Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts†

Georgios C. Vougioukalakis‡ and Robert H. Grubbs*§

Institute of Physical Chemistry, National Centre of Scientific Research "Demokritos", 15310 Agia Paraskevi, Greece, and Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received July 6, 2009

The fascinating story of olefin (or alkene) metathesis (eq 1) began almost five decades ago, when Anderson and Merckling reported the first carbon—carbon double-bond rearrangement reaction in the titanium-catalyzed polymerization of norbornene.1 Nine years later, Banks and Bailey reported "a new disproportionation reaction ... in which olefins are converted to homologues of shorter and longer carbon chains ...".2 In 1967, Calderon and co-workers named this metal-catalyzed redistribution of carbon double bonds olefin metathesis, from the Greek word "μετάθεσις", which means change of position.3 These contributions have since served as the foundation for an amazing research field, and olefin metathesis currently represents a powerful transformation in chemical synthesis, attracting a vast amount of interest both in industry and academia.4–6

The generally accepted mechanism for olefin metathesis was originally proposed by Chauvin and Hérisson in 1970.7 According to this mechanism, olefin metathesis proceeds through metallocyclobutane intermediates, generated by the coordination of the olefin(s) to a metal alkylidene, via a series of alternating [2 + 2]-cycloadditions and cycloreversions (Scheme 1).8 Because of the reversibility of all individual steps in the catalytic cycle, an equilibrium mixture of olefins is obtained. For the metathesis to be productive and useful, it is necessary to shift the equilibrium in one direction. These inceptive mechanistic explorations, followed by highly sophisticated attempts to synthesize metal alkylidenes and metallocyclobutanes, eventually led to the synthesis of the first well-defined olefin metathesis catalysts. However, as will be also discussed in the following sections, there are many details of the olefin metathesis mechanism that still remain unclear.

The most important olefin metathesis subtypes are presented in Scheme 2. The ring-opening metathesis polymer-
The ring-strain release also determines the irreversible nature of ROMP, as the pathway back to the cyclic compound(s) has to overcome a significant thermodynamic barrier. Ring-closing metathesis (RCM) is widely used in organic synthesis. The driving force for RCM is primarily entropic, because one substrate molecule affords two molecules of product; furthermore, since the small molecules released from this reaction are volatile (if not gaseous), RCM is practically irreversible and can proceed to completion. On the other hand, cross metathesis (CM) is more challenging than both RCM and ROMP, as it lacks the entropic driving force of RCM and the ring-strain release of ROMP, which can lead to relatively low yields of the desired cross-product. For these reasons, CM has been an underutilized metathesis transformation. Other types of olefin metathesis reactions include acyclic diene metathesis polymerization (ADMET), ring-opening cross-metathesis (ROCM), ring-rearrangement metathesis (RRM), and ethenolysis (ethenolysis is the cross-metathesis of ethylene with an internal olefin).

Early metathesis catalysts were multicomponent systems formed in situ from transition-metal halides and main-group metal alkyl cocatalysts. Some representative examples include WCl₆/EtAlCl₂, WCl₆/BuSn₄, and MoO₃/SiO₂. Occasionally, a third component had to be added to the catalytic system as an activator, e.g., the Calderon catalyst (WCl₆/EtAlCl₂/EtOH). However, these catalytic systems were of limited use in organic synthetic applications, mainly because of the harsh reaction conditions they require and their prolonged initiation periods. Additionally, the propagating species were neither quantitatively nor uniformly formed, resulting in lack of reaction control. The first single-component metathesis catalysts were based upon titanium, tantalum, and tungsten, with the synthesis of the first members of these catalytic families reported in the late 1970s. Later on, well-defined molybdenum-based catalysts were also synthesized. Unfortunately though, despite the high catalytic activity of these early transition-metal catalysts, their somewhat limited functional group tolerance and high sensitivity toward oxygen and moisture render them difficult to use in many cases. In addition to the necessity for careful handling, time-consuming protecting-group strategies have to be utilized when substrates bear alcohols or aldehydes. Many of the functional group tolerance and oxophilicity problems in these early transition-metal systems were adressed by the development of well-defined ruthenium-based metathesis catalysts. Although the first reports regarding...
ill-defined ruthenium-catalyzed ROMP were published as early as the 1960s, using RuCl₃(H₂O)₆, this late transition metal had to wait 20 more years until it came back into the metathesis game in the late 1980s. Unlike its early transition-metal counterparts, ruthenium was remarkably tolerant toward oxygen, water, and functional groups, at least in these early ill-defined systems. Furthermore, one of the most important findings in these studies was the suggestion that the active species was a ruthenium alkylidene. On this basis, the synthesis of the first metathesis-active ruthenium alkylidene complex (1, Figure 1) was accomplished in 1992; nevertheless, catalyst 1 showed relatively low reactivity and was only effective in the ROMP of highly strained olefins.

Although the basic structure of the currently used ruthenium-based catalysts still resembles that of the original complex, composed of a ruthenium alkylidene along with two anionic and two neutral ligands, contemporary catalysts (2–5, Figure 2) are much more robust and functional group tolerant. For example, first-generation catalyst 2 has much better functional group compatibility than all of the early transition-metal olefin metathesis initiators. Substitution of one of the tricyclo-hexylphosphine ligands with the bulky N-heterocyclic carbene (NHC) ligand H₂IMes produced ruthenium complex 3, which displays improved catalytic activity, maintaining the high functional group tolerance and thermal stability of 2. This improvement has been attributed to the increased affinity of the NHC-substituted ruthenium center for π-acidic olefins relative to σ-donating phosphines (vide infra). Furthermore, substitution of the second phosphine ligand for a bidentate alkylidene (complexes 4 and 5) led to ruthenium-based catalysts with even higher thermal stability. More recent studies have led to the development of ruthenium catalysts that, among others, initiate asymmetric olefin metathesis reactions, with applications in aqueous and protic solvent systems, or even carry out the challenging formation of tetrasubstituted carbon–carbon double bonds.

All the above-mentioned developments in the field of heterocyclic carbene-coordinated ruthenium-based metathesis catalysts will be extensively discussed in the following sections of this article.

Figure 1. First well-defined metathesis-active ruthenium alkylidene complex.

Figure 2. First- and second-generation ruthenium-based metathesis catalysts.
Figure 4. The most successful and well-studied ruthenium catalysts bear either symmetrical or unsymmetrical imidazol- or imidazolin-2-ylidenes. Triazol-5-ylidenes, tetrahydropyrimidin-2-ylidenes, and a four-membered ring diaminocarben have also been utilized, to afford the corresponding complexes. More recently, a series of ruthenium complexes coordinated with cyclic (alkyl)(amino)carbenes and thiazol-2-ylidenes have been synthesized. The synthesis, structure, and the catalytic activity of all (pre)catalysts families in Figure 4 will be thoroughly discussed in the following sections.

3. Heterocyclic Carbene Frameworks Used in Ruthenium-Based Metathesis Catalysts

3.1. Symmetrical Imidazol- and Imidazolin-2-ylidenes

In 1998, Herrmann and co-workers reported the synthesis of the first heterocyclic carbene-containing ruthenium-based metathesis catalysts (9–13, Figure 5) in which both phosphine ligands were replaced by NHCs.58 Despite their high stability, these complexes did not show a significant improvement in metathesis activity, mostly due to their slow initiation rates, attributed, in these carbene biscoordinated complexes, to one of the NHCs (less labile than phosphines),53,59 which has to dissociate from the metal center for the catalyst to be initiated (vide infra).

Soon thereafter, the synthesis of heteroleptic ruthenium complexes 14a and 14b (Figure 6), by combining a nonlabile (1,3-dimesityl-imidazol-2-ylidene) with a labile (tricyclohexylphosphine or triphenylphosphine) ligand, was published.60–62 Species 14a and 14b exhibited not only higher RCM activity affording even tetrasubstituted cycloolefins, at that time out of reach of ruthenium catalysts,60 but also improved thermal stability compared to the parent bis(tri-
generation catalyst (2), by substituting one of the phosphine ligands with the in situ generated free carbenes. Complex 3 expanded the scope of ruthenium metathesis catalysts significantly, as it was proved to be not only air-, water-, and functional group-tolerant but also highly efficient in significantly, as it was proved to be not only air-, water-, and functional group-tolerant, but also highly efficient in the RCM of sterically demanding dienes, in the ROMP of low-strain substrates, and in the realization of challenging CM reactions. This kind of reactivity was previously possible only with the more active, though highly air- and water-sensitive, early transition-metal catalysts. What is more, 3 remains efficient at catalyst loadings as low as 0.05 mol % for RCM and 0.0001 mol % for ROMP reactions. An alternative, one-pot synthesis for complex 3 was published a couple of years later. According to this report, potassium t-amylate can be used for the deprotonation of the carbene precursor, an imidazolinium salt, whereas isolation of 3 can be achieved by simple filtration. Another route toward the preparation of 3 was reported in 2003. In this work, the NHC−alcohol or −chloroform adducts were used as carbene precursors. These easy-to-synthesize and easy-to-use “protected” forms of NHCs are air-stable and easier to handle than their free carbene analogues, while the used as carbene precursors. These easy-to-synthesize and easy-to-use “protected” forms of NHCs are air-stable and easier to handle than their free carbene analogues, while the desired carbenes can be readily released in solution, providing direct access to the metal−NHC complexes.

The reasons for the increased activity of the second-generation phosphine-containing catalysts, compared to their first-generation analogues, have been investigated both experimentally and theoretically. Initially, it was assumed that the higher activity of the second-generation catalysts originates from the higher electronic trans-influence of the NHCs, compared to the phosphine ligands, that was in turn expected to lead to a lower barrier to phosphine dissociation (faster initiation). However, a series of mechanistic studies later on confirmed by gas-phase experiments showed that this is not the case. Thus, whereas both the first- and second-generation tricyclohexylphosphine-containing catalysts were found to initiate via a dissociative mechanism (Scheme 4), the initiation rate \( k_1 \) of 2 was measured to be 2 orders of magnitude higher than that of 3. Nevertheless, the overall catalytic activity of 3 was found to be about 2 orders of magnitude higher than that of 2. To account for these contradictory observations, it was proposed that the partitioning \( k_f/k_{-f} \) between the coordination of the alkene substrate \( k_f \) and the phosphine ligand \( k_{-f} \), return to the resting state of the catalyst), by the corresponding 14-electron ruthenacylclobutane intermediates (Scheme 4), is about 4 orders of magnitude greater for 3 relative to 2. Therefore, the increased activity of the second-generation catalyst(s) was rationalized on the basis of an increased affinity of the NHC-

substituted ruthenium center for \( \pi \)-acidic olefins relative to \( \sigma \)-donating phosphines. It should be noted that improvement of initiation alone does not necessarily lead to a better catalyst, since catalyst efficiency depends on initiation, phosphine rebinding, reaction of the 14-electron ruthenium intermediate with olefin, and rate of catalyst decomposition.

As mentioned above, there are also a number of theoretical studies, sometimes contradictory to each other, dealing with the increased activity of the second-generation catalysts. For instance, differences in the barriers to the rotation of the ancillary neutral ligands (phosphine or NHC), in the 14-electron ruthenacylclobutane intermediates, were initially proposed as the source of the observed differences in activity between the first- and second-generation catalysts. Later on, it was suggested that these differences in reactivity originate from the difference in the energy of the 14-electron benzylidenes and the corresponding 14-electron ruthenacylclobutane intermediates. Other studies showed that both steric and electronic effects dictate the differences in reactivity. Finally, in a more recent work, it was proposed that the difference in the initiation rates for phosphine- and NHC-coordinated catalysts is determined by attractive non-covalent interactions.

In another significant contribution to the field of ruthenium-based metathesis, the Hoveyda group reported the synthesis of isopropoxystyrene-coordinated catalyst 5 in 2000, one year after the report of its first-generation analogue 4 (Figure 8). The Blechert group published the synthesis of the same phosphine-free catalyst almost simultaneously. Compared to its phosphine-containing analogue 3, catalyst 5 shows improved thermal stability, oxygen- and moisture-tolerance. On the other hand, the decreased initiation rate of 5 quite often comprises a major disadvantage. A variety of steric and electronic modifications of the chelating benzylidene...
ether ligand were aimed at resolving this problem. These efforts will be discussed in section 4.1, which is exclusively dedicated to the chelating benzylidene ether ligands.

The proposed catalytic mechanism of the chelating benzylidene ether ruthenium complexes is slightly different from that discussed above for the phosphine-containing complexes. Initially, 14-electron intermediate II is formed through the dissociation of the benzylidene ether chelating group (Scheme 5). Coordination of the alkene substrate, followed by metathesis, leads to the formation of the catalytically active species III and a molecule of isopropoxystyrene (or a related derivative).25,26,79 Therefore, the initial catalyst, or precatalyst, exists in equilibrium with the catalytically active species, and when the olefin is completely consumed, the catalyst may return to its resting state by rebinding the isopropoxystyrene that was eliminated at the first step (release/return mechanism).25,26 Also note that both phosphine-containing (Scheme 4) and phosphine-free catalysts (Scheme 5) provide the same propagating species (III, Scheme 5) after a single turnover.

In 2000, Nolan and co-workers reported the synthesis of complex 21 (Figure 9), bearing two bulky aryl groups (2,6-diisopropylphenyl), in an effort to study the influence of the bulkiness of the NHCs on the catalytic activity of the corresponding complexes.80 Likewise, the groups of Fürstner,81 Mol,82 and Wagener83 reported the synthesis and the catalytic activity evaluation of complexes 22 and 23 (Figure 9), the saturated phosphine-containing and phosphine-free analogues of 21. At ambient temperature, catalyst 22 shows effective turnover numbers 6 times higher than those of 3,82 along with very high initiation rates (turnover number is defined as the number of substrate molecules that are converted into product per catalyst molecule); nevertheless, its decomposition rate is also increased,83 especially when utilized in challenging transformations.84 In sharp contrast, phosphine-free catalyst 23 displays increased thermal stability and improved ADMET polymerization efficiency compared to complex 22,83

The Fürstner group has also published the preparation of complex 24 (Figure 10).81 Remarkably, substitution of the backbone of this unsaturated NHC with two chlorine atoms has little effect on the reactivity of the resulting complex, despite the obviously altered electronics of the ligand. The synthesis of complexes 2585 and 2686, presented in Figure 10, was published in 2005; 25, bearing an internal double bond, was prepared in order to be used as a starting point for the preparation of further functionalized NHC-coordinated catalysts.85 The unsaturated backbone in 25 remains intact even at elevated temperatures, most probably due to the low metathesis reactivity of unstrained cycloolefins such as cyclohexenes. The reactivity of 25 in the RCM of N,N-diallyl tosylamine was found to be slightly lower than that of the second-generation isopropoxystyrene-coordinated ruthenium catalyst 5 (Figure 8). Triphenylphosphine-containing complex 26 was reportedly purified by simple hexane washings (i.e., there was no need for column chromatography).86 Its catalytic efficiency was evaluated in the self-CM of acrylonitrile, where it showed activity similar to the second-generation catalyst 3 (Figure 7). Complex 27 (Figure 10), bearing the deuterated analogue of the NHC in 26, was prepared to investigate the mechanism of olefin isomerization in metathesis reactions carried out by H2IMes-containing ruthenium catalysts.87

Complexes 28 and 29 (Figure 11), bearing o-fluorinated aryl groups on the NHC ligand, were reported in 2006.88

![Scheme 5. Proposed Catalytic Mechanism of Isopropoxystyrene-Coordinated Ruthenium Catalysts](image)

![Figure 9. Ruthenium catalysts 21–23 bearing sterically demanding NHCs.](image)

![Figure 10. NHC-coordinated ruthenium-based catalysts 24–27.](image)

![Figure 11. Fluorinated ruthenium-based catalysts 28 and 29.](image)
Phosphine-containing 28 catalyzes the RCM of diethyl diallylmalonate with a significantly increased reaction rate compared to both parent complexes 3 (Figure 7) and 5 (Figure 8), whereas, in the same benchmark reaction, phosphine-free 29 shows a slower rate than both 3 and 5. This contradictory behavior of 28 and 29 was ascribed to an unprecedented fluorine–ruthenium interaction (Ru–F distance = 3.2 Å) observed in the solid-state structure of 29 (IV, Figure 11) via X-ray diffraction.

