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Review

Preparation of NHC–ruthenium complexes and their catalytic activity in metathesis reaction

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Abstract

A detailed overview on the synthesis of four-, five- and six-membered, saturated and unsaturated *N*-heterocyclic carbenes used in the preparation of their corresponding ruthenium complexes (Grubbs' second-generation, Fischer-type, Hoveyda–Grubbs, homo and hetero-bimetallic) is presented both in solution and on solid support. The catalytic activity of the different complexes in ruthenium-catalyzed metathesis reaction is compared and explained by their structural features.

Keywords: *N*-Heterocyclic carbenes; Homogeneous ruthenium catalysts; Supported ruthenium catalysts; RCM mechanism

1. Introduction

Olefin metathesis has proven to be a powerful technique for the formation of C–C bonds in both polymer and small molecule synthesis [1–3]. The development of the ruthenium complexes bearing sterically demanding phosphines such as the well-defined and highly efficient metathesis precatalyst $RuCl_2$(=C(H)Ph)(PCy_3)$_2$ (**1**) (Fig. 1) (Grubbs' first-generation catalyst) [4], tolerating an array of functional groups has triggered an avalanche of interest in this transformation, allowing significant progress in the field of olefin metathesis [5–18].

Since at elevated temperature phosphines suffer from significant P–C bond degradation [19–23] the development of sterically demanding ligands that can mimic the phosphine behavior and at the same time show stability at higher temperatures would prove useful [24]. *N*-Heterocyclic carbene (NHC) ligands of the type imidazol-2-ylidene, *symmetrically* or *unsymmetrically* substituted, are phosphine mimics [20,21,25] with a particularly strong σ-donor but poor π-acceptor character. They show little tendency to dissociate from the metal center [26,27]. Since they can be easily endowed with sterically hindered substituents on their N-atoms, they are able to stabilize the catalytically relevant intermediates by electronic and steric means against uni- as well as bimolecular decomposition pathways. These properties translate into catalysts of greatly improved reactivity as well as higher stability, which outperform the parent-complex **1** (Fig. 1) in many cases.

In this context, by replacing one or both of the PCy_3 ligands in **1** by imidazolyl-2-ylidenes (Grubbs' second-generation catalyst), complexes such as **2** [28], the closely related mixed NHC/phosphane ruthenium–alkylidene complex (**3**) [23,29], dihydroimidazole carbene ruthenium complex (**4**) [30,31], and

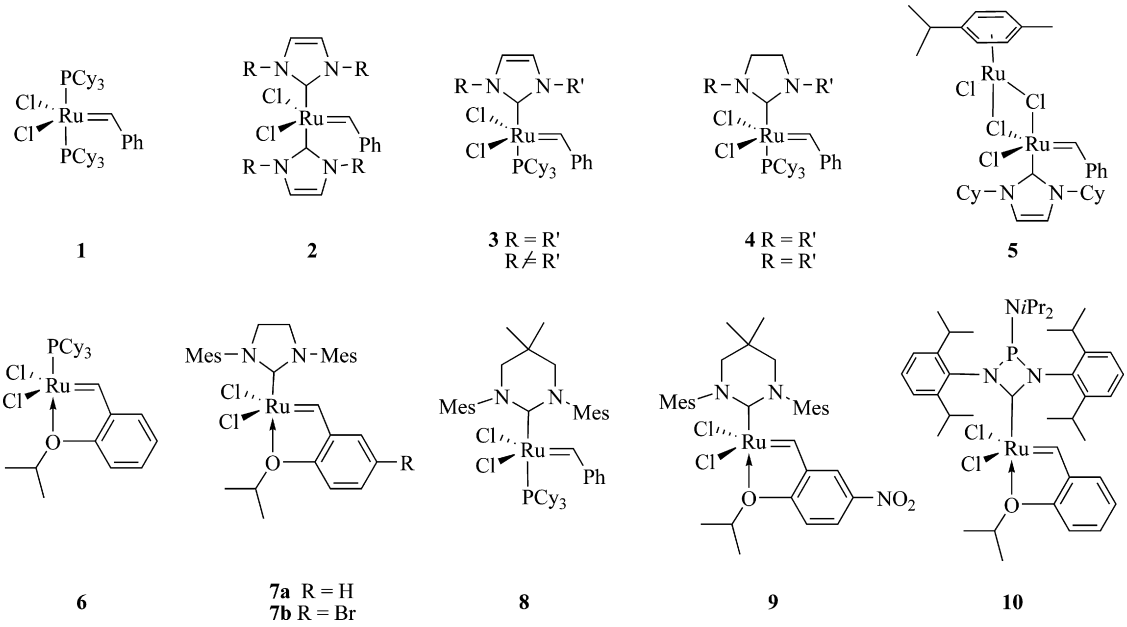


Fig. 1. Ruthenium catalysts for olefin metathesis.

homobimetallic ruthenium complex (**5**) [30,32], may allow a fine tuning of the reactivity pattern by systematic variations of the R groups (Fig. 1).

Another significant advance in this area is the discovery by Hoveyda and co-workers of the Ru catalysts **6** [33], **7** [34] that bear an isopropoxy ether ligand tethered to the benzylidene group. The unique bidentate nature of this ligand provides catalysts **6** and **7** with a number of interesting and useful properties [35].

The aim of this review is to discuss the preparation, structure and reactivity of metathesis catalysts, including complexes on solid supports and to present the mechanistic aspects behind the olefin metathesis.

2. Mechanism of ruthenium olefin metathesis

2.1. Mechanism of Grubbs' second-generation catalysts

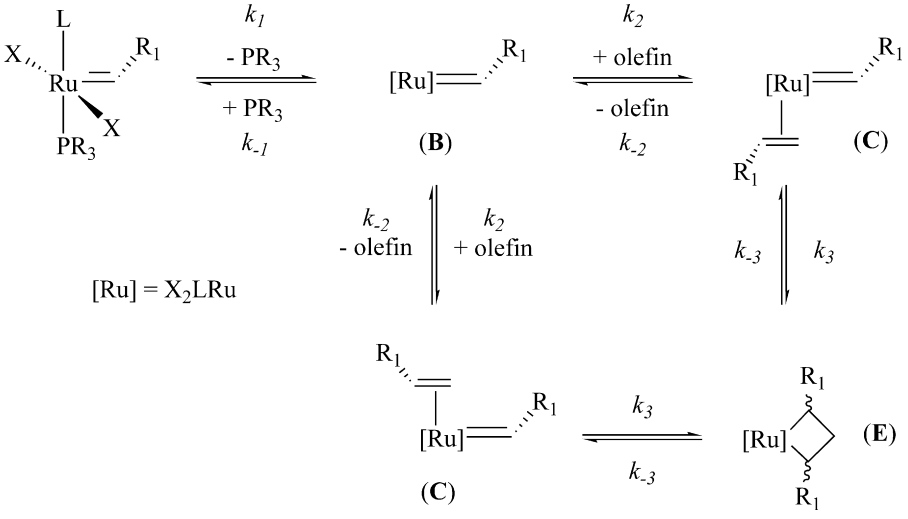
The mechanistic studies [23,36,37] and the theoretical investigation [38] on model systems, indicate that olefin metathesis reactions proceed in a dissociative fashion according to the mechanism outlined in Scheme 1.

The first step of the reaction involves dissociation of bound PCy_3 to form a 14-electron intermediate of the general form $L(Cl)_2Ru{=}CHPh$ (**B**). This intermediate can be trapped by free PCy_3 to regenerate the starting alkylidene, or bind the substrate [(**C**), with *trans* olefin coordination to L] [38]. Rearrangement of the resulting π complex to give the ruthenacycle (**E**) by migratory insertion undergoes metathesis. The 14-electron ruthenacyclobutane (**E**) is an observable intermediate [39] in NHC-stabilized Grubbs catalysts, in which the strongly σ donating carbene ligand is able to stabilize this Ru(IV) species which has a symmetrical C_{2v} structure [39].

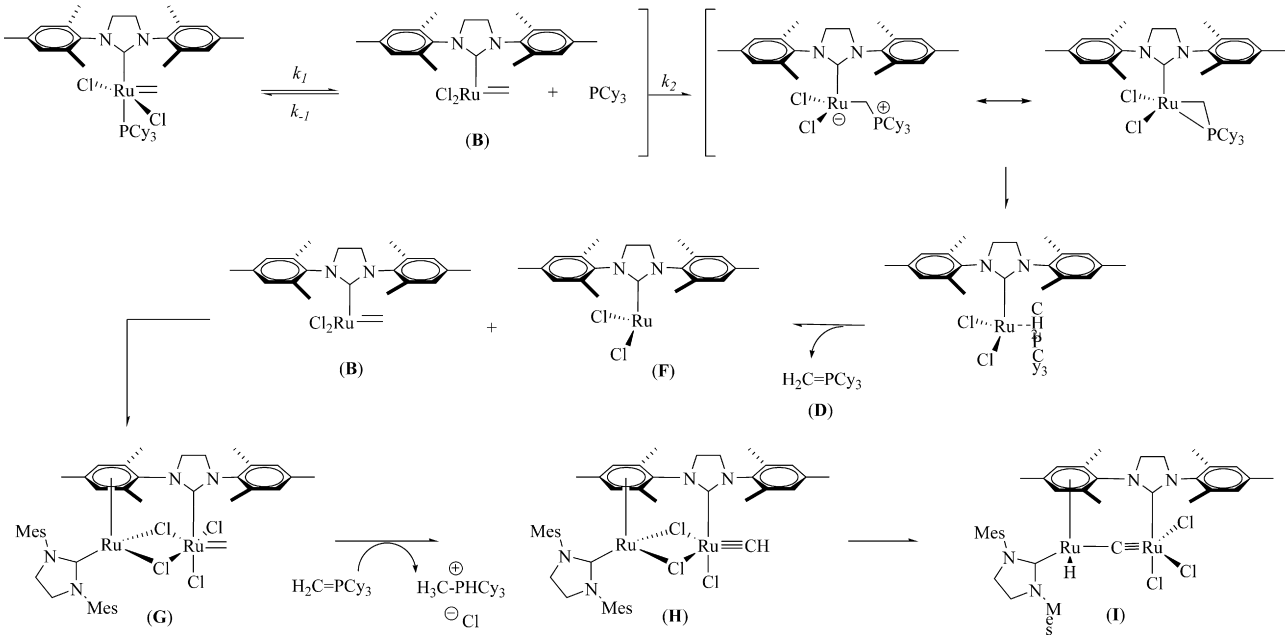
The activity of catalyst is not only related to the phosphine dissociation rate k_1 but also to the ratio k_{-1} to k_2 which determines whether the catalyst binds the olefin or returns to its resting state. While NHC complexes do not efficiently loose a phosphine (initation, k_1 small), a small amount of initiated 14-electron species is capable of cycling through multiple olefin metathesis reactions before it is deactivated by the rebinding of PCy_3. However, once the phosphine comes off, coordination of olefin is facile compared to re-binding of PCy_3 ($k_{-1}/k_2 \sim 1$ and [olefin] is high). For a given phosphane PR_3, an increasing σ-donor ability of L facilitates the initial dissociation of PR_3 and destabilizes the intermediate π complex. This makes the insertion more favorable. Electronically, the most efficient catalysts are expected to contain one weak and one strong σ-donor ancillary ligand to promote, respectively, dissociation and insertion. For this reason, the role of NHC is two-fold: (i) being a better donor than PCy_3, as expected from simple electronic arguments, catalyst performance is enhanced and (ii) steric hindrance helps to prevent (or slow down) bimolecular carbene decomposition [23]. The catalytic activity depends on the donor properties of aryl substituted NHC, the lone pair donation from the carbene carbon and the transfer of electron density of the aromatic π-face of the NHC aryl groups towards the metal [40]. It is also worth noting that the *para*-substituents to the nitrogen atom also have an effect on the stability of the respective ruthenium complexes. The more electron donating substituents, especially OR, lead to a significant destabilization of the respective Grubbs II and Grubbs–Hoveyda complexes, as evidenced by some decomposition during chromatographic purification [40].

The thermal decomposition of catalysts has been proposed to occur *via* phosphine dissociation followed by bimolecular coupling of two ruthenium fragments [37,41,42] suggesting that catalyst initiation and decomposition proceed through the common intermediate (**B**) (Scheme 2).

According to the mechanism proposed by Grubbs and co-workers [42], the decomposition of the catalyst occurs mainly by attack of the dissociated tricyclohexylphosphine **D** on the methylidene of **B**. The 12 electron species **F** formed upon elimination of phosphine ylide would bind one of the mesityl rings of **B**. Through two chloride bridges between



Scheme 1.



Scheme 2.

two ruthenium centers and HCl abstraction by the phosphine ylide **D**, the terminal alkylidyne complex **H** could be obtained. Formation of **I** can be explained by oxidative addition of the terminal alkylidyne in **H** with migration of two chlorides. However, the authors report that none of these intermediates have been observed by NMR spectroscopy [42].

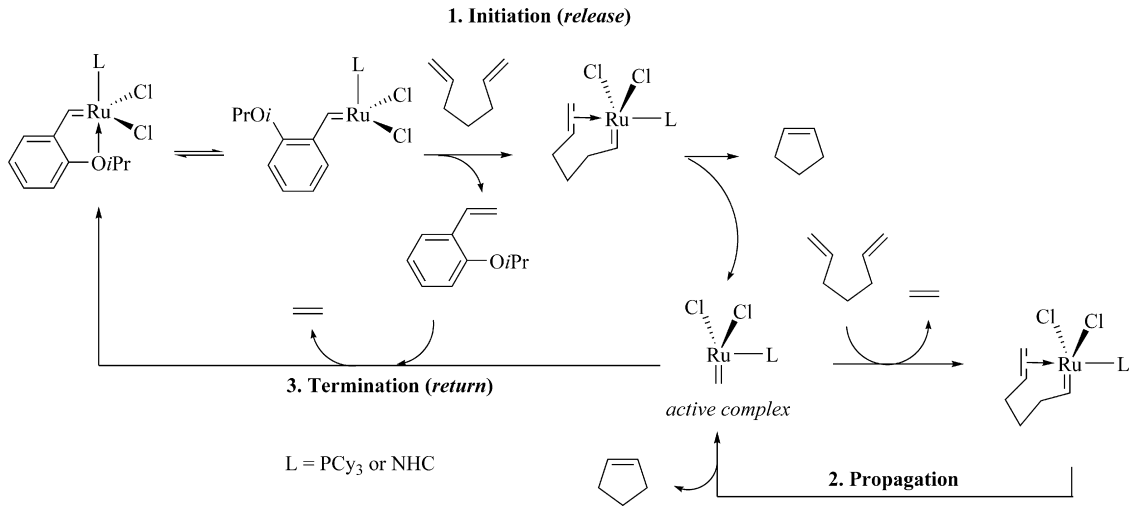
2.2. Mechanism of Hoveyda–Grubbs' catalysts

In contrast to Grubbs' second-generation precatalysts, which are likely activated by the loss of PCy_3, bidentate carbenes such as **6** or **7** (Fig. 1) are converted to the catalytically active 14-electron Ru complex through the dissociation of the Ru–O chelation. This is followed by olefin metathesis involving a substrate molecule leading to the formation of isopropoxystyrene (or a related derivative) (Scheme 3) [33,34,43].

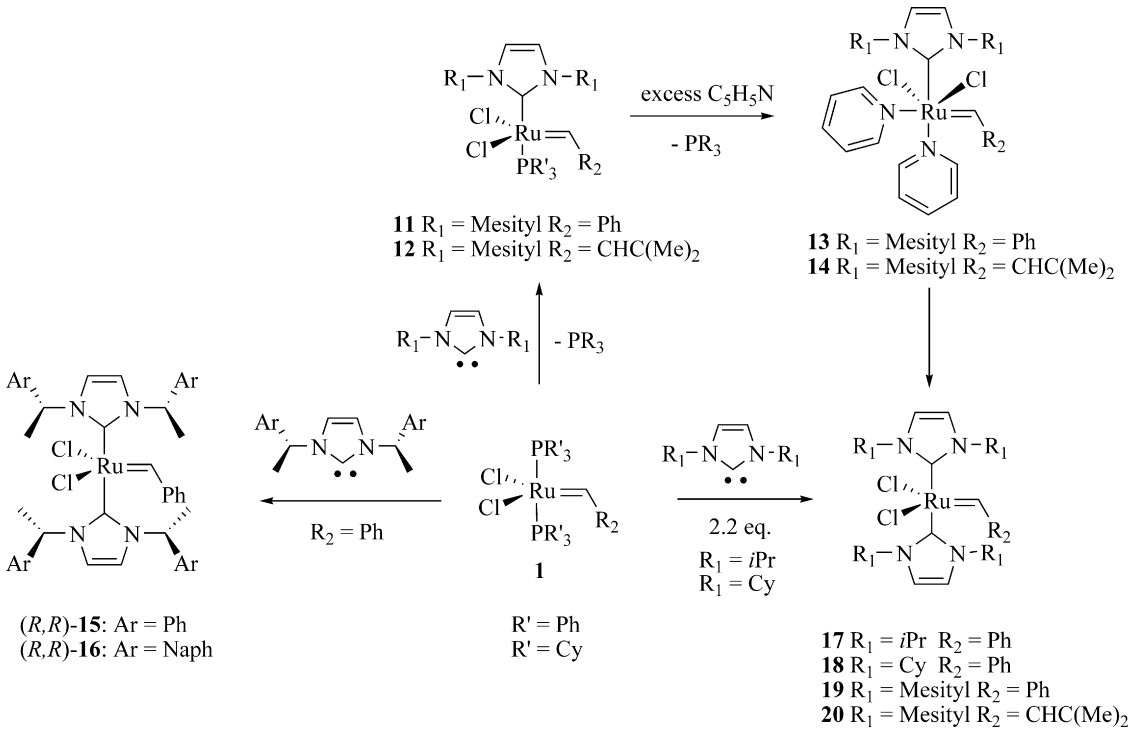
The absence of released phosphine, which can intercept and deactivate certain Ru carbene (such as the *active complex*) [44,45] is one of the key reason for the unique reactivity profiles observed for complex **6** or **7**. Ruthenium complexes such as **6** or **7** operate by a release/return mechanism (Scheme 3) [33,34]. It is possible that the initial Ru complex can exist in equilibrium with the *active complex* (release).

After initiating several catalytic olefin metathesis cycles (propagation), and upon complete consumption of the olefin, the methylidene *active complex* encounters the initially released isopropoxystyrene to regenerate the starting catalysts **6** or **7** (termination of the catalytic cycle) (Scheme 3) [33].

Intermolecular as well as intramolecular mechanism of enyne metathesis, catalyzed by Grubbs ruthenium carbene complexes has been modeled in a DFT study by Lippstreu and Straub [46].



Scheme 3.



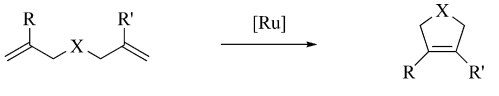
Scheme 4.

3. Ruthenium carbene complexes bearing two unsaturated imidazolin-2-ylidene ligands (type 2)

The first examples of ruthenium-based complexes in which both phosphines are replaced by more Lewis basic imidazolin-2-ylidene groups were reported by Hermann and co-workers [28]. The phosphane complex $[RuCl_2(PR_3)_2(=CHPh)]$ [47] reacts with the appropriate imidazolin-2-ylidene to yield compounds **15**–**18** (Cy = cyclohexyl, Naph = 1-naphthyl) as air-stable solids [48] (Scheme 4).

A pathway to **19** [49] and **20** [49] is *via* complex $(IMes)(Cl)_2(C_5H_5N)_2Ru{=}CHPh$ [50] (**13**) [49] and $(IMes)(Cl)_2(C_5H_5N)_2Ru{=}CHCHC(Me)_2$ [50] (**14**) respectively [IMes = 1,3-bis(2,4,6-mesityl-imidazol-2-ylidene], in which the IMes ligand is preinstalled and which contains labile pyridine and chloride ligands (Scheme 4).

Compounds **17** and **18** catalyze the conversion of *N*,*N*-diallyl-*N*-tosylamide **21** into the corresponding dihydropyrrole **27** in quantitative yield; a lower activity has been reported for compounds (*R*,*R*)-**15** and (*R*,*R*)-**16**, which exhibit *chiral* imidazolin-2-ylidene ligands (Scheme 5).



Scheme 5.

Compounds **15**–**18** show high tolerance towards functional groups and they are remarkably active catalyst in ring-opening metathesis polymerization (ROMP) and for any kind of ring-closing metathesis (RCM) [28,32,51]. Even though their activity is lower compared to the bisphosphine complex **1** [28,31] probably because the catalytically active 14e$^-$ species is formed more slowly, they show excellent performance in the formation of tri- and even of tetra-substituted cycloalkene products [51] due to the stronger carbene metal bond [23,30].

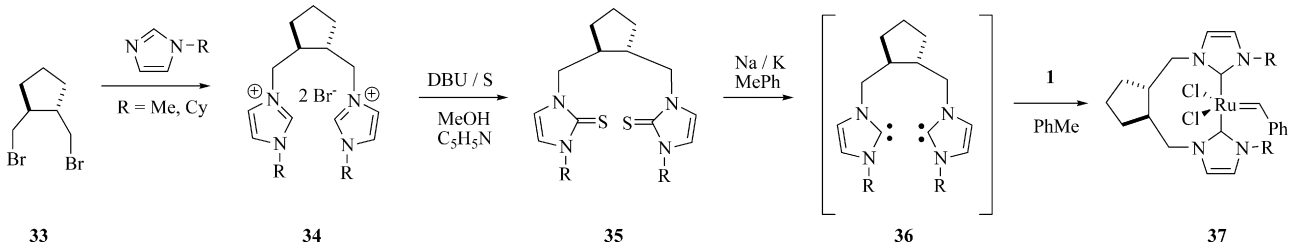
Marshall et al. [52] have recently prepared the first *chiral* nine-membered NHC complex of ruthenium **37** for potential stereodifferentiating alkene metathesis reactions (Scheme 6).

The new chiral ligands (1*S*,2*S*)- and (1*R*,2*R*)-1,2-bis-(1-alkylimidazol-2-yliden-3-methyl)cyclopentane (**36**) were prepared *in situ*: this was achieved by transformation of a chiral cyclopentane dibromide backbone **33** to the bisimidazolium salt **34**. Conversion of the salt to the crystalline bis(imidazol-2-thione) revealed existence of two forms of the molecule in the asymmetric unit with the same chirality. Reduction of the thione functionality gave access to the bis(imidazol-2-ylidene) (**36**), which reacted with Grubbs catalyst **1** to afford the air-stable chiral chelating bidentate NHC ruthenium benzylidene complexes **37** (Scheme 6).

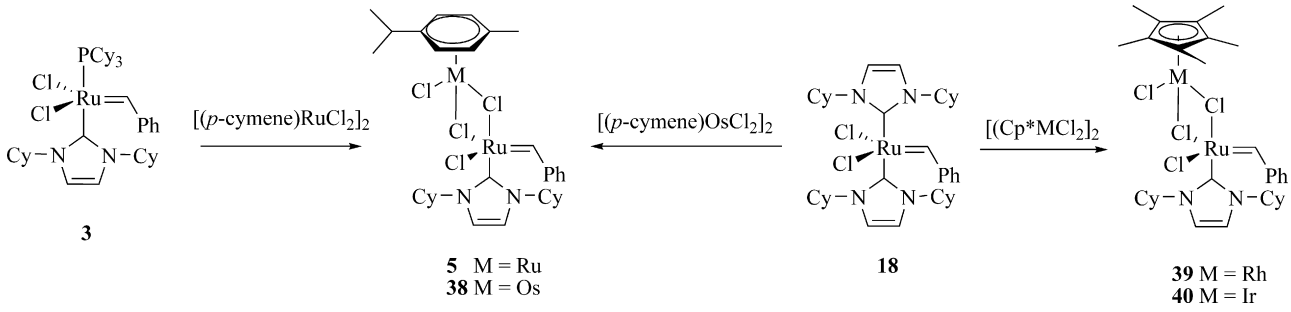
4. Homo- and heterobimetallic ruthenium alkylidene complexes (type 5)

Herrmann and co-workers [30,32] synthesized the first example of bimetallic ruthenium NHC complexes **5**, **38**–**40** (Scheme 7).

Differences in reactivity of the chloro-bridged organometallic precursors give an interesting insight into the affinity of



Scheme 6. Synthesis of dicarbene ruthenium complexes **37**.



Scheme 7. Homo- (**5**) and heterobimetallic (**38**–**40**) ruthenium NHC complexes.

different metal fragments to NHCs. For example, compound **5** can only be obtained from **3** and [(*p*-cymene)$RuCl_2$]$_2$, which selectively substitutes the phosphane ligand of **3**, leaving NHC unchanged. Starting from **18** reveals no conversion. In contrast, **38**–**40** have to be synthesized from **18**; starting from **3** leads to a mixture of heterobimetallic phosphane and NHC complexes. The decisive criterion for the reactivity is the different affinity of the NHC to the chloro-bridged compounds: Rh(III) > Ir(III) > Os(II) > Ru(II) (no reaction).

Complexes **5**, **38**–**40** (Scheme 7), show a very high catalytic activity in ROMP of 1,5-cyclooctadiene and RCM of tetra-substituted cycloalkenes [51], not accessible by using complex **1**. The chloride bridged cymene and cyclopentadienyle ruthenium templates are prone to decoordination and thereby open the required vacant site on the active species in solution.

5. Ruthenium carbene complexes bearing one unsaturated nucleophilic imidazolin-2-ylidene ligand (type 3)

Independent and almost simultaneous publications on 'second-generation' metathesis catalysts, report complexes in which *one* of the PCy_3 groups of **1** is replaced by an NHC [22,23,29–31,51,53].

