cm) of neutral alumina (Acros, 50-200 μm), containing 15 g of alumina per 100 ml of 1-Octene, into a Schlenk flask, thereafter, 1-octene was deoxygenated. In an empty 15 ml reaction vessel, an appropriate quantity of the catalyst under investigation and solvent was transferred under a constant Ar-flow. Thereafter the substrate was added and the vessel was immersed in an oil bath allowing to equilibrate to the desired temperature before timing. All reactions were thoroughly stirred, using a magnetic stirrer bar. Before GC-analysis, the reaction mixture was purified over a silica filter in order to remove the catalyst. Hexane was used as solvent to prepare the GC samples and 1-dodecane was added as internal standard.

3.2.2 Preparation of Schiff base ligand

In the first step, the Schiff bases were prepared and purified readily by using conventional methods.[35] In our protocol condensation of salicylaldehydes with aromatic amines was conducted

in ethanol (80 °C, 2 hr.). The resulted crude products were isolated as yellow solids (at 0 °C), which were further purified by washing with cold pentane and drying *in vacuo* to afford salicylaldimines in quantitative yields. The spectroscopic properties[36] of the synthesized Schiff bases, see Scheme 3.5, are in agreement with data published earlier.[35]



R = H	R′= 2-Me-phenyl	(a)	R = NO2	R′= 2-Me-phenyl	(e)
R = H	R′= 4-tBu-phenyl	(b)	R = NO2	R′= 4-tBu-phenyl	(f)
R = H	R′= 2,6-dimethylphenyl	(c)	R = NO2	R′= 2,6-dimethylphenyl	(g)
R = H	R′= 4-bromo-2,6-dimethylphenyl	(d)	R = NO2	R′= 4-bromo-2,6-dimethylphenyl	(h)

Scheme 3.3 Synthesis of Schiff Base.

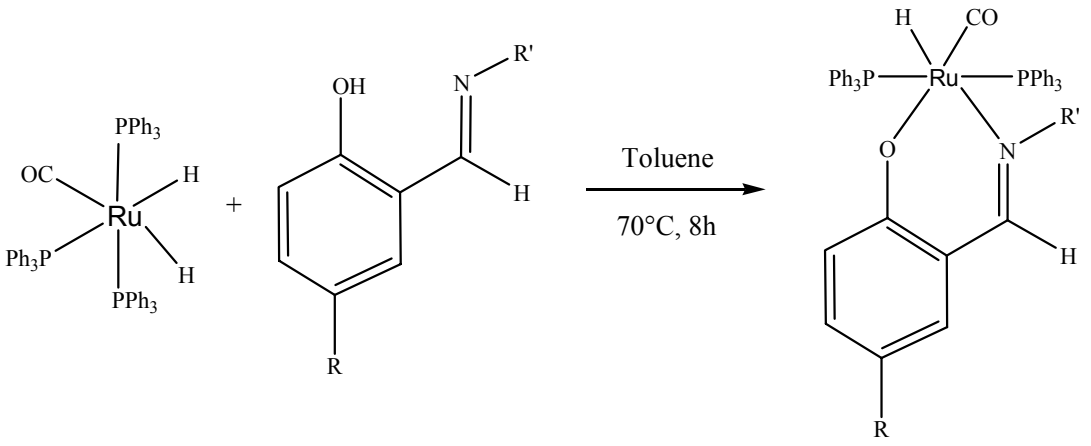
3.2.3 Preparation of ruthenium hydride precursor

The precursor $RuH_2(CO)(PPh_3)_3$ was prepared according to a modified method from the literature.[34] The characterization of the pure ruthenium complex $RuH_2(CO)(PPh_3)_3$ was in agreement with the literature data.[34]

3.2.4 Preparation of Schiff Base ruthenium hydride complexes

By attempting to develop a synthetic route to Schiff base ruthenium hydride complexes using $RuH_2(CO)(PPh_3)_3$ as precursor, we avoid the use the carcinogenic solvent benzene as reported by Viswanathamurthi.[33] The new hexa-coordinated ruthenium (II) complexes of the type $RuH(CO)(PPh_3)_2(L)_n$ (L = Schiff base ligand, n=a-h) have been prepared according the reaction depicted in Scheme 3.4.

To a solution of the bidentate salicylaldimine ligand a-h (1.1 equiv.) in dry toluene was added drop-wise a solution of $RuH_2(CO)(PPh_3)_3$ (1 equiv.) in distilled toluene. After the addition, the mixture was heated to 65-80 °C for about 5 hr to afford a pale yellow solution. The new species were evidenced by ^{1}H and ^{31}P NMR (Fig. 3.1) and the yield varies between 50-90%. Unfortunately, although many attempts were made to separate the new species, we were not successful.



R = H	R'= 2-Me-phenyl	(1)	R = NO_2	R'= 2-Me-phenyl	(5)
R = H	R'= 4-tBu-phenyl	(2)	R = NO_2	R'= 4-tBu-phenyl	(6)
R = H	R'= 2,6-dimethylphenyl	(3)	R = NO_2	R'= 2,6-dimethylphenyl	(7)
R = H	R'= 4-bromo-2,6-dimethylphenyl	(4)	R = NO_2	R'= 4-bromo-2,6-dimethylphenyl	(8)

Scheme 3.4 Synthesis of the ruthenium hydride Schiff base catalysts.

3.3 Results and discussion

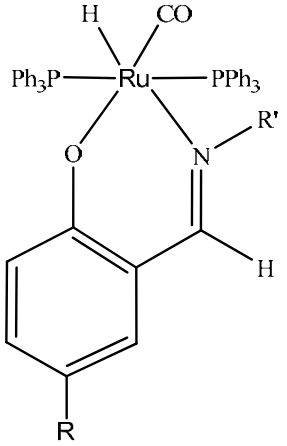
3.3.1 Synthesis and characterization

Since ruthenium hydrides were found to be active catalysts for isomerization, a series of ruthenium hydride Schiff base complexes $RuH(PPh_3)_2(CO)(L^n)$ with n=a-h have been developed. One has to mention that compound **1** has been reported by Vart A. et al., however using a different synthesis method and without any further application exploration .[28]

Since efforts to isolate the pure compounds were not successful, and because of the absence of an X-ray crystal structure determination, it is impossible to establish a definitive stereochemistry. Nevertheless, on the basis of valuable NMR information (Table 3.1), the stereochemical structure of compounds **1**-**8** was supposed as in the Figure 3.1. From the ^{1}H NMR data (^{1}H, δ_{RuH} *ca*. -10 ppm, ^2J(PH) ca. 20-22Hz, ^4J(HH) ca. 2Hz), especially, the coupling ^4J(HH') between hydridic and azomethine (-N=CH-) protons favors the structure in Fig. 3.1 between the alternative arrangements with the hydride *trans* to the O-donor site. The ^{31}P NMR resonances (^{31}P{^{1}H}, δ_{PPH3}, *ca*. 38.9 -43.0 ppm (s)) were found to be singlets. From the reported literature, when the phosphines are bulky (e.g., PPh_3), effectively no coupling is observed between the two phosphine ligands (^{31}P-^{31}P). [37] These observations indicate that the phosphine ligands are orientated *trans* to each other. Reports in the literature describe that these Schiff base ligands usually coordinate in a bidentate fashion with the N, O donors forming a six-membered chelating ring. All above elucidations support the structure in Fig. 3.1.

Table 3.1 The ^{1}H and ^{31}P NMR data of $RuH_2(CO)(PPh_3)_3$ and $RuH(PPh_3)_2(CO)(L^n)$ (n=a-h).

$RuH(CO)(PPh_3)_2(L)^n$	^{1}H (ppm)	^{31}P(ppm)
$RuH_2(CO)(PPh_3)_3$	-6.885(t), -8.905(m)	58.245(d), 45.732(t)
1	-11.336(t)	38..936(s)
2	-10.931(t)	41.273(s)
3	-16.394(t)	40.213(s)
4	-14.364(t)	38.075(s)
5	-11.263(t)	38.940(s)
6	-10.891(t)	41.657(s)
7	-16.748(t)	40.205(s)
8	-14.534(t)	39.926(s)



R = H R'= 2-Me-phenyl (1)
R = H R'= 4-tBu-phenyl (2)
R = H R'= 2,6-dimethylphenyl (3)
R = H R'= 4-bromo-2,6-dimethylphenyl (4)
$R = NO_2$ R'= 2-Me-phenyl (5)
$R = NO_2$ R'= 4-tBu-phenyl (6)
$R = NO_2$ R'= 2,6-dimethylphenyl (7)
$R = NO_2$ R'= 4-bromo-2,6-dimethylphenyl (8)

Figure 3.1 Structure of the ruthenium Schiff base hydride complexes.

The respective ^{1}H resonances relative to the hydride in the complexes $RuH(PPh_3)_2(CO)(L^n)$ (n=a-h) were strongly shifted downfield or upfield (-10.9 ~-16.7 ppm), depending on the electronic properties of the R´-group on the Schiff base.

A number of features of Schiff base ligands make them attractive for catalytic applications and particularly the decreased liability and/or higher stability in comparison to the precursor compound. For the new species, no changes were found in the NMR spectrum after a few days, even in open air. Moreover, the new compounds are more stable than most of the reported Ruthenium hydrides.

3.3.2 Isomerization activities

Since the hydride complex has been corroborated in literature as an isomerization catalyst,[38-42] by using the different R or R' groups in Schiff base ligands, the influence of the electronic, steric factors of the ligands in the ruthenium hydride complexes was subject of this study. To elucidate

the source of the activity differences and establish relative stabilities of the various complexes, the reactivity of the ruthenium hydrides **1**-**8** were examined using 1-octene and allylbenzene.

Treatment of **1**-**8** with an excess of 1-octene at different temperatures (60, 80 and 100 °C) for 12 h has been investigated. The results are summarized in 3.2, 3.3 and 3.4. To compare and optimize their activity, different catalyst/substrate ratio (1:1000, 1:5000 and 1:10000) and different solvents were applied.

Table 3.2 1-Octene conversion by $RuH_2(CO)(PPh_3)_3$ (precursor) and $RuH(CO)(PPh_3)_2(L^n)$ (n=a-h) without solvent.

T (°C)	Precursor	1	2	3	4	5	6	7	8
C:S[a] Ratio 1:1000									
60	42,0	62,5	90,6	96,9	95,2	89,6	97,1	95,7	98,1
80	86,5	96,1	96,6	96,3	97,3	97,4	97,4	97,4	97,4
100	88,7	94,8	96,5	97,5	97,4	97,3	97,4	96,9	97,4
C:S[a] Ratio 1:5000									
60	36,0	39,6	86,4	71,4	93,2	73,1	96,7	60,2	96,6
80	40,4	87,6	96,5	91,5	97,0	97,3	96,2	92,1	96,7
100	60,3	92,3	94,6	94,9	96,8	97,2	97,1	95,6	97,2
C:S[a] Ratio 1:10000									
60	1,8	32,9	20,4	10,3	20,3	42,6	89,4	24,7	89,9
80	19,1	26,2	87,0	35,9	84,0	91,2	91,2	85,9	96,1
100	40,3	81,7	92,7	86,2	94,3	92,3	96,9	95,6	97,2

a. C:S ratio = Catalyst/ Substrate mol ratio

During the isomerization reaction, three products can be generated, 2-octene, 3-octene and 4-octene, indicating that **1**-**8** catalyzed the isomerization of 1-octene. Initial GC and NMR results prove that neither metathesis nor dimerization takes place.

All the new species performed better than the precursor under any experimental condition. In most of the cases, the advantage is obvious and high conversions are reached by the new complexes. Moreover, the increased activity of these catalysts did not result in the loss of inertness toward air and moisture. This observation was emerged from the contribution of the Schiff base ligand --- two donor atoms, N and O, in the ligated Schiff base exert opposite electronic effects: the phenolate oxygen is a hard donor known to stabilize the higher oxidation state of the ruthenium atom whereas the imine nitrogen is a softer donor and, accordingly, will better stabilize the lower oxidation state of the ruthenium. In this way a flexible interplay between these two binding sites can be achieved, the Schiff base ”dangling” ligand stabilizes the resting state of the catalyst while one coordination site becomes available.

From table 3.2 the observed trend is that the higher catalyst loading, the higher the substrate conversion. However, the variance is not linear and some differences are less than 1%. i.e. there are no significant differences between these two mol ratios (1:1000 to 1:5000), moreover, the lower catalyst loading is very attractive for isomerization reactions. Compared with the other reported catalysts, it is a noteworthy improvement. [43-45]

Performing experiments at different temperatures, it follows that increasing the temperature is not always equal with increased conversion. A higher temperature can promote the decomposition of the catalyst resulting in a decrease of the yield. Complexes **1**, **2**, **5**, **6** and **7** show the best performance at 80 °C, while complexes 3 and 4 need 100 °C to fulfill the isomerization reaction. Only complex **8** shows an excellent performance at 60°C.

Fig. 3.2 depicts the isomerization results of 1-Octene in the presence of $RuH_2(CO)(PPh_3)_3$ and $RuH(PPh_3)_2(CO)$ (L^n) (n=a-h) without solvent. Except for complex **1** and **2**, all the other complexes achieved over 95% conversion. Using complex **8** a 1-Octene conversion of 98.1% is generated. Complex **3**, **4**, **6**, **7** and **8** execute fast initiation, in contrast to complexes **1**, **2** and **5**. All the Nitro-containing complexes display a higher activity compared to the non-nitro-containing compounds.

As discussed above, it seems that after adjusting the steric and electronic effects around the ruthenium centre through an appropriate selection of the substituents on the Schiff base unit, the activity of ruthenium hydride complexes appeared to depend on the R'-group of the Schiff base. Experimental data suggests that the electronic influence of the Schiff base has a greater impact on catalytic performance compared to the steric bulk of the Schiff base.

As comparison, the control experiments for the precursor without solvent were also carried out by using microwave irradiation. Using a microwave power of 800 watts and the same ratio as described above at 100°C for 1 hour, a %-conversion of 23.6%, 7.8% and 0.6% respectively was obtained. The corresponding %-conversion of 1-octene obtained by heating was 47.3%, 15.7% and 4.8% respectively. The results using microwave were not promising and prevent us to the further investigate the use of microwave irradiation.

Based on the study discussed above, most of the catalysts demonstrate an excellent performance at Catalyst/ Substrate mol ratio 1:1000. The same ratio is used to study the influence of the solvent.

Comparing the %-conversion of 1-octene (table 3.3), it follows that the various solvents affect the isomerization in a different way.

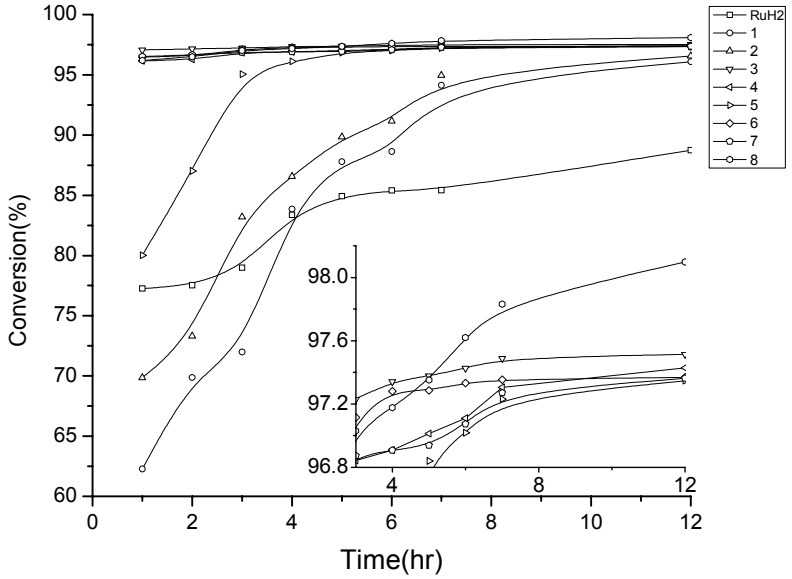


Figure 3.2 Optimized Isomerization results of 1-Octene using $RuH_2(CO)(PPh_3)_3$ (= RuH_2) and $Ru(PPh_3)_2$ $(CO)H(L^n)$ (n=a-h). No solvent was used.

2-Butanol is manifesting itself as the unique solvent for all catalysts. For the other solvents, it is difficult to observe a general trend. Moreover, the solvent effect on this series of catalysts is not tackled by the temperature.

Because of the different thermal stability in different solvents, the best performance of the catalyst did not always appear at higher temperature, the same catalyst can generate the highest conversion at a different temperature depending on the solvent. For instance, catalyst **1** showed 97.4% and 95.2% conversion in CH_3Cl and $CH_3CH_2ClCH_2Cl$ respectively at 60°C, while in methanol and 2-butanol, the highest conversion 87.2% and 95.9% appeared at 80 °C. This phenomenon appears for all catalysts.

Analyzing the data, it seems that the solvent effect improved the activity of catalysts containing a small substituent on the Schiff Base (**1** and **5**).

Using allylbenzene as substrate, 2-butanol is still the solvent of choice since all the catalysts are promoted. Varying the solvent results in a significant change in conversion, e.g. for catalyst **1** a conversion of 6.6% is obtained in CH_2Cl_2 at 60 °C, while using 2-butanol a conversion of 86.6% is reached at 60°C. For catalyst **7**, at all temperatures high conversions are obtained when $CHCl_3$ or 2-Butanol is used as solvent. For catalysts **6**, the solvent of choice is here 2-Butanol, at 60°C full conversion is achieved.

Table 3.3 %-conversion for the isomerization of 1-octene by $RuH(PPh_3)_2(CO)$ (L^n) (n=a-h) with solvent.

Solvent T (°C)	No Solvent	CH_2Cl_2	$CHCl_3$	CH_2Cl CH_2Cl	CH_3CH_2 $ClCH_2Cl$	MeOH	2-Butanol	PhCl	Toluene
Catalyst 1									
60	62.5	36.0	92.2	97.4	95.2	37.9	92.1	67.8	92.1
80	96.1	50.6	96.7	97.3	91.0	87.2	95.9	80.5	96.4
100	94.8	47.3	97.0	96.5	92.9	60.8	94.0	82.4	96.9
Catalyst 2									
60	90.6	35.0	65.1	43.8	57.7	96.1	93.2	77.0	50.2
80	96.6	41.5	58.0	72.0	74.0	89.8	89.5	70.6	66.4
100	96.5	46.6	83.0	77.6	74.0	94.0	95.3	77.4	61.7
Catalyst 3									
60	96.9	97.0	95.8	76.0	72.5	52.0	97.8	82.6	38.3
80	96.3	95.2	92.3	87.4	88.5	65.8	96.5	84.5	54.4
100	97.5	96.1	96.3	86.5	77.8	76.0	96.3	76.3	75.3
Catalyst 4									
60	95.2	93.5	89.9	70.6	75.1	97.2	90.8	59.2	15.8
80	97.3	91.9	98.0	75.3	77.9	97.7	95.5	85.0	17.0
100	97.4	96.8	98.8	77.8	80.8	95.7	96.6	93.0	36.4
Catalyst 5									
60	89.6	96.1	71.3	95.6	59.2	45.1	94.1	56.4	72.5
80	97.4	93.7	88.4	96.5	67.7	62.6	98.6	72.4	86.8
100	97.3	92.4	84.0	97.4	59.3	63.7	96.4	84.5	90.6
Catalyst 6									
60	97.1	82.0	93.2	78.2	85.5	56.3	96.2	53.8	69.3
80	97.4	83.5	93.2	84.8	96.0	63.2	96.7	79.1	75.0
100	97.4	85.7	94.4	85.0	96.3	60.3	97.1	80.0	85.8
Catalyst 7									
60	95.7	50.6	77.5	81.1	53.3	91.1	87.4	41.8	57.9
80	97.4	43.6	74.8	80.2	54.3	95.5	87.9	63.9	61.3
100	96.9	28.0	75.6	83.1	66.3	96.4	94.5	56.7	60.9
Catalyst 8									
60	98.1	70.3	91.0	85.7	71.2	43.9	96.2	67.5	63.9
80	97.4	73.3	91.0	87.2	59.9	33.3	96.6	67.1	76.3
100	97.4	68.1	100.0	88.8	68.9	19.5	95.8	83.5	76.9

In general, it can be concluded that 2-butanol seems the preferred solvent for this series of ruthenium Schiff Base hydrides.

Because many hydride complexes, such as $RuH_4(PPh_3)_3$ and $RuH(BH_4)(PMe_2Ph)_3$ are able to decarbonylate alcohols, it was expected that also here this decarbonylation would occur. Some analogous reactions were reported in the earlier literature, describing the decarbonylation of methanol applying $RuHCl(PPh_3)_3$, where a ruthenium hydride complex $RuH_2(\eta^2\text{-}HCHO)(PPh_3)_3$ was suggested as an intermediate[46]. Furthermore, adding methanol to $WH(\eta^2\text{-}CH_2PMe_2)(PMe_3)_4$, a well-characterized η^2-formaldehyde complex $WH_2(\eta^2\text{-}HCHO)(PMe_3)_4$ was formed.[47] Therefore, notwithstanding that a number of intermediates, regarding the active pathway of the catalyst,

have not yet been elucidated by some evidences, based on the ^{1}H NMR observation (Fig. 3.3a, b and c), it is reasonable to suppose that the alcohol decarbonylation occurs by a metal-aldehyde dihydride-complex RuH(η^2-OCH_2R)(PPh_3)$_2$(L^n).

Table 3.4 %-conversion for the isomerization of allylbenzene by RuH(PPh_3)$_2$(CO)(L^n) (n=a-h) with solvent.

Solvent T (°C)	**CH_2Cl_2**	**$CHCl_3$**	**CH_2Cl CH_2Cl**	**CH_3CH_2 $ClCH_2Cl$**	**MeOH**	**2-Butanol**	**PhCl**	**Toluene**
				Catalyst 1				
60	6.6	33.4	63.9	32.3	56.7	86.6	32.5	50.7
80	10.8	27.6	89.9	62.5	69.7	97.6	72.4	75.6
100	16.5	61.2	93.1	50.2	76.3	93.0	52.6	84.6
				Catalyst 2				
60	15.9	12.8	22.7	15.3	69.1	99.8	17.1	10.9
80	12.2	17.4	45.0	45.9	53.1	97.8	35.6	15.4
100	11.2	37.2	43.4	65.1	48.6	99.7	57.6	18.8
				Catalyst 3				
60	99.9	99.7	13.4	57.9	95.5	98.4	24.6	18.2
80	99.8	99.9	40.1	58.1	95.7	99.7	47.0	29.8
100	99.5	96.4	45.6	59.2	92.1	99.6	41.3	34.1
				Catalyst 4				
60	69.7	81.5	32.4	82.5	21.7	99.4	7.8	15.0
80	77.9	96.6	41.5	97.2	51.2	99.7	7.2	35.7
100	44.7	95.2	73.6	99.7	76.7	99.8	3.7	26.8
				Catalyst 5				
60	45.4	26.0	84.5	23.4	80.1	90.9	15.0	10.6
80	42.0	56.8	85.3	45.4	85.2	99.8	31.3	71.4
100	41.8	52.9	93.8	66.2	95.9	99.4	78.7	82.9
				Catalyst 6				
60	38.9	49.3	58.9	46.9	15.6	99.8	33.3	30.8
80	55.5	40.3	73.3	75.3	18.7	99.9	52.1	57.1
100	63.6	64.1	91.5	70.6	13.2	99.9	77.2	72.2
				Catalyst 7				
60	52.4	92.6	33.6	47.8	98.9	77.0	25.4	14.0
80	60.6	92.9	42.0	53.0	94.9	65.2	27.2	20.9
100	81.1	92.5	35.4	50.6	99.2	79.3	26.2	27.4
				Catalyst 8				
60	31.7	95.7	22.5	9.6	59.0	75.7	16.4	9.8
80	42.9	94.0	29.9	17.7	47.1	85.5	60.5	39.1
100	55.1	89.9	54.9	43.8	73.8	96.2	66.0	34.9

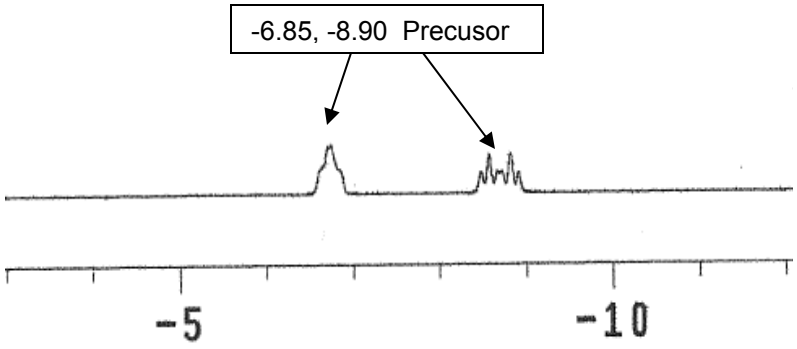


Figure 3.3a Hydride region of the ^{1}HNMR spectrum of precursor-$RuH_2(CO)(PPh_3)_3$.

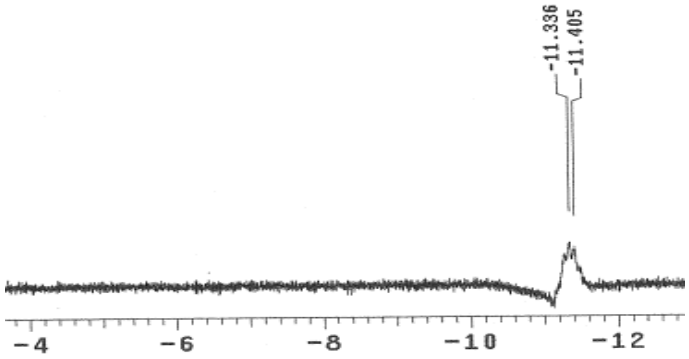


Figure 3.3b. Hydride region of the ^{1}HNMR spectrum of catalyst **1**-$RuH(CO)(PPh_3)_2(L^1)$.

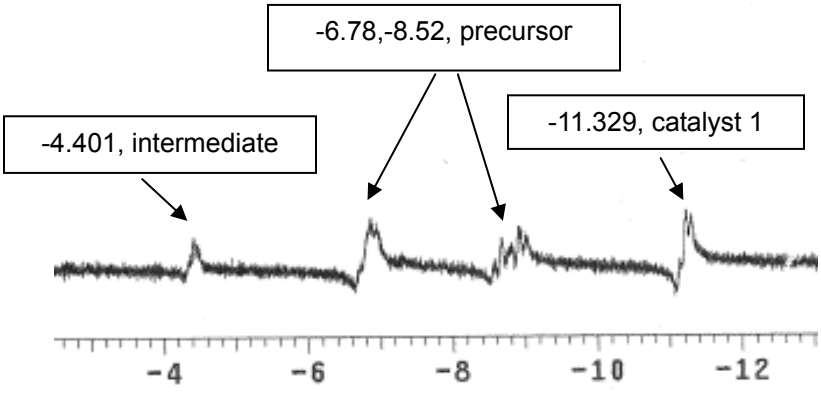


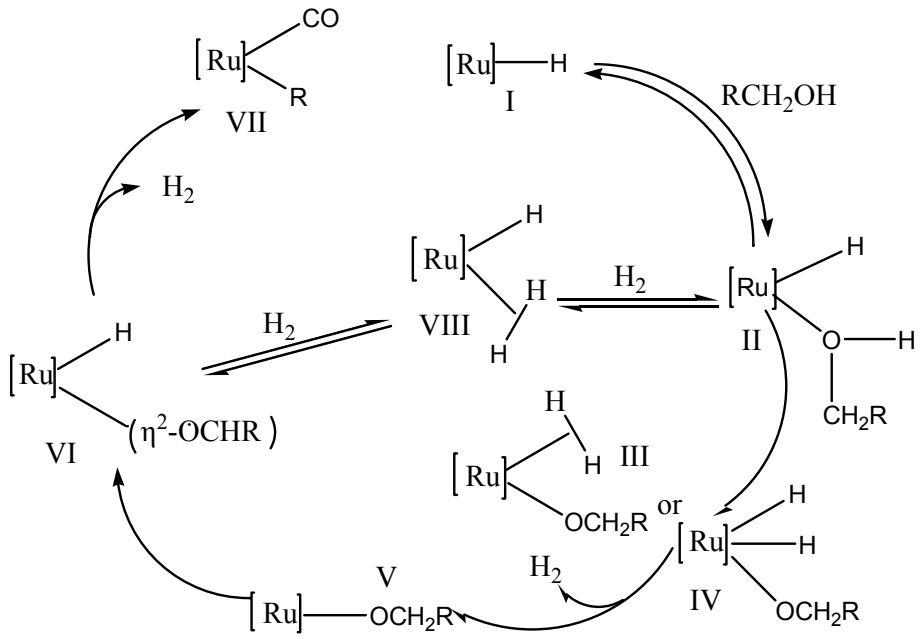
Figure 3.3c Hydride region of the ^{1}HNMR spectrum of intermediate, catalyst **1**-$RuH(CO)(PPh_3)_2(L^1)$ and precursor-$RuH_2(CO)(PPh_3)_3$.

Furthermore, after the elimination of hydrogen from the catalyst, the intermediate can react with H_2, produced during the reaction, to recover the catalysts. All these possibility supported higher activities in alcohol.

A proposed mechanism for the reaction of the ruthenium hydride with alcohol is depicted in scheme 3.5.

The fact that the activity in methanol was not as high as in 2-butanol as solvent is a consequence of the difference in vapor pressure. At 80°C, methanol exists as vapor and excluding the above described mechanism almost fully.

Moreover, performing experiments using solvents and substrates directly from the bottle (as received) and working in open air, similar conversion were obtained. This is evidencing the stability of the new catalyst making the reaction conditions very convenient. Since the new catalysts posses an attractive stability, the catalyst life-time is enhanced resulting in the use of low catalyst loadings.



$$[Ru] = [Ru(CO)(PPh_3)_2(L^n)]$$

Scheme 3.5 Proposed mechanism for decarbonylation of RCH_2OH with ruthenium hydride.

3.4. Conclusion

In conclusion, a series of Ruthenium hydride complexes $RuH(PPh_3)_2(CO)(L^n)$ (n=a-h) incorporating a Schiff base ligand have been developed and investigated as isomerization catalysts. In contrast to what is observed for ruthenium hydride catalysts described in literature, a noteworthy advantage of these new catalysts is their inertness toward air and moisture. This

advantage is related to the coordination of a Schiff base ligand. This also results in a catalyst lifetime enhancement and thus a lower catalyst loading can be applied. Also careful pretreatment of solvents and substrates is unnecessary, since the reaction can be performed in the open air whereupon monitoring of the reaction progress becomes very convenient.

The complexes have been tested on their isomerization performance without and with various solvents and the different behavior of the Ruthenium catalysts has been explained. All the new species revealed higher activities than the parent precursor.

Furthermore, these observations show that modification of the Schiff Base ligand can induce substantial changes in the reactivity of the corresponding catalyst. The obtained results, that all the nitro-substituted complexes performed better than the non-nitro-substituted ones and that all catalysts showed the highest activity in 2-butanol suggest that the catalytic activity strongly depends on the steric and electronic environment of the Ruthenium as well as on the solvent used. Further fine-tuning of the Schiff Base ligands will further improve the potential of these catalytic systems in the field of isomerization.

Finally, the results of the present investigation suggest a promising application of a new family of organoruthenium (II) hydride Schiff base complexes. The fact that hydride catalysts have been reported for transfer hydrogenation and exhibit good isomerization activities (our work) would allow them to combine these two methodologies to some interesting properties by using new substrate combinations. Further studies concerning these points are currently under investigation.

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Chapter 4
O,N-bidentate Ruthenium Azo Complexes as Catalysts for Isomerization Reactions

In this chapter, a series of Ruthenium complexes [(η^6-*p*-Cymene)RuCl(L)] (L incorporate an azo group (**1-5**) or an imine group (**6-7**)) have been investigated and reported for the first time as catalysts for the isomerization, using allylbenzene and 1-Octene as model substrates. Temperature and catalyst/substrate mol ratio have been taken into account as parameters to optimize the isomerization reaction conditions. By using ^{1}H, ^{13}C NMR, FT-IR and element analysis, the new complexes have been characterized and the molecular structure of complex **4** has been determined by crystal analysis.

4.1 Introduction

Olefin isomerization with transition-metal catalysts is well established in organic chemistry in terms of both academic curiosities and industrial interests.[1] Today, the available catalysts have proven their value in many conditions, some of them are even frequently used, for example, the Wilkinson catalyst [$(PPh_3)_3RhCl$] is employed in the isomerization of allylic ethers.[2] However, there is still a high request for cheaper, readily available and highly selective transition metal systems. Furthermore, systems providing especially mild and efficient conditions are required ensuring the C=C bond is only isomerized to a certain position.

During recent years the chemistry of half-sandwich (η^6-arene)ruthenium(II) complexes has been the subject of intense research in the field of organometallic chemistry.[3-6] Except for isomerization, the catalytic properties of these complexes have been investigated in various fields ranging from hydrogen transfer [7-11] to ring-closing metathesis[4, 12-14] ,etc.

The extension of the catalytic activities towards isomerization depends on the metal itself and its structure. Tuning of the ligand environment with the aim to develop catalysts for the isomerization is of our concern. Herein, as an addition of previous investigations on the ruthenium Schiff base chemistry,[15] analogous ligands e.g. Sudan compounds are selected as ligands to investigate.

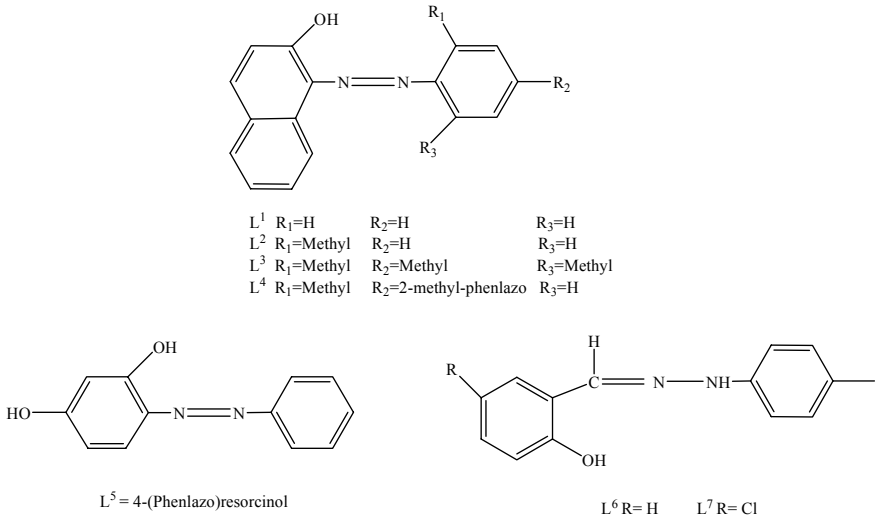
The interest for these ligands is mainly based on three reasons. Firstly, because of the π-acidic nature of the azo function, the ligands are able to form M-C bonds or metallacycles[16]. Moreover, the azo group (-N=N-) can stabilize ruthenium in lower oxidation states due to its strong π-acidic character, while naphtholate/phenolate oxygen, being a hard base, stabilizes the higher oxidation states of the metal ion.[15]

Secondly, the naphthol based ligands are not only potential ligands that can coordinate with the metal by oxygen and nitrogen in a bidentate mode, but they are also better electron donating agents and provide more steric crowding compared to the phenyl group. Naphthol based azo compounds have not been used very often as ligands, although recent work has gone some way to redress the balance. Until now, only three reports could be found in respect to these ligands in combination with ruthenium(II)[17] and ruthenium(III)[18, 19]. Two reports describe the ligands as mono-anionic O,N-bidentate donor ligands, while the third report describes the ligand as a di-anionic C, O, N-tridentate donor ligand.

Thirdly, we expect that some of the selected ligands can act as a tridentate donor with the capability of generating an extra vacancy on the metal center during the catalytic reaction.

As reported earlier in literature, azonaphthol and azophenyl complexes have been extensively used as catalysts for transfer hydrogenation of ketones. [17, 20] Among the different metals catalyzing this reaction, ruthenium-based systems are found to be effective.[21-23] However, in many cases, double bond isomerization occurs as an undesired side reaction meaning that two reactions can be performed by the same catalyst.[24-26]

In this study we focused on the synthesis, characterization and isomerization performance of half sandwich ruthenium azo and imine complexes. To the best of our knowledge, this is the first time these compounds are studied as isomerization catalysts.



Scheme 4.1 Structure of the azo and imine ligands.

4.2 Experimental

4.2.1 General

Unless otherwise stated, all reactions were carried out under a dry Argon atmosphere following conventional Schlenk techniques. All solvents were distilled from the appropriate drying agents and deoxygenated prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 spectrometer in $CDCl_3$ (δ ppm). The NMR spectral data suggest a 1:1 molar ratio of the *p*-cymene and the O,N ligand in **1**–**7**. Elemental analysis was performed using a Perkin–Elmer-2400 CHNS/O analyzer. The Sudan ligands were purchased from Aldrich and used as such. [(*p*-cymene)$RuCl_2]_2$ [27] and the ligands 1-(2,4,6-Trimethylphenylazo)-2-naphthol [28] (5-Chloro-2-hydroxybenzenyl)(*p*-methylphenylazo)[29] were prepared according to the literature. All other chemicals used were of analytical grade without further purification.