Despite the development of the highly active and functional group-tolerant catalysts described above, RCM to form tetrasubstituted olefins remained one of the weaknesses of ruthenium-catalyzed metathesis until 2007, when a series of new catalysts with increased activity for this transformation was published. On the basis of an earlier observation, according to which catalysts with reduced bulk at the ortho position of the two N-bound aryl groups of the NHCs exert increased efficiency in the formation of sterically demanding substrates, catalysts 30 and 31 (Figure 12) were designed and synthesized. Indeed, these two catalysts, along with complex 29 in Figure 11, performed significantly better than all the ruthenium catalysts available at the time in the RCM formation of many tetrasubstituted olefins. Further improvements led to the syntheses of complexes 32–34 (Figure 12), bearing the unsaturated analogue of the NHC in 31. Overall, 34 was the most efficient catalyst in that work regarding RCM to afford tetrasubstituted olefins. It is also worth mentioning that the diphenyl group on the isopropoxybenzylidine moiety of complex 34 is known to afford rapidly initiating phosphine-free catalysts (refer to section 4.1).

Unfortunately, however, the difficult preparation of catalyst 34 rendered its large-scale production uneconomical and imposed significant drawbacks regarding its commercialization. Research in the direction of more easily prepared catalysts eventually led to the evolution of 35–40 (Figure 13), the syntheses of which can be easily performed on a large scale. Catalysts 35–40 proved to be very efficient in the RCM of dimethallylmalonates, a family of sterically demanding benchmark substrates, while N-tolyl complexes 35 and 38 were the most successful catalysts in that work. Later on, 38 was also found to exert increased efficiency for the formation of sterically challenging disubstituted olefins by CM. On the basis of solution- and solid-state structural data, and in conjunction with a series of theoretical calculations, the outstanding catalytic activity of 35 and 38 toward sterically demanding substrates was proposed to result from a significantly more open steric environment around the ruthenium center. This was suggested to originate from the accessibility of conformations in which the N-tolyl rings are rotated away from approaching and coordinating olefins.

In two other recent reports, the syntheses of ruthenium-based catalysts 41–45 were described (Figure 14). Complexes 41 and 42 were initially targeted with the aim of increasing the diastereoselectivity of ring-rearrangement metathesis reactions. Although both 41 and 42 were found to be of limited stability in solution, even in the absence of olefin substrates, 41 indeed showed some promising results in diastereoselective ring-rearrangement metathesis reactions, affording improved E/Z selectivities. In addition, 42 led to the isolation of a ruthenium complex relevant to the deactivation of NHC-coordinated ruthenium-based metathesis catalysts (refer to section 11). On the other hand, 43–45 were proven to be efficient RCM catalysts in benchmark reactions: 43 and 44 showed reactivity similar to that of the existing second-generation phosphine-coordinated catalysts (3), whereas 45 outperformed 3 by about an order of magnitude, in terms of turnover frequencies for complete conversion.
A series of decomposition studies concerning NHC-substituted ruthenium complexes, extensively discussed in section 11 of the present article, has shown that N-aryl-substituted NHC complexes without ortho-substituents on the N-aryl groups are more prone to degradation compared to complexes bearing ortho-substituted N-aryl NHCs. This lack of stability has been attributed to an easier rotation of the N-aryl groups in the former, which brings the ortho-aryl C–H bonds closer to the ruthenium center, thereby facilitating degradation through C–H bond activation. For this reason, it was anticipated that, by placing bulky substituents on the backbone of the NHC, the rotation of the N-aryl groups (about the N–C bond) should be restricted, thereby rendering this decomposition pathway unfavorable. In this context, complexes 46 and 47 (Figure 15), bearing a tetramethyl-substituted NHC ligand, were synthesized, and 47 was the first stable ruthenium metathesis catalyst coordinated with an N,N-diphenyl-substituted NHC with a saturated backbone. Species 47 was proven to be an efficient olefin metathesis catalyst, carrying out a series of model RCM, CM, and ROMP reactions. 47 is also one of the most efficient catalysts in the RCM of the sterically demanding diethyl dimethallylmalonate.

A subsequent more-detailed study, concerning the effects of NHC-backbone substitution on the efficiency of ruthenium metathesis catalysts, led to the synthesis of complexes 48–53 (Figure 15). In that work, the catalytic activities of 48–53 were evaluated by the use of a highly sensitive Symyx robotic system. Both backbone and aryl substitution were found to significantly impact catalyst stability and activity. Thus, low N-aryl bulk on the NHC ligand led to increased activity and decreased stability, while increased backbone substitution increased catalyst lifetimes and decreased reaction rates. Furthermore, the relative importance of catalyst stability and activity on efficiency was found to depend on the steric encumbrance of the specific RCM reaction. Whereas for substrates with low steric demands catalyst stability is important for success at low catalyst loadings, for sterically hindered substrates catalyst activity becomes more important than catalyst stability.

In other work, based mostly on electrochemical and NMR studies, imidazolylidene- and imidazolinylidene-coordinated complexes 54–71 (Figure 16) were synthesized. The major goal of this study was to investigate the existence of intramolecular π–π interactions and whether such interactions influence the electronic density at the ruthenium center as well as the catalytic activity of the corresponding complexes. The reactivity of some representative complexes in selected RCM and CM reactions was found to systematically depend on the electronic properties of substituents R (Figure 16). Complex 54, bearing the electron-donating Me2N group, was the most catalytically active complex. It was furthermore suggested by the authors that the differences in reactivity between saturated and unsaturated NHCs do not originate from different electron densities at the ruthenium center, and that the electron-donating abilities of the saturated and the unsaturated NHCs (bearing the same substituents R) are similar.

Complexes 72 and 73 (Figure 16), bearing a pH-responsive NHC ligand, have also been prepared by Schanz and co-workers. In organic solvents, and in the absence of acid, 72 and 73 show reactivity similar to that of the parent H2IMes complexes 3 and 5 (Figures 7 and 8, respectively) in representative RCM and ROMP transformations. Upon addition of HCl, the NMe2 groups in 72 and 73 get protonated, affording the corresponding dicaticonic complexes, which show increased decomposition rates. A protocol was developed to remove the residual ruthenium from RCM reaction mixtures by acidification and subsequent filtration of protonated 73 (refer also to section 10 dedicated to this issue).

Phosphine-free complexes 74 and 75 (Figure 17) were the first reported isolable ruthenium-based catalysts bearing aliphatic side groups on both nitrogen atoms of their saturated NHC ring. Despite their higher catalytic activity in the ROMP of 1,5-cyclooctadiene, compared to the parent bis(mesityl)-substituted catalyst 5 in Figure 8, both 74 and 75 show decreased activity in model RCM and CM reactions. The authors suggested that this low efficiency originated from
the increased steric bulk of the alkyls relative to the usual aromatic groups.

3.2. Unsymmetrical Imidazol- and Imidazolin-2-ylidenes

The first report on ruthenium complexes coordinated with unsymmetrical NHCs came from the Fürstner group in 2001. Specifically, 76–78 (Figure 18) were targeted as complexes able to metathesize their own heterocyclic carbene ligands, affording the corresponding chelates, with the goal of regenerating themselves after the quantitative consumption of the substrate. In that same work, complexes 79 and 80 (Figure 18), incorporating a silyl ether and a perfluoroalkyl chain, respectively, were also reported. Complexes 76–80 are efficient in the RCM of $N,N$-dimethallyl-$N$-tosylamide to form the corresponding tetrasubstituted carbon–carbon double bond. The catalytic activity of 76–78 also showed a systematic dependence on the tether length between the alkene group and the ruthenium center. This effect was postulated to depend on the different capacities of the side-chains of their NHC ligands, were synthesized in an attempt to prepare catalysts capable of undergoing immobilization on various supports (for a discussion on ruthenium metathesis catalysts tagged with insoluble materials or soluble functionalities, refer to section 10). An unanticipated molecular rearrangement was observed during the deprotection of 82d under acidic or mildly basic conditions. Thus, instead of the expected 83d, rearranged 84c with its neutral ligands in a cis-configuration was isolated in high yield (Figure 19). The same phenomenon was observed during immobilization attempts of 83b and 83c on silica gel, when rearranged complexes 84b and 84a were respectively isolated. It was speculated that this reorganization process is promoted by the terminal hydroxyl groups. The ability of the hydroxyl function to effect this transformation becomes increasingly facile as this group is brought closer to the ruthenium center. cis-Configured 84a–84c are active metathesis catalysts at elevated temperatures, where, as suggested by $^{31}$P NMR data, they reconvert into their trans-isomers 83b–83d.

The design of complexes 85–88 (Figure 20) was based on the anticipation that the unsymmetrical nature of their NHC ligands might alter the environment of key intermediates in the metathesis pathway, leading to improved $E/Z$ selectivity in CM reactions and diastereoselectivity in RCM reactions. Moreover, the enhanced electron-donating ability of alkyl substituents was anticipated to lead to increased catalyst activity. Complexes 85–88 were synthesized from commercially available reagents in good to high yields. NOE-difference NMR experiments (NOE = nuclear overhauser effect) suggest that only one rotational isomer exists for both 85 and 86 in solution, with the benzylidene moiety located directly under the mesityl ring of the NHC. Similarly, in the solid state, a single isomer was isolated for 87 and 88, with the mesityl group situated directly above the benzylidene proton. In a model RCM reaction, complexes 85–88 showed...
activities similar to those of their parent bis(mesityl)-substituted complexes 3 and 5 (Figures 7 and 8, respectively). Moreover, 85 and 87 showed significantly different $E/Z$ ratios in selected CM transformations and improved selectivities in a diastereoselective RCM reaction compared to the parent complexes 3 and 5.

Ledoux, Verpoort, and co-workers synthesized and evaluated another series of ruthenium catalysts coordinated with $N$-alkyl-$N$-aryl-substituted NHCs ($89 - 98$, Figure 21).100,104,105 Phosphine-containing $89$, $91$, and $92$ were demonstrated to surpass the parent second-generation catalyst (3) in the ROMP of 1,5-cyclooctadiene,104 whereas $93$ showed only fair metathesis activity.105 The decreased catalytic activity of $90$ was attributed to its increased steric bulk in close proximity to the metal center.104 Phosphine-free complexes $94$, $96$, and $97$ display reduced catalytic activity compared to the parent bis(aryl) $N$-substituted symmetrical catalysts (5 and 23, Figures 8 and 9, respectively).100

A family of ruthenium-based complexes bearing unsymmetrical NHCs with fluorinated $N$-aryl groups ($99 - 106$, Figure 22) has been also synthesized.106,107 These complexes are readily accessible in one or two steps from commercially available first-generation catalyst 2. Among others, $99 - 106$ promote the RCM of diethyl diallylmalonate and diethyl allylmethallylmalonate, the ROMP of 1,5-cyclooctadiene, and the CM of allyl benzene with cis-1,4-diacetoxy-2-butene, in some cases surpassing the existing second-generation catalysts 3 and 5 in efficiency. Especially in the CM of allyl benzene with cis-1,4-diacetoxy-2-butene, complexes $99 - 106$ demonstrate similar or higher activity than the second-generation ruthenium catalysts and, more importantly, afford improved $E/Z$ ratios of the desired cross-product at conversion above 60%. This was quite an important finding, since, as mentioned in the Introduction, compared to RCM and ROMP, CM is an underutilized olefin metathesis transformation, not only because it lacks the entropic driving force of RCM and the ring-strain release of ROMP, but also because it often leads to relatively low statistical yields of the desired cross-product, as well as poor $E/Z$ cross-product selectivity.108

The $E/Z$ selectivity in CM reactions at high conversion is usually governed by thermodynamic factors; that is, secondary metathesis promotes isomerization of the product to the favored $E$ isomer, with the $E/Z$ selectivity being controlled by the stability of the olefin isomers rather than the selectivity of the catalyst.

The influence of the unsymmetrical NHC ligands in $99 - 106$ on the initiation rate of the irreversible reaction of these ruthenium complexes with butyl vinyl ether was also studied.106,107 The measured rate constants and activation parameters for all phosphine-containing catalysts in Figure 22 suggest rate-determining phosphine dissociation. On the contrary, rate constants and activation parameters for the phosphine-free catalysts 5, 100, 102, 104, and 106 are indicative of an associative mechanism.106,107,109 Finally, the synthesis of the related Rh($CO_2$)$_2$Cl(NHC) complexes allowed for the study of the electronic properties of all unsymmetrical NHC ligands in $99 - 106$, by measuring the corresponding carbonyl stretching frequencies.107

Complexes $107 - 109$, coordinated with the 1-mesityl-3-phenyl-substituted NHC ligands presented in Figure 23, have been also synthesized. $107$ and $108$ were prepared as model complexes during a series of catalyst decomposition studies.
In 1999, the first asymmetric metathesis reaction catalyzed by these kinds of complexes was published two years later.29 Chiral complexes 113–116 (Figure 25) were reported in 1999,23 the first asymmetric metathesis reaction catalyzed by these kinds of complexes was published two years later.29 Chiral complexes 113–116 (Figure 25) were reported in 1999,23 the first asymmetric metathesis reaction catalyzed by these kinds of complexes was published two years later.29

Chiral Monodentate N-Heterocyclic Carbenes

Although the first ruthenium-based catalysts bearing chiral monodentate NHCs110 (19 and 20, Figure 25) were reported in 1999,23 the first asymmetric metathesis reaction catalyzed by these kinds of complexes was published two years later.29 Besides 19 and 20, chiral complexes 113–116 (Figure 25) were synthesized and evaluated. In these asymmetric complexes, the chirality is transferred from the 4- and 5-positions of the NHC imidazolyl ring to the N-bonded aromatic groups, forcing the ortho-substituents of the N-aryl rings to reside on the NHC-face opposite to the bulky groups on the backbone (a so-called “gearing” effect). Complexes 113, 114a, 115a, and 116a are air-stable solids easily purified on the bench by column chromatography, whereas 114b–116b and 114c–116c can be generated in situ by the addition of excess LiBr or NaI (vide infra). Crystallographic evidence of the conformation of these chiral NHCs was obtained by conversion of 114a to the corresponding bis(pyridine) complex (see section 4.3).

Complexes 19, 20, and 113–116 were evaluated in the enantioselective desymmetrization of achiral trienes (3-allyloxy-2,4-dimethylpent-1,4-dienes), also known as asymmetric ring-closing metathesis (ARCM).29 It was found that catalysts encompassing the (1R,2R)-1,2-diaminocyclohexane group (19, 113, and 115) exhibit lower enantioselectivities than those having the (1R,2R)-1,2-diphenylethyldiamine moiety (20, 114, and 116). Replacement of the mesityl substituents (in 19 and 20) with o-methylaryl (in 113 and 114) or o-isopropylaryl groups (in 115 and 116) also increases the enantioselectivity. Finally, changing the halide ligands from chlorides to iodides improves the enantioselectivity; however, the conversion to the metathesized products is simultaneously reduced, supposedly due to the lower stability of the diiodide ruthenium intermediates. None of these catalysts showed a significant temperature- or solvent-dependent change in its enantioselectivity. Catalyst 116c afforded the highest enantiomeric excess measured in that study.

