Development of Ruthenium Indenylidene Olefin Metathesis Catalysts

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Preface

Synthetic organic chemistry aims to develop cost-efficient and *green* routes towards drugs, natural products, fine chemicals, agro-chemicals and polymeric products, and skeletal transformations are often key in this respect. A great deal of attention of synthetic organic chemists has consequently focused on the development of straightforward synthetic strategies towards the formation of carbon-carbon single, double and triple bonds.

The olefin metathesis reaction is a carbon-carbon double bond breaking and reforming sequence which results in the thermodynamically determined redistribution of alkylidene units at carbon-carbon double bonds. As many further developments on its road, the discovery of the olefin metathesis reaction was a matter of serendipity. In days that the Ziegler-Natta polymerization proclaimed the start of organo-transition-metal chemistry, Eleuterio at DuPont found that polymerization of propylene with a molybdenum-on-aluminum catalyst resulted in an ethylene-propylene copolymer. The same catalyst transformed cyclopentene to a polymer with carbon-carbon double bonds in its chain. In 1967, Calderon rationalized that these observations are mechanistically identical and named the reaction *olefin metathesis*.

Although Chauvin proposed the metal carbene mechanism in 1971, the 1970's witnessed a feverish debate on the actual mechanism. The succeeding decades revealed high-oxidation state early transition-metal alkylidene catalysts by Schrock and ruthenium alkylidene catalysts by Grubbs. The importance of their seminal contributions was subscribed by the Nobel Prize Committee in 2005.

In the field of ruthenium olefin metathesis catalysts, ruthenium indenylidene complexes take a unique position due to their ease of synthesis and their high catalytic activity. In 2006, state-of-the-art in ruthenium indenylidene olefin metathesis catalyst development was limited to phosphine-based catalysts and catalysts bearing an unsaturated N-heterocyclic carbene ligand. It is known, however, that the ligand environment of the transition-metal catalyst has a profound influence on its resulting catalytic activity and consequently, further elaboration of the design of ruthenium indenylidene catalysts is of high interest.

Our efforts initially focused on the development of a family of ruthenium indenylidene complexes bearing a saturated N-heterocyclic carbene ligand and the determination of their activity towards selected olefin metathesis reactions. Furthermore, we have taken advantage of their synthetic accessibility as a means to synthesize olefin metathesis catalysts bearing a chelating arylether alkylidene ligand. In this respect, we developed a polymer-assisted solution phase approach that allows for a *green* synthesis of highly active olefin metathesis catalysts. Eventually, we have illustrated the usefulness of a latent catalyst in a reaction-injection molding process for the ring-opening metathesis polymerization of dicyclopentadiene.

Outline

This dissertation is mainly build up from three parts. Part 1 comprises chapters 1 to 3 and supplies an overview of the relevant literature concerning olefin metathesis, the development of ruthenium indenylidene complexes and latent ruthenium-based olefin metathesis catalysts. Part 2 contains the experimental results obtained during the doctoral research and their discussion in chapters 4 to 8. Part 3 encloses chapters 9 and 10 and summarizes the general conclusions obtained from Part 1 and 2, provides an outlook for further research and supplies a Dutch summary of this work.

Chapter 1 presents a general introduction to olefin metathesis and the aspects related to its mechanism, various catalytic transformations and selected highlights concerning catalyst development.

Chapter 2 covers the synthetic efforts towards well-defined ruthenium olefin metathesis catalysts bearing an alkylidene ligand. In view of this background, the development of ruthenium indenylidene complexes bearing phosphine and N-heterocyclic carbene ligands is discussed in more detail, as well as the mechanistic details of their synthesis.

Chapter 3 provides an overview of latent ruthenium-based olefin metathesis catalysts, their advantages and drawbacks, catalytic performance and methods of activation.

Chapter 4 describes the synthesis of ruthenium indenylidene complexes bearing a saturated N-heterocyclic carbene ligand. Their characteriza-

tion by means of NMR spectroscopy is discussed and their potential as olefin metathesis catalysts is evaluated in comparison with Grubbs type olefin metathesis catalysts.

Chapter 5 examines the effect of the N-heterocyclic carbene ligand in ruthenium indenylidene type catalysts in an effort to yield a catalyst with enhanced initiation efficiency.

Chapter 6 aimed at the application of the catalysts obtained in Chapter 4 as scaffolds for the preparation of olefin metathesis catalysts bearing a chelating arylether alkylidene ligand. In this respect, a polymer-assisted solution-phase synthetic protocol was successfully established by application of a polymer-supported sulfonic acid resin, acting as an efficient phosphine scavenger. Ruthenium indenylidene type complexes were straightforwardly converted to Hoveyda type catalysts which were readily isolated.

Chapter 7 extends the methodology described in Chapter 6 to a ruthenium indenylidene complex bearing ^{i}butyl-phosphabicyclononane ligands. The obtained Hoveyda-like catalyst proved to be highly active towards the formation of challenging trisubstituted olefins via ring-closing metathesis.

Chapter 8 provides a novel activation methodology in view of a reaction-injection molding process for the ring-opening metathesis polymerization of dicyclopentadiene. In the newly established protocol, hydrochloric acid - which was determined as the co-catalyst of choice - was formed *in situ* from the reaction of alcohols and chloride-based Lewis acids. In addition, an in-depth NMR study was performed in order to reveal the mechanism of the catalyst activation.

Chapter 9 briefly summarizes the conclusions obtained in the previous chapters and provides suggestions for future research.

Chapter 10 affords a Dutch summary of the thesis.

Contents

Part I

Introduction

1

Introduction to Olefin Metathesis

The formation of carbon-carbon bonds has been subject of intense research by synthetic organic chemists and in view of this endeavor olefin metathesis, the exchange of alkylidene units at carbon-carbon double bonds, has matured from a "black box" laboratory curiosity to a useful synthetic methodology for the synthesis of carbon-carbon double bonds. [1–14] The awarding by the Nobel Prize Committee of Chauvin for postulating the now generally accepted olefin metathesis mechanism, and of Schrock and Grubbs for availing a significant number of efficient early transition-metal and and easy-to-handle ruthenium olefin metathesis catalysts, respectively, subscribes to the immense impact of this reaction on the academic and industrial chemical community. [15–17]

While, at that time, the olefin metathesis reaction was predominantly believed to proceed according to a pair-wise mechanism in which

two olefins enter the metal's coordination sphere, [18, 19] Hérisson and Chauvin postulated a non-pair-wise mechanism in which metal carbenes and metallacyclobutanes represent key intermediates. Basically, the overall mechanism was understood in terms of a [2+2]-cycloaddition/-cycloreversion sequence of an olefin to a metal carbene specie (Figure 1.1). [20] Further experimental support for the proposed mechanism was later availed by Katz [21–23] and Grubbs [24, 25].

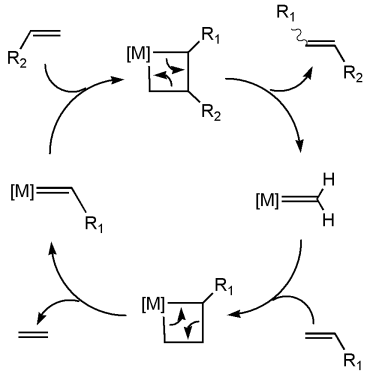

Figure 1.1: Chauvin's mechanism for olefin metathesis reactions.

From a mechanistically point of view, the outcome of the olefin metathesis reaction is strongly dependant on the olefin feed (Figure 9.1). Indeed, strained cyclic olefins undergo Ring-Opening Metathesis Polymerization (ROMP) while cyclohexene remains unaltered. [26–30] On the other hand, α,ω-dienes will Ring-Close (RCM) to form five-, six- or higher-membered hetero- [31–34] or carbocyclic olefins in presence of a suited olefin metathesis catalyst. [35–39] In high substrate concentrations, however, longer-chain acyclic α,ω-dienes are subjected to a stepwise Acyclic Diene Metathesis (ADMET) condensation polymerization. [40–44] Under ethylene atmosphere or in presence of acyclic olefins, cyclic olefins form acyclic dienes, a process known as Ring-Opening Metathesis (ROM) [45] or Ring-Opening/Cross Metathesis (RO/CM). The intermolecular alkylidene exchange between two distinct olefins is designated as Cross Metathesis (CM). [46–49] The versatility of the olefin metathesis method has significantly contributed to its success as a synthetic methodology. Moreover, olefin metathesis catalysts are re-

ported to be efficient catalysts for various mechanistically related reactions, *i.e.* enyne metathesis [50–55] and ring-rearrangement metathesis (RRM) [56]. In addition, selected olefin metathesis catalysts exhibit catalytic activity towards non-metathetical transformations [57, 58] such as Karash addition reactions [59] or have been applied in tandem-catalysis [60–63].

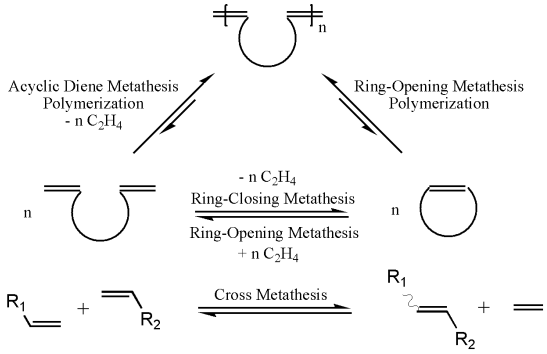

Figure 1.2: Mechanistically related olefin metathesis reactions.

Development of efficient catalysts for the olefin metathesis reaction, originally observed for olefins in presence of transition-metal salts with main group metal alkyl co-catalysts, initially focused on the activity of ill-defined early transition-metal catalyst systems. In this regard, Calderon reported on the highly active WCl_6 / $EtAlCl_2$ / EtOH. [64] Although these systems did not contain a carbene unit, it is supposed that the carbene ligand was formed in the initial stage of the reaction. These catalytic systems turned out to be cheap, however, the application of harsh reaction conditions, strong Lewis acids and the occurrence of side-reactions limited their scope. The lack of reaction control prompted the development of well-defined early transition-metal catalysts.

As soon as the Chauvin mechanism was accepted, it was clear that highly active, well-defined single-component catalysts had to be found among stable transition-metal alkylidenes or metallacyclobutanes. Early examples in this respect were the pentacarbonyl tungsten diphenylcarbene by Katz in 1976 [22] and the titanocyclobutane by Grubbs in 1980 [65]. The development of synthetically modular high oxida-

tion state tungsten, tantalum and molybdenum alkylidene complexes by Schrock evoked the discovery of the highly active olefin metathesis catalyst **1** [66] (Figure 1.3). [67–71] The sensitivity of molybdenum alkylidene complexes to air and moisture and their intolerance towards functional groups long impeded its widespread applicability in organic synthesis. [7, 37] However, recent developments have yielded molybdenum alkylidene analogues exhibiting functional group tolerance [69] while maintaining a high degree of enantiomeric selectivity. [72]

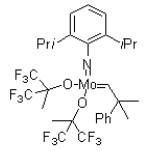

Figure 1.3: Schrock's molybdenum imido-alkylidene catalyst.

Tolerance to functional groups, however, improves with the group number of the incorporated transition-metal. [2] Seminal reports by Novak and Grubbs illustrated that ruthenium not only serves as an interesting candidate for executing olefin metathesis reactions, but also that the reactions were successful in water. [73] This suggested that the catalytically active ruthenium compound might be tolerant towards moisture. Indeed, it was later confirmed that Grubbs catalysts tolerate a wide array of functional groups, such as alcohols, amides, carboxylic acids and aldehydes and are easier to handle than Schrock's catalysts. Moreover, recent developments remain to focus on performing olefin metathesis reactions in water. [74–77]

A major breakthrough in ruthenium-based olefin metathesis catalysis was established during the mid-nineties with the synthesis of ruthenium benzylidene compounds. [78–80] In its most widely known embodiment, two tricyclohexylphosphines and two chlorides coordinate to the ruthenium benzylidene moiety (**2**, Figure 1.4). Commercialization of this catalyst, commonly known as the Grubbs 1^{st} generation catalyst, elicited an emerging interest from synthetic organic and polymer chemists and allowed organometallic chemists to fine-tune the ligand environment. Related to the latter aspect, the replacement of one phos-

phine ligand in Grubbs catalyst **2** with a bulky N-heterocyclic carbene (NHC) [81] ligand established a novel milestone, allowing an increase in thermal stability and catalytic activity and selectivity in several olefin metathesis reactions. [82–85] Systems incorporating an imidazol(in)-2-ylidene ligand are known as Grubbs 2^{nd} generation catalysts (**3** and **4** in Figure 1.4). [82, 86–88] It was shown that these ruthenium precatalysts enter the metathesis cycle after phosphine dissociation. The corresponding 14-electron complexes are highly electron-deficient and are stabilized by coordination of an olefin and subsequent formation and decomposition of the ruthenacyclobutane ring.

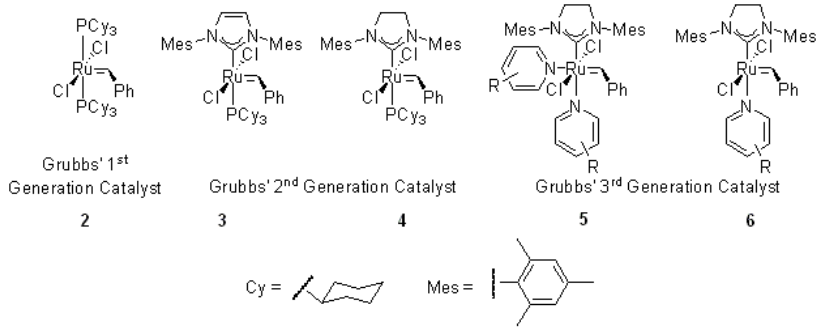

Figure 1.4: Grubbs type ruthenium olefin metathesis catalysts.

Exchange of the other phosphine in the 2^{nd} generation Grubbs catalyst with pyridine afforded higher initiation rates (Grubbs 3^{rd} generation catalysts, **5** and **6** in Figure 1.4). [89–91] The fortuitous incorporation of a chelating carbene ligand by Hoveyda resulted in a family of fairly stable aryl-ether chelated complexes, **7** and **8**, with high activity and improved selectivity compared with Grubbs catalysts in CM and RCM reactions (Figure 1.5). [92, 93]

Modification of the isopropoxy fragment with a more bulky chelating group (**10**) resulted in very high initiation rates indicating that this bulky moiety forces the decoordination of the leaving group. [94, 95, 95, 96] Grela *et al.* introduced a strong electron-withdrawing group on the phenyl ring of the aryl-ether ligand (**11**) obtaining a much higher catalytic activity (Figure 1.5). [97, 98]

Nowadays, more active, efficient and highly selective catalysts re-

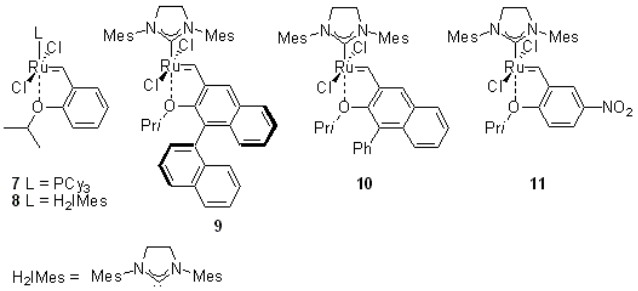

Figure 1.5: Grubbs-Hoveyda type catalysts.

main the focus of intensive research and novel catalyst are continuously developed leading to a large number of metathesis catalysts described in literature. [28, 99, 100] In addition, many aspects related to latent catalysts, [101, 102] chiral catalysts, [103] catalyst immobilization [104–107] or use in alternative reaction media [77, 108, 109] or chemical biology [110] have been extensively studied. In the following sections, we will focus on the aspects related to the preparation of well-defined ruthenium olefin metathesis catalysts featuring a ruthenium-carbon double bond and more specifically on alternative ruthenium indenylidenes based olefin metathesis catalysts.

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2

Ruthenium 3-Phenylindenylid-1-ene Complexes for Olefin Metathesis

2.1 Introduction

The elucidation of the olefin metathesis mechanism by Chauvin was a first but not the determining step towards rational catalyst development. In fact, it is the merit of Katz of recognizing the validity of the proposed carbene mechanism and of concluding that if the mechanism was correct, well-defined, isolable olefin metathesis catalysts had to be found among metal carbenes or metallacyclobutanes. Whereas initial efforts focused on high-oxidation state early transition-metal carbenes, Grubbs showed that ruthenium alkylidene complexes provide a more practical alternative in view of their tolerance towards air, moisture and functional groups. The synthesis of late transition-metal alkyli-

dene complexes, however, was rather unexplored. The following section provides an overview of rational attempts towards isolable ruthenium alkylidene complexes exhibiting olefin metathesis activity. Against this background, section 2.3 discusses an alternative route towards highly active ruthenium alkylidene complexes.

2.2 Preparation of Ruthenium Alkylidene Complexes for Olefin Metathesis

The seminal report on the isolation of a stable ruthenium carbene complex by Grubbs *et al.* upon the reaction of the commercially available ruthenium precursor $Cl_2Ru(PPh_3)_{3-4}$ with 3,3-diphenylcyclopropene afforded the first well-defined olefin metathesis active ruthenium catalyst **12a** (Figure 2.1). [1] The observation that ruthenium salts were active for the ROM polymerization of strained cyclic olefin such as norbornenes [2, 3] was of paramount importance in this respect, and it was anticipated that the active ruthenium alkylidene compound could be caught in the first stage of the reaction in case of the extremely strained cyclopropene. This complex exhibited activity towards the ROMP of strained cyclic olefins, *i.e.* norbornenes, in organic media, and it was soon thereafter recognized that exchange of the coordinatively labile PPh_3 ligands by stronger electron-donating trialkyl phosphines (**12b**) significantly improved its catalytic activity, thus capable of polymerizing unstrained cyclic olefins and formation of five- to eight-membered olefinic hetero- and carbocycles. [4, 5] However, difficulties associated with the large scale synthesis of the cyclopropene precursor contained the germ for further research towards more straightforward procedures for the preparation of five-coordinate ruthenium alkylidene complexes.

As soon as 1995, the same laboratory reported on the synthesis of olefin metathesis active ruthenium catalysts upon reaction of phenyl diazomethane with $Cl_2Ru(PPh_3)_3$. The accordingly obtained catalyst **13**, after ligand exchange with PCy_3, is now generally known as the Grubbs 1^{st} generation catalyst **2** (Figure 2.1). The comparable ease of preparing the synthetically modular diazo carbene precursors allowed for the synthesis of a *family* of well-defined ruthenium-based olefin metathesis catalysts, which were found to exceed the activity of the Grubbs-Nguyen

catalyst **12b** significantly. [6, 7] Later, Hoveyda applied a similar procedure for the preparation of the so-called Hoveyda 1^{st} generation catalyst **7** (Figure 2.1). [8] However, handling of the hazardous diazo compounds requires special care and new, more accessible routes towards well-defined ruthenium olefin metathesis catalysts remained the focus of subsequent research.

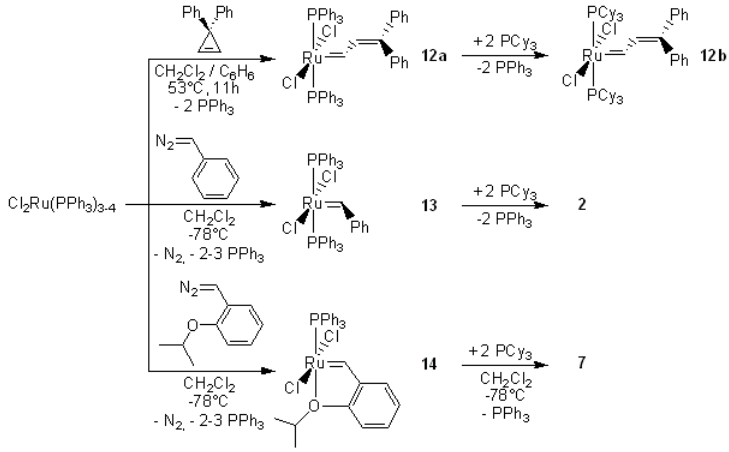


Figure 2.1: Diazo compounds as carbene precursors for the preparation of Grubbs and Grubbs-Hoveyda type complexes.

In view of these demands, Werner *et al.* developed a procedure for the preparation of vinylidenes and alkylcarbenes. Treatment of $[(RuCl_2(COD)]_n$ with P^iPr_3 under H_2 atmosphere in refluxing 2-propanol yielded a *red solution* which, upon recrystallization from diethyl ether, afforded the expected dichloro dihydrido ruthenium compound **15** in high yield (93%)(Figure 2.2). [9] Importantly, the compound in the *red solution* was obviously different from the isolated product and was tentatively taken for the monohydride dihydrogen complex **19**. The isolated complex **15** was found to be an efficient precursor for the development of a ruthenium vinylidene compound **16a** upon reaction with phenyl acetylene at room temperature in dichloromethane (Figure 2.2). The benzylcarbene compound **17**, found as a side product in a 10:1 ratio, was the exclusively formed product when the *red solution* was treated at -78°C with 2 equiv phenyl acetylene and was efficiently converted

to the ruthenium vinylidene complex **16a** upon reaction with phenyl acetylene at 80℃. Treatment of the *red solution* with acetylene at room temperature afforded a ruthenium methylcarbene **18** as the sole product (Figure 2.2). [9] In sharp contrast, reaction of the isolated complex **15** with acetylene did not afford the methyl carbene complex **18**, but rather the ruthenium vinylidene compound **16b**. Interestingly, it was also found that reaction of propargylic alcohols or its derivatives, typically used for the synthesis of allenylidene complexes (*vide infra*), yields vinylcarbenes analogous to **12b** upon reaction with the dichloro dihydro ruthenium compound **15** (Figure 2.2). [10, 11]

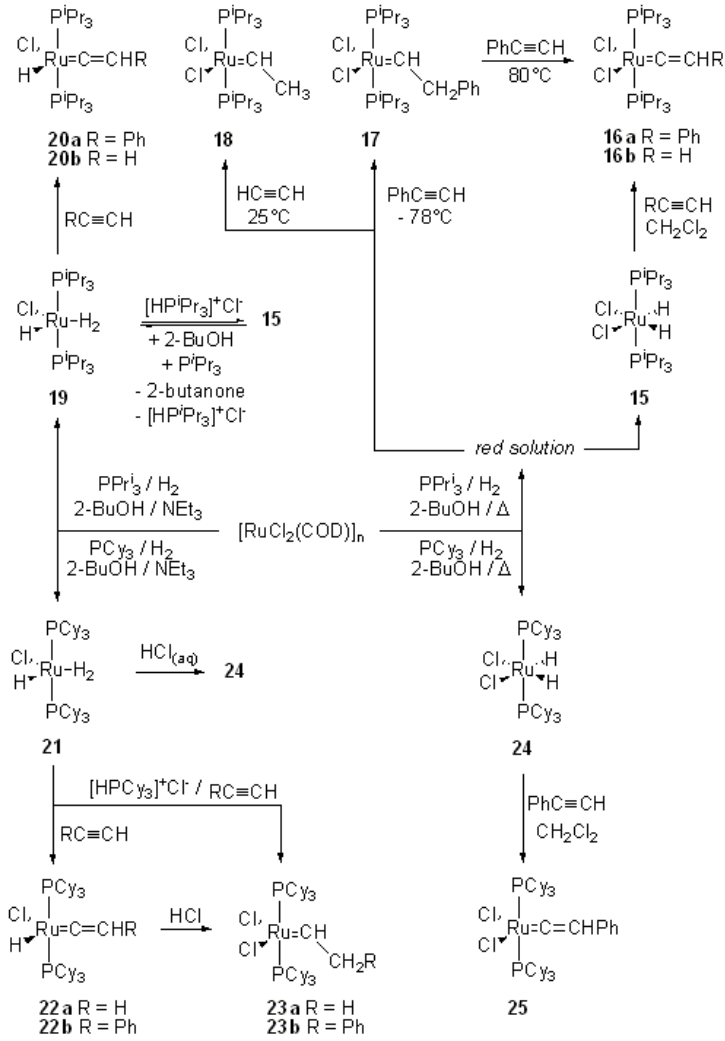


Figure 2.2: $[RuCl_2(COD)]_n$ as a source for the synthesis of ruthenium vinylidene and alkylidene complexes.

Under otherwise identical conditions but in presence of NEt_3, $[RuCl_2(COD)]_n$ is converted to a hydrido dihydrogen ruthenium complex **19** which yields a hydridovinylidene compound **20** upon reaction with terminal acetylenes (Figure 2.2). Of note, complex **15** can also be converted to compound **19** in 2-butanol with loss of butanone and P^iPr_3 acting as hydrochloride scavenger. The reverse reaction is mediated by $[HP^iPr_3]^+Cl^-$ as a chloride and proton source.

Later, Werner *et al.* further demonstrated that the bistricyclohexylphosphine hydrido dihydrogen ruthenium compound **21** reacts with terminal acetylenes to afford the analogous hydridovinylidene complexes **22a** and **22b**. However, when the reaction was performed in presence of $[HPCy_3]^+Cl^-$, ruthenium alkylidenes **23a** and **23b** are isolated. Reaction of the hydrido vinylidenes **22** with hydrochloric acid or $[HPCy_3]^+Cl^-$ also affords the corresponding alkylidene complexes **23**. It was assumed that addition of HCl occurs across the carbon-carbon double bond in the vinylidene ligand, followed by a carbene insertion into the ruthenium hydride bond with subsequent α-chloride shift to form **23**. In a similar way as described above, a ruthenium dichloro dihydrido complex **24** bearing two PCy_3 ligands was prepared which affords the analogous ruthenium vinylidene complexes **25a** and **25b**. [12] Additionally, a one-pot procedure which affords the desired carbene ruthenium catalyst **23a** in about 75% yield was developed starting from the commercially available $RuCl_3 \cdot 3\,H_2O$. Reduction of the ruthenium precursor in presence of PCy_3 and $Mg/ClCH_2CH_2Cl$ under H_2 atmosphere at 60°C-85°C and subsequent addition of 2 equiv acetylene and a small excess of water at -40°C yielded the desired ruthenium alkylidene **23a** upon warming to room temperature. [12]

At the same time, Grubbs reported on an resourceful strategy to prepare the air-sensitive $ClHRu(H_2)(PCy_3)_2$, **21**, from $[(RuCl_2(COD)]_n$, PCy_3, H_2 and NEt_3 in 94% isolated yield, the former compound being a rewarding precursor for the preparation of ruthenium vinylcarbene complexes. **26a** was formed quantitatively at 30°C within 10 min. upon reaction with the commercially available 3-chloro-3-methyl-1-butyne and could be isolated in 95% yield (Figure 2.3). Other propargylic halides were found to be suitable carbene precursors as well, albeit with the formation of trace amounts of complex **24** as a side-product as the steric bulk of the propargylic halide decreases. To account for the carbene formation, an insertion of the alkyne in the ruthenium-hydride bond with a subsequent rearrangement and a formal addition of the chloride to ruthenium was proposed. Although alkylcarbene complexes **27** were observed during the reaction of **21** with an excess vinyl chloride, it should be stated that these reactions were significantly less productive and yielded various ruthenium carbene complexes and complex **24** as a

side-product (Figure 2.3). [13]

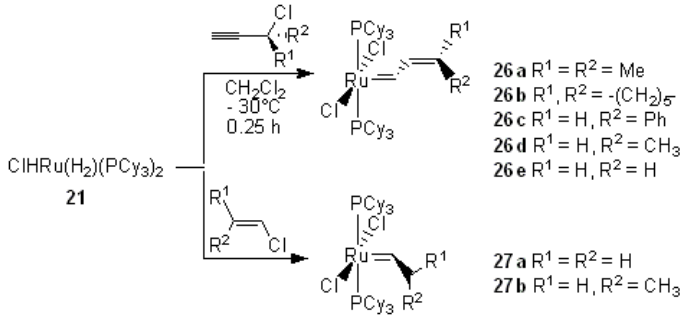


Figure 2.3: Propargylic and vinylic chlorides as hydrocarbon precursor of the carbene ligand.

Caulton *et al.* showed that ruthenium hydride dihydrogen chloride or iodide complexes bearing two P^tBu_2Me ligands react in a 1:2 stoichiometric amount with terminal alkynes, RCCH (R = Ph; $SiMe_3$) - 1 equiv alkyne serving as carbene precursor, 1 equiv alkyne serving as hydrogen acceptor -, to afford hydridovinylidene ruthenium complexes analogous to **22** and 1 equiv of the corresponding alkene. The reaction of $IHRuH_2(P^tBu_2Me)_2$ with DCCPh showed that the only products formed are *cis*-HDC=CHPh and $(P^tBu_2Me)_2IDRu(=CCHPh)$, which is consistent with a mechanism comprising addition of the Ru-H across the alkyne forming a π-acetylenic complex and subsequent α-D migration. [14]

Hofmann *et al.*, in search of olefin metathesis catalysts bearing a chelating bisphosphine ligand which are relevant to the experimental investigation of the phosphine ligand dissociation behavior in Grubbs 1^{st} generation catalyst, applied a similar procedure for the reduction of $[RuCl_2(COD)]_n$ in presence of bis(di-^{t}butyl-phosphanyl)-methane (btbpm) instead of PCy_3 and obtained an electronically unsaturated dihydride ruthenium dimer **28** which formed a ruthenium vinylcarbene complex **29a** with a *cis*-dichloro arrangement upon reaction with 2 equiv propargyl chloride at 70°C in toluene as an air-stable green powder in 62% yield (Figure 2.4). [15] Initial screening of the catalyst's activity towards the ROMP of norbornene and cyclopentene showed that com-

plex **29** was significantly less active than the Grubbs catalysts **2**, as can be rationalized by the strongly decreased tendency to phosphine ligand dissociation due to the chelate effect. Later, it was shown that allenyl and vinyl chlorides were also suitable precursors for the preparation of ruthenium complexes featuring a metal-carbon double bond **29c-d**. [16] Of note, biscationic bimetallic ruthenium carbene complexes obtained from **29** after chloride abstraction using trimethylsilyl triflate were found to be highly active catalysts towards the ROMP of cyclooctene. [16]

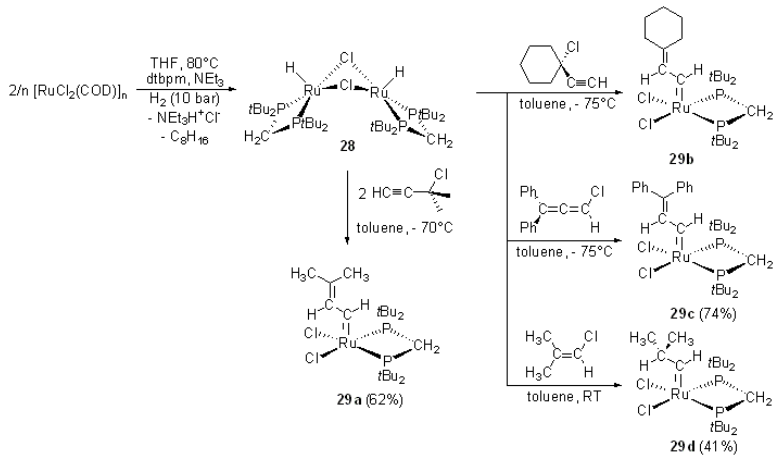


Figure 2.4: A bimetallic ruthenium dihydride as precursor for the preparation of ruthenium alkenylcarbene complexes bearing a bidentate bisphosphine ligand.

In 2000, van der Schaaf *et al.* reported on a one-pot procedure for the preparation of Grubbs 1^{st} generation catalyst **34**. Most importantly, the reduction of $[RuCl_2(COD)]_n$ was successful in refluxing 2-propanol in presence of 2 equiv P^iPr_3 and 1 equiv NEt_3 without use of dihydrogen gas. Upon slow cooling of the obtained *red solution* previously described by Werner *et al.*, [9] orange crystals formed which turned out to be a tetracoordinate, 14-electron ruthenium monohydride species $ClHRu(P^iPr_3)_2$, **30**, as determined by single crystal X-ray analysis. Simultaneously, 3 equiv of 2-propanol were converted to acetone as a result of ruthenium hydride formation (1 equiv) and reduction of cycloocta-1,5-diene to cyclooctane (2 equiv). Cooling of the *red solution*

to 20℃, addition of 1 equiv of hydrochloric acid to form the proposed ruthenium dichloro dihydrogen complex **31** and subsequent addition of 1 equiv phenyl acetylene and 2 equiv styrene led to the isolation of Grubbs 1^{st} generation catalyst **34** in 75% yield on a multigram scale. The proposed mechanism is depicted in Figure 2.5. [17]

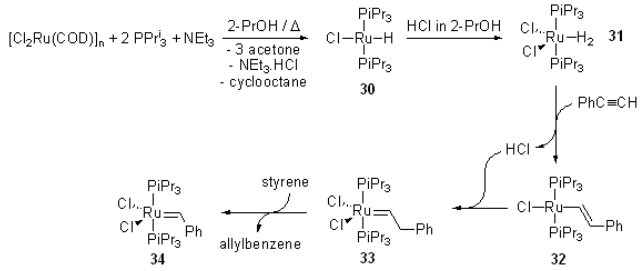


Figure 2.5: Synthesis of Grubbs catalyst **34** from a 14-electron ruthenium hydride.

Interestingly, a similar procedure using 1-hexyne instead of phenyl acetylene was successfully applied for the synthesis of complexes **35a** (78%), **35b** (72%) and **36a-f** (55-68%) (Figure 2.6), which were found to be latent catalysts for the controlled polymerization of dicyclopentadiene. [18]

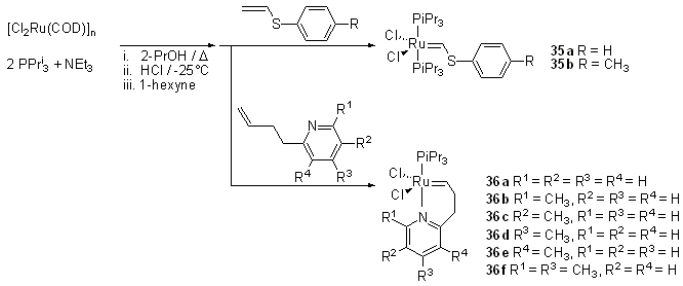


Figure 2.6: Synthesis of latent olefin metathesis catalysts from $[RuCl_2(COD)_n]$.

Hofmann *et al.*, acknowledging its accessibility and ease of handling, showed that the Wilkinson's hydride $ClHRu(PPh_3)_3$, **37**, [19] a

16-electron analogue to the 14-electron hydride intermediate reported by van der Schaaf, readily reacts with propargyl chlorides in CH_2Cl_2 to yield the vinylcarbene **38** in good yield (75%) (Figure 2.7). Alternatively, the reaction is performed with subsequent addition of PCy_3 or the sterically demanding 1,2-bis(di-^{t}butylphosphino)ethane (dtbpe) in a one-pot process. When the reaction was performed in CH_2Cl_2:CH_3CN in a 3:1 ratio, a hexacoordinate ruthenium alkenylcarbene complex **39** was isolated as a yellow-green powder in 69% yield bearing a labile CH_3CN ligand *trans* to the carbene moiety. Although vinyl chlorides did not react in a similar way, the reaction was successful in case of 3-chloro-1,1-diphenyl-1,2-propadiene to afford Grubbs-Nguyen catalyst **12a** (Figure 2.7). [20]

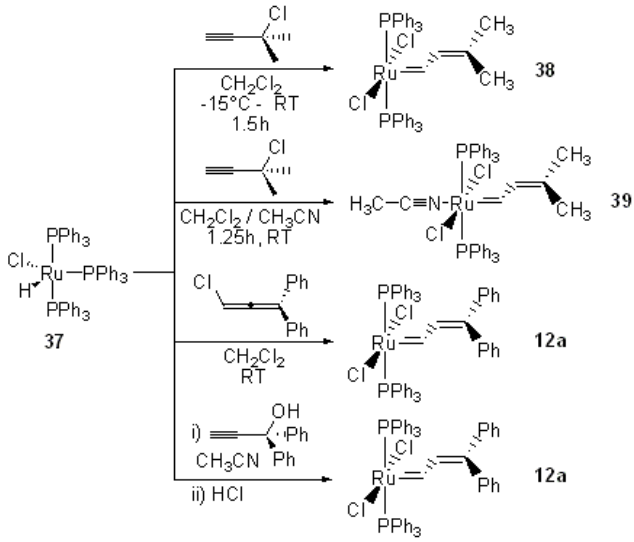


Figure 2.7: Preparation of ruthenium alkenylcarbene complexes from Wilkinson's hydride **37**.

Hill *et al.* showed that reaction of **37** with propargylic alcohol in acetonitrile presumably forms a γ-hydroxyvinylidene compound which, upon workup with hydrochloric acid, yields compound **12a** (83%), as well. [21]

An optimized procedure for the preparation of the Wilkinson's hy-

dride complex **37** from $RuCl_2(PPh_3)_3$ and 1 equiv 4-^{t}butyl-aryloxide in refluxing benzene/2-propanol was later reported by Fogg *et al.* and afforded the desired complex in quantitative yield (97-99%). A mechanism was postulated comprising metathesis of the aryloxide for the chloride, protonolysis of the formed aryloxide complex with 2-propanol and subsequent β-H-elimination in the isopropoxide ligand, thus eliminating acetone, the driving force of the reaction (Figure 2.8). The obtained complex **37** was later converted to $Cl_2Ru(PCy_3)_2(=CHCHCMe_2)$ **38** upon reaction with 1 equiv 3-chloro-3-methyl-1-butyne at room temperature in CH_2Cl_2 within 30 min. (Figure 2.7) and subsequent phosphine ligand exchange in a one-pot reaction afforded a metathesis active ruthenium compound in 88% isolated yield. [22] Of note, a ruthenium alkenylcarbyne complex was formed as a minor side-product during the reaction of **37** with 3-chloro-3-methyl-1-butyne and this carbyne complex was isolated in 75% yield when the reaction was performed in THF with a fourfold excess of 3-chloro-3-methyl-1-butyne.

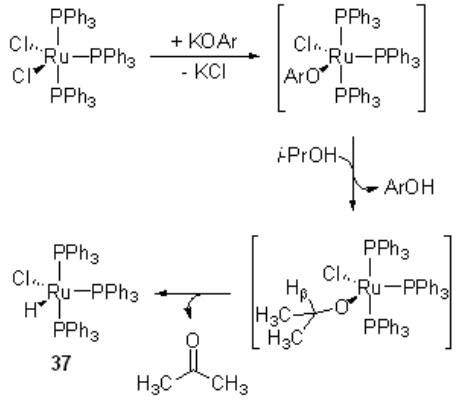


Figure 2.8: Optimized synthesis of Wilkinson's hydride **37**.

