1

N-Heterocyclic Carbene–Ruthenium Complexes in Olefin Metathesis

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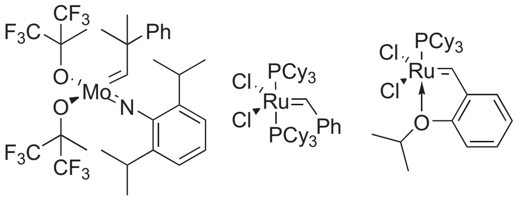
1.1

Introduction

Metal-catalyzed olefin metathesis has established itself as a powerful tool for carbon–carbon bond formation in organic chemistry [1]. The development of catalysts since the initial discoveries of the early 1990s has been tremendous: molybdenum [2], tungsten [3] and ruthenium catalysts have proved to be very fruitful metals for this reaction (Fig. 1.1).



Schrock's catalyst **1** Grubbs I **2** Hoveyda-Grubbs **3**

Fig. 1.1 Metathesis catalysts.

Ruthenium-based olefin metathesis catalysts have been the focus of great attention. The first major breakthrough for ruthenium-catalyzed metathesis was from the work of Grubbs, which developed catalyst **2**, known as Grubbs I catalyst [4], which is less reactive than the Schrock molybdenum-based alkylidene complexes but has greater functional group tolerance and simplified handling characteristics. However, these species still show relatively low thermal stability and suffer significant decomposition at elevated temperatures through P–C bond degradation [5]. Hoveyda and coworkers have serendipitously discovered catalyst **3** [6], which contains an internal metal–oxygen chelate. This Ru-carbene complex offers excellent stability to air and moisture and can be recycled in high yield by silica-gel column chromatography. The ability of catalyst **3** to be recycled is based on a release–return mechanism. Considerable evidence that this mechanism is at least partially

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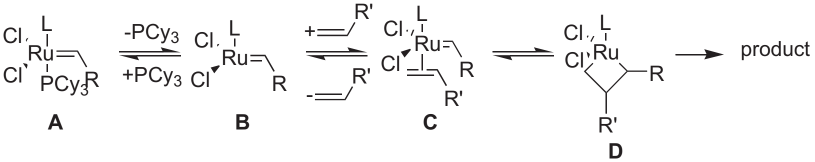
supported has been given recently [7]. After the first turnover, the styrene moiety is released from the ruthenium core but can return at the end of the sequence. However, despite this progress, ruthenium complexes **2** and **3** do not generally allow the formation of tri- and tetra-substituted double bonds by ring-closing metathesis (RCM); only Schrock's tetra-coordinated alkylidene species, such as **1**, can promote such reactions efficiently.

1.2
N-Heterocyclic Carbene–Ruthenium Complexes

1.2.1
Introduction of N-Heterocyclic Carbenes

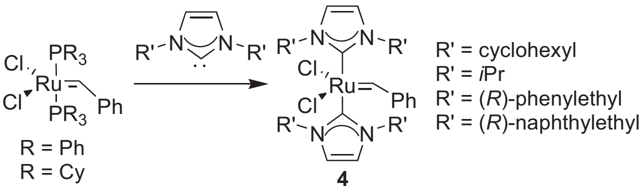
Intimate understanding of the mechanism of the metathesis reaction promoted by ruthenium complexes was crucial for the development of more efficient catalysts. The mechanism of olefin metathesis promoted by **2** and its analogues has been the subject of extended theoretical [8] and experimental [9] studies. There is consensus on the mechanism depicted in Scheme 1.1. Phosphine dissociation was critical to the process and a low ratio of phosphine reassociation to the ruthenium species was necessary for high activity.



Scheme 1.1 Metathesis mechanism.

In addition, catalyst activity is directly related to the electron-donating ability of the phosphine ligands [1h]. The steric bulk of the ligand may also play an important role, contributing to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex. An understanding of the mechanism has made clear that a highly active but unstable 14-electron mono(phosphine) intermediate **B** is formed during the catalytic cycle. To have more stable and active catalysts it was necessary to incorporate more basic and sterically demanding ligands than PCy_3. N-Heterocyclic carbenes (NHC) were perfect candidates.

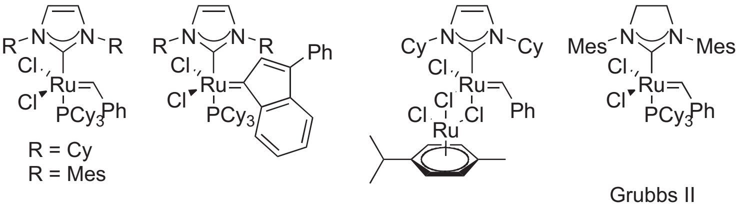
The second breakthrough in ruthenium catalysts was the introduction of NHCs as ligands to the ruthenium complex. The use of nucleophilic NHCs is an attractive alternative to phosphine ligands since they are relatively easy to prepare. NHCs are strong σ-donors but poor π-acceptor ligands and bind strongly to the metal center with little tendency to dissociate from it. Solution calorimetry has shown that the NHC ligand binds by approximately 5 kcal mol^{-1} more than PCy_3 to ruthenium [10]. Herrmann reported the first such complex [11]. Both PCy_3 moieties were replaced by N,N′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene units



Scheme 1.2 The first NHC-Ru complexes (reported by Herrmann [11]).

to give ruthenium complex **4** (Scheme 1.2). The product is stable but the catalytic activity was not considerably improved.

The lack of improved catalytic activity is due to the strong bonding between the NHC and the ruthenium core, which renders the dissociative pathway less likely and leads to a low concentration of the catalytically active 14-electron species in solution. However, the combination of a strongly binding, electron-donating NHC ligand with a more labile ligand should afford the desired effect, leading to a more active and more stable species. Both the 14-electron catalyst species **B** and the 16-electron olefin complex should be stabilized by the NHC ligand due to its strong σ-donor ability. Three groups independently and almost simultaneously reported the synthesis and catalytic properties of such ruthenium complexes (Fig. 1.2) [10, 12, 13].



