

Single-Site Ruthenium Metathesis Catalysts

PROGRESS IN THEIR DESIGN AND SYNTHESIS

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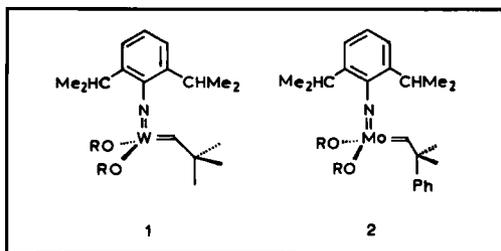
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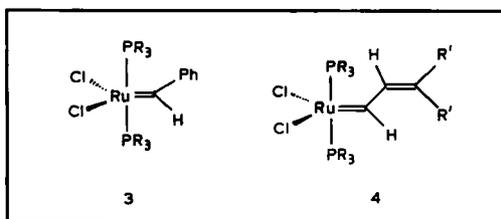
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This paper presents an up-to-date investigation relating to the design and synthesis of the recently disclosed single-site ruthenium carbene metathesis catalysts. Created as a convenient counterpart of the earlier tungsten and molybdenum carbene catalysts, these novel ruthenium carbene complexes bear specific heterocyclic ligands and display comparable activity and selectivity in metathesis reactions, as well as good tolerance toward organic functionalities, air and moisture. Due to their unique properties, they can be successfully applied in numerous organic and polymer syntheses involving cross-metathesis, ring-opening and ring-closing metatheses, as well as ring-opening metathesis polymerisation. This paper updates our previous review on metathesis reactions published in this Journal last year.

At present, single-site ruthenium carbene catalysts have an important role in metathesis chemistry (1). The earlier, well-defined tungsten and molybdenum alkylidene complexes, 1 and 2, successfully prepared by Schrock (2, 3), are very active and quite stereoselective in the alkene metathesis and ring-opening metathesis polymerisation (ROMP) of cycloolefins.



$R = C(CH_3)_3, C(CF_3)(CH_3)_2$ or $C(CF_3)_2(CH_3)$



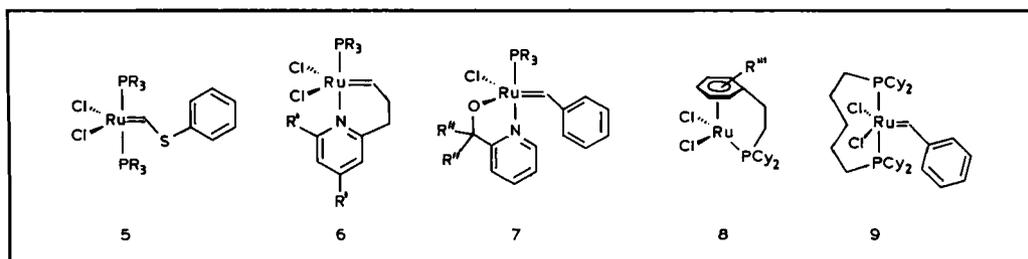
In 3, $R =$ isopropyl (*i*-Pr), phenyl (*Ph*), cyclopentyl (*Cyp*); in 4, $R =$ *Ph*, *Cyp*, cyclohexyl (*Cy*); $R' =$ methyl (*Me*), *Ph*

However, the new ruthenium alkylidene complex, 3, and ruthenium vinylalkylidene complex 4, more recently disclosed by Grubbs (4, 5), exhibit, along with good activity and stability, an improved tolerance towards many organic functionalities, as well as to air and moisture. Therefore, they are of great use in a variety of organic and polymer syntheses (6, 7).

Because of these new catalysts, the metathesis reaction has finally been accepted for widespread use by both synthetic organic and polymer chemists. Currently, this process is being utilised across a vast spectrum of organic syntheses yielding functional organic compounds and natural products. It is also being used in syntheses of specialty and functional polymers.

