

N-Heterocyclic carbenes as highly efficient ancillary ligands in homogeneous and immobilized metathesis ruthenium catalytic systems

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Dedicated to Professor Alexandru T. Balaban on the occasion of his 75th birthday anniversary, in acknowledgement of his significant contribution to advancement in theoretical and synthetic organic chemistry

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Abstract

This general overview focuses on novel N-heterocyclic carbene (NHC) Ru complexes, now at the forefront of research in metathesis chemistry, and on their derived multiple applications in targeted organic, polymeric and natural compound synthesis. This outstanding, large class of ruthenium precatalysts combines high activity and selectivity with increased stability and good tolerance towards organic functionalities, air and moisture. The NHC ancillary ligands allow manipulation of the catalytic performance through adjustment of electronic and steric parameters in the ruthenium coordination sphere, facilitate introduction of chiral motifs, and enable convenient immobilization of homogeneous initiators onto solid supports. A broad spectrum of practical applications is discussed.

Keywords: N-Heterocyclic carbenes, ruthenium complexes, ring-closing metathesis, rotaxanes, natural products, acyclic diene metathesis

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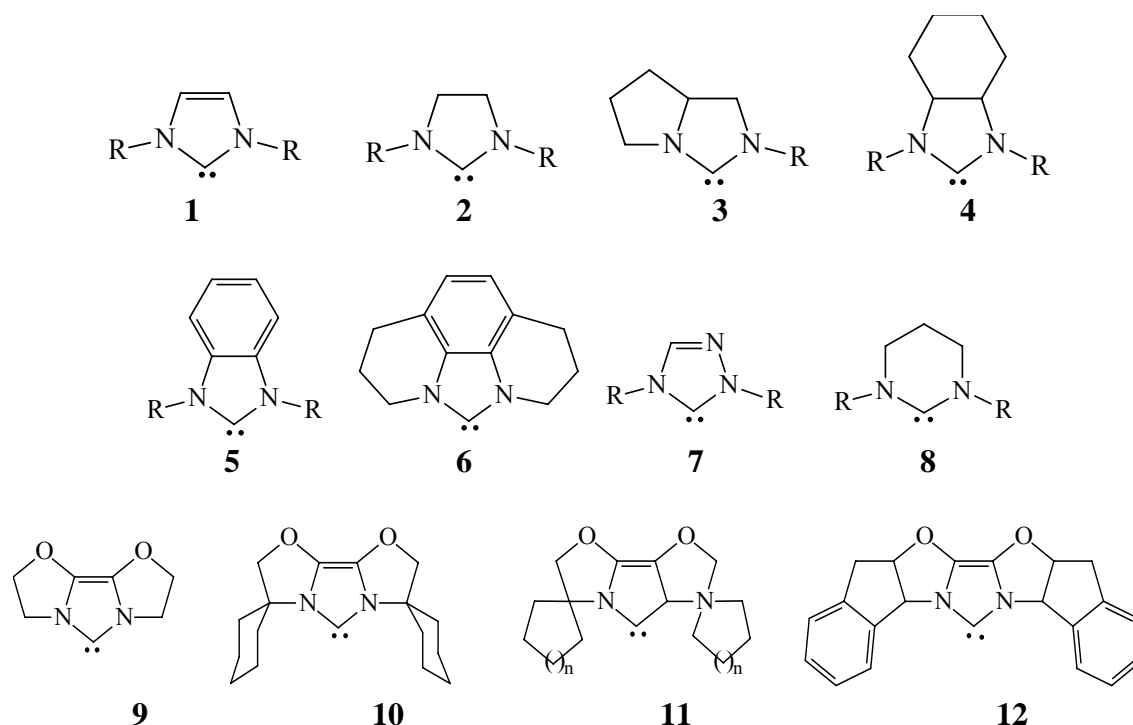
1. Introduction

In the past few years, N-heterocyclic carbenes (NHCs)¹ emerged as ligated versatile building blocks for a large variety of organometallic and coordination compounds.^{2,3} These ligands show a high propensity to act as excellent σ -donors and to generate rather stable metal-carbon bonds.⁴ As with other donor ligands (*e.g.* phosphane, amine, alkoxy, Schiff base), substituent group manipulations allow fine-tuning of the steric and electronic properties of the NHC ligand thus conferring special attributes to the metal complex.⁵ Most NHCs have turned out to be quite efficient ancillary ligands in transition metal complexes widely used as highly active and rather selective catalysts (or precatalysts) in numerous fundamental chemical transformations such as hydrogenation,⁶ hydrogen transfer,⁷ hydroformylation,⁸ hydrosilylation,⁹ isomerization,^{10,11} telomerization,¹² Kharash addition,¹³ Pauson-Khand cyclization,¹⁴ olefin metathesis¹⁵ and various C-C coupling reactions.¹⁶⁻¹⁸ Of these catalytic processes, olefin metathesis has recently undergone spectacular development, becoming a powerful synthetic protocol in organic and polymer chemistry.¹⁹ In the ever-increasing metathesis field, design of new Ru catalysts containing NHC ligands has been seen as an attractive challenge for many research groups. This triggered an avalanche of investigations resulting in innumerable applications of the novel generation of NHC-based metathesis catalysts in organic synthesis.²⁰ The present paper gives a summary of the most important types of these new Ru complexes and their successful application in olefin metathesis, ring-opening metathesis polymerization and related radical reactions (*e.g.* atom transfer radical polymerization (ATRP)).

2. N-Heterocyclic carbenes (NHC). Synthesis and properties

There exists nowadays a variety of nucleophilic N-heterocyclic carbenes employed as ligands in organometallic and coordination chemistry.²¹ Initially, five-membered rings such as imidazolin-2-ylidenes (**1**), and imidazolidin-2-ylidenes (**2**) of the Arduengo²² and Wanzlick²³ ligand families have been prepared and exploited in metal complexes. Following Arduengo's discovery of isolable carbenes, the library of NHCs has expanded to the pyrazole, triazole and thiazole series

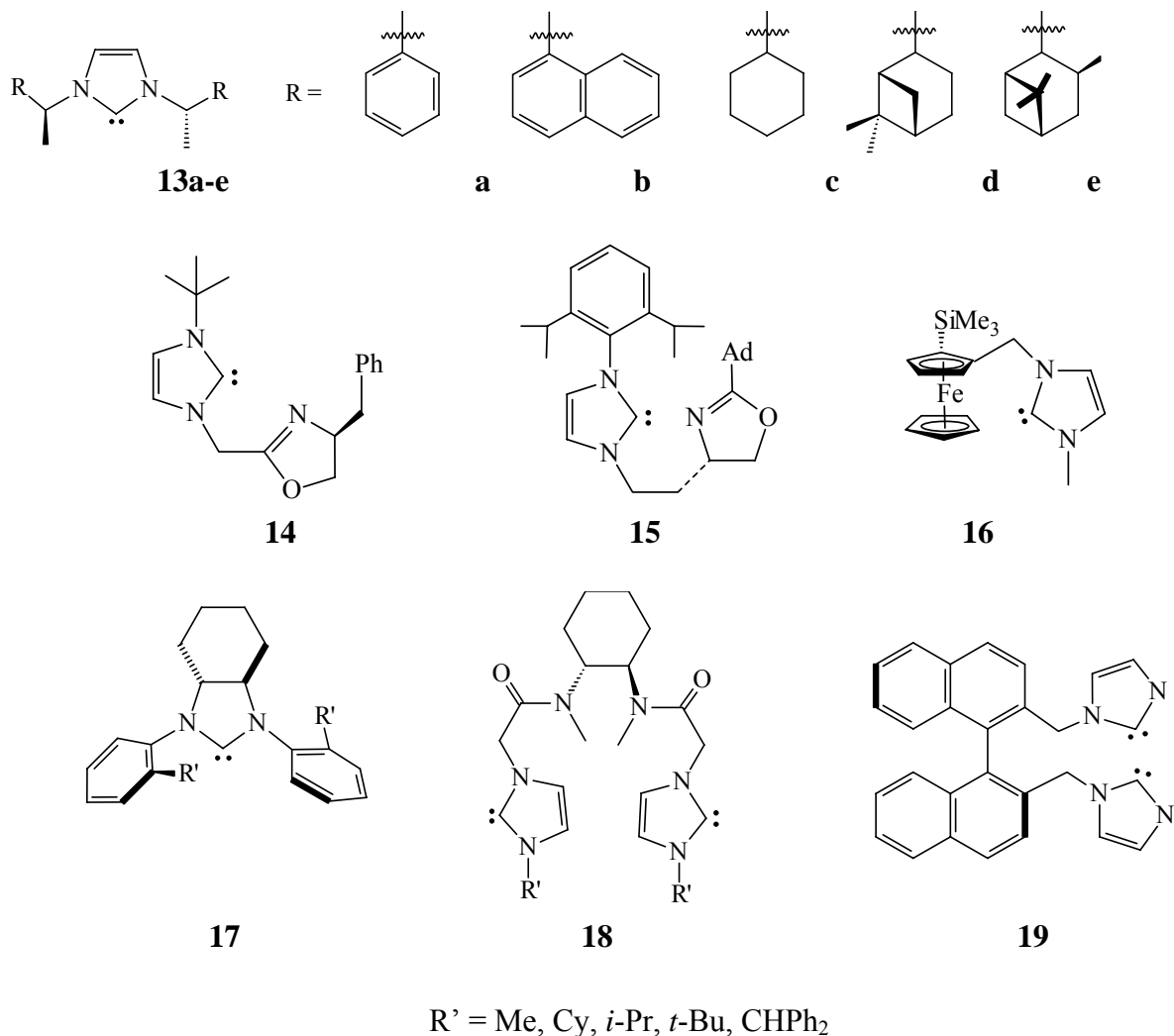
and, more recently, to other heterocyclic compounds including large rings and polycyclic fused systems.²⁴ (Scheme 1).



Scheme 1. Representative N-heterocyclic carbene (NHC) ligands.

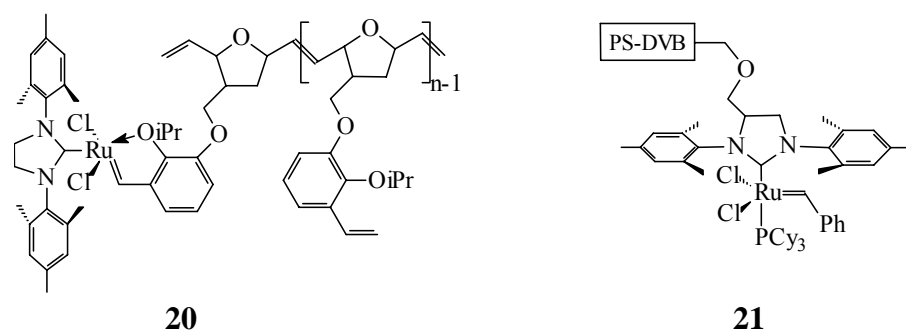
Substituents on nitrogen may be identical (symmetrical NHC ligands) or different (unsymmetrical counterparts). Typically, unsymmetrical NHC ligands are prepared by alkylating the monosubstituted derivatives, at the second nitrogen atom, with the appropriate alkylating agent.²⁵ Symmetrical N-heterocyclic carbenes tend to form stronger coordination bonds to the metal than unsymmetrical ones. Of the former type of ligand, N,N-dialkyls are found to have stronger metal-carbon bonds than the N,N-diaryls of a comparable size.

Chiral²⁶ and immobilized²⁷ N-heterocyclic carbene ligands have opened new ways for creating modular catalytic systems of a high synthetic utility in organic chemistry. Along these lines, NHC structures **13-19** for NHC ligands reflect ubiquitously applied motifs in asymmetric catalysis: pinene- or camphor-derived chiral auxiliaries, oxazolines from optically active amino acids, atropisomerism in binaphthyl systems and the planar chirality of ferrocene. (Scheme 2).



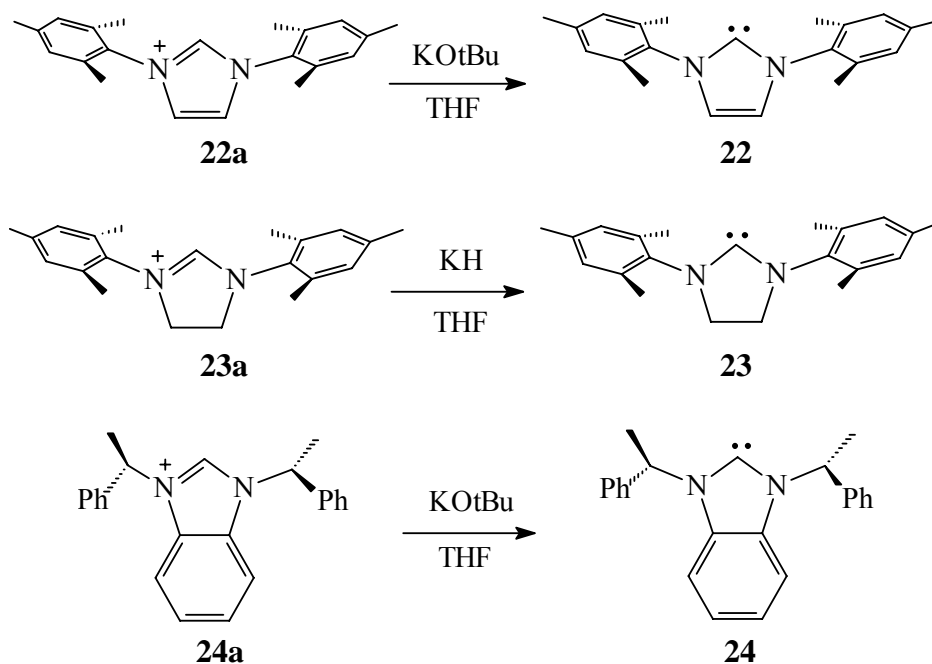
Scheme 2. Chiral ligands encountered in NHC-based metal complexes.

The valuable property of NHC ligands of being suitable for incorporation in immobilized complexes (*e.g.* **20**), and even for helping anchor the complex onto the polymer support (*e.g.* **21**), illustrates the potential of emerging heterogeneous methodologies for ruthenium complex applications (Scheme 3).

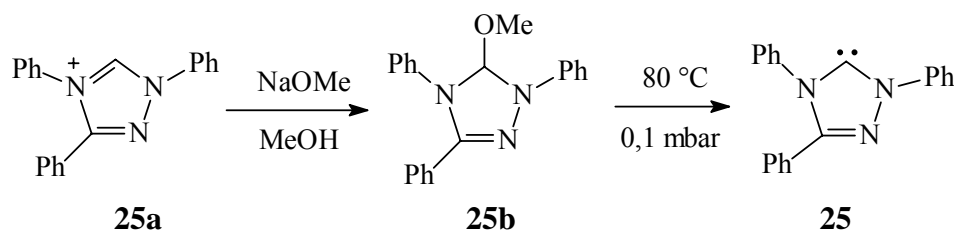


Scheme 3. Immobilized NHC-based Ru complexes.

There are several routes for preparing N-heterocyclic carbenes from the corresponding azolium salts.²⁸ The most common method consists of deprotonation of their respective azolium salts with an appropriate base which generates the free carbene (Scheme 4 and 5).



Scheme 4. Preparation of imidazolin-2-ylidene, imidazolidin-2-ylidene and benzoimidazolin-2-ylidene ligands *via* deprotonation of imidazolium salts (Mes = 2,4,6-trimethylphenyl).



Scheme 5. Synthesis of triazolin-2-ylidene ligands from triazolium salts, by deprotonation and trapping.