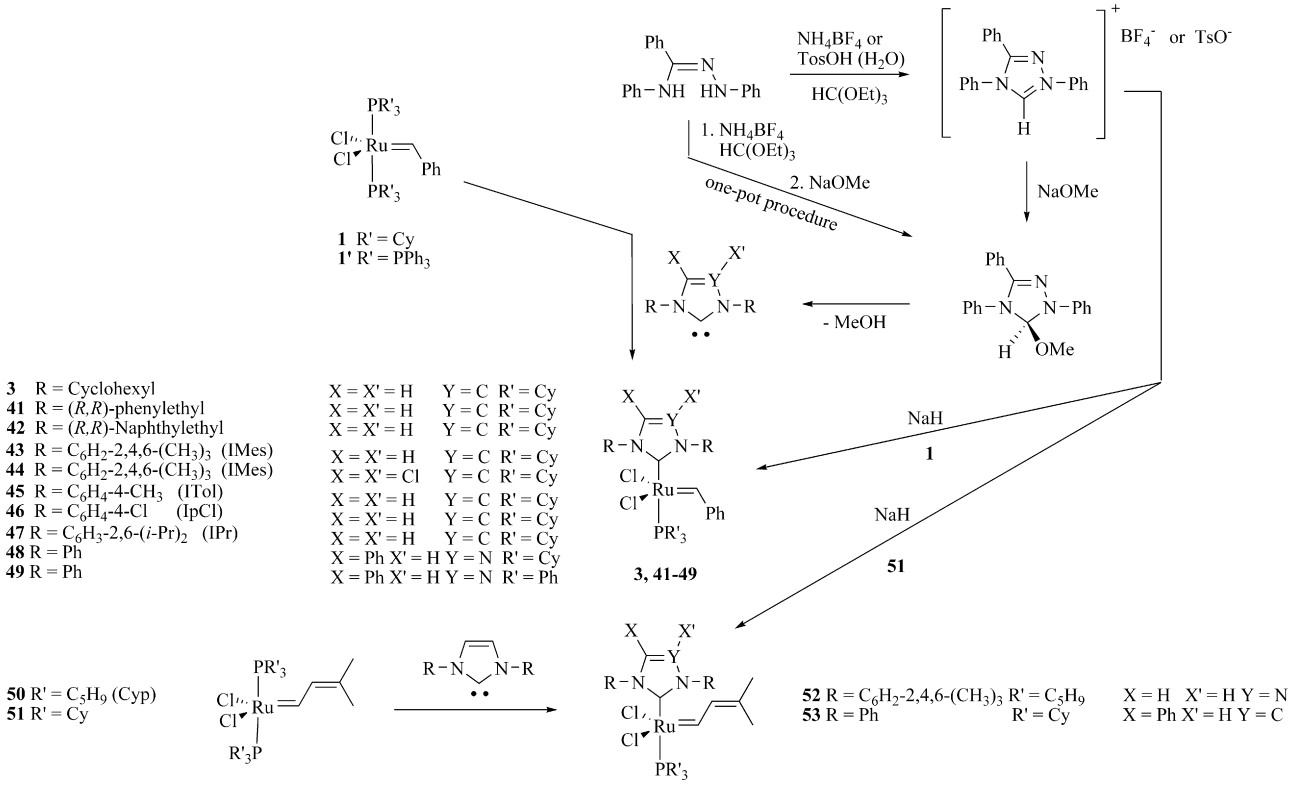
Metal carbenes are generally classified as being nucleophilic (electron-rich) or electrophilic (electron-poor) in character of the carbene carbon atom, but an effective olefin-metathesis catalyst exhibits behavior between these two extremes. The Grubbs-catalyst portfolio [9] consists of a variety of ruthenium-based systems of general formula $[Cl_2(L)(L')Ru{=}C(H)R]$ (Fig. 1). Successful improvements to the 'Grubbs first-generation catalyst' $[Cl_2(PCy_3)_2Ru{=}C(H)R]$ (**1**) are modifications that either encourage loss of L′ [45] (initiation of catalytic reaction) or reduce the tendency of $[Cl_2(L)Ru{=}C(H)R]$ to re-capture the liberated L′ [37] (propagation), which competes with the olefin substrate for the unsaturated metal center in $[Cl_2(L)Ru{=}C(H)R]$.

Nucleophilic heterocyclic carbene ligands of the imidazol-2-ylidene-type have proven to be phosphine mimics [21] more particularly those sterically hindered developed by Arduengo et al., which bear aryl group on the nitrogen positions and prevent (or slow down) bimolecular carbene degradation [24].

5.1. Symmetrically substituted NHC entities (R = R′)

The first NHC/phosphane complexes **3**, **41**–**42** were reported by Herrmann and co-workers [30], by reacting the appropriate NHC (1.2 equiv.) with **1** in THF (Scheme 8). Low temperature is crucial for the selectivity of the phosphane/NHC substitution reaction. At room temperature the selectivity is lowered and mixtures with a significant amount of the corresponding type **2** (Fig. 1) dicarbene complexes were generated [30]. The catalytic activity for all types of RCM reactions is very high but still lower with respect to the parent compound **1** [51].

In the same year, parallel studies by Grubbs and co-workers [29] and Nolan and co-workers [23,54] described the exchange reaction of one phosphine ligand of compound **1** with the sterically demanding carbene ligand 1,3-bis(2,4,6-mesityl)imidazol-2-ylidene (IMes) leading to the isolation of the new complex $(PCy_3)(IMes)Cl_2Ru{=}C(H)Ph$ (**43**) [55] (Scheme 8). According to the same reaction scheme, the new complexes $(PCy_3)(ITol)Cl_2Ru{=}C(H)Ph$ (**45**) [54] $(PCy_3)(IpCl)Cl_2Ru{=}C(H)Ph$ (**46**) [54] (PCy_3)-$(IPr)Cl_2Ru{=}C(H)Ph$ (**47**) [56] and $(PCy_3)(Ph_3Tri)$-$Cl_2Ru{=}C(H)Ph$ (**48**) [57] of the sterically hindered carbene ligands 1,3-bis(4-methylphenyl)imidazol-2-ylidene (ITol), 1,3-bis(4-chlorophenyl)imidazolyd-2-ylidene (IpCl), 1,3-bis-(2,3-diisopropyl)imidazol-2-ylidene (IPr) and 1,3,4-triphenyl-



Scheme 8.

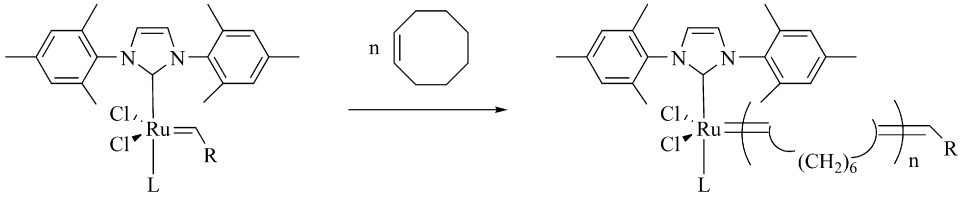
4,5-dihydro-l*H*-l,2,4-triazol-5-ylidene [58] (Ph_3Tri) were synthesized (Scheme 8).

Grubbs and co-workers [59] reported an alternative route to **48**, **49** and **53** that employs NCH-alcohol as protected form of the NHC ligand, easier to handle compared to their free carbene counterparts (Scheme 8). When compounds **48** and **53** were unstable in solution due to the Ph_3Tri ligand dissociation from the metal center and the phosphine reassociation to yield the more stable $(PCy_3)_2(Cl_2)Ru{=}CH{-}CH{=}C(CH_3)_3$, complex **49**, generated *in situ* from $(Ph_3Tri)(H)(OMe)$ and $(PPh_3)_2(Cl)_2Ru{=}CHPh$ **1′**, catalyses the ROMP reactions of COD and bulk dicyclopentadiene at a fast rate [59]. The decomposition pathway of **48** and **53** is both accelerated at elevated temperature and under catalytic turnover conditions, making them poor olefin metathesis catalysts [59].

As it was the case for **43**, one IMes can be substituted by one $PCyp_3$ in $(PCyp_3)_2(Cl_2)Ru{=}CH{-}CH{=}C(CH_3)_3$ (**50**; Cyp = cyclopentyl, C_5H_9) [28] to produce $(PCyp_3)$-$(IMes)Cl_2Ru{=}CH{-}CH{=}C(CH_3)_3$ **52** [54] (Scheme 8).

Complex **3** promotes a better ROMP of 1,5-cyclooctadiene [30], with respect to the parent compound **1**, and presents an excellent activity for the synthesis of tetra-substituted cycloalkenes by RCM [29,51]. The IMes-containing derivatives **43** and **52** are efficient as catalysts for the polymerization of cyclic olefins contained in cyclostomes (COE) [54] [Scheme 9(a)]. They show enhanced polymerization propaga-

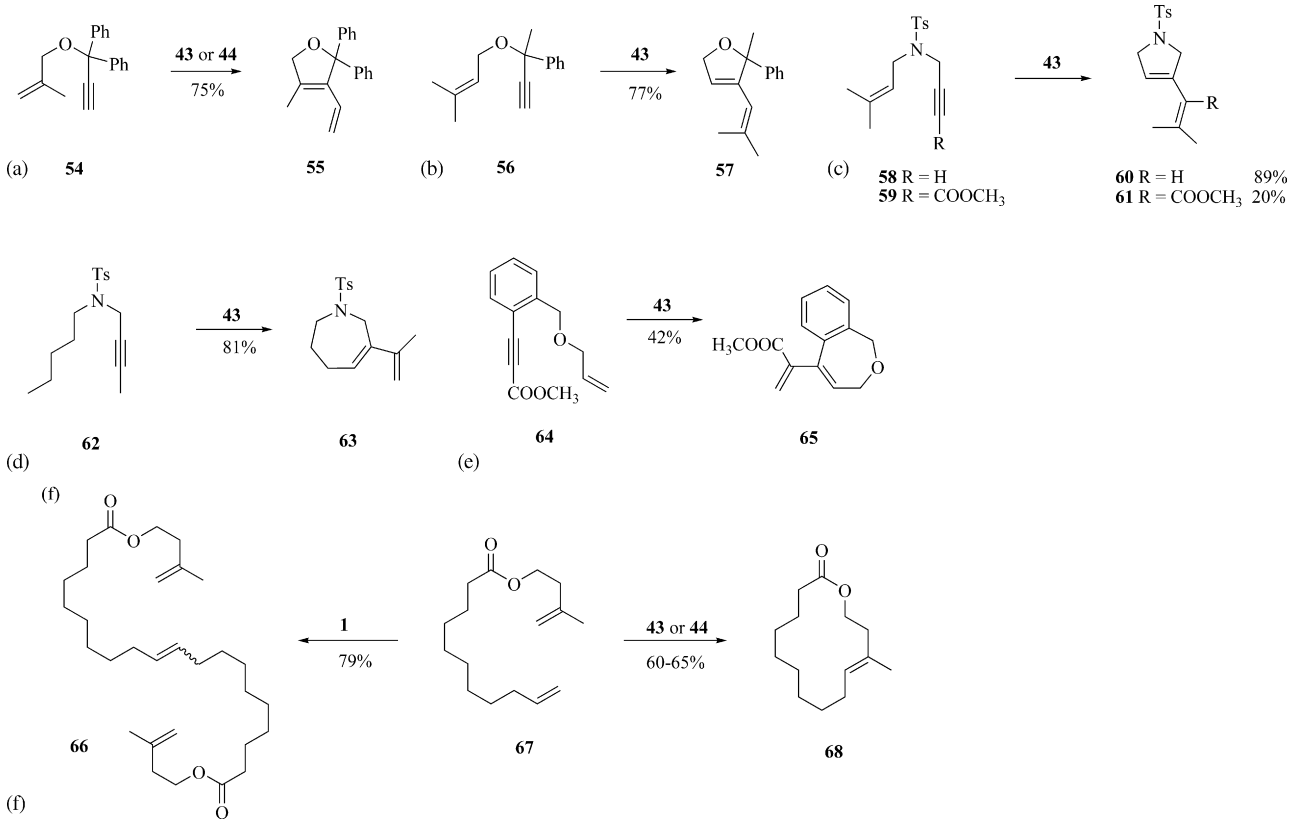
(a) *Ring-opening metathesis polymerization* (ROMP)



43 R = Ph, L = PCy_3
52 R = $CH{=}C(CH_3)_2$ L = $PCyp_3$

(b) *Cross metathesis* (CM)

Scheme 9.



Scheme 10.

tion compared to their precursors **1** and **50**. The improved electron donor properties of the IMes ligand lead to a better stabilization of the reactive site, which is formed by phosphine abstraction from the metal center. Moreover, the PCy_3-benzylidene complex **1** and **43** display a significantly more rapid polymerization behavior than the $PCyp_3$-vinylmethylene complexes **50** and **52**, which is obviously the result of the benzylidene replacement by the vinylmethylene moiety at the metal center.

For the RCM of diethyl diallylmalonate [23,54] (**25**, Scheme 5), the ITol (**45**) and IpCl (**46**) ligands lead to significantly slower reactions, because of poor electron-donating ligand ability to the ruthenium center and lower steric protection because of the lack of substitutions at the aryl *ortho* positions. $PCyp_3$-vinylmethylene complexes **50** and especially **52** are less efficient under these conditions. Complex **43** exhibits high RCM of macrocyclic ethers, comparable to that of complex **1** [29,57].

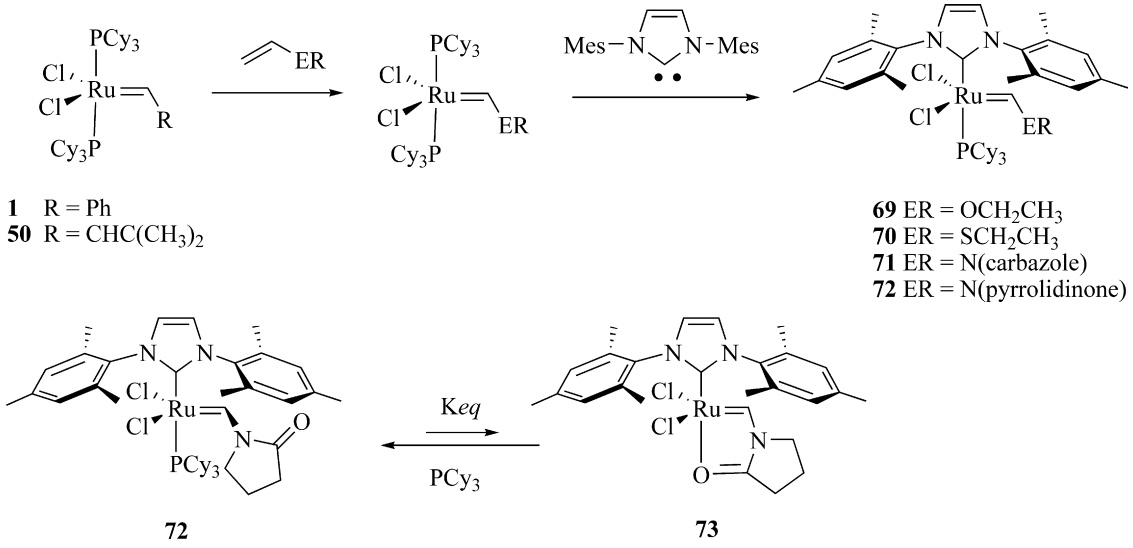
In the cross-metathesis (CM) of *cis*-2-pentene [Scheme 9(b)] complex **43** is twice more efficient as catalyst **1**; the vinylmethylene complex **52** is slower than **43**, but still better than **53**, which shows a very low activity [54].

Complexes **43** and its chloro-substituted analogue **44** are almost indistinguishable in their reactivity toward enyne **54** [Scheme 10(a)]; terminal as well as internal alkynes can be used; various substitution of the alkene entities are tolerated and even tri-substituted olefins are found to undergo efficient cycloisomerization in the presence of complex **43**, thereby transferring a dimethylmethylidene unit [Scheme 10(b) and (c)]. Catalyst **43** also allows formation of six-membered rings and even the seven-membered heterocycle **63** is obtained in excellent yields [57] [Scheme 10(d)]. Formation of product **65** [Scheme 10(e)], in lower yield, is particularly noteworthy as the required substrate **64** is an electron-deficient and highly conjugated alkyne derivative. Another stringent test is the formation of the 14-membered ring lactone **68** [Scheme 10(f)] containing a tri-substituted double bond, formed in good yield in the presence of **43** and **44**; all attempts to run the same transformation using catalyst **1** afford only homo-dimerization at the least substituted site with the formation of the acyclic dimer **66** [57].

When catalyst **47** was tested by using diethyl diallylmalonate **25** or its substituted analogues **23**, **24** and **26** (Scheme 5), RCM reaction was complete after 15 min at room temperature [56]; under identical conditions complex **1** showed 85% conversion [23,29,51]. The catalyst **48** affords a 85% conversion of diethyl diallylmalonate **25** and diallyltosylamide **21** in RCM reactions, within 2 h. However, a prolonged stirring did not lead to further conversion, most likely because of the limited lifetime of complex **48** in solution [57].

A number of recent reports have indicated that [Ru]=C(H)OR-type complexes may be active olefin metathesis catalysts [60–62]. A series of well-defined carbenes complexes $(PCy_3)(IMes)(Cl)_2Ru$=C(H)ER (**69**–**72**) bearing electron-rich (ER) olefins have been prepared by Louie and Grubbs [63] (Scheme 11). Complex **72** in solution was shown to behave in equilibrium with its chelate form **73**.

All Ru Fischer-type carbene complexes initiated the ROMP of strained cyclic olefins (e.g. norbornene and 1,5-cyclooctadiene) affording quantitative yield of polymer, complex **71** being the one with the highest catalytic activity. In



Scheme 11. Synthesis of Ru Fischer-type complexes **69–72**.

the presence of diethyl diallylmalonate **25**, **69–72** afforded the cyclized product **31** (Scheme 5). The activity of Ru Fischer-type carbene complex heavily depends on the α-heteroatom of the carbene moiety. The rates of ROMP and RCM suggest that relative activities of $(PCy_3)(IMes)(Cl)_2Ru{=}C(H)ER$ complexes follow the general trend E = C > N > S > O.

To study the effect of replacing a phosphine donor with the IMes or IPr ligand in RCM reactions, Nolan and co-workers [64] prepared (*p*-cymene)$RuCl_2$(IMes) (**75**) (*p*-cymene)$RuCl_2$(IPr) (**76**) and $[(p\text{-cymene})RuCl(IMes)(=C=C=CPh_2)]^+PF_6^-$ (**77**), stable at elevated temperature (Scheme 12).

The catalytic activities of **75–77** in ring-closing metathesis (RCM) of diethyl diallylmalonate **25** showed that the IMes-containing complexes **75** and **77** are the best catalyst precursors compared to the phosphine-containing complexes (*p*-cymene)$RuCl_2(PCy_3)$ and (*p*-cymene)$RuCl_2(P\textit{i}\text{-}Pr_3)$, whereas the ruthenium complex incorporating the IPr ligand **76**, showed similar reactivity.

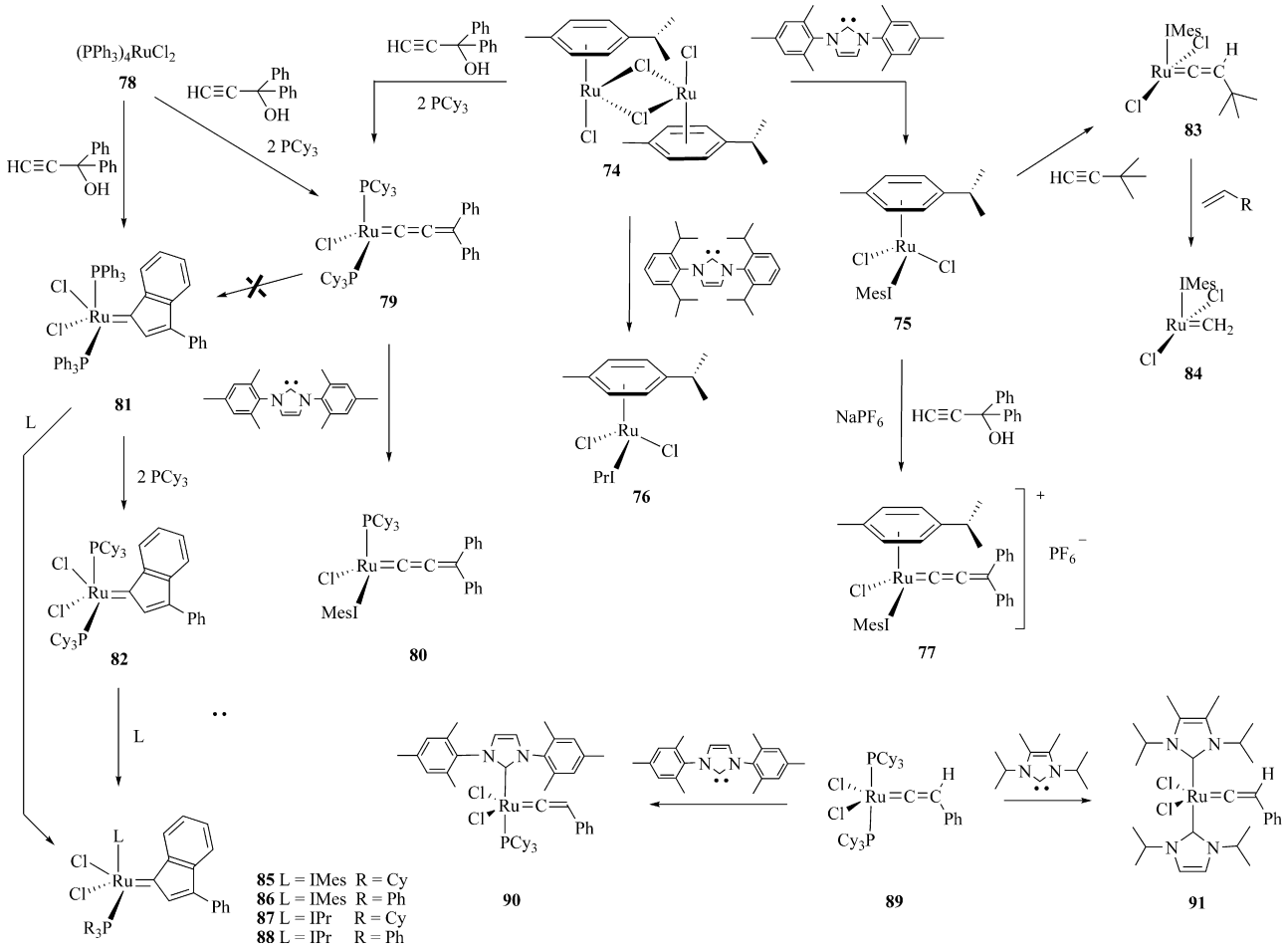
The first coordinative unsaturated 16-electron ruthenium allenylidene complex **79** is easily prepared by *one-pot* reaction of $(PPh_3)_4RuCl_2$ (**78**) or [(*p*-cymene)$RuCl_2$] (**74**) with 2 equivalents of PCy_3 and 3,3-diphenylpropyn-1-ol [65]. The exchange of one PCy_3 ligand for IMes afforded **80** in high yields (Scheme 12). When $(PPh_3)_4RuCl_2$ (**78**) reacts in the sole presence of 3,3-diphenylpropyn-1-ol, the 3-phenyl-1-indenylidene complex **81** (indenylidene) is formed by intramolecular rearrangement. The PPh_3 ligands can be substituted by the better electron-donating ligand such as PCy_3 to afford **82**. In the case of complex $(PCy_3)_2RuCl_2(=C=C=CPh_2)$ (**79**), the higher electron density at the metal center provided by the PCy_3 ligand inhibits the rearrangement of the allenylidene backbone to afford **81**.

Unfortunately, both complexes **79** and **80** are not very efficient in RCM of diethyl diallylmalonate **25** and diallyltosylamide **21** compared to cationic 18-electron arene-ruthenium allenylidene complexes [66]. The significantly higher bonding energy of allenylidene moiety of the metal center might be at the origin of the lower catalytic activity [65].

The imidazolynilidene analogues of the previously described Ru–allenylidene complexes $RuCl_2(=C=C=CPh_2)(PR_3)$ [**81**, R = Ph; **82**, R = Cy] [65] can be prepared *via* substitution reactions with IMes or IPr ligands, to afford complexes **86** and **88** (R = Ph) or **85** and **87** (R = Cy), respectively [67]. The compounds containing PPh_3 were less stable and decomposed on heating, while those incorporating PCy_3 were robust at elevated temperature even after 10 days. This result is surprising because if the decomposition pathway involves dissociation of phosphines (other ligands are less likely to dissociate), the less electron-releasing and hence the less tightly bound PPh_3 ligand should undergo dissociation faster than the more tightly bound PCy_3 moiety.

The complexes **81**, **82**, **85–88** were tested in the RCM reaction of diethyl diallylmalonate **25** and diallyltosylamide **21**: **81** showed no activity, while its derivatives **86** and **88** were efficient in this transformation, at 40 °C and room temperature, respectively. With more hindered substrates such as diethyl(2-methylallyl)malonate (**23**, Scheme 5) the yield of the reaction was poor, even at 80 °C, because the catalyst was disabled after a certain period of time at higher temperature [67]. Complexes **82**, **85** and **87** catalyzed the RCM reaction of diethyl diallylmalonate **25** with comparable yields (75–88%) [67] at room temperature. When the substrate was diallyltosylamide **21**, a common trend of reactivity was displayed by complexes **82** and **87** (yields 89–96%) [67] at room temperature. Only 30% yield was obtained with complex **85** [67]. The indenylidene complexes **82** and **85–88** are good catalyst precursors in RCM of sterically unhindered substrates, comparable to types **1** and **50** alkylidene complexes (Scheme 8) developed by Grubbs and co-workers [4,47,68] and Herrmann and co-workers [28], respectively. They show much higher activity compared to their allenylidene analogues **79** [65] and **80** (Scheme 12). In summary, complexes **85–88** are active catalyst precursors in the RCM reactions of dienes.