%-Yield and selectivity of the isomerization reactions were obtained via capillary GC using a Finnigan Trace GC Ultra with an Ultra Fast Column Module (PH-5 5% diphenyl/95% dimethyl poly-siloxane capillary, helium carrier gas, 1ml/min) column (10 m x 0.10 mm, 0.40 µm) and a FID detector. The temperature program starts at 50°C increasing with 20°C/min. until the end temperature (255°C) is reached.

4.2.2 Isomerization procedure

Pretreatment of 1-octene was necessary before screening. Therefore 1-octene was passed through a column (20 cm x 1.5 cm) of neutral alumina (Acros, 50-200 µm), containing 15 g of alumina per 100 ml of 1-octene, collected in a Schlenk flask and degassed. In an empty 15 ml reaction vessel, an appropriate quantity of the catalyst under investigation was transferred

together with toluene as solvent followed by the substrates. The vessel was immersed in an oil bath and allowed to equilibrate to the desired temperature before timing. Before GC-analysis, the reaction mixture was purified over a silica filter in order to remove the catalyst. Distilled, degassed hexane was used as solvent to prepare the GC samples and 1-dodecane was taken as internal standard.

4.2.3 General procedure for the preparation of thallium salts

To a solution of the ligands **1-7** in dry THF (15 ml) was added drop-wise a solution of thallium ethoxide in THF (5 ml) at room temperature. Immediately after the addition, a yellow solid formed and the reaction mixture was stirred for 2 h. Filtration of the solid under an Argon atmosphere gave the thallium salts in quantitative yields. The salts were used without further purification.

4.2.4 Preparation of [(η^6-*p*-CymeneRuCl(L^n)] (1- 7,n=1-7)

To a solution of [(η^6-*p*-cymene)$RuCl_2$]$_2$ (0.1 g, 0.16 mmol) in THF (5 ml) was added a solution of the corresponding appropriate thallium salt in THF (5 ml) and stirred for 6-8 h at room temperature. Thallium chloride was removed via filtration. After evaporation of the solvent, the residue was dissolved in a minimal amount of toluene and cooled to 0 °C. Hexane was used to precipitate the desired compound. The product was filtered, washed with hexane and dried *in vacuo*. The novel ruthenium complexes appeared as red-brown to dark-brown solids. Yields between 90-98%. All the complexes were found to be air stable in the solid state and moderately stable in solution.

1). [(η^6-*p*-CymeneRuCl(L^1)] (**1**) Although this complex has been reported by Rakesh et al.[17] a modified procedure have been used to realize a high yield. Yield: 96%, red-brown powder. Anal. Calc. for **1** $C_{26}H_{25}ClN_2ORu$, C, 60.28; H, 4.87; N, 5.41; Found: C, 59.95; H, 4.47; N, 5.13.

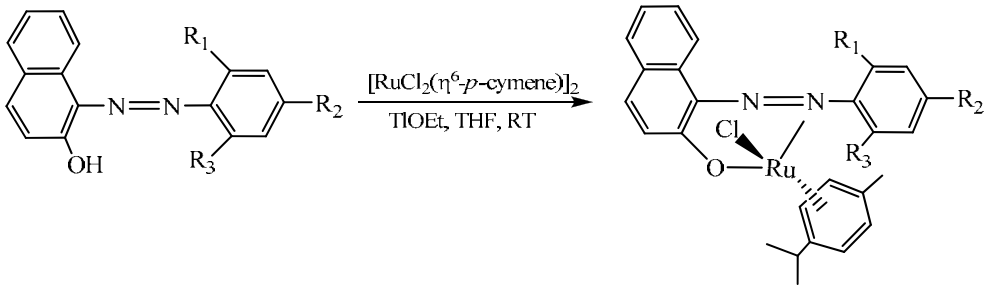
IR spectral data: $\nu_{(-N=N-)}$ 1371.63 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1312.31 cm^{-1}. ^{1}H NMR: 1.05, 1.12 (2d, 2x3H, $2CH_3$- on isopropyl of *p*-cymene, *J*HH=7 Hz), 2.25 (s, 3H, CH_3- on *p*-cymene), 2.56 (sp, 1H, *J*HH=7 Hz, -CH- on isopropyl), 4.59, 4.96 (2d, 2×1H, *J*HH=6 Hz, ring H of *p*-cymene), 5.40 (s, 2H, ring H of *p*-cymene), 7.14–7.56 (m, 7H, ring H), 7.67 (d, H, *J*HH=9 Hz, naphthol ring H), 7.90 (d, 2H, *J*HH=7 Hz, naphthol ring H), 8.26 (d, H, *J*HH=8 Hz, naphthol ring H). ^{13}C NMR: 18.79 (-CH- on isopropyl), 21.89, 22.72 ($2CH_3$- on isopropyl), 30.50 (Me on *p*-cymene), 83.41, 83.72, 85.83, 88.08, 101.14, 101.80 (ring of *p*-cymene), 121.95, 123.46, 124.49, 124.79, 127.19, 127.64, 127.71, 127.77, 128.28, 130.11, 134.89, 137.26, 153.12 (Carbon on L^1), 162.29 (Carbon next to oxygen).

2). [(η^6-*p*-CymeneRuCl(L^2)] (**2**) Yield: 93%, red-brown powder. Anal. Calc. for **2** $C_{28}H_{29}ClN_2ORu$ C, 61.58; H, 5.36; N, 5.13; Found: C, 62.01; H, 5.81; N, 5.34.

IR spectral data: $\nu_{(-N=N-)}$ 1372.15 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1310.99 cm^{-1}. ^{1}H NMR: 1.12, 1.24 (2d, 2x3H, $2CH_3$- on isopropyl of *p*-cymene, *J*HH=7 Hz), 2.16 (s, 3H, CH_3- on phenyl), 2.33 (s, 3H, CH_3- on phenyl), 2.44 (s, 3H, CH_3, on *p*-cymene), 2.64 (sp, 1H, -CH- on isopropyl), 4.31 (s, H, ring H of *p*-cymene), 5.02 (s, H, ring H of *p*-cymene), 5.38, 5.45 (2d, 2×1H, *J*HH=21 Hz, ring H of *p*-cymene), 7.13–7.21 (m, 4H, ring H), 7.32 (d, H, *J*HH=6.9 Hz, naphthol ring H), 7.51 (d, H, *J*HH=7.8 Hz, naphthol ring H), 7.64 (d, H, *J*HH=9.3 Hz, naphthol ring H), 7.93 (d, H, *J*HH=9 Hz, naphthol ring H), 8.13 (d, H, *J*HH=8.4 Hz, naphthol ring H). ^{13}C NMR: 18.94 (-CH- on isopropyl), 22.15, 22.45 ($2CH_3$- on isopropyl), 27.23 (CH_3- on phenyl), 30.63 (Me on *p*-cymene), 31.51 (CH_3- on phenyl), 77.94, 78.71, 80.51, 81.30 (ring of *p*-cymene), 121.92, 123.43, 124.31, 125.66, 127.79, 128.67, 128.91, 129.67, 133.48, 134.89, 153.67 (Carbon on L^2), 162.24 (Carbon next to oxygen).

3). [(η^6-*p*-CymeneRuCl(L^3)] (**3**) Yield: 95%, red-brown powder. Anal. Calc. for **3** $C_{29}H_{31}ClN_2ORu$ C, 62.18; H, 5.59; N, 5.00; Found: C, 61.77; H, 5.16; N, 4.77.

IR spectral data: $\nu_{(-N=N-)}$ 1376.87 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1308.22 cm^{-1}. ^{1}H NMR: 1.26, 1.35 (2d, 2x3H, $2CH_3$- on isopropyl of *p*-cymene, *J*HH=7 Hz), 2.03, 2.06 (s, 2x3H, $2CH_3$- on phenyl), 2.28 (s, 3H, CH_3- on phenyl), 2.60 (s, 3H, CH_3- on p-cymene), 2.75 (sp, 1H, , -CH- on isopropyl), 4.46, 4.91 (s, 2×1H, ring H of *p*-cymene), 5.33, 5.38 (d, 2×1H, ring H of *p*-cymene, *J*HH=7 Hz), 6.96–7.17 (m, 5H, ring H), 7.49 (d, *J*HH=9 Hz, naphthol ring H), 7.58 (d, *J*HH=7 Hz, naphthol ring H), 7.95 (d, *J*HH=8 Hz, naphthol ring H). ^{13}C NMR: 17.68, 18.02 ($2CH_3$- on phenyl), 19.08 (-CH- on isopropyl), 20.98 (CH_3- on phenyl), 22.09, 22.53 ($2CH_3$- on isopropyl), 30.92 (Me on *p*-cymene), 79.40, 83.67, 87.31, 91.33 (ring of *p*-cymene) 121.91, 123.37, 124.14, 127.54, 127.69, 128.46, 129.47, 130.48, 130.88, 136.84, 154.70 (Carbon on L^3), 162.23 (Carbon next to oxygen).



[(η^6-*p*-CymeneRuCl(L^n)] (n=1-4)

L^1	R_1=H	R_2=H	R_3=H
L^2	R_1=Me	R_2=H	R_3=H
L^3	R_1=Me	R_2=Me	R_3=Me
L^4	R_1=Me	R_2=2-Me-phenylazo	R_3=H

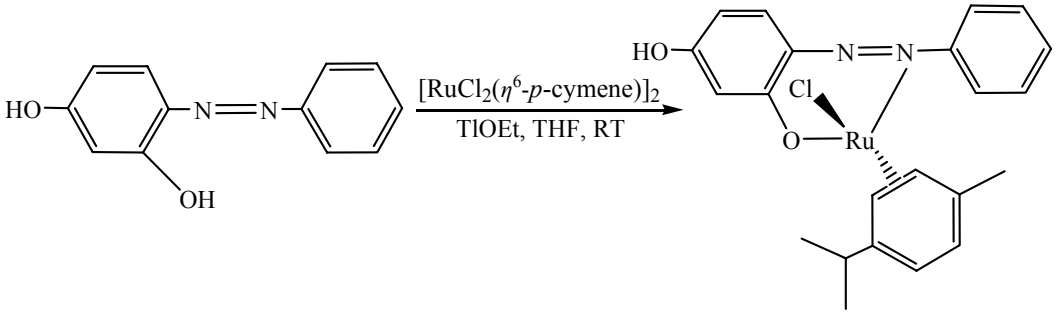
Scheme 4.2 Synthesis procedure for catalysts **1- 4**.

4). [(η^6-*p*-CymeneRuCl(L^4)] (**4**) Yield: 93%, red-brown powder. Anal. Calc. for **4** $C_{34}H_{33}ClN_4ORu$ C, 62.80; H, 5.13; N, 8.62; Found: C, 62.57; H, 5.24; N, 8.23.

IR spectral data: $\nu_{(-N=N-)}$ 1370.93 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1294.59 cm^{-1}. ^{1}H NMR: 1.13, 1.26 (2d, 2x3H, $2CH_3$- on isopropyl of *p*-cymene, *J*HH=6.6 Hz), 2.20 , 2.49 (s, 2x3H, $2CH_3$- on phenyl), 2.80 (s, 3H, CH_3- on *p*-cymene), 3.90 (sp, 1H, , -CH- on isopropyl), 4.43, 5.01 (s, 2×1H, ring H of *p*-cymene), 5.42, 5.51 (d, 2×1H, ring H of *p*-cymene, *J*HH=5.7 Hz), 7.20–7.40 (m, 8H, ring H), 7.53 (d, *J*HH=6 Hz, naphthol ring H), 7.56 (d, *J*HH=9 Hz, naphthol ring H), 7.93 (d, *J*HH=6.6 Hz, naphthol ring H), 8.14 (d, *J*HH=6.4 Hz, naphthol ring H), 8.25 (d, *J*HH=7 Hz, naphthol ring H). ^{13}C NMR: 17.63 (CH_3- on phenyl), 18.32, 18.43 ($2CH_3$- on phenyl), 21.52, 22.89 ($2CH_3$- on isopropyl), 30.60 (Me on *p*-cymene), 79.68, 80.60, 83.29, 86.71, 87.69, 89.09 (ring of *p*-cymene), 115.31, 121.09, 121.64, 121.95, 122.75, 123.58, 123.78, 124.31, 124.58, 125.20, 126.51, 127.19, 127.85, 128.917, 130.40, 131.23, 131.39, 134.69, 136.744, 137.76, 151.26 (Carbon on L^5), 161.77 (Carbon next to oxygen).

5). [(η^6-*p*-CymeneRuCl(L^5)] (**5**) Yield: 90%, red-brown powder. Anal. Calc. for **5** $C_{22}H_{23}ClN_2O_2Ru$: C, 54.60; H, 4.80; N, 5.79; Found: C, 55.02; H, 4.99; N, 5.44.

IR spectral data: $\nu_{(-N=N-)}$ 1364.14 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1278.24 cm^{-1}. ^{1}H NMR: 1.24, 1.97 (2d, 2x3H, $2CH_3$- on isopropyl of *p*-cymene, *J*HH=4.5 Hz), 2.18 (s, 3H, CH_3- on p-cymene), 2.32 (sp, 1H, , -CH- on isopropyl), 4.60 (s, 2H, ring H of *p*-cymene), 4.99, 5.20 (d, 2×1H, ring H of *p*-cymene, *J*HH=6 Hz), 6.91, 7.00 (d, 2×1H, ring H, *J*HH=9 Hz), 7.12 (s, 1H, ring H), 7.23–7.42 (m, 5H, ring H), 9.79 (s, H of hydroxy). ^{13}C NMR: 18.01 (-CH- on isopropyl), 22.85, 23.67 ($2CH_3$- on isopropyl), 31.15 (Me on *p*-cymene), 79.88, 81.91, 83.30, 84.34, 97.18, 98.56 (ring of *p*-cymene), 113.54, 121.46, 123.57, 127.72, 135.07, 140.01, 146.94, 152.26, 156.36, 165.36, (Carbon next to oxygen).



Scheme 4.3 Synthesis procedure for catalyst **5**

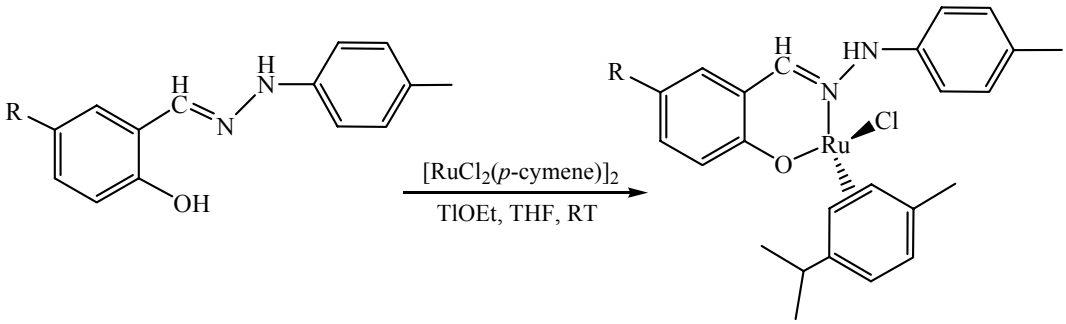
6). [(η^6-*p*-CymeneRuCl(L^6)] (**6**) Yield: 92%, red-brown powder. Anal. Calc. for **6** $C_{24}H_{27}ClN_2ORu$: C, 58.11; H, 5.50; N, 5.65; Found: C, 58.38; H, 5.48; N, 5.46.

IR spectral data: $\nu_{(-N=N-)}$ 1377.76 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1278.21 cm^{-1}. ^{1}H NMR: 1.13, 1.22 (d, 2x3H, $2CH_3$- on isopropyl of p-cymene, *J*HH=1.2 Hz), 2.28 (s, 3H, CH_3- on *p*-cymene), 2.37 (s, 3H, CH_3- on

phenyl), 2.77 (sp, 1H, -CH- on isopropyl), 4.96, 5.17 (s, 2×1H, ring H of *p*-cymene), 5.28, 5.45 (d, 2×1H, ring H of *p*-cymene, *J*HH=6 Hz), 6.48–7.85 (m, 8H, ring H). ^{13}C NMR: 17.48 (CH_3- on phenyl), 18.62 (-CH- on isopropyl), 22.64, 23.40 ($2CH_3$- on isopropyl), 29.71 (Me on *p*-cymene), 65.45 (-CH-N=N), 81.52, 82.56, 85.74, 86.17 (ring of *p*-cymene), 113.09, 115.34, 121.28, 123.79, 128.23, 131.30, 132.43, 135.28, 160.85, 161.76 (Carbon next to oxygen).

7). [(η^6-*p*-CymeneRuCl(L^7)] (**7**) Yield: 91%, red-brown powder. Anal. Calc. for **7** $C_{24}H_{26}Cl_2N_2ORu$: C, 54.34; H, 4.95; N, 5.28; Found: C, 54.73; H, 4.59; N, 5.49.

IR spectral data: $\nu_{(-N=N-)}$ 1380.96 cm^{-1}, $\nu_{(-c-o-Ru)}$ 1293.15 cm^{-1}. ^{1}H NMR: 1.25，1.32 (d, 2x3H, $2CH_3$- on isopropyl of p-cymene, *J*HH=6 Hz), 1.86 (s, 3H, CH_3- on *p*-cymene), 2.17 (sp, 1H, , -CH- on isopropyl), 2.36 (s, 3H, CH_3- on phenyl), 3.75 (s, 2×1H, ring H of *p*-cymene), 4.77, 5.23 (d, 2×1H, ring H of *p*-cymene, *J*HH=3.6 Hz), 7.18–7.36 (m, 9H, ring H). ^{13}C NMR: 18.42 (CH_3- on phenyl), 18.94 (-CH- on isopropyl), 21.65, 22.99 ($2CH_3$- on isopropyl), 30.60 (Me on *p*-cymene), 66.54 (-CH-N=N), 80.52, 81.31, 83.21, 88.09 (ring of *p*-cymene), 114.02, 118.05, 122.34, 129.37, 129.82, 134.738, 135.14, 136.23, 164.16, 165.33 (Carbon next to oxygen).



Scheme 4.4 Synthesis procedure for catalysts **6** and **7**.

4.2.5 Procedure for the preparation of 1-(2,4,6-Trimethylphenylazo)-2-naphthol (L^3)

7.3g (54mmol) of 2,4,6-trimethyl aniline is dissolved in a solution containing 16 ml of concentrated hydrochloric acid and 16 ml of water. By addition of a solution of 4.0g sodium nitrite in 20 ml water in small portions and keeping the solution below 10°C diazotizing occurs. The temperature is kept below 10 °C till the moment that by dipping a potassium iodide–starch paper becomes immediately blue. A cooled solution (5°C) of 7.8 g β–naphthol in 45 ml of 10% sodium hydroxide solution is vigorously stirred and added very slowly to the cold diazonium salt solution. A red color develops and red crystals of 1-(2,4,6-trimethylphenylazo)-2-naphthol (Scheme 1) precipitates. The filtered product is recrystallized using glacial acetic acid, yielding 26% **L^3**.

Elemental analysis: Found: C, 78.20; H, 5.95; N, 9.31. $C_{19}H_{18}N_2O$, calc.: C, 78.58; H, 6.26; N, 9.65].

^{1}H NMR: 2.35 (s, 3H, CH_3-), 2.601 (s, 6H, $2CH_3$-), 6.92 (s, 1H, naphthol ring H), 6.95 (s, 1H, naphthol ring H), 7.003 (s, 2H, phenyl ring H), 7.47 (t, 1H, J-7.5 Hz, naphthol ring H), 7.63 (t, 1H, J-7.2 Hz, naphthol ring H), 7.24 (d, 1H, J-6.6 Hz, naphthol ring H), 7.82 (d, 1H, J-9.6 Hz, naphthol ring H), 8.41 (d, 1H, J-6.6 Hz, hydroxy).

4.2.6 Procedure for the preparation of (2-hydroxybenzenyl)(*p*-methylphenyl azo) (L^6)

Triethylamine (4 equiv. 25.2mmol) is added to a 50 mL methanol solution of the appropriate tolylhydrazine hydrochloride (1 equiv, 6.3 mmol) resulting in a bright yellow solution followed by a drop-wise addition of a 10 ml methanol solution of salicylaldehyde (1 equiv, 6.3 mmol). An orange-yellow solution is obtained after 5-6h stirring at room temperature. Thereafter the solvent was evaporated till precipitation occurred. (Scheme 1). Filtering the solid and recrystallizing using ethyl acetate/hexane (1:8) yields 38% of **L^6**.

Elemental analysis: Found: C, 74.48; H, 6.52; N, 12.01. $C_{14}H_{14}N_2O$ calc.: C, 74.30; H, 6.25; N, 12.38.

^{1}H NMR: 2.29 (CH_3-, s, 3H), 6.86 ~ 7.25 (aromatic-ring, m, 4H), 7.40 (NH, m, 3H), 7.82 (-CH-, s, 1H), 10.91 ((-OH, s, 1H);]

4.2.7 Procedure for the preparation of (5-Chloro-2-hydroxybenzenyl)(*p*-methylphenylazo) (L^7)

The same procedure was used as for **L^6** except that 5-chloro salicylaldehyde was applied instead of salicylaldehyde. The yield after recrystallization is 39%.

Elemental analysis: Found: C, 64.11; H, 4.97; N, 10.31. $C_{14}H_{13}N_2OCl$ calc.: C, 64.49; H, 5.04; N, 10.75.

^{1}H NMR: 2.30 (s, 3H), 6.905 (aromatic-ring, s, 1H), 7.10 (aromatic-ring, s, 1H), 7.26 (aromatic-ring, s, 1H), 7.51 (NH, s, 1H), 7.75 (-CH-, s, 1H), 10.85 (-OH, s, 1H);]

4.2.8 General procedure for the catalytic testing

A mixture of the catalyst (**1**–**7**), and the appropriate amount of substrate (1-octene or allylbenzene) was solved in toluene (1 ml) and heated to the desired temperature for 12 h. After the reaction time, the mixture was cooled to room temperature. The catalyst was removed by addition of 2 ml of Hexane followed by filtration through a silica filter.

4.3 Results and discussion

4.3.1. Synthesis

A series of ruthenium (II) complexes, general formula [(η^6-*p*-CymeneRuCl(L^n)] (n=1-7) incorporating an azo group (**1-5**) or an imine group (**6-7**) have been synthesized conveniently in a high yield.

It follows that all ligands act as bidentate ligands, although some ligands, especially ligand **4** have been assumed to act as a tridentate N, N, O donor ligand, This was not the case here. All the complexes are found to be air stable in both the solid and the liquid states at room temperature and are non-hygroscopic in nature.

4.3.2. Characterization

For ruthenium compounds, the methyl (singlet) of the *p*-cymene ligand appears in the ranges of 2.1–2.96 and the isopropyl protons (two doublets) of the *p*-cymene ligand appear in the ranges of 0.7–1.32 ppm. The isopropyl CH proton appears as a septet in the range of 2.2–4.0 ppm. The protons of *p*-cymene ring show as either four doublets (4H) or two doublets (2H) and a singlet (2H) in the range of 4.3–5.5 ppm. In ^{13}C NMR spectra, the *p*-cymene resonances are assignable to four distinctive ranges of 17.5–21.9, 21.3–22.9, 30.4–31.5 and 77.9–110.8 ppm. The other spectral features are as expected. In complexes **1**–**7**, a similar peak in the range of 160–167 ppm is corresponding to the phenolato/naphtholato carbon.

The IR bands from the azo group of the metal complexes [(η^6-*p*-CymeneRuCl(L^n)] (n=1-5) are most useful to determine the coordination mode. For instance, all of them exhibit many sharp and strong vibrations within the region of 500–1700 cm^{-1}. To confirm the ligand coordination IR-spectra of the ligands were analyzed and compare with the spectra of the complexes. The infrared spectra of the ligands show bands around 1446–1476 cm^{-1} and 1266–1278 cm^{-1} corresponding to the azo group $\nu_{(-N=N-)}$ and the aromatic $\nu_{(C-O)}$ stretch vibrations respectively. In the coordinated compounds, the azo vibration, $\nu_{(-N=N-)}$, exposes peaks at lower frequency 1364–1380 cm^{-1}. This supports the assumption that the coordination of the nitrogen atom can reduce the electron density in the azo frequency due to the (d-π) Ru (II)→π*(L) back bonding effect.[30] Meanwhile, in all the compounds, a shift to higher frequency occurs for the aromatic $\nu_{(C-O)}$ stretch confirming the coordination of the aromatic oxygen. [19]

4.3.3 X-ray crystallography

In order to determine the coordination mode of the ligands in the ruthenium complexes and the stereochemistry of the complexes, the crystallization of the complex [(η^6-*p*-CymeneRuCl(L^4)] (**4**) has been proceeded by slow evaporation of a MeOH-Hexane solution at 0-4°C. It follows from X-ray analysis that one MeOH molecule (solvent) is enclosed in the crystal, resulting in a crystal [(η^6-*p*-CymeneRuCl(L^4)]·CH_3OH. The X-ray analysis results and refinements are given in table 1 and 2. The complex essentially has an octahedral coordination geometry, as shown in Fig. 1. The molecular structure shows that the O_1, N_2-donor in the arylazo-naphtholate ligand adopts a bidentate chelating mode and the *p*-cymene carbons occupy one face of the octahedron. The Ru-C(arene) distances vary considerably from 2.182 to 2.212 Å. Compared with earlier reported work, the distances of Ru_1-O_1, Ru_1-N_2 and Ru_1-C are within the normal range.[17] A six-membered ring planar with the naphtholate ligand is generated by the two carbon atoms from naphtholate group, the two nitrogen from coordinated diazo group, the oxygen from phenolic group and ruthenium.The dihedral angle of the naphthalene plane and the benzene plane C_{21} to C_{26} in arylazo-naphtholate ligand is 64.0°. Comparing the crystal data with the one reported by Rakesh, most of the bond angles of the crystal [(η^6-*p*-CymeneRuCl(L^4)]·CH_3OH were larger due to the increased steric congestion around the Ru center.

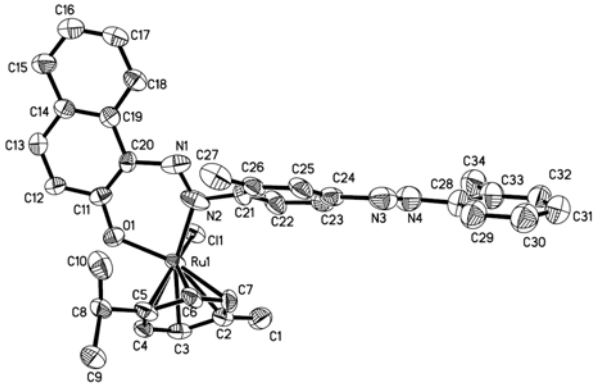


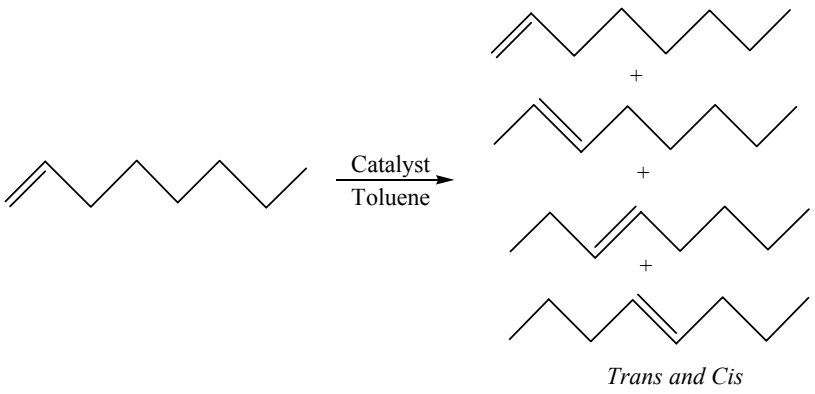
Figure 4.1 The molecular structure of complex **4,** the solvent molecule MeOH has been omitted for clearity. (30% thermal probability ellipsoids)

4.3.4. Isomerization activity

Allylbenzene is used as a model substrate for the isomerization applying all kinds of catalysts, such as transition metals – Ti, Zr,[37] Co,[38] Rh,[39, 40] Ir,[41] Au,[42] and Ru,[43-46] , mean metal – Mg,[47] and even some non-metal compound – P.[48] While 1-octene is also extensively used as a model substrate [35], these two compounds are selected as representatives alkenes to evaluate the performance of the complexes [(η^6-*p*-CymeneRuCl(L^n)] (n=1-7).

Table 4.1 Crystal data and structure refinement for [(η^6-*p*-CymeneRuCl(L^4)]·CH_3OH.

Molecular formula	C_{35} $H_{37}ClN_4O_2Ru$
Molecular weight	682.21
Molecular size(mm)	0.18 x 0.16 x 0.10
Molecular color	brown
Crystal system	Monoclinic
Space group	*P*2(1)/*n*
a(Å)	15.845(3)
b(Å)	14.337(3)
c(Å)	17.406(4)
β	116.27(3)
V	3545.8(12)
Z	4
*D*c	1.278
F (000*)*	1408
Absorption correction T_{max}/T_{min}	0.9469/ 0.9073
Goodness-of-fit on F^2	1.139
Absorption coefficient (mm^{-1})	0.551
Largest diff. peak and hole(e $Å^{-3}$)	0.667/-0.629
Data/restraints/parameters	6189 / 326 / 452
R_1, $wR_2[I > 2\sigma(I)]$	0.0993 0.2325
R_1, wR_2 (all data)	0.1324 0.2548



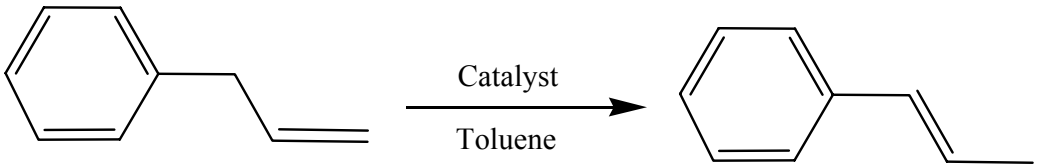
Scheme 4.5 Isomerization reaction for 1-octene.

To investigate the catalytic activity, all ligands and precursor complexes have been screened under identical reaction conditions and no isomerization activity could be observed. Compound **6** and **7** are also found to be totally inactive for the isomerization of both substrates.

Table 4.2 Selected bond lengths (Å) and angles (°) for complex **4**

Bond Distances Å			
Ru(1)-O(1)	2.038(4)	Ru(1)-N(2)	2.051(5)
Ru(1)-C(4)	2.181(5)	Ru(1)-C(6)	2.183(5)
Ru(1)-C(7)	2.191(6)	Ru(1)-C(5)	2.202(6)
Ru(1)-C(3)	2.205(5)	Ru(1)-C(2)	2.211(6)
Ru(1)-Cl(1)	2.4095(15)	O(1)-C(11)	1.308(6)
Bond Angles º			
O(1)-Ru(1)-N(2)	88.9(2)	C(4)-Ru(1)-C(6)	66.8(2)
O(1)-Ru(1)-C(4)	88.39(19)	N(2)-Ru(1)-C(5)	116.3(2)
O(1)-Ru(1)-C(6)	122.2(2)	N(2)-Ru(1)-C(2)	121.8(3)
N(2)-Ru(1)-C(4)	153.8(2)	N(2)-Ru(1)-Cl(1)	84.16(15)
N(2)-Ru(1)-C(6)	92.98(19)	C^0-Ru(1)-Cl(1)	128.33(19)
N(2)-Ru(1)-C(7)	95.7(2)	C^0-Ru(1)-O(1)	125.62(12)
N(2)-Ru(1)-C(3)	159.8(3)	C^0-Ru(1)-N(2)	129.97(13)
O(1)-Ru(1)-Cl(1)	85.16(11)		

To optimize the reaction conditions, the different catalyst:substrate mol ratios and temperature were chosen as parameters and the results are summarized in Table 3 and 4.



Scheme 4.6 Isomerization reaction for allylbenzene.

From Table 3 and 4 it follows that changing the C:S ratio from 1:1000 to 1:2000, the reaction still proceeds smoothly accompanied by a moderate drop in conversion. Compared with the raise of the C:S ratio, the decrease of conversion is much less than half in most cases. Higher catalyst concentrations favored the formation of the *cis*-alkene; as the catalyst concentration was lowered, more *trans*-isomer was formed. Comparing the different catalysts it follows that the change in selectivity is related to the bulkiness of the aniline part of the azonaphthol ligand. This signifies that the less steric hindering in the ortho positions, the higher the *cis* ratio.

Table 4.3 Isomerization of 1-octene by [(η^6-*p*-cymeneRuCl(L^n)] (n=1-5). %- conversion is measured after 12 h.

Cat.	T (°C)	C/S Ratio[B]	1-Octene[A]	2-Octene	3-Octene	4-Octene	
						Trans	*Cis*
1	60	a	90.6	14.9	49.8	0	25.8
		b	87.9	51.0	28.2	1.2	7.5
	80	a	87.0	10.5	55.4	3.5	17.6
		b	75.6	14.0	51.0	1.6	8.9
	100	a	80.4	10.0	11.3	2.1	57.0
		b	68.8	10.0	46.0	2.5	10.3
2	60	a	68.8	42.4	17.4	0	9.0
		b	59.8	59.7	0.1	0	0
	80	a	92.2	8.3	51.1	6.9	25.6
		b	78.7	9.5	59.0	3.2	7.0
	100	a	86.9	7.3	55.6	4.5	19.5
		b	84.2	6.7	55.5	4.2	17.9
3	60	a	37.6	5.9	27.3	0.6	3.9
		b	36.0	3.8	28.1	0.5	3.6
	80	a	92.2	8.2	52.4	7.1	24.5
		b	78.8	9.4	59.1	3.2	7.0
	100	a	87.1	7.2	55.7	4.6	19.6
		b	84.2	6.6	55.5	4.2	17.9
4	60	a	44.6	8.3	31.6	0.3	4.4
		b	27.8	3.4	21.0	0.51	2.9
	80	a	82.2	8.8	51.2	4.52	16.8
		b	73.7	10.4	51.7	1.67	10.1
	100	a	74.1	10.8	51.1	1.99	10.2
		b	56.9	6.9	42.7	1.32	6.0
5	60	a	32.1	4.7	24.0	0.93	2.4
		b	0.8	0.1	0.2	0.07	0.4
	80	a	1.4	0.2	0.6	0.057	0.5
		b	1.3	0.2	0.5	0.093	0.5
	100	a	1.2	0.2	0.5	0.06	0.5
		b	0.7	0.1	0.2	0.040	0.4

A. Here is the conversion of 1-octene

B. Catalyst/ Substrate ratio: a=1:1000, b=1:2000.

Table 4.4 Isomerization of allylbenzene by [(η^6-*p*-CymeneRuCl(L^n)] (n=1-5).). %- conversion is measured after 12 h.

Catalyst	C/S Ratio[A]	60°C	80°C	100°C
[(η^6-*p*-CymeneRuCl(L^1)]	a	89.2	95.6	98.4
	b	73.0	93.4	96.3
[(η^6-*p*-CymeneRuCl(L^2)]	a	27.2	90.9	86.3
	b	25.4	85.9	70.2
[(η^6-*p*-CymeneRuCl(L^3)]	a	10.8	90.8	86.2
	b	10.1	85.9	70.1
[(η^6-*p*-CymeneRuCl(L^4)]	a	34.1	81.1	76.9
	b	27.6	66.5	31.5
[(η^6-*p*-CymeneRuCl(L^5)]	a	6.5	5.7	3.4
	b	2.3	1.6	0.4

A Catalyst/ Substrate mol ratio: a=1:1000, b=1:2000

For both substrates, catalysts **2**-**4** show higher activity when temperature is enhanced from 60°C to 80°C. Mounting the temperature to 100°C diminished the final conversion. From these results, it is clear that a temperature of 80°C is the best compromise for catalysts **2**-**4**.

When 1-octene is taken as substrate, the higher the temperature, the lower the substrate conversion becomes for catalyst **1** and **5**. This phenomenon can be related to the thermal stability of the catalysts. While using allylbenzene, the behavior of catalyst **1** is consistent with the temperature however, a contrasting behavior of catalyst **5** is observed.

If only the conversion of 1-octene is taken into account, the catalytic actvity of catalysts **1**-**3** is similar (yield 92-90%) without dimerization and polymerization. Considering the selectivity, catalysts **1**-**4** all catalyze 1-octene to n-octene in yields higher than 50% by controlling the C:S ratio, temperature and reaction time. For the catalyst **2**, using a C:S=1:2000, preferentially 2-octene was generated and the highest product selectivity was reached.