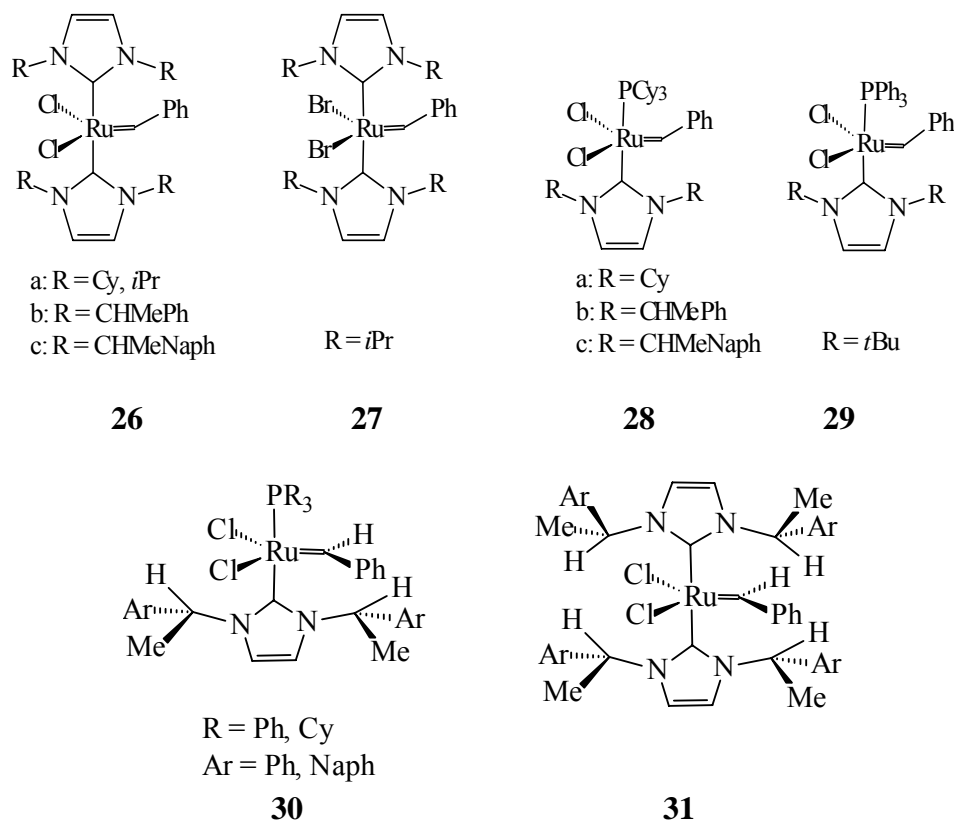
While certain stable carbenes can be isolated and characterized prior to reaction with a complex precursor, the majority react usually *in situ* to provide the desired metal complex. Thermodynamic considerations estimate the dimerization of imidazolinylidene carbenes to be enthalpically favored by ca. 4 kcal/mol, but this apparently does not offset the higher unfavorable entropic factor for the reaction to occur.²⁹ By contrast, imidazolidinylidene carbenes readily dimerize to the corresponding electron-rich alkenes whereas benzimidazolinylidenes have an intermediate behavior. In the latter case, the corresponding carbene – alkene (carbene dimer) equilibrium has been shown to favor the alkene formation by approximately 5 kcal/mol, though the position of the equilibrium will be obviously affected by steric factors associated with the substituent groups.³⁰

Nucleophilic N-heterocyclic carbenes readily displace different types of commonly encountered ligands in metal complexes including bridging halides, phosphines, carbonyls, aryl and alkenes. By such substitution reactions occurring in the coordination sphere of the metal entity, production of a wide variety of metal complexes becomes possible.

The class of nucleophilic carbenes displays very good σ -donor properties forming strong coordination bonds within the metal complexes.³¹ At the same time, they are rather poor π -acceptors because proximal nitrogen atoms preferentially donate electron density into the empty orbital on the carbene carbon.³² As a consequence, introduction of NHC ligands into metal complexes will make metal centers more electron-rich resulting in a pronounced activation effect on the functional bonds crucial for many catalytic processes. Electron density and reactivity of the functional bonds in the catalytic species can be gradually tuned by a rational choice of substituent groups on the NHC ligand. These complexes are quite robust and useful precatalysts that promote different types of reactions, depending mainly on the nature of the coordinated metal. As we shall point out in the following sections, both homogeneous and immobilized NHC-based ruthenium complexes are highly active and chemoselective in olefin metathesis reactions facilitating, by the metathesis user-friendly procedure, the synthesis of a broad spectrum of organic and polymer compounds.

3. Well-Defined Homogeneous NHC Ru Complexes

Almost simultaneously three independent groups reported the synthesis of metathesis ruthenium benzylidene precatalysts containing nucleophilic N-heterocyclic carbenes (NHCs) as ancillary ligands.³³⁻³⁵ Thus, Herrmann et al.³³ published the synthesis of NHC ruthenium complexes **26-31** by ligand exchange reactions of the diphosphane ruthenium benzylidene complex **32**, $\text{RuCl}_2(\text{PR}_3)_2(=\text{CHPh})$ ($\text{R} = \text{Ph}$ or Cy), with the corresponding imidazolin-2-ylidenes.

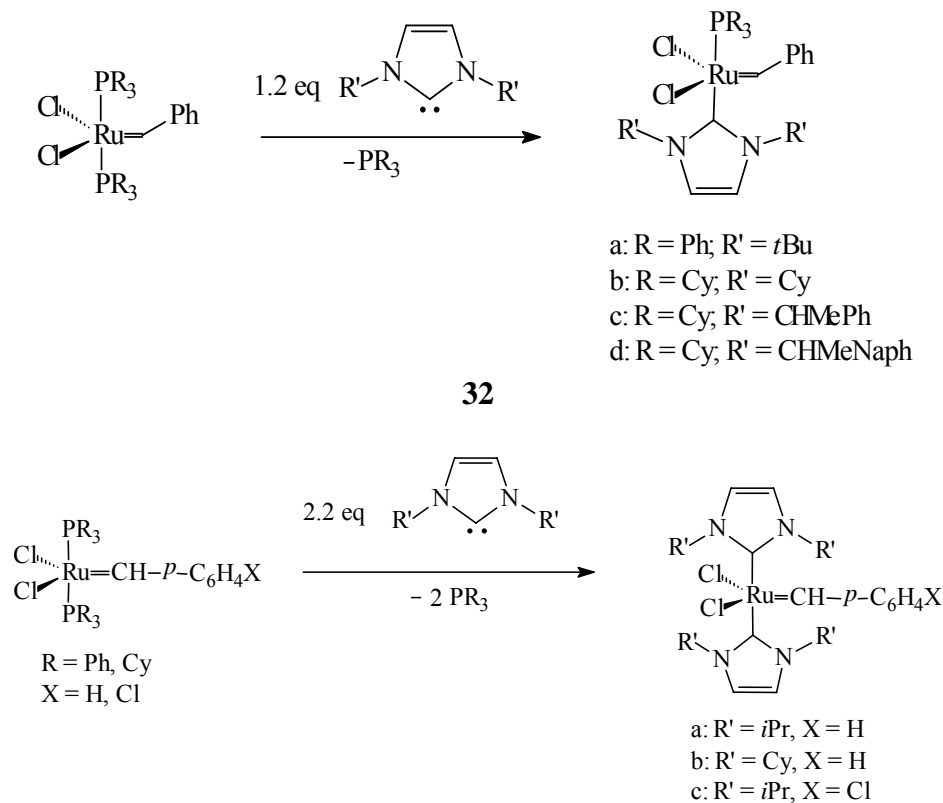


Scheme 6. NHC ruthenium benzylidene complexes.

These non-labile, sterically demanding ligands, were shown to stabilize both the 16-electron complexes and the highly electron deficient metathesis intermediates, resulting in precatalysts with increased metathesis activity as compared to the parent diphosphane congeners. Moreover, this class of ligand is easily accessible, they are stronger Lewis bases than the phosphane counterparts thus improving the stability of the ruthenium complex, and allow a fine-tuning of the reactivity of the catalyst by systematic variation of R groups in the imidazolin-2-ylidene moiety. By the above approach even several chiral imidazolin-2-ylidene ruthenium complexes have been prepared, such as (*R,R*)-**30** and (*R,R*)-**31** ($\text{Ar} = \text{Ph}$ or Naph), from the diphosphane ruthenium benzylidene complex **32** and selected chiral imidazolin-2-ylidene ligands. These

types of chiral compounds make quite promising candidates for convenient precursors to be used in enantioselective metathesis reactions starting from prochiral substrates.

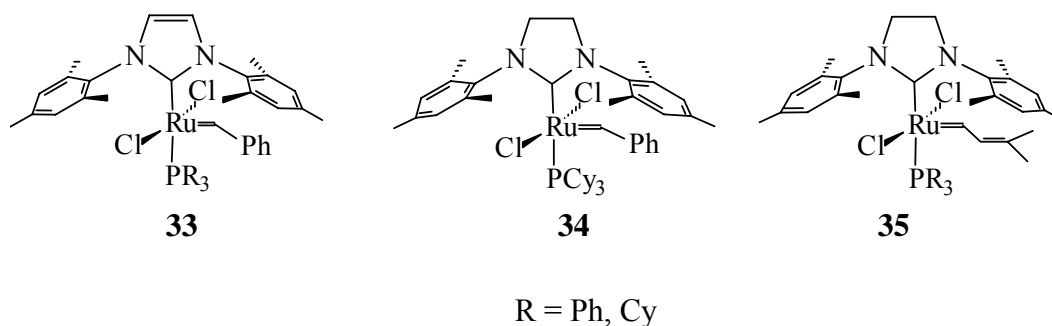
Synthesis of these NHC-ruthenium complexes occurs readily in toluene or tetrahydrofuran, at room temperature, leading in high yield (80-90 %) to products with either one or two imidazolin-2-ylidene ligands, depending on the employed molar ratio between complex **32** (R = Ph or Cy) and N,N-disubstituted imidazolin-2-ylidene (in practice a molar ratio of 1:1.2 or 1: 2.2 is used)³³ (Scheme 7).



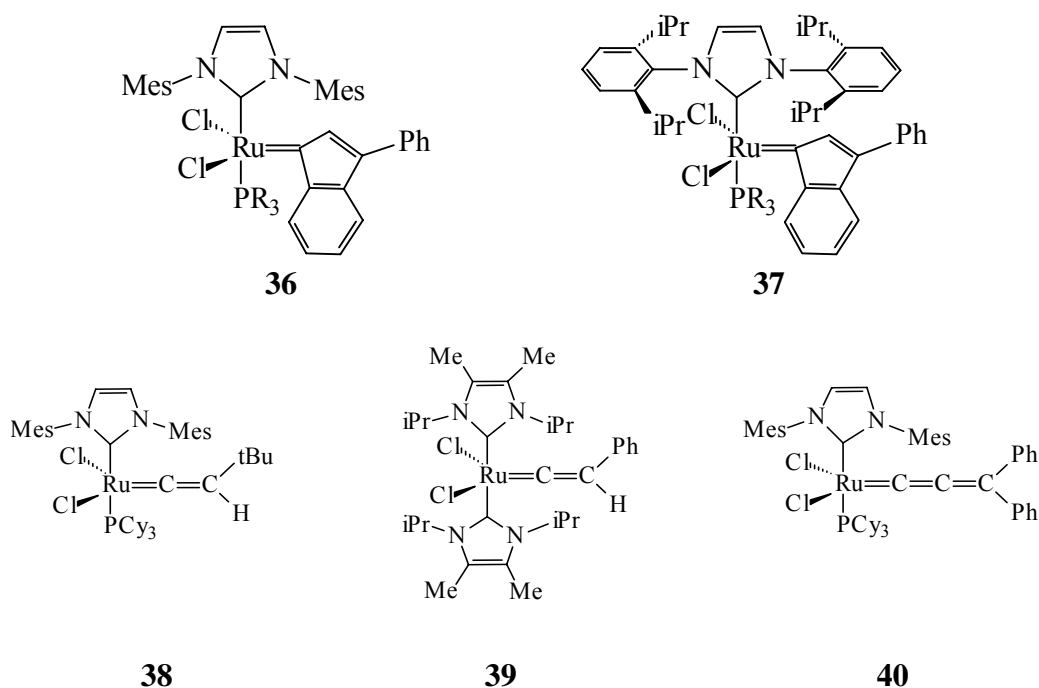
Scheme 7. Synthesis of heteroleptic and homoleptic NHC Ru alkylidene complexes.

Significantly, single-crystal X-ray analysis of the bisimidazolin-2-ylidene *p*-chlorobenzylidene ruthenium complex revealed a lower degree of distortion of the square-pyramidal coordination than the analogous diphosphane complex with R = Cy. Moreover, the Ru-C bond lengths of the alkylidene and the N-heterocyclic carbene moieties showed a fundamentally different nature of the metal-“carbene” bonds.

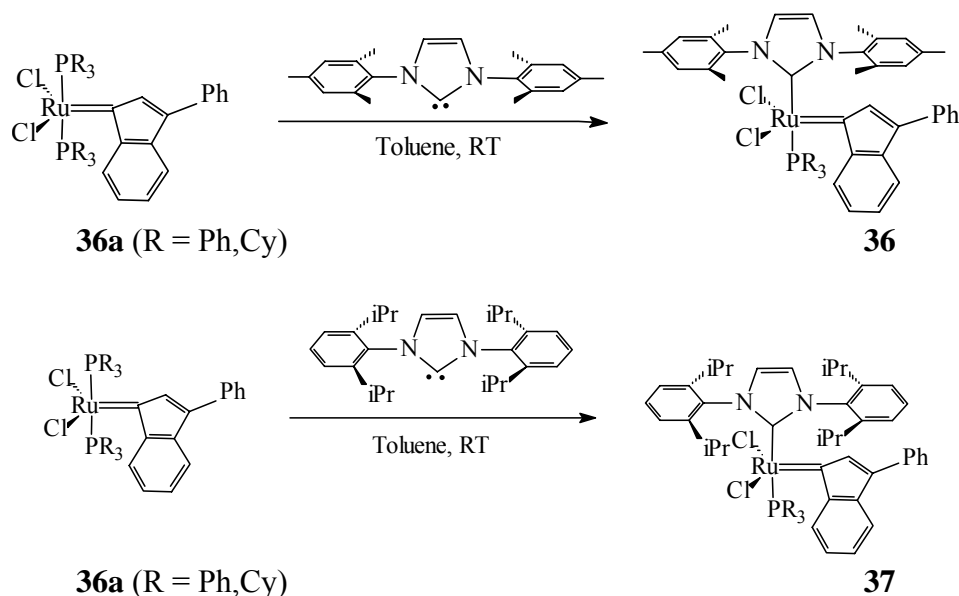
Practically at the same time, Grubbs³⁴ and Nolan³⁵ reported synthesis of the 1,3-dimesitylimidazolin-2-ylidene complex **33** and shortly thereafter of its 4,5-dihydroimidazolin-2-ylidene analogues **34** and **35**, that use another nucleophilic N-heterocyclic ligand of the Arduengo type.²²

**Scheme 8.** NHC ruthenium carbene complexes.

Complexes **33-35** show superior reactivity and increased stability but their metathesis activity strongly depends on the nature of the N-heterocyclic ligand, solvent and substrate, the saturated complex being generally more active than the unsaturated one. Soon after these significant findings, the family of ruthenium complexes containing N-heterocyclic ligands rapidly expanded to the ruthenium indenylidene compounds **36** and **37**³⁶ as well as to the analogous ruthenium vinylidene derivatives **38** and **39**³⁷ and the allenylidene complex **40**.³⁸

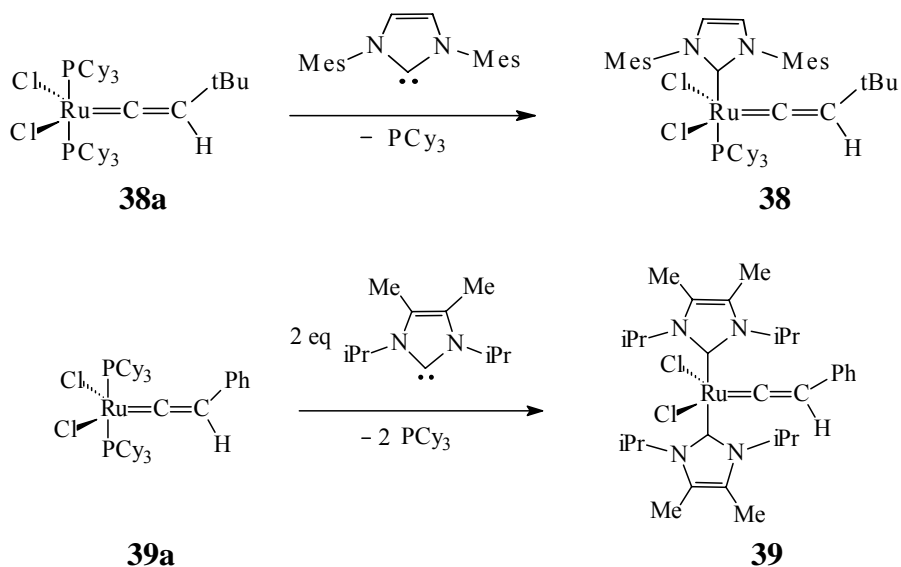
**Scheme 9.** NHC Ru indenylidene, vinylidene and allenylidene complexes.