The reaction of carbenes 1,3-diisopropyl-4,5-dimethylimidazol-2-ylideme (*i*Prim) [69] and IMes with $(PCy_3)_2Cl_2Ru{=}$



Scheme 12.

C=CHPh (**89**) [70,71] respectively afforded (*i*PrIm)$_2$Cl$_2$Ru=C=CHPh (**91**) [72] and (PCy$_3$)(IMes)Cl$_2$Ru=C=CHPh (**90**) (Scheme 12).

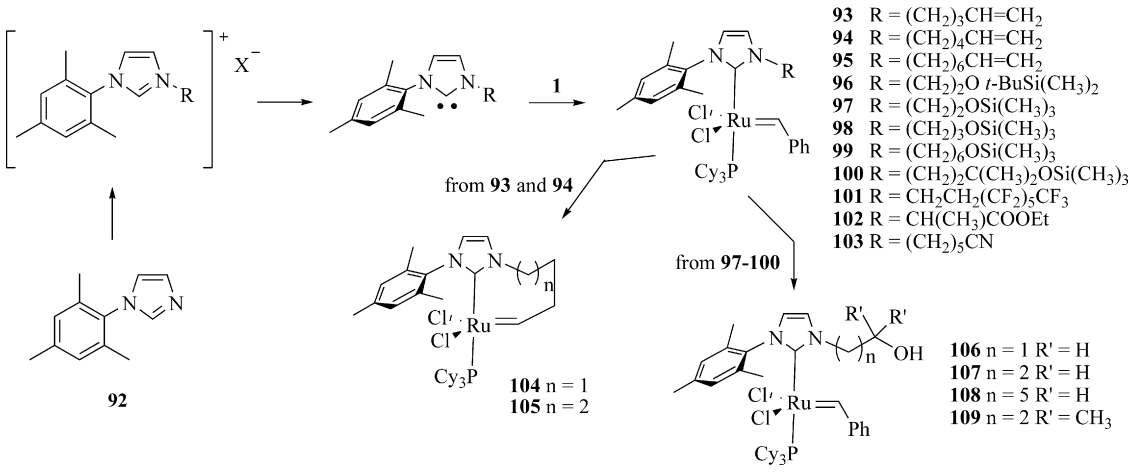
The RCM of diethyl diallylmalonate using **91** was not observed, even under harsh conditions. This is somewhat surprising since the analogous bisimidazolyl benzylidene complex **19** (Scheme 4) is a known RCM catalyst [30,51]. The same reaction, in the presence of **90** as catalyst afforded high yield, although the reaction rate was much slower than with the ruthenium carbene complexes **1** (Fig. 1) and **43** (Scheme 8). The slow rate of the reaction may result from a slow initiation since the propagating species, presumably methylidene, should be the same as that produced by carbene **43**. Noteworthy is that replacement of a phosphane with an imidazolylidene in neutral allenylidene complexes (e.g. **80**, Scheme 12) does not provide a metathesis active catalyst [65]. These results indicate that increased ligand dissociation (i.e. of phosphane) was necessary to accelerate initiation and thereby enhance the catalytic activity. The alternative approach involves the direct generation of the phosphane-free active species *in situ* [72], avoiding the use of phosphane scavengers such as copper salts or acids. Ruthenium vinylidene complexes can be conveniently prepared by adding to the dimer [(*p*-cymene)RuCl$_2$]$_2$ (**74**, Scheme 12), the ligand IMes and *t*-butylacetylene, to afford a phosphane-free complex **83** (Scheme 12) as a catalyst precursor which catalyses the RCM of diethyl diallylmalonate **25** with 95% yield. The complex formed *in situ* displayed higher catalytic activity than the vinylidene complex **90** [72] (Scheme 12).

5.2. *Unsymmetrically substituted NHC entities ($R \neq R'$)*

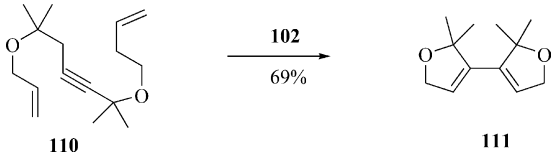
The unsymmetrically substituted NHC's metathesis catalysts **93–104** of 'second generation' are prepared *in situ* in presence of *t*-BuOK [57,73,74] after quaternization of *N*-mesitylimidazole **92** [75]. This approach is particularly justified especially for the preparation of complexes **93–95**, to minimize possible side reactions between the carbene center and the alkene groups in the lateral chains of the corresponding NHC derivatives (Scheme 13).

Their unique ability to *metathesize their own ligands* allows the preparation of compounds **104** and **105** from **93** and **94** [57] respectively, in which the NHC and the 'regular' carbene unit Ru=CHR are tethered to a metallacycle [73] (Scheme 13).

The design of these species is based on the idea that they might be able to regenerate themselves after the metathesis reaction is over and the substrate in solution has been quantitatively consumed. Desilylation of **97–100** afforded ruthenium–NHC complexes **106–109** [74] bearing unprotected hydroxyl groups



Scheme 13.



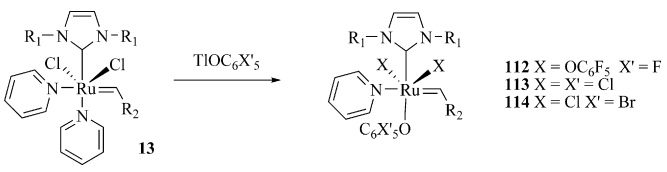
Scheme 14.

in their side chains, which might allow their immobilization on various supports.

All complexes **93–96** and **101** are able to promote cyclization of **22** to **28** (Scheme 5), although the catalytic activity of the homologous series **93–95** shows a significant dependence of reactivity related to the tether length between the alkene entity and the metal core. This effect is likely associated to their different ability to form *in situ* chelate complexes such as **104** and **105**. The analogous malonate derivative **23** is more reluctant toward cyclization catalyzed by **93–96** and **101** [57], while complex **102** is efficient with **24** (Scheme 5) and **110** in the RCM reaction (Scheme 14) [73].

Fogg and co-workers [76] prepared the first halide-free ruthenium catalyst for olefin metathesis, by reacting complex $(py)_2(IMes)(Cl)_2Ru{=}C(H)Ph$ **13** [49] (Scheme 4) with $TlOC_6X_5$ (X = F, Cl, Br) in a selective *trans*-metallation reaction, to afford complexes bis(perfluorophenoxide) **112**, and mono(aryloxides) **113** (X = Cl) and **114** (X = Br) because of the ligand bulk (Scheme 15) [77].

Catalysts **112–114** show high activity at low catalyst loading for ring-closing of diethyl diallylmalonate **25** (Scheme 5) and **67** (Scheme 10) with a 100% yield in only 15 min [77]. RCM of ene-yne **54** (Scheme 10) is facile, even at catalyst loadings an order of magnitude lower than those reported for **43** or **44**. The aryloxide catalysts have high affinity for silica, enabling



Scheme 15.

their efficient removal in a simple column filtration, without any incubation with charcoal, lead or phosphine [77].

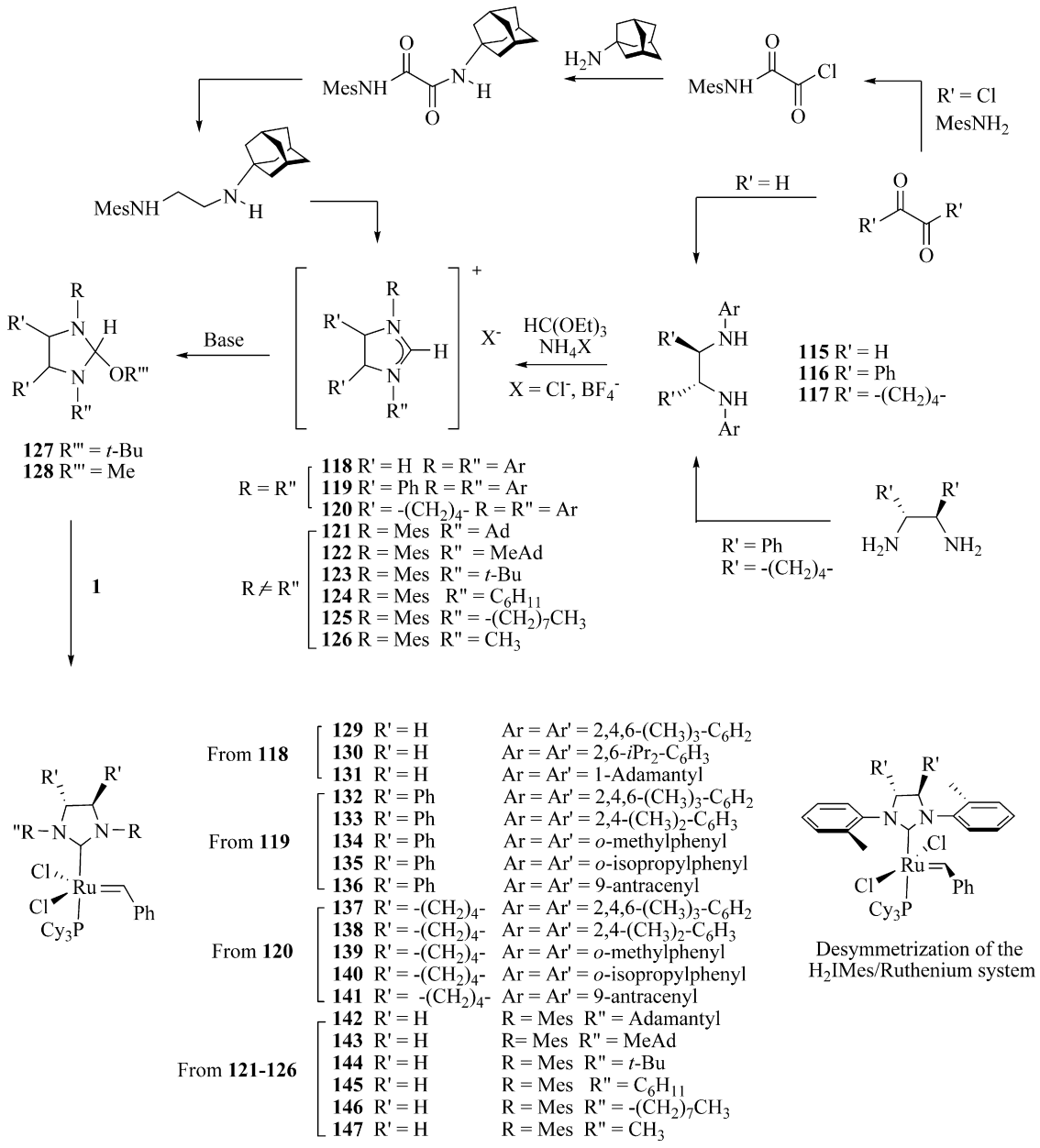
6. Ruthenium carbene complexes bearing one saturated nucleophilic imidazolin-2-ylidene ligand (type 4)

6.1. Symmetrically substituted NHC entities (R = R′)

To increase the utility of the ruthenium family of complexes by increasing their catalytic activity, Grubbs and coworkers [31,59,78–80] prepared ruthenium-based complexes coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (H_2IMes). Due to the lack of carbene stabilization, resulting from the absence of π-interactions, these saturated imidazole ligands are more basic than their unsaturated analogues. The stronger basicity of these ligands should in turn translate into an increased catalytic activity [68].

The ethane-1,2-diamines **115** [81] (R′ = H), and 1,2-disubstituted ethane-1,2-diamines **116** [82] (R′ = Ph) and **117** [82] (R′ = alkyl) were converted into the corresponding imidazolium salts **118–120** by treatment with triethylorthoformate in the presence of ammonium tetrafluoroborate. All attempts to deprotonate **118–120** by a metal hydride to generate the free carbene to be coupled with the benzylidene ruthenium complex **1** failed. The alternative approach consisted in the protection of carbene as 2-alkoxy-4,5-dihydroimidazoles **127–128**; the free carbene, extremely air and moisture sensitive, can be generated *in situ* in the presence of potassium *tert*-butoxide [80] (*t*-BuOK) or potassium *tert*-amylate [55] [$CH_3(CH_2)_3COK$] and directly trapped by complex **1**, by heating to 60–80 °C, to afford ruthenium complexes **129–141** (Scheme 16).

When replaced by mono-*o*-substituted aryl groups, the mesityl substituents of **132** and **137**, afford complexes **134**, **135** and **139**, **140** respectively. The desymmetrization of the H_2IMes ligand was performed in the development of chiral ruthenium metathesis catalysts [79]. A steric effect was expected to more effectively transfer the stereochemistry of the ligand close to the metal center by placing the *o*-substitutents of the aryl group in an *anti* arrangement to the substitutents on the imidazole ring.



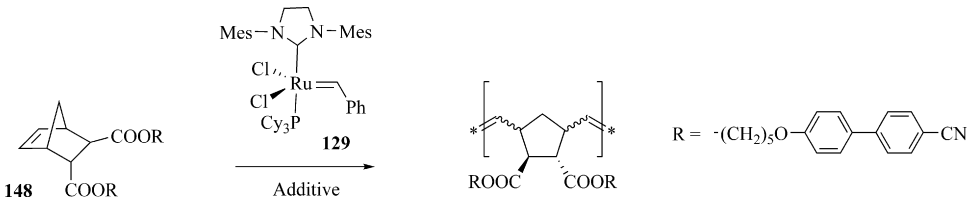
Scheme 16.

The RCM reaction of complexes **129** and **137** produces a quantitative yield for the cyclization of diethyl diallylmalonate **25**, comparable to **1**. In the case of 2-substituted α,ω-dienes, the increased ring-closing metathesis activity is evident: compound **24** (Scheme 5) is converted in a quantitative within minutes into the corresponding tri-substituted cycloolefin **30** using complexes **129** and **137**, with a quantitative yield. Complex **1** in the same reaction conditions afforded only a 20% conversion [31]. A more dramatic illustration of the RCM activity of complexes **129** and **137** is the quantitative conversion of compounds **23** and **26** into the corresponding tetra- and tri-substituted cyclolefins **29** and **32** (Scheme 15), while complex **1** completely failed to promote the cyclization [31]. The 2,6-di-isopropylphenyl-substituted complex **130** diplays considerably superior activity than **129** for the metathesis of terminal olefins [83].

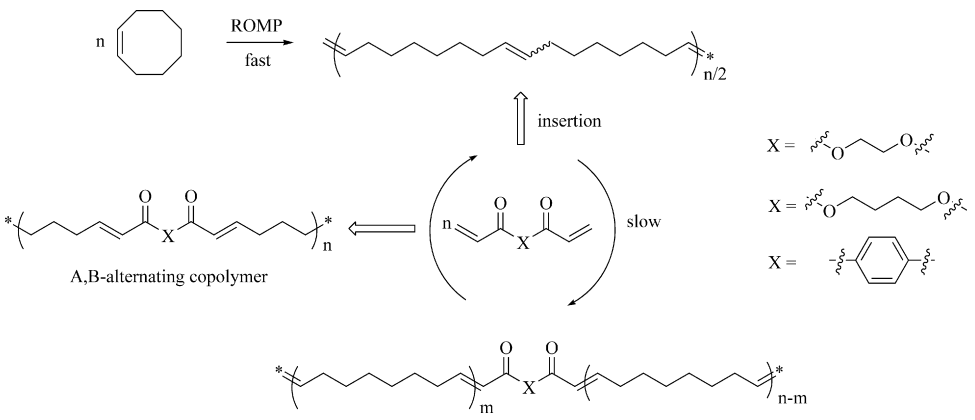
Complex **129** was used also as initiator for the polymerization of (±)-*exo,endo*-bis{5-[(4′-cyanobiphenyl-4-yl)oxy]pentyl}bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **148** [84] in the presence of additives such as pyridine or acetonitrile (Scheme 17).

Complex **129** was also used in the high-yielding synthesis of A,B-alternating copolymers by ring-opening-insertion-metathesis polymerization [85] (ROIMP), where the ROMP of the cycloalkene initially produces an unsaturated polymer scaffold to which subsequent insertion of the diacrylate produces the final A,B-alternating structure (Scheme 18). A 1:1 mixture of 1,4-butanediol diacrylate and cyclooctene gave a copolymer with up to 99% A,B-alternation.

Catalysts **132**, **134**, **135**, **137**, **139** and **140** were used for enantioselective desymmetrization of triene **149** to dihydrofurans



Scheme 17.



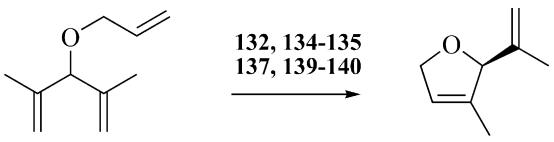
Scheme 18. Proposed mechanism for ROIMP [85].

150 [79], with higher enantioselectivity for those prepared from (1*R*,2*R*)-diphenylethylenediamine (**132**, **134–135**, up to 23% ee) than those prepared from (1*R*,2*R*)-1,2-diaminocyclohexane (**137**, **139–140**, less than 9% ee), more particularly when the mesityl groups (**132**, 15% ee) were replaced by *o*-methyl- (**134**, 23% ee) or *o*-isopropylaryl groups (**135**, 23% ee) (Scheme 19).

The 4,5-dihydroimidazol-2-ylidene-substituted ruthenium-based complexes extend the potential of the ruthenium family complexes. Di-, tri- and tetra-substituted cycloolefins can be prepared in moderate to excellent yields. Moreover, the catalyst loading is two orders of magnitude lower than that for parent complex **1** (approximately 0.05 mol%) and tolerates functional groups such as nitriles or amines, known to poison complex **1** in ROMP reactions [84].

6.2. Unsymmetrically substituted NHC entities ($R \neq R'$)

Replacement of the currently ubiquitous mesityl-substituted NHC ligand with a 1-adamantyl-substituted one afforded complex **142** (Scheme 16) [78]. The mixed mesityl/1-adamantyl NHC ligand 1-(1-adamantyl)-3-mesityl-4,5-dihydroimidazol-2-ylidene (H_2IAdMes) (rapidly generated *in situ* from **121** and potassium *tert*-pentoxide) was added to a solution of **1** (Scheme 16) to afford complex (PCy_3)-(H_2IAdMes)(Cl_2)Ru=CHPh **142** [78].

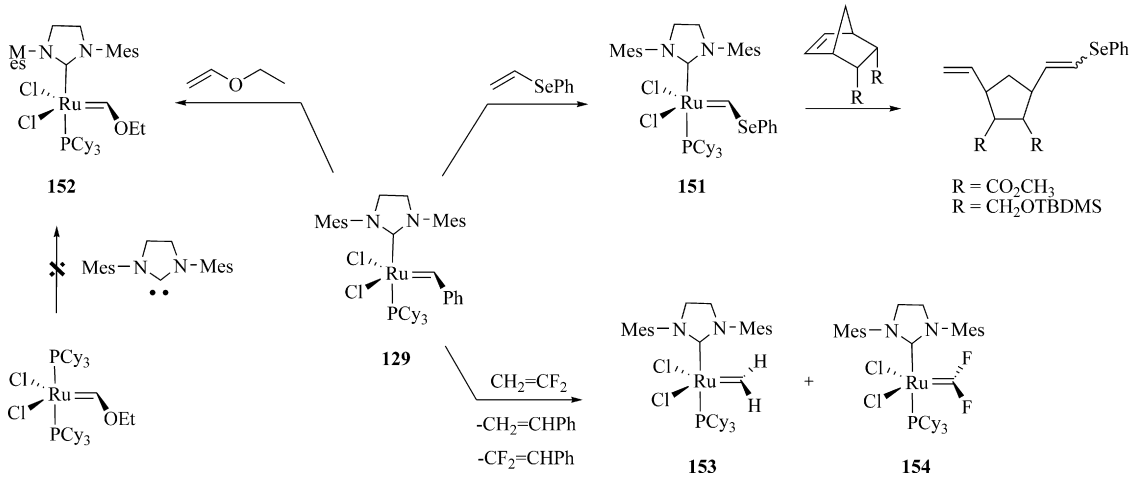


149 (*S*)-**150**

Scheme 19. Enantioselective desymmetrization of triene **149**.

The metathesis activity is very limited, considerably lower than the parent complex **1**. Indeed, **142** was unable to initiate the metathesis of 1-octene in the absence of the phosphine scavenger (CuCl), and even in the presence of CuCl, very low turnover numbers could be obtained.

The mesityl group, being flat, is bulky in only two dimensions; the adamantyl is bulky in three dimensions. The extra bulkiness might induce more rapid dissociation of the phosphine ligand, an essential step for the initiation of the 'precatalyst' to the four coordinate 14-electron metathesis active species [37], and might also provide greater shielding of the metal center. The aliphatic adamantyl group is more electron-donating than the aromatic mesityl, which should make adamantyl-substituted NHC's better σ-donors than the mesityl analogues [78]. It seems that the steric hindrance of the *trans* position to the benzylidene group provided by the adamantyl substituents is the most convincing explanation for the observed decrease in metathesis activity of **142**, compared to closely related catalysts [78]. Single crystal X-ray analysis of complex **145** [86] (Scheme 16) shows intramolecular π–π stacking between the benzylidene carbene unit and the *N*-mesityl substituent on the NHC residue. The same structural element has been observed for complexes **143–144**, and **146–147** [86], originated respectively from **122–123**, and **125–126** in the presence of catalyst **1**. With the exception of catalyst **144**, catalysts **143**, and **145–147** were found to be superior to the parent complex **1** for the ROMP of cycloocta-l,5-diene, furthermore, the less hindered complex **147** is the most active in this family for RCM of diethylallylmalonate **25**. This fact clearly demonstrates that modification of the NHC ligand can induce substantial changes in the reactivity pattern



Scheme 20.

of the corresponding catalyst and that systematic variation of the *N*-substituents may eventually allow fine-tuning.

6.3. Ruthenium Fisher-type complex (PCy_3)(H_2IMes)(Cl_2)-Ru=C(H)ER

A series of well-defined carbene complexes (PCy_3)-(H_2IMes)(Cl)$_2$Ru=C(H)ER (**151**, **152**) bearing electron-rich (ER) olefins have been prepared from **129**, by Ozawa and co-workers [62] (**151**, ER=SePh), and Louie and Grubbs [63] (**152**, ER=OEt) by addition of vinyl phenyl selenide and vinyl ethyl ether, respectively (Scheme 20).

The successful metathesis of 1,1-difluoroethylene with ruthenium catalyst **129** affords the corresponding methylidene [(H_2IMes)(PCy_3)(Cl_2)Ru=CH_2] [37] **153** and difluorocarbene [(H_2IMes)(PCy_3)(Cl_2)Ru=CF_2] [87] **154** complexes (Scheme 20).

Catalyst **151** promotes ring-opening/cross-metathesis [62] (ROCM) reactions of *endo*-5,6-disubstituted norbornenes, with high yields (Scheme 20). Complex **152** initiates: (i) the ROMP of norbornene and norbornene derivatives at room temperature, affording quantitative yield of polymers; (ii) ROMP reaction of 1,5-cyclooctadiene within only 2 h at 60 °C, with almost quantitative yield; (iii) the RCM reaction of diethyl diallylmalonate **25** within 4 h at 60 °C, with quantitative yield. As expected, complex **152**, containing an imidazolylidene ligand was more active than its unsaturated analogue **69** (Scheme 11). The activity of **154** in ROMP reaction of 1,5-cyclooctadiene is low (yield: 9% at room temperature) with respect to catalyst **129** yield: 100% at room temperature). Higher temperatures and additives to promote phosphane dissociation improve the activity of **154** to afford 72% yield [87].

6.4. Ruthenium complex type [(p-cymene)(H_2IMes)-Ru(Cl_2)] **155** [88,89]

A three-component combination of the ruthenium(II) source [(*p*-cymene)$RuCl_2$]$_2$, 1,3-bis(mesityl)-4,5-dihydroimidazolium chloride (H_2IMes) and Cs_2CO_3 as a base produces *in situ* a catalytic system **155** for the intramolecular metathesis of O–Si containing enynes under mild conditions [89].

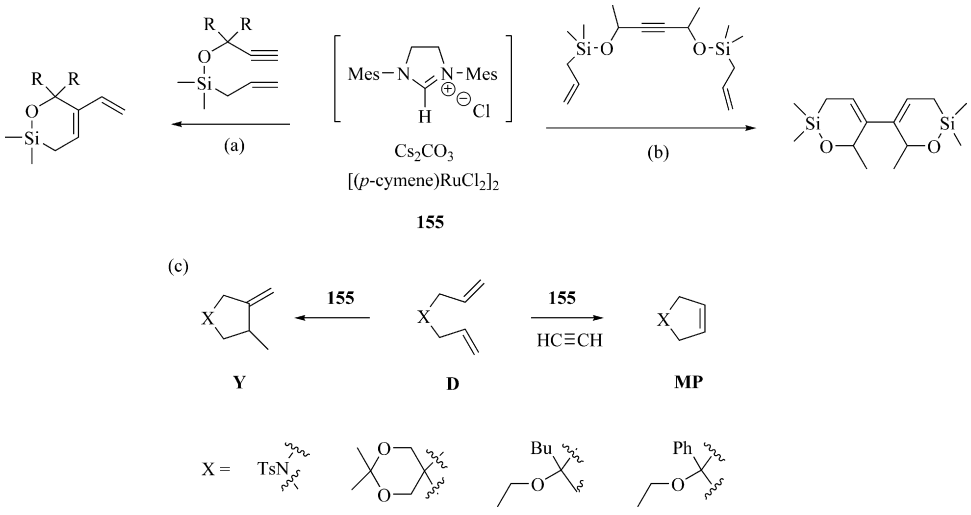
The transformation was extended to other silylated enynes containing a terminal triple bond and various alkyl and aryl substitutents, with a complete transformation of substrates into 1,3-diene six-membered siloxanes. This catalytic system is also efficient for disubstituted C–C triple bonds containing enynes [Scheme 21(a) and (b)].