Olivan and Caulton reported on the first double oxidative addition of dichloromethane, a *geminal* dihalocompound, to a single ruthenium center using $(H)_2Ru(H_2)_2(PCy_3)_2$ as a formal source for the coordinatively unsaturated Ru^0 compound, $[Ru(PCy_3)_2]$, after reductive elimination of the hydride ligands and loss of the H_2 ligands. Accordingly, $Cl_2Ru(=CH_2)(PCy_3)_2$ was obtained in good yields upon reaction

of $(H)_2Ru(H_2)_2(PCy_3)_2$ with a small excess of dichloromethane after merely 15 min. at 60℃ (67%) or after 3 h at room temperature using a fourfold excess of dichloromethane (63%). [23] When the reaction was performed in a closed NMR-tube, however, $Cl_2Ru(=CH_2)(PCy_3)_2$ further reacted with the released H_2 to give $ClHRu(H_2)(PCy_3)_2$ and no reaction occurred when the reaction was performed under a 1 atm H_2 atmosphere, indicating dissociation of H_2 as the initial step of the reaction and $(H)_2Ru(H_2)(PCy_3)_2$ as the actual reactive partner. Alternatively, $(H)_2Ru(N_2)_2(PCy_3)_2$ readily affords $Cl_2Ru(=CH_2)(PCy_3)_2$ upon reaction with 4 equiv CH_2Cl_2 within 20 minutes at room temperature precluding inhibition and side-reactions. In case of vinylic *gem*-dichloride as carbene precursor, a ruthenium ethylidene compound is observed, a result of a double oxidative addition with subsequent selective reduction of the vinylic carbon-carbon double bond. Reaction of benzylidene chloride with $(H)_2Ru(N_2)_2(PCy_3)_2$ yields the formation of Grubbs 1^{st} generation catalyst **2** in 65% with $(H)_2(Cl)_2Ru(PCy_3)_2$ (7%) and $ClHRu(H_2)(PCy_3)_2$ (28%) as side-products. The isolation of $Cl(PhCH_2)Ru(H_2)(PCy_3)_2$ from the same reaction with benzyl chloride suggests a two-step mechanism with "ClRuCHRCl" as an intermediate. A ruthenium propylidene, initially formed during the reaction of 1,1-dichloropropane with $(H)_2Ru(N_2)_2(PCy_3)_2$, appeared to be the thermodynamically unfavored product since $ClHRu(N_2)(PCy_3)_2$, the product of a β-hydride migration after the first oxidative addition of a C-Cl bond is exclusively obtained after 24 h while no traces of the ruthenium propylidene could be observed. [24]

Independent from the research of Olivan and Caulton, Grubbs *et al.* reported on the preparation of Grubbs 1^{st} generation catalyst **2** upon reaction of $Ru^0(COD)(COT)$ with $PhCHCl_2$ in presence of 2 equiv PCy_3 according to a mechanism which was designated as an oxidative addition - α-chloro elimination sequence. However, the preparation of Ru(COD)(COT) was quite tedious and the procedure could not be applied to the synthesis of other carbenes. Alternatively, the hydrido alkyl complex **41**, a formal source of a Ru^0 species upon reductive elimination of the hydride and alkyl ligand obtained from $(H)_2Ru(H_2)_2(PCy_3)_2$, **40**, under ethylene atmosphere, reacts with Cl_2CHR (R = Ph, COOMe) to afford the ruthenium methylidene complex **42** instead of the ex-

pected benzylidene **2** or methylester carbene **43**, obviously the result of subsequent metathesis of the latter compounds with ethylene (Figure 2.9). Indeed, styrene and methyl methacrylate were observed in the reaction mixture. In case cyclohexene is used instead of ethylene, a pale yellow precipitate, presumably a bis(hydrido)(olefin)Ru^{II} compound, is obtained which affords the Grubbs 1^{st} generation catalyst **2**, the methylidene complex **42** and the methylester carbene complex **43** in near to quantitative yields upon reaction with Cl_2CHPh, CH_2Cl_2 and $Cl_2CHCOOMe$, respectively. The methylester carbene complex **43** further reacts with styrene to afford **2** and in case styrene is used instead of ethylene or cyclohexene, a red solution is obtained which reacts with $Cl_2CHCOOMe$ to afford Grubbs 1^{st} generation catalyst **2** in 54% yield on a multigram scale. [25] Of note, ester carbene complexes were found active in the thermodynamically unfavored ring-opening metathesis of cyclohexene, metathesis of trisubstituted olefins and acrylates. [26, 27]

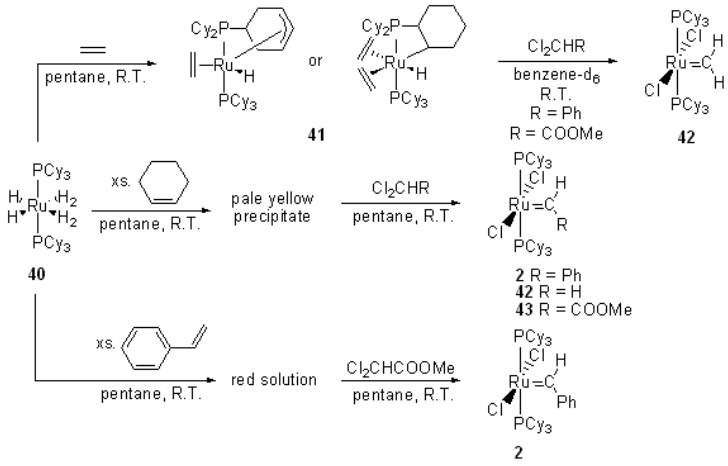
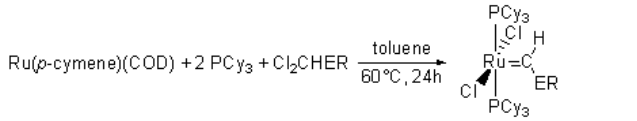


Figure 2.9: Synthesis of ruthenium carbene complexes from *gem*-dichloro-compounds.

Ozawa and coworkers showed that Fischer-type ruthenium carbene complexes are straightforwardly accessible from Ru^0(*p*-cymene)(COD) and dichloromethyl chalcogenides in presence of 2 equiv PCy_3 (Figure 2.10). In contrast to Ru(COD)(COT), the comparably air and moisture stable Ru(*p*-cymene)(COD) is readily obtained from commercially

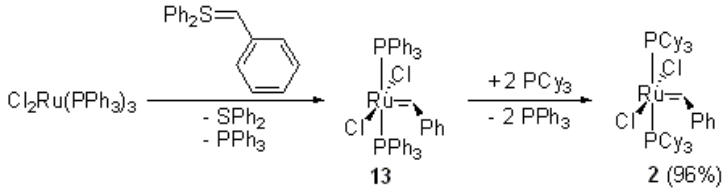
available products in 83% isolated yield. Other Ru^0-complexes, *i.e.* Ru(benzene)(1,3-cyclohexadiene), proved to be successful precursors to ruthenium carbene complexes as well. Ozawa *et al.* further exemplified the use of catalysts **44a** and **44e** as highly selective catalysts for ring-opening/cross metathesis of norbornene and oxanorbornene derivatives with thio and seleno vinyl substrates. [28]



44a ER = SPh (80%)
44b ER = SPh-*p*-Me (47%)
44c ER = SPh-*p*-Cl (56%)
44d ER = SPh-*p*-OMe (77%)
44e ER = SePh (71%)

Figure 2.10: Synthesis of ruthenium Fischer-carbene complexes from Ru^0(*p*-cymene)(COD).

A distinct and general methodology for the incorporation of carbene ligands in transition-metal complexes was elaborated by Gandalman *et al.* Diphenyl sulfur-ylide, prepared upon the deprotonation of a benzyl diphenylsulfonium salt with 1 equiv $KN(SiMe_3)_2$, was reacted with $RuCl_2(PPh_3)_3$ at -30°C. Subsequent exchange of the PPh_3 ligands with PCy_3 afforded Grubbs 1^{st} generation catalyst **2** in 96% yield. [29] In addition, the reaction was also successful in a polymer-assisted solution-phase (PASP) synthetic approach (Figure 2.11). [30]



13 **2** (96%)

Figure 2.11: One-pot synthesis of Grubbs catalyst **2** from a sulfur-ylide.

The preparation of transition-metal alkylidene complexes has long been limited to α-elimination from a transition-metal alkyl complex or

the use of diazo precursors. The seminal finding that ruthenium carbene complexes are active olefin metathesis catalysts prompted the search for straightforward synthetic strategies towards these compounds. In spite of the above summarized developments, many of these strategies remain unattractive in terms of toxicity, stability or accessibility of the ruthenium- or hydrocarbon-precursor. In the following sections, we will focus on the development and application of ruthenium indenylidene based olefin metathesis catalysts. In contrast to the above described approaches, it will be evidenced that these systems are readily obtained from cheap and commercially available resources in near to quantitative yields under soft reaction conditions. In addition, these catalysts are readily modified by ligand exchange reactions to avail new ruthenium based olefin metathesis catalysts with specific characteristics. As such, they have gained a lot of industrial and academic interest and their performance in olefin metathesis reactions is exemplified by selected examples from literature.

2.3 Development of Ruthenium Indenylidene Complexes

In recent years, the development and application of ruthenium indenylidene type catalysts [31–36] has received widespread attention due to their high activity in various olefin metathesis reactions and their comparable ease of synthesis. [37] We have previously stressed out the importance of straightforward synthetic routes to ruthenium alkylidene complexes, and ruthenium indenylidene complexes, readily prepared upon reaction of propargylic alcohol and $Cl_2Ru(PPh_3)_{3\text{-}4}$, are interesting candidates in this respect. Moreover, most of the reported ruthenium indenylidene complexes exhibit high air and moisture stability, good thermal stability and excellent tolerance towards functional groups. Furthermore, this class of olefin metathesis catalysts has proved useful for application in the total synthesis of various natural products. [38–45] In the following sections, we will take a closer look at the discovery and the development of ruthenium indenylidene olefin metathesis catalysts.

2.3.1 Synthesis of Ruthenium Indenylidene Complexes - from Allenylidene to Indenylidene

The chemistry of ruthenium indenylidene complexes started with the serendipitous synthesis of the first ruthenium indenylidene complex by Hill and co-workers, who were actually elaborating the synthesis of ruthenium diphenylallenylidene complexes. [46] They found that upon refluxing a mixture of propargylic alcohol and $Cl_2Ru(PPh_3)_{3\text{-}4}$ for 2 hours in THF, only one signal was found in ^{31}P NMR spectrum and erroneously attributed this to the corresponding ruthenium allenylidene complex (Figure 2.12). Later, it was recognized that the obtained complex was not an allenylidene specie, but the ruthenium 3-phenylindenylid-1-ene complex, **44** (Figure 2.12). [42, 47] Two-dimensional NMR spectroscopy indeed allowed for the unambiguous characterization of the indenylidene moiety. However, details about its synthetic pathway, whether the indenylidene complex is formed through an allenylidene intermediate or generated directly from starting products, could not be ruled out. This question was rather relevant indeed since 1,3-diphenylindenyl ligands appeared to form on Ru_3-clusters (see Figure 2.13). [48, 49] Of note, a recent report by Whitwood *et al.* shows that the formation of an allenylidene complex, and consequently its rearrangement to an indenylidene complex, is prohibited in case of bisacetate ruthenium complexes due to a hydrogen bond induced charge transfer in the hydroxyvinylidene intermediate. [50]

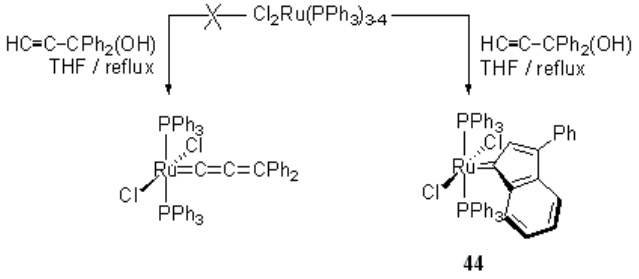


Figure 2.12: Serendipitous discovery of ruthenium indenylidene complex **44**.

While studying the ring-closing metathesis reaction of N,N-diallyl

tosylamide with cationic ruthenium allenylidene arene complexes at moderate temperature (33℃), Dixneuf *et al.* observed that the consumption of the substrate is linear in time, indicating that a highly active species is slowly formed *in situ* while the RCM reaction is comparably fast. They proposed a thermally promoted rearrangement of the allenylidene to indenylidene moiety to account for these observations. Indeed, UV-Vis studies in toluene at 50℃ revealed the disappearance of the allenylidene band (at 518 nm) and the appearance of new bands at 358 nm and 409 nm, due to the formation of a new metal alkylidene moiety, presumably a 3-phenylindenylidene moiety. Elaborating these results, bearing in mind that the addition of strong acids such as HBF_4 and CF_3SO_3H significantly enhance the activity of these cationic ruthenium allenylidene arene complexes, Dixneuf *et al.* found that upon addition of 1.2 equiv of triflic acid to the ruthenium allenylidene arene complex **15b** (Figure 2.13) at -40℃ in CH_2Cl_2, color changed from dark red to dark orange, accompanied by the appearance of a new signal in the ^{31}P NMR spectrum at δ 78.6 ppm *vs.* δ 57.6 ppm for the starting complex. ^{13}C and ^{1}H NMR spectra revealed that the newly formed complex is a biscationic ruthenium alkenylcarbyne complex (Figure 2.13) [51] derived from the protonation of the C_β of the allenylidene moiety. When temperature was allowed to rise to -20℃, color changed to violet and the ^{31}P NMR spectrum revealed a new peak at δ 48.3 ppm. Further NMR spectroscopic data were consistent with a ruthenium 3-phenylindenylidene complex **45** (Figure 2.13) derived from phenyl substitution by the electrophilic C_α. [52, 53] Although very unstable at room temperature, complex 45 and two analogues bearing a PPh_3 and P^iPr_3 ligand, respectively, could be isolated at lower temperature. The isolated catalyst **45** exhibited a lower initial catalytic performance toward the RCM of 200 equiv N,N-diallyl tosylamide compared to the acid activated catalyst **15a**, but managed almost quantitative completion of the reaction after 10 min. while conversion is abruptly stopped for reactions with the acid activated allenylidene complex after 1 min. The isolated catalyst **45** further operated successfully in the ROMP of cyclooctene and cyclopentene and in RCM and enyne metathesis reactions. [53] Interestingly, Bruce *et al.* previously reported on the cyclization of allenylidene to indenyl ligands on Ru_3-clusters. [48, 49] The Ru_3-allenylidene cluster (Figure 2.13) shows a markedly resemblance to the biscationic ruthenium alkenylcarbyne

complex reported by Dixneuf, therefore giving support to the suggested intermediates.

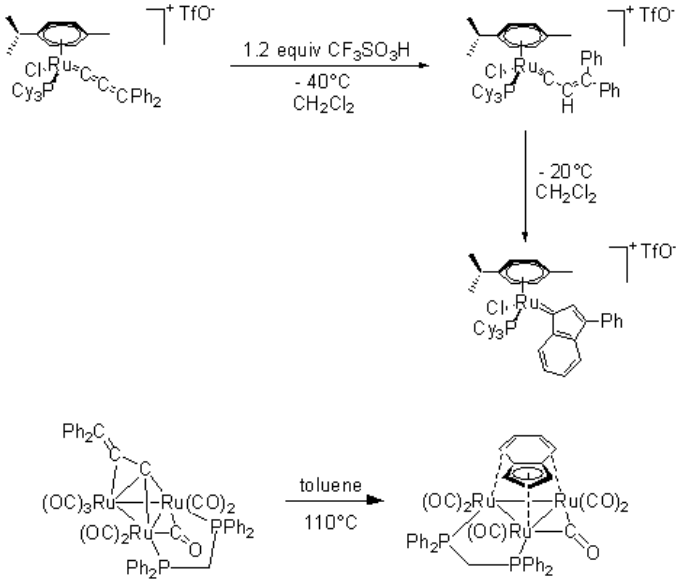


Figure 2.13: Formation of ruthenium indenylidene complex **45** from ruthenium allenylidene complex **15b** through an alkenylcarbyne complex.

Although at that time, several ruthenium indenylidene complexes were reported in literature (*vide infra*) and mechanistic details about their synthesis were revealed, Schanz *et al.* correctly stated that the synthesis of such complexes is not always straightforward and that even though applying the same procedure, sometimes a ruthenium indenylidene species is obtained, but more often an unidentified species containing 4 different kinds of phosphine ligands. [54] The latter specie was identified as a μ_3-chloro-bridged bimetallic ruthenium allenylidene complex **11.1** (Figure 2.14). It is worth noting that this complex can be obtained from equimolar quantities of ruthenium allenylidene and starting complex and can be converted to a ruthenium indenylidene complex upon refluxing for 4 hours in THF in presence of acetyl chloride (Figure 2.14, route A). When adding a catalytic amount of acetyl chloride to $Cl_2Ru(PPh_3)_{3-4}$ - forms HCl *in situ* from reaction of the acetyl chloride with water generated upon formation of the allenylidene ligand - to

speed up the allenylidene-to-indenylidene rearrangement (*vide supra*), indeed, the indenylidene complex **46** could be isolated directly (Figure 2.14, route B). When adding an excess of HCl to the starting product and refluxing for 90 min. in CH_2Cl_2, a stable yellow compound is obtained which was characterized as a ruthenium carbyne complex, **11.2** (Figure 2.14), obviously the result of a 1,3-addition of HCl across the proposed ruthenium allenylidene intermediate. Further refluxing of this complex in THF affords ruthenium indenylidene complex **46** (Figure 2.14, route C and D). It should be noted that the same reaction in CH_2Cl_2 did not yield compound **46**, which leads to the assumption of a cationic THF-ruthenium carbyne complex, **11.3** (Figure 2.14) which contains a more electrophilic carbon in the α-position, therefore being more susceptible to nucleophilic attack of the phenyl group. Of note, complexes **11.1** and **11.2** were isolated from the reaction mixture and their structures were determined by single crystal X-ray analysis.

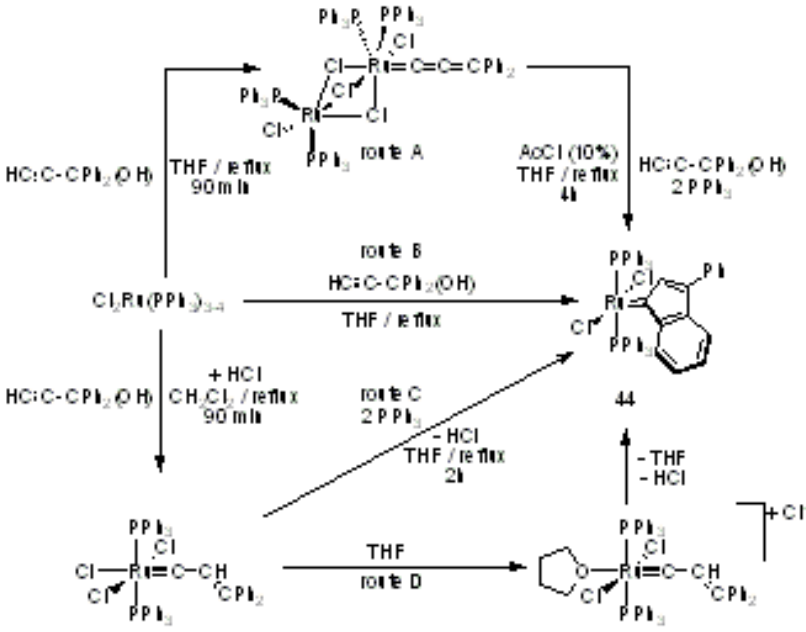


Figure 2.14: Synthetic pathways to ruthenium indenylidene complex **44**.

2.3.2 Development of Ruthenium Indenylidene Type Catalysts

Ruthenium Indenylidene Catalysts bearing Phosphine Ligands

As soon as the synthesis of ruthenium indenylidene complexes was well-documented and they were fully characterized, their further application in the development of ruthenium olefin metathesis catalysts was exploited. The first relevant example in this respect was the ligand exchange of PPh_3 with PCy_3. It was known from Grubbs type catalysts that such an exchange had a pronounced influence on catalytic activity and catalyst stability. [4, 5] In this respect, Fürstner reported on the multi-gram scale synthesis of compound **47** (Figure 2.15) and on the synthesis of its bimetallic congener, **48**. Indeed, catalyst **47** was found to be a highly active catalyst, exhibiting high activity towards the RCM of allyl methallyl malonate and diallyl tosylamide and its activity was found to be comparable to Grubbs type catalyst. In contrast, catalyst **48** showed limited activity. However, Sauvage *et al.* later reported on almost quantitative conversion of diethyl diallylmalonate within merely 15 min. [55] Further elaboration of the catalytic activity of these complexes showed that they were tolerant towards a range of polar functional groups, such as ethers, esters, amides, silyl ethers, sulfonamides, ketones, urethanes, alcohols and furan and pyrrole rings. [42] Of note, the bimetallic ruthenium indenylidene complex was previously also synthesized by Hill, but speciously taken for a homobimetallic ruthenium allenylidene complex. [46] With regard to complex **47**, Kunkely and Vogler reported on the reversible release of the indenylidene ligand after MLCT excitation (λ_{max} = 490 nm), eventually resulting in formation of anthracene and catalyst degradation in air-saturated solvents. [56] Complex **44** undergoes transmetallation in presence of $Hg(ptpy)_2$ with consequent elimination of the indenylidene ligand. [57]

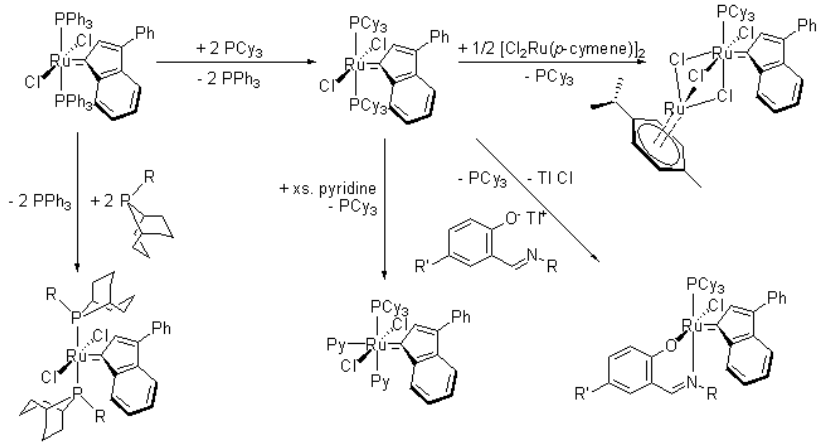


Figure 2.15: Ruthenium indenylidene complexes derived from parent complex **44**.

Interestingly, Forman *et al.* reported on the ligand exchange from **46** to $(PhobCy)_2Cl_2Ru$(3-phenylindenylidene), the so-called phoban-indenylidene catalyst, **49a** (R = Cy) (PhobCy = 9-cyclohexyl-9-phospha-9*H*-bicyclononane). [58] They had previously shown that incorporation of the phoban ligand in Grubbs type complexes induces a comparably high air and moisture stability and good thermal stability, even in a 2M HCl solution. Furthermore, they illustrated that this catalyst excels in efficiency and selectivity towards the self-metathesis of 1-decene and methyl oleate, the ethenolysis of methyl oleate and the RCM of diethyl diallyl malonate compared to Grubbs 1^{st} and 2^{nd} generation catalysts, **2** and **4**. [59] Likewise its benzylidene congener, the phoban indenylidene catalyst **49a** exhibited higher catalytic activity towards the self-metathesis and ethenolysis of methyl oleate, enabling substrate-to-catalyst ratios up to 200,000:1 for the self-metathesis reaction and 20,000:1 for the ethenolysis of methyl oleate. In addition, the ethenolysis of methyl oleate with **49a** proved to proceed even at higher temperatures (65℃) while maintaining its activity.

Elaboration of this new class of catalysts, together with comparison of the new isobutyl phoban catalyst **49b** (R = ^{i}Bu) in RCM reaction revealed good activity of **49b** in RCM of simple five- and six-membered ring substrates, with exception of enyne metathesis reactions. In general, catalyst **49b** performed better than its cyclohexyl-based congener **49a**

and, except for the formation of substituted alkenes, good activities were reported for all reactions. During the self-metathesis of 1-octene, however, catalyst **49a** performed notably better. [60, 61]

Nolan *et al.* reported on the synthesis and catalytic activity of the bis(pyridine) adduct $Cl_2Ru(PCy_3)(py)_2$(3-phenylindenylidene) **50** as an air and moisture stable catalyst. This compound, readily prepared upon treatment of **47** with an excess of pyridine, performed well in the initial stage of the RCM reaction of diethyl diallylmalonate. However, catalytic activity dropped significantly after 30 min. indicating degradation of the catalytically active specie. Similar behavior was concluded for the RCM of more sterically demanding substrates such as diethyl allylmethallylmalonate, eventually resulting in low turn-over numbers. [62]

Application of Schiff base ligands has been a well-documented strategy towards the development of thermally stable, efficient catalysts. Verpoort *et al.* reported on the isolation, characterization and catalytic activity of ruthenium indenylidene Schiff base complexes, **51**. [63–66] These catalysts exhibited high thermal stability ($\tau_{1/2-degradation}$ = 3-6 h at 80℃ in benzene-d_6) with moderate room temperature activity. However, upon heating to 60℃, cyclization of diallyl tosylamide is quantitative within one hour and good to quantitative conversions are reported for the RCM of the more sterically demanding allyl methallyl tosylamide within 3 hours under otherwise identical conditions. In addition, rigorous choice of the Schiff base ligands allows for high activity in the cross metathesis reaction of 5-hexenyl acetate with methyl acrylate. As a result, activities surpassing those obtained with Grubbs-Hoveyda 1^{st} generation catalyst, **7**, can be achieved.

Sauvage *et al.*, elaborating homobimetallic ruthenium ethylene complexes, **13.1** (Figure 2.16), reported on the alternative synthesis of a bimetallic indenylidene complex, **48**, formed upon the reaction of propargylic alcohol or its *n*-propyl ether adduct in presence of acid and a drying agent (*e.g.* molecular sieves 3Å). [67]

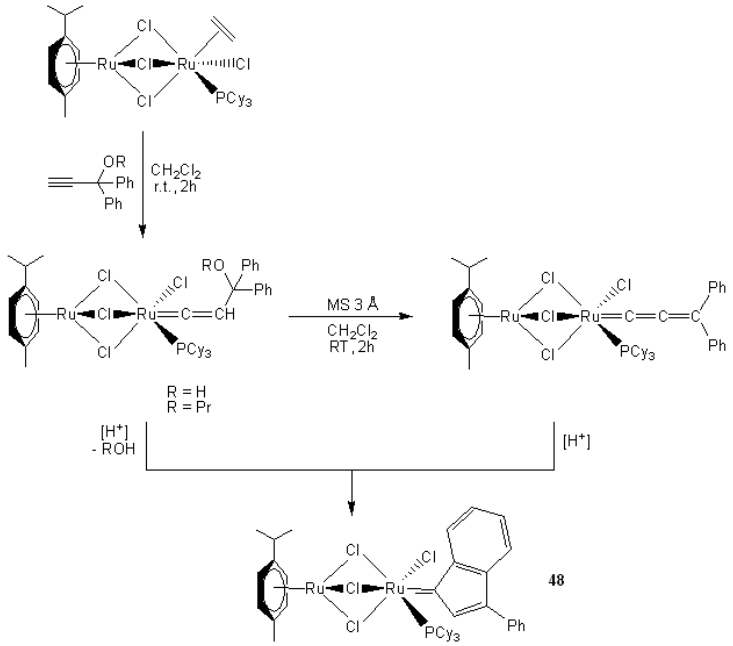


Figure 2.16: A ruthenium-ethylene complex as precursor for the synthesis of homobimetallic ruthenium vinylidene, allenylidene and indenylidene complexes.

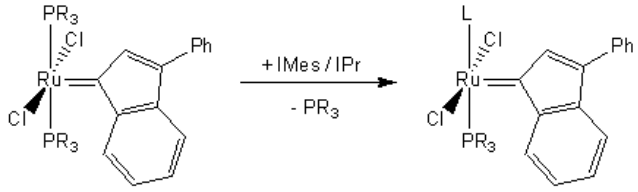
X-ray crystallographic data unambiguously proved that the obtained complex **48** was an indenylidene complex and characterization by means of NMR and IR spectroscopy corresponded to data previously reported by Hill. [46] Interestingly, Sauvage also showed that a bimetallic ruthenium vinylidene complex, **13.2**, could be isolated upon reaction of the bimetallic ethylene complex with propargylic alcohol or its *n*-propyl ether adduct and that it forms the bimetallic ruthenium allenylidene complex **13.3** upon addition of drying agents such as molecular sieves. Subsequent addition of trifluoroacetic acid or alternatively *p*-toluenesulfonic acid monohydrate yielded the bimetallic ruthenium indenylidene complex, **48**. Thus, full characterization of key intermediates observed during the transformation of vinylidene-to-indenylidene through a proposed ruthenium carbyne complex was obtained. When applied in characteristic olefin metathesis reactions, **48** exhibited high catalytic activity toward the ROMP of cyclooctene and the RCM of diethyl diallylmalonate. Catalytic tests for the cross metathesis of styrene

yielded poor conversions, attributed to the reduced stability of the corresponding bimetallic ruthenium methylidene complex.

Development of Ruthenium Indenylidene Complexes bearing a N-Heterocyclic Carbene Ligand

It is well-documented that phosphines used in the above discussed catalysts induce considerable degradation at elevated temperature. The advent of N-heterocyclic carbenes which act as phosphine mimics was found to be of paramount importance toward the development of highly active and stable olefin metathesis catalysts. In this respect, Nolan *et al.* reported on the incorporation of the IMes and IPr ligand in complexes **46** and **47**, respectively (Figure 2.17). [68] Indeed, high thermal stability was observed for the newly obtained NHC ligated catalysts. More importantly, PCy_3 based complexes were more robust compared to their PPh_3 based congeners, basically showing no signs of decomposition after 10 days at 80℃ in toluene. In standard RCM experiments, NHC ligated catalysts notably performed better than their phosphine analogues. RCM of diethyl diallylmalonate and diallyl tosylamide proceeded smoothly with catalyst **55** whereas catalyst **52** required heating to 40℃. However, higher conversion was obtained for **53** when applied to RCM of the sterically demanding diethyl di(methallyl)malonate.

Determination of catalytic activity of catalysts **47**, **55** and **56** (*vide infra*) in the cross metathesis reaction of ^{t}butyl(hex-5-enyloxy)dimethylsilane and methylacrylate revealed significantly improved catalytic activity for reactions performed with catalyst **55**, basically conducting the reactions to full conversion under ambient conditions. Further screening of the catalytic activity of **55** in various cross metathesis reactions showed a definite substrate dependency. [69]



46 R = Ph
47 R = Cy

52 L = IMes; R = Ph
53 L = IMes; R = Cy
54 L = IPr; R = Ph
55 L = IPr; R = Cy

Figure 2.17: Synthesis of ruthenium indenylidene complexes bearing an imidazol-2-ylidene ligand.

Elaborating the application of catalyst **53**, Fürstner noted that di-, tri- and tetrasubstituted small to medium and macrocyclic alkenes are isolated in high yields upon RCM of the corresponding dienes and it was concluded that catalyst **53** could be regarded as equipotent to its Grubbs type congener, **3**. [70]

In 2007, Nolan reported on the application of catalyst **56** bearing a saturated imidazolin-2-ylidene ligand in olefin metathesis reactions. [62] Catalyst performance in RCM experiments using diethyl diallylmalonate as a substrate proved a fast and almost quantitative conversion in case of catalyst **47** while NHC bearing catalysts **56** and **53** needed significantly longer reaction times. However, **56** performed notably better compared to **47** and **53** in case of RCM of the more sterically demanding diethyl allylmethallylmalonate. Discrepancies in catalytic activities observed were rationalized by the difference in rate determining step between phosphine- and NHC-based catalysts, respectively. It was reasoned that while NHC-containing catalysts suffer from a reduced initiation rate, phosphine-based catalysts exhibit fast initiation with a reduced propagation rate. Definite causes for the different activity of catalyst **53** and **56** however could not be ruled out. In addition, formation of tetrasubstituted olefins with catalyst **56** was found to proceed with excellent isolated yields whereas the benzylidene congeners yielded moderate conversions. Further elaboration of the catalytic activity of catalysts **53** and **56** proved that under optimized conditions these catalysts are suitable for RCM of malonate- and tosyl-containing and ether- and amide-

based substrates and that high catalytic activity was observed in enyne metathesis reactions. In addition, good activities were obtained in the self-metathesis reaction of undecylenic aldehyde, a renewable derived from castor oil cracking. [71]

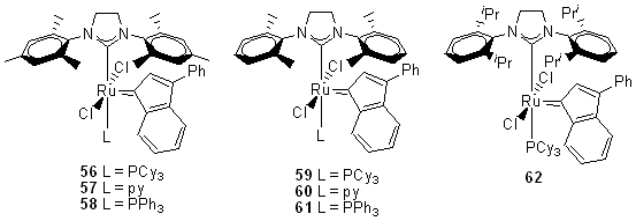


Figure 2.18: Ruthenium indenylidene type catalysts bearing saturated N-heterocyclic carbenes.

The synthesis and characterization by means of ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis of the ruthenium indenylidene catalyst **56** bearing a saturated N-heterocyclic carbene ligand was shortly thereafter reported by Verpoort *et al.* [72] From known methodologies for the introduction of the NHC ligand in ruthenium olefin metathesis catalysts, solely the application of the thermally decomposing SIMes $\cdot$ $CHCl_3$ adduct afforded compound **56** in high isolated yields (82%). In addition, synthesis and characterization of the pyridine (**57**) and PPh_3 (**58**) containing analogues were reported. In agreement with catalytic data reported by Nolan (*vide supra*), a slow initiation rate was observed for **56** in both RCM and ROMP reactions, a trend which was successfully offset by application at higher temperatures. Catalysts bearing the more labile PPh_3 ligand performed excellent in RCM of diethyl diallylmalonate and ROMP of cylooctadiene. While the pyridine containing catalyst **57** excelled its Grubbs type congener in ROMP reactions using cylooctadiene as monomer, moderate activity is obtained when applied in RCM reactions. Interestingly, it was evidenced that the Grubbs type congener suffered from an increased initiation period towards the RCM of diethyl diallylmalonate when higher catalyst loadings were applied, a phenomenon which was not observed with catalyst **57** and for which, to the best of our knowledge, no precedents have been reported so far. An in-depth study of the application of ruthenium

indenylidene catalysts **47**, **53**, **56**, **52** (py_2) and **57** (py_2) in ROM polymerizations of cylooctadiene was later reported by Nolan. [73] In this respect, it is interesting to note that the pyridine containing complexes reported bear two pyridine ligands, in contrast to reports by Verpoort and Slugovc, who independent from Verpoort *et al.*, reported on the synthesis of **57** and its application in controlled living ROMP of norbornene and oxanorbornene derivatives. [74] Alternatively, the SIXyl ligand (SIXyl = N,N'-(2,6-dimethylphenyl)-imidazolin-2-ylidene) was successfully introduced in ruthenium indenylidene type catalysts after reaction with merely 1.15 equiv of its pentafluorobenzene adduct whereas 2 equiv of SIMes $\cdot$ $CHCl_3$ were necessary for the synthesis of **56**. It was concluded that although these catalysts exhibit a roughly similar activity compared to their SIMes-based congeners, slightly lower activity was observed when exposed to challenging reactions such as the RCM of diphenyl diallylsilane or cross metathesis reactions. [75]

A convenient method for the preparation of ruthenium-based olefin metathesis catalysts bearing an N-heterocyclic carbene ligand based on the thermal decomposition of imidazol(in)ium-2-carboxylates was later reported by Sauvage *et al.* Accordingly, **53** and **56** were prepared in 89% and 86% yield in isolated product, respectively. [76]

A useful and practical guide to application of olefin metathesis catalysts was recently availed by Grela and co-workers. They examined the effectiveness of ruthenium indenylidene complexes in standard olefin metathesis reactions and compared their activity to those of Grubbs and Grubbs-Hoveyda type catalysts. [77] Indenylidene catalysts **53** and **56** were found to be practically inactive toward the RCM of diethyl diallylmalonate at room temperature using catalyst loadings as low as at 0.05 mol%, in sharp contrast to Grubbs and Grubbs-Hoveyda catalysts. However, conversions dramatically increased when the reaction was performed at elevated temperature (70°C) rendering them competitive to the most active catalysts reported. Similar conclusions were drawn from experiments aiming at the formation of tetrasubstituted olefins. In contrast, enyne cycloisomerization was significantly more effective using Grubbs or Grubbs-Hoveyda type complexes. Cross metathesis of various olefins with (*Z*)-1,4-diacetoxy-2-butene, however, did not exemplify significant discrepancies in catalytic activity. In addition, application

of 2^{nd} generation indenylidene type catalysts, **53** and **56**, to challenging substrates such as diethyl di(methallyl)malonate in fluorinated aromatic hydrocarbon solvents resulted in a remarkable enhancement of catalytic activity. This approach was successfully extended to the RCM of natural products and the cross metathesis formation of trisubstituted alkenes. [78]

The synthesis and activity of a ruthenium indenylidene complex bearing a saturated IPr ligand was recently reported by Nolan. [79] In contrast to comparable ruthenium indenylidene complexes bearing NHC ligands, **63** exhibited limited thermal stability, essentially decomposing over the course of 24 hours in solution. However, high initial activity was reported, allowing for the fast and complete consumption of sterically unhindered substrates in ring-closing and enyne metathesis reactions, in due contrast to application in RCM of sterically more demanding substrates, eventually affording poor isolated yields.

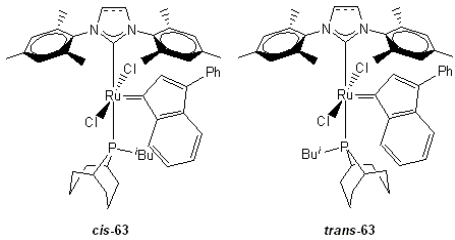


Figure 2.19: 2^{nd} generation phoban indenylidene ruthenium catalysts.

