# Ruthenium-Based Olefin Metathesis Catalysts Bearing *N*-Heterocyclic Carbene Ligands

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## Contents



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Michał Bieniek was born in Płock, Poland in 1979. He obtained his MSc Eng. degree in 2003 from the Warsaw University of Technology. In 2004, as a Marie-Curie fellow, he spent five months with Guy Lavigne in Laboratoire de Chemie de Coordination, CNRS, Toulouse, France. Bieniek received a PhD degree from IChO PAN in 2008, under the supervision of Karol Grela. He is currently working in Grela's group at Department of Chemistry, Warsaw University, where he is carrying out research on the development of new efficient catalyst for olefin metathesis.

## 1. Introduction

*N*-Heterocyclic carbene (NHC) ligands, introduced as analogues to phosphines, are recently getting wide attention in the design of diverse homogeneous catalytic systems.[1−6]

During recent years, olefin metathesis has gained a position of increasing significance.[7−9] The ruthenium complex $(PCy_3)_2(Cl_2)Ru{=}CHPh$ **1** (Cy = cyclohexyl) developed by Grubbs et al.[10] constitutes a highly efficient metathesis catalyst[11] tolerating most functional groups. In spite of the generally superb application profile of **1**, its limited stability and the low activity toward substituted double bonds are major drawbacks. The initial success of olefin metathesis has spurred the intense investigation of new catalysts for this transformation. Inter alia, the recent introduction of NHCs

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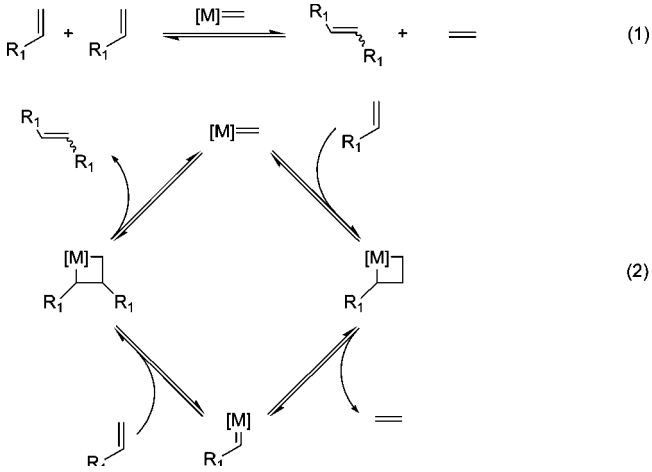
**Scheme 1. Mechanism of Metathesis Proposed by Chauvin**

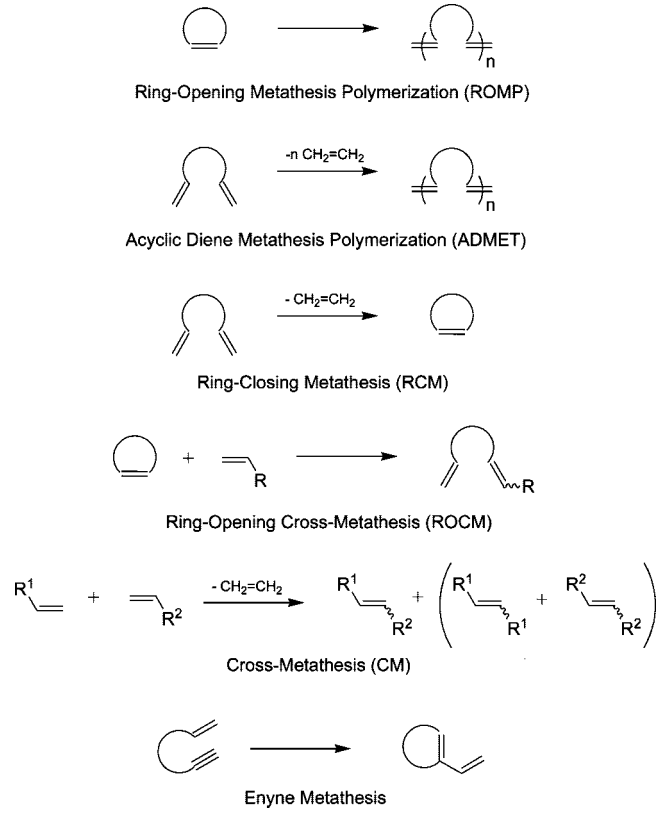


as ligands for ruthenium olefin metathesis catalysts allowed to extend the scope of this reaction far beyond the initial expectations.[12]

## 1.1. Mechanism of Olefin Metathesis

Several mechanistic hypotheses were in existence during the early period of olefin metathesis exploration.[13−15] Although, the mechanistic ideas explained the exchange process of the reactions, they did not match the results of some metathesis experiments.[16−18] It was in 1971 that Yves Chauvin and his student Jean-Louis Hérisson published their proposition of a mechanism subsequently found to be consistent with experimental observations, and now referred to as "Chauvin mechanism" (Scheme 1).[16] They pinpointed the important metallacyclobutane step, which is common to all olefin metathesis catalysts. First, as illustrated in Scheme 1, the initiating metal alkylidene reacts with an olefin, forming a metallacyclobutane intermediate. This intermediate subsequently flips open either into the initiating species or, productively, into ethylene and a new metal alkylidene. The ethylene formed contains one methylene from the catalyst and one from the starting olefin. The new metal alkylidene contains the metal with its ligands (indicated by the brackets around the metal) and an alkylidene from the substrate

**Scheme 2. Different Types of Olefin Metathesis Reactions**




alkene. Now a new olefin can react at the alkylidene center to ultimately give the metathesized product and the alkylidene initiator, which restarts the cycle. Finally, this reversible process leads to a thermodynamic equilibrium of the reaction products but in this case removal of ethene drives the reaction to completion.

Chauvin and co-workers also presented experimental support for the mechanism which could not be explained by other proposed mechanisms. The mechanism has also experimental support by Grubbs, Katz, Schrock, and others and is now generally accepted as the mechanism for metathesis. The proposed mechanism influenced work on catalyst development in that it provided both a design rationale and a way to begin to understand catalyst activity.

## 1.2. Types of Metathesis Transformations

With the advent of efficient catalysts, olefin metathesis has emerged as a powerful tool for the formation of C−C double bonds in organic synthesis. One of the most intriguing aspects of this reaction is that several types of chemistry can be performed with the same alkylidene catalysts depending on the reaction conditions and on the structural features of the substrates. Since the metathesis process is energetically neutral and thus reversible, one can obtain a mixture of both substrates and products coexisting in a thermodynamical equilibrium. However, by the judicious choice of substrates and/or reaction conditions this intrinsic problem can be circumvented, so one product can be made selectively. As illustrated in Scheme 2, metathetical transformations can be categorized by the kind of starting materials used and the outcome of the reaction.

Selected practical examples of typical metathesis transformations are shown in Scheme 3. These reactions are frequently used in the literature as benchmark tests to compare activity of various catalysts.[19,20]

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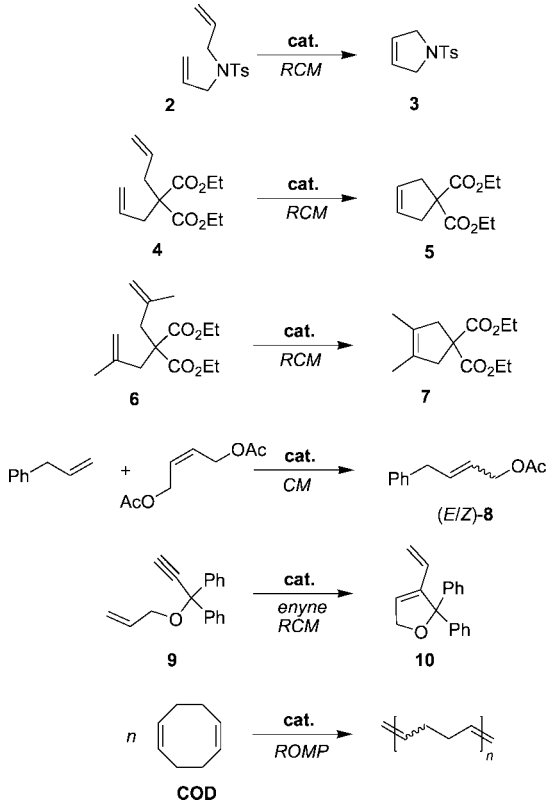
**Scheme 3. Benchmark Transformations in Olefin Metathesis**




## 2. Early Ruthenium Alkylidene Complexes Bearing Two NHC Ligands

A spectacular progress in Ru-alkylidene catalyst design was achieved when *N*-heterocyclic carbenes (NHCs) were introduced as ancillary ligands.[21−25] Ligands of this type show high propensity for acting as typical $\sigma$-donors, yet manifest a slight $\pi$-back bonding tendency, moreover are strong Lewis bases and generate rather stable metal−carbon bonds.[26−28] In fact, the NHC−Ru bond strengths were calculated to be 20−40 kcal/mol stronger than $R_3P$−Ru bond strengths.[29]

Hermann was the first to propose a modification of Grubbs catalyst consisting in the replacement of the two phosphines by imidazolin-2-ylidene ligands (Figure 1). Compounds **11**−**14** show high tolerance toward functional groups and they are remarkably active catalysts in ROMP and RCM.[30−32] Even though their activity turned out to be lower than that of the original Grubbs catalyst **1**,[30,33] probably because the NHC ligands are less labile than the phosphines and the catalytically active 14e$^-$ species are formed more slowly (compare Scheme 4), these results suggested that NHCs might be indeed interesting ligands for ruthenium based olefin metathesis catalysts.

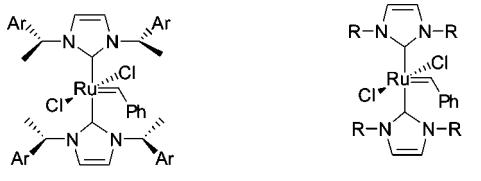



**Figure 1.** Catalysts bearing two NHC ligands.

## 3. Modern Ruthenium Alkylidene Complexes Bearing One NHC Ligand

Mindful of the stabilizing effect of NHC ligands, the groups of Nolan,[34] Grubbs,[35] and Fürstner and Herrmann,[32] independently and almost simultaneously proposed the idea of combining a labile phosphine group for rapid metathesis initiation with a nonlabile NHC ligand. The resulting mixed phosphine/NHC complexes (**15**−**17**), proved to be superior to the bis(NHC) and bis(phosphine) complexes in overall metathesis activity (Figure 2).

Grubbs subsequently discovered that catalyst **17**, which contains an *N*-heterocyclic carbene with a saturated backbone (SIMes), even further improved catalytic ability as compared with its unsaturated (IMes) antecedent (**16**).[33] These new ruthenium catalysts containing *N*-heterocyclic carbene ligands, in a number of cases, display performances that were previously accessible only to the most efficient molybdenum catalysts,[36−39] while maintaining the stability and functional group compatibility that is typical of the late metal catalysts. Complexes **16** and **17** catalyze the RCM of diethyl diallylmalonate[72] and the ROMP of cyclooctadiene[40] at rates approximately 100−1000 times greater than those observed for **1**. Remarkably, **17** remains effective at loadings as low as 0.05 mol % for RCM reactions and 0.0001 mol % for ROMP.[72] Both catalysts **16** and **17** are capable of effecting the RCM of tri- and tetra-substituted olefins.[33,35]

In addition, catalyst **17** provided the first example of CM to afford a trisubstituted olefin,[41] as well as Ru-catalyzed CM and RCM reactions, where one partner is directly functionalized with electron-withdrawing group, such as carbonyl,[42] cyano,[43] perfluoroalkyl,[44] phosphine oxide,[45,46] or sulfone.[47−50]

Importantly, besides excellent catalytic performance of **16** and **17**, they are also more thermally stable than the first-generation catalysts.[33−35,51] Because of these amazing improvements, this class of catalysts has been called second-generation Grubbs' catalysts. A possible explanation of the remarkable performance of these catalysts is that the nonlabile, bulky NHC ligand provides the metal center with considerable steric protection, and as a good-donor, stabilizes both the precatalyst and the coordinatively unsaturated, catalytically relevant intermediate. Unfortunately, NHC-containing complexes similarly to the first-generation Grubbs' catalysts are susceptible to oxidative decomposition.[52] Nevertheless, the commercially available complex **17** is currently the second most used catalyst for metathesis reactions. The improved catalytic properties of these second-generation catalyst systems were initially attributed to increased phosphine exchange rates. However, detailed investigation established that **16** and **17** initiate more slowly than the parent complex **1**. The same study demonstrated that catalysts containing NHC ligands possess a much higher preference, as compared with **1**, for coordination of olefinic substrates relative to phosphine (i.e., they propagate the catalytic cycle faster and more efficiently). The stronger-donor character of the NHC ligand and the greater kinetic stability of the unsaturated active species are responsible for the higher reactivity. In addition, these properties allow catalyst **17** to effect metathesis of olefins for which **1** is ineffective, such as electron-poor and sterically demanding olefins.[52]

Ruthenium complexes bearing bidentate Schiff base ligands,[53,54] P,O-, N,O-, and O,O-chelates[55−58] and other chelating ligands constitute another important classes of

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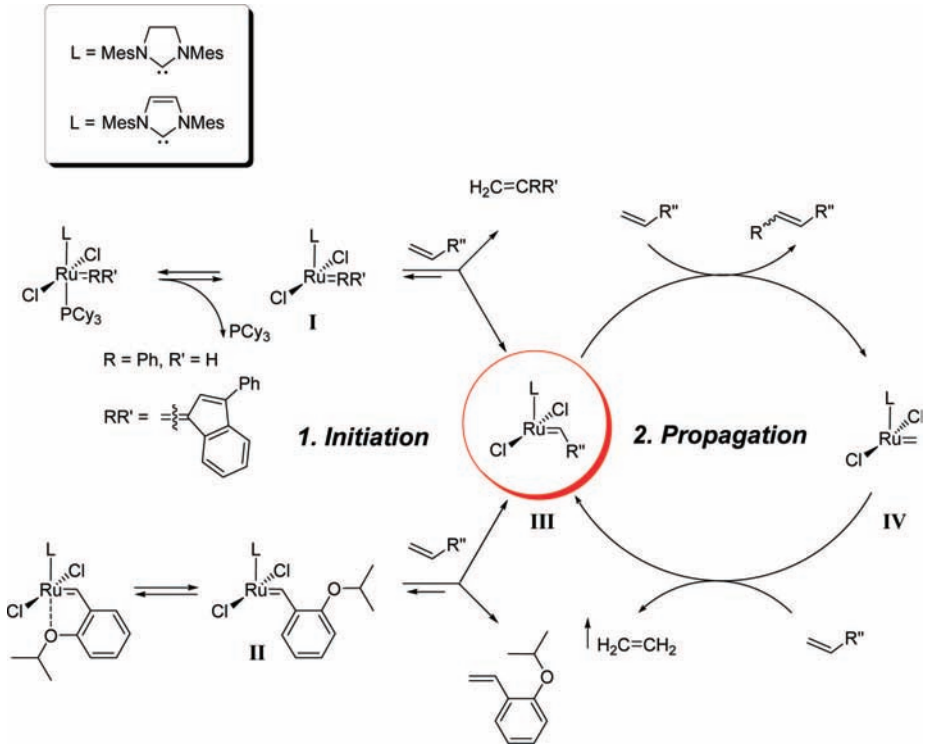
**Scheme 4. Mechanism of Metathesis Catalyzed by Common Ru Precatalysts**




NHC-bearing catalysts.[59] Many of them found applications in polymer syntheses.[60,61]

As an alternative to Ru-benzylidene catalysts, NHC bearing Ru-3-phenylindenylidene complexes,[62] such as **19** and **20**, were developed and widely used in natural product synthesis (Figure 3).[63,64] The Ru−indenylidene complexes showed a higher thermal stability than their benzylidene counterparts and, at the same time, showed a good catalytic activity and selectivity. A further improvement in terms of catalyst longevity was made by the serendipitous discovery of Hoveyda and co-workers that the introduction of styrenyl ether moiety produces a new complex (**21**) of a particular stability.[65,66] In 2000, the groups of Hoveyda[67] and Blechert[68] simultaneously reported the phosphine-free, NHC-bearing catalyst **22**. This so-called "Hoveyda" or "Hoveyda−Grubbs" catalyst, in addition to being extremely robust, demonstrated improved activity toward electron deficient alkenes, such as acrylonitriles,[44] fluorinated alkenes,[43] vinyl phosphine oxides, and sulfones.[45−47] Moreover, metathesis reactions involving vinyl chlorides[69] and trisubstituted alkenes catalyzed by complex **22** showed better outcomes than those obtained with benzylidene or indenylidene complexes. Ease of handling, stability to air and moisture, and the possibility for immobilization and catalyst reuse also conferred additional advantages to the catalyst **22**.

Mechanistic studies have played an important role in the evolution of ruthenium-based olefin metathesis catalysts. Detailed mechanistic investigation of ruthenium complexes has guided the development of new ligand systems that provide increased activity, improved functional group tolerance, and higher thermal stability. According to the generally accepted mechanism (Scheme 4) phosphine bearing catalysts are initiated by the dissociation of a $PCy_3$ group to form the 14-electron complex **I**, while in the case of the Hoveyda-type complexes the initiation requires breakage of the O → Ru chelation as a first step.[70,71]

This simple mechanistic scheme can be used to explain observed differences between the second-generation Grubbs and indenylidene complexes. The release of 1-methylene-3-phenyl-1*H*-indene and the formation of the common propagating species **III** and **IV** (Scheme 4) proceeds much

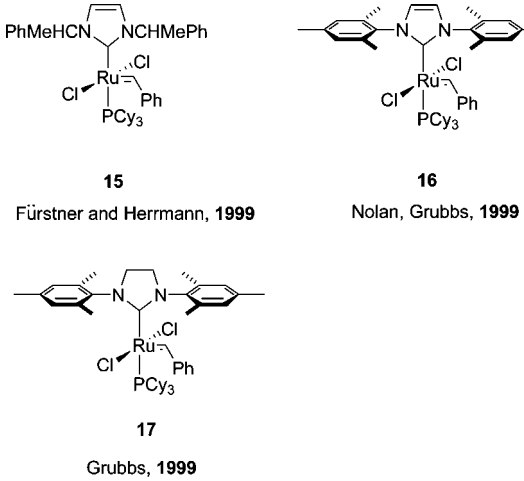



**Figure 2.** First catalysts bearing one NHC ligand.

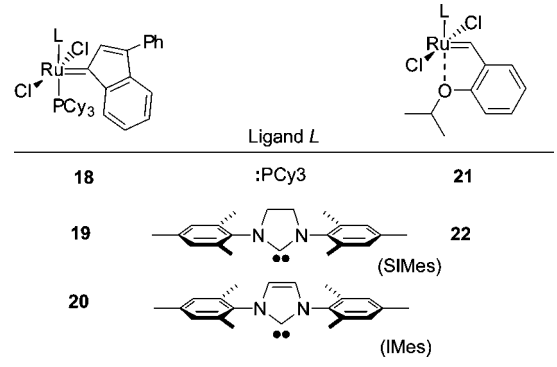



**Figure 3.** Indenylidene (**18**−**20**) and 2-isopropoxybenzylidene (**21**−**22**) catalysts.

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more slowly in the case of **19** and **20**, whereas **16** and **17** easily lose styrene in the analogous transformation. Therefore, catalysts **19** and **20** initiate much more slowly than **16** and **17** and need a higher temperature to reach reasonable activity.

It is believed that both the Grubbs and Hoveyda-type catalysts generate identical propagating species (**III** and **IV**, Scheme 4) after a single turnover.[70,71] However, the well-documented differences in scope between these two catalysts (especially toward electron-deficient substrates) suggest that the mode of propagation might also be different, leading to the observed nonidentical reactivities. In a recent publication, Farina and Wei reported on NMR analyzes of some metathesis reactions promoted by 30 mol % of the first-generation Hoveyda catalyst; they observed no discrete intermediates of type **III**, which are typically present in the case of Grubbs catalysts.[72] It was suggested, that only a small portion of the Hoveyda precatalysts present in the reaction mixture initiates to form active species **III** and **IV**. However, results reported in the literature unambiguously proved that Hoveyda-type catalysts are not by-standers but actually all the amount of the catalysts used takes part in the reaction.[19,67] Based on these facts, it is reasonable to assume that in reactions promoted by Hoveyda-type catalysts the propagation proceeds through a dynamic equilibrium involving the intermediacy of the self-regenerating 14-electron species (**II**, Scheme 4) and that this is responsible for the observed differences in reactivity of these catalysts toward some substrates.

Given that the activity and stability of a given catalyst are depending not only on neutral ligands (L) but also on the nature of alkylidene and anionic ligands, as well as on substrate and reactions conditions used, it is quite difficult to compare the influence of various NHC ligands on the activity of Ru catalysts.[19] In the following review, we are trying to compare only catalysts belonging to the same class (e.g., Hoveyda, Grubbs), using the same model reaction and conditions, where it was possible.

## 3.1. Complexes Bearing Imidazol-2-ylidene or Imidazolin-2-ylidene Ligands

Definitely, the most frequently studied second-generation olefin metathesis catalysts are complexes bearing either imidazol-2-ylidene or imidazolin-2-ylidene NHC ligands. A number of such catalysts is already available commercially (**17**, **19**, **20**, **22**, and variations) and used widely in various applications, both in basic research and in industry.[73]

### *3.1.1. Steric and Electronic Influences on Catalyst Activity*

It is generally agreed that IMes bearing catalyst **16** is considerably less active (with respect to turnover numbers) than SIMes bearing **17**.[10,40,74,75] This observed difference in activity can only be attributed to the saturated (in **17**) versus unsaturated (in **16**) NHC "roof", since these catalysts are otherwise identical. Interestingly, this significant difference in catalytic activity between IMes and SIMes-containing catalyst is still not explained on theoretical grounds.[76] Geometrical analyses in the solid state show rather small differences between the corresponding IMes and SIMes-containing ruthenium based catalysts (Figure 4).

It is clear that the overall availability of the ruthenium center is dependent on a combination of steric and electronic properties of the NHC ligand in a given coordination

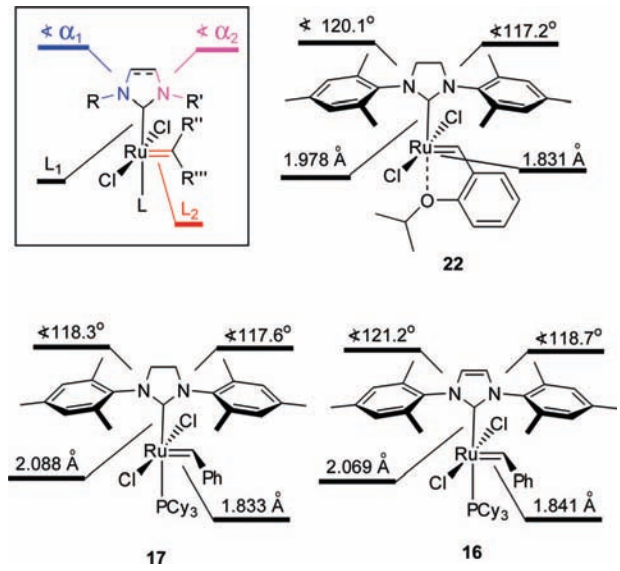


**Figure 4.** Selected crucial geometrical features of NHC Ru catalysts.

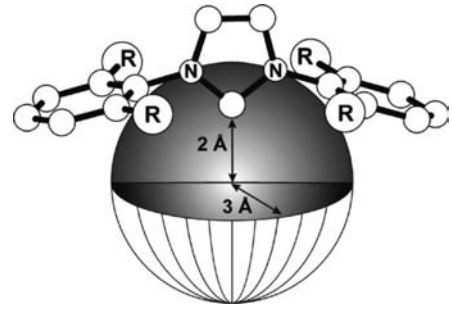


**Figure 5.** Representation of the sphere dimensions for steric parameter determination (%$V_{Bur}$) of NHC ligands. (Reproduced with permission from ref. 77. Copyright 2005 Elsevier.)

environment. In general, based on structural studies, one can only conclude that bulkiness of the groups bound to the nitrogen atoms of the NHC ligand, and more importantly, the shortened length of the Ru−carbene carbon distance ($L_1$) in these complexes, increase the steric congestion around the metal center when compared to $PCy_3$ ligand of the first generation complexes.

While it is common to characterize the steric demand of $PR_3$ ligands using the Tolman cone angle, in the case of NHC ligands it is more reasonable to use the %$V_{Bur}$ molecular descriptor (Figure 5), which was introduced by Cavallo et al.[76,77,200] In fact, NHC ligands are usually highly asymmetric, and steric demand in the direction of the N−R bonds can be very different from steric demand in the direction perpendicular to the imidazolyl NHC ring plane.

Various attempts have been made to quantify the electronic properties of NHC ligands.[6,78−81] The Cp*Ru(L)Cl system (Cp* = $\eta^5$-$C_5Me_5$) has been used for the establishment of a relative scale of Ru−$C_{(NHC)}$ bond dissociation energy (BDE). The higher catalytic activity of **17** over **16** in alkene metathesis has been attributed to a greater donor ability of saturated carbenes. Calorimetric studies showed that, contrary to expectations, differences in reaction enthalpies between unsaturated and saturated ligands (IMes vs SIMes, as well as IPr vs SIPr, see Figure 10) were of only 1 kcal/mol.[78] These results tend to indicate that such small differences in the donor capacities of NHC ligands can be responsible for significant enhancements in catalytic activity. However,

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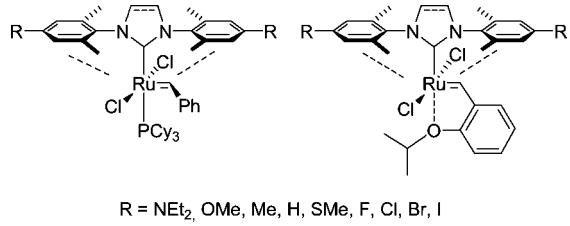



**Figure 6.** $\pi$-Face donor properties of NHC ligands, according to Plenio.

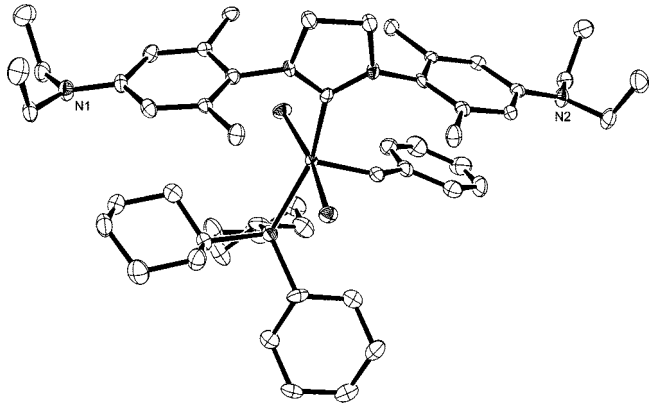



**Figure 7.** ORTEP view of **23** (R = $NEt_2$). Selected bond lengths and angles: $L_1 = 2.058(4)$ Å, $L_2 = 1.841(4)$ Å, $\alpha_1 = 117.7(3)°$, $\alpha_2 = 117.4(3)°$ (refer to Figure 4).

subtle geometrical differences (Figure 4) may also play an important role.