The behavior of catalytic system **155** is dichotomous: in the presence of a diene **D**, it spontaneously promotes cycloisomerization to methylene five-membered cyclic ylidenes **Y**, whereas, in the presence of acetylene the activity of catalyst **155** is oriented toward the exclusive formation of the RCM metathesis product (**MP**), with loss of ethylene. Thus, acetylene can tune the activity of catalytic system **155** and modify its standard catalytic role [88] [Scheme 21(c)].

6.5. η^6-Mesityl,η^1-imidazolinylidene–carbene–ruthenium(II) complexes [90]

Reaction of electron-rich carbene-precursor olefins containing at least one 2,4,6-trimethylbenzyl group (R = CH_2Mes) linked to a nitrogen atom, with [$RuCl_2$(arene)]$_2$ (arene = *p*-cymene, hexamethylbenzene) selectively leads to two types of complexes. The cleavage of the chloride bridges occurs first to yield the expected (carbene)(arene)ruthenium(II) complex **158**. Then, a further arene displacement reaction takes place to yield the chelated η^6-arene,η^1-carbene–rutheniun(II) complexes **159** and **160**. An analogous η^6-arene,η^1-carbene complex with a benzimidazole frame **162** was isolated from an *in situ* reaction between [(*p*-cymene)$RuCl_2$]$_2$ **74**, the corresponding benzimidazolium salt **161** and cesium carbonate. By reaction with AgOTf and propargylic alcohol, compounds **159**, **160** and **162** were transformed into the corresponding ruthenium allenylidene intermediates **163**–**165** [90] (Scheme 22).

In situ generated intermediates **163**–**165** were found to be selective catalysts for RCM or cycloisomerization reaction of 1,6-dienes. Catalytic reactions proceed with good efficiency and selectivity under relatively mild conditions. However, the



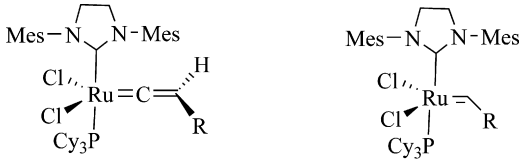
Scheme 21.

chemoselectivity of the reaction dramatically depends on both diene and solvent nature.

Like **80** (Scheme 12), other ruthenium vinylidene complexes can be prepared from commercially available terminal alkynes and ruthenium sources such as the dimer $[RuCl_2(p\text{-cymene})]_2$ **74**, in presence of PCy_3 [71]. Reaction of these vinylidene complexes with the carbene ligand H_2IMes produces a clean mono-substitution for complexes **166–168** [91] (Fig. 2). Low-strained and high-strained cyclic monomers were converted in excellent yields using the three complexes although significant differences in their behavior were observed. Catayst **167** is the most active system toward ROMP because quantitative conversions are reached from cyclooctene. Conversions for **166** and **168** are, respectively 54% and 90%. Quantitative conversions with catalyst **167** are also obtained from norbornene, ethyl-, butyl-, hexyl-, decyl-, ethylidene-, triethoxysilyl-norbornene. The RCM of diethyl diallylmalonate, 1,7-octadiene and diallylether yields quantitatively the cyclic product using catalysts **167** and **168**, with a good activity on tri- and tetra-substituted double bonds.

6.6. Linear alkylcarbene complexes [92]

Alkyl carbene second-generation ruthenium olefin metathesis catalysts are synthesized by reaction of $(PCy_3)(H_2Mes)(Cl_2)Ru{=}C(H)Ph$ (**129**) with 2-butene gas and *trans*-2-hexene to afford $(PCy_3)(H_2Mes)(Cl_2)Ru{=}C(H)Me$ [92] (**169**) and



166 R = Ph
167 R = $Si(CH_3)_3$
118 R = *t*-Bu

169 R = Me
170 R = Et

Fig. 2. Vinylidene and linear alkyl carbene complexes.

$(PCy_3)(H_2Mes)(Cl_2)Ru{=}C(H)Et$ [92] (**170**) (Fig. 2). These complexes were found to active for ROMP of cyclooctene and for acyclic diene metathesis (ADMET) polymerization of 1,9-decadiene, resulting in polymers with well-defined vinyl end groups [1].

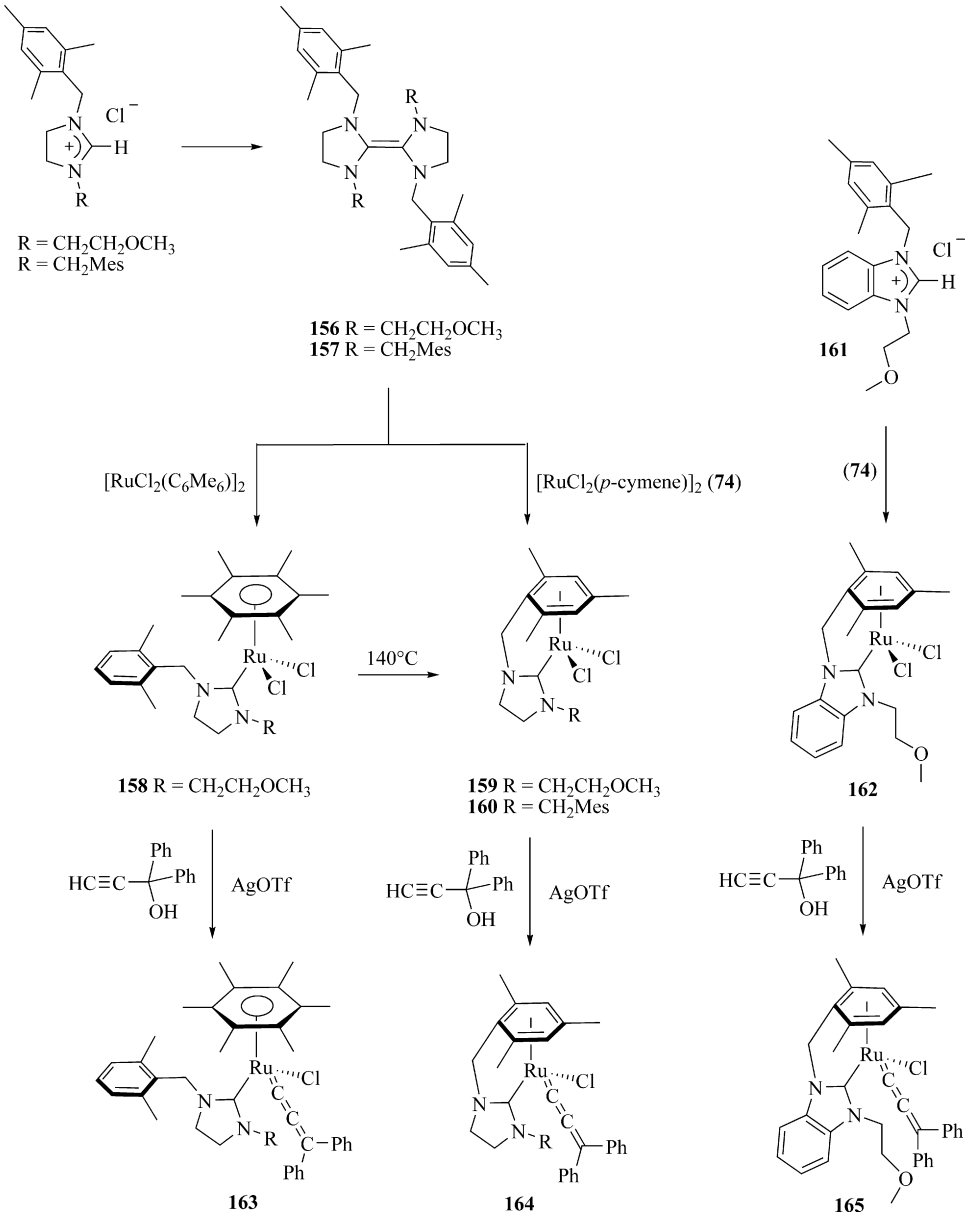
6.7. Ruthenium indenylidene complex bearing a bidentate Schiff-base [93]

The mixed-ligand ruthenium-(3-phenyl-1-indenylidene) Schiff base complex **171** was synthesized in two steps: the addition of the parent Schiff base **172** [94] to **82** [65] afforded **173** [94]. The reaction of **173** with H_2Mes ligand [95] according to well-established procedures [67] afforded complex **171** [93] (Scheme 23).

Both complexes **173** and **171** exhibit catalytic activity for the ROMP of cyclopentene and cyclooctene, with a quantitative conversion of cyclooctane in few minutes at room temperature, **171** having more pronounced effect. Moreover, in contrast to the second-generation Grubbs-type catalysts, **171** give access to well-controlled high-molecular weight polymers [93].

6.8. $(H_2IMes)(Cl_2)(XC_5H_4N)_2Ru{=}C(H)R$: a precursor for new ruthenium catalysts

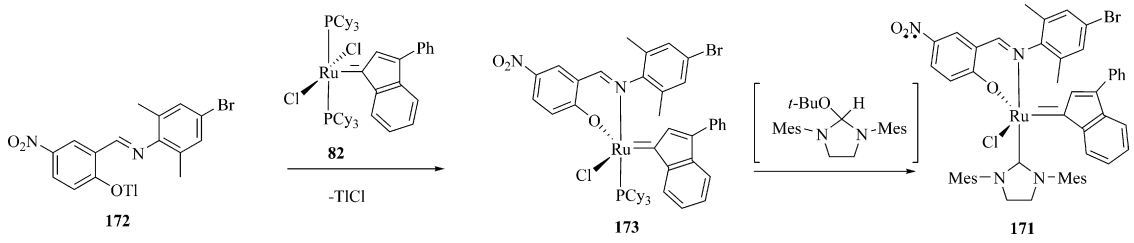
An effort to modify the ligand environment of **129** or **174** to produce new metathesis catalysts with improved stability, activity, selectivity and functional group tolerance $(H_2IMes)(Cl_2)(3\text{-}XC_5H_4N)_2Ru{=}C(H)Ph$ [(**175**) [37,45,50,96,97] X = H; (**176**) [44,92] X = 3-Br; (**177**) [44] X = 4-Ph] $(H_2IMes)(Cl_2)(3\text{-}XC_5H_4N)_2Ru{=}C(H)C(H){=}C(CH_3)_2$ [(**178**) [98] X = H; (**179**) [98] X = 3-Br] and $(H_2IMes)(Cl_2)(3\text{-}BrC_5H_4N)_2Ru{=}C(H)CH_3$ (**180**) [92] were synthesized. They are versatile starting materials, containing labile pyridine and chloride ligands. Catalysts **174**, **181–187** [45,50] and **188** [98] are synthesized by adding the appropriate phosphine to the solution of bis(pyridine) complexes (Scheme 24).



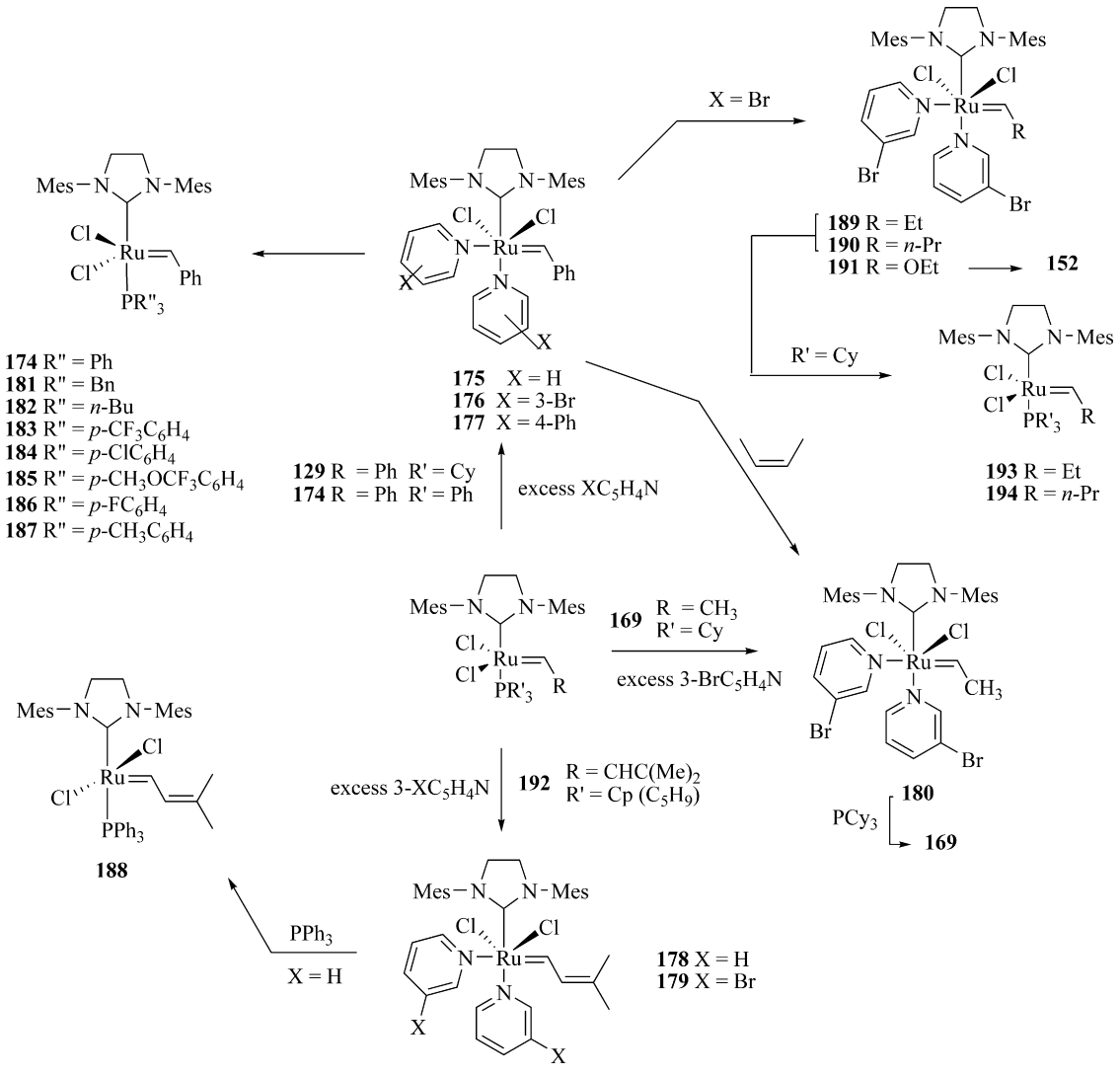
Scheme 22.

Reaction of **176** with *cis*-butene affords ethylidene **180** [99] the propylidene and butylidene complexes **189** and **190** being prepared in a similar fashion by using respectively *trans*-3-hexene and *trans*-4-octene [99]. These complexes are not very stable in solution, but when treated with PCy_3, they rapidly react to afford the corresponding complexes [99] **169**, **193** and **194** (Scheme 24). In the presence of vinyl ethyl ether, complex **176** affords **191** [99] precursor for the synthesis of ruthenium Fischer-type complex **152** (Scheme 20) obtained by adding PCy_3.

Complex **175** was found to efficiently catalyze the selective CM of 1-hexene and acrylonitrile. High yields were obtained



Scheme 23.



Scheme 24.

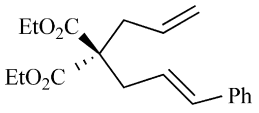
only with high loading of catalyst (10 mol%). Reactions between acrylonitrile with various functionalized olefins, such as allyl alcohols, acrolein, and acrylic acid and ester, were performed in good yields (55–77%), the *Z*-isomer predominating in the mixture of products [96]. In order to prevent the coordination of the cyano group towards the ruthenium carbene intermediates, some Lewis acids as co-catalyst were introduced: Ti(O-*i*-Pr)$_4$ was the best promoter for CM of acrylonitrile, the product was obtained in 60% yield [97].

Complexes **175–177** were compared for their ability to mediate CM between acrylonitrile and allylbenzene. **175** and **177** provided only modest yield of cross-product (26% and 29%, respectively), while the 3-bromopyridine derivative **176** provided a yield of 67%, presumably because dissociation of the electron-deficient 3-bromo-pyridine ligand was extremely rapid and/or because rebinding was slow, both of them contributing to favor turnover conditions [44]. (±)-*Exo,endo*-bis{5-[(4′-cyanobiphenyl-4 - yl)oxy]pentyl}bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**148**) was polymerized with initiator **175** [84] which also promoted the controlled living polymerization for norbornene and 7-oxonorbornene derivatives, not achievable with other catalysts, and producing AB-diblock and ABC-triblock copolymers from sequential addition of monomers [100].

The linear alkyl carbene complexes (H_2IMes)(3-Br$C_5H_4N)_2$-(Cl_2)Ru=C(H)Me (**180**) and (H_2IMes)(3-Br$C_5H_4N)_2$(Cl_2)Ru=C(H)Et (**189**) catalyzes the ROMP of cyclooctene, with a higher catalytic activity **189** compared to that of (H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Me (**169**) [92].

Catalyst (H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Et (**193**) more efficient than (H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Ph (**129**) in the ROMP of dicyclopentadiene [99,101] but is not active in the RCM of diethyl diallylmalonate, compared to **129** which promoted complete conversion. A possible explanation for the lack of catalytic activity is that the faster PCy_3 of **193** leads to a higher PCy_3 concentration and faster deactivation of the propagating methylidene catalyst (H_2IMes)(Cl_2)Ru(=CH_2) [99].

(H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Et (**193**) was used to polymerize 1,9-decadiene at 70 °C under vacuum (ADMET) and the properties of this polyoctenamer were quite similar to those of



195

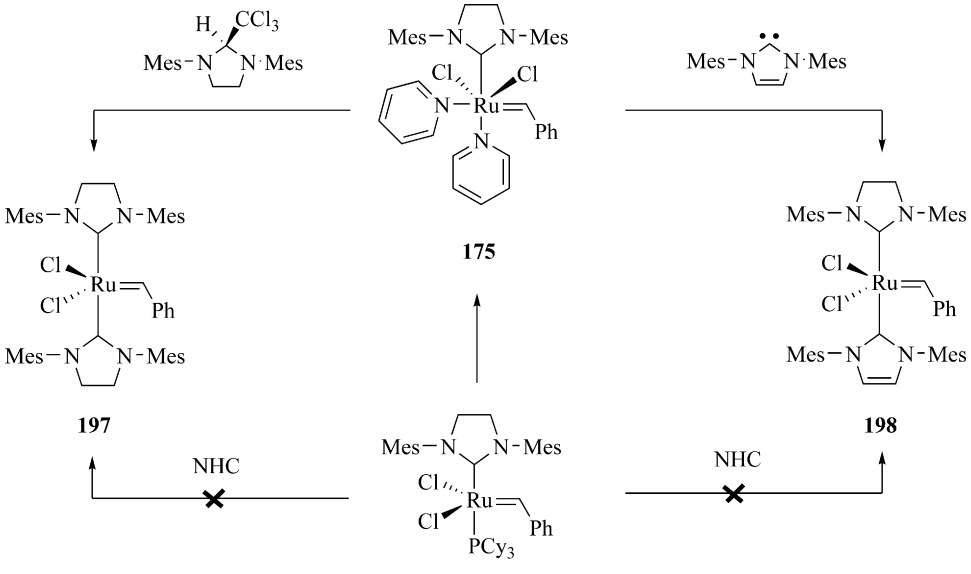
Fig. 3. Diene for RCM.

the one produced with $(H_2IMes)(PCy_3)(Cl_2)Ru{=}C(H)Ph$ (**129**), but a lower molecular weight was obtained [92]. All the aryl phosphines containing ruthenium complexes **174**, **183–187** are more active than **129** in the ROMP of cyclooctadiene. They completely initiate during the course of polymerization (i.e. complete conversion of the starting benzylidene into a new alkylidene), suggesting that loading of aryl-phosphine-based catalyst can be lower with respect to **129** [45]. The rate difference for the RCM of diene **195** (Fig. 3) using **174**, **183–187** compared with **129** is not so dramatic as they are for ROMP suggesting that the ROMP kinetics are primarily affected by phosphine dissociation, whereas the RCM kinetics are also affected by differences in phosphine rebinding. Complexes **174**, **183–187** proved to be more active than **129** for the RCM of diene **195** [45].

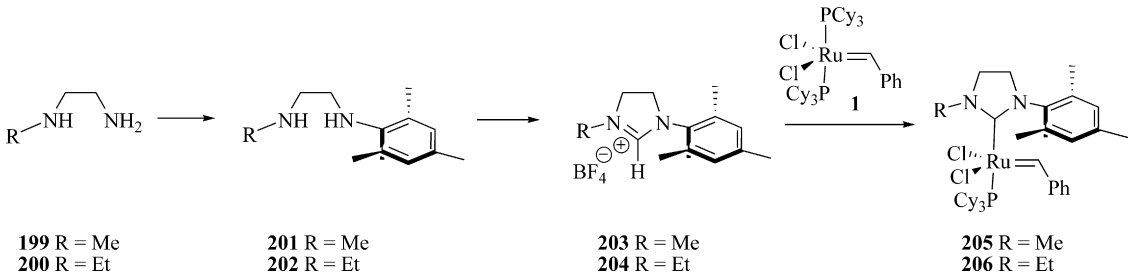
In contrast to the bis-phosphine ruthenium dimethylvinyl carbene complexes, the mixed ligand complex $(H_2IMes)(PPh_3)(Cl_2)Ru{=}C(H){=}C(H)C(CH_3)_2$ (**196**) is a useful catalyst for ADMET of terminal dienes and ROMP of low-strain cyclic monomers as demonstrated by the polymerization of 1,9-decadiene, 1,5-hexadiene, cyclooctene and 1,5-cyclooctadiene. It produces polymers with high *trans*-olefin contents (94%), whereas the PCy_3 complex produces ADMET polymers with lower trans content (80%). **196** is also useful for ROMP of low-strain olefins and produces high molecular weight polyoctenamer. Bis-pyridine, phosphine-free $(H_2IMes)(3\text{-}BrC_5H_4N)_2(Cl_2)Ru{=}C(H){=}C(H)C(CH3)_2$ (**179**) was shown to react rapidly and completely with ethyl vinyl ether, indicating that the poor initiation characteristics of these dimethylvinyl carbene complexes are overcome with pyridine ligation; however, polymerization of 1,5-cyclooctadiene shows that the activity of $(H_2IMes)(3\text{-}BrC_5H_4N)_2(Cl_2)Ru{=}C(H){=}C(H)C(CH_3)_2$ (**179**) is inferior to that of $(H_2IMes)(3\text{-}BrC_5H_4N)_2(Cl_2)Ru{=}C(H)Ph$ (**176**). Despite the incomplete initiation and relatively slow polymerization rate $(H_2IMes)(PCp_3)(Cl_2)Ru{=}C(H){=}C(H)C(CH_3)_2$ (**192**) polymerizes cyclooctene in bulk monomer to form a polymer with higher melting point and crystallinity. In this respect **192** is better [98].

6.9. $(H_2IMes)(Cl_2)(L)_2Ru{=}C(H)Ph$ (L = H_2IMes or IMes) [59]

In the synthesis of catalyst **129**, the monosubstituted $(NHC)(PCy_3)(Cl_2)Ru{=}C(H)R$ is exclusively observed, even when a large NHC excess of is present. The bis-substituted product $(NHC)_2(Cl_2)Ru{=}C(H)R$ can also form as observed when NHC is 1,3-dicyclohexyl-imidazoline-2-ylidene [28]. The phosphine exchange rate decreases dramatically when one of the PCy_3 ligands in $(PCy_3)_2(Cl_2)Ru{=}C(H)Ph$ (**1**) is replaced by an H_2IMes [37]. This slow phosphine exchange rate in **129** may effectively prevent further PCy_3 substitution by the accepted dissociative ligand substitution pathway. Nevertheless, bis-substitution can be achieved by using $(H_2IMes)(C_5H_5N)_2(Cl_2)Ru{=}C(H)Ph$ (**175**) [50] with more labile ligands replacing the tricyclohexylphosphine. Addition of the free IMes carbene to $(H_2IMes)(C_5H_5N)2(Cl_2)Ru{=}C(H)Ph$ (**175**) cleanly provides the mixed H_2IMes–IMes complex $(H_2IMes)(IMes)(Cl_2)Ru{=}C(H)Ph$ (**198**) [59]. Similarly, the reaction of **175** with the chloroform adduct $H_2IMes(H)(CCl_3)$ provides the bis(H_2IMes) complex $(H_2IMes)_2(Cl_2)Ru{=}C(H)Ph$ **197**() [59] (Scheme 25). Complex **192** showed slight activity for RCM of 4,4-dicarboethoxy-2-methyl-1,6-heptadiene at 40 °C to the corresponding 4,4-dicarboethoxy-1-methyl-cyclopentene



Scheme 25.



199 R = Me
200 R = Et

201 R = Me
202 R = Et

203 R = Me
204 R = Et

205 R = Me
206 R = Et

Scheme 26.

product, and no activity in the ROMP of cyclooctadiene was observed [59].

6.10. Ruthenium catalysts with unsymmetrical N-heterocyclic carbene ligands

The replacement of one mesityl ring with a more electron donating alkyl group led to enhanced σ-donor properties. Increased σ-donation has was suggested to explain the higher activity of second-generation complexes compared to the first-generation [1].