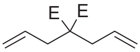
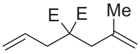
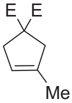
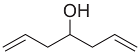
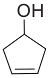
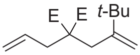
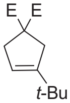
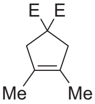
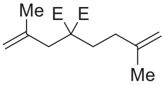
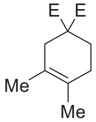
5 **6** **7** **8**

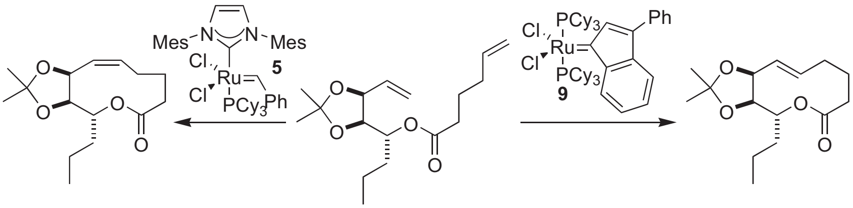
Fig. 1.2 Initial second-generation ruthenium complexes for metathesis.

As expected, this new generation of catalysts proved to be very stable, combined with greater reactivity than the Grubbs I catalyst, which opened new possibilities for organic synthesis. The NHC-ruthenium complexes are stable to air and have reactivity that can even surpass, in some cases, that of molybdenum catalyst **1**. Formation of tri- and even tetra-substituted double bonds, which were generally only possible using Schrock's catalyst, were now possible using NHC-ruthenium complexes (Table 1.1).

Differences in reactivity with Grubbs I catalyst and analogues were not only noticeable in terms of rates of reaction but also in terms of E/Z selectivity in RCM. Fürstner and coworkers, during the total synthesis of herbarumin I and II, discovered that the use of the ruthenium indenylidene complex **9** leads only to the lactone with E-geometry. Whereas catalyst **5** favors the corresponding Z-geometry with good selectivity [14]. This selectivity reflects kinetic control versus thermodynamic control; catalyst **9** is not active enough to equilibrate the E-isomer of the lactone to its more thermodynamically favored Z-isomer (Scheme 1.3).

Table 1.1 Comparison of reactivity of first- and second-generation Ru and Mo catalysts.

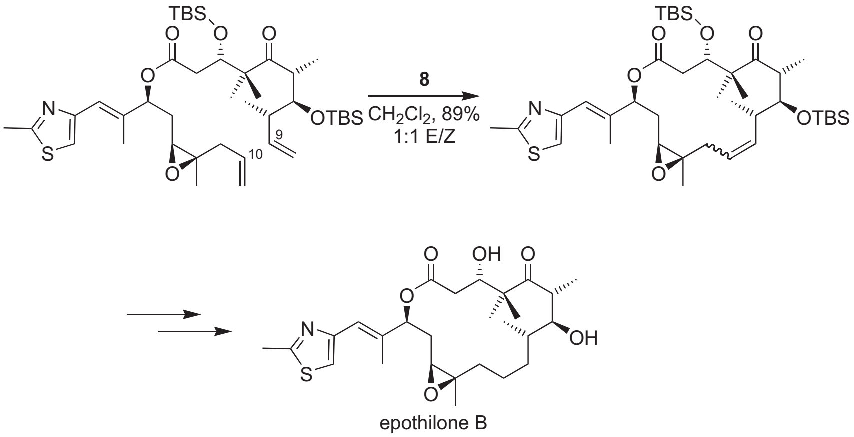
Entry	Substrate	Product	Time (min)	Yield (%)		
				1	**2**	**8**
1			10	Quant.	Quant.	Quant.
2			10	Quant.	20	Quant.
3			10	0	0	Quant.
4			60	37	0	Quant.
5			24 h	93	0	31
6			90	52	0	90



Scheme 1.3 Differences in E/Z selectivity between first and second-generation Ru complexes in RCM.

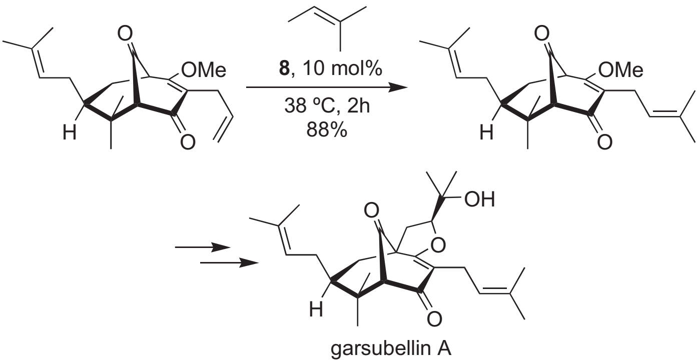
The NHC-ruthenium complex **8**, commonly called Grubbs II, was the most active catalyst of these early second-generation complexes [15]. Due to the absence of a π-system in the NHC the carbene is not stabilized by resonance. This makes the carbene more basic than the unsaturated analogue and this higher basicity translates into an increased activity of the resulting ruthenium complex. Nolan and coworkers have directly compared the NHC ligand SIMes to its unsaturated analogue IMes with respect to steric bulk and electron donor activity with calorimetric and structural investigations [16]. In view of the relatively important difference of reactivity between **5** and **8**, surprisingly minor differences in donor ability were found.

The increased reactivity of this new generation of ruthenium catalysts was highlighted in the total synthesis of epothilones by Sinha's group [17]. The synthesis of epothilones via a C9–C10 disconnection was first explored in Danishefsky's group. Unfortunately, the attempted connection of C9–C10 by RCM using either the Grubbs I catalyst **2** or Schrock's molybdenum catalyst **1** was unsuccessful [18]. However, Sinha showed that this strategy was viable using the Grubbs II catalyst **8**. The ring-closed product was obtained in 89% yield. The mixture of geometric isomers was of no consequence since the double bond was subsequently hydrogenated (Scheme 1.4).



Scheme 1.4 Epothilone B synthesis.