Comparison of the catalysts reveals that catalyst **1** has a better performance for allylbenzene, implicating an excellent yield (more than 98%) and a high selectivity (*trans*-β-methylstyrene exclusively). Contrary to the results from late transition metal complexes in which the isomerized products are in equilibrium, this interesting result — no *cis*-β-methylstyrene — indicate the lack of isomerization between the *cis* and *trans*-β-methylstyrenes.[49] The conversion obtained from catalyst **5** was much lower in comparison to the other catalysts indicating that the structure of naphthol plays a significant role in isomerization.

It is known from literature that the ruthenium azonaphthol/azophenyl complexes are used as catalysts for transfer hydrogenation of carbonyl compounds with *iso*-propanol as a hydrogen

source. In this classical pathway, the ruthenium complexes dehydrogenate the alcohol and deliver the hydrides to a ketone or an α,β-unsaturated ketone.[50, 51] However, the coordination of the substrate to the hydride ruthenium metal intermediate is not suitable here.

Moreover, studies by other teams dealing with metathesis reactions mediated by ruthenium-arene complexes have shown that the release of the arene ligand is crucial and is responsible for the generation of the catalytic active species.[52-54] Nonetheless, in this study, a careful NMR monitoring of the isomerization revealed no ligation of the cymene ligand. (see Figure 2) Comparing the ^{1}H-NMR spectra of the cymene region of the catalyst before and during reaction (Figure 2), it was observed that the four doublet peaks of the cymene ring remain during the catalytic reaction. The shift of the peaks can be understood as a result of the nitrogen dissociation and the substrate coordination. Therefore, it is plausible to state that the proposed mechanism depicted in Scheme 7 is responsible for the formation of the catalytic active species during the isomerization reaction.

The proposed pathway for this reaction is the decoordination of the nitrogen generating a vacant coordination site followed by the substrate coordination to the metal center. Subsequently, following the less common π-allyl mechanism, an oxidative addition of an activated allylic C-H bond to the metal yields a π-allyl metal hydride and generates the desired isomerization product.[55-57]

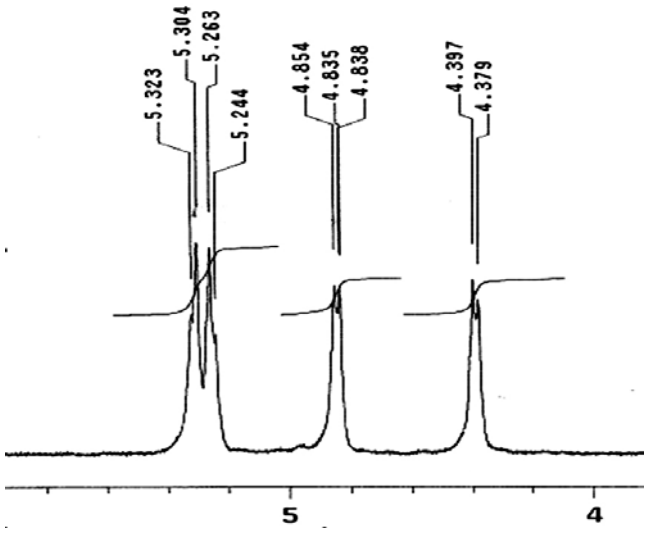


Figure 4.2 a) ^{1}H NMR spectrum of the cymene region of the catalyst.

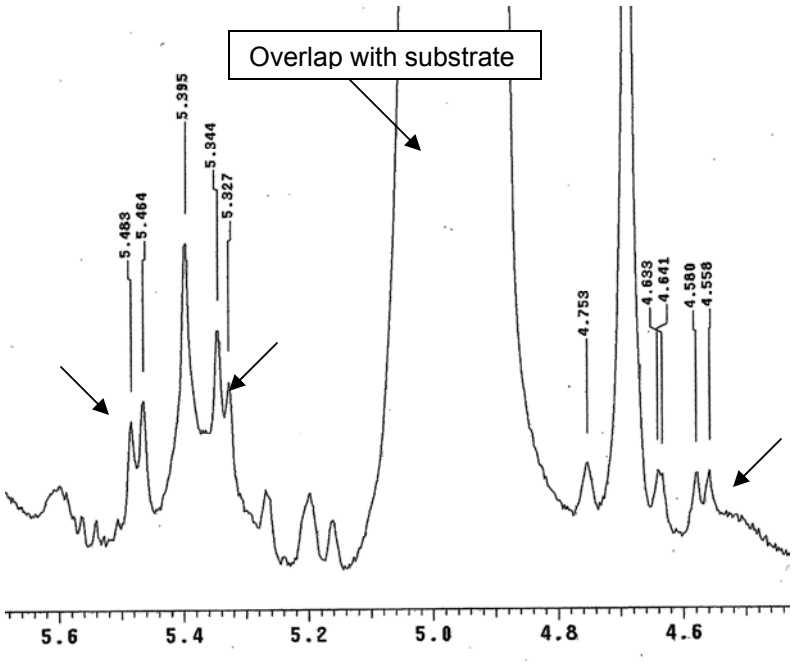


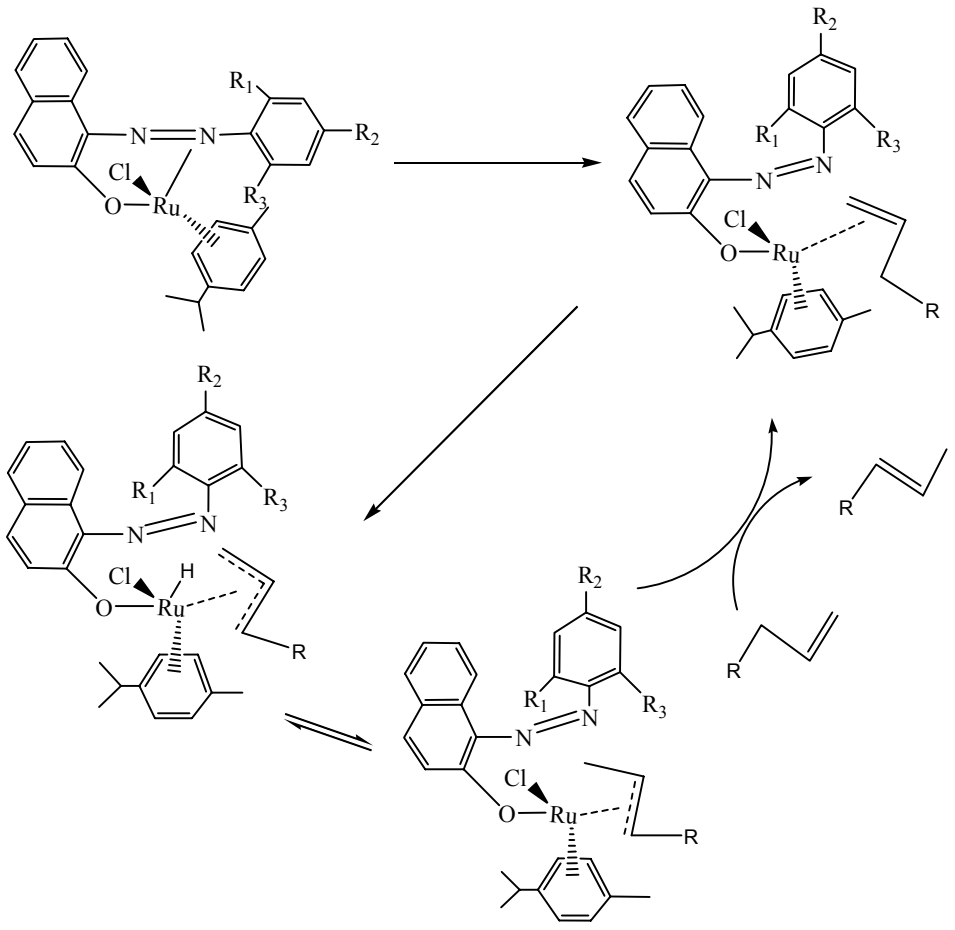
Figure 4.2 b) ^{1}H NMR spectrum of the cymene region of the catalyst during reaction.

Furthermore, results obtained from experiments in which the influence of moisture and air sensitivity was studied proved that the isomerization using catalyst **1-5** is not affected and so, the isomerization can be executed using solvents form the bottle and in open air.

4.4. Conclusions

In conclusion, a new class of ruthenium-based catalysts useful for isomerization has been synthesized. The X-ray crystal structure of the complex (**4**) reveals an octahedral environment around ruthenium. In contrast to what is observed for most other described catalysts, a noteworthy advantage of these catalysts is their inertness toward air and moisture preventing a meticulous pretreatment of solvents and substrates. This benefit makes the set-up of the experiment and the monitoring of the reaction progress very convenient.

The ruthenium complexes have been tested on their isomerization activity and their different behavior has been explained. Catalysts (**1-4**) are effectively active for the isomerization without any dimerization or oligomerization. The obtained results imply that the naphthol part plays a significant role in the isomerization suggesting that the catalytic activity for 1-octene strongly depends on the steric and electronic environment of the ruthenium. So, the prospective of these catalysts in the field of isomerization can be further improved by fine-tuning of the ligand environment. The isomerization activity of complex **1** for allylbenzenyl is superior to most of the reported systems. [41, 44, 58-61]



Scheme 4.7 Proposed mechanisms for the isomerization by catalysts **1-5**.

In general, the results of the present exploration suggest a promising application of a new family of organoruthenium (II) complexes containing an azonaphthol/azophenyl group. Furthermore, the fact that these catalysts have been reported for transfer hydrogenation and exhibiting good isomerization activities (this work) allows them to combine these two methodologies to some interesting properties by using new substrate combinations. Further studies concerning these points are currently under investigation.

Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC reference number 719359. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: C44 1223/336 033; e-mail: deposit@ccdc.cam.ac

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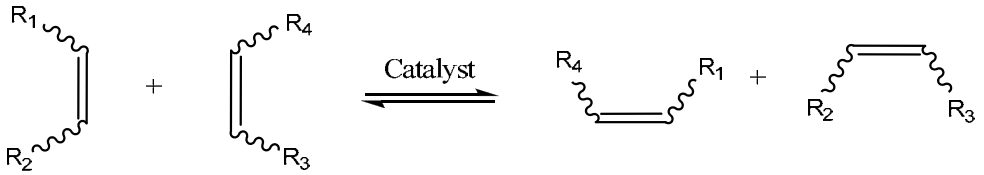
Chapter 5
Olefin Metathesis

5.1 Introduction

Although many chemists such as Ziegler, Tebbe, Eleuterio, Natta, Chauvin, Grubbs, Schrock and etc, never stop their steps to design a better performing catalyst systems for olefin metathesis, nobody would have thought before half a century ago, that olefin metathesis would belong once to the standard repertoire of the organic chemist. Last two decades, a rapid development of catalysts has been achieved. Today the multiplicity of metathesis examples from the current literature with applications from total synthesis and medical chemistry are a rich source for every chemist. Since the importance of this kind of reaction still will increase, herein the aim is only to focus on the overview of the metathesis transformations and a brief outline of the mechanistic pathway. Furthermore, some selected examples of catalyst systems and commercial applications will be highlighted.



Scheme 5.1 A model reaction of olefin metathesis.

'Metathesis' is a word derived from the two Greek words *meta* (change) and *thesis* (position).[1] The metathesis chemistry includes olefin metathesis,[2-19] alkyne metathesis,[2-6] and enyne metathesis.[25-35] Olefin Metathesis - a transalkylidenation allows the exchange of alkylidene

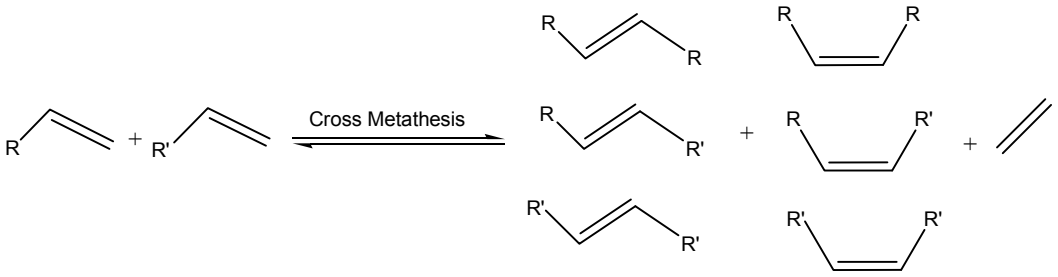
fragments between different olefins. A model reaction of the interchanged double bonds between the carbon atoms is depicted below.

Olefin metathesis is a popular, synthetically useful and high-yield procedures reaction for both lab and industry use. In the presence of certain transition-metal compounds, especially various metal carbenes, alkylidene exchange results in several outcomes:

• CM (Cross Metathesis): straight exchange of groups between two acyclic olefins [7-19]
• RCM (Ring-Closing Metathesis): ring closure of acyclic dienes[7-19]
• ROM (Ring-Opening Metathesis): formation of dienes from cyclic and acyclic olefins[20-22]
• ROMP (Ring-Opening Metathesis Polymerization): polymerization of cyclic olefins [2-6]
• ADMET (Acyclic Diene Metathesis Polymerization) : polymerization of acyclic dienes [7, 8]

The power of olefin metathesis is that it transforms the carbon-carbon double bond. With certain catalysts, new carbon-carbon double bonds are formed at or near room temperature even in aqueous media from starting materials that bear a variety of functional groups. The catalysts are available commercially, making the reaction accessible even to novice researchers.

Among these reactions, cross metathesis is the intermolecular catalyzed reaction of terminal vinyl groups releasing ethylene. Cross metathesis deals with linear transformations and the substitution pattern determines the equilibrium of homo-dimerization vs. hetero-dimerization. Statistically, the reaction can lead to three possible pairs of geometric isomers, i.e. *E/Z* pairs for two homo-couplings and the cross-coupling (RCH=CHR, R'CH=CHR', and RCH=CHR') - a total of 6 products. (Scheme 5.2)

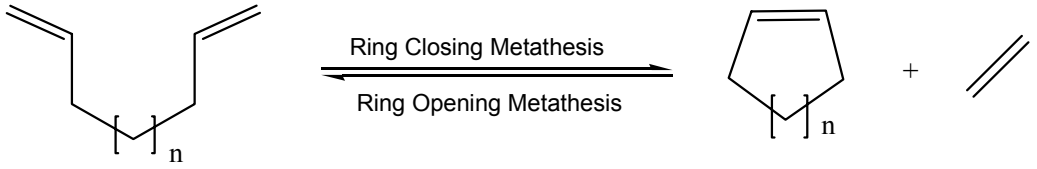


Scheme 5.2 Cross metathesis transformations.

Because of the various examples in which two alkenes with different reactivity give the cross-coupled product with different yields and selectivity, the selectivity of this reaction is currently undergoing further study.

Ring closure between terminal vinyl groups and ring opening of strained alkenes are reversible process reactions. (Scheme 5.3) The ring closing metathesis is a valuable synthesis tool for preparing from 5- up to 30-membered rings.

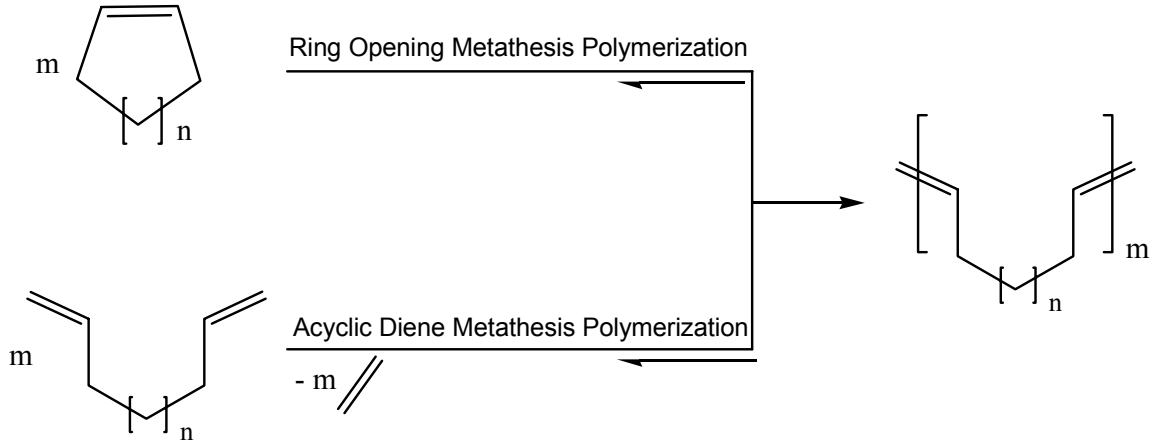
When molecules with terminal vinyl groups are used, the equilibrium can be driven by the ready removal of the product ethylene from the reaction mixture. While with the development of the ring closing reactions, the variety of possibilities has been pointed out, i.e. these reactions are no longer limited to the metathesis of terminal double bonds. Current examples of alkene-alkyne metathesis as well as alkyne-alkyne metathesis and domino metathesis show the unbelievable variety of possibilities, from which research and development can select today.



Scheme 5.3 Ring-Closing Metathesis and Ring-Opening Metathesis transformations.

Strained rings may be opened by a catalyzed reaction with a second olefin following the mechanism of the cross metathesis. The driving force is the relief of ring strain. As the products contain terminal vinyl groups, further reactions of the cross metathesis variety may occur. Therefore, the reaction conditions (time, concentrations,...) must be optimized to favor the desired product. Ring opening metathesis can employ an excess of a second olefin (e.g. ethylene), but can also be conducted as a homo- or co-polymerization reaction. The driving force in this case is the loss of ring strain.

In absence of excess of a second reaction partner, polymerization occurs (Scheme 5.4).



Scheme 5.4 Ring-Closing Metathesis Polymerization and Acyclic Diene Metathesis Polymerization transformations.

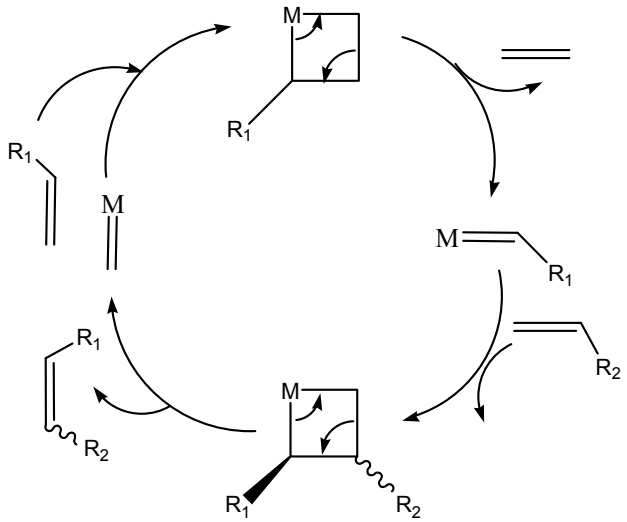
It is the same as in RCM and CM, the formation of a volatile compound and an internal olefin is also the driving force in ADMET reactions. In order to favors RCM, low concentrations of substrate can be used to prevent oligomerization obtained by the competitive ADMET reaction. Meanwhile, because the formation of stable rings favors RCM, the stability of the ring is of principal importance in this competition. On the other hand, in ROMP and ROM a high ring strain is necessary to overcome the loss in entropy during the reaction.

From the theory, since the very high energies of the potential TS's (Transition State) exist, no classical orbital attack is possible to obtain above reactions. All of these applications have been made possible by the development of homogeneous catalysts. It is important to note that a catalyst can only speed up the reaction to thermodynamic equilibrium but can never change that particular equilibrium.

5.2 Mechanism

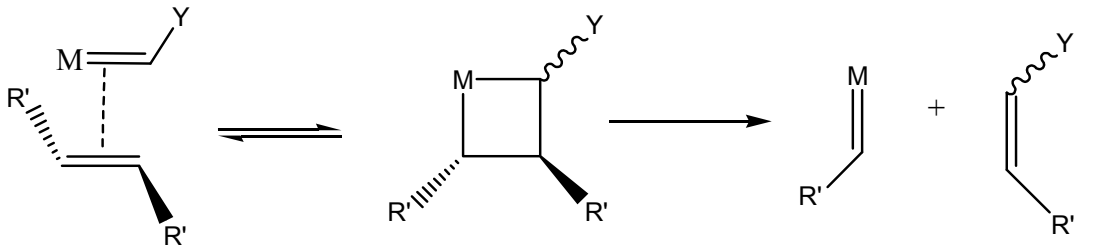
For all the catalyzed reactions, the understanding of mechanism of the catalyst functions in the reaction must provide some basic information to develop novel, more efficient catalysts. The study on metathesis reaction has shown that the new catalysts should be found among isolable metal-carbene complexes.

One of the culminations in the history of the development of olefin metathesis was the awarding in 2005 of the Nobel Prize for chemistry to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for their development in the field of olefin metathesis.

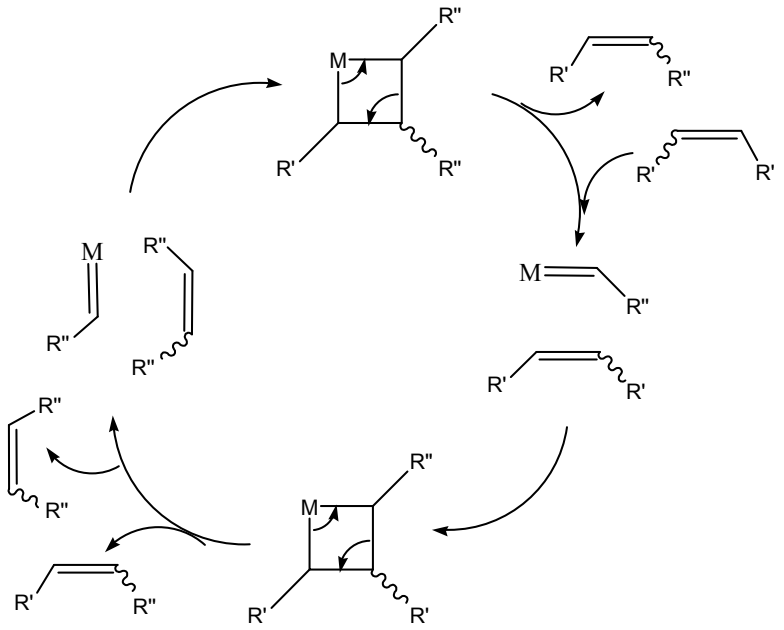


Scheme 5.5 Chauvin-Herisson Mechanism.

Initiation:



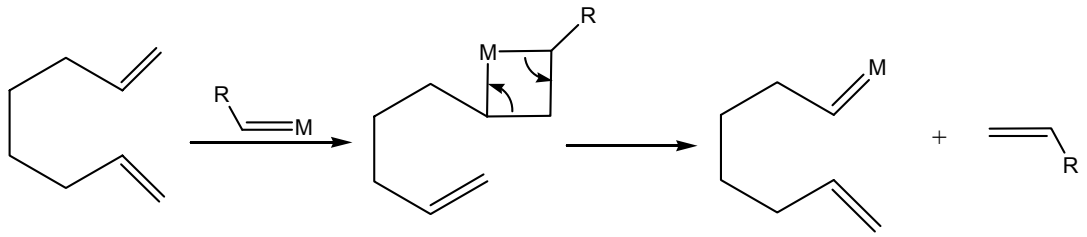
Catalytic Cycle:



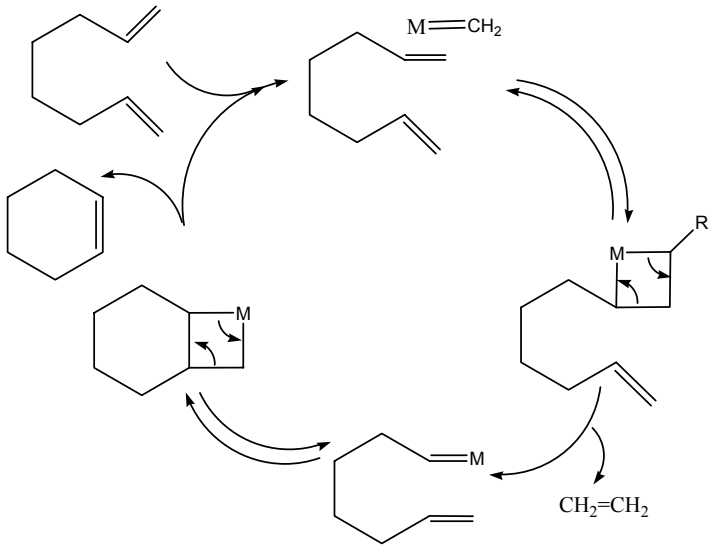
Scheme 5.6 Mechanism of cross metathesis.

In 1971, Y. Chauvin and J.-L. Herisson of the French Petroleum Institute, suggested an unraveling mechanism (Scheme 5.5) that olefin metathesis reaction is initiated by a metal carbene and goes through a cycle of reversible steps.[9] At beginning, the metal carbene reacts with an olefin in a concerted mechanism to form a metallacyclobutane ring. Subsequently the metallacyclobutane ring opens either into the initiating species or creatively into a new metal carbene fragment. Another substrate olefin can react with the carbene centre to ultimately get the metathesized product and the carbene initiator. Then new carbene reinitiate a new catalytic cycle. The reaction is characterized by a series of reversible steps, which lead to a thermodynamic equilibrium of reaction products.

Initiation:



Catalytic Cycle:

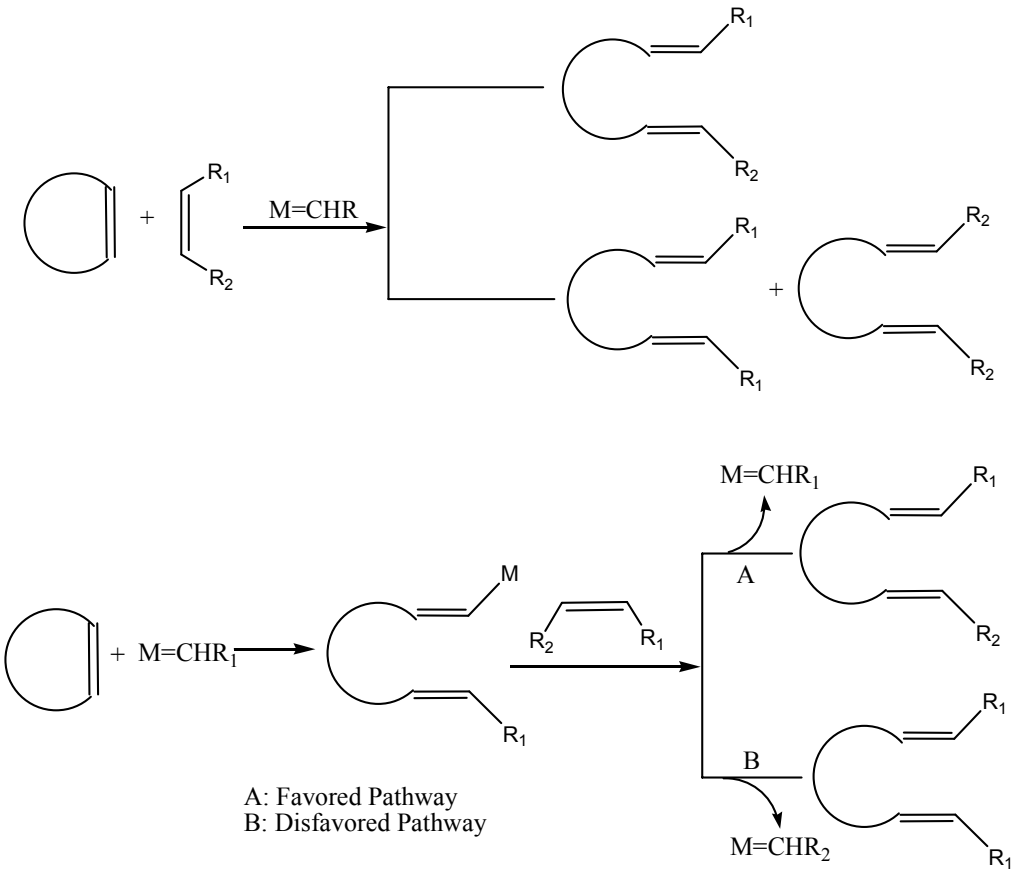


Scheme 5.7 Mechanism of ring closing metathesis.

Since then, the supporting discussion to the Chauvin-Herisson mechanism has been published in some important publications. [10-15] For instance, Katz et al. has described the olefin metathesis kinetics and it was the first time to give full evidence for the metal carbene mechanism. [10] From the later experiments reported by Grubbs, [11] and Schrock, [12] it also has been proved.

Base on the Chauvin-Herisson mechanism, the following catalytic cycle for olefin metathesis can be proposed. Regarding cross metathesis, which in former times due to the reduced E/Z selectivity and the statistic product distribution is rather a stepchild, evolved more and more to a useful method. (Scheme 5.6)

In RCM, the key intermediate is a metallacyclobutane, which can undergo cyclo-reversion either towards products or back to starting materials. When the olefins of the substrate are terminal, the driving force for RCM is the removal of ethylene from the reaction mixture. (Scheme 5.7)



Scheme 5.8 Possibility of two metal carbenes.

On the base of mechanistic studies and various experimental data, it has been shown that reactions of cycloalkenes with acyclic internal olefins give two additional products, while from the reaction between cycloalkenes and terminal olefins only one product could be obtained. When a metal carbene reacts with an olefin, two metal carbenes can be generated. (Scheme 5.8) If the groups around the double bond of the acyclic olefin are sufficiently different, one metal carbene product will be favored over the other. Namely, which products are formed depends on the substituents of the acyclic olefin.

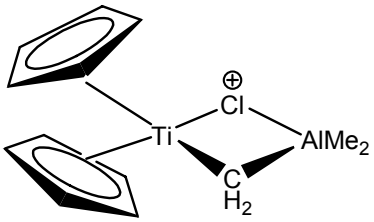
5.3 Catalyst systems

After Ziegler discovered the metal-catalyzed olefin polymerizations the polymer science was changed forever, the science surrounding it supplied the motivation for the development of olefin metathesis catalysts. Thereupon, a great number of catalysts has been introduced into olefin metathesis. Compared with the black box catalysts in the early stage, after the Chauvin mechanism had been established, it was the outset for the development of well-defined catalysts.

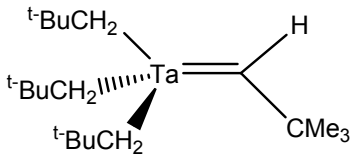
The common feature of the catalysts in the early systems is ill-defined, namely, without any mechanistical understanding. Early transition metals supported on oxide supports (e.g. WO_3/SiO_2) and mixtures of various components (early transition metal halides and reducing/alkylating agents; e.g.$MoCl_5/Et_3Al$ or WCl_6/Et_3Al) are all used in the industrial applied metathesis. Due to a low amount of active species, the ill-defined catalysts are inefficient. Because of the Lewis acidic feature of these catalysts they were readily deactivated by common Lewis basic functional groups, they are only useful for reactions involving unfunctionalized hydrocarbons.

”well-defined” catalysts refer to the isolable catalytic systems which can be characterized by a stoichiometric composition and for which the actual propagating species is well known. During the development of olefin metathesis catalyst, the different metals had been involved, such as Ti, Ta, Rh, Mo, W and Ru. Among them, Mo, W and Ru have emerged as the key elements to achieve highly active and selective catalysts. Generally, they can be divided in two categories: Mo and W-based systems are typically high oxidation state d^0 alkylidene complexes; they contain a set of ligands which can increase the electrophilicity of the metal center. While Ru-based systems are d^4 metal complexes with basic ligands which assist in the dissociation of one ligand to generate the active species.

The comprehensive use of olefin metathesis in organic synthesis has been directly correlated to improvements in metal-carbene catalysts. Before Tebbes' complex (Fig 5.1) has been reported, none of the known carbene complexes at that time showed any metathesis activity, the complex provided an excellent model for metathesis reaction although this titanium catalyst showed very low activity. Concurrently, Richard R. Schrock developed tantalum carbene complexes (Fig 5.2). Later, based on the better insights in the metathesis reaction, a serials of W-based (e.g. $W(O)(CH\text{-}^{t}Bu)(PMe_3)_2Cl_2/AlCl_3$), [13] $[W(CH\text{-}^{t}Bu)(OCH_2\text{-}^{t}Bu)_2X]^+ AlX_4^-$, [14] $(OR)_3W{\equiv}C\text{-}^{t}Bu$, [12] $W{=}CH\text{-}^{t}Bu(NAr)(OR)_2$), [15] and etc.) and Mo-based catalysts (e.g. $Mo{=}CHR(NAr)(OTf)_2(dme)$ [16] and etc.) were reported as metathesis active complexes.



Tebbe Complex



R.Schrock Complex

Figaure 5.1 Tebbes' Complex and Schrocks' Complex.

The chemists most responsible for developing metal-carbene catalysts for the broad use to olefin metathesis are professors Robert H, Grubbs at California Institute of Technology andRichard R. Schrock at Massachusetts Institute of Technology. Together with Yves Chauvin, these two professors were also awarded the Nobel Prize at the same time. Richard R. Schrock got the Prize for being the first to have discovered an alkylidene complex and for having developed a whole family of tungsten and more important molybdenum alkylidene complexes.[17] Robert Grubbs was honored for his development of ruthenium catalysts, which up till now are by far the most tolerant catalysts towards functional groups and simultaneously compete with the most active Schrock catalysts regarding catalytic activity.

The so-called Grubbs and Schrock catalysts were developed through focused research programs going back to the 1970s. In the mid-1980s, Schrock came up with highly reactive systems based on tungsten and on molybdenum. The latter were less reactive and therefore more selective in reacting with olefins rather than with other functional groups. The widely known Schrock Catalyst depicted in Fig. 5.2.[16] Due to the high oxophilicity of the early transition metal center, this Mo-catalyst is sensitive to ambient air and moisture and difficult to store because of the easily decomposition. The tolerancy of the catalyst towards protic compounds such as alcohols and aldehydes is also very poor.

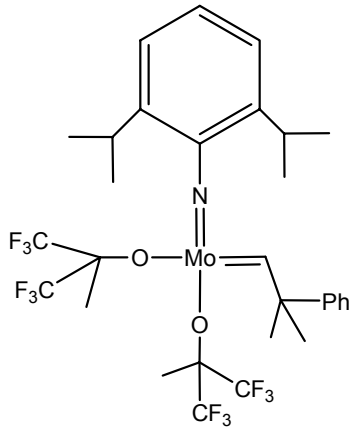
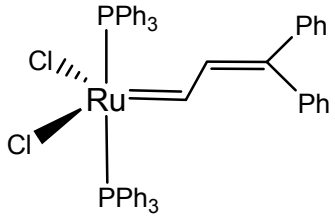


Figure 5.2 Schrocks' Catalyst.

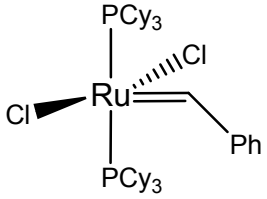
It is found that the tolerance to functional groups can be improved with increasing group number of the incorporated metal. Compared with other late transition metals which also allow the formation of metal-carbon double bonds, ruthenium seems to be the optimal metal. [2] The ruthenium carbene complexes developed by Grubbs et al. demonstrate good chemo-selectivity for carbon-carbon double bonds with a good functional group tolerance, such as to alcohols, amides, aldehydes, and carboxylic acids.

To compare Schrock's molybdenum catalysts with Grubbs' catalysts, the later one shows a better stability towards functional groups, and are easier to handle. For instance, the Schrock catalysts are air and moisture sensitive and can not be used in ordinary laboratories; vacuum lines and dry boxes are always necessary; while these strict conditions can be avoid using Grubbs' catalysts. Schrock catalysts are more active and are useful in the conversion of sterically demanding substrates, while the Grubbs catalysts tolerate a wide variety of functional groups. The second generation Grubbs catalysts are even more stable and more active than the original versions. [2 56-58]

The first member of the Grubbs catalysts (Fig. 5.3) was developed by Nguyen in 1992 and it is the first well defined ruthenium species which is active for metathesis. [18] One year later, it was refined into Grubbs 1st generation catalyst (Fig. 5.3) by the substitution of the $P(Ph)_3$ ligands with better σ-donating alkyl ligands like PCy_3 or $P(^{i}Pr)_3$. [19] Further by the exchange of one phosphine ligand with a bulky Nitrogen-heterocyclic carbene (NHC) ligand enhancement of the activity and selectivity in some olefin metathesis reactions was found. Many catalysts derived from both unsaturated and saturated NHC ligands were investigated by Grubbs, Herrmann and Nolan et al. [61-66]



First Member of the Grubbs Catalysts



Grubbs 1st Generation Catalyst

Figure 5.3 First member of the Grubbs catalysts and Grubbs 1st generation catalyst.

Among these NHC derived catalysts, the commercially available 2nd Grubbs generation catalyst (Fig. 5.4) was a result of the substitution of a phosphine ligand in Grubbs 1st catalyst with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (SIMES or H2IMES). [20] Further, in 2001, Grubbs's et al. reported by replacing another phosphine ligand with weakly bound heterocyclic ligands such as pyridine, that the slow initiation step of the Grubbs 2nd generation catalyst has been improved drastically.[21] This Grubbs 2nd generation derived catalyst is a 18-electron bis-pyridine adduct and often referred to as the Grubbs 3rd generation catalyst (Fig. 5.4).[22, 23] These Ru-catalysts tolerate a variety of functional groups and the modern Grubbs 2nd and 3rd Generation Catalysts are more versatile compared with molybdenum catalysts.