Types of Catalysts, Syntheses and Catalytic Properties

Following this significant breakthrough in organoruthenium chemistry, a variety of ruthenium carbene catalysts has been prepared, characterised and used by many research teams as a convenient strategy in the synthesis of various organic compounds and polymeric materials (8–15). A first group of catalysts concerns ruthenium alkylidene complexes, such as 5, bearing a



In **5**, **6**, **7**, $R = i\text{-Pr}$; in **6** $R' = \text{H}, \text{CH}_3$; in **7** $R'' = \text{CH}_3, \text{C}_6\text{H}_5$; in **8** $R''' = \text{an alkyl group}$

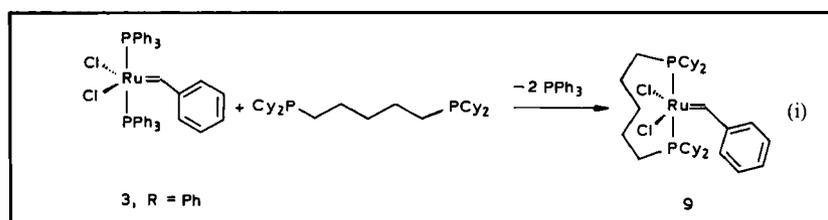
heteroatom-containing carbene ligand (**12**), the ruthenium bridged complexes **6** and **7** (**13**) all developed by Ciba SC, **8** by Abele *et al.* (**14**) and **9** by Mol and coworkers (**15**).

One advantage offered by these new ruthenium alkyldiene catalysts **5–9** is that, for the first time, it is possible to apply them to the ring-opening

metathesis polymerisation (ROMP) of cycloolefins (for example to dicyclopentadiene) using the reaction injection moulding (RIM) technique and also to immobilise them on solid supports. In addition, the synthesis of such ruthenium carbene complexes involves a convenient one-step procedure starting from the ruthenium phosphine benzylidene complex **3**. For instance, the reaction of two equivalents of complex **3** with one equivalent of phenyl vinyl sulfide gives the ruthenium complex with an S-containing ligand **5** whereas the equimolar reaction of **3** with 2-(3-butenyl)pyridine leads to the bridged ruthenium complex **6**, see Scheme I.

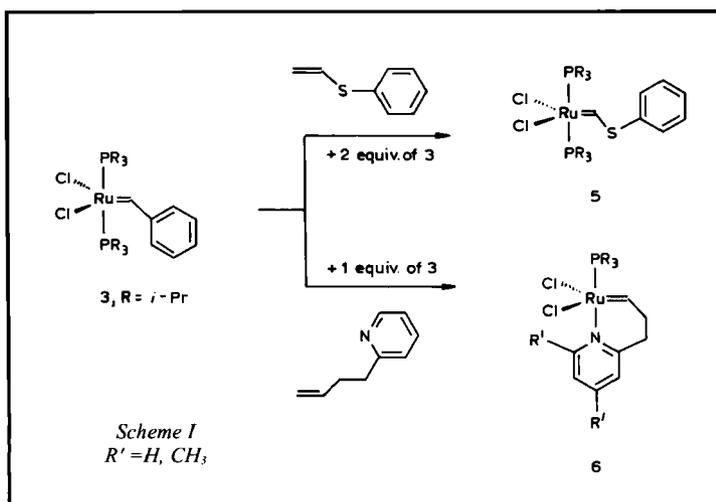
Similarly, bidentate phosphines with large natural bite angles (for example based on xanthene or $\text{Cy}_2\text{P}(\text{CH}_2)_n\text{PCy}_2$ ($n = 3–5$))

