Ruthenium–indenylidene complexes: powerful tools for metathesis transformations

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Ruthenium–indenylidene complexes represent a class of robust and efficient pre-catalysts for olefin metathesis reactions. In this feature article, we provide an overview of the various complexes belonging to this family and summarise their use in various applications. The relation between the nature of ancillary ligands around the metal coordination sphere of these complexes and their catalytic activity is also discussed.

1. Introduction

Ruthenium-catalysed olefin metathesis has become a preferred synthetic method in polymer and organic synthesis for the formation of new carbon–carbon double bonds.[1] Thus, many efforts have focused on the development of novel more active and more stable catalysts.[2] Among the several metal-based complexes enabling olefin metathesis transformations, ruthenium–benzylidene[3] pre-catalysts are the most widely used in light of their stability and their tolerance towards functionalised substrates (Fig. 1). These complexes include first, second and third generation Grubbs catalysts **1**, **3** and **4**, complex **2** developed by Nolan, but also boomerang-type pre-catalysts **5** and **6**. However, other pre-catalysts yielding the same active species, such as ruthenium–indenylidene complexes, have also proven to be efficient facilitators of olefin metathesis.[4] Indeed, these pre-catalysts, first identified as allenylidene species,[5] are accessible through a straightforward synthesis and are quite resistant to harsh reaction conditions (temperature and functional group tolerance) and can be used as an attractive alternative to benzylidene-based pre-catalysts. In the present article, the structures and syntheses of ruthenium–indenylidene complexes will first be presented and their performance in catalytic reactions will be discussed.

2. Synthesis of Ru–indenylidene complexes

The majority of late transition metal indenylidene complexes are synthesised through an intramolecular rearrangement of allenylidene or cumulenylidene complexes.[6] The general synthetic strategy involves the introduction of a preformed C3 skeleton containing a leaving group. The most common approach is to use the dehydration of 2-propyn-1-ols which affords cumulenylidene complexes. Of note, this groundbreaking concept was first reported by Selegue[7] in 1982 and then further studied independently by Dixneuf, Hill, Fürstner and Nolan.[5,8] In this section, we will present the different existing indenylidene-containing ruthenium complexes and their corresponding synthesis.

2.1 Bisphosphine-containing pre-catalysts

Originally, the product formed from the reaction of $[RuCl_2(PPh_3)_3]$ and 1,1-diphenylpropargyl alcohol was identified as the diphenylallenylidene complex **7a**.[5] However, more detailed studies demonstrated that the stable product isolated was the rearranged indenylidene ruthenium complex **8a** (Scheme 1).[9,10] It should be noted that this Ru–indenylidene

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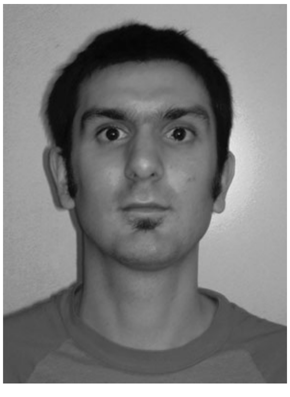


Fabien Boeda was born in 1980 in Le Mans, France. He received his MSc in organic chemistry from the Université du Maine (France). In 2003, he joined the Ecole Nationale Supérieure de Chimie de Rennes where he worked on asymmetric catalysis under the supervision of Drs Christophe Crévisy and Paul Mosset. He completed his PhD in 2006 and accepted a post-doctoral position with Professor Steven P. Nolan in 2007. He is currently working on the use of NHC in homogeneous catalysis.

Hervé Clavier was born in Vannes, France in 1979. He graduated from the Ecole Nationale Supérieure de Chimie de Rennes and received his MSc in organic chemistry from the Université de Rennes I (France) where he completed his PhD in 2005 under the supervision of Drs Jean-Claude Guillemin and Marc Mauduit. Then, he joined the research group of Professor Steven P. Nolan as post-doctoral fellow and followed him to the ICIQ in Tarragona (Spain) where he is currently working on the synthesis and applications of NHC-containing complexes.

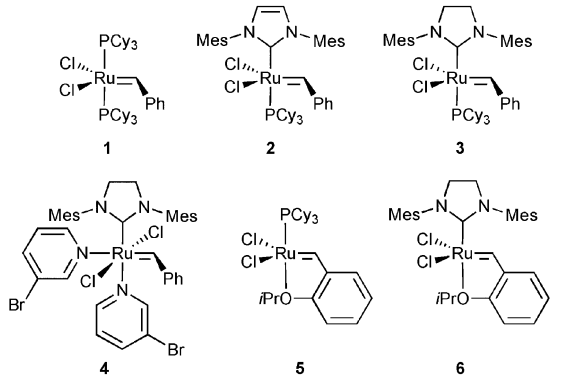
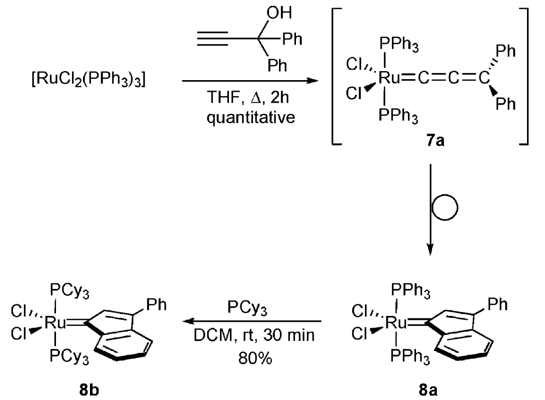


Fig. 1 Representative ruthenium–benzylidene pre-catalysts.



Scheme 1 First synthesis of indenylidene-containing ruthenium complexes.

bisphosphine pre-catalyst can lead to complex **8b** by a simple ligand exchange reaction between PPh_3 and the more donating phosphine PCy_3.

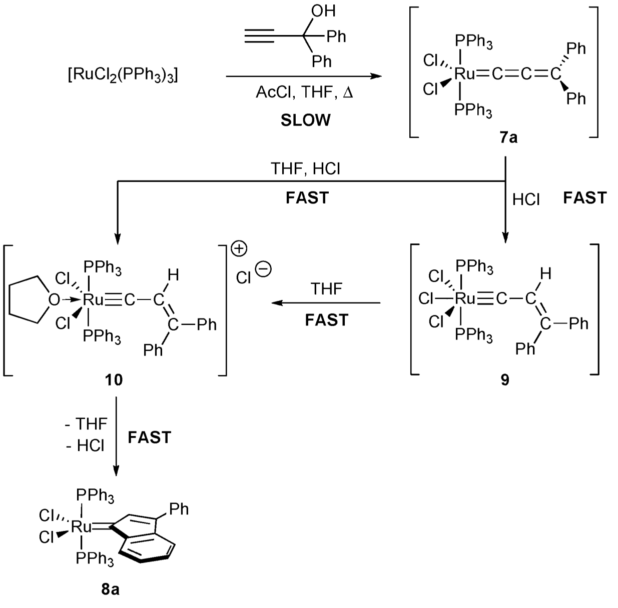
Interestingly, Nolan showed that complex **8b** can be obtained using a simple one-step procedure starting from $[RuCl_2(PPh_3)_3]$ by an *in situ* exchange of PPh_3 with PCy_3 on the crude complex **8a**.[11]

Recently, Schanz reported an improved procedure for the synthesis of complexes **8a** and **8b**.[10] It has been suggested that the rearrangement pathway should be promoted by an acid source, as already interestingly proven with 18-electron (*p*-cymene)–Ru complexes.[12] Indeed, acetyl chloride, which can provide HCl and some amount of acetic acid, as an additive for this synthesis was found to catalyse the formation of the indenylidene moiety. Of note, the acylation of propargylic alcohol could also provide a good leaving group and as a consequence facilitate the rearrangement. Moreover, the authors succeeded in crystallising some intermediates and proposed the mechanism depicted in Scheme 2. The allenylidene **7a** and the carbyne **9** compounds were isolated and characterised by X-ray techniques. It was observed that the α-carbon atom of intermediate **10** has an elevated electrophilicity and thus enables the rearrangement of the allenylidene into the phenylindenylidene group.

Phosphabicyclononane (phoban) ligands, initially developed by Shell[13] in the 1960's, are interesting candidates for developing active catalysts. Indeed, these phosphines fulfil the requirements of steric bulk and basicity required for metathesis reactions. Thus, the first synthesis of a Ru–phoban complex was reported in 2004 by Forman and co-workers[14] using the relatively inexpensive 9-cyclohexyl-9-phosphabicyclononane as ligand for the synthesis of complex **11** (Scheme 3). This compound was prepared by treatment of a 3 : 1 mixture of cyclohexylphoban with indenylidene derivative **8a**, followed by precipitation from pentane. It is noteworthy that pre-catalyst **12**, bearing an isobutyl substituent on the phoban instead of a cyclohexyl group, is now commercially available but its synthesis has not yet been referenced in the literature (Fig. 2).