The Grubbs II catalyst was also the first catalyst to enable the formation of tri-substituted alkenes by cross-metathesis (CM) [19]. This was of prime importance since tri-substituted carbon–carbon double bonds are a recurring motif in a wide array of organic molecules. Grubbs and coworkers at Caltech reported the formation of tri-substituted double bonds in good yield with moderate to excellent E-selectivity [12c, 20]. The CM of α,β-unsaturated compounds (ester, aldehydes and ketones) and simple terminal olefins in the presence of **8** (5 mol%) was remarkably efficient. This particular reactivity was used by Spessard and Stoltz towards the total synthesis of garsubellin A, a potential Alzheimer therapeutic [21]. The CM between the bicyclo[3.3.1]nonane core and 2-methylbut-2-ene highlighted this reactivity as it gave the CM product in 88% yield (Scheme 1.5).



Scheme 1.5 Towards the synthesis of garsubellin A.

Mechanistic studies have shown an interesting feature of this new family of catalysts. Initially, the improved catalytic properties were ascribed to the exacerbated ability of the phosphine moiety to dissociate owing to the presence of the bulky NHC. Conversely, phosphine dissociation from **8** was two orders of magnitude slower than from **2**, which makes the Grubbs II catalyst a slower initiator than Grubbs I [9b, 22]. However, **8** showed an increased preference for coordination of olefinic substrates relative to phosphines compared to the Grubbs I catalyst. This is certainly due to the increased σ-donor character of NHCs in comparison to phosphines [1i]. Hence, Grubbs II catalyst **8** remains longer in the catalytic cycle even if it initiates slower. The strong donor ability of NHCs leads to overall faster rates of catalysis and enables the metathesis of olefins for which **2** was ineffective.

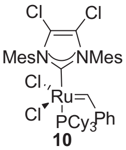
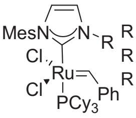
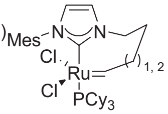
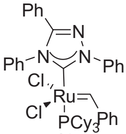
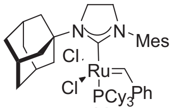
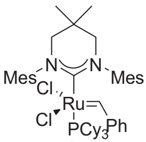
1.3
Second-generation NHC-Ru Catalysts

These new vistas of reactivities prompted an impressive amount of research towards the development of new NHC-ruthenium catalysts for metathesis reactions. Research was directed towards the use of new types of NHCs and also to variations of moieties around the ruthenium core.

1.3.1
Variations on the NHC Group

Several "second generation" metathesis catalysts have been prepared from Grubbs I catalyst 2 and various NHCs (Table 1.2). The influence of the N-substituent on both imidazol-2-ylidene and 5,5-dihydroimidazol-2-ylidene has been studied by different groups [10b, 23–27]. The SIMes analogue bearing two 2,6-diisopropylphenyl groups displayed even greater activity than 8 for the metathesis of terminal olefins [23]. Other analogues generally displayed lower reactivity. Substitution on the backbone of the NHC ligand with two chlorides (entry 1) afforded little change

Table 1.2 Variation of the NHC.

Entry	Catalyst	Catalytic activity	Ref.
1	 **10**	RCM, enyne metathesis	[29]
2	 **11** R = $(CH_2)_nCH{=}CH_2$ (n = 3,4,6) R = CH_2CH_2OTBS R = $CH_2CH_2(CF_2)_5CF_3$  **12**	RCM, enyne metathesis	[29]
3	 **13**	RCM	[29, 30]
4	 **14**	–	[31]
5	 **15**	RCM, ROMP	[32]

in reactivity compared with catalyst 5. Fürstner and coworkers also showed that asymmetrically substituted NHC-ruthenium (entry 2) complexes promote the formation of tetra-substituted double bonds by RCM in moderate to good yields. Complex 11, bearing a pendant terminal olefin, was shown to form tethered carbene 12, which potentially could regenerate once the substrate is subjected to metathesis and has been completely consumed.

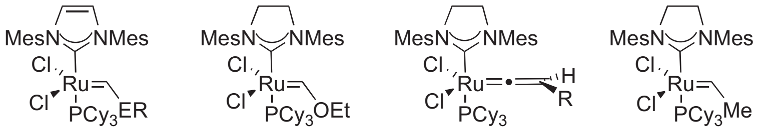
The NHC complex using the triazol-5-ylidene carbene developed by Enders [28] exhibits good catalyst activity; however, its limited lifetime in solution does not enable the reaction to reach completion in demanding cases. Adamantyl-substituted NHC-Ru complex (entry 4) was a poor metathesis catalyst, most likely because of the steric hindrance of the trans position to the benzylidene moiety by the adamantyl group. Catalyst 15 (entry 5), bearing a six-membered NHC, was synthesized by the Grubbs group. This catalyst showed limited reactivity for RCM and ROMP (ring-opening metathesis polymerization) compared with its five-membered NHC-Ru complex analogues.

To date, the SIMes ligand is still the ligand of choice as it affords the most potent NHC-ruthenium catalyst for olefin metathesis.

1.3.2
Variation on the Benzylidene Group

The effect of the variation or the replacement of the benzylidene group has also been studied. The Grubbs group have prepared a series of NHC-Ru complexes with electron-donating groups on the carbene carbon [33]. These carbenes are often referred to as Fischer-type carbenes. Complexes **16–19** (Fig. 1.3) were prepared from the reaction between the Grubbs I catalyst and an excess of the corresponding vinylic compound followed by treatment with the free IMes carbene in benzene.

Analogue **20** was prepared directly by treatment of Grubbs II catalyst **8** with an excess of ethyl vinyl ether. These complexes initiated the ROMP of norbornene and norbornene derivatives and gave the corresponding polymer in quantitative yield. However, polymerization was significantly slower than with the parent NHC-Ru complexes **5** and **8**. They also promoted the RCM of diethyl diallylmalonate in good yield. The rates of RCM and ROMP suggest that the reactivity follows a general trend: E = C > N > S > O.



16 ER = OEt
17 ER = SEt
18 ER = N(carbazole)
19 ER = N(pyrroldinone)

20

21 R = Ph
22 R = $SiMe_3$
23 R = *t*-Bu

24

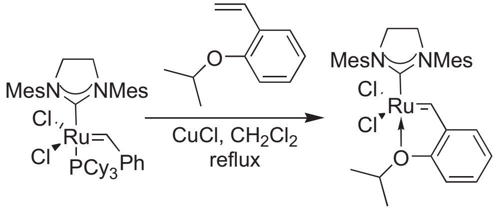
Fig. 1.3 Variation on the benzylidene group.