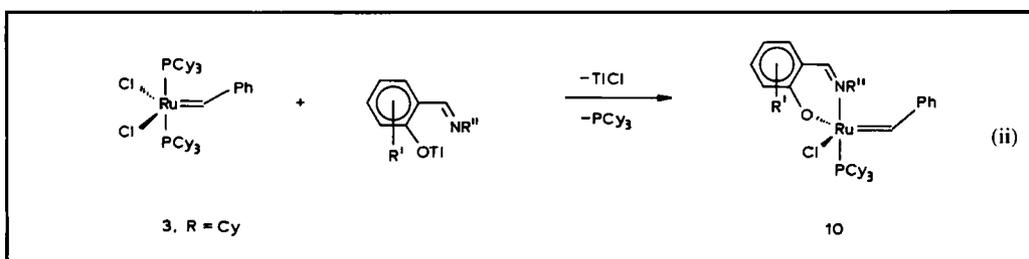
have been obtained by reaction of ruthenium complex **3** with 1, ω -bis(dicyclohexylphosphine)alkanes (for example 1,5-bis(dicyclohexylphosphine)pentane) (**15**), (Equation (i)).



In order to prepare novel hydrogenised catalysts, bidentate phosphine ligands of this type could also be used to attach the ruthenium alkyldiene complexes to solid supports.

A new class of efficient ruthenium catalysts, **10**, contains bidentate Schiff base ligands and can be prepared by a single-step procedure starting from





In 10, R' = NO₂, R'' = substituted phenyl group, Tl = thallium

the ruthenium complex 3 (16), see Equation (ii).

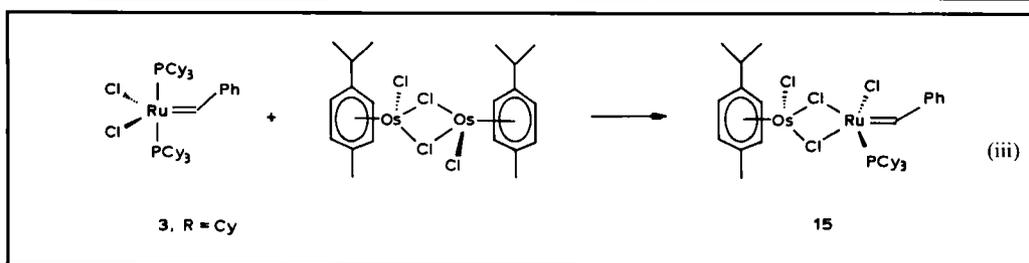
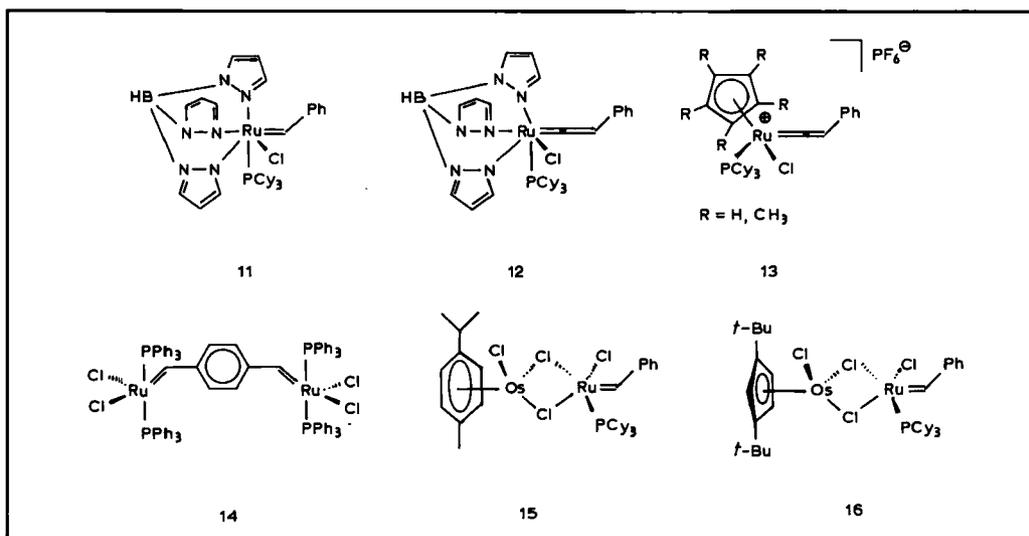
Schiff base ligated ruthenium carbenes are important as raw materials for the manufacture of supported catalysts. Other alkylidene and vinylidene ruthenium complexes, 11, 12 and 13, contain tris(pyrazolyl)borate, cyclopentadienyl and penta-methylcyclopentadienyl ligands (17).