On the basis of the ligand effects described above and the stereochemical outcome of the studied reactions, a bottom-face (trans to the NHC) olefin binding pathway (intermediate V in Figure 26) was excluded. Among the two-side-on (cis to the NHC) olefin binding pathways in Figure 26, intermediate VII was favored, although VI was not excluded.29 On the contrary, theoretical work published in 2004 suggested bottom-face olefin binding (V, Figure 26), given that the other two intermediates (VI and VII) were calculated to be of remarkably higher energy.111 For a more detailed discussion on olefin coordination and the geometry of ruthenacyclobutane intermediates, the reader may refer to section 4.6.

Subsequent studies, aimed at the enhancement of the enantioselectivity displayed by 116, together with the goal of expanding the substrate scope of ARCM, led to the synthesis of chiral complexes 117–120 (Figure 27).34,35 While 117 and 118 showed enantioselectivities similar to those of catalyst 116, 119 displayed increased enantioselectivity to the extent that, in a number of substrates, even its dichloride version (119a) could be used at very low catalyst loadings (<1 mol %) to afford high enantiomeric excesses and conversions.34 Thus, 116c and 119a were utilized to ring-close alkyl ether- and silyl ether-prochiral trienes, affording five- to seven-membered rings; conversions up to >98% and enantiomeric excesses up to 92% were obtained. The

Figure 24. Unsymmetrical NHC-coordinated complexes 110–112.

Figure 25. Ruthenium complexes 19, 20, and 113–116 coordinated with chiral monodentate NHCs.

Figure 26. Possible geometries of the intermediate olefin complex.
influence of solvent and temperature on conversion and enantiomeric excess was also studied. Finally, according to the olefin-binding pathways proposed, if the incoming olefin binds cis to the NHC, the stereodefining interaction is the face of the ruthenium to which the olefin binds. If, on the other hand, the incoming olefin binds trans to the NHC, the stereodefining interaction is the position of the alkylidene under the N-bound aryl ring. Either way, the position of the pendant olefin in the forming ring also plays an important role in the transition state.

116–120 (Figures 25 and 27) were later proven to also be highly active in asymmetric ring-opening cross-metathesis (AROCM) reactions. 118a was found to be the most selective of dichloride catalysts 116–120, whereas the use of diiodide catalyst 118b slightly improved the enantiomeric excess values (up to 82% in the AROCM of norbornene derivatives with styrene). Nevertheless, since diiodide catalysts are generally less reactive than their dichloride counterparts, the loading of 118b had to be increased to 3 mol % to achieve activity similar to that observed with 1 mol % loading of 118a. A ruthenium benzylidene, rather than a ruthenium methylidene as the propagating species, along with a trans coordination pathway were proposed to be operative in these AROCM reactions. Moreover, in the same work, the first examples of asymmetric cross-metathesis (ACM) reactions, the most challenging of the asymmetric metathesis (AM) reactions, were reported by the groups of Buchmeiser, Blechert, and Grisi. 114,115 The catalytic activity of 125 was not investigated extensively, since it was essentially prepared as the precursor of the corresponding phosphine-free, pyridine-coordinated complex, utilized in alternating copolymerizations (refer to section 4.3). 126–128, bearing saturated NHCs with two nonaromatic N-substituents, were found to promote RCM, ARCM, CM, and ROMP reactions. 113 In these benchmark ROMP and CM reactions, 126–128 showed activities between that of the first- and second-generation phosphine-containing catalysts (Figure 2, catalysts 2 and 3, respectively), with 127 being the most catalytically active complex in the series. In the CM of allyl benzene with cis-1,4-diacetoxy-2-butene, 126–128 afforded improved E/Z ratios toward Z double bond formation. It should be noted that 126, which does not have chirality in the backbone of the NHC, was completely unable to give enantiodinduction in ARCM, whereas, in the same transformation, 128 afforded modest enantioselectivities (33%). This difference in reactivity was a key observation and highlights the significance of chiral substitution on the backbone and the minor role of the chiral N-substituents in chirality induction with this catalyst type.

3.4. Chiral Bidentate N-Heterocyclic Carbenes

Hoveyda and co-workers have developed a series of ruthenium complexes coordinated with bidentate NHC
ligands, bearing biphenolate or binaphtholate moieties that displace one of the chlorides in the coordination sphere of ruthenium. More specifically, in 2002 they reported the synthesis of chiral complex 129 (Figure 30), bearing a bidentate binaphthol NHC moiety.30 This was the first report regarding a ruthenium-based metathesis catalyst in which the chiral information of the NHC ligand is transferred directly to the ruthenium center. Complex 129, isolated in >98% diastereo- and enantiomeric purity without resolution, is air- and moisture-stable and can be recycled at the end of the reaction, by column chromatography, with up to 96% catalyst recovery. Because of the less electronegative nature and the increased steric bulk of the naphthoxide ligand in 129, compared to the corresponding chloride ligand in parent complex 5, 129 is less active, requiring longer reaction times and elevated temperatures for the same transformations. Nevertheless, 129 was proven to efficiently catalyze a series of AROCM reactions to afford high enantioselectivities.30

Aiming at the enhancement of the activity of 129, by increasing the electronegativity of the naphtholate moiety, the Hoveyda group developed the trifluoromethyl-substituted chiral NHC ligand incorporated in complexes 134 and 135 (Figure 31).31 Indeed, 134 and 135 showed reactivities more than 2 orders of magnitude higher than parent complex 129. A number of modifications of the chelating isopropoxybenzylidene ligand (in complexes 130–133 and 135), addressing the low initiation rate of 129, were also reported in that same work for a detailed discussion on this issue, see section 4.1. Complexes 130–135 showed enhanced catalytic activity, in general requiring lower catalyst loadings than 129, and in some cases promoting asymmetric reactions that cannot be effected by 129.31,116 More recently, complex 136 (Figure 31), the iodide-containing analogue of complex 133, was also reported.32 Both 133 and 136 were found to be efficient and highly enantioselective, affording up to 98% enantiomeric excesses in the AROCM of low-strain oxabicyclic olefins, allowing access to a variety of 2,6-disubstituted pyrans.32 136 was shown to catalyze these AROCM reactions with significantly higher asymmetric induction than 133.

The most significant drawback to the synthesis and, therefore, the extensive use of the above binaphthyl-based catalysts is their lengthy, chiral auxiliary directed synthesis. To overcome these difficulties, Hoveyda and co-workers synthesized biphenolate, NHC-coordinated complexes 137 and 138 (Figure 31).33 The synthetic route to the precursor of the asymmetric carbene contained in 137 and 138 is considerably shorter and, more significantly, does not require the use of optically pure, axially chiral amino alcohols. Although 137 is not stable to chromatography, it can be prepared and in situ catalyze a series of AROCM reactions.33 On the contrary, iodide-containing 138, while less active than 137, can be chromatographically purified and promotes a variety of AROCM reactions, in many cases affording higher enantioselectivities than its binaphthyl-based analogues, 133 and 136.33,36,117

3.5. Four- and Six-Membered Ring N-Heterocyclic Carbenes

With the purpose of investigating the role of the NHC ring size on the activity of ruthenium-based catalysts, additional structural modifications of the diaminocarbene family led to the synthesis of complexes 139–141 (Figure 32). 139, coordinated with a six-membered NHC, was synthesized in moderate yield via a four-step synthetic route.118 Unfortunately, however, 139 displayed lower catalytic activity than its counterparts with five-membered NHCs, most probably due to the increased steric bulk of its six-membered NHC in close proximity to the ruthenium center. This pronounced steric influence, clearly observed in the X-ray structure of 139, was proposed to disfavor olefin formation.
binding and/or ruthenacyclobutane formation, resulting in reduced activity. Soon thereafter, complex 140, featuring a six-membered NHC similar to that in 139 along with a chelating benzylidene ether ligand, was also reported.\textsuperscript{110} 140 is highly active in benchmark RCM and ROCM reactions and moderately active in enyne metathesis. The significantly different activity of 139 and 140 is most probably related to the existence of the chelating benzylidene ether ligand in 140, versus the tricyclohexyolphosphate in 139, rather than to the difference in the backbone structure of the corresponding NHCs.

In order to study the impact of employing more strained diaminocarbene frameworks than in the ordinary five-membered NHCs, complex 141 was synthesized.\textsuperscript{120} X-ray crystallographic analysis of 141 showed that the geometry around the nitrogen atoms is not strictly planar, indicating a reduced π overlap between the carbenic carbon atom and the adjacent nitrogen atoms. Moreover, by measuring the carbonyl stretching frequencies in the corresponding Rh(CO)\textsubscript{2}Cl(NHC) complex, it was found that the four-membered NHC ligand in 141 is a slightly less effective σ-donor than its dihydroimidazol-2-ylidene analogue. This difference was attributed to the more bent carbene angle in the former. Complex 141 was shown to catalyze selected RCM, CM, and ROMP transformations, albeit in a slower rate than the parent, phosphine-free second-generation catalyst (5).

3.6. 1,2,4-Triazol-5-ylidenes, Cyclic (Alkyl)(amino) Carbenes, Thiazol-2-ylidenes, and Other Heterocyclic Carbene Ligands

The first report of the employment of a carbene structure, other than the typical diaminocarbene framework in a ruthenium-based metathesis catalyst, was published in 2001 by Fürstner et al. (complex 142, Figure 33).\textsuperscript{81} Despite the straightforward synthesis of 142, given that the 1,2,4-triazol-5-ylidene is commercially available, this complex is not an efficient metathesis catalyst, due to its high instability in solution.\textsuperscript{53,81} The rapid decomposition of 142 was proposed to originate from the facile dissociation of the triazolylidene from the metal center.\textsuperscript{53} Nevertheless, 142 was shown to exert a high initial activity in the formation of tetrasubstituted cycloalkenes,\textsuperscript{81} providing one of the first hints regarding the creation of a “more open” steric environment around the ruthenium center in order to accommodate more sterically demanding substrates; this effect is discussed above for complexes 30–40 (Figures 12 and 13) and complexes 46, 47, and 51–53 (Figure 15).

In a more recent work, a series of ruthenium catalysts bearing cyclic (alkyl)(amino) carbenes was synthesized and characterized (143–145, Figure 33).\textsuperscript{121} Cyclic (alkyl)(amino) carbenes are more σ-electron-donating than their conventional NHC counterparts and, at the same time, introduce a unique \(C_5\)- or \(C_7\)-symmetric steric environment. These unusual steric properties of cyclic (alkyl)(amino) carbenes may have implications for the microscopic reversibility of the olefin binding and cycloreversion steps along the metathesis catalytic cycle. Complexes 143–145 are air- and moisture-stable compounds that can be isolated and purified by column chromatography in low (145) to high (144) yields. In the solid state, 143–145 position the \(N\)-aryl rings of their cyclic (alkyl)(amino) carbenes above the benzylidene moiety and the quaternary carbon adjacent to the carbenic center over the empty coordination site.\textsuperscript{1}\textsuperscript{H} NMR spectroscopy data suggest that the solid-state conformation of 143–145 is maintained in solution. The catalytic activity of 143–145 was evaluated in RCM,\textsuperscript{121} CM, and ethenolysis reactions.\textsuperscript{122} The RCM efficiency of 143–145, in the formation of representative di- and trisubstituted cycloalkenes, was found to be comparable to that of the second-generation complexes 3 and 5 (Figures 7 and 8, respectively).\textsuperscript{121} In the CM of allyl benzene with \textit{cis}-1,4-diacetoxy-2-butene, 143–145 exhibit lower \(E/Z\) ratios relative to most NHC-substituted complexes.\textsuperscript{122} Furthermore, in the ethenolysis of methyl oleate, 143–145 afford good selectivity for the formation of terminal olefins versus internal olefins (originating from undesired self-metathesis and secondary metathesis), with complex 145 being the most efficient ethenolysis catalyst examined to date, achieving 35 000 turnover numbers.

Another family of ruthenium-based metathesis catalysts, coordinated with a series of thiazol-2-ylidene ligands (146–152, Figure 34), was reported in 2008.\textsuperscript{123} The steric

![Figure 33: 1,2,4-Triazol-5-ylidene-coordinated complex 142 and cyclic (alkyl)(amino) carbone-coordinated complexes 143–145.](image)

![Figure 34: Ruthenium-based complexes 146–152 bearing thiazol-2-ylidene ligands.](image)
that should, upon reaction with the appropriate 35) were designed as “double-centered” metathesis catalysts merization.124 Indeed, although promote cyclodimerization rather than cyclization or oligomerization.124,125,126 environment of the thiazol-2-ylidene encompassed in 146–152 is unique, in the sense that they bear only one exocyclic substituent adjacent to the carbenic center. The synthesis of the thiazol-2-ylidene precursors, namely, the corresponding 3-aryl-4,5-dimethylthiazolium chlorides, is a two-step, straightforward procedure, while 146–152, which are stable to chromatography, can be prepared in one step from commercially available 2 or 4 (Figure 2). In the solid state, the N-aryl substituents of the thiazol-2-ylidene ligands are located above the empty coordination site of the ruthenium center. This is a rather interesting find, since all phosphate-free ruthenium complexes bearing unsymmetrical carbenes with only one exocyclic aryl substituent adjacent to the carbenic center, reported thus far, are isolated with this aryl group located directly above the benzylidene proton. Despite the decreased steric protection of their ligands, complexes 146–152 were demonstrated to efficiently promote a series of benchmark RCM, macrocyclic RCM, ROMP, and CM reactions, showing stability and activity comparable to the conventional NHC-containing ruthenium catalysts.123 The phosphate-free catalysts of this family were found to be more stable than their phosphate-containing counterparts. Upon removing the steric bulk from the ortho-positions of the N-aryl group of the thiazol-2-ylidenes, the phosphate-free catalysts lose stability, but when the substituents become too bulky, the resulting catalysts show prolonged induction periods. Among the five thiazol-2-ylidene ligands examined, 3-(2,4,6-trimethylphenyl)- and 3-(2,6-diethylphenyl)-4,5-dimethylthiazol-2-ylidene afforded the most efficient and stable catalysts (148 and 149). Unlike all previously evaluated catalysts, the steric bulk of these thiazol-2-ylidene-containing complexes is correlated to the observed E/Z ratio of the cross-product in the cross-metathesis reaction of allyl benzene with cis-1,4-diacyteto-2-butene. Thus, decreasing the steric demand of the ortho substituents on the N-aryl groups from i-Pr to H results in an increased kinetic E-selectivity from ~4 to ~6.5. In addition, in the macrocyclic ring-closing of a 14-membered lactone, the E/Z profile of catalysts 146–152 is completely different than that of H2IMes catalysts 3 and 5 (Figures 7 and 8, respectively) and more similar to the stereoselectivity displayed by the first-generation catalyst 2 (Figure 2).

Homodinuclear ruthenium complexes 153 and 154 (Figure 35) were designed as “double-centered” metathesis catalysts that should, upon reaction with the appropriate α,ω-dienes, promote cyclodimerization rather than cyclization or oligomerization.124 Indeed, although 153 is unstable and decomposes after some hours in solution, phosphate-free 154 was shown to competently promote dimer ring-closing metathesis of dienes with the appropriate length, at the suitable effective molarity. A trapping experiment suggested that both ruthenium centers in homobimetallic 154 are simultaneously metathetically active.