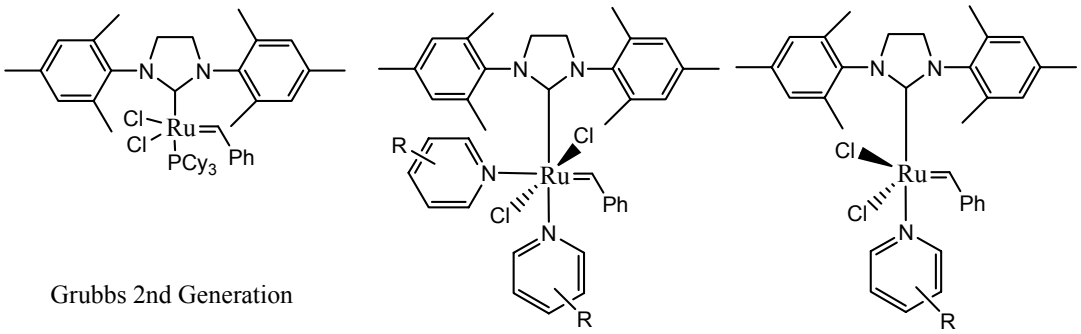


Figure 5.4 Grubbs catalysts 2nd and 3a-b (R = H, Br, Ph, NO_2).

Now Grubbs 2nd generation catalyst is the most widely used catalyst.[50-52] In the shadow of Grubbs catalysts, over the years a numerous of literatures described the search for other ruthenium based metathesis active catalysts.[24-37] Verpoort has reported a systemic work to incorporate an alkyl substituted NHC onto the Grubbs complex. Since the alkyl ligands can enhance the ability of electron donation of the NHC lone pair it has been found that the catalytic activity was affected by this modification. [38] Fürstner et al. prepared a series of unsaturated imidazoles to make a comparative activity study.[39]

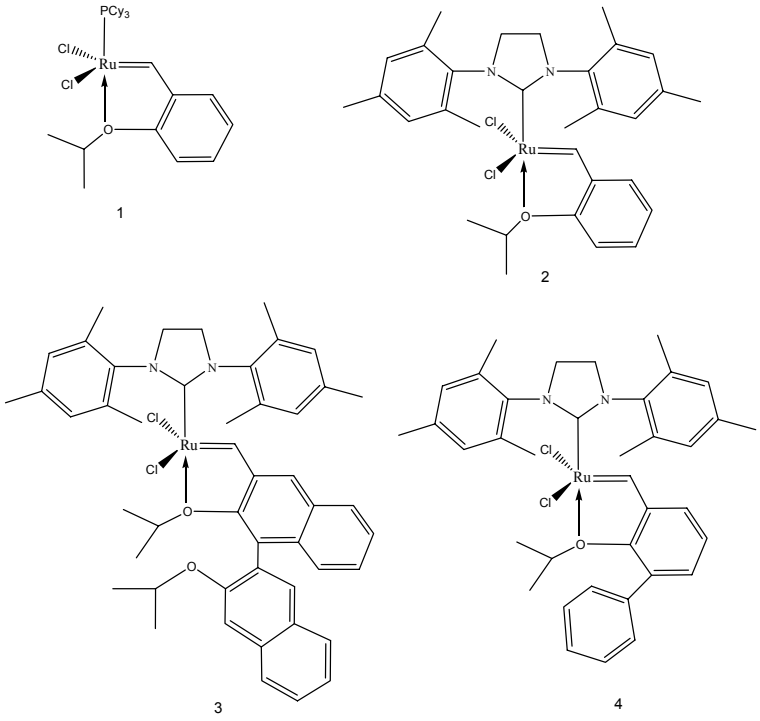


Figure 5.5 Grubbs-Hoveyda Catalysts.

Except Grubbs' catalysts mentioned above, the second most important improvement of the Grubbs catalysts is definitely the incorporation of a chelating carbene ligand. Hoveyda et al. reported the substitution of PPh_3 in $Cl_2Ru(PPh)_3$ by using PCy_3 and (2-isopropoxyphenyl)-diazomethane resulting in the Grubbs-Hoveyda catalyst (Fig. 5.5)[40, 41] One year later the analogue of the Grubbs 2nd generation catalyst has been reported by both Hoveyda[40] and Blechert.[41](Fig. 5.5)

Compared with the Grubbs 1st generation catalyst, the aryl-ether chelated complex (**1** in Fig. 5.5) offers much better stability, although the same active species is generated as with Grubbs 1st generation catalyst. The extra robust and recyclable character of the catalyst even allowed it to be recovered in high yield after a reaction using silica gel chromatography. A release/return mechanism was proposed that the isopropoxystyrene can decoordinate during metathesis procedure and then react again with a Ru-intermediate to regenerate the original catalyst.[42] The 2nd generation Grubbs-Hoveyda (**2** in Fig. 5.5) shows a similar efficient activity as the Grubbs 2nd Generation Catalyst, while the selectivity in CM and RCM catalyzed by Grubbs-Hoveyda is better than Grubbs 2nd Generation. [40] In order to improve the slow initiation rate, the stability and the reaction rate of **2** in Fig. 5.5, the variations on the chelating ligand has been implemented by Blechert et al. and **3** and **4** in Fig. 5.5 has been obtained as much faster initiators.[43, 44] Also the BINOL-derived catalyst **3** in Fig. 5.5 showed a significantly higher catalytic activity than complex **1** in Fig. 5.5. The complex **4** was proved to be very active catalyst for RCM and confirmed that the presence of steric bulk adjacent to the chelating unit is decisive. [44, 45] The higher structural integrity and congested molecular environment made by steric bulk can force the leaving group to dissociate and form a 14-electron active species.

The variations on the electronic changes in the chelating ligand have been performance at the same period by Grela et al. It was found when a strong electron-withdrawing group (such as nitro group) was introduced in the isopropoxystyrene ligand, a much higher activity can be obtained.[48-50] In case the introduced group on the styrene fragment is methoxy, little rate improvement was shown.[46] The location of strong electron-withdrawing group is also crucial, except the para position towards the oxygen is enhancing, placing the nitro group on any other position could not improve the activity, because the structural integrity of the catalysts could be reduced by affection between the steric bulk and electron withdrawing group.[47]

All above findings reveal evidently that by using a modest variations of ligand structure, a noticeably difference on the catalytic activity can be achieved.[48]

In the last decades, olefin metathesis, as a powerful, atom-efficient, synthetic strategy, for C-C bond forming, has met with great success, mainly because of outstanding advances in catalyst performance. [49] In the quest for better catalyst, the class of organmetallic ruthenium and

molybdenum catalysts has made enormous progress and since the challenge still remains, a constant improvement still continues. The well-defined, high reactivity, commercial available and functional group tolerance metathesis catalysts are widely used in industrial production of specific molecules. This will be briefly discussed in the next section.

Except the catalysts mentioned above, some other ruthenium based metathesis initiators have been developed and became commercially available at industrial relevant scale during the last couple of years. (Figure 5.6)

Catalyst Ciba 1st - Ruthenium (phenylthio)methylene complex has been developed by van der Schaaf et al. of Ciba Specialty Chemicals from Switzerland in 2000 and was optimized and commercialized by Ozawa et al. in 2003.[28, 50, 51] Now, the 2nd generation analogue is also distributed.

A serial of air stable Hoveyda-derived catalysts - Zhan catalysts have been launched by a Chinese company Zannan® Pharma Ltd from Shanghai. The catalysts can perform well in ring-closing metathesis reactions. [52]

In 2006, CatMETium® IMesPCy has been introduced by Degussa Homogeneous Catalysts (DHC) from Degussa-Huls AG, Germany. This catalyst performs well in cross metathesis, ring-closing, ring-opening, and eneyne metathesis reactions, all of which are important in pharmaceutical syntheses and the catalyst is only offered for pharmaceutical applications. DHC has obtained technology licenses from Herrmann et al. [53, 54]

Umicore AG&CO.KG from Germany produces the world wide patent-free catalyst Neolyst® M1, that is an air-stable complex and was first reported by Furstner et al[30]. Catalyst Neolyst® M2 launched to market by Umicore after taking licenses of patents of Nolan et al. This catalyst is expected to be more reactive in outside polymerization reactions than CatMETium® due to the saturated nature of its NHC ligand.[55, 56] A ruthenium indenylidene complex with two phobane ligands named as Neolyst® M3 joined Umicore metathesis catalysts in 2007. This catalyst was licensed by Sasol Technology from United Kingdom and shown improved air, moisture, and heat resistance. In the same year, Umicore signed a licensing and cooperation agreement to commercialize a new type of Schiff base substituted indenylidene complexes – Verpoort Catalyst which has been developed by Viacatt, a spin-off company of Ghent University, Belgium.

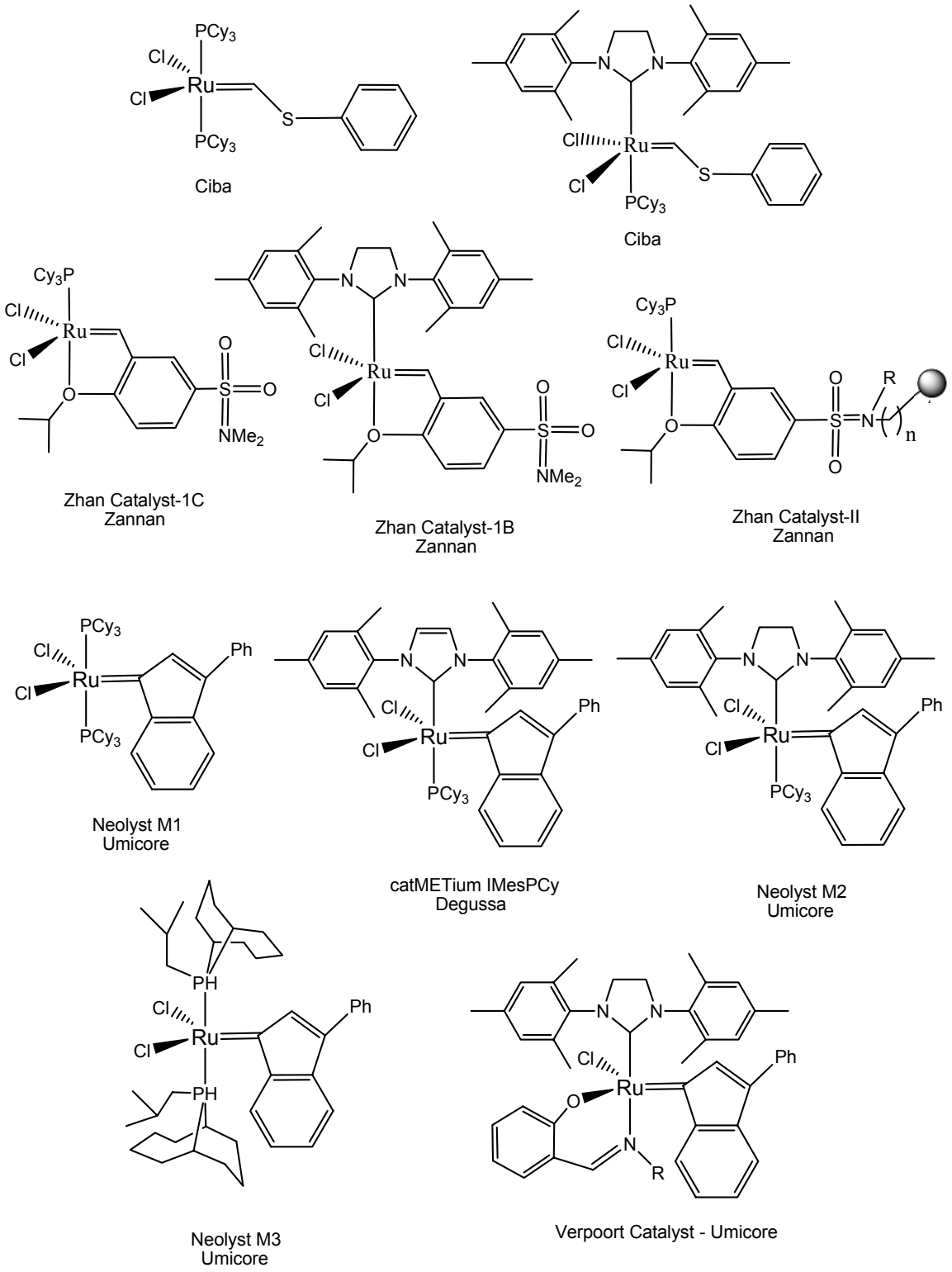
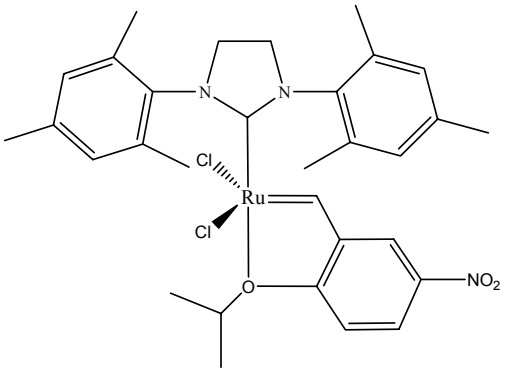


Figure 5.6 Other commercial olefin metathesis catalysts.



Figuare 5.7 Grela's Nitro Catalyst

In 2007, Grela's nitro catalyst (Fig. 5.7) attracted the Boehringer Ingelheim's interest in view of its successful use[47] and its own process chemistry to produce macrocyclic drug and anticipated commercializing.[57]

5.4 Applications

Olefin metathesis has asserted itself as a powerful strategy for obtaining fine chemicals, biologically active compounds, architecturally complex assemblies, new materials, and functionalized polymers. The field of olefin metathesis has served as an important area of interaction within inorganic, polymer, organic chemistry and chemical engineering for both lab and industry use. As such it has had an important influence on all these disciplines. Over the past few years, the applications of olefin metathesis have fulfilled much of the promises of this catalytic process.

5.4.1 Lab application

Since more selective catalysts are available, scientists began to use them in organic chemistry. For example, in 1992, Grubbs and MIT chemistry Professor Gregory C. Fu used the widely known Schrock catalyst in ring-closing metathesis to form oxygen and nitrogen heterocycles. Another spectacular example is in 1995, Professor Amir H. Hoveyda from Boston College used the same catalyst in a stereospecific 14-membered macrocyclization in the enantioselective total synthesis of an antifungal compound. This application set the stage for use of olefin metathesis to close big rings carrying much functionalities.

Olefin metathesis catalyzed by Grubbs catalysts have been credited in the forefront of organic synthesis. These ruthenium compounds have high preference for carbon-carbon double bonds and are indifferent to alcohols, amides, aldehydes, and carboxylic acids. More important, their use does not require stringent conditions. They can be used by organic chemists applying

standard techniques. The vacuum lines and dry boxes are needed when working with Schrock's molybdenum catalysts, while they are not necessary when using the Grubbs' type catalysts.

Since 1996 the Grubbs catalyst was introduced in organic synthesis, many groups such as groups of Samuel J. Danishefsky from Columbia University, K. C. Nicolaou from the University of California, all used the catalyst in the synthesis of epothilones. At the University of Wisconsin, the Grubbs catalyst was used to prepare carbohydrate-containing polymers with significant biological activities. At MIT, Peter H. S. used the catalyst to cleave linkers in solid-phase oligosaccharide synthesis. At Tohoku University in Japan, olefin metathesis catalyzed by the Grubbs catalyst was a key step in the total synthesis of the natural product ciguatoxin by Masahiro Hirama. Mainly applications of the metathesis reaction related to medicinal chemistry, including solid phase synthesis and combinatorial chemistry were presented.

5.4.2 Industrial application

A benifit to organic synthetic chemists, olefin metathesis also promises cleaner, cheaper, and more efficient industrial processes. In general, the olefin metathesis reaction has opened up new routes in three important fields of industrial chemistry:[58]

5.4.2.1 Production of petrochemicals

Industrial production of olefins is based on cross-metathesis using heterogeneous catalysts, such as the Phillips triolefin process, which produces polymerization-grade propene by cross-metathesis of ethylene and 2-butene, and a process for the production of neohexene, an intermediate in the synthesis of musk perfume. Later on, because propene is used for making polypropene, and further for producing acrylonitrile, oxo alcohol, acrylic acid, etc, a high global demand for propylene prompted petrochemical companies to improve the yield. Since olefin metathesis is a reversible reaction, by using the process, known as olefin conversion technology (OCT), propylene can be produced from ethylene and 2-butene and this technology currently used by Lyondell Petrochemical and BASF Fina Petrochemicals.

1-Hexene and neohexene (3,3-dimethyl-1-butene) are also made by cross-metathesis. A semi-work unit using the above mentioned OCT process for the metathesis of butene to produce 3-hexene, which is then isomerized into 1-hexene the later is a high-value co-monomer used in the production of polyethene.

A large-scale industrial process incorporating olefin metathesis (cross-metathesis) is the Shell Higher Olefins Process (SHOP) producing linear higher olefins from ethylene. In the U.S. and England, Shell Chemicals can produce up to 1.2 million tons of linear higher olefins per year from

ethylene through SHOP. The process takes place in three stages. In the third step, a cross metathesis catalyzed by heterogeneous catalyst ---alumina supported molybdate metathesis catalyst, results in the linear internal alkenes.

5.4.2.2 Polymer synthesis

Another wide application of olefin metathesis is the synthesis of polymer. Most olefin-metathesis-derived polymers are made with complex homogeneous systems.[59] Several industrial processes involving homogeneous catalyzed ROMP have been developed and brought into practice, such as the ROMP of cyclooctene, norbornene and dicyclopentadiene, leading to useful polymers --- polyoctenamer, polynorbornene, and polydicyclopentadiene (PDCPD). [60]

Polyoctenamer (Fig. 5.8) is prepared from cyclooctene over a tungsten-based polymerization catalyst. Since 1980, Degussa-Hüls AG has been producing Vestenamer® 8012, the metathesis polymer of cyclooctene. This polymer also goes under the name TOR (*trans*-polyoctenamer). This polymer is mainly used as a processing aid in the rubber industry to manufacture tires, profiles, tubes, all kinds of molded rubber articles, and roller coatings.

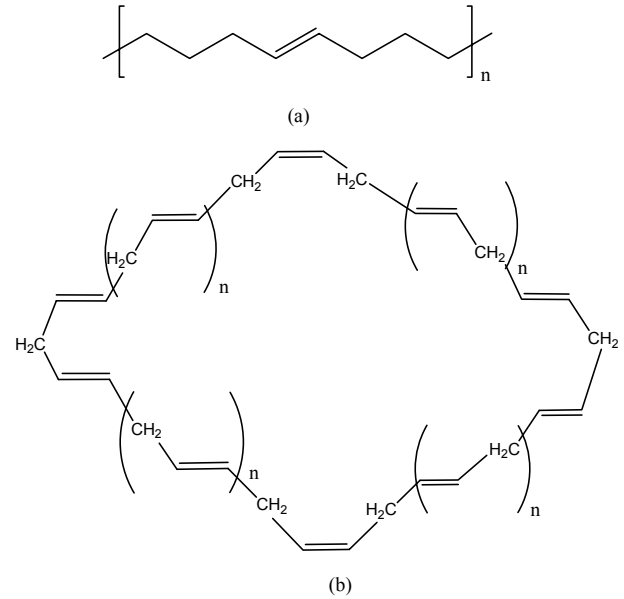
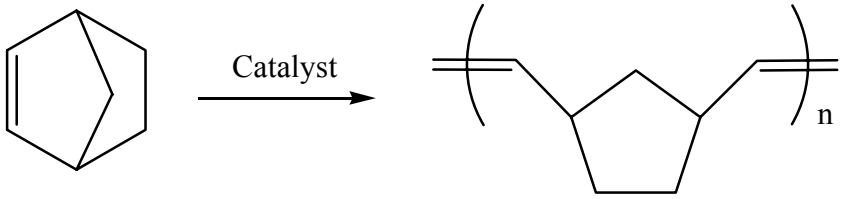


Figure 5.8 Polyoctenamer.

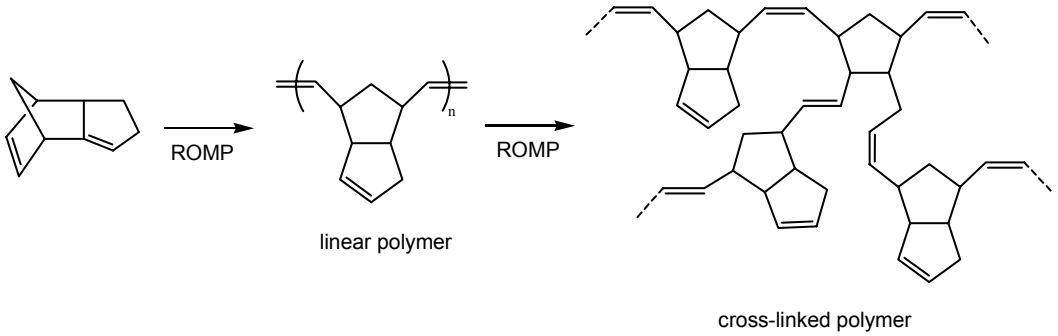
Polynorbornene (Scheme 5.9) was introduced under the name Norsorex in 1976 in Europe and in 1978 in the United States and Japan. It is the first commercially available metathesis polymer and to be used as a rubber. One of the unique characteristics of this polymer is the oil absorption ability. A process using a $RuCl_3$/HCl catalyst produces an elastomer which proved to be useful for oil spill recovery and as a sound or vibration barrier.



Scheme 5.9 Polynorbornene.

When only the highly strained norbornene moiety of dicyclopentadieen (DCPD) is ring opened, a linear polymer is formed shown in Scheme 5.10. On the other hand, it is also possible to metathesize the double bond in the cyclopentene ring to give rise to cross-linking. By using the Reaction Injection Molding (RIM) technology, this cross-linked polymer can industrially be processed to produce large objects such as bathroom modules, lawn and garden equipment, construction machinery, body panels for trucks…

DCPD is an inexpensive, readily available byproduct of the petrochemical industry obtained from naphtha crackers. In the polymer field, ring-opening metathesis polymerization (ROMP) of cycloalkenes is an attractive process for making linear polymers when based on cheap monomers or possessing special properties compensating for a high price. Poly-DCPD (Fig. 5.10) is based on the former rule. Although the widely used homogeneous catalysts such as Grubbs' and Schrock's, they do not play a major role in industrial scenarios. For PDCPD production, the Verpoort ruthenium technology is very reliable and the robust catalysts are enabling various applications, and some products emerged.



Scheme 5.10 poly-DCPD.

The commercial production of molded objects from DCPD-based feed using RIM technology has been developed mainly by the BF Goodrich Co., under the trade name Telene®, and by Hercules Inc. under the trade name Metton®. The latter is now produced by Metton America, Inc. at La Porte (USA) and Teijin-Metton Co. in Japan. In the Telene® process, a molybdenum based precatalyst is activated by a mixture of Et_2AlCl, alcohol and $SiCl_4$. The Metton® process utilizes a WCl_6 + $WOCl_4$ precursor, which is initiated by the addition of $EtAlCl_2$.

5.4.2.3 Fine chemistry

The olefin metathesis reactions, during the last decade, have provided new indispensable synthetic methods for difficult or even impossible conventional ways.[61 66-73] Catalyzed by the well-defined catalysts, they now induce a substantial boost in this particular research area and constitute an emerging field for the selective preparation of fine chemicals.

In the field of fine chemicals, from life saving pharmaceuticals to renewable based chemicals and from specialty materials to commodity plastics, Materia, Inc., a company found in 1998 is changing the scope of chemistry through the utilization of olefin metathesis technology. The technology holds by this company includes the exclusive worldwide rights of metathesis catalysts from Grubbs, Schrock, and Hoveyda. These catalysts have already shown remarkable utility in the production of fine chemicals on an industrial scale.

Meanwhile olefin metathesis reactions are significant to reformation processes in the pharmaceutical industry, the industry utilizes olefin metathesis methodologies in the pursuit of complex active pharmaceutical ingredients or as one of their intermediate steps, examples are Mevinolin (drug used to lower cholesterol rates), Ambruticin (anti-fungal antibiotic), and Nonenolide (anti-malarial).[62] During the research procedure to develop the pharmaceuticals for diseases such as HIV/AIDS, hepatitis C, cancer, Alzheimer's disease, Down's Syndrome, osteoporosis, arthritis, fibrosis, migraine,. . . olefin-metathesis-based reactions will hopefully become a powerful synthetic tool.

Olefin metathesis can also be used to improve the synthesis of insect pheromones, which are more ecological alternatives to chemical pesticides, useful as environmentally friendly pest-control agents and in intermediate reactions to produce flavor and fragrance chemicals. Since, pheromones have been very expensive to produce in traditional synthetic methods, applying Grubbs' catalyst, some olefin-metathesis-based routes to produce various pheromones has been invented and some insect pheromones, such as (*E*)-5-decenyl acetate, a mixture of (*E*)- and (*Z*)-11-tetradecenyl acetate, and a different mixture of (E)- and (Z)-11-tetradecenyl acetate has been registered by the Environmental Protection Agency.

The development of well-defined catalysts leads olefin metathesis to spectacular advances over the past 10 years. The various incarnations of the reaction have now acquired first rank importance in synthesis. Clearly, the emergence of a similar, generic efficient catalytic system to controlled reaction would contribute enormously to their popularity among the community of organic chemists. Although some proposed activation processes are still controversial, this will presumably follow from a better understanding of the mechanisms of these highly complexes reaction.

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Chapter 6
First FT-Raman and ^{1}H-NMR Comparative Investigations in Ring Opening Metathesis Polymerization

Kinetics of ring-opening metathesis polymerization (ROMP) of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, promoted by the Grubbs' 1st generation pre-catalyst, has been effectively monitored by FT-Raman and NMR spectroscopy. Both techniques evidenced similar monomer conversions to be attained under the same reaction conditions. The present FT-Raman study provided information on the polymer steric configuration, the Raman bands at 1670 and 1677 cm^{-1} being specifically assigned to stretching vibrations of double bonds from the *cis*- and *trans*-polymer, respectively. The *trans/cis* ratio observed by FT-Raman parallels the corresponding result from ^{1}H NMR. For the first time, a comparison was made on application of these complementary methods on the same ROMP reaction, evidencing their assets and disadvantages and reliability of FT-Raman.

6.1. Introduction

Transition metal catalyzed C–C bond formation falls into the area of most important reactions applied in organic and polymer synthesis. Within this category olefin metathesis (mainly as ring closing metathesis, cross-metathesis and ring-opening metathesis polymerization (ROMP)), has won a leading position owing to its success in yielding various natural products, specialty polymers, pharmaceuticals and otherwise hard-to-get organic compounds. [1-13]

ROMP involving cyclic alkenes is particularly favored in the case of strained substrates. It is the reaction of choice to access diversely functionalized polymers in high demand due to their unique characteristics. Materials ranging in properties from soft rubber to hard and tough thermoplastics and highly cross-linked thermosets can be prepared by this chemistry.[14,15] The burgeoning area of ROMP-based ‘‘designer materials’’ needs to always find an efficient solution for reconciling the high reaction rates in ROMP with the precise control over polymer chain lengths.

Because of its importance, ROMP kinetics and mechanism, as well as characterization of the reaction products, have been thoroughly examined and/or continuously monitored by a variety of physical techniques at the forefront of modern research, frequently used in combination, such as gas-chromatography, ^{1}H NMR, ^{13}C NMR, ESR, FT-IR, MALDI-TOF MS, molecular mass analysis (gel permeation chromatography, light scattering, osmometry, viscometry), etc..[16–22]

Of all these analytical methods, Fourier transform Raman spectroscopy can be easily applied to real world samples, therefore with no need for special sample preparation. Through coupling of the FT-Raman spectrometer by optical fiber bundles, remote examination of samples (located at a certain distance from the spectrometer) becomes possible. It should be kept in mind, however, that for successful recording of FT-Raman spectra of small samples a compromise between large lateral resolution and a large signal/noise ratio has to be found.

Raman has obvious advantages over the IR absorption spectroscopy, a technique which along with Raman accomplishes the full vibrational characterization of a molecule. [23–26] The scattering FT-Raman is usually less complicated, and the interpretation of data is more straightforward, yet the Raman signal is frequently weaker than in FT-IR. If we now compare Raman with the NMR spectroscopy, some of Raman’s valuable features have to be highlighted: no solvent and no special analysis tubes are needed, a smaller amount of substrate is necessary, no viscosity changes can influence accurateness of kinetics measurements, as is the case with bulk polymerizations monitored by NMR.

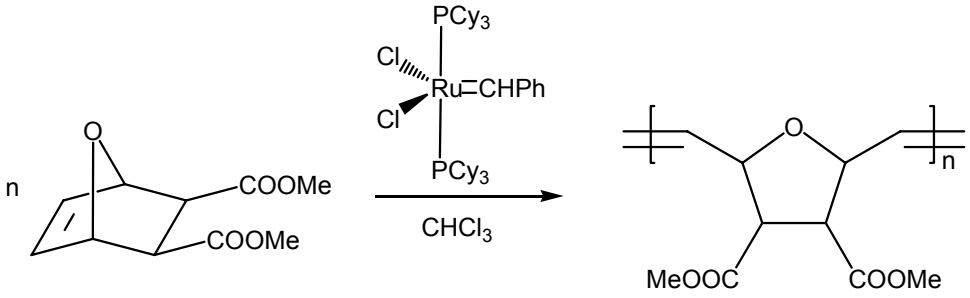


Figure 6.1 ROMP of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene using Grubbs’ 1st generation catalyst.

Investigation of catalytic reactions by Raman spectroscopy is widely used. [27] As Raman spectroscopy has high sensitivity to non-polar species (C=C) which make-up polymer chains, this method has long been employed for characterization of various polymers or to follow polymerization kinetics. [28–33] Discrimination between *cis* and *trans* C=C vibrations is also possible. However, following ROMP by FT-Raman can be successfully performed only if there are characteristic $\nu_{C=C}$ bands in the monomer and polymer whose intensities change during polymerization. [34] In spite of these assets, there are to date only few reports on ROMP based on such deserving analytical tools (e.g. ROMP of norbornene by in-line fibre-optic NIR-FT-Raman, [32] real-time mid-IR monitoring of ROMP of 1,5-cyclooctadiene by fibre-optic FT-IR.[35,36]). In the present research we propose to monitor kinetics of ROMP of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene (exo-ONDAMe), initiated by the well-defined Grubbs' 1st generation catalyst (Fig. 6.1). The main goal is to assess, for the first time, the merits of FT-Raman and ^{1}H NMR in providing complementary information on the chemistry of the ROMP catalytic process. To the best of our knowledge there is no previous report on such a comparative kinetic study.

6.2 Experimental

6.2.1 Materials

Exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene (exo-ONDAMe) was prepared according to literature (yield:41%). [37]

Grubbs' 1st generation catalyst is commercially available (Strem Chemicals, Inc.) and was used as received.

6.2.2 Spectroscopic conditions

A Bruker FT spectrometer Equinox 55S with Raman module FRA 106, a hybrid FT-IR/FT-Raman spectrometer, fitted with a germanium high sensitivity detector D418-T (cooled by nitrogen at 77 K) was used. During the monitoring of ROMP, the excitation laser wavelength of 1064 nm was produced by an air cooled diode pumped neodynium–yttrium aluminium garnet laser (Nd:YAG). The spectral coverage extends from 100 to 4000 cm^{-1} with a spectral resolution of 4 cm^{-1}, number of scans (100), laser power (350 mW). Spectra were recorded at 3 min intervals. Data transfer, collection and processing were fully automated using a Bruker OPUSTM software.

^{1}H NMR spectra were recorded using a Varian 300 MHz spectrometer. Chemical shifts are reported in ppm vs. TMS, in the range 0–10.

6.2.3 Choice of the solvent

In this ROMP study limiting conditions on the solvent are imposed. The solvent must not deactivate the catalyst and in Raman spectra no interference from the solvent with the $\nu_{C=C}$ band of the monomer and/of the polymer should occur (no solvent peaks in the range 1500–1800 cm^{-1} are admissible). No traces of moisture or oxygen are acceptable because of the sensitivity of the catalyst.[1] Furthermore, a suitable solubility of the monomer and polymer has to be assured for a homogeneous polymerization reaction. Chloroform was chosen as the ideal solvent in Raman and deuterated chloroform in ^1H NMR measurements, respectively.

6.2.4. Calibration curve

To determine the relationship between the intensity of the Raman signal and the concentration of the monomer we had to first construct a calibration curve. The same methodology as previously applied for Raman evaluation of ROMP of norbornene has been followed. [32] To minimize variations in intensity of the excitation laser line we used, as necessary, a reference band from the spectrum (668 cm^{-1}) which remains constant during the ROMP reaction.

Five standard solutions with different monomer concentrations (0, 0.493, 0.972, 1.298, and 2.001 mol/l) were prepared and measured five times each by in-line Raman. Measurement conditions for building the calibration curve were the same as those listed above for monitoring ROMP of exo,exo-ONDAMe (50 scans, laser power: 200 mW, room temperature, 4 cm^{-1} resolution), with the monomer peak appearing at 1573 $cm^{-1}$and the reference peak ($CHCl_3$) at 668 cm^{-1}.

For each measurement the height of the monomer peak was corrected by that of the reference (solvent). For every standard solution the average of the corrected peak height (resulting from five successive measurements) was considered. Eventually a calibration curve was obtained in which the relative intensity, *y* (i.e. intensity of the monomer peak/intensity of the reference peak) was plotted as a function of the monomer concentration, *x*.[32] In the investigated domain of concentrations a linear relationship was found, $y = 0.044x - 0.0004$ ($R^2 = 0.9998$).

Based on this calibration curve, the degree of monomer conversion could be calculated from the known initial monomer concentration and the transient monomer concentration (above the detection limit), as determined by Raman at a time t.

6.3 Results and discussion

6.3.1 Monitoring of polymerization by FT-Raman

The ROMP reaction was carried out in a glass vessel (7 ml) equipped with a magnetic stirring bar. The monomer, exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, was solved in 1 ml $CHCl_3$ under magnetic stirring and the FT-Raman spectrum was recorded to obtain the intensity of its $\nu_{C=C}$ band at time t = 0. Next, the catalyst was added to the monomer solution, the vial containing the reaction mixture placed in the sample compartment of the FT-Raman spectrometer, and evolution of polymerization (Table 6.1) was monitored under the following measurement conditions: 50 scans; laser power, 200 mW; resolution, 4 cm^{-1}; temperature, 17 °C (Fig. 6.2).

Table 6.1 Reaction conditions for ROMP of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo [2.2.1]hept-2-ene, used in experiments monitored by FT-Raman and ^{1}H NMR.

Monomer (M)	***exo*-ONDAMe**	
Spectroscopic Method	^{1}H-NMR	Raman
Temperature (°C)	17	17
Solvent	$CDCl_3$	$CHCl_3$
[M] (mol/l)	2.08	2.092
Catalyst initiator (I)	Grubbs 1st gen.	Grubbs 1st gen.
$[M] / [I]_0$	105	104

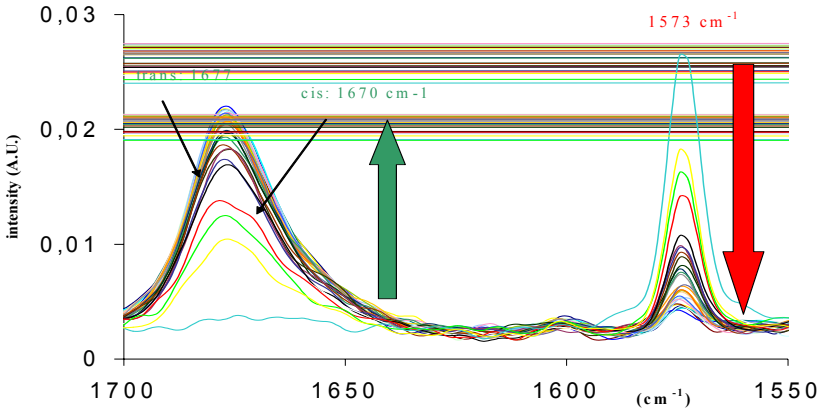


Figure 6.2 FT-Raman spectra (1550–1700 cm^{-1}). Spectra were collected at 3 min intervals.

Conversions have been determined from the ratio between the height of the monomer peak (1573 cm^{-1}), relative to the height of the reference peak, at a time t and at the time zero (t = 0, i.e. in the initial monomer solution). The reference peak (668 cm^{-1}) is used for spectral intensity normalization and in this study is that of the solvent. The area under the peak varies linearly with the peak height if resolution is considerably better than the band half-width, which is the case here (Fig. 6.2). A small error in placing the background greatly affects the area integral, but less so the peak height, so use of peak heights rather than peak areas is more reliable.[32]

6.3.2 Monitoring of polymerization by ^{1}H NMR

Due to the good solubility of exo-ONDAMe in chloroform it was possible to monitor the progress of our ROMP reaction also by ^{1}H NMR (in deuterated chloroform).