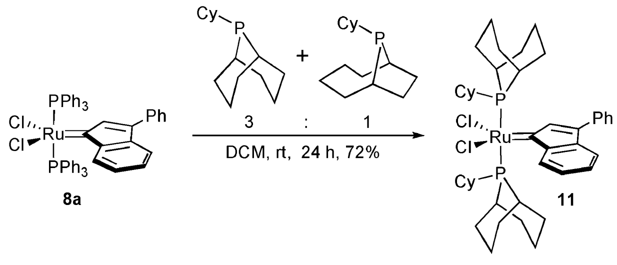
2.2 N-heterocyclic carbene (NHC)-containing pre-catalysts

Compared to phosphine-containing complexes which often suffer from thermal degradation due to the lability of the phosphine ligand, NHC ligands have allowed for improved thermal stability of these second-generation congeners.[3b,15,16] Such sterically demanding ligands have been used for the synthesis of NHC–ruthenium indenylidene complexes.[3b–d] Hence, pre-catalysts **13–14** were synthesised by treatment of



Scheme 2 Proposed mechanism for the indenylidene formation.

Steven P. Nolan received his BSc in chemistry from the University of West Florida and his PhD from the University of Miami where he worked under the supervision of Professor Carl D. Hoff. After a postdoctoral stay with Professor Tobin J. Marks at Northwestern University, he joined the Department of Chemistry of the University of New Orleans in 1990. He is now Group Leader and ICREA Research Professor at the ICIQ in Tarragona (Spain). His research interests include organometallic chemistry and homogeneous catalysis.



Scheme 3 Synthesis of phoban–ruthenium pre-catalyst **11**.

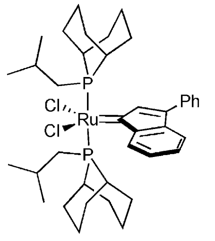


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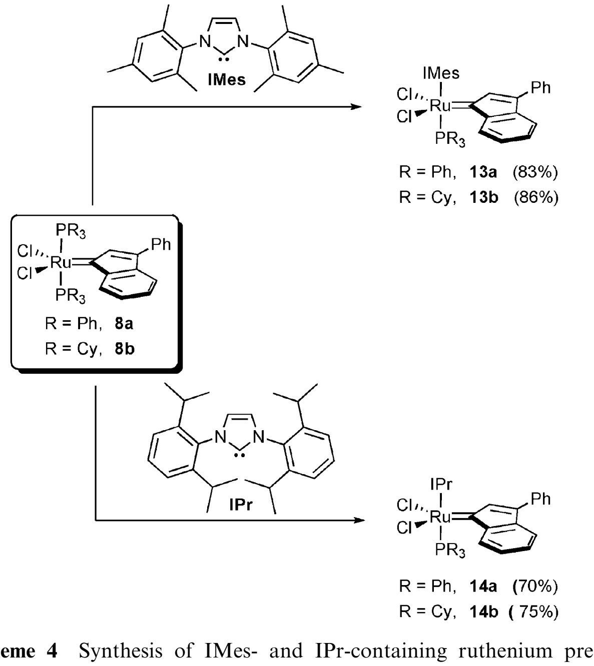
Fig. 2

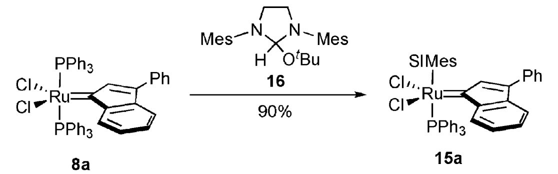
complexes **8a** and **8b** with free carbene IMes (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and free carbene IPr (*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (Scheme 4).[4b] Of note, this report was the first disclosure of the complete and correct characterisation of the indenylidene moiety.



Scheme 4 Synthesis of IMes- and IPr-containing ruthenium pre-catalysts.

Thermal stabilities of complexes **8a**, **8b** and **13–14** were investigated to finally highlight that IPr ligand in the coordination sphere of ruthenium significantly stabilised the complex. Moreover, these investigations showed that pre-catalysts bearing PCy_3 ligands were also thermally stable in solution even at 80 °C for 10 days. Thus, this property hints at the potential use of such complexes in transformations requiring harsher reaction conditions; transformations in which benzylidene pre-catalysts are often not suitable.

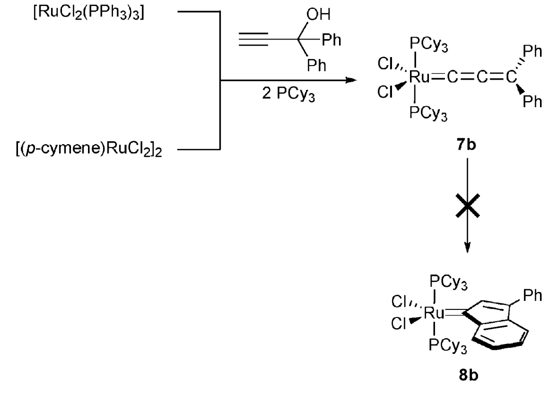
On the other hand, pre-catalyst **15a** bearing a SIMes (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) ligand has been obtained alternatively by treatment of complex **8a** with imidazolidine **16** (Scheme 5).[17] It should be noted that, even though the PCy_3 counterpart of **15b** is commercially available[18] and has been used in atom transfer radical polymerisation,[19] to the best of our knowledge no reference describes its detailed synthesis.



Scheme 5 Synthesis of SIMes-containing ruthenium pre-catalyst.

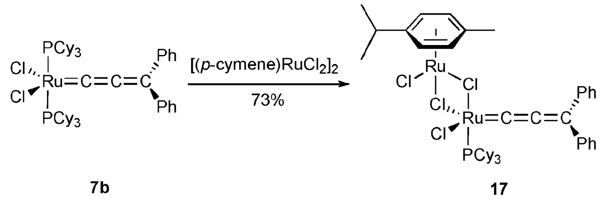
2.3 η^6-Arene-containing pre-catalysts

Several studies have been carried out with *p*-cymene Ru-precursors to develop metathesis pre-catalysts bearing allenylidene as well as indenylidene moieties.[20] The reaction of propargylic alcohol $HC\equiv C–CPh_2OH$ and $[(p\text{-cymene})RuCl_2]_2$ in presence of tricyclohexylphosphine yielded a stable diphenylallenylidene complex **7b** and not the expected rearranged phenylindenylidene product **8b**. Similar results were observed with $[RuCl_2(PPh_3)_3]$ (Scheme 6).[5a,8c]

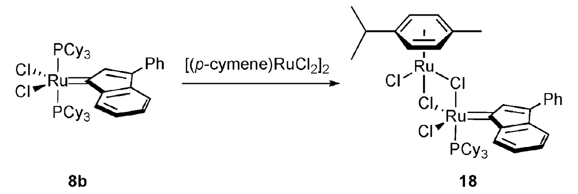


Scheme 6 Synthesis of stable diphenylallenylidene complex **7b**.

It is noteworthy that the reaction between complex **7b** and $[(p\text{-cymene})RuCl_2]_2$ afforded a bimetallic compound **17**, in which no intramolecular rearrangement is observed (Scheme 7).[5b]



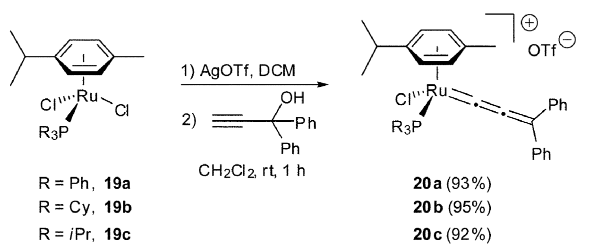
Scheme 7 Synthesis of homobimetallic diphenylallenylidene complex **17**.



Scheme 8 Synthesis of homobimetallic phenylindenylidene complex **18**.

The formation of homobimetallic phenylindenylidene complex **18** was detected in the reaction between complex **8b** and $[(p\text{-cymene})RuCl_2]_2$ (Scheme 8).[9,21] Nevertheless, to the best of our knowledge, neither synthetic procedure nor characterisation has been reported in the literature.

Interestingly, the rearrangement of allenylidene to indenylidene η^6-arene–ruthenium complexes has been extensively studied by Dixneuf and co-workers.[12,22] The cationic allenylidene arene–ruthenium complexes **20a–c**,[8b,23] conveniently synthesised from 18-electron complexes $[(\eta^6\text{-arene})RuCl_2(PR_3)]$, were found to be intermediates in the synthesis of indenylidene complexes (Scheme 9).