3.7. Carbene Biscoordination

Ruthenium-based complexes bearing two heterocyclic carbenes are prepared in one or two steps via the substitution of two or more labile ligands by the corresponding carbenes. The ease of this carbene biscoordination has been suggested to depend both on the steric and the electronic properties of the utilized carbene(s).53,123 Moreover, according to the established mechanistic model, one of the carbenes has to dissociate from the metal center for a bircarbene ruthenium complex to initiate.24–26,71,79 In this regard, although it is generally accepted that carbone ligands bind strongly to the metal centers,10,53 carbene dissociation/transfer have been repeatedly proven feasible.53,100,105,125,126

As mentioned earlier, the first heterocyclic carbene biscoordinated ruthenium complexes were reported in 1998 (9–13, Figure 5).58 These complexes were applied in the ROMP of functionalized norbornenes,127 as well as in benchmark RCM reactions,128 albeit displaying slow initiation rates due to the relatively low lability of the corresponding NHCs. Later on, carbene biscoordinated ruthenium complexes 155 and 156 (Figure 36) were also prepared.53 The complexes 155 and 156 could not be obtained directly from first-generation catalyst 2 (Figure 2), even when a large excess of the NHC was used. This was attributed to the significant decrease of the phosphine exchange rate when one of the tricyclohexylphosphine ligands was replaced by a NHC.53 Nevertheless, bis-substitution was achieved using complex 157 (Figure 36) bearing two labile pyridine ligands (see section 4.3).129 Both 155 and 156 are highly stable and can be purified by column chromatography on silica gel.53 In the solid state, both of the Ru–NHC distances in 156 are longer than those in either of the corresponding monocarbene complexes (complexes 14 and 3 in Figures 6 and 7, respectively), which was suggested to originate from the greater steric congestion in 156 and possibly also from a more electron-rich ruthenium center. 155 shows low RCM and ROMP activities below 40 °C, but this picture significantly improves at 80 °C. Therefore, elevated temperatures are required for an efficient initiation of 155 to occur. When 155 is heated in the presence of PCy3 or the first-generation
catalyst 2 (Figure 2), the heteroleptic, second-generation catalyst 3 (Figure 7) is formed, confirming NHC dissociation. It should also be noted that a bimolecular NHC transfer mechanism has been similarly proposed by Herrmann and co-workers for the formation of complex 16 (Figure 6).63 Arylphosphines are generally weaker donor ligands and bind more weakly to the metal centers than their alkylphosphine analogues (for a related discussion, refer to section 6). On this basis, complexes 158–160 (Figure 37) were prepared in one step by simply reacting their corresponding bis(triphenylphosphine) precursors with the appropriate NHC ligand.126,130 158 was isolated as a crystalline, air-stable solid and was fully characterized, whereas the isolation of 159 was proven impossible and was only observed in situ, because of its high solubility.130 The metathetical catalytic activities of 158 and 159 have not been evaluated. Moreover, 160 shows a rather low RCM activity at 40 °C, ascribed to its slow initiation, but at 80 °C it efficiently ring-closes diethyl diallylmalonate and diallyl malononitrile.

Carbene biscoordinated complexes 161–163 (Figure 38) have also been prepared.131,132 161 and 162, bearing two 9-membered chiral bidentate NHCs, were isolated as air-stable solids, but their metathesis activity has not yet been evaluated.131 On the other hand, the catalytic activity of “pincer” pyridine–dicarbene complex 163 was examined in benchmark RCM and ROMP reactions.132 Both the first- and the second-generation phosphine-containing catalysts (complexes 2 and 3, respectively, Figure 2) outperformed 163, as the same metathesis transformations required higher catalyst loadings and longer reaction time with 163.

More recently, the synthesis of complexes 164 and 165 (Figure 39) was accomplished by substituting both tricyclohexylphosphine ligands in the first-generation catalyst 2 (Figure 2) in one step.105 The exclusive formation of the NHC biscoordinated complexes 164 and 165, when even an equimolar amount of the corresponding heterocyclic carbene was utilized, was assigned to a higher phosphine exchange rate in the heteroleptic (phosphine–NHC) intermediate complex compared to its precursor 2. Interestingly, it was also found that both NHCs on biscoordinated complexes 164 and 165 can be exchanged with an excess of tricyclohexylphosphine, affording the initial bis(phosphine) complex (2). 164 and 165 were found to be catalytically active in the ROMP of 1,5-cyclooctadiene at elevated temperatures, and initiation was proposed to occur via NHC dissociation.

An analogous situation was observed during a series of attempts to isolate the tricyclohexylphosphine-containing ruthenium complex bearing a 3-(2,6-diisopropylphenyl)-4,5-dimethylthiazol-2-yldene, when only the formation of the carbene biscoordinated complex 166 (Figure 39) was observed by 1H NMR and high-resolution mass spectroscopy.123 In that case, it was proposed that the coordination of the first bulky thiazol-2-yldene ligand at the ruthenium center, followed by the dissociation of the remaining tricyclohexylphosphine and coordination of a second thiazol-2-yldene, is highly energetically favorable due to the formation of an “empty pocket” in the coordination sphere of the intermediate complex. This empty pocket was suggested to better accommodate the second unsymmetrical carbene ligand compared to the C3 symmetric tricyclohexylphosphine. Complex 166 is not stable enough to be purified by column chromatography.

4. Phosphine-free Heterocyclic Carbene-Coordinated Ruthenium Catalysts

4.1. Chelating Alkoxybenzylidene Ligands

As mentioned in section 3.1, the synthesis of the first isopropoxystyrene-containing heterocyclic carbene-coordinated catalyst (5, Figure 8) was independently and almost
simultaneously published by the Hoveyda and the Blechert groups in 2000.\textsuperscript{26,27} Compared to its phosphine-containing counterpart (3, Figure 7), catalyst 5 displays enhanced oxygen- and moisture-tolerance; however, its decreased initiation rate presents a major disadvantage. To increase initiation rate, either the bulk around the ether moiety is increased or a \textit{para}-electron-withdrawing substituent that decreases the basicity of the ether group is introduced. In all these cases, the catalyst activity is controlled by initiation. After the first turnover, the properties of the catalytically active species are the same for all. The modifications of the chelating benzylidene ether moiety’s sterics and electronics that have been attempted thus far are comprehensively discussed below.

The first and rather adventitious advancement in this direction came from the group of Blechert in 2002.\textsuperscript{133} Highly active and air-stable 167 (Figure 40), bearing a binol-based ruthenium alkylidene, was prepared as a potent ARCM catalyst. Despite the absence of asymmetric induction in ARCM, 167 showed a large improvement in catalytic activity. This high reactivity was suggested to originate from an improved leaving group ability of the binol-substituted isopropoxystyrene, because of its increased steric bulk in comparison with the isopropoxystyrene in the parent complex (5, Figure 8). Soon thereafter, the synthesis of catalyst 168, showing a markedly greater catalytic efficiency than either 5 or 167, and without any loss of stability in air, was published.\textsuperscript{89} Again, the enhanced reactivity of 168 was attributed to the faster dissociation of the phenyl-substituted isopropoxystyrene ligand, owing to a weakening of the chelation bond as a result of steric crowding. This assumption was later confirmed via a series of ligand-exchange experiments.\textsuperscript{134} A more efficient and practical synthetic route to 168 was also reported in the same work.

In order to obtain more detailed information regarding the effect of the steric and the electronic environment of the chelating isopropoxybenzylidene ligands on the rate of metathesis, Blechert and co-workers prepared complexes 169–176 (Figure 40).\textsuperscript{135} By comparing the RCM activity of 5 and 168–176, and by taking into account the \(\sigma_m^+\) and \(\sigma_p^+\) values of the corresponding substituents, they concluded that an increase in the electrophilicity of either substituent (R') through R', namely, decreasing the electron density at both the Ru=C and the Ru–O bonds, leads to a faster initiation rate, with the electronic character of the Ru=C bond being the dominant factor. As expected, increased steric hindrance \textit{ortho} to the isopropoxy group was also found to enhance initiation rates. In another publication, addressing the lower catalyst loading limit that can effect a RCM transformation, complexes 177–180 (Figure 41) were reported.\textsuperscript{136} 177–179 were found to deliver similar turnover numbers to each other, whereas the sterically modified 180 delivered lower turnover numbers, perhaps due to its faster initiation rate, which was proposed to result in faster decomposition.

A variety of electronically and sterically modified catalysts, bearing chelating alkoxystylenedene ligands, have been also synthesized by Grela and co-workers. Thus, 181 (Figure 42) was found to be significantly more reactive than its parent complex (5, Figure 8), without being less air- or moisture-stable.\textsuperscript{137} The drastically increased reactivity of 181 was rationalized in terms of a reduced chelating ability of the isopropoxy fragment, due to a decrease in the electron density of the corresponding oxygen atom. Moreover, complex 182 (Figure 42), encompassing an inexpensive and easily accessible chelating methoxystyrene fragment, was synthesized as a cheap alternative of the parent catalyst (5, Figure 8).\textsuperscript{138} 182 was successfully tested in RCM, CM, and enyne metathesis reactions, showing slightly improved reactivities in comparison with 5. A more detailed study regarding the activity of catalysts bearing nitro-substituted chelating alkoxystyrenes (181 and 183–187, Figure 42) in RCM, CM, and enyne metathesis reactions was subsequently published.\textsuperscript{139} It was found that catalysts coordinated with \textit{meta-} and \textit{para}-nitro-substituted isopropoxybenzylidenes (181 and 183) are significantly more active than the parent catalyst 5, although not as reactive as 168 (Figure 40). On the other hand, attempts to combine electronic and steric activation in the same isopropoxybenzylidene induced a drastic decrease in the stability of the resulting complexes (184–186); furthermore, 187 proved to be a less efficient catalyst than its isopropyl counterpart (181). Subsequently, an improved synthetic route to various 3- and 5-substituted alkoxystyrenes, and a practical, large-scale preparation of the corresponding NHC-coordinated alkoxystylenedene complexes, was also published.\textsuperscript{140,141}

Further research led to the synthesis of phosphine-free complexes 188 and 189 (Figure 43), the initiation efficiency
of which can be controlled on demand. Thus, in the absence of acid, 188 shows no activity in the RCM of diethyl allylmethallylmalonate, whereas its in situ formed salts (VIII) via the addition of 1 equiv of organic acids are highly active, in one case outperforming even the parent complex 5 (Figure 42). Similarly, the reactivity of 189 can be dramatically enhanced using Ph2SnCl2, due to the formation of carbocation IX (Figure 43). Complexes 190–192 have been also prepared. 190 and 191 are slightly less efficient than the parent catalyst 5, while the metathetical catalytic behavior of 192 has not been reported.

In complexes 193–195 (Figure 44), the aliphatic end group of the styrenyl ether has been functionalized by the attachment of an ester or an acid moiety. Scorpio catalysts 193 and 194 were shown to be highly efficient in model RCM and CM reactions, sometimes outperforming even the very active 168 (Figure 40). Interestingly, 194, which combines a coordinating ester function with an electron-withdrawing NO2 group, requires 10 times lower catalyst loadings than the parent NO2-bearing complex 181 (Figure 42) in order to afford the same result under identical conditions in a model CM reaction. Moreover, during an attempt to prepare the free carboxylic acid analogue of 193, ruthenium carboxylate 195 was isolated in 84% yield. Although catalytically dormant, 195 can be chemically (via the addition of 1 equiv of acid) and thermally activated in situ, promoting a series of RCM and CM reactions. 196 and 197 (Figure 44) were also synthesized and evaluated in benchmark RCM reactions, mainly because their isoproxybenzylidene moiety can be simply prepared in three steps from inexpensive starting materials. Both 196 and its dimeric analogue 197 show catalytic activity higher than that of the parent complex 5.

Additional studies led to the synthesis of complexes 198–205 (Figure 45). 198 was prepared with the purpose of carrying out metathesis reactions both in organic and aqueous solvents, as well as in ionic media (for a survey on water-soluble and ionic liquid tagged catalysts, see sections 9 and 10, respectively). However, although highly active in model RCM reactions, the recyclability levels of 198 in ionic solvents were very low. Complexes 199, 201, and 202 were also shown to be significantly more active than the
parent complex 5 (Figure 8);148 nevertheless, 201 and 202 are also less thermally- and air-stable and, therefore, less efficient than both 199 and 5. Finally, phosphine-free catalysts 203–205 were targeted in view of the tunable steric and electronic properties of their aminocarbonyl group (amide or carbamate).149

In 2008, Barbasiewicz et al. reported the preparation of complexes 206–210 (Figure 46), bearing five different isopropoxyarylidene chelates.139–205 initiate faster than 5, while 204 is the best-performing and 203 is the worst-performing catalyst in the series. These differences in the initiation rates were rationalized on the basis of the switchable electronic properties of the aminocarbonyl function.

In 2008, Barbasiewicz et al. reported the preparation of complexes 206–210 (Figure 46), bearing five different isopropoxyarylidene chelates,150 207, which was found to be the most efficient RCM catalyst in the series, showed metathesis activity similar to 5 (Figure 8). On the contrary, systems 206 and 208 were found to be latent, initiating only at temperatures above 110 °C. These pronounced differences in the catalytic activity of 206–210, also taking into consideration a series of structural and spectroscopic studies, were attributed to the partially aromatic character of the ruthenafurane ring, present in all ruthenium alkoxybenzylidene, which inhibits initiation and thereby decreases the catalytic activity of the complexes.

An analogous class of NHC-coordinated complexes bearing carbonyl- or carboxyl-substituted chelating benzylidene ligands (211–215) is presented in Figure 47. 211 is significantly less metathesis active than both first-generation catalyst 2 (Figure 2) and its heteroleptic (phosphine-NHC) analogues 14a and 14b (Figure 6).151 On the contrary, complexes 212–215, which have an unusual cis-dichloro arrangement, most commonly observed in complexes bearing strong chelating ligands such as pyridyl or quinoline (vide infra), were found to be thermally switchable in the ROMP of functionalized norbornenes.152 For example, aldehyde derivative 212, which showed the lowest initiation efficiency in this study, is barely active at room temperature but is an efficient polymerization catalyst at temperatures higher than 45 °C. In the ester series (213–215), initiation efficiencies were found to increase with the decreasing steric bulk of the alkoxy substituent (R). It should be noted that the development of thermally switchable, chemically switchable, or photoswitchable catalysts is highly important in polymer chemistry, as quite often the mixing of the monomer with the catalyst and the polymerization reaction have to be carried out at different times (and/or reactors) and, therefore, accurately controlled. This is vital in processes such as spraying or inkjet printing, where a constant and low viscosity is required, or when the monomer/catalyst mixture has to be shaped and profiled prior to polymerization (“curing”).

4.2. Chelating Thioether and Chelating Sulfoxide Benzylidene Ligands

In 2008, Lemcoff and co-workers published the synthesis of ruthenium-based complexes 216a and 217–220 (Figure 48) bearing a series of chelating thioether benzylidene ligands.153,154 As demonstrated by NMR experiments and single-crystal X-ray analysis data, these complexes display a cis-dichloro arrangement similar to that of 212–215 (Figure 47). 216a and 217–220 are highly stable toward oxygen and moisture and, equally importantly, thermally switchable. For example, catalyst 216a could be repeatedly switched on and off in the RCM of diethyl diallylmalonate by heating to 80 °C and cooling to 25 °C, respectively.153 It was also found that the initiation efficiency of 216a and 217–220 systematically depends on the steric bulk of substituent R, with 218 being the most reactive catalyst in the series.
More recently, Grela and co-workers reported the synthesis and catalytic activity evaluation of complexes 221–227 and 216b, an isomer of 216a having the usual trans-dichloro arrangement (Figure 48).155 221–227, which are coordinated with chelating sulfoxide benzylidene ligands, were proven to be metathetically inactive at room temperature but showed good diene and enyne RCM catalytic activity at elevated temperatures. 227 was found to be the most efficient metathesis catalyst in this study, combining thermal and air stability with good catalytic activity.