The catalyst, and next the monomer, were weighed in the tube before starting the reaction by adding the solvent. The tube was swirled to ensure complete mixing of its contents, then placed in the NMR spectrometer in order to monitor the polymerization process (at 17 or 19°C) by taking spectra of the reaction mixture at constant time intervals. Fifteen spectra were recorded at 2 min intervals (Fig. 6.4), that is during the most rapid phase of ROMP (the reaction is essentially complete after 24 h).[38]

To enable a fair comparison between the two sets of data, from the Raman and the NMR spectroscopy, the same reaction conditions (Table 6.1) have been applied in both cases.

In kinetic measurements performed by Raman spectroscopy, we focused primarily on the stretching vibrations of double bonds which, owing to their significant polarizability, exhibit strong signals in FT-Raman spectra. The intense bands at 1573 and 1677 cm^{-1}, clearly evidenced in our FT-Raman spectra taken during polymerization of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene where both the monomer and its polymer are present (Fig. 6.2), have been, respectively, assigned to $\nu_{C=C}$ vibrations in the monomer and the polymer. The lower value of the $\nu_{C=C}$ in the monomer may be rationalized by the considerable strain of the bicyclic oxanorbornene ring system, while the higher nC C observed for the polymer results from release of this ring strain during ring-opening polymerization yielding the sterically more favourable structure of the polymer Q1.[39]

As the reaction proceeds, the concentration of the polymer increases at the expense of the monomer concentration and this development is reflected in Raman spectra by the evolution of intensity of the respective $\nu_{C=C}$ vibrations: the 1573 cm^{-1} continuously diminishes while the 1677 cm^{-1} band increases. Therefore, measuring the intensity of the 1573 cm^{-1} band, it is possible to calculate the monomer concentration $[M]_t$ at any time during the reaction, and thereupon build the

evolution of the monomer conversion as a function of time. The curve is characterized by a fast conversion in the beginning of the reaction (the first 20 min.). Then conversion slows down as should be anticipated from the kinetic characteristic behaviour of the Grubbs' 1st generation catalyst,[1] known to exhibit fast initiation and slower propagation (Fig. 6.3).

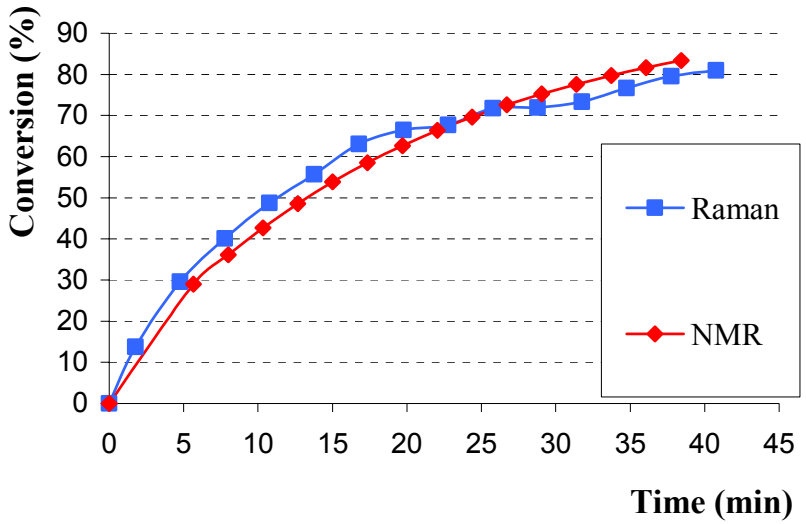


Figure 6.3 Comparison of monomer conversions (%; at 17°C) vs. time, as obtained by Raman and NMR spectroscopy.

Conclusive results in NMR, that compare well with literature data (Table 6.2),[38] were obtained by following polymerization of exo,exo-5,6-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, when carried out directly in the NMR-tube. Spectra consist of monomer and polymer signals (sharp for the monomer and somewhat broadened for the polymer), along with the distinctive signal due to the carbene proton (from the initiating and propagating ruthenium species) which appears considerably downfield from the organic proton region of interest and therefore was omitted from Fig. 6.4.

Change of spectra in time clearly illustrates progress of polymerization through a decrease in intensity of the monomer signals (at 6.46 ppm (Ha), 5.28 ppm (Hb) and 2.83 ppm (Hc)) and a simultaneous increase of the characteristic signals for the corresponding protons in the growing polymer (at 5.82 (*trans*) and 5.52 (*cis*); 4.95 (*cis*) and 4.59 (*trans*); 2.98) (Table 6.2, Fig. 6.4).

Integration of these signals for each spectrum enabled us to establish the monomer conversion at the time t when the spectrum was recorded.

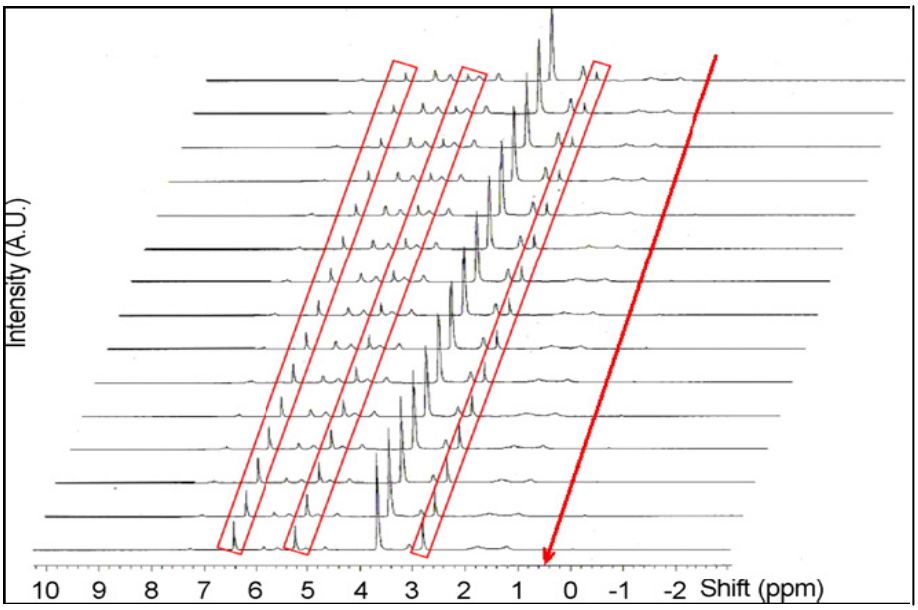
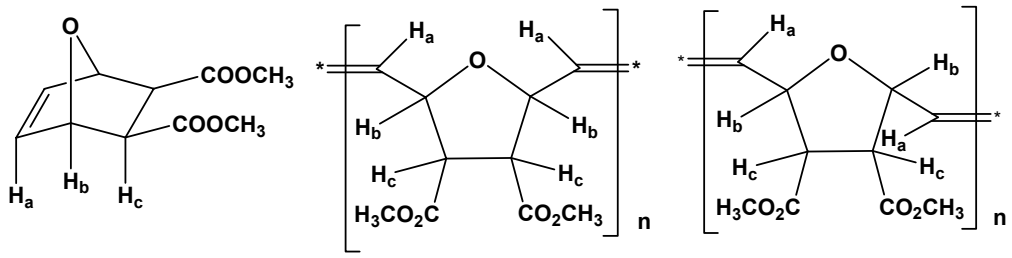


Figure 6.4 NMR spectra collected during the polymerization of exo-ONDAMe (at 19 °C; M/catalyst = 105 mol/mol).

As clearly apparent from Table 6.2, the solvent employed plays a great influence on the chemical shift at which various protons are found. However, a change of solvent from C_6D_6 to $CDCl_3$ results in a negligible effect on this reaction (Table 6.2). Our NMR study on kinetics of ROMP of exo,exo-ONDAMe (Fig. 6.4) leads to very similar polymer spectra as earlier reported. [38,40,41] indicating that our choice of $CDCl_3$ as the solvent for NMR does not bear on the ROMP itself. Checking our NMR results against literature is a crucial requirement in view of our intended parallelism and a reliable comparison with results from Raman spectroscopy.

The present FT-Raman study on ROMP of exo,exo-5,6-bis(-methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene also allowed relevant information to be obtained on the stereospecific configuration of the polymer. The stretching vibration at 1670 cm^{-1} was attributed to double bonds from the *cis*-polymer and the band at 1677 cm^{-1} from the *trans*-polymer, on the basis of previous findings in Raman investigations on ROMP of norbornenes. [32,42] Further rationale for this assignment is that the higher steric interference between the substituents at the double bond in the *cis*-polymer should translate into easier vibrating and hence lower wavenumbers in the Raman spectra, as compared to the *trans*polymer. Although it is impossible to exactly determine the *trans*/*cis* ratio in the resulting polymer, because of partial overlapping of the above two bands in the spectra acquired during this ROMP study, preponderance of the *trans* configuration is obvious. This conclusion perfectly correlates with our NMR data, as fully illustrated by Fig. 6.4 and Table 6.2, and is in total agreement with the ample literature information on the preferred formation of the *trans* isomer in ROMP initiated by Grubbs' 1st generation catalyst. [1,43]

Table 6.2 Chemical shifts (ppm) of protons from exo,exo-ONDAMe and its ROMP polymer in $CDCl_3$ and C_6D_6.



exo-ONDAMe *cis*-Polymer *trans*-Polymer

	Monomer		Polymer		
H	**δ(ppm) $CDCl_3$**	**δ*(ppm) C_6D_6**	**δ(ppm) $CDCl_3$**	**δ*(ppm) $CDCl_3$**	**δ*(ppm) C_6D_6**
H_a	6.46	5.64	5.82(*trans*) 5.52(*cis*)	5.88 (*trans*) 5.59 (*cis*)	6.07(*trans*) 5.58(*cis*)
H_b	5.28	4.97	4.95(*cis*) 4.59 *trans*)	5.05 (*cis*) 4.69 (*trans*)	5.41(*cis*) 4.98(*trans*)
CH_3	3.71	3.37	3.60	3.68	3.34
H_c	2.83	2.34	2.98	3.08	3.05

Comparative kinetics of ROMP of exo,exo-5,6-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, determined by the two spectroscopic techniques applied in this research, was illustrated in Fig. 6.3. It can be observed that values for monomer conversions at a given time are close, be it that they result from Raman or NMR data. Small deviations of conversions determined by FT-Raman vs.NMR, visible at the beginning and end of the monitoring period, can be accounted for by differences in stirring of the reaction mixture imposed by the two types of instrumentation. Increasing viscosity with progress of the reaction emphasizes the role of adequate agitation for assuring homogeneity; whereas stirring in our Raman experiment was more vigorous than in the NMR tube, the Raman effect only occurs at the place of the radiation incidence.

The obvious similarity of conversion curves determined by FT-Raman and ^{1}H NMR (Fig. 6.3) is irrefutable proof that the much less exploited Raman methodology is a valuable tool for monitoring ROMP kinetics, reliably comparing with kinetics [44,45] from NMR spectroscopy. Useful information from the vast library of existing NMR data on ROMP of a variety of cyclic monomers [14,15,46] could thus be transferred to Raman, in anticipation of new results.

6.4 Conclusions

Kinetics of ring-opening metathesis polymerization of exo,exo-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, in the presence of the Grubbs' 1st generation precatalyst, has been effectively monitored using successively FT-Raman and NMR spectroscopy. Under the same reaction conditions, both techniques evidenced that similar monomer conversions (vs. time) were attained. The FT-Raman study provided relevant information on the stereospecific configuration of the polymer, the Raman bands at 1670 and 1677 cm^{-1} being specifically assigned to stretching vibrations of double bonds from the *cis*- and *trans*-polymer, respectively. The *trans/cis* ratio observed by FT-Raman parallels the corresponding result from ^{1}H NMR.

The Raman technique was proved to be a worthy approach for evaluating kinetics of ROMP reactions and an attractive alternative to the traditional ^{1}H NMR spectroscopy. For the first time, a comparison was made on application of these complementary methods on the same ROMP reaction, evidencing their assets and disadvantages. Raman spectroscopy can use cheaper solvents, and furthermore experimental wavenumbers in Raman spectra are independent of the solvent which is not the case in NMR spectroscopy, yet solvents not interfering with Raman bands of the polymer and monomer are recommended.

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Chapter 7
Cyclopropanation

7.1 Introduction

Since this smallest three-membered carbocyclic structure is found as a basic structural in a wide range of natural and unnatural products, cyclopropanes have always been fascinating to chemists.[1] The high ring strain of cyclopropanes means they are very sensitive for ring opening reactions in the presence of nucleophiles and electrophiles. This feature makes them very useful to test the bonding features of the highly strained cycloalkanes and to probe the reaction mechanism. They can be used as versatile synthetic intermediates in the preparation of complex molecules via vinylcyclopropane and homo-Cope rearrangements.[2-6] In view of the fact that normal sp^3-hybridized carbon atoms' bond angle is approximately 109°, while in cyclopropanes, the bond angles of each sp^3-hybridized carbon atom in the ring is only 60°, it is difficult to synthesize these compounds.

In recent years, most of the effort has been focused on the enantioselective synthesis of cyclopropanes.[2-4] Althought new and more effective methods for the preparation of these entities are evolving, the challenge is still retained. After several decades of study, it could be found that cyclopropanation could be achieved by the following methods:

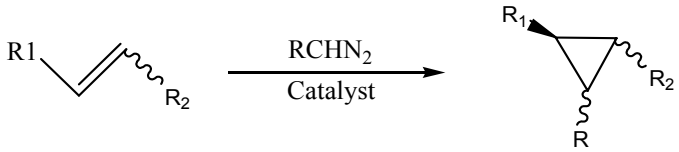
7.2 The Mechanism of Cyclopropanation

For the different synthesis methods, various mechanisms have been proposed. Herein, some of the wide accepted mechanisms are introduced.

a. Halomethylmetal (Zn, Sm, Al)-Mediated cyclopropanation reactions

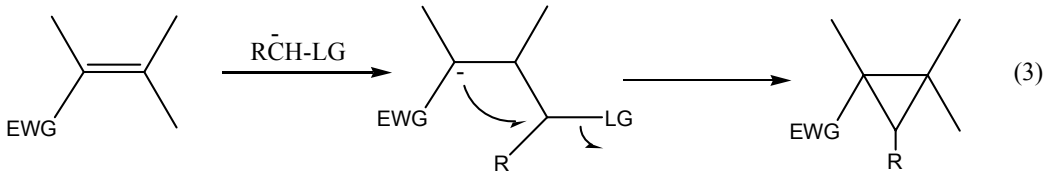
(1)

b. Transition Metal-Catalyzed decomposition of diazoalkanes

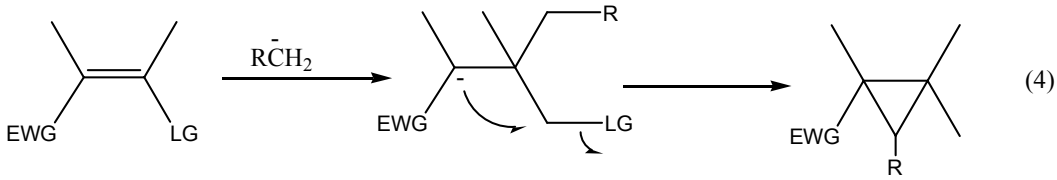


(2)

c. Michael-Initiated ring closure

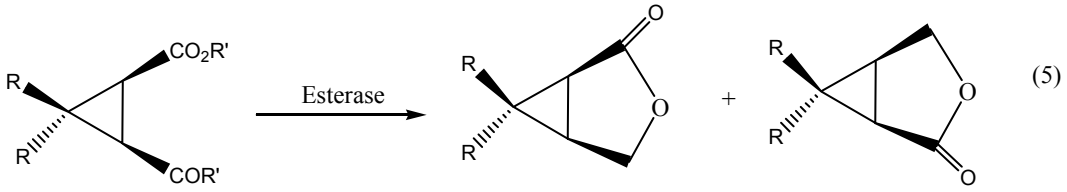


(3)



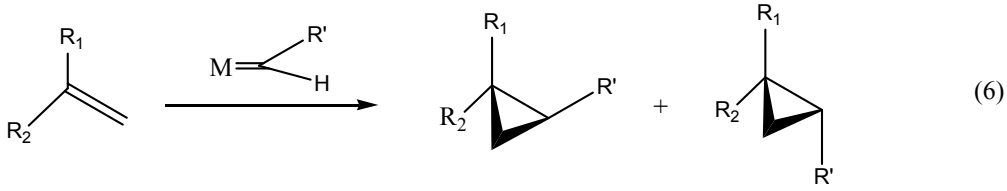
(4)

d. Enzymatic methods



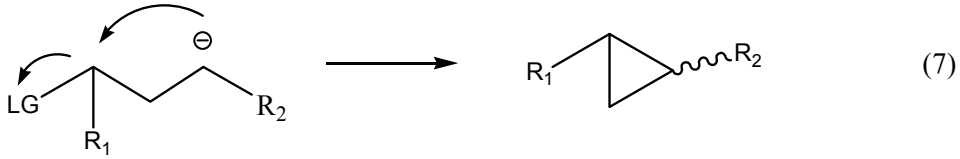
(5)

e. Chiral stoichiometric carbenes



(6)

f. Other ring-closing reaction of chiral precursors

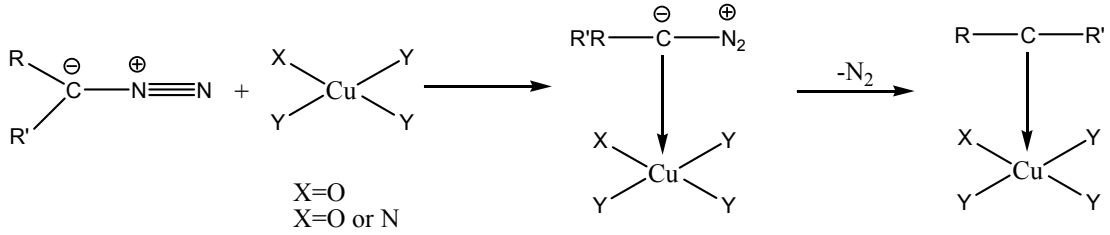


(7)

Scheme 7.1 Different methods to synthesize cyclopropane compounds.

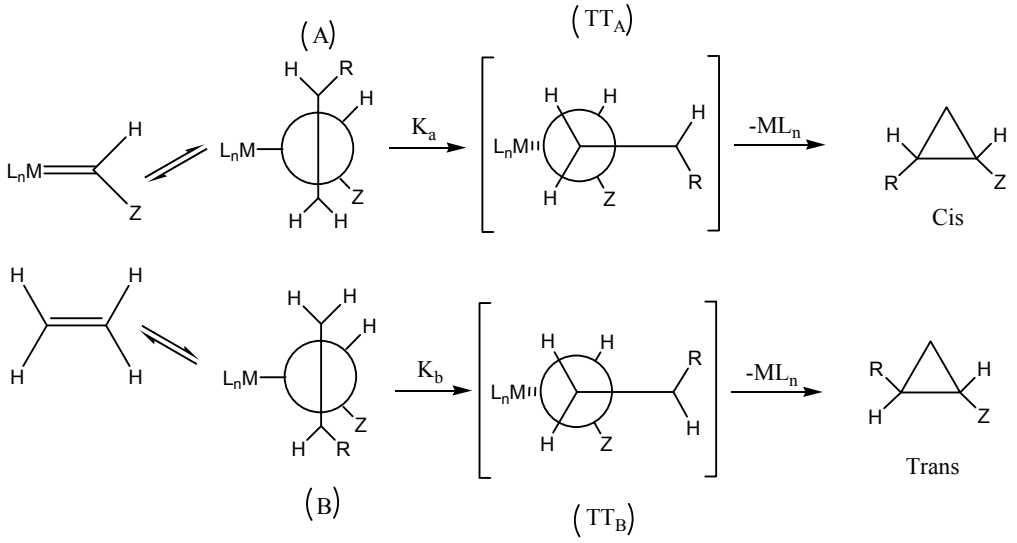
In case of the transition metal catalyzed cyclopropanation, the mechanism of decomposition of α-diazocarbonyl compounds is believed to initially proceed via the formation of a metal carbene complex (Scheme 7.6).[2]

For Evans catalyst, an oxazoline-copper complex, one of the proposed mechanism is given below.[3] Due to the chelating ligands, the copper metal has a square-planar geometry. The axial positions of this complex are free and they can undergo easily an electrophilic attack. Diazo compounds have nucleophilic character due to the presence of a carbene carbon. The diazo compound attacks the copper metal followed by releasing nitrogen gas resulting in a carbene copper complex. The possibility of back-donation from the metal atom to the empty p_z orbital of the carbene carbon may stabilize the complex. The next step involves the transfer of the carbene to an olefin. The formation of the carbene-copper complex is depicted in scheme 7.2:



Scheme 7.2 Cyclopropanation mechanism using a copper catalyst.

Another mechanism for the cyclopropanation of olefins is proposed by Doyle.[4] (see Scheme 7.3) Cyclopropanation generally results in two *cis*- and *trans*- isomers of cyclopropanes, generally *trans*- cyclopropane is the major product. This proposed mechanism can be explained as follows. The olefin can coordinate with the metal via π bond. This olefin bond is almost perpendicular to metal-carbene bond (Scheme 7.3(A)). While cyclopropanation reaction proceeds, *cis*- and *trans*-transition state occur simultaneously. The *trans*- form has a rather low transition state energy, because there is no interaction between the R and Z group. In the *cis*- form steric hindrance between the R and Z groups increases the transition state energy. Because of this, the *trans*-product is generally obtained as major product at the end of the reaction.



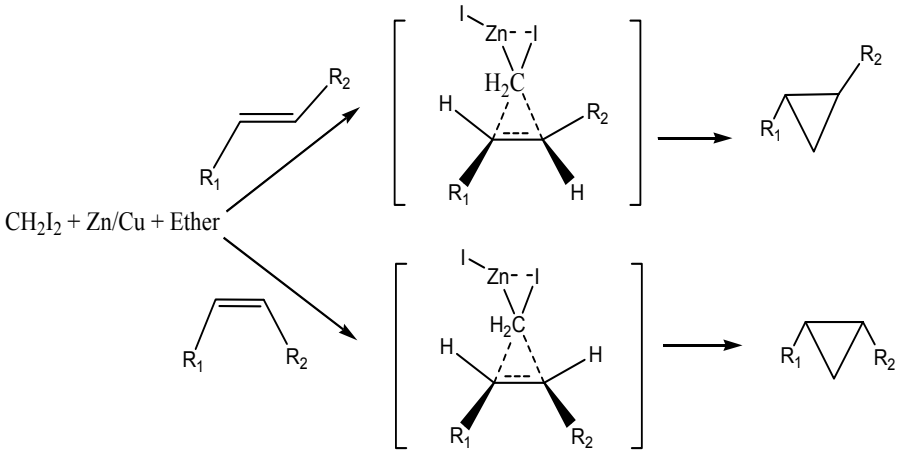
Scheme 7.3 Intermolecular cyclopropanation mechanism proposed by Doyle.[4]

7.3 Review for cyclopropanation

7.3.1 Halomethylmetal mediated cyclopropanation reactions

Many halomethylmetal reagents have been discovered as effective cyclopropanating reagents with unique properties and reactivities. From a historical perspective it is interesting to note that the seminal work for cyclopropanation was reported by Simmons and Smith in 1973, (Scheme 7.4)[5] although the iodomethylzinc species was first reported in 1929 by Emschwiller. [6] By using stoichiometric amounts of Simmons-Smith reactant, asymmetric cyclopropanation of olefins can be achieved. The organozinc intermediate shows an electrophilic character and excellent chemoselectivity.

After Simmons and Smith, Wittig, Furukawa, Denmark and many other chemists the development of several alternative methods to prepare efficient cyclopropanation reagents rapidly followed. The structures of these halomethylmetal reagents have been characterized over the years.[11, 12] In general, the classic Simmons-Smith reagent is mainly based on the zinc-mediated cyclopropanation reaction. It has to be mention here, that in case less nucleophilic alkenes were used, Furukawa's reagent is preferred since noncomplexing solvents are more suitable (higher electrophilicity of the reagent in non-complexing solvents).



Scheme 7.4 Simmons-Smith reaction.

A series of complexes with a proposed general structure"MCH_2X" can be catalogued here also, such as a samarium carbenoids reported by Molander.[7, 8] Often this kind of reagents displays an unique reactivity. For instance, the samarium-based compound promotes cyclopropanation of allylic alcohol, while the aluminum reagent only performs cyclopropanation on isolated olefinic groups.

Coordinating zinc or samarium reagent with the hydroxyl group or the corresponding metal alkoxide to direct the addition of methylene to the neighboring alkenes prior, the reaction rate was increased and the stereochemical outcome of cyclopropanation could be controlled.

If a catalytic amount of non-covalently bonded chiral auxiliary was added to the reacting holomethylmetal reagent, optically active cyclopropane could be obtained with an enhanced yield. There are four general classes of chiral auxiliary developed for various halomethylmetal reagents. (A) Carbohyrate-derived chiral auxiliaries act as bidentate ligand to the zinc reagent.[15-19] (B) Acetal-derived auxiliaries, especially tartaric- acid-derivatives were the most efficient ones. Diisopropyl tartrate was particularly effective with (*E*)-disubstituted and –trisubstituted acyclic substrates, because more auxiliaries were readily cleaved to produce the cyclopropyl ketone or aldehyde. (C) The chiral α,β-unsaturated carbonyl derivatives are the third class of auxiliaries. Because of the electrophilic nature of these reagents, they would prevent the cyclopropanation of the substrates. [9] It is not so common to be used for cyclopropanation reaction however the aluminum-derived reagent was superior with these auxiliaries.[21-23] (D) Enamines and enol ethers are the last class of auxiliaries. These compounds could generate enantiomerically enriched cyclopropyl alcohols and amines.[11-19]

The use of a stoichiometric amount of chiral ligand for the enantioselective cyclopropanation of allylic alcohol was reported by Fujusawa and co-workers.[10] A most important breakthrough in this area, based on a simple bifunctional, chiral, non-racemic ligand, containing both acidic and basic sites would allow simultaneous chelation of the acidic halomethylmetal reagent and the basic zinc alkoxide.[11, 12]

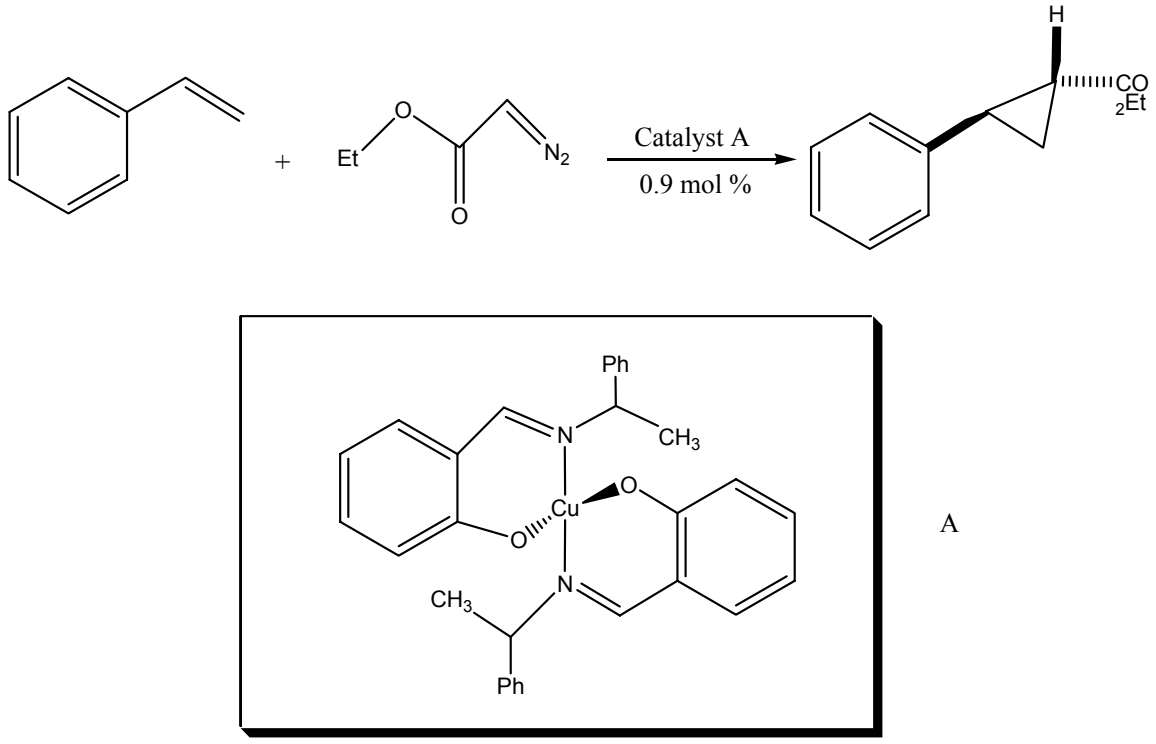
Kobayashi and Denmark developed an alternative protocol for the Lewis acid-catalyzed cyclopropanation reaction of allylic alcohol. Their comprehensive study highlighted the effect of the many variables to optimize the enantiomeric excesses of the product. [22-27]

7.3.2 Transtion Metal-Catalyzed decomposition of Diazo-Compound as carbene source

The cyclopropanation of olefins using the transition metal catalyzed decomposition of diazoalkanes is one of the most extensively studied reactions in organic chemistry. A wide range of metal catalyst derived from Cu, Rh, Co, Pd, Fe, Cr, Pt, Ru, lanthanum metal,[13] etc. have been reported to catalyze the diazo reagent decomposition. Usually, Cu, Rh, Co and Ru metal catalysts prefer to react with electron-rich alkene, while Pd-based catalyst show a high preference for electron-deficient ones.[14]

Herein, it is worth recalling that the asymmetric cyclopropanation, reported in 1966 by Noyori and co-workers, of decomposition of ethyl diazoacetate with a chiral copper(II) salicylaldimine complex in the presence of styrene is the first example of a transition metal catalyzed enantioselective reaction initiating a field of endeavor which still today represents one of the major enterprises in chemistry.[15] (Scheme 7.5) In view of the enormous growth in the field of asymmetric catalysis over the past five decades, it is somewhat ironic that significant advances in cyclopropanation have only emerged in the past twenty years.

The search for highly stereoselective and enantioselective olefin addition reactions has a long and continuing history, and cyclopropanation reactions of olefins using diazoacetates are core elements in this quest. Catalytic methodologies, especially those built upon a platform of transition metals having chiral ligands, have stimulated developments that today offer diastereocontrol and enantioselectivities that approach the limits of stereoisomer detection.[16] These reactions have been developed and exploited for synthesis in both inter- and intra-molecular.

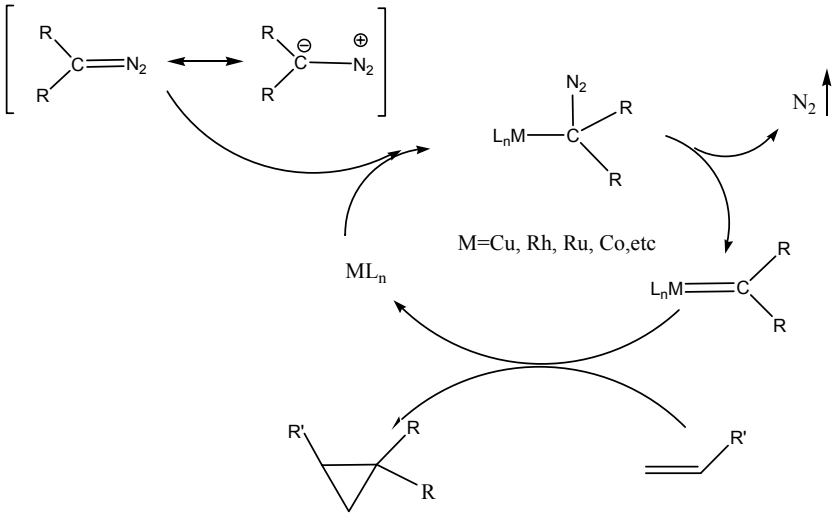


Scheme 7.5 Styrene cyclopropanation catalyzed by decomposition of Ethyl Diazoacetate with copper(II) salicylaldimine.

Diazao compounds are widely used as a carbene source for this reaction. Since diazo compounds have a resonance structure, the carbon atom connected to the nitrogen carries a partial negative charge while the nitrogen carries a partial positive charge. Because of this partial negative charge the carbon atom posses a carbenoid nature. As a consequence this carbon atom can interact with a metal atom by donating its electrons. As a result of this interaction N_2 is released easily from the diazo compound. In the next step the carbene can be transferred to the olefin. Selectivity control during the carbene transfer step is the main goal for cyclopropanation with diazo compounds. The nature of the diazo reagent is critical in the selection of the catalyst. Resonance structure and carbene transferring is shown in Scheme 7.6

Today many different transition metals with different ligands under different conditions have been tested. Many mechanisms have been proposed for the transition state of the carbene to an olefin. Unfortunately, the active species can not be separated and the nature of the intermediary's species remains unclear. The carbene formation and its transfer towards an olefin depend on the many aspects in the reaction i.e. the nature of the transition metal, the steric and electronic ligand periphery, the type of diazo compounds, the properties of olefin and the reaction conditions, e.g. temperature, reaction time, concentration, solvent, etc. A general observed trend is that the more

stable the complex the slower the carbene formation occurs but the more selective the transfer of this generated carbene towards an olefin proceeds.

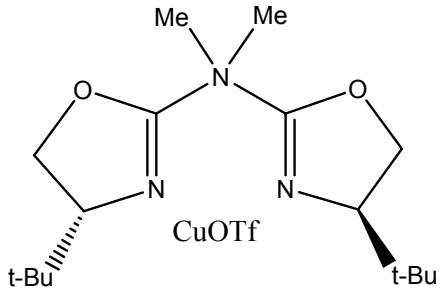


Scheme 7.6 Catalytic cycle of the cyclopropanation using a diazo compound.

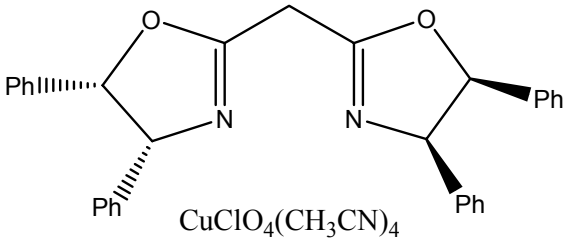
Among the reactions that decompose the α-diazoesters, by chiral transition metal complexes to cyclopropanate chiral alkenes in an intermolecular fashion, some general conclusions can be drawn. Firstly, the most effective catalysts for the preparation of the *trans* isomer with the widest reaction scope are the copper-based catalysts. Although Rhodium-based catalysts are very effective, they generally produce lower enantio- and diastereomeric ratios. Secondly, ruthenium-based catalysts are very efficient, but the scope is usually narrower compared to the best copper-based systems. Finally, cobalt-based catalysts are usually used in *cis*-selective cyclopropanation reactions.[6]

7.3.2.1 Copper(I) based catalysts[17-26]

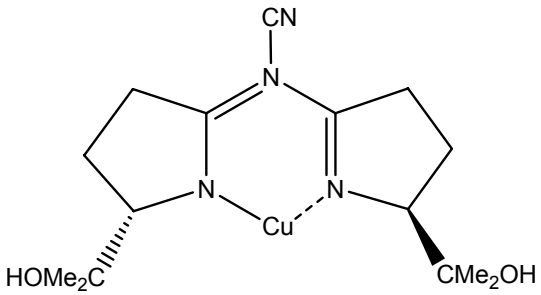
From the literature, copper-base catalysts have played a prominent role in the *in-situ* generation of metal carbenes (or carbenoids) from diazo compounds. [18-22, 27, 28] Beginning with copper catalysts having chiral salen (salen=*N*,*N'*-bis(salicylidene)ethylene diamine) ligands [29] and progressing to chiral semicorrin [37, 38] and bisoxazoline [30 23]ligands, rapid advances were made in enantio-controlled intermolecular addition reactions of diazoacetates. For instance, by using the C_2 symmetrical ligand bis(oxazolines) as a chiral ligand to obtained asymmetrical cyclopropanation products in high yields, the studies show that a bulky chiral ligand could improved the enantioselectivity of cyclopropanes. Some reported bidentate ligands are depicted in Figure 7.1. [31 34-37]



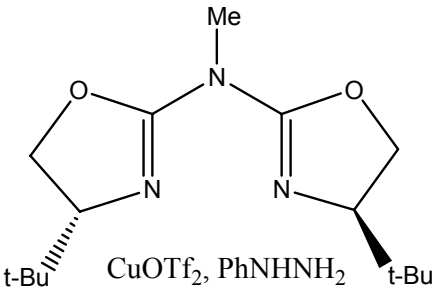
A) Catalyst by Evans



B) Catalyst by Masamune



C) Catalyst by Pfaltz



D) Catalyst by Reiser

Figure 7.1 Bis(oxazoline)copper(I) catalyst by Evans(a), Masamune (b), Pfaltz (c), Reiser (d).