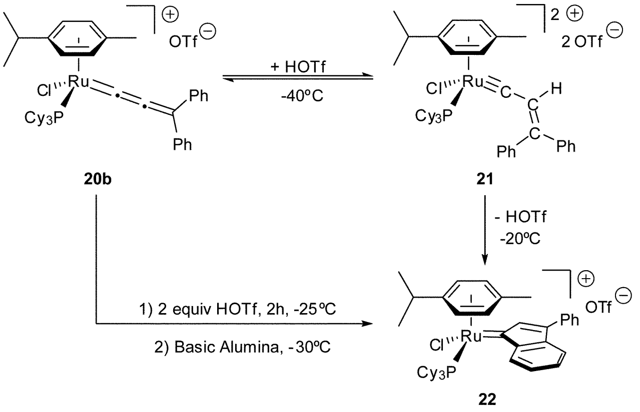
Scheme 9 Synthesis of cationic allenylidene arene–ruthenium complexes.

In the course of kinetic studies of metathesis reactions using complex **20b**, other organometallic species were observed and assumed to act as the active catalyst.[22a] Moreover, it was observed that the addition of a strong acid such as trifluoromethanesulfonic acid to **20b** led to a dramatic increase of the catalytic activity in several metathesis transformations. To understand the real nature of the catalytic species and also control their synthesis, NMR studies at low temperatures were performed by Dixneuf and co-workers.[12,22b] These showed that after addition of 2 equiv. of triflic acid to a CD_2Cl_2 solution of **20b** at −40 °C, the ionic compound **21** can be clearly identified (Scheme 10). Then, upon slight warming to −20 °C, complex **21** was completely converted into phenylindenylidene arene–ruthenium complex **22**.

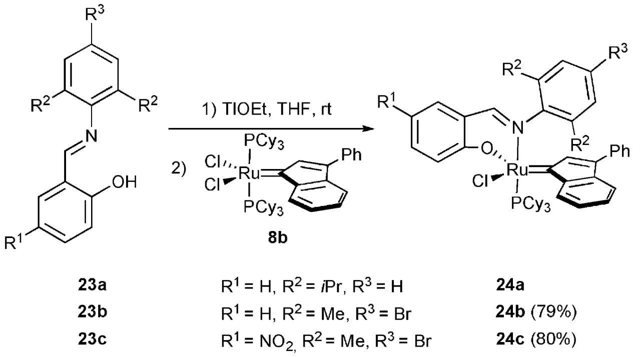
These observations suggest that the α-carbon atom of the protonated intermediate **21** displays an elevated electrophilicity and thus facilitates the electrophilic *ortho* substitution of the phenyl group.

2.4 Schiff base-containing pre-catalysts

During their investigation on Schiff base-containing ruthenium pre-catalysts,[24] Verpoort and co-workers incorporated salicylaldimidato type ligands into indenylidene-based complexes. Treatment of salicylaldimines **23a–c** with thallium ethoxide in THF afforded the corresponding thallium salts which were then reacted with complex **8b**. Upon substitution of an anionic chloride and a neutral phosphine, complexes **24a–c** can be isolated in high yields (Scheme 11).[19,25]



Scheme 10 Rearrangement of allenylidene to indenylidene arene–ruthenium complexes.



Scheme 11 Synthesis of Schiff base Ru–indenylidene complexes **24a–c**.

Such ligands[3f,26] bear two donor atoms having opposite character. Indeed, the phenolate oxygen atom is a hard donor and is known to stabilise the higher oxidation states of ruthenium,[27] whereas the imine nitrogen atom is in comparison soft and is a stabiliser of the lower oxidation states.[28]

Then, a combined NHC–bidentate salicylaldimine complex was synthesised in order to obtain an adequate compromise between catalyst stability and activity. The IMes (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) ligand was chosen for the synthesis of complex **25** (Fig. 3).[25a]

2.5 Pyridine-containing pre-catalysts

Recently, Nolan reported the synthesis of pyridine adducts of ruthenium–indenylidene complexes (Scheme 12).[29] Treatment of precursors **8b**, **13b** and **15b** with excess pyridine and

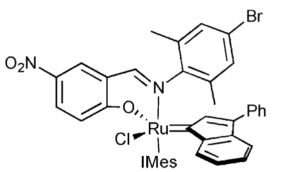


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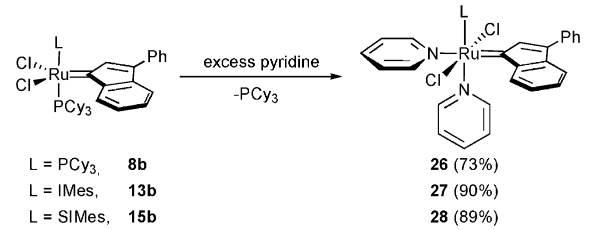
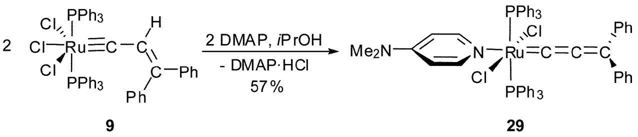
Fig. 3



Scheme 12 Synthesis of pyridine-containing Ru–indenylidene complexes **26–28**.

subsequent addition of hexanes resulted in the formation of a precipitate which can be isolated by filtration at −40 °C in good yields. It should be noted that these cleanly produced bis(pyridine) adducts are air- and moisture-sensitive.

A dimethylaminopyridine (DMAP)-containing Ru–allenylidene complex **29** was prepared by treatment of complex **9** with 2 equiv. of DMAP in isopropanol.[10] However, in that case no rearrangement into the indenylidene compound was observed, which is in good accordance with an acid catalysed pathway for this transformation (Scheme 13).



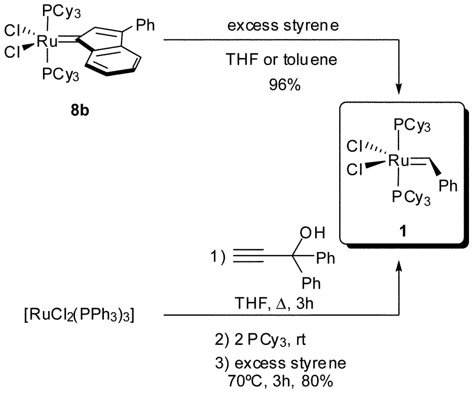
Scheme 13 Synthesis of DMAP-containing Ru–allenylidene complex **29**.

On the other hand, it should be noted that the ^{31}P NMR spectrum of a CD_2Cl_2 solution of **29** revealed the existence of several secondary species in trace amounts (Scheme 14), but once again no indenylidene species were detected.

2.6 Indenylidene-containing pre-catalysts as starting materials for complexes synthesis

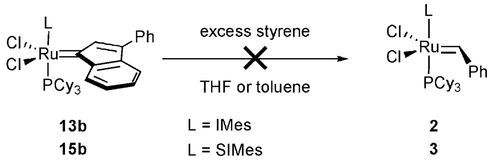
One major drawback of complexes **1**, **2** and **3** is their non-straightforward synthesis.[30] Alternative routes and methods leading to these ruthenium complexes have been examined, especially to do away with the use of diazo reagents which are known for their instability and their explosive nature. Thus, Ru–phenylindenylidene complex **8b** has been used as starting material to form Grubbs first generation catalyst **1** and also Hoveyda boomerang pre-catalyst **6**.

Nolan and co-workers have shown that the reaction of compound **8b** with excess styrene gave catalyst **1** in nearly quantitative yield (Scheme 15) whereas complex **8a** did not exhibit any activity in the cross metathesis reaction with styrene.[11] The procedure may be performed in a single step starting from commercially available compounds $[RuCl_2(PPh_3)_3]$ and HC≡C–CPh$_2$OH. The desired product is isolated in good yield and high purity.



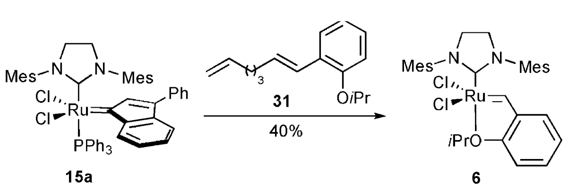
Scheme 15 Conversion of a ruthenium indenylidene complex into Grubbs catalyst.

Surprisingly, Ru–indenylidene complexes **13b** and **15b** bearing NHC ligands did not show good reactivities toward the cross metathesis with styrene and as a consequence did not afford second generation pre-catalysts **2** and **3** (Scheme 16).

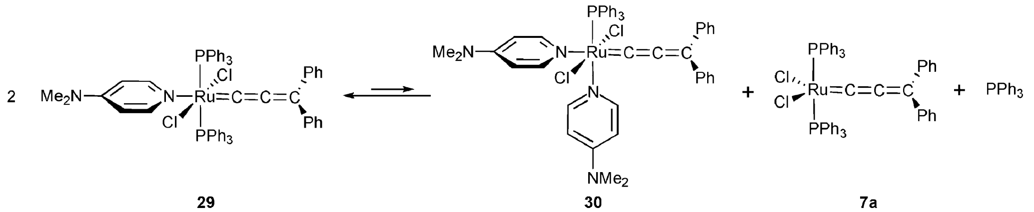


Scheme 16 Reactivity of indenylidene complexes towards styrene metathesis reaction.