4.3. Mono- and Bis(pyridine)-Coordinated Catalysts

Further modifications of the ligand environment in heterocyclic carbene-coordinated ruthenium complexes led to the synthesis of catalysts 157 and 228–230 (Figure 49), bearing one or two pyridine ligands. As mentioned earlier, because of the lability of these pyridine ligands, mono- and bis(pyridine)-coordinated complexes can be used as versatile starting materials for the synthesis of other NHC-coordinated ruthenium complexes. Complexes 157, 229, and 230 can be easily prepared and purified on a multigram scale, requiring little or no solvent, by simply adding an excess of the appropriate pyridine to 3 (Figure 7).120,157 As shown in Figure 49, pyridine ligands bind in a cis geometry, occupying the coordination sites trans to the benzylidene and the NHC ligands. In the solid-state structure of 157, the Ru–N bond of the pyridine located trans to the benzylidene is more than 0.15 Å longer than the Ru–N bond of the pyridine positioned trans to the NHC, indicating that the benzylidene exerts a significantly larger trans influence than the NHC.129 Besides being the precursor of bis(NHC)-coordinated complexes 155 and 156 (Figure 36), 157 reacts instantaneously with PCy3 to regenerate the parent complex 3, with NaI to afford mono(pyridine) complex 231, with potassium tris(pyrazolyl)borate to give 232, or with potassium t-butoxide to afford complex 233 (Figure 50).129 Mono(pyridine) complex 228 can be prepared from 157 upon loss of one pyridine ligand under vacuum.

Probably even more importantly, bis(pyridine) ruthenium benzylidenes were proven to be efficient in the challenging CM of acrylonitrile, and they are among the fastest-initiating ruthenium systems studied thus far.157 Specifically, the initiation rate in the irreversible reaction of complex 229 with ethyl vinyl ether is at least 6 orders of magnitude higher than the corresponding initiation rate of second-generation catalyst 3. This very fast initiation of catalyst 229 has proven to be extremely useful in the production of polymers with very narrow polydispersity and for the synthesis of block copolymers.158

The procedure for the preparation of complexes 234–240 (Figure 51) is analogous to that of 157 and 229.159 The isolation of mono(pyridine)-coordinated 234, instead of the expected bis(pyridine) complex, was rationalized on the basis of the increased steric bulk and donor ability of the ancillary six-membered NHC ligand, compared to the five-membered NHC in 157 (Figure 49).159 234 was used in the ROMP of two enantiomerically pure norbornene derivatives. Bis(pyridine)-coordinated 235 was shown to be highly efficient in the CM of acrylonitrile with various functionalized alkenes,159a,b The activity of 235 decreases in coordinating solvents, whereas utilization of Lewis acids, which prevent the coordination of the cyano functionality with the ruthenium center, improves both the reaction rate and the yield of the CM reactions. In another more detailed study, mono(pyridine) complexes 236–239 were prepared from the corresponding triphenylphosphine-containing NHC-coordinated 26 (Figure 10).159c Complex 236 can also be prepared from
bis(pyridine)-coordinated 235 under vacuum, and conversely, 236 can be transformed into 235 in the presence of an excess of pyridine. The metathetic catalytic activity of complexes 235 and 236 was shown to be quite similar, while 238 was the most catalytically active complex studied, namely, among complexes 235-240, in the RCM of diallyl malononitrile and the CM of acrylonitrile with terminal olefins.

On a different note, pyridine-containing tethered catalysts 241-243 (Scheme 6) initiate slowly, but since the same propagating species is provided after one turnover, they maintain the high activity of parent catalyst 3 (Figure 7).160

As mentioned earlier, metathesis catalysts exerting attenuated initiation rates are very important in a number of ROMP applications, because they allow for longer fabrication times of the monomer/catalyst mixture and, therefore, for a more uniform polymeric material to be synthesized.161 Complexes 241a and 241b, of C1 and C3 symmetry, respectively, are isomers in equilibrium, with 241b being the thermodynamically favored species. Also, 241a and 241b are both latent initiators relative to complexes 3, 5 (Figures 7 and 8, respectively), and 157 (Figure 49), with 241b initiating much slower than 241a in RCM and ROMP transformations. The difference in initiation rate between 241a and 241b was attributed to the fact that the tethered pyridine ligand in 241a is trans to the strongly σ-donating NHC ligand and, as a result, dissociates to give the active 14-electron species much more quickly than that in 241b. Substitution on the pyridine ring was found to have a much less significant effect on catalytic activity, and 243 was found to be a faster initiator than 241 and 242, presumably due to the steric crowding of the α-methyl group on the tethered pyridine.

A series of other heterocyclic carbene-coordinated ruthenium complexes bearing pyridine or pyridine-based ligands are presented in Figure 52. Cationic complex 244 was isolated in an attempt to enforce intramolecular displacement of one of the chloride atoms, by the hydroxyl group in the side chain, to form a chelate structure.102 244 is metathesis inactive in standard RCM reactions, supposedly due to the pyridine ligands that are tightly bound to the cationic metal center and cannot be released even upon addition of p-toluenesulfonic acid. On the other hand, the tridentate carbene in 245 was designed as a more labile and less rigid alternative of the pincer NHC ligand in 163 (Figure 38) and was anticipated to lead to an improved metathesis catalyst compared to 163.132 Nevertheless, 245 was isolated in a very low yield, preventing evaluation of its catalytic activity. Pyridine adducts 246 and 247 (Figure 52) were also isolated, during attempts to prepare the corresponding (not observed) tricyclohexylphosphine complexes.121 Complexes 246 and 247, coordinated with cyclic (alkyl)(amino)carbenes, showed relatively low RCM efficiency, which was suggested to result from increased catalyst decomposition. Finally, 248 was targeted as a catalyst with improved initiation efficiency compared to its tricyclohexylphosphine-containing counterpart 125 (Figure 29).114 Indeed, 248 was shown to be an efficient ROMP initiator in sequence-selective copolymeriza-
tions. This alternating ROMP selectivity by 248 was attributed to the steric interaction of the 2-phenethyl substituent of the NHC with the growing polymer chain.

The concept of using labile pyridine ligands to prepare faster-initiating and highly active ruthenium metathesis catalysts that do not suffer from incomplete initiation has been also employed in complexes 249–253 (Figure 53), which bear alkylidene ligands other than benzylidene (note that section 5 is dedicated to the systematic variation of the alkylidene ligand in heterocyclic carbene-coordinated catalysts). Thus, Wagener and co-workers developed catalysts 249 and 250, bearing a ruthenium ethylidene and a ruthenium dimethylvinylidene, respectively, and successfully used them in ADMET and ROMP transformations.162,163 In other work, 251 was prepared by treatment of the corresponding tricyclohexylphosphine-coordinated indenylidene complex with an excess of pyridine.164 Displacing the phosphine ligand by pyridine in the indenylidene precursor of 251 is significantly slower than the same substitution reaction in benzylidene-bearing complex 3 (Figure 7). This was attributed to the stronger electron-donating ability and, therefore, trans influence, as well as to the increased steric bulk of the indenylidene, as compared to the benzylidene ligand. Nevertheless, 251 is also more thermally stable and, furthermore, more active in both RCM and ROMP compared to its benzylidene counterpart 228 (Figure 49).164,165 Quite similarly, both pyridine-coordinated ruthenium indenylidenes 252 and 253 were shown to be highly active in the ROMP of 1,5-cyclooctadiene.166

Finally, polyvinyl-, poly(ethylene glycol)-, and phospho-}

rylcholine-substituted pyridine ligands, in complexes 254, 255, and 256, respectively (Figures 54 and 55), have been successfully utilized to prepare immobilized (254)167 (see section 10) or water-soluble metathesis catalysts (255 and 256)168 (see section 9).

4.4. Chelating Quinolin- and Quinoxalin-ylidenes

Quinoline- and quinoxaline-containing tethered complexes 257 and 258 (Scheme 7), bearing five-membered chelate rings, have also been prepared.169 Similarly to their pyridine-containing counterparts 241–243 (Scheme 6),160 these complexes are initially isolated in the trans-dichloro geometry (257a and 258a); nevertheless, upon prolonged storage in solution they isomerize to the thermodynamically favored
cis-dichloro isomers (257b and 258b, respectively). Both 257 and 258 are air-stable in solution, showing RCM, enyne metathesis, and thermally triggered ROMP activity.\textsuperscript{169,170} Moreover, trans-dichloro complexes 257a and 258a initiate faster than their cis-dichloro isomers 257b and 258b, while the quinoxaline-containing 258a is faster than its quinoline analogue (257a) in model RCM and enyne metathesis reactions.\textsuperscript{169}

### 4.5. Bidentate Alkylidenes Chelated through Imine Donors

The first NHC-coordinated ruthenium alkylidenes containing an imine donor tethered to the alkylidene (259 and 260, Figure 56) were reported in 2005 by Slugovc et al.\textsuperscript{171} These air- and moisture-stable complexes exert thermally switchable ROMP behavior, showing high efficiency at temperatures around 110 °C and very low initiation rates at room temperature. 260 has a higher switching temperature and a lower polymerization rate than 259. This difference in the initiation rates of 259 and 260 was ascribed to the varying chelate ring sizes (five- versus six-membered, respectively).\textsuperscript{171} However, this hypothesis was challenged one year later, by the suggestion that the placement of the imine bond (exocyclic in 259 versus endocyclic in 260) is the factor that primarily determines the initiation behavior.\textsuperscript{172} In that study, complexes 261–270 (Figure 56) were prepared and evaluated in RCM and ROMP transformations. Exocyclic imine catalysts 261 and 262 were found to be highly active, and certainly not latent, in the RCM of diethyl diallylmalonate, and 261 initiated somewhat faster than 262. On the contrary, endocyclic imine complexes 264–267 are thermally triggered latent catalysts that show an almost on/off polymerization behavior in the ROMP of dicyclopentadiene. This different initiation behavior among the exocyclic and the endocyclic imine frameworks was attributed to unfavorable steric interactions in the exocyclic case with the rest of the catalyst framework. Thus, a weaker Ru–N bond results in a more efficient initiator and, ultimately, leads to a higher activity. Moreover, endocyclic imine complexes 263–267 efficiently ring-close diethyl diallylmalonate at elevated temperatures, with an order of activity 263 > 264 > 265 > 266 > 267. This result was rationalized on the basis of the relative donating ability and steric demand of the imine substituents. Namely, the electron-poor phenyl substituent affords the fastest-initiating catalyst and the small methyl group affords the slowest-initiating catalyst. The three-point chelating alkylidenes in 269 and 270 were designed as potentially even slower metathesis initiators since two successive ligand dissociation events must take place before a catalytically active fragment is generated. However, 268 and 269 show essentially identical RCM activities, indicating that the oxygen atom does not bind tightly enough to measurably impact the catalysis. Complex 270, on the other hand, shows a lower initiation rate than both 268 and 269, which suggests that incorporating an appropriate third point of attachment may indeed have a major impact on catalysis.

### 4.6. 14-Electron Phosphonium Alkylidenes

In 2004, Piers and co-workers published the synthesis of NHC-coordinated ruthenium complex 271 (Figure 57) bearing a 14-electron phosphonium alkylidene.\textsuperscript{173} Surprisingly, the four-coordinate complex 271, which models the presumed active species formed upon dissociation of the labile ligand in NHC-coordinated catalysts, is air- and moisture-stable and, furthermore, highly active in model RCM reactions. More importantly, this system provides rapid metathesis initiation, outperforming even bis(3-bromopyridine) complex 229 (Figure 49). Initiation in these 14-electron phosphonium alkylidenes is more energetically favorable than in the classic five- or six-coordinated systems, as it consists of a low-barrier olefin-binding event without the need for a ligand to dissociate. Soon after the synthesis of 271, the analogous 14-electron complexes 272 and 273 (Figure 57) were also prepared.\textsuperscript{174,175}

The ability of these phosphonium alkylidenes to initiate at very low temperatures has additionally proven useful in a series of low-temperature mechanistic studies that resulted in the direct observation of ruthenacyclobutane intermediates relevant to olefin metathesis.\textsuperscript{174–177} Given that ruthenacyclobutanes are known to play a key role in the determination of the regio- and stereochemical outcome of metathesis, a better understanding of their geometry is essential to the rational design of diastereo- and enantioselective catalysts. These studies are suggestive of bottom-face olefin coordina-
tion and metallacycle generation, that is, \textit{trans} to the NHC ligand. Spectroscopic data for all reported ruthenacyclobutanes are consistent with a symmetric structure with a flat, kite-shaped four-membered ring (species XII, Scheme 8).\textsuperscript{174–178} Ruthenacyclobutanes show dynamic structure, proceeding through a series of nonproductive metallacycle formations/cycloreversions prior to olefin exchange. However, most systems studied to date are relatively simple, and therefore, one should be very careful in generalizing these observations to more complicated ruthenacyclobutane species. Also note that there has been a long-standing debate regarding the site of olefin coordination to the ruthenium catalyst that leads to ruthenacyclobutane formation (side- or bottom-bound). Thus, in 1997 Snapper and co-workers reported the isolation of complex 274 (Scheme 9) in which a chelating olefin coordinates \textit{trans} to the PCy3 ligand (bottom face).\textsuperscript{179} Complexes 275a and 275b (Scheme 9) were also subsequently isolated, suggesting a side-bound olefin intermediate.\textsuperscript{180} In a similar vein, the reaction between 1,2-divinylbenzene and a series of NHC-coordinated ruthenium complexes led to the formation of two types of side-bound olefin adducts (XIII and XIV, Scheme 9) that undergo dynamic interconversion.\textsuperscript{181,91}

5. Ruthenium Alkylidene Variation: Fischer-Type Carbenes, Indenylidenes, Vinylidenes, Cyclic Ruthenium Alkylidenes, and Other Alkylidene Ligands

The first NHC-coordinated ruthenium indenylidenes \textsuperscript{(276–279, Figure 58)} were reported in 1999 by Nolan and co-workers.\textsuperscript{182,183} These complexes were demonstrated to be highly thermally stable and efficient in the RCM of benchmark \textit{α},\textit{ω}-dienes, forming five-, six-, and seven-membered \textit{di}-, tri-, and tetrasubstituted cycloalkenes, in the ROMP of 1,5-cyclooctadiene, as well as in a series of CM transformations.\textsuperscript{166,182–186} The preparation of indenylidene complexes 280, 281, and 282 (Figure 58), bearing NHC ligands with saturated backbones, was published in 2001, 2008, and 2009, respectively.\textsuperscript{184,187,188} Complex 280 was found to initiate the ROMP of 1,5-cyclooctadiene faster than both 281 and 3 (Figure 7), due to the more labile nature of the PPh\textsubscript{3} ligand as compared to the PCy\textsubscript{3} (also refer to section 6). Moreover, 281 shows an increased induction period compared to its benzylidene analogue 3 (Figure 7) and, therefore, lower activity in both RCM and ROMP transformations. It should also be noted that (pre)catalysts 3, 280, and 281, as well as all H\textsubscript{2}IMes-coordinated ruthenium complexes, provide the same propagating species (X, Scheme 8) after a single turnover. That is, as long as ligand “L” and the two anionic ligands in X are the same in two (pre)catalysts, the catalytic behavior of these species will only differ in the initiation step. Finally, complex 282 was found to be more competent than both 276 and 281 in the RCM of unhindered and moderately hindered dienes and enynes.