After initial development, the copper carbenes have never been characterized by X-ray analysis, until 2001 a NMR study has been carried out.[32] This study proved the mechanistic picture is fully consistent with the proposed mechanism by Pfaltz and co-workers.[33] Furthermore, an important aspect for copper catalysts in cyclopropanation reaction is that although Cu(II) salts are usually used as catalysts precursors, the real catalytic active species is Cu(I).[34, 35]

Another example of Cu (I) catalyst bearing entities contains bisferrocenyldiamine ligands and also this complex has a C_2 symmetry. By using these ligands (Fig. 7.2), an enantioselectivity range between [ee(*trans*)=48-96%] was found depending on the olefin and the electronic properties of the ligands.

The high selectivity of enzymes is largely caused by their concave geometry and this idea has been implemented in some copper based catalysts. Numerous classes of concave acids, concave bases and concave ligands have been synthesized and besides used as carriers, these complexes have been used to enhance selectivities in cyclopropanation. [36] Due to the concave shielding of the copper the least hindered approach of the alkene to the carbenoid is the unproductive orthogonal approach, see Figure 7.3. A clockwise rotation of the alkene diminishes the steric interactions, favouring the formation of the *trans*-products. [37]

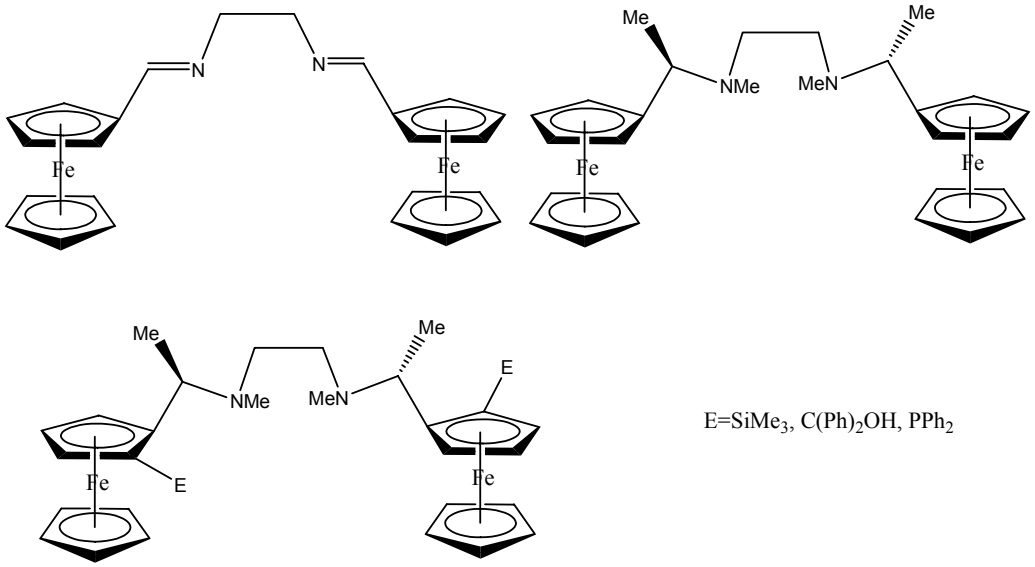


Figure 7.2 Bisferrocenyldiamine ligands used in cyclopropanation catalysts.

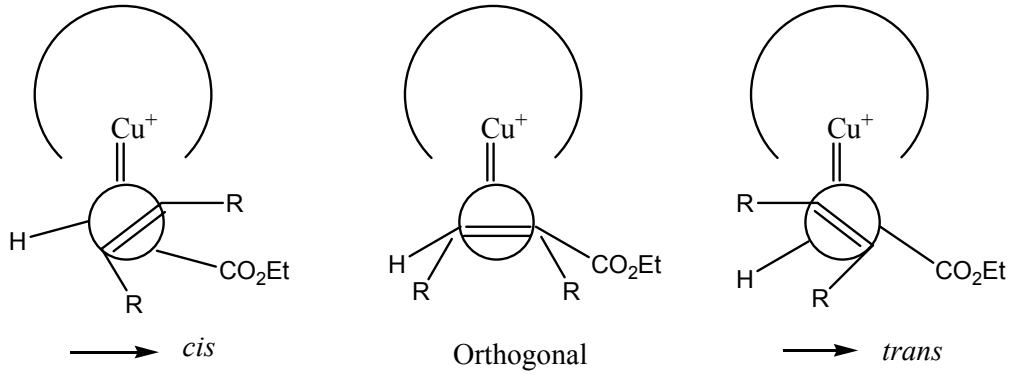


Figure 7.3 Due to the concave shielding of the copper the least hindered approach of the alkene to the carbenoid is the unproductive orthogonal approach.

Recently catalytic cyclopropanations reactions were carried out using copper(I) diphosphinoamine $(PPh_2)_2N(R)$ (R =*i* -Pr, H, Ph and $-CH_2C_6H_4CH=CH_2$) and high yields of the cyclopropanes were obtained in all cases. The reaction rate was influenced by the nuclearity of the complex and the binding mode of the ligand which was either bridging or chelating. [38] Copper(I) 2,2'-bipyridine complexes, $[Cu(bpy)(\pi\text{-}CH_2CHC_6H_5)A]$ (A = $CF_3SO_3^-$, PF_6^-, ClO_4^-) have been synthesized and characterized. In cyclopropanation reactions, catalyzed by these complexes, a similar product distribution was obtained.[39]

7.3.2.2 Rhodium based catalysts

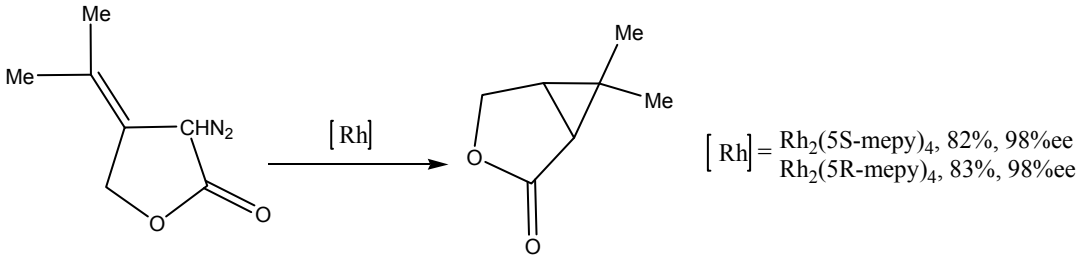
In the 1970s, new transition metal complexes were discovered that widened the range of catalyzed diazocompound applications while proceeding under much milder reaction conditions. In 1977, Mansuy et al. reported the formation of the first metalloporphyrin carbene complex. Three years later, Callot and Piechocki found that rhodium porphyrins catalyze the cyclopropanation of alkenes with ethyl diazoacetate to form cyclopropyl esters in 60–71% yields with a striking *cis*-selectivity. [40] The *cis*-selectivity can be rationalized by the intermediacy of a rhodium porphyrin carbene species in the catalytic process. These works first demonstrate the close relevance of metalloporphyrin carbene complexes to both biological systems and metal-catalyzed organic reactions. Up to now, the rhodium porphyrin-catalyzed alkene cyclopropanations have been dramatically enriched by Kodadek and co-workers. [41]

A better insight into the possible reaction mechanism promoted further investigations on the catalytic behavior of transition metal complexes that culminated in the discovery of dirhodium(II) tetracarboxylate[42] and later of the corresponding carboxamides.[43] These are the first really efficient and air-stable complexes. Recently *trans*-directing ability of amide groups in cyclopropanation catalyzed by a rhodium complex, has been reported in asymmetric cyclopropanation of alkenes with a diazo reagents bearing two carboxy groups.[44] Recently, the mechanism of $Rh_2(carboxylate)_4$-catalyzed cyclopropenation and cyclopropanation via two different pathways has been investigated computationally.[45]

The dimeric rhodium(II) complex with the chiral ligands, [N-(arenesulfonyl)prolinate], induced good selectivity and high yields with diazoesters. In this study, it was mentioned that the distance between the reaction centre and the chiral subsituents at the N atoms of the dirhodium (II) complexes is important for the selectivity of the reaction. This dimeric catalyst is also used for the synthesis of an intermediated product using another type of diazo compound.[46]

Chiral dirhodium(II) carboxamidates fulfilled a role in intramolecular reactions. [45, 46] For instance, rhodium carboxamindes possessing the chiral ligand pyrrolidone or oxazolidinone are effective catalysts for the olefin cyclopropanation with diazoacetate esters, optical yields higher than 90% are obtained.[47, 48] The basis for this high yield has been attributed to the organization of the chiral ligands around the dirhodium nucleus and the electronic orientation and stabilization of the intermediate metal-carbene.

When the diazoalkanes bear two electron-withdrawing groups, more active catalysts are required to generate the metal carbene. $Rh_2(5S\text{-}mepy)_4$ and $Rh_2(5R\text{-}mepy)_4$ were reported as efficient dimeric chiral catalysts for this type of cyclopropanation by Doyle. [47]



Scheme 7.7 Cyclopropanation Catalyzed by $Rh_2(5S\text{-mepy})_4$ and $Rh_2(5R\text{-mepy})_4$

In an early report, rhodium complexes have been taken as the best catalyst for the decomposition of vinyldiazoesters in the cyclopropanation of alkenes with a high diastereocontrol.[49] After development of chiral auxiliary on the ester, the enantiomerical ratio enlarged. Davies reported that by changing the chiral auxiliary with chiral ligands, e.g. $Rh_2(DOSP)_4$, this system provides the highest enantiocontrol.[50]

When the diazo unit and the alkene functionality are in the same molecule, intramolecular cyclopropanation is possible. Sarkar described the synthesis of the tricarbocyclic framework using $Rh_2(OAc)_4$ as a highly diastereoselective catalyst.[51]

In 2002, a novel dirhodium catalyst, with L-menthyl ester-derived azetidine was reported by Doyle. The cyclopropanation of substituted styrenes with tert-butyl diazoactate resulted in a good *cis* diastereo-control and excellent enantio-control, however with a low yield.

Recently, a structurally characterized Rh(I) iminocarbene complex (N,C)Rh(CO)Cl activated with AgOTf act as a highly *cis*-selective catalyst for the cyclopropanation of substituted styrenes. Other alkenes with ethyl diazoacetate has been reported as a novel development of a Rh-base catalyst in cyclopropanation reaction.[52]

Immobilized chiral catalysts for cyclopropanation has been a novel development direction recently. Immobilization of ortho-metalated dirhodium(II) compounds has been achieved by a carboxylate interchange reaction between $Rh_2(L\text{-protoS})_2[(p\text{-}XC_6H_3)P(p\text{-}XC_6H_4)_2]_2$ diastereoisomers and carboxyethylpolystyrene polymer ($PS\text{-}C_6H_4(CH_2)_2CO_2H$).

7.3.2.3 Palladium based catalysts

Diazomethane (CH_2N_2) is the simplest diazoalkane that has been used in cyclopropanation reactions. Due to some disadvantagyes and limitations linked with the preparation and transport of diazomethane, the more stable trimethylsilyl analogue ($TMSCHN_2$)[53] and phenyldiazomethane ($PhCHN_2$)[54] have been used. Although a large number of metal salts interact with diazomethane, [55] palladium salts are very effective at decomposing diazomethane in the presence of an alkene to lead to cyclopropane formation.

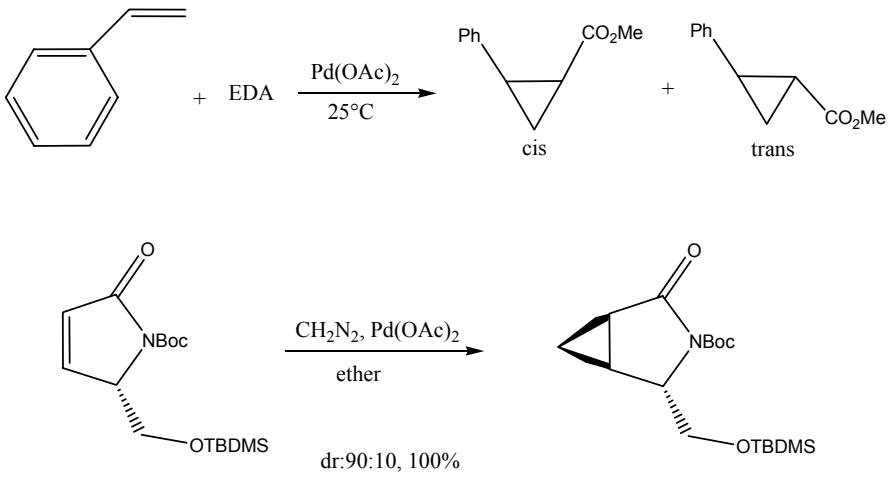
The available literature support the assumption that the outcome of the methylene cycloadditions depends to a large extent on the ability of the olefin to be coordinationed to the palladium center. In that respect, the mechanism of palladium catalyzed cyclopropanation appears to differ significantly from the rhodium (II) catalyzed cyclopropanation. Most probably the palladium (II) catalyst precursor is initially reduced to palladium (0), [56] and a subsequent reaction with diazomethane would produce the palladium carbene.[57]

One advantage of using palladium catalysts with diazomethane is associated with the possibility of synthesizing polycyclopropane adducts. Moreover, the reactivity of the double bond depends both on their position in the linear hydrocarbon chain and on their configuration.

One of the earlier studies on cyclopropanation of olefins reported by R. Paulissen, A.J.Hubert and Ph. Teyssie includes $Pd(OAc)_2$ as catalyst. They obtained almost quantitatively cyclopropane products of styrene in the presence of EDA under very mild conditions. [58, 59] Nevertheless, the selectivity was very low because of the absence of chiral entities within the catalyst periphery. While, by using the same catalyst in combination with substrates bearing sterically demanding groups, the cyclopropanation of the chiral cyclic alkene proceeds with good diastereo-control.

Recently, the asymmetric cyclopropanation of cinnamoyl amides derived from amino acids with CH_2N_2 in the presence of catalytic $Pd(OAc)_2$ has been studied. The reaction proceeded with moderate to excellent diastereoselection. However, the selectivity depends upon the amino acid side chain as well as the electronic nature of the cinnamoyl moiety.[60]

In order to get pure enantiomeric cyclopropane derivatives, chiral ligands have been introduced on the metal complex. Although a great number of chiral palladium compounds have been investigated by Denmark and co-workers, and all catalysts were very active, but up to now, no enantio-selectivity was observed.[2]



Scheme 7.8 Palladium catalyst cyclopropanation

7.3.2.4 Cobalt(II) based catalysts

The chiral cobalt(II)-dioximato complex derived from camphor was the first successes in enantioselective intermolecular cyclopropanation reported by Nakamura et al.. [61] Although results from many transition metals and chiral ligands have been reported, none have surpassed the overall stereocontrol provided by copper and dirhodium catalysts until the recent emergence of cobalt (II)-porphyrin catalysts.

The early report regarding these catalysts established that they are constructed as a double-edged sword. On one hand, the common weaknesses for the breakthrough of these catalysts are that at least one of the key ingredients, i.e. one of the factors among yield, diastereoselectivity, or enantioselectivity is missing. On the other hand, the advantage of these catalysts compared with copper and dirhodium catalysts is, that both later catalysts promote additions to simple and conjugated olefins and not to unsaturated esters, nitriles, and ketones, while cobalt catalysts showed activity even with unsaturated esters and nitriles. Furthermore in 1999, Yamada reported that 3-oxobutylideneaminato cobalt(II) complexes were very effective in a *trans*-selectivity reaction.[62 63]

Katsuki and co-workers[64] reported intriguing results in *trans*-or-*cis*-selectivity for cyclopropanation reactions by using chiral cobalt(III)-salen complexes. (Fig. 7.4) Both of them show excellent diastereomeric ratios and enantiomeric excess.

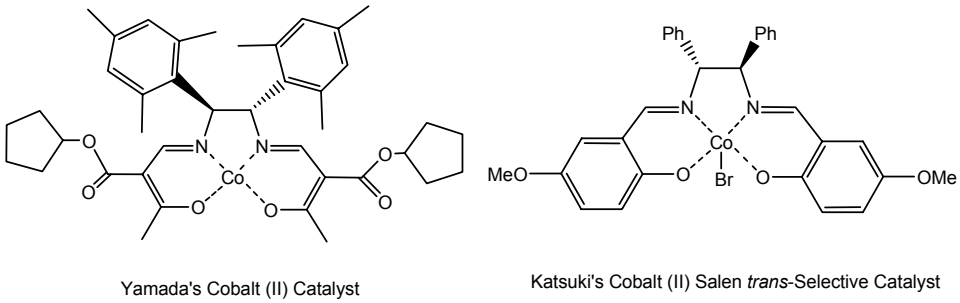
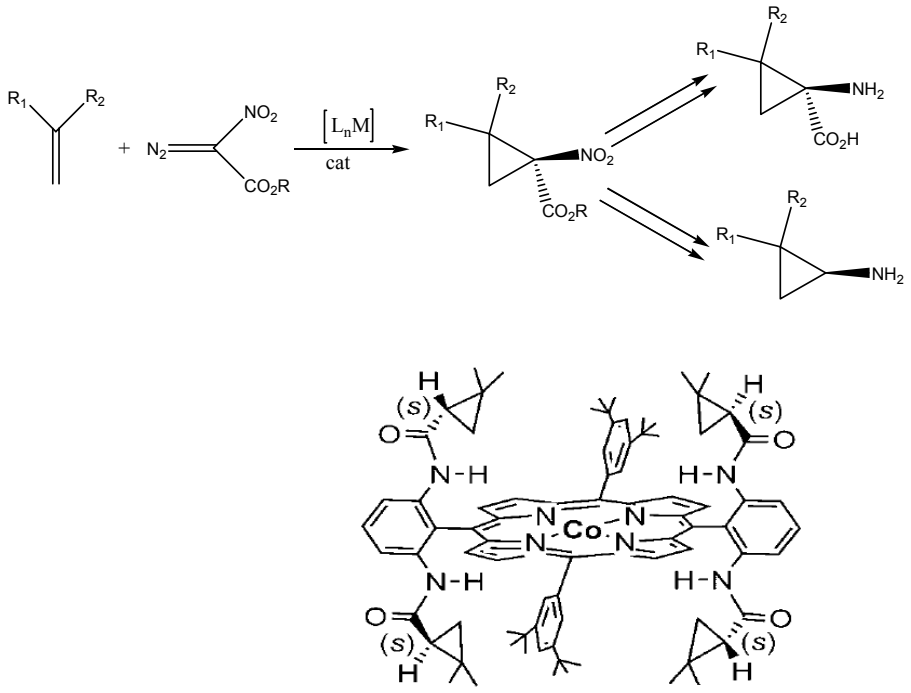


Figure 7.4 Chiral Cobalt(II)-Based catalysts.

Zhang and co-workers combined cobalt (II) with chiral porphyrins to produce catalysts that exhibit unique reactivities and exceptional selectivities.[45-48] Recently, the same group have reported applications using α-nitro-diazoacetates to prepare *cis*-cyclopropanes in high yield with exceptional diastereo- and enantioselectivity (Scheme 7.15).[65] With these catalysts, all kinds of olefin, i.e. electron-sufficient, electron-neutral, and electron-deficient olefins can be used.



Scheme 7.9 Cyclopropanation of Olefins Catalyzed by a cobalt(II)–porphyrin catalyst

Recently, Cobalt(II) complexes of chiral bis-binaphthyl porphyrins were prepared, and their catalytic activity in the asymmetric cyclopropanation of alkenes with ethyl diazoacetate was examined. Good yields and enantioselectivities were observed with *cis/trans* ratios reaching 11:89. UV-vis and ^{1}H-NMR studies suggest that the axial nitrogen ligand N-methylimidazole could play a role in changing the enantioselectivity of the reaction.[66]

7.3.2.5 Ruthenium(II) based catalysts

The common strategic element found in approaches to designing catalysts for inducing enantioselective carbenoid transformations has consisted of attaching chiral ligands to a central metal atom.[17] To this end, ruthenium based catalysts containing asymmetric ligand have been designed that achieve high levels of enantioselectivity for the cyclopropanation reaction.

I. Ruthenium Catalysts with a Pybox Ligand

The first very effective ruthenium-based chiral catalyst system was reported in 1994 by Nishiyama[67] and the effect of electronic properties of the pybox ligand on cyclopropanation was studied in their work.[68] The pybox-Ru catalytic system is probably the most studied Ru-based catalyst for cyclopropanation and many structural variations of the ligands have been tested.

A chiral 4-substituted bis-(4-isopropyloxazolinyl)pyridine ligand (4-X pybox) was synthesized (Fig. 7.4). When an electron withdrawing group (X=Cl, COOMe) is presented at 4-position, the catalytic activity could be increased. While, if an electron donating group (X=OMe, NMe_2) was presented at that position, the catalytic activity would be decreased. The quantity of enantiomeric excess of the products seems to depend on the substituent as well. In the intramolecular cyclopropanation of olefins reaction, the same trend has been found.

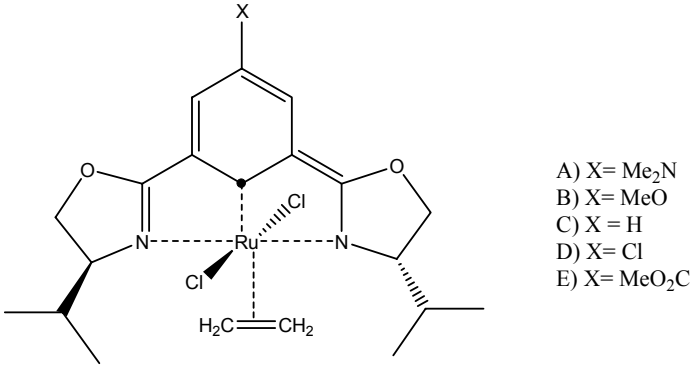
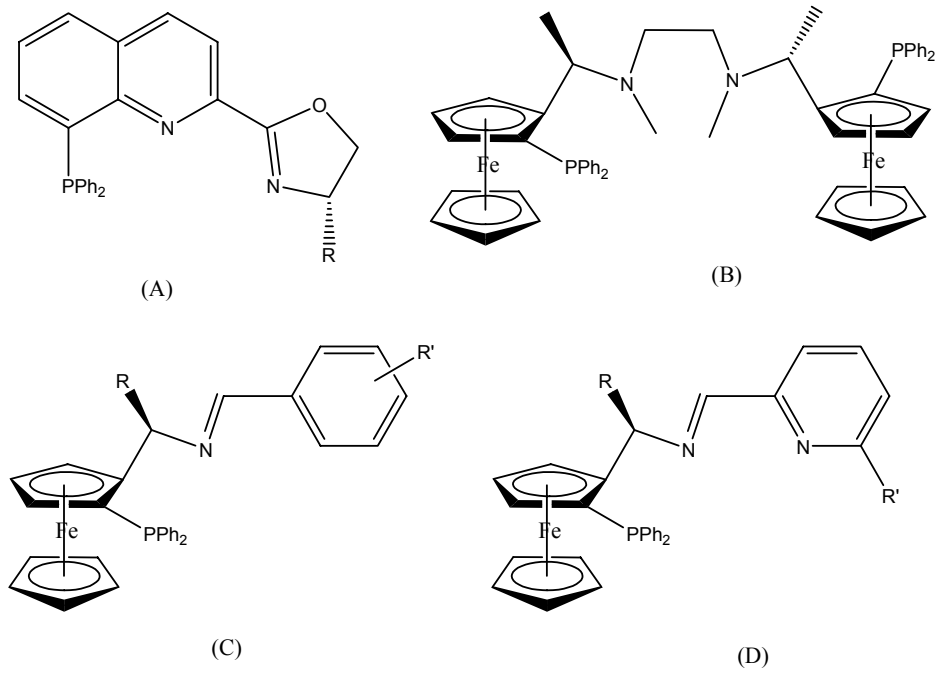


Figure 7.5 Ruthenium pybox catalyst reported by Nishiyanma

II. Ruthenium catalysts with a P,N,N-type ligand

A new ferrocenylphosphinimine (P,N,N-type) ligand was synthesized by Zhou Zheng and co-workers used as an asymmetric ligand for cyclopropanation of styrene resulting in high enantiselectivities. Because of the central and planar chirality of this ligand, a different behavior was expected for the catalytic reaction. Using ethyl diazoacetate as a carbene precursor, a high *trans:cis* diastereoselectivity (up to 81:19) and high enantioselectivity (up to 95% for *cis* isomer) was obtained.

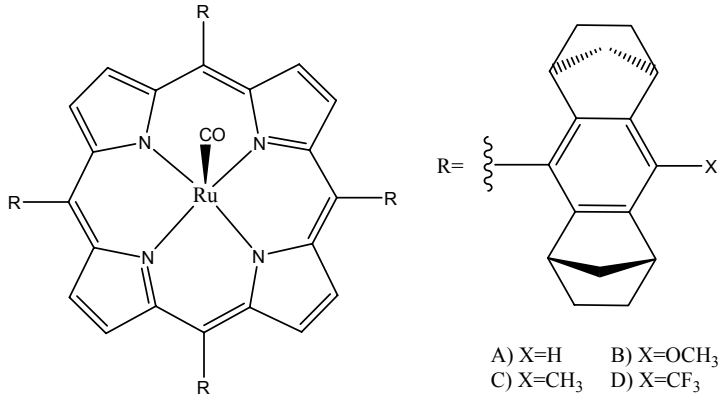


A) R=Me, R'=H B) R=Me, R'=Me
C) R=Et, R'=H D) R=Ph, R'=H

Figure 7.6 P,N,N ligands in ruthenium cyclopropanation catalysts

III. Ruthenium Catalyst with Porphyrin Ligand

Ru(II) with a porphyrin ligand, reported by M. Frauenkron and A. Berkessel, resulted in a high increase of selectivity for the cyclopropanation of olefins using diazo compounds.[69] Almost quantitative cyclopropanation products were obtained by using a very low catalyst loading (0.15 mol%). Because of the bulky chiral ligand, a very good diastereoselectivity (*trans:cis* 96:4) and a large enantiomeric excess (up to 91%) were obtained[70]



A) X=H B) X=OCH_3
C) X=CH_3 D) X=CF_3

Figure 7.7 Chiral ruthenium carbonyl porphyrin complex.

IV. Ruthenium Catalyst with Schiff Base

The chiral ruthenium complexes discovered for cyclopropanation include many ruthenium chiral Schiff base complexes.[71, 72]

In 2002, another type of highly enantioselective and diastereoselective cyclopropanation catalyst was reported by J.A. Miller and co-worker. [73] Schiff base ligands containing chiral centers were prepared, and implemented on ruthenium resulting in chiral Ru(II)-complexes. These complexes have two pyridine ligands at the axial positions. By using EDA, *trans*- isomers in a highly enantioselective way were obtained (in all case at least 10.6:1). These compounds are also very efficient catalysts for the asymmetric cyclopropanation of both electron rich and electron deficient olefins. It was observed that side reactions did barely occur (dimerization products<1%).

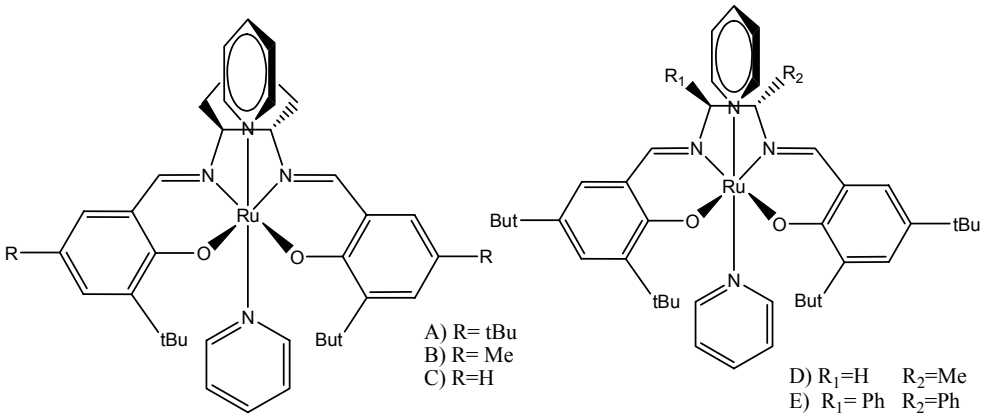


Figure 7.8 Chiral Schiff base ruthenium complexes

V. Ruthenium Catalyst with P,N,N,P Ligand

A Ru (II) catalyst with a chiral PNNP-type ligand was reported to highly increase *cis* enantioselectivity in cyclopropanation when styrene or its derivatives were used as substrates; especially, when they carry an electron donating group at the para- position.[42, 56-5974] From this result, the electronic tuning of the ligands could optimize the results for asymmetric cyclopropanation. Also the detection of an intermediate by ^{1}H and ^{31}P NMR was successful.

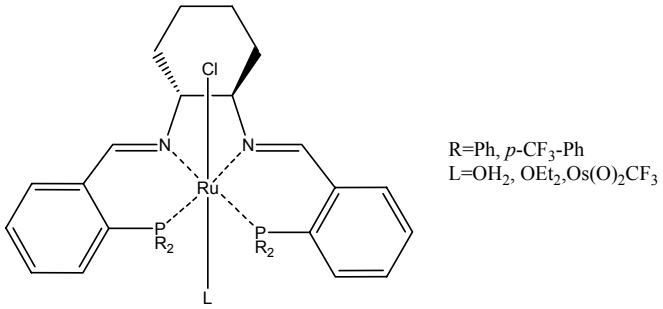


Figure 7.9 Catalyst reported by Mezzetti

VI. Ruthenium Catalyst with 2,6-bis(imino)pyridyl

Another efficient Ru(II)-catalyst containing a chiral imino pyridyl ligand for cyclopropanation has been reported by H.M.Lee and C.Bianchini.[75] When taken stryrene as olefin and EDA as diazocompound, cyclopropanation products were obtained. The carbene intermediate could be isolated in this reaction. Apparently the *cis*-Ru carbene can be thought as a kinetic product and the *trans*-Ru carbene as the thermodynamic product. The kinetic product was intercepted at low temperature. The yield and stereo-selectivity increase in the presence of $AgPF_6$. In most cases *trans*- products were formed as the major compounds.

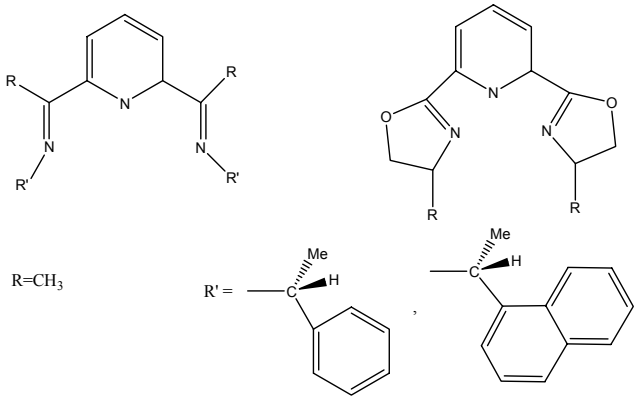


Figure 7.10 Catalyst with 2,6-bis(imino)pyridyl ligand

VII. Ruthenium Catalyst with Carbene

Generally, compared with the copper and rhodium complexes, which bearing chiral ligands, ruthenium carbenes bearing chiral ligands are less reactive. Most of them will efficiently convert aryl-substituted alkenes to their corresponding cyclopropane, but lower yields are observed when alkyl-substituted alkenes are used.

In recently years, the nitrogen heterocyclic carbenes (NHCs) complexes became a hot topic. Many non-metathesis reactions, such as hydrogenation epimerization, co-cyclopropanation, [3+2] cycloaddition, and cycloisomerization have been investigated using ruthenium carbene catalysts. [76-78] One of the utilities focus on tandem reactions, e.g. preparation of substituted vinylcyclopropanes using a ruthenium NHC catalyst is a tandem three-component coupling between an olefin, alkyne, and diazoester; [79, 80] Ruthenium-carbene catalyzed cyclopropanation was also used as one procedure of stepwise macrocyclization.[81]

Recently, RuCl(COD)Cp was applied as a catalyst precursor generating an alkenylruthenium-carbene, which promotes the cyclopropanation. A direct comparison of the energy profiles with respect to those involving the Grubbs catalyst is discussed in literature, [82-84] proving that cyclopropanation is favored with respect to the metathesis.

7.3.2.6 Gold based catalysts

Recently gold has been investigated as a novel metal-catalyzed cyclopropanation catalyst. The selectivity of the cyclopropanation of olefins with ethyl phenyldiazoacetate has been tested using different gold complexes bearing phosphine, phosphite or N-heterocyclic ligands. A comparative study with related copper, silver and other metal complexes as catalysts is described.[80, 85-87] Furthermore, the activity of the gold-based catalysts in ionic liquid has been also investigated. [88]

7.3.3 Michael-Initiated ring closure

Cyclopropanation reactions which involve a conjugate addition to an electrophilic alkene producing an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael initiated ring closure (MIRC) reactions. [89]

The cyclopropanation via the MIRC reaction are usually non-stereospecific, and both (*E*)- and (*Z*)-olefins give the *trans*-cyclopropanes. Two types of substrates are useful in MIRC reactions. The nucleophiles, such as alkoxides, thiolates, cyanides, enolates, Grignard reagents, hydrides, phosphites, and phosphonites[90] are added to the electrophilic substrates containing a leaving group to form the cyclopropanes is the first type. (Scheme 7.4).

Cyclopropane-forming reactions, in which the leaving group is present on the nucleophile (include the α-halo carbanions[91], the heteroatom-derivative), constitute the other class of the MIRC reactions (Scheme 7.3)

Recently, Taylor and co-workers established that stabilized phosphonates could be used and represent a viable alternative to ylides in the cyclopropanation reaction involving 1,2-dioxine.[92] Stabilized arsonium ylides, such as carbomethoxy and benzoyl-methylene- triphenyl-arsorane, are also known to react with conjugated esters and ketones leading to cyclopropanes.[93] An efficient oxidative cyclopropanation of the Michael adducts of nitroolefins with activated methylene compounds by combining of iodobenzene diacetate and tetrabutylammonium iodide is reported. Highly functionalized nitrocyclopropanes are synthesized in moderate to good yields via the Michael addition and cyclopropanation with high diastereoselectivity and enantioselectivity under mild conditions.[94]

7.3.4 Enzymatic methods

Enzymes, such as lipases and esterases have been used in the synthesis of chiral cyclopropanes frequently. Many processes were reported in the 1980s and early 1990s for the desymmetrization of diester cyclopropanes. The enantiomeric excess depends on the substituents and the esterase

source. Sometimes, better selectivities are observed with substituted substrates or substrates containing chiral centers other than the cyclopropane moiety.[95]

7.3.5 Chiral stoichiometric carbenes

Except metal carbene produced as intermediate in the transition metal-catalyzed cyclopropanation of olefins with diazo reagents, in parallel to this process, the development of chiral stoichiometric metal carbene systems as cyclopropanating reagents has also been investigated. [95-97] Iron and chromium-derived carbene systems [96, 97] have been used successfully.

Brookhart[100, 101], and Hossain[98, 99] reported that high enantioselectivities could be achived when the chiral metal carbene such as [$CpFe(CO)_2$] is used to catalyze cyclopropanation.[100] A variety of substituted cyclopropanes have been synthesized from chromium carbenes and alkenes.[101-103] Barluenga also reported that chiral oxazolines could be used as chiral auxiliaries for the cyclopropanation with chromium complex, but the chiral auxiliary could not be removed without destroying the cyclopropyl moiety.[104]

7.3.6 Other ring-closing reaction of chiral precursors

Many chiral 1,2-electrophiles such as epichlorodrins, epibromohydrins, glycidol derivatives, cyclic 1,2-sulfates[105] and a variety of nucleophiles, including malonate-, β-phosphonate-, ketone-, sulfone-, and nitrile-derived carbanions[110-112] were studied for synthesis of chiral cyclopropanes.

Two presumable pathways have been established for the double displacement which is dependent on the nature of the leaving group.[106] In one of them, the direct displacement of the leaving group is followed by the ring opening of the epoxide, whereas in the other, the ring opening of the epoxide is the first step followed by the Payne rearrangement to generate a new epoxide, and then cyclization. The two pathways gives rise to the opposite enantiomer.