Synthesis of these complexes occurs readily by direct phosphane displacement in the respective bisphosphane indenylidene, vinylidene or allenylidene complex by the bulky 1,3-dimesitylimidazolylidene group, under mild conditions (Schemes 10-12).



Scheme 10. Synthesis of imidazolin-2-ylidene ruthenium complexes **36** and **37** by reaction of the diphosphane ruthenium indenylidene complex with bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene and bis(2,6-diisopropylphenyl)imidazolin-2-ylidene, respectively.

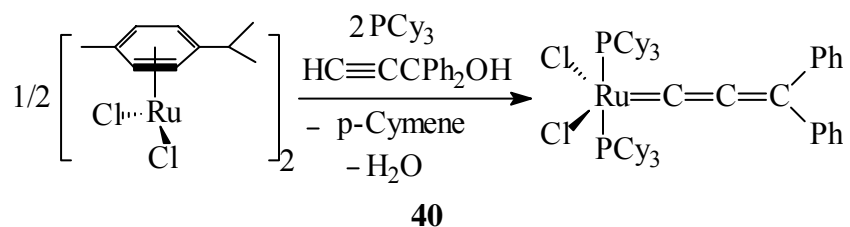
This synthetic protocol afforded imidazolin-2-ylidene ruthenium vinylidene complex **38** in high yield (85%), from the corresponding diphosphane vinylidene complex **38a** (Scheme 11). The complex is a brown solid which exhibited appreciable activity in RCM of diethyl diallylmalonate.³⁷



Scheme 11. Synthesis of imidazolin-2-ylidene ruthenium complexes **38** and **39** by reaction of the diphosphane ruthenium vinylidene complex with bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene and bis(2,6-diisopropylphenyl)imidazolin-2-ylidene, respectively.

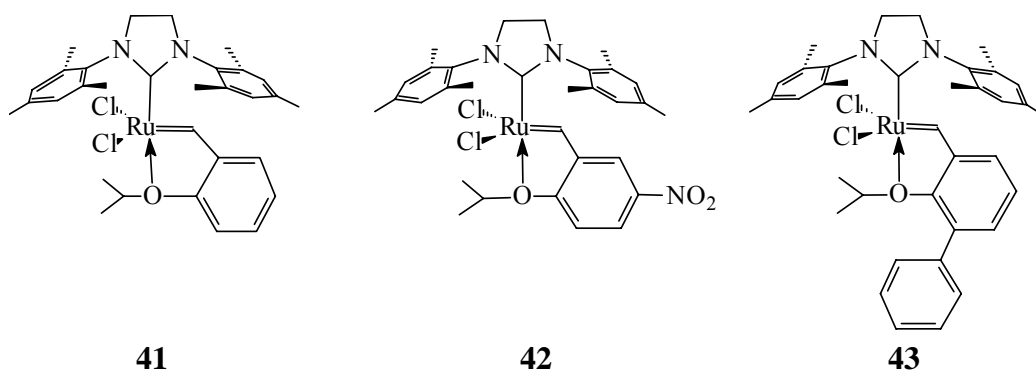
When two equivalents of the imidazolin-2-ylidene ligand precursor are employed, the bisimidazolin-2-ylidene complex **39** is easily accessible by this procedure. Surprisingly, this complex did not manifest the expected metathesis activity in ring-closing of diethyl diallylmalonate, although the analogous bisimidazolin-2-ylidene benzyldiene complex **27** is a recognized RCM precatalyst.³³

The imidazolin-2-ylidene ruthenium allenylidene complex **40** can be prepared in appreciable yield from the ruthenium dimer $[(p\text{-cymene})\text{RuCl}_2]_2$, 3,3-diphenylpropyn-3-ol and PCy_3 , followed by replacement of one PCy_3 by 1,3-dimesitylimidazoline³⁶ (Scheme 12).



Scheme 12. Synthesis of imidazolin-2-ylidene ruthenium allenylidene complex **40** from the ruthenium *p*-cymene dimer, 3,3-diphenylpropyn-3-ol and bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene.

A valuable and easily accessible set of NHC ruthenium complexes, **41-43**, with a chelating isopropoxybenzylidene ligand which augments the catalyst stability, have been synthesized and conveniently applied by several research teams in a broad range of metathesis reactions (Scheme 13).⁴⁰⁻⁴²

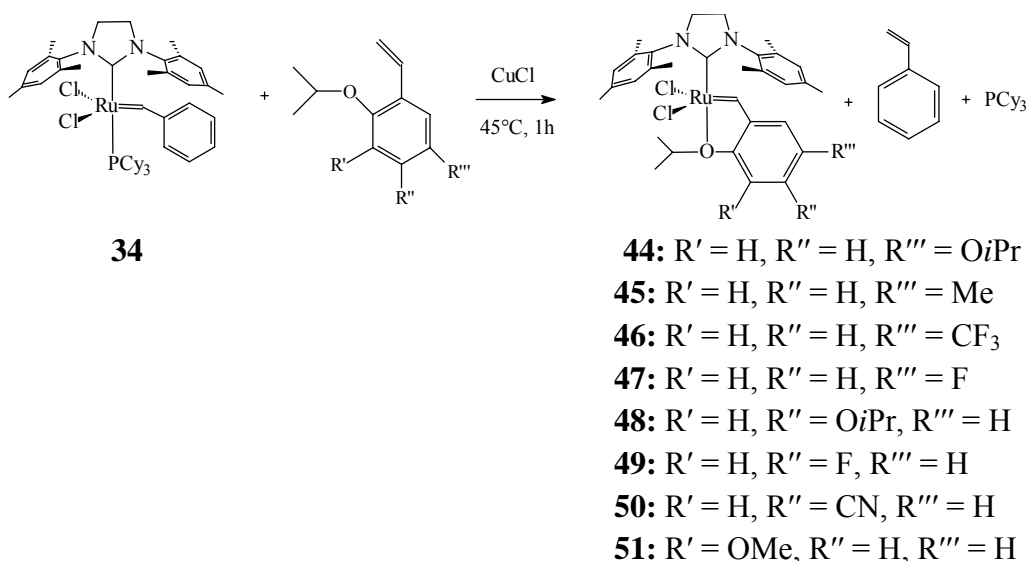


Scheme 13. NHC Ru isopropoxybenzylidene complexes.

Precatalysts bearing such entities can be purified by column chromatography, allowing for precatalyst recycling after the reaction. Immobilization on solid supports of suitably substituted variants of these complexes *via* the isopropoxybenzylidene ligand will be considered in a later section. Significantly, the activity of this type of compound in metathesis reactions can be

adjusted through appropriate structural choices in both the N-heterocyclic carbene and the chelating isopropoxybenzylidene ligand. In this respect, it should be pointed out that complexes containing substituents other than hydrogen *ortho* to the isopropoxy show dramatically improved initiation rates across a wide range of olefin metathesis reactions.⁴³ For instance, in complex **43** having a phenyl substituent in the *ortho* position to the isopropoxy group, the increased steric bulk is supposed to weaken the Ru-O chelate bond, thus facilitating a faster ligand dissociation generating the catalytically active 14-electron intermediate species while also hindering the ligand reassociation, hence catalyst deactivation. On the other hand, by introducing electron withdrawing or donating substituents in various positions of the benzylidene moiety, the electron density on the isopropoxy group and, consequently, the strength of the Ru-O bond can be drastically changed, resulting in a pronounced effect on the catalytic activity. As an example, the analogue **42** of the Hoveyda complex **41**, having a nitro group *para* to isopropoxy, proved to be more active and stable than the parent series head **41**.⁴²

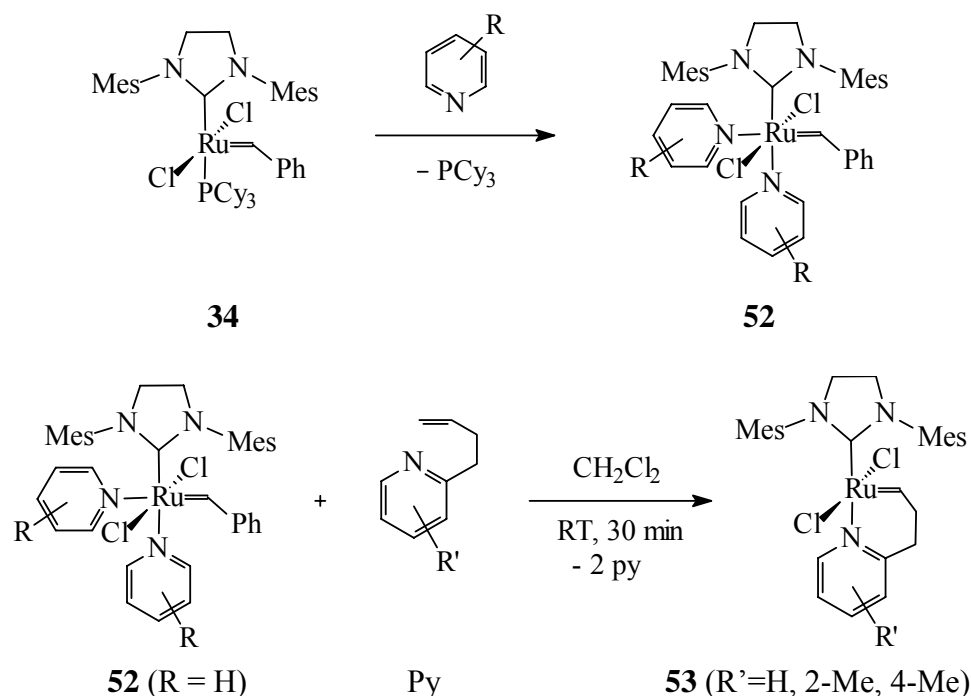
Interesting results have been reported also with other members, **44-51**, pertaining to the same class of ruthenium isopropoxybenzylidene complexes, prepared by reacting Grubbs' second generation ruthenium precatalyst **34** with a set of substituted styrenes (Scheme 14).⁴⁴ Detailed studies on the effect that each isopropoxybenzylidene ligand in **44-51** induced on activity in the ring-closing metathesis (RCM) of N-containing dienes validated the previous assumption that increased steric hindrance *ortho* to the isopropoxy group considerably enhances reaction rates. Again, decreasing electron density both at the chelating oxygen atom and the Ru=C bond appreciably accelerated metathesis reactions.⁴⁴



Scheme 14. Synthesis of NHC Ru substituted isopropoxybenzylidene complexes.

Highly active bispyridine complexes [(H₂IMes)(R-py)₂(Cl)₂Ru=CHPh] (R = H, 3-Br, 4-Ph) (**52**) have been prepared by Grubbs⁴⁵ through addition of a large excess of pyridine or

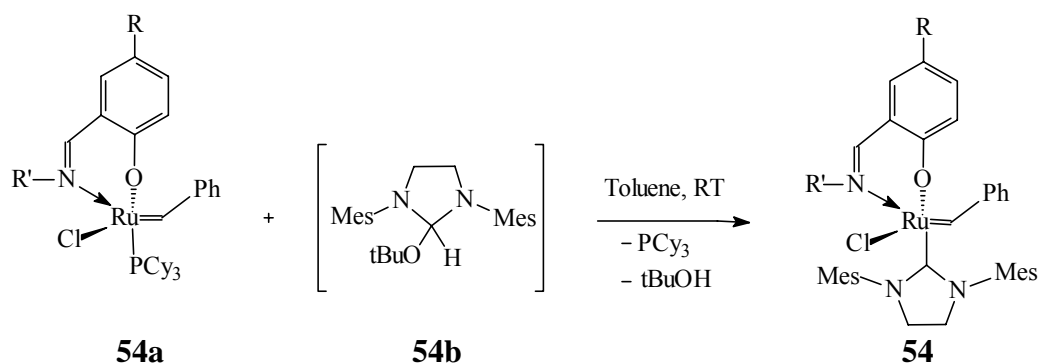
appropriately substituted pyridine to the complex **34**. These reactions are complete within minutes, require little or no solvent and can be performed with commercial grade reagents. For instance, reaction of **34** with 3-bromopyridine provides $[(\text{H}_2\text{IMes})(3\text{-Br-py})_2(\text{Cl})_2\text{Ru}=\text{CHPh}]$ within minutes (yield 89%). This precatalyst proved to be of great value in acrylonitrile cross metathesis (CM) as well as an exceptionally fast initiator for the metathesis of simple olefins (Scheme 15).



Scheme 15. Synthesis of NHC Ru complexes with N-donor (**52**) and chelating ligands (**53**).

Starting from complex **52** ($R = \text{H}$), Grubbs and coworkers⁴⁶ prepared a new heterocyclic carbene ruthenium complex **53** ($R' = \text{H}, 2\text{-Me}, 4\text{-Me}$), in high yield (ca. 80%), by metathesis reaction with 1.5 equiv. of 2-(3-butenyl)pyridine in dichloromethane, at room or slightly elevated temperature. NHC and pyridine ligands are *trans* in **53** and *cis* in its isomer formed on heating **53** at 40°C. In contrast to catalyst **52**, the new ruthenium complex **53** has a low initiation rate for metathesis reaction and consequently is more latent in RCM and ROMP processes. This behavior is particularly beneficial when performing ROMP reactions because it allows for longer handling of the monomer/catalyst mixture before the actual polymerization starts.

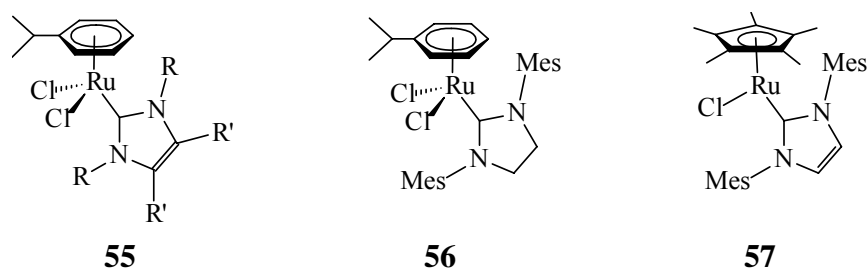
Valuable NHC ruthenium complexes **54**, having as ligands 1,3-dimesityl-4,5-dihydroimidazolin-2-ylidene along with Schiff bases in which the catalytic activity could be controlled by altering electronic and steric demands in the metal coordination sphere, have been prepared by Verpoort and coworkers⁴⁷ *via* substitution of the phosphane ligand with 4,5-dihydroimidazolin-2-ylidene group (Scheme 16).



Scheme 16. Synthesis of NHC Schiff-base Ru complex **54**.

The protected imidazolin-2-ylidene intermediate, **54b**, was prepared *in situ* directly from imidazolium tetrafluoroborate and *t*-BuOK and employed further in the reaction with complex **54a** to produce the imidazolin-2-ylidene ruthenium precatalyst **54**. Studies on RCM and ROMP reactions induced by this type of catalytic precursors indicated high activity and excellent stability as compared to the phosphane counterparts.⁴⁸

In the context of these exceptional achievements it is worth noting that imidazolin-2-ylidene ligands have also been employed in design and synthesis of an interesting class of arene ruthenium complexes, **55-57**, the first two compounds being of a special importance for both radical and metathesis reactions due to their easy accessibility from the commercially available ruthenium dimer [(*p*-cymene)RuCl₂]₂⁴⁹ (Scheme 17).