$SIMes \cdot CO_2$ and $IMes \cdot CO_2$ betaines have previously proven their suitability as stable precursors to free N-heterocyclic carbenes which readily coordinate to ruthenium upon phosphine ligand exchange. [76] Upon refluxing a mixture of $SIMes \cdot CO_2$ or $IMes \cdot CO_2$ betaines and **49b** in THF, Sauvage *et al.* showed that 2^{nd} generation phoban indenylidene catalysts, **63**, are obtained in high yield. (Figure 2.19)Acquisition of the ^{31}P NMR spectrum at -40°C allowed for the observation of two distinct peaks, assigned to the *cis-* and *transoidal* conformation of the phoban ligand with respect to the indenylidene moiety. Activity of these catalysts was rather low at room temperature. In contrast, ring-closing of diethyl diallylmalonate was quantitative after 3 hours at 50°C. In addi-

tion, relatively high TONs were obtained for RCM of di(2-methallyl)-malonate at 80℃ in toluene; 15 and 10 for the IMes and SIMes based catalyst, respectively.

2.3.3 Ruthenium Indenylidene Complexes as Scaffolds for the Development of New Ruthenium Olefin Metathesis Catalysts

Besides their immediate application in olefin metathesis reactions, advantage has been taken of the synthetic straightforwardness of the preparation of ruthenium indenylidene complexes to use as scaffolds for the synthesis of novel olefin metathesis catalysts (Figure 2.20).

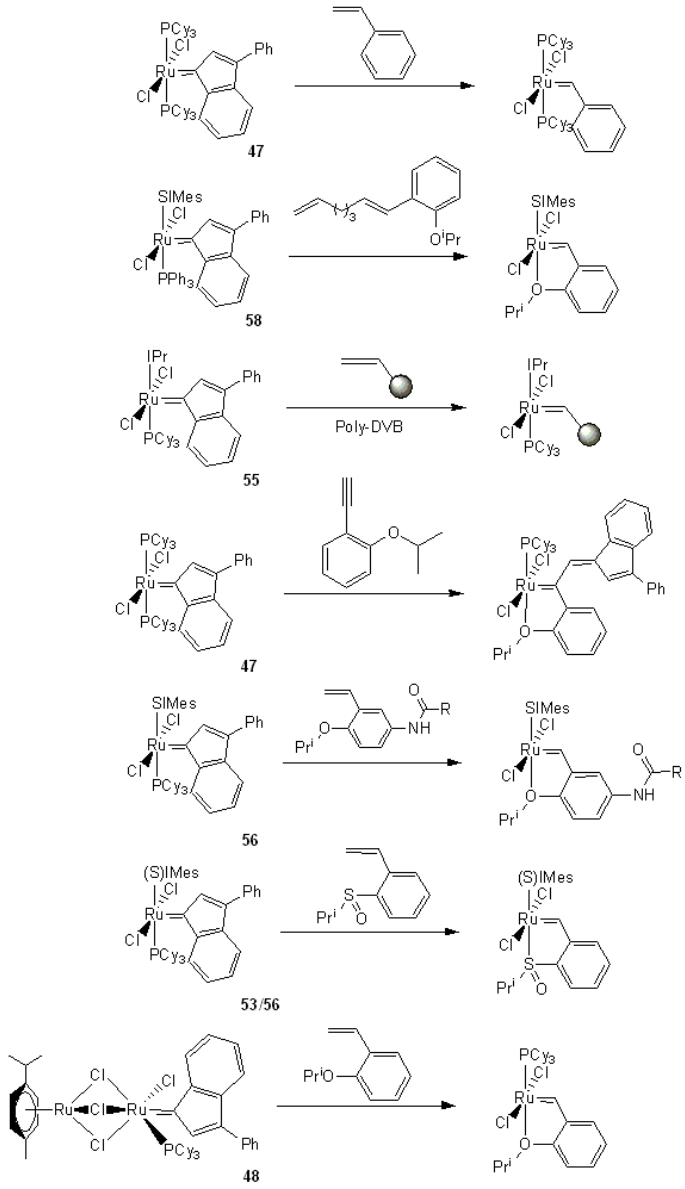


Figure 2.20: Ruthenium indenylidene complexes as scaffolds for the synthesis for new ruthenium olefin metathesis catalysts.

We have previously stressed out the hazardousness of diazo compounds and the fact that their use during the preparation of Grubbs

1^{st} generation catalyst **2** is therefore to be avoided. Nolan anticipated that Grubbs catalyst **2** can be obtained after cross metathesis of styrene with 1^{st} generation indenylidene catalyst, **47**. [80] Indeed, high yields in isolated product can be obtained for this reaction using a 20-fold excess of styrene. Interestingly, a one-pot procedure for the synthesis of indenylidene 1^{st} generation catalyst **47** is reported.

Blechert recognized the utility of ruthenium indenylidene complexes as useful scaffolds for the synthesis of 2^{nd} generation Grubbs-Hoveyda catalyst **8** upon a ring-closing metathesis inspired alkylidene exchange with an alkenylisopropoxystyrene. [81]

Nolan used poly-divinylbenzene (poly-DVB) for the immobilization of **55** on a heterogeneous polymer support. [82] Interestingly, the polymer-supported catalyst exhibits higher catalytic activity for RCM of diethyl diallylmalonate compared to its homogeneous parent complex, **55**, and leaching after 4 catalytic cycles was determined to merely 2% of the initial catalyst loading. Unfortunately, RCM activity was less impressive for diallyl tosylamide and activity for diethyl di(methallyl) malonate was disappointing.

Fürstner adopted the formal insertion of an alkyne into the Ru=C bond for the synthesis of Grubbs-Hoveyda type catalysts. Addition of 2-isopropoxyphenyl acetylene to 1^{st} generation indenylidene catalyst in presence of AgCl as phosphine scavenger indeed afforded the desired κ^2-(O,C) bidentate complex in moderate yield (59%). Although no catalytic activities were reported for the thus obtained complex, it is worth mentioning that comparable vinylcarbene complexes exhibited good activity towards the RCM of diethyl diallylmalonate in CH_2Cl_2 at reflux. [83]

Cross metathesis of 4-aminocarbonyl-2-isopropoxystyrene derivatives with ruthenium indenylidene catalyst **56** by Mauduit led to the isolation of 4-aminocarbonyl-substituted Grubbs-Hoveyda type catalysts. [84] An unequivocal influence of the carbonyl substituent was derived from kinetic studies using the RCM of 2-allyl-2-methallyl malonate as a benchmark reaction, thus allowing for fine-tuning of the catalyst activity. More importantly, ruthenium contamination of the reaction products

was reported to be significantly below 10 ppm after a single pass through a silica column, a vast advantage when thinking of the synthesis of biologically active compounds.

In search of catalysts with a more controllable activity profile, Grela reported on ruthenium olefin metathesis catalysts bearing a chelating κ^2-(*C,S*) sulfoxide ligand. [85] These complexes were obtained in good yields upon adding 2-isopropylsulfinylstyrene to ruthenium (S)IMes indenylidene complexes in presence of CuCl (toluene, 80°C). Good activity was reported toward RCM of model substrates, however not being competitive to the commercially available Grubbs 2^{nd} generation catalyst, **4**. In addition, the SIMes containing analogue was slightly more active than its IMes based congener. Modification of the alkyl substituent on the sulfur atom showed that steric effects conclusively determine the catalytic activity. RCM of diethyl di(methallyl)malonate to form the challenging tetrasubstituted carbon-carbon double bond proved satisfactory, albeit only at elevated temperatures (110°C).

Sauvage *et al.* successfully converted the bimetallic ruthenium indenylidene complex **48** to the Grubbs-Hoveyda catalyst **7** by means of cross metathesis of the indenylidene moiety with 2-isopropoxyystyrene. Alternatively, a one-pot procedure starting from the homobimetallic ruthenium ethylene complex **13.1** was availed by subsequent addition of i) propargylic alcohol; ii) *p*-toluenesulfonic acid and anhydrous $CaCl_2$; and iii) 2-isopropoxystyrene. It is worth noting that the reported procedure excludes the use of a sacrificial phosphine while the ruthenium dimer side product was effectively recycled. [55]

2.4 Conclusion

With regard to ruthenium indenylidene complexes, the mechanism of formation of the indenylidene ligand from reaction between propargylic alcohol and a ruthenium precursor including formation of ruthenium vinylidene, allenylidene and alkenylcarbene intermediates is now well-understood. These insights led to reliable and reproducible procedures for the synthesis of ruthenium indenylidene complexes under ambient conditions. Prominent characteristics of this class of olefin metathesis catalysts are their ease of preparation, high thermal stability, air

and moisture stability, functional group tolerance, and high intrinsic catalytic activity. Altering the application profile of the catalysts is readily obtained by varying or exchange of phosphine ligands, substitution of halide ligands with *e.g.* Schiff base ligands, incorporation of N-heterocyclic carbene ligands or ultimately a cross metathesis based exchange of the indenylidene ligand with styrene or its derivatives. Consequently, the class of ruthenium indenylidene complexes gradually begins to fulfill its potential as viable olefin metathesis catalysts.

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3

Development of latent olefin metathesis catalysts

3.1 Introduction

The success of the olefin metathesis reaction can thus be greatly attributed to its versatility and the development of well-defined catalysts stable to demanding reaction conditions. As these catalysts became commercially available and were exposed to a myriad of potentially interesting applications, the field was faced with renewed challenges, *e.g.* catalysts yielding high enantioselectivity in reaction products, catalysts with enhanced thermal stability or catalysts immobilized on heterogeneous supports were strongly demanded for.

A class of task-specific olefin metathesis catalysts which has recently

attracted increasingly attention is that of latent catalysts. Several key concepts should be kept in mind during the design of potential latent olefin metathesis catalysts. Firstly, the ideal latent olefin metathesis catalyst exhibits no catalytic activity in the presence of monomer or substrate at room temperature, but can be triggered quantitatively to a highly active form by thermal, chemical or photochemical activation to initiate the metathesis reaction. Most metathesis catalysts are operative at room temperature and are therefore not well-suited for applications where catalyst latency is beneficial. Additionally, catalyst stability towards decomposition or thermal degradation should be guaranteed by the rigorous choice of ligand environment.

The last decade, Ring-Opening Metathesis Polymerization attracted increasing interest by polymer chemists since it is a straightforward method for the synthesis of functionalized, polymeric materials in a "living" way. [1, 2] Additionally, ruthenium-based olefin metathesis catalysts are easy to handle and the catalytically active species are relatively stable compared to those used in classical living polymerizations. The advantages of latent initiators for anionic polymerizations or controlled radical polymerizations are widely recognized, and the use of similar methodologies for the Ring-Opening Metathesis Polymerization are justified there from.

The advent of latent olefin metathesis catalysts was mainly driven by the need for Ring-Opening Metathesis Polymerization catalysts that can be mixed with the monomers without concomitant polymerization, which should allow for longer handling of the catalyst/monomer mixtures or even storage of the formulation for longer periods. Furthermore, commercially available catalysts suffered from considerable degradation during metathesis reactions and it was anticipated that the elaboration of latent catalysts, which generally exhibit higher thermal stabilities, could yield *a catalyst that lives forever*.

This section aims to provide a comprehensive introduction to the state-of-the-art of latent ruthenium olefin metathesis catalysts.

3.2 Ill-defined latent catalysts

Contrary to well-defined latent olefin metathesis catalysts, ill-defined latent catalysts can be defined as transition-metal complexes without an alkylidene fragment. In case of ruthenium, the active alkylidene is formed *in situ* by the addition of a carbene source or it is formed by coordination of the substrate to the coordinatively unsaturated complex and subsequent 1,2-H-shift. Although these ill-defined systems were originally used due to lack of well-defined catalysts, they regained interest, having several advantages compared to the former ones. *E.g.*, these catalysts are generally cheaper and readily commercially available or easily prepared from commercially available compounds. Furthermore, they sometimes exhibit comparable performance and allow for straightforward synthetic procedures.

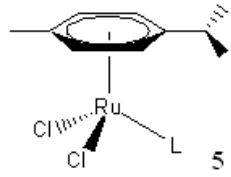


Figure 3.1: Ruthenium *p*-cymene complexes as latent olefin metathesis catalysts.

In the late 1980s, it was shown that $Ru(H_2O)_6(tos)_2$ polymerizes norbornenes within the range of minutes and low-strain cyclic olefins were readily polymerized when ethyl diazoacetate was added to the reaction. [3] Noels *et al.* reported on the use of trimethylsilyl diazomethane (TMSD) as a more efficient carbene precursor in combination with ruthenium arene complexes **5** (Figure 3.1, L = PCy_3, $PPhCy_2$, P^iPr_3), either preformed or prepared *in situ* upon mixing $[RuCl_2(p\text{-cymene})]_2$ with the corresponding phosphine, to form the highly active [Ru]=$CHSiMe_3$ *in situ* for the polymerization of functionalized norbornenes and cyclooctenes. Gelation occurred within minutes after activation of the complexes with TMSD and TON higher than 2,000 were readily reached. Interestingly, proof of the formation of the [Ru]=$CHSiMe_3$ complex and the propagating species derived there from upon addition of monomer

could be observed by ^{1}H and ^{13}C NMR spectroscopy, and the content of original ruthenium activated accordingly was determined to 15-20%. Metathesis activity was attributed to the highly active, coordinatively unsaturated ruthenium monophosphine complex formed upon the TMSD induced release of the *p*-cymene ligand. [4, 5]

In 1997, Hafner *et al.* described the use of osmium and ruthenium arene complexes bearing various phosphine ligands. [6] Type **5** osmium complexes (Figure 3.1, L = PCy_3, P^iPr_3) are highly active ROMP catalysts when irradiated by UV (200-W Hg lamp, 5 min), while inactive towards thermally induced polymerization. In contrast, similar complexes based on ruthenium mostly exhibited room temperature activity towards the polymerization of norbornene. However, clear-cut photoactivity was determined for complex **5** (Figure 3.1, L = P^nBu_3), yielding traces of poly(NBE) after 1 h at 80°C but affording 80% conversion upon irradiation for 5 minutes at room temperature. Furthermore, complex **5** (Figure 3.1, L = PCy_3) exhibited latent properties towards the polymerization of dicyclopentadiene (DCPD), being stable for weeks as a solution in DCPD and thermally activated upon heating to temperatures above 80°C. This was an important precedent since poly(DCPD) is an attractive, oxidatively stable thermoset with exquisite electrical and mechanical properties, and no ruthenium catalysts for the ROMP of DCPD were available at that time. In fact, poly(DCPD) was classically obtained using early transition-metal catalysts and the observation that ruthenium complexes are suitable catalysts opened the field of poly(DCPD) chemistry to the incorporation of filler materials and additives. Additionally, this complex, either preformed or formed *in situ*, exhibits high catalytic activity towards the RCM synthesis of small to large, functionalized cyclic olefins when heated to reflux in CH_2Cl_2 and exposed to neon light or strong daylight. [7]

De Clercq *et al.* reported on the incorporation of a bidentate κ^2-(*O*,*N*) Schiff base ligand in complex **5**. Results showed that these complexes exhibit rather low activity towards the ROMP of norbornene and cyclooctene but high activity is observed after chemical activation with TMSD. [8]

The isolation of N-heterocyclic carbenes in the early nineties [9]

marked an important milestone in late transition-metal organometallic chemistry. When incorporated in olefin metathesis catalysts, they function as strong electron-donating and sterically demanding phosphine mimics. Delaude *et al.* reported on the visible light-induced ROMP of cyclooctene with complexes **5** (Figure 3.1, L = IMes = 1,3-dimesitylimidazol-2-ylidene, Dipp = 1,3-di(2,6-diisopropylphenyl)-imidazol-2-ylidene). [10] These complexes exhibited high catalytic activity, even at room temperature and without the addition of TMSD as a carbene precursor. However, the need for photochemical activation was indisputably evidenced from experiments in darkness (22%), normal daylight (93%), irradiation with neon light (99%) or with a 250 W incandescent light bulb (>99%), being of possible interest when thinking of dental applications or surface modification. Surprisingly, these complexes exhibit no photochemical activity for the RCM of diethyl diallylmalonate. Although the mechanism of ruthenium alkylidene formation remained elusive, UV-Vis and NMR spectroscopy confirmed the release of the *p*-cymene-ligand (absorption at 450 nm) after visible light irradiation of the complex in PhCl, thus forming a highly coordinatively unsaturated ruthenium complex.

Buchmeiser *et al.* studied complexes **5** (Figure 3.2, L = PPh_3, PCy_3, IMes, SIMes) where the chlorides are replaced by trifluoro acetate ligands and subjected them to thermally induced polymerization of enantiomerically pure norbornene derivatives. [11] *Exo*-norbornene derivatives were polymerized faster than their *endo*-congeners, but the non-quantitative nature of the initiation of the ruthenium precatalysts yielded non-"living", though controlled polymerizations. Replacement of the chlorine ligands by trifluoro acetate ligands, as well as the incorporation of N-heterocyclic carbene ligands, furthermore proved to be substantial for the straightforward *in situ* formation of the active catalyst. In addition, quantum chemical calculations supported the idea that the active catalyst is formed upon coordination of norbornene and a subsequent 1,2-H-shift, and allowed for rationalization of discrepancies in catalytic activities observed.

Hafner *et al.* studied the use of cationic (half-)sandwich Ru^{II} and Ru^{II} nitrile complexes as potential photoinitiators since they are known to possess a high activation energy barrier towards the dissociation of

an arene or nitrile ligand and therefore were suspected to exhibit high thermal latency. Indeed, a mechanistic study revealed the release of arene ligands upon UV irradiation to form solvated Ru^{II} complexes, $[Ru(solvent)_6]_2^+$, which are ought to be responsible for high polymerization activity. A similar study using ^1H NMR spectroscopy for the ruthenium nitrile complexes in D_2O revealed the release of acetonitrile from $[Ru(NC{-}Me)_6]_2^+$ to form $[Ru(NC{-}Me)_{6-x}(D_2O)_x]^{2+}$ complexes. Experimental results illustrated that indeed only weak activity was observed for the thermally induced ROMP of norbornene and 7-oxa-2-norbornene-6,7-dicarboxylic acid dimethyl ester in ethanol using different nitrile complexes. However, activity of the complexes increased effectively upon irradiation with a 200 W Hg lamp. More importantly, ruthenium sandwich complexes exhibited no thermal activity at all, but proved to be highly active catalysts upon short irradiation. Analysis of the polymers thus obtained revealed high PDI's (typically higher than 2.0) for both ruthenium (half-)sandwich and nitrile complexes, basically indicating that the polymerization is not "living". Additionally, their cationic character limited their applicability to polar solvents such as water and ethanol. [12, 13]

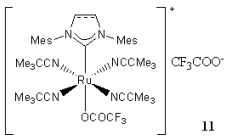


Figure 3.2: A latent ruthenium NHC complex bearing coordinatively stable nitrile ligands.

Only recently, Buchmeiser *et al.*, [14] elaborating the initial efforts of Hafner *et al.*, reported on the incorporation of an N-heterocyclic carbene ligand (Figure 3.2, NHC = IMes, SIMes) in cationic Ru^{II} nitrile complexes, illustrating the use of such complexes as photoactive initiators for ROMP of functionalized norbornenes, DCPD and 1,5-cyclooctadiene. Analogous to the results obtained by Hafner *et al.* no catalytic activity was observed upon mixing these photocatalysts with cyclic olefins (after 24 h at room temperature). However, a 308 nm light source clearly induced catalytic activity when exposed to the catalyst/monomer mixtures in $CHCl_3$. Interestingly, yields increased significantly when a 254

nm Hg lamp was used instead. Furthermore, the newly explored methodology proved applicable for the surface functionalization of glass plates with poly(DCPD). A quantum chemical study provided mechanistic understanding of the photo-formation of the ROMP-active specie. Thus, it was explained that in accordance to mechanistic studies by Hafner *et al.*, irradiation induces the dissociation of one ^{t}Bu−CN ligand. Although, either dissociation of a second ^{t}Bu−CN ligand or coordination of a monomer proved to be energetically unfavored, excitation to the triplet state by UV irradiation weakens the Ru-N bond and consequently enables decoordination of a second ^{t}Bu−CN. Coordination of an olefinic substrate molecule to form a π-complex and subsequent 1,2-H-shift allows for the formation of the ruthenium alkylidene and consequent polymerization. In addition, theoretical studies were supported by laser flash and steady-state photolysis experiments.

3.3 Well-defined latent catalysts

A major shortcoming of ill-defined catalyst systems is their lack of initiation efficiency which results in broad molecular weight distributions of the obtained polymers and the need for high catalyst loadings which limits commercial application. Polymerizations with ill-defined latent catalysts can therefore not be considered as "living" polymerizations. However, the advent of well-defined, highly active ruthenium catalysts and the fact that they were commercially available, urged the development of latent catalysts incorporating a ruthenium alkylidene motif. Different approaches towards the design of well-defined latent catalysts are presented in Figure 3.3. [15]

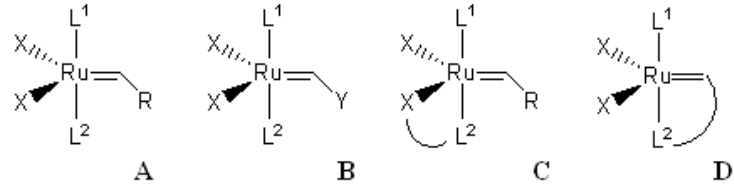


Figure 3.3: Modular approaches to latent well-defined ruthenium catalysts.

A first class of catalysts retain the classic morphology of Grubbs first

and second generation catalysts (Class A). When applying heteroatom substituted carbene ligands, so-called Fisher carbenes, no catalytic activity is observed. However, these catalysts can be activated thermally or photochemically (Class B). Catalysts with motif C or D make use of the chelate effect to reduce catalysts initiation. When activated, class C catalysts open the coordination site by the dissociation of L^2. Although this approach can stabilize the catalyst towards decomposition, a competitive coordination between the dangling ligand and olefinic substrates can reduce the propagation speed. Such a competition is avoided when using catalysts with motif D.

3.3.1 Latent Grubbs type catalysts

In the search for the isolation of highly reactive, 14-electron ruthenium alkylidenes intermediates, Grubbs *et al.* reported on coordinatively unsaturated, trigonal pyramidal ruthenium complexes after exchange of both chlorine ligands in first generation Grubbs catalyst by more π-donating and sterically demanding tertiary alkoxide ligands (Figure 3.4). [16] Although being highly electron-deficient, these complexes exhibit no catalytic activity for the RCM of diethyl diallylmalonate at room temperature, and only moderate activity is obtained after 12-96 h at 60℃. Furthermore, substantial catalyst decomposition is observed after entering the catalytic cycle. However, catalysts **12** can be triggered by the addition of 2 equiv of hydrochloric acid, yielding almost quantitative conversions for the RCM of diethyl diallymalonate at room temperature after about 1 h. The idea that HCl could protonate the alkoxide moieties with subsequent release of those ligands and post-end coordination of the two chlorines to ruthenium was supported by ^{19}F NMR spectroscopy and the fact that Grubbs 1^{st} generation catalyst was regenerated upon consecutively acid (2 equiv) and PCy_3 (1 equiv) addition.

In 2007, P'Pool and Schanz reported on the use of Grubbs first generation catalyst in a reversible inhibition/activation sequence by readily available N-donors such as methyl imidazole (MIM), dimethylamino pyridine (DMAP) and pyridine as inhibitors and phosphoric acid as activator. [17] A high degree of latency was found since no activity was

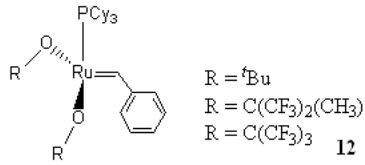


Figure 3.4: A latent tetra-coordinate ruthenium benzylidene catalyst.

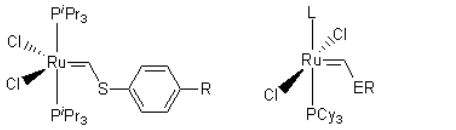
observed after 24 h at room temperature for the ROMP of 50 equiv of cyclooctene upon addition of 1-5 equiv of MIM or DMAP, while successfully reactivated upon addition of an excess of H_3PO_4. In addition, a dramatic increase of initiation rate was found for the reactivated complexes compared to non-inhibited Grubbs first generation catalyst. Interestingly, an in-depth NMR investigation allowed for studying the equilibria governing the inhibition and reactivation processes and the experimental results observed could thus be clarified.

In another study focused on Grubbs first generation catalyst, Kunkely and Vogler [18] have shown that UV-Vis irradiation of the square pyramidal complex induces a geometrical distortion which increases sterical hindrance between phosphine and chlorine ligands, thus facilitating phosphine dissociation. Such a methodology was recognized to be of potential interest for less efficient or latent first generation Grubbs catalyst analogues.

3.3.2 Catalysts bearing Electron-Rich Carbene Ligands

Although heteroatom substituted ruthenium carbenes were initially believed to be inactive for olefin metathesis reactions, van der Schaaf *et al.* illustrated that ruthenium complexes bearing arylthio substituted carbene ligands, **13** (Figure 3.5), efficiently polymerized 12,000 equiv DCPD, with gel times ranging from 10-12 min, thus allowing for adequate handling of the monomer/catalyst mixture in contrast to Grubbs first generation catalyst. [19] Additionally, reactions were completed within 60 seconds by application of these catalysts in a plate polymerization experiment using a preheated mold at 60°C and monomer/catalyst ratio's of 4,700/1, allowing for fast polymerization and high exotherms,

a semiquantitative indication for conversion.



13 R = H, R = Me

14 L = PCy$_3$, IMes, SIMes; ER = OEt, SEt, SPh, N(carbazole), N(pyrrolidinone)

Figure 3.5: Ruthenium Fischer-carbenes as latent metathesis catalysts.

This approach was further elaborated by Grubbs *et al.* with the synthesis of complexes **14** (Figure 3.5). [20] These complexes proved applicable for the ROMP of norbornene at room temperature, albeit with significantly decreased initiation rates; $\tau_{1/2}$ ranges within minutes whereas $\tau_{1/2}$ ranges within seconds for comparable complexes bearing alkylidene or benzylidene ligands, thus allowing for rigorous mixing of catalyst and monomer. In contrast to the IMes and SIMes (4,5-dihydro-1,3-dimesitylimidazol-2-ylidene) substituted catalysts, ROMP of the more challenging COD revealed only moderate to low activity for the phosphine bearing analogues, even when heated to 60°C. Interestingly, all complexes were active for the RCM of diethyl diallylmalonate and a distinct reactivity trend was concluded; activity of (L)(PCy_3)Cl_2Ru=C(H)ER catalysts increased in the series E = C > N > S > O.

3.3.3 Catalyst bearing Dangling Ligands

Although application of the discussed catalysts exhibits notable advantages for certain applications, efforts were directed towards the exploration of different catalyst designs which are more readily altered. In this discussion, the use of hemilabile ligands is of major importance. Hemilabile ligands occupy two or more coordination sites at the metal center *via* donating groups with preferably significantly different steric and electronic properties. Thus, one coordinating group can dissociate from the catalytically active center to yield a coordination vacancy

for substrate molecules while the other donor group remains attached to the transition-metal and consequently stabilizes the reactive species. Furthermore, steric and electronic properties of these ligands are easily varied over a wide range by the proper choice of the constituting coordinating groups, thus allowing for advanced fine-tuning of the properties of the precatalyst.

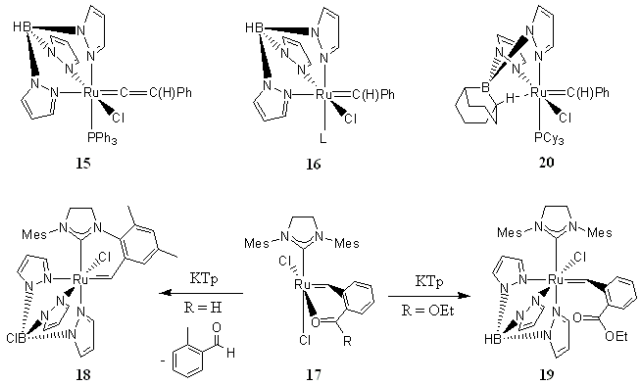


Figure 3.6: Ruthenium complexes bearing a Tp or Bp ligand.

In 1998, Ozawa *et al.* [21] and Grubbs *et al.* [22] described the use of a tridentate, 6-electron donating, anionic hydrido tris(pyrazolyl)borato ligand (κ^3-Tp) to enhance thermal stability of rutheniumvinylidene, **15**, and -benzylidene, **16**, complexes respectively (Figure 3.6). In contrast to Cp ligands, which are also 6-electron, anionic ligands occupying three coordination sites, these Tp ligands are more sterically demanding and stronger electron-donors. The 18-electron vinylidene ruthenium complex, **15**, described by Ozawa exhibited moderate catalytic activity towards the ROMP of norbornene, however, long reactions times (72 h) and high temperatures (80℃) were required. More importantly, these complexes were shown to be triggered by the addition of 3 equiv $BF_3 \cdot Et_2O$, allowing to achieve the same results at only 40℃. The incorporation of a Tp ligand in the first generation Grubbs catalyst, **2**, straightforwardly affords complex **16** (Figure 3.6, L = PCy_3), which was found not to facilitate the RCM of diethyl diallylmalonate or ROMP of norbornene, even after several days at 70℃. Although the addition of phosphine scavenging agents such as HCl, CuCl or $AlCl_3$ yields higher

catalytic activity for RCM of diethyl diallylmalonate, the use of complex **16** (L = PCy_3) was restricted by the high catalyst loading required (20 mol%).

Following the efforts of Ozawa and Grubbs, Slugovc *et al.* tried to implement Tp ligands in κ^2-(C,O) complexes **17** with a *cis*-dichloro configuration (Figure 3.6). [23] Interestingly, addition of KTp to complex **17** (R = H) led to the formation of the κ^2-(C,C)-κ^3-(N,N,N) complex **18**, through a double C-H activation of the *ortho*-methyl substituents of the SIMes ligand and the simultaneous elimination of 2-formylbenzylidene ligand as 2-methylbenzaldehyde. Additionally, the proton in the Tp ligand appeared to have been substituted by a chlorine which was originally coordinated to ruthenium. In case of **17** (R = OEt), the rather expected κ^3-(N,N,N) complex **19** was obtained. Monitoring the catalytic activity of complexes **18**, **19** and **16** (L = SIMes) towards the ROMP of norbornene-2,3-dicarboxylic acid diethyl ester using DSC revealed that high '*switching temperatures*' (the temperature at which the initiation of the polymerization reaction is observed) were reached (109°C, 128°C and 138°C for catalysts **18**, **19** and **16** (L = SIMes), respectively).

Another approach, reported by Patel *et al.*, involved the incorporation of an anionic, bidentate bis(pyrazolyl)borate ligand (κ^2-Bp) in Grubbs first generation catalyst, **2**. [24] Interestingly, single-crystal structure determination revealed the presence of an agostic interaction from the Bp ligand to ruthenium. Furthermore, complex **20** exhibited high thermal stability in solution, even in acetone; no indication of decomposition was observed over several weeks. When subjected to catalyst **20**, no traces of RCM of diethyl diallylmalonate were detected after 1 h in toluene at 80°C, and only moderate conversion (36%) was obtained after 1 h at reflux. Addition of CuCl increased the catalytic activity substantially (81%), but the need for high catalyst loadings (8 mol%) render this methodology unfavorable.

As can be concluded from the experimental results discussed above, Tp- and Bp-type ligands induce a high degree of catalyst stability and latency towards RCM of dienes and ROMP of strained cyclic olefins. However, thermal activation of Tp- and Bp-based catalysts proved to be difficult, an inconvenience often remedied by the use of higher cata-

lyst loadings. For these reasons, these type of complexes are unsuitable candidates as potential latent catalysts, hence other approaches are required.

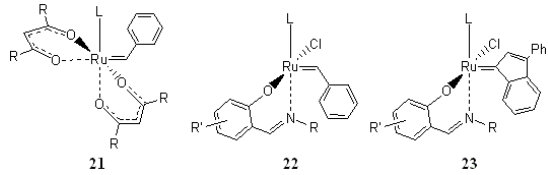


Figure 3.7: Ruthenium complexes bearing bidentate κ^2-(O,O) and bidentate κ^2-(O,N) ligands.

In this respect, a series of latent olefin metathesis catalysts bearing bidentate κ^2-(O,O) and κ^2-(O,N) ligands were synthesized (Figure 3.7). Complex **21** (Figure 3.7, L = PCy_3), straightforwardly obtained from first generation Grubbs catalyst, **2**, and 2 equiv Tl(alkyl-acac), proved to be inactive for the solvent-free polymerization of DCPD and the polymerization of 7-oxanorbornene-2,3-dimethoxymethyl in methanol at room temperature. However, addition of organic or inorganic acids, *e.g.* hydrochloric acid, enabled reactivation of the catalyst and reactions were completed within minutes, basically surpassing the activity of the parent complex **2**. It was furthermore illustrated that complex **21** (Figure 3.7, L = PCy_3, SIMes) is readily activated upon irradiation of a catalyst/monomer mixture containing a photoacid generator and was found applicable in RCM and ROMP. [25] The authors noticed that such behavior could be of supreme interest in a Reaction Injection Molding process where the catalyst can be stored together with the monomer while a second monomer stream contains acid to activate the catalyst.

In another approach towards rationally designed thermally stable olefin metathesis catalysts, efforts were directed towards the development of an O,N-bidentate Schiff base ligated Ru-carbene catalysts. [26] These ligands are especially feasible for fine-tuning of ligand parameters since their steric and electronic environment can be easily tailored by the proper choice of aniline and salicyladehyde. The catalysts thus obtained proved to exhibit high air and moisture stability. Furthermore, the authors noticed that the catalytic activity of these catalysts for the RCM

of diethyl diallylmalonate was substantially lower than that of the first generation Grubbs' catalyst, **2**, but that *the reactivity increases dramatically at higher temperatures.* In addition, high activity was observed for the RCM of diallylamine hydrochloride in methanol (catalyst loading: 5 mol%, 40°C, 12 h, 95% yield).

This type of catalysts was further elaborated by Verpoort *et al.*, incorporating an N-heterocyclic carbene which generally accounts for enhanced thermal stability combined with a definite increase of catalytic activity (Figure 3.7, **22**, L = SIMes). [27] It was shown the such complexes are extremely inactive at room temperature towards the polymerization of low-strain, cyclic olefins such as 1,5-cyclooctadiene and can be thermally activated to yield high activity for the bulk-polymerization of DCPD. [28] Quantitative conversions were enabled for ROMP of COD mediated by various Schiff base catalysts; the high temperature (90°C) and long reaction times (4 - 24 h) required illustrate that these catalysts combine latency and high thermal stability. Additionally, activation of the catalyst was facilitated by the addition of soft Lewis acids, *e.g.* $HSiCl_3$, [29] yielding extremely high catalytic activity for the ROMP of COD and TON's up to 630,000. It was reasoned that coordination of the Lewis acid to the N of the Schiff base ligand yields a vacancy at the ruthenium center thus allowing for ROMP, while the dangling phenoxide moiety was believed to prevent or significantly reduce bimolecular decomposition of the activated catalyst. Analogous complexes bearing an indenylidene, **23** (Figure 3.7, L = PCy_3, SIMes) [30], or allenylidene [31] ligand were also found to exhibit high thermal stability combined with high activity upon thermal or acid activation in various challenging olefin metathesis reactions.

A pyridinyl-alcoholato ligand (Figure 3.8, **24**) can be regarded as a 5-membered ring alternative to Schiff base ligands in complexes **22**. Their use was first described by Herrmann *et al.* who reported on enhanced activity for complex **24** (Figure 3.8, L = ICy) for ROMP of cyclooctene and norbornene upon thermal activation. [32] Vosloo *et al.* further elaborated this approach for the self-metathesis of 1-octene by catalysts **24** (Figure 3.8, L = PCy_3; L = SIMes) and concluded on an enhanced temperature dependent selectivity. [33] Hahn *et al.* focused on improving the catalyst design by substituting the halide ligands by

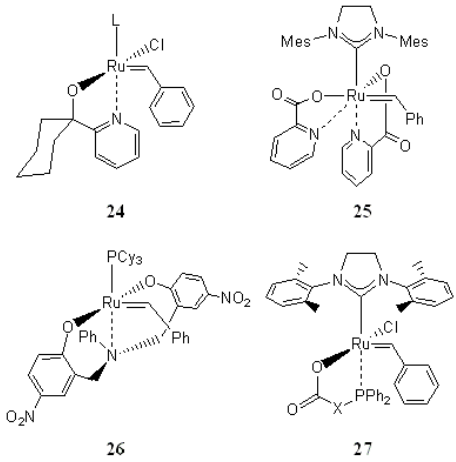


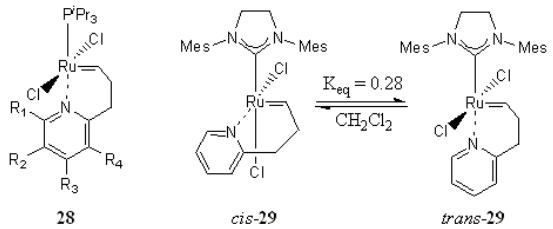
Figure 3.8: Latent ruthenium catalysts bearing chelating alkoxy and aryloxy ligands.

bidentate pyridinecarboxylato ligands (Figure 3.8, **25**). [34] This complex showed no activity for the RCM of diethyl diallylmalonate. In contrast, addition of 2 equiv of hydrochloric acid yielded quantitative conversion within 2 hours. Mass spectroscopy elucidated that either one or both Ru-O bonds can be cleaved. When targeting the RCM of diallylamine hydrochloride in methanol, the precatalyst not only proved to be stable in this solvent for weeks, in contrast to second generation Grubbs catalyst, **4**, which exhibits only limited lifetime, but also a 70% conversion was attained within 12 h at 40°C upon addition of hydrochloric acid. Alternatively, Jensen *et al.* reported on the use of chelating κ^3-(O,O,N) amine ligands (Figure 3.8, **26**) in RCM of diethyl diallylmalonate. [35] They concluded on a remarkably low room temperature activity of these precatalysts but illustrated the use of Brønsted acids, such as HCl or H_2SO_4 to activate the catalyst. Zhang *et al.* elaborated the possibility of a bidentate phosphinocarboxylato ligand, envisioning the dissociation of the phosphine from the ruthenium at elevated temperatures to initiate olefin metathesis while the carboxylate group remains coordinated to the ruthenium center (Figure 3.8, **27**). [36] While these complexes are straightforwardly obtained from reaction of a second generation Grubbs type complex with the corresponding sodium phosphine-carboxylates, they exhibit medium to high activity for the RCM of diethyl diallyl-

malonate at 40℃ and 70℃. Especially complexes with X = CH_2 or *ortho*-C_6H_4 yielded a good combination of high reactivity and catalyst stability at elevated temperatures. Moreover, these complexes excel second generation Grubbs catalyst, **4**, for the RCM of diallylmalononitrile, a challenging RCM substrate since the cyano-group is known to deactivate olefin metathesis catalysts. Additionally, isomerization of substrate and product is strongly reduced since the phosphine ligand protects the catalytically active center from decomposition.

