N-Heterocyclic Carbenes in Synthesis

Edited by
Steven P. Nolan

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Contents

Preface

This project was begun after a symposium organized at the fall 2004 ACS meeting in Philadelphia. The occasion appeared timely to gather some of the most important developments in the use of N-heterocyclic carbenes (NHCs) in catalysis and synthesis and find a home for them. This project has developed quite rapidly, as has the area, and we hope the reader will find the emerging science useful and stimulating.

The seminal work of Arduengo is key to the development of NHCs as ligands in transition metal chemistry and as reactive entities. The importance of this development, involving the isolation and characterization by X-ray diffraction of a free carbene, cannot be overstated. It opened the door to the most recent developments in the use of NHCs as catalyst modifiers and organic catalysts. The earlier work of Michael Lappert is also of note as the chemistry developed in Sussex was the first concerted effort to use NHCs as ligands for transition metal systems. Even earlier developments by Wanzlick at the Technical University in Berlin are at the origin of the ideas associated with the possible intermediacy and existence of a "stable carbene".

The work described in this book is, as with most science, not done in a vacuum but "built on the shoulders of giants". Ranging from developments of catalysts that have become known as "second-generation olefin metathesis catalysts" to the use of NHCs in palladium cross-coupling to the role of NHCs in organic catalysis, the areas described in the following chapters are quite diverse. We hope the work described here will encourage others to investigate this area and to proceed in new and exciting directions.

Ottawa, Canada
August 2006

Steven P. Nolan

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1
N-Heterocyclic Carbene–Ruthenium Complexes in Olefin Metathesis

Samuel Beligny and Siegfried Blechert

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).

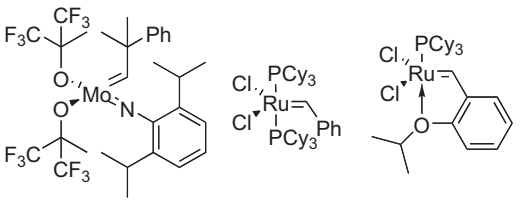


Fig. 1.1 Metathesis catalysts.

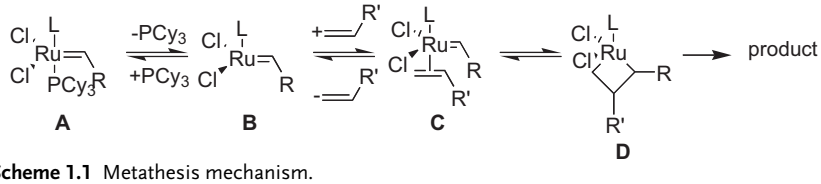
Ruthenium-based olefin metathesis catalysts have been the focus of great attention. The first major breakthrough for ruthenium-catalyzed metathesis was from the work of Grubbs, which developed catalyst **2**, known as Grubbs I catalyst [4], which is less reactive than the Schrock molybdenum-based alkylidene 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

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

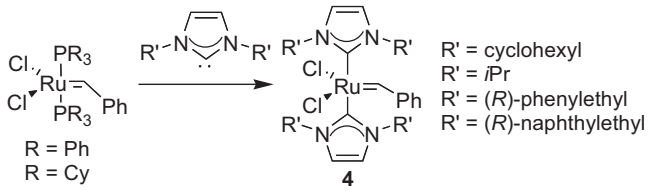
Intimate understanding of the mechanism of the metathesis reaction promoted by ruthenium complexes was crucial for the development of more efficient catalysts. The mechanism of olefin metathesis promoted by **2** and its analogues has been the subject of extended theoretical [8] and experimental [9] 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].

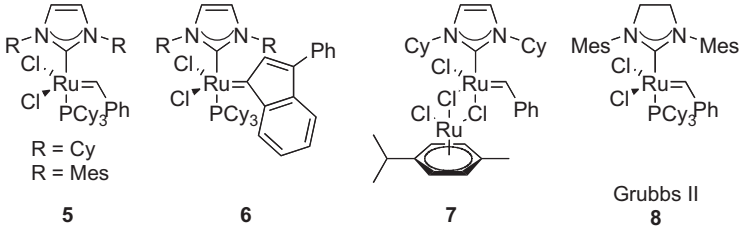
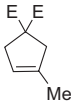
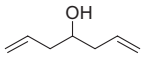
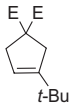
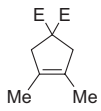
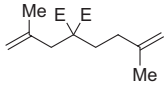
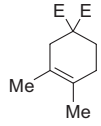


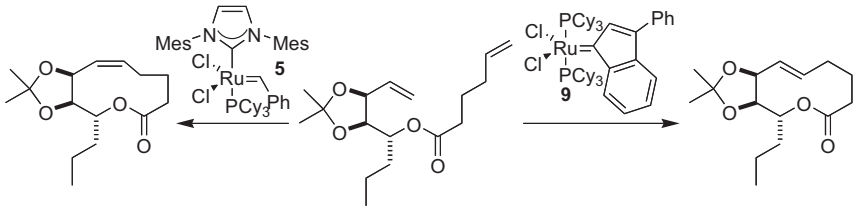
Fig. 1.2 Initial second-generation ruthenium complexes for metathesis.