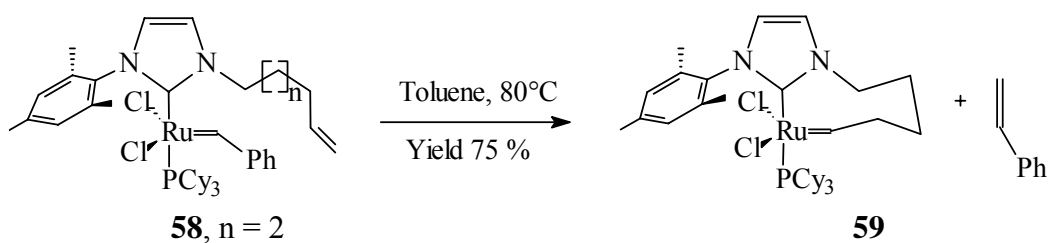


Scheme 17. Some NHC Ru arene complexes.

In addition, such imidazolin-2-ylidene arene complexes have high potential as precursors for further arene ruthenium compounds with pronounced catalytic properties in various organic reactions.

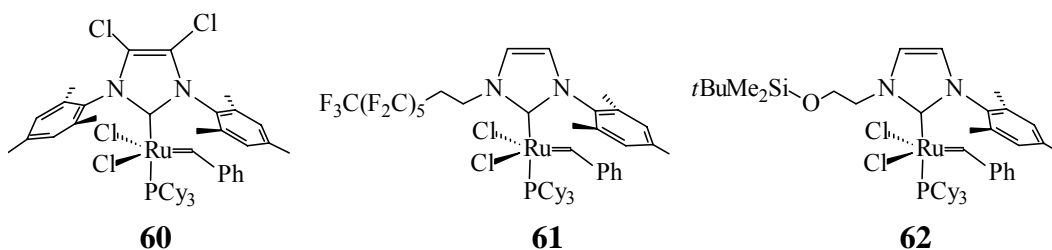
Unsymmetrically substituted complexes **58** ($n = 1, 2, 4$) readily metathesize their own ligands to form chelated NHC ruthenium complexes in which the N-heterocyclic carbene and the “regular” carbene unit Ru=CHR are tethered by a variable “cyclic” structure. In one example, heating a solution of complex **58** ($n = 2$) in refluxing toluene afforded “metallacyclic” complex **59** in 75% isolated yield⁵⁰ (Scheme 19). It was assumed that the catalytic species might be able

to regenerate itself after the productive metathesis is over and the substrate in solution has been quantitatively consumed.



Scheme 18. Synthesis of cyclic NHC Ru complex **59**.

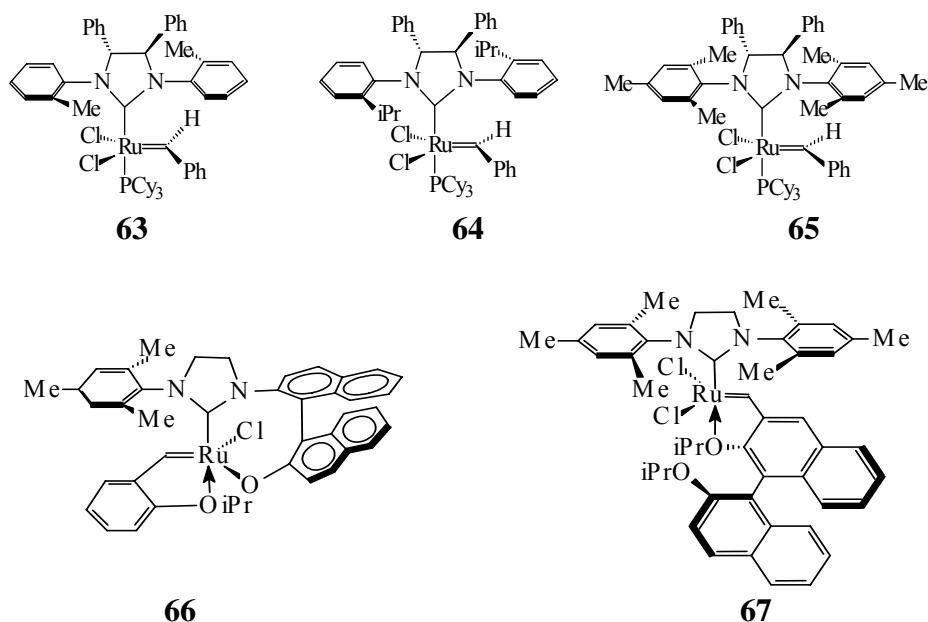
Complex **60**, prepared from diphosphane complex **32** and 4,5-dichloroimidazolinyldene according to the procedure described above, displayed good thermal stability and catalytic activity in various metathesis reactions.⁵⁰ (Scheme 19).



Scheme 19. Symmetrical and unsymmetrical NHC Ru complexes.

The same strategy afforded the unsymmetrically substituted NHC complexes **61** and **62** containing a perfluoroalkyl chain or a silylether side-chain.

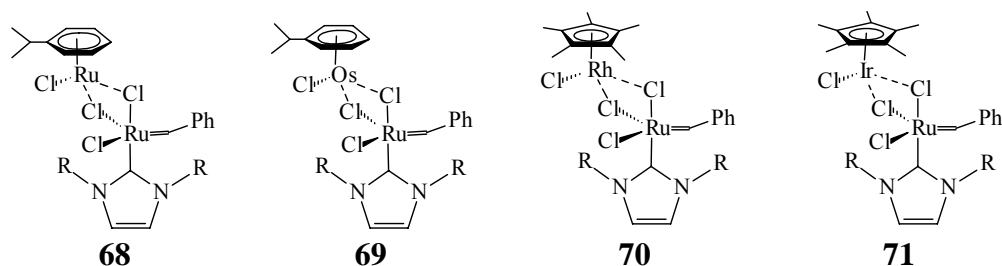
As a bonus for asymmetric catalysis, the new chiral NHC ruthenium benzylidene complexes **63-67** could be synthesized and screened for their metathesis enantioselectivity.⁵¹⁻⁵³ (Scheme 20).



Scheme 20. Chiral NHC-based ruthenium complexes.

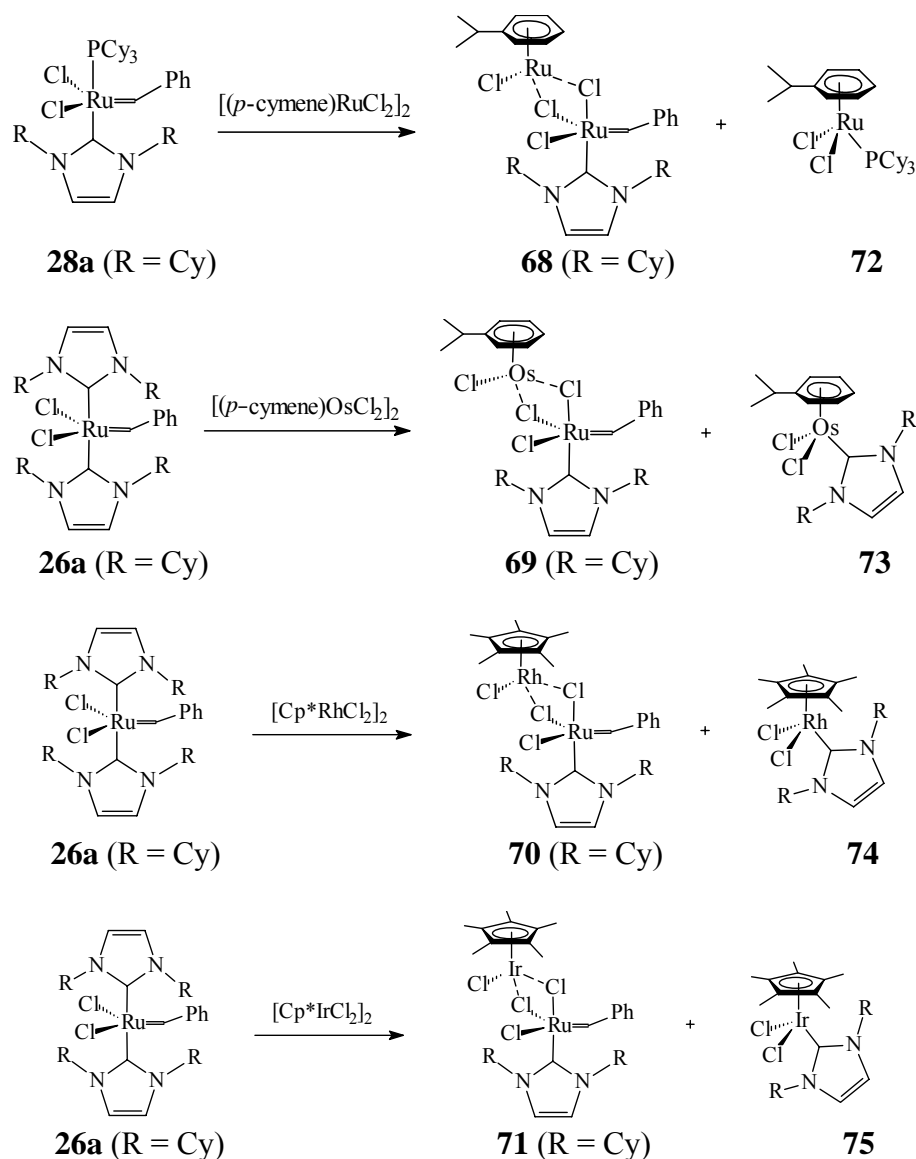
Both complexes **63** and **64** ingeniously use backbone stereogenicity to induce atropisomeric chirality in the unsymmetrical N-aryl substituents. Of these two chiral ruthenium benzylidene complexes, compound **64** showed a wide range of metathesis activity and a particularly high enantioselectivity in RCM of dienes.⁵² More recently, novel chiral ruthenium complexes bearing different alkylidene moieties, *e.g.* **66** and **67**, have been prepared and investigated in enantioselective metathesis processes. Complex **66**, stereogenic at the metal center, has been obtained in >98% diastereoselectivity and readily purified by chromatography on silica gel. Its structure suggests that the peripheral phenolic oxygen coordinates to the ruthenium and locks the aromatic group into a chiral, twisted conformation. This chiral complex proved to be a highly effective catalyst in promoting both asymmetric ring-closing (ARCM) and cross-metathesis (CM) as well as ring-opening metathesis (ROM).⁵³

An interesting panel of very active NHC homo- and heterobimetallic complexes containing Ru, Os, Rh and Ir, such as **40-44**, resulted from selective ligand substitution in mono- or bisimidazolin-2-ylidene ruthenium complexes using appropriate chloro-bridged organometallic dimers⁵⁴⁻⁵⁶ (Scheme 21).



Scheme 21. Examples of dinuclear NHC Ru complexes.

The procedure followed for the synthesis of complexes **68-71** is based on the difference in affinity of the Ru-, Os-, Rh- and Ir-dimer fragments for either the imidazolin-2-ylidene or phosphane ligand. Thus, **68** can only be obtained starting from the heteroleptic **28a** because the affinity of the $[(p\text{-cymene})\text{RuCl}_2]$ fragment for the phosphane ligand is high enough to selectively abstract the phosphane alone leaving the imidazolin-2-ylidene ligand untouched⁵⁵ (Scheme 22).



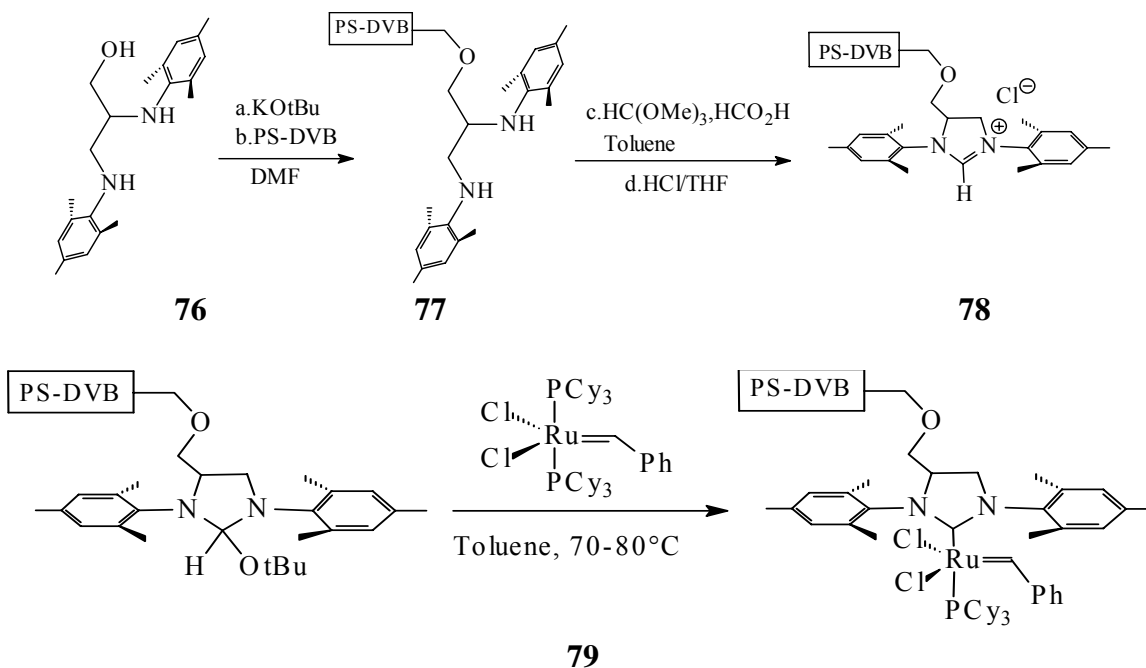
Scheme 22. Synthesis of dinuclear NHC Ru complexes.

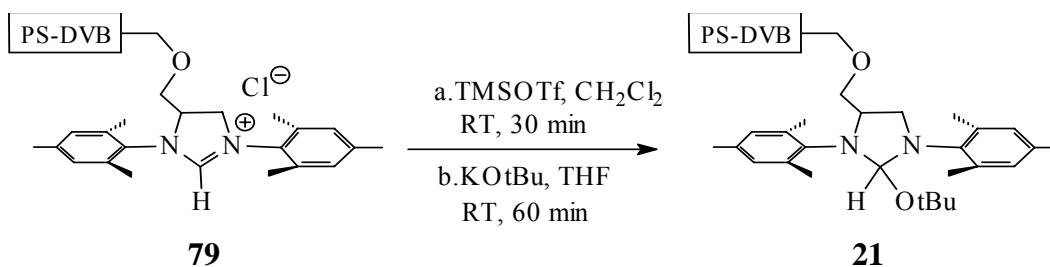
By contrast, **69-71** can be obtained preferentially from **26a** (R = Cy) and the corresponding organometallic dimers, as reaction of **28a** will lead to a mixture of bimetallic complexes with phosphane or NHC.⁵⁵

4. Immobilized NHC Ru complexes

In catalysis, immobilization of well-defined homogeneous complexes is a sagacious policy that combines benefits from both heterogeneous and homogeneous catalytic systems.⁵⁷⁻⁵⁹ This technique offers several assets to organic synthesis such as simplification of reaction procedures, easy separation of products, recyclability of expensive catalysts, possibility to operate in continuous flow processes, good control of morphology of polymers and high polymer bulk density.⁶⁰ Taking advantage of the propensity of N-heterocyclic carbenes to generally form strong σ -bonds with the metal, these ligands may serve as suitable linkers for immobilizing metal complexes onto solid supports.⁶¹