The benzylidene group has also been replaced by vinylidene groups [34]. Complexes **21–23** display good metathesis activity for the ROMP and RCM, yet the reactivity is still inferior to the benzylidene analogues.

To install a linear alkyl end group on ROMP polymers, NHC-Ru complex **24** was prepared from Grubbs II (**8**) and but-2-ene gas [35]. These complexes are again slightly less active than the parent benzylidenes but are suitable for ROMP and acyclic diene metathesis (ADMET).

1.3.3
Phosphine-free NHC-Ruthenium Complexes

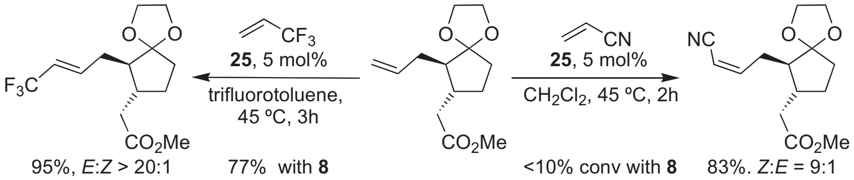
Tremendous efforts have been made to obtain phosphine-free NHC-ruthenium complexes. The first breakthrough was reported almost simultaneously by the Hoveyda [36] and the Blechert [37] groups and was based on the Hoveyda–Grubbs and the Grubbs II catalyst. This new catalyst (**25**) is now one of the most widely used ruthenium catalysts for metathesis reactions, alongside both Grubbs I and II and the Hoveyda–Grubbs catalyst, and is prepared from the Grubbs II catalyst and 2-isopropoxystyrene (Scheme 1.6).



8 **25**

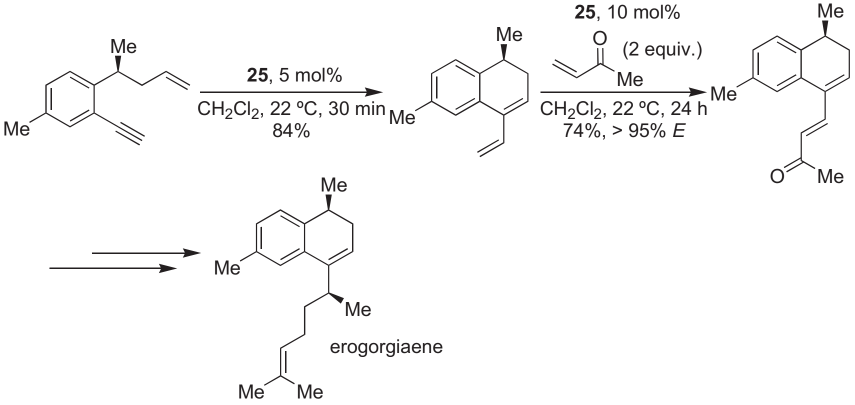
Scheme 1.6 Synthesis of phosphine-free catalyst **25**.

NHC-ruthenium complex **25** opened up new possibilities in organic synthesis. Most noticeably it made possible CM involving electron-deficient olefin partners such as acrylonitrile [38] and fluorinated olefins [39]. The CM of acrylonitrile with terminal alkenes was problematic with the phosphine-containing catalyst **8** [40]; however, Blechert and coworkers in Berlin have shown that catalyst **25** promoted such reactions in high yield and with good to excellent Z-selectivity (Scheme 1.7).



Scheme 1.7 Reactivity of phosphine-free catalyst **25**.

Catalyst **25** also made possible the efficient synthesis of biologically interesting molecules. Hoveyda et al. have reported the enantioselective total synthesis of erogorgiaene, an inhibitor of *Mycobacterium tuberculosis* [41]. This synthesis involves two metathesis steps: an enyne metathesis and a CM. Both catalysts **8** and **25** promote the enyne metathesis; however, the Grubbs II catalyst led to the formation of side products and a lower reaction rate in the CM step with methyl vinyl ketone (MVK) and only **25** gave the desired product in good yield and with excellent E-selectivity (Scheme 1.8).

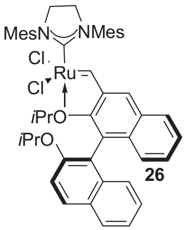
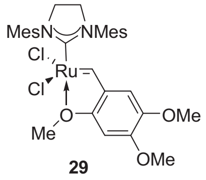
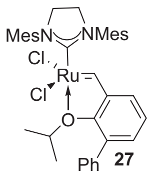
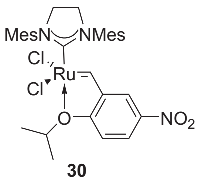
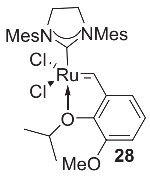


Scheme 1.8 Synthesis of erogorgiaene.

The activity and reactivity profile of catalyst **25** is greatly affected by the released phosphine, which is able to intercept and deactivate the 14-electron active species [22, 42].

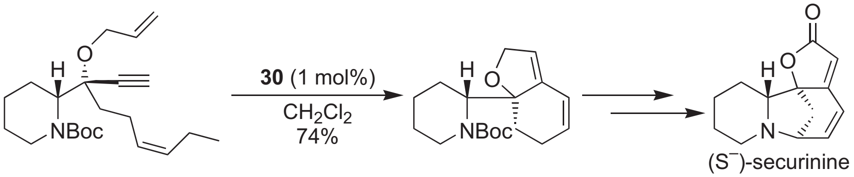
To improve further the reactivity of phosphine-free NHC-Ru complexes, the groups of Blechert and Grela both embarked on systematic studies on the effect of substitution on the 2-isopropoxystyrene ligand. Blechert's group have shown that increased steric hindrance adjacent to the chelating isopropoxy group is crucial for increasing the catalytic activity. Replacing the benzylidene ligand in **25** with BINOL- or biphenyl-based ligands results in a large improvement in initiation (Table 1.3). These catalysts, especially **27**, were shown to initiate significantly more rapidly than **8** and **25**. Formation of the 14-electron active species is, presumably, facilitated by the increased bulk of the ligand, which helps dissociation. Analogue **28**, which displays a similar reactivity profile as **27** (entry 3), is particularly interesting since its synthesis is more facile than the other analogues, starting with *o*-vanillin. Systematic studies on the effect of substituents on the styrene showed that decreased electron density on both the chelating oxygen and the Ru═C bond had a significant effect on the rate of acceleration [48]. Reassociation to the metal center, which deactivates the catalyst, is also suppressed. Grela and coworkers have developed catalyst **29**, derived from inexpensive *α*-asarone, which showed catalytic activity comparable to the parent catalyst **25** [46, 49]. They also

Table 1.3 Phosphine-free NHC-Ru complexes.