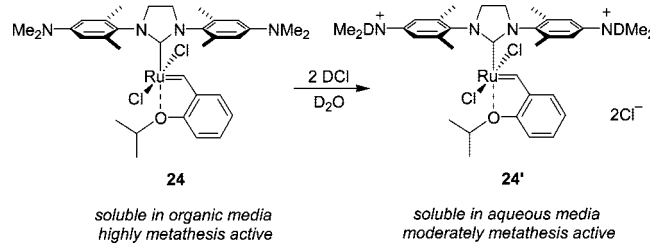
To quantify the electron density transfer from the NHC ligand to the metal, stretching frequencies $\nu_{(CO)}$ of NHC-containing carbonyl transition metal complexes, such as $(NHC)Ni(CO)_3$ were studied.[79,80,82−88] These results suggested that the saturated NHC ligands are slightly less electron-donating than their unsaturated analogues and that alkyl-substituted NHCs are only marginally more electron donating than their aryl-substituted counterparts, which contradicts again the accepted dogma.[76]

With the aim to gain information on the electronic situation at the metal center of Ru-alkylidenes, Plenio et al. determined the Ru(II)/Ru(III) redox potential of Grubbs and Hoveyda complexes by cyclic voltametry. Thus, they synthesized a number of Grubbs and Hoveyda type complexes with modified NHC ligands and determined their redox potentials.[89,90]

The variation of remote para-substituents R (e.g., R = $NEt_2$, OMe, Me, H, SMe, F, Cl, Br, I) on the phenyl ring of *N*-heterocyclic carbenes (Figures 6 and 7) has a significant influence on the redox behavior of Grubbs and Hoveyda-type complexes. As reported by Plenio, the electronic properties of NHC ligands are not exclusively governed by the $\sigma$-donation from the carbene carbon atom to the metal, but also by a direct transfer of electron density between the Ru=CHR unit and the phenyl rings. Unfortunately, no correlation between electronic properties of substituent R and the catalytic activity in RCM of such modified complexes was observed.[89] Although the direct relationship has yet not been found, these results are of importance for further design of NHC bearing Ru catalysts. Recently, Jensen and co-workers studied electronic and steric effects computationally.[91]

Schanz et al. synthesized Grubbs- and Hoveyda-type complexes bearing $Me_2N$-substituted NHC ligand, similar to **23** obtained previously by Plenio[89] (Scheme 5).[92] Both

**Scheme 5. pH Responsive Catalyst Obtained by Schanz et al.**




**24** *soluble in organic media highly metathesis active*

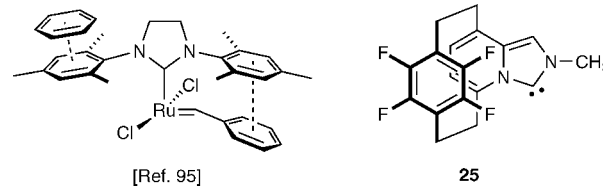
**24′** *soluble in aqueous media moderately metathesis active*

catalysts performed ROMP of cyclooctene at faster rates than their commercially available counterparts **17** and **22** and acted at similar rates during RCM of diethyldiallylmalonate (**4**). Hoveyda-type catalyst **24** can be protonated with 2 equiv of HCl leading to moderately water-soluble complex **24′**. The formed complex is stable in aqueous solution in air for >4 h, but over prolonged periods of time shows signs of degradation. Interestingly, **24′** was active during the RCM of diallylmalonic acid in protic media at 50 °C; however, the reaction proceeded at low rate and did not afford complete conversion. The authors concluded that the NHC ligand in its protonated form is likely less $\sigma$-donating, which leads to lowering the catalytic activity of the dicationic Ru complex.[92]

Despite the difficulties in understanding the stereoelectronic peculiarities of the NHC-ruthenium complexes,[76] it is clear that the specific $\sigma$-donor and $\pi$-acceptor character of NHCs exerts an influence on the catalytic activity, resulting in particular on an increased stability of 14-electron complexes. The steric influence of NHC ligand in olefin metathesis transformations is still the subject of controversy but the nonplanarity of the imidazolinium backbone of SIMes seems to be of major importance.[76]

It was reported that some RCM reactions promoted by the second generation catalyst **16** in toluene at 80 °C were not only faster than those in dichloromethane at 40 °C but also faster than the reactions conducted in 1,2-dichloroethane at 80 °C.[93−95] Recently, Ledoux has noted that in ring-opening metathesis polymerization (ROMP) of cyclooctadienie, the catalyst **17** was unambiguously more active in $C_6D_6$ than in $CDCl_3$ *at the same temperature*.[95] A proposed explanation for this doping effect[93,95] was based on $\pi-\pi$ interactions of the *N*-mesityl group with the aromatic solvent molecules (Figure 8).[93,95] This effect can be formally classified as *in situ electronic modification of NHC donating properties* and could also influence the reactivity of the catalyst. Therefore, the authors decided to discuss it in the review.

It should be argued that, since the mesityl units in IMes and SIMes ligands in second generation Ru catalysts are perpendicular to the NHC five-membered ring, no electronic communication between these two parts is possible. However, it was shown that the nature of the aromatic "flaps" of the NHC ligands has a significant influence on the electron



[Ref. 95] **25**

**Figure 8.** Aromatic solvent−NHC interactions according to Ledoux and cyclophane−NHC ligand obtained by Fürstner.

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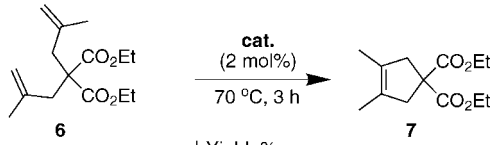
**Scheme 6. Solvent Effect in Model RCM Reaction**




| | | Yield, % | | | | |
|---|---|---|---|---|---|---|
| | solvent | 17 | 16 | 19 | 20 | 22 |
| "classical" solvents | $C_2H_4Cl_2$ | 21 | nd | 28 | 38 | 4 |
| | $C_6H_5CH_3$ | 20 | nd | 27 | 56 | 33 |
| fluorinated solvents | $C_6F_6$ | 61 | 77 | 91 | 74 | 58 |
| | $C_6F_5CF_3$ | 72 | nd | 94 | 85 | 72 |

density at Ru center and on the catalytic properties of Grubbs-type complexes. The above-described work by Plenio,[89] supports the assumption that a through-space donation of electron density of the aromatic $\pi$-face of the NHC aryl groups toward the metal can be (at least in part) responsible for this effect.

In 2007, Kadyrov and et al. disclosed that fluorinated aromatic solvents, such as trifluoromethylbenzene, perfluorobenzene, and perfluorotoluene can modify properties of commercially available II-generation catalysts in a significant manner, allowing them to reach much higher activities in various metathesis transformations, including the challenging formation of tetrasubstituted C−C double bonds.[96] It was found that the observed activating effect is of quite general nature, as all the second generation catalysts studied lead to higher yields and selectivities in fluorinated aromatic solvents as compared to "classical" conditions (Scheme 6). The same doping effect of perfluorobenzene was also observed by Blechert and Collins in some metathesis reactions promoted by new olefin metathesis catalysts bearing modified NHC ligands (see section 3.1.2 and 3.1.5 for more details).[97,98] This effect seems to be specific for aromatic solvents, since no rate enhancement was noted in aliphatic fluorinated solvents.[99,100] Carbene **25**, recently developed by Fürstner et al. can serve as related example of modulation of the donor properties of a NHC ligand by "through-space" interactions with the fluorinated cyclophane scaffold (Figure 8).[101]

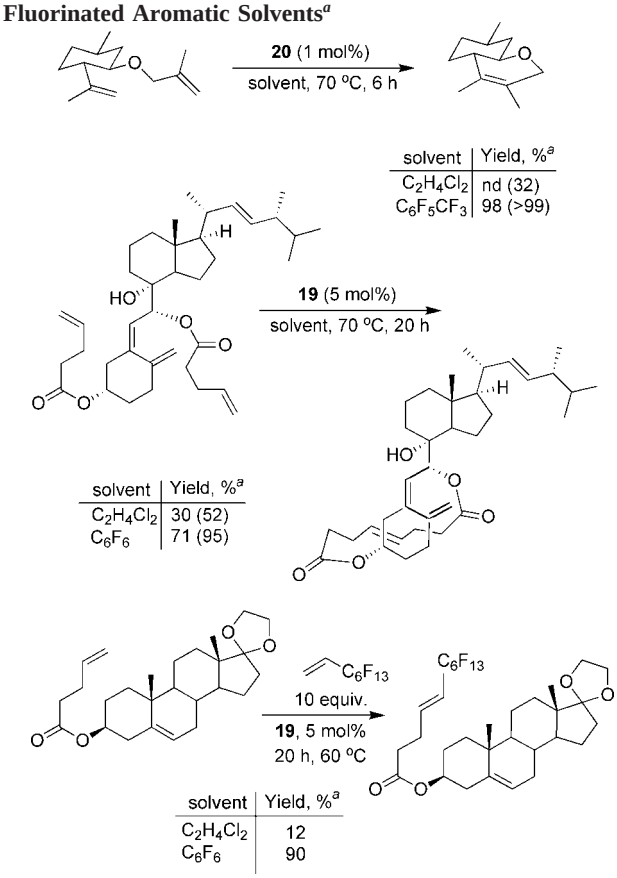
Even though most authors explain this doping effect by $\pi-\pi$ stacking between a NHC and fluorinated solvents, direct fluorine−ruthenium interactions, that could reduce the activation energy of the rate-limiting phosphine dissociation, can also be responsible for rate enhancement of the reaction in some cases. Such interactions have previously been described in literature and are discussed in the next chapter of this review (see Scheme 9 and 10).

Although the exact nature of the observed effect is not yet clear, its practical value as a method for the in situ activation of commercial NHC-bearing metathesis catalysts is obvious. For example, this technique can find applications in the synthesis of advanced natural and biologically active compounds, where any increase in yield is of high importance, especially when the metathesis step is applied in the last stages of a given total synthesis.[102] Accordingly, Grela et al. have recently shown that this technique can be applied for the activation of standard metathesis catalysts (**19** and **20**) during the course of the preparation of biologically active or natural-like compounds (Scheme 7).[103]

### *3.1.2. Influence of Substituents Modification at 1,3-Positions*

Further improvements in activity of the imidazol- and imidazolin-2-ylidene Ru complexes might be attained by the

**Scheme 7. Preparation of Biologically Active Compounds in Fluorinated Aromatic Solvents[a]**




[a] Isolated yields after column chromatography. Conversions calculated by $^1$H NMR are in parentheses.

incorporation of better donor substituents with larger steric requirements. Both ligand-to-metal-donation and bulkiness of the NHC force the active orientation of the carbene moiety and thus contribute to the rapid transformation into metallacyclobutane species. Both of these goals can be realized by incorporation of various groups in 1,3- and 4,5-position of the five-membered ring ligand.

**Symmetrically 1,3-Substituted Imidazol- and Imidazolin-2-ylidene Ligands.** The current literature shows a number of examples where 1,3-substituents in imidazol- and imidazolin-2-ylidene ligands were altered with the aim to establish the structure−activity relationships (SAR) in the resulting Ru-complexes. Typically, imidazol- and imidazolin-2-ylidene ligands with aliphatic substituents were either not formed or were unstable and displayed reduced catalytic activities. For example, Grubbs and Louie described the preparation of a 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene Ru complex (**26**, Scheme 8).[104] Although **26** (a bright blue solid) was obtained in quantitative yield, the RCM of diethyl diallylmalonate (**4**, Scheme 3) using this complex was not observed, even under forcing conditions. The same reaction, in the presence of **27** as a catalyst proceeded in high yield.

Mol et al. noted that 1,3-di(1-adamantyl)-4,5-dihydroimidazol-2-ylidene ruthenium complex **28** cannot be formed (Scheme 8).[105] (However, the immobilized ruthenium catalyst bearing a di(1-adamantyl)-substituted NHC ligand was reported in the literature. See section 3.1.4, structure **107**). Similarly, Verpoort and Ledoux reported on the low stability of Grubbs benzylidene complexes **29a** and **29b**, which prevented their isolation. The lack of stability was attributed

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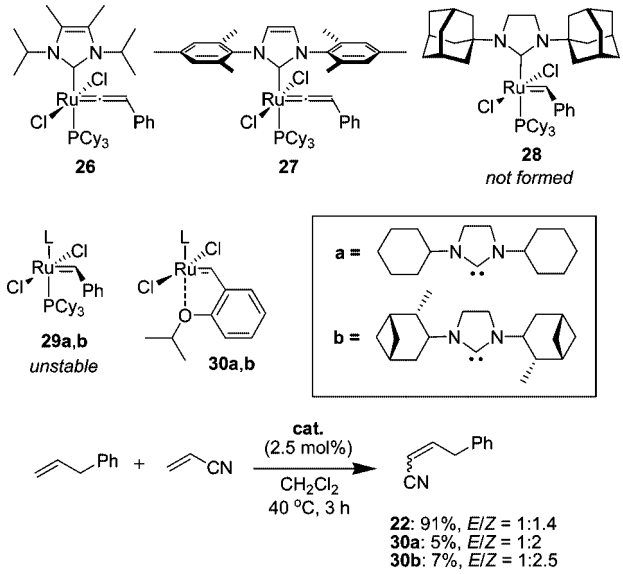
**Scheme 8. Selected 1,3-Dialkyl Substituted NHC−Ru Complexes**




to steric effects resulting in a weakened NHC−metal bond.[95] Fortunately, the sterically less demanding Hoveyda-type complexes could be substituted with NHC ligands bearing two aliphatic N-substituents, yielding **30a** and **30b** as olive and bright green solids (Scheme 8, Figure 9).[106]

Compared with the standard Hoveyda catalyst **22**, a slightly decreased Ru−$C_{(NHC)}$ bond length (1.972 vs 1.981 Å in **22**) was noted in **30a**. This may indicate a stronger $\sigma$-donation of the NHC ligand caused by the aliphatic *N*-groups. Although more active in ROMP of *cis,cis*-cycloocta-1,5-diene (COD), in RCM of **4** and CM of acrylonitrile,[107] these modified complexes displayed lower activity than the parent Hoveyda complex **22**, It should be noted, however that in the CM reaction these complexes led to slightly higher *Z* selectivity.

A relatively large number of reports have appeared on 1,3-diaryl substituted NHC complexes. In addition to the above-described electronic modifications,[89,90] steric effects caused by altering the aryl substituents were thoroughly investigated and found to exert a strong influence on catalyst activity (Figure 10).

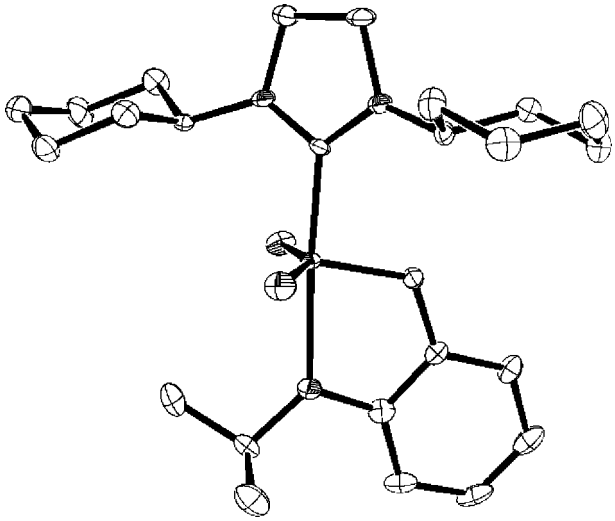


**Figure 9.** ORTEP view of **30a**. $L_1 = 1.972(3)$ Å, $L_2 = 1.824(3)$ Å, $\alpha_1 = 121.5(3)°$, $\alpha_2 = 119.2(3)°$.

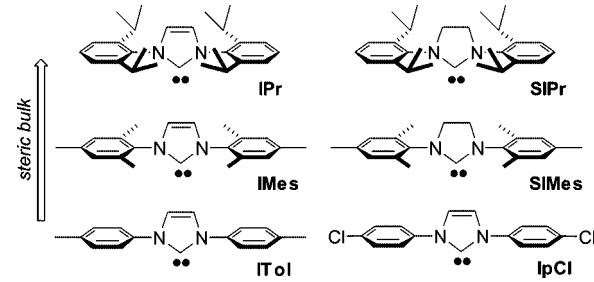



**Figure 10.** Common 1,3-diaryl substituted NHC.

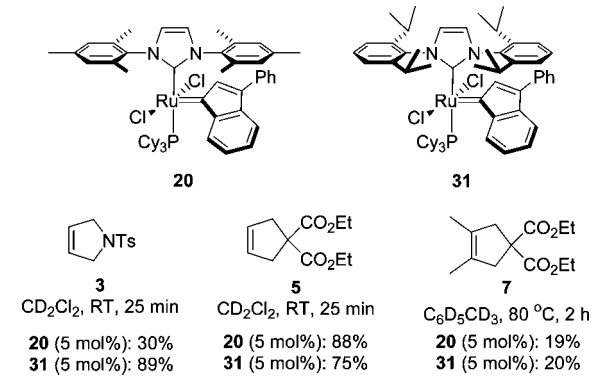



**Figure 11.** RCM results using **20** and **31**.

In 1999, Nolan et al. reported on the synthesis and characterization of Ru-imidazolylidene complexes bearing 1,3-bis(2,4,6-trimethylphenyl)imidazol2-ylidene (IMes) and a sterically more demanding 1,3-bis(2,6-diisopropylphenyl)imidazol2-ylidene (IPr) ligands.[63] Complexes **20** and **31** were synthesized as air stable orange microcrystalline solids, by the addition of **18** to free IMes or IPr in toluene at room temperature. In the formation of **3** by RCM (see Scheme 3) much higher conversion was obtained with **31**. However, in other model reactions, both complexes show rather similar catalytic activities (Figure 11).[19]

One year later, Nolan reported on the benzylidene Ru complex **32**[108] bearing an IPr ligand. This complex was obtained in moderate yield as a brown, thermally stable, and air-stable solid in the reaction of **1** with **IPr** in hexane at 60 °C. The identity of this complex was further confirmed by a single-crystal X-ray diffraction study, revealing that the Ru−$C_{(NHC)}$ bond is longer (2.088 vs 2.069 Å in **16**), which shows the distinct difference between IMes and IPr ligands. The isopropyl groups on the phenyl rings of the IPr ligand are pushed back indicating a fairly congested environment. The catalytic activity of **32** was tested by using the standard RCM substrate, diethyl diallylmalonate (**4**). When **32** was used as a catalyst precursor, the ring closure was complete (>99%) after 15 min at room temperature. Under identical conditions, **17** showed slightly lower (92%) conversion.

In 2001, Fürstner et al. attempted a more broad comparative reactivity study of a number of second-generation Ru catalysts. Complex **32** was found to be slightly more active than **16** and **17**, at least for the more challenging transformation (Figure 12).[94] In the same paper, Ru-complex (**34**) with the saturated ligand, 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazoline (SIPr), was disclosed, although its catalytic activity was not reported.[19] Mol and Dinger decided to check if the significant increase in steric bulk of SIPr relative to SIMes, might give rise to a highly active metathesis initiator.[109] In the self-metathesis of 1-octene at ambient

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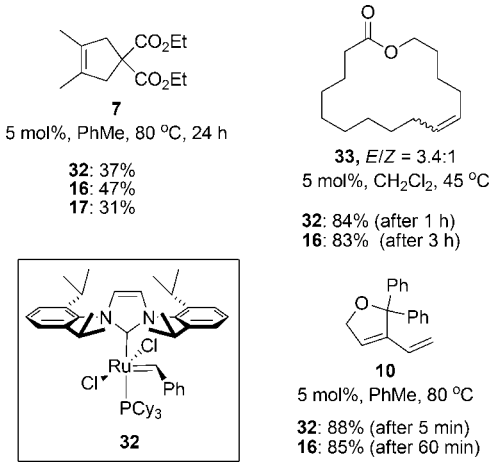



**Figure 12.** Activity profile of complex **32**, according to Fürstner.

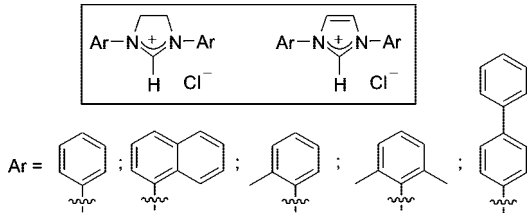


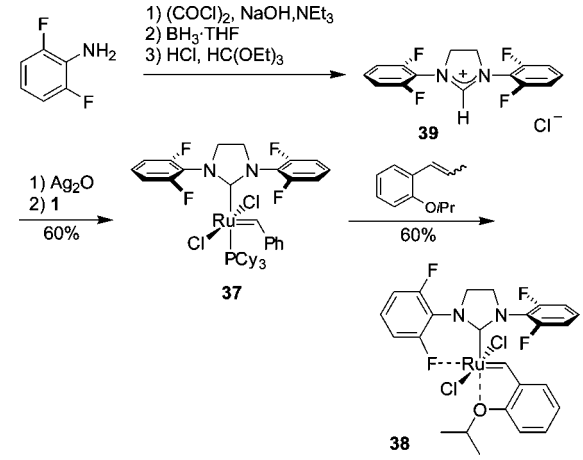

**Figure 13.** NHC salts tested by Noels.

temperature, **34** exhibited significantly higher activity and productivity than those of **16**. The improved efficiency of **34** for terminal olefins metathesis does not fully translate to the CM of substrates bearing internal C−C double bonds, such as *trans*-4-decene and methyl oleate, where catalyst **34** gave visibly lower conversions. The authors speculated that the bulkier SIPr ligand in **34** hinders the approach of internal olefin molecules to the Ru center, resulting in lower catalytic activity. In the case of RCM of diethyl diallymalonate (**4**), the initiator **34** showed a slightly better activity than **17**.[109]

New Ru complexes, bearing ITol and IpCl carbene ligands were prepared by Nolan et al. by a direct reaction between free carbenes and **1** in toluene.[110] The catalysts were isolated in high yields (80−87%) as green solids[111] and characterized by $^{1}H$ and $^{31}P$ NMR and elemental analysis. For the RCM of diethyl diallylmalonate (**4**), the precatalysts bearing ITol (**35**) and IpCl (**36**) ligands lead to significant reactivity decrease as compared with the precatalyst bearing IMes ligand (**16**), These results were rationalized by poor electron-donating ligand ability to the ruthenium center and lower stability as a result of the lack of substitutions at the aryl ortho-positions (see section 4).[110]

Noels et al. reported on preparation of some imidazol- and imidazolinium chlorides bearing various 1,3-diaryl substituents (Figure 13). These salts were combined with $[RuCl_2(p\text{-cymene})]_2$ and potassium *tert*-butoxide or sodium hydride to generate the corresponding ruthenium-NHC complexes in situ.[112] The catalytic activity of these species in the photo-induced ROMP of cyclooctene was investigated, using corresponding IMes and SIMes ligand precursors as benchmarks. The authors concluded that the (un)saturation of the C4−C5 double bond in the imidazole ring is not crucial to achieve high catalytic efficiencies. On the other hand, the presence or the absence of alkyl groups on the ortho-positions of the phenyl substituents in NHC ligands had a more pronounced influence. Blocking all the ortho positions was

**Scheme 9. Preparation of 37 and 38**




a requisite for obtaining efficient catalysts. According to the authors, the presence of the ortho-substituents prevents the intramolecular metalation of the phenyl ring in a NHC ligand, thus changing the fate of the catalytic species (see section 4).[112]

In 2006, Grubbs et al. reported on synthesis, structure, and performance of new ruthenium-based olefin metathesis catalysts featuring fluorinated NHC ligands.[113] The synthesis of complexes **37** and **38** was accomplished in a few steps from commercially available 2,6-difluoroaniline (Scheme 9). Deprotonation of **39** by various bases in the presence of the ruthenium source **1** did not afford the desired complex **37**. The use of silver(I) oxide furnished **37** in 60% yield (the reaction preceded via transmetalation of Ag−NHC complex). The phosphine-free analogue **38** was prepared from **37** in reaction with *o*-isopropoxymethylstyrene in 75% yield (Scheme 9). These compounds are air stable in the solid state.[113]

Crystallographic analysis revealed two significant differences in the structures of these two new catalysts. Complex **37** displays a geometry similar to those observed for the parent benzylidene complex **17** (Figure 14). However, the Hoveyda-type complex **38** shows a rotation of the entire NHC ligand around the Ru−C bond by 40° compared to **37** (Figure 15). An additional rotation of one of the two fluorinated aryls by 26° around the $N-C_{(aryl)}$ bond moves one of the fluorine atoms closer to the ruthenium atom,

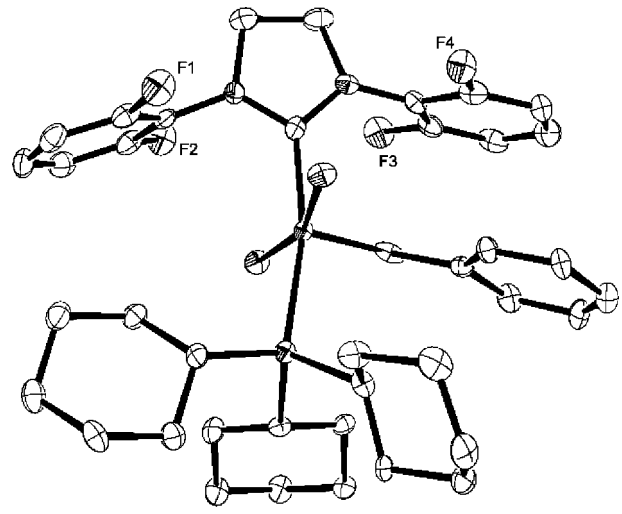



**Figure 14.** ORTEP view of **37**. $L_1 = 2.055(5)$ Å, $L_2 = 1.814(5)$ Å, $\alpha_1 = 119.1(4)°$, $\alpha_2 = 118.9(4)°$.