The synthesis of unsymmetrical NHC ligands was easily accomplished through Buchwald–Hartwig coupling of commercially available monosubstituted diamines **199**, **200** and 2-bromomesitylene [102] followed by cyclization, affording in high yields **203**, **204** as tetrafluoroborate salts.

Complexes **205**, **206** were formed by reaction of $(PCy_3)_2(Cl_2)Ru{=}C(H)Ph$ (**1**) with the free carbene generated *in situ* from **203**, **204** [103] (Scheme 26).

The catalytic activity of **205** in RCM reactions was tested using diallyltosylamide, with a 56% conversion, compared to 50% conversion with **129**. **205** gave significantly different *E*:*Z* ratio in CM reactions and improved selectivity in diasteroselective RCM reactions, since unsymmetrical ligands alter the steric environment of key metathesis intermediates. Some examples are reported in Scheme 27.

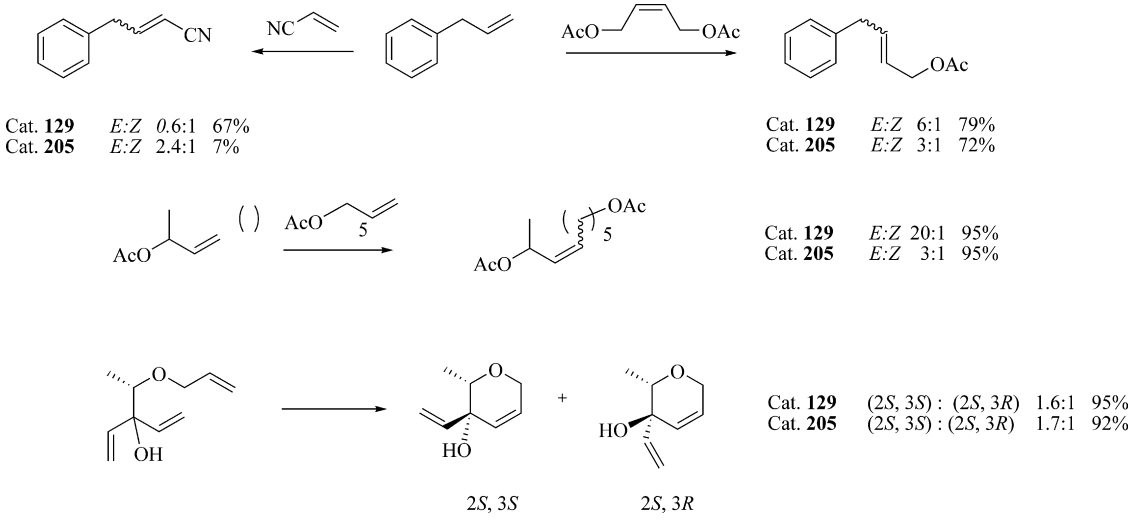
7. Ruthenium complexes with a bidentate carbene moiety: Hoveyda–Grubbs' catalysts (type 7)

7.1. Hoveyda–Grubbs catalysts: $(H_2IMes)(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ 7 and tetramer 208

Hoveyda and co-workers have developed catalysts $(PCy_3)_2(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ (**6**) and $(H_2IMes)(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ (**7**) (Fig. 1), bearing *O*-chelating benzylidene moieties and exhibiting extraordinary stability against water and oxygen. They promote olefin metathesis by a unique 'release-return' (boomerang) mechanism, allowing efficient metal recovery without significant loss of activity [33,104,105].

Two different synthetic strategies were used for the synthesis of the styrenyl complex $(H_2IMes)(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ (**7**): depending on the substrate used either $(H_2IMes)(PCy_3)(Cl_2)Ru{=}C(H)Ph$ [34] (**129**) or $(PCy_3)_2(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ [48] (**6**) (Scheme 28).

Formation of the intermediate $(H_2IMes)(PCy_3)(Cl_2)Ru{=}CH(o\text{-}iPrOC_6H_4)$ (**207**) from **6** suggests that the H_2IMes ligand replaces the isopropoxygroup which in turn replaces the phophine by prolonged stirring at room temperature, to afford **7**. **7** is an effective catalyst for the RCM of dienes, hetero- (allylic alcohols and acetates) and carbocycles. Tri-substituted alkenes were obtained from the corresponding dienes in the presence of 5 mol% catalyst at room temperature; the catalyst was recovered after simple silica gel column chromatography, and used



Cat. **129** *E*:*Z* 0.6:1 67%
Cat. **205** *E*:*Z* 2.4:1 7%

Cat. **129** *E*:*Z* 6:1 79%
Cat. **205** *E*:*Z* 3:1 72%

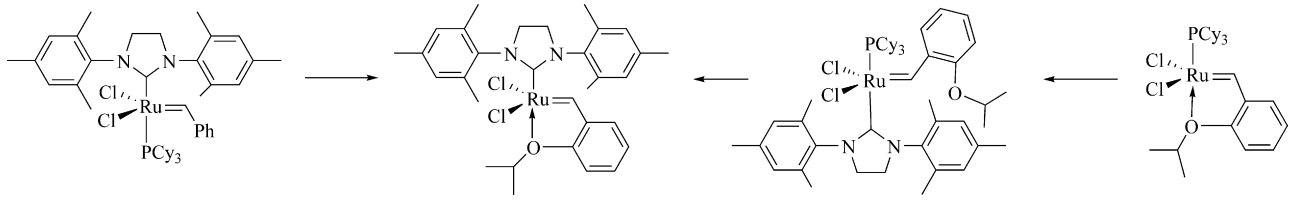
Cat. **129** *E*:*Z* 20:1 95%
Cat. **205** *E*:*Z* 3:1 95%

2*S*, 3*S*

2*S*, 3*R*

Cat. **129** (2*S*, 3*S*) : (2*S*, 3*R*) 1.6:1 95%
Cat. **205** (2*S*, 3*S*) : (2*S*, 3*R*) 1.7:1 92%

Scheme 27.



Scheme 28.

in subsequent metathesis reactions with equal efficiency. All the reactions proceeded with a conversion up to 98% and total recovery of the catalyst (Scheme 29) [34].

Catalyst **7** is an efficient catalyst in ROM/RCM [34] and ROM/CM [34] processes but separation of the desired products from the recovered catalyst was unsuccessful [Scheme 29(c) and (d)].

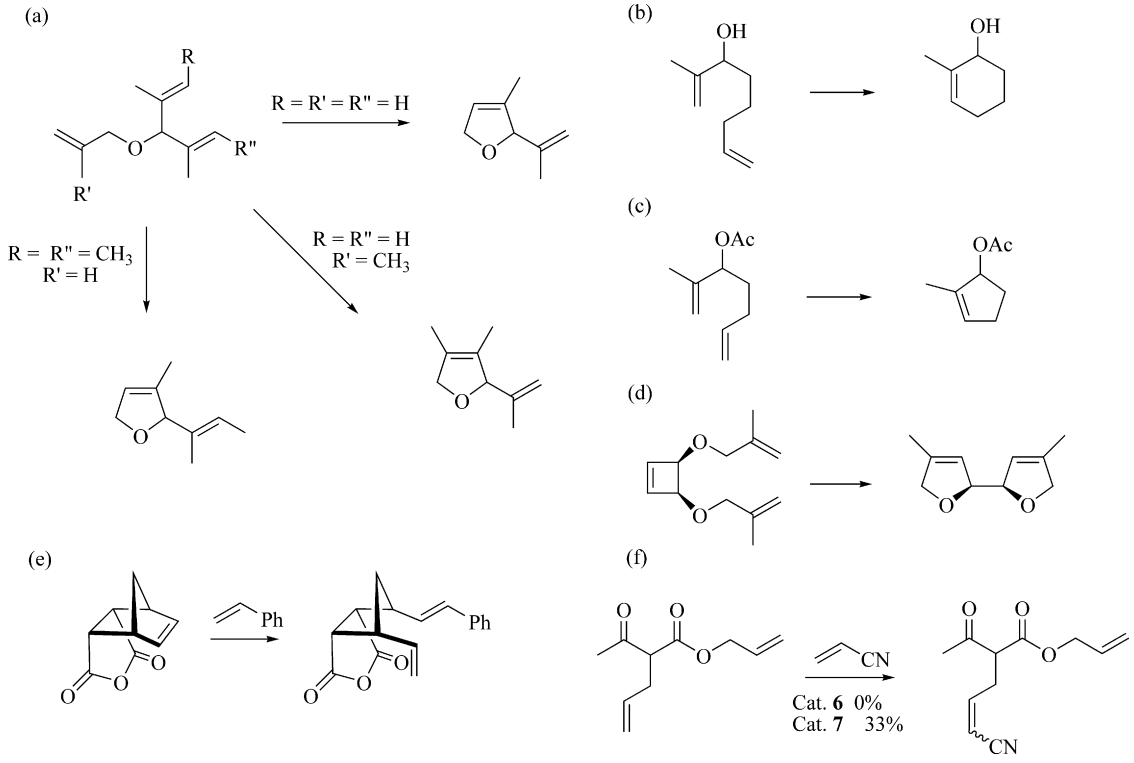
To separate the catalyst from the reaction products, macromolecular ruthenium tetramers were designed. The active Ru–carbene leaves the ligation site and returns to the macromolecule more efficiently because the terminal sites within a soluble structure are more exposed and accessible [34].

The key feature for the synthesis of **208** (Scheme 30) includes the attachment of the vinyl group through a Pd-catalyzed Stille coupling (**211**) [106] and preparation of the tetramer backbone by Pt-catalyzed hydrosilylation/alkylation/hydroboration sequence (**212–213–214**). Coupling of **214** with **211**, followed by incorporation of the ruthenium center through treatment with **129**, affords the tetramer **208** [34] (Scheme 30).

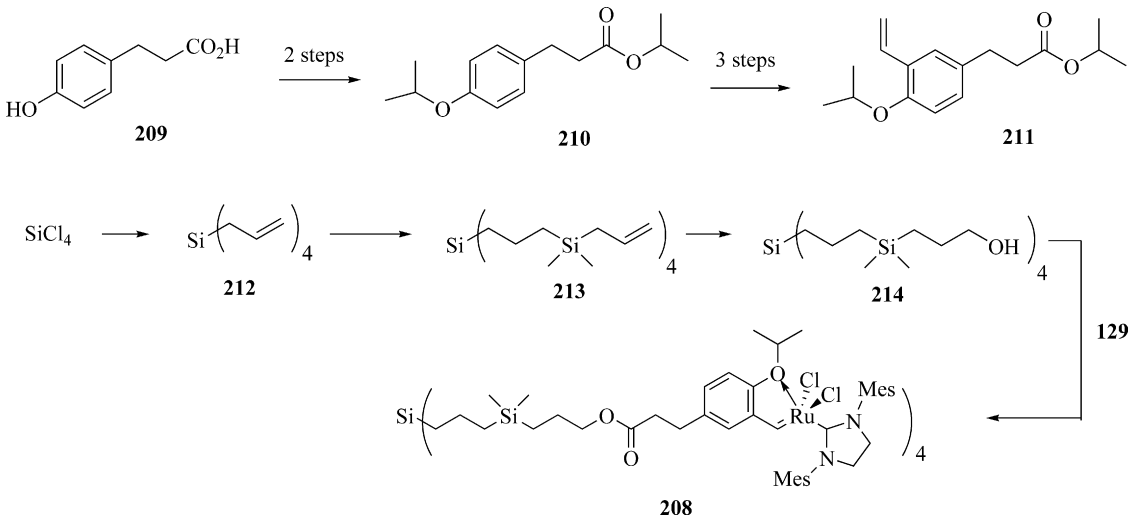
Unlike **6**, but similarly to **7**, tetrameric **208** efficiently promoted the formation of tri-substituted allylic alcohol [Scheme 29(b)]; in addition to the desired product (78%), the tetramer was recovered in 90% yield after silica gel column chromatography, with only 8% loss in Ru loading. Moreover, like **7**, tetramer **208** effectively catalyzed tandem ROM/RCM of cyclobutene derivatives [Scheme 29(d)] with 94% yield and ROM/CM reactions of bicycloheptene derivatives [Scheme 29(e)] with 98% yield. In each case, owing to its high polarity, isolation of tetramer was a straightforward operation, retaining the high catalytic activity of monomeric **129**.

7.2. BINOL- and biphenyl-based ruthenium alkylidene catalyst

The difference in reactivity associated with the use of catalysts **6** and **7** can be explained with a stabilizing interaction between the isopropoxy group and the metal center during metathesis. The replacement of the isopropoxystyrene ligand in **7** by BINOL-based styrene **217** results in a chiral chelating isopropoxystyrene complex (**218**) [107]. Ligand **217** was prepared from commercially available 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) **215** by treatment with *i*PrBr



Scheme 29.



Scheme 30.

followed by monoformylation and Wittig olefination. Complex **218** [107] was then obtained by reaction of **217** with (H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Ph (**129**) (Scheme 31).

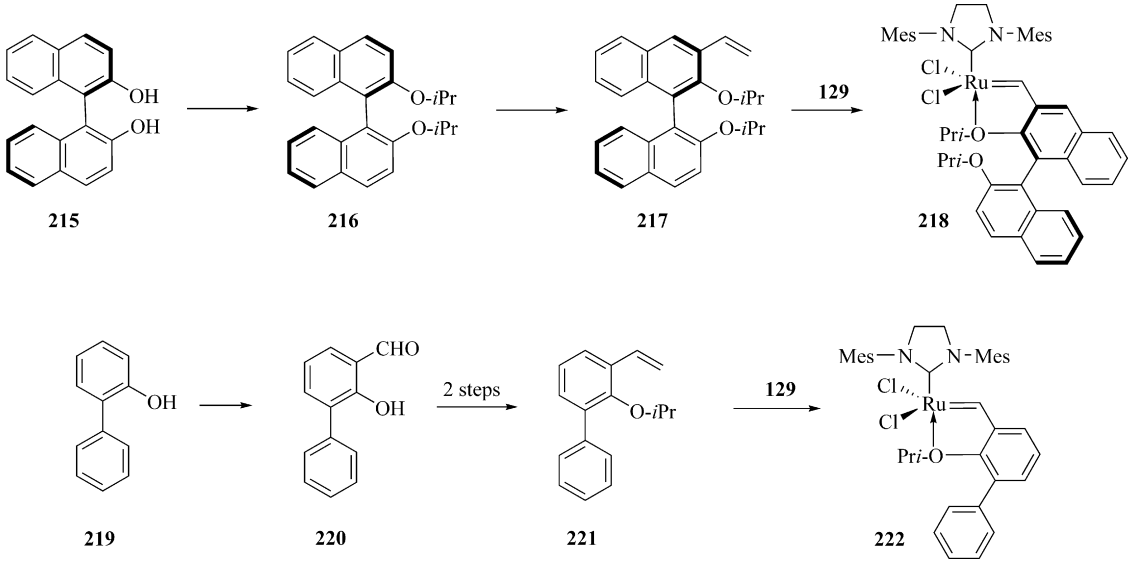
According to the same sequence of reactions described for the synthesis of catalyst **218**, a biphenyl-based complex **222** [108] was synthesized from 2-hydroxyphenyl-3-carbaldehyde (**220**) (Scheme 31).

Data for RCM reaction of diallyltosylamide **21** showed that catalyst **218** exhibits a drastically higher activity than **129** or **7**, and excellent stability to air. The superiority of complex **218** compared to complex **129** in term of turnover frequencies is evident in seven- or eight-membered ring formation [Scheme 32(a) and (b)] [107], known to be difficult, and in CM reaction, even with electron-deficient olefins [Scheme 32(c) and (d)] [107]. The increase in steric bulk improves the leaving group ability of the ligand, thus facilitating formation of the catalytically active 14-electron species, and suppressing reassociation to the metal center, which deactivates the catalyst.

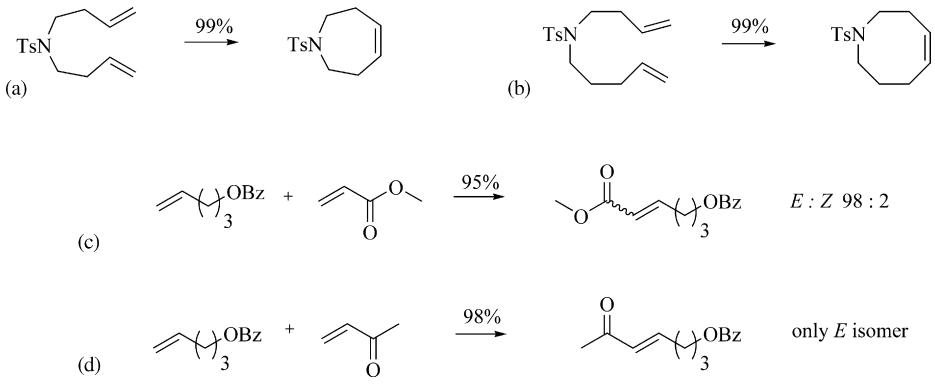
Catalyst **222** exhibits higher activity than **129** in RCM, CM and ROMP reactions, under identical conditions [108]. Oxanorbornene derivatives, in the presence of allyltrimethylsilane and only 0.005 mol% of catalyst **222** afford high yields of the ring-opened product (Scheme 33).

7.3. Nitro-substituted Hoveyda–Grubbs catalysts

Catalysts related to **7** can be significantly improved by changing not only the steric but also the electronic character of the Ru-chelating isopropoxy fragment. Introduction of a strong electron-withdrawing group at the 2-isopropoxy styrene ring of (H_2IMes)(Cl_2)Ru=CH(*o*-*i*PrOC_6H_4) (**7**), leads to complexes **229**, **230** and **234** [109,110], prepared like **218** and **222** from commercially available **223**, **224** and **231**, respectively. An alternative route to **229** involves the treatment of **83**, generated *in situ*, with styrene derivative **167a** (Scheme 30). Complex **165a** is equally stable but dramatically more reactive than the parent



Scheme 31.



Scheme 32.

catalyst **7**. The enhancement of reactivity is somewhat lower than that observed for sterically activated **222**.

Decrease in the electron density at the oxygen atom of the isopropoxy fragment reduces its chelating ability, thus facilitating formation of the catalytically active 14-electron Ru–carbene species, and suppressing reassociation to the metal center. This mode of catalyst activation is, in fact, similar to that of **218** and **222**, in which the increase in bulkiness improves the leaving-group ability of the styrene 'ligand' (Scheme 34).

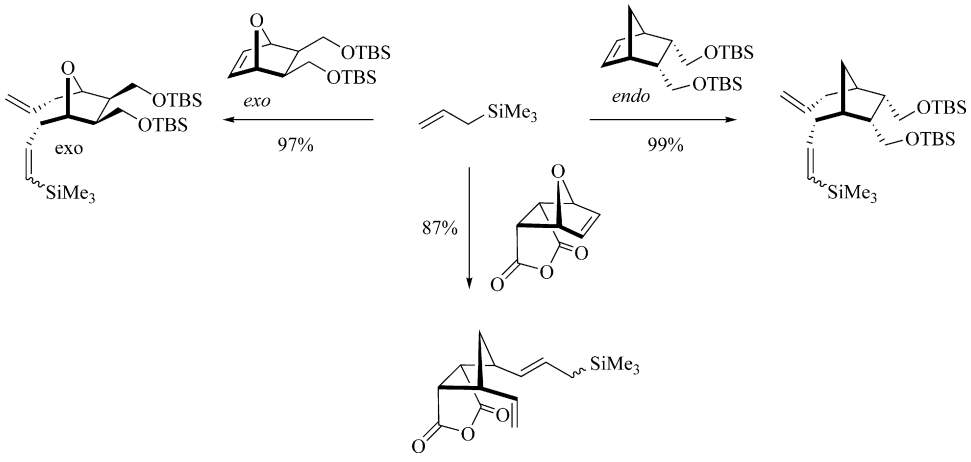
The RCM and enyne variant of the metathesis reaction could be performed efficiently at 0 °C [Scheme 35(a)]; various degrees of substitution of the double bond are tolerated, and even tri-substituted olefins can be synthesized in good yields at room temperature [Scheme 35(b)]; the CM reaction of terminal alkenes with internal olefins and α,β-unsaturated compounds can also be performed at room temperature [Scheme 35(c)]; the CM reaction of phenyl vinyl sulfone [Scheme 35(d)] and acrylonitrile [Scheme 35(e)], showed that complex **229** was superior to **129** and **7**: higher conversions of the substrates were realized at lower temperature and with lower loading of catalyst [110].

7.4. Other electron-withdrawing and electron-donating substituents on Hoveyda–Grubbs catalysts

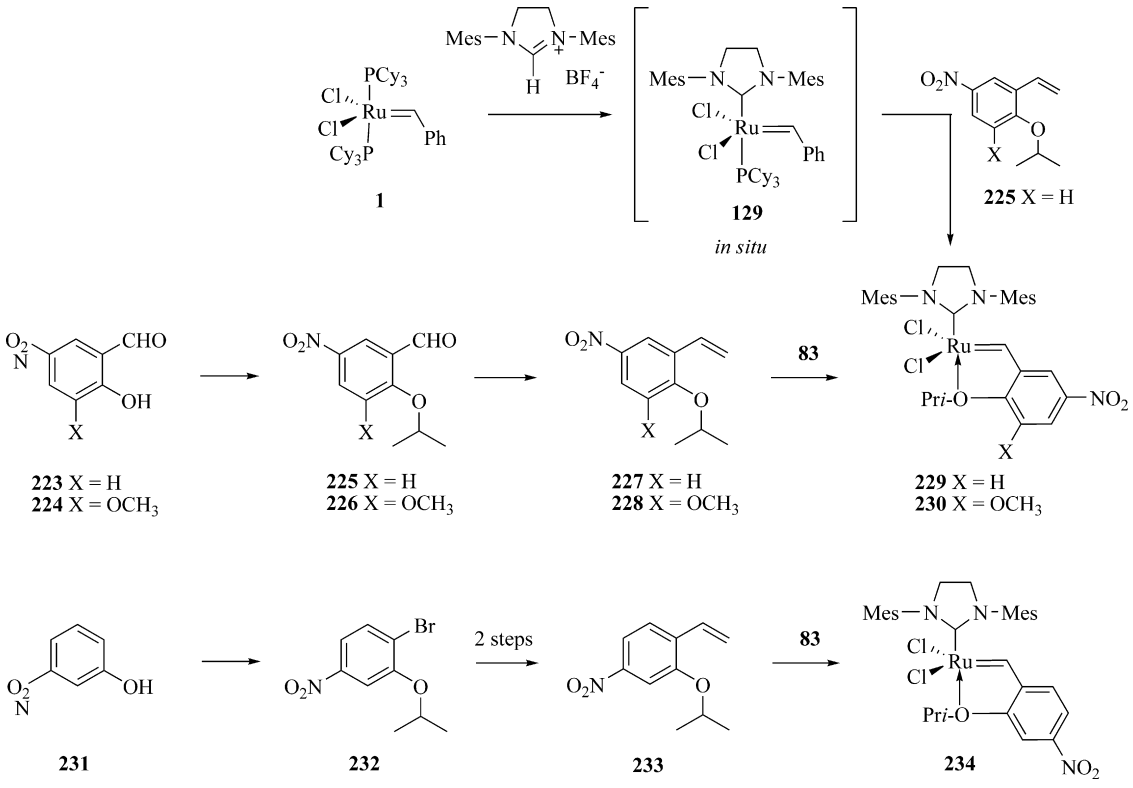
The high catalytic activity of complex **222**, which contain an *ortho*-substituent to the isopropoxy group, opened the way to the conception and synthesis of new catalysts **236**–**245** [111,112] and **245** [113] (Scheme 36).

The order of catalytic activity in the RCM reaction of diallyltosylamide **21** was found to be **222** > **242** > **243**, **129**, **238** > **239**, **241** > **7** > **236** ≫ **237** ≫ **240**. Catalysts bearing electron-withdrawing groups led to faster reaction rates than the reference catalyst **7** and analogues substituted with electron donating groups. The rate of catalysis is largely but not entirely governed by electron density at the benzylidene moiety. In the case of catalyst **236**, the non-chelating isopropoxy group would be expected to have a strong electron donating effect on its chelated counterpart while having little or no influence on benzylidene electrophilicity. Conversely, the regioisomeric **240** possesses a relatively electron-rich Ru=C bond while the Ru–O bond should have similar electronic characteristics than the corresponding moiety of **7**. Therefore, the observation that **240** leads to slower reaction times compared to **236** strongly indicates that benzylidene electrophilicity is the dominant factor. It is also interesting that **236** has a lower initial activity than **7**; thus, tighter Ru–O bonding due to an increased electron density at the chelating isopropoxy group also influences activity, albeit to a lesser extent. The fastest non-hindered variants of **7** are those which bear substituents capable of reducing the electron density at both *meta* and *para* positions.