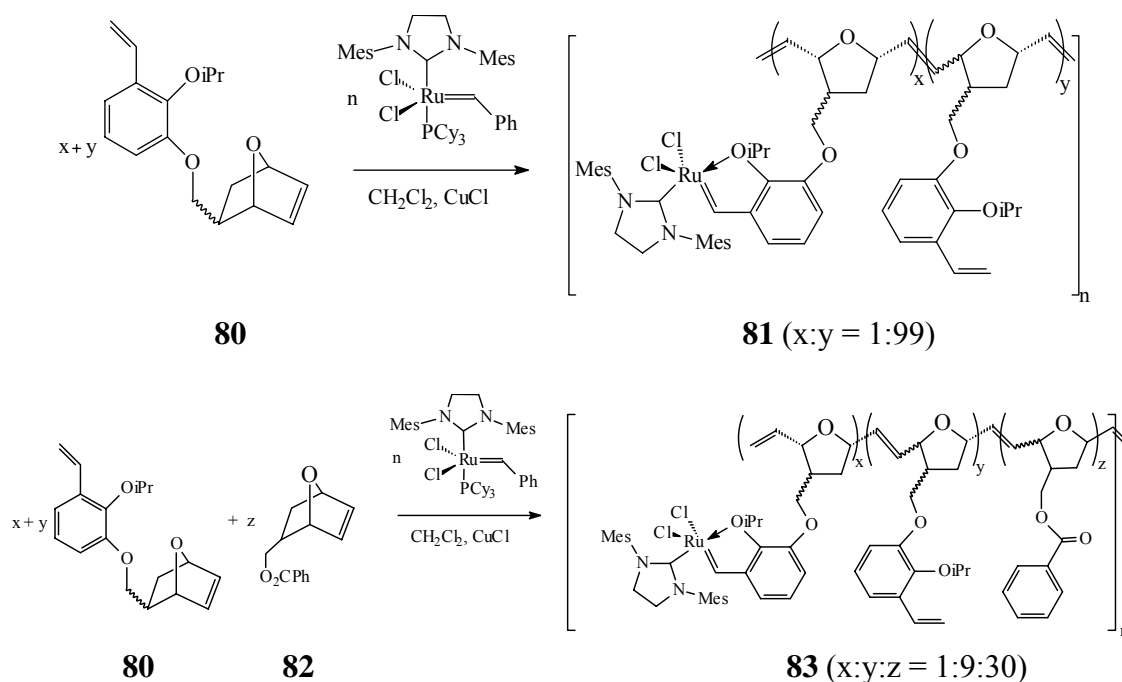
This favorable feature has been successfully exploited by Blechert²⁷ to prepare a permanently immobilized and highly active NHC ruthenium benzylidene complex **21** by attaching **34**, through its NHC ligand, to a polymeric support. The approach developed consists in synthesis of an immobilized suitable ligand precursor **78**, starting from the diamine **76** (see Scheme 23). Compound **76**, in turn prepared from 2,3-dibromo-1-propanol and 2,4,6-trimethylaniline, was attached, after deprotonation of the hydroxyl group, to Merrifield polystyrene (1% divinyl benzene (DVB)) by an ether linkage yielding quantitatively the immobilized compound **77**; this diamine was cyclized under acidic conditions and, after anion exchange, gave the support-bound 3,4-dimesityl-4,5-dihydroimidazolium salt **78**. Precursor **78** was converted into the protected carbene **79** (2-*tert*-butoxy-4,5-dihydroimidazoline), which through *in situ* deprotection in the presence of diphosphane ruthenium benzylidene complex **32** ($\text{RuCl}_2(\text{PPh}_3)_2(=\text{CHPh})$), yielded the support-bound NHC ruthenium complex **21**.





Scheme 23. Synthesis of immobilized NHC ruthenium complex **20**.

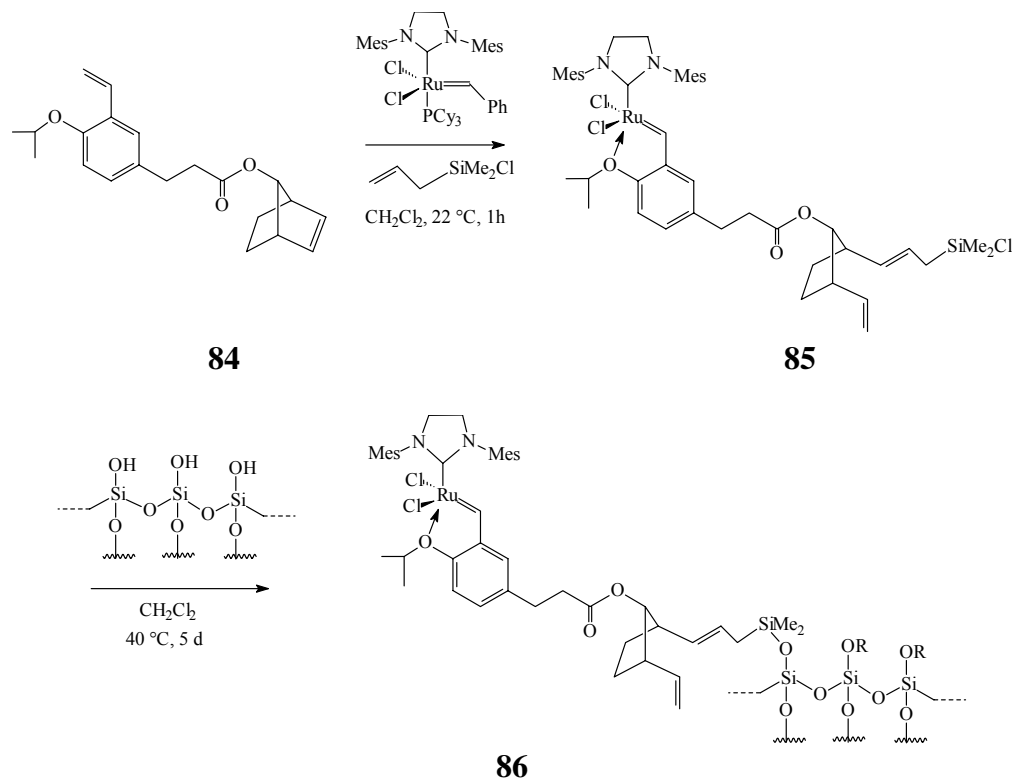
A polymer-bound, homogeneous, recyclable and highly active NHC ruthenium catalyst **81** has also been prepared by the same authors⁶² *via* ROMP of the norbornene derivative **80**, in the presence of complex **34** (Scheme 24).



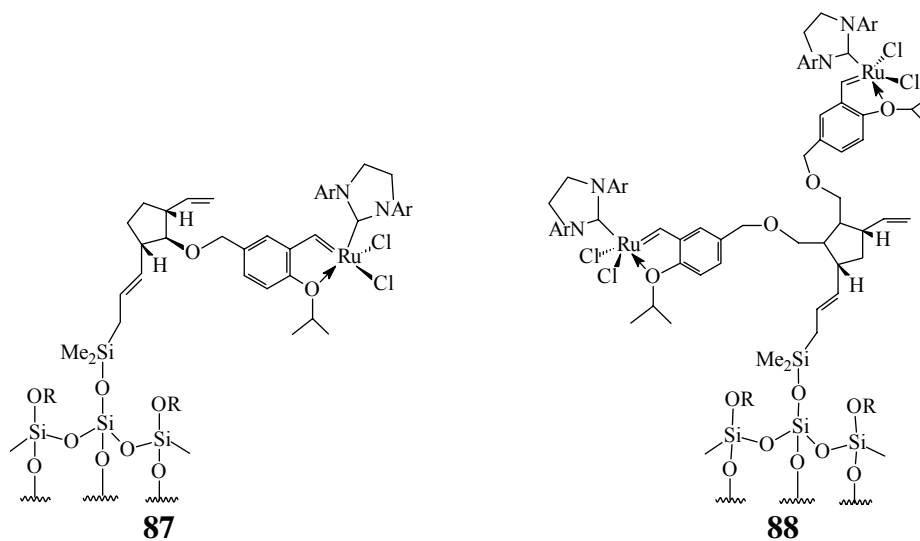
Scheme 24. Synthesis of immobilized NHC ruthenium complexes **81** and **83**.

The procedure was further conveniently extended to the synthesis of supported catalyst **83** using an oxanorbornene benzoate co-monomer, **82**; **82** was employed in conjunction with compound **80** and the ruthenium complex **34**. Excellent conversions in RCM of a variety of diene substrates have been attained producing carbo- and heterocyclic compounds with five-, six-, seven- and higher-membered rings, in several cases hitherto unreachable. It is important to note that the recyclability of these catalysts in metathesis reactions is remarkable, some of them (e.g. **83**) allowing high conversions (>98%) of diallyl tosyl amide to 1-tosylpyrroline, even after 7 reaction cycles with total recovery of the catalyst.

On using an appropriate linker, generated from the styrene ether **84**, to bind the NHC isopropoxy benzylidene Ru complex on a monolithic sol-gel, Hoveyda and coworkers⁶³ prepared in a "one-pot" procedure the series of highly active and recyclable supported Ru complexes **86-88** (Scheme 25 and 26).



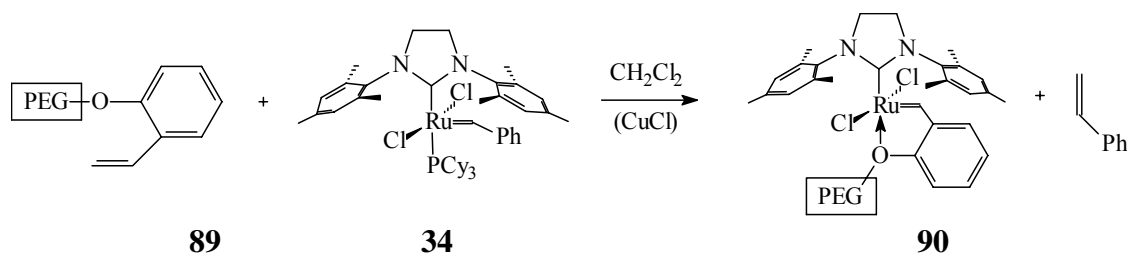
Scheme 25. Synthesis of supported NHC ruthenium complex **86**.



Scheme 26. Supported NHC ruthenium complexes **87** and **88**.

Practically, these supported catalysts provided products in RCM and tandem ring-opening/cross metathesis that are of excellent purity even before silica gel chromatography or distillation. They are recommended for use in combinatorial synthesis in air and with reagent-grade commercial solvents.

An interesting soluble, polymer bound NHC ruthenium carbene catalyst **90** was prepared by Lamaty et al.⁶⁴ through exchange of benzylidene from the commercially available Grubbs' catalyst **34** with the supported ligand **89** (PEG = polyethylene glycol) (Scheme 27).



Scheme 27. Synthesis of soluble-polymer bound NHC ruthenium complex.

This catalyst was fully characterized by solution NMR and MALDI mass spectrometry and tested in RCM reactions. It proved to be particularly active and could be used in parallel synthesis of cyclic amino esters. ¹H NMR analysis provided key information concerning the recovery of the catalyst at the end of the reaction. Most significantly, catalyst **90** could be recovered and recycled in this kind of reaction.

5. Manifold synthetic applications of NHC Ru complexes

5.1. Synthesis of carbocycles and heterocycles

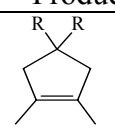
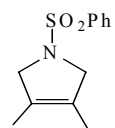
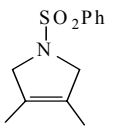
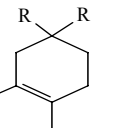
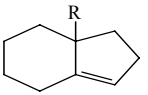
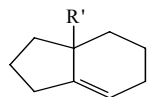
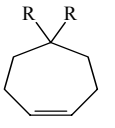
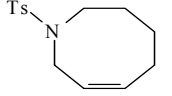
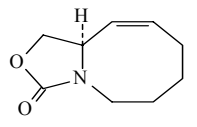
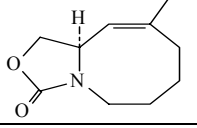
Carbocycles and heterocycles are ubiquitous constituents of architecturally complex natural products and, therefore, synthesis of a large number of carbocyclic and heterocyclic compounds using well-defined transition metal alkylidene initiators has been a productive field in metathesis chemistry. With the advent of the highly active and user-friendly NHC ruthenium precatalysts, functionalized carbocycles and heterocycles with variable size and molecular architecture have become easily accessible by RCM of dienes bearing a diversity of substituents. Moreover, whereas synthesis of tri- and tetrasubstituted cyclic olefins and of specialty, functionalized polymers was possible previously only with the efficient and sensitive Schrock molybdenum alkylidene catalysts,⁶⁵ nowadays a wide variety of such structures have become available by means of the new class of NHC-based ruthenium catalysts. Representative examples, selected from the extensive work of Furstner et al.⁶⁶ on RCM of an array of dienes leading to a multitude

of carbocycles and heterocycles, in the presence of complexes **33** and **36** (R = Cy) as initiators, are summarized in Table 1.

As can be observed from Table 1, reactivity of the benzylidene complex **33** and indenylidene complex **36** in CH₂Cl₂ is sufficiently high to easily allow synthesis of di- and trisubstituted alkenes in good to excellent yields. By this approach all ring sizes, including medium-sized and macrocyclic rings, could be prepared. This behavior was verified even for tetrasubstituted alkenes (entries 1-4) as well as in the case of annulation reactions (entries 9 and 10). From all data it is obvious that the two ruthenium initiators **33** and **36** display a rather similar activity in the studied reactions yet the latter is particularly attractive because of its convenient preparation based on commercially available propargyl alcohol as the carbene source. The sharp difference in product yield for annulation reactions leading to compounds **98** and **99** (entries 9 and 10) is striking if we take into account that the starting materials differ only by a methyl substituent.

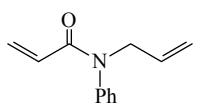
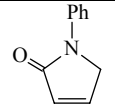
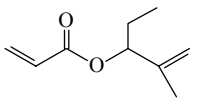
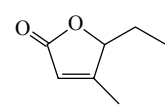
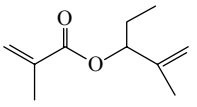
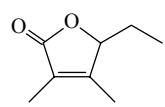
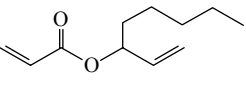
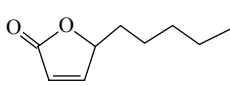
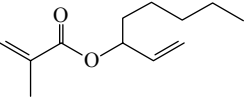
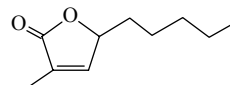
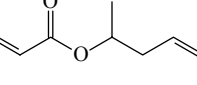
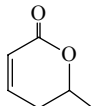
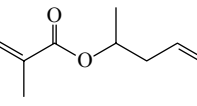
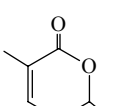
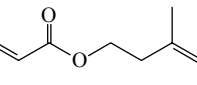
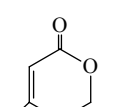
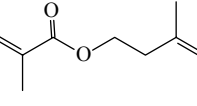
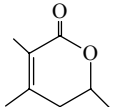
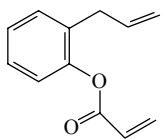
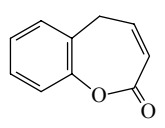
Of particular significance for their preparative value, metathesis reactions of acrylates and other electron deficient alkenes^{67,68} readily proceed in the presence of NHC ruthenium precatalysts.⁶⁶ As illustrated in Table 2, synthesis of a large number of tri- and tetrasubstituted α,β -unsaturated lactones of variable ring size succeeds with complex **33**. Tertiary acrylic amides also proved to take part in ring-closing metathesis in the presence of **33** whereas a residual H-atom on amide nitrogen was reported to lead exclusively to isomerization product, under the same conditions.

Table 1. Carbocycles and heterocycles obtained by ring-closing metathesis of various dienes using precatalysts **33** and **36** in refluxing CH₂Cl₂^a

Entry	Product	Catalyst (mol%)	Yields (%) ^b
1		34 (8 %)	77 ^c
2		34 (2.5%)	96 ^c
3		36 (2.5%)	97 ^c
4		36 (2.5%)	89 ^c
5		34 (5%)	98
6		34 (5%)	93
7		36 (5%)	71
8		34 (1%)	64
9		34 (1%)	62
10		34 (5%)	93

^a Data from Ref. ⁶⁶. ^b Isolated yield. ^c Solvent toluene, reaction temperature 80°C; R = COOEt, R' = COOMe)

Table 2. Ring-closing metathesis of α,β -unsaturated esters and amides initiated by **33** in toluene at 80°C^a

Entry	Substrate	Product		Yield (%)
1			100	82
2			101	78
3			102	63
4			103	93
5			104	92
6			105	95
7			106	79
8			107	73
9			108	42
10			109	89

^a Data from Ref. ⁶⁶

Both inter- and intramolecular enyne metatheses have recently become productive methods for preparing cyclic compounds that had been difficult to obtain by conventional routes.^{69,70} Application of NHC ruthenium complexes in this area was fruitfully expanded to a large range of sterically demanding substrates for which the previously used phosphane ruthenium complexes were practically inactive.⁵⁰ The results presented in Table 3 adequately illustrate the outstandingly wide scope of this approach. Thus, this new methodology afforded five- and six-membered heterocycles in appreciable yields, on conducting metathesis induced by complex **33** (R = Cy) with enynes bearing different heteroatoms. It is noteworthy that, various degrees of substitution on the alkene entity are tolerated by the NHC-based ruthenium precatalyst **33**. Even trisubstituted alkenes are found to undergo efficient cycloisomerization with this precatalyst.