Entry	Catalyst	Entry	Catalyst
1 [43]	 **26**	4 [46]	 **29**
2 [44]	 **27**	5 [47]	 **30**
3 [45]	 **28**		

synthesized catalyst **30**, which contains the electron-withdrawing group (EWG) NO_2 [47]. It is assumed that the NO_2 group weakens the *i*PrO→Ru bond and therefore renders the initiation more facile. This catalyst, which showed enhanced activity, has been used in the total synthesis of (−)-securinine and (+)-viroallosecurinine [50]. This example illustrates the potency of complex **30** as it promotes the tandem enyne-RCM of a dienyne system, enabling the formation of three rings of the core of securinine in excellent yield (Scheme 1.9).

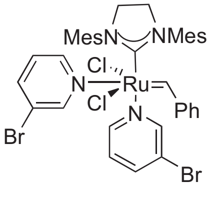
The Grela group then embarked on a program to study the effect of combining an EWG, to decrease the electronic density of the styrene moiety, and steric bulk close to the chelating isopropoxy substituent, in the hope of combining the effects



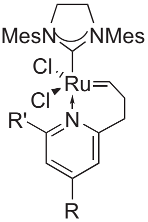
Scheme 1.9 Synthesis of (−)-securinine.

shown in **27** and **30** to increase still further the catalytic activity [51]. Unfortunately, combination of those two modes of activation, steric and electronic, resulted in a significant decrease in stability.

Grubbs and coworkers have prepared phosphine-free catalysts **31** [42] and **32** [52] (Fig. 1.4). Catalyst **31** was initially developed to promote CM with acrylonitrile. This catalyst is easily obtained in good yield from treatment of Grubbs II catalyst **8** with an excess of 3-bromopyridine and has been shown to be a very fast initiator. It initiates at least six orders of magnitude faster than **8**. Presumably, dissociation of the electron-deficient 3-bromopyridine is extremely rapid and the rebinding is slow, which contributes to an excellent turnover. This catalyst was also found to be an excellent promoter of living polymerization, not only with norbornene but also with oxo-norbornene derivatives, which do not undergo living polymerization with other catalysts [53].



31

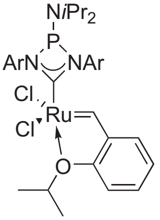


32

Fig. 1.4 Phosphine-free NHC-Ru complexes.

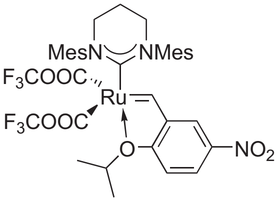
In contrast, phosphine-free catalyst **32** was a much slower catalyst than **8**.

Recently, Grubbs [54] and Buchmeiser [55] have also prepared NHC-ruthenium complexes **33** and **34** (Fig. 1.5). Catalyst **33** is the first NHC-Ru complex bearing a four-membered cyclic NHC and has been synthesized in moderate yield and showed slow reactivity towards olefin metathesis. Presumably, this arises from the less basic character of the NHC, which makes it a lesser α-donor than the SIMes NHC. Buchmeiser and coworkers disclosed the preparation of catalyst **34** based on tetrahydropyrimidin-2-ylidenes. This catalyst and its analogue with two chlorides have been shown to be very potent catalysts for RCM and ROCM.



Ar: o-(iPr)$_2$C$_6$H$_3$

33



34

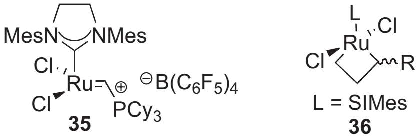
Fig. 1.5 More phosphine-free NHC-Ru complexes.

1.3.4
Variation of the Anionic Ligands

Exchange of the anionic chlorine ligand has been studied at length in the Buchmeiser and Fogg laboratories [56, 57]. The chlorine ions were substituted by strongly electron-withdrawing ligands. Buchmeiser has prepared analogues of catalyst **25** and of Grela's variation **30** with $CF_3(CF_2)_xCOO$ ($x = 0$–2) and showed that these catalysts displayed great activity, enabling the cyclopolymerization of diethyldipropargylmalonate, for which the chloride analogues were inactive. These catalysts also proved to be highly stable.

1.3.5
14-Electron NHC-Ruthenium Complexes

To have a fast initiating catalyst, Piers and coworkers prepared a 14-electron ruthenium catalyst [58]. This compound is isoelectronic with the active species in the olefin metathesis and possesses a vacant coordination site in direct analogy to it. This catalyst (**35**) is prepared from the corresponding Grubbs II catalyst **8**. It is reasonably stable and was found to be extremely potent. The rate for RCM is qualitatively comparable to the best Blechert catalyst (**27**) (Fig. 1.6).



35

L = SIMes

36

Fig. 1.6 Fourteen-electron NHC-Ru complexes.

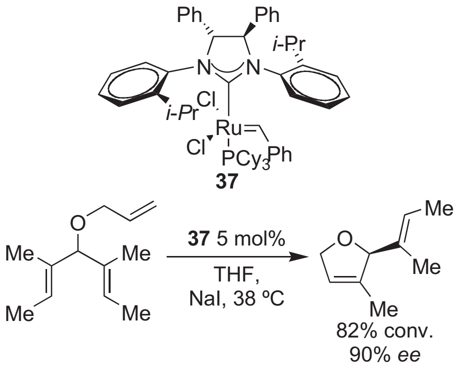
The reason for such high reactivity is that there is no need for the ruthenium complex to dissociate a ligand to enter the catalytic cycle and that the initiation binding of the C=C substrate to the ruthenium core is now energetically more favorable. This catalyst has also enabled direct observation of the long postulated 14-electron ruthenocyclobutane metathesis intermediate **36** [59].