Nitrile-substituted **242** is even more efficient than the hindered catalyst **243** in the initiation speed, while also



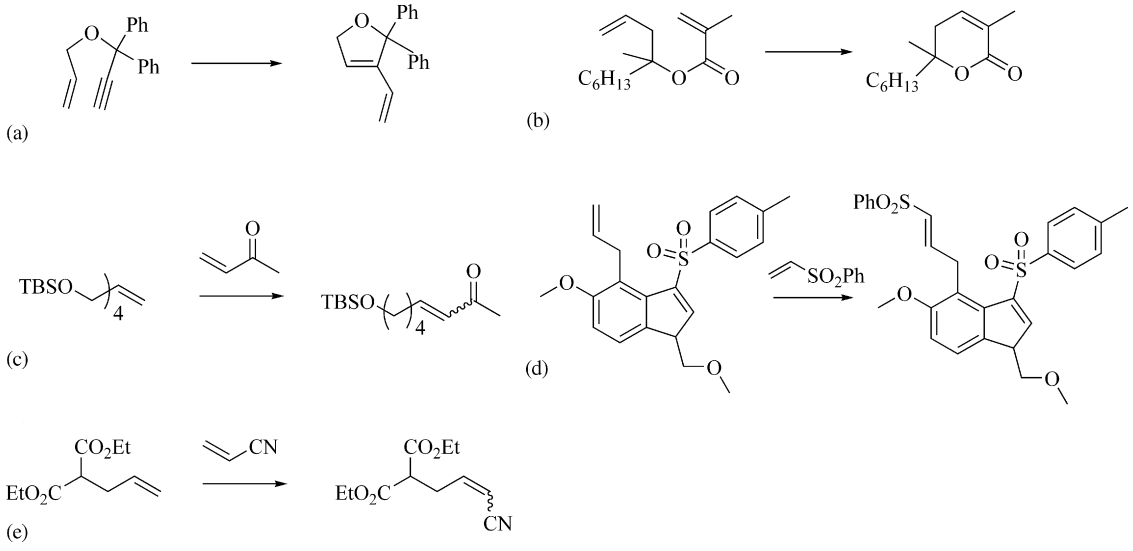
Scheme 33.



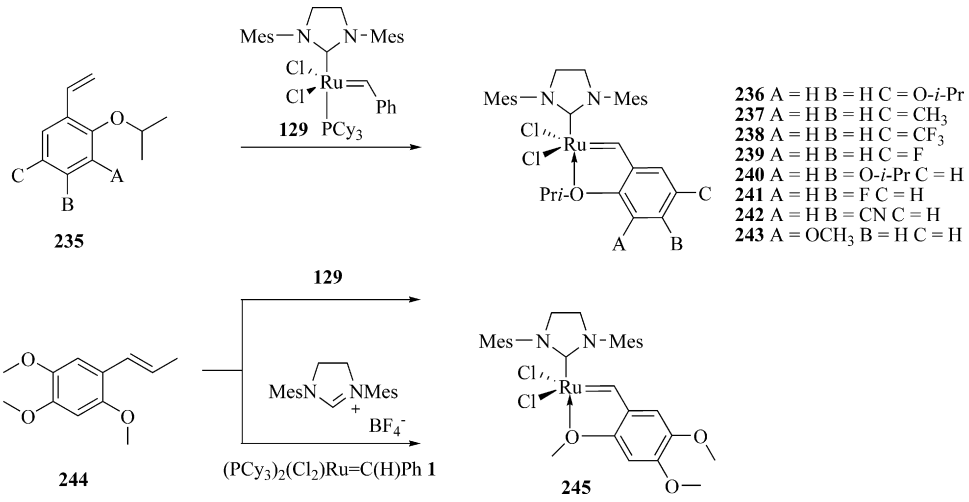
Scheme 34.

converting the substrate to a greater extent. ROM-CM of the *exo*-oxanorbornene derivative (Scheme 33), in the presence of allyltrimethylsilane and catalyst **243** (0.05 mol%) shows nearly quantitative conversion within a few minutes [111]. Catalyst **238** is also highly active, while **239** and **241**, which bear fluorine atoms in positions allowing electron withdrawal from either the benzylidene or the isopropoxy moiety (but not both) are less effective, although both are predictably faster than **7**. RCM reaction of (b) [Scheme 32] to form the eight-membered ring product under identical conditions is faster than the RCM of diallyltosylamide when isopropoxybenzylidene-based catalysts are employed. Blechert and co-workers [112] explains this observation on the premise that *N*-allylic moiety in diallyltosylamide is less reactive towards metathesis catalysts due to electronic or chelating effects that might sequester the catalyst in an unproductive form (Fig. 4).

Replacement of 2-isopropoxybenzylidene by 2,4,5-trimethoxybenzylidene leads to a recyclable catalyst **245** [113], which is not only very stable. It is more reactive than **129** for the formation of carbo- and heterocycles bearing a



Scheme 35.



Scheme 36.

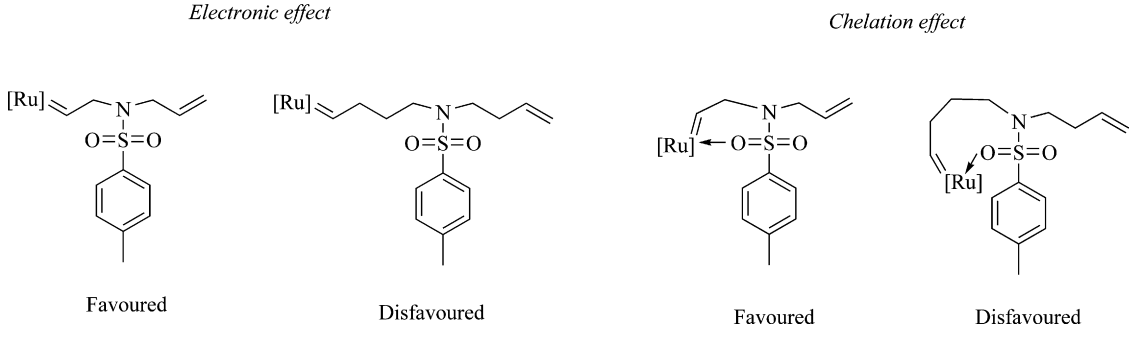


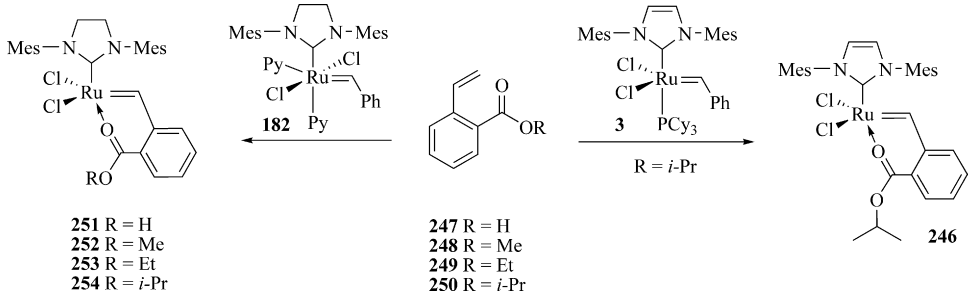
Fig. 4. Electronic and chelating effect on Ruthenium catalyst.

di- or tri-substituted double bonds, and for challenging CM reactions.

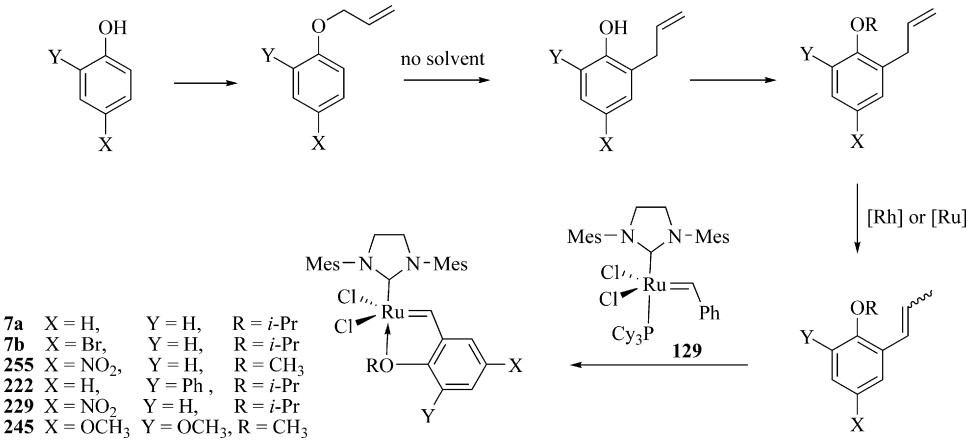
The assumption that formation of stable chelate complexes attenuates the reactivity of the metathesis catalysts is further supported by Fürstner et al. [114] They showed in a set of representative RCM reactions (e.g. cyclization of diallyl dimethyl malonate) the lower catalytic activity of complex **246** compared to the parent compound **3** (Scheme 37).

The carbene exchange reaction of $(H_2Mes)(Py_2)(Cl_2)$-Ru=C(H)Ph (**182**) and chelating ligands derived from 2-vinylbenzaldeyde **247** or 2-vinylbenzoic acid ester **248**–**250**, affords complexes **251**–**254** [115] (Scheme 37). The peculiarity of these complexes lays on the *cis*-dichloro arrangement and a chelating carbene ligand oriented parallel to the mesityl moiety of the H_2IMes coligand. The application of the complexes as initiators for ROMP of norbornene derivatives revealed that elevated temperature were necessary to provide a reasonable initiation. The advantage of these kind of complexes, thermally switchable, is that monomers and initiator(s) can be mixed and stored without concomitant polymerization events [115].

Grela and co-workers [116] developed an efficient and general synthetic route, based on a solvent-free Claisen rearrangement and catalytic isomerization by means of rhodium or ruthenium trichloride, with high *trans* selectivity. This protocol was used to prepare the highly active *ortho*- and *para*-substituted catalysts **7b**, **255**, **222**, **229**, **245** as well as parent Hoveyda–Grubbs carbene **7** in multigrams quantities (Scheme 38).



Scheme 37.

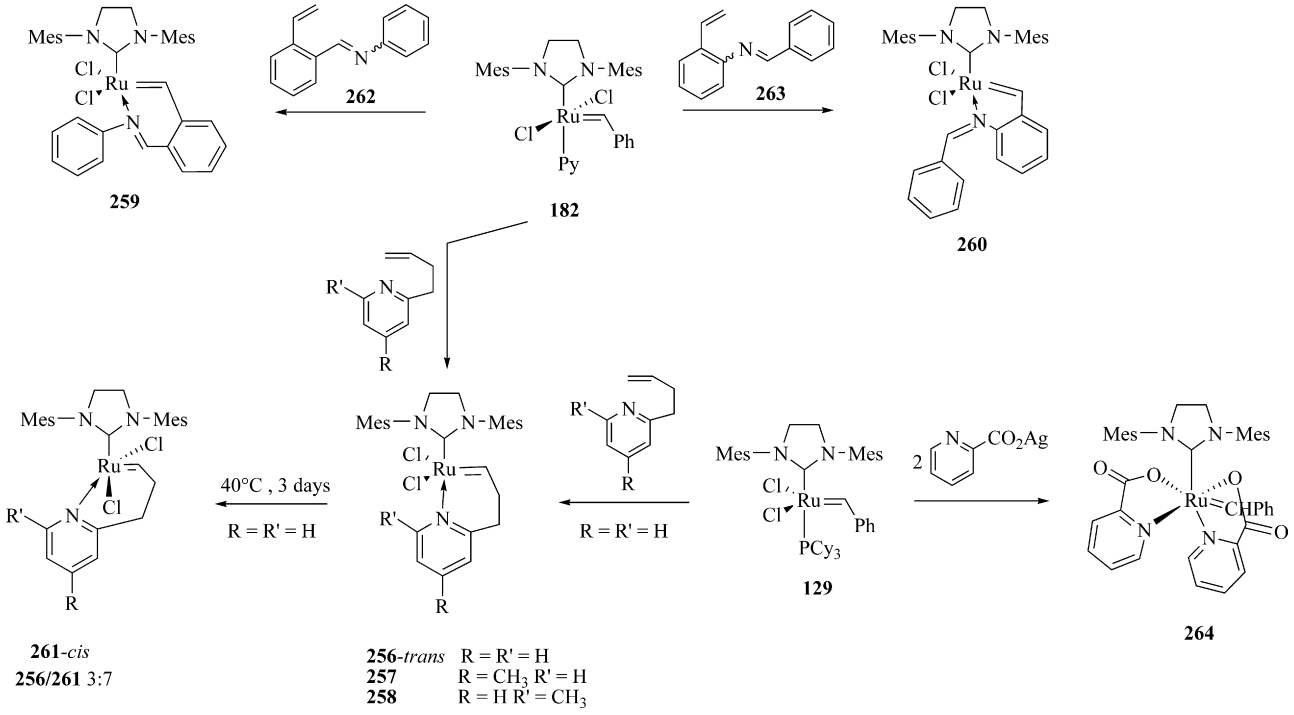


Scheme 38.

7.5. Switchable catalysts

When the oxygen donor is exchanged for a nitrogen donor in the chelating carbene ligand, more inert initiators **256–258** [117] and **259–260** [118] are accessible (Scheme 39): they initiate slowly while maintaining the high activity associated with NHC-based catalysts. When heated in dichloromethane, **256**, in which NHC and pyridine ligands are *trans*, is slowly converted into its *cis* isomer **261** [117] which is more reactive than **256**. The **261** is less reactive than **129** in RCM of diethyl diallylmalonate **25** and ROMP of dicyclopentadiene. Substitution on the pyridine ring has a much less dramatic effect on catalytic activity, since **256** and **257** show similar reactivity in RCM, but **258** proves to initiate faster than **256** and **257**. In the ROMP, the three complexes **256–258** were found to have similar catalytic properties [117].

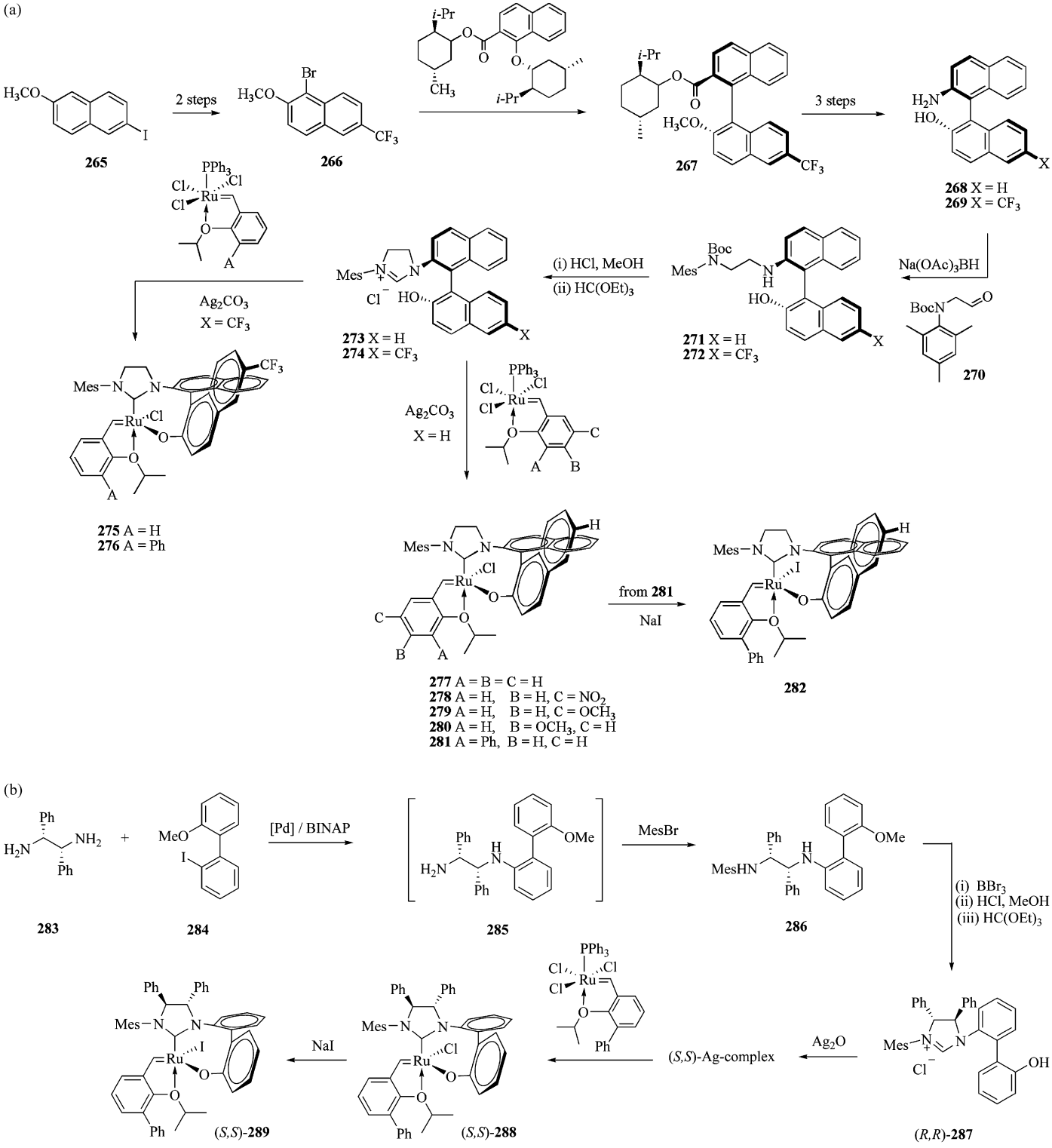
The two ruthenium-based metathesis initiators bearing chelating carbene ligands with imine functionalities [119] and NHC ligands **259** and **260** [118] were prepared by a carbene exchange reaction of phenyl(2-vinylbenzylidene)amine (**262**) and benzylidene(2-vinylphenyl)amine (**263**) with $(H_2IMes)(py_2)(Cl_2)Ru{=}C(H)Ph$ (**182**), forming respectively a six- and a five-membered chelating carbene (Scheme 39). The two initiators exhibit different rates of polymerization in the ROMP of (±)-*exo,endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxilic acid diethyl ester (**148**) (R = Et, Scheme 17), but in all cases the polymerization was complete within 5 min. Both compounds revealed pronounced latency at room temperature and very fast polymerization rates at temperature around 110 °C. The latency for the six-membered chelating ring system in **259** is more pronounced than the latency of the five-membered-ring system **260**. This explains a higher "switching temperature"



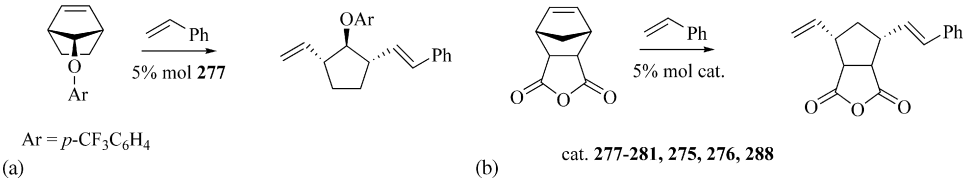
Scheme 39.

and a lower polymerization rate for **259** compared to **260** [118].

Precatalyst **264** [120] was obtained by heating a stoichiometric mixture of **129** and silver 2-pyridine-carboxylate in THF: both the phosphine ligand and the two halide ligands of **129** are substituted by two 2-pyridinecarboxylate ligands which are coordinated in a *cis* fashion (Scheme 39). Complex **264** does not promote the RCM reaction of diethyl diallylmalonate **25**, but the reaction is initiated upon addition of two equivalents of HCl, which protonate at least one of the pyridine-2-carboxylate ligands. However, **264** remains less active than **129** which catalyzes the RCM in shorter time and lower loading of catalyst.



Scheme 40.



Scheme 41.

7.6. Unsymmetrical NHC ligands: chiral ruthenium-based catalysts

Hoveyda and co-workers [121–124] developed chiral Ru-based catalysts **275–282** [Scheme 40(a)] and **288–289** [Scheme 40(b)], bearing a bidentate chiral imidazolinylidene, for enantioselective olefin metathesis (Scheme 41). The pivotal step in the synthesis scheme proved to be the conversion of **273** and **274** to optically and diasteromerically pure **275–281** [121,122,124] and **288** [123] catalysts. The corresponding chiral Ru–iodide complexes **282** and **289** are obtained by treatment with NaI.

Ruthenium complex **277** promotes the RCM of diene and enyne substrates (>98% conversion), but is less reactive than the achiral parent **7**. Longer reaction time and elevated temperatures are required for complete conversion. The replacement of a chlorine with the less electronegative phenoxyde of the chiral ligand and the increased steric bulk of the binaphthyl are responsible for the diminished activity. However, **277** can be recovered in high yield and reused without significant loss of activity or enantioselectivity. Catalyst **277** promotes asymmetric ring-opening/cross-metathesis (AROM/CM) in air, with undistilled solvents of 7-oxonorbornenes in 96% ee, 66% yield and 86% recovered catalyst (>98% *trans*) [121] [Scheme 41(a)]. The AROM/CM reaction of tricyclic norbornene [Scheme 41 (b)] in presence of catalysts **278–281**, **275**, **276**, **282** shows that complex **278** (because of the presence of NO_2 group), is three times more active than **277**, but less powerful than **229** (Scheme 34). Furthermore, the presence of electron-donating OMe group in **279** results in a catalyst that is still twice as active as its parent complex, but the catalytic activity of isomeric **280** is not affected by the presence of the OMe group. The steric alteration that results in the highly active achiral catalyst **222** [108] (Scheme 34) also seems to enhance significantly the efficiency of chiral complex **281**, while the electronic factors influences the reactivity of catalyst **275**. Both promote the AROM/CM more than **100** and three times faster than **277**, respectively.

Electronic and steric effects result to be additive, since the doubly modified complex **276** exhibits the highest level of potency among those studied. If the reaction is promoted by complex **288**, prepared and used *in situ* [123] higher enantioselectivity and shorter period of time are exhibited, compared to **281**, while the biphenyl-based ruthenium complex **289** shows higher levels of reactivity versus the corresponding binaphtyl complex **282**.

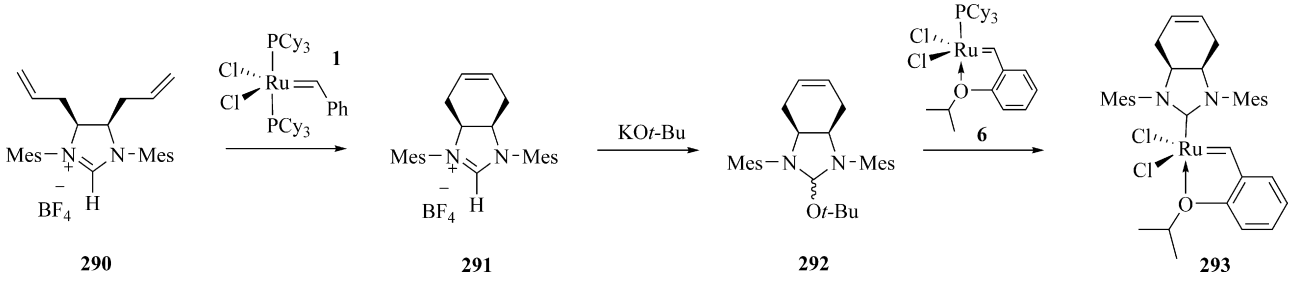
7.7. NHC ligand with annelated cyclohexene moiety

The functionalization of the NHC at the C-4 and C-5 position is interesting, since the substitution will be quite remote from the catalytically active metal site. Any potentially disturbing effect from those substituent groups on the catalytic reaction is therefore minimized. The reaction of (4*R*,5*S*)-4,5-diallyl-1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-3*H*-imidazol-l-ium-tetrafluoroborate (**290**) with the first-generation Grubbs catalyst **1** leads to RCM of the two allylic groups to afford **291** [125]. Subsequent reaction of this new imidazolium salt with a base, followed by phosphine substitution reaction with **6**, forms **293** [125] (Scheme 42).

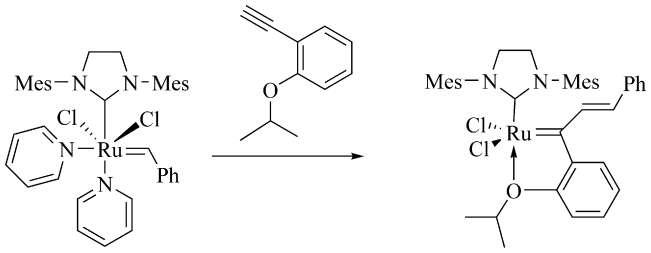
The intriguing feature is the presence of an inert C=C bond, even at elevated temperature, that is part of a highly active olefin metathesis catalyst. The RCM of diallyl tosylamide **21** is only slightly lower than the parent compound **7**.

7.8. Bidentate ruthenium vinylcarbene complex

Exposure of terminal alkynes to a suitable metal carbene complex results in the insertion of the alkyne into the M=C bond of the metal alkylidene *via* a possible elementary step of "enyne metathesis". The phenylacetylene, bearing the *ortho* isopropoxy group, terminates the grooving polymer chain by chelation to the metal center. Treatment of the bis-pyridine adduct **174** [44,50] with phenylacetylene, affords the bidentate vinylcarbene complex **294** [126] stable in the solid state for extended period of



Scheme 42.



175 294

Scheme 43.

time (Scheme 43). The RCM of diethyl diallylmalonate **25** is complete within 5 min, with 95% yield.

7.9. Fluorinated ligands for second-generation Grubbs–Hoveyda (f-GH) ruthenium carbene complexes

The replacement of one or both chlorines in the Grubbs second-generation catalyst **129** and Hoveyda–Grubbs **7** by trifluoroacetates, trifluoromethansulfonates, fluoroalkylcarboxylates, perfluorated phenoxyde, results in catalysts **295** [127] and **296–302** [127,128] respectively (Scheme 44).

Catalysts **297** and **298** display lower activities than the parent compound in the RCM of diethyl diallylmalonate **25**, 1,7-octadiene, diallyldiphenylsilane, *trans*-3-methylpentanoate, *N*,*N*-diallyltrifluoroacetamide, and *N*,*N*-diallyl-*tert*-butylcarbamide. However, in various RCM, enyne metathesis and ROM/CM experiments, catalyst **296** revealed the highest activity ever reported both at room and elevated temperature, with high turnover numbers (TONs), sometimes exceeding those obtained with **129** or **7** [128]. In general, the reactivity of NHC-based catalysts bearing electron-withdrawing ligands **295**, **299–302** [127] is generally equal or lower than that of the parent chlorine-containing systems. With catalysts **295–302** electron-poor double bonds give lower TONs, whereas electron-rich double bonds tend to give higher TONs.