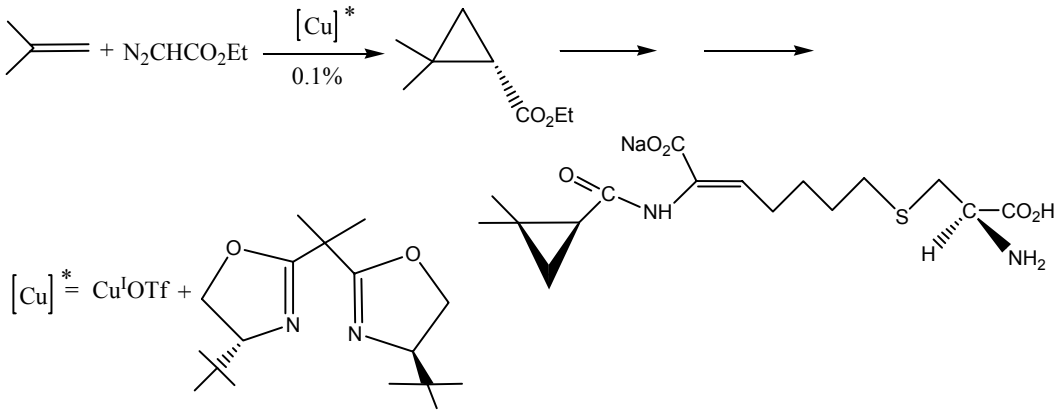
Pirrung, [107] Burgess, [108, 109] Otera and Furukawa, [110] Shuto and Co-workers[111, 112] have reported their investigation on this study.

The application of novel sulfonamides in enantioselective organocatalyzed cyclopropanation has been reported recently. Three new aryl sulfonamides derived from (2S)-indoline-2-carboxylic acid have been obtained and used as organocatalysts. The catalysts incorporate diverse functionality on the phenyl ring, enabling steric, and electronic fine tuning of the catalysts. The catalysts facilitate the reaction between a range of alpha, beta-unsaturated aldehydes and sulfur ylides, thus providing cyclopropane products in enantiomeric excesses of up to 99%. [113]

7.4 The Application of Cyclopropanation

Cyclopropanation reactions are among the most important tools for synthesis in organic chemistry, since these reaction are vital to the modern synthesis of natural products. The interest in the synthesis and chemistry of the cyclopropane subunit may also be attributed to number of other factors. Such as, these compounds generally are optically active and often show a significant and specific biological activity. Its ability to act as a probe for the reaction mechanism studies is widely employed. Meanwhile, in organic chemistry the cyclopropane entity is used as a strategic element for developing a synthesis of optically active molecules. Therefore, cyclopropanes are often used as intermediary compounds in organic synthesis via vinylcyclopropane and homo-Cope rearrangements.[2, 6, 48-53]

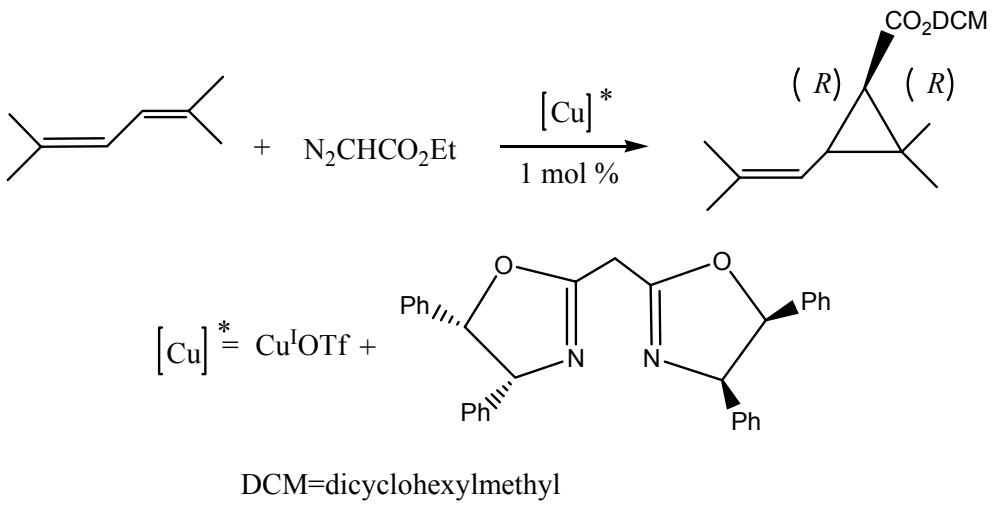
Practical application include the synthesis of 2,2-dimethylcyclopropane carboxylate from isobutene, [30] a key step in the commercial production of cilastatin (Scheme. 7.6) and of the esters of chrysanthemic acid. (Scheme. 7.7).[15, 24]



Scheme 7.10 Syntheis of Cilastatin

Cilastatin is a dehydropeptidase and acts as an in-vivo stabilizer of the carbapenem antibiotic imipenem with achiral diazoeasters.

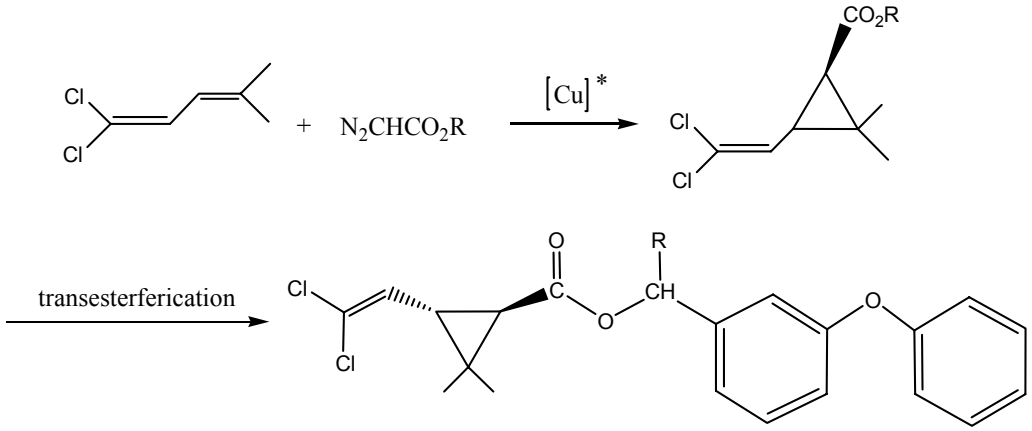
After modification and stabilization of chrysanthemic acid derivatives, the pyrethroids have been discovered as the most important class of environmentally friendly insecticides.



DCM=dicyclohexylmethyl

Scheme 7.11 Synthesis of ester of Chrysanthemic acid

Cypermethrin is highly effective against a wide range of parasitic insects in various crops and also active to against mosquitoes.

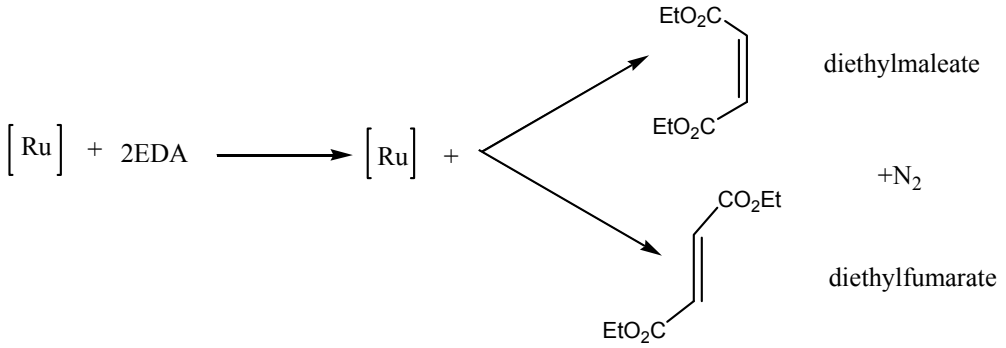


Scheme 7.12 Synthesis of Cypermethrin

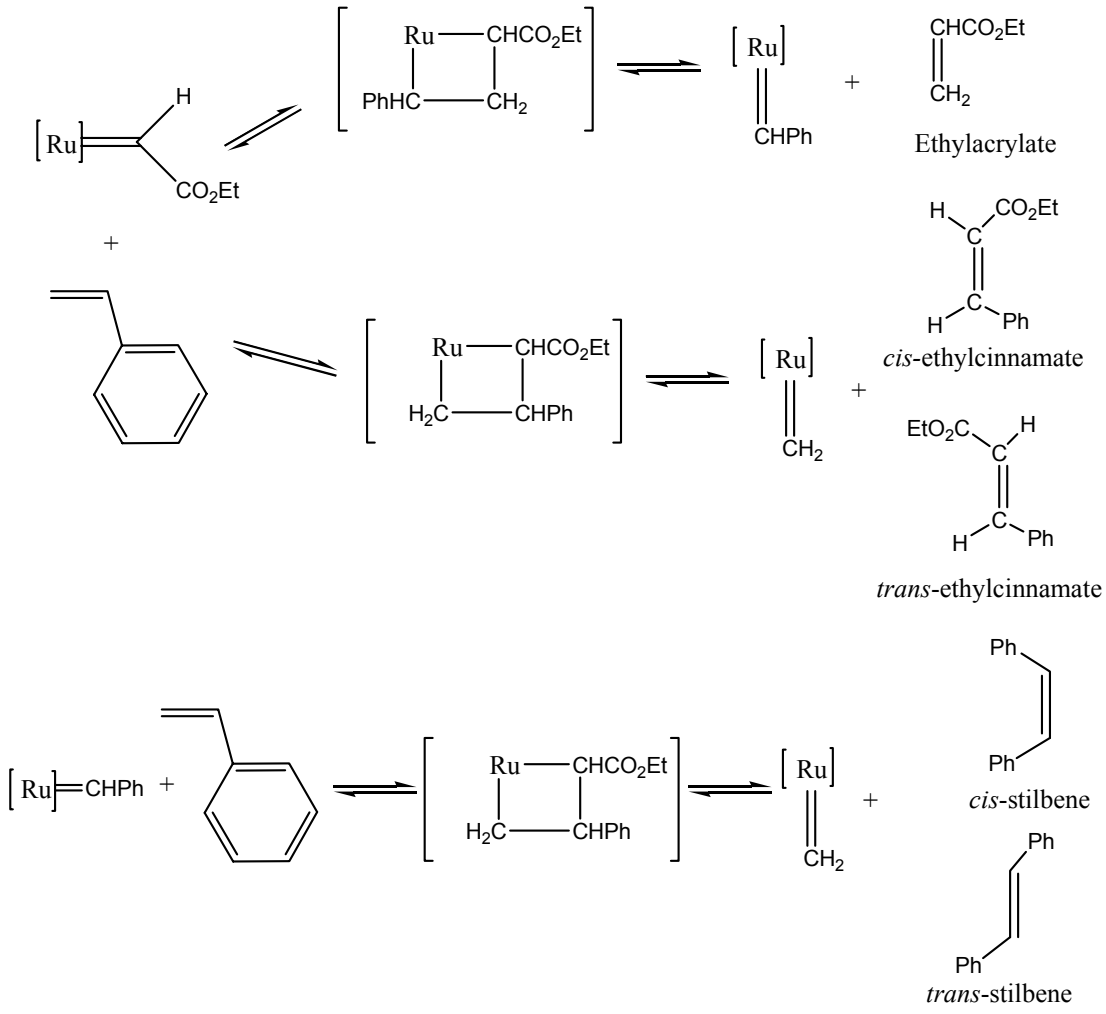
7.5 The side reaction of cyclopropanation

By using the most common method for cyclopropanation, i.e. a reaction of olefins with a diazo compound, three major side reactions can occur under these conditions. Dimerization of the diazo compound can be seen as the major side reaction. When the olefins coordinate with the metal the metathesis reaction could occur but metathesis products are generally observed in inferior amounts. The amounts of side products can be controlled by adjusting the reaction conditions. Dimerization can be surpressed by manipulation of the addition rate of the diazo-compound and by use of an excess of olefin. Metathesis can be repressed by working in an inert solvent instead of pure olefin.

Because of the complicity of the reaction mixture and the possible side reaction a mixture of products is obtained at the end of the reaction. The side reaction can be summarized as follows:



Dimerization



Metathesis Products of Styrene Using EDA

Scheme 7.13 The side reaction of cyclopropanation reaction

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Chapter 8
The Kinetic Study of Grubbs' 1st Generation Catalyst on Cyclopropanation

In this chapter, Grubbs 1st generation catalyst is evaluated in relation to the cyclopropanation of olefins using ethyl diazoacetate. From a fundamental study of the reaction by means of FT-IR, GC and NMR, some elementary kinetic parameters are calculated and based on these findings, a mechanism is proposed. It is found that the catalyst shows good activity for the cyclopropanation of styrene. An effort is made to suppress the most common side reactions by modifying the ligand sphere and the nature of the carbene.

8.1 Introduction

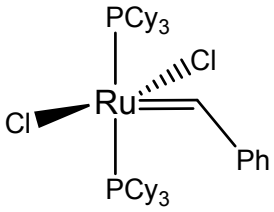
Cyclopropane structures have always been of wide interest since they are frequently found in natural products[1] and since they are of high biological significance[2]. Moreover, since Simmon and Smith have reported the synthesis of a cyclopropane structure in 1958[3], this unit became a valuable synthetic intermediate in organic synthesis[4]. Many efforts have been made ever since in an attempt to introduce a cyclopropane unit in the most complex molecules. In terms of academic curiosities and industrial interests, catalytic cyclopropanation of olefins using diazocompounds has been one of the highlights since Nozaki and co-workers introduced the use of transition metal catalysts for this purpose about 40 years ago[5].

Over the last 20 years many excellent, metal-based methodologies have been developed for the cyclopropanation of olefins. Catalysts based on cobalt[6], palladium[7], osmium[8], iron[9] but especially copper[10] and rhodium[11] are found to be very efficient in terms of activity and selectivity[12] among the wide variety of catalytic systems described. Inspired by the success and

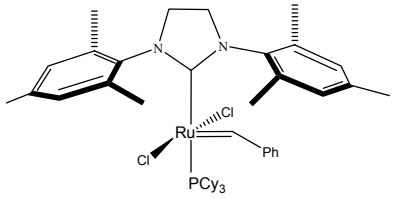
the versatility of these catalysts, the central metal ion was expanded towards Ru, as a cheaper alternative for Rh. Although $Ru_3(CO)_{12}$ has been reported already in 1981[13] to catalyze the cyclopropanation reaction with diazoacetates, the potential usefulness of Ru-catalysts - with different possible oxidation states of the metal ion and a variety of ligand systems – for carbene transfer reactions has started to emerge as novel catalysts only the last decade[14].

Today, the available catalysts have proven their value in many conditions, but the need for cheaper, readily available and highly selective transition metal systems which catalyze carbene transfer from a diazo compound towards a (substituted) olefin remains largely unmet.

The well defined, commercially available Grubbs' systems, $(PCy_3)_2Cl_2Ru=CHPh$ (1st generation) and $(PCy_3)(H_2IMes)Cl_2Ru=CHPh$ (2nd generation) (Fig 8.1) are very attractive due to their ease of resistance to a variety of functional groups, air and moisture. The share of Ru-complexes for the cyclpropanation reaction has grown significantly over the last years and the Grubbs systems should be classified in this category.



(1)



(2)

Figure 8.1 Grubbs 1st Generation $(PCy_3)_2Cl_2Ru=CHPh$ (1) and Grubbs 2nd Generation $(PCy_3)(H_2IMes)Cl_2Ru=CHPh$ (2)

Up till now, the mechanism of the cyclopropanation reaction is not known into detail and although different theoretical suggestions and predictions are described, the detection of some crucial intermediaries to prove the theory has not been succeeded. Also the factors governing the activity of the catalyst are not always fully understood. We were interested whether the Grubbs' systems would be able to catalyze the cyclopropanation of olefins with diazocompounds. Based on our experimental findings and with the knowledge of known mechanism of olefin metathesis together with the nature of the catalyst active carbene, we tried to pose a mechanism for the cyclopropanation. In a next stage, a first attempt is made to take advantage of the catalysts activity towards olefin metathesis by combining this property with the activity for cyclopropanation of the generated olefins in a so called 'tandem catalysis' system. Thus, as a part of our continuing efforts[15], we undertake a fundamental approach with the Grubbs catalyst system in order to elucidate the mechanistic aspects of the cyclopropanation. Therefore, the Grubbs catalysts have been examined for their activity towards the reaction of

terminal olefins with diazocompounds. Our further study to qualify the Grubbs catalyst as a valuable candidate for 'tandem catalysis' was proved by the reported article[16]. Moreover, because the activity of Grubbs I for cross metathesis is largely understood, we are more interested in its activity towards other reaction and we propose that 1st gen. Grubbs is a valuable candidate for tandem catalysis in a one-pot system, i.e. a catalyst for cross metathesis and cyclopropanation in one reaction mixture.

8.2 Results and discussion

8.2.1 FT-IR Kinetic measurements

During the cyclopropanation procedure catalyzed by transition metals, a diazo compound is needed besides an olefin. Dimerisation and cross metathesis, involving the carbene centre, are the most undesired side reactions during transition metal catalyzed cyclopropanation. Since both reactions can be assumed to act as competitive reactions with the cyclopropanation, it is the challenge to study whether it is possible to manipulate the reaction parameters in such a way that the cyclopropanation reaction is favoured and that, in a following stage, it is possible to switch between two reactions by adjusting the reactions parameters. In order to explore the activity of the 1st generation Grubbs catalyst for this type of chemistry, we assessed a kinetic study by means of *in situ* FT-IR by following the typical N≡N vibration at 2110 cm^{-1}.

In a first stage, the inherent catalytic decomposition of diazocompounds by Grubbs I is monitored. This is accomplished in the absence of an olefin. In this way, only one reaction, the dimerisation of the diazo compound, will occur. Ethyl diazoacetate (EDA) is used as the diazo agent and a significant thermal decomposition in toluene is observed above 80°C. Therefore, all catalytic experiments are run at lower temperature. It is believed that the decomposition of EDA will continue until it is depleted since the irreversible nature of the reaction due to the release of N_2 gas. It is confirmed that the decomposition of EDA indeed follows an exponential-like decay over time and that no more EDA is detected in the end.

In a first set of experiments, a study is performed by changing different parameters as the catalyst concentration, the initial concentration of EDA, the presence of an olefin and the temperature. At 45°C, it is found that initially [EDA] drops dramatically and a 90% conversion is reached after 150 minutes. The reproducibility of the experiment is very high (Fig 8.2).

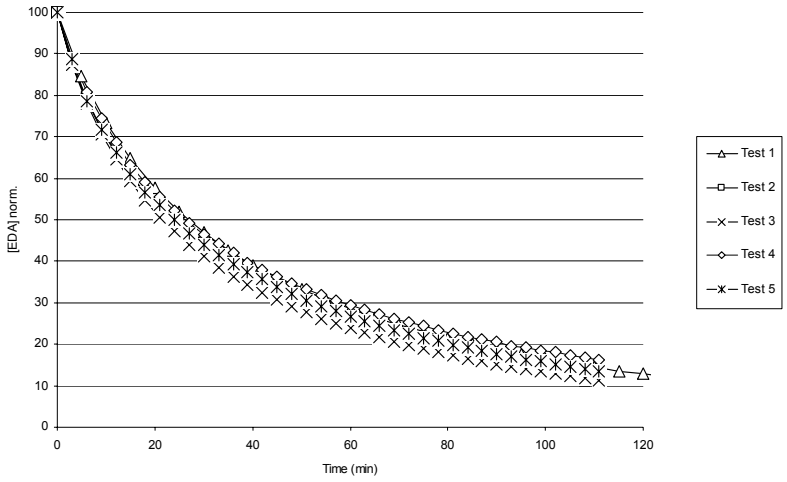


Figure. 8.2 Decomposition of EDA at 45 □ (3 μmol Grubbs I)

It is also observed that the presence of styrene promotes the decomposition (Fig 8.3).

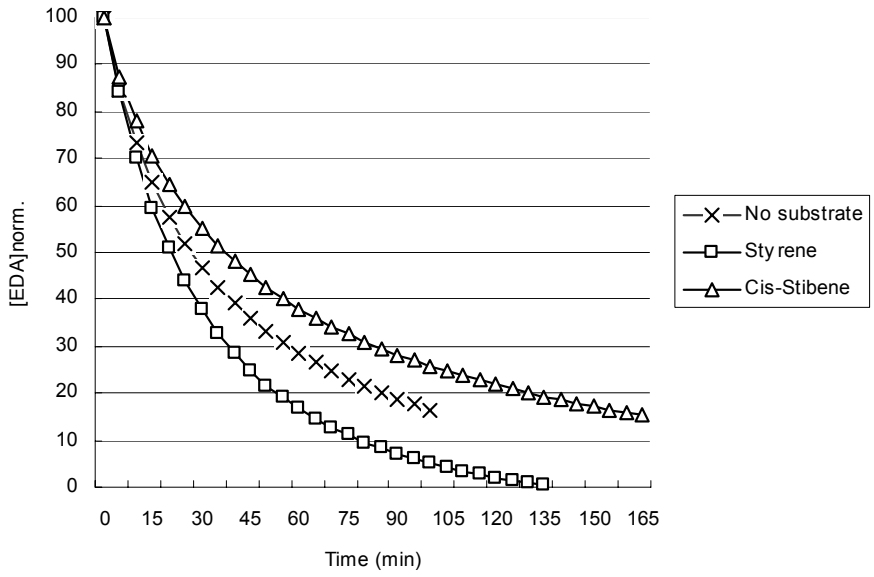


Figure 8.3 The influence of substrate on EDA decomposition

By plotting the logarithm of [EDA] versus time (equation *2*), it is found that, apart from the initial deviations, ln[EDA] shows a linear behaviour, indicating a first order in [EDA] (Fig 8.4). The slope of this line can be taken as the observed rate constant k_{obs}.

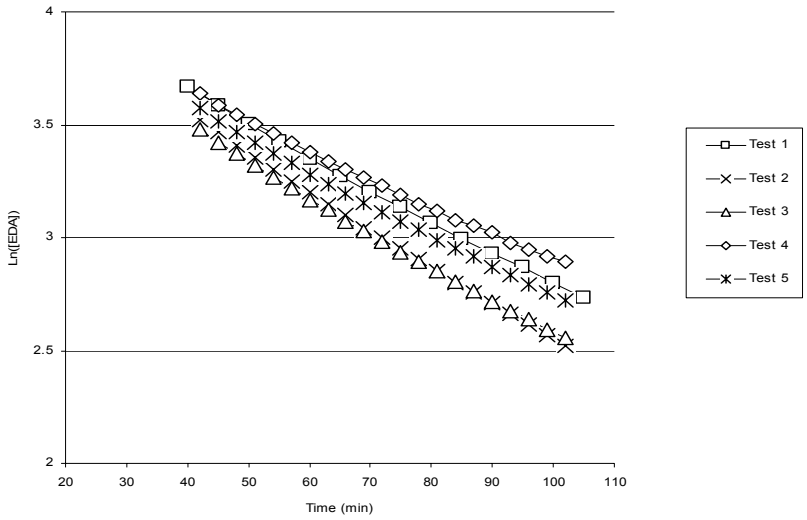


Figure 8.4 Plot based on Ln[EDA] *vs* Time shows a first order reaction in EDA

$$v = -\left(\frac{d[EDA]}{dt}\right) = k_{obs}.[EDA]^{x} \qquad (1)$$

$$\ln[EDA] = \ln[EDA]_{t=0} - k_{obs}.t \qquad (2)$$

At this point, the deviations occurring at the early stage of the experiments are thought to originate from the homogenisation of the experimental setup (see experimental section). It is therefore that the initial part of the reaction is not used in further calculations. Only the linear part of the plot is used.

By monitoring the decomposition in function of temperature it was possible to make use of the Arrhenius equation and to calculate a value for the activation energy (Fig.8.5).

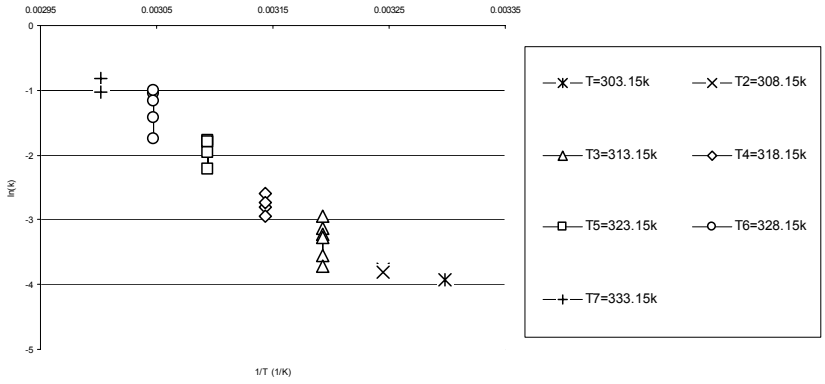


Figure 8.5 (a)The influence of temperature on EDA decomposition

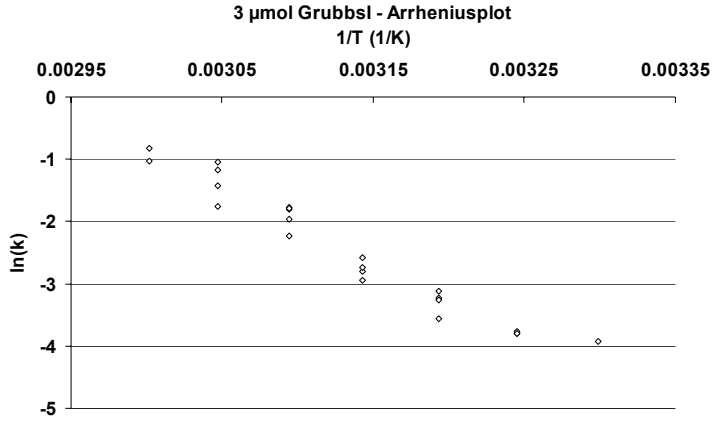


Figure 8.5 (b) The influence of temperature on EDA decomposition

$$\ln k_{obs} = \ln A - \frac{E_a}{R.T} \qquad (3)$$

$$E_a = 105 \, {}^{kJ}\!/_{mole}$$

More activation parameters can be calculated from an Eyring plot (Fig. 8.6).

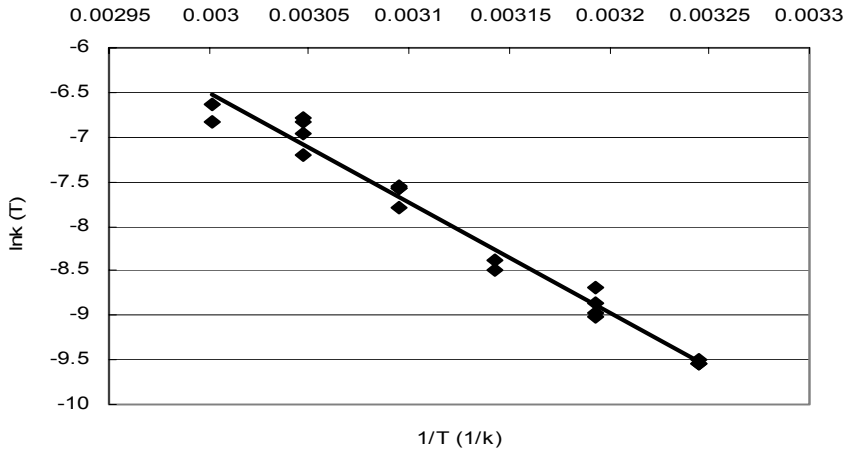


Figure 8.6 Eyring plot of Grubbs I

$$\ln\left(\frac{k_{obs}}{T}\right) = \ln\left(\frac{k_b}{h}\right) + \frac{\Delta S^{\neq}}{R} - \frac{\Delta H^{\neq}}{R.T} \qquad (4)$$

$$\Delta H^{\neq} = 103 \, {}^{kJ}\!/_{mole}$$

$$\Delta S^{\neq} = 56.3 \, {}^{J}\!/_{mole.K}$$

A positive value for the activation entropy is found and it is suggested that, despite the fact a bimolecular assembling between catalyst and EDA takes place, this might be related to the release of N_2 gas. This implies that the N≡N fragment is already released in the activated complex.

To have a more profound view on the kinetics, the relation between the reaction rate and the amount of catalyst is studied. An unexpected result is found when the value of the observed rate constant, k_{obs}, is plotted versus the initial catalyst concentration, $[Ru]_0$. Based on the equation (5) below, a linear behaviour is expected while a non-linear plot is obtained (Fig 8.7).

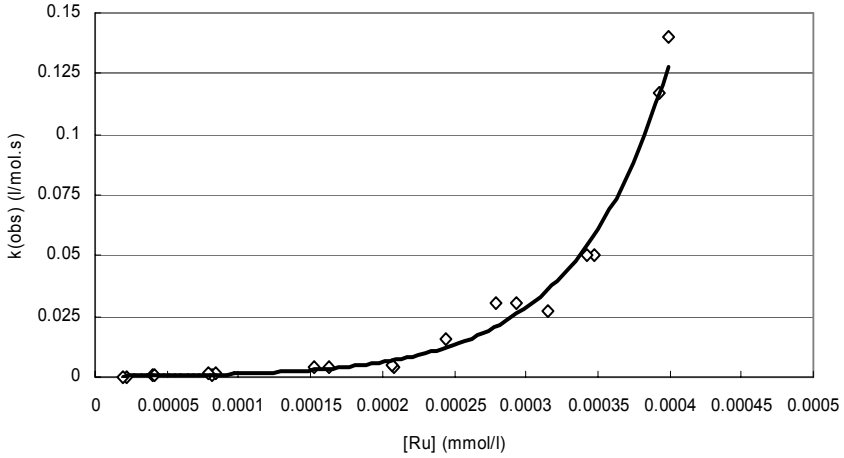


Figure 8.7 k_{obs} in the function of [Ru]

$$v = k_{obs}.[EDA] = k_{eff}.[Ru]^x{}_0.[EDA] \qquad (5)$$

$$k_{obs} = k_{eff}.[Ru]^x{}_0$$

$$\ln(k_{obs}) = \ln(k_{eff}) + x.\ln([Ru]_0)$$

Plotting $\ln(k_{obs})$ versus $\ln([Ru]_0)$ approaches first order kinetics in the catalyst concentration (x = 1) only at low catalyst concentrations (Fig 8.8).

Two effects are postulated as a provisional explanation. On one hand, the exothermic event that is caused by the decomposition of EDA induces a non-isothermal event and thus a variation of the value of the rate constant k_{eff}. This effect increases with the amount of catalyst. On the other hand, high excess of EDA (relative to $[Ru]_0$, i.e. at low $[Ru]_0$) may promote unknown side reactions, partly deactivate the catalyst or induce a change of the catalytic species. It is confirmed by a NMR-study that the relative amount of EDA present strongly

influences the kinetics (see *NMR kinetic measurements*). A new set of FT-IR experiments with a fixed $[EDA]_0/[Ru]_0$ ratio is performed to determine the prevailing effect by excluding the issue of catalyst concentration. Under these conditions, the order of the catalyst is found to be very close to 1, except at high $[Ru]_0$ where some small deviations remained. From these experiments it can be said that the second posing, i.e. that high relative excess of EDA may promote unwanted side reactions, partly deactivate the catalyst or induce a change of the catalytic species, is ruling over the non-isothermal event caused by the decomposition of EDA. A search towards more evidence for this posing is assessed by NMR experiments.

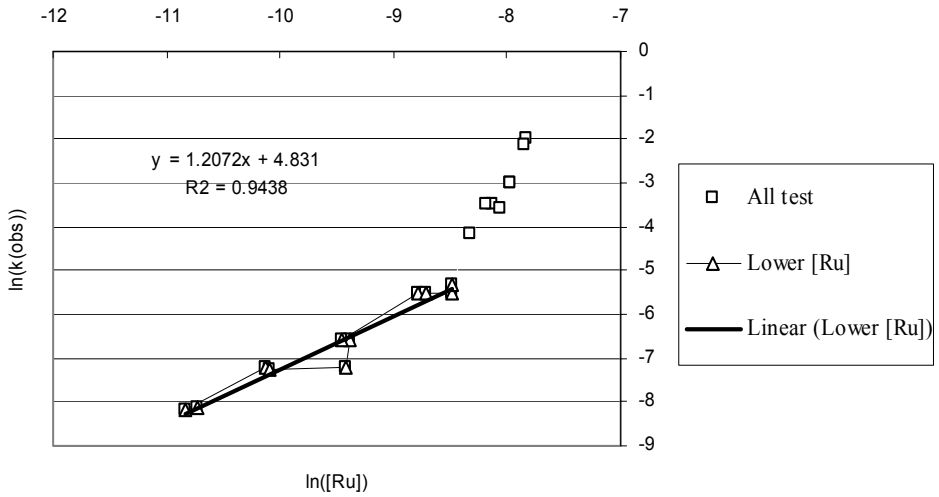


Figure 8.8 $\ln(k_{obs})$ *vs* ln[Ru]

In a second stage, a first attempt towards the tandem reaction is made. The idea is that when the reactivity of the catalyst can be controlled, it might lead to a key to switch between olefin metathesis and cyclopropanation. The reactivity of the catalyst is a result of the interactive combination between the central metal ion, the ligand sphere and, in this case, the reactive catalytic site, i.e. the carbene functionality. Since the Grubbs systems are taken as a base set, the nature of the metal ion is fixed. The parameters that are investigated in order to reveal some clues about the catalyst reactivity for these reactions are the nature of the carbene and the ligand periphery. It is already known that a metathesis reaction catalyzed by Grubbs systems can be easily aborted by destroying the active carbene site. This is accomplished by the addition of an olefin, like ethyl vinylether (EVE), resulting in a Fisher carbene which is inert towards metathesis. This knowledge can be used as a first tool to switch off the metathesis activity and to activate the cyclopropanation properties. Therefore, a set of experiments is performed by using a modified Grubbs I catalyst bearing a Fischer carbene instead of the original benzyl carbene. The new complex is preliminary prepared and isolated by adding an excess of EVE to a solution of Grubbs I in toluene. This reaction can be easily followed since a

shift of colour from purple to orange takes place. The exchange is more closely monitored by NMR and will be discussed below (*NMR kinetic measurements*). The activity of the Fisher carbene complex towards the decomposition of EDA is screened by a set of similar FT-IR kinetic measurements. It is found that the ethylvinylether complex enhances the decomposition of EDA when compared to the Grubbs I system (Fig 8.9).

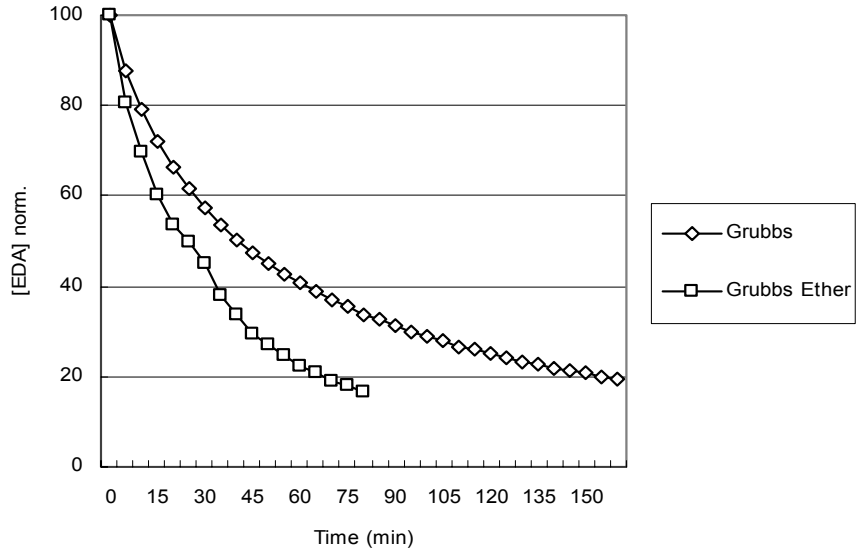


Figure 8.9 EDA decomposition at 40 □ catalyzed by Grubbs I and Grubbs ether

A second tool to manipulate the catalyst' activity is its ligand periphery. A key structure in the mechanism of metathesis,[17] is a metallacyclobutane compound. This structure is formed after creation of a vacancy in the coordination sphere followed by coordination of an olefin. According to this reasoning, metathesis should be obstructed in case no vacancy for coordination to the metal centre is available. In contrast, according to the proposed mechanism of cyclopropanation,[18,10b] coordination of the olefin does not require a vacancy but occurs directly to the electrophilic carbon atom of the carbene. Thus cyclopropanation activity should be independent of the presence of a coordination vacancy. This idea is found to be worthwhile to investigate in more detail since it might offer a second tool to switch between metathesis and cyclopropanation activity. This is assessed by studying the influence of the addition of extra phosphine ligand, PPh_3, to the cyclopropanation reaction and to evaluate the rate of EDA decomposition. In a first step, it is seen that the decomposition of EDA is enhanced with increasing equivalents of PPh_3 (Fig 8.10).

Moreover, a linear correlation is found by plotting the observed rate constant, k_{obs}, versus the equivalents of PPh_3 (Fig 8.11).