1.4
Enantioselective Ruthenium Olefin Catalysts

Reactions requiring high e.e. are still the domain of molybdenum-based Schrock catalysts [60]. However, asymmetric Ru-catalysts are starting to show promising results.

1.4.1
Grubbs II Analogues

The Grubbs group reported an early example of a chiral NHC-ruthenium complex for the enantioselective metathesis reaction [61]. Ruthenium complex **37** was shown to promote desymmetrization of achiral trienes in up to 82% conversion with 90% e.e. in the presence of NaI, which gives the iodine analogue *in situ* (Scheme 1.10). The asymmetric induction is clearly dependant on the degree of substitution of the olefins [62]. The stereocenters of the NHC are too remote from the reaction center to have any noticeable effect. The mesityl groups were replaced by o-substituted aryl groups to afford a steric effect, which was expected to transfer the stereochemistry of the ligand nearer the metal center by placing the aryl group in an arrangement anti to the substituent on the imidazole ring. Crystal studies showed that the NHC ligand was approximately C_2-symmetric. The increased steric bulk generated by replacement of the two chloride atoms with iodine also plays an important role in the enantioselectivity.

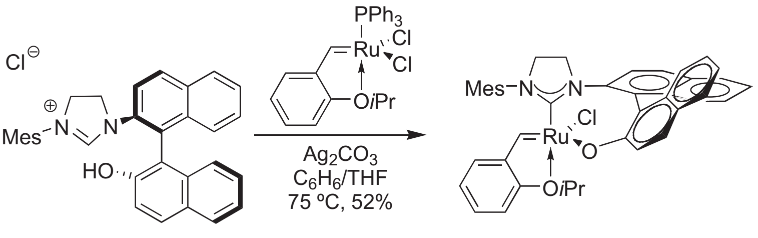


Scheme 1.10 Grubbs chiral NHC-Ru complex.

1.4.2
Phosphine-free Chiral NHC-Ruthenium Complexes

1.4.2.1 First-generation Catalysts

Hoveyda and coworkers have developed a series of chiral catalysts for enantioselective olefin metathesis. These catalysts are particularly efficient for asymmetric ring-opening/cross metathesis reactions. The first generation of such catalysts was prepared in 2002 [63]. The optically pure phosphine-free complex **38**, isolated as a single enantiomer, is air-stable and can be purified by silica-gel chromatography. It was prepared from an unsymmetrical NHC and the triphenylphosphine analogue of the Hoveyda I catalyst (Scheme 1.11). The Hoveyda group chose a bidentate chiral imidazolidene on the hypothesis that such a ligand would induce

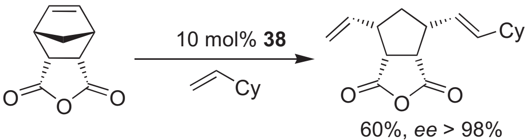


38

Scheme 1.11 Synthesis of Hoveyda's chiral NHC-Ru complex.

enantioselectivity more efficiently than a monodentate ligand. The fact that one of the chloride ions was substituted for an aryl oxide ligand was not too much of a concern in terms of the effects on activity since there have been some reports of active Ru catalyst bearing a bidentate phenolic base [64]. However, catalyst **38** is less active than its achiral parent **25**.

The combination of replacing a chlorine ion with a less electronegative phenoxide and the increased steric bulk due to the presence of the binaphthyl group is probably responsible for this loss of reactivity. Yet, catalyst **38** showed excellent selectivity in AROM/CM (Scheme 1.12). The catalyst was efficient even when the reaction was performed in air and with non-distilled solvents. The catalyst was recovered in excellent yields and could be reused without significant loss of activity.

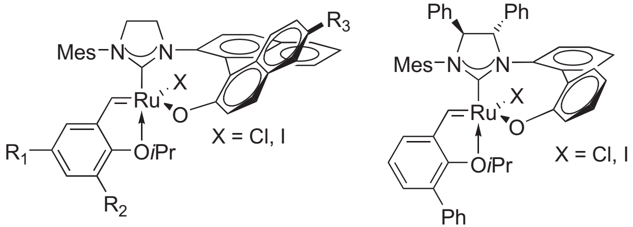


Scheme 1.12 AROM/CM with catalyst **38**.

1.4.2.2 **Second-generation Chiral Ru Complexes**

To compensate the loss of reactivity resulting from the bulk of the binaphthyl ligand and the replacement of a chlorine ion by an aryl oxide group, Hoveyda's group studied the effect of sterics and electronic alteration on the parent catalyst **38**. Modifications of the benzylidene by installing the EWG NO_2, an electron-donating OMe, or a bulky phenyl group were performed to see if the effect observed by Blechert and Grela on the achiral analogue (Section 2.2.3) was translated to the present class of chiral Ru catalysts (Fig. 1.7) [65]. Enantiomerically pure catalysts **39d** and **39e** were prepared to study the influence on the catalytic activity of reduced electron donation of the aryl oxide oxygen to the Ru core.

Compounds **39c** and **39d** were the more potent catalysts as their reactivity levels are three orders of magnitude higher than catalyst **37**. Catalyst **39d** promotes AROM/CM of **41** in good yield with excellent e.e. (Scheme 1.13). Catalyst **38** leads to less than 10% conversion and chiral Mo catalysts result in rapid polymerization



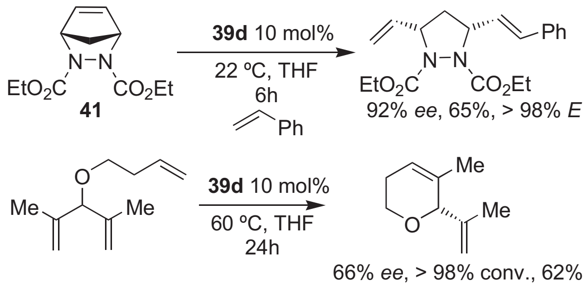
39a	R_1 = OMe	R_2 = H	R_3 = H
39b	R_1 = NO_2	R_2 = H	R_3 = H
39c	R_1 = H	R_2 = Ph	R_3 = H
39d	R_1 = H	R_2 = H	R_3 = CF_3
39e	R_1 = H	R_2 = Ph	R_3 = CF_3

40

Fig. 1.7 Second-generation chiral Ru complexes.