3.3.4 Catalysts bearing Chelating Alkylidene Ligands

Catalysts bearing so-called 'dangling' ligands exhibit desirable characteristics; that is, low to negligible room temperature activity, high thermal stability of the catalysts and simple activation either through addition of Brønsted or Lewis acids or through application at higher temperatures. When applied in ROM polymerization, however, one can prefer the cleavage of the chelating ligand to prevent its competitive coordination and thus allowing for a fast propagation after retarded initiation. Therefore, a class of ruthenium catalysts bearing chelating alkylidene ligands has been developed and gains increasingly attention.



28 *cis*-**29** *trans*-**29**

Figure 3.9: N-heterocyclic alkylidene ligands for controlled polymerization reactions.

A first important report in this respect was the implementation of a substituted 2-pyridylethanyl alkylidene ligand by van der Schaaf (Figure 3.9, **28**). [19] It was clearly shown that variations in substitution pattern of the pyridine ligand of these catalysts influences gel times and T_gs of the obtained polymers during the bulk-polymerization of DCPD. Unfortunately, activities of the reported complexes were undesirably low;

restricted to 12,000 equiv DCPD. Consequently, N-heterocyclic carbene ligands, known to induce higher catalytic activities, were adopted in the catalyst design by Schrodi *et al.* (Figure 3.9, **29**). [37, 38] Interestingly, the corresponding complex exhibited an isomerization between the *cis*- and *trans*-dichloro configuration with a solvent dependent equilibrium (78:22 ratio in CD_2Cl_2). More importantly, both isomers could be isolated and the *cis*-isomer displayed a distinctly higher room temperature latency, *i.e.* towards the RCM of diethyl diallylmalonate and the ROMP of DCPD. It was reasoned that decoordination of the pyridine moiety, the initial step towards the formation of the catalytically active 14-electron species, is more facilitated by the stronger *trans*-influence of the N-heterocyclic carbene ligand in the *trans*-isomer *vs.* that of the chlorine ligand in the *cis*-isomer. In addition, mixtures of these isomers allowed for tuning of the induction period in bulk-polymerizations of DCPD, while high catalytic activities were availed; up to 40,000 equiv of DCPD were successfully converted.

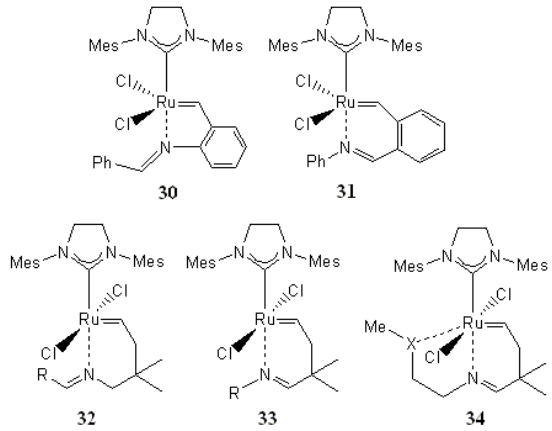


Figure 3.10: Latent ruthenium catalysts with a Schiff base alkylidene ligand.

In search of thermally switchable catalysts which allow for further fine-tuning, Slugovc reported on the synthesis of 5- and 6-membered, bidentate Schiff base benzylidene ligands, taking advantage of synthetically modular Schiff base ligands. [15] One member of each family was synthesized (see Figure 3.10, **30**, **31**) and proved to be stable in solution (solvent = $CDCl_3$) at room temperature for at least 2 months

and only moderate activity was observed towards the polymerization of norbornene-2,3-dicarboxylic acid diethyl ester; conversions were 20% and 29% for the polymerization of 50 equiv norbornene-2,3-dicarboxylic acid diethyl ester with catalysts **30** and **31**, respectively, after 15 days. Additionally, the '*switching temperature*' for these catalysts was determined by means of DSC at 48°C and 55°C for the 5- and 6-membered Schiff base catalysts **30** and **31**, respectively. Alternatively, endo- and exocyclic Schiff base alkylidene ligands were applied by Grubbs *et al.* as a structural motif towards latent catalysts (Figure 3.10, **32** and **33**). [39] Although the exocylic Schiff base catalysts did not behave like latent catalysts, performing well at room temperature for the RCM of diethyl diallylmalonate, endocyclic imine catalysts exhibited a distinctly reduced room temperature activity, thus confirming their latent character. The authors further illustrated the versatility of their approach; *i.e.*, when subjected to the polymerization of DPCD, a more pronounced induction of the catalyst was found in the series R = Cy, ^{i}Pr, Ph, without observable influence on the overall catalyst activity. Furthermore, it is worth noting that this particular approach allowed for the straightforward synthesis of various latent catalysts with a 3-point chelates. Indeed, latency of type **34** catalysts decreases in the series X = S > > O ∼ CH_2 (Figure 3.10).

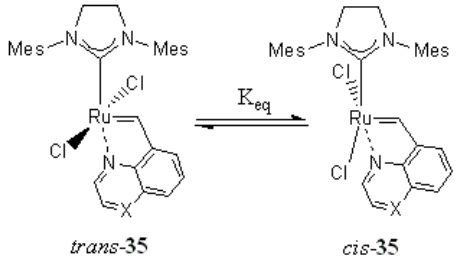


Figure 3.11: Ruthenium quinoline and quinoxazoline complexes.

Grela *et al.* envisaged that more rigid chelates will enhance the catalysts latency and consequently reported on the latent properties of quinoline **35** (Figure 3.11, X = CH) and quinoxaline **35** (Figure 3.11, X = N) alkylidene complexes. [40] In analogy to the 2-pyridylethanyl alkylidene complexes reported by Grubbs (Figure 3.9, **29**), these air sta-

ble complexes exhibited *cis*/*trans*-isomerization, and *cis*-isomers were less active when applied in RCM or enyne metathesis reactions. Additionally, these complexes were found to be excellent latent catalysts for ROM polymerizations of various norbornene derivatives, no activity was observed for at least 2 weeks at room temperature and the catalysts exhibited high activity after thermal activation. [41]

Finally, we want to conclude with some examples of latent catalysts specifically designed for application in organic synthesis.

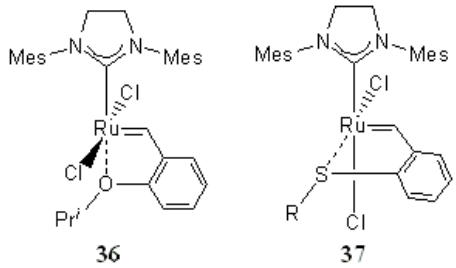


Figure 3.12: A thermally latent ruthenium sulfur-alkylidene catalyst.

A first important achievement in this respect is the development of a S-containing Grubbs-Hoveyda-type catalyst by Lemcoff *et al.* (Figure 3.12, **37**). [42] In contrast to the Grubbs-Hoveyda catalyst, **36**, its sulfer-containing congener has a *cis*-dichloro arrangement comparable to previous reports by Grubbs, Slugovc and Grela (*vide supra*). Both of these complexes exhibit high room temperature stability, but contrary to **36**, a highly active olefin metathesis catalyst often used for the synthesis of small or complex molecules, catalyst **37** displays a reversible *thermoswitchable behavior*; high activity is obtained for the RCM of diethyl diallylmalonate upon heating to 80°C, but activity drops upon cooling the reaction mixture to room temperature. In addition, variation of the S-substituent allowed for altering the activation temperature. [43]

Grela *et al.* further elaborated the Grubbs-Hoveyda catalyst motif and introduced acid-base sensitive functionalities on the isopropoxybenzylidene ligand **38**, **39** (Figure 3.13). [44] Activation by Brønsted and Lewis acids, respectively, induced a strong electron-withdrawing effect,

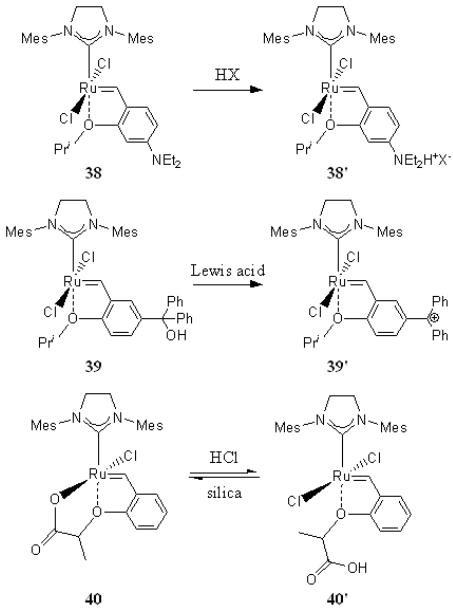


Figure 3.13: Latent Hoveyda-type ruthenium catalysts.

thus destabilizing the Ru-O bond and facilitating decoordination of the oxygen atom. In addition, catalyst **38** was straightforwardly immobilized on a polymeric phase containing Brønsted acidic functionalities and allowed for high catalytic activity with minimal ruthenium contamination of the reaction products, a requisite when focusing on the synthesis of biologically active compounds. In another report, Grela described the synthesis of a tridentate κ^3-(C,O,O)-complex, **40** (Figure 3.13) and its use as a chemically switchable catalyst with high regeneration efficiency. [45] Catalyst **40** suffers from a strongly diminished activity, but the carboxylate can be cleaved with hydrochloric acid, thus allowing for high catalytic activities. More importantly, purification of the reaction mixture on silica gel allowed for the selective retention of **40'** (Ru contamination in the reaction products were as low as 48 ppm), while subsequent washing of the silica gel with ethyl acetate yielded **40** in 95%.

3.4 Conclusions

We have described the rational design, study and application of one- and multicomponent, ill- and well-defined latent ruthenium-based olefin metathesis catalysts. These catalysts are of prominent importance for Ring-Opening Metathesis Polymerizations of low- and high-strained cyclic olefins, where they allow for rigorous mixing of monomer and catalyst without concomitant gelation or microencapsulation of the precatalyst, but they are also promising for applications in synthetic organic chemistry, where they give support to the idea of an olefin metathesis *catalyst that lives forever*.

It is now well established that ill-defined catalysts form an alkylidene ligand *in situ* after addition of a carbene precursor or coordination of an olefin to ruthenium and subsequent 1,2-H-shift. Well-defined catalysts bear an alkylidene ligand in their coordination sphere and are straightforwardly isolable. These catalysts are basically inactive towards metathesis of olefins either induced by inhibition, by heteroatom substituted carbene ligands or by chelating ligands occupying the active site of the catalyst, but they can be triggered upon addition of Lewis or Brønsted acids or are activated at higher temperatures.

Regardless of the increasing number of reports on latent ruthenium olefin metathesis catalysts and the advances that are made along these lines, we can state that the development of ill- and well-defined catalysts remains challenging.

Finally, we can conclude that although application of well-defined latent ruthenium olefin metathesis catalysts is often restricted to the advanced organometallic chemists with a profound interest in polymer chemistry, commercialization of these catalysts will most probably accelerate their use in high profile applications.

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Part II

Results and Discussion

4

Ruthenium Indenylidene Complexes bearing a saturated N-Heterocyclic Carbene: synthesis and catalytic investigation in Olefin Metathesis reactions

4.1 Introduction

In the quest for better catalysts, the class of Ru-indenylidene [1–6] complexes with different ancillary ligands has proven to be a class of straightforwardly accessible ruthenium alkylidenes, and their catalytic activity has elaborately been compared to the ruthenium-benzylidene Grubbs catalysts (**1a-c**). [7–12] (Figure 4.1)

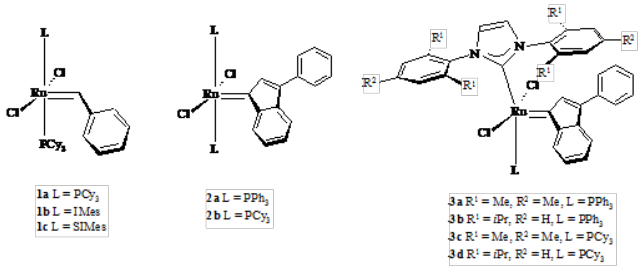

Figure 4.1: 1^{st} and 2^{nd} generation Ru-benzylidene (**1**) and -indenylidene (**2**, **3**) precatalysts.

Introduction of a sterically demanding N-heterocyclic carbene ligand into ruthenium complexes was an important milestone on the metathesis road of success. The logical approach to further advancement in the indenylidene series along these lines, *i.e.* ligand exchange in **2** with an unsaturated N-heterocyclic carbene moiety (IMes and IPr), was first achieved by Nolan [1] through synthesis of complexes **3a-d**. It was evidenced that these ruthenium catalysts display higher thermal stability than their benzylidene counterparts. In addition, good catalytic activities in ring-closing metathesis reactions [1, 13] and ring-opening metathesis polymerization [5, 14] have been reported. Among olefin metathesis catalysts, the combined high catalyst stability and activity is a unique beneficial feature of indenylidenes. In view of the improved performance of SIMes- *vs.* IMes-Ru-benzylidene catalysts, it came to our attention that no reports were published on the parent complexes bearing a saturated N-heterocyclic carbene ligand (**5**).

Here, we describe the synthesis of five-coordinate ruthenium indenylidene complexes (**5**, **6** and **7**) bearing a saturated N-heterocyclic carbene ligand as viable precatalysts, performing efficiently in the ring-closing metathesis of α,ω-dienes and the ring-opening metathesis polymerization of cycloolefins. To determine the activity of this class of indenylidene catalysts relative to the analogous Grubbs catalysts in classic olefin metathesis reactions, the benzylidene family was used as a bench mark and activities were compared mutually. We believe that such an examination is relevant for the understanding of the importance of the carbene unit and the synergetic effect of ancillary ligands around the

Ru-centre.

4.2 Results and Discussion

4.2.1 Catalyst synthesis

While **3c** is readily obtained from **2b** and the free IMes carbene in hot hexane, [1] an analogous approach is to be avoided in the case of **5**. Because of the comparatively higher air- and moisture sensitivity of the *unmasked* saturated carbene, SIMes, an *in situ* generation protocol is to be used instead. An overview of well-established strategic approaches towards the *in situ* formation of the N-heterocyclic carbene is given in Figure 4.2. Most commonly, KO^tBu is added to a solution of the $SIMesH^+Cl^-$ salt. The alcohol adduct thus formed decomposes at elevated temperature to release the *unmasked* N-heterocyclic carbene *in situ*. Alternatively, potassium bis(trimethylsilyl)amide (KHMDS) is used to deprotonate the $SIMesH^+Cl^-$ salt and form the free N-heterocyclic carbene. It was also shown that this approach can be applied in presence of an organometallic precursor, *i.e.* Grubbs 1^{st} generation catalyst. [**?**] A third approach uses imidazolinium-2-carboxylates that form NHC-metal complexes upon release of CO_2. [15] 2-(trichloromethyl)- and 2-(pentafluorophenyl)imidazolidines offer a practical alternative since they are readily soluble in common organic solvents and they easily decompose upon gentle heating with the release of the volatile $CHCl_3$ or C_6F_5H. Another well-established method is the transmetallation of Ag-NHC complexes.

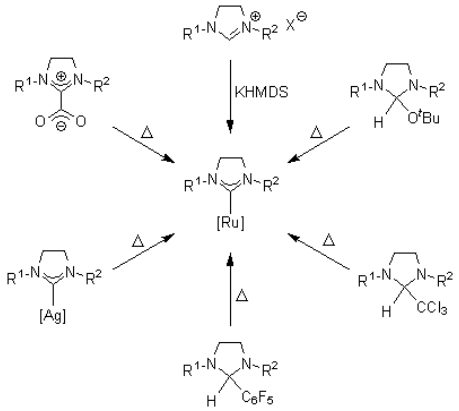

Figure 4.2: Synthetic pathways to *in situ* formed imidazolin-2-ylidenes.

From the methodologies described above, the application of KO^tBu proved to be unsuccessful for the synthesis of **5** from **2b** in terms of incomplete conversion of the starting complex. Analogously, KHMDS allows for the deprotonation of $SIMesH^+Cl^-$ but conversion of the starting compound was limited. Eventually, the most suitable method for converting **2b** into its 2^{nd} generation analogue appeared to be the "one-pot" thermal decomposition of the chloroform adduct **4** (Figure 4.3).

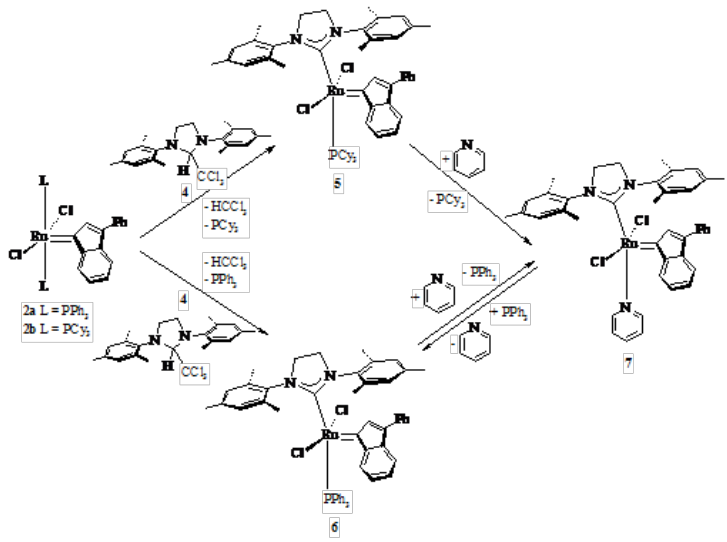

Figure 4.3: Synthetic pathways to 2^{nd} (**5**, **6**) and 3^{rd} generation Ru indenylidene (**7**) metathesis catalysts.

Progress of the reaction was monitored by ^{31}P NMR following the increase of a new, upfield peak at δ 27.0 ppm, *vs.* δ 33.5 ppm for the starting complex **2b**. Complete reaction was observed within 1.5 h and the complex was isolated in excellent yield (82%). Of note, a rather large excess (2 equiv) was required in order to obtain full conversion of the starting compound. In agreement with the proposed structure, NMR spectra showed peaks characteristic for the indenylidene unit (^{1}H NMR: doublet at δ 9.13 ppm (**5**), *vs.* δ 9.08 ppm in **2b**, and singlet at δ 7.81 ppm (**5**), *vs.* δ 7.80 ppm in **2b**) and the imidazolin-2-ylidene ligand (^{1}H NMR: complex multiplet at δ 3.41-3.12 ppm, and ^{13}C NMR: doublet at δ 216.34 ppm for the carbene-*C*). (Figure 4.4)

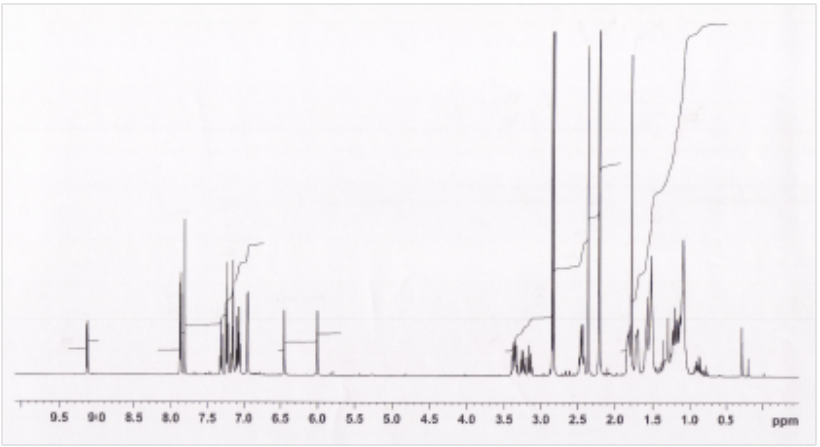

Figure 4.4: ^{1}H NMR spectrum of complex **5**.

Synthesis of **7** proceeded easily by treatment of **5** with an excess of pyridine. However, while for the synthesis of Grubbs third generation catalyst **8** the phosphine ligand in **1c** was readily displaced by pyridine (*via* an associative mechanism [16]), ligand substitution in the SIMes-indenylidene series proved to be significantly slower. The indenylidene complex, **7**, was isolated in good yield (70%) as a clear brown powder. Different from the Grubbs (**8a**, **9**) [16, 17] and Nolan (**10**) [18] complexes which incorporate two pyridine ligands (Figure 4.5), the ^{1}H and ^{13}C NMR spectra indicated undoubtedly coordination of only one pyridine. Elemental analysis confirmed this statement indisputably. Unlike **8a** and **8b**, complex **7** is stable in dichloromethane (clear red solution) for several days, at room temperature. This enhanced thermal stability is likely a result of the steric and electronic robustness of the indenylidene ligand, which prevents dimerization, the initial step towards catalyst decomposition. [19] This robustness is a unique feature for a third generation catalysts while the labile pyridine ligand is an asset for fast initiation in ROM polymerizations [20].

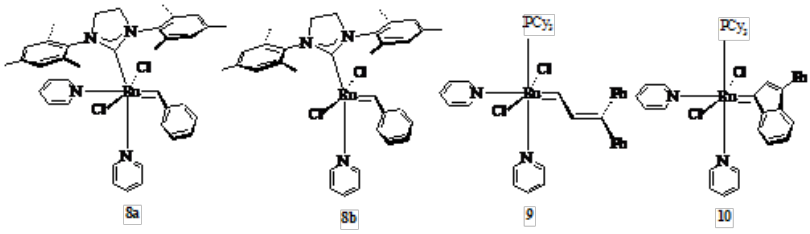

Figure 4.5: Pyridine containing Ru-precatalysts.

Complex **6** was obtained from **7** by simple ligand exchange and isolated in 89% yield as a clear red powder. In addition, it was straightforwardly obtained from reaction of **2a** with **4** (1 h in refluxing THF). The high thermal stability of **2a** prevents decomposition under these conditions and thus provides a cheap and economical way to this second generation type catalyst.

4.2.2 Catalytic activity

Challenged to establish how the properties of the indenylidene ligand translate into catalyst activity, we investigated the catalytic behavior of the indenylidene complexes **2b**, **5**, **6** and **7** for two standard reactions, the ring-opening metathesis polymerization of 1,5-cyclooctadiene (COD, **11**) (Figure 4.6) and the ring-closing metathesis reaction of diethyl diallylmalonate (**13**) (Figure 4.11), usually employed for the characterization of olefin metathesis catalysts. [21] Parallel screening with their benzylidene counterparts **1a**, **1c** and **8b** has been performed in order to gain insight into particularities concerning the carbene ligand behavior.

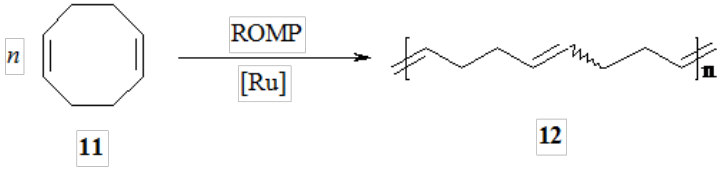

Figure 4.6: Ring-opening metathesis polymerization of 1,5-*cis*,*cis*-cyclooctadiene (**11**).

As a catalyst for the polymerization of 3,000 equiv *cis*,*cis*-1,5-cylooctadiene, complex **5** suffers from a strongly increased initiation period in comparison to its benzylidene analogue, **1c** (Figure 4.7). Regardless of this observation, full conversion is achieved after 5 h, illustrating the stability of the precursor. The lower rate of initiation of **5** relative to **1c** is in accordance with observations in ring-closing metathesis reactions (*vide infra*). The replacement of the strong electron-donating PCy_3-ligand (**5**) by the coordinatively more labile PPh_3-ligand (**6**) rationally enhances the initiation rate and drastically improves monomer consumption, reaching full conversion within a few minutes.

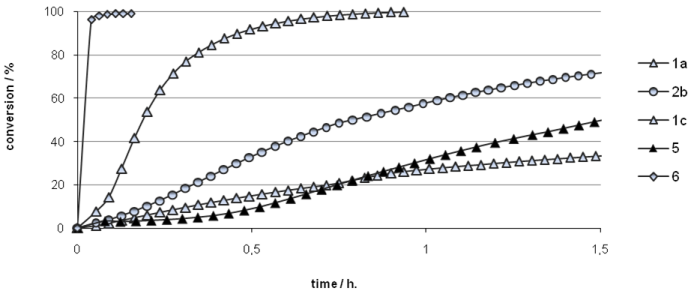

Figure 4.7: ROMP of 3,000 equiv *cis*,*cis*-1,5-cylooctadiene (**11**) using catalyst **1a**, **1c**, **2b**, **5** and **6**.

For the first generation catalysts, we encountered a strikingly better activity for catalyst **2b** *vs.* **1a**. Since the propagating species is the same for both catalysts, a fundamental difference has to be native to the precatalysts. Surprisingly, at a monomer/catalyst ratio of merely 300/1 (Figure 4.8), the benzylidene catalyst demonstrates superior activity compared to the indenylidene analogue, which is at first sight contradictory to the results depicted in Figure 4.7.

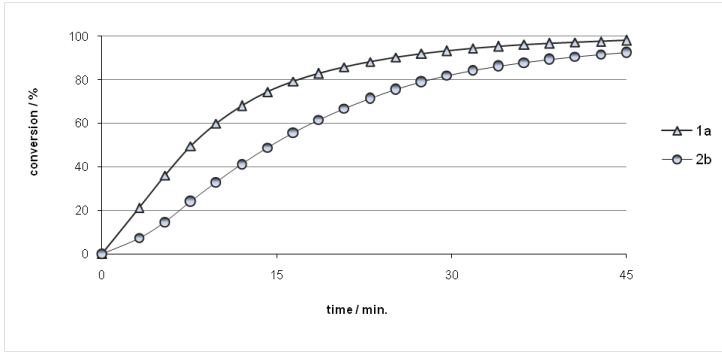

Figure 4.8: ROMP of 300 equiv *cis,cis*-1,5-cylooctadiene (**11**) using catalyst **1a** and **2b**.

In fact, catalyst **2b** displays an initiation period after which activity increases to reach 97% conversion after 1 h. Contrary to the observations, the bulkier indenylidene unit would predict faster PCy_3-ligand dissociation as a result of steric repulsion between the carbene unit and the phosphine ligand (Figure 4.9, a). On the other hand, it is reasonable to accept that the activation energy for olefin coordination is higher for **2b** compared to **1a** because of (i) the enhanced steric hinderance of the indenylidene ligand, preventing facile approach of olefin substrate molecules (Figure 4.9,b), (ii) the enhanced delocalization of electron density in the indenylidene ligand relative to the benzylidene ligand which reduces the rate of metallacyclobutane ring formation (Figure 4.9, c), or (iii) a combination of these factors. These arguments account for the prolonged initiation period of **2b** and illustrate how olefin coordination, the second step of the initiation process, can play a determining role on the initiation rate of the catalyst and accordingly demonstrates the importance of the steric and electronic characteristics of the carbene unit. We tentatively take the faster initiation of the benzylidene catalyst, **1a**, as a cause to higher concentrations of the active species which is more vulnerable to decomposition *via* bimolecular decomposition.

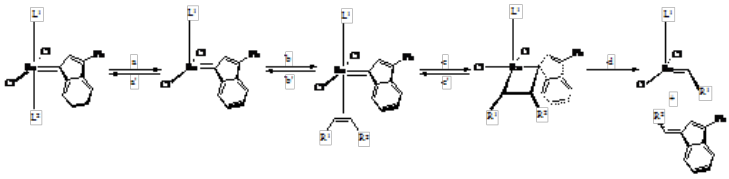

Figure 4.9: Mechanism of initiation for indenylidene type precatalysts.

For the third generation catalysts, addition of the monomer to the catalyst solution in a 3,000/1 ratio yielded immediate formation of the polymeric product, preventing monitoring of the reaction using NMR spectroscopy. The monomer/catalyst ratio was consequently extended to 10,000/1 and the results are depicted in Figure 4.10.

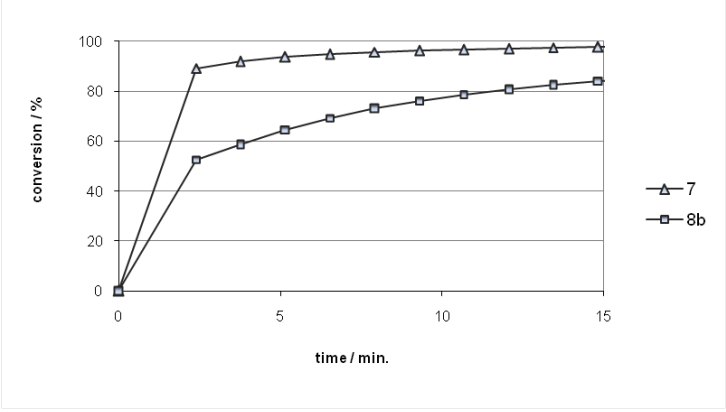

Figure 4.10: ROMP of 10,000 equiv *cis*,*cis*-1,5-cyclooctadiene using 3^{rd} generation catalysts Ru-indenylidene, **7**, *vs.* Ru-benzylidene, **8b**.

Quite successfully, at these low catalyst loadings, **7** reached full monomer conversion in less than 15 min. surpassing at all times the 3^{rd} generation Grubbs catalyst **8b** (Figure 4.10), the ROMP catalyst of excellence up to date. The polymers obtained from these reactions display similar characteristics (Mn = 52,000; PDI = 1.6; $\sigma_c = 0.47$ for **8b** and Mn = 50,000; PDI = 1.6; $\sigma_c = 0.42$ for **7**). Summarizing the results for the ring-opening metathesis polymerization of cyclooctadiene, the electronic and steric robustness of the indenylidene ligand raises the barrier

for catalyst initiation and decomposition. The lower initiation rate is particular disadvantageous in view of 'living' polymerizations with catalysts **2b** and **5**, while the enhanced stability is beneficial for complexes **6** and **7**. Aiming at a more elaborate exploration of the catalytic potential of the newly reported complexes and encouraged by the high rates of initiation for complex **7**, our research was extended to the application in the ring-closing metathesis reaction of diethyl diallylmalonate, **13** (Figure 4.11).

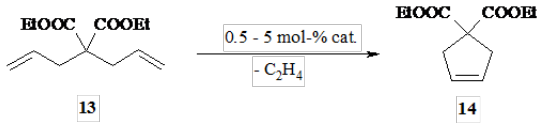

Figure 4.11: Ring-closing metathesis of diethyl diallylmalonate (**13**).

The results for the ring-closing metathesis of **13** using catalysts **1a**, **1c**, **2b**, **5** and **6** are depicted in Figure 4.12. Remarkably, under these conditions, first generation catalysts, **1a** and **2b**, clearly afford higher conversions at shorter reaction times than their second generation counterparts, **1c** and **5**, which obviously originates from an increased ligand dissociation. [22] Within the class of 1^{st} generation catalysts, the indenylidene catalyst performs a faster quantitative consumption of the substrate. Both catalysts show a high initial activity to move over to a phase of slow proceeding towards full conversion, a highly unusual reaction profile also described by Grubbs *et al.* for **1a**. [21]

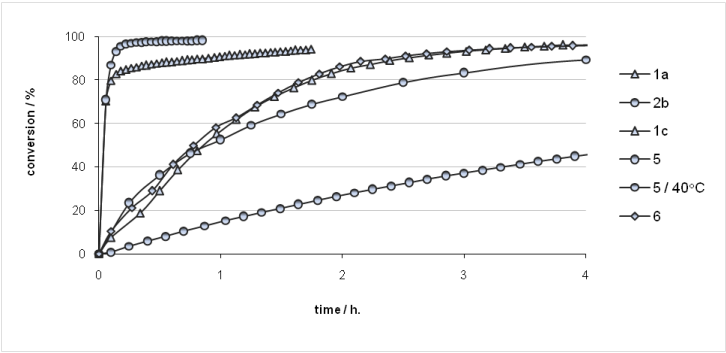

Figure 4.12: Conversions in the RCM of diethyl diallylmalonate (**13**) using catalysts **1a**, **1c**, **2b**, **5** and **6**.

Using a catalyst loading as low as 0.5 mol%, precursor **5** shows only 45% conversion in the ring-closing metathesis of **11** after 4 h, a result which is clearly excelled by the Grubbs 2^{nd} generation catalyst **1c**. A further increase of conversion to 76% after 16 h and 90% after 24 h indicates that the catalyst has a very long lifetime; yet, at room temperature a low rate of initiation prevents a faster conversion. The reaction rate expedites when the temperature is raised to 40°C (Table 4.1). The higher temperature allows for a better ligand dissociation, and hence yields a higher initiation rate for **5**. Whereas the indenylidene unit in **2b** proved beneficial, incorporation of the NHC ligand decreases the initial catalytic activity for RCM dramatically. In search of better ligand dissociation, the exchange of the PCy_3-ligand in **5** for the more labile PPh_3 ligand logically improves the rate of reaction. Remarkably, the activity of **6** is identical to that of **1c**. In spite of the more labile PPh_3 ligand, allowing for better ligand dissociation, the activity of **6** does not surpass the activity of **1c**. While **6** initiates clearly faster in the ROMP of **11**, its activity is equal to that of **1c** in the RCM of **13**.

Table 4.1: Influence of temperature on the proceeding of the ring-closing metathesis reaction of diethyl diallylmalonate with catalyst **5**.

Entry	**Reaction time / h**	**Conversion / %**	
		22℃	40℃
1	1	15	52
2	2	27	72
3	4	45	89
4	8	-[n.d.]	97
5	16	76	-[n.d.]
6	20	83	-[n.d.]
7	24	90	-[n.d.]

[n.d.] not determined.

In order to clarify the behavior of the third generation catalysts in RCM, both catalysts were subjected to catalytic tests at various catalyst loadings (0.5-5 mol%) and compared mutually (Figure 4.13 and 4.14).

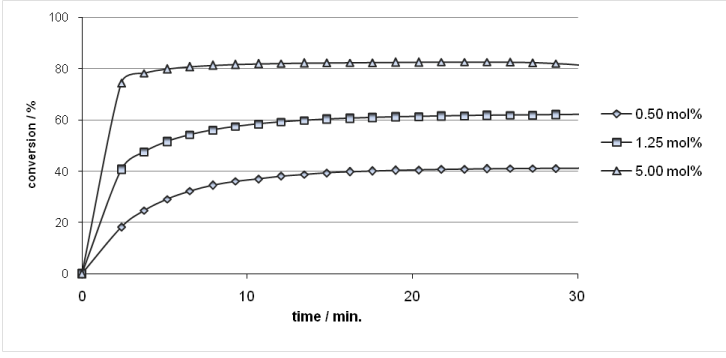

Figure 4.13: Conversion of diethyl diallylmalonate (**13**) using catalyst **8b** at different catalyst loadings.

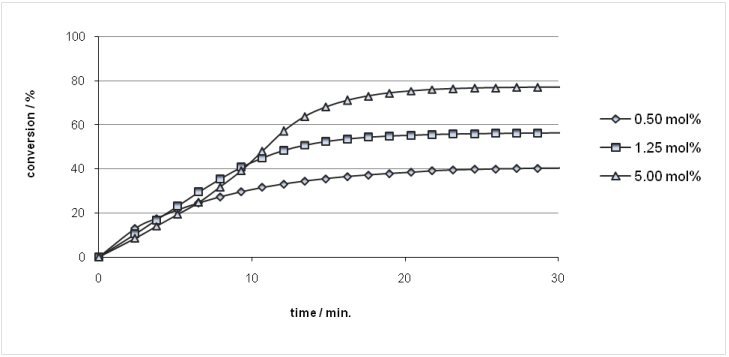

Figure 4.14: Conversion of diethyl diallylmalonate (**13**) using catalyst **7** at different catalyst loadings.

While the previously discussed catalysts (Figure 4.12) tend to perform the reaction to full conversion, catalysts **7** and **8b** complete the reaction only partially (Figure 4.13 and 4.14). The weak donating properties of the pyridine ligand in complexes **7** and **8b** are visibly insufficient to stabilize the catalytically active species during the course of the reaction, and as a result, catalyst decomposition prevents a successful fulfillment of the reaction. Similar reaction profiles are reported for analogous pyridine containing complexes **9** and **10**. [17, 18] Results further illustrate that, for all tested catalyst loadings, the indenylidene catalyst **7** enables very good conversions at short reaction times (5-10 min.), undoubtedly superior to those attained with the benzylidene analogue **8b** in the same time period. Contrary to the 1^{st} and 2^{nd} generation catalysts, this indenylidene catalyst initiates faster than its benzylidene analogue. Astoundingly, at distinct catalyst loadings, there is no significant differentiation in conversions after longer reaction times ($>$ 20 min.) between the catalysts mutually. This indicates an unusual catalyst behavior in the initial stage of the reaction. It was even more conspicuous to perceive that in the beginning of the reactions with catalyst **8b**, conversions are lower in case of higher catalyst loadings. To gain insight in this discernible fact, a detailed look at the TON/s of both catalysts was undertaken (Figure 4.15 and 4.16).

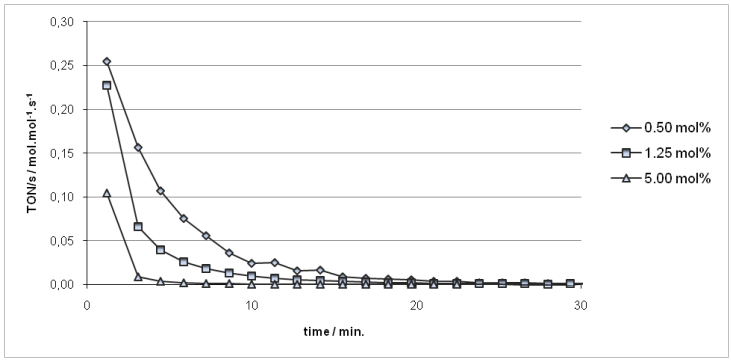

Figure 4.15: TON/s during RCM of diethyl diallylmalonate (**13**) using catalyst **7** at different catalyst loadings.

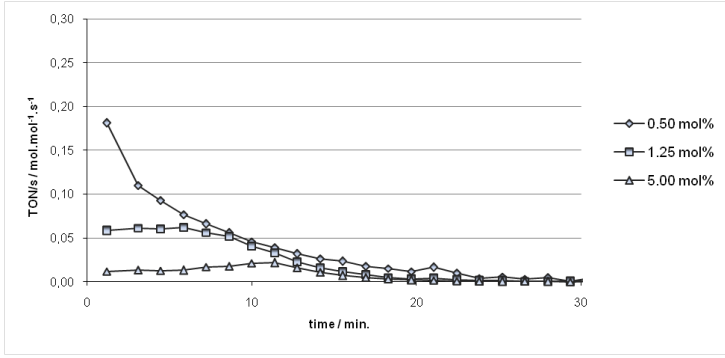

Figure 4.16: TON/s during RCM of diethyl diallylmalonate (**13**) using catalyst **8b** at different catalyst loadings.