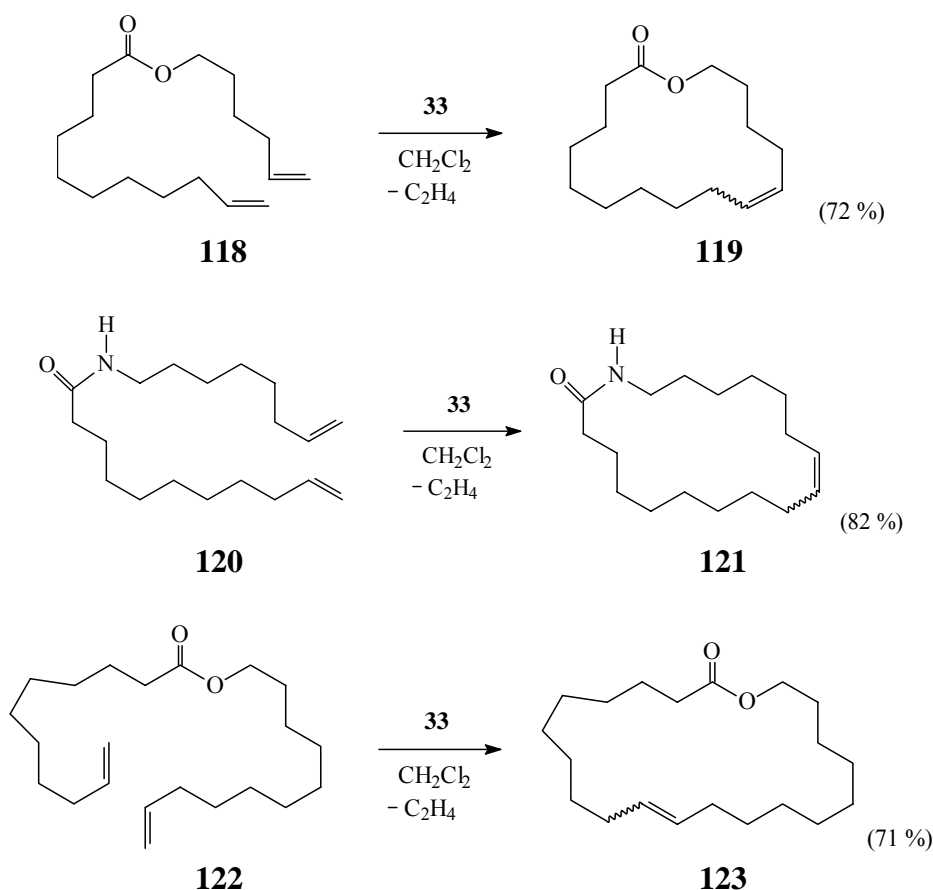
Table 3. Cycloisomerization of substituted enynes induced by **33**, in toluene at 80°C^a

Entry	Substrate	Product	Yield (%)
1			89
2			75
3			67
4			97
5			81 ^b
6			66
7			81
8			42

^a Data from Ref.⁵⁰. ^b Under reflux in CH₂Cl₂; R = COOEt

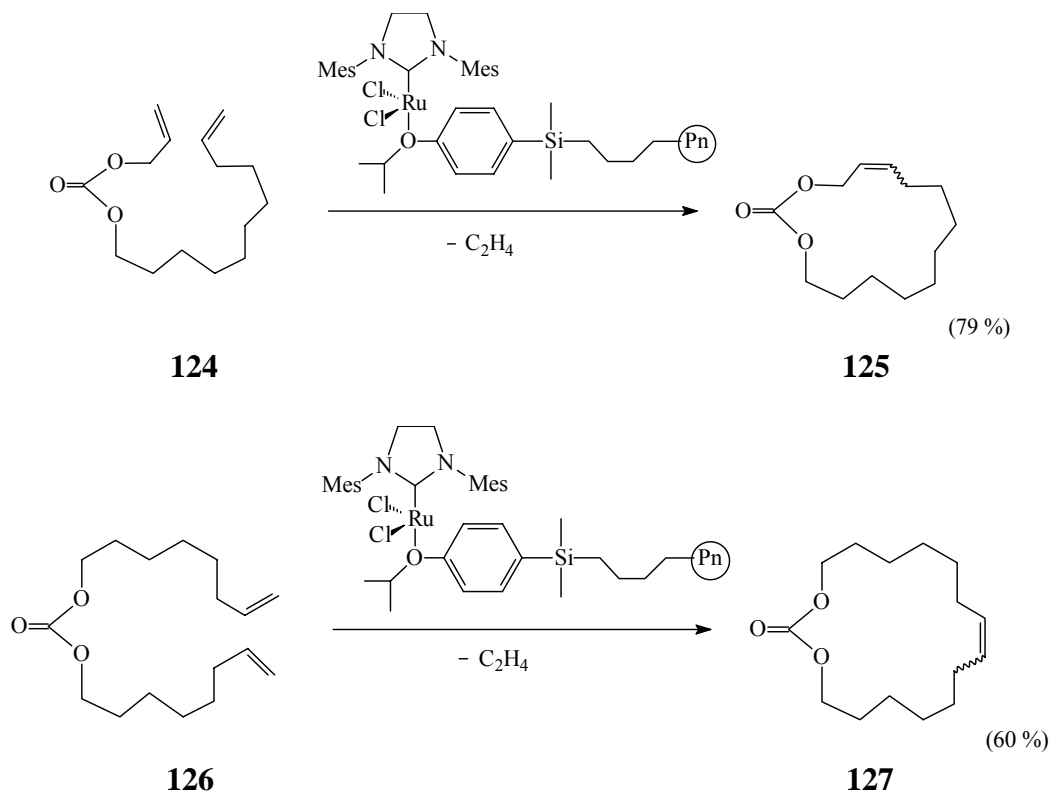
5.2. Synthesis of macrocyclic compounds

NHC-based ruthenium precatalysts perform very well in macrocyclization reactions of linear dienes promoting synthesis, in good to excellent yields, of a wide palette of heteroarom-containing macrocycles, some of which, *e.g.* the musk-odored lactone **119**, are of a high practical value (Scheme 28).



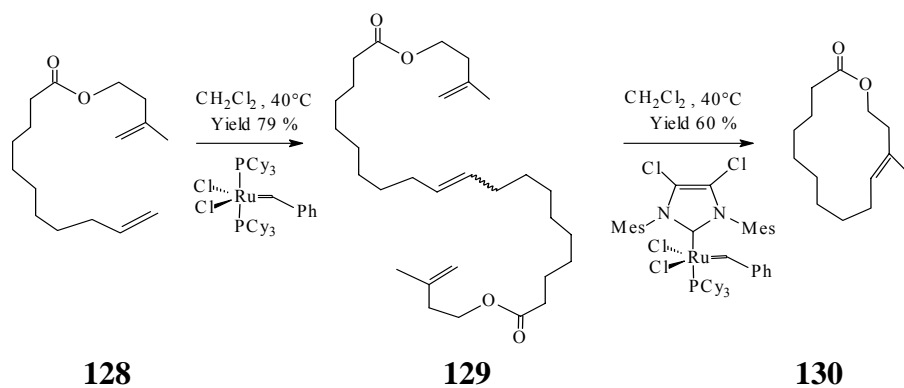
Scheme 28. Macrocyclization reactions initiated by the NHC complex **33**.

Large ring cyclic carbonates with musk odor, extremely attractive ingredients in many perfumes, *e.g.* **125** and **127**, also have been obtained in appreciable yield by RCM of the corresponding unsaturated linear carbonates⁷¹ in the presence of a recyclable Hoveyda-type polymer-supported precatalyst⁷² (Scheme 29). Unexpectedly, the unsupported - otherwise very active heteroleptic NHC-based Ru precatalysts, **34**, **41** and **42** - gave only a low conversion of the starting unsaturated carbonates, leading under forcing conditions to oligomers and polymers with undefined structure. By contrast, diphosphane complex **32** produced cyclic carbonates with ring sizes between 15-23 atoms in very good yields.



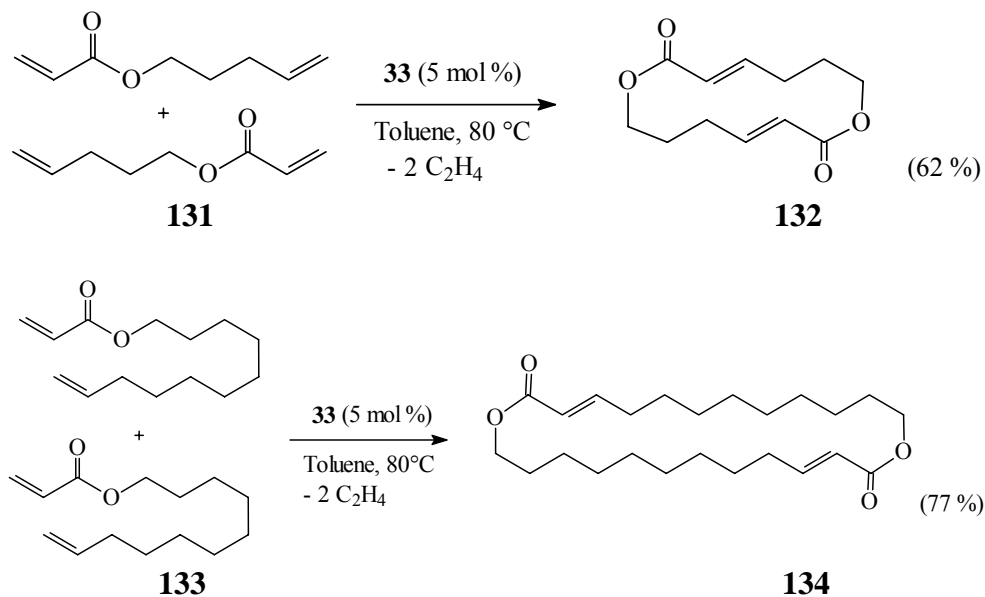
Scheme 29. Synthesis of macrocyclic carbonates *via* RCM.

An interesting result is the formation of the 14-membered ring lactone **130** containing a trisubstituted double bond, from diene **128**, in the presence of several NHC-based ruthenium complexes. In contrast, cyclization could not be achieved with the parent diphosphane Ru precatalyst **32** which effected only metathesis dimerization at the least substituted end, with formation of the acyclic dimer **129**. Significantly, the saturated NHC complex **34** displayed a similar reactivity in this cyclization as did its unsaturated congeners.



Scheme 30. Dimerization and macrocyclization reactions of linear dienes induced by diphosphane and heteroleptic NHC ruthenium complexes.

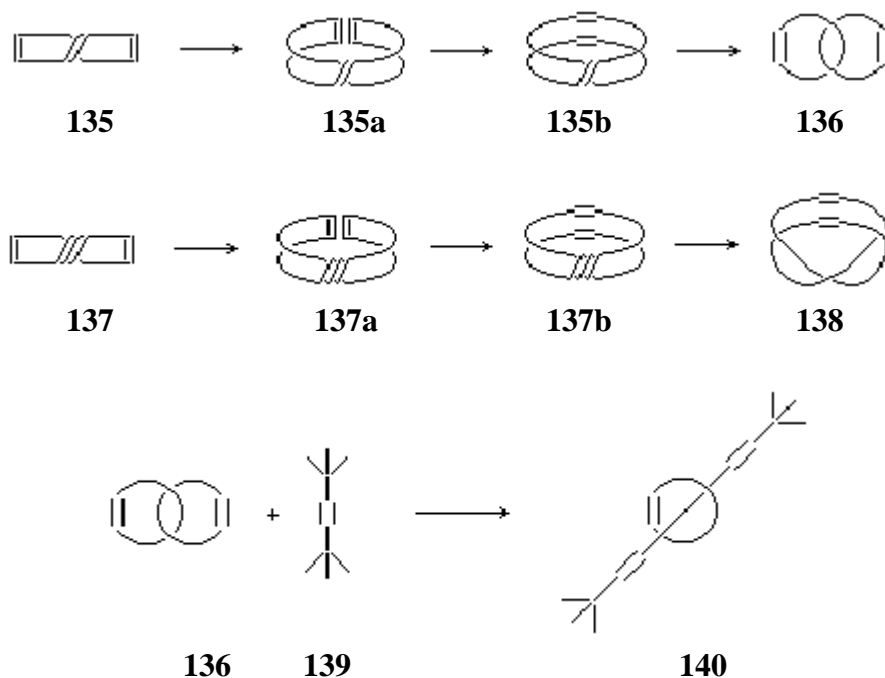
Production of larger cycles from acrylates is sometimes difficult and results in formation of cyclic dimers, *e.g.* **132** and **134**, each obtained as a single isomer with head-to-tail connected monomer units and *E*-configured double bonds (Scheme 31).



Scheme 31. Synthesis of macrocyclic compounds by cyclodimerization.

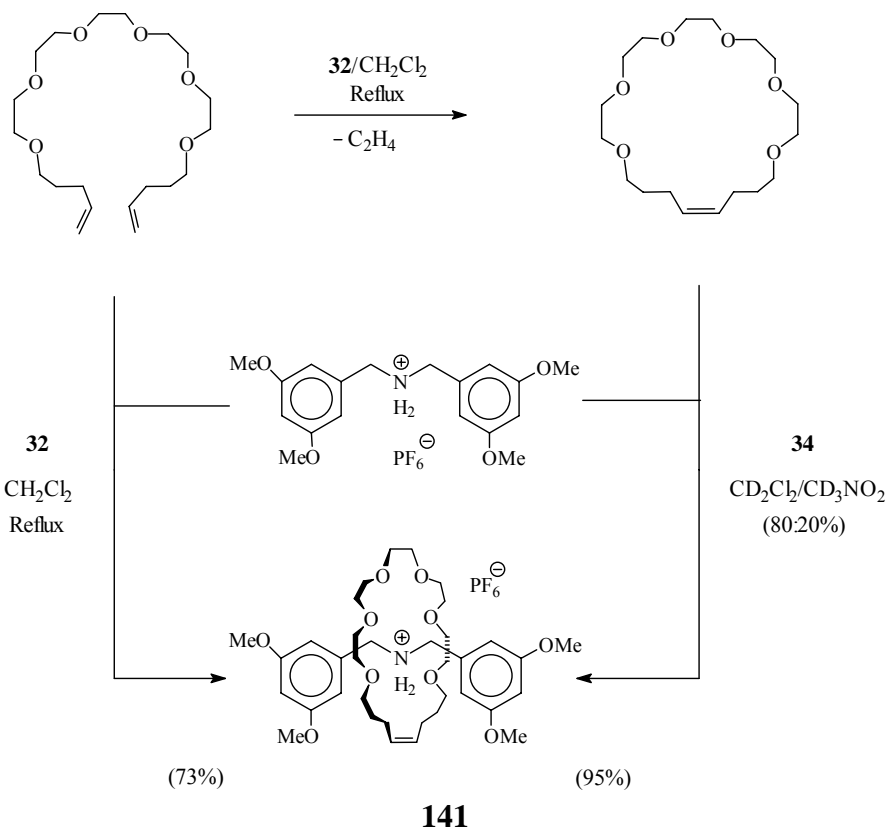
5.3. Synthesis of catenanes, knots and rotaxanes

Olefin metathesis opened a new and elegant route for the synthesis of catenanes, knots and rotaxanes as well as of other supramolecular assemblies, starting from cycloolefins and proceeding *via* macrocyclization.^{73,74} (Scheme 32).



Scheme 32. Synthesis, by metathesis, of catenanes, knots and rotaxanes from cycloolefins.