[66]. Chiral complex **39d** also promoted ARCM in good yield with good e.e. However, notably, chiral Mo-based catalysts are still generally the complexes of choice for such reactions.

The synthesis of these catalysts is lengthy. However, a new, more readily available chiral bidentate NHC-Ru complex has recently been reported by the Hoveyda group [67]. The synthesis is considerably shorter than that of the parent catalyst **39**. The chloride version is not stable on silica but can be prepared *in situ*. The iodine analogue **40**, though, is more stable. Previous studies have shown the effect of substitution of the chloride group by an iodine on the reactivity and the stability of **39** [68]. The iodine analogues are generally less active than their chlorine counterparts; however, they give the product with higher enantioselectivity.



Scheme 1.13 Reactivity of the second-generation chiral Ru complexes.

1.5
Solid Supported NHC-Ru Complexes

There has been an increased demand for supported versions of modern catalysts in recent years and NHC-ruthenium complexes for metathesis are no exception. There are various reasons for this interest: to reduce metal contamination, especially in medicinal chemistry, the possibility of recovering the catalyst to reuse it is also very important in terms of cost and, finally, solid supported catalysts offer access to high-throughput chemistry and continuous flow reactors. There are two classes of solid supported catalysts:

- Heterogeneous catalysts, which are covalently attached to an insoluble polymer support; filtration enables the recovery of the catalyst.
- Homogenous catalysts, which are covalently attached to a soluble polymer support. Addition of solvent selectively precipitates the polymer supported catalyst and filtration enables the recovery of the catalyst.

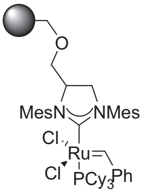
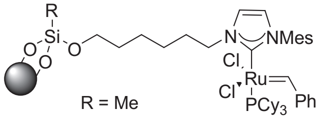
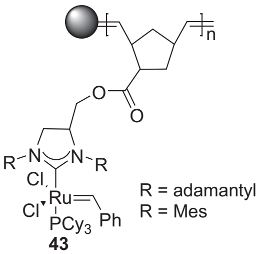
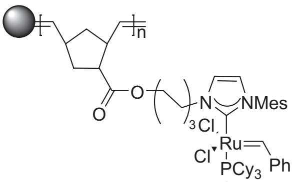
These classes of catalysts can be further classified by the type of attachment:

- attachment to the permanently bound ancillary NHC ligand,
- attachment through the anionic ligand directly to the Ru metal,
- attachment to the alkylidene moiety.

1.5.1
Immobilization via the NHC Ligand

The first such catalyst was reported by Blechert and coworkers (Table 1.4, entry 1). This Merrifield-supported version of the Grubbs II catalyst was successful in RCM and enyne metathesis and was easy to handle. The same group also reported a supported version of the phosphine-free catalyst **25** bearing the same attached NHC [69]. The supported version of the Grubbs II catalyst **42** showed excellent reactivity for RCM but, disappointingly, proved to be a mediocre promoter for

Table 1.4 Immobilization via the NHC ligand.

Entry	Catalyst	Entry	Catalyst
1 [70]	 **42**	3 [72]	 **44**
2 [71]	 **43**	4 [73]	 **45**

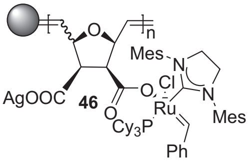
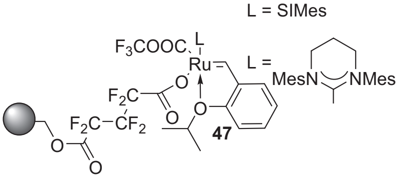
CM. This is probably because the 14-electron active species remained immobilized and suffers diffusion problems. This factor is not important for RCM as only one substrate is involved but had a noticeable effect on CM when two substrates were involved. Buchmeiser's group have worked on the development of non-porous supports suitable for continuous flow experiments (entry 2). These catalysts showed high activity for RCM and ROMP and the cis/trans ratio of the polymer is the same as that obtained with homogeneous systems. These monolithic systems can be used as cartridges for combinatorial chemistry; the products obtained are also virtually ruthenium free, with a ruthenium content of only ≤70 ppm. A silica-based version of **43**, also prepared by the same group, gave good results in RCM.

Fürstner and coworkers have prepared a solid supported version of catalyst **11**, which they previously developed in their laboratory (entry 3). This solid supported catalyst is attached to the silica gel support via one nitrogen of the NHC and exhibits similar reactivity for RCM as the homogeneous non-attached version. A monolith-immobilized version of this catalyst was also prepared by Fürstner and Buchmeiser (entry 4). It showed moderate activity in metathesis reactions.

1.5.2
Attachment Through the Anionic Ligand

The Buchmeiser group has devoted a lot of research to this type of solid supported catalyst. Work was conducted toward monolith- (Table 1.5, entry 1) and silica- (entry 2) supported catalysts. These catalysts displayed high RCM activity, demonstrating high turnover numbers (TON) at elevated temperatures, and also led to a unprecedented low content of ruthenium in the RCM products at <70 ppb. These catalysts also showed high activity for enyne and ring-opening cross metathesis, giving the final products in high yields.

Table 1.5 Attachment through the anionic ligand.