Whereas **7** shows an expected TON/s-plot for all catalyst loadings, **8b** demonstrates an initiation period which prolongs with increasing catalyst loadings. This type of behavior is a fingerprint of intermolecular self inhibition of the catalyst while the overall conversion, being roughly equal for both catalysts, excludes major decomposition of the starting complex in this stage of the reaction. NMR investigation on this event revealed the ascent of a new signal at δ 8.84 ppm in the ^{1}H NMR spectrum (pyridine-*ortho*-C*H*) and two distinct peaks at δ 152.3 ppm and δ 150.1 ppm in the ^{13}C NMR spectrum (pyridine-*ortho*-*C*) (Figure 4.17),

characterizing unambiguously the formation of the bispyridine complex, **8a** [16].

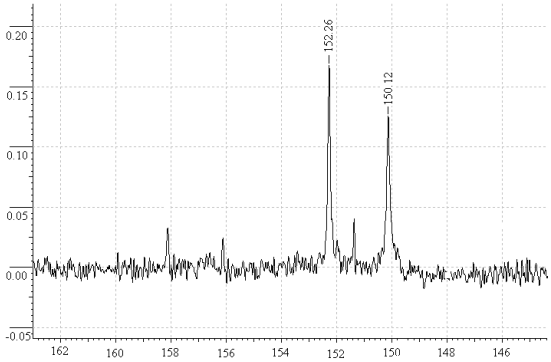

Figure 4.17: Detail of the ^{13}C NMR of a concentrated solution of **8b** in $CDCl_3$.

Based on these observations, we propose a mechanism where the starting compound **8b** partially disproportionates into a bispyridine complex and a proposed unidentified dimeric species. [23] We previously emphasized on the steric and electronic robustness of the indenylidene unit which disfavors dimerization and decomposition of the precatalyst. It is conceivable to accept that due to enhanced steric crowding of the indenylidene ligand, the driving force for the formation of a dimeric species and a bispyridine complex has decreased to such an extent that this phenomenon does not occur spontaneously and as a result, the catalyst displays a different behavior in the initial phase of the reaction. The propagating species being identical for both catalyst precursors, and thus being equally vulnerable to decomposition, results in similar conversions in the end. In search for further support of this statement, we reasoned that if the bispyridine complex formation accounts for the observed initiation periods, such an initiation period should be absent in case of the bispyridine catalyst, **8a**. Figure 4.18 and 4.19 show that indeed the bispyridine complex **8a** exhibits no visible initiation period.

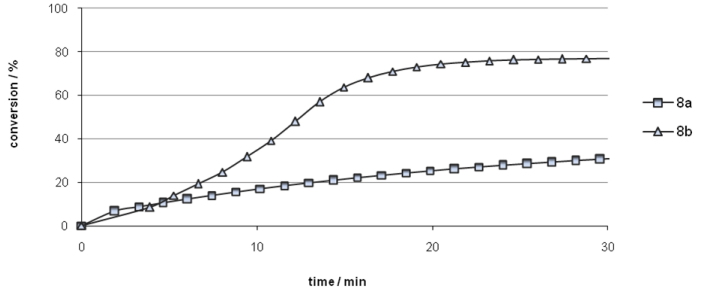

Figure 4.18: Conversions in RCM of diethyl diallylmalonate (**13**) using catalyst **8a** and **8b**.

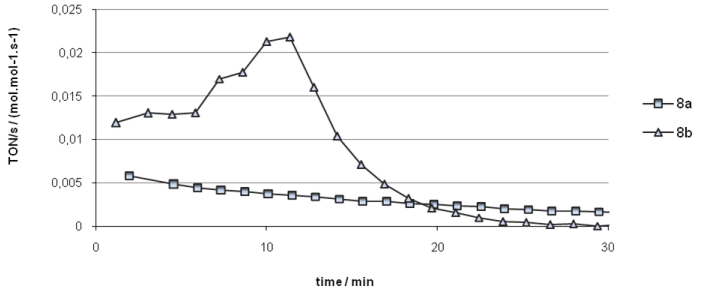

Figure 4.19: TON/s in RCM of diethyl diallylmalonate (**13**) using catalyst **8a** and **8b**.

Most remarkably, the results obtained from Figure 4.18 not only show that the monopyridine catalyst **8b** exhibits an initiation period, but also that this phenomenon evokes a higher conversion for **8b** (77%) *vs.* **8a** (31%) after 30 min.

Conclusively, we can state that although in 1^{st} and 2^{nd} generation catalysts the indenylidene unit evokes a decreased initiation rate in the ring-closing metathesis reaction of diethyl diallylmalonate, full conversion of the substrate can be obtained. In case of 3^{rd} generation catalysts, the indenylidene unit stabilizes the precatalyst and prevents it from self-inhibition.

4.3 Conclusions

In conclusion, in this chapter new and robust 2^{nd} and 3^{rd} generation Ru-indenylidene complexes **5**, **6** and **7**, all isolated in high yields, have been disclosed as air- and moisture-stable compounds. Together with the 1^{st} generation catalyst, this family of Ru-indenylidenes was screened on their activity for RCM and ROMP of model substrates, with their benzylidene counterparts as bench marks. Based on kinetic investigations, the alkylidene ligand was shown to play a decisive role on the activity of the catalysts, more specifically a decreased rate of catalyst initiation for the indenylidene complexes was observed. For 1^{st} generation catalysts, the retarded initiation of the indenylidene catalyst affords higher activity in RCM, while the activity in ROMP is more dependent on the reaction conditions. The second generation indenylidene catalyst **5** exhibits lower activity than its benzylidene analogue, in RCM reactions as well as in ROM polymerizations; clearly a result of decreased catalyst initiation. While catalyst **6** shares the activity of the 2^{nd} generation Grubbs catalyst for RCM, it initiates ROMP significantly faster. Evaluating the results for the third generation catalysts, we observed a better performance of the indenylidene catalyst **7** both in RCM and ROMP. The higher activity and stability of **7** *vs.* **8b** supports the idea that properties such as catalyst activity and stability, seemingly antagonistic, can be innate features of one single catalyst. Serendipitously, determining the activity of **8b** for RCM at different catalyst loadings revealed the unexpected partial formation of the bispyridine complex **8a** from **8b**, which results in the self-inhibition of the catalyst.

4.4 Experimental Section

General remarks

All synthetic manipulations were performed under argon (oxygen free) using the Schlenk technique. Argon was dried by passage through drierite. Tetrahydrofuran (THF), toluene, dichloromethane, hexane, benzene-d_6 and chloroform-d, dried by standard methods, were degassed by a standard three freeze-pump-thaw cycles. Methanol and pyridine was neither dried nor degassed before use. PPh_3 was purchased from Acros. Catalysts **1c** [10] and **8b** [16] were prepared according to litera-

ture. **1a** and diethyl diallylmalonate were purchased from Aldrich and used as received. **2b** was supplied by Umicor AG and used as received. 1,5-Cyclooctadiene was purchased from Aldrich and distilled, dried and degassed before use. ^{1}H NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer and ^{13}C and ^{31}P NMR spectra were recorded on a Bruker 300 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS. In ^{31}P NMR spectra, PPh_3 was used as an internal standard (δ = - 4.27 ppm in C_6D_6). Kinetic experiments were conducted on a Varian Unity 300 MHz NMR spectrometer.

Synthesis of (SIMes)(PCy_3)Cl_2Ru(3-phenylindenylid-1-ene), **5**: Complex **2b** (398 mg; 0.432 mmol) and the chloroform adduct **4** (357 mg; 0.863 mmol) were admitted into a previously flame dried flask, solved in THF (15 mL) under stirring, and the solution refluxed for 1.5 h. The reaction mixture was allowed to cool down, solid materials filtered of and the filtrate concentrated in vacuo. The residue was suspended in MeOH (5 mL) and dissolved under ultrasound; the precipitate formed when ultrasound is disconnected was filtered off, washed on the glass frit with another 5 mL MeOH and dried in vacuo to afford 334.5 mg (82% yield) of **5** as a red powder. ^{31}P NMR (300.18 MHz; 22°C; C_6D_6), δ (ppm): 27.0 (s). ^{1}H NMR (500.13 MHz; 22°C; C_6D_6; Me_4Si), δ (ppm): 9.13 (d, 1H); 7.88 (s, 1H, phenyl); 7.86 (s, 1H, phenyl); 7.81 (s, 1H); 7.31 (t, 1H, phenyl); 7.23 (t, 2H, phenyl); 7.16 (td, 1H); 7.10 (td, 1H); 7.06 (dd, 1H); 6.96 (s, 1H, SIMes-*m*-C*H*); 6.95 (s, 1H, SIMes-*m*-C*H*); 6.45 (s, 1H, SIMes-*m*-C*H*); 6.00 (s, 1H, SIMes-*m*-C*H*); 3.41-3.32 (m, 2H, N-C*H*); 3.28-3.22 (m, 1H, N-C*H*); 3.18-3.12 (m, 1H, N-C*H*); 2.85 (s, 3H, SIMes-CH_3); 2.83 (s, 3H, SIMes-CH_3); 2.45 (q, 3H, PCy_3); 2.36 (s, 3H, SIMes-CH_3); 2.22 (s, 3H, SIMes-CH_3); 2.21 (s, 3H, SIMes-CH_3); 1.82 (m, 3H, PCy_3); 1.78 (s, 3H, SIMes-CH_3); 1.71 (m, 3H, PCy_3); 1.57 (m, 3H, PCy_3); 1.52 (m, 6H, PCy_3); 1.36-1.09 (m, 15H, PCy_3). ^{13}C NMR (300.18 MHz; 22°C; C_6D_6; Me_4Si), δ (ppm): 291.4 (d, 1C, C1); 216.3 (d, 1C, SIMes-C_2); 144.1; 140.1; 138.1; 136.9; 136.9; 136.4; 136.1; 135.6; 135.2; 134.7; 129.0; 128.9; 128.44; 128.04; 127.95; 127.6; 127.4; 127.0; 126.6; 126.3; 125.8; 125.3; 115.0; 51.1; 50.5; 32.1; 31.9; 30.3; 28.8; 28.5; 26.9; 26.8; 26.7; 25.8; 25.3; 21.6; 19.8; 19.7; 19.3; 17.8; 17.6. $C_{54}H_{69}Cl_2N_2PRu$ (949.10): calcd. C 68.34, H 7.33, N 2.95; found C 67.97, H 6.95, N 3.19%.

Synthesis of (SIMes)(PPh_3)Cl_2Ru(3-phenylindenylid-1-ene), **6**: Method A: 1.00 g (1.34 mmol) of **7** and 387 mg (1.47 mmol) PPh_3 were dissolved in 50 mL dichloromethane and stirred for 30 min. at room temperature. The solvent was removed by evaporation and the residue recrystallized from dichloromethane/hexane. Filtration and washing with hexane afforded 1.11 g of compound **6** (89%). Method B: 1.00 g (1.13 mmol) of **2a** and 935 mg (2.26 mmol) of the chloroform adduct **4** were charged into a flame dried reaction flask and dissolved in 50 mL of toluene. The mixture was heated for 2.5 h at 65℃. After cooling down to room temperature, the solid materials were filtered of and the filtrate was concentrated by evaporation. Suspending in hexane, filtering of and washing intensively with 100 mL hexane yielded compound **6** as a deep red powder in 86% yield. ^{31}P NMR (300.18 MHz; 22℃; CD_2Cl_2), δ (ppm): 27.3 (s). ^{1}H NMR (300.18 MHz; 22℃; CD_2Cl_2; Me_4Si), δ (ppm): 7.87 (d, 1H); 7.54-6.96 (br. multiple peaks, 20H, PPh_3, phenyl); 6.56 (s, 1H, SIMes-*m*-C*H*); 6.41 (s, 1H, SIMes-*m*-C*H*); 6.03 (s, 1H, SIMes-*m*-C*H*); 4.09-4.03 (m, 2H, N-C*H*); 3.89-3.78 (m, 2H, N-C*H*); 2.69 (s, 3H, SIMes-CH_3); 2.66 (s, 3H, SIMes-CH_3); 2.47 (s, 3H, SIMes-CH_3); 2.13 (s, 3H, SIMes-CH_3); 2.01 (s, 3H, SIMes-CH_3); 1.84 (s, 3H, SIMes-CH_3). ^{13}C NMR (300.18 MHz; 22℃; CD_2Cl_2; Me_4Si) δ: 300.3 (d, 1C, C1); 215.2 (d, 1C, SIMes-C_2); 143.3; 141.2; 140.8; 139.6; 139.4; 138.6; 138.2; 137.2; 136.9; 136.8; 136.4; 135.8; 134.8; 134.5; 134.4; 134.0; 133.7; 132.2; 132.0; 131.5; 130.1; 130.0; 129.9; 129.5; 129.2; 129.1; 129.0; 128.93; 128.86; 128.7; 128.2; 127.6; 127.5; 127.3; 126.6; 116.4; 21.3; 20.9; 20.4; 20.3; 18.7; 18.6. $C_{54}H_{51}Cl_2N_2PRu$ (930.96): calcd. C 69.67, H 5.52, N 3.01; found C 69.78, H 5.43, N 3.19%.

Synthesis of (SIMes)(py)Cl_2Ru(3-phenylindenylid-1-ene), **7**: A flame dried reaction flask was charged with 1.00 g (1.05 mmol) of **5** and 5.0 ml of pyridine. The resulted solution was stirred for 2 h during which time the colour change from red to yellowish-brown. 20 mL hexane was added and upon cooling the mixture to - 40℃, brown solid precipitated. The solid was filtrated, washed several times with cold hexanes (3×10 mL) and dried under vacuum to afford **7** as an orange-brown solid. Yield: 552 mg (70%). ^{1}H NMR (300.18 MHz; 22℃ ; C_6D_6; Me_4Si), δ (ppm): 9.05 (d, 1H); 8.13 (br. s., 2H, py-*o*-C*H*); 7.81-6.04 (br. multiple peaks, 16H, py, Mes-C*H*); 3.56-3.17 (m, 4H, N-CH_2); 2.99 (s, 3H, SIMes-CH_3);

2.72 (s, 3H, SIMes-CH_3); 2.48 (s, 3H, SIMes-CH_3); 2.13 (s, 3H, SIMes-CH_3); 1.99 (s, 3H, SIMes-CH_3); 1.70 (s, 3 H, SIMes-CH_3). ^{13}C NMR (300.18 MHz; 22°C C_6D_6; Me_4Si) δ: 300.6 (s, 1C, C1); 215.13 (s, 1C, SIMes-C_2); 152.2 (s, 2 C, py-*o*-*C*); 143.6; 141.5; 141.0; 140.6; 139.5; 139.3; 138.8; 137.6; 137.4; 137.2; 137.1; 136.6; 136.2; 134.2; 134.6; 129.8; 129.5; 129.2; 128.6; 128.2; 127.9; 127.6; 126.6; 123.2; 116.8; 52.1; 50.6; 21.5; 21.2; 21.04; 20.95; 18.8; 18.6. $C_{41}H_{41}Cl_2N_3Ru$ (747.77): calcd. C 65.68, H 5.53, N 5.62; found: C 65.22, H 5.87, N 5.43%.

General procedure for the ring-opening metathesis polymerization of *(*cis),*(*cis)-1,5-cyclooctadiene: The appropriate amount of catalyst is dissolved in 0.60 mL $CDCl_3$ and transferred to an NMR tube. 1,5-Cyclooctadiene (0.10 mL; 0.82 mmol) is then added under Ar and the NMR tube is capped. Conversion is monitored by integration of the allylic methylene peaks in the ^{1}H NMR spectrum of the monomer and polymer.

General procedure for polymer synthesis: A small oven-dried glass vial with septum was charged with a magnetic bar and the appropriate amount of catalyst under an inert atmosphere of Ar. The catalyst is dissolved (5.0 mL CH_2Cl_2) and 2.0 mL of *cis*,*cis*-1,5-cylooctadiene was transferred to the vial *via* syringe, under vigorous stirring at room temperature. The polymerization was terminated after 1 h through addition of 0.1 mL ethyl vinyl ether and a small amount of BHT was added to prevent the polymer from oxidation. The polymer was precipitated with methanol and isolated by filtration and drying in vacuo. Mn and polydispersities (PDI) are determined by size-exclusion chromatography (SEC) with polystyrene calibration. σ_c is determined by ^{13}C NMR spectroscopy (allylic carbon *cis*: δ 27.6 ppm, allylic carbon *trans*: δ 32.9 ppm).

General procedure for the ring-closing metathesis of diethyl diallylmalonate: The appropriate amount of catalyst is dissolved in 0.60 mL $CDCl_3$, left to equilibrate for 2 min. at room temperature and transferred to an NMR tube. Diethyl diallylmalonate (0.10 mL; 0.41 mmol) is then added under Ar and the NMR tube capped and sealed with Parafilm. Conversion is monitored by integration of the allylic methylene peaks in the ^{1}H NMR

spectrum of the substrate and the product.

NMR-investigation on catalyst **8b**: An NMR tube is charged with a 34.5 mM solution of **8b** in $CDCl_3$ under an inert atmosphere of Ar and the NMR tube is capped and sealed with Parafilm. The catalyst transformation is monitored at room temperature by ^{1}H and ^{13}C NMR.

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5

Ruthenium Indenylidene Complexes with a Modified N-Heterocyclic Carbene Ligand

5.1 Introduction

In the previous chapter, we have shown that the low initiation rate of second generation ruthenium indenylidene catalysts can be offset by application at higher temperatures or by exchange of the PCy_3 ligand trans to the N-heterocyclic carbene with a more labile PPh_3 or pyridine ligand. The current research was focused on the influence of the substitution pattern of the aryl moiety in the N-heterocyclic carbene ligand. Mol *et al.* [1] and more recently Schrodi *et al.* [2] have shown that altering this substitution pattern can strongly affect the olefin metathesis activity of ruthenium benzylidene catalysts (Figure 5.1).

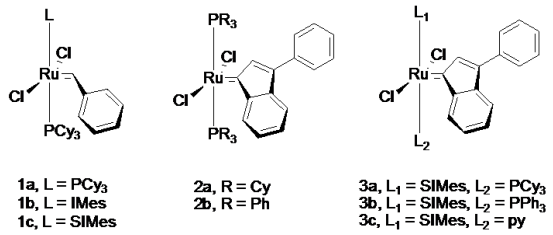

Figure 5.1: Well-defined olefin metathesis catalysts **1**, **2** and **3**.

Preliminary research has shown that the absence of the *para*-methyl substituent on the aryl moiety of the N-heterocyclic carbene results in a strongly improved initiation rate of ruthenium benzylidene type catalysts, especially in ring-opening metathesis polymerizations (Figure 5.2 and 5.3).

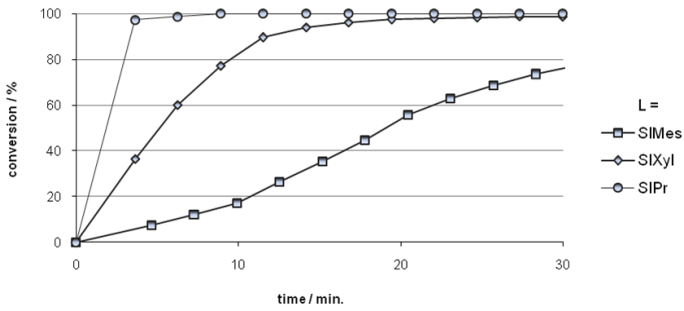

Figure 5.2: Influence of the N-heterocyclic carbene ligand in Grubbs type catalysts, $Cl_2Ru(=CHPh)(L)(PCy_3)$, on the proceeding of the ring-opening metathesis polymerization of *cis*,*cis*-1,5-cyclooctadiene.

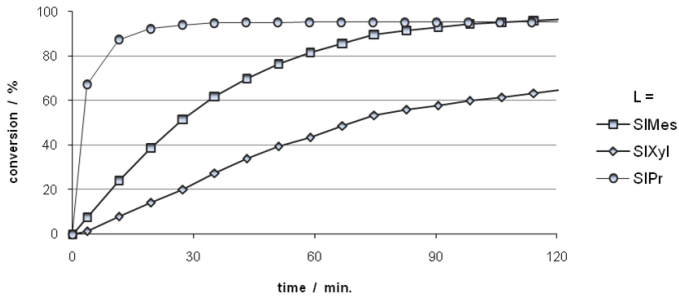

Figure 5.3: Influence of the N-heterocyclic carbene ligand in Grubbs type catalysts, $Cl_2Ru(=CHPh)(L)(PCy_3)$, on the proceeding of the ring-closing metathesis of diethyl diallylmalonate.

5.2 Results and Discussion

5.2.1 Synthesis of 2nd generation indenylidene complexes with a modified N-heterocyclic carbene ligand

In chapter 4, we reported the synthesis of ruthenium indenylidene complexes with a N,N'-bis-(mesityl)imidazolin-2-ylidene ligand from **2a** or **2b** and the thermolysis of the corresponding 2-(trichloromethyl)imidazolidine. The ease of performing synthesis and purification of the obtained catalyst prompted us to verify whether an analogous approach would apply for the synthesis of similar complexes bearing an SIPr ligand. Unfortunately, we found that a rather large amount of ligand precursor (4 to 8 equiv) was required and that the high thermolytic temperature needed (90°C) resulted in the decomposition of the target ruthenium compound before the starting compound was fully consumed. Eventually, we were unable to isolate the desired compound since other approaches described in section 4.2.1 (page 87) turned out to be unsuccessful as well. Regardless of our attempts, Clavier *et al.* later reported on the synthesis of this compound from **2a** and 2 equiv SIPr, and the obtained compound was indeed reported to be a faster initiator, but also thermally unstable at room temperature in solution. [3] We thus turned our attention to the synthesis of ruthenium indenylidene complexes bearing a SIXyl ligand. A similar approach using a

pentafluorobenzene adduct **5** was applied for the synthesis of **4a** from **2a** (Figure 5.4). Monitoring the reaction of **2a** and **5** using ^{31}P NMR showed that the reaction was complete after 1.5 h of reaction at 100°C in toluene. Surprisingly, merely 1.15 equiv of the pentafluorobenzene adduct **5** proved satisfactory, suggesting a much less sterical hindrance thwarting the complex formation, and thus a much less sterically demanding ligand environment. The complex was easily purified by evaporation of all volatiles and subsequent suspending in MeOH. Filtration and drying afforded **4a** as a red powder in moderate yield (56%). NMR analysis of **4a** showed a single peak up-field to the starting complex in the ^{31}P NMR spectrum at δ 26.1 ppm. The ^{1}H NMR spectrum revealed a doublet at δ 9.20 ppm for **4a**, which is typical for indenylidene complexes. The ethylene backbone of the imidazolin-2-ylidene ligand in **4a** forms a complex multiplet (at δ 3.35 - 3.06 ppm for **4a** *vs.* at δ 3.41 - 3.12 ppm for **3a**) which indicates the complexes' asymmetry. The ^{13}C NMR spectrum further proved presence of the imidazolin-2-ylidene ligand, with a doublet at δ 215.27 ppm for **4a**. Elemental analysis showed that the obtained compound is indeed **4a**, and that it was obtained as a pure compound. The complex was found to be air-stable as a powder and was stable for days as a solution in dichloromethane.

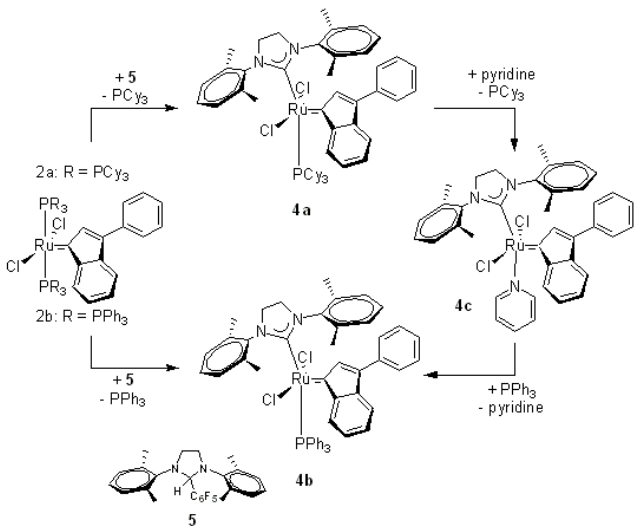

Figure 5.4: Synthesis of new generations Ru indenylidene metathesis catalysts with saturated N-heterocyclic carbene ligands.

Synthesis of **4c** proceeded easily by treatment of **4a** with an excess of pyridine. The indenylidene complex **4c** was isolated in good yield (60%) as an orange-brown powder. Complex **4b** was obtained from **4c** by simple ligand exchange and isolated in 53% yield as clear red powder. In addition, it was straightforwardly obtained from reaction of **2b** with **5** (1 h in refluxing THF) in good yield (74%).

5.2.2 Ring-closing metathesis activity

Next to the ring-closing metathesis of diethyl diallylmalonate, we now also selected the ring-closing metathesis of N,N-diallyl tosylamide (Figure 5.5). In order to depict the catalytic activity of this new class of olefin metathesis catalysts, we confronted their activity with the performance of complexes **2a** and **3a-c**.

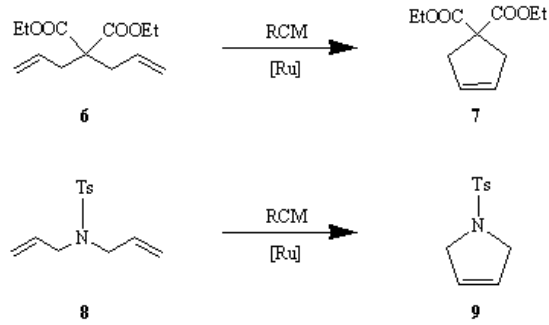

Figure 5.5: Representative metathesis reactions.

First generation indenylidene catalyst **2a** unequivocally displays the best activity for the RCM of diethyl diallylmalonate, converting 200 equiv of the substrate almost quantitatively within 30 minutes. Second generation type complexes with a PCy_3-ligand *trans* to the N-heterocyclic carbene moiety, **3a** and **4a**, suffer from a dramatic decrease in activity, which may be rationalized by a reduction of the catalysts initiation efficiency. Complex **3a** shows 50% conversion after 5 hours for the RCM with **6**. The conversion proceeds to 89% after 24 hours, which indicates a long lifetime of the complex. Full conversion could not be attained due to the low initiation rate. **4a** exhibits the same behaviour but exceeds the activity of **3a**; after 24 hours **4a** reaches al-

most full conversion (99%). The stability of catalyst **4a** bearing a PCy_3 ligand at room temperature is implied by the requirement for elevated temperatures in order to achieve high activity, as we reported earlier for indenylidene catalysts **3a**.

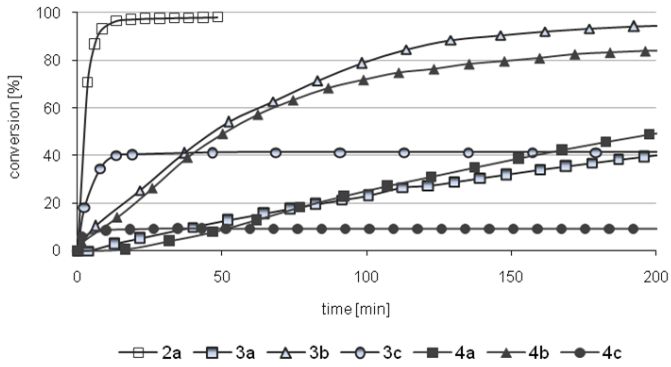

Figure 5.6: RCM of **6** with catalysts **2a**, **3a-c** and **4a-c**.

In case the complexes bear a weaker donating PPh_3-ligand, **3b** and **4b**, a definite increase in the catalyst's activities is observed. Complexes bearing a pyridine ligand *trans* to the NHC-ligand, **3c** and **4c** exhibit a high initial activity, succeeded by a strong activity drop-off which suggests dramatic catalyst decomposition. Although no discernible effect of the NHC-ligand on the catalytic activity is observed for phosphine ligated complexes, a profound effect is perceived for the pyridine complexes **3c** and **4c**. While the SIMes ligated catalyst **3c** attains 40% conversion, SIXyl ligated catalyst **4c** manages to convert only 9% of the substrate. A profound influence of the N-aryl substitution pattern in the N-heterocyclic carbene ligand on the stability of the active species can thus be assumed.

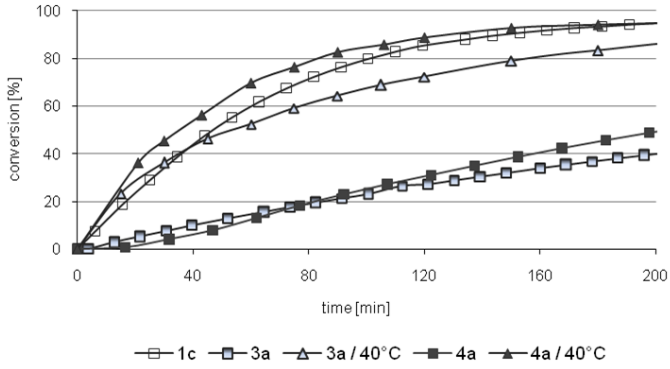

Figure 5.7: RCM of **6** with catalysts **1c**, **3a** and **4a**.

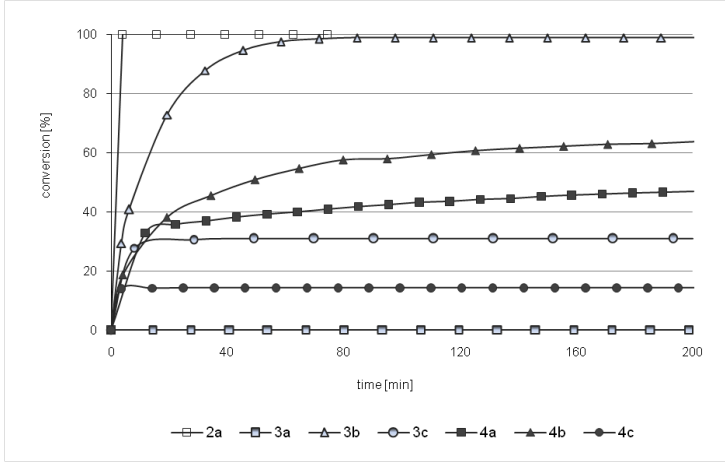

Figure 5.8: RCM of N,N-diallyl tosylamide (**8**) with catalysts **2a**, **3a-c** and **4a-c**.

Similar to the RCM of diethyl diallylmalonate, the RCM of N,N-diallyl tosylamide proceeds smoothly using first generation type catalyst **2a**, affording quantitative conversion within 4 minutes. More strikingly is the negligible activity of **3a** towards the RCM of **8**. A comparable catalyst with the SIXyl ligand, **4a**, still manages 40% conversion. Catalysts **3b** and **4b** with a PPh_3 ligand again allow for higher activities, converting 98% and 58% of the substrate respectively within one hour.

The pyridine ligated complexes again exhibit a high initial activity followed by a dramatic decrease in catalyst activity, comparable to the results obtained for the RCM of diethyl diallylmalonate.

5.2.3 Ring-opening metathesis polymerization

Figure 5.9 displays the catalytic performance for ROMP of *cis*,*cis*-1,5-cyclooctadiene with with catalysts **3a**, **3b**, **4a** and **4b** in a catalyst to monomer ratio of 1/3,000.

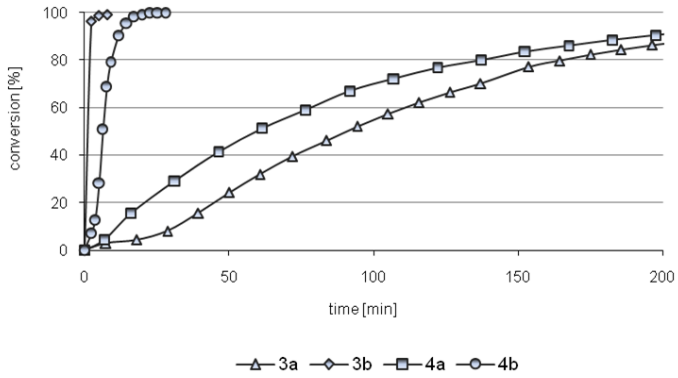

Figure 5.9: Ring-opening metathesis polymerization of *cis*,*cis*-1,5-cyclooctadiene with catalysts **3a**, **3b**, **4a** and **4b**.

Third generation ruthenium indenylidene complexes **3c** and **4c** yield full monomer conversion within two minutes at a monomer to catalyst ratio of 1/3,000, a performance far beyond that of the 2^{nd} generation indenylidene Ru catalysts **3a** and **4a**. Even though our 2^{nd} generation complexes with PPh_3 ligands **3b** and **4b** initiate ROMP slower than **3c** and **4c**, they still manage 100% conversion within 20 min. Lower catalyst loadings (10,000 equiv of COD) of **3c** and **4c** afford total monomer conversion within 15 min. It has previously been described, that the polymerization of cyclooctadiene (COD) is initially not stereoselective. Since only one double bond of *cis*,*cis*-COD is opened, a 75:25 *cis*/*trans* ratio represents the theoretically predicted non-selective polymerization. Although olefin metathesis catalysts show no preference for the *trans*-orientation in the initial stage of the polymerization, a secondary

metathesis event transforms the polymer into a polymer with higher *trans* content. [4] Moreover, upon formation of the *cis,trans*-polymer by secondary metathesis, a tertiary metathesis event occurs, which transforms *trans*-1,4-polybutadiene into *t,t,t*-1,5,9-cyclododecatriene (CDT) (Figure 5.10, Table 5.1). [4]

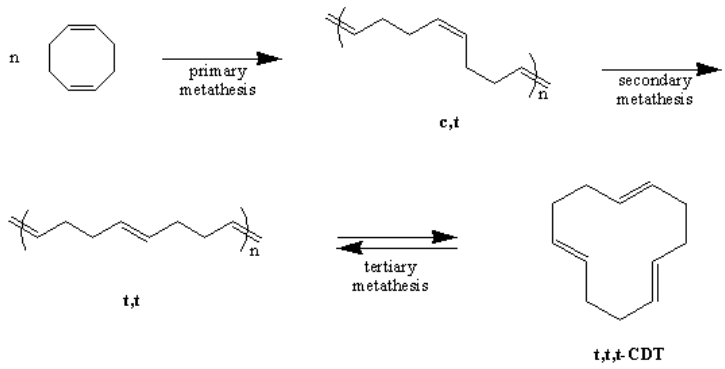

Figure 5.10: Ring-opening metathesis polymerization of *cis,cis*-1,5-cyclooctadiene with catalysts **3a**, **3b**, **4a** and **4b**.

Transformation of the 1,4-polybutadiene chain into *t,t,t*-CDT is not observed in case of catalysts **3a**, **4a** and **1c** (Figure 5.10). Contrary to the indenylidene-type catalysts **3a** and **4a**, catalyst **1c** exhibits moderate secondary metathesis activity as reflected by the higher *trans*-content. Catalysts **3bc** and **4bc** yield high conversions in very short reaction times accompanied by high percentages of *cis,trans*-polymer, a result of their excellent initiation and propagation rates. The high performance of these catalysts further allowed tertiary metathesis to occur transforming the *cis,trans*-1,4-polybutadiene into *t,t,t*-CDT.

Table 5.1: Formation of *t,t,t*-1,5,9-cyclododecatriene (CDT) during the polymerization of *cis,cis*-1,5-cyclooctadiene.

Entry	**Catalyst**	***cis*** / %	CDT / %	TON
1	**1c**	54	0	2,900
2	**3a**	75	0	3,000
3	**3b**	17	4.7	3,000
4	**3c**	8	10	10,000
5	**4a**	75	0	3,000
6	**4b**	20	1	3,000
7	**4c**	9	10	10,000

5.3 Conclusions

In this part, we presented the synthesis and screening results for a series of 2^{nd} and 3^{rd} generation indenylidene olefin metathesis catalysts applied to a set of ring-closing metathesis transformations. The aim of this study was to reveal the relative efficacies of different catalysts containing a SIMes or a SIXyl ligand. We have compared six of the ruthenium-indenylidene olefin metathesis catalysts in a set of metathesis reactions and described them in terms of their performance. During this comparison, it became evident that a small modification of the substituents on the NHC ligand influence the catalyst initiation rate. Nevertheless, as ligand (phosphine, pyridine) dissociation promotes catalyst decomposition, complexes bearing SIXyl ligand decompose faster. It was evidenced that second generation type indenylidene catalysts suffer from low initiation efficiency. Therefore, first generation type catalyst **2a** often excels other studied catalysts for RCM transformations. Third generation type catalysts exhibit a high initial activity, ensued by a definite drop in activity, a fingerprint of their fast decomposition. Second generation type indenylidene catalysts bearing a SIXyl ligand generally surpass the activity of those bearing a SIMes ligand, since the latter suffer from a more pronounced initiation period. Third generation type catalysts bearing a SIXyl ligand suffer to a larger extent from decomposition, compared to their SIMes ligated counterparts. Therefore, their RCM activity is rather marginally.

5.4 Experimental Section

General remarks Reactions were performed under inert argon atmosphere using the Schlenk technique. Argon was dried by passage through drierite. Solvents like tetrahydrofuran (THF), toluene, dichloromethane (CH_2CL_2), *n*-hexane, benzene$-d_6$, chloroform-d were dried by standard methods and degassed by a standard three freeze-pump-thaw cycles. Methanol was not dried before use. Pyridine was nor dried nor degassed before use. Diethyl diallylmalonate was purchased from Aldrich and used as received. Complexes **2a**,**b** [5] and **3a-c** [6] were synthesized as described in literature.

Synthesis of N,N-bis-(2,6-dimethylphenyl-2-pentafluorophenyl)imidazolidine, **5** Preparation of Glyoxal-bis-(2,6-dimethylphenyl)imine: 10.0 mL (80.2 mmol) 2,6-dimethylaniline and 5.0 mL (43.6 mmol) of a 40 wt% solution of glyoxal in water were reacted overnight in 30 mL n-propanol, catalyzed by 2 drops of formic acid. The yellow precipitate was filtered off and dried in vacuo to afford 8.00 g (30.3 mmol; 76%) glyoxal-bis-(2,6-dimethylphenyl)imine. 1H NMR (300 MHz, 22°C, $CDCl_3$): δ 2.18 (s, o-CH3, 12 H), 6.98-7.10 (aryl-CH, 6 H), 8.12 (s, NCH, 2 H).