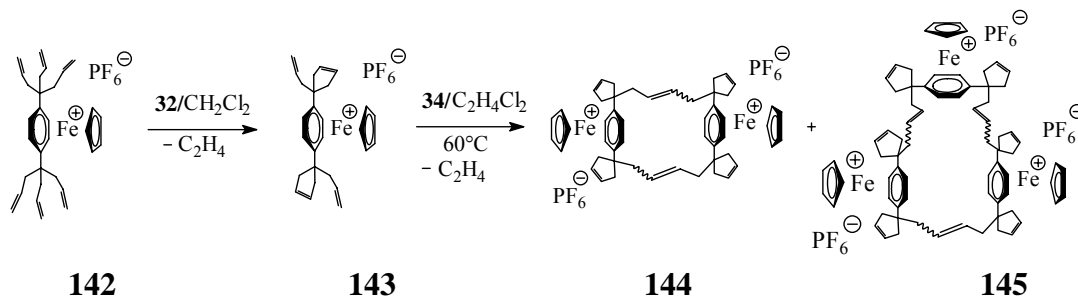
Functional-group tolerant ruthenium alkylidenes mediate the thermodynamically controlled synthesis of [2]catenanes, **136**,⁷⁵ and the anion-templated formation of rotaxanes, **140**.⁷⁶ By employing one of the best established supramolecular principles in the construction of rotaxanes, the mutual recognition exhibited by secondary dialkylammonium ($R_2NH_2^+$) ions and suitably sized crown ethers like dibenzo[24]crown-8 (DB24C8)⁷⁷, Grubbs and coworkers⁷⁸ prepared [2]rotaxanes by a reversible ring-closing metathesis (RCM) reaction, under thermodynamic control. Thus, starting from a terminal diolefin or the 24-membered olefinic crown ether (*E* and *Z* isomers) derived from it, in conjunction with dibenzylammonium hexafluorophosphate (DBA.PF₆), both the expected [2]rotaxane (73 % yield) and “magic-ring” rotaxane^{75b} (95 % yield) (**141**.PF₆) have been obtained with precatalysts **32** or **34**, respectively (Scheme 33).



Scheme 33. Synthesis of “magic ring” [2]rotaxanes with ruthenium alkylidene precatalysts **34**.

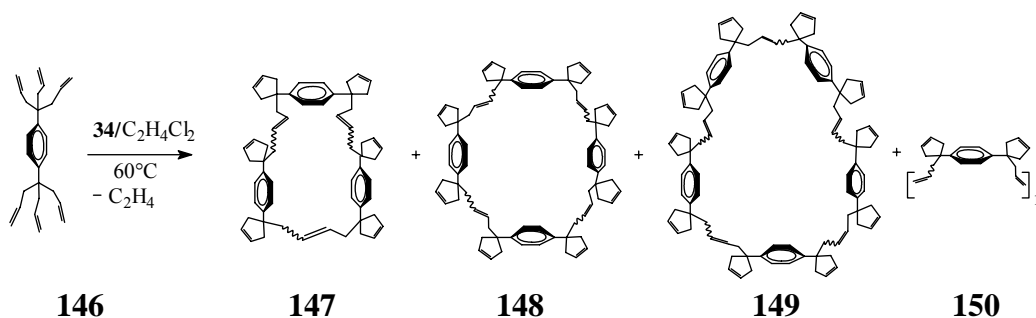
5.4. Synthesis of architecturally complex organic molecules

Architecturally complex organic molecules including polyaromatic cyclophanes, organoiron cyclophanes, capsules and polymers have been prepared by Astruc and coworkers⁷⁹ through a very simple and economic pathway starting from common and cheap raw materials such as toluene, *o*-xylene and mesitylene. These aromatic compounds form readily robust sandwich complexes of the type $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\eta^6\text{-arene})]^+$, in high yield, by reaction with ferrocene, in the presence of aluminum chloride. For instance, the sandwich complex of *p*-xylene, after CpFe^+ -induced polyallylation (allyl bromide, KOH, DME) of the two methyl groups, gave **142** which by RCM with **32** led to compound **143**. The latter, when heated in the presence of complex **34**, at 60°C for 6 days, is transformed into a mixture of [6,6]- and [6,6,6]-paracyclophanes (**144** and **145**), in 45 % yield, along with traces of [6,6,6,6]-paracyclophane (Scheme 34).



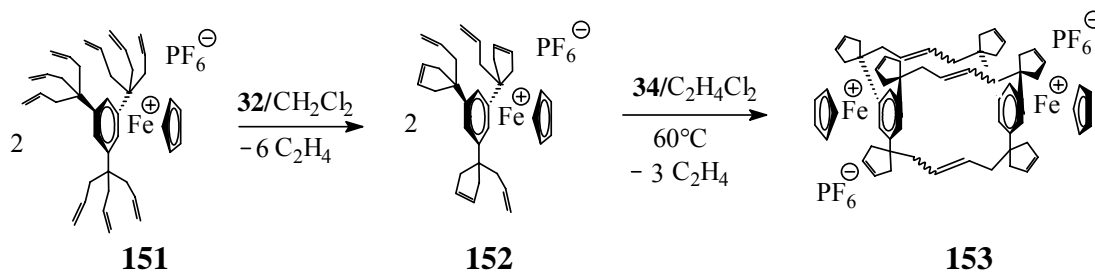
Scheme 34. Synthesis of iron paracyclophanes by metathesis.

Under these conditions, the iron-free arene compound **146** gives a mixture of three paracyclophanes, the [6,6,6]-, [6,6,6,6]- and [6.6.6.6.6]-paracyclophanes (**147**, **148** and **149**), and linear tris-arene and tetra-arene compounds (**150**, $n = 3$ and 4), identified by MALDI-TOF mass spectrometry (Scheme 35).



Scheme 35. Synthesis of paracyclophanes by metathesis.

When starting from the mesitylene iron complex the same process, implying CpFe^+ -induced nona-allylation at room temperature to **151**, ring-closing metathesis of the latter (in the presence of precatalyst **32**) to the sandwich complex **152**, and further metathesis reaction with precatalyst **34** (at 60°C for over a week), gave almost exclusively the triply bridged organoiron [6₃](1,3,5) cyclophane **153**, a molecular capsule, and only traces of other compounds (Scheme 36).



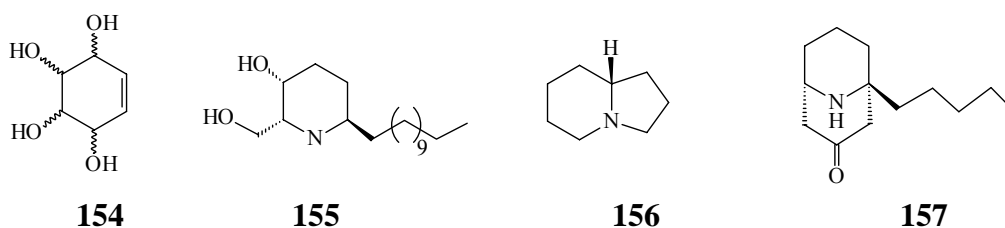
Scheme 36. Synthesis of molecular capsules by metathesis.

As required by the thermodynamic control, the outcome of this process is strongly concentration dependent: at higher concentrations amounts of oligomers are larger, with the final equilibrium favoring these oligomers. When metathesis is carried out on the iron-free non-allylated arene obtained by decomplexation of **151**, reaction proceeds more readily and selectively to form the corresponding metal-free triply bridged cross-metathesis product **153**. The triply-bridged compound was isolated as a mixture of isomers that, by subsequent hydrogenation with H₂/Pd/C in CH₂Cl₂, yielded the corresponding saturated capsule as the single product.

5.5. Total synthesis of natural compounds

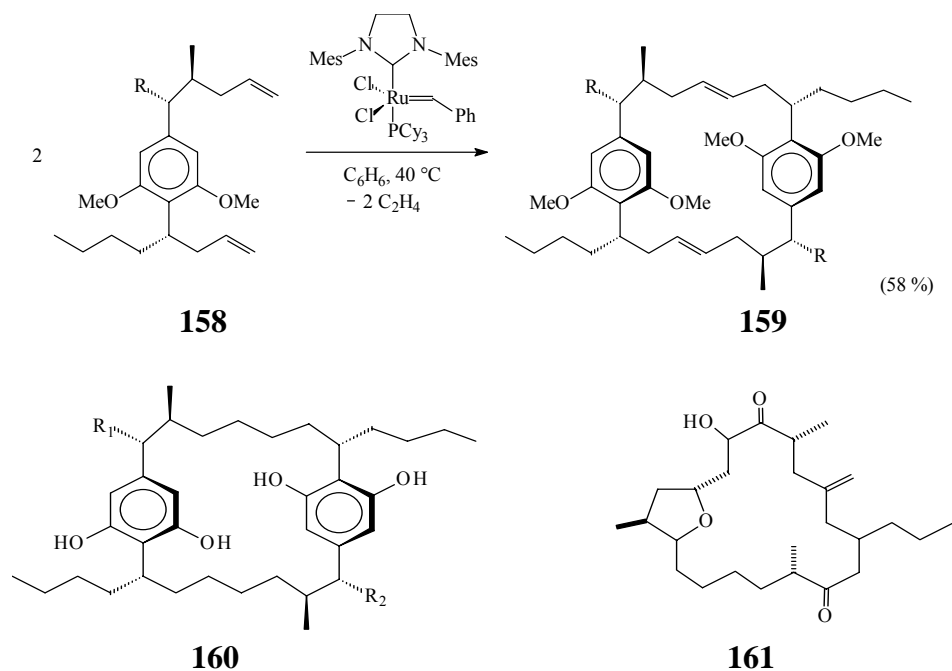
Manufacture of natural compounds and biologically active assemblies has been for long a fascinating challenge for numerous research groups. Of the multiple applied strategies, olefin metathesis has emerged as one of the most powerful tools for constructing the ubiquitous carbo- and heterocyclic units and subunits from such compounds. The diversity and large number of total syntheses of natural products and other complex molecules that have recently benefited from this versatile process as a key synthetic step stand proof to this statement.

Synthesis of conduritol derivatives (**154**) starting from galactitol, D-mannitol and D-glucitol, through a Tebbe olefination, followed by ring-closing metathesis in the presence of the NHC-based ruthenium complex **33**, revealed a superior activity of the second generation Grubbs' precatalyst as compared to the bisphosphane congener **32**.⁸⁰ High yields (70-90 %) of polyhydroxylated compounds, from the corresponding dienes, have been readily attained with **33**, sometimes comparable with those obtained with the very active and sensitive Schrock imido alkoxide molybdenum alkylidene complex.⁶⁵ Total synthesis of a trisubstituted piperidine, (-) 3-*epi*-deoxoprosopinine (**155**), was finalized in 8 steps, from Garner aldehyde (overall yield 27 %), involving as the key step the construction of the piperidine moiety by ring-closing metathesis of an intermediate diene, induced by the ruthenium complex **34**.⁸¹ (-) Coniceine (**156**), the simplest indolizidine alkaloid having a pronounced biological activity, has been prepared by several routes, starting from different sources and using the ruthenium complex **34** in ring-closing metathesis of the intermediate diene to form the indolizidine moiety.⁸² Furthermore, the same complex **34** proved to be quite efficient in building bridged bicyclic alkaloids containing a nitrogen atom in the one-atom bridge, as illustrated by the synthesis of (-) adaline (**157**), a major alkaloid found in the chemical defense secretion of the European two-spotted ladybird *Adalia bipunctata*.⁸³ (Scheme 37).



Scheme 37. Selected natural compounds prepared by RCM.

The naturally occurring 22-membered carbocyclic [7,7]-paracyclophanes that are postulated to arise biosynthetically *via* dimerization involving an electrophilic aromatic substitution at C(2) of 5-substituted resorcinol with an olefin group appropriately positioned in the side chain, have been prepared recently *via* olefin cross-metathesis dimerization as the key step, using precatalyst **34** (Scheme 38).⁸⁴

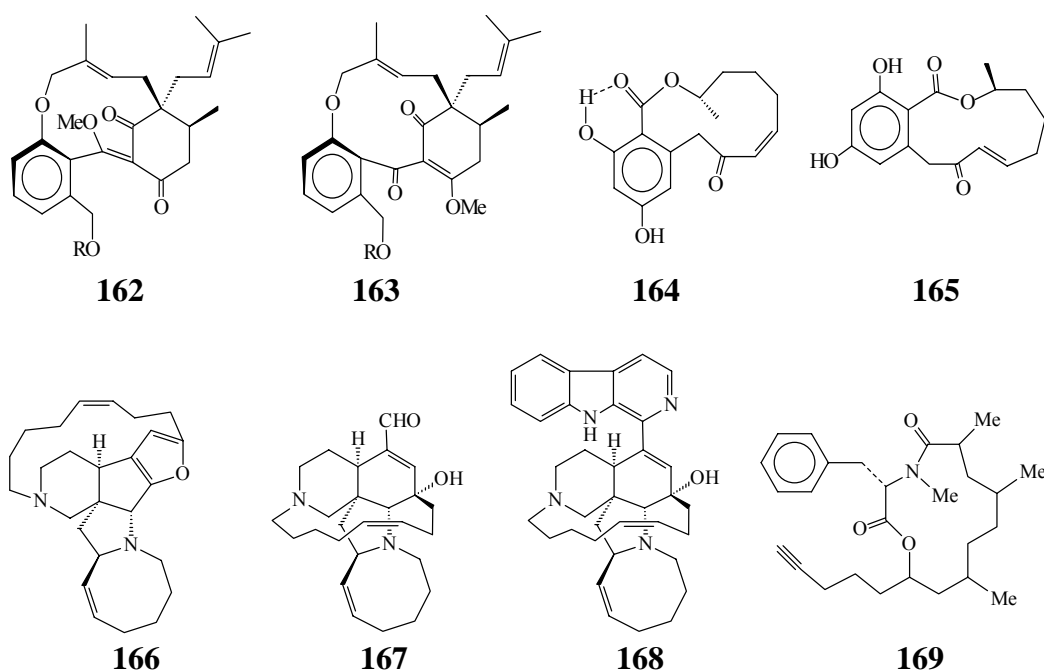


Scheme 38. Applications of NHC Ru complexes in synthesis of natural compounds.

Heterogeneous hydrogenation of diene **159** with Pd/C, followed by cleavage of the methyl ethers with BBr_3 , led to cylindrocyclophane **160**, which was identical in all respects with an authentic sample. The first total synthesis of amphidinolide T4 (**161**), a natural compound with a pronounced cytotoxicity against various cancer cell lines, has been achieved using the second generation NHC ruthenium complex **33** in order to close the 19-membered lactone core.⁸⁵ Hydrogenation, olefination and further deprotection of the intermediate compounds finally gave synthetic amphidinolide T4 having all characteristics in excellent agreement with those of the natural compound.

An elegant synthesis of coleophomones B and C precursors (**162** and **163**) has been reported by Nicolaou et al.⁸⁶ by highly stereoselective ring-closing metathesis of the corresponding dienes (*E* for **162**, 86% yield, and *Z* for **163**, 80% yield) induced by the NHC ruthenium complex **34**. Also, stereospecific synthesis of the pair of natural macrolides, *cis*- and *trans*-resorcyllide, **164** and **165**, both acting as plant growth inhibitors, was performed by Couladuros et al.⁸⁷ using ring-closing metathesis of the corresponding diene precursors induced by **34**. Although differences in reactivity between the two diene substrates in the presence of this catalyst have been observed,

optimization of the reaction parameters (substrate concentration, reaction temperature) allowed stereoselective cyclization of the two enolizable enones (Scheme 39).



Scheme 39. Representative natural compounds prepared by RCM.