The preparation of Hoveyda's pre-catalyst **6** starting from Ru–phenylindenylidene complex **8a** has been described by Blechert *et al.*[17] After the introduction of the NHC ligand by treatment of complex **8a** with imidazolidine **16** (Scheme 5), the second PPh_3 ligand was replaced by an isopropoxybenzylidene moiety. This exchange reaction was performed by RCM (ring closing metathesis) of compound **31** which gives rise to pre-catalyst **6** and cyclopentene as a byproduct (Scheme 17).

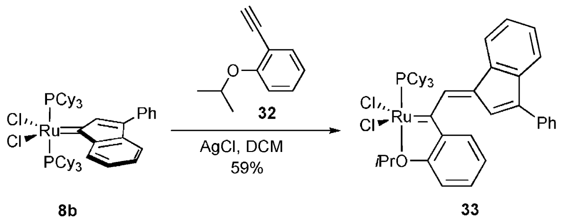


Scheme 17 Conversion of a ruthenium indenylidene complex into Hoveyda's catalyst.



Scheme 14 Equilibrium between DMAP-containing complexes **29** and **30**, **7a** and PPh_3.

The conversion of ruthenium indenylidene compound **8b** into Hoveyda-type complex **33** was achieved *via* an enyne metathesis process (Scheme 18).[31] Reaction of phenylacetylene derivative **32** with **8b** in the presence of silver chloride (phosphine scavenger) afforded complex **33** in moderate yield. It is noteworthy that the presence of the isopropoxy group allowed for a suitable chelation on the metal centre and indeed stabilised the resulting complex.



Scheme 18 Preparation of a bidentate ruthenium vinylcarbene complex.

3. Applications of Ru–indenylidene complexes

Similarly to their benzylidene counterparts, the Ru–indenylidene complexes show excellent catalytic performance in several metathesis transformations. Polymerisation reactions such as ring-opening metathesis polymerisation (ROMP) and atom-transfer radical polymerisation (ATRP) have been investigated, as well as ring-closing metathesis of diene and enyne. As testimony to their high efficiency, these catalysts were used in numerous total syntheses of natural compounds. Moreover, they found applications in scarcely examined reactions with metathesis catalysts, for example in the nucleophilic addition to alkynes or in the hydrosilylation of alkynes.

3.1 Polymerisation reactions

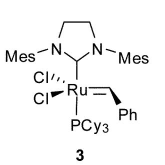
3.1.1 Ring-opening metathesis polymerisation (ROMP). Olefin metathesis was discovered while examining the polymerisation of olefins mediated by transition metal pre-catalysts. Catalysts were later developed specifically for this reaction which is of significant industrial interest. The ROMP of an olefin is the model polymerisation carried out with metathesis catalysts and has been extensively studied.[2b] Verpoort reported the ROMP of benchmark low-strain cyclic olefins *i.e.* cyclooctene and cyclopentene using the Schiff base-containing complexes **24a** and **25**.[25a] Both catalysts were found to be highly active at room temperature. Complex **25** bearing an NHC exhibited the best activity since full conversion of cyclooctene was obtained in less than 15 min with a ratio monomer/catalyst = 10 000/1 (Table 1, entries 2 and 3). For comparison, 2nd generation Grubbs catalyst **3** required 30 min for this reaction to give an insoluble polymer (entry 1).[32] Analyses of the resulting polymer revealed a high molecular weight and a good reaction control. For the more challenging cyclopentene, 17 h were required to convert 78% of the monomer with a ratio monomer/catalyst = 5000/1 leading to a lower molecular weight polymer, yet fitting the theoretical predictions.

Dixneuf and Castarlenas also reported on the activity of Ru–indenylidene complexes for ROMP of cyclooctene and cyclopentene.[12,22b] The indenylidene was generated *in situ* from Ru–allenylidene and a strong acid such as HBF_4 or triflic acid. Of note, in the absence of acid, the indenylidene formation occurred slowly since some activity in catalysis was observed (entry 4). Using the ionic complex **20b** bearing a PCy_3, 5 equiv. of acid and 10 000 equiv. of cyclooctene, complete conversion to polymer was obtained in 5 min at room temperature (entry 5). Reaction with 100 000 equiv. led to an impressive turnover frequency of 1 056 000 h^{-1} with a low polydispersity of the polymer (entry 6). Whereas investigations of the effects of phenyl moieties or η^6-arene substituents showed only slight modifications of the catalytic performances, complex **20a**, the triphenylphosphine counterpart of **20b**, displayed a significantly lower efficiency (entry 7).

Table 1 Cyclooctene polymerisation at room temperature

Entry	Catalyst	Ratio Cyclooctene/Cat.	Time	Conv. or yield (%)	M_n (10^3)[a]	PDI (M_n/M_w)
1	**3**	10 000	30 min	nd[b]	nd	nd
2	**24a**	10 000	17 h	53	855	1.79
3	**25**	10 000	<15 min	100	1210	1.60
4	**20b**	1	15 h	95	143	1.9
5	**20b**, HOTf (5 equiv.)	10 000	5 min	97	387	1.5
6	**20b**, HOTf (100 equiv.)	100 000	5 min	88	857	1.4
7	**20a**, HOTf (5 equiv.)	10 000	8 h	25	107	1.9

[a] Determined by size exclusion chromatography or gel-permeation chromatography. [b] nd = not determined.



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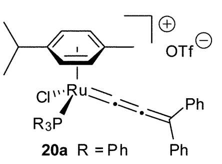
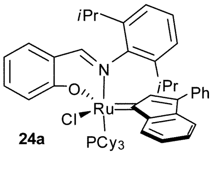
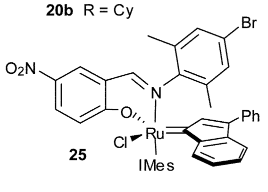


20a R = Ph
20b R = Cy



24a



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These results were confirmed by experiments carried out with the less reactive cyclopentene. Once again, the catalytic system **20b**–HOTf was found to be superior to the 2nd generation Grubbs catalyst **3**. Moreover, the cyclopentene ROMP was achieved at −40 °C with extremely low catalyst loading (ratio monomer/catalyst = 10 000). Recently, it has been demonstrated by kinetic studies that this *in situ* generated complex displayed a high initial activity, which rapidly stopped probably due to complex degradation. On the other hand, the isolated complex **22** allowed for reduced primary efficiency but reaction continued until reaching almost full conversion.[12] Complex **22** also gave good results for ROMP of unstrained monomers.

3.1.2 Atom-transfer radical polymerisation (ATRP).

A few groups have reported that Ru–benzylidene complexes could catalyse the addition of chlorinated alkanes to olefins under atom transfer radical conditions.[33] When the ratio olefin/halide was increased, controlled ATRP occurred. Verpoort and Opstal explored this reaction using several indenylidene complexes: phosphine-containing catalysts **8a** and **8b**, their NHC counterparts **15a** and **15b** and the Schiff base-containing complexes **24a** and **24c**.[19] The atom transfer radical reaction was investigated for addition of carbon tetrachloride and chloroform to several olefins (methyl methacrylate, styrene, acrylonitrile, 1-octene...). The highest Kharasch activity was obtained with catalyst **8a** bearing two triphenylphosphines. On the other hand, higher ATRP activities were observed with the NHC-containing complexes **15a** and **15b** and a good correlation between experimental and theoretically predicted molecular weights was observed (Table 2, entries 1–4). The living character of the polymerisation was verified by linear kinetic plots of $\ln([M]_0/[M])$ *versus* time.

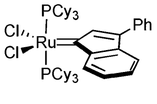
In order to improve the activity of the previous catalytic systems, a few strategies have been examined. Addition of dibutylamine to the reaction mixture allowed for a dramatic increase of the polymerisation conversion with high molecular weight of the polymer (entry 5). Unfortunately, the molecular weight distribution was also found to be significantly broadened. Alternatively, 14-electron enhanced active species have been generated *in situ* by chloride abstraction with $AgBF_4$ (Scheme 19). It was shown that catalysts **34** and **35** are more efficient for ATRP of methyl methacrylate than their neutral analogues, especially when reactions were carried out in a toluene–water mixture (entries 6 and 7). It is noteworthy that a higher polymerisation rate was obtained when the indenylidene moiety was replaced by an ethyl vinyl ether pattern.

Schiff base-containing complexes **24a** and **25** also displayed good activity for the controlled radical polymerisation of methyl methacrylate initiated by ethyl 2-bromo-2-methylpropionate at 85 °C.[25a] Complex **24a** was found to be moderately active but the resulting polymer was well-controlled with a low polydispersity index. **25** exhibited a better activity with still an excellent control of the reactivity as well as a narrow molecular weight distribution. Interestingly, treatment of both catalysts with $AgBF_4$ led also to the formation of more active 14-electron complexes. The general trend was an increase of the activity accompanied by a slight broadening of the molecular weight distribution.