Preparation of N,N-bis-(2,6-dimethylphenylamino)ethane: 4.00 g (15.2 mmol) of glyoxal-bis-(2,6-dimethylphenyl)imine was stirred overnight with 2.28 g (60.3 mmol) NaBH4 in 50 mL THF. Then, 50 mL ice water was added and the solution was cooled to 0C. Subsequently, 50 mL of a 3 M HCl solution in water was added drop wise. The colorless precipitate was filtered off, washed with 2 x 15 mL THF and dried in vacuo to yield 4.82 g (14.1 mmol; 93%)

N,N-bis-(2,6-dimethylphenylamino)ethane dihydrochloride: 4.00 g (11.7 mmol) N,N-bis-(2,6-dimethylphenylamino)ethane dihydrochloride was suspended in 150 mL of a 1 N NaOH solution in water and N,N-bis-(2,6-dimethylphenylamino)ethane was extracted subsequently by 150 mL and 100 mL dichloromethane. Drying of the organic phase on MgSO4 and evaporation of the solvent yielded 2.65 g (9.9 mmol; 84%) of the N,N-bis-(2,6-dimethylphenylamino)ethane as a beige solid. 1H NMR (300 MHz, 22°C, $CDCl_3$) : 2.31 (s, o-CH3, 12 H), 3.21 (s, N-CH2, 4 H), 3.41 (bpeak, NH, 2 H), 6.84 (t, aryl-p-CH, 2 H), 7.00 (d, aryl-m-CH, 4

H).

Preparation of 1,3-bis-(2,6-dimethylphenyl-2-pentafluorophenyl)imidazolidine: 0.81 g (4.15 mmol) pentafluorobenzaldehyde is dissolved in 5 drops of glacial acetic acid and 5 mL dichloromethane. 1.13 g (4.22 mmol; 1.04 equiv) N,N-bis-(2,6-dimethylphenylamino)ethane is added and the mixture is stirred for 30 min. at room temperature. The adduct is purified by crystallization from dichloromethane and methanol and dried in vacuo to afford 1.01 g (2.27 mmol; 55%) of a colorless powder. 1H NMR (300 MHz, 22°C, $CDCl_3$) : 2.38(s, o-CH3, 12 H), 3.57 (s, N-CH2-, 2 H), 3.95 (s, NCH2-, 2 H), 6.45 (s, C2-H, 1 H), 6.99 (s, m-CH, 6H).

Synthesis of (SIXyl)(PCy_3)Cl_2Ru(3-phenylindenylid-1-ene), **4a**: A flame dried reaction flask is charged with 286.0 mg (0.3098 mmol) of compound **2a** and 159.3 mg (0.3568 mmol; 1.15 equiv) of the pentafluorobenzene adduct **5**. The mixture is dissolved in 10 mL toluene, stirred and heated to 100°C for 1.5 h. The reaction mixture is allowed to cool down to room temperature and filtered off. All volatiles are removed by evaporation and the residue is suspended in 5 mL MeOH. After filtration, the residue is washed with another 5 mL MeOH and dried *in vacuo* to afford 160.5 mg (0.1743 mmol; 56 %) of **4a** as a red powder.

Synthesis of (SIXyl)(PPh_3)Cl_2Ru(3-phenylindenylid-1-ene), **4b**: Method A: Under an inert atmosphere of Ar, 35.1 mg PPh_3 (0.134 mmol; 1.10 equiv) is added to 87.3 mg **4c** (0.121 mmol) in dichloromethane (10 mL) and the mixture is stirred for 30 minutes at room temperature. After evaporation of all volatiles, the residue is suspended in *n*-hexane and filtered off. Thoroughly washing with 3x5 mL *n*-hexane and drying *in vacuo* yielded 57.7 mg of **4b** (0.064 mmol; 53%) as a deep red powder. Method B: Under an inert atmosphere of Ar, a flame dried reaction flask is charged with 275.3 mg (0.3105 mmol) of complex **2b** and 159.4 mg (0.3571 mmol; 1.15 equiv) of the pentafluorobenzene adduct **5**. The mixture is dissolved in 10 mL toluene, stirred and heated to 100°C for 1 h. The reaction mixture is allowed to cool down to room temperature and filtered off. All volatiles are removed by evaporation and the residue is suspended in 5 mL MeOH. After filtration, the residue is washed with another 5 mL MeOH and dried in vacuo to afford 211.7 mg (0.2299

mmol; 74%) of **4b**.

Synthesis of (SIXyl)(py)Cl_2Ru(3-phenylindenylid-1-ene), **4c**: 152.0 mg (0.165 mmol) of complex **4a** is dissolved in pyridine (2.0 mL) and stirred at room temperature for 2 hours. A brown precipitate is formed upon addition of *n*-hexane (10mL) and subsequent cooling to -40°C. Filtration of the precipitate, washing with 3x5 mL *n*-hexane and drying *in vacuo* yielded 87.3 mg (0.121 mmol; 73%) of compound **4c** as an orange powder.

Monitoring ROMP of *cis*,*cis*-cycloocta-1,5-diene (COD): An NMR-tube is charged with the appropriate amount of catalyst, dissolved in 0.60 mL of $CDCl_3$. 0.10 mL *cis*,*cis*-cycloocta-1,5-diene is added, the NMR-tube is closed and the conversion is determined by integration of the olefinic ^{1}H signals of the formed polymer and the consumed monomer.

Monitoring RCM of diethyl diallylmalonate and N,N-diallyltosylamide (**10**): An NMR-tube is charged with the appropriate amount of catalyst, dissolved in 0.60 mL $CDCl_3$. 0.10 mL of the substrate is added, the NMR-tube is closed and the conversion is determined by integration of the allylic ^{1}H signals of the formed product and the consumed substrate.

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6

A Polymer-Supported Scavenger Approach towards the Synthesis of Grubbs-Hoveyda Olefin Metathesis Catalysts

6.1 Introduction

Combinatorial chemistry, and more specifically its inherent need for high-throughput synthesis and purification of chemical libraries, availed novel purification techniques based on solid-phase and solution-phase synthetic strategies. [**?**, 1–8] Whereas the initial *modus operandi* focused on an immobilization-cleavage sequence of target molecules, new methods such as solid-phase extraction [9] and reactive filtration [10]

endeavour scavenging the excess of reagents or side products while the target molecule is readily isolated. These methods are often associated with ease of product purification while tedious column chromatography is avoided. Up to date, these techniques have been successfully applied for the synthesis of organic molecules. [11–15] Gandelman and coworkers have shown that the principles of polymer-phase methodologies can be successfully transferred to the synthesis of $[Cl_2Ru(PPh_3)_2(=CHPh)]$ (**13**), [16] a precursor for the preparation of Grubbs 1^{st} generation catalyst **1a**. [17–19] However, the full potential of these techniques for the synthesis of organotransition-metal compounds has not yet been recognized. The development of well-defined ruthenium catalysts has rendered olefin metathesis an efficient and reliable tool for the formation of carbon-carbon double bonds. [**?**, **?**, 20–23] Grubbs type catalysts **1a** and **1b** [24, 25] have found numerous applications in synthetic chemistry and ruthenium indenylidene type catalysts **2a** [26–28] and **2b** [29–32] have proven to represent splendid alternatives (see Figure 6.1). Grubbs-Hoveyda catalyst **3a** [33] and its phosphine-free congener **3b** [34] exhibit enhanced activity in various reactions compared to catalysts **1** and **2** and hold as a bench mark for further catalyst development.

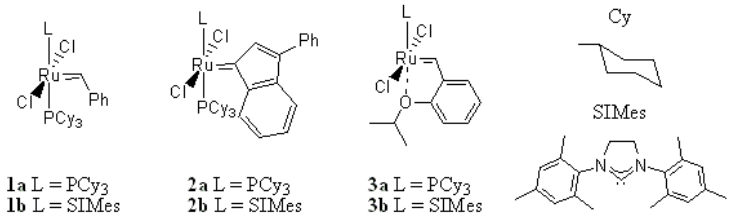

Figure 6.1: Ruthenium based olefin metathesis catalysts.

Grubbs-Hoveyda type catalysts **3a** and **3b** are generally prepared from reaction of **1a**/**b** or **2a**/**b** with 2-isopropoxystyrene in presence of CuCl. In this reaction, CuCl acts as a phosphine scavenger, shifting the reaction towards closure of the κ^2-(C,O)-chelate. Unfortunately, CuCl is easily oxidized in presence of atmospheric oxygen which complicates handling during preparation of metathesis catalysts and long-term storage. In addition, application of the non-innocent CuCl requires specific workup since it can not be quantitatively retained using column

chromatography. In this regard, Cu scavenging packings have been proposed. Alternatively, some publications report on the use of AgCl as an efficient phosphine scavenger. [35, 36] Such procedures necessitate use of column chromatography, a tedious and solvent intensive protocol. In this respect, Blechert prepared **3b** by introduction of SIMes into **3a** and subsequent stirring of the catalyst in chloroform, thus avoiding use of the air sensitive CuCl. [37] Alternatively, **3b** was prepared from second generation ruthenium olefin metathesis catalysts bearing a more labile PPh_3 ligand. [38] Grela reported on a procedure for the large scale preparation of **3b** circumventing use of column chromatography. [39] Sauvage *et al.* elaborated an alternative route via homobimetallic ruthenium indenylidene complexes. [40] These alternative procedures, however, require multiple preparative steps and/or post-end column chromatography. We envisaged that a new and general procedure for the preparation of Grubbs-Hoveyda type catalysts eluding usage of CuCl is strongly demanded for. The combichem promise for clean and simple procedures prompted us to verify whether such methodologies apply to the synthesis of Grubbs-Hoveyda catalysts. CuCl accelerates the conversion of the starting complex by lowering the free phosphine concentration in solution and prevents coordination of phosphine to the target ruthenium catalyst. Circumventing application of CuCl consequently demands an efficient phosphine scavenging reagent. Falchi and Taddei reported on PEG-dichlorotriazine as a soluble polymer-supported scavenger for alcohols, thiols, phosphines and phosphine oxides. [9] Although its activity as a phosphine scavenger was evidenced from its successful application in the workup after Appel reactions, we were reluctant towards its application for our purposes since the necessity for preparative steps towards the scavenger polymer limits its applicability. Alternatively, our attention was drawn towards the application of Amberlyst 15-A, a cross-linked polystyrene-co-divinylbenzene sulfonic acid polymer, previously applied for the removal of tertiary amines from the reaction mixture after Pfitzner-Moffatt oxidation. [2] Subsequent filtration of the resin allows for high-yielding isolation of the corresponding ketones. In regard of its complementary molecular reactivity, we anticipated that this resin might prove useful as a scavenger resin for the removal of PCy_3 from the reaction mixture during the preparation of Grubbs-Hoveyda type catalysts (see Figure 10.3) while shifting the reaction in the direction of

closure of the κ^2-(C,O)-chelate. In addition, this resin is commercially available and should be straightforwardly reactivated after the sequestration step bringing about recovery of the valuable phosphines.

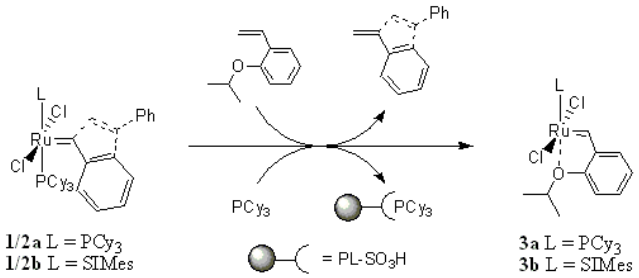

Figure 6.2: Alternative synthesis of Grubbs-Hoveyda type catalysts **3a** and **3b**.

6.2 Results and discussion

6.2.1 A novel method for the synthesis of Grubbs-Hoveyda catalysts

In a first set of experiments, we attempted to depict the potential of our selected resin as an *in situ* phosphine sequestration reagent for directing the reaction towards the synthesis of Grubbs-Hoveyda 1^{st} generation catalyst **3a** upon reaction of ruthenium indenylidene complex **2a** with 1.05 equiv 2-isopropoxystyrene. Progress of the reaction of **2a** to **3a** in dichloromethane (CH_2Cl_2) (c_{Ru} = 0.01 M) at 40°C in presence of various amounts of sulfonic acid groups of the Amberlyst 15-A resin was conveniently monitored by ^{31}P NMR analysis of the crude reaction mixtures at selected time intervals. The results are depicted in Figure 6.3. Figure 6.4 shows the disappearance of the signal at δ 30.4 ppm (**2a**), with the coincident clean formation of a new peak at δ 58.4 ppm (**3a**), in presence of 4 equiv sulfonic acid groups as monitored by ^{31}P NMR spectroscopy. Simultaneously, the reaction mixture colors from clear red to brown.

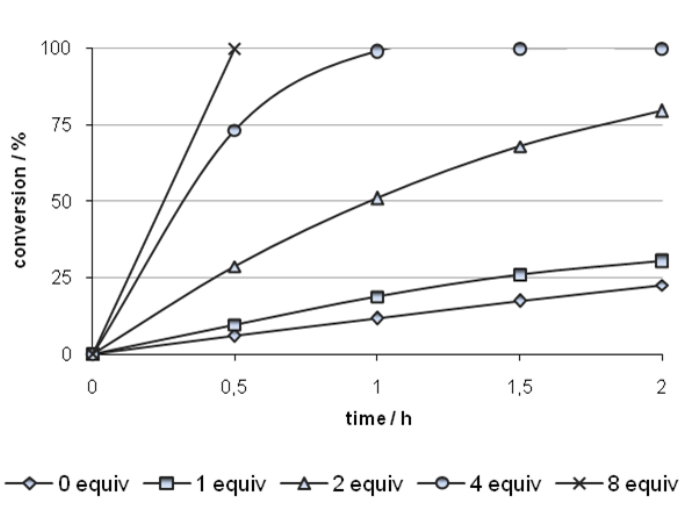

Figure 6.3: Conversion of ruthenium indenylidene catalyst **2a** to Grubbs-Hoveyda catalyst **3a** in refluxing dichloromethane as a function of polymer-supported sulfonic acid and time.

Figure 6.3 clearly shows the impact of the polymer resin on the proceeding of the reaction. In absence of Amberlyst 15-A resin, merely 23% of starting material is consumed after 2 hours. Due to the lack of a phosphine scavenging agent, the Grubbs-Hoveyda catalyst **3a** is present as its bis-phosphine adduct **3a**·$\mathbf{PCy_3}$ (δ 36.3 ppm). Upon raising the amount of Amberlyst 15-A to 1 or 2 equiv, modest improvement of the reaction rate is observed. However, application of 4 to 8 equiv affords clean conversion of complex **2a** to **3a** within 1 hour.

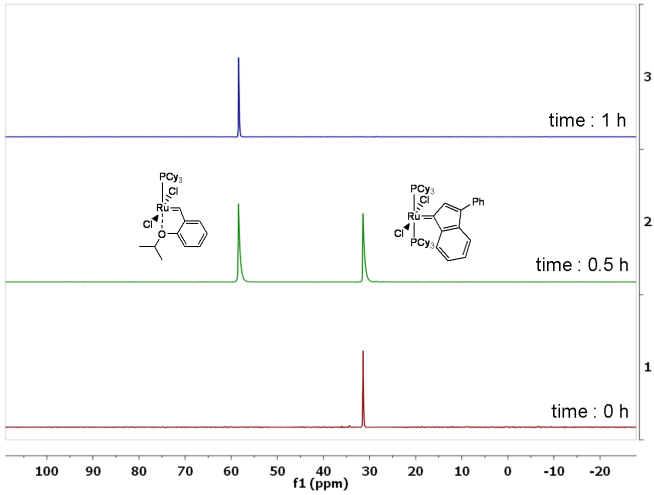

Figure 6.4: Monitoring the reaction of 2-isopropoxystyrene with complex **2a** in presence of 4 equiv Amberlyst 15-A resin in dichloromethane at reflux using ^{31}P NMR spectroscopy.

With these results at hand, we studied the influence of the solvent on the reaction rate. THF, toluene and CH_2Cl_2, three commonly used solvents for the preparation of olefin metathesis catalysts were selected together with chloroform and 1,2-dichloroethane (DCE). Ruthenium concentration was as low as 0.01 M and reactions were monitored by integration of characteristic peaks in the ^{31}P NMR spectrum.

Table 6.1: Influence of solvent on the rate of formation of Grubbs-Hoveyda catalyst **3a**[a]

Entry	Solvent	Catalyst	Reaction time (h)	Conversion (%)a
1	THF	**1a**	1	98
2			1.5	100
3		**2a**	1	30
4			2	93
5			2.5	100
6	CH_2Cl_2	**1a**	1	100
7		**2a**	1	99
8			1.5	100
9	toluene	**1a**	1	35
10			2	53
11			4	81
12			8	100
13		**2a**	1	5
14			2	13
15			4	22
16			8	42
17	DCE	**1a**	1	90
18			1.5	100
19		**2a**	1	45
20			2	79
21			3	100
22	$CHCl_3$	**1a**	1	100
23		**2a**	1	79
24			2	100

[a] Determined by integration of characteristic peaks in ^{31}P NMR spectrum.

The results summarized in Table 1 show that good conversions are obtained for reactions performed in THF, CH_2Cl_2, DCE and chloroform. Generally, full conversion is obtained within 2 hours. Reactions performed with Grubbs 1^{st} generation catalyst **1a** are faster than those per-

formed with ruthenium indenylidene complex **2a**. Reactions in toluene were significantly slower. It was observed that upon stirring, the polymer resin sticks to the edges of the vial and accordingly, contact between the phosphine scavenger and the reaction mixture is significantly reduced. We tentatively attributed this observation to the comparably lower polarity of toluene. Eventually, the reaction was performed on a 1 mmol scale. We selected CH_2Cl_2 as the solvent of choice since reaction is complete within one hour and the solvent is readily removed after reaction by evaporation. Indeed, full conversion was obtained after 1 hour at reflux using 1.05 equiv 2-isopropoxystyrene, 4 equiv Amberlyst 15-A and 25 mL CH_2Cl_2. The reaction mixture was allowed to cool to room temperature and was subsequently sent through a Pasteur pipette equipped with a cotton plug. Figure 6.5a shows the simplicity of the experimental setup. Figure 6.5b and 6.5c depict the polymer resin before and after reaction, respectively. After reaction, the resin colors to brown. It is reasonable to assume that swelling of the polymer particles evokes microencapsulation of the catalyst. The yield of the reaction, however, was not affected to a large extent (*vide infra*). Upon evaporation of CH_2Cl_2, the residue is suspended in 20 mL *n*-hexane and filtered off on a glass frit. The brown product is extensively washed with *n*-pentane (3× 10 mL) to remove all traces of 1-methylene-3-phenyl-1*H*-indene. After extensive drying of the product in vacuo, the yield was determined to 91%. ^{1}H NMR spectroscopy further confirmed that the obtained complex was indeed complex **3a**, and no spectral indications were found that traces of 1-methylene-3-phenyl-1*H*-indene or 2-isopropoxystyrene were still present in the obtained powder.

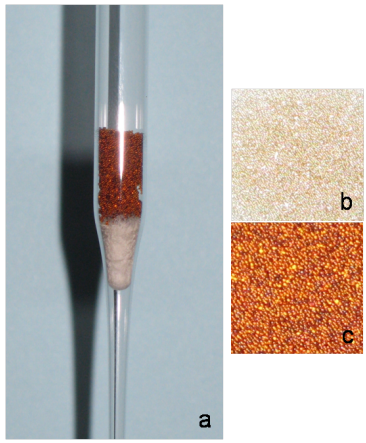

Figure 6.5: a. A Pasteur pipette equipped with a cotton plug suffices to separate the polymer resin from the reaction mixture; b. polymer resin Amberlyst 15-A before reaction; c. polymer resin Amberlyst 15-A after reaction.

6.2.2 Synthesis of 2^{nd} generation Grubbs-Hoveyda catalyst

Encouraged by the straightforwardness of the above described protocol, we were interested to see if the established procedure also applies to the preparation of Grubbs-Hoveyda type catalysts bearing an N-heterocyclic carbene ligand, so-called 2^{nd} generation Grubbs-Hoveyda catalyst **3b**. Reactions were performed using Grubbs catalyst **1b** or indenylidene catalyst **2b** with 1.05 equiv of 2-isopropoxystyrene and 4 equiv of Amberlyst 15-A. The influence of the solvent on the proceeding of the reaction is recorded in Table 2. In accordance to the results described above, good conversions were obtained when Grubbs catalyst **1b** was used as starting material. Reactions in THF and CH_2Cl_2 were quantitative after 1.5 hours at 40°C while the reaction mixture colored from pink to green. In agreement with previous conclusions, toluene proved to be an unfavorable solvent for this reaction. No full conversion was obtained after 8 hours of reaction. When complex **2b** was used as starting material, no conversion was observed after 2 hours at 40°C in THF. However, when the reaction was carried out in THF at reflux, 80% conversion was obtained after 0.5 h and the reaction was complete within 1 hour. Analogously, the reaction in CH_2Cl_2 did not afford **3b** and raising tem-

perature was disabled by the low boiling point of the solvent. Again, the reaction in toluene did not yield full conversion after 8 hours. From these experimental results, THF turned out to be the solvent of choice for the synthesis of **3b**.

Table 6.2: Influence of solvent on the rate of formation of Grubbs-Hoveyda catalyst **3b**[a]

Entry	Catalyst	Solvent	Reaction time (h)
1	THF	**1b**	1.5
2		**2b**	1[b,c]
3	CH_2Cl_2	**1b**	1.5
4		**2b**	-[b]
5	toluene	**1b**	-[d]
6		**2b**	-[d]

[a] Determined by integration of characteristic peaks in ^{31}P NMR spectrum. Ph_3PO (20% relative to Ru) used as internal reference. [b] No conversion at 40°C. [c] Reaction performed at 68°C. [d] No full conversion after 8 hours.

Stirring 1 mmol of **2b** in 25 mL THF with 1.05 equiv 2-isopropoxystyrene and 4 equiv Amberlyst 15-A for 1.5 hours at reflux allowed for the straightforward synthesis of **3b**. The workup procedure described above for the preparation of Grubbs-Hoveyda catalyst **3a** was applied to the purification of **3b** from the reaction mixture. Complex **3b** was obtained in 94% yield. The ^1H and ^{13}C NMR spectral data of the dried greenish powder were in accordance to literature reports.

6.2.3 A Grubbs-Hoveyda catalyst bearing an amino-amido N-heterocyclic carbene ligand

In 2008, Allaert reported on the incorporation of an amino-amido N-heterocyclic carbene ligand in Grubbs 1^{st} generation catalyst. The resulting complex, **4**, was found to be a good catalyst for the ring-opening metathesis polymerization of cyclooctadiene with relation to initiation kinetics. In view of the above described protocol, we were interested to

find out whether a Hoveyda-type catalyst bearing an amino-amido NHC can be prepared as well.

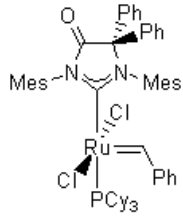

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Figure 6.6: Grubbs catalyst bearing an amino-amido N-heterocyclic carbene ligand.

In our selected approach, 1.5 equiv KHMDS (0.5M solution in toluene) was added to 1.5 equiv of the amino-amido imidazolium salt in THF. Upon addition of the base, the solution colored immediately to pink and the solution was allowed to stir for an additional 15 min. Then, a solution of Hoveyda 1^{st} generation catalyst in THF was added to the fluorescent pinkish solution of the unmasked amino-amido NHC. The ^{31}P NMR spectrum showed the appearance of a new signal at δ 30.28 ppm while the signal of Hoveyda 1^{st} generation catalyst (δ 60.29 ppm) disappeared completely. Conversion of the starting complex was quantitative after 1 hour. Although the formed compound was neither isolated nor characterized, we presume that this compound contains both the amino-amido NHC ligand and the PCy_3 ligand. For comparison, the analogous compound containing a SIMes ligand and a PCy_3 ligand was isolated and characterized by Blechert *et al.* and the signal of PCy_3 in the ^{31}P NMR spectrum was located at δ 29.36 ppm. Sauvage *et al.* monitored the reaction of Hoveyda 1^{st} generation catalyst with SIMes $\cdot$ CO_2 in toluene at 90°C and located the same compound at δ 30.7 ppm. [41] Remarkably, Allaert reported on the formation of two isomers of compound **4** with ^{31}P NMR shifts at δ 28.74 and δ 27.87 ppm, respectively. Under the selected reaction conditions reported here, the similar compound bearing a *ortho*-isopropoxy group shows no isomeric forms. Eventually, 4 equiv PL-SO_3H were added to the solution. The solution colored from pinkish to green within 5 minutes of stirring. The reaction mixture was stirred for an additional 30 min. and was subsequently sent through a Pasteur

pipette to filter of the polymer resin. Evaporation of all volatiles and suspending of the obtained residue in methanol allowed for the filtration of the green powder on a glass frit. Drying of the powder *in vacuo* afforded the desired compound in good yield (88%). Likewise compound **4**, which was obtained as a mixture of two isomeric compounds in a 2:3 ratio, compound **5** was obtained as a mixture of two isomers in a 1:3 ratio. The major isomer exhibited a downfield singlet in the ^{1}H NMR spectrum at δ 15.91 ppm while the minor isomer showed a signal at δ 16.31 ppm. These shifts are significantly upfield compared to the analogous chemical shift for catalyst **3b** (δ 16.56 ppm) and **3a** (δ 17.44 ppm). Other indicative chemical shifts, *i.e.* δ 9.03 ppm and δ 8.36 ppm (phenyl-C*H*), and δ 5.00 ppm and δ 4.12 ppm (O-C*H*(Me)$_2$), were found in a 1:3 ratio as well.

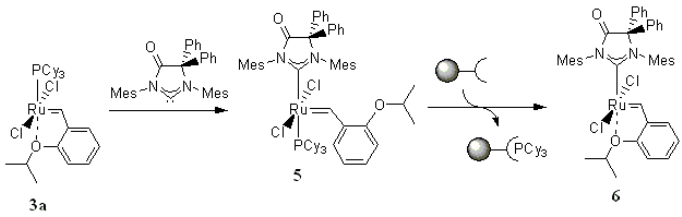

Figure 6.7: Preparation of a Grubbs-Hoveyda catalyst bearing an amino-amido N-heterocyclic carbene ligand.

6.3 Conclusions

As the chemical society is faced with new challenges towards environmentally benign processes, the olefin metathesis community has addressed these novel needs by exploiting catalyst selectivity and activity, immobilization and recovery and application of alternative reaction media. Other aspects concerning green chemistry are reduction of solvent use and chromatography, use of simple, preferably one-step, and straightforward procedures with quantitative reactions affording high isolated yields. Up to date, these aspects have been extensively translated to the application of olefin metathesis catalysts. In sharp contrast, less attention has been devoted to the green preparation of the catalysts themselves. However, few examples stress out the importance of green procedures that afford the desired catalysts in high

yields. Here, a novel strategy is presented for the preparation of Grubbs-Hoveyda type catalysts (**3**) from 1^{st} or 2^{nd} generation Grubbs (**1**) or indenylidene (**2**) type ruthenium catalysts using a heterogeneous polymer-supported phosphine scavenger reagent, *i.e.*, the commercially available polystyrene sulfonic acid resin. Optimized reaction conditions conclude on the 4-fold use of the phosphine scavenging reagent to afford quantitative conversions within 1.5 hours. The reported protocol can be easily up-scaled to a 1 mmol scale and the phosphine containing polymer resin is readily removed from the reaction mixture by passage through a Pasteur pipette equipped with a cotton plug. Further workup involves simple precipitation and filtration of the complexes and the use of tedious and solvent intensive column chromatography is avoided. The target ruthenium olefin metathesis catalysts are obtained in high yield ($> 90\%$) and purity.

6.4 Experimental Section

Monitoring the reaction of **1a**/**b** or **2a**/**b** with 2-isopropoxystyrene to **3a**/**b** in presence of Amberlyst 15-A: To a 7 mL vial equipped with a stir bar, a 0.01 M solution of catalyst **1a**/**b** or **2a**/**b** in the appropriate solvent with the apt amount of Amberlyst 15-A resin is added 1.05 equiv 2-isopropoxystyrene. The vial is heated to 40°C and the reaction is monitored by ^{31}P NMR spectroscopy. In case of 2^{nd} generation catalysts, **1b** and **2b**, Ph_3PO is used as an internal reference.

1 mmol scale preparation of Hoveyda catalyst **3a** from **2a**: A flame-dried Schlenk reaction flask is charged with a stir bar and put under an Ar atmosphere. 923 mg **2a** (1.00 mmol), 173 mg 2-isopropoxystyrene (1.05 mmol; 1.05 equiv) and 1026 mg Amberlyst 15-A resin (4.00 mmol; 4 equiv) was loaded into the reaction flask and 25 mL CH_2Cl_2 is added. The reaction was stirred at 40°C for 75 minutes and the solution colored from red to brown. Subsequently, the reaction mixture is sent through a Pasteur pipette equipped with a cotton plug to remove the polystyrene-supported sulfonic acid resin. Evaporation of all volatiles, suspending in 20 mL *n*-hexane and subsequent percolation and drying *in vacuo* afforded 548 mg of the desired compound (yield: 91%).

1 mmol scale preparation of Hoveyda catalyst **3b** from **2b**: A flame-dried Schlenk reaction flask is charged with a stir bar and put under an Ar atmosphere. 949 mg **2b** (1.00 mmol), 173 mg 2-isopropoxystyrene (1.05 mmol; 1.05 equiv) and 1026 mg Amberlyst 15-A resin (4.00 mmol; 4 equiv) was loaded into the reaction flask and 25 mL THF is added. The reaction was stirred at 68°C for 1 hour, during which the reaction mixture colors from red to green. Then, the reaction mixture is sent through a Pasteur pipette equipped with a cotton plug to remove the polystyrene sulfonic acid resin. Evaporation of all volatiles, suspending in 20 mL *n*-hexane and subsequent percolation and drying *in vacuo* afforded 576 mg of the desired compound as a green air-stable product (yield: 94%).

0.25 mmol scale preparation of complex **5** from **3a**: A flame-dried Schlenk reaction flask is charged with a stir bar and put under an Ar atmosphere. 200.1 mg of the amino,amido-imidazolium salt (0.37 mmol; 1.5 equiv) is dissolved in 15 mL THF and 0.75 mL KHMDS (0.5 M solution in toluene) (0.37 mmol; 1.5 equiv) is added. The solution colored immediately to pink and the reaction was allowed to stir for 30 min. Then, 150 mg **3a** (0.25 mmol; 1.0 equiv) was added and the solution colored to pink. The mixture was additionally stirred for 15 min. and 258 mg Amberlyst 15-A resin (1.00 mmol; 4 equiv) was loaded into the reaction flask. The reaction was stirred at 40°C for 1 hour, during which the reaction mixture colors from pink to green. Then, the reaction mixture is sent through a Pasteur pipette equipped with a cotton plug to remove the polystyrene sulfonic acid resin. Evaporation of all volatiles, suspending in 20 mL *n*-hexane and subsequent percolation and drying *in vacuo* afforded 156 mg of the desired compound as a green air-stable product (yield: 88%).

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7

A Polymer-Assisted Solution Phase Approach Towards the Synthesis of a Phoban-Hoveyda Ruthenium Catalyst for Olefin Metathesis Reactions

7.1 Introduction

In Chapter 1, we have stressed out that the groundbreaking report on ruthenium catalyst **1** by Grubbs in the mid-nineties was most influential for the development of efficient ruthenium alkylidene olefin metathesis catalysts. Further developments included 2^{nd} generation catalysts bearing an N-heterocyclic carbene ligand and the discovery of the ruthenium indenylidene catalyst **2**. Last decade, olefin metathesis catalyst

development has most prominently been influenced by the serendipitous discovery of ruthenium catalyst **3** by Hoveyda, bearing a chelating 2-isopropoxybenzylidene ligand. [1, 2] Ever since their disclosure in literature, research on development of ruthenium olefin metathesis catalysts has focused primarily on the elaboration of 2^{nd} generation Grubbs-Hoveyda type catalysts.

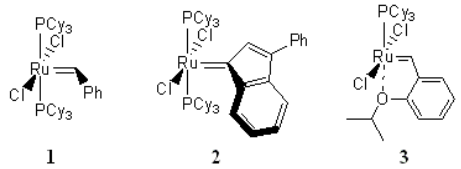

Figure 7.1: First generation Grubbs and Grubbs-Hoveyda catalysts.

In 2004, however, Forman *et al.* recognized the importance of the phosphine ligands as a means to efficient catalyst design and reported on phosphabicyclononane (phoban) ligands which impart rather unexpected catalyst properties. *I.e.*, catalyst **4** was found to be surprisingly air and moisture stable compared to **1**. Furthermore, **4** was relatively stable in acetonitrile and remained unaltered upon treatment with a 2M HCl solution while **1** almost immediately decomposed. In addition, **4** is stable to column chromatography and can be recycled after reaction. It was shown that **4** acts as a selective catalyst for the self-metathesis of 1-decene and methyl oleate, even at elevated temperatures. Thus, it was suggested that rigid bicyclic phosphine ligands hold the promise of a stable and selective olefin metathesis catalyst. [3] In this respect, it should be noted that previous attempts to modify the trialkyl phosphine ligand in ruthenium alkylidene complexes were either insignificant (*i.e.* PCp_3 or P^iPr_3) or unsuccessful (*i.e.* $PCoc_3$) [4]. Following up on this seminal report, the same group reported on the analogous cyclohexyl-phoban ruthenium indenylidene catalyst **5** and its application in the metathesis of renewable unsaturated fatty acid esters. [5] Most recently, Meyer and Nolan reported on the application of catalyst **4**, **5** and **7** in ring-closing and ring-closing enyne metathesis reactions, and the self-metathesis of 1-octene. [6] Of note, catalyst **7** is now commercially available from Umicore AG. (Figure 7.2)

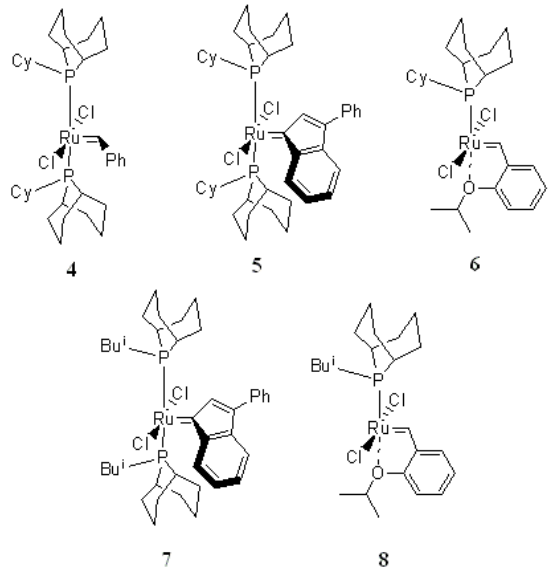

Figure 7.2: Phoban ruthenium olefin metathesis catalysts.

While performing a study on TONs of ruthenium catalysts **1**, **G2**, **3** and **H2** in ring-closing metathesis reactions using very low catalyst loadings, Blechert *et al.* reported on extremely high TONs. More importantly, this report also disclosed the application of a cyclohexyl-phoban Hoveyda catalyst **6** towards the RCM of diallyl tosylamide. [7] Selected catalytic data are provided in Table 7.1.

Table 7.1: Ring-closing metathesis of diallyl tosylamide with (pre)catalysts **1**, **3** and **6**. Catalyst loading = 0.006 mol%. [7]

Entry	Catalyst	Conversion /%	TON
1	**1**	21	3500
2	**3**	59	9894
3	**6**	40	6667

These results show that the phoban-Hoveyda catalyst excells the activity of Grubbs 1^{st} generation catalyst **1** while its activity is lower than the classical Grubbs-Hoveyda catalyst **3** bearing a PCy_3 ligand. However, the catalytic data provided for catalyst **6** were rather limited,

and further elaboration of such catalysts is desirable.

In recognition of the beneficial aspects related to phoban-ligands in ruthenium-based olefin metathesis catalysts, we describe here the synthesis and application of a Grubbs-Hoveyda 1^{st} generation catalyst bearing an ^{i}Bu-phoban ligand. With respect to the synthesis, we verified whether a synthetic methodology comprising a phosphine scavenging polymeric resin reported in the previous chapter applies to the synthesis of the new catalyst. Furthermore, its activity towards standard olefin metathesis reactions [8] was studied and compared to catalytic activities observed for catalysts **1**, **2**, **3** and **7**. In addition, the kinetic behavior of catalyst **7** in ring-closing metathesis reactions and the ring-opening metathesis polymerization of 1,5-*cis*,*cis*-cyclooctadiene is studied for the first time.

7.2 Results and discussion

7.2.1 Catalyst Synthesis

In the preceding chapter, we reported on a polymer-assisted solution-phase approach towards the synthesis of Grubbs-Hoveyda type complexes **3** and its 2^{nd} generation congener using Amberlyst 15-A as a phosphine scavenger in stead of CuCl. Encouraged by the ease of either performing the reaction and the synthetic workup, we were interested to verify whether an analogous approach would prove beneficial for the synthesis of a Grubbs-Hoveyda catalyst bearing a phosphabicyclononane ligand. Preliminary experiments using the polymer-supported sulfonic acid resin, however, learned that the desired complex **8** was formed in merely 19% after 2 hours in refluxing dichloromethane using 16 equiv PL-SO_3H. Forman *et al.* have previously reported on the high stability of ruthenium carbene complexes bearing a cyclohexyl phoban ligand in a 2M HCl solution, and it is reasonable to assume that the phoban ligands are highly resistant towards Brønsted acids, either towards HCl or towards the polymer-supported sulfonic acid. Accordingly, the polymer-supported sulfonic acid is not capable of efficiently scavenging the phoban phosphine ligands.