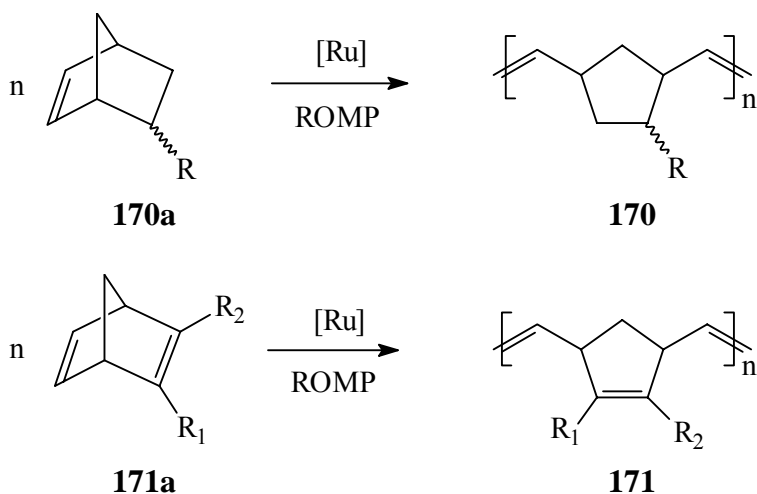
Asymmetric total synthesis of (-)-nakadomarin A (**166**), a natural compound of the class of ircinal and manzamine alkaloids **167** and **168**, having cytotoxic activity against murine lymphoma cells as well as antimicrobial activity, has been performed recently by means of ring-closing metathesis of the diene precursors, with complexes **32** and **34** in the key reaction steps.⁸⁸ In this process, the difference in reactivity between the bisphosphane and NHC/phosphane precatalysts was significant, the former leading to the 15-membered azacycle in 26% yield whereas the latter gave the 8-membered azacycle, in 83% yield. Spongidepsin, **169**, a remarkable natural compound with cytotoxic and antiproliferative activities against several cancer cell lines, has been synthesized recently through a stereodivergent ring-closing strategy.⁸⁹ The corresponding diene amide precursors were cyclized under the action of the second generation Grubbs' precatalyst and, after separation of stereoisomers by flash column chromatography and hydrogenation over Pd/C, the saturated macrolides were obtained. The structural assignment was based on appropriate spectroscopic investigations.

Obviously, ring-closing metathesis has proven to be a successful key step in the synthesis of a large number of natural compounds or precursor thereof, the majority of them using first and second generation Grubbs' catalysts. Some further representative examples are: brefeldin A (13 membered ring, *E*-isomer),⁹⁰ epothilone,⁹¹ zearalenone (14-membered ring, *E*-isomer),⁹² lasiodiplodin,⁹² radicicol,⁹³ salicylihalamides,⁹⁴ aspiciillin (18-membered ring, *E/Z*=3:1),⁹⁵ griseoviridin (20-membered ring, *E*-isomer).⁹⁶

5.6. Synthesis of specialty polymers

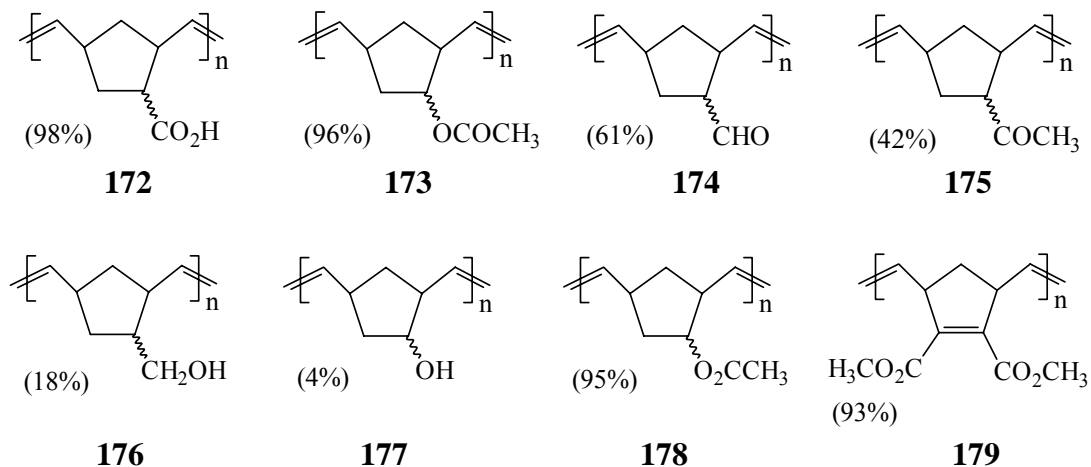
Ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) of a variety of substrates have had a strong impact on polymer synthesis after the disclosure of well-defined molybdenum, tungsten and ruthenium alkylidene precatalysts. Additionally, atom transfer radical polymerization (ATRP) of polar monomers expanded its scope through successful application of ruthenium alkylidene complexes in this reaction. With introduction of the highly active and functional-group-tolerant NHC-based ruthenium complexes, the potential of these chemical transformations increased dramatically.

Norbornene and norbornadiene, substituted with a broad range of functional groups (R = hydroxyl, hydroxymethylene, aldehyde, carbonyl, carboxyl, acyl, ester etc.), have been converted to the respective ROMP polymers working under normal conditions, with the above ruthenium precatalysts^{97,98} (Scheme 40).



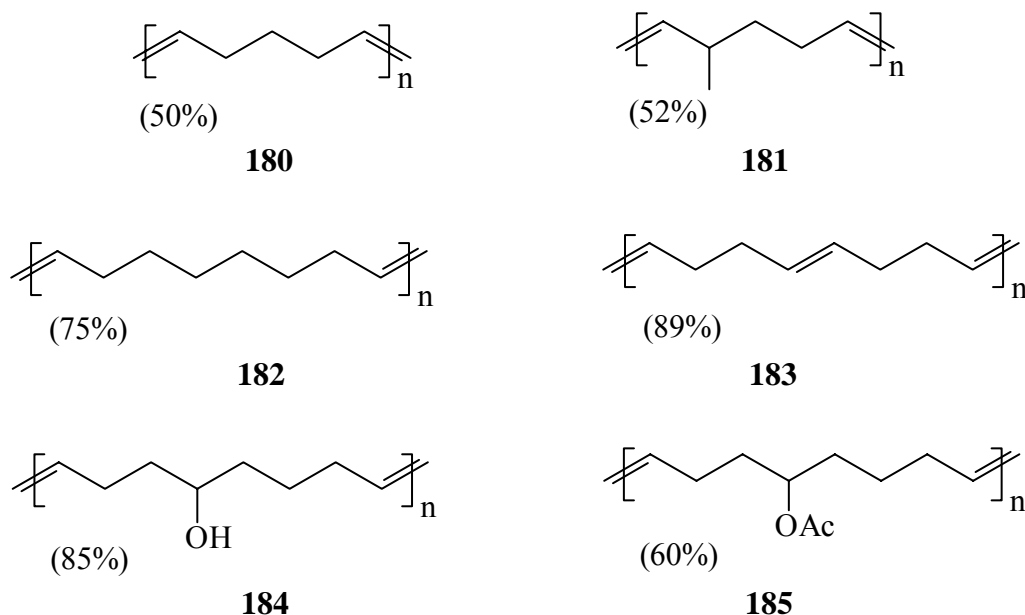
Scheme 40. ROMP of substituted norbornene and norbornadiene induced by ruthenium precatalysts [Ru].

Selected examples for various functionalized polymers obtained by ROMP of substituted norbornene and norbornadiene, mainly induced by bisimidazolin-2-ylidene ruthenium precatalyst **26**, are summarized in Scheme 41.⁹⁸



Scheme 41. Functionalized polymers prepared by ROMP of substituted norbornene and norbornadiene.

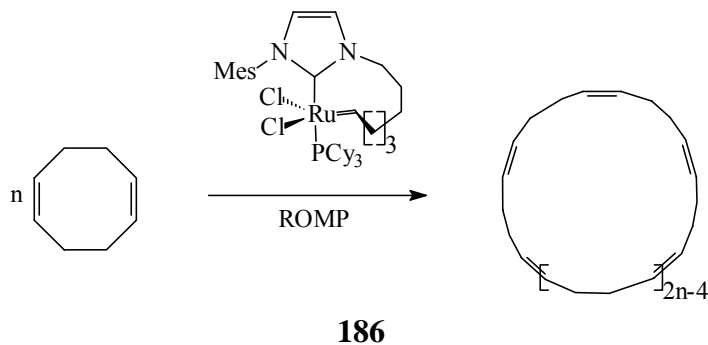
The superior activity of NHC-based Ru catalysts implies high rates in ROMP of low strain, substituted and unsubstituted cycloolefins such as cyclopentene, cyclooctene and cyclooctadiene and even the ROMP of sterically hindered substrates containing trisubstituted olefins such as 1,5-dimethylcyclooctene.^{99a} Good to excellent conversions of the cyclooctene and cyclooctadiene monomers have been reached readily using precatalysts **33** or **34** under mild conditions (Scheme 42).



Scheme 42. Linear polymers obtained by ROMP of low strain cycloolefins.

Under visible light irradiation, Ru-arene complexes bearing NHC ligands, **55** and **56**, either preformed or generated *in situ*, are very active catalyst precursors for ROMP of cyclooctene, already at room temperature.^{99b}

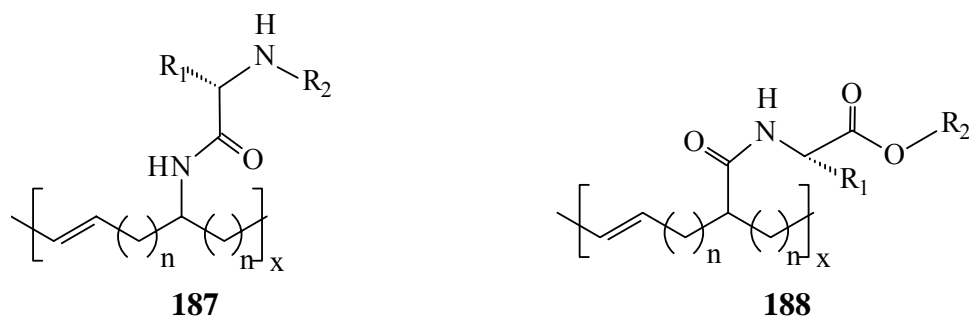
By using a ‘cyclic’ olefin metathesis precatalyst, **59**, Grubbs and coworkers¹⁰⁰ obtained by ROMP a series of cyclic polymers from low-strain cycloolefins. The topological restrictions imposed upon this class of polymers result in a set of particular physical properties that distinguishes them from their linear counterparts. Thus, cyclic polymers are less viscous, possess increased glass transition temperatures (T_g) and have smaller hydrodynamic volumes and radii (R_g) than their linear analogs. The currently applied multistep procedure for synthesis of cyclic polymers involves a conventional polymerization process leading to the linear polymeric precursors, containing reactive end-groups, followed by intramolecular cyclization under highly diluted conditions. Gratifyingly, the ROMP of cycloolefins with the ‘cyclic’ initiator occurs effectively and under mild conditions. As illustrative examples of the new approach should be mentioned the cyclic polyoctenamer (produced by ROMP of *cis*-cyclooctene), and the cyclic polyethylene resulting from it through hydrogenation, and the cyclic polybutadiene **186**, obtained by ROMP of 1,5-cyclooctadiene.¹⁰⁰ (Scheme 43).



Scheme 43. Synthesis of cyclic polybutadiene by ROMP of 1,5-cyclooctadiene.

Acyclic diene metathesis (ADMET), that is the condensation of terminal dienes to unsaturated high polymers with removal of ethylene, under the action of metathesis initiators, has become a versatile method for production of new polymeric materials.¹⁰¹ Depending on the nature of the catalyst employed, unsaturated polymers containing a wide range of functional groups can be prepared.¹⁰² In this productive field of research, Wagener and coworkers have recently extended ADMET chemistry from simple hydrocarbons to a variety of functionalized dienes including amino acid and dipeptide branched monomers¹⁰³. The incorporation of a high content of amino acid functionality and chirality in the polymer repeat unit is bound to increase the solubility of the material and enhance its potential to form secondary structures such as α -helices and β -sheets. This types of polymers can be useful as drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, metal ion absorbents and biocompatible materials. Using the second generation of Grubbs’ catalysts, Wagener prepared an interesting

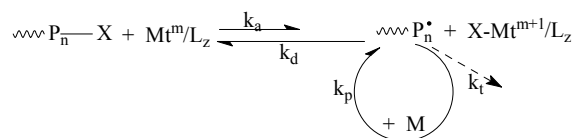
series of “C-terminus” and “N-terminus” amino acid and peptide branched, chiral polyolefins, termed “bioolefins”. Representative examples of lysine branched polymer attached through the C-terminus (**187**), and alanine, leucine and lysine-branched polymer, attached through N-terminus (**188**) are shown in Scheme 44.



Scheme 44. Amino acid branched polymers attached through the C-terminus and N-terminus.

These polymers offer the possibility of having amine or carboxylic acid functionalities on the surface of the material. To enhance both the monomer polymerizability and the polymer solubility, the carboxylic acid functional groups were protected, in the last set of monomers, with methyl, benzyl and *tert*-butyl esters. Remarkably, this class of bioolefin has properties uncharacteristic of typical branched polyolefins, revealing new aspects regarding the structure-properties relationship.

Atom transfer radical polymerization (ATRP) of vinyl monomers (styrene, dienes, (meth)acrylates and other polar vinyl monomers) is an important radical process widespread in polymer chemistry.¹⁰⁴ The process is based on the reversible formation of radicals from alkyl halides, in the presence of transition metal complexes, *e.g.* Ru(II) complexes with phosphines or Cu(I) complexes with bipyridines and aliphatic polyamines (Scheme 45).



Scheme 45. Reversible formation of radical species in ATRP.

Intriguingly, certain ruthenium alkylidene complexes promote ATRP without cocatalyst activation.¹⁰⁵ This unexpected finding rapidly extended the application potential of ruthenium metathesis precatalysts for synthesis of new polymers with particular topologies, compositions and functionalities in bulk, solution, emulsion etc. Catalysis by metathesis ruthenium complexes in ATRP raised many questions regarding the intimate mechanism of these two catalytic processes, metal-carbene induced olefin metathesis and transition metal initiated ATRP.¹⁰⁶

Surprisingly, some of the most active ruthenium initiators for ring-opening metathesis polymerization, *e.g.* ruthenium benzylidene complexes **32** and **33** or the saturated indenylidene complexes **36** (R = Ph and Cy), are found among the best catalysts for ATRP reactions too.^{107,108}

For instance, polymerization of styrene in the presence of the indenylidene complex **36** (R = Ph or Cy), in toluene at 110°C, has been reported to give polymer yields of 71 and 75%, when R = Ph and Cy, respectively.^{108b} Under the same conditions, the bisphosphane indenylidene analogues gave lower yields in polystyrene (37 and 44%, respectively). A similar trend has been observed in polymerization of methyl methacrylate carried out with the NHC catalytic system **36**; ATRP of this monomer with **36** (R = Ph and Cy), carried out in toluene at 85°C, attained 67 and 73% yields in poly(methyl methacrylate), respectively. Parallel runs using the bisphosphane indenylidene congeners as initiators gave 40 and 54% yields of polymer for R = Ph and Cy, respectively. Kinetic considerations revealed that the ATRP of both monomers exhibited a “living” character and proceeded in a controlled manner resulting in moderately narrow molecular weight distributions ($M_w/M_n = 1.30$ for styrene and 1.24 for methyl methacrylate). Addition of dibutyl amine to the reaction mixture accelerated considerably the polymerization process increasing the yield in polystyrene to 96 and 98%, and to 75 and 81% in poly(methyl methacrylate), when R = Ph and Cy, respectively. However, on employing amine as additive, molecular weight distributions were broader ($M_w/M_n = 1.42$ for styrene and 1.60 for methyl methacrylate) and the polymerization proceeding in an uncontrolled manner.

6. Conclusions

In less than a decade, an extensive class of ruthenium complexes bearing as ancillary ligands a wide range of nucleophilic N-heterocyclic carbenes (NHC) emerged as outstanding organometallic precatalysts. Rationally designed and skilfully prepared, they were immediately applied in the synthesis of a multitude of organic and polymeric compounds. In comparison to their bisphosphane ruthenium congeners, the novel complexes manifest superior reactivity and increased thermal stability, along with high chemoselectivity. Additionally, these exceptionally successful ruthenium complexes display good tolerance towards many organic functionalities, and also to air, moisture and impurities, thus widening the application potential in straightforward syntheses of many natural and functionalized organic compounds or polymers. The catalytic performance of the new Ru initiators depends strongly on the structure of the complex, solvent and olefinic substrate and can be finely tuned by changing the electronic and steric properties of the N-heterocyclic carbene ligand(s). With their unique attributes, the N-heterocyclic carbene Ru precatalysts are ready for further chiral exploitation and advantageous immobilization by anchoring on polymers or solid supports.

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