Ruthenium vinylalkylidene complexes \textsuperscript{283–285} (Figure 59) have also been isolated.\textsuperscript{66a,130,162} 283 was successfully utilized in the RCM and CM of a variety of electron-deficient olefins,\textsuperscript{56a} whereas 285 and ruthenium ethylidene 286 were shown to be efficient ADMET and ROMP catalysts.\textsuperscript{162,163} Ruthenium alkylidienes \textsuperscript{286–288} (Figure 59) initiate faster than the parent benzylidene complex 3 (Figure 7).\textsuperscript{189} While, in contrast, methylidene 289 is a very poor metathesis catalyst, in part as a result of its extremely low phosphine
dissociation rate. 294 289 represents an important intermediate of low stability in metathesis reactions of terminal olefins initiated by H2IMes catalyst 3, but can be isolated and purified by column chromatography. 24 All related catalyst decomposition studies are discussed in section 11.

Ozawa and co-workers were the first to report the preparation of an NHC-coordinated ruthenium complex bearing a Fischer-type carbene (290, Figure 60), 190 shown to be efficient in the RCM of endo-5,6-disubstituted norbornenes using phenyl vinyl selenide as an acyclic olefin. Soon thereafter, Fischer-type ruthenium complexes 291–295 (Figure 60) were also synthesized and were demonstrated to be structurally similar, but inherently more stable than their carbon analogues. 191 In solution, complex 294 exists in a temperature-dependent equilibrium with the chelate complex 296 and free PCy3. Complexes 291–295 efficiently catalyze a series of model RCM and ROMP reactions, although with significantly lower rates than their corresponding alkylidene counterparts. The rate of the RCM reaction of diethyl diallylmalonate was found to be highly dependent on the α-heteroatom; complex 293 was proven to be the most active catalyst in the series with the relative activities following the trend E = C > N > S > O. Along these lines, care should be taken when ethyl vinyl ether is used as the quenching agent in ROMP reactions, since complex 295 is metathesis active, at least under some conditions.

Furthermore, ruthenium allenylidene 297 (Figure 61), reported in 1999, shows high thermal stability but very low RCM activity, supposedly due to the relatively high bonding energy of the allenylidene moiety. 192 However, vinylidenes 298−300 (Figure 61) are efficient RCM and ROMP catalysts, although not as reactive as the corresponding benzylidene complex 3 (Figure 7). 193

Despite the great progress that has been made in the field of ruthenium-catalyzed metathesis, ruthenium catalysts do not efficiently carry out the metathesis of directly halogenated alkenes (i.e., vinyl halides and related substrates), because of the electron-withdrawing nature of the pendent halogens. This is especially true in CM, since there are some examples of RCM transformations involving α-chloro- and α-fluoro-α,ω-dienes. 194 The first example of a successful metathesis reaction between an NHC-coordinated ruthenium complex and a vinyl halide was reported in 2001, where ruthenium difluoromethylidene 301 (Figure 62) was prepared by treating the parent benzylidene complex 3, Figure 7 with an atmosphere of 1,1-difluoroethylene. 195 Although the F2C=CH2 double bond was cleaved metathetically, this reaction was proven not catalytic. Nevertheless, 301 effects the ROMP of 1,5-cyclooctadiene, albeit significantly less efficiently than 3. The poor catalytic activity of 301 was attributed to its insufficient initiation and, therefore, could be slightly improved by additives that promote phosphine dissociation.

On the basis of another study, Johnson and co-workers published a procedure toward the synthesis of monofluoromethylidene complexes 302 and 303 (Figure 62). 196 302 and 303 are significantly more reactive than 301, but slow compared to 3, in the RCM and CM of model alkenes. Bis(pyridine) complex 303 initiates more quickly than 302, as anticipated; however, it also suffers from a higher decomposition rate. Isolation of the monochloromethylidene analogue of 302 was not possible, even though its transient formation could be observed at −70 °C by NMR. 197 Instead, terminal carbide 304 and phosphoniomethylidene 305 (Figure 63) were formed upon reaction of ruthenium benzylidene 3 with vinyl chloride.

In 2001, Fürstner et al. reported the synthesis of complexes 306 and 307 (Figure 64), featuring a chelating N-to-Ru tether, as catalysts that could be regenerated upon consumption of monomer; nevertheless, the catalytic activities of 306 and
307 were not evaluated in that early work.81 Later on, however, catalyst 309 (Figure 64) was found to mediate the synthesis of cyclic polymers via ROMP of strained cyclic monomers such as cis-cyclooctene,198 1,5-cyclooctadiene, and 1,5,9-trans-cis-trans-cyclooctadecatriene.199 In brief, this ring-expansion metathesis polymerization (REMP) was suggested to proceed via a ring-expansion initiation event, from a cyclic ruthenium alkylidene catalyst, and propagate as cyclic monomers are incorporated into the growing cyclic polymer (XV, Figure 64) that remains attached to the metal center throughout the entire polymerization process. This approach circumvents the problems involved in other more typical routes to cyclic polymers, which require the intramolecular macrocyclization of linear precursors at very low concentrations. Further investigations, with the aim of systematically studying the impact of the tether length and the electronic properties of the NHC, via backbone saturation, on different aspects of the polymerization mechanism, led to the synthesis of cyclic catalysts 307–312, presented in Figure 64.200 Whereas increasing the N-to-Ru tether length was found to result in enhanced rates of polymerization, shorter tethers were more efficient for catalyst release from the polymer. Utilizing a saturated NHC backbone (311 and 312) was shown to boost polymerization rates to a greater extent than increasing the length of the tether.

Attempts to prepare active chelated catalysts led to the preparation of an unusual imidazolium-substituted ruthenium alkylidene (314, Figure 65).201 Complexes 313 and 314 were isolated during attempts to synthesize a ruthenium alkylidene complex monocoordinated with the corresponding bidentate aryloxy–NHC ligand. 313 and 314 were purified by column chromatography and fully characterized, although in very low isolated yields (6 and 12%, respectively). As expected, 314 proved to be a poor olefin metathesis catalyst.

The isolation of alkynyl-substituted alkylidene ruthenium complexes 315–317 (Figure 65) was reported in 2009.202 In that work, Lee and co-workers showed that substituents on alkynyl ruthenium alkylidenes can efficiently adjust their reactivity and metallocotropic [1,3]-shift behavior. 315, characterized via single-crystal X-ray analysis, was proved to be moderately active in the RCM of a model enyne substrate.

### 6. Variation of the Phosphine Ligand

With regard to phosphine-containing NHC ruthenium catalysts, it should be re-emphasized that complexes which are different only in their phosphine ligand provide the same propagating species (X, Scheme 8) upon phosphine dissociation. Consequently, by varying the phosphine, one can manipulate initiation and phosphine rebinding without changing the metathesis ability of the catalyst. Accordingly, phosphine-containing complexes 318–327 (Figure 66) were prepared for a systematic study of the effect of different phosphine ligands.24,129,156,203 The data obtained for complexes 322 (bearing phosphine ligands with the same cone angle) by either magnetization transfer experiments or by the stoichiometric initiation with ethyl vinyl ether revealed the existence of a linear free energy relationship between the phosphine dissociation rate constant and the Hammett constant $\sigma_p$ (that is, phosphine $\sigma$-donor strength), with the more electron-rich phosphines dissociating at slower rates than electron-poor ones.156 Moreover, arylphosphine...
dissociation was generally found to be faster than alkylphosphine dissociation. Thus, initiation in H2IMes phosphine-containing catalysts can be easily adjusted by tuning phosphine electronics. On the other hand, phosphine reassociation showed no direct correlation with phosphine electronics. In addition to electronics, the steric properties of phosphine ligands have a major impact on phosphine dissociation, and thus complex 318 was essentially metathesis inactive at room temperature.  

Recently, complexes 328–330 (Figure 66), coordinated with a series of chelating phosphine-carboxylate ligands, were prepared. These chelated complexes exhibit slow initiation rates at temperatures up to 40 °C; nevertheless, at elevated temperatures, 328 and 330 efficiently ring-close diethyl diallylmalonate and diallyl malononitrile, outperforming 329.

7. Anionic Ligand(s) Variation

7.1. Halides

It has been already mentioned that, in some cases, changing the halide ligands from chlorides to iodides improves the enantioselectivity of chiral ruthenium metathesis catalysts (sections 3.3 and 3.4). In the case of chiral monodentate NHCs, the diiodide complexes are prepared in situ, by dissolving the dichloride catalyst in THF in the presence of NaI, whereas chiral bidentate iodide complexes are stable enough to be isolated and chromatographically purified. Additionally, halide ligands have been shown to have a significant impact on the initiation rates of second-generation catalysts. For example, dibromide 331 and diiodide 332 (Figure 67) initiate 3 and 250 times faster than the dichloride parent complex 3 (Figure 66), respectively. This initiation rate enhancement was predominantly attributed to the increased steric bulk of bromide or iodide ligands, since cis electronic effects (i.e., between the halide(s) and the phosphine ligand) are generally relatively small in dissociative ligand-substitution reactions. However, despite the increased initiation efficiency of 332, its olefin metathesis activity is comparable to, or even lower than, that of the parent dichloride complex 3 due to slower turnover rates.

7.2. Monodentate and Bidentate Aryloxides

Motivated by the easily tunable steric and electronic properties of Fogg and co-workers developed “pseudohalide” ruthenium catalysts 333–337 (Figure 68). “Halide-free” 333, the first NHC-coordinated complex of this type to be reported, proved to be a highly active metathesis catalyst, efficiently carrying out the ring-closing of model \(\alpha,\omega\)-dienes, even at very low catalyst loadings. Equally efficient metathesis catalysts 334–337 bearing aryloxide ligands.

Figure 68. Ruthenium-based catalysts 333–337 bearing aryloxide ligands.

7.3. \(N,O\), \(P,O\), and \(O,O\)-Bidentate Ligands

The first ruthenium catalysts featuring this class of ligands to be reported are complexes 338–341 (Figure 69), prepared by exchanging tricyclohexylphosphine with the corresponding chelating pyridinyl alcoholate ligand, which display low metathesis activity at room temperature. This effect was attributed to the chelate stabilization induced by the dangling pyridine ligand. Nevertheless, at 60 °C, 338–341 effect the ROMP of both norbornene and cyclooctene, showing activities similar to the tricyclohexylphosphine-containing parent complexes. In a more recent study, Jordaan and Vosloo prepared the structurally similar complex 342 (Figure 69) and evaluated its catalytic performance in the self-metathesis of 1-octene in the absence of a solvent. Complex 342 displays a lower initiation rate than phosphine-containing 3 (Figure 66); however, at 60 °C, 342 has a higher activity and stability compared to 3.

Schiff base \(N,O\)-bidentate ligands were introduced for the first time in NHC-coordinated ruthenium complexes by Vervoort and co-workers. Utilizing this ligand framework is quite appealing, not only because of the fine-tuning
possibility of both the steric and electronics at the ruthenium center but also because of the high-yielding and usually single-step procedures by which they are accessible. Thus, complexes 343-349 (Figure 70) were synthesized and shown to efficiently catalyze the RCM and ROMP of a series of benchmark substrates.\(^{213,214,216}\) The catalytic activity of 343-348 was proved to depend strongly and systematically on the steric and electronic environment of the Schiff base, with an order of activity 343 > 344 > 345 > 346 > 347 > 348. In addition, complexes 346-349 initiate extremely slowly compared to their phosphine-containing analogue 3 (Figure 66), showing very low metathesis activity at room temperature. Nevertheless, at 90 °C, 346-349 are very efficient ROMP initiators, on account of their very high thermal stability.\(^{216}\) It was also found that the initiation efficiency of latent 346 can be chemically controlled on demand.\(^{217}\) Specifically, upon addition of Brønsted or Lewis acids, such as HSiCl\(_3\), HSiMeCl\(_2\), BF\(_3\), or AlCl\(_3\), at room temperature, 346 can be transformed into a very reactive catalyst, affording high turnover numbers in the ROMP of both 1,5-cyclooctadiene and dicyclopentadiene, as well as in the RCM of diethyl diallylmalonate. The triggering mechanism was proposed to involve the reversible formation of an adduct between the acid and the electron pair on the nitrogen of the Schiff base. Ruthenium indenylidene 350 (Figure 70), with both ROMP and controlled radical polymerization reactivity, has been also prepared.\(^{218}\)

In 2005, Hahn et al. reported the synthesis of halide-free 351 (Figure 71), coordinated with two bidentate 2-pyridine-carboxylato ligands.\(^{219}\) Although complex 351 is metathesis inactive, upon addition of 2 equiv of HCl it generates a catalytically active species by protonation of at least one of the 2-pyridine-carboxylato ligands. While less active than second-generation catalyst 3 (Figure 66), this in situ generated species effects the RCM of model \(\alpha,\omega\)-dienes in CH\(_2\)Cl\(_2\) and MeOH.

In another approach, \(\mathrm{N},\mathrm{O},\mathrm{P},\mathrm{O}\)-, and \(\mathrm{O},\mathrm{O}\)-bidentate complexes 352-354 (Figure 71) were developed.\(^{220}\) Quite similar to many of the above-reported chelated catalysts, 352-354 exert low metathesis activity at room temperature, while \(\mathrm{O},\omega\)-chelate 354 also suffers from a high decomposition rate. Interestingly, however, the initiation of both 352 and 353 is significantly enhanced upon addition of CuCl. Whereas CuCl-activated 352 shows reduced stability, CuCl-activated 353 is a quick-initiating and highly efficient catalytic system in the RCM of diethyl diallyl and diethyl allylmethylmalonate. Additionally, intermediate trapping experiments suggest that this CuCl-assisted initiation mechanism involves reversible coordination of the prolinate ligand to CuCl, thereby facilitating an open coordination site on ruthenium.