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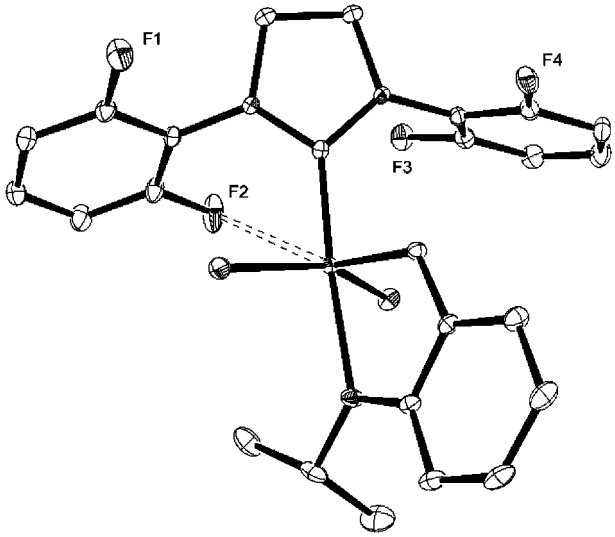



**Figure 15.** ORTEP view of **38**. $L_1$ = 1.9628(11) Å, $L_2$ = 1.8311(11) Å, $\alpha_1$ = 121.24(9)°, $\alpha_2$ = 116.94(9)°.

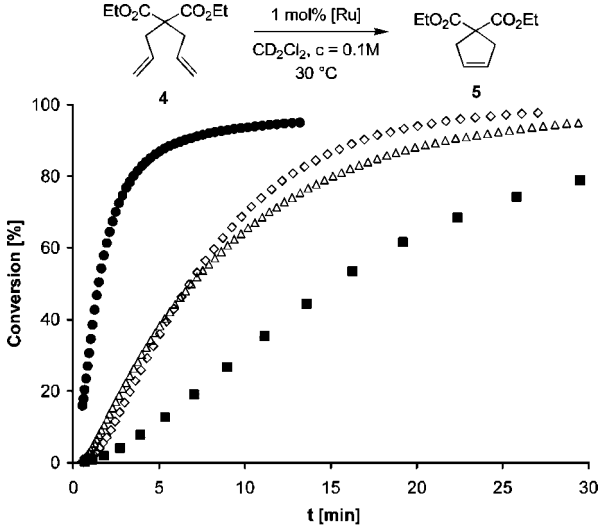
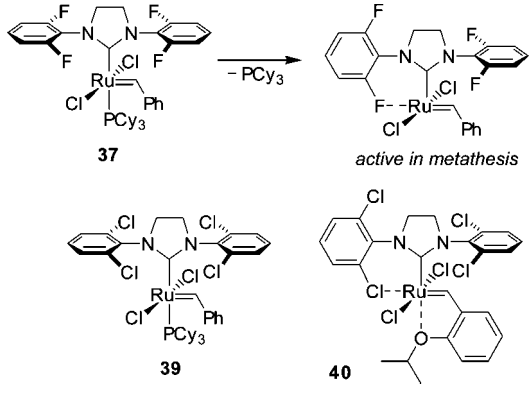



**Figure 16.** Relative activities of **17** (△), **22** (◊), **37** (•), and **38** (■) in RCM. (Reproduced with permission from ref. 113. Copyright 2006 American Chemical Society.)

**Scheme 10. Fluorine−Ru Interaction Facilitating Initiation of 37, and Chloro-Containing Complexes 39 and 40**




making it hexacoordinate via an additional fluorine−ruthenium interaction (Ru−F distance 3.2 Å, Scheme 9). The absence of analogous interaction in **37** was explained by steric congestion of the NHC aryl substituent with the large $PCy_3$ ligand. The isopropoxy group in **38** is significantly smaller, leaving space for the fluorine atom to coordinate.[113]

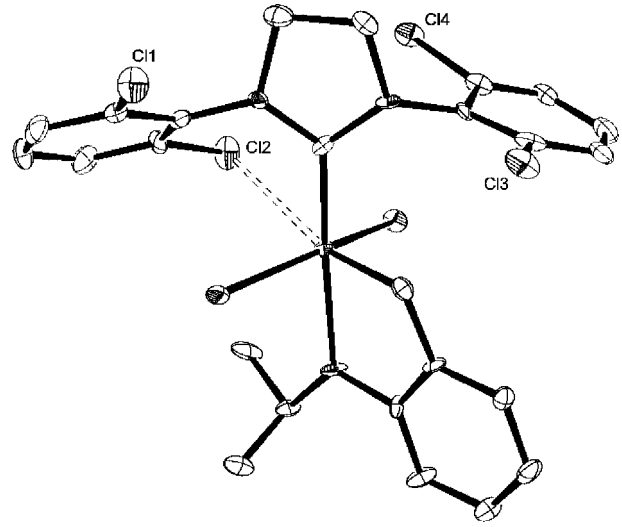
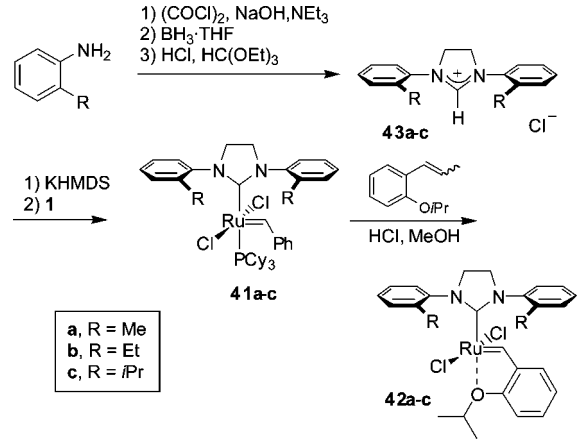



**Figure 17.** ORTEP view of **40**. $L_1$ = 1.972(6) Å, $L_2$ = 1.827(6) Å, $\alpha_1$ = 119.1(5)°, $\alpha_2$ = 118.7(5)°.

**Scheme 11. Preparation of 41 and 42**




The catalytic activity of these new catalysts was then tested using standard RCM of **4** (Figure 16). The previously mentioned[91] theoretical investigations suggested that the withdrawing capacity of the electronegative fluorine atoms would lead to a decrease in catalyst activity, which was in good agreement with the observed reaction profile of **38**, which catalyzed the reaction at a slower rate than the parent SIMes-containing complex **22**. The phosphine-containing catalyst **37**, however, showed a significantly increased reaction rate compared to parent **17**. To explain this intriguing dissimilar behavior of **37** and **38**, the authors proposed that in case of **37** a fluorine−ruthenium interaction facilitates phosphine dissociation from the complex, which is the rate-limiting step in Grubbs-type catalyst initiation (Scheme 10).[113]

Because the Cl−Ru interactions should be even stronger, analogues **39** and **40** bearing NHC with dichlorophenyl substituents were also prepared, in hope to lower the free energy of activation even further.[113] As expected, the crystal structure of the Hoveyda analogue **40** shows a strong ruthenium-chlorine interaction (Ru−Cl distance 3.0 Å, Figure 17). The chloro-substituted catalysts, however, are less stable than the corresponding fluoro-counterparts and thus not suitable for catalysis.[113]

A series of ruthenium-based metathesis catalysts with less bulky NHC ligands were prepared by Schrodi et al. (Scheme 11).[114] These new catalysts offered an increased activity in the RCM of sterically cumbersome substrates.

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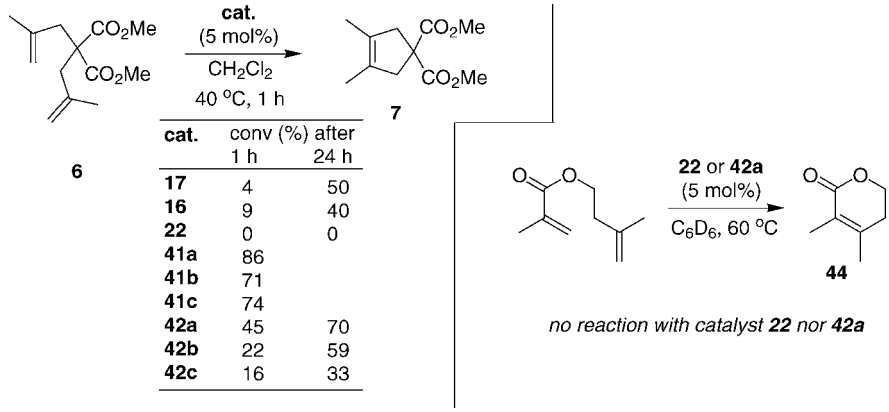
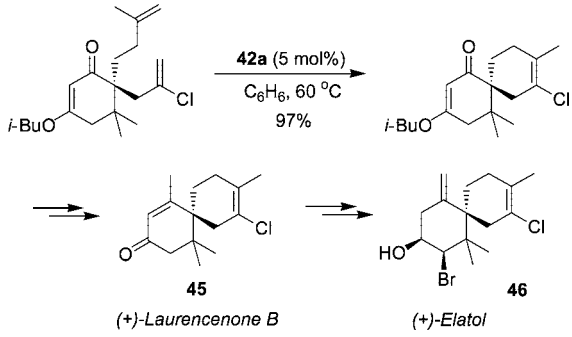
**Scheme 12. Comparative RCM Experiments**




| cat. | conv (%) after 1 h | 24 h |
|---|---|---|
| **17** | 4 | 50 |
| **16** | 9 | 40 |
| **22** | 0 | 0 |
| **41a** | 86 | |
| **41b** | 71 | |
| **41c** | 74 | |
| **42a** | 45 | 70 |
| **42b** | 22 | 59 |
| **42c** | 16 | 33 |

**Scheme 13. RCM Step in the Total Synthesis of (+)-Laurencenone B and (+)-Elatol**




A panel of catalysts (**41a**−**41c** and **42a**−**42c**) was tested in the ring-closing of dimethallylmalonate **6** (Scheme 12). Phosphine-based catalysts **41a**−**41c** gave high conversions under mild conditions within very short reaction times. Methyl-substituted catalysts **41a** and **42a** performed better than their ethyl- and isopropyl-substituted analogues. According to expectations, the Hoveyda-type complexes **42a**−**42c** were found to require longer reaction times to reach good conversions (Scheme 12). These less substituted systems were sufficiently stable to provide efficient conversions to highly substituted products.[115] Unfortunately, despite the higher reactivity offered by these catalysts, the ring closing of tetrasubstituted ester **44** was not realized.

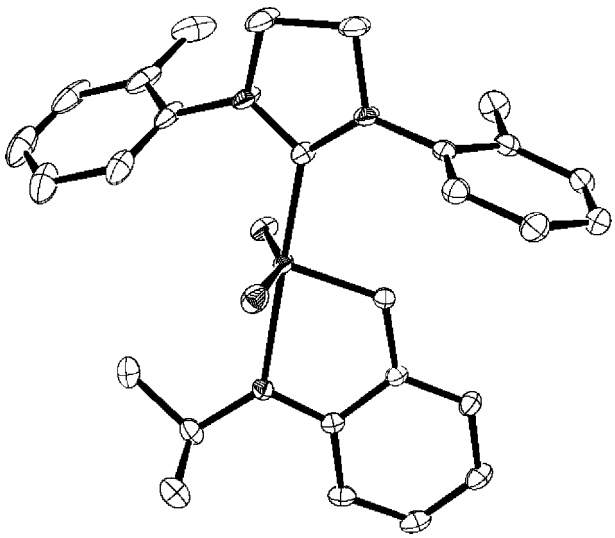
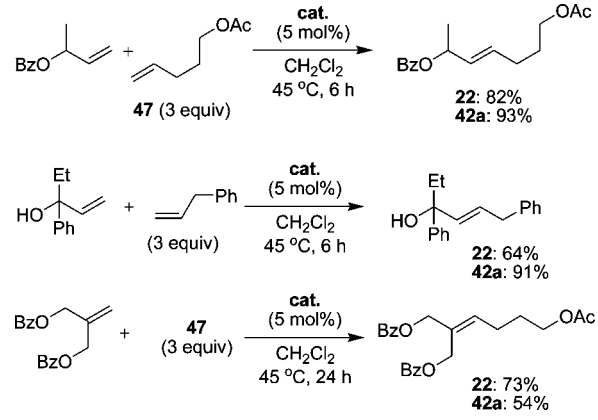
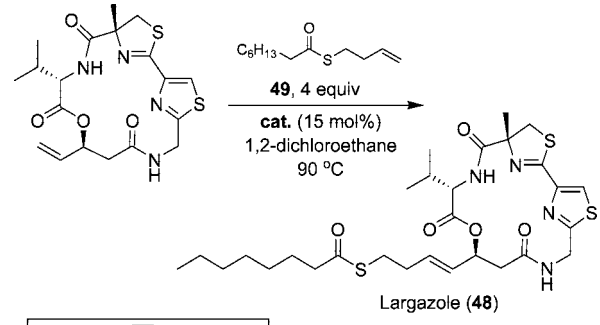


**Figure 18.** ORTEP view of **42a**. $L_1 = 1.9611(11)$ Å, $L_2 = 1.8329(11)$ Å, $\alpha_1 = 119.80(10)°$, $\alpha_2 = 119.52(8)°$.

**Scheme 14. Comparative CM Reactions**




**Scheme 15. Final Step in Synthesis of Largazole (48)**




The authors proposed that the remarkable increase in catalytic activity of **41a** and **42a** compared to the parent systems **17** and **22** for the formation of tetrasubstituted olefins results from the significantly more open steric environment around the ruthenium center, which allows the catalytic site to accommodate larger organic fragments. The X-ray crystal structure of **42a** illustrates the reduced steric hindrance around the metal compared to that in **22** (Figure 18).

In 2008, the catalyst **42a** was successfully used in the first total syntheses of (+)-laurencenone B (**45**) and (+)-elatol (**46**), allowing for highly efficient preparation of a tetrasubstituted chlorinated C−C double bond via RCM (Scheme 13).[116]

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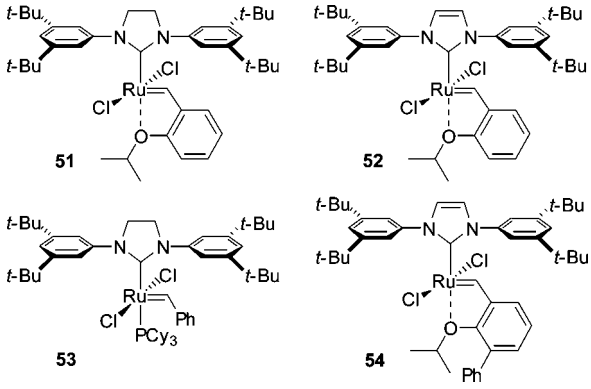
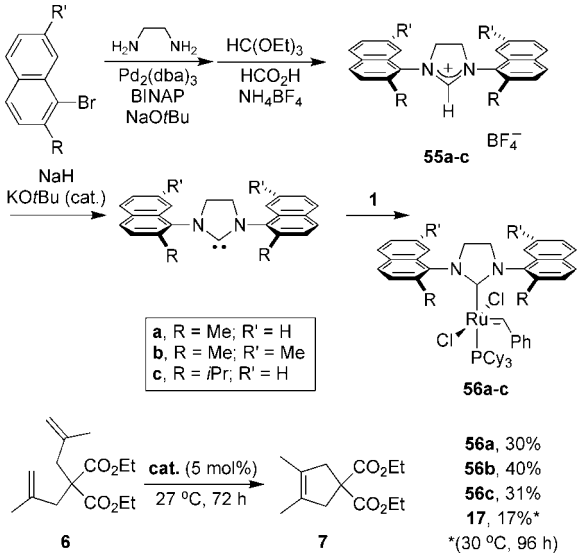



**Figure 19.** Catalysts **51**−**54**.

**Scheme 16. Synthesis and Activity Test of Complexes 56a−56c**



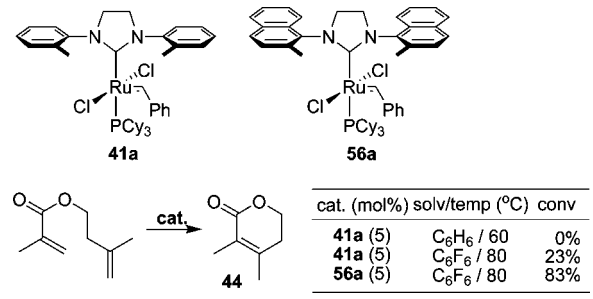

In the same year, the efficiency of catalyst **42a** in olefin cross-metathesis reactions was studied by Grubbs.[117] It was found that for the formation of disubstituted olefins **42a** bearing smaller *N*-tolyl groups is more efficient than the corresponding SIMes bearing **22**. In contrast, in the formation of trisubstituted olefins the latter catalyst was visibly more potent (Scheme 14).

The sterically less demanding variant **42a** was also tested in total synthesis of largazole, a natural product exhibiting broad anticancer activity.[118] In the chosen synthetic approach, it was planned to assemble the final product (**48**) by a cross-metathesis reaction between alkene **49** and the largazole highly functionalized cyclic core. On the basis of the results of model studies presented in Scheme 14, one can expect that the sterically less demanding **42a** should show high activity in this reaction. Interestingly, this catalyst gave the CM product in considerably lower yield than the SIMes-containing catalyst **50**[119,120] (Scheme 15).[118]

Even though the application profile of **42a** seems to be strongly substrate dependent (which is characteristic feature of all modern Ru systems),[19] this new family of sterically less demanding catalysts presumably will find wide application in a target oriented organic synthesis.

In another paper, Grubbs et al. examined the consequences of a further reduction of the steric bulk of the imidazolin-2-ylidene by removal of both ortho-substituents (Figure 19).[121] The authors hypothesized that the absence of ortho

**Scheme 17. Doping Effect of $C_6F_6$ on Metathesis with 41a and 56a**




substituents on each *N*-aryl ring shall bring the additional space necessary for formation of the more sterically demanding tetrasubstituted olefins. To reduce this assumption to reality, a panel of ruthenium complexes with modified NHC ligands was prepared, using similar routes as the one shown in Scheme 11.

Diethyl dimethallylmalonate (**6**, see Scheme 3) was used for activity comparisons. Catalyst **51** performed significantly better in this reaction than either **17** or **22**. Catalyst **52** promoted the reaction more slowly than **51**, as was expected because the IMes-bearing **16** is less active than the SIMes-bearing **17**. Catalyst **53** showed a dramatically enhanced rate of initiation, reaching 43% conversion in 60 min, but also displayed dramatically reduced stability, as the maximal conversion was only 51%. The recent Blechert's concept of steric activation of Hoveyda-type systems[122] was used to prepare the activated catalyst **54**, which exhibited excellent activity (90% conversion after just 1.5 h) combined with good stability.[121]

An interesting class of imidazolin-2-ylidenes bearing 1,3-naphthyl substituents was studied by Dorta and co-workers.[123] Synthesis and structural properties of ligands derived from salts **55a**−**55c** were described in details. Catalysts **56a**−**56c** were synthesized according to Scheme 16 and tested in model RCM reactions with **2** and **4**. While the reactivities of **56a** and **56b** closely resemble that seen with SIMes-bearing **17**, catalyst **56c** showed visibly higher activity toward these substrates. Interestingly, these catalysts were slightly more active toward RCM of the more challenging diethyldimethallyl malonate, **6** (Scheme 16).

In 2008, Blechert et al. reported on the highly efficient formation of tetrasubstituted olefins in RCM using the independently synthesized[124] catalyst **56a**. The authors showed that hexafluorobenzene used as a solvent shows a substantial promoting effect on this reaction (Scheme 17).[97] Under these conditions, high conversions were obtained in a number of challenging RCM reactions, including the formation of electron deficient tetrasubstituted C−C double bonds. Interestingly, the structurally related complex **41a** was less potent in the same reaction (compare Scheme 12). Intermolecular $\pi-\pi$ stacking (see section 3.1.1) or direct fluorine−ruthenium interactions were discussed by the authors as possible reasons for the increased efficiency observed under these conditions.[127] The authors claimed to have obtain a crystalline complex of **56a** and hexafluorobenzene, although no relevant X-ray structure determination was presented.[127]

**Unsymmetrically 1,3-Substituted NHC Entities.** Unsymmetrical NHC frameworks, especially those with one aliphatic side *N*-group, were initially used in order to increase the electron-donating ability and to control the steric bulk

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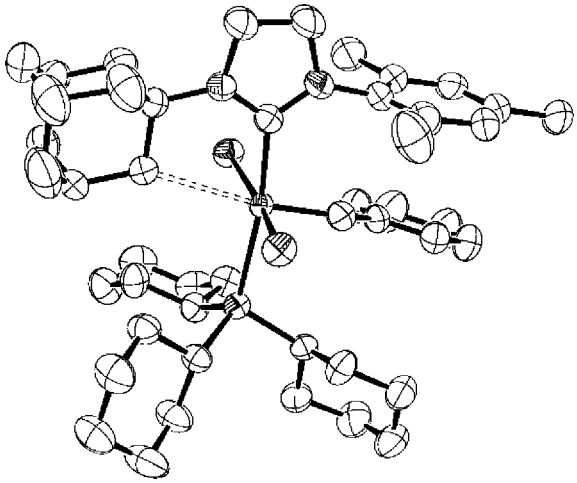
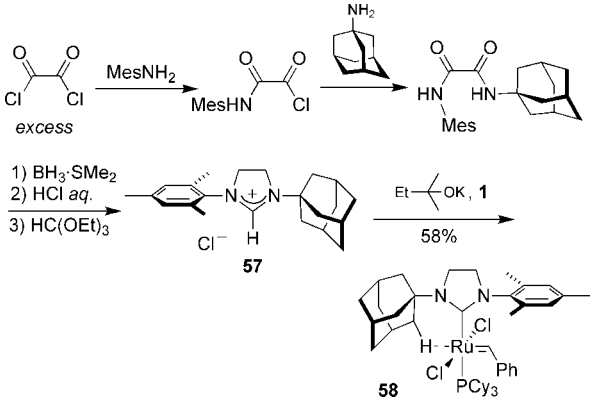
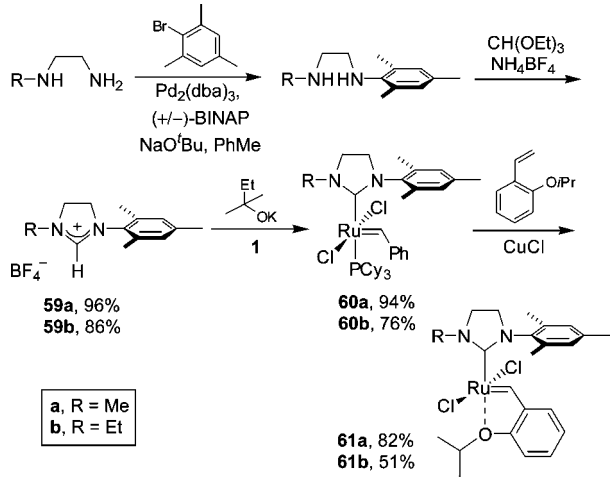


**Figure 20.** X-ray structure of **58**. $L_1 = 2.083(5)$ Å, $L_2 = 1.851(5)$ Å, $\alpha_1 = 117.3(4)°$, $\alpha_2 = 116.7(4)°$.

**Scheme 18. Synthesis of 58**



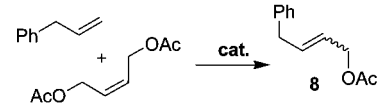

**Scheme 19. Synthesis of 60a and 60b and 61a and 61b**



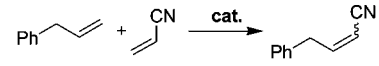

of the NHCs, and consequently to enhance the catalytic activity of the corresponding complexes. In addition, it was found that the utilization of unsymmetrical NHCs alters the selectivity in diastereoselective RCM reactions and the *E*/*Z* selectivity in CM reactions. Examples of such complexes bearing saturated unsymmetrical ($C_1$-symmetry) NHC moieties were disclosed by Hoveyda et al. and are described in section 3.1.5.[125−127]

Mol et al. introduced a large sterically encumbered mixed adamantyl/mesityl based NHC ligand.[128] (The catalysts bearing bis(adamantyl) NHC ligand, **28**, could not be formed). Complex **58** bearing the bulky 1-(1-adamantyl)-3-mesityl-4,5-dihydroimidazol-2-ylidine NHC ligand was obtained in moderate yield as depicted in Scheme 18.

**Scheme 20. Comparative CM reactions**




| cat. | *E*/*Z* | conv (%) |
|---|---|---|
| **17** | 6:1 | 79 |
| **60a** | 3:1 | 72 |
| **22** | 6:1 | 84 |
| **61a** | 6:1 | 78 |




| cat. | *E*/*Z* | conv (%) |
|---|---|---|
| **17** | 0.6:1 | 67 |
| **60a** | 2.4:1 | 7 |
| **22** | 0.6:1 | 95 |
| **61a** | 1.8:1 | 20 |

The air-stable catalyst **58** exhibits a green color what is a bit surprising as the parent Grubbs catalyst **17** is red-brownish in appearance. Interestingly, the X-ray structure of **58** showed a possible week interaction of one of the adamantyl carbons with the metal center (2.883 Å), Figure 20.

Complex **58** completely failed to initiate even the simple self-metathesis of 1-octene, the self-metathesis of methyl oleate, and the ring-closing metathesis of diethyl diallylmalonate. This lack of activity persisted even at higher temperatures; in fact, **58** failed to produce even trace amounts of any metathesis products of 1-octene at 60 or even 100 °C, with isomerization being the only reaction that took place in these cases. The same reactions carried out in the presence of some copper (I) chloride afforded 7-tetradecene with only 12% conversion (12 turnovers per mol of catalyst), whereas catalysts **17** and **37** are capable of turnover numbers of ∼300 000 and over 600 000, respectively, for the metathesis of 1-octene.[129] This negligible metathesis activity was ascribed to excessive steric crowding imparted by the 1-adamantyl moiety toward the position trans to the benzylidene group.

Further studies of unsymmetrical saturated NHC ligands were made by Blechert et al.[130] The authors postulated that replacement of one mesityl ring with a more electron donating alkyl group could lead to enhanced $\sigma$-donor properties of the NHC. Additionally, it was anticipated that unsymmetrical ligands could alter the steric environment of key metathesis intermediates to effect *E*/*Z* selectivity in cross-metathesis (CM) reactions and diastereoselectivity in some ring-closing metathesis (RCM) reactions.[131] Synthesis of ligand precursors commenced with Buchwald−Hartwig coupling of commercially available monosubstituted diamines with 2-bromomesitylene, followed by cyclization, furnished **59a** and **59b** as their tetrafluoroborate salts in high yields. Complexes **60a** and **60b** were isolated in excellent yields by reaction of free NHC (generated in situ from **59a** or **59b** with potassium *tert*-amylate) with **1** in *n*-hexane. Treatment of **60a** or **60b** with 2-isopropoxystyrene in the presence of CuCl afforded the Hoveyda-type complexes **61a** and **61b** in good isolated yields as green air-stable solids (Scheme 19).