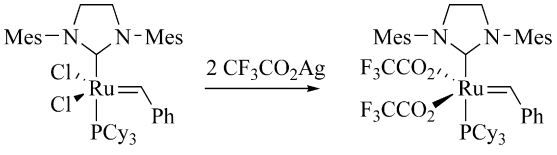
8. Ruthenium complexes bearing six-membered NHC carbene ligands (types 8 and 9)

Introduction of bulky 5,5′-dimethyl-1,3-dimesityl-1,4,5,6-tetrahydropyrimidin-2-ylidene as six-membered NHC ligand [129] gives access to a new class of ruthenium carbene catalysts (Mes_2-THP)(PCy_3)(Cl_2)Ru=C(H)Ph (**8**) [129] (Mes_2-THP)(Cl_2)Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**9**) [130] (Mes_2-THP)(CF_3CO_2)$_2$Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**306**) [130] and (Mes_2-THP)(C_5H_5N)(Cl_2)Ru=C(H)Ph (**307**) [131] (Scheme 45).

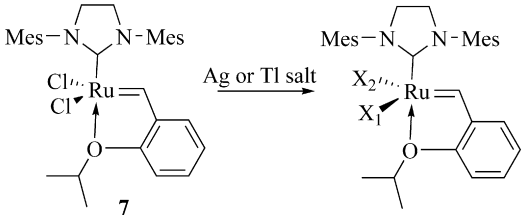
The tetrahydropyrimidinium salt **305** is prepared by reacting dimethylmalonyl chloride with mesitylamine to give the bis(amide) **303**, followed by reduction to **304** and cyclization to **305**. Carbene is generated by KHMDS which is reacted *in situ* with (PCy_3)$_2$(Cl_2)Ru=C(H)Ph (**1**) to produce **8**. The tetrahydropyrimidinyl NHC **8** adopts a half-chair conformation. The synthesis of (Mes_2-THP)(Cl_2)Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**9**) [130] is achieved by introduction of the ligand isopropoxystyrene. Its bis(trifluoroacetate) analogue (Mes_2-THP)(CF_3CO_2)$_2$Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**306**) [130] is obtained by substitution of both chloro ligands in the presence of silver salt (Scheme 45). In the reaction of **8** with an excess of pyridine, only one pyridine ligand coordinates the ruthenium center, in contrast to (H_2IMes)(Cl_2)(3-Br-C_5H_4N)$_2$Ru=C(H)Ph (**177**) (Scheme 24) which requires two molecules of 2-bromopyridine to be stable. This maybe due to the increased donor ability of pyridine compared to 2-Br-pyridine, the increased donor ability of the tetrahydropyrimidin-2-ylidene ligand and its increased steric factor.

(Mes_2-THP)(PCy_3)(Cl_2)Ru=C(H)Ph (**8**) demonstrates moderate reactivity for both RCM and ROMP in comparison with (H_2IMes)(PCy_3)(Cl_2)Ru=C(H)Ph (**129**), due to a larger steric environment around the metal atom, which may disfavor olefin binding or metallacyclobutane formation.

(Mes_2-THP)(Cl_2)Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**9**) and (Mes_2-THP)(CF_3CO_2)$_2$Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**306**) are the most reactive catalysts for the RCM of diethyl



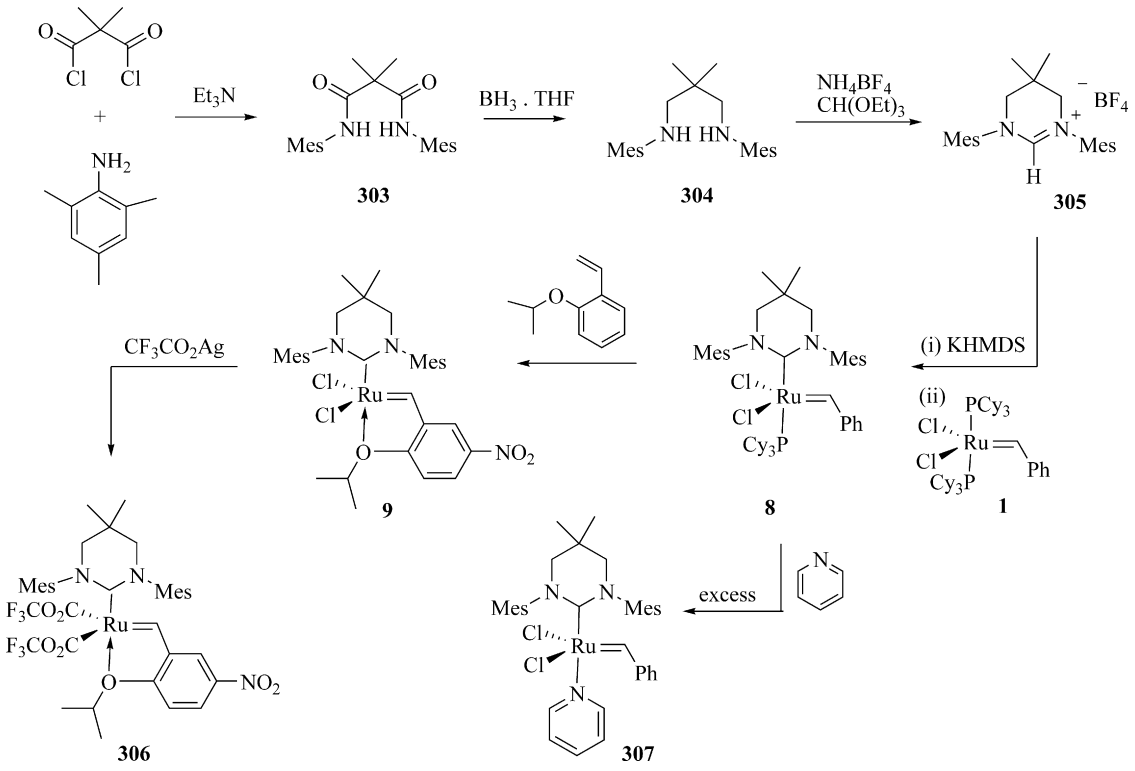
129 295



7

296 $X_1 = X_2 = CF_3CO_2$
297 $X_1 = CF_3SO_3$ $X_2 = Cl$
298 $X_1 = X_2 = CF_3SO_3$
299 $X_1 = X_2$ $C_2F_5CO_2$
300 $X_1 = X_2 = C_3F_7CO_2$
301 $X_1 = X_2 = C_6F_5CO_2$
302 $X_1 = X_2 = C_6F_5O$

Scheme 44.



Scheme 45.

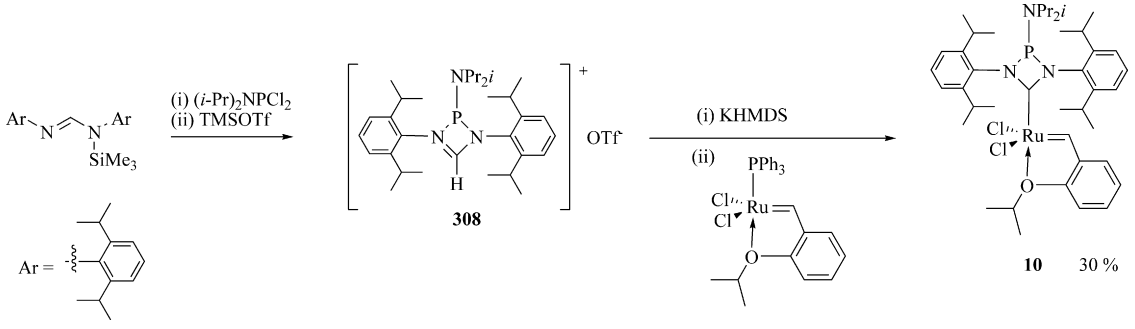
diallylmalonate **25**. However, the reactivity for diethyl bis(2-methylallylmalonate) **23** was poor. Their high reactivity in metathesis reactions involving electron-rich alkenes and their low reactivity for disubstituted and electron-poor alkenes offers in principle access to selective metathesis reactions with molecules containing both types of alkenes. ROM/CM reaction with 7-oxanorborn-5-ene are quantitative at room temperature with 2 mol% catalyst, and in most cases exceeds those reported in the literature [130].

Polymerization of enantiomerically pure monomers *exo-N*-(norborn-2-ene-carboxyl)-L-phenylalanine ethyl ester mediated by (Mes_2-THP)(Cl_2)Ru=CH(*o*-*i*PrO-5-NO_2-C_6H_3) (**9**) and (Mes_2-THP)(C_5H_5N)(Cl_2)Ru=C(H)Ph (**307**) proceeds in a living manner with good control over molecular weight; polymerization of *endo*,*endo*-*N*,*N*-(norbom-5-ene-2,3-dicarbimido)-L-valine ethyl ester yields a polymer with an exclusive all-*trans* structure [131].

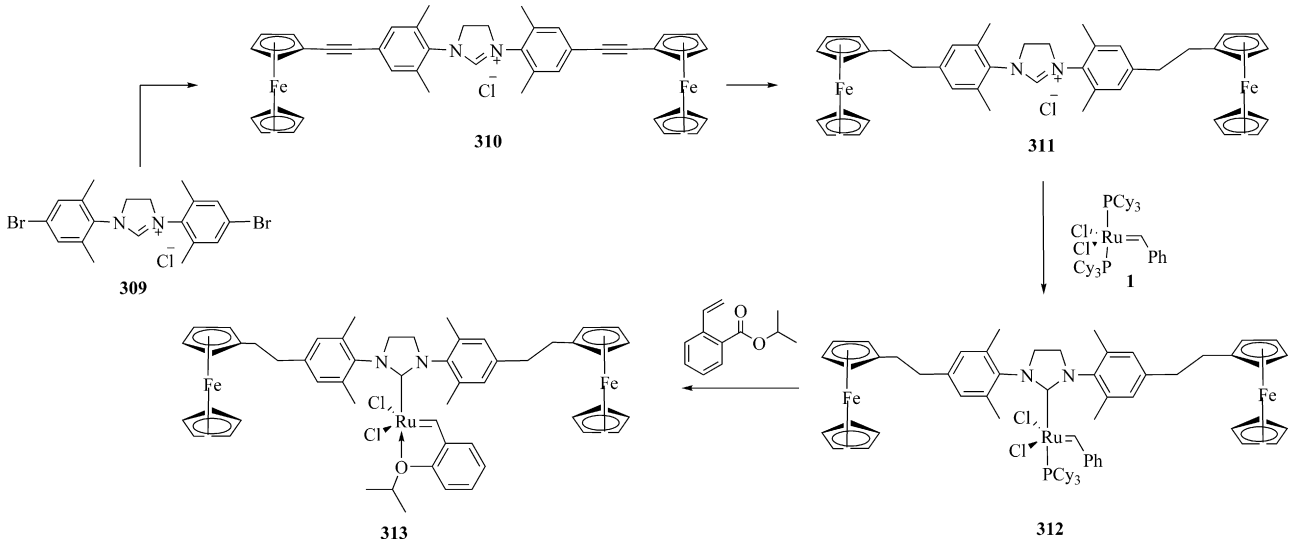
9. Ruthenium complexes bearing four-membered NHC carbene ligand (type 10)

The diaminocarbene family was extended to a more strained system, by introducing a four-membered NHC. The iminium salt **308** [132] was prepared in 66% yield from the silylamidine by addition of (diethylamino)-dichlorophosphine and trimethylsilyl-trifluoromethanesulfonate at room temperature. Deprotonation of **308** with potassium hexamethyldisilazide at room temperature generates the carbene *in situ*, which reacts in the presence of (PPh_3)$_2$(Cl_2)Ru=CH(*o*-*i*PrOC_6H_4) to afford the first ruthenium complex bearing a four-membered NHC ligand [133] (Scheme 46).

In the CM reaction of allylbenzene with *cis*-l,4-diacetoxy-2-butene, the conversion is comparable to that obtained with complexes **129** and **7**, and longer reaction times are required. A similar trend is observed in the RCM of diethyl diallylmalonate;



Scheme 46.



Scheme 47.

high temperatures are required to promote the ROMP of *cis*,*cis*-cycloocta-1,5-diene.

10. Supported metathesis catalysts

Recent interest in the development of environmentally benign synthesis has evoked a renewed interest in developing polymer bound or supported metal catalysts that maintain high activity and selectivity. In an ideal case, the supported complexes can be recovered from reaction mixtures by simple filtration, they do not contaminate the reaction solution, they can be recycled, and they can increase selectivity. As transition-metal complexes are often expensive to prepare or purchase, the immobilization on a support, thereby enabling simple extraction and recyclability, makes a commercial advantage as well as an easy manipulation. Previously, a review on the synthesis of supported metathesis catalyst has been published [134]. Herein the state of art and the recent developments in the synthesis of supported metathesis catalysts are reviewed.

10.1. Redox-switchable ferrocenyl-tagged second-generation Grubbs carbene complex

A strategy for the separation of homogeneous catalysts from the reaction products, is based on redox-switchable phase tags, which mutate from neutral (lipophilic) into charged (lipophobic) tags and vice versa. The synthesis of ferrocenyl-tagged olefin-metathesis catalyst is shown in Scheme 47. The redox tag is constituted by a monoalkylated ferrocene [40]. The imidazolinium salt **309** undergoes Sonogashira coupling to ferrocenylacetylene **310**, the acetylene linker is reduced to **195**, followed by deprotonation with KO*t*Bu and treatment with **1**, to afford **312**. The remaining PCy_3 ligand and the benzylidene are substituted with 2-isopropoxystyrene to yield the desired redox-tagged Grubbs–Hoveyda-type catalyst **313**.

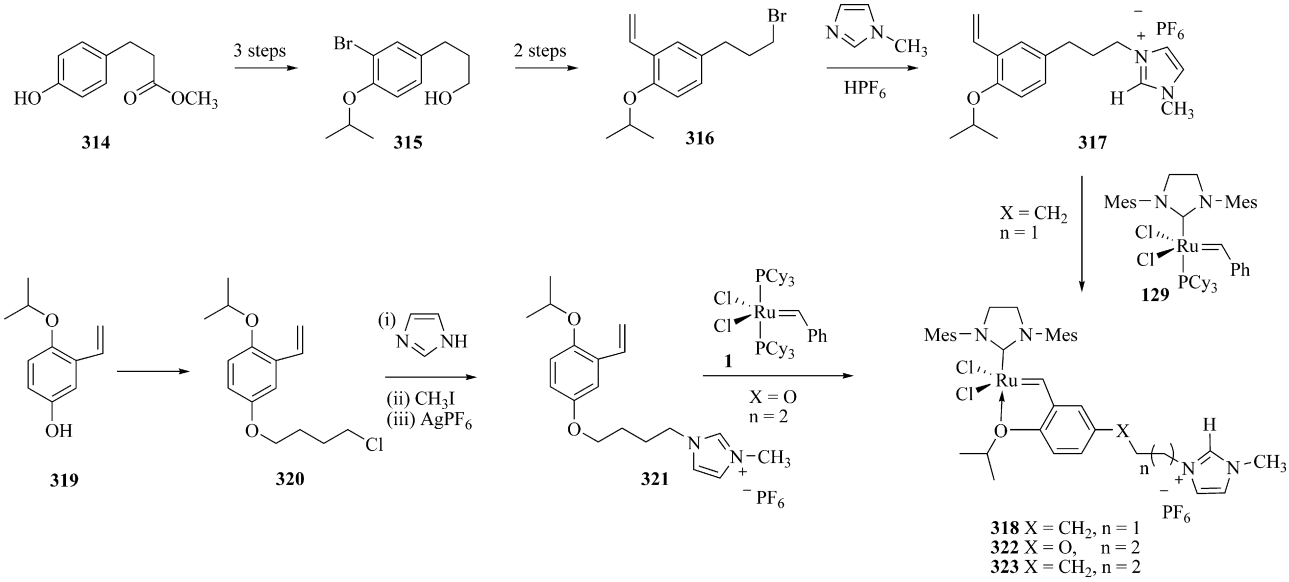
The RCM reaction of *N*-tosyldiallyl amide **21** proceeds to completion as expected for such catalyst; by adding the oxidation reagent $[FeCOCH_3]/[CF_3SO_3]$ the two ferrocenyl tags were oxidized and the resulting dication $\mathbf{313}^{2+}$ precipitates from the solution within a few seconds. The product of the catalytic reaction can be separated by filtration and the catalyst reactivated by addition of a reducing agent [1,1′,2,2′,3,3′,4,4′-octamethylferrocene ($FcMe_8$)]. The catalyst can be switched off and on several times after completion of the RCM reaction, thus allowing multiple recycling of the catalyst [40].

10.2. Ionic liquid-tagged second-generation Hoveyda–Grubbs ruthenium carbene complexes

The use of homogeneous catalysts is associated with two disadvantages: poor recyclability and difficulty to remove the ruthenium waste from the final products. To solve this problems ruthenium catalysts have been immobilized in the 1-butyl-3-methylimidazolium hexafluorophosphate (BMI·PF6).

The synthetic route to the imidazolinium-bound ligand **318** [135,136] starts from esterification of the commercially available methyl-3-(4-hydroxyphenyl)propionate, to afford **314**. Selective *ortho*-bromination of the aromatic ring, reduction of the ester group with $LiAlH_4$ followed by Pd-catalyzed Stille coupling to introduce the vinyl group, affords the styrenyl ether **315**. The alcohol function is then converted into the corresponding bromide **316**, *via* a standard nucleophilic substitution performed by treatment of LiBr on the mesitylate intermediate. The imidazolium tag **317** is obtained by alkylation of 1-methylimidazole by **316** followed by the ion exchange with an aqueous HPF_6 solution. The imidazolium-tagged ruthenium catalyst **318** is synthesized from the second-generation Grubbs catalyst **129** by a simple exchange of the styrenyl group [33,34] (Scheme 48).

Preparation of **321** [137] started from the hydroxyl-functionalized isopropoxystyrene **319** [138], followed by alkylation with 1-chloro-4-iodobutane to **320**. Reaction with imidazole, methylation and anion exchange of iodide with $AgPF_6$ yields the imidazolium hexafluorophosphate **321**.

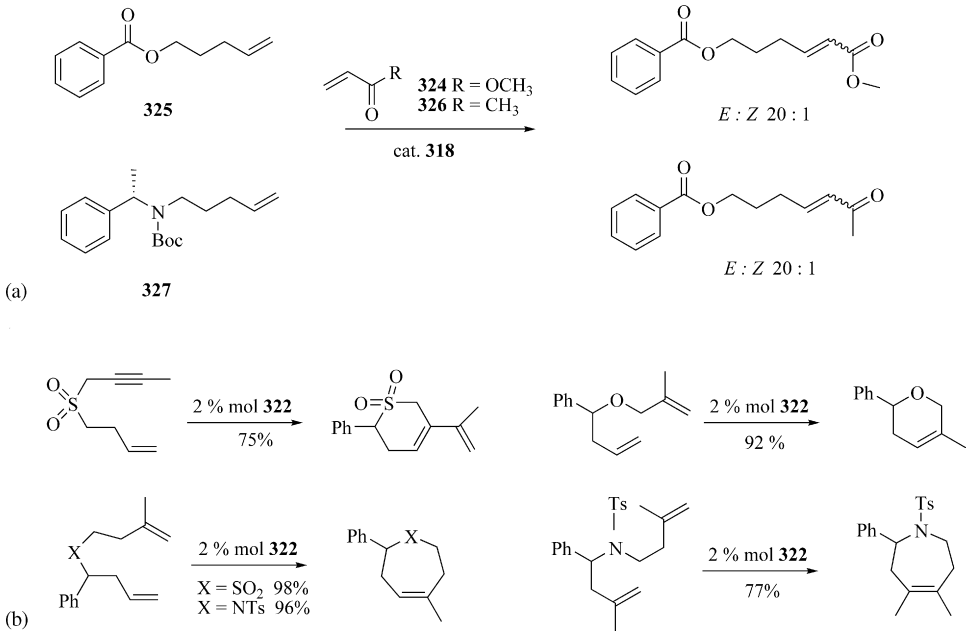


Scheme 48.

Treatment with first-generation Grubbs catalyst **1** affords catalyst **322** [139].

The second-generation of NHC ruthenium complex **318** appears to be more suitable to perform RCM reactions of less reactive substrates in harsher conditions, under biphasic conditions (BMI·PF_6/Toluene 25/75): excellent conversions at room temperature (>95%) are obtained for diethyl diallylmalonate **25** and diallyltosylamide **21** for up to six cycles, but a poor reactivity is exhibited against highly hindered substrates such as $[CH_2{=}CH(CH_3)CH_2]_2C(CO_2Et)_2$ (**23**) and $[CH_2{=}CH(CH_3)]_2$ NTs (**22**) (Scheme 5). The CM reactions of methylacrylate **324** with olefin **325** in the biphasic system BMI·PF_6/Toluene (20/80), and of methyl vinyl ketone **326** and chiral homoallylamine **327** at room temperature are achieved with 80% yield. However, the conversion decreased rapidly after the third and the second run respectively, without any possibility to recycle the catalysts [Scheme 49(a)]. A better yield (94%) for CM of **326/327** is obtained in the biphasic system BMI·PF_6/CH_2Cl_2 developed for **323** [137] but no improvement in the recycling was observed for this system.

Ruthenium-tagged complex **322** is a highly efficient catalyst for the RCM of di-, tri- and tetra-substituted diene and enyne substrates in minimal ionic solvent systems, with high reactivity and high level of recyclability, up to ten runs [139]



Scheme 49.

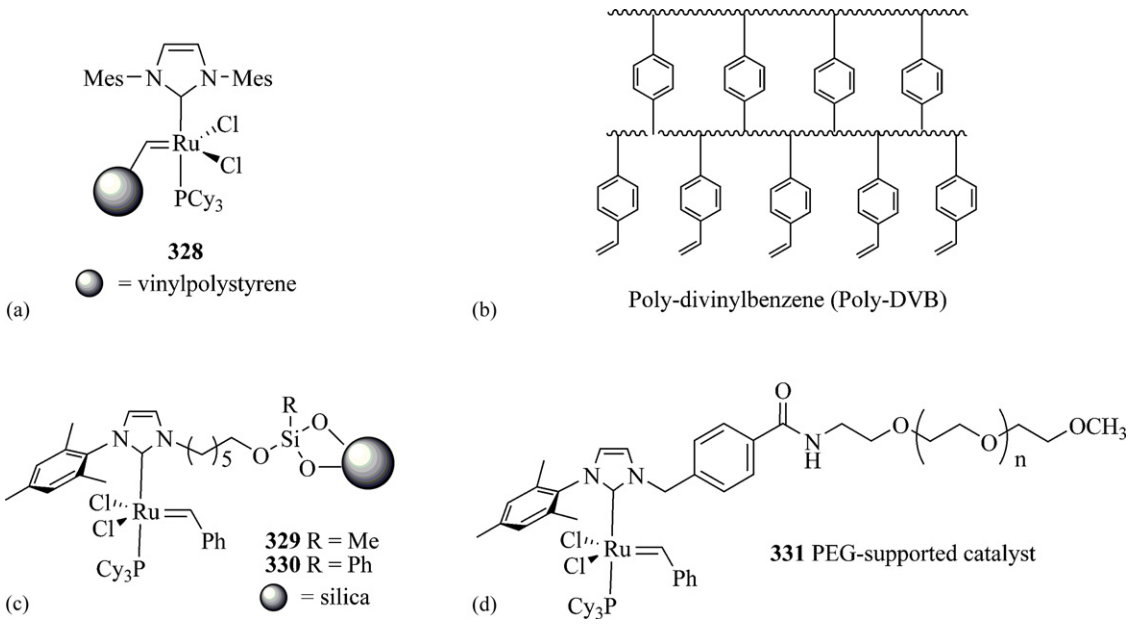


Fig. 5. Immobilized ruthenium carbene complexes.

[Scheme 49(b)]. Diethyl diallylmalonate **25** undergoes RCM quantitatively after 1 h in an homogeneous mixture of biphasic system BMI·PF_6/CH_2Cl_2 (10/90), at 45 °C with 1 mol% of **322**.

*10.3. Immobilization of ruthenium carbene complex (IMes)(PCy_3)(Cl_2)Ru=C(R′) (type **3**)*

Barrett and co-workers [140] have prepared a polymer supported version by shaking **3** (Scheme 8) with vinylpolystyrene leading to the formation of **328** [Fig. 5(a)], with complete incorporation of the metal. **328** exhibits increased metathesis activity and more stability air and moisture over their phosphine analogues. Complex **328** is termed "boomerang" catalyst since the active alkylidene is released from the support into solution during the course of the reaction and then recaptured on completion.

Nolan and co-workers [141,142] have also reported the preparation of boomerang-type supported catalyst by the immobilization of the metal complex on a macroporous polymer rather than cross-linked supports such as those derived from Merrifield's resin. The advantage of such immobilization is that swelling is not necessary to ensure accessibility of pore sites. The resin used was prepared from divinylbenzene using toluene as a porogen, the bulk polymer having a high degree of cross-linking (55%) [Fig. 5(b)].

Metal complexes **3** (Scheme 8) and **85** (Scheme 12) were immobilized on the support using a simple impregnation protocol involving heating the metal complex with the support in toluene for 1 h followed by filtration. In RCM reactions the supported complex containing **3** shows a similar activity to that of its homogeneous analogue. In the case of **85** the activity of the metal complex is often increased by immobilization, although a significant loss of activity after its initial use is displayed. The supported complexes however poorly perform with substrates such as oxygen-containing dienes, in which a stable oxygen-ligated ruthenium carbene complex can be formed. This complex is more stable and less reactive than the supported ruthenium carbene complex. As a result, the metal stays in solution rather than remaining attached back onto the polymer support. Consequently, the active sites on the polymer support are depleted, leading to a loss of activity in subsequent cycles.