Consequently, we turned our attention to acylating and tosylating

agents which potentially scavenge the phosphine ligand irreversibly. In order to verify whether such an approach could be successful, we monitored the reaction of **7** with 2-isopropoxystyrene (1.05 equiv) in presence of a large excess (8 equiv) tosyl chloride and acetyl chloride. Reactions were performed in CD_2Cl_2 at 40°C and 70°C, respectively, and the conversion was determined by integration of the characteristic peaks in the ^{1}H NMR spectrum. Results are depicted in Figure 7.3. Analysis of the conversion of **7** to **8** revealed zero-order kinetics, which is in agreement with the large excess of phosphine scavenging agent. From these results, it can be concluded that the scavenging of the phosphine ligand is the rate-determining step, while the cross metathesis reaction is comparably fast. Experiments performed at 40°C show that full conversion is obtained within 4 hours in case tosyl chloride is applied as phosphine scavenging agent. Although conversion of complex **7** to **8** is less successful in case of acetyl chloride, results were notably better compared to the polymer-supported sulfonic acid resin as phosphine scavenger. It is known that reaction of a tertiary amine with acetyl chloride results in the formation of a ketene and the corresponding trialkyl ammonium chloride *via* an acyl ammonium chloride intermediate which undergoes HCl elimination. The chemical properties of acyl phosphonium salts are rather undocumented and it is therefore unclear whether the product of the reaction of trialkyl phosphines with acetyl chloride undergoes HCl elimination. In terms of a polymer-supported acetyl chloride, such an event would transform the polymer-supported reagent to a ketene while the phosphonium chloride remains in solution. In case of tosyl chloride, however, no α-hydrogens are available and the tosyl phosphonium salt should therefore be stable against decomposition. Therefore, we anticipated that the application of *p*-toluene sulfonic acid chloride as a phosphine scavenging agent should allow for the straightforward sequestration of the phosphine by-product. In addition, the polymer-supported sulfonic acid chloride is commercially available, in contrast to a polymer-supported carboxylic acid chloride. Furthermore, reactions performed at 70°C show that full conversion is obtained within 1.5 hours (Figure 7.3).

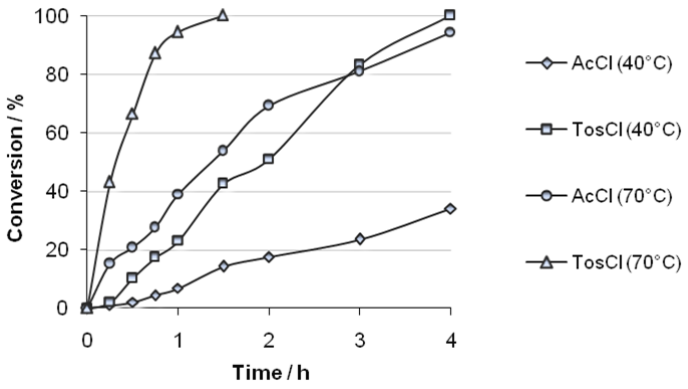

Figure 7.3: Conversion of complex **7** to complex **8** using tosyl or acetyl chloride as phosphine scavenger.

With these results at hand, we endeavored the synthesis of complex **8** on a 1 mmol scale from the reaction of **7** with 1.05 equiv 2-isopropoxystyrene in presence of 8 equiv of the polymer-supported sulfonic acid chloride, PL−SO_2Cl in THF at 70°C(Figure 10.4). The reaction was complete within 2 hours as determined by ^{31}P NMR spectroscopy. The reaction mixture was filtered through a Pasteur pipette equipped with a cotton plug and the solvent was stripped off *in vacuo*. ^{1}H NMR spectroscopy of the resulting residue, however, revealed the presence of various hydride species. We tentatively attribute this observation to the large excess of tosyl chloride. The lone electron-pairs at the oxygen-atom of the isopropoxy-benzylidene group in complex **8** can coordinate to the acidic sulfur-atom of the residual tosyl chloride on the surface of the polymer resin, and therefore destabilize the κ^2-(C,O)-chelation. As such, tosyl chloride can force the decoordination of the oxygen ligand, leaving the highly unstable 14-electron ruthenium species vulnerable to decomposition with formation of unidentified hydrido ruthenium complexes. Further purification of the residue using silica gel chromatography yielded the desired complex **8** as a brown powder in 72% isolated yield.

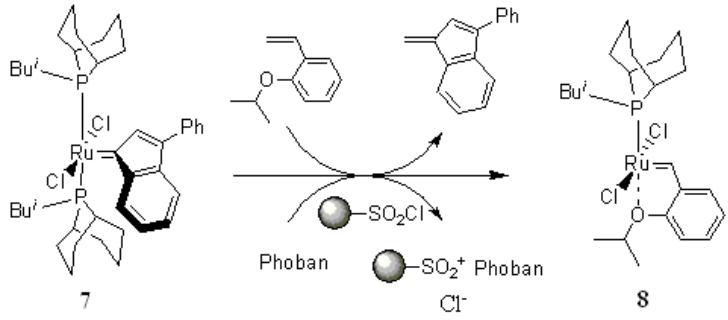

Figure 7.4: Synthesis of complex **8** using a polymer-supported tosyl chloride as phosphine scavenger.

NMR analysis of the obtained powder reveals a downfield shifted singlet at δ 17.56 ppm in the ^{1}H NMR spectrum, assigned to the Ru=CH_α, which is in the characteristic region for Grubbs-Hoveyda type complexes. The ^{31}P NMR spectrum shows one singlet at δ 39.04 ppm, which is significantly upfield compared to Grubbs-Hoveyda 1st generation catalyst (δ 59.17 ppm) [1] but in the range of the reported chemical shift for complex **6** (δ 37.64 ppm) [7]. The ^{13}C NMR spectrum shows a significantly downfield shifted doublet at δ 282.20 ppm, indicative for the Ru=C$_\alpha$-carbon in the chelating isopropoxy-alkylidene ligand.

7.2.2 Olefin Metathesis Experiments

We have previously pointed out that the potential of Grubbs-Hoveyda type olefin metathesis catalysts bearing a phoban ligand is virtually unexplored. In order to straightforwardly assess the scope of catalyst **8** in standard olefin metathesis reactions, [8] we performed a bench mark study using catalysts **1**, **2**, **3** and **7**. Kinetic plots were recorded in order to reveal information on the catalytic behavior. Results are given in Figures 7.5-7.7.

Under the reaction conditions applied, Grubbs 1st generation catalyst **1** performed the ring-closing metathesis of diethyl diallylmalonate to completion within one hour at a catalyst loading of 1 mol% whereas other catalysts attained a 87-95% conversion after the same period. Tricyclohexyl phosphine based 1st generation catalysts **1** and **2** exhibited a significantly higher initial reaction rate compared to their phoban-

based congener **7**. Regardless of its lower initial catalytic activity, the substrate conversion using **7** equalled that of catalyst **2** after 1 h. In contrast, the phoban-Hoveyda catalyst **8** showed a higher initial activity compared to the PCy_3-based **3**, albeit at the expense of a lower over-all conversion after one hour.

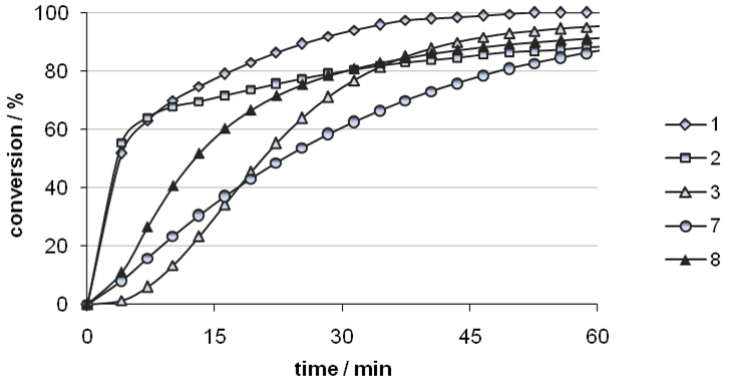

Figure 7.5: Ring-closing metathesis of diethyl diallylmalonate with catalysts **1**, **2**, **3**, **7** and **8**.

The conclusion that bis-phosphine catalysts **1** and **2** show a higher initial activity compared to their Hoveyda type congener **8** holds for the ring-closing metathesis of the more challenging diethyl allyl methallylmalonate. Bis-phosphine catalysts **1** and **2** convert 12% and 15%, respectively, of the substrate within 4 minutes. This high initial activity is followed by a modest further increase of substrate conversion. In contrast to the ring-closing metathesis reaction of diethyl diallylmalonate, catalyst **7** now exhibits a high initial catalytic activity (14% after 4 min.) and likewise catalysts **1** and **2**, conversion futher increases at a constant rate. Interestingly, the slope of the conversion curve between 15 and 60 min. is nearly equal for PCy_3-based catalysts whereas the slope for the phoban catalyst is significantly higher. Eventually, catalysts **1**, **2** and **7** converted 25%, 30% and 45% of the substrate after one hour, respectively.

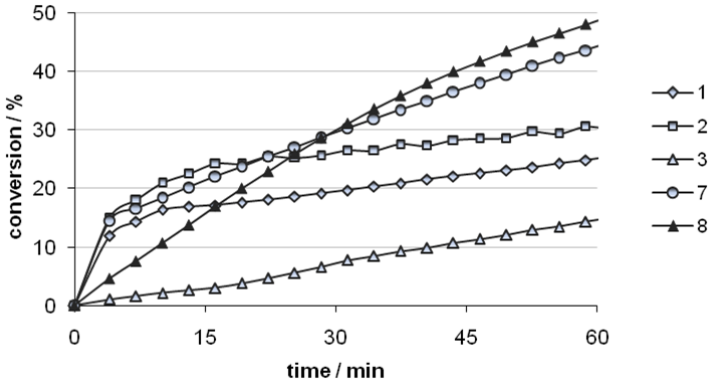

Figure 7.6: Ring-closing metathesis of diethyl allylmethallylmalonate with catalysts **1**, **2**, **3**, **7** and **8**.

Again, the Hoveyda type catalysts **3** and **8** show a significantly lower initiation rate, but the difference in catalytic activity between **3** and **8** is now more striking. Whereas catalyst **3** converts merely 15% of the substrate after 1 hour, **8** converts almost 50% of substrate after the same period. Conversion of the reaction using catalyst **8** further increased gradually to 90% after 48 hours (Table 7.2). It should also be noted that in spite of it lower initial activity compared to catalysts **1**, **2** and **7**, catalyst **8** exhibited the highest turn-over after 1 hour.

Table 7.2: Ring-closing metathesis of diethyl allyl methallylmalonate with catalyst **8**.

Entry	Time / h	Conversion /%
1	1	49
2	2	64
3	4	73
4	8	82
5	48	90

As standard reaction conditions for the ring-opening metathesis polymerization of cyclooctadiene, Grubbs proposed a 0.1 mol% catalyst loading. Bearing in mind that 1^{st} generation type olefin metathesis

catalysts exhibit a significantly lower polymerization activity than their 2^{nd} generation congeners - especially Hoveyda 1^{st} generation type catalyst exhibit poor polymerization activities - we decided to enhance the catalyst loading to 0.4 mol%. Results are summarized in Figure 7.7. Grubbs catalyst **1** and indenylidene catalyst **2** exhibit catalytic activities which are in line with results reported in section **??**. Catalyst **7** exhibits very poor polymerization activity and converts less than 5% of the monomer after 1 hour. This discrepancy in catalytic activity, especially in the initial stage of the reaction, between PCy_3 and phoban type catalysts is in accordance with the results found for the ring-closing metathesis reaction of diethyl diallylmalonate. Most notably, regardless of the enhanced catalyst loading, Grubbs-Hoveyda type catalysts **3** and **8** were devoid of any polymerization activity. The same conclusion was drawn for catalyst **3** by Grubbs *et al.* [8]

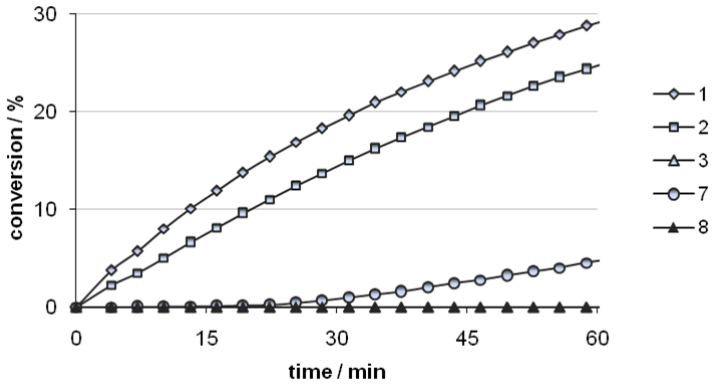

Figure 7.7: Ring-opening metathesis polymerization of 1,5-*cis*,*cis*-cyclooctadiene with catalysts **1**, **2**, **3**, **7** and **8**.

7.3 Conclusion

In this chapter, we reported the synthesis of a Hoveyda-type catalyst bearing a phosphabicyclononane ligand using a polymer-assisted solution phase synthetic approach. Although the polymer-supported sulfonic acid did not afford the straightforward synthesis of compound **8**, an analogous approach using a polymer-supported sulfonic acid chloride

proved satisfactory. Regardless of the minor decomposition observed during this reaction, **8** was isolated as a pure compound after purification on silica gel. The activity of the novel catalyst **8** in standard olefin metathesis reactions was compared to catalysts **1**, **2**, **3** and **7**. From these results, **8** proved to be an excellent catalyst for the formation of trisubstituted olefins *via* ring-closing metathesis. In ring-opening metathesis polymerizations, however, **8** exhibited no catalytic activity.

7.4 Experimental section

Monitoring the reaction of **7** with 2-isopropoxystyrene to **8** in presence of Amberlyst 15-A: A 7 mL vial containing 1.7 mg of 2-isopropoxystyrene (1.05 equiv) and equipped with a stir bar was charged with 1.00 mL of a 0.01 M stock solution of catalyst **7** in dichloromethane and 16 equiv (41.0 mg) of Amberlyst 15-A resin. The vial is put under an Ar atmosphere, capped and heated to 40°C. The reaction is monitored by ^{31}P NMR spectroscopy.

Monitoring the reaction of **7** with 2-isopropoxystyrene to **8** in presence of 8 equiv acetyl chloride: 0.50 mL of a stock solution containing 0.01 M of complex **7** and 0.0105 M of 2-isopropoxystyrene in CD_2Cl_2 was charged into an NMR-tube. 2.8 µL acetyl chloride (8.0 equiv; 8.0 mmol) is added and the NMR-tube is capped and sealed with Parafilm. The vial is heated to 40°C/70°C and the reaction is monitored by ^{1}H NMR spectroscopy.

Monitoring the reaction of **7** with 2-isopropoxystyrene to **8** in presence of 8 equiv tosyl chloride: 0.50 mL of a stock solution containing 0.01 M of complex **7** and 0.0105 M of 2-isopropoxystyrene in CD_2Cl_2 was charged into an NMR-tube. 7.6 mg tosyl chloride (8.0 equiv; 8.0 mmol) is added and the NMR-tube is capped and sealed with Parafilm. The vial is heated to 40°C/70°C and the reaction is monitored by ^{1}H NMR spectroscopy.

1 mmol scale preparation of Hoveyda catalyst **8** from **7**: A flame-dried Schlenk reaction flask is charged with a stir bar and put under an Ar atmosphere. 759 mg **7** (1.00 mmol), 173 mg 2-isopropoxystyrene (1.05

mmol; 1.05 equiv) and 1.72 g PL-SO_2Cl resin (8.00 mmol; 8 equiv) was loaded into the reaction flask and 25 mL CH_2Cl_2 is added. The reaction was stirred at 70°C for 1.5 h and the solution colored from red to brown. Subsequently, the reaction mixture is sent through a Pasteur pipette equipped with a cotton plug to remove the polystyrene-supported sulfonic acid chloride resin. After evaporation of the solvent, the residue was purified on a silica column using EtOAc/*n*-hexane : 1/19 $\longrightarrow$ 1/4 as eluent. After evaporation of all volatiles, the residue is suspended in 20 mL *n*-hexane and subsequently filtered off on a glass frit. Drying of the brownish powder *in vacuo* afforded 373 mg of the desired compound (yield: 72%). ^{31}P NMR (300.18 MHz, 22°C, $CDCl_3$, Me_4Si): δ 39.04 (s) ppm. ^{1}H NMR (300.18 MHz, 22°C, $CDCl_3$, Me_4Si): δ 17.56 (s, 1H, Ru=C*H*); 7,66 (d, 2H, J_α = Hz, phenyl-*H*); 7.09 (q, 2H, J_α = Hz, phenyl-*H*); 5.32 (sept, J_α = Hz, O-C(*H*)$(Me)_2$); 2.82 (); 1.79 (d, 13H); 2.16-2.42 (); 1.29 (d, 9H). ^{13}C NMR (300.18 MHz, 22°C, $CDCl_3$, Me_4Si): δ 282.80 (d, J_α = Hz, Ru=*C*);130.12; 123.30; 123.04; 113.67; 75.80; 35.35; 35.04; 28.88; 28.38; 28.30; 27.69; 26.26; 26.05; 25.95; 25.89; 22.25; 22.10; 21.67; 21.60.

Ring-closing metathesis of diethyl diallymalonate: An NMR tube was charged with 50 µL (0.50 µmol, 1 mol%) of a 0.010 M catalyst stock solution in CD_2Cl_2 and 450 µL (80 µmol) of a 0.11 M stock solution of diethyl diallylmalonate in CD_2Cl_2 was added. The reaction was performed at room temperature (25°C) and the conversion was monitored by integration of the allylic signals of diethyl diallylmalonate (δ 2.61 ppm) and 4,4-dicarboxylic acid cyclopent-1-ene diethyl ester (δ 2.98 ppm) in the ^{1}H NMR spectrum.

Ring-closing metathesis of diethyl allylmethallylmalonate: An NMR tube was charged with 50 µL (0.50 µmol, 1 mol%) of a 0.010 M catalyst stock solution in CD_2Cl_2 and 450 µL (80 µmol) of a 0.11 M stock solution of diethyl allylmethallylmalonate in CD_2Cl_2 was added. The reaction was performed at room temperature (25°C) and the conversion was monitored by integration of the allylic signals of diethyl allylmethallylmalonate (δ 2.64-2.67 ppm) and 1-methyl-4,4-dicarboxylic acid cyclopent-1-ene diethyl ester (δ 2.88-2.93 ppm) in the ^{1}H NMR spectrum.

Ring-opening metathesis polymerization of 1,5-*cis*,*cis*-cyclooctadiene:

Synthesis N,N'-dimesitylformamidine: 26.7 mL mesitylamine (212 mmol; 2 equiv), 17.6 mL triethyl orthoformate (106 mmol; 1 equiv) and 0.30 mL acetic acid (5.30 mmol; 0.05 equiv) is charged into a 100 mL flask with reflux cooler. The mixture is allowed to stir for 3 h at 140°C and subsequently for 0.5 h at 160°C. Upon cooling, a colorless solid precipitated. After filtration and washing of the solid, the product is dried *in vacuo* (yield: 85%). ^{1}H NMR (300 MHz, C_6D_6); δ (ppm), major isomer: 6.99 (s, 1H), 6.93 (s, 2H), 6.58 (s, 2H), 5.00 (d, 1H), 2.35 (s, 6H), 2.27 (s, 3H), 2.06 (s, 3H), 1.89 (s, 6H); minor isomer: 6.85 (s, 1H), 6.78 (s, 4H), 2.19 (s, 12H), 2.15 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm): 147.4, 134.2, 129.6, 129.2, 129.1, 128.6, 98.8, 86.3, 86.3, 78.1, 45.8, 21.0, 19.2, 18.9, 18.1.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 8.33 (s, 1H, N=C*H*), 7.35 (s, 10H, Ph-*H*), 6.96 (s, 2H, Ph-*H*, mesityl), 6.65 (s, 2H, ph-*H*, mesityl), 2.32 (s, 6H, CH_3), 2.27 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.73 (s, 6H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm): 169.3 (*C*=O), 149.8, 145.4, 140.1, 138.4, 135.4, 133.3, 132.6, 129.8, 129.2, 128.8, 128.7, 128.6, 127.9, 21.4, 20.9, 18.6, 18.3.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 11.81 (s, 1H, *H*CNN), 7.51-7.31 (10H, Ph-*H*), 7.04 (s, 2H, Ph-*H*, mesityl), 6.77 (s, 2H, Ph-*H*, mesityl), 2.48 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.80 (s, 6H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm): 172.8 ,(*C*=O), 168.3 (*C*NN), 141.7,141.7, 137.5, 135.9, 131.0, 131.0, 130.8, 130.6, 130.0, 129.3, 126.0, 21.3, 21.1, 20.7, 19.6.

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8

A Highly Controllable Latent Ruthenium Schiff Base Olefin Metathesis Catalyst

8.1 Introduction

Attention of synthetic polymer chemists, both from academy and industry, has long been attracted to polydicyclopentadiene (PDCPD), a high-tech polymer synthesized through the ROMP of DCPD. [1–8] Unfortunately, application of the relatively fast initiating Grubbs catalysts **1**-**3** (Figure 8.1) proved disadvantageous since they do not allow for longer handling or shelf-life of the monomer/catalyst mixture.

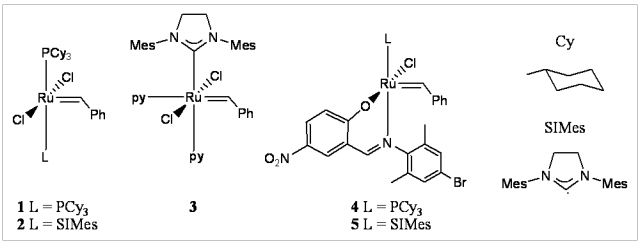

Figure 8.1: Highly active Ru olefin metathesis catalyst **1-3** and Schiff base catalysts **4**, **5**.

In this respect, latent ruthenium catalysts enabling on-demand catalyst activation have been investigated in order to avoid room temperature activity. [9] Although various approaches are reported, most widely applied strategies comprise incorporation of chelating ligands that allow for adjourning the chelate after thermal, chemical or photoactivation. Grubbs, Slugovc and Grela disentangled the field of thermally stable κ^2-(C,N) type ruthenium catalysts. [10–15] Lemcoff *et al.* reported on the thermal and photochemical activation of chelating κ^2-(C,S) ruthenium catalysts. [16–18] Grubbs illustrated the applicability of photo-acid generators (PAG's) for the photo-chemical activation of latent bis-κ^2-(O,O) ruthenium complexes. [19] Sijbesma explored the possibility of mechanical activation of latent ruthenium catalysts bearing N-heterocyclic carbene ligands with a pTHF N-substituent. [20] Recent developments heading for enhanced thermal stability were inspired by an early report of Grubbs, describing a catalytic system substituted with a bidentate κ^2-(O,N) Schiff base ligand **4** (Figure 1). [21] Schiff base substituted ruthenium complexes bearing an N-heterocyclic carbene ligand, *e.g.* **5**, (Figure 1) were first investigated by our group and compound **5**turned out to be a very latent precatalyst towards monomers such as COD and DCPD. [7, 22–26] At higher temperature, the catalytic activity increased, but activities comparable to the corresponding complexes without a Schiff base ligand could not be reached. [7] Gentle activation of these catalysts using Lewis acids afforded high activity towards ROMP of COD, [24] however merely moderate activity was observed when applied to the ROMP of DCPD. Therefore, more competent activation methodologies for these catalysts are still in demand. Ledoux

also commented on the activity of catalyst **5** for the ROMP of COD after chemical activation of the catalyst using hydrochloric acid. A such methodology has been successfully applied for the chemical activation of various latent olefin metathesis catalysts. [**?**, 19, 27–32] We here validate a similar approach for the ROMP of DCPD. Catalyst latency towards DCPD is depicted through the monitoring of the viscosity of a DCPD-catalyst mixture. Furthermore, a convenient protocol for the activation of the catalyst is reported, based on the *in situ* generation of hydrochloric acid from the reaction of alcohols with Lewis acids. Mechanistic insight on the activation of catalyst **5** is provided through a ^{1}H NMR study.

8.2 Results and discussion

8.2.1 Latent catalyst activation

Ring-opening metathesis polymerization of DCPD

Ledoux and Verpoort have previously studied the activity of catalyst **5** and concluded on its latency towards the ring-opening metathesis polymerization of cyclooctadiene. However, this catalysts was transformed to a highly active form upon activation with hydrochloric acid. Consequently, fast polymerization of high monomer/catalyst ratios were obtained. These features, a latent catalyst which can be activated on demand for polymerization with high monomer to catalyst ratios in a short period of time, suggest the possibility of application in Reaction Injection Molding (RIM) processes. This RIM technology is of particular interest for the ROMP of DCPD (**8**) to PDCPD, a rigid thermoset with exquisite chemical and physical properties (Figure 2). [33] In this process, two monomer streams (one containing the latent catalyst and one containing the co-catalyst) are injected and mixed under pressure in a mixing head before the mixture is squirted into the mold where polymerization and curing occurs at atmospheric pressure. Preliminary investigations into the possibility of establishing a RIM procedure for the ROMP of DCPD using catalyst **5** led to similar observations obtained from ROMP of COD. This Schiff base bearing catalyst **5** was inactive for the ROMP of DCPD at room temperature while high activity was observed upon the addition of hydrochloric acid as co-catalyst.

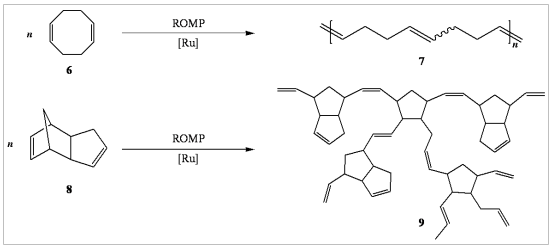

Figure 8.2: Ring-opening metathesis polymerization of 1,5-cyclooctadiene (**6**) and dicyclopentadiene (**8**).

Figures 8.3 and 8.4 show thermoplots for the exothermal polymerization of DCPD using the acid activated catalyst **5** at room temperature. The plots indicate that rather large excesses (20 to 40 equivalents) of HCl were required to give way to excellent catalyst activation. An optimized ratio appeared at about 30 equivalents of co-catalyst. Moreover, turn over numbers up to 60,000 were readily achieved (Figure 6). In all cases the exothermal temperatures reached were very high (160-190℃) and were found to depend on the amounts of acid and on the DCPD/catalyst ratio.

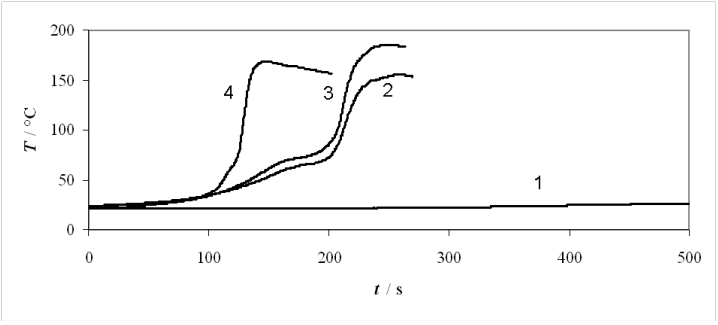

Figure 8.3: Exotherm plot for ROMP of DCPD. Conditions: **5**/DCPD = 1/30,000. 1: **5**/HCl = 1/10; 2: **5**/HCl = 1/20; 3: **5**/HCl = 1/30; 4: **5**/HCl = 1/40; r.t.

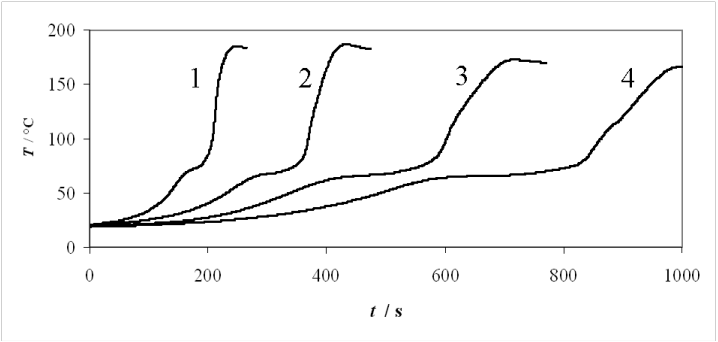

Figure 8.4: Exotherm plot for ROMP of DCPD. Conditions: **5**/HCl = 1/30. 1: **5**/DCPD = 1/30,000; 2: **5**/DCPD = 1/40,000; 3: **5**/DCPD = 1/50,000; 4: **5**/DCPD = 1/60,000; r.t.

Latency

The latency and stability of the precatalyst **5** are relevant in relation to facile handling and shelf-life of the catalyst-monomer mixture. Two formulations with respectively a monomer/catalyst ratio of 15,000/1 and 30,000/1 were prepared and the viscosity, as a semi-quantitative indication for the degree of polymerization, was monitored. Results show that regardless of the unequivocal increase of viscosities, viscosities do not excess the threshold for further processing of these formulations (Figure 8.5).

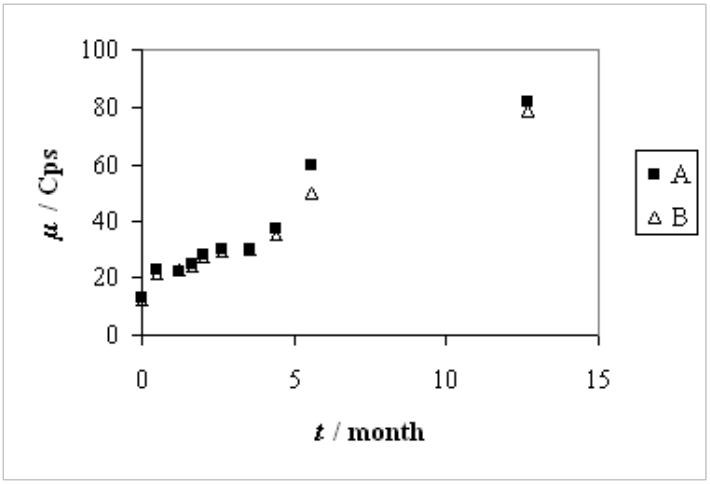

Figure 8.5: Monitoring viscosities of DCPD/catalyst formulations. Temperature = 5℃; A: monomer/catalyst ratio = 15,000; B: monomer/catalyst ratio = 30,000.

Figure 8.6 shows the activity of precatalyst **5** activated with hydrochloric acid compared to the activity of precatalyst **5** stored for one year in DCPD at a monomer/catalyst ratio of 15,000/1. These results show that similar peak temperatures are obtained for both solutions, which lead us to the conclusion that despite of its shelf-life, the precatalyst lasts unimpaired. The mere discrepancy observed regarding the initiation time ($\sim$ 200 sec) is still acceptable towards processing. To the best of our knowledge, no reports on latent ruthenium metathesis catalysts exhibiting one year shelf-life towards ROMP of DCPD preceded.

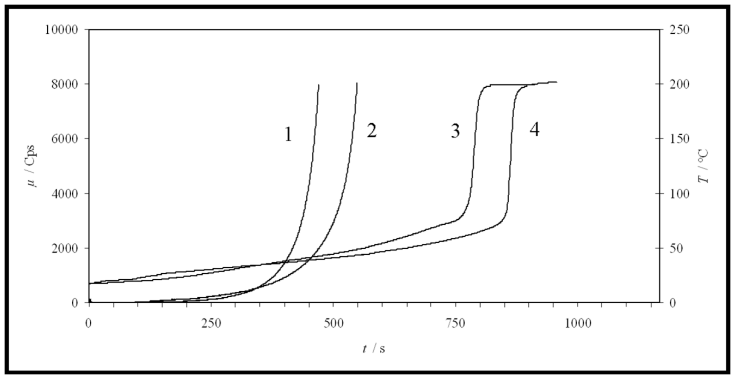

Figure 8.6: Exothermic graphs and viscosity plots during ROMP of DCPD with precatalyst **5**. 1: μ (original formulation); 2: μ (after 1 year); 3: T (original formulation); 4: T (after 1 year). r.t.

In situ generation of the co-catalyst

The use of hydrochloric acid limited the reach of the technology due to low vapor pressure of the co-catalyst and lack of reaction control. The application of Bronsted acids other than hydrochloric acid generally led to deteriorate results and application of Lewis acids such as $HSiCl_3$, a highly potent co-catalyst for the ROMP of COD, gave no satisfactory results (see Table 8.1). As such, reaction control is limited to variation of mold temperature. In contrast, an *in situ* generation protocol for hydrochloric acid may prove advantageous instead. The usefulness of a catalyst system for the ROMP of DCPD with *in situ* generation of HCl from reaction of alcohols or carboxylic acids and the appropriate Lewis acids is illustrated in Table 8.2.1, page 164. Since injection into the mold occurs within the range of seconds, we reasoned that study of the gelation time is of minor importance. The exothermal temperature reached and the time to exotherm, on the other hand, are a *semiquantitative indication of the extent of the polymerization* [1] and are relevant for the cycle time in RIM processes.

Table 8.1: Effect of Brønsted acid on the Bulk Polymerization of DCPD.[a]

Entry	Co-catalyst	acid/Ru mol/mol	Exotherm Maximum	
			Time / min	Temperature / °C
1	HCOOH	30	-[b]	-[b]
2	CF_3COOH	20	27.8	37
3	CF_3COOH	40	16.1	54
4	CF_3COOH	80	12.9	64
5	CF_3COOH	160	14.6	66

[a] catalyst/monomer ratio = 1/30,000; Brønsted acid added to monomer stream; catalyst **5** dissolved in 0.10 mL CH_2Cl_2; [b] no exotherm.

Most importantly, the results (Table 3, entry 1-4) shows excellent exothermal temperatures, a clear evidence for the assumption that *in situ* generation of HCl could lead to efficient catalyst activation. Moreover, no significant differences in exotherms are witnessed and a clear control of the co-catalyst system on the induction period is observed. Selecting the appropriate alcohol or carboxylic acid enables variation of the catalyst activation over a time range of 8 minutes.

Entry	MCl_x	MCl_x/Ru (mol/mol)	ROH	ROH/Ru (mol/mol)	Exotherm Time (min)	Maximum T (°C)
1	$MeHSiCl_2$	30	*n*-propanol	60	8.2	176
2	$MeHSiCl_2$	30	3,5-dimethylphenol	60	4.8	176
3	$MeHSiCl_2$	30	acetic acid	60	7.6	174
4	$MeHSiCl_2$	30	benzoic acid	60	12.8	177
5	$SiCl_4$	22.5	*n*-propanol	90	4.0	184
6	$HSiCl_3$	30	*n*-propanol	90	5.4	185
7	$MeHSiCl_2$	45	*n*-propanol	90	6.5	171
8	Me_2SiCl_2	45	*n*-propanol	90	16.0	161
9	Me_3SiCl	90	*n*-propanol	90	55.0	61
10	$^tBuMe_2SiCl$	90	*n*-propanol	90	-[b]	-[b]
11	$FeCl_2$	45	-	-	164.8	29
12	$FeCl_2$	45	*n*-propanol	90	64.7	24
13	$FeCl_2$	45	3,5-dimethylphenol	90	19.6	28
14	$TiCl_4$	22.5	-	-	7.7	29
15	$TiCl_4$	22.5	*n*-propanol	90	2.0	201
16	$TiCl_4$	22.5	3,5-dimethylphenol	90	1.1	202

Entry	MCl_x	MCl_x/Ru (mol/mol)	ROH	ROH/Ru (mol/mol)	Exotherm Time (min)	Maximum T (°C)
17	$SnCl_4$	22.5	*n*-propanol	90	2.8	178
18	$SnCl_4$	22.5	3,5-dimethylphenol	90	29.7	107
19	BF_3	30	*n*-propanol	90	_[b]	_[b]
20	BF_3	30	3,5-dimethylphenol	90	_[b]	_[b]
21	$AlCl_3$	30	1-propanol	90	3.3	163
22	$AlCl_3$	30	3,5-dimethylphenol	90	1.2	170
23	PBr_3	30	*n*-propanol	90	73.7	59
24	PBr_3	30	3,5-dimethylphenol	90	11.3	156
25	$AlCl_3$	30	isonox	90	1.0	172
26	$SiCl_4$	22.5	isonox	90	6.5	184
27	PBr_3	30	isonox	90	27.8	39
28	$SnCl_4$	22.5	isonox	90	18.8	27
29	$FeCl_2$	45	isonox	90	24.4	28
30	$TiCl_4$	22.5	isonox	90	27.6	29

[a] catalyst/monomer ratio = 1/30,000; ROH added to catalyst stream, Lewis acid added to monomer stream; catalyst **5** dissolved in 0.10 mL CH_2Cl_2. [b] no exotherm.

Elaboration of the newly established protocol shows that the strength of the Lewis acid is determining for the efficiency of *in situ* generation of the hydrochloric acid and consequent catalyst activation. On varying the Lewis acid in the series $SiCl_4$, $HSiCl_3$, $MeHSiCl_2$, Me_2SiCl_2, Me_3SiCl and $^tBu(Me)_2SiCl$ (Table 3, entry 5-10), a definite decrease of exothermal temperature and an increased initiation period is observed. Efficient generation of HCl leads to improved exotherms and will consequently yield better physical properties of the polymeric end-product. The importance of the Lewis acidity strength on the extent of the reaction is further illustrated by the use of $FeCl_2$ and $TiCl_4$ respectively (see Table 3, entry 11-16) in combination with 1-propanol and 3,5-dimethylphenol. In the case of $FeCl_2$, there is no significant rise of temperature, leading to the conclusion that the catalyst in not activated sufficiently. In case of $TiCl_4$, which is a stronger Lewis acid compared to both $FeCl_2$ and $SiCl_4$, the reaction temperature boosts to 202°C within one minute. On the other hand, the results show that in the absence of alcohols, the catalyst is not activated, neither by $TiCl_4$ nor by $FeCl_2$ (Table 3, entry 11, 14). This indicates that the formation of HCl from of the reaction of these Lewis acids and the alcohol is a requisite for efficient catalyst activation. Reactions performed with $WOCl_4$, WO_2Cl_2 or $NbCl_5$ were unsuccessful, probably due to their insolubility in the monomeric product. Further examples (Table 3, entry 17-22) illustrate the flexibility in the co-catalyst generation system and the control on the polymerization reaction resulting thereof.

Reproducibility of the RIM process using catalyst 5

Industrial processing not only requires sufficient catalyst latency and the ability to control the catalyst activity upon activation. A well-defined catalyst system requires reproducibility of the results in terms of time and exothermal temperature of the polymerization reaction. In order to depict the reproducibility of the results, ten polymerization reactions using 45 equiv $MeHSiCl_2$ and 90 equiv *n*-propanol to generate the co-catalyst *in situ* were performed. Results for catalyst **5** are summarized

in Table 8.2.

Table 8.2: Reproducibility of the results for the Bulk Polymerization of DCPD using catalyst **5**[a]

Entry	Exotherm Maximum Time (min)	T (℃)
1	6.10	168
2	6.05	171
3	5.20	179
4	5.39	172
5	6.22	173
6	6.03	170
7	5.17	173
8	4.84	173
9	5.25	175
10	6.53	171

From these results, the average exothermal temperature was determined to 172.5℃ (standard deviation = 1.9℃); the average time required to finish the reaction was 5.68 min. (standard deviation = 0.51 min.). To better understand the significance of these numbers, we performed an analogous experiment using 2^{nd} generation Grubbs catalyst **2**. Results are summarized in Table **??**.