In the RCM reaction of **2**, the novel metathesis initiators displayed activities similar to those of their symmetrical counterparts (**17** and **22**). Analogous results were obtained when CM was the subject of investigation. Interestingly, greater amounts of the (*Z*)-**8** isomer were obtained with **60a**, whereas **61a** gave a *E*/*Z* ratio comparable, to that one obtained with **17** and **18** (Scheme 20). CM with acrylonitrile

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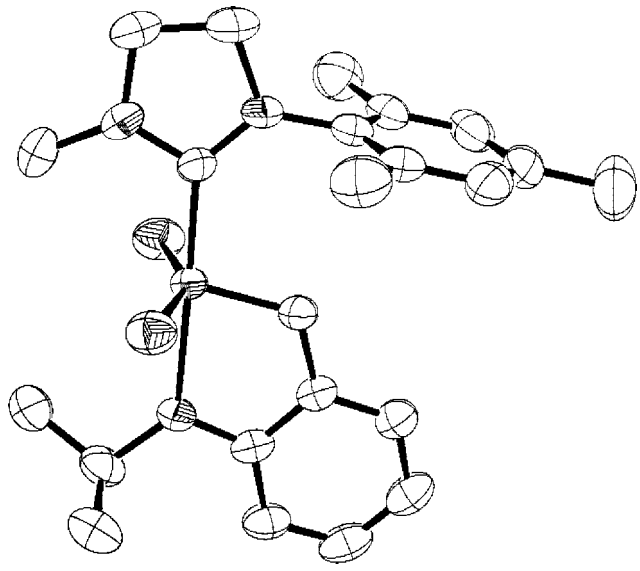


**Figure 21.** ORTEP view of **61a**. $L_1 = 1.978(3)$ Å, $L_2 = 1.821(3)$ Å, $\alpha_1 = 120.2(3)°$.

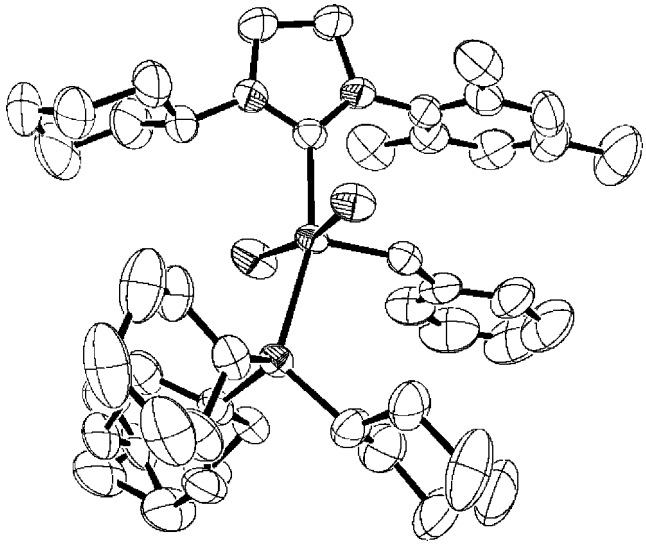


**Figure 22.** ORTEP view of **63c**. $L_1 = 2.060(5)$ Å, $L_2 = 1.830(6)$ Å, $\alpha_1 = 118.2(4)°$, $\alpha_2 = 121.8(4)°$.

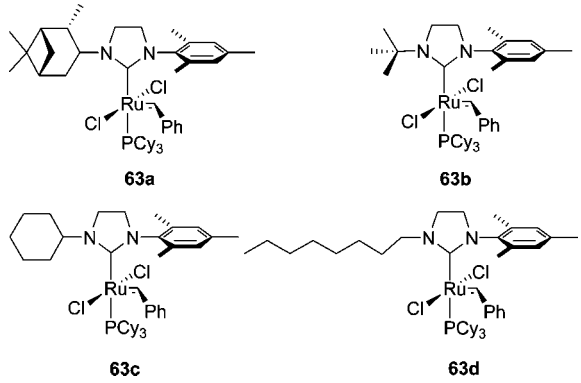



**Figure 23.** Catalysts **63a**−**63d**.

proceeded in low conversion when the new catalysts were utilized; however, a *complete* reversal of selectivity was observed (Scheme 20). Additionally, catalysts **60a** and **61a** induce higher selectivity in some diastereoselective ring-closing metathesis.

Blechert et al.[132] also reported on a ruthenium-based catalyst bearing unsymmetrical NHC containing *N*-phenyl-*N*′-mesityl flaps, but unfortunately this complex undergoes fast decomposition (see section 4).

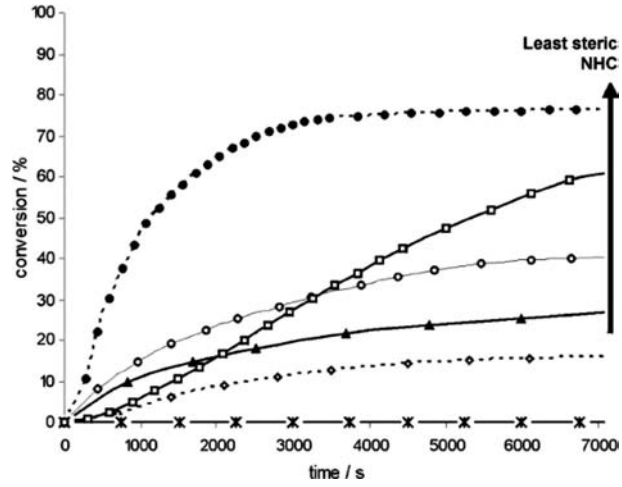
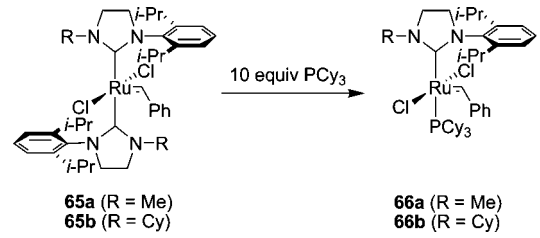



**Figure 24.** Relative activity of **17** (□), **60a** (●), **63d** (○), **63a** (◊), **63c** (▲), and **63b** (*) in RCM of **4** (catalyst 0.5 mol %, $C = 4.5$ mM, $CH_2Cl_2$, 20 °C). (Reproduced with permission from ref. 95 Copyright 2006 Wiley-VCH.)

**Scheme 21. NHC Exchange in 65**




Aiming at further improvement of the application profile of the Grubbs second-generation catalysts,[95] Ledoux et al. decided to test dihydroimidazolium NHC ligands bearing (in addition to a mesityl "flap") an aliphatic group with greater steric bulk than Me and Et tested by Blechert. The preparation of NHC salts was straightforward, following a synthetic pathway described by Grubbs et al. Exposure of the **1** to these unsymmetrically substituted NHC precursors and KHMDS as a base afforded the complexes **63a**−**63d** under mild reaction conditions (Figure 23). The "benchmark" complex **60a** was also synthesized by the authors and used in a comparative study. The X-ray crystallographic analysis of **63c** demonstrated that the mesityl group is coplanar with the phenyl ring of the benzylidene (Figure 22). This result shows again that $\pi-\pi$ interactions between the mesityl arm and the benzylidene moiety constitute an important structural element of NHC-bearing benzylidene complexes.

Catalysts obtained by Ledoux et al. (Figure 23) were tested in ROMP and RCM. Catalytic performance in the polymerization of *cis*,*cis*-cycloocta-1,5-diene (COD, Scheme 3) was compared to the reactivity of **1** and **17**, using different solvents and monomer/catalyst ratios. The RCM activity of the new complexes was tested on the standard substrate diethyl diallylmalonate **4**. A significant dependence of the reactivity on the bulkiness of the NHC entities was observed. The most crowded NHCs correspond to the lowest RCM activity, while activity increases considerably for complexes bearing less bulky NHCs. The most active catalyst system was found to be complex **60a**, bearing an NHC ligand with the smallest methyl moiety. This complex was found to be substantially more active than the parent complex **17**. It is therefore undeniable that the steric bulk of the *N*-side group

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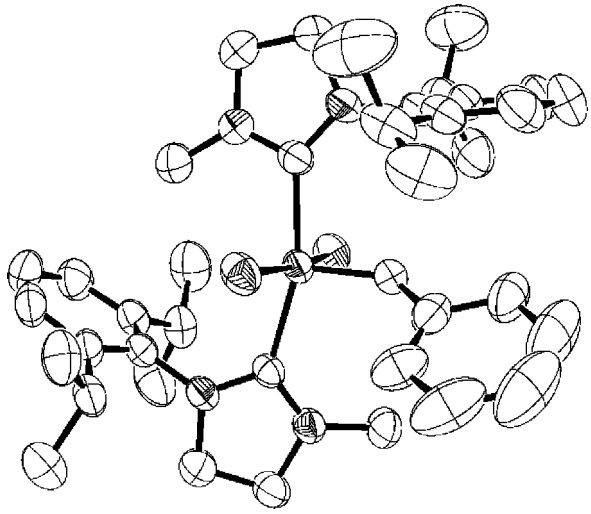

**Figure 25.** X-ray structure of **65a**. $L_1 = 2.073$ Å and 2.121 Å, $L_2 = 1.818$ Å $\alpha_1 = 130.31°$, $\alpha_2 = 118.94°$.

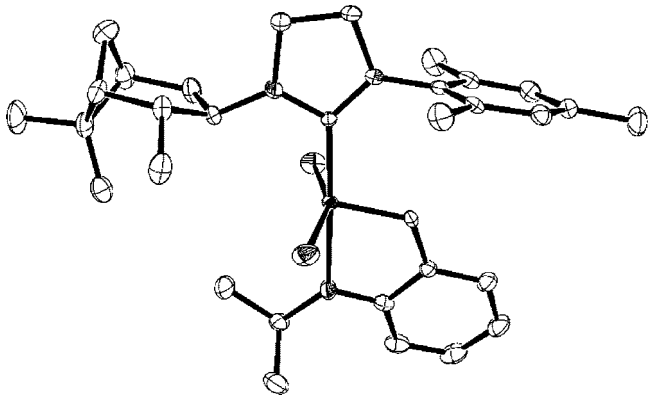

**Figure 26.** X-ray structure of **67d**. $L_1 = 1.973(3)$ Å, $L_2 = 1.832(3)$ Å, $\alpha_1 = 120.7(3)°$, $\alpha_2 = 119.4(2)°$.

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is of great importance. The new catalysts were found to surpass the parent complex **17** in the ROMP of COD. Catalyst **63b**, bearing a *t*-Bu-*N* substituted NHC, was considerably less metathesis active than other tested catalysts. Furthermore the observation that the least sterically congested complex **60a** is the most active for RCM (Figure 24), clearly demonstrates that modification of the NHC ligand can induce substantial changes in the reactivity pattern of the corresponding catalysts and that systematic variation of the *N*-substituents may eventually allow fine-tuning.

Ledoux et al. reported on preparation and utility of some bis(NHC) ruthenium complexes (compare section 2).[133] *N*-(Alkyl)-*N*′-(2,6-diisopropylphenyl) carbenes display an exceptional tendency toward substitution of both phosphine ligands in the reaction with the benzylidene complex **1** (Scheme 21, Figure 25). The resulting bis(NHC) catalysts **65** show substantial olefin metathesis activity at elevated temperature. One NHC ligand is expected to dissociate from the metal center for the catalyst to be activated. This NHC ligand lability is confirmed by the observation that both NHCs are exchangeable when the complexes are treated with an excess of $PCy_3$. In addition, the isolation of new mono(NHC) complexes **66** was described, as well as their reactivity in the ROMP of COD and RCM of diethyl diallylmalonate (**4**).

The bis(NHC) complexes **65a**,**b** and NHC-$PCy_3$ counterpart **66a** display substantial ROMP activity at room temperature. In the RCM of diethyl diallylmalonate (**4**), complex

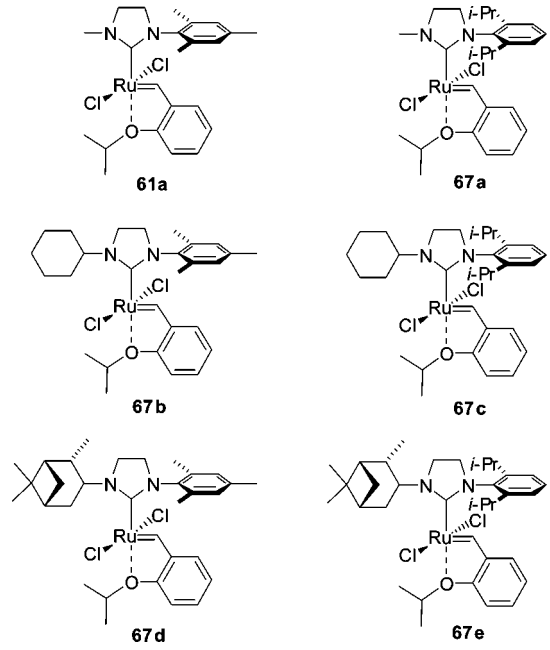


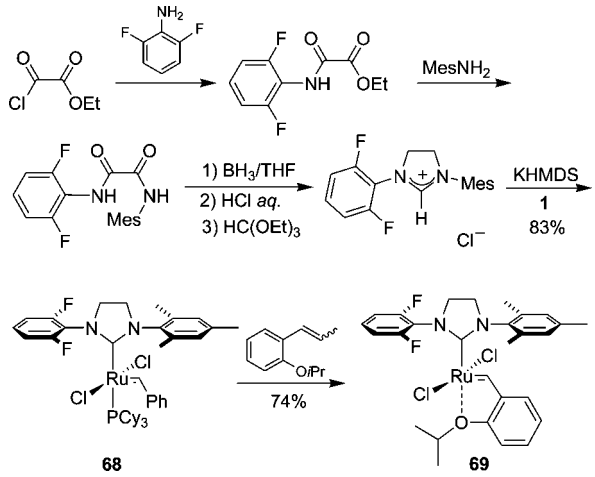

**Figure 27.** Catalysts **61a** and **67a**−**61e**.

**66a** exhibits faster initial reaction than the benchmark catalyst **17**. Even though we are not able to provide full evidence, one could presume that the higher initiation rate of **66a** goes together with a higher lability of its phosphine ligand.

Ledoux and Verpoort[106] described also the preparation, characterization and catalytic behavior of Hoveyda type complexes featuring modified *N*-heterocyclic carbenes. The introduction of an aliphatic amino side group into the NHC framework profoundly altered the catalytic activity and selectivity of the resulting complexes. Since the *N*-(alkyl)-*N*′-(2,6-diisopropylphenyl) heterocyclic carbenes induce preferential bis-coordination in their reaction with **1**, the authors worked out an unconventional synthetic strategy which uses the bis(NHC) complexes **65a** and **65b** as the starting material. Reaction with an excess of 2-isopropoxystyrene at elevated temperature allows for the decoordination of one NHC ligand with formation of the desired complexes in good yield (Figure 27). To explore the catalytic potential of the new complexes,[106] a series of comparative tests were attempted. The authors anticipated that changing the electronic nature of the NHC through the introduction of aliphatic groups might positively affect the catalytic activity of the corresponding complexes.[106] However, they came to conclusion that the influence of the steric bulk plays a much more compelling role in developing the RCM activity. As the steric bulk of the NHC ligand increases, a decrease in catalyst activity was found. In the CM reactions these modified complexes display lower activity than the classic **17** and **22**, yet induce different *E/Z* selectivities.

In summary, a comparison between the classical Hoveyda complex **22** and complexes **61a** and **67a**−**67e** demonstrates that the introduction of one aliphatic group into the NHC framework does not improve really the catalytic activity. However, the observed different stereoselectivities are intriguing. These results confirm that the NHCs side groups play a pivotal role in determining the reactivity and selectivity of the corresponding catalysts. While small differences in donor capacities might cause a significantly different catalytic behavior, it is plausible that subtle steric differences exert a more determining influence on the activity of the catalysts.

**Scheme 22. Synthesis of 68 and 69**




As a continuation of the previously described work on a significant rate enhancement of ruthenium catalyst **37** bearing *o*-fluorinated aryl groups on the NHC ligand Grubbs et al. developed catalysts **68** and **69**, (Scheme 22), bearing the unsymmetrical 1-(2,6-difluorophenyl)-3-(mesityl)-4,5-dihydroimidazolin-2-ylidene ligand.[134]

The synthesis of 1-(2,6-difluorophenyl)-3-(mesityl)-4,5-dihydroimidazolium chloride was straightforward, following a modification of a previously reported synthetic pathway. Reaction of commercially available 2,6-difluoroaniline affords an oxanilic acid ethyl ester, which, upon condensation with mesitylaniline, reduction with $BH_3 \cdot THF$ and treatment with triethyl orthoformate yielded the corresponding imidazolinium chloride. Complex **68** was isolated in 83% yield by in situ generation of the free carbene and reaction with **1** in benzene. Treatment of **68** with *o*-isopropoxy-$\beta$-methylstyrene afforded the phosphine-free analogue **69** in 74% yield after crystallization (Scheme 22). Complexes **68** and **69** are both air stable in the solid state and were fully characterized spectroscopically, as well as by single-crystal X-ray analysis (Figure 28).

The catalytic performance in RCM, CM, and ROMP reactions has been evaluated. The activity of **68** in RCM reactions surpasses that of the commercially available catalysts **17** and **22**. In the same set of model RCM reactions, the phosphine-free complex **69** exhibited similar or even lower activity than complexes **17** and **22** because of slower initiation. In model CM and ROMP reactions both new

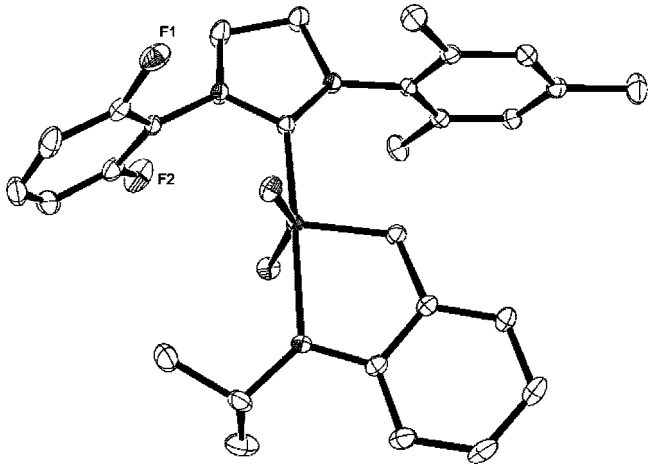



**Figure 28.** ORTEP view of **69**. $L_1 = 1.9688(12)$ Å, $L_2 = 1.8337(12)$ Å, $\alpha_1 = 121.45(10)°$, $\alpha_2 = 118.20(10)°$.

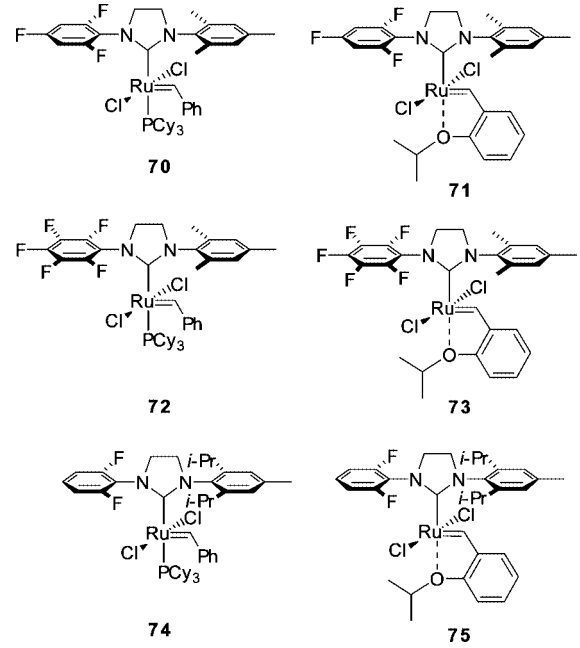



**Figure 29.** Ru-catalysts **70**−**75**.

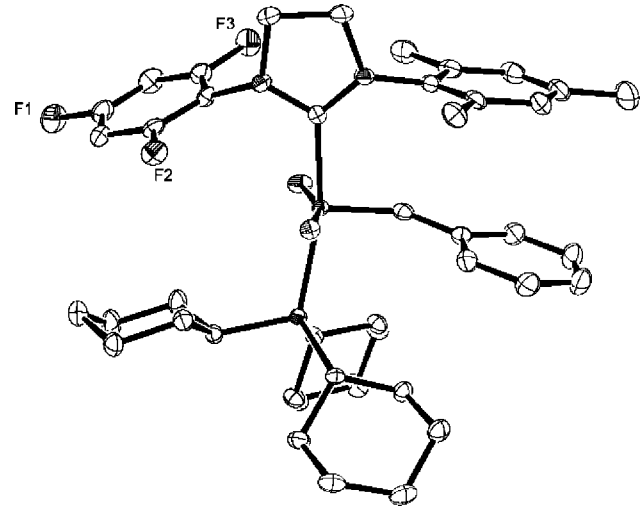



**Figure 30.** ORTEP view of **70**. $L_1 = 2.0602(18)$ Å, $L_2 = 1.826(2)$ Å, $\alpha_1 = 118.40(15)°$, $\alpha_2 = 117.99(15)°$.

catalysts show similar or even lower reactivity than **17** and **22**. Interestingly, however, in the CM reaction of allyl benzene with *cis*-1,4-diacetoxy-2-butene, both **68** and **69** give improved *E/Z* selectivities at conversions above 60%, comparing to commercial available catalysts.

A longer series of ruthenium-based olefin metathesis catalysts coordinated with unsymmetrical *N*-heterocyclic carbene (NHC) ligands containing one fluoroaryl substituent (Figure 29) was prepared and fully characterized by Grubbs and co-workers.[135] All of the complexes reported herein were tested in a set of model reactions, such as RCM of diethyldiallyl and diethylallylmethallyl malonates, ROMP of COD, and CM of allyl benzene with *cis*-1,4-diacetoxy-2-butene, in some cases surpassing in efficiency the existing second generation catalysts.

The synthesis of carbene precursors is straightforward, following a modification of previously reported procedures.[30] Compounds **70**−**75** are air stable in the solid state and can be purified by silica gel chromatography. As in the previous case, phosphine-free catalysts were less efficient than the

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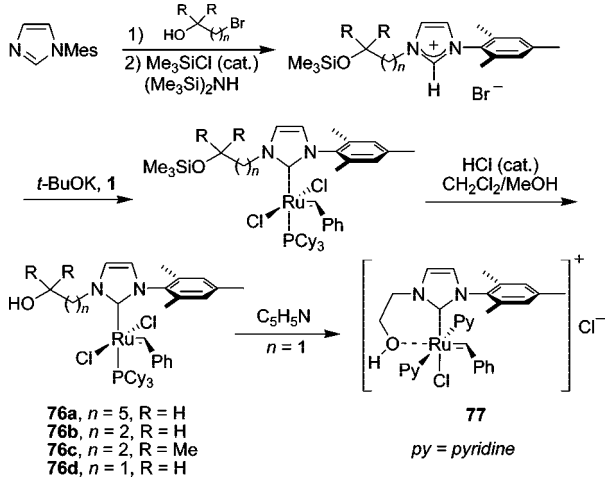
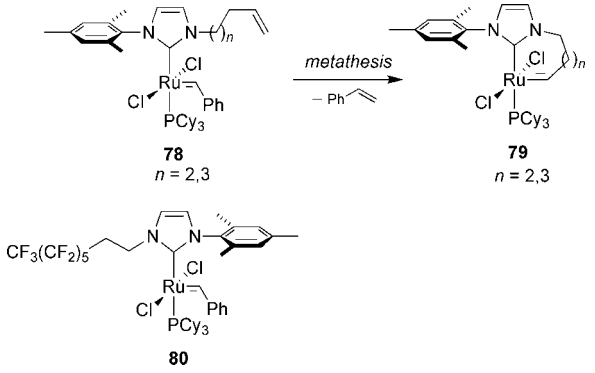
**Scheme 23. Catalysts Obtained by Fürstner et al.**




**Scheme 24. Catalysts 78−80**




parent complex **22**. In fact, increasing the number of fluorine atoms on the *N*-aryl substituent, in going from complex **69** to **71** and eventually to **73**, results in lower activity, with catalyst **73** being the least efficient of all in this series.

Fürstner and co-workers reported on the preparation of some ruthenium benzylidene complexes bearing hydroxyalkyl chains on their *N*-heterocyclic carbene ligands (Scheme 23).[136] These complexes exhibit very interesting structural peculiarities being prone to rearrange their ligand sphere such that the chloride ligands get *cis*- rather than *trans*-disposed. Moreover, treatment of complex **76d** with pyridine results in an unprecedented ionization by loss of one of its chloride ligands. The resulting cationic complex **77** (Figure 31), though devoid of catalytic activity, is the first member of a new type of ruthenium carbene complexes characterized by

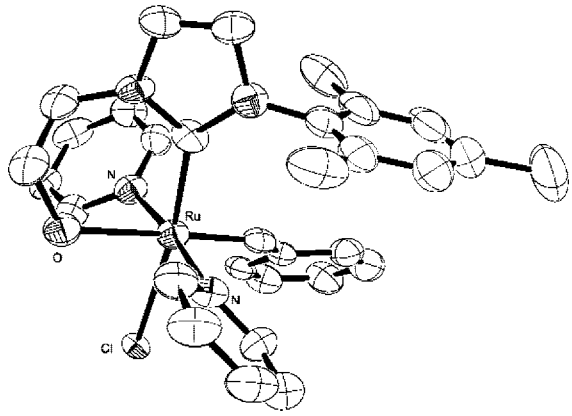
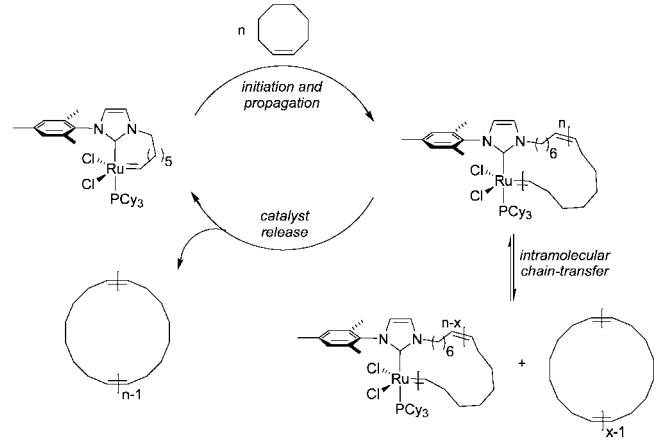
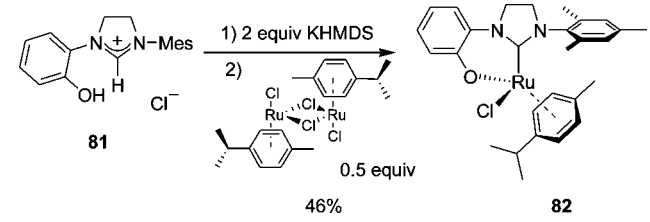



**Figure 31.** ORTEP view of complex **77**.

**Scheme 25. Mechanism of REMP**




**Scheme 26. Bidentate Catalyst Precursor 82**




an octahedral coordination geometry and a donor/acceptor interaction between the metal center and the tethered hydroxyl group. Complex **76a** can be covalently immobilized on silica using the hydroxyalkyl chain (see section 3.1.4 for more details).