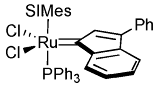
Table 2 ATRP of methyl methacrylate catalysed by Ru–indenylidene complexes[a]

Entry	Catalyst	Yield (%)	M_n (10^3)[b]	PDI (M_n/M_w)
1	**8b**	54	23.6	1.25
2	**15a**	67	30.6	1.24
3	**15b**	73	29.4	1.21
4	**24c**	54	23.5	1.19
5	**15b**–nBu$_2$NH (1/4)	81	105.2	1.67
6	**35b** (toluene)	70	34.3	1.21
7	**35b** (toluene–H_2O)	80	39.3	1.45

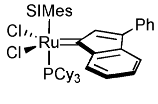
[a] General conditions: ratio monomer/cat./initiator = 800/1/2, 85 °C, 17 h. [b] Determined by size exclusion chromatography.



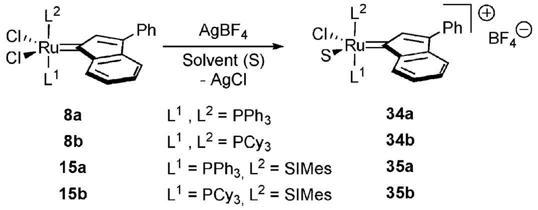
8b



15a



15b



Scheme 19 *In situ* formation of cationic complexes.

3.2 Ring-closing reactions (RCM)

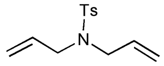
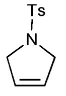
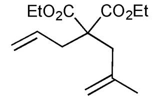
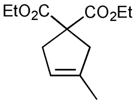
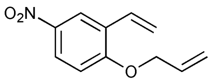
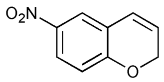
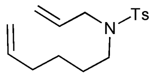
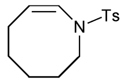
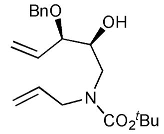
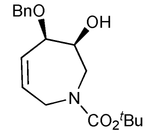
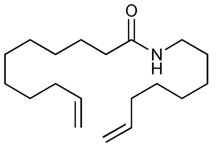
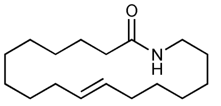
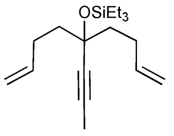
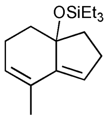
One of the most fascinating features of olefin metathesis is the access to numerous reactions achieved depending on the substrates and reaction conditions albeit with the same metal–carbene complex. Among these transformations, ring-closing metathesis is one of the most popular.

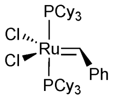
3.2.1 Evaluation and comparison of catalytic performances.

Very early on, the catalytic activity of Ru–indenylidene complex **8b** was investigated for RCM reactions[5b] and compared to that of its benzylidene counterpart.[9] As shown in Table 3, activities provided by **8b** and 1st generation Grubbs catalyst **1** were found to be quite similar. Applied to a set of RCM reactions, **8b** showed a high tolerance to a wide array of functionalities such as amide (entries 1 and 4), ester (entry 2), ether (entry 3), alcohol (entry 5), silyl ethers (entry 7)... Moreover, **8b** was found to be efficient in forming medium (entries 1–3) and larger rings (entries 4 and 5) as well as macrocyclic derivatives, for example the 18-membered ring product presented in entry 6. **8b** was also shown to be quite competent for enyne metathesis (entry 7). However, it has been reported that some RCM reactions leading to dihydropyrans using **8b** required thermal activation whereas with **1** reaction occurred at room temperature.[34] Surprisingly, pre-catalyst **8a** does not exhibit any activity in RCM transformations.[4b]

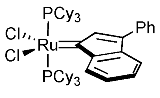
Benzylidene- and indenylidene-based catalysts have rarely been compared in terms of activity, but even more infrequently from a reactivity point of view. In 2000, Schmidt reported that the metathesis reaction on the allyl ether **36** mediated by the pre-catalyst **1** led to the spiro product **37** in low yield due to

Table 3 Comparison between catalysts **1** and **8b** in RCM reactions for various substrates (1–5 mol% of catalyst loading)

Entry	Substrate	Product	Yield (%)	
			1	8b
1			93	98
2			93	83
3			97	97
4			68	70
5			64	87
6			83	82
7			95	79



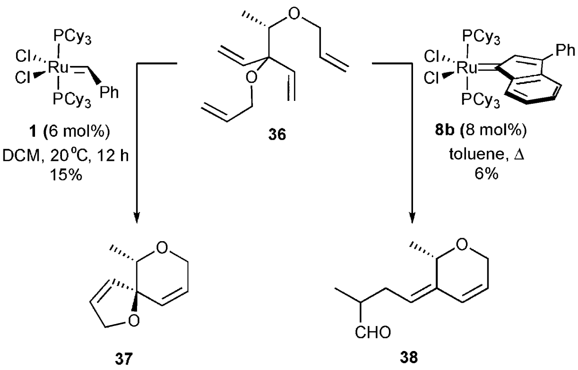
1



8b

the competition with intermolecular metathesis (Scheme 20).[35] When the 1st generation indenylidene complex **8b** was used, the double RCM sequence did not occur and only the dihydropyran **38** was isolated in poor yield. The formation of **38** can be explained by a sequence of RCM reaction, double bond isomerization, and then Claisen rearrangement. Unfortunately, no precise explanation was given as to the cause of this reactivity difference (complex or/and temperature).

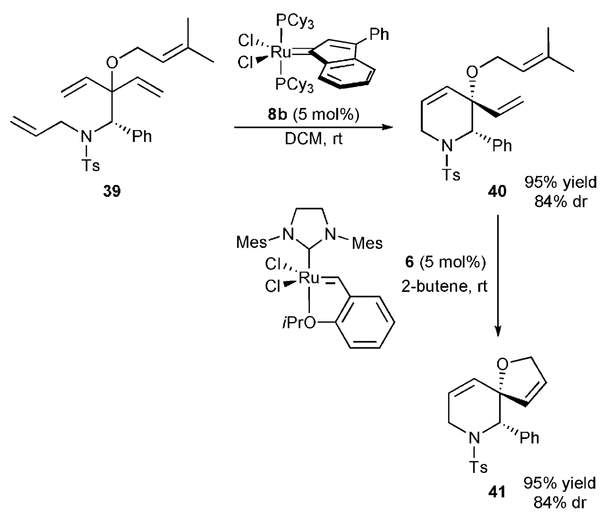
The activity of catalyst **8b** has been found to be low for some sterically hindered substrates. Nevertheless, Wallace took advantage of this lack of activity towards particular olefins to perform a diastereoselective double RCM reaction (Scheme 21).[36] Treatment of tetraene **39** with the Ru–indenylidene complex **8b** gave cleanly the monocyclised product **40** with a good diastereoselectivity (84% dr). The second RCM leading to the spiro compound **41** was achieved quantitatively with the more active 2nd generation Hoveyda catalyst **6**. When tetraene **39** reacted with **6**, final product **41** was directly isolated without diastereoselectivity.



Scheme 20 Difference of reactivity between benzylidene and indenylidene ruthenium-based catalysts.

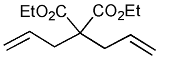
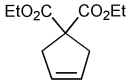
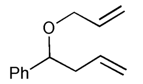
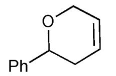
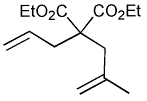
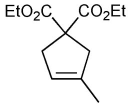
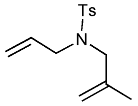
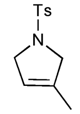
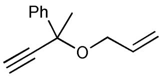
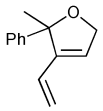
Recently, the catalytic performances in RCM of phoban-containing catalysts **11** and **12** were investigated.[37] For non-hindered substrates, **11** and **12** exhibited similar activities (Table 4, entries 1 and 2), nevertheless for these types of olefins, the first generation Grubbs and indenylidene catalysts **1** and **8b** proved to be more competent.[38] However, for trisubstituted dienes, **12** was found to possess significantly improved activity over **11** and was also better than **1** and **8b** (entries 3 and 4). This activity difference related to the phosphine could be explained by the ligand symmetries and their conformational behaviour.[39] More surprisingly, for other substrates such as enynes (entry 5), **11** displayed much better activity than **12**. This study highlighted that the relationship between ruthenium complexes, catalyst efficiency, and the substrate was difficult to predict.

The 2nd generation catalyst **13b**, bearing an unsaturated NHC and having an excellent thermal stability,[4b] proved competent in RCM involving very sterically hindered substrates such as tetrasubstituted dienes for which high temperature reactions are required (Table 5).[4a] Tosylamine- and malonate-based substrates were cyclised in good to excellent yields using a catalyst loading of only 2.5 mol% (entries 1 and 2). When the ring formed was larger, 5 mol% were required, but the isolated yield still remained acceptable (entry 3).