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.

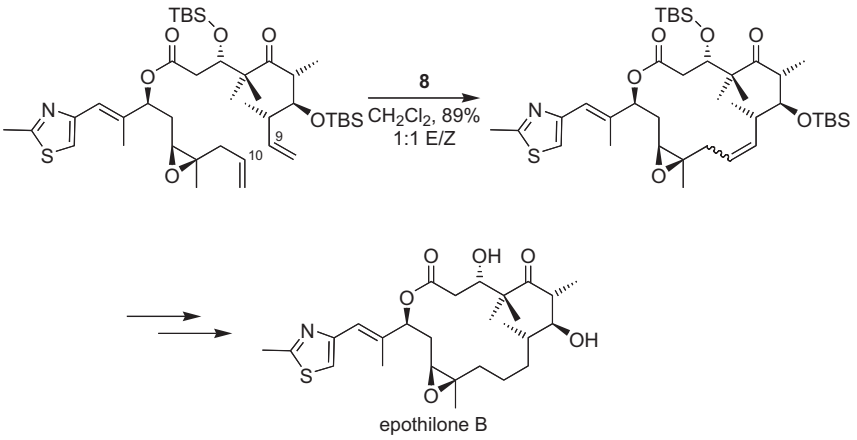
Entry	Substrate	Product	Time (min)	Yield (%)		
				1	**2**	**8**
1			10	Quant.	Quant.	Quant.
2			10	Quant.	20	Quant.
3			10	0	0	Quant.
4			60	37	0	Quant.
5			24 h	93	0	31
6			90	52	0	90



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.

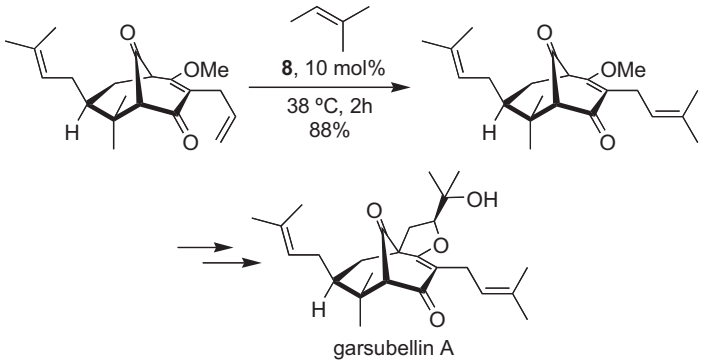
The increased reactivity of this new generation of ruthenium catalysts was highlighted in the total synthesis of epothilones by Sinha's group [17]. The synthesis of epothilones via a C9–C10 disconnection was first explored in Danishefsky's group. Unfortunately, the attempted connection of C9–C10 by RCM 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 trisubstituted 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.

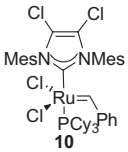
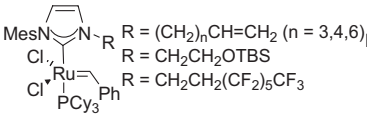
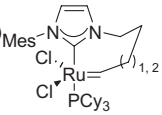
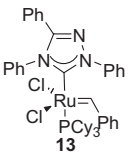
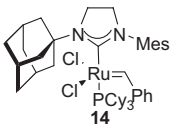
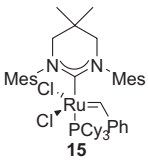
1.3 Second-generation NHC-Ru Catalysts

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	 R = $(CH_2)_nCH{=}CH_2$ (n = 3,4,6) R = CH_2CH_2OTBS R = $CH_2CH_2(CF_2)_5CF_3$  **11** **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.

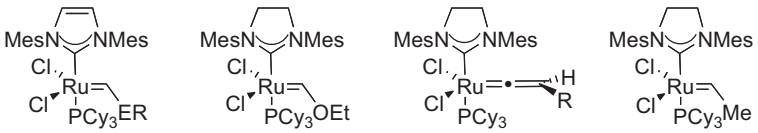


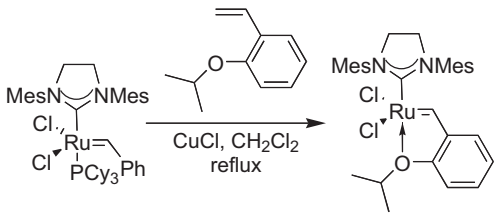
Fig. 1.3 Variation on the benzylidene group.