The same strategy, based on the alkylation of mesitylimidazole by an olefinic chain, led to functionalized NHCs, which were used in the construction of Grubbs type catalysts being able to metathesize their own olefinic arm.[137] The same authors also obtained ruthenium catalysts bearing unsymmetrical NHC with perfluorinated alkyl chains which can be potentially useful in fluorous phases (Scheme 24).[94] Although no example of such application of pony-tailed **80** was presented, this possibility is of future interest.[138]

Later Grubbs et al.[139] utilized similar "cyclic" catalysts **79** (e.g., $n = 5$) for the preparation of cyclic polymers in ring-expansion metathesis polymerization (REMP) process.[140] Such catalysts react with *cis*,*cis*-1,5-cyclooctadiene to provide cyclic polybutadiene with no contamination by linear product. This is in contrast with commercially available **17**, which gave in this reaction only linear high-molecular weight product. The REMP methodology provides access to polymers of different physical properties, which are difficult to obtain via alternate synthetic routes. The mechanism of REMP has been proposed in due course (Scheme 25). It should be noted that the catalyst design is modular in nature, which provided access to Ru complexes having various tether lengths, as well as electronically different NHC ligands. From these studies, it was deduced that while increasing the tether length of the catalyst leads to enhanced rates of polymerization, shorter tethers were found to facilitate intramolecular chain transfer and release of catalyst from the polymer. Electronic modification of the NHC via backbone saturation was found to enhance polymerization rates to a greater extent than was possible by homologation of the tether. Finally, cyclic Ru complexes incorporating 5- or 6-carbon tethers and saturated NHC ligands were found to be also highly active catalysts for REMP.

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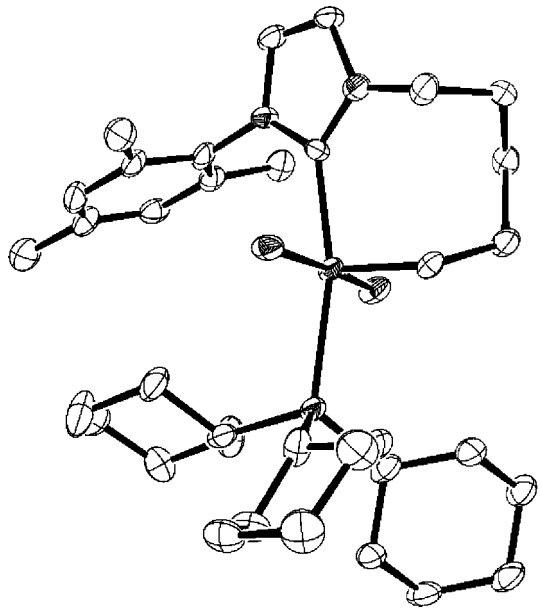


**Figure 32.** ORTEP view of **79** ($n = 3$). $L_1 = 2.091(6)$ Å, $L_2 = 1.806(6)$ Å, $\alpha_1 = 122.0(6)°$, $\alpha_2 = 123.5(5)°$.

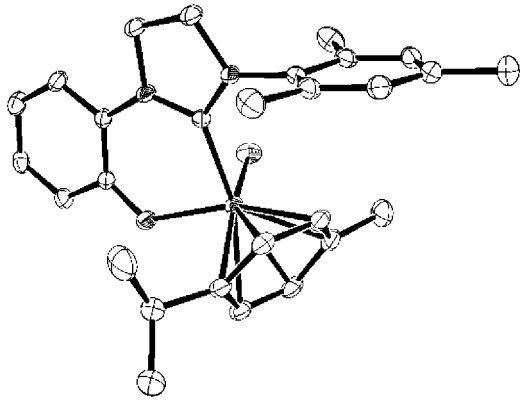
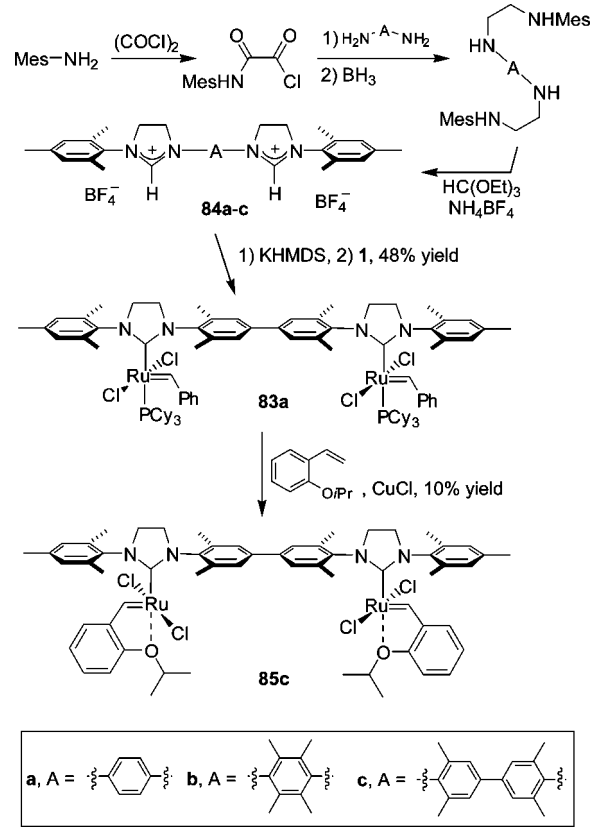


**Figure 33.** ORTEP view of **82**. $L_1 = 2.0596(19)$ Å, $\alpha_1 = 118.14(16)°$, $\alpha_2 = 116.85(16)°$.

Ledoux et al. were looking for patent free ruthenium complexes active in olefin metathesis.[141] These authors reported a straightforward synthesis of the bidentate NHC precursor **81**, which after deprotonation and in situ reaction with a dimeric Ru−cymene complex, produced the desired product **82** (Scheme 26). In the ROMP of norbornene, complex **82** displayed very poor activity as initiator (only 20% of norbornene polymerized during a reaction time of 3 h at 85 °C), comparing to the commercially available **17**. Recently, another ruthenium complex coordinated by a bidentate aryloxy−NHC ligand was reported by Jensen et al.[142]

Lemcoff et al. designed a very interesting homodinuclear ruthenium catalysts (**83**) for dimer ring-closing metathesis (DRCM) applications.[143] The bis-NHC ligand precursors **84** were readily synthesized, as shown in Scheme 27. Significantly, ligands **84a** and **84b**, built on shorter spacers, did not allow the corresponding di(ruthenium) catalysts **83a** and **83b** to be obtained, probably because the significant steric constraints due to the large $PCy_3$ ligands.[67,144] Catalyst **83c** was isolated and characterized but was proved to be relatively unstable and decomposed after some hours in solution. The reaction of **83c** with isopropoxystyrene and copper(I) chloride led to the formation of the isopropoxy chelated bis-catalyst **85c** of improved stability (Scheme 27, Figure 34).

**Scheme 27. Synthesis of bis-NHC catalyst 83c and 85c**




In a model diethyl diallylmalonate (**4**) RCM, both catalysts **83c** and **85c** exhibited similar reactivity to the mono-Ru catalyst **22**. More importantly, in metathesis of diene **86**, catalysts **83c** and **85c** preferentially afforded DRCM product, when in the case of monomeric catalysts **17** and **22** a preference toward formation of an ADMET product was observed (Scheme 28).

### *3.1.3. Influence of Substituents Modification at 4,5-Positions*

The ruthenium benzylidene **87** bearing 4,5-dichloro-substituted imidazol-2-ylidene was disclosed by Fürstner (Scheme 29).[94] Exposure of the parent Grubbs complex **1** to **88** (obtained on treatment of IMes with $CCl_4$ as outlined by Arduengo et al.)[145] in toluene at ambient temperature afforded **87**, which was found to be thermally stable, rather inert toward oxygen, and could be stored for extended periods of time without any appreciable loss of reactivity. The catalytic activity of **87** was tested in a set of model reactions (Scheme 3), revealing that substitution of the backbone of the NHC

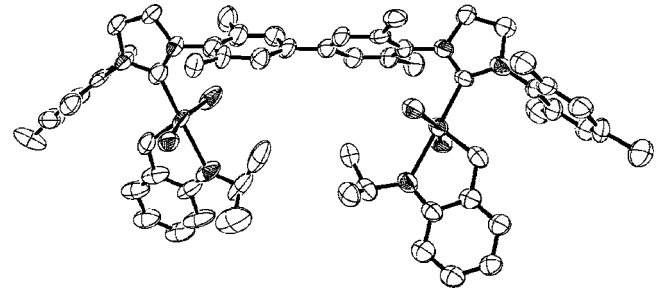
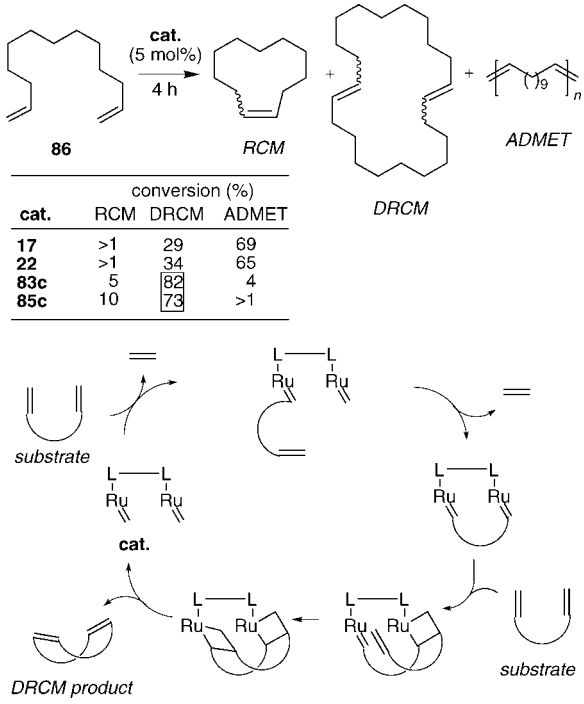
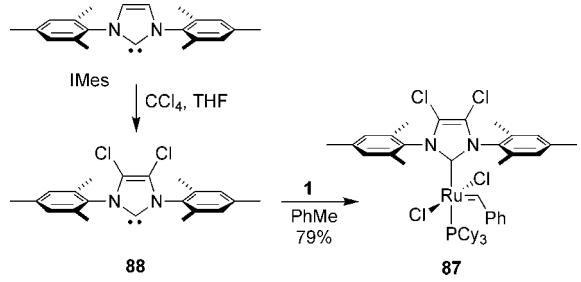


**Figure 34.** ORTEP view of **85c**. $L_1 = 1.965(8)$ Å and 1.963(10) Å, $L_2 = 1.813(10)$ Å and 1.836(11) Å, $\alpha 1 = 120.9(8)°$ and 121.0(9)°, $\alpha 2 = 121.4(7)°$ and 120.7(7)°.

**Scheme 28. Metathesis of 86 and Mechanistic Explanation Proposed by Lemcoff**




**Scheme 29. Synthesis of Catalyst 87**




ligand with two chlorine atoms has surprisingly little effect on the reactivity of the resulting complex, since **87** and its parent IMes analogue **16** were almost indistinguishable in their catalytic activity.[144]

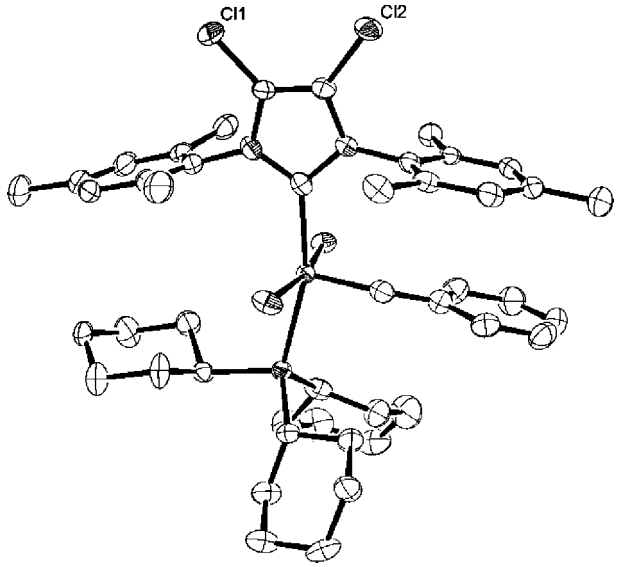



**Figure 35.** ORTEP view of **87**. $L_1 = 2.092(5)$ Å, $L_2 = 1.846(5)$ Å, $\alpha_1 = 122.0(4)°$, $\alpha_2 = 121.0(4)°$.

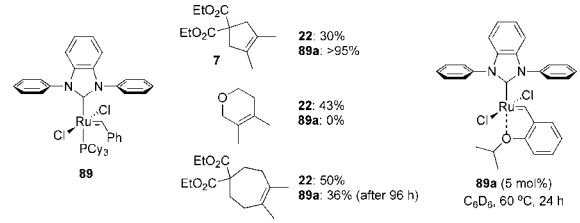



**Figure 36.** RCM to form tetrasubstituted olefins.

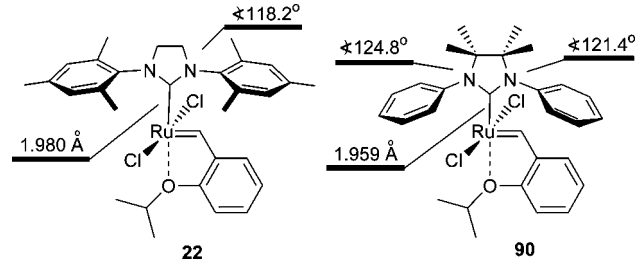
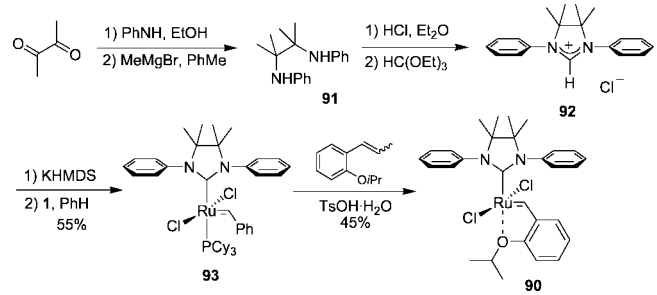



**Figure 37.** Effect the neighboring *gem*-dimethyl groups.

**Scheme 30. Synthesis of Ruthenium Complexes 90 and 93**




Grubbs' group has recently demonstrated[114,116,117] that decreasing the size of the aryl groups on the imidazolin-2-ylidene ligand by the removal of one ortho substituent was beneficial for the ring closing metathesis (RCM) and cross metathesis (CM) of hindered substrates. However, attempts to further enhance the efficiency of the catalyst by removing both ortho substituents on the NHC ligand led to catalyst instability through the activation of ortho C−H bonds of the *N*-phenyl groups (see section 4). Although the 1,3-diphenylbenzimidazol-2-ylidene bearing complex (**89**) shows good catalytic activity for some hindered olefins, this complex is rather unstable and decomposes easily under metathesis reaction conditions (Figure 36).[121]

To check if restricting rotation of the *N*-aryl group would prevent catalyst decomposition Chung and Grubbs synthesized a variant of Hoveyda-catalyst (**90**) bearing bulky substituents on the backbone of the NHC ligand.[146,201]

The synthesis of **90** began with the condensation of 2,3-butandione with aniline (Scheme 30). Treatment of the resulting diimine with a Grignard reagent furnished diamine **91**, which was subsequently converted to salt **92**. The corresponding free carbene (generated with potassium hexamethyldisilazide at room temperature) mixed with **1**, afforded complex **93**, which was finally transformed to phosphine-free complex **90**. The latter was stable under air in the solid state. The crystal structure showed that the length of the $C_{(NHC)}$−Ru is shorter in **90** (1.959 Å) than in **22** (1.980 Å), indicating a stronger NHC−ruthenium interaction. Notably, the two phenyl substituents are tilted away from the top *gem*-dimethyl groups as can be seen from the bond angles (124.83° and 121.36°, respectively, compared with 118.33° and 118.22° for **22**, Figure 38).

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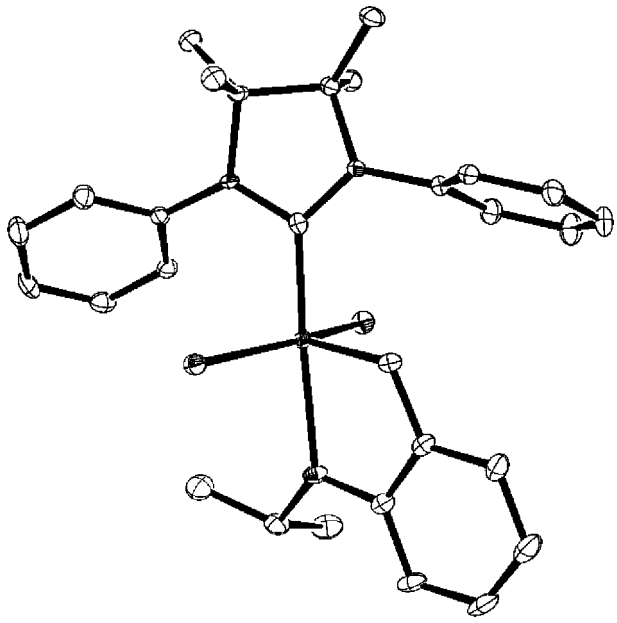
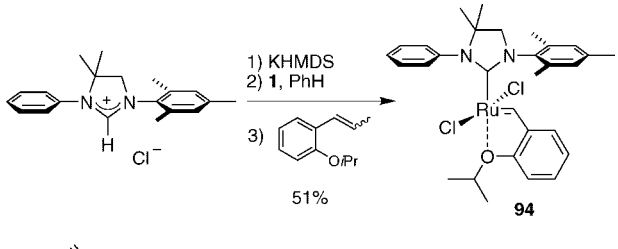


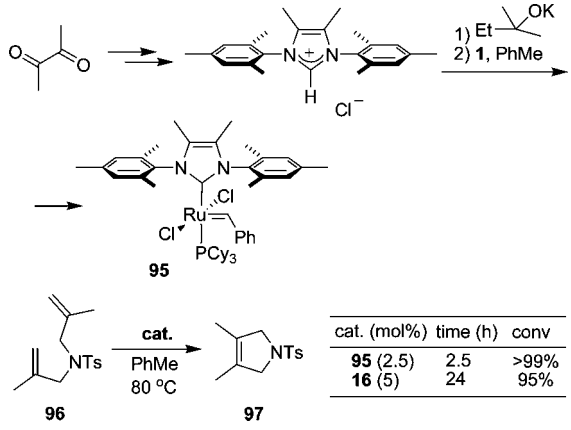
**Figure 38.** ORTEP view of **90**. $L_1 = 1.959(2)$ Å, $L_2 = 1.822(2)$ Å, $\alpha_1 = 124.83(15)°$, $\alpha_2 = 121.36(15)°$.

**Scheme 31. Synthesis of 94 and Catalytic Activity Screening of 90 and 94**




| catalyst | time (h) | conv (%) |
|---|---|---|
| **22** | 24 | 30 |
| **90** | 0.3 | 98 |
| **94** | 31 | 55 |

**Scheme 32. Preparation and Screening of 95**




| cat. (mol%) | time (h) | conv |
|---|---|---|
| **95** (2.5) | 2.5 | >99% |
| **16** (5) | 24 | 95% |

Next, an unsymmetrical analogue (**94**) with 1-mesityl-3-phenyl-substituted NHC was synthesized by the same authors using the similar synthetic route (Scheme 31). The catalytic activity of these backbone-substituted complexes was tested

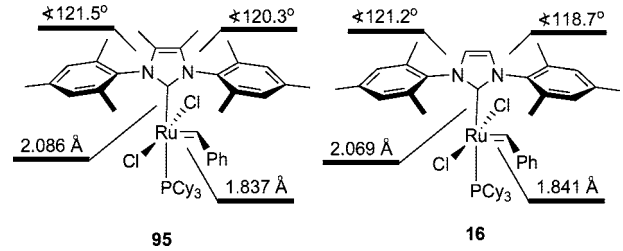



**Figure 39.**

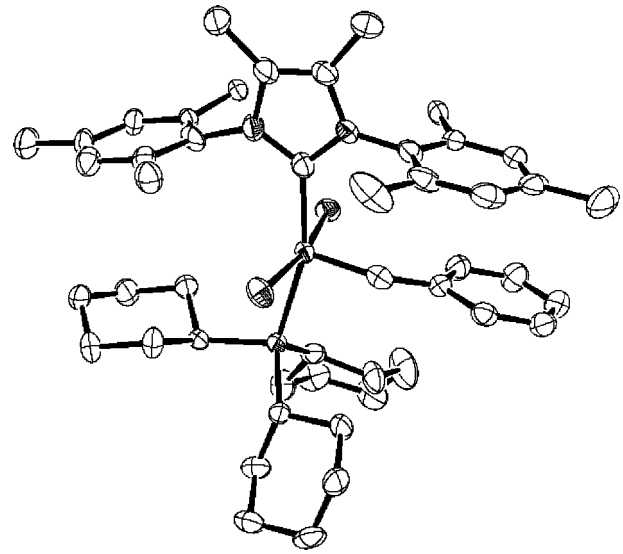


**Figure 40.** ORTEP view of **95**. $L_1 = 2.087(4)$ Å, $L_2 = 1.837(4)$ Å, $\alpha_1 = 121.5(3)°$, $\alpha_2 = 120.5(1)°$.

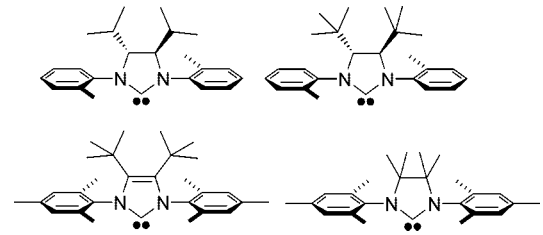


**Figure 41.** Ligands predicted to provide highly active Ru-catalysts.

in RCM, CM, and ROMP reactions, and **90** emerged as one of the most efficient catalysts in the tetrasubstituted olefin forming RCM reaction. Contrary to the high reactivity of **90** in hindered olefin formation, the unsymmetrical complex **94** failed to cyclize **6** at 30 °C. However, at higher reaction temperature (60 °C in benzene), **94** afforded **7** in 55% conversion after 31 h.

Interestingly, yet another approach to increase the activity of second generation Ru catalysts in the formation of tetrasubstituted C−C double bonds in RCM has recently been disclosed by researchers working in industry. Starting from 2,3-butandione, Kadyrov and Rosiak prepared new complex **95**.[147] This catalyst, like the parent IMes and SIMes complexes **16** and **17** is stable in the presence of air and moisture.

The efficiency of catalyst **95** was examined in the ring closing metathesis of a challenging substrate **96**. Full conversion of **96** was achieved after heating to 80 °C for 2.5 h with a catalyst loading of 2.5 mol %. The larger scale run furnished 80% isolated yield of the desired dihydropyrrole **97** (Scheme 32). Interestingly, the solid-state structure

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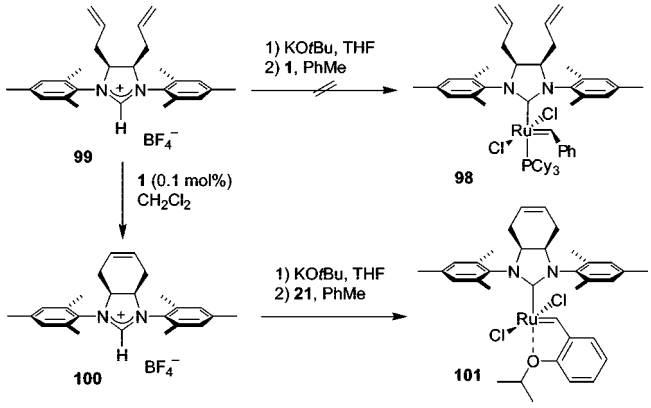
**Scheme 33. Ring-Closing Metathesis of 100 and Preparation of Catalyst 101**




of **95** resembles very closely the parent IMes complex **16** (Figure 39, Figure 40). Therefore the reason for the observed enhanced activity is not clear. These preliminary results are of future interest, since good activity levels for hindered substrates were achieved without decreasing the size of the *N*-aryl groups on the NHC ligand, therefore without diminishing the catalyst's stability.

It should be noted that in 2006 Jensen et al. presented a quantitative structure−activity relationship (QSAR) model based on density functional theory (DFT) calculations on a large set of 14-electron complexes, $LCl_2Ru{=}CH_2$, with different dative ligands, L, including over 30 different NHC ligands.[126]

Based on the results, the authors selected a number of ligands predicted to provide highly active catalysts for the olefin metathesis (Figure 41, note some structural similarities with complexes **90**, **95**). Without doubts such in silico screening strategy can be an useful alternative for developing new NHC-bearing olefin metathesis catalysts.[126]

In 2005, Köhler et al. attempted the preparation of a ruthenium metathesis catalyst **98**, bearing a SIMes ligand substituted with two allylic groups at the backbone C-4 and C-5 positions. However, in reaction of a free carbene (generated in situ from salt **99** and KO*t*Bu), with one equivalent of the first-generation Grubbs catalyst **1** none of the expected product **98** was isolated (Scheme 33).[148]

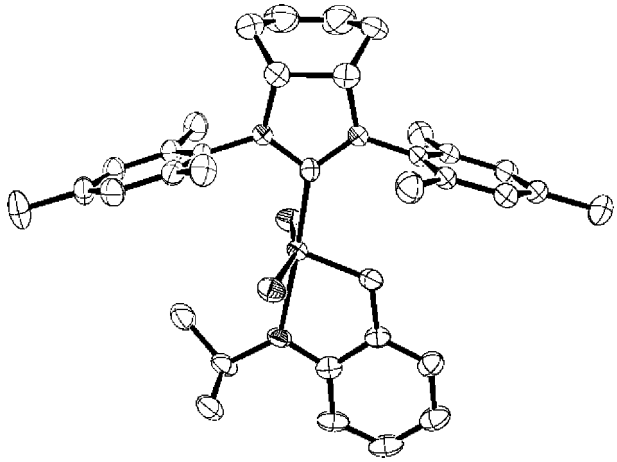
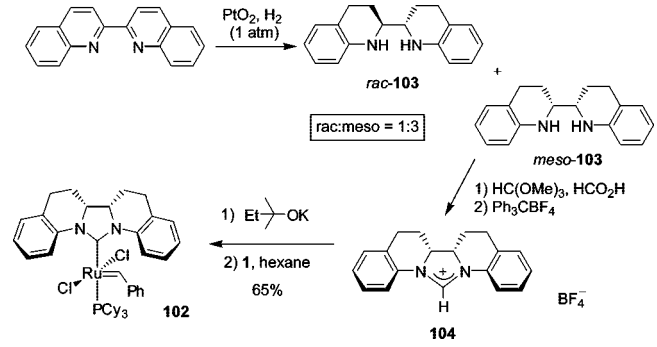


**Figure 42.** ORTEP view of **101**. $L_1 = 1.967(4)$ Å, $L_2 = 1.833(4)$ Å, $\alpha_1 = 119.3(3)°$, $\alpha_2 = 117.4(3)°$.