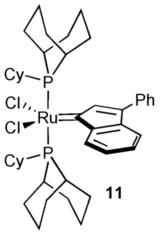


Scheme 21 Diastereoselective double ring-closing metathesis reaction.

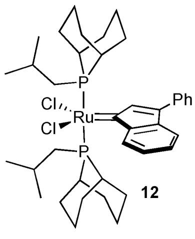
Table 4 Comparison between catalysts **11** and **12** in RCM reactions for various substrates[a]

Entry	Substrate	Product	Complex	*t*/h	Yield (%)
1			**11**	3	>98
			12	2	96
2			**11**	5	98
			12	5	>98
3			**11**	8	80
			12	2	98
4			**11**	8	98
			12	5	>98
5			**11**	5	98
			12	10	68[b]

[a] Reaction conditions: 2 mol% of catalyst, DCM, rt. [b] Reaction performed at 40 °C.



11



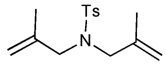
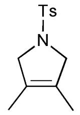
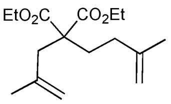
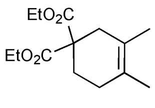
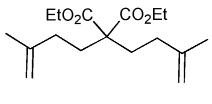
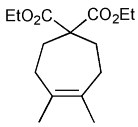
12

Recently, Nolan and Clavier reported the activity of the SIMes-containing Ru–indenylidene **15b** and carried out a thorough comparison between the 1st generation catalyst **8b**, its IMes counterpart **13b** and their benzylidene analogues.[40] Interestingly, kinetic studies using **8b**, **13b** and **15b** in RCM of di- and trisubstituted dienes reveal that phosphine- and NHC-containing complexes possess a distinct rate-determining step for the formation of the 14-electron active species. For **8b**, the activity is a function of the substrate steric hindrance, implying that its rate-determining-step is the formation of the metallacyclobutane. On the other hand, kinetic studies with catalysts **13b** and **15b**, both bearing NHC ligands, showed their activity not to be related to the substrate and that the rate-determining step is likely to be the formation of the 14-electron species by loss of the phosphine ligand. Of note, **15b** bearing the saturated NHC was found to be more efficient than **13b**, probably due to their different stereoelectronic properties leading to easier phosphine displacement from **15b**.

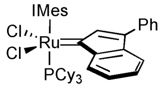
Broadening the scope to various substrates showed the catalysts to exhibit good tolerance to various functional groups: ester (Table 6, entry 1), tosylamines (entries 2 and 3), amide (entry 4), ethers (entries 5 and 6) and also for enynes (entries 7 and 8). For some unhindered substrates, the phosphine-containing catalyst **8b** was found to be more efficient than **15b** (entries 1, 5 and 7). However, when the steric congestion around the reactive moieties of the substrate increased the various catalysts' activity was found comparable (entry 2) or superior in the case of **15b** (entries 4 and 6). Importantly, the cyclisation of very hindered olefins could not be achieved using **8b**, whereas **15b** gave excellent results (entries 3 and 8).

In order to favour the formation of 14-electron active species and hence increase the activity of the Ru–indenylidene complexes, Nolan and co-workers substituted phosphine ligands by more labile pyridine.[29] The activity of pyridine adducts **26–28** was investigated on benchmark malonate substrates using kinetics studies (Table 7). In spite of promising initiation rates, only poor to moderate activities were observed. Due to a rapid degradation of the active species, complex **26** gave only low conversions even for an unchallenging substrate (entry 1). NHC ligands allowed for enhanced stability of the active species, but still the catalytic

Table 5 RCM of sterically hindered substrates using catalyst **13b**[a]

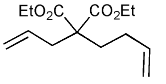
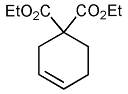
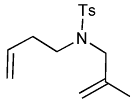
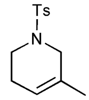
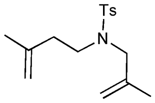
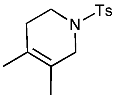
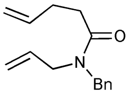
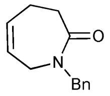
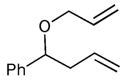
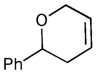
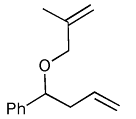
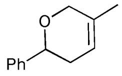
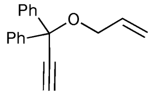
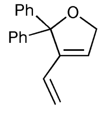
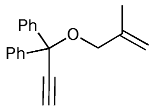
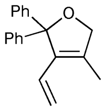
Entry	Substrate	Product	Catalyst loading (mol%)	Yield (%)
1			2.5	97
2			2.5	89
3			5	71

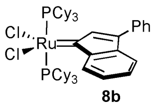
[a] Reaction performed in toluene at 80 °C.



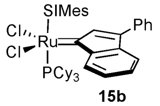
13b

Table 6 Activity comparison between catalysts **8b** and **15b**

Entry	Substrate	Product	Complex (loading (mol%))	$T/°C$	t/h	Yield (%)
1			**8b** (2) **15b** (2)	25 25	0.25 5	>98 >98
2			**8b** (2) **15b** (2)	25 25	6 6	95 >98
3			**8b** (5) **15b** (5)	80 80	5 0.5	<2 95
4			**8b** (2) **15b** (2)	40 40	3 3	54 81
5			**8b** (2) **15b** (2)	25 40	2 5	98 94
6			**8b** (2) **15b** (2)	40 40	2 2	42 98
7			**8b** (2) **15b** (2)	25 40	5 5	89 99
8			**8b** (5) **15b** (5)	80 80	5 5	<2 85



8b



15b

performances were found to be moderate since no full conversion could be reached for either diallylmalonate (entry 1) or methallylallylmalonate (entry 2). Of note, the complex bearing SIMes showed once again a significantly improved activity over its IMes relative.

η^6-Arene complexes such as **20** and **22** have been demonstrated to catalyse very efficiently the RCM of dienes and enynes. As shown in Table 8, **20d** allowed for the cyclisation of common substrates (entry 1), dienynes (entry 2) and, more interestingly, catalysed the formation of larger rings (entries 3–6).[23] It should be noted that the counterion altered both the reactivity and the selectivity of the reaction. PF_6^-, BPh_4^- or OTf^- led to excellent results whereas BF_4^- or $B(C_6F_5)_4^-$ gave only low yields due to side reactions (isomerisation and cycloisomerisation).

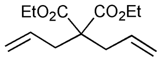
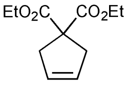
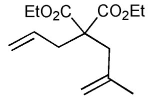
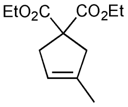
Nevertheless, **20d** required an important thermal activation (80 °C), even if it has been proven that reaction occurred at lower temperature with longer reaction time. The authors found that the addition of $HBF_4{\cdot}Et_2O$ or CF_3SO_3H as additives led to a critical enhancement of the activity. Since the rearrangement of allenylidene to indenylidene is known to occur under acid conditions, this study also emphasises the superiority of Ru–indenylidene catalysts over the allenylidene complexes. As depicted in Table 9, the isolated cationic complex **22** was able to cyclise a diene leading to the expected five-membered ring in short reaction times at room temperature (entry 1).[12] On the other hand, the study focused more specifically on rearrangement of enynes into alkenylcycloalkenes by enyne RCM. This reaction occurred rapidly, and to complete conversion, at room temperature (entry 2). Nevertheless, longer reaction times were required for more valuable products such as myrtenal and menthone derivatives (respectively, entries 3 and 4).

RCM of diallyltosylamide carried out using the homobimetallic indenylidene **18** highlighted the poor activity of the catalyst.[9] Surprisingly, this trend is in contrast with its analogous benzylidene which possesses a higher activity than the 1st generation Grubbs catalyst **1**.[41]

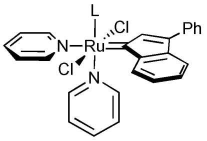
3.2.2 Applications to total synthesis of natural products.

Since ring-closing metathesis is one of the most powerful reactions giving access to large rings and macrocycles,

Table 7 Activity in RCM of pyridine adducts **26–28**[a]

Entry	Substrate	Product	Catalyst	t/h	Conv. (%)[b]
1			**26** **27** **28**	2 2 2	38 71 87
2			**26** **27** **28**	2 2 2	17 50 60

[a] Reaction conditions: 1 mol% of catalyst, DCM, room temperature. [b] Determined by NMR analysis.