### 7.4. Carboxylates and (Alkyl)sulfonates

Substitution of the anionic chloride ligand(s) by perfluorosulfonates and, more often, perfluorocarboxylates, in ruthenium metathesis catalysts is typically connected with the preparation of immobilized catalysts on solid supports (see section 10). However, homogeneous catalytic applica-
tions of this family of complexes turned out to be quite successful as well. Thus, catalysts 355–357 (Figure 72) were prepared and found to be efficient in the RCM of diethyl diallylmalonate, 1,7-octadiene, diallyldiphenylsilane, N,N-diallyltrifluoroacetamide, and other related substrates, as well as in enyne metathesis and ROCM reactions.221 In other work, 357–362 were tested in a series of benchmark RCM transformations.222 These complexes proved to exert similar or lower reactivity compared to the parent chlorine-containing systems (catalysts 3 and 5, Figures 66 and 8, respectively). Quite similarly, 363–368 (Figure 72) were prepared by substituting one or two of the chloride ligands in complex 5 with 1 or 2 equiv of the corresponding silver carboxylates, respectively.223,224 Note that this rather typical substitution reaction is usually complete within minutes, driven by the precipitation of silver(I) chloride. In terms of catalytic efficiency, monosubstituted catalysts (363, 365, and 367) outperform those in which both chloride ligands are exchanged (364, 366, and 368), with the most efficient, 363, showing activity similar to the parent dichloride catalyst 5. Complex 369 was shown to be a highly active metathesis catalyst in both RCM and ROCM transformations.119

In 2006, Braddock and co-workers published a related study on Cl-, Br-, CF3CO2-, and C2F5CO2-substituted ruthenium isopropoxybenzylidenes, the results of which reveal significant implications for all kinds of anionic substituents in these types of ruthenium complexes.225 In solution, all examined complexes were shown to constantly undergo anionic ligand exchange, under mild conditions typical for olefin metathesis reactions. The mechanism that was proposed to account for this ligand exchange involves the intermediacy of halide-bridged dimers, which are more easily accessible in the case of carboxylate-containing complexes due to steric reasons. This effect should be taken into consideration in the design of both homogeneous and heterogeneous ruthenium catalysts in the case of immobilization through the anionic ligand(s). One year later, the same group reported the vacuum-driven anionic ligand exchange of free perfluorocarboxylic acids with ruthenate-bound perfluorocarboxylates.226

7.5. Nitrile- and Isonitrile-Coordinated Alkylidene-Free Ruthenium Catalysts

This class of compounds was targeted by Buchmeiser and co-workers with the aim of developing phototriggered ROMP catalysts. Whereas both 370 and 371 (Figure 73) were shown to initiate the ROMP of norbornene at room temperature in the absence of irradiation, therefore being unsuitable phototriggered initiators for this monomer, polymerization of norborn-5-ene-2-ylmethanol required UV irradiation (172 nm) and concurrent heating at 40 °C.227 Thus, 370 and 371 are in principle suitable for the UV-initiated ROMP of this monomer. Initiation of 370 and 371 was postulated to involve the phototriggered dissociation of at least two of the three phenyl isonitrile groups. Although structurally similar to 370 and 371, carboxylate-containing catalysts 372 and 373 (Figure 73) decompose upon heating in the presence of a series of functionalized norbornenes, supposedly due to an imine metathesis-type reaction of dissociated phenyl isonitrile with any in situ generated ruthenium alkylidene complex.228 Nevertheless, the turning point in this family of catalysts occurred with the preparation of nitrile-coordinated cationic complexes 374 and 375 (Figure 73).229 These two complexes proved to be the first thermally stable, UV-initiated ROMP catalysts. Both 374 and 375 can be handled in air and, in the absence of light, are completely unreactive toward cyclooctene, dicyclopentadiene, and a number of norbornene derivatives up to 45 °C. Exposing mixtures of either 374 or 375 with these same monomers to 308 or 254 nm irradiation, at room temperature, led to the formation of the correspond-

![Figure 72. Ruthenium-based catalysts 355–369 coordinated with carboxylate and (alkyl)sulfonate ligands.](image)

![Figure 73. Nitrile- and isonitrile-coordinated ruthenium-based complexes 370–375.](image)
ing polymers, with 254 nm excitation being considerably more efficient. On the basis of NMR data, laser flash and steady-state photolysis experiments, and a series of theoretical calculations, the mechanism shown in Scheme 10 was used to account for the phototriggered ROMP activity of 374. According to their proposal, photolysis of the precatalyst (374) initially leads to the formation of species XVI, which then binds one monomer molecule to form intermediate XVII. In the key step for the alkylidene formation, a 1,2-hydrogen atom shift on the carbon–carbon double bond of the alkene $\pi$-complex (XVII) affords the active ruthenium(IV) species (XVIII) that initiates the ROMP cascade.

8. N-Heterocyclic Carbone-Coordinated ($\eta^6$-Arene)ruthenium Metathesis Catalysts

Complexes 376–378 depicted in Figure 74 were the first ($\eta^6$-arene)ruthenium species bearing NHC ancillary ligands to be reported. These half-sandwich complexes, which are isolated in high yields and display high thermal stability, outperform their phosphine-containing counterparts in the RCM of diethyl diallylmalonate. It should be noted that aryl-substituted imidazol- and imidazolin-2-ylidene-coordinated ruthenium species have no effect on the RCM of diethyl diallylmalonate discussed above. Alternatively, visible light irradiation was observed to lead to $p$-cymene decoordination, generating highly reactive, coordinatively unsaturated ruthenium species that were suggested to trigger metathesis. In the absence of trimethylsilyldiazomethane, the ROMP of cyclooctene by 376 and 377, as well as 387–389, was found to depend on the presence of light, in contrast to the RCM of diethyl diallylmalonate discussed above. Photoinitiation only required an ordinary 40 W “cold white” fluorescent tube or a 250 W incandescent light bulb placed 10 cm from the Pyrex reaction flasks. The most efficient ROMP catalyst in this study proved to be 376, slightly outperforming the second most efficient, 377. In related more recent work, Ledoux et al. reported that preparation of 389 is extremely problematic due to its high decomposition rate. Instead, they prepared chelated complexes 390 and 391 (Figure 75), the phenolate ligand of which dissociates.
imidazolium chloride corresponding NHC, which is also obtained in situ from and imidazolinium chlorides

1776 Chemical Reviews, 2010, Vol. 110, No. 3 Vougioukalakis and Grubbs

[52x194] KO

imidazolium and imidazolinium chlorides

that the presence of a C4 monodentate analogues of upon treatment with HCl to afford the corresponding

chemical Reviews, 2010, Vol. 110, No. 3 Vougioukalakis and Grubbs

Figure 76. Ruthenium complex 392, imidazolium chloride 393, and imidazolinium chlorides 394a–394h.

upon treatment with HCl to afford the corresponding monodentate analogues of 389. These species were highly unstable as well.

Interestingly, it was also found that preformed 376 is almost as catalytically efficient as when generated in situ from the homobimetallic complex 392 (Figure 76) and the corresponding NHC, which is also obtained in situ from imidazolium chloride 393 (Figure 76) by deprotonation with KOt-Bu.234,236 This three-component catalytic system (i.e., [RuCl2(p-cymene)]2/NHC-precursor salt/base) is simpler and more straightforward to utilize, as it requires only stable and commercially available reagents to generate the active species. Subsequently, the same approach was utilized with imidazolium and imidazolinium chlorides 394–396(Figures 76 and 77) as NHC ligand precursors.237–239 It was found that the presence of a C4–C5 double bond in the imidazole ring of the NHC ligand is not a prerequisite for high catalytic activities in the photoinduced ROMP of cyclooctene and norbornene.237,238 However, blocking all the ortho positions on the N-aryl substituents of the NHCs is necessary to afford efficient photoinitiating ROMP polymerization catalysts. This effect was proposed to originate from the tendency of ruthenium complexes lacking ortho substituents to undergo orto-metalation240 of the N-aryl moiety (also refer to section 11). Moreover, changing the sterics and the electronics of the remote aryl groups of the biphenyl units in imidazolium chlorides 395a–395h and imidazolinium chlorides 396a–396e (Figure 77) had only limited influence on the polymerization activity.239 Mesityl-based in situ generated 376 and 389 were the most efficient catalysts in these studies. Finally, Buchmeiser and co-workers prepared complexes 397 and 398 (Figure 78), which are the trifluoroacetate-coordinated analogues of 376 and 389, and examined their thermally initiated and photoinitiated ROMP activity.227,228 While 397 and 398 were indeed shown to be suitable for the UV-triggered polymerization of norborn-5-ene-2-ylmethanol, norbornene was uncontrollably polymerized by both 397 and 398 in the absence of irradiation at room temperature.

Dixneuf and co-workers utilized a quite similar, though thermally initiated rather than photoinitiated, three-component catalytic system (i.e., [RuCl2(p-cymene)]2/NHC-precursor salt/Cs2CO3) to carry out enyne metathesis and RCM reactions.241–244 The presence of a terminal alkyne as an activator was necessary in the latter set of transformations. Furthermore, the same in situ prepared three-component system was found to promote the ROMP of cyclooctene.245 Thus, heating of [RuCl2(p-cymene)]2(NHC-precursors 394g or 394h, and Cs2CO3 at 80 °C in chlorobenzene led to high- and moderate-yielding cyclooctene polymerization with 394g and 394h, respectively. Two different experimental procedures were used, with addition of cyclooctene to the catalytic system either before or after its activation process. Cs2CO3 was proposed not only to deprotonate the NHC precursor but also to modify the catalyst, possibly by substituting the chloride ligand(s) and/or favoring the dissociation of p-cymene.

Figure 77. Imidazolium chlorides 395a–395i and imidazolinium chlorides 396a–396e.

Figure 78. NHC-coordinated half-sandwich ruthenium complexes 397 and 398.
Scheme 11. NHC-Coordinated (η⁶-Arene)ruthenium Complexes 399–405


In addition to the potential environmental and economic benefits of aqueous olefin metathesis, successful materialization of such a process would also be important for numerous biological applications. In this context, water- and protic solvent-soluble NHC-coordinated ruthenium catalysts were targeted in an attempt to overcome the relatively low stability and activity of the early bis(phosphine) water-soluble catalysts.37–39,250 In fact, the first report of olefin metathesis utilizing NHC-coordinated complexes in protic media involved the use of conventional 3 and 5 (Figures 66 and 8, respectively), which were shown to effect the RCM and, to a lesser extent, CM of model substrates in MeOH, as well as in MeOH–water and DMF–water mixtures.251

Two kinds of functionalities have been employed thus far to solubilize the desired NHC-bearing (pre)catalysts in water: (i) poly(ethylene glycol) (PEG) chains (406 and 407, Figure 79),40,41 and (ii) quaternary ammonium groups (408–411, Figure 79).43,99,168,252,253 As can be seen in Figure 79, these solubilizing moieties have been attached: (i) to the NHC ligand, as in 406–407; (ii) through the benzylidene, as in 408–410; or (iii) via the anionic ligand, as in 411. In particular, 406 efficiently initiates the ROMP of strained cyclic olefins in both water and methanol.40 In the former case, the presence of 1 equiv of HCl, relative to 406, is necessary in order to protonate the dissociated tricyclohexylphosphine, thereby inhibiting its reassociation to the ruthenium center and preventing catalyst decomposition by base. Phosphine dissociation in water was proposed to be disfavored due to the energetic cost of solvating two neutral molecules. Catalyst 406, which remains in solution throughout the entire metathesis reaction in water or MeOH, was also found to catalyze the RCM of benchmark dienes in MeOH. With the intention of avoiding the incorporation of the PEG–carbamoyl–benzyl moiety, which was suggested to reduce the stability of 406, the PEG group (number average molecular weight ≈ 2600) has been alternatively appended on the backbone of the NHC ligand (407).41 Indeed, water-soluble complex 407, which is also soluble in common organic solvents such as dichloromethane and toluene, exerts improved stability and activity in water, compared to both 406 and all previously reported water-soluble bis(phosphine) catalysts. Thus, 407 efficiently carried out the ROMP of norbornene derivatives, the unprecedented RCM of a series of water-soluble α,ω-dienes, and the self-CM of cis-2-butene-1,4-diol. In an analogous fashion, complexes 255 and 256 (Figures 54 and 55, respectively), bearing PEG- and phosphorylcholine-substituted pyridine ligands, were more recently shown to initiate the ROMP of a PEG-containing oxanorbornene monomer under a variety of conditions.168

Further studies have furnished small-molecule catalysts 408 and 409,252 as well as 410253 and 41143 (Figure 79). In brief, 408 and 409 efficiently mediate a series of ROMP and RCM transformations in water,252 whereas 410 performs RCM and CM reactions in water (only for X = I), alcohols, and homogeneous alcohol–water mixtures, even in the presence of air.253 In micellar solutions, 410 acts both as an initiator and a surfactant promoting RCM and CM under heterogeneous aqueous conditions. Complex 411 also proved to be an efficient RCM catalyst in alcohols and homogeneous alcohol–water mixtures in air.43 Complex 73 (Figure 16) can be transformed into its moderately water-soluble bisprotonated analogue by the addition of 2 equiv of HCl.99 Unfortunately though, this bisprotonated complex suffers from a high decomposition rate, owing to the hydrolysis of the NHC–ruthenium bond.

Olefin metathesis in water can also be carried out by occluding existing homogeneous ruthenium catalysts in a hydrophobic matrix of polydimethylsiloxane and then using the resulting polydimethylsiloxane slabs in heterogeneous reactions.32,254 For a more detailed discussion of heterogeneous olefin metathesis, refer to section 10. Finally, note that Raines and co-workers successfully utilized conventional

Figure 79. Ruthenium metathesis catalysts 406–411 for use in water and protic solvents.
NHC-coordinated catalysts 3 and 5 (Figures 66 and 8, respectively) in RCM and CM reactions in homogeneous water/organic mixtures, achieving high conversions for a variety of substrates.255

10. Removal of Ruthenium Impurities from Metathesis Products and Ruthenium Recycling Strategies

Despite the widespread use of ruthenium-catalyzed metathesis, removal of ruthenium byproducts at the end of the reaction is still rather challenging. In addition to pharmaceutical chemistry applications, where the acceptable ruthenium content is <10 ppm in the final compound, efficient purification of olefin metathesis products is also highly important in the case of polymeric materials, especially when these are to be used in electronics and other technologically advanced applications. Of equal importance is the unsuccessful exclusion of ruthenium impurities during the production of fine chemicals, which invokes the danger of undesired side-reactions in subsequent steps. Another closely related and very significant issue, from both an environmental and an economic point of view, is catalyst recycling and regeneration.

The most common strategies that have been thus far employed to address these problems are based on ruthenium catalyst tagging with (i) inorganic materials (e.g., silica gel); (ii) insoluble polymers; (iii) ionic liquid functionalities; (iv) perfluorinated hydrocarbons; or (v) soluble polymers or small-molecule functionalities. Ideally, these modified catalysts can be easily recovered from reaction mixtures by filtration (supports i and ii above) or by extracting the catalyst into the ionic liquid or fluorous phase (functionalities iii and iv, respectively), resulting in reduced ruthenium impurities. Another procedure involves precipitation controlled on demand, or purification via a chromatographic procedure (approach v). As illustrated in Figure 80, attachment of NHC-coordinated ruthenium catalysts with the above-mentioned functionalities can be achieved through the NHC nonlabile ligand (positions R1 or R2), anionic ligand(s) X1 and/or X2, the benzylidene moiety (Ar), or phosphine- or pyridine-based labile ligand(s) L. Besides affecting recycling along with easier and more efficient purification, immobilizing the catalytic complex onto a solid support has also been proposed to improve catalyst stability and prevent the undesirable bimolecular decomposition pathways, by inhibiting intermolecular catalyst–catalyst interactions via a phenomenon known as site isolation.256 In view of the fact that this research field has been very well described in a series of recent review articles,257 herein we only briefly discuss some representative examples.258

Catalysts of the types shown in Figure 81 (412–417)102,259–262 are immobilized onto solid insoluble supports and are utilized in heterogeneous catalysis. Thus, 412 was prepared by immobilizing the precursor alcohol adduct on commercial silica gel, which was pretreated with MeSiCl3 or PhSiCl3 in order to install the necessary chlorosilane anchoring functionalities on its surface. 412 effects the RCM of a series of α,ω-dienes and could be reused up to three times; however, it was proved to exert lower catalytic activity compared to its homogeneous analogue.102 413, immobilized onto nonporous silica with a 0.5 wt % ruthenium loading, also shows modest RCM activity in slurry-type reactions.259 On the other hand, catalyst 414, prepared with a loading of 1.4 wt %, efficiently promotes both ROMP and RCM transformations, while ruthenium contamination of the products was found to be as low as 70 ppm.260 Silica-supported catalysts 416 and 417 were shown to competently catalyze a variety of model RCM and CM reactions.261 416 and 417 can be efficiently recycled multiple times and, most importantly, do not leach ruthenium, as revealed by inductively coupled plasma–mass spectrometry (ICP-MS) analysis of filtered reaction solutions (ruthenium contamination of filtrate < 5 ppb). 415 also could be recycled up to five times with no significant loss of activity in the CM of a series of highly electron-deficient alkenes;262 other ruthenium isopropoxy-
benzylidenes, supported on monolithic silica discs, were reportedly reused in 20 cycles. Note that in the case of “boomerang-type” catalysts resembling (i.e., anchored through the benzylidene ligand), the active species are homogeneous. Nevertheless, it is proposed that a large fraction of these catalytically active ruthenium species are recaptured during metathesis, forming the more stable chelating isopropoxybenzylidenes, whereas complexes that decompose remain in solution.