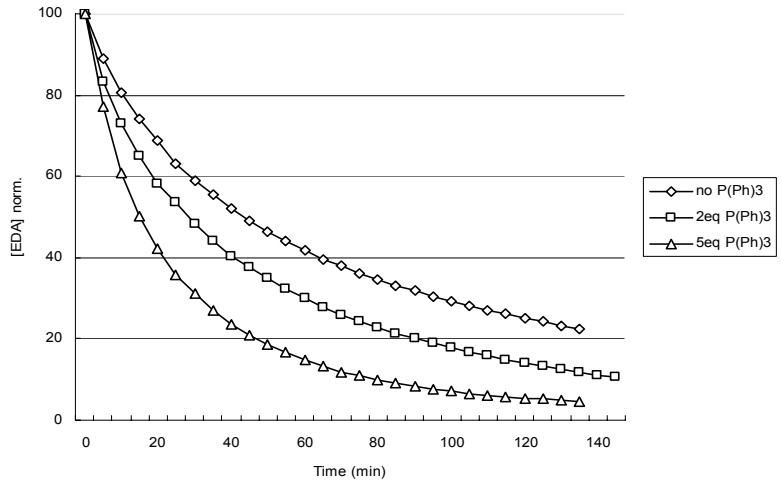


Figure 8.10 The influence of Adding $P(Ph)_3$ on EDA decomposition (in Grubbs I and EDA system)

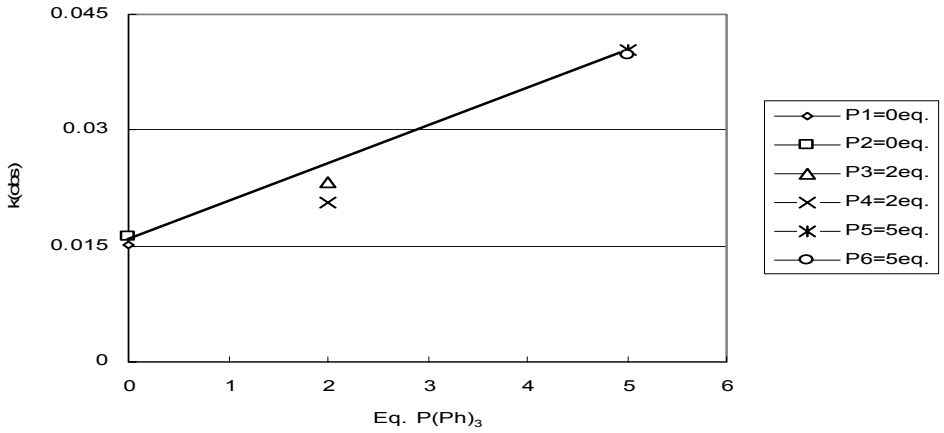


Figure 8.11 k_{obs} in function of equivalent of $P(Ph)_3$

It is thought that PPh_3 possesses an intrinsic catalytic activity and an experiment in absence of Grubbs I is run, but is found that the phosphine does not contribute directly to the EDA decomposition (Fig 8.12).

Based on these findings it seems that PPh_3 is capable of hindering the creation of vacancies rather than being capable of promoting the EDA decomposition.

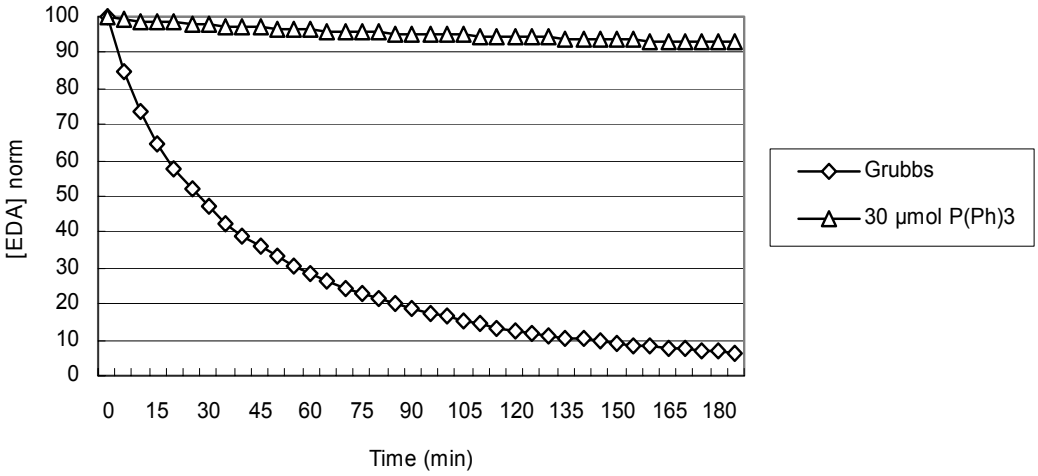


Figure 8.12 The function of $P(Ph)_3$ on EDA decomposition

8.2.2 NMR kinetic measurements

The widely described and proposed mechanism[18,10b] of cyclopropanation follows a reaction pathway where an electrophilic carbene intermediary compound plays a crucial role. It has been found experimentally that among the different types of transition metal based reactants described, carbene complexes are among the most versatile,[19] whether they are applied as a stoichiometric reactant or as a catalytic species. To our best knowledge, there is no intermediary compound detected for the cyclpropanation catalyzed by Grubbs I, while for other catalysts, it has been reported.[20, 21]

In our study, we made an effort to bring some clarity in the mechanism of the cyclopropanation by use of the Grubbs catalyst. In a first experiment, an attempt is made to look at the beginning of the reaction. This is experimentally done by adding only 1 equivalent EDA to a solution of Grubbs I. Under these conditions, the reaction proceeds much slower compared to the FT-IR kinetic measurements. The decomposition is monitored over time and two different carbene signals are observed: the original benzyl carbene and a new signal at 17.128 ppm (Fig 8.12).

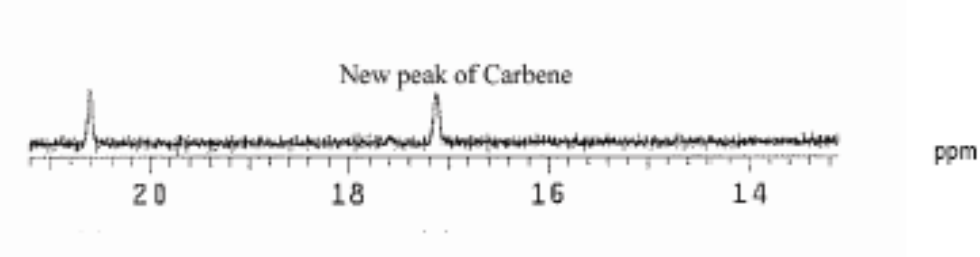


Figure 8.13 NMR ^1H of Grubbs I and Grubbs Ether

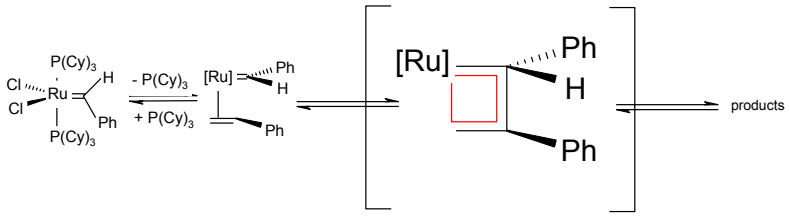
Although reported,[17] it seems to be very unlikely that two carbene functionalities are formed on the same centre. In that case, a shift of the original carbene centre towards lower field is expected which is not observed. Therefore it is thought that the new signal originates from two different centres implying that two different catalytic species are present, already from the start of the decomposition reaction. When fresh amounts of EDA are added to the sample, it is seen that that both signals disappear over time. When 50 eq. of EDA are applied, no carbene signals could be seen at any moment. From these findings it can be postulated that at low EDA concentrations the original phenyl carbene is substituted by another carbene, but that at high EDA concentrations a new 'carbene-free' species becomes present or a highly reactive carbenoid species is formed instead. The deviations observed at the initial stage of the EDA decomposition in the FT-IR measurements can thus be explained from the idea that a change of active species takes place when a large excess of EDA is applied (or an excess EDA is added all at once at the beginning), and not only from homogenization of the reaction mixture.

More evidence for the change of catalytic species is found from our NMR study. The formation of cinnamate esters is observed implying that an attack on the benzyl carbene by EDA occurs. Off course, from another point of view, this means that the original catalyst is deactivated. The formation of cinnamate esters is confirmed by GC.

Based on the results gathered from FT-IR experiments and the NMR study, we can conclude that a new catalytic species is formed soon after the start of the reaction and which inhibits a lower catalytic activity than the original Grubbs catalyst. More proof for the deactivation of the catalyst is received from a new set of FT-IR experiments. In the experiments, an equal portion of new EDA is dosed and it is depleted once all. From these measurements, it is seen that $t_{1/2}$ decreases dramatically after the first cycle, which can also serve as an explanation for the initial drop of the EDA concentration.

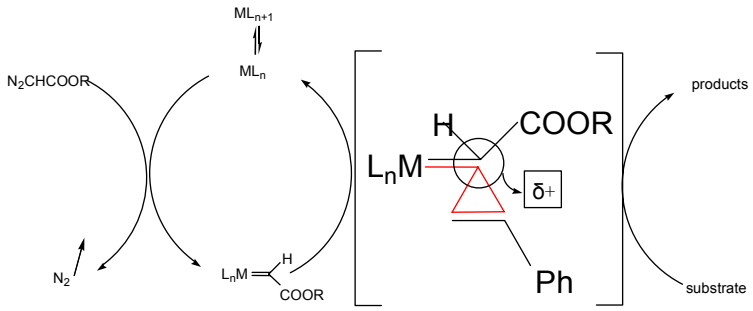
Thirdly, Phosphine can be oxidized due to the addition of EDA that the oxygen is present in the EDA solution and ^{31}P-NMR reveals the formation of oxidized phosphine. This fact is another indication for the formation of a new catalytic species during the reaction.

Besides the mechanistic research of the cyclopropanation reaction, we studied the possibilities to engage the Grubbs catalyst as a valuable candidate in tandem catalysis. As described above, see FT-IR experiments, some tools are available to inhibit the intrinsic metathesis properties of the catalyst. Switching between metathesis and cyclopropanation can be achieved by using these tools properly. The classical mechanism of metathesis by Grubbs I includes a preliminary dissociation step in which a phosphine ligand is removed from the metal centre. The vacancy thus created is used for the coordination of an olefin. Via a metallacyclobutane ring, a 16-electron monophosphine/olefin intermediary compound is generated (scheme 8.1).



Scheme 8.1 The Classical mechanism of metathesis of Grubbs catalyst

In contrast, in the accepted mechanism for cyclopropanation, already reported in 1968 (scheme 8.2),[18, 10b] a diazo molecule attacks the transition metal centre with release of nitrogen gas.

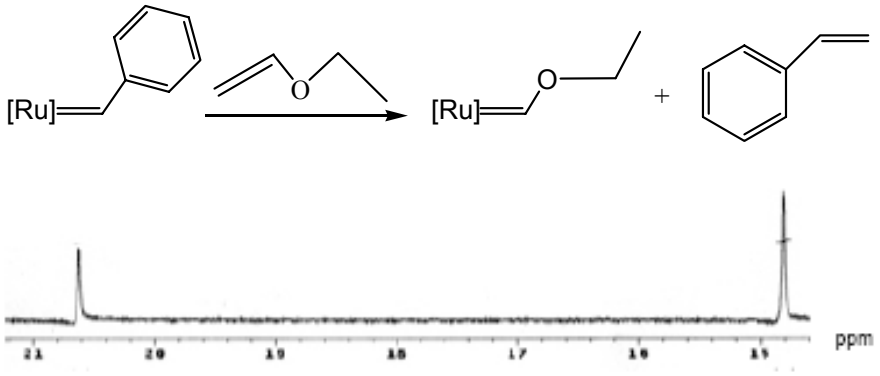


Scheme 8.2 Mechanism of the transition-metal catalyzed cyclopropanation with diazo compounds

The intermediary electron deficient carbene thus created is highly reactive and undergoes easily a nucleophilic attack from an olefin. In this case, no extra vacancy for the coordination of the olefin is required and a cyclopropane-like structure is proposed as transition state. The main differences between both mechanisms lie in the electrophilicity of the carbene and the presence of a vacancy on the metal centre.

In order to gain an improved understanding of the mechanism and in a search towards some adaptable tools for the tandem catalytic activity, we performed a substitution of the original phenyl carbene with a new inert ethyl vinyl ether carbene by adding an electron rich olefin to a solution of Grubbs I (Scheme 8.3).

It is known that the reaction between EVE and Grubbs I proceeds rapid, quantitative, selective and irreversible with formation of a Fisher carbene complex and styrene. The new carbene is inadequate to maintain the metathesis cycle. As such, this substrate serves to trap all Ru species which are active for metathesis. The reaction scheme is shown in scheme 8.3. The substitution reaction is monitored by ^{1}H- and ^{31}P-NMR (Fig 8.14 & 8.15).



Scheme 8.3 The substitution reaction between Grubbs I and ethyl vinyl ether (EVE)

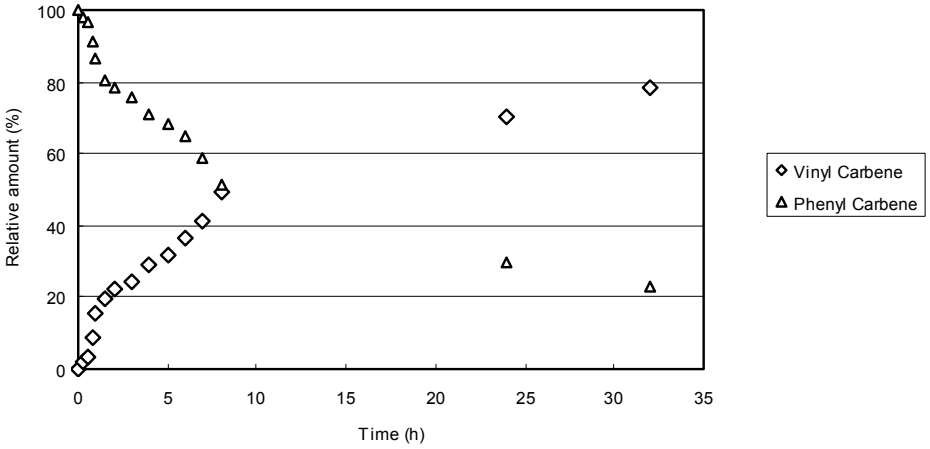


Figure 8.14 The reaction between Grubbs I and EVE in benzene monitored by NMR

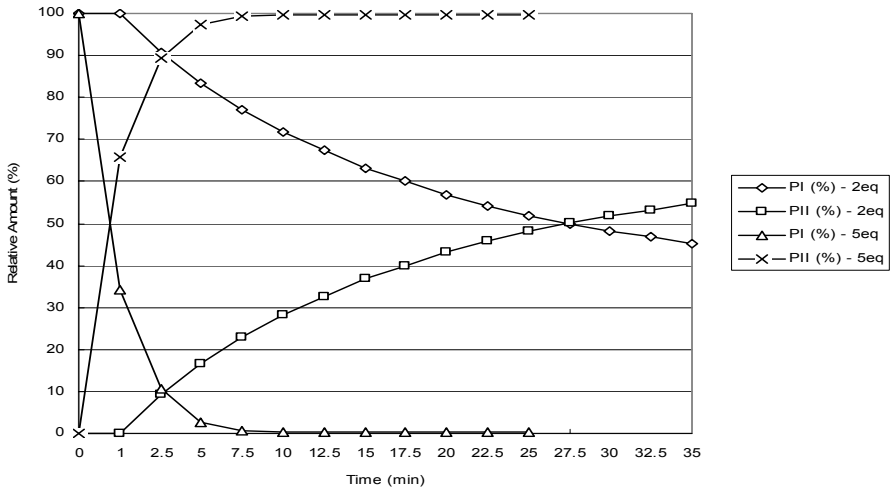


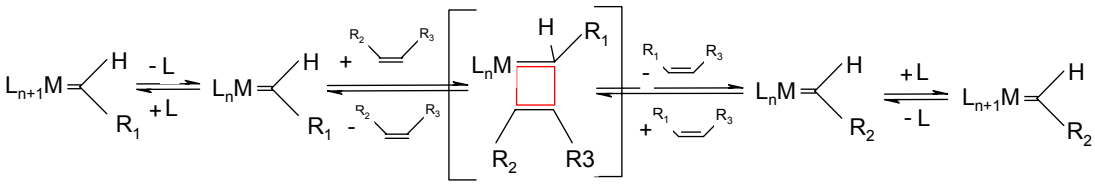
Figure 8.15 NMR ^{31}P of the reaction between Grubbs I and EVE in benzene.

The disappearance of the phenyl carbene at 19.95 ppm and the appearance of the new Fisher carbene signal at 14.49 ppm) are followed over time.[22, 8b] This carbene cross metathesis reaction is also followed in the presence of PPh_3. It is found that $P(Ph)_3$ strongly inhibits the reaction by preventing ligand dissociation. It is calculated that, when 2 equivalents of PPh_3 are added, the reaction proceeds 300 times slower

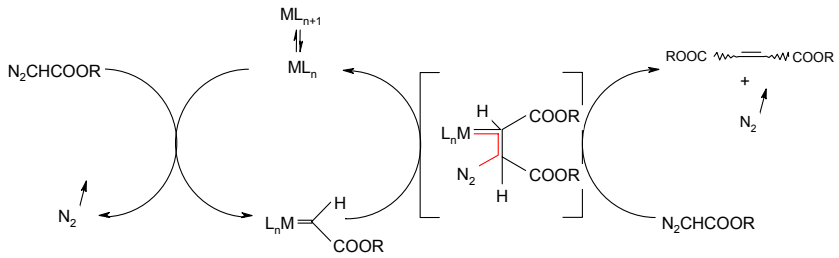
$$t_{\frac{1}{2},noP} = 300.t_{\frac{1}{2},2eqP}$$

8.2.3 GC measurements

Alkene metathesis (Scheme 8.4) and dimerization (Scheme 8.5) will take place as major side reaction of the cyclopropanation when transition metal catalysts are used on various types of unsaturated substrates under mild conditions. The same is observed when Grubbs I catalyst is applied. Dimerization becomes significant when too much EDA is present per time unit and the metathesis reaction will mainly depend on the nature of the carbene and the olefin. Dimerization can thus be surpressed by dosing EDA slowly over time and metathesis can be limited by use of a proper carbene. In order to get an idea about the extend in which these side reactions occur, the reaction mixtures are analyzed by GC. In contrast with the FT-IR and the NMR experiments, EDA is added dropwise over a large period of time in these experiments and the mixtures are analyzed after an extra post reaction time.



Scheme 8.4 Mechanism of the transition-metal catalyzed olefin cross metathesis



Scheme 8.5 Mechanism of the transition-metal catalyzed dimerisation

In a first set of experiments, the cyclopropanation of styrene by Grubbs I and EDA is performed at 50°C. The yield is calculated to exceed 80 mole% (Fig 8.16).

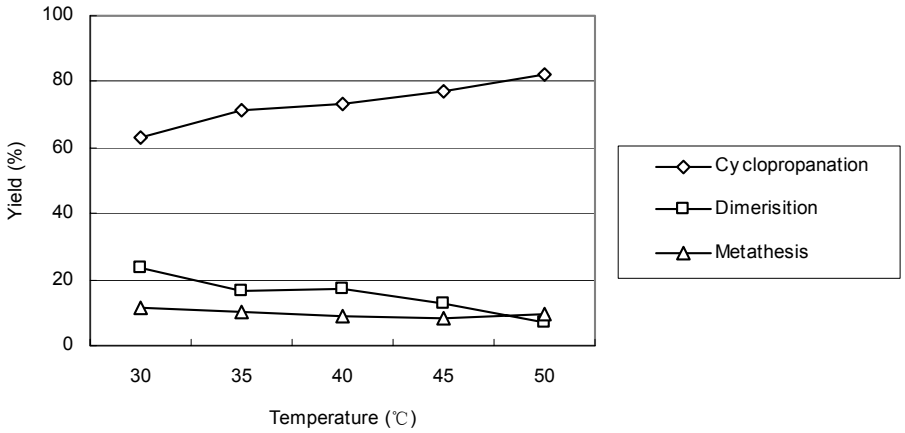


Figure 8.16 Selectivity of Grubbs I for cyclopropanation of styrene

Dimerization with formation of maleate and fumarate is represented as the largest side reaction while metathesis of styrene towards stilbene is minimal. Concerning the selectivity a double amount of the *trans* cyclopropane isomer is formed. It is found that the *trans/cis* ratio is independent of temperature (Fig 8.17 & 8.18).

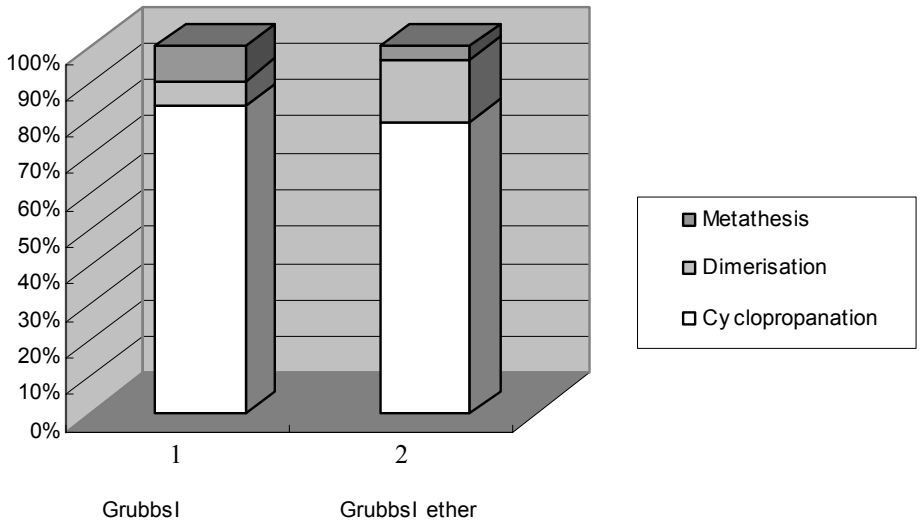


Figure 8.17 Selectivity of Grubbs I and Grubbs Ether for cyclopropanation of styrene

Since we attempt to achieve tandem catalysis between metathesis and cyclopropanation, the suggestion is made to investigate the cyclopropanation of stilbene, which is the metathesis product of styrene. Unfortunately, the outcome of the cyclopropanation of *cis*-stilbene was negative since 90 mole% of the EDA is converted in the dimerization reaction. A minor part of

the styrene is converted in a metathesis cycle with formation of *trans*-stilbene. Nevertheless, tandem catalysis is already reported by Snapper et al.[16] and according to their findings, tandem catalysis by Grubbs I is limited by the substrate.

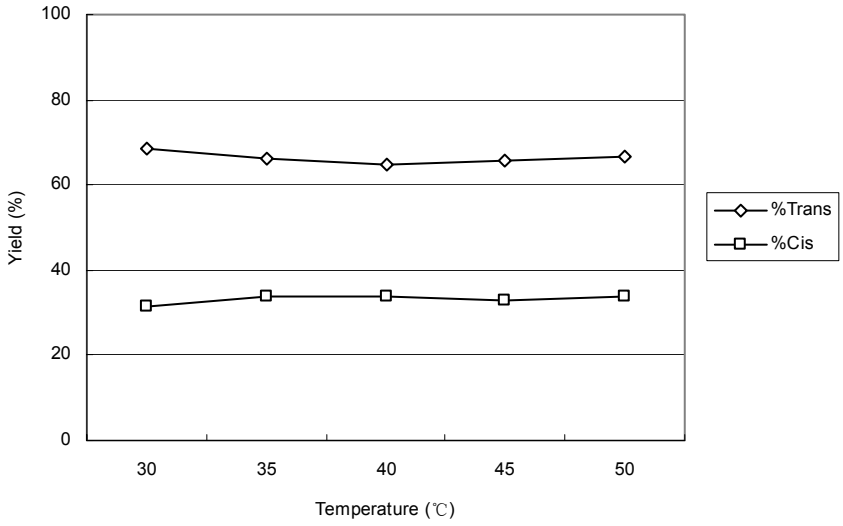


Figure 8.18 Diastereoselectibity of Grubbs I

After a preliminary reaction between Grubbs I and EVE, it is found that the olefin metathesis is suppressed from a relative point of view, while the dimerization reaction tended to increase. From our experience, it is presumed that the increase of the dimerization of EDA can be avoided by decreasing the addition rate of EDA even further.

8.3 Conclusion

From our kinetic experiments, some indications about the mechanism of the EDA decomposition are obtained. It is found that the EDA, when present at large excess, attacks the initial benzyl carbene of the Grubbs I catalyst with formation of a new carbene or carbenoid like species. This new catalytic species has a lower intrinsic catalytic activity. The assumption that a change of catalyst structure occurs, is confirmed by the detection of oxidized phopshine after ligand loss. This change of catalyst structure is, in our opinion, the major factor which induces a non linearity in the kinetic measurements. Other factors are proposed like the homogenization of the reaction mixture, the exothermicity at the start of the reaction resulting in a non-isothermal event, increase over time of metathesis of the dimerization products. Although still active, it is seen from repeated measurements that the catalytic activity towards the decomposition of EDA dramatically decreases when an excess of EDA is dosed repeatedly and

all at once. Once the benzyl carbene species are converted, a linear behaviour in our kinetic measurements is found. Nevertheless, no exact chemical structure of the new catalytic species can be proposed.

The addition of free PPh_3 enhances the decomposition of EDA while the free phosphine does not show any catalytic activity itself.

Although it has been reported that the cyclopropanation is disfavoured since it requires the overcoming of larger activation energy barriers than those found for the metathesis reaction,[23] it is found from our experiments that the Grubbs 1st generation catalyst is active towards the cyclopropanation of styrene and that the metathesis with formation of stilbene is strongly limited. Metathesis can be suppressed by preliminary converting the benzyl carbene into a Fisher carbene inert towards metathesis. Moreover, this Fisher carbene also promotes the decomposition of EDA. Other substrates than styrene, like stilbene and 2,5-dimethyl 2,4-hexadiene are screened but are found to be not susceptible towards cyclopropanation under the conditions tested.

We believe that Grubbs systems can be adapted for the tandem catalysis metathesis-cyclopropanation but more fundamental research and experimental work is required to obtain a clear and profound view on the activity and mechanism of the reaction(s).

8.4 Experimental

8.4.1 General

All materials were of analytical grade and used without further purification. During the catalytic decomposition of EDA, precautions need to be taken since a hazard for pressure building exists due to the release of N_2(g).

8.4.2 FT-IR measurements

Most of kinetic measurements of the diazo compounds decomposition were assessed by using a Bruker FT-Raman/FT-IR spectrometer with a Nernst glowing element as the IR source and a DTGS detector. The flow-through IR-cell consists of KBr windows with a 2 mm inner separation.

Following operations were undertaken in a typical FT-IR experiment. From a preliminary prepared solution of catalyst in freshly distilled toluene, with known concentration, 3 µmol of catalyst is transferred under a continuous Ar-flow to an empty 15 ml vessel. The solvent is then evaporated under vacuum resulting in a small amount of solid catalyst. Next, 12 ml of extra dry toluene is added to dissolve the catalyst. The vessels are sealed with a septum and stored at -

18°C. For an experiment, the vessel is put into a heating block at the desired temperature and 400 µmol EDA is added with a syringe. A needle is put through the septum to prevent pressure building. The reaction mixture is circulated through the IR cell in a closed circuit by use of a peristaltic pump. All measurements are performed by following the typical v (N≡N) stretch at 2110 cm^{-1}. Each experiment is repeated at least 5 times. All spectra are baseline corrected, normalized to a solvent signal, integrated and correlated to a concentration by means of a calibration curve.

When an additive is used, this is added before placing the sample in the heating device. In case a substrate is applied, the amount typically is 4 mmol. For other additives (ethylvinylether, PPh_3) is refferd to the text.

8.4.3 GC- measurements

To measure the yield and selectivity of cyclopropanation, the capillary GC measurements were obtained by using a Trace GC Ultra (ultra fast GC) with a RTX-1 type capillary (5 m x 0.32 mm, 0.25 µm 100% dimethylpolysiloxane) column and a FID detection system. The temperature program starts at 40°C and heats at 180°C/min ing And then the analyses were performed on a FID detection system.

Following operations were undertaken in a typical GC experiment. From a preliminary prepared solution of catalyst in freshly distilled toluene, with known concentration, 2.5 µmol of catalyst is transferred under a continuous Ar-flow to an empty 15 ml vessel. The solvent is then evaporated under vacuum resulting in a small amount of solid catalyst. Next, substrate (10 mmol) is added to obtain a solution of catalyst in substrate. EDA (1 mmol) is dissolved in substrate (10 mmol) and the solution is added very slowly (typically over a period of 4 h using a peristaltic pump.). After addition of a few drops of EDA solution, the mixture is heated from room temperature to the reaction temperature. After complete addition, the mixture is kept at reaction temperature overnight. Before GC-analysis, the reaction mixture is purified by pouring over a silica filter in order to remove the catalyst. The silica is washed with 20 ml toluene/EtOAc (1/1). Diethyl adipate is taken as internal standard.

The composition of the reaction mixture is fully characterized by MS and by use of authentic samples of the compounds.

8.4.4 NMR- measurements

The proton and phosphine NMR spectra were recorded in C_6D_6 on a Bruker DPX-300 spectrometer. Following operations were undertaken in a typical NMR experiment. The catalyst Grubbs I (20 µmol) is dissolved deuterated benzene (500 µl). If an additive is used, it is added

at this point (ethylvinylether, PPh_3. The amount depends on the experiment, referring to the text for the exact amount of additive used). For the experiments without EDA, the sample is recorded from the moment the additive is added.

For the cyclopropanation experiments EDA (min. 1 eq.) is added as well (the amount depends on the experiment, referring to the text for the exact amount of EDA used). A needle is put through the cap to avoid pressure building. The samples are recorded in an array mode with a given time interval.

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Chapter 9
Conclusion and Outlook

9.1 Summary

In this dissertation, the presented research addresses the development of O,N-bidentate ruthenium catalysts to explore their applicability in isomerization and the kinetic studies of ruthenium carbenes for C=C coupling reactions. The stability, reactivity, and selectivity of the catalyst are the properties to determine the efficiency of a catalyst (Figure 9.1). Therefore, a minor change in the ligand sphere of the catalyst can significantly alter one of these three aspects, and thus improve or diminish its efficiency.

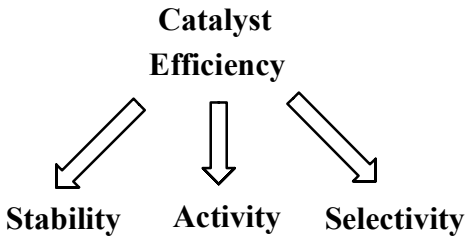

Figure 9.1 Related properties of the catalyst efficiency.

During this study we concentrated on ruthenium complexes bearing O,N-bidentate ligands, since over the past few years ruthenium complexes have opened up enormous possibilities for a variety of catalytic organic processes, due to the great advances in the design and synthesis of efficient

and selective catalysts. Meanwhile the electron donating ability and size of the ligands on the Ru center were found to be the key in optimizing the catalytic efficiency of these complexes. All the progress was attributed to the introduction of ligands such as Schiff bases, N- or N, S, P-, bi- or multidentate donor ligands, O-donor ligands, etc. When combined with traditional ligands they donate targeted catalytic properties to the resulting ruthenium systems. In addition, some ligands induce extraordinary catalyst tolerance towards organic functional groups, air, moisture and impurities, thus largely expanding the scope of utilization of the corresponding metal complexes.

The work done in this dissertation was divided into three main parts. In the first part, O,N-bidentate ligands are used to replace the phosphine and hydrogen from the dihydride ruthenium precursor $[Ru(H)_2(CO)(PPh_3)_3]$ and the chloride from dimeric ruthenium precursor $[RuCl(p\text{-cymene})]_2$, several new ruthenium O,N-bidentate ligand catalysts were prepared. The series of ruthenium arylazo ligand complexes $[(\eta^6\text{-}p\text{-Cymene})RuCl(L)]$ (L incorporate an arylazo /azonaphthol groups and azophenyl group) have been characterized by ^1H, ^{13}C NMR, FT-IR and element analysis. The series of Ruthenium hydride complexes $Ru(PPh_3)_2(CO)H(L^n)$ (n=a-h) incorporating a Schiff base ligand has been characterized by ^1H-NMR to confirm the new hydride species in combination with ^{31}P-NMR.

Furthermore, examination of the isomerization ability of the new complexes, the activity and the thermal stability stressed out that considerable improvements were achieved. Allylbenzene and 1-Octene have been used as model substrates. Temperature, solvents and catalyst/substrate mol ratio have been taken into account as parameters to optimize the isomerization. The ruthenium arylazo series complexes were reported for the first time as catalysts for isomerization. The chelating O, N-bidentate ligand is responsible for a high stability of the complexes leading to a catalyst lifetime enhancement and finally to lower catalyst loadings. Also careful pretreatment of solvents and substrates is unnecessary, since the ismerization can be performed in open air whereupon monitoring of the reaction progress becomes very convenient.

Regarding the ruthenium hydride complexes, all the nitro-substituted complexes performed better than the non-nitro-substituted ones and all catalysts showed the best performance in 2-butanol as solvent. This suggests that the catalytic activity strongly depends on the steric and electronic environment of the ruthenium as well as on the solvent used. Because many hydride complexes are able to decarbonylate alcohols, based on the ^1H NMR observation, it is reasonable to suppose that the alcohol decarbonylation occurs by a metal-aldehyde dihydride-complex $RuH(\eta^2\text{-}OCH_2R)(PPh_3)_2(L^n)$. Furthermore, after the elimination of hydrogen from the catalyst, the intermediate can react with H_2, produced during the reaction, to recover the catalysts. All of these facts support the higher activities in alcohol.

Concerning the ruthenium arylazo complexes, the X-ray crystal structure of the complex reveals an octahedral environment around ruthenium. Some complexes are highly active in isomerization without any dimerization or oligomerization. From the obtained results it is clear that naphthol plays a significant role in the isomerization suggesting that the catalytic activity for 1-Octene strongly depends on the steric and electronic environment of the ligand. To the best of our knowledge, the isomerization activities of complex **1** for allylbenzenyl are the highest reported until now.

Studies dealing with ruthenium-arene complexes have shown that based on a careful NMR monitoring, during the isomerization reaction, no ligation of the cymene ligand occurs. From the ^{1}H NMR analysis of the cymene region of the catalyst, it follows that the shift of the peaks is the result of the dissociation of the nitrogen followed by the coordination of the substrate. This means that due to heating, the O, N-bidentate ligand imine moiety is decoordination to generate a vacant coordination site. Thereafter, the substrate can easily coordinate to the metal centre to form an octyl/allylbenzenyl intermediate. Following the less common π-allyl mechanism, oxidative addition of an activated allylic C-H bond to the metal yields a π-allyl metal hydride and generates the desired isomerization product.

A second part of this work deals with the kinetics of ring-opening metathesis polymerization (ROMP) of *exo,exo*-5,6-di(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, promoted by the Grubbs' 1st generation catalyst.

Here it was proven that the metathesis reaction can be effectively monitored by FT-Raman and NMR spectroscopy. Both techniques evidenced similar monomer conversions under the same reaction conditions. The present FT-Raman study provided information on the polymer steric configuration. The Raman bands at 1670 cm^{-1} and 1677 cm^{-1} are assigned to the stretching vibrations of the double bonds from the *cis*- and *trans*- polymer, respectively. The *trans/cis* ratio observed by FT-Raman is in excellent agreement with the result from ^{1}H-NMR. For the first time, a comparison was made on the application of these complementary methods for the ROMP reaction, evidencing their assets and disadvantages and reliability of FT Raman.

In a third part, the evaluation of Grubbs 1st generation catalyst in relation to the cyclopropanation of olefins using ethyl diazoacetate was addressed. Although, it has been reported, that the cyclopropanation is disfavored since it requires to overcome a larger activation barrier than found for the metathesis,[28] from a fundamental study of the reaction by means of FT-IR, GC and NMR, the Grubbs 1st generation is active in the cyclopropanation of styrene.

Stilbene is taken as the substrate for cyclopropanation reaction and successful results were obtained. It was proven that the molecular structure of catalyst changed by losing the phenyl-carbene. Research towards suppression of the most common side reactions has been done by modifying the ligand sphere and the nature of the carbene, such as substitution of phenyl carbene and addition of $P(Ph)_3$.

Some elementary kinetic parameters are calculated. The initial kinetic deviation is caused due to several reasons. Firstly, although the reaction mixture was circulating, the homogenization still took some time. Secondly, other apparent initial mechanism exists, i.e. different order in [EDA]. The classic kinetic approach of catalyzed second order reactions shows an apparent zero order in [EDA] at the initiation. Using high [EDA] concentration, an increase of the temperature due to the exothermic nature is also a reason. Catalyst deactivation is proved and NMR-study confirms the loss of carbenes due to the EDA attack or due to exothermicity. At last, metathesis of the dimerized products is responsible for the reduction in decomposition rate.

9.2 Outlook

The results of the present investigation suggest that for the ruthenium isomerisation catalyst described above, are very promising to be applied on big scale and for commercialisation. The fact that these catalysts and their analogous complexes have been reported for transfer hydrogenation and exhibit good isomerization activities (our work) would allow them to combine these two methodologies to some interesting properties by using new substrate combinations.