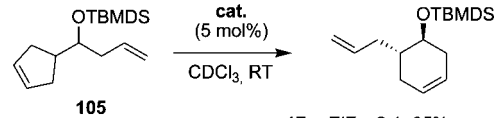
**Table 1. RCM of *N*,*N*-Diallyl-4-toluenesulfonamide (2) promoted by 101 and 22**

| | conversion (%) | |
|---|---|---|
| loading (mol %) | catalyst **101** | catalyst **22** |
| 0.05 | 100 | 100 |
| 0.02 | 81 | 97 |
| 0.005 | 20 | 52 |
| 0.002 | 14 | 34 |

**Scheme 34. Synthesis of Ruthenium Complex 102**




**Scheme 35. Diastereoselective RRM of 105 Using Catalysts 17 and 102**




**17**: *E*/*Z* = 2:1, 95%
**102**: *E*/*Z* = 9:1, 58%

On the other hand, the imidazolium salt **99** can be converted into the new imidazolium salt **100** by RCM in the presence of Grubbs catalyst **1** (0.1 mol %) in $CH_2Cl_2$ at 25 °C (Scheme 33).[148] The latter proved to be a valuable NHC precursor for the synthesis of new catalysts that feature an olefinic moiety in the ligand backbone. Imidazolium salt **100** was reacted with KO*t*Bu in THF at 25 °C and with the first generation Hoveyda catalyst **21** to afford **101** as an air-stable green solid in 63% yield (Scheme 33).[148] Crystals suitable for X-ray crystallographic analysis were grown, and the solid-state structure was measured (Figure 42) and found to correspond to that of Hoveyda type catalysts.

Surprisingly, the ring-closing olefin metathesis using **2** ($CH_2Cl_2$ at 25 °C, 17 h) revealed that **101** is slightly less active than the benchmark catalyst **22** (especially at low loadings, Table 1).[148]

The explanation for a decreased productivity of **101** is not clear, however, it cannot be excluded that the double C−C bond at the backbone is not innocent under the metathesis conditions.

Recently, Blechert et al. focused on the development of a ruthenium carbene complex (**102**) for diastereoselective ring rearrangement metathesis reactions (dRRM).[132] To increase the diastereoselective interaction between the olefin moiety and the catalytically active ruthenium species, in the presented design the authors decided to connect the *N*-aryl substituent with the *N*-heterocyclic carbene C2 unit. Unlike in standard IMes or SIMes ligands, the NHC moiety in this new ruthenium complex (**102**, Scheme 34) should exert a much stronger steric influence on the ruthenium alkylidene moiety. The synthesis of the NHC ligand started from commercially available 2,2′-biquinoline. After hydrogenation using $PtO_2$ and $H_2$ (*rac*-**103** was separated by chromatography on silica gel), the *meso*-diamine **103** was converted

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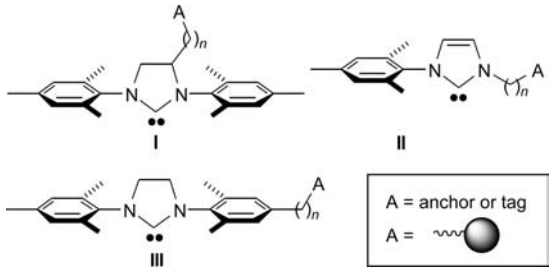
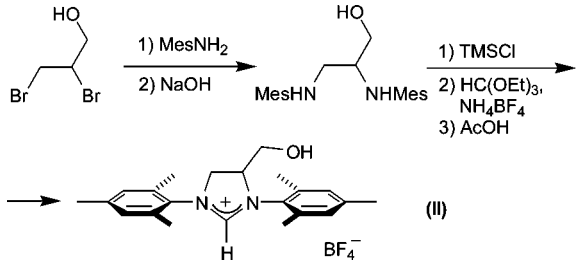



**Figure 43.** Possible attachment points in NHC ligands.

**Scheme 36**




into the desired imidazolium salt **104**, subsequently used to prepare complex **102** by a standard procedure. The latter was obtained as a green[149] microcrystalline solid in 65% yield (Scheme 34).

The novel catalyst **102** was tested in selected metathesis reactions (RCM, CM). A model diastereoselective ring rearrangement showed very promising results (Scheme 35).[150] Unfortunately, complex **102** was found to be of limited stability in solution, which may account for the much lower conversion rates than those obtained with **17**. Intrigued by this observation, the authors initiated a mechanistic study of possible deactivation pathways for this complex (see section 4 for more details).

### *3.1.4. Immobilization via NHC Ligands*

The use of supported catalysts appears to be the easiest method to avoid contamination of the product with metal-containing catalysts. Therefore the design of recoverable catalysts has become a central field of catalysis research. Various immobilization/tagging approaches in metathesis are discussed in recent reviews.[151−156]

The specific "dissociative" mechanism of action of olefin metathesis ruthenium catalysts (see Scheme 4)[7,10] makes the immobilization of these catalysts a non trivial task. As it was described in section 3, it is believed that both Grubbs and Hoveyda-type precatalysts provide identical propagating species: $L'X_2Ru{=}CH_2$ and $L'X_2Ru{=}CRR'$ after a single metathesis turnover. So, if one tries to immobilize/tag a Ru-precatalyst via the ligand, which is dissociating during reaction course (neutral ligand L or an alkylidene), after the reaction the most of the Ru shall be detached from the tag/support. Interestingly, a big number of Hoveyda-type catalysts were immobilized via (dissociating) 2-alkoxy-benzylidene ligands.[151−154,157] In the most successful cases up to 10−12 recycles were possible in a batch setup. These surprisingly good results can be explained by so-called boomerang mechanism (catalyst goes to the solution and returns to the supported ligand after the reaction, Scheme 4). Unfortunately, when metathesis is conducted under continuous flow conditions, such benzylidene-immobilized catalysts usually fail.[158]

Therefore, the alternative strategy, based on immobilization/tagging via a nondissociating neutral ligand $L^2$ or anionic ligands seems to be more justified. It should be also noted, that in contrast to the coordinatively saturated precatalysts (16-electron complexes) the propagating species (14-electron) are rather unstable (Scheme 4). Also, the stability of Ru methynylidene complexes ($LL'X_2Ru{=}CH_2$) is much lower than the benzylidene or indenylidene ones ($LL'X_2Ru{=}CRR'$).[10] Therefore, after loosing some "vital" ligands, the supported Ru-methylidene would decompose fast. Despite this potential problem, the later strategy seems to be more fruitful. The excellent coordinative properties of NHC ligands predispose them to be used as anchoring points in design of robust Ru immobilized catalysts. Polymers or phase-tags can be attached to the NHC backbone (**I**) or to *N*-side groups (**II**, **III**, Figure 43).

The synthesis of a ligand suitable for the catalyst attachment via NHC backbone (**I**) is presented in Scheme 36, while the previously described complexes **76a** and **80** are representative for the second tagging strategy (**II**).

Different tags/anchors were used for immobilization of Ru catalysts *via* NHC ligands, the most prominent one being a solid phase based on inorganic materials or polymers.[151−154] Polymers of choice can be either insoluble in the reaction medium, or soluble therein (e.g., polyethylene glycol (PEG)), in which case they are often removed by precipitation or extraction. Other catalyst tags include ionic or polar groups. This strategy made use of the high affinity of these tags to alternative reaction media such as ionic liquids (ILs),[155] or aqueous media.[156]

In 2000, Blechert and co-workers[159] reported the synthesis of a second-generation catalyst attached to Merrifield polystyrene by an ether linkage (**106**, Figure 44). This catalyst was found to be efficient for olefin metathesis reactions, however, the only four successive cycles could be performed. Buchmeiser and co-workers reported on a catalyst anchored to monolithic material (**107**). The synthesis of **107** involved preparation of a imidazolium salt immobilized on a polymer, formation of the free NHC upon action of a base, and a final phosphine−NHC displacement leading to immobilization of the Ru complex.[160] It should be noted that benzylidene **107** is the only example of a ruthenium-based metathesis catalyst containing 1,3-bis(1-adamantyl)imidazol-2-ylidene NHC ligand (interestingly, a homogeneous analogue, complex **28**, could not be formed, see Scheme 8) The resulting immobilized catalyst promoted ROMP and RCM reactions, allowing for rather low levels of residual Ru in the final products (70 ppm). Catalysts **108**[161] and **109**[162] were anchored through a *N*-substituent (strategy **II**, Figure 43) and used in some RCM and enyne metathesis reactions, exhibiting moderate to good activities and recyclabilities. Immobilization of NHC-containing catalysts on silica has been achieved by using both the backbone (e.g., **110**)[163] and the *N*-substituents (e.g., **111**)[136] as anchoring points (strategies **I** and **II**). In general, these complexes exhibited lower activities than their homogeneous counterparts, suffering from diffusion phenomenon associated to the use of insoluble supports. Lee et al. proposed the interesting concept of a *self-supported* Hoveyda catalyst (**112**).[164] The resulting oligomeric, insoluble ruthenium catalyst was tested in the RCM of simple diene **2** (refer to Scheme 3). Despite relatively high loadings used, the reported contamination of product **3** with ruthenium was only 16 ppm.

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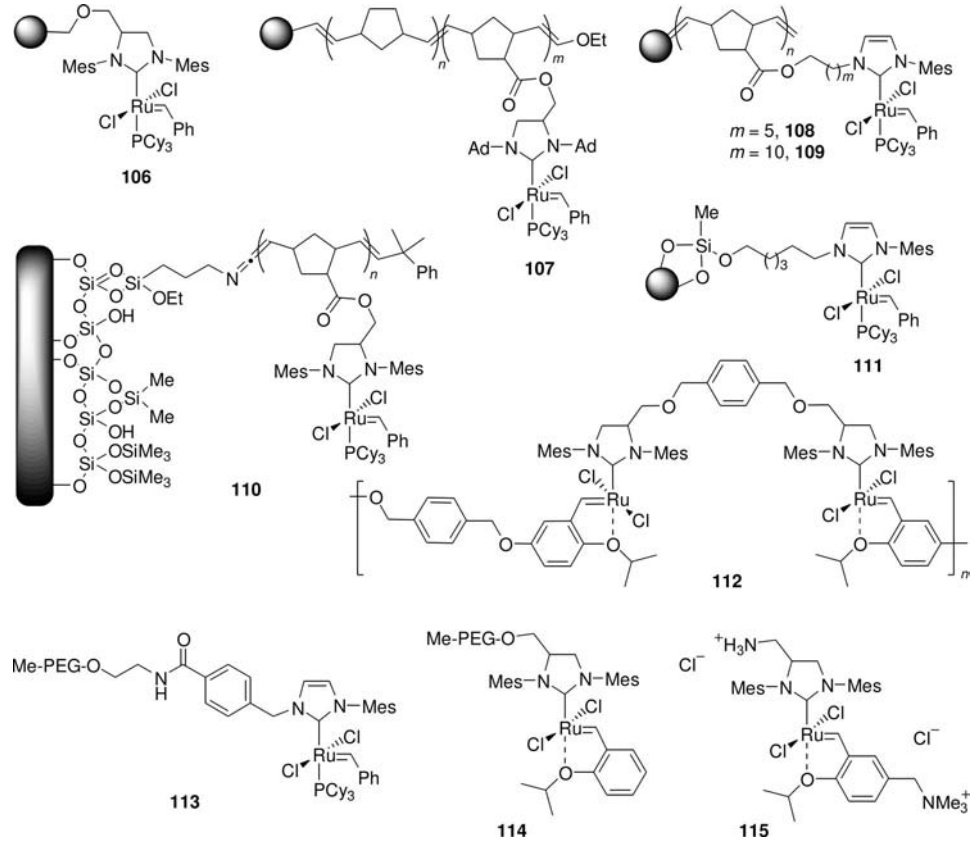
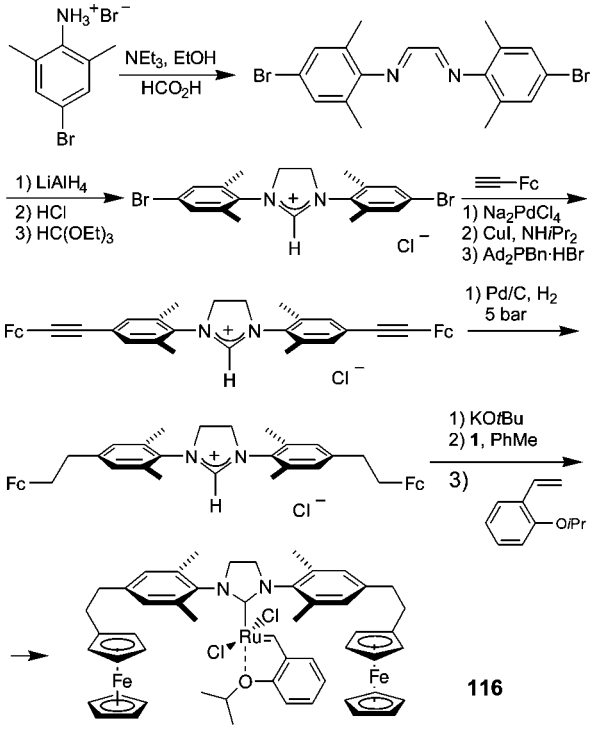



**Figure 44.** Selected NHC-immobilized ruthenium catalysts

**Scheme 37. Redox-Switchable Catalyst 116**




In an attempt to compensate for the moderate activity associated with solid supports, Grubbs and co-workers recently developed complexes anchored to soluble supports (**113** and **114**, Figure 44). Catalyst **113** was found to be a very good initiator for ROMP in acidic water/methanol solvent mixture, whereas showed rather moderate efficiency and stability in more challenging RCM reactions.[165] The addition of diethyl ether allowed for removal of about 97% of this PEG-tagged catalyst. The highly water-stable catalyst **114** was found to be more efficient than **113** for ROMP, RCM, and CM reactions in aqueous media.[166] Notably, when this NHC-tagged initiator was used in $CH_2Cl_2$, removal of **114** from olefin metathesis products was possible by simple aqueous extraction.[167] The water-soluble amonium-tagged catalyst **115** showed high activity in numerous ROMP, RCM, and CM of water-soluble alkenes and dienes.[168]

A very interesting example of the third tagging strategy (**III**, Figure 43) was reported by Plenio and Süssner.[169] Separation from the reaction products and recycling of homogeneous catalyst **116** was based on a redox-switchable phase tag (Scheme 37). The ferrocene pattern attached to the NHC part of **116** can be easily oxidized in situ, triggering its precipitation in the reaction media, and subsequently can be reduced, leading to the recovery of the active soluble catalyst.[202−205]

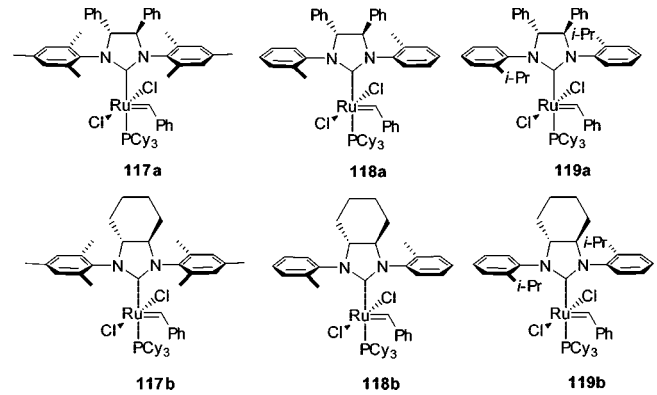



**Figure 45.** Family of catalysts **117**−**119**.

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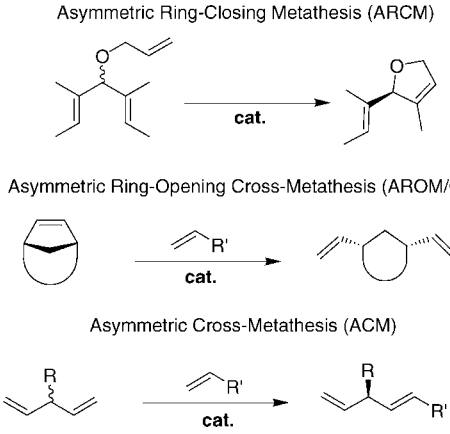
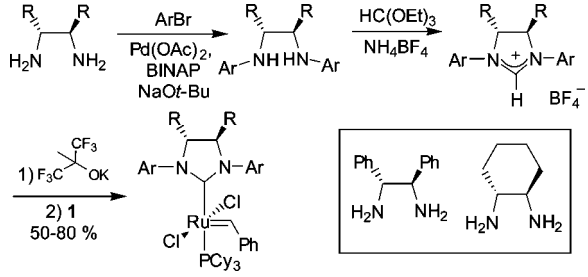
**Scheme 38. Selected Asymmetric Reactions in Olefin Metathesis**

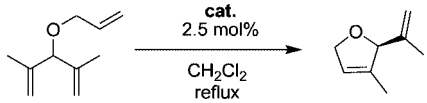



### 3.1.5. Complexes With Chiral NHC Ligands: Applications

**Scheme 39. Synthesis of Chiral Complexes 117−119**




**Scheme 40. Desymmetrization Reaction of a Model Triene**




| catalyst | ee (%) | conv (%) |
|---|---|---|
| **117a** | 13 | 57 |
| **118a** | 23 | 95 |
| **119a** | 23 | 96 |
| **118a**+NaI | 38 | 18 |
| **119a**+NaI | 39 | 20 |

### in Enantioselective Metathesis

During the past years, a variety of chiral, ruthenium-, and molybdenum-based alkylidene catalysts have been developed and used in small molecules synthesis. Two classes of chiral ruthenium catalysts bearing NHC were respectively considered by Grubbs and Hoveyda, namely, those containing monodentate *N*-heterocyclic carbenes (NHCs) with chirality in the backbone of the carbene and those containing chiral, bidentate NHC/binaphtyl, and biphenyl ligands.

The first enantioselective ruthenium olefin metathesis catalysts bearing NHC ligands with $C_2$-symmetry were disclosed in 2001 by Grubbs et al.[170] A set of NHC ligand precursors was obtained from commercially available chiral nonracemic 1,2-diamines in a convenient way and converted into corresponding Ru-complexes (Scheme 39). Low to satisfactory enantiomeric excesses (13−90% *ee*) were observed in ARCM desymmetrization of achiral trienes (Scheme 38). Interestingly, catalysts prepared from (1*R*,2*R*)-diphenylethylenediamine exhibited higher enantioselectivity than those prepared from (1*R*,2*R*)-1,2-diaminocyclohexane (Figure

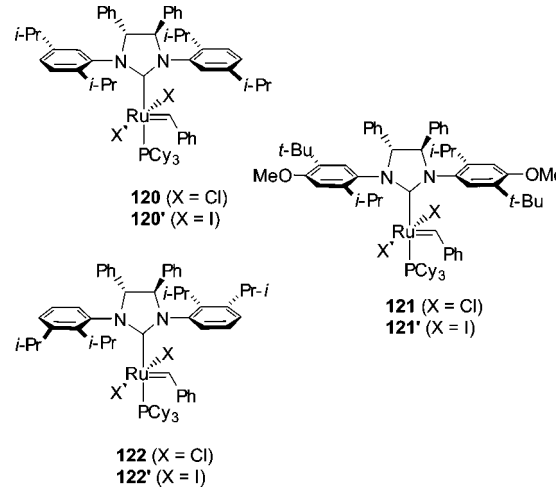
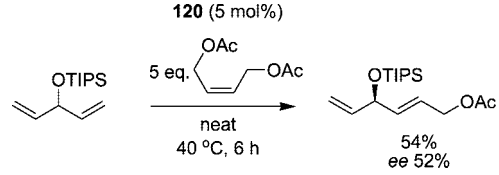


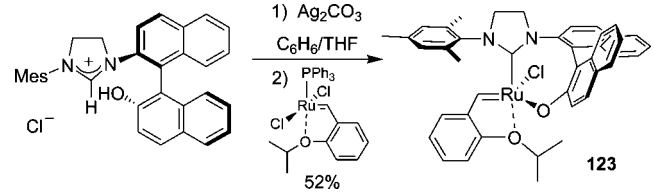

**Figure 46.** Improved catalysts **120**−**122**.

**Scheme 41. Asymmetric Cross-Metathesis with 120**[a]




[a] TIPS = tri(isopropyl)silil.

**Scheme 42. Synthesis of Bidentate Chiral Ru-Catalyst 123**




45). While dichloro-ruthenium complexes led typically to low *ee*, the dramatic increase in enantioselectivity was observed upon changing the halide from $Cl^-$ to $Br^-$ to $I^-$. (The bromide and iodide analogues were generated *in situ* by the addition of excess LiBr and NaI, respectively.) A model consistent with the stereochemical outcome of the reactions was described and suggests side-on olefin binding and reorganization of the halide ligands.

The crystal structure of one of such catalysts derived from (1*R*,2*R*)-diphenylethylenediamine was solved and showed that the NHC ligand is approximately $C_2$-symmetric with the *o*-methyl group oriented anti to the phenyl substituent of the imidazolium ring. Additionally, the phenyl group of the benzylidene is oriented anti to the *o*-methyl substituent of the proximal aryl ring. This anti−anti arrangement is indicative that the stereochemistry of the phenyl substituents on the imidazolium ring is effectively transferred to the metal center. Series of reactions of a model triene, reveal that replacement of the mesityl groups (**117a**) with *o*-methyl-(**118a**) and *o*-isopropylaryl groups (**119a**, Scheme 40) increases the enantioselectivity. Again, changing the halide ligands of catalyst **119a** from chloride to iodide further improves the enantioselectivity.

Importantly, the enanctioselectivity of these systems was neither influenced by the nature of the solvent (THF, dichloromethane, benzene) nor by the temperature (−15 °C, 0 °C, 38 °C).

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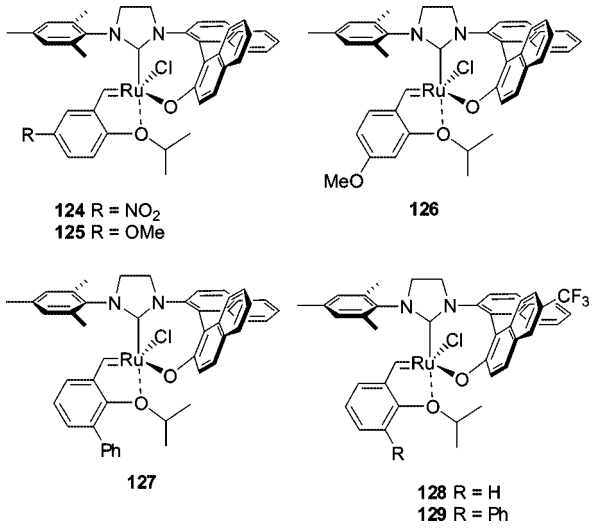



**Figure 47.** Improved bidentate chiral catalysts **124**−**129**.

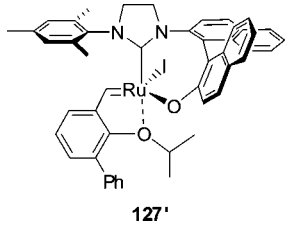
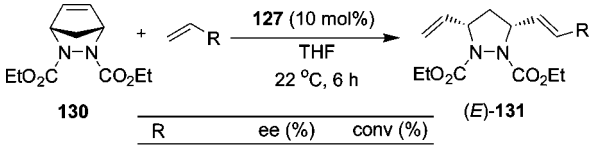



**Figure 48.** Catalyst **127′**.

**Scheme 43. ARCM/CM Promoted by 127**



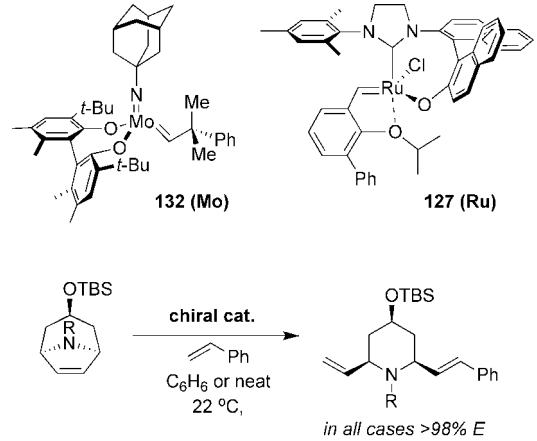

| R | ee (%) | conv (%) |
|---|---|---|
| Ph | 92 | 65 |
| *n*-$C_6H_{13}$ | 68 | 55 |
| Cy | 87 | 53 |

Further improvement to this family of catalysts was made five years later by Grubbs et al.[171] The authors showed that while catalysts containing substitution on the NHC's *N*-aryl flap *para* to the *o*-isopropyl group (**120** and **121**) lead to enantioselectivites very similar to those of the parent chiral catalyst **119a**, the substitution of the same side of the *N*-phenyl ring as the *o*-isopropyl group (**122**) results in a huge increase in enantioselectivity.

Importantly, Grubbs and co-workers[172] proved that these monodentate chiral Ru-catalysts (Figure 46) give excellent results not only in ARCM and AROM/CM but are also suitable for the most challenging asymmetric cross-metathesis reactions (Scheme 41). Even the obtained *ee* values (ranging from 37% to 52%) still need improvements, the overall efficiency of the improved catalysts **120**−**122** is a landmark.