Fürstner and co-workers [74] reported also silica-immobilized versions of **108** (Scheme 13), which offer considerable advantages over other support materials due to low cost, thermal stability, broad solvent compatibility, minimal swelling and ease of handling. Although longer reaction times are necessary to reach complete conversion in RCM, the yields are comparable to those obtained with catalysts **106** and **108** (Scheme 13), which constitute the homogeneous analogues of **329** and **330** [Fig. 5(c)]. This system was reported to be reusable up to three times with TONs in the range of 15–20.

Grubbs and co-workers [143] reported a water soluble ruthenium-based olefin metathesis catalyst **331** supported by a poly(ethylene glycol) conjugated NHC ligand [Fig. 5(d)]. The catalyst initiates the ring-opening metathesis polymerization of strained cyclic olefins in both water and methanol, as well as the polymerization of hindered monomers in water.

*10.4. Immobilization of ruthenium carbene complex (H_2lMes)(PCy_3)(Cl_2)Ru=C(R′) (type **4**)*

The first ruthenium-based metathesis catalyst immobilized *via* the NHC was reported by Blechert and co-workers [144] by constructing the NHC ligand on the support and then appending the metal. Loadings of metal complexes of 0.14–0.40 mmol/g are reported. This supported version [Fig. 6(a); **332**] of Grubbs' second-generation catalyst **129** (Scheme 16) was successfully used in RCM and enyne metathesis reactions and was easy to handle. The Merrifield polystyrene support (1% divinylbenzene-

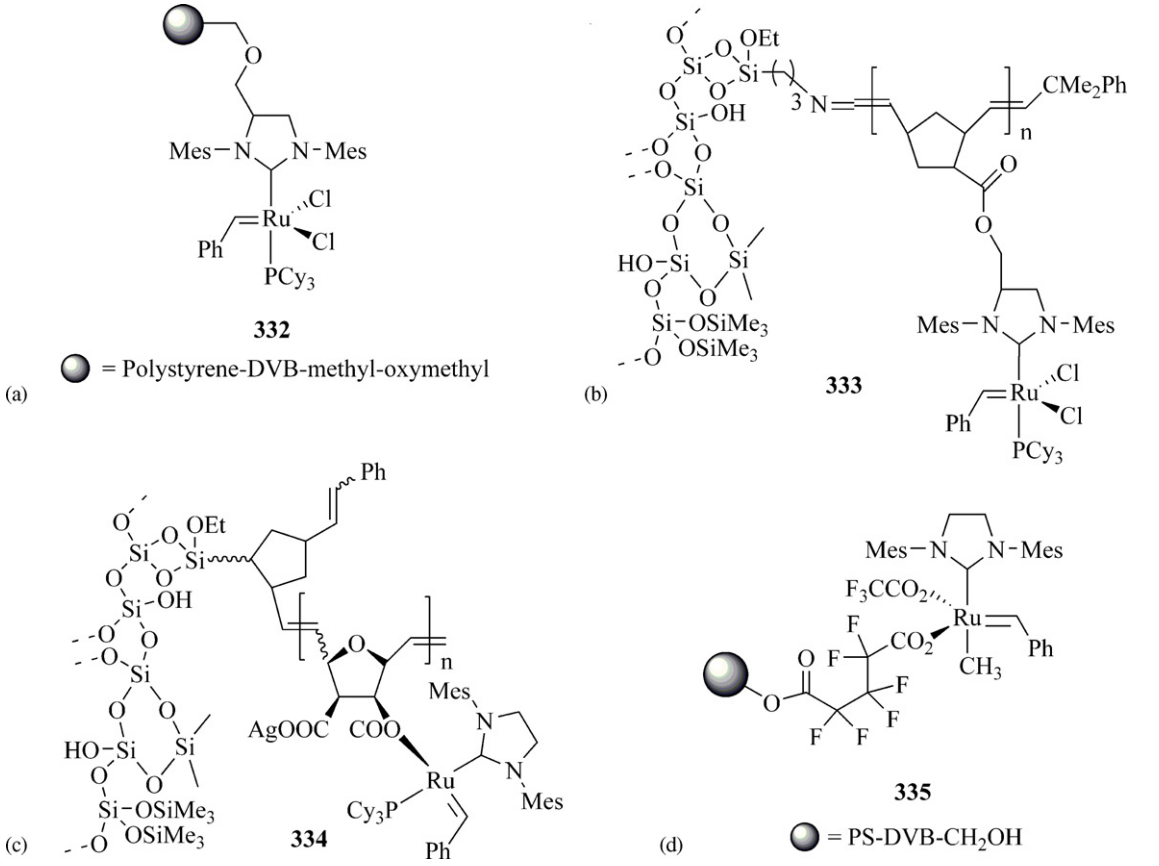


Fig. 6. Immobilized ruthenium carbene complexes on monolithic support.

DVB) represents a swollen, low cross-linked network. Consequently, reactions are diffusion controlled and increased reaction times are required.

To overcome this problem, second-generation Grubbs catalyst was immobilized on both non-porous (monolithic supports) and porous silica, designed in such a way that only interparticle porosity was generated, whereas the structure forming microglobules were virtually non-porous [145,146] [Fig. 6(b) and (c)]. The silica-based systems can be used in slurry reactions and for making cartridge systems for RCM. Both systems turned out to be stable, allowing high TON's in RCM for a large number of compounds. Ruthenium leaching being low, the stability and the activity make them attractive for both combinatorial chemistry and large-scale industrial applications.

The technique of microencapsulation has been used to envelop catalyst **129** in a polymer film (polystyrene) [147]. The resulting material is catalytically active and may be easily used and recycled over four cycles. Like catalysts **3** and **85**, complex **129** (Scheme 16) has been grafted onto poly-DVB [141,142] and found to be effective heterogeneous catalyst for RCM. In some cases, the complex can be recycled, showing comparable reactivity to its homogeneous counterpart. It tolerates functional groups and performs very well with diene but is less efficient with highly hindered substrates.

The perfluoroglutaric acid-derivatized poly(styrene-co-divinylbenzene) (PS-DVB) support (silver form) has been used for the synthesis of complex **335** [127] [Fig. 6(d)]. The catalyst shows higher activity in RCM compared to its homogeneous analogue, with a TON up to 4200. Leaching of ruthenium into the reaction mixture was low, resulting in ruthenium content $<85\ \mathrm{ng\ g^{-1}}$ in the final RCM-derived final products.

10.5. Immobilization of ruthenium carbene complex (H_2IMes)(Cl_2)Ru=CH(o-iPrOC_6H_4) (type 7)

The methodology used for the immobilization of **332** was also used for the preparation of the supported analogue of (H_2IMes)(Cl_2)Ru=CH(*o*-*i*PrOC_6H_4) (**7**), with the support grafted either to the NHC (**336**) [148] or to the styrene ligand (**337**) [148] [Fig. 7(a)].

Hoveyda-type catalyst **7** has been immobilized also on butyldiethylsilyl polystyrene (PS-DES) [Fig. 7(b); **338**] [149]. It is stable and could be recycled 5–6 times, resulting in TONs of up to 110 in the synthesis of cyclic structures based on trisubstituted double bonds. No activity was observed in the RCM of dienes with two non-terminal alkene groups.

Monolayer-protected gold cluster (Au-MPC)-bound-Ru–carbene complex [150] has been synthesized. The complex showed high reactivity and high levels of reusability in RCM suggesting that the monolayer-protected nanoparticles could have a high potential as support-materials for recyclable catalysts.

Connon and Blechert [151] bound the catalyst to a highly hydrophilic, commercially available ω-amino-

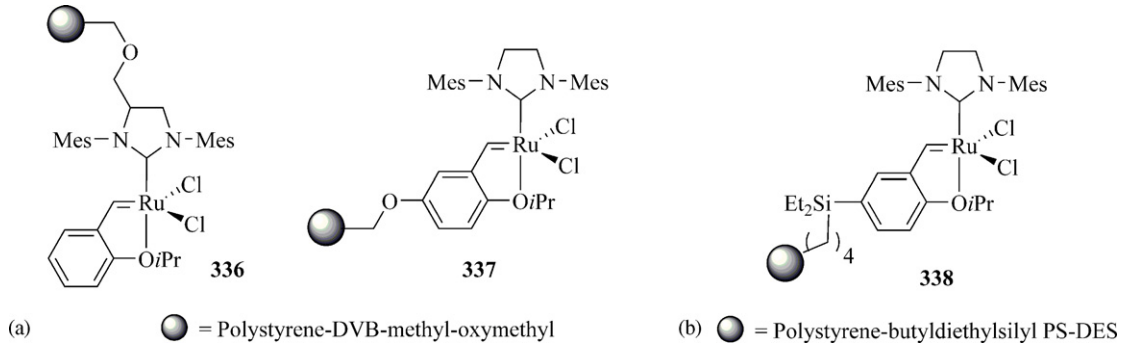


Fig. 7. Immobilized ruthenium carbene complexes on cross-linked polymers.

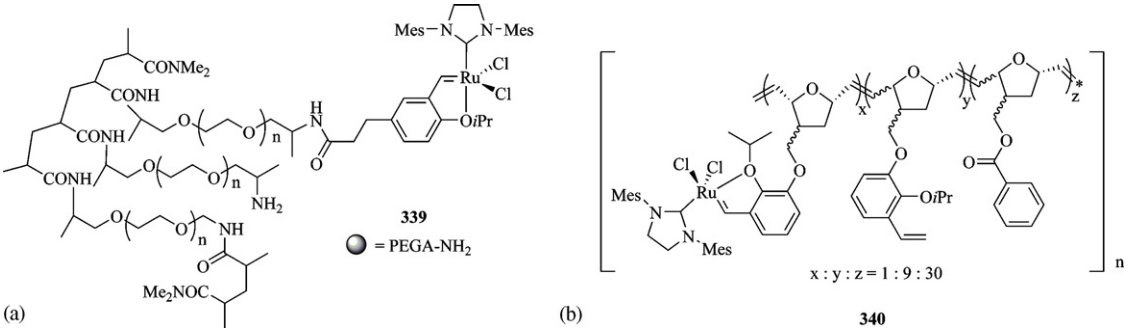


Fig. 8. Immobilized ruthenium carbene complexes on (a) PEGA-NH_2 support; (b) poly(7-oxanorbornene).

poly(ethyleneglycol)amide (PEGA-NH_2) support [Fig. 8(a)]. The heterogeneous catalyst **339** promotes relatively efficient RCM and CM reactions in both methanol and water, with only 5 mol% of catalyst.

A 'self-supported' version of Hoveyda catalyst has been obtained by reaction of 7-oxanorborn-2-ene-substituted Hoveyda catalyst. It undergoes spontaneous polymerization to form a polar matrix of poly(7-oxanorbornene) bearing the catalyst [152] [Fig. 8(b)]. In the RCM of diallyltosylamine **25**, this system could be recycled 7 times with a total TON of 760.

Inorganic sol–gels were used for immobilization of the catalyst [153]. These porous glasses retain a rigid and exposed surface area, whereas conventional polymer beads typically swell and shrink variably in different media, often resulting in unpredictable effects on catalyst activity. Moreover, surface functionalization of a monolithic gel results in a bulk catalyst sample; obviating the filtration step [Fig. 9; **341**]. For the formation of tri-substituted olefins, the catalyst retained its activity after up to 15 cycles affording product that often are of high purity.

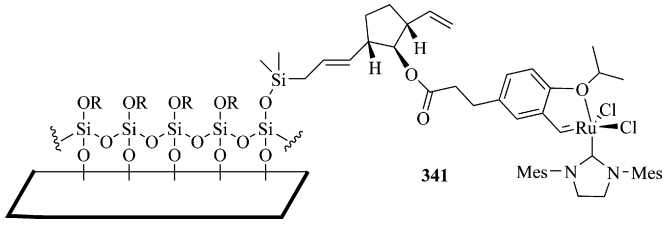


Fig. 9. Immobilized ruthenium carbene complexes on monolithic gel.

A supported version of catalyst **296** (Scheme 44) bound to hydroxymethyl-polystyrene (PS-DVB-CH_2OH) has been described [127,128] [Fig. 10(a); **342**]. Excellent activity in RCM was observed. TONs up to 1100 were achieved in stirred batch RCM experiments. Leaching of ruthenium into the reaction mixture was low, resulting in a ruthenium content <70 ng g^{-1} in the final RCM-derived products.

Perfluoroalkyl polymer bearing a bidentate isopropoxystyrene ligand has been used as support for catalyst **343** [154] [Fig. 10(b)]. The poly(fluoroalkyl acrylate) support was synthesized from commercially available fluoroacrylate and acryloyl chloride. Complex **343** proved to be reactive toward the RCM of tetra-substituted dienes, albeit higher loading and longer reaction times were required to reach high conversion. The recovered catalyst remains highly active, confirming its stability and recyclability.

Trans-metathesis of commercially available **344** with standard Grubbs second-generation catalyst **129**, gives light-fluorous tagged second-generation Hoveyda–Grubbs (f-GH) catalyst **345** [155] thermally stable, insoluble in fluorous solvents, and easily dissolved in common organic solvents [Fig. 10(c)]. The light-fluorous version of second-generation Grubbs–Hoveyda metathesis catalyst **345** reacts under similar conditions and shows similar reactivity profiles to the nonfluorous analogue for RCM and CM. They are readily separated and recovered from reaction mixtures by fluorous solid phase extraction (fspe), and can be routinely reused five or more times [155].

A supported version of catalyst **296** (Scheme 44), was prepared by attaching it to a poly(2-oxazoline) derived block

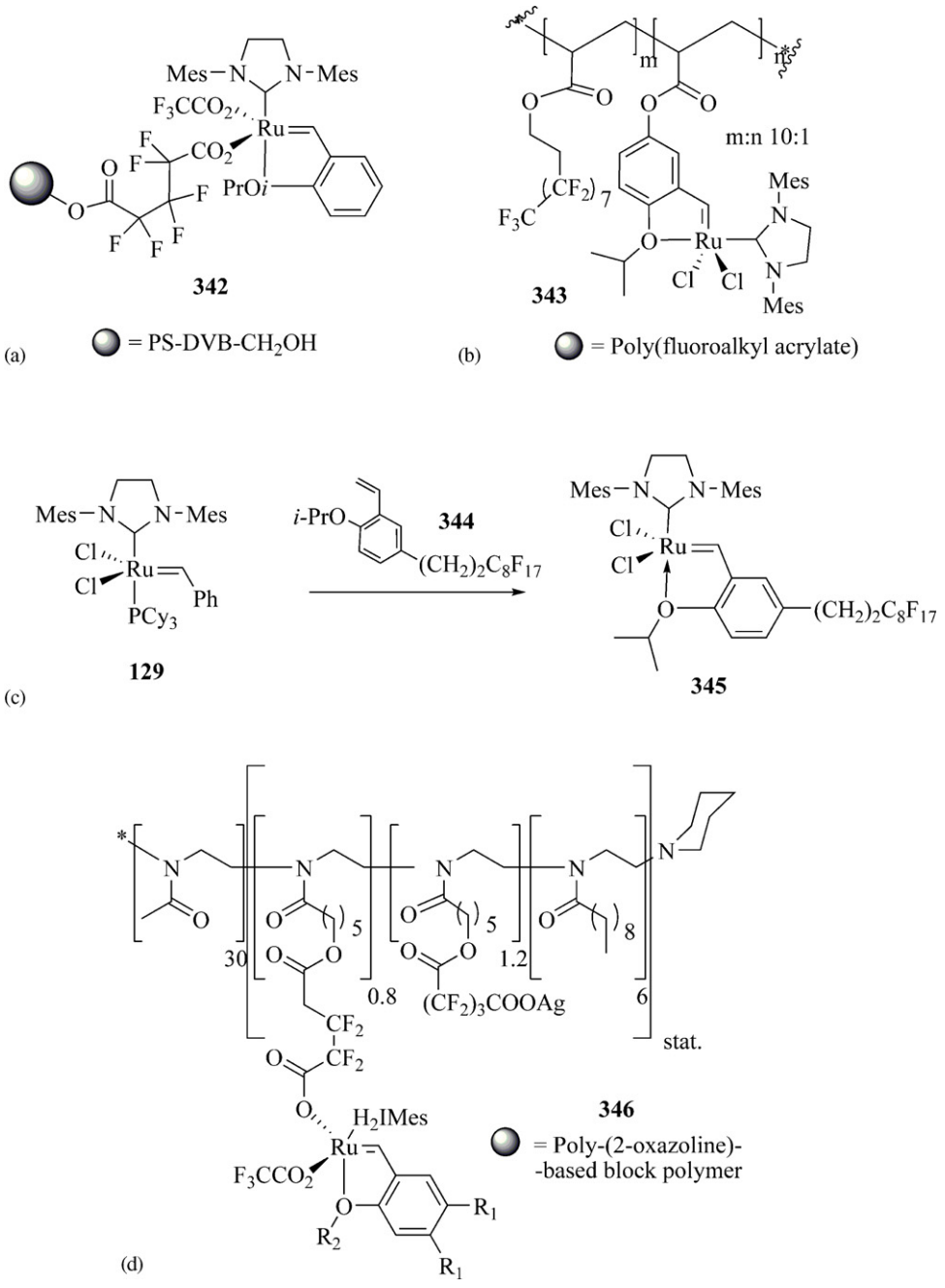


Fig. 10. Immobilized ruthenium carbene complexes on poly(fluoroalkyl acrylate) support.

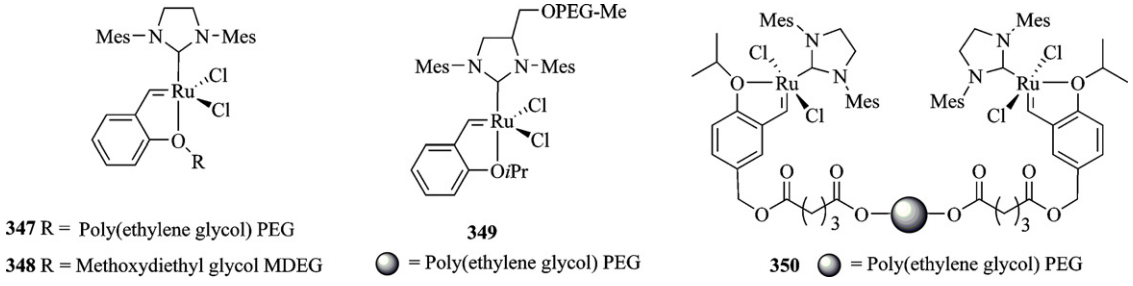


Fig. 11. Immobilized ruthenium carbene complexes on poly(ethylene glycol) support.

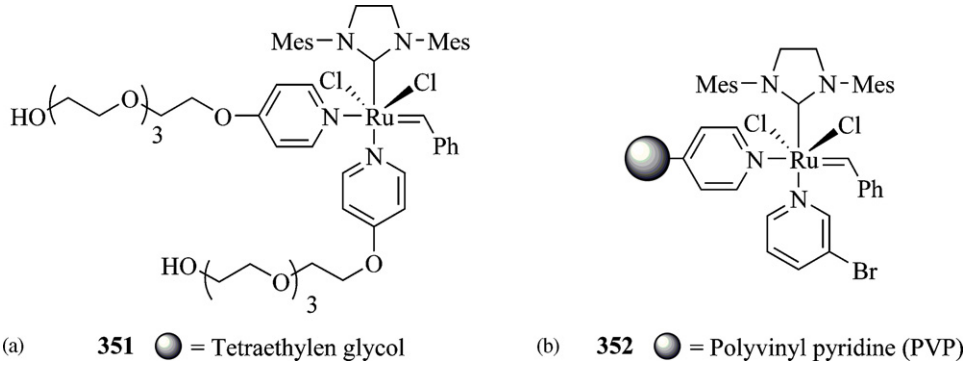


Fig. 12. Immobilized ruthenium carbene complexes on tetraethylene glycol and poly(vinylpyridine).

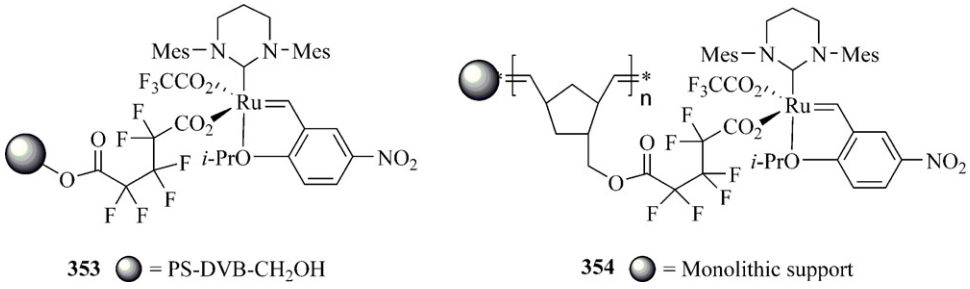


Fig. 13. Poly(fluoroalkyl acrylate) ruthenium carbene complexes immobilized on monolithic support.

copolymer [Fig. 10(d); **273**]. This supported catalyst allowed the first ever reported Ru-catalyzed cyclopolymerization of diethyl dipropargylmalonate (DEDPM), in water under micellar conditions, allowing class VI living polymerization [156].

Immobilization of second-generation Hoveyda–Grubbs complex on poly(ethylene glycol) (PEG) affords complexes **347** [157], **349** [158], **350** [159] (Fig. 11). It constitutes an alternative to insoluble supports. To evaluate the effect of the support in **347**, structurally similar catalyst **348**, in which the polymer was replaced by the shorter PEG methoxydiethylene glycol (MDEG) (Fig. 11), was also prepared [157]. Soluble polymer like PEG facilitates the accessibility to reactive sites and reduces diffusion rate problems within the polymer as well as provides access to structural information using classical solution spectroscopic methods (NMR [160] or mass spectrometry [161–165]).

In the case of PEG-supported RCM catalyst **347** [157] it is possible to characterize a supported precatalyst, to monitor the advancement of a reaction, and finally to evaluate the ccatalyst recovering ability at the end of a reaction. Boomerang catalysts **347–348** and **350** proved to be highly reactive and recyclable respectively in RCM of a wide variety of diene substrates, yielding di-, tri- and tetra-substituted carbocyclic and heterocyclic olefins [159] including cyclization of electron-deficient olefins to cyclic amino esters [157]. They are also very efficient in CM and ROM/CM [159]. Appending PEG on the backbone of NHC ligand renders catalyst **349** [158] soluble in organic solvents and water, while maintaining stability and activity of the well-known H_2IMes-based ruthenium metathesis catalysts. The catalyst shows unprecedented activity in ROMP, RCM with water-soluble α,ω-dienes yielding the corresponding five- and six-membered rings in good to excellent yields and CM in aqueous media.

10.6. Immobilization of ruthenium carbene complex $(H_2IMes)(Cl_2)(XC_5H_4N)_2Ru{=}C(H)Ph$

The amphiphilic version **351** [166] of the ruthenium benzylidene catalyst **175** (Scheme 24), containing *para*-substituted tetraethyneglycol pyridine ligands [Fig. 12(a)] shows efficiency in ROMP of cyclic olefins in both dichloromethane and water.

The supported version of catalyst **176** (Scheme 24) is obtained by direct coordination of ruthenium to polyvinyl pyridine (PVP) as a part of a monolithic highly porous polymer/glass composite material which was obtained by precipitation polymerization of vinyl pyridine and divinylbenzene as a crosslinker, to afford complex **352** [167] [Fig. 12(b)]. The solid-phase bound catalyst shows very good chemical reactivity in RCM, enyne and CM reactions, good recyclability and can easily be reactivated with fresh catalyst.

*10.7. Immobilization of ruthenium carbene complex $(Mes_2\text{-}THP)(CF_3CO_2)_2Ru{=}CH(o\text{-}iPrO\text{-}5\text{-}NO_2\text{-}C_6H_3)$ (**306**)*

$(Mes_2\text{-}THP)(CF_3CO_2)_2Ru{=}CH(o\text{-}iPrO\text{-}5\text{-}NO_2\text{-}C_6H_3)$ (**306**) [130] was immobilized on hydroxymethyl-Merrifield resin through a perfluoroglutaric anhydride linker (loading $10\,mg\,g^{-1}$) to afford catalyst **280** [130] (Fig. 13). As an alternative to the Merrifield support, a monolithic support was synthesized by ROMP of norborn-2-ene (NBE) and $(NBE\text{-}CH_2O)_3SiCH_3$ in a suitable mixture of porogens with

the first-generation Grubbs catalyst **1** [130]. Catalyst **354** [130] is grafted on the monolithic support to the perfluoroalkyl chain, as for **353** (Fig. 13).

Excellent reactivity for RCM was observed for the Merrifield supported catalyst **353** with TONs in the range of 80–3200. The monolithic disk immobilized catalyst **354** showed somewhat reduced TONs in the range of 80–960. This clearly stems from the fact that reactions within these disks were not stirred and therefore depended on diffusion of the substrates to the catalytic site.

11. Conclusion

The difference in reactivity of the presented catalysts, clearly underlines that no catalyst is equally good one for every substrate. Reactivity in RCM (and other metathesis-based reactions) depends on distinct catalyst–substrate issues [168]. Moreover, the structural diversity of ruthenium metathesis catalysts can be expanded with no influence of the catalyst performance.

There is now ample evidence that in the new generation of organometallic catalysts the established ligand class of organophosphanes will be supplemented and, partly replaced by NHCs, which have become universal ligands in organometallic and inorganic coordination chemistry. Because of their specific coordination chemistry, NHCs both stabilize and activate metal centers in olefin metathesis, giving higher catalytic performance than organophosphane ligand congeners. Their structural diversity can be obtained easily since the synthesized stable transition metal complexes are tolerant to different functional groups and working at room temperature. However, modification of the NHC ligand can induce substantial changes in the reactivity pattern of the corresponding catalysts and the systematic variation of *N*-substituents may allow fine-tuning of the catalytic activity.

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