The average exothermal reaction temperature using catalyst **2** was determined to 178.2℃ (standard deviation = 4.1℃); the average reaction time needed to perform the reaction was 15.34 min. (standard deviation = 3.08 min.). These results illustrate that the average exothermal temperature obtained with catalyst **2** was 5.6℃ higher compared to that obtained with catalyst **5**. Being a semiquantitative indication for the extend of the polymerization reaction, these results suggest that catalyst **2** performs the reaction better than catalyst **5**. The standard deviation on the exothermal temperature, on the other hand, calculated from the results obtained for catalyst **2** is significantly higher than that obtained with catalyst **5**. The standard deviation on the exothermal temperature immediately relates to the deviation on the properties of the polymeric product obtained and therefore should preferable be low. In addition,

Table 8.3: Reproducibility of the results for the Bulk Polymerization of DCPD using catalyst **2**[a]

Entry	Exotherm Maximum Time (min)	T (°C)
1	13.73	180
2	9.71	186
3	12.40	180
4	16.42	179
5	19.96	176
6	15.23	165
7	13.93	180
8	13.53	182
9	11.90	181
10	26.59	173

cracks were observed in the polymeric product obtained with catalyst **2**. No such polymer cracking was observed in polymers prepared with catalyst **5**. A typical thermogram for the reaction performed with catalyst **5** shows a gradual increase of temperature from 20°C to 70°C followed by slow increase from 70°C to 80°C and eventually a steep increase of temperature from 80°C to 170°C. Thus, the increase of temperature is spread over the full reaction time. In case of 2^{nd} generation Grubbs catalyst **2**, however, the thermogram reveals a slow increase of temperature from 20°C to 45°C followed by a steep increase from 45°C to 180°C within 1 min. Of note, Dinger and Mol reported significantly higher TONs for catalyst **2** for the self-cross metathesis of 1-octene when the temperature surpasses the thermal threshold of 45°C and this temperature can thus be regarded as the threshold for thermal activation of catalyst **2**.[1] [34] It is reasonable to assume that the thermal strain from the reaction using catalyst **2** is responsible for the cracking of the polymer.

The average time to reach the maximum exothermal temperature is relevant with respect to cycle time in a RIM process. Again, this value

[1] In case no co-catalyst was used, reaction time for catalyst **2** was typically around 60 min. Thus, although the reaction is presumably excecuted by thermal activation of catalyst **2**, the co-catalyst significantly reduces the reaction time.

was significantly lower in case of Schiff base catalyst **5**. Moreover, the standard deviation of the reaction time was more than 6 times lower when reactions were conducted with catalyst **5**. In these respects, the Schiff base catalyst **5** is obviously the preferred catalyst.

In many respects, we can state that the described catalyst system stands unparalleled in literature through its control on the initiation rate of the polymerization, high catalyst activity and latency and reproducibility of the obtained results. Varying the alcohol used for the co-catalyst generation allows for enhanced control on the polymerization initiation period. We illustrated that the polymerization with this catalyst system offers good results in case of ratios up to 60,000/1. Furthermore, this newly established catalyst system exhibits a high degree of catalyst latency for at least 1 year without observable loss of activity.

8.2.2 Mechanism

NMR-scale experiments were performed to gain mechanistic understanding of the precatalyst activation. Since water and oxygen can not be excluded during industrial application, we were eager to find out about the activation mechanism in case of neat solvents and in case solvents were not pretreated. Spectra are included as supporting information. In a first experiment, catalyst **5** was dissolved in dry $CDCl_3$ in a NMR tube and 5 equivalents of HCl (solution in Et_2O) were added and the activation reaction was monitored by ^1H NMR spectroscopy. Immediately upon addition of HCl, new signals appeared between δ 8.40 ppm and δ 8.60 ppm corresponding to the protonated Schiff base ligand and a new, weak signal from the α-benzylidene proton appeared at δ 16.89 ppm. This new alkylidene signal suggests the formation of a 14-electron ruthenium complex bearing a monodentate Schiff base ligand, **10**. Although isolation of stable 14-electron ruthenium complexes under ambient conditions have previously been reported in literature, their observation remains rare. [27, 35, 36] These spectroscopic findings support the idea that monodentate aryloxide moieties contribute significantly to the stability of electron-deficient ruthenium species. [37, 38] The original alkylidene signal remains present for weeks in solution and no indications were found that neither the precatalyst **5** nor the activated species **10** decompose.

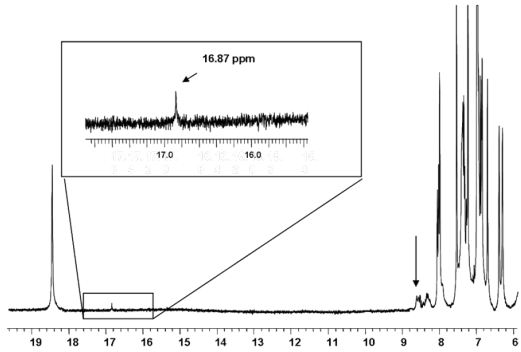

Figure 8.7: ^{1}H NMR spectrum of **5** after addition of 5 equivalents of etheral HCl in dry conditions. Conditions: time: 30 min., solvent: $CDCl_3$, temperature: r.t. For clarity only part of the spectrum is shown.

In case solvents were not pretreated, immediately upon addition of 5 equivalents of HCl to a solution of catalyst **5**, four new peaks were observed at δ 13.97 ppm assigned to a protonated phenoxide moiety of the Schiff base, at δ 11.62 ppm from the proton of the hydroxyl group from 4-nitrosalicylaldehyde, at δ 10.03 ppm assigned to the aldehyde proton (s, Ar-C(=O)H), and multiple peaks at δ 8.56 - 8.29 ppm resulting from the aromatic protons of 4-nitrosalicylaldehyde, respectively.

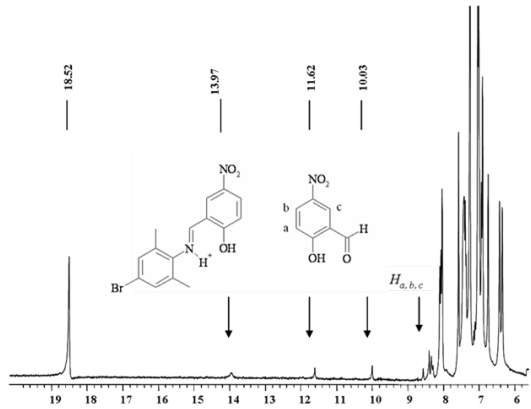

Figure 8.8: ^{1}H NMR spectrum of **5** after addition of 5 equivalents of ethereal HCl. Conditions: time: 30 min., solvent: $CDCl_3$, temperature: r.t. Solvents not pretreated prior to use. For clarity only part of the spectra is shown.

Increasing the amount of acid up to 20 equivalents gives rise to a new peak at δ 16.89 ppm which was recognized as the α-benzylidene proton of the activated species. It is reasonable to assume that the newly formed alkylidene compound corresponds to the 14-electron ruthenium complex **10** previously observed during the activation of complex **5** in neat solvents. At this point, full consumption of trace amounts of water can be assumed and a similar behavior of complex **5** towards hydrochloric acid is observed consequently. Further addition of hydrochloric acid results in a further increase of the signal at δ 16.89 ppm, indicating generation of a higher amount of active species. Although no spectroscopic evidence for the presence of complex **12** is observed, its formation is conclusive from the formation of protonated salicylaldimine (δ 13.97 ppm). Thus, its role towards catalytic activity can not be ruled out, especially in case of catalyst activation in bulk conditions. However, various hydride species had formed, witnessed by the appearance of two new peaks at δ -0.4 ppm and δ -3.9 ppm, a plausible indication for partial or full decomposition of **12** under the conditions studied. Although we were not able to identify these compounds, the region is characteristic for hydrido complexes and its role in the establishment of the *cis*/*trans* ratio through isomerisation should therefore be considered. Thus, it may be concluded that the presence of trace amounts of water is tolerated, albeit at the expense of sacrificial ruthenium precatalyst. Importantly, these results point out that the catalyst activation using hydrochloric acid is not quantitative. The requirement of excessive use of hydrochloric acid is in agreement with the results obtained from the catalytic tests (*vide supra*). The alkylidene peak from the starting complex **5** at δ 18.52 ppm persisted even after 24 hours, which indicates that complete activation did not took place.

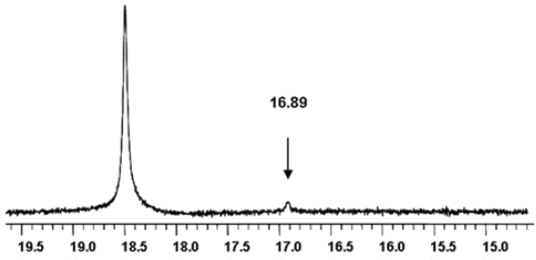

Figure 8.9: ^{1}H NMR spectrum of **5** after addition of 20 equivalents of ethereal HCl. Conditions: time: 2h, solvent: $CDCl_3$, temperature: r.t. Solvents not pretreated prior to use. For clarity only part of the spectra is shown.

Subsequently, *cis*-cyclooctene was added to the NMR tube, which resulted in immediate formation of polymer. This experiment enabled us to follow the creation of the propagating specie, **11**, with a new alkylidene resonance at δ 18.01 ppm while the signal of the activated specie, **10**, at δ 16.89 ppm disappeared completely. From these observations and the fact that the unactivated complex **5** is not active towards ROMP of unstrained cyclic olefins and the consideration that complex **10** proved to be stable for hours, we concluded that complex **10** acts as a catalyst in the above described experiment and that its initiation was quantitative as determined from the ^{1}H NMR spectrum.

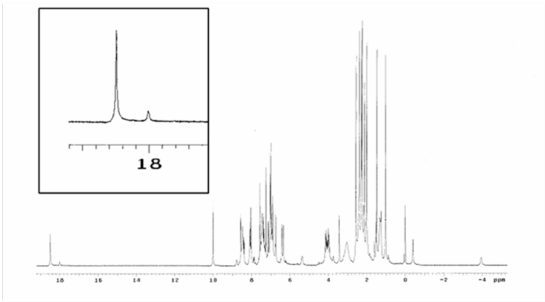

Figure 8.10: ^{1}H NMR spectrum of **5** after addition of 20 equivalents of ethereal HCl and subsequent addition (after 2h pre-activation) of 100 equiv cyclooctene. Conditions: time: 0.05h, solvent: $CDCl_3$, temperature: r.t. Solvents not pretreated prior to use. For clarity only part of the spectra is shown.

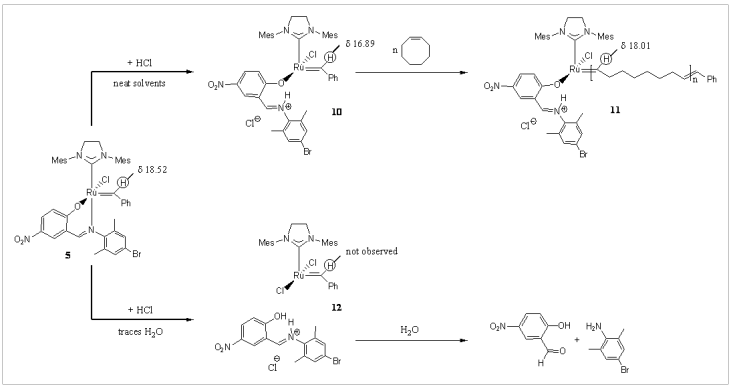

Figure 8.11: Proposed mechanism for the activation of the Schiff base ruthenium catalyst **5** in neat solvents (above) and in solvents not treated prior to use (below).

From these data, one can propose the following activation mechanism (Figure 1). In dry conditions, the acid protonates the N-atom of the Schiff base. This causes the generation of a vacancy at the ruthenium center and the active species can initiate ROMP when a cyclic olefin is added. In case traces of water are present in the solvent, a cleavage of the Ru-O bond occurs, [27, 31] generating a protonated phenoxide moiety of the Schiff base and a 14-electron ruthenium complex which supposedly initiates ROMP in presence of cyclic olefins or decomposes with formation of hydride complexes in case no cyclic olefins are present. Furthermore, the imine bond of the Schiff base condensates in presence of trace amounts of water resulting in the aldehyde and the aniline. When trace amounts of water are fully consumed, catalyst activation occurs according to activation in neat conditions.

8.3 Conclusions

In conclusion, the tested Schiff base catalyst, **5**, displays excellent stability and latency towards cyclic olefins and acts as precatalyst which is on-demand activated by the addition of hydrochloric acid. Extremely high TONs were reached for the ROMP of COD using the activated catalyst. Additionally, this feature, on-demand chemical activation, showed applicable for the polymerization of DCPD *via* a RIM procedure. *In*

situ generation of HCl, from the reaction of alcohols and the appropriate Lewis acids, gives way to excellent reaction control. A ^{1}H NMR study elucidated the activation mechanism of Schiff base ligated olefin metathesis precursors, comprising protonation of the Schiff base ligand with the formation of a stable 14-electron ruthenium complex. In case trace amounts of H_2O are present in the solvent, condensation of the imine bond and cleavage of the Ru-O bond occurs. Addition of excesses of hydrochloric acid to catalyst **5** allows for the observation of the activated catalyst, **10**. Upon subsequent addition of a cyclic olefin, the propagating specie, **11**, can be observed by ^{1}H NMR spectroscopy.

8.4 Experimental

General remarks

All synthetic manipulations were performed under an oxygen free argon atmosphere using Schlenk techniques. Argon was dried by passage through drierite. Reactions were carried out in dried, distilled and degassed solvents. Liquids were transferred by syringe and introduced into the Schlenk flasks through rubber septa or through a stopcock under positive argon pressure. NMR spectra were recorded with a Varian Unity-300 spectrometer, chemical shifts were reported in parts per million (δ) and referenced to TMS. COD was dried over calcium hydride, distilled and degassed by three standard freeze-pump-thaw cycles. $CDCl_3$ was dried on P_2O_5 and degassed prior to use. HCl was purchased from Acros as a 1N solution in Et_2O. Grubbs 1^{st} generation catalyst **1** was purchased from Aldrich. Catalysts **2** [39] **3**, [40] **4** [21] and **5** [7] were prepared according to literature procedures.

Ring-opening metathesis polymerization reactions

Representative procedure for ROMP tests of DCPD (containing 3.5 % tricyclopentadiene) using catalyst **5** (Figures 5, 6 and 8): The tests were performed conform to Reaction Injection Molding procedures, at room temperature (20℃) under adiabatic conditions, comprising the catalyst and the co-catalyst in separate monomer streams; monomer stream ratio = 1:1. The appropriate amount of catalyst **5** was dissolved

in 0.10 mL CH_2Cl_2 before addition of 5 mL DCPD. In a second vial, the appropriate amount of co-catalyst (1N solution of HCl in Et_2O) was added to 5 mL DCPD and was mixed thoroughly. Upon mixing, a thermogram is recorded with a Brookfield DV-II+Pro thermocouple in order to monitor the polymerization reaction temperature. Viscosities were determined with a Brookfield DV-II+Pro rotational viscosimeter which was removed from the reaction mixture once μ (Cp) > 8.000. Tests were performed on a 10 mL scale. Further details are reported together with the thermograms.

Representative procedure for ROMP tests of DCPD (containing 3.5 % tricyclopentadiene) using catalyst **5** in an *in situ* HCl generation protocol (Table 3): The tests were performed conform to Reaction Injection Molding procedures, at room temperature (20°C) under adiabatic conditions, comprising catalyst **5** and ROH and the Lewis acid in separate monomer streams; monomer stream ratio = 1:1. The appropriate amount of catalyst **5** and ROH was dissolved in 0.10 mL CH_2Cl_2 before addition of DCPD. In a second vial, the appropriate amount of Lewis acid was added to 5 mL DCPD and was mixed thoroughly. Upon mixing, a thermogram is recorded with a Brookfield DV-II+Pro thermocouple in order to monitor the polymerization reaction temperature. Tests were performed on a 10 mL scale. The maximum temperature and the time to reach this maximum are reported. Further details are given in Table 3.

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Part III

Conclusions

9

Summary and Outlook

9.1 Summary

9.1.1 Introduction

Olefin metathesis or alkene metathesis is a fundamental transformation of carbon-carbon double bonds which affords the formal exchange of alkyl substituents. In view of the fact that many organic molecules contain one or more carbon-carbon double bonds, the scope of potential applications of olefin metathesis is very wide. Moreover, if the final product does not contain a carbon-carbon double bond, it is very probable that a double bond is to be broken or made in one of the previous steps of the total synthesis. The power of olefin metathesis is in its versatility. Figure 9.1 shows an overview of the diverse mechanistically related olefin metathesis transformations.

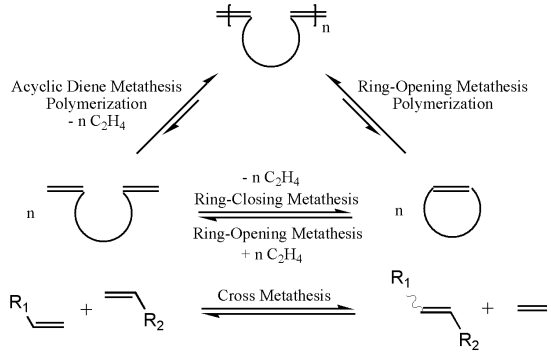

Figure 9.1: Mechanistically related olefin metathesis transformations.

In 1971, Chauvin postulated a mechanism in which a transition-metal carbene and a metallacyclobutane are key in this transformation, and it is the merit of Schrock and Grubbs that the olefin metathesis reaction is now well-known in virtually every synthetic organic lab. In 2005, the Nobel Prize Committee for Chemistry recognized these merits as a fundamental contribution to science.

In despite of these contributions, the accessibility of well-defined ruthenium catalyst remains a critical point in the development of this synthetic method. In this respect, ruthenium indenylidene complexes take a unique position since they are straightforwardly prepared and exhibit high intrinsic catalytic activity.

The developments in catalyst design have found numerous applications in organic and polymer-syntheses. A side-effect of this development was that researchers strived to an optimal ligand-environment. As such, the emphasis shifted from the development of ruthenium olefin metathesis catalysts to the development of task-specific catalysts. One class of task-specific catalysts is latent catalysts. These catalysts exhibit no catalytic activity at room temperature in presence of the aimed substrate or monomer, but can be triggered thermally, chemically or photochemically to yield high catalytic activity.

In the first part of this thesis, new ways towards novel ruthenium indenylidene catalysts were explored. In a second part, we attempted to take advantage of the synthetic accessibility of ruthenium indenylidene catalysts for the synthesis of highly active olefin metathesis catalysts. In a last section, an efficient activation methodology for latent Schiff base

olefin metathesis catalysts was explored.

9.1.2 Ruthenium Indenylidene Complexes with a saturated N-Heterocyclic Carbene: synthesis and catalytic activity in olefin metathesis reactions

Contrary to Grubbs-type catalysts, the optimization of the ligand environment in ruthenium indenylidene catalysts is significantly less studied. At the start of the doctoral research, catalysts **1** and **2** were the most widely known examples of ligand optimization in ruthenium indenylidene catalysts (Figure 10.2). The logical further step to catalysts of type **3** was not yet reported. Efforts to prepare this new type of olefin metathesis catalysts appeared successful by application of thermolytic degradation of imidazolidines.

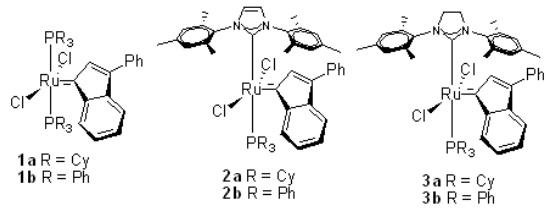

Figure 9.2: Ruthenium indenylidene type olefin metathesis catalysts.

The thus obtained catalysts **3** were thermally stable and appeared to be a good precursor for the synthesis of analogous complexes bearing a pyridine ligand *trans* to the N-heterocyclic carbene ligand. Their application in ring-closing metathesis reactions and ring-opening metathesis polymerization reactions revealed a good activity for the obtained catalysts. A comparative study with Grubbs type catalysts showed, however, that these catalysts suffer from a strongly diminished initiation rate.

9.1.3 Ruthenium Indenylidene Complexes with a Modified N-heterocyclic Carbene Ligand

Initiation kinetics of type **3** catalysts improved upon gentle heating or by exchange of the *trans* ligand with a coordinatively more labile ligand. An effort was undertaken to improve the initiation kinetics by modification of the N-heterocyclic carbene ligand. Introductory results had

shown that the suited modification of the N-heterocyclic carbene ligand in Grubbs-type catalysts strongly improves the initiation kinetics, especially for ring-opening metathesis polymerizations. Analogously as described above, a new *family* or ruthenium indenylidene catalysts was obtained. These catalysts exhibited a high catalytic activity as well, but a clear N-heterocyclic carbene ligand influence - like in Grubbs-type catalysts - could not be concluded.

9.1.4 A Polymer-Assisted Synthesis of Grubbs-Hoveyda Olefin Metathesis Catalysts

The obtained complexes were subsequently applied for the synthesis of the highly active Grubbs-Hoveyda catalysts (Figure 10.3). In this respect, CuCl is commonly applied for the scavenging of the phosphine ligand. The use of CuCl, however, put some limits. *I.e.*, CuCl is sensitive to oxygen which is problematic for handling and storage. In addition, the removal of CuCl from the reaction mixture after reaction is not straightforward and requires purification of the catalyst on silica gel. Column chromatography, however, is a solvent intensive protocol, which is not in line with the values of *green* chemistry. The here described alternative protocol uses a polymer-supported sulfonic acid for the scavenging of the liberated phosphines. Phosphine is thus readily removed from the reaction mixture by filtration of the polymeric material. Further workup of the obtained Grubbs-Hoveyda catalyst yields the desired product in high yield (+90%) and purity. Furthermore, this approach proved to be successful for the synthesis of related Grubbs-Hoveyda catalysts.

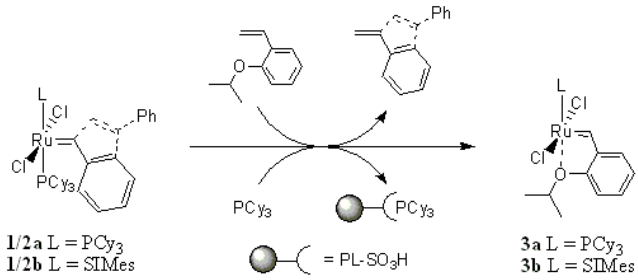

Figure 9.3: Synthesis of Grubbs-Hoveyda type catalysts by scavenging the liberated phosphine from the reaction mixture.

9.1.5 A Polymer-assisted Synthesis of a Phoban-Hoveyda Olefin Metathesis Catalyst

Although olefin metathesis catalysts bearing a N-heterocyclic carbene ligand are elaborately studied in literature - and also take a central role in this doctoral research - ruthenium catalyst with a phosphabicyclononane (phoban) ligand take a prominent position in the development of olefin metathesis catalysts. A Hoveyda-type catalyst bearing a phoban ligand was previously reported in literature, but its catalytic activity was virtually unreported. From the results obtained from the previous chapter, we described the application of a polymer supported paratoluene sulfonyl chloride as a phosphine scavenger for the synthesis of complex **8**.

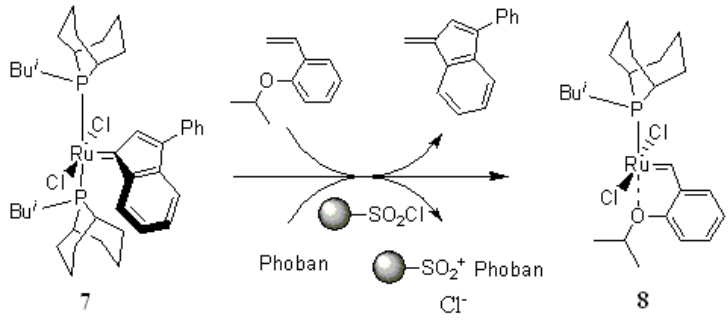

Figure 9.4: Synthesis of complex **8** using polymer supported paratoluene sulfonyl chloride as phosphine scavenger.

Although the obtained catalyst exhibited no catalytic activity towards ring-opening metathesis polymerizations, a high catalytic activity was observed in ring-closing metathesis reactions, especially for the metathesis of substituted olefins.

9.1.6 A Highly Controllable Latent Ruthenium Schiff Base Olefin Metathesis Catalyst

The last section of the doctoral research was devoted to the search for an effective manner for the activation of a latent ruthenium Schiff base catalyst for the ring-opening metathesis polymerization of dicyclopentadiene. The studied catalyst exhibited a remarkable latency towards the polymerization of cyclic olefins and it was shown that activation occurs preferably using hydrochloric acid. Since this acid did not prove applicable in an industrial reaction injection molding process, an *in situ* generation protocol of the hydrochloric acid was developed. The results showed that good reaction control and reproducibility was obtained. As such, these results stand unparalleled in literature.

9.2 Outlook

Looking at the fundamental developments witnessed in the last two decades, advances in the field of ruthenium based olefin metathesis chemistry have often been surprising or serendipitous. In an attempt to forecast evolutions in this field for the coming decade, one will certainly miss out on the most promising advancements. This does not prevent, however, that one can predict that certain fields of research will remain to attract academic and/or industrial interest or will be endowed with an increasing deal of attention.

The most relevant advances in olefin metathesis catalyst development have centered around catalyst stability, activity and selectivity, and improvements along these lines will most probably continue to be the focus of rational catalyst development. With respect to catalytic activity, the multitude of reports on olefin metathesis catalysts screened for various reactions under non-standardized reaction conditions prevents the straightforward comparison of catalytic activities across literature. This evolution holds the danger of ending up with a myriad of olefin metathe-

sis catalysts but loosing the overview of their potential. An attempt of the group of Grubbs to uniform the catalytic characterization conditions was in this respect *noble*, but did not catch on in literature. With respect to catalytic activity, it will be interesting to see how researchers will tackle the metathesis of olefins with a hetero-atom substituent. It has long been a myth that ruthenium carbene complexes with a hetero-atom at the carbene-atom are inactive for olefin metathesis reactions. Recently, however, it has been shown that these complexes are active olefin metathesis catalyst but their potential remains to be elaborated. The rational development of highly selective ruthenium olefin metathesis catalysts requires an advanced knowledge of the influence of the ligand environment on the catalytically active species and further research in this direction will be required. With the advent of ruthenium-based olefin metathesis catalyts, the issue on catalyst stability has extended from its stability in solid state to its stability during the olefin metathesis reaction, or in presence of strongly demanding substrates. Many efforts in this direction have focused on the understanding of the decomposition mechanism, but rational approaches to suppress catalyst decomposition are limited.

Furthermore, an evolution of the development of olefin metathesis catalysts of general applicability to metathesis catalysts specifically designed for a particular task can be observed. Prominent examples in this respect are the development of latent olefin metathesis catalysts and catalyst for olefin metathesis in aqueous environment or ionic liquids. Olefin metathesis in alternative reaction media or using a catalyst immobilized on a heterogeneous support hold the promise of a *green* technology, and this will continue to be the focus of various research.

From the above discussed considerations, it may be clear that research in the field of olefin metathesis remains to throw up interesting problems. From this perspective, we can state that the full potential of this interesting reaction is still to be established. We hope that some of the catalyst developments or tools discussed in this doctoral thesis can assist future research.

10

Nederlandstalige Samenvatting

10.1 Inleiding

Olefine metathese, ook wel alkeen metathese, is een fundamentele transformatie van een koolstof-koolstof dubbele binding die de formele uitwisseling van de alkyl-substituenten bewerkstelligt. Gezien vele organische moleculen een of meerdere koolstof-koolstof dubbele bindingen bevatten kent de olefine metathese reactie tal van toepassingen. Zelfs indien het eindproduct van een organische synthese geen dubbele binding bevat, is het vrij waarschijnlijk dat een dubbele binding dient gebroken of gemaakt worden in een van de vorige stappen. De kracht van de olefine metathese reactie ligt in haar veelzijdigheid. Figuur 9.1 toont een overzicht van diverse mechanistisch identieke olefine metathese transformaties.

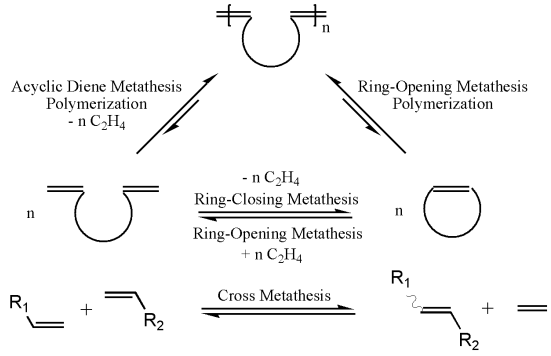

Figure 10.1: Mechanistisch gerelateerde olefine metathese reacties.

Chauvin postuleerde in 1971 een mechanisme waarin een transitiemetaal carbeen en een metallocyclobutaan de sleutelcomponenten vormden van deze transformatie, en het is de verdienste van Schrock en Grubbs dat de olefine metathese reactie nu in vrijwel elk synthetisch organisch laboratorium bekend is. In 2005 erkende het Nobel Prijs Comite voor de Chemie deze verdiensten als een fundamentele bijdrage tot de wetenschap.

Ondanks deze bijdragen blijft de toegankelijkheid van goedgedefinieerde ruthenium katalysatoren een kritisch punt in de ontwikkeling van deze synthetische methode. Ruthenium indenylideen complexen nemen in dit verband een unieke positie in gezien ze zeer gemakkelijk kunnen worden bereid, zelfs op industriele schaal, en een hoge intrinsieke katalytische activiteit hebben.

De ontwikkelingen in katalysator design hebben hun toepassingen gevonden in tal van organische en polymeer-syntheses. Een neveneffect van deze ontwikkeling was dat steeds meer naar een optimale ligand-sfeer werd gezocht. Op die manier verschoof de klemtoon van de ontwikkeling van ruthenium olefine metathese katalysatoren naar de ontwikkeling van taak-specifieke katalysatoren. Een klasse van taakspecifieke katalysatoren zijn de latente katalysatoren. Deze vertonen geen katalytische activiteit bij kamertemperatuur in aanwezigheid van het beoogde substraat of monomeer, maar kunnen thermisch, chemische of fotochemisch worden geactiveerd waardoor ze een hoge katalytische activiteit vertonen.

In een eerste deel van de thesis werd gezocht naar manieren om

nieuwe ruthenium indenylideen katalysatoren te bereiden. In een tweede deel werd betracht om gebruik te maken van de synthetische toegankelijkheid van ruthenium indenylideen complexen om nieuwe olefine metathese katalysatoren te bekomen. In een laatste deel werd het gebruik van een taak-specifieke, latente ruthenium katalysator aangetoond voor de ring-opening metathese polymerisatie van dicyclopentadieen.

10.2 Ruthenium Indenylideen Complexen met een verzadigd N-Heterocyclisch Carbeen: synthese en katalytisch onderzoek in olefine metathese reacties

In tegenstelling tot Grubbs-type ruthenium katalysatoren, is de optimalisatie van de ligand-sfeer in ruthenium indenylideen katalysatoren veel minder bestudeerd. Bij het begin van dit doctoraatsonderzoek waren katalysatoren **1** en **2** de meest bekende types van ligand-optimalisatie in ruthenium indenylideen katalysatoren (Figuur 10.2). De logische stap naar katalysatoren van het type **3** was echter nog niet gerapporteerd. Pogingen om dit nieuwe type ruthenium indenylideen katalysatoren te bereiden bleken slechts succesvol door het gebruik van thermolytisch degradeerbare imidazolidines.

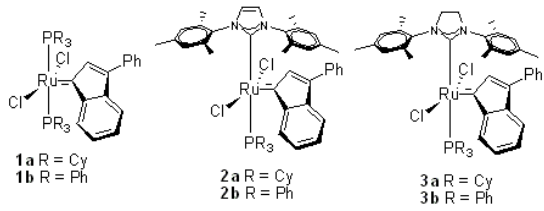

Figure 10.2: Ruthenium indenylideen type olefine metathese katalysatoren.

De aldus bekomen katalysatoren **3** waren thermisch stabiel en bleken een goede precursor voor de synthese van analoge complexen met een pyridine ligand *trans* ten opzichte van het N-heterocyclisch carbeen ligand. Hun toepassing in ring-sluiting metathese en ring-opening metathese polymerisatie reacties toonde dat deze katalysatoren een goede activiteit vertonen. Een vergelijkende studie met Grubbs type katalysatoren toonde echter dat deze katalysatoren een sterk vertraagde initiatiekinetiek vertonen.

10.3 Ruthenium Indenylideen Complexen met een Gemodificeerd N-Heterocyclisch Carbeen Ligand

De initiatiekinetiek van katalysatoren van het type **3** verbeterde sterk bij licht verhoogde temperatuur of door uitwisseling van het *trans*-ligand voor een coordinatief labieler ligand. Een poging werd ondernomen om de initiatiesnelheid te verhogen door aanpassing van het N-heterocyclisch carbeen ligand. Een inleidende studie toonde dat de geschikte aanpassing van het N-heterocyclisch carbeen ligand de initiatie sterk bevorderd in analoge Grubbs-type katalysatoren, vooral in ring-opening metathese polymerisaties. Op een analoge manier als hierboven beschreven werd aldus een nieuwe *familie* ruthenium indenylideen katalysatoren bekomen. Ook deze katalysatoren toonden een hoge olefine metathese activiteit, maar een duidelijk onderscheid - zoals in Grubbs-type katalysatoren - kon niet worden besloten.

10.4 Een Polymeer-Geassisteerde Synthese van Grubbs-Hoveyda Olefine Metathese Katalysatoren

Vervolgens werden de bekomen katalysatoren aangewend voor de synthese van hoog-actieve Grubbs-Hoveyda katalysatoren (Figuur 10.3). In dit verband is het gebruik van CuCl voor het wegnemen van het vrijkomende fosfine de meest gangbare aanpak. Het gebruik van CuCl stelt echter ook een aantal praktische problemen. Zo is CuCl gevoelig voor lucht (zuurstof), wat problemen stelt bij de handelbaarheid en bewaring. Daarenboven is het verwijderen van CuCl uit het reactiemengsel problematisch en dient de katalysator gezuiverd te worden *via* kolomchromatografie. Dit laatste is dan weer solvent-intensief, wat niet strookt met de principes van *groene* chemie. De hier aangewende aanpak maakt gebruik van paratolueen sulfonzuur op een polymere drager. Dit sulfonzuur laat toe dat de vrijkomende fosfines na reactie eenvoudig uit het reactiemengsel kunnen worden verwijderd door filtratie van het polymere materiaal. Verdere opzuivering van de bekomen Grubbs-Hoveyda katalysator levert het gewenste product in hoge opbrengst (+90%) en zuiverheid. Daarenboven toonde deze aanpak zich robust voor de synthese van gelijkaardige Grubbs-Hoveyda type katalysatoren.

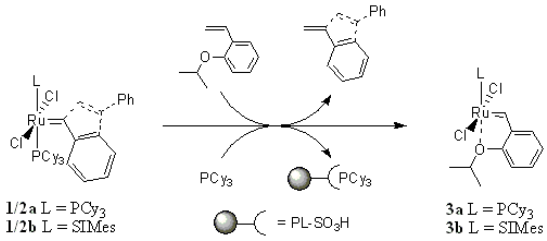

Figure 10.3: Synthese van Grubbs-Hoveyda type katalysatoren met het wegnemen van vrijkomende fosfines door paratolueen sulfonzuur op een polymeer dragermateriaal.

10.5 Een Polymeer-Geassisteerde Synthese van een Phoban-Hoveyda Olefine Metathese Katalysator

Hoewel olefine metathese katalysatoren met een N-heterocyclisch carbeen ligand uitvoerig worden bestudeerd in de literatuur - en ook in dit doctoraatsonderzoek een centrale rol opeisen - nemen ruthenium katalysatoren met een bicyclofosfanonaan (phoban) ligand steeds meer een prominente plaats in bij de ontwikkeling van olefine metathese katalysatoren. Een Hoveyda-type katalysator met een dergelijk phoban ligand werd eerder in de literatuur beschreven, maar de katalytische activiteit van dergelijke katalysatoren is amper gerapporteed. Aan de hand van de resultaten uit vorig hoofdstuk, beschrijven we in dit hoofdstuk het gebruik van paratolueen sulfonyl chloride op een polymere drager als fosfine isolator in de synthese van complex **8**.

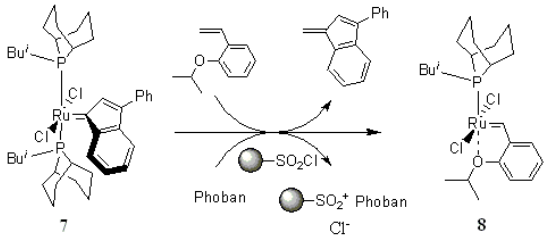

Figure 10.4: Synthese van complex **8** met paratolueen sulfonyl chloride op een polymere drager als fosfine isolator.

Hoewel de bekomen katalysator niet actief was in ring-opening

metathese polymerisaties, toonde deze een zeer hoge activiteit in de ring-sluitingsmetathese reacties, met nadruk op de metathese van gesubstitueerde olefines.

10.6 Een Latente Ruthenium Schiffse Base Katalysator voor de Gecontrolleerde Ring-Opening Metathese Polymerisatie van Dicyclopentadieen

In een laatste sectie van het doctoraatsonderzoek werd gezocht naar een effectieve manier voor de activering van een latente olefine metathese katalysator voor de ring-opening metathese polymerisatie van dicyclopentadieen. De bestudeerde katalysator vertoonde een hoge latentie en er werd aangetoond dat activering best gebeurd met zoutzuur. Gezien dit zoutzuur niet toepasbaar bleek in een reactie injectie molding, werd een *in situ* generatie protocol ontwikkeld. De resultaten toonden dat op deze manier een hoge graad van reactiecontrole en reproduceerbaarheid werd bekomen. Dergelijke resultaten zijn werden tot op heden nog niet geevenaard in de literatuur.

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Patent applications

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- NATO symposium Antalya (Turkey) 2006: "HCl activation of a phosphine free ruthenium complex bearing a bidentate Schiff base ligand"

Poster presentations

- ISOM XVII Pasadena (Ca, USA) 2007: "2^{nd} and 3^{rd} Generation ruthenium indenylidene complexes bearing saturated NHC's: efficient and robust catalysts for RCM"
- NCCC VIII Amsterdam (Noordwijkerhout, The Netherlands) 2007: "2^{nd} and 3^{rd} Generation ruthenium indenylidene complexes bearing saturated NHC's: efficient and robust catalysts for RCM"
- NCCC VIII Amsterdam (Noordwijkerhout, The Netherlands) 2007: "HCl activation of a phosphine free ruthenium complex bearing a bidentate Schiff base ligand"
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