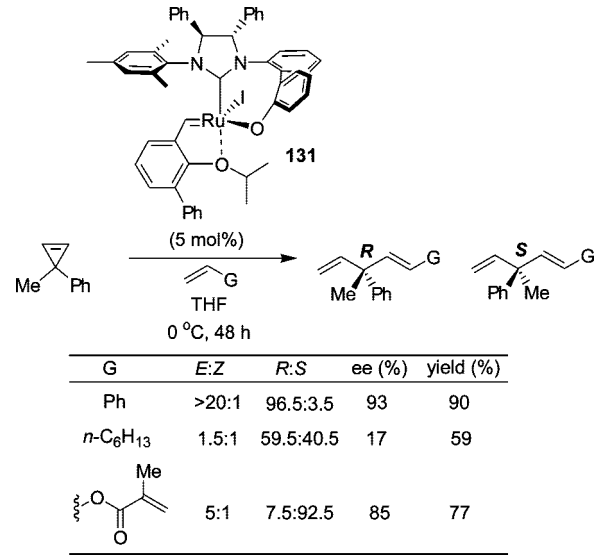
The first report on a chiral ruthenium based catalyst bearing a bidentate NHC (with $C_1$-symmetry) was published by Hoveyda et al.[173] The authors were prompted to test if such bidentate ligand would induce chirality more effectively than a $C_2$-symmetric monodentate ligand. According to this expectation, catalyst **123** gave excellent enantiomeric excesses in many reactions. Unfortunately, **123** was catalytically less active (Scheme 42) than the achiral parent **22**, and longer reaction times and elevated temperatures were required to achieve good conversions with **123**. The electronic influence:

**Scheme 44. Study on Mo- and Ru-Based Chiral Catalysts**




| R | cat. | time (h) | ee (%) | yield (%) |
|---|---|---|---|---|
| Me | **Mo** 5 mol% | 1 | 94 | 95 |
| Me | **Ru** 5 mol% | 36 | 33 | n.d. |
| Bn | **Mo** 5 mol% | 1 | 21 | 85 |
| Bn | **Ru** 5 mol% | 24 | 98 | 80 |

**Scheme 45. Reactivity of Bidentate Ru-Catalyst 131 in AROM/CM Process**




| G | *E*:*Z* | *R*:*S* | ee (%) | yield (%) |
|---|---|---|---|---|
| Ph | >20:1 | 96.5:3.5 | 93 | 90 |
| *n*-$C_6H_{13}$ | 1.5:1 | 59.5:40.5 | 17 | 59 |
|  | 5:1 | 7.5:92.5 | 85 | 77 |

the replacement of a chloride with the less electronegative phenoxide of the chiral ligand and the increased steric bulk of the binaphthyl are likely the factors responsible for the diminished activity.

To solve this limitation, Hoveyda and co-workers applied several alterations to the benzylidene and NHC parts of **123** (Figure 47).[174] Methods to activate the Hoveyda type catalysts by electronic[119] and steric[122] factors were studied in details by Grela and Blechert. Results obtained by Hoveyda in activation of **123** show that the steric hindrance exhibits a more pronounced effect in this specific case. For example, while the introduction of a $NO_2$ group[119] led to a complex **124** that is 3 times more potent than an unmodified catalyst **123**, a sterically hindered one (**127**) acts more than 100 times faster in the same model reaction. However, both modes of activation can be successfully combined in this case, as the doubly modified (sterically in the benzylidene part and electronically in the NHC ligand) chiral complex **129** possessed the highest level of potency among those studied. Selected members of the new generation of chiral Ru

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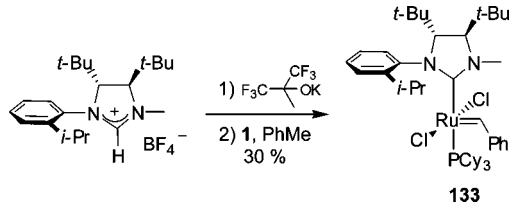
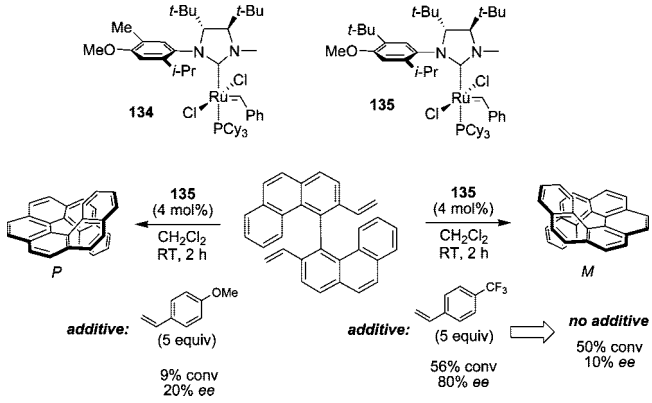
**Scheme 46. Monodentate Chiral Ru-Catalyst 133**




**Scheme 47. Choice of Additive Provides Access to Either Enantiomer of [7]Helicene**




catalysts were tested in AROM and ARCM transformations, giving very high levels of enantioselectivity. Furthermore, the authors showed that reactions may be carried out in air and with commercial grade solvents. Chiral complexes after reaction cycle can be recovered and reused in a new catalytic reaction.

Grubbs reported that addition of NaI to a solution of chiral-NHC Ru-dichloride benzylidene complex leads to enhancement in enantioselectivity asymmetric olefin metathesis reactions. The increase in asymmetric induction was attributed to the formation of a Ru-diiodide, although a discrete catalyst was not isolated and characterized. Following this observation, Hoveyda et al. developed an iodide analogue of **127** (Figure 48), which promotes asymmetric metathesis with improved enantioselectivity.[126] The authors indicated that AROM/CM can be made in neat mixtures of substrates with shorter time without decrease of *ee*. It was also demonstrated that the chiral catalyst **127′** can be isolated after each reaction and reused for up to five cycles without diminishing its activity and selectivity.

A comparative study (Scheme 43) on ability of selected chiral Mo- and Ru-based catalysts to promote enantioselective synthesis of 2,6-disubstituted pyrans and piperidines through asymmetric ring-opening/cross-metathesis (AROM/CM) reactions were presented by Hoveyda and Schrock (Scheme 44).[175] Although Mo catalyst **132** initiates much faster, in some cases low yields or selectivities were observed. Mo-catalyzed olefin metathesis reactions has to be carried out in solvents that are strictly oxygen and moisture free, while the less reactive chiral Ru-complex (**127**) is air-stable and can be used without a solvent. These studies demonstrate that these distinct classes of initiators are complementary in respect of particular substrates and conditions used.

In another work, Hoveyda and co-workers studied a chiral Ru-based catalyst bearing bisphenyl phenoxide based NHC ligand. Ru-complex **131** was successfully applied in AROM/CM desymmetrisation of cyclopropenes allowing to obtain high enantiomeric excesses (Scheme 45).[176]

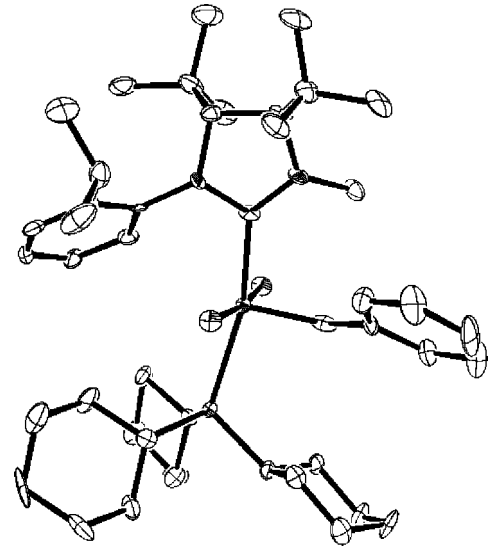


**Figure 49.** ORTEP view of **133**. $L_1 = 2.077(5)$ Å, $L_2 = 1.840(7)$ Å, $\alpha_1 = 125.4(5)°$, $\alpha_2 = 122.9(5)°$.

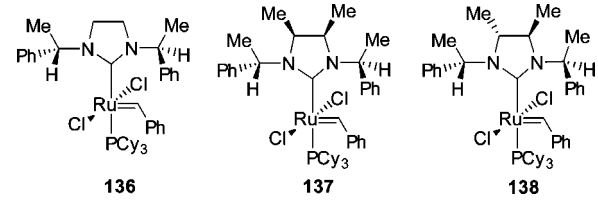



**Figure 50.** Chiral catalysts **136**−**138** obtained by Grisi et al.

Collins et al. synthesized an interesting class of chiral Ru-based olefin metathesis catalysts (**133**−**135**) bearing $C_1$-symmetric monodentate NHC ligands (Scheme 46 and 47).[177] The catalysts showed increased reactivity in comparison to existing Grubbs' chiral Ru-based catalysts that possess a $C_2$-symmetric NHC, and successfully induced various desymmetrization reactions.

This design extends the family of chiral Ru-based catalysts bearing monodentate NHC ligands. The newly developed complex **135** was applied in asymmetric synthesis of [7]helicenes.[178] The synthetic challenge associated with an asymmetric synthesis of carbohelicenes is associated with induction of chirality while forming a new carbon−carbon bond. The authors found that various additives play a significant role in this transformation, allowing to access both antipodes of [7]helicene. A positive influence of aromatic fluorinated solvents was also noted by the authors. Using the chiral-NHC Ru catalyst under carefully optimized conditions led to the enantioselective synthesis of [7]helicene of up to 56% *ee* (Scheme 47).

Many useful chiral Ru-based catalysts have been synthesized (monodentate and bidentate NHCs of $C_1$- and $C_2$-symmetry) and successfully used in asymmetric olefin metathesis. However, still some substrates are not compatible with the present catalysts. As a result, the enantioselective metathesis still suffers of low yield or *ee* in some cases. A theoretical study was initiated[179] to understand the role of NHCs in these transformations, using the previous mechanistic models developed by Grubbs et al.[170] The computational analysis indicated that the origin of enantioselectivity in the ring-closing metathesis of achiral trienes is correlated to the chiral folding of the *N*-bonded aromatic groups, which is imposed by the Ph groups in positions 4 and 5 of the NHC ligand imidazole ring. This chiral folding of the catalyst

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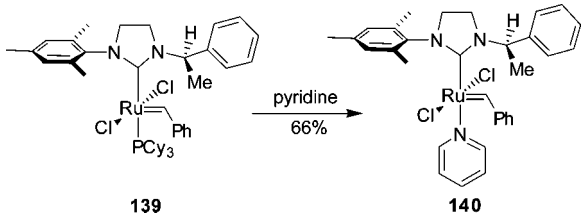
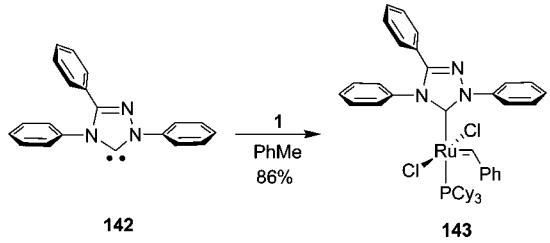
**Scheme 48. Synthesis of Ruthenium Initiator 140 from 139**




**Scheme 49. Synthesis of Catalyst Bearing 1,2,4-Triazol-5-ylidene**




imposes a chiral orientation around the Ru=C bond, which, in turn, selects between the two enantiofaces of the substrate. In the ring-closing transition state, the geometry in which additional groups on the forming ring are in pseudoequatorial positions is favored over transition states in which this additional group is in a pseudoaxial position. These combined effects explain well the enantiomeric excesses experimentally obtained.[179]

The synthesis of chiral Ru-based catalysts,[180] presenting saturated chiral $C_2$ symmetric (**136** and **138**) and $C_1$ symmetric (**137**) *N*-heterocyclic carbene (NHC) ligands bearing *N*-(*S*)-phenylethyl groups (Figure 50), was presented by Grisi et al. Variable-temperature NMR studies and DFT calculations were conducted to investigate the interconversion of atropisomers in solution. The complex behaviors were rationalized evaluating the rotation barrier of alkylidene and NHC groups around the C−Ru bonds. Comparison between NMR data and DFT calculations suggested that interconversion between different atropisomers, which occurs at room temperature, is due to the free rotation of the benzylidene group around the Ru=C bond. The activity and stereoselectivity of **136**−**138** were investigated in ring-closing metathesis (RCM), asymmetric ring-closing metathesis

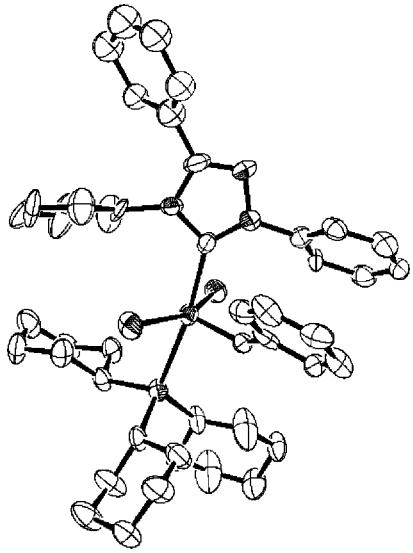
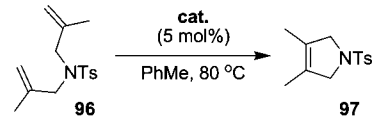


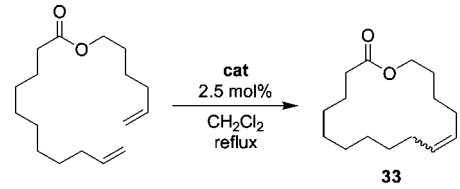
**Figure 51.** ORTEP view of **143**. $L_1 = 2.085(9)$ Å, $L_2 = 1.819(9)$ Å, $\alpha_1 = 127.5(8)°$, $\alpha_1 = 114.9(8)°$.

**Scheme 50. RCM to Form Tetrasubstituted C−C Double Bond**



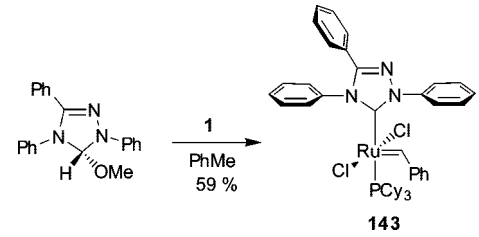

| catalyst | time (h) | conv (%) |
|---|---|---|
| **16** | 24 | 95 |
| **87** | 3 | 85 |
| **143** | 2 | 80 |

**Scheme 51. RCM to Form 14-Members Macrocycle**




| catalyst | time (h) | conv (%) |
|---|---|---|
| **16** | 3 | 83 |
| **87** | 5 | 71 |
| **143** | 5 | 78 |

**Scheme 52. Synthesis of 143**




(ARCM), cross-metathesis (CM), and ring-opening metathesis polymerization (ROMP). Complex **137** showed the highest activity in all reactions and gave a significantly lower *E*/*Z* ratios in tested CM reactions. Modest enantioselectivity in the ARCM of an achiral triene was observed in the presence of the chiral non racemic $C_2$ symmetric catalyst **138**.

Buchmeiser and Blechert applied a ruthenium-based initiator bearing an unsymmetrical, chiral NHC ligand in alternating copolymerizations.[181] Reports on alternating copolymers prepared by metathesis copolymerization of two different monomers are relatively rare.[182] Catalyst **139** was obtained with 90% yield, in standard procedure starting with deprotonation of a NHC precursor and using **1** as ruthenium source. Catalyst **139** was used in copolymerization of different norbornenes with cyclooctene or cyclopentene mixtures. Because the catalyst **139** revealed poor initiation efficiencies, the authors decided to prepare a monopyridine adduct (**140**), in analogy to known "third generation Grubbs catalyst", $(py)_2(SIMes)Cl_2Ru{=}CHPh$ (**141**),[183] by the reaction of **139** with excess of pyridine (Scheme 48). The fact that *only one* pyridine ligand is capable of coordinating Ru is indicative of the significant steric demand of the NHC ligand.

## 3.2. Complexes Bearing 1,2,4-triazol-5-ylidene Ligands

In 2001, Fürstner et al. reported the synthesis and full characterization of ruthenium 1,2,4-triazol-5-ylidene complex. In the reaction of **1** with commercially available 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene (**142**), the

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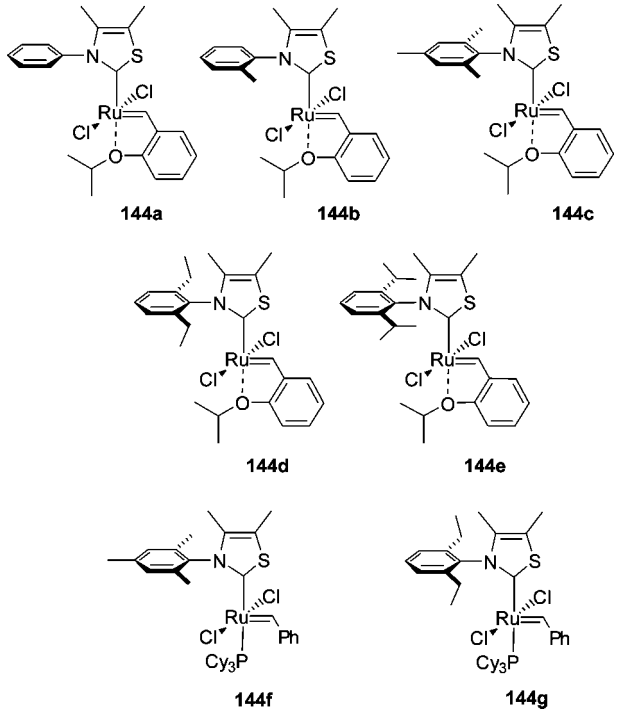



**Figure 52.** Complexes bearing thiazol-2-ylidene ligands.

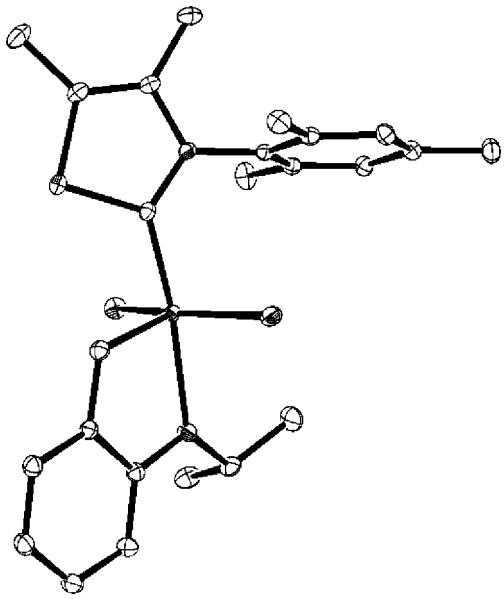


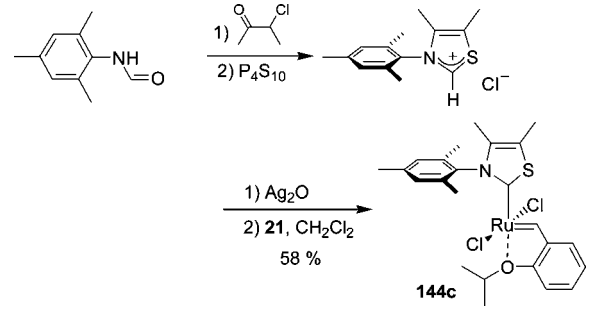
**Figure 53.** ORTEP view of **144c**. $L_1 = 1.9535(11)$ Å, $L_2 = 1.8296(11)$ Å, $\alpha_1 = 120.39(9)°$.

authors obtained the desired product **143** in 86% yield (Scheme 49).[94]

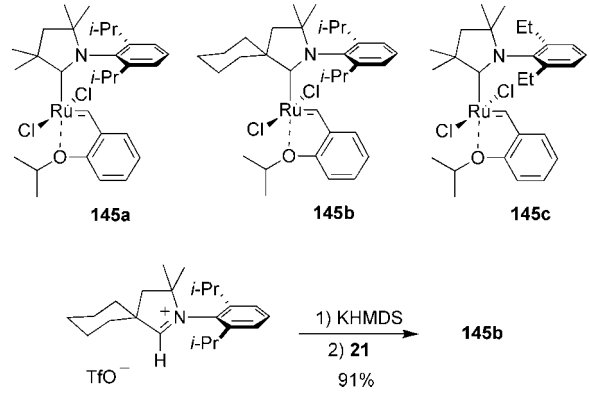
In a crystalline form (Figure 51) this compound can be stored under Ar for several weeks, but when kept in chlorinated solvents it decomposes rapidly to unidentified products. The significantly lower stability of **143** in solution is limiting factor for its practical utility.

In the formation of **97** triazol-5-ylidene containing catalyst **143** provided a satisfactory yield of 80% in just 2 h. Prolonged reaction, however, did not lead to further conversion, most likely because of the limited lifetime of complex **143**. In contrast, IMes bearing complex **16** was active over much longer periods, thereby leading to an almost quantitative formation (95%) of the desired product.

**Scheme 53. Synthesis of 144c**




**Scheme 54. Catalysts Bearing (Alkyl)(Amino)Carbenes**




In RCM of 16-membered macrocycle catalyst **143** gave slightly lower yield 78%, as compared to **16** which gave 83% (Scheme 51).

It is remarkable, however, that the triazolyl substituted complex **143** was unable to effect a rather straightforward cycloizomerization of enyne **9** (Scheme 3), although it was not clear to which extent this failure is caused by the limited stability of the complex in solution and/or to an inherent lack of reactivity toward this particular substrate.

Grubbs et al. showed that catalyst **143** can be prepared in the reaction of **1** with a NHC-MeOH adduct (Scheme 52).[184] The authors confirmed that catalyst **143** is unstable in a solution. After several hours in $C_6D_6$ or $CD_2Cl_2$ at room temperature under an $N_2$ atmosphere, significant decomposition was visible by NMR. Among the decomposition products the bis(phosphine) ruthenium complex **1** was observed, which suggests that the NHC ligand can dissociate from the metal center allowing for a phosphine reassociation to yield the more stable complex, **1**. This decomposition pathway seems to be accelerated at elevated temperatures and under catalytic turnover conditions.

## 3.3. Complexes Bearing Thiazol-2-ylidene Ligands

A family of ruthenium-based olefin metathesis catalysts (**144**) bearing a series of thiazole-2-ylidene ligands has recently been prepared by Grubbs and Vougioukalakis (Figure 52).[185]

The X-ray crystal structures (e.g., Figure 53) of four of these complexes are described. In the solid state, the aryl substituents of the thiazole-2-ylidene ligands are located above the empty coordination site of the ruthenium center. Almost all family of catalysts was synthesized by transmetalation of silver-NHC complexes with the appropriate ruthenium source (Scheme 53). Interestingly only one complex was synthesized by treatment **21** with the appropriate carbene

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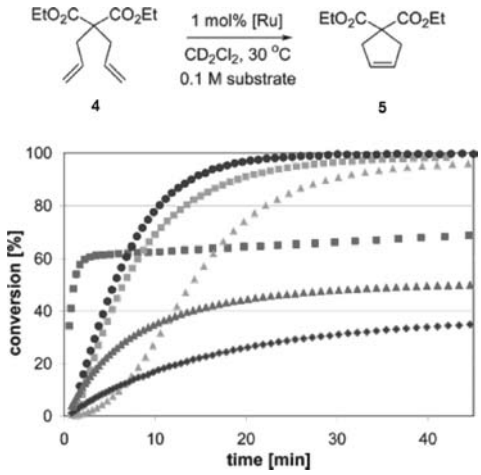


**Figure 54.** Relative activity of **1** (black box), **22** (gray box), **21** (gray triangle), **22** (black circle), **144f** (black triangle), and **144g** (black diamond) in RCM of **4**. (Reproduced with permission from ref. 185. Copyright 2006 American Chemical Society.)

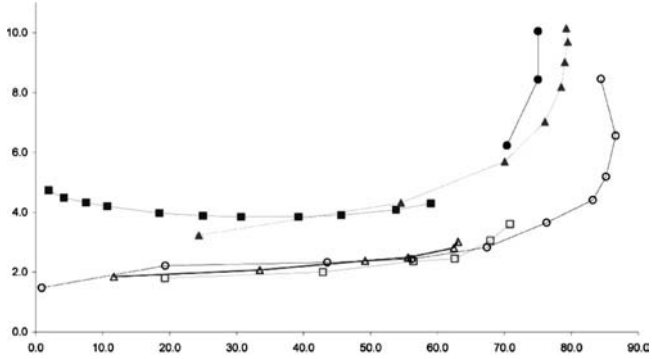

**Figure 55.** Plot of *E/Z* ratio of CM product 8 vs % conversion for catalysts **1** (■), **17** (▲), **22** (•) in comparison with **145a** (□), **145b** (Δ) and **145c** (○). (Reproduced with permission from ref. 187. Copyright 2006 American Chemical Society.)

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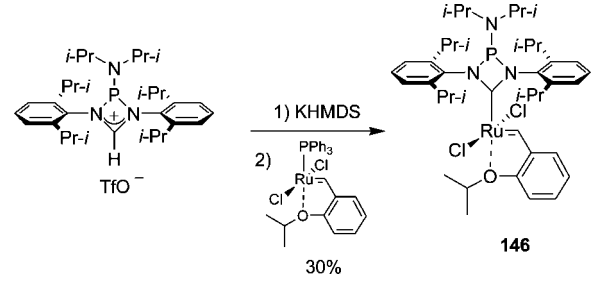
ligand, prepared in situ by deprotonation of a dimethylthiazolium salt with KHMDS.

Despite the decreased steric bulk of these NHC ligands, all of the complexes reported by Grubbs efficiently promoted benchmark olefin metathesis reactions, such as RCM of diethyldiallyl malonate (**4**, Scheme 17) and ROMP of 1,5-cyclooctadiene and norbornene, as well as the cross metathesis of allyl benzene with *cis*-1,4-diacetoxy-2-butene and other.

The phosphine-free catalysts of this family are more stable than their phosphine-containing counterparts, exhibiting pseudo-first-order kinetics in the ring-closing of diethyldiallyl malonate (**4**). Upon removing the steric bulk from the ortho positions of the *N*-aryl group of the thiazole-2-ylidene ligands, the phosphine-free catalysts lose stability, but when the substituents become too bulky, the resulting catalysts show prolonged induction periods. Among five thiazole-2-ylidene ligands examined, 3-(2,4,6-trimethylphenyl)- and 3-(2,6-diethylphenyl)-4,5-dimethylthiazol-2-ylidene afforded the most efficient and stable catalysts. In the cross-metathesis reaction of allyl benzene with *cis*-1,4-diacetoxy-2-butene increasing the steric bulk at the ortho positions of the *N*-aryl substituents results in catalysts that are more *Z*-selective.