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

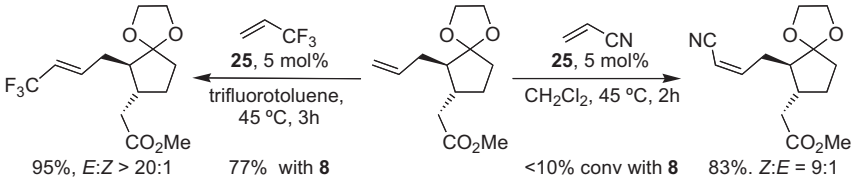
Tremendous efforts have been made to obtain phosphine-free NHC-ruthenium complexes. The first breakthrough was reported almost simultaneously by the Hoveyda [36] and the Blechert [37] groups and was based on the Hoveyda–Grubbs and the Grubbs II catalyst. This new catalyst (**25**) is now one of the most 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**.

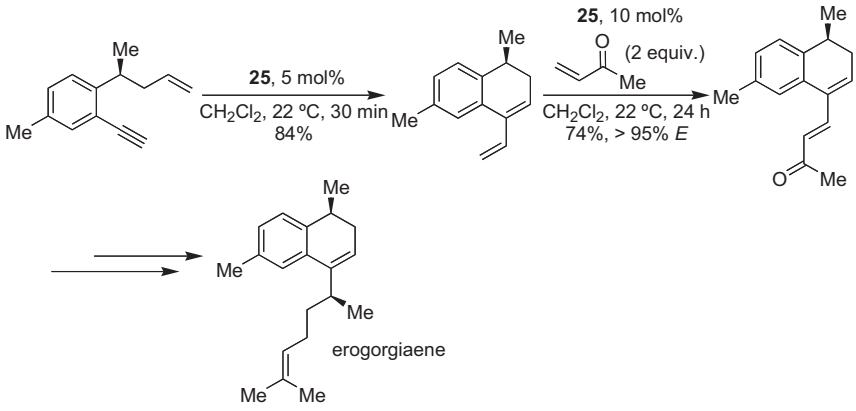
NHC-ruthenium complex **25** opened up new possibilities in organic synthesis. Most noticeably it made possible CM involving electron-deficient olefin partners such as acrylonitrile [38] and fluorinated olefins [39]. The CM of acrylonitrile with terminal alkenes was problematic with the phosphine-containing 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).



95%, *E*:*Z* > 20:1 77% with **8** <10% conv with **8** 83%. *Z*:*E* = 9:1

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).

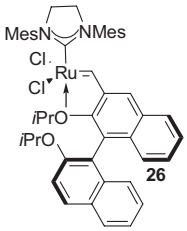
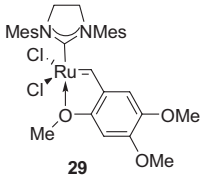
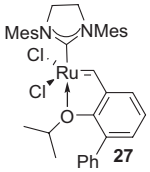
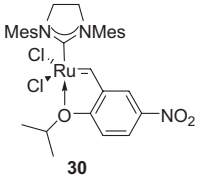
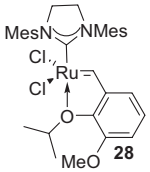


Scheme 1.8 Synthesis of erogorgiaene.

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].

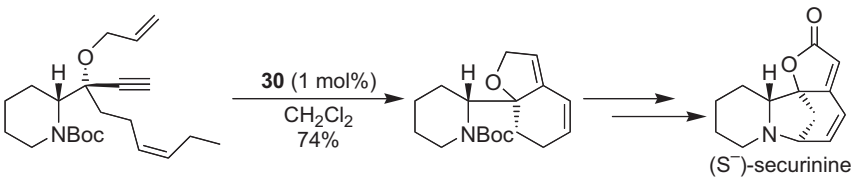
To improve further the reactivity of phosphine-free NHC-Ru complexes, the groups of Blechert and Grela both embarked on systematic studies on the effect of substitution on the 2-isopropoxystyrene ligand. Blechert's group have shown that increased steric hindrance adjacent to the chelating isopropoxy 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].

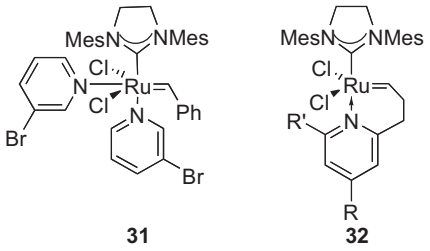


Fig. 1.4 Phosphine-free NHC-Ru complexes.

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 σ-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.

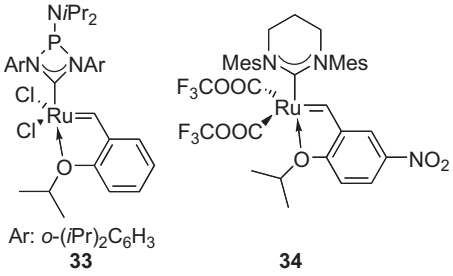


Fig. 1.5 More phosphine-free NHC-Ru complexes.