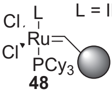
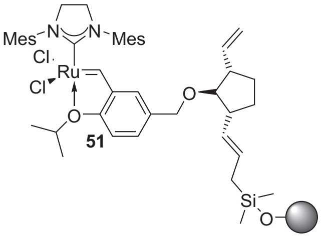
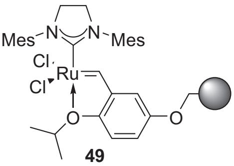
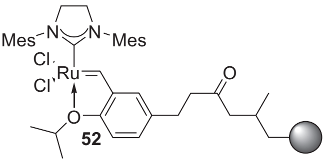
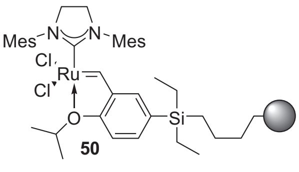
Entry	Catalyst	Entry	Catalyst
1 [74]	 **46**	2 [55, 75]	 **47**

1.5.3
Attachment Through the Alkylidene Moiety

The most versatile and most widely used method for attaching catalysts to the solid support has been through the alkylidene moiety. This is due to the ease of functionalization. After one catalytic cycle, the catalyst is detached from the solid support – the active species is then in solution. This is one reason why this type of solid supported catalyst exhibits activities comparable to homogenous catalysts. However, for this technology to be valid and viable as a solid support technology, the catalysts have to reattach to the solid support at the end of the sequence (see Section 1.1 and [7]).

The first such catalysts were prepared by the Nolan group (Table 1.6, entry 1). The catalysts were attached to poly-divinylbenzene (poly-DVB), a macroporous resin polymer. The catalysts have been shown to be recoverable and to display an activity comparable to their homogenous analogues for the RCM of unsubstituted dienes. However, they performed poorly with substrates that have different coordination modes competitive with ruthenium recapture by DVB, such as highly hindered substrates. Catalysts **49**–**52** (entries 2–5), analogous to catalyst **25**, all showed high activity for RCM and CM with 5 mol% loading. They are usually highly recyclable, generally 5–6×, and up to 15× under inert conditions for the Hoveyda version **51**. This particular catalyst has also been shown to display high reactivity for ROM-CM and ring rearrangement metathesis (RRM).

Table 1.6 Attachment through the alkylidene moiety.

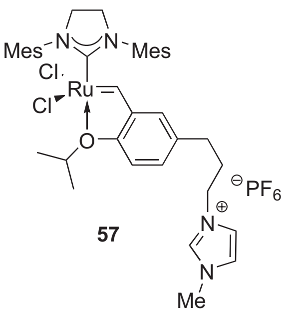
Entry	Catalyst	Entry	Catalyst
1 [76]	 **48** L = IMes, SIMes	4 [78]	 **51**
2 [69]	 **49**	5 [79]	 **52**
3 [77]	 **50**		

1.5.4
Homogenous Catalysts

Homogenous versions of this type of catalyst have also been prepared. The advantage of homogenous supported catalysts is that their reactivity profile corresponds to their unattached analogues. They usually display higher overall activity than their heterogeneous counterparts. However, much solvent waste is generated due to the techniques used for their recovery. A change of solvent polarity is necessary to precipitate the catalyst. Catalyst **53** (Table 1.7, entry 1) has been shown to be efficient for RCM, ROM-CM and RRM, including the synthesis of tri-substituted double bonds with only 1 mol% of loading. It can be reused up to eight times without loss of activity and gave the final products with very low ruthenium contamination (0.0004% in the first four cycles). Catalyst **54** (entry 2) promotes RCM and EYM and can lead to the formation of tri-substituted double bonds. However, high loadings of catalyst are necessary (10 mol%) and it can be recycled only twice before there is a noticeable loss of activity. Catalyst **55** was shown to be highly recyclable as it could be used 17× in RCM and was particularly active as it can lead to tetra-substituted double bonds. The light fluorous catalyst **56** displayed activities similar to its non-fluorous analogue **25** (entry 4). It can be recovered either by fluorous solid-phase extraction or by filtration when it is initially added on fluorous silica gel. It can be used up to five times without significant loss of activity.

1.5.5
Ionic Liquids

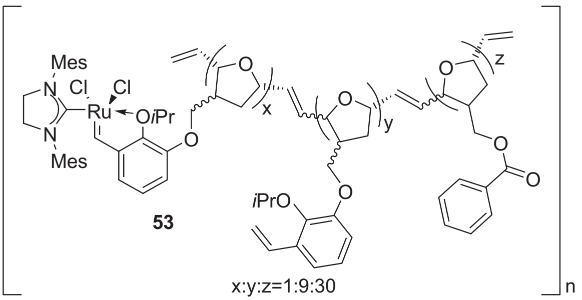
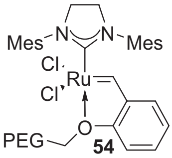
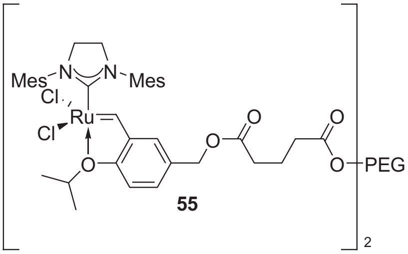
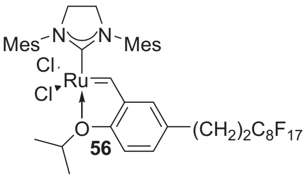
An alternative to solid supported reagents that is environmentally friendly, and with the potential for recyclability, is to use ionic liquids. Recently, Mauduit and Guillemin in Rennes have developed the phosphine-free NHC ruthenium complex **57** (Fig. 1.8) to perform metathesis in a BMI·PF_6/toluene biphasic medium [84]. High reactivity was observed in RCM. The catalyst was reused up to eight times without significant loss of reactivity and the final product had ruthenium contamination as low as 1 ppm.



57

Fig. 1.8 NHC-Ru complex for reactions in ionic liquids.

Table 1.7 Homogenous catalysts.

Entry	Catalyst
1 [80]	 **53** x:y:z=1:9:30
2 [81]	 **54**
3 [82]	 **55**
4 [83]	 **56**

1.6
Conclusion and Outlook

In a relatively short period, an impressive amount of research has been done towards the synthesis of potent NHC-ruthenium complexes for olefin metathesis. The advent of such metal catalysts has had a tremendous impact in organic synthesis, enabling transformations not possible before. No single catalyst performs better than all the other catalysts in all possible reactions. Phosphine-free catalysts are generally the catalysts of choice for CM whereas the phosphine analogues are more potent in the formation of tetra-substituted double bonds. We can be sure that further improvements will arise in the near future with perhaps the introduction of novel NHCs.

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