L = PCy_3 **26**
L = IMes **27**
L = SIMes **28**

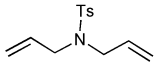
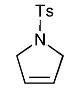
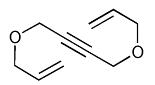
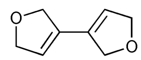
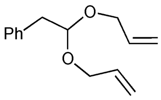
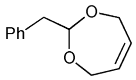
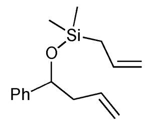
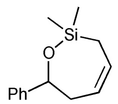
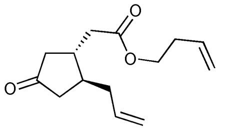
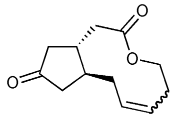
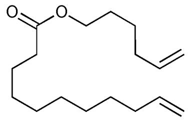
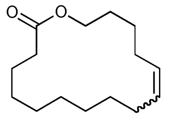
Ru-based olefin metathesis complexes have been employed for the synthesis of biologically relevant molecules. The first application of a Ru–indenylidene catalyst to total synthesis was described by Fürstner.[42] The formation of the macrocyclic ring in the total synthesis of the cyclic tripyrrole pigment nonylprodigiosin **44**, which is a potential lead compound for the development of immunosuppressive agents, was achieved by RCM (Scheme 22). Whereas the RCM of **42** with 1st generation Grubbs catalyst **1** gave only 42% of the cyclised product **43**, the use of indenylidene complex **8b** improved the yield to 65% ($E:Z \geq 10:1$). Although high catalyst loading was required, Wilkinson's catalyst promoted the hydrogenation of the newly formed double bond. This synthetic pathway has also been applied to the synthesis of various nonylprodigiosin analogues.[43]

(−)-Balanol **48** is an alkaloid representing an interesting lead as a selective inhibitor of protein kinase C. For its total synthesis, the formation of the seven-membered ring was achieved by RCM of diene **46** (Scheme 23).[44] Grubbs catalyst **45** and **1** allowed for the isolation of the desired tetrahydroazepine **47** in only satisfactory yield (64–69%) whereas catalyst **8b** advantageously afforded the product in 87% yield.

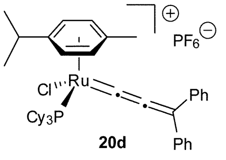
Turrianes possess a cyclophane structure arising from the C–C coupling of phenol rings of non-isoprenoid lipid derivatives. It was speculated that these compounds might display DNA-cleaving properties similar to those of already known substances. For the total synthesis of the 20-membered macrocycle **50**, Fürstner *et al.* employed an RCM strategy (Scheme 24).[45] Either the 1st generation Grubbs catalyst **1** or the indenylidene **8b** was found competent to promote the cyclisation of **49**. Nevertheless, **8b** gave both higher isolated yield (73% for **1**) and higher selectivity in the double bond geometry ($E:Z = 5.8:1$ for **1**). Interestingly, such a good selectivity was unexpected since substrates similar to **49** did not lead to any E/Z selectivity.

Few families of large membered lactones such as microcarpalides, pinolidoxin, didemnilactones, or herbarumin have

Table 8 Cyclisation of dienes and dienyne promoted by **20d**[a]

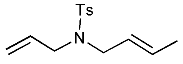
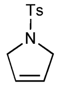
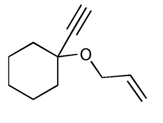
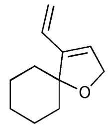
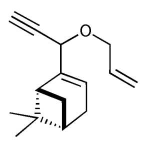
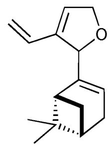
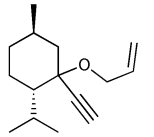
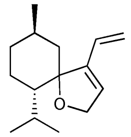
Entry	Substrate	Product	Yield (%)
1			83
2			86
3			88
4			77
5			40
6			90

[a] Reaction conditions: 2.5–5 mol% of catalyst, toluene, 80 °C.

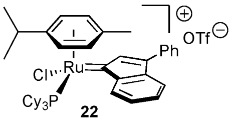


20d

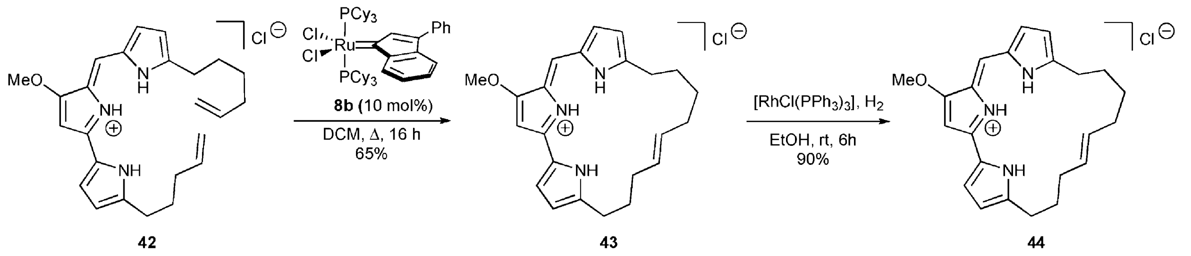
Table 9 Cyclisation of dienes and enynes promoted by **22**[a]

Entry	Substrate	Product	t/h	Yield (%)
1			0.5	95
2			1.5	93
3			24	72
4			24	96

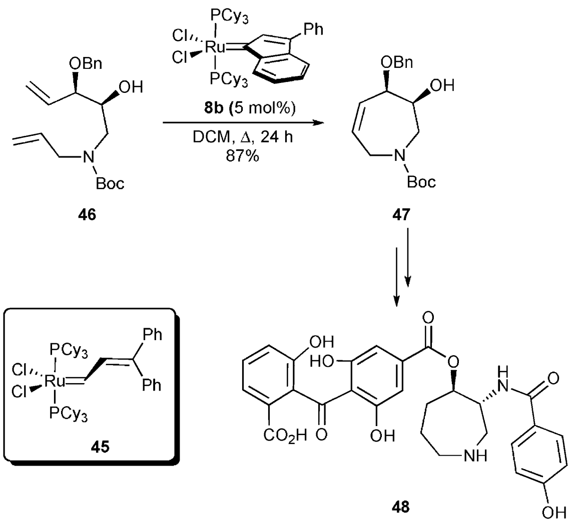
[a] Reaction conditions: 2 mol% of catalyst, chlorobenzene, rt.



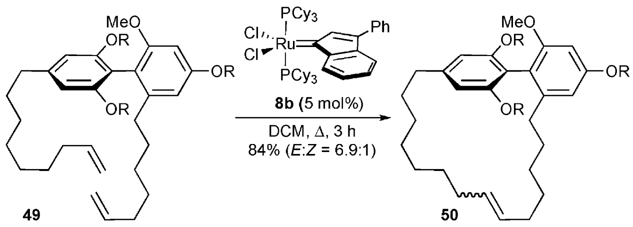
22



Scheme 22 Metathesis key-step for the synthesis of cyclic tripyrrole pigment nonylprodigiosin **44**.

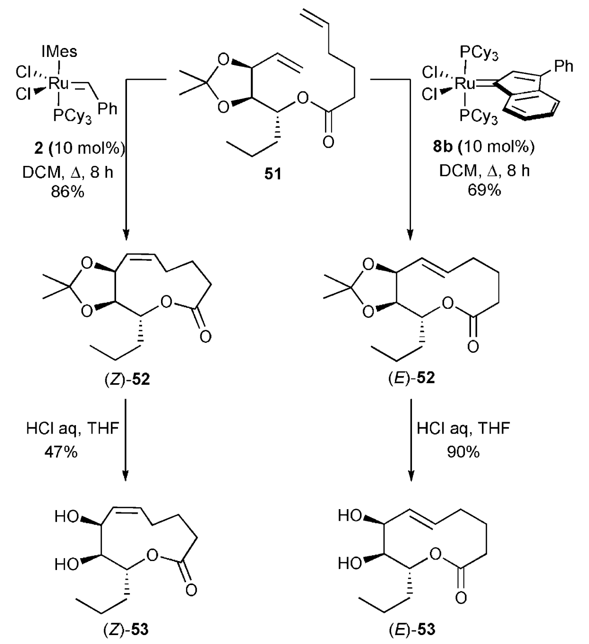


Scheme 23 RCM step in the synthesis of (−)-balanol **48**.



Scheme 24 Macrocyclisation step by RCM in the synthesis of turrianes.

been isolated from natural resources and due to their biological significance, their synthesis has attracted the attention of many groups. Some of these have employed approaches using RCM as a key step.[46] As illustrated in Scheme 25, the RCM of substrate **51** was achieved using benzylidene catalyst **2** and the ruthenium–indenylidene **8b**. A catalytic amount of **8b** in refluxing DCM afforded the desired (*E*)-lactone **52** as the major product; only 9% of the (*Z*)-isomer was detected. The non-time evolution of the ratio (*E* : *Z*) indicated that the formation of the thermodynamically less stable (*E*)-isomer resulted from a kinetic control. In contrast, when **51** was treated with benzylidene catalyst **2** bearing an NHC, the selective formation of the *Z* isomer occurred in excellent yield. In order to explain this difference, the authors proposed that the higher activity of the 2nd generation pre-catalyst allowed for the formation of the thermodynamically favoured product, particularly due to the reversibility of this reaction. Subsequent cleavage of acetyl groups was performed by treatment with dilute aqueous HCl providing herbarumin I (*E*)-**53**.