The use of ionic liquids as alternative solvents provides many potential advantages over their conventional counterparts. These advantages include their high chemical and thermal stability, extremely low vapor pressure, insolubility or immiscibility with either aqueous or organic reaction media, and good ability to solvate both polar and nonpolar species. In this context, specially designed catalysts incorporating an ionic moiety into their structure, such as or in Figures 45, 79, and 82, respectively, have been exploited in ruthenium-catalyzed biphasic (i.e., organic solvent/ionic liquid) olefin metathesis reactions, aiming at the recovery and reusability of the catalyst. In brief, or efficiently promote olefin metathesis in organic solvents, aqueous media, and ionic liquids, leading to levels of ruthenium contamination in the products as low as 25 and 12 ppm, respectively, after a simple filtration through silica gel; however, they both display poor recyclability, and their activity is significantly reduced in the second cycle. On the contrary, complexes and are very efficient RCM catalysts and display relatively high recyclability (i.e., they can be reused up to 8 and 17 times, respectively, with no significant loss of activity). Furthermore, affords low ruthenium contamination levels in the ring-closed products (1–22 ppm).

As noted above, attempts to eliminate ruthenium contamination have been carried out by utilizing ruthenium complexes bearing fluorous tags, either via filtration through a short pad of fluororous-phase silica gel or by fluororous-phase extraction. For example, complex (Figure 82) was found to be efficient in the RCM of benchmark $\omega$-dienes under both monophasic (CH$_2$Cl$_2$) and biphasic (CH$_2$Cl$_2$/fluorous solvent mixtures) conditions; the rate acceleration observed in the latter case was proposed to arise from phase transfer of the dissociated fluororous phosphate. Moreover, could be recycled up to three times with no significant loss of activity, by extracting the reaction mixtures with perfluoro(methylcyclohexane). Fluorous-tagged complex (Figure 82) was also shown to be highly active in RCM and CM transformations of terminal olefins. Removal of ruthenium residues from the metathesized products was achieved either by fluorous-phase extraction or by filtration through fluorous-phase silica gel, resulting in ruthenium contamination levels as low as 500 ppm.

An alternative, on-demand purification and recycling strategy, employing the redox-switchable ferrocenyl moieties in complex (Figure 83), was published by Süßner and Plenio in 2005. In particular, after utilizing soluble catalyst to catalyze the RCM of $N,N$-diallyl tosylamine, they were able to in situ oxidize its two ferrocenyl moieties, causing its precipitation and separation from the reaction products; precipitated and washed could then be easily redissolved by reduction. By repeating the same protocol, could efficiently perform up to three consecutive metathesis-redox cycles.

Ruthenium contamination levels as low as 41 ppm were achieved by simply extracting the RCM reaction mixtures carried out by (Figure 79) with water. Furthermore, treatment of the ring-closed products with activated carbon after aqueous extraction led to ruthenium levels below 0.04 ppm (ICP-MS). Other published strategies, attempting to address the difficulties in removing ruthenium residues...
coming from homogeneous metathesis catalysts, include (i) purification of the products on silica gel along with treatment with activated carbon (ruthenium contamination levels as low as 60 ppm);273 (ii) use of ruthenium scavengers, such as dimethyl sulfoxide,274 Ph₃P or lead tetraacetate,275 in combination with column chromatography (residual ruthenium levels as low as 240 ppm); (iii) treatment of the metathesized products with amine-modified silica (ruthenium contamination less than 2000 ppm);276 and (iv) treatment of the metathesis product(s) mixture with isocyanide CNCH₂CO₂K (residual ruthenium as low as 120 ppm)277 or tris(hydroxymethyl)phosphine.278

11. Decomposition Studies

Understanding the decomposition pathways of existing ruthenium-based metathesis catalysts is crucial for the development of new, more efficient catalysts, by rationally designing and utilizing adjusted ligand environments that reduce reactions that result in alkylidene loss. Along these lines, hydridocarbonyl chlorides 424—426 and phenylcarbonyl chlorides 427 and 428 (Figure 84), formed in basic alcoholic solutions upon prolonged heating of the corresponding benzylidene, comprise the first reported family of heterocyclic carbene-coordinated ruthenium catalyst degradation adducts.53,279,280 Note that 424 is also formed upon prolonged heating of parent complex 3 (Figure 66) in the presence of oxygen-containing substrates such as ethyl vinyl ether;53 and 427 can also be produced by the reaction of solid 3 with oxygen in 29% isolable yield.279 Complexes 424—428 are derived through alcohol decarbonylation, although the exact mechanism of this process is still unknown. Moreover, while many of these complexes are highly efficient hydrogenation- and olefin isomerization catalysts, they usually do not impose significant problems on olefin metathesis reactions carried out in alcoholic solvents, due to the high temperatures and prolonged reaction times needed for their production.279,280 Structurally similar species 429 (Figure 84), encompassing an H₂IMes ligand that has undergone C—H bond activation on one of its ortho-methyl groups, is formed when 3 is prepared under a moderately rigorous inert atmosphere.53 However, it should be noted that none of the above decomposition adducts (424—429) are formed from typical metathesis conditions employing aprotic solvents (e.g., dichloromethane, benzene, or toluene), and consequently, their generation cannot be considered universal.

On the contrary, by taking into consideration that ruthenium methylidenes such as 289 (Scheme 12) are common intermediates in most metathesis reactions, studying their decomposition was expected to shed some light on ruthenium catalyst degradation in general. Initial investigations revealed that 289 decomposes rapidly ($t_{1/2} = 5$ h 40 min) compared to the parent benzylidene complex 3 (Figure 66), via a unimolecular pathway, despite exhibiting very low initiation rates.24,281 While decomposition of 3 was found to be inhibited by adding free phosphines, this was certainly not
the case with 289. Subsequent studies led to the isolation of the first well-characterized decomposition products of 289, namely, 430 and 431 (Scheme 12). As shown by X-ray crystallographic analysis, dinuclear ruthenium hydride 431 bears a bridging carbide between the two ruthenium centers (Ru1 and Ru2), whereas the complete loss of phosphine ligands is accompanied by η6-binding of Ru2 to one of the mesityl rings in the NHC on Ru1. The proposed mechanism for the formation of methyltricyclohexylphosphonium chloride (430) and binuclear complex 431 is illustrated in Scheme 12. Decomposition of 289 commences by nucleophilic attack of dissociated tricyclohexylphosphine on the methylidene moiety of XXI. Next, the 12-electron species XXII, formed upon elimination of phosphonium ylide CH2PCy3, binds one of the mesityl rings of XXI to afford XXIII. Terminal alkylidyne species XXIV, along with 430, are then generated through HCl abstraction by CH2PCy3. In the final step, insertion into the alkylidyne C–H bond in XXIV with concomitant migration of the two chlorides leads to the formation of 431, isolated as an orange–yellow crystalline solid in 46% yield. It is important to emphasize that complex 431 was found to catalyze alkene isomerization under metathesis conditions, suggesting that the above-described decomposition route of methylidene 289, and accordingly (pre)catalyst 3, could be responsible for competing unwanted alkene isomerization reactions during olefin metathesis transformations carried out by 3.

Expanding this decomposition study, to include other heteroleptic (phosphine–NHC) model ruthenium methylidenes, confirmed the assumption of phosphine attack on the methylidene carbon along the major decomposition pathway. This was also found to be the case in decomposition experiments performed in the presence of ethylene as a model olefin substrate. Thus, after five days at room temperature, in a toluene solution under an atmosphere of ethylene, complex 322 (Scheme 13) was found to quantitatively afford methyltricyclohexylphosphonium chloride 430 along with binuclear complex 432 (in about 70% yield). With the exception of the necessary ortho-methyl C–H bond activation step of the NHC ligands, the proposed mechanistic pathway for the generation of 432 was essentially the same as for complex 431. Finally, tris(pyridine) decomposition adduct 433 (Scheme 13) was isolated in 29% yield during attempts to prepare the corresponding bis(pyridine) ruthenium methylidene.

In related studies, N-phenyl-substituted NHC-coordinated ruthenium complexes were shown to also be prone to C–H bond activation. In particular, when complex 434 (Scheme 14) was heated in benzene at 60 °C for 3 days, decomposition adduct 435 precipitated in 58% yield, together with traces (<2%) of 436 (Scheme 14). When 434 was heated in dichloromethane at 40 °C, the isolated yields of 435 and 436 after 12 h were 24% and 38%, respectively. The structures of both 435 and 436 were elucidated by X-ray crystallographic analysis, and the mechanism proposed to rationalize their generation is illustrated in Scheme 14. Intermediate XXVI, formed by the oxidative addition of an ortho C–H bond of one of the N-phenyl NHC substituents to the ruthenium center, undergoes hydride insertions at the α-carbon atom of the benzylidene to afford XXVII. This is followed by reductive elimination between the metalated phenyl carbon atom of the NHC and the α-carbon atom of benzylidene to yield complex 435. Decomposition adduct 436 is finally generated via a second C–H insertion and PCy3-mediated elimination of HCl.

NHC-coordinated alkoxybenzylidene complexes lacking ortho substituents on the N-aryl groups of the NHCs show a high decomposition tendency via ortho C–H bond activation. Hence, in 2007, Blechert and co-workers reported the
isolation of oxidative degradation products 437 and 438, derived from solutions of complexes 42 and 108, respectively, in the presence of oxygen (Scheme 15). As expected, 437 and 438 were found to be completely metathesis inactive. The proposed mechanistic pathway for the formation of 438 (Scheme 15) begins with a pericyclic cyclization reaction of valence structure XXVIII leading to XXIX. Reaction with oxygen (XXX) followed by elimination and rearomatization (XXXI) affords the final insertion product 438. As also mentioned in section 3.1, this deactivation route, involving \textit{ortho} C–H bond activation of \textit{N}-phenyl groups in \textit{N}HC-coordinated ruthenium complexes, can be shut off by placing bulky substituents on the backbone of the \textit{N}HC, thereby restricting the intramolecular rotation of the \textit{N}-aryl groups that brings the \textit{ortho}-aryl C–H bonds closer to the ruthenium center.96

In 2008, Piers and co-workers published a detailed work on the thermal decomposition of 14-electron phosphonium alkylidene species 271 and 272 (Scheme 16).283 During their studies, in which they utilized 1,1-dichloroethylene as a trapping agent, the formation of cationic trichloride-bridged dimer 439 (Scheme 16) was observed in 40–45% NMR yield, along with methylphosphonium chloride \([\text{H}_3\text{CPR}_3]^+\cdot [\text{Cl}]^-\). As can be seen in Scheme 16, 439 contains a dichloromethylidene and a vinyl-modified \textit{N}HC ligand at each ruthenium center. The mechanism proposed to account for all findings (characterization of decomposition adducts as well as kinetic isotope effects and deuterium-labeling studies) includes the C–H bond activation of an \textit{ortho}-methyl group of one of the \textit{N}-mesityl substituents (XXXII), followed by elimination of the methylphosphonium species (isolated) to yield the cyclometalated ruthenium benzylidene XXXIII. Intermediate species XXXIV, formed after the CM reaction of highly reactive XXXIII with 1,1-dichloroethylene, eventually undergoes loss of a chloride anion and dimerization to afford the final degradation product 439.

H\textsubscript{2}IMes-coordinated ruthenium complexes bearing phosphine ligands have been also found to undergo carbon monoxide- and aryl isocyanide-promoted alkylidene insertion into the aryl substituent of their H\textsubscript{2}IMes ligand.277,284,285 In fact, catalyst degradation adducts of this kind (440–455, Scheme 17) were initially observed during attempts to develop a rapidly quenching procedure for metathesis reactions by blocking any available coordination sites with carbon monoxide. Aryl isocyanides promote the same insertion reaction for isopropoxybenzylidene-coordinated H\textsubscript{2}IMes ruthenium complexes, but only after initial displacement of the coordinated ether by a phosphine (456, 457, Scheme 17).285 Ruthenium complexes 440–457 were reported to form through carbon monoxide or aryl isocyanide coordination-triggered carbene cyclopropanation of the closest “double bond” of the mesityl ring, followed by electrocyclic ring-opening of the resulting cyclopropene derivative to afford the final cycloheptatriene.284,285 As discussed in section 10, this isocyanide-promoted degradation route has also been utilized as a “cleanup” procedure for metathesis transformations.277 Finally, it should be noted that a number of theoretical calculations have dealt with the decomposition of ruthenium olefin metathesis catalysts.286 For example, on the basis of a series of DFT calculations, van Rensburg and co-workers have suggested a substrate-induced decomposition mechanism involving a \(\beta\)-hydride transfer from a ruthenacyclobutane intermediate.286a,b

To summarize, the most important decomposition modes of \textit{N}HC-coordinated catalyst precursors and intermediates include (i) degradation with primary alcohols, producing...
Scheme 17. Carbon Monoxide- or Aryl Isocyanide-Promoted Transformation of H$_2$IMes-Substituted Ruthenium Alkylidenes

12. Conclusions and Perspectives

As discussed above, nearly 400 ruthenium heterocyclic carbene-coordinated olefin metathesis catalysts have been prepared. They offer a wide array of structures and activities that will benefit specific applications such as azeoquous and asymmetric reactions. In spite of all these structures, it is pleasing to recognize that, for most applications, a few structures will provide excellent results. The N-mesityl and N-tolyl NHC-coordinated complexes bearing alkoxybenzylidene ligands provide an excellent starting point for most applications. It also appears as though the mechanisms of all the complexes involve the formation of a 14-electron species that adds an olefin to initiate the reaction. The general reactivity can be understood in terms of the effect of a ligand on the initiation formation of the 14-electron species and the turnover of the olefin complex. Given the increasing rate at which new catalysts are now appearing, we look forward to further surprises and control mechanisms.

13. Acknowledgments

The authors are grateful for financial support provided by the National Science Foundation, the National Institutes of Health, and the 6th European Community Framework Programme.

14. References


(22) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. Angew. Chem., Int. Ed. Engl. 1995, 34, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. J. Am. Chem. Soc. 1996, 118, 100. Ruthenium-based metathesis catalysts (LₓRu═CHR) are usually divided into two families: the first- and the second-generation ones. In the first-generation catalysts, both neutral ligands (L) are phosphines, while...
in the second-generation ones, one of the neutral ligands is a heterocyclic carbene.

(23) Schönherr, H.; Angew. Chem., Int. Ed. 1968, 7, 141.


On the basis of element-specific X-ray spectroscopies and theoretical calculations, the increased initiation rate of the phosphine-coordinated metathesis catalysts was rationalized on the basis of a higher electron density. 

For a review article on the use of chiral NHCs in transition-metal complexes, see: Snead, D. R.; Seo, H.; Hong, S. Curr. Org. Chem. 2008, 12, 1370.