**Scheme 55. Synthesis of Catalyst 146**




## 3.4. Complexes Bearing Cyclic (alkyl)(amino)carbene Ligands

Grubbs and co-workers obtained ruthenium catalysts bearing cyclic (alkyl)(amino)carbenes (Scheme 54).[186] The synthesis of cyclic (alkyl)(amino)carbenes, in which one amino group from an NHC has been replaced by an alkyl group, was reported. The greater $\sigma$-donor ability of carbon versus nitrogen resulted in more electron-donating ligands. The exchange of an $sp^2$-hybridized nitrogen atom for an $sp^3$-hybridized carbon atom also changes the steric environment relative to NHCs. $^1$H NMR spectroscopy data provide a view on conformation of these complexes in solution. 2D-ROESY experiments performed on complexes **145a** and **145b** in $C_6D_6$ at 22 °C demonstrate Overhauser effects between the benzylidene resonance and the aryl protons on the *N*-diisopropylphenyl moiety, the equivalent methine resonances of the aryl isopropyl groups, and the enantiotopic Me groups facing the benzylidene proton.

Cyclic (alkyl)(amino)carbenes are more electron-donating than their traditional NHC counterparts and have unique steric properties. It was observed that catalyst **145a** and **145b** require elevated temperatures and extended reaction times to complete ring-closing metathesis reactions, whereas

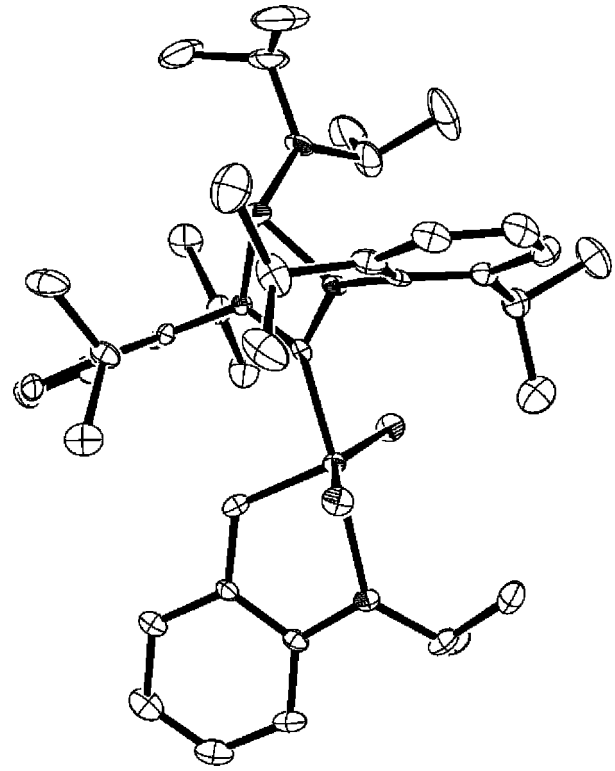
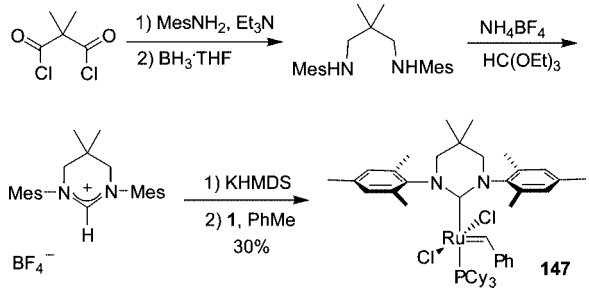


**Figure 56.** Ortep view of **146**. $L_1 = 1.921(4)$ Å, $L_2 = 1.832(4)$ Å, $\alpha_1 = 126.8(2)°$, $\alpha_1 = 126.8(2)°$.

**Scheme 56. Synthesis of Catalyst 147**




catalyst **145c** exhibited activity comparable to catalysts **17** and **22** (Figure 55).

A comparative study of cross-metathesis reaction of *cis*-1,4-diacetoxy-2-butene with allybenzene (see Scheme 3) catalyzed by these new catalysts was reported.[187] Complexes **145a**−**145c** demonstrated increased selectivity for the formation of *Z*-olefins, as compared with commercially available catalysts **17** and **22** (Figure 55). The authors stated that higher *E* selectivity observed is not simply the result of lower activity of catalyst that is slow to isomerize olefins, but rather the result of the inherent catalyst selectivity.

## 3.5. Complexes Bearing Four-Membered Ring Carbene Ligands

Ruthenium olefin metathesis catalyst **146** bearing a four-membered *N*-heterocyclic carbene was synthesized by Grubbs and co-workers (Scheme 55).[188]

Compound **146** was obtained with moderate yield (30%) and was fully characterized by NMR spectroscopy and X-ray crystallography (Figure 56). The catalytic activity of the new complex was explored in the cross-metathesis (CM) of allylbenzene with *cis*-1,4-diacetoxy-2-butene. The reaction was carried out in dichloromethane at ambient temperature. The conversion afforded by **146** (73%) was comparable to those obtained with complexes **17** (79%) and **22** (72%). However, a longer reaction time was required for **146** (35 h vs <30 min for **17** and **22**). A similar trend was observed in RCM of diallyldiethyl malonate (**4**) at 40 °C. With **146**, the

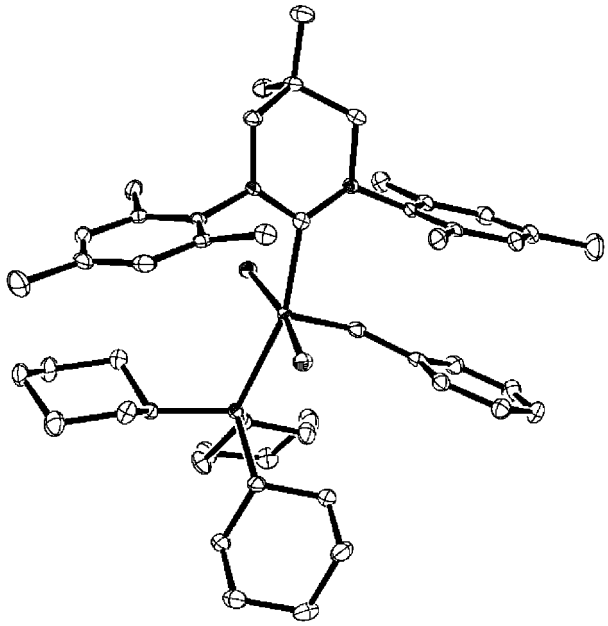


**Figure 57.** ORTEP view of **147**. $L_1 = 2.1059(17)$ Å, $L_2 = 1.8353(18)$ Å, $\alpha_1 = 108.95(13)°$, $\alpha_1 = 110.99(13)°$.

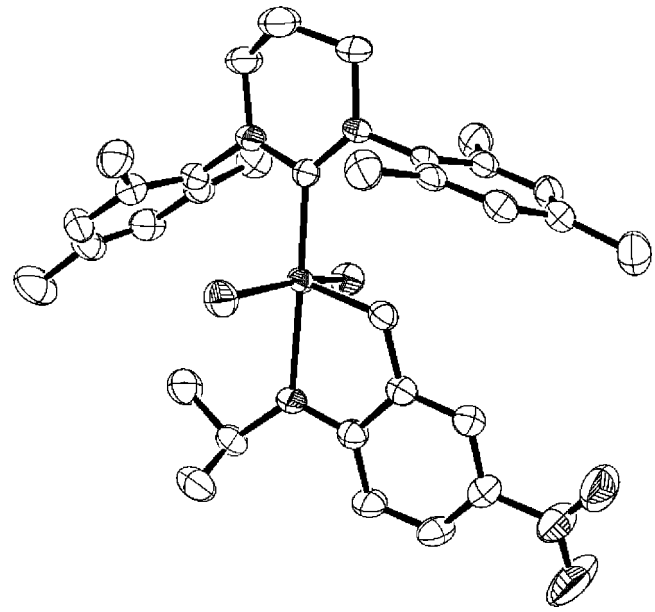
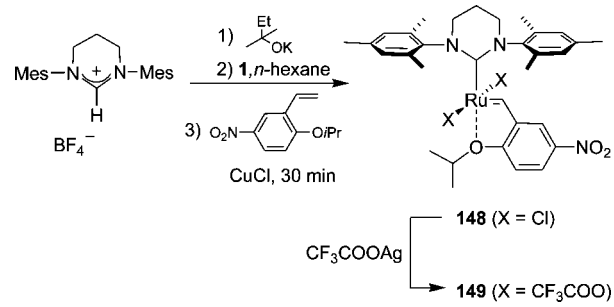
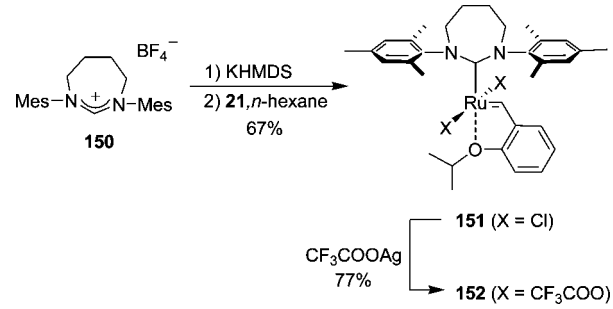


**Figure 58.** ORTEP view of **148**. $L_1 = 2.013(2)$ Å, $L_2 = 1.825(3)$ Å, $\alpha_1 = 114.0(2)°$, $\alpha_1 = 112.7(2)°$.

**Scheme 57. Synthesis of Catalysts 148 and 149**




**Scheme 58. Ru Complexes Bearing Seven-Membered NHC**




reaction reached completion within 20 min, whereas less than 10 min is necessary for SIMes bearing **17** and **22**. Catalytic studies on ROMP of *cis*,*cis*-cycloocta-1,5-diene (COD) were also carried out. Interestingly, at 25 °C, using the monomer to catalyst ratio of 10 000:1, complex **146** afforded only oligomers after 24 h. However, at 55 °C polymer formation was observed for the neat COD or in a solution.

## 3.6. Complexes Bearing 1,4,5,6-Tetrahydropyrimidin-2-ylidene Ligands

The ruthenium olefin metathesis catalyst **147** bearing a 5,5-dimethyl-1,3-dimesityl-1,4,5,6-tetrahydropyrimidin-2-ylidene ligand was synthesized (Scheme 56) by Grubbs et al.[189] Interestingly, attempts to generate the carbene using KO*t*-Bu as a base were unsuccessful under a variety of conditions. However, using KHMDS in toluene at 100 °C the appropriate

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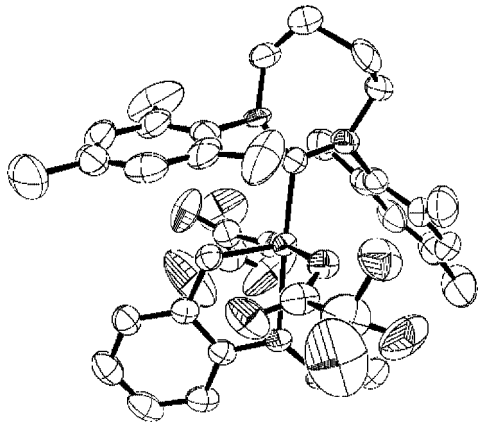


**Figure 59.** ORTEP view of **152**. $L_1 = 1.999(4)$ Å, $L_2 = 1.821(4)$ Å, $\alpha_1 = 111.2(3)°$, $\alpha_1 = 117.4(4)°$.

carbene was generated and subsequently reacted in situ with **1** at room temperature to produce complex **147** in 30% isolated yield.

The solid state structure of complex **147** (Figure 57) was determined and shows that the *N*-mesityl group of the six-membered carbene ligand and the benzylidene moiety are in close proximity (2.9 Å). Catalyst **147** demonstrates moderate reactivity for both RCM and ROMP. The ring-closing metathesis of diethyl diallylmalonate (**4**) at 50 °C resulted in 72% conversion after 30 min and 83% after 1 h. In comparison, the reaction goes to completion with catalysts **16** and **17** after 10 and 30 min, respectively, which indicates that the increased steric interactions present in **147** result in less active catalyst, as compared to its SIMes and IMes cousins. The authors next checked the reactivity of **147** for ROMP of *cis*,*cis*-1,5-cyclooctadiene (COD). The polymerization proceeds to a conversion of 85% after 10 min and 96% after 20 min at room temperature (the monomer to catalyst ratio of 300:1). Under similar conditions, catalyst **17** goes to completion in 10 min, while catalyst **16** proceeds to 35% after 10 min and to 60% after 20 min. Overall, catalyst **147** exhibits lower reactivity in comparison to **17**. It was assumed that the lower reactivity of **147** is caused by a larger steric crowding around the metal atom, which may disfavor olefin binding or metallacyclobutane formation.

The synthesis of ruthenium-based metathesis catalyst (**148**, Figure 58) containing the saturated 1,3-bis(2,4,6-trimethylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene ligand was described by Buchmeiser et al.[190] Catalyst **149** was synthesized by treatment of **148** with silver trifluoroacetate (Scheme 57). Both catalysts were highly active in ring-closing metathesis and ring-opening cross-metathesis (ROCM), but, unlike Grela's nitro catalyst **50**,[119,120] showed moderate activity in CM metathesis of acrylonitrile. Importantly, complex **149** exhibited high activity in the cyclopolymerization of diethyl dipropargylmalonate.[160]

## 3.7. Complexes Bearing Tetrahydro-1,3-diazepin-2-ylidenes Ligands

Novel 1,3-dimesityl-4,5,6,7-tetrahydro-[1,3]-diazepin-2-ylidene coordinated Ru-alkylidene complexes **151** and **152** were synthesized by Buchmeiser et al. from the first-generation Hoveyda catalyst, **21** and the 7-membered NHC ligand precursor **150**[191] (Scheme 58).[192]

Pure **151** was isolated as a light yellow-green solid in 67% yield, while **152** was obtained as a dark brown solid. Crystals

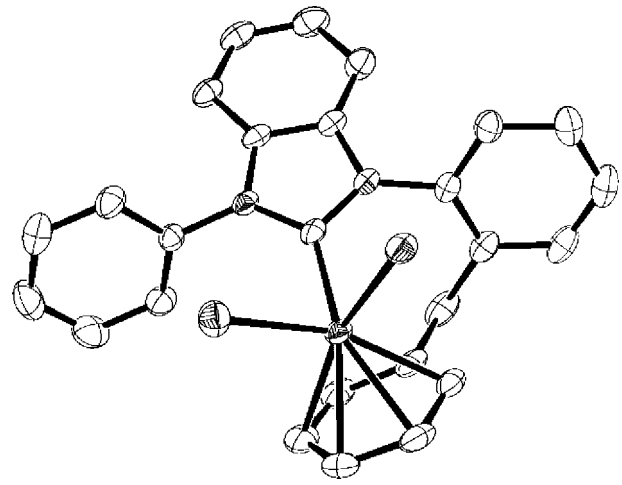


**Figure 60.** ORTEP view of **153a**.

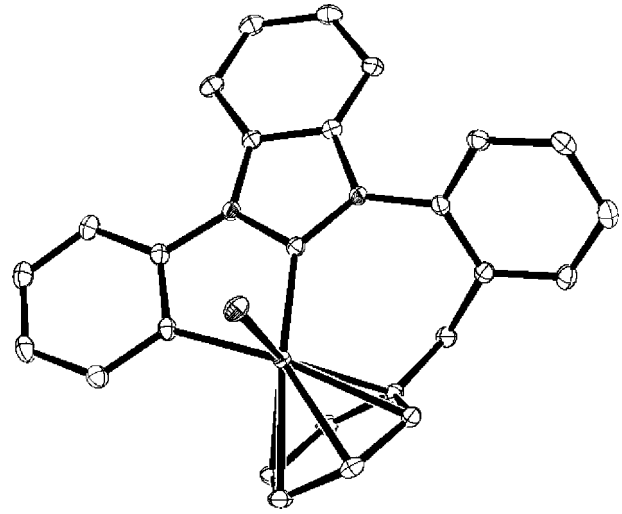
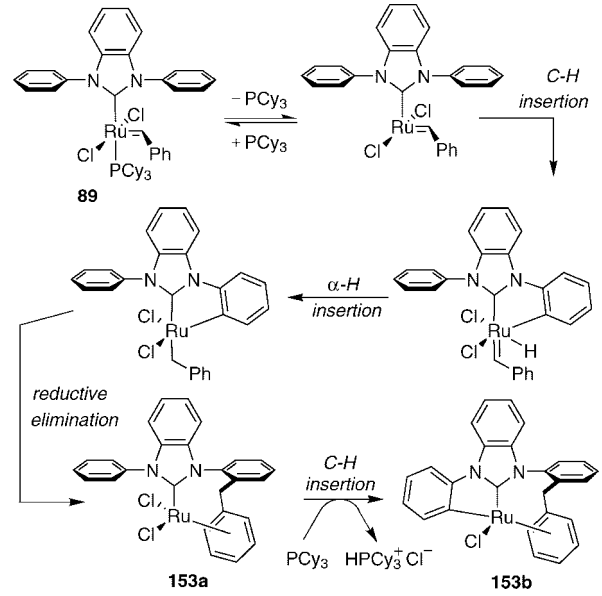


**Figure 61.** ORTEP view of **153b**.

**Scheme 59. Plausible Mechanism of 89 Deactivation**




of **152** suitable for the X-ray analysis were obtained via the layering of *n*-hexane over a concentrated dichloromethane solution. Despite the smaller angle defined by the two mesityl groups at the NHC, the distance between the Ru and the $C_{(NHC)}$ in **152** was comparable to the ones in the correspond-

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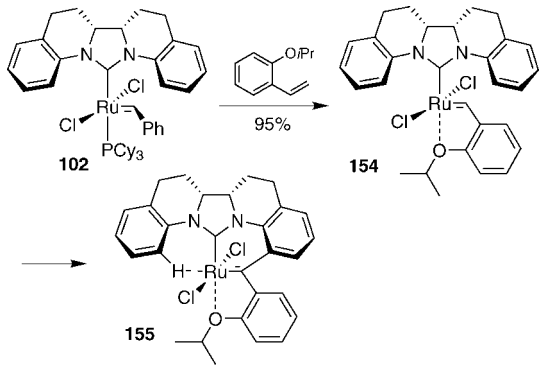
**Scheme 60. Synthesis of Catalyst 154 and Its Deactivation**




ing imidazolin-2-ylidene and tetrahydropyrimidin-2-ylidene complexes.[190]

Compound **151** showed excellent reactivity in ROMP of **COD**, yielding polymers with a high trans-content. Compound **152** was also an active initiator for ROMP. However, a lower trans-content was found for poly-COD prepared by this initiator. Both seven-membered NHC-Ru complexes turned out to be good catalysts for cross-metathesis, while showed moderate activity in ring-closing metathesis (no activity at all was observed in the RCM of tetrasubstituted dienes).

## 4. Decomposition Pathways via NHC

Generally, the *N*-heterocyclic carbene ligands can be seen as noninterfering neutral ligands in metathesis reactions. However, it has been demonstrated that NHCs occasionally[193] participate in side reactions, such as activation of C−C and C−H bonds.[194] This type of C−H or C−C bond activation of the *ortho*-methyl groups of SIMes and IMes ligands has been previously observed in some ruthenium olefin metathesis catalysts.[184] Recently, a carbene insertion promoted by a donor ligand was reported by Diver.[195]

To explain rather low stability of *N*,*N*′-diphenylbenimidazol-2-ylidene containing catalyst **89**[19] Grubbs et al. attempted more detailed investigation on the possible mechanism of catalyst deactivation.[196]

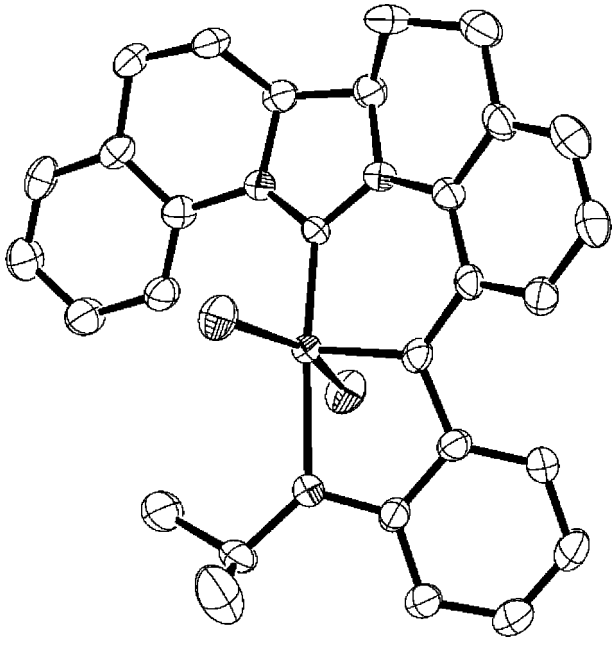
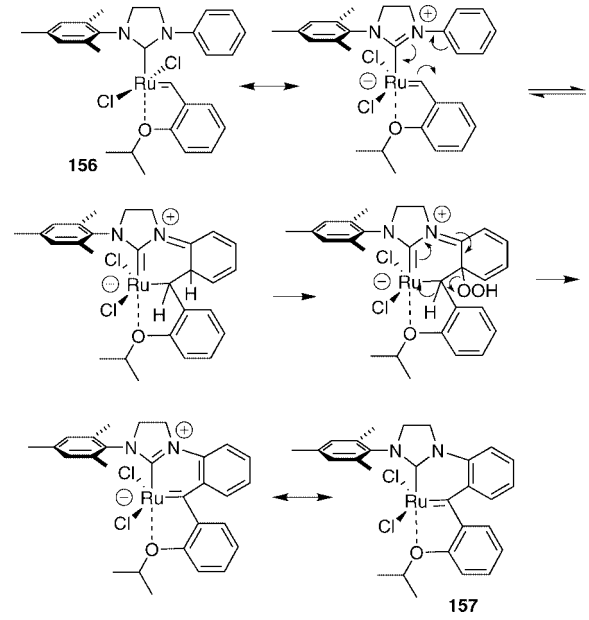


**Figure 62.** ORTEP view of **155**.

**Scheme 61. Proposed Mechanism for the Deactivation Reaction**




The structures of deactivation products **153a** and **153b** were elucidated by X-ray crystallography (Figures 60 and 61). The crystal structure of **153a** showed that the benzylidene carbon atom of **89** had inserted into an ortho C−H bond of one of the *N*-phenyl rings of the NHC ligand. In complex **153b**, the ruthenium center has further inserted into another ortho C−H bond of the other *N*-phenyl ring of the NHC ligand to give a new Ru−C bond. This further C−H activation occurred with the assistance of the dissociated phosphine. These observations suggest that NHC ligands containing phenyl groups (as opposed to mesityl groups) produce ruthenium-based olefin metathesis catalysts that are more vulnerable to decomposition by C−H activation.[196]

Recently, Suresh et al. carried out a mechanistic study to explore the structural and energetic features leading to the decomposition pathways of **89** using density functional theory.[197] The mechanistic study proved that the deactivation of this catalyst takes place through C−H activation followed by C−H agostic interactions and $\sigma$-bond metathesis (Scheme 59).

Trying to increase the stability of the newly developed catalyst for diastereoselective RRM, Blechert et al. attempted

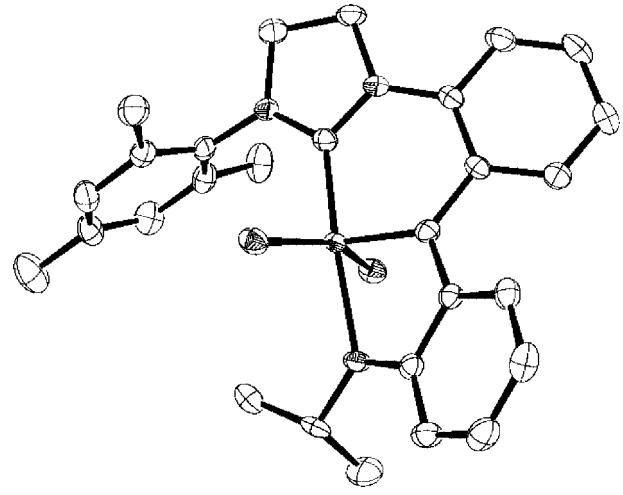


**Figure 63.** ORTEP view of **157**.

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to obtain the Hoveyda-type analogue of **102**. Reaction of **102** and 2-isopropoxystyrene without CuCl[198] resulted in the formation of the desired ruthenium catalyst **154** as an air-stable, olive green solid in 95% yield (Scheme 60). Unfortunately, the stability of this complex was limited, leading after two weeks to complete disappearance of Ru=C*H* signal. The newly formed complex **155** was fully characterized by spectrometric and X-ray crystallographic analysis (Figure 62).

This unexpected C−H insertion prompted the authors to synthesize a related phosphine-free second-generation ruthenium complex **156** (olive green solid) with similarly unsubstituted ortho-positions on one of the *N*-aryl ligands. It was observed that in $CH_2Cl_2$, in the presence of atmospheric oxygen, **156** converts completely into **157** within a few hours. Interestingly, no reaction was observed in solutions stored under inert atmosphere. The dark green, crystalline C−H insertion product **157** was characterized by X-ray crystallographic analysis. Based on these observations, a mechanism of deactivation was proposed, including a pericyclic cyclization, oxidation with $O_2$, elimination, and rearomatization steps (Scheme 61).

The results discussed here show that ruthenium catalysts bearing *N*-aryl substituted NHC ligands lacking steric hindrance in the ortho position of the arene ligand, although generally more potent in formation of tetrasubstituted C−C double bonds, can also give rise to intramolecular C−H insertion, leading to formation of metathesis-inactive ruthenium complexes. This observation is of importance for further development of olefin metathesis catalysts.

## 5. Summary and Outlook

The results presented in this review suggest that the application profile of the olefin metathesis catalysts (including, but not limited to factors such as stability, activity, selectivity and recoverability) can be controlled by a proper choice of a *N*-heterocyclic carbene ligand. For an example, a rather simple modification, the removal of an ortho substituent from the *N*-aryl ring of a standard NHC ligand, has resulted in complexes that efficiently catalyze various challenging olefin metathesis transformations, however at the cost of slightly limited stability. In many other cases, surprisingly, the 2,4,6-mesityl substituents, present in "standard" SIMes and IMes bearing catalysts, were found to be still the most optimal.

In the case of large-scale applications of metathesis technology, considerable attention shall be given to economical aspects (i.e., price of precious metals); therefore, development of new NHC-ruthenium complexes characterized by high turnover numbers and high turnover frequencies is required. It is hoped that the future development of new highly active catalysts with even better recyclability will help to overcome the crucial problem of ruthenium contamination in the pharmaceutical industry. It is also believed that the main future focus in this area of research will rest on the development of new catalysts for (stereo)selective metathesis.

We are confident that further experimental and computational exploration will bring to new generations of these very versatile and useful ligands.[199]

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