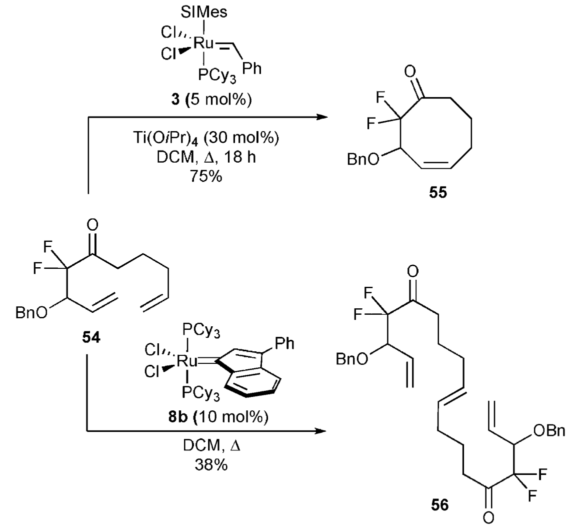


Scheme 25 Metathesis key-step for the synthesis of herbarumin I **53**.

3.3 Olefin cross metathesis and related reactions

Cross metathesis transformations have rarely been investigated using Ru–indenylidene complexes. Recently, Percy reported the synthesis of difluorinated pentopyranose analogues involving an RCM step.[47] With 2nd generation Grubbs catalyst **3** and Ti(O*i*Pr)$_4$ as co-catalyst, diene **54** was cyclised to the eight-membered ring **55** in good yield (Scheme 26). However, when the indenylidene catalyst **8b** was used, significant quantities of homodimeric cross metathesis product **56** were isolated. Only traces of the expected product **55** (4%) were observed. This is one of the rare examples of a reactivity difference between indenylidene and benzylidene ruthenium-based catalysts.

Fatty acid esters, such as methyl oleate **57**, represent promising alternatives to fossil fuel derived feedstocks for the production of raw materials. By self-metathesis or ethenolysis, derivatisations of methyl oleate could produce useful raw materials (Scheme 27).[48] For these reactions requiring a thermal activation (50 °C), the performance of robust ruthenium–indenylidene complexes was found satisfactory. It is of note that equilibria were reached at 50% conversion. For the

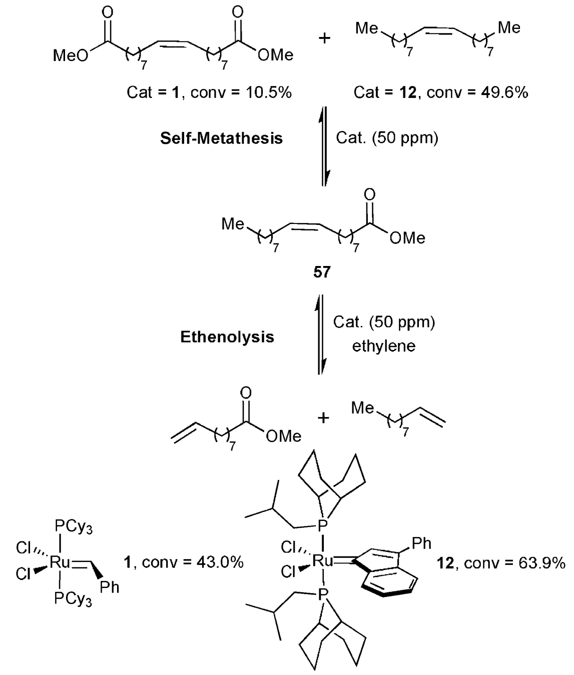


Scheme 26 Reactivity difference between benzylidene and indenylidene catalysts.

self-metathesis of **57**, the phoban-containing catalyst **12** gave significantly higher conversions compared to Grubbs catalyst **1**. Interestingly, in this type of reaction the Ru–methylidene species are not reaction intermediates, suggesting that degradation of ruthenium metathesis catalysts occurs without involving Ru–methylidene species. Slightly better results with phoban catalyst **12** were also obtained for ethenolysis of methyl oleate.

3.4 Non-metathesis reactions

In addition to olefin metathesis, Ru–indenylidene complexes have been used in other reactions such as nucleophilic additions and hydrosilylation of alkynes.

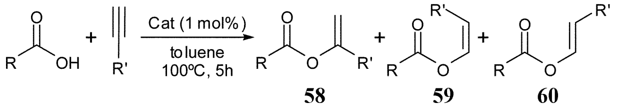


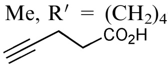
Scheme 27 Metathesis of renewable unsaturated fatty acid esters.

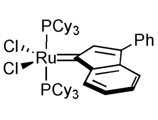
3.4.1 Nucleophilic addition to alkynes.

In 2002, Verpoort reported the Markovnikov addition of carboxylic acids to alkynes catalysed by Ru(II) indenylidene complexes.[24] The activities of phosphine-containing catalyst **8b** and complex **61**, bearing a Schiff base, were compared in the addition of formic acid to phenylacetylene (Table 10, entries 1 and 2). The use of **61** led to significantly better conversion; moreover, advantageously with this catalyst no anti-Markovnikov product (compounds **59** and **60**) was detected. The examination of the reaction scope showed that, depending on the substrates,

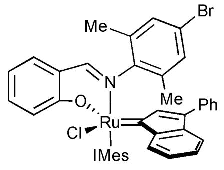
Table 10 Ruthenium catalysed nucleophilic addition of acid to alkynes



Entry	Substrate	Cat.	Conv. (%)	Product composition (%)		
				58	**59**	**60**
1	R = H, R′ = Ph	**8b**	68	41	56	—
2	R = H, R′ = Ph	**61**	80	97	—	—
3	R = CH_2CHMe_2, R′ = Ph	**61**	77	74	11	3
4	R = Ph, R′ = Ph	**61**	98	84	4	8
5	R = Me, R′ = ^{t}Bu	**61**	66	65	28	7
6	R = Me, R′ = $(CH_2)_4CCH$	**61**	79	80	18	2
7		**61**	79	80	18	2

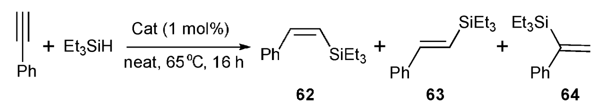


8b

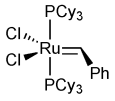


61

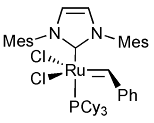
Table 11 Ruthenium catalysed hydrosilylation of alkynes



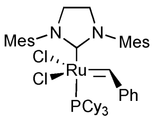
Entry	Cat.	Conv. (%)	Product composition (%) **62**	 **63**	 **64**
1	**1**	90	100	—	Traces
2	**2**	53	95	—	5
3	**3**	40	94	—	6
4	**13b**	31	94	—	6



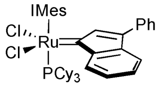
1



2



3



13b

this undesired reaction occurred. For example, in the reaction of acetic acid with the sterically hindered *tert*-butylacetylene (entry 5), in addition to a lower conversion, significant amounts of **59** were formed. However, considering that under these reaction conditions side reactions like alkyne homocoupling may occur (small quantities were obtained), **61** promoted efficiently the Markovnikov addition of carboxylic acids to alkynes with good selectivities.

3.4.2 Hydrosilylation of alkynes. In the course of studies on the ability of ruthenium metathesis catalysts to promote hydrosilylation of alkynes, Lee investigated the activity of 2nd generation indenylidene **13b** and compared its activity to that of other catalysts (Table 11).[49] For the addition of triethylsilane to phenylacetylene, in spite of good selectivity for the formation of the product **62**, complex **13b** provided lower conversions than other catalysts tested. Of note, in all cases, after 16 h at 65 °C, phenylacetylene consumption was complete and with catalysts **2**, **3** and **13b** significant amounts of tail-to-tail dimer (alkyne dimerisation) were formed, probably due to the higher activity of these complexes bearing an NHC ligand. Since 1st generation catalyst **1** was found to be the best catalyst for this reaction, it would be interesting to test its indenylidene cousin **8b**.

4. Conclusion and outlook

An overview of the syntheses of ruthenium–indenylidene complexes as well as their applications was presented in this *feature article*. The great accessibility and robustness of indenylidene-containing pre-catalysts were highlighted. Moreover, it was mentioned that these complexes can bear various ancillary ligands including, for instance, tertiary phosphines, NHCs or pyridines. As a consequence, the resulting 'tunable' catalysts constitute interesting candidates for metathesis transformations. The observed catalytic activities of the indenylidene systems are often similar to those of their benzylidene counterparts and in some cases good complementarity exists. We believe that indenylidene-containing ruthenium catalysts are promised a bright future. A number of these are commercially available which should result in an increase in their use and of work performed on this ruthenium platform.

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