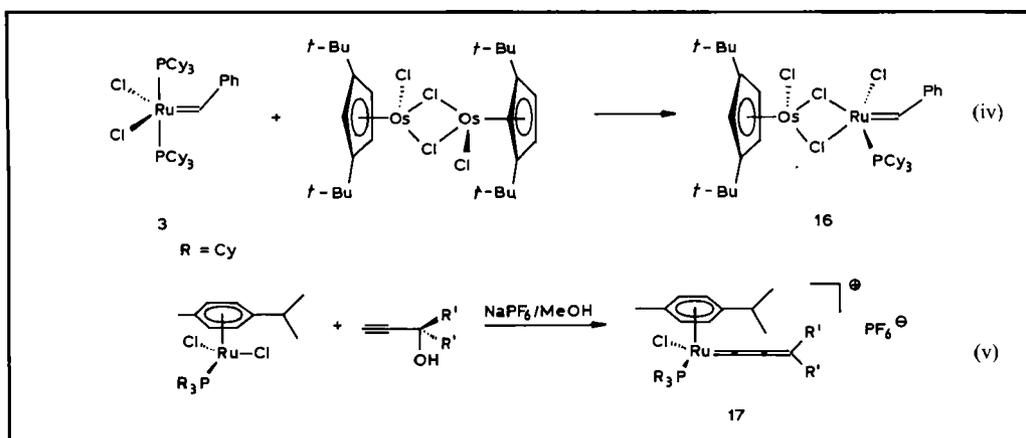
Binuclear ruthenium complexes such as 14, easily obtained from RuCl₂(PPh₃)₃ and 1,4-benzene-bis(diazomethane), provide ready access, by ROMP of cycloolefins, to particular polymer

architectures, like ABA block copolymers (18).

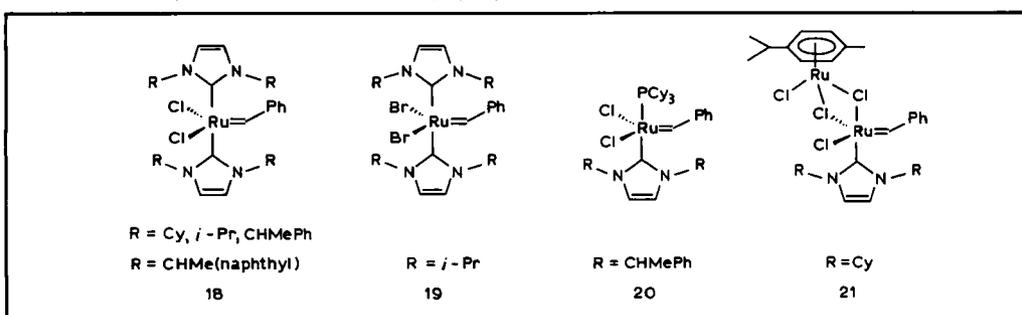
Other heterobimetallic ruthenium catalysts, for example compounds 15 and 16, which contain both osmium and ruthenium, were conveniently obtained from the reaction of complex 3 with the corresponding binuclear osmium complexes (19) (Equations (iii) and (iv)). These complexes were reported to possess significantly enhanced activities in ROMP of 1,5-cyclooctadiene and 2,2-bis(trifluoromethyl)norbornene (19).

Recently, Dixneuf and coworkers reported that





In (v) $R = i\text{-Pr}$ or Cy ; $R' = \text{Ph}$ or a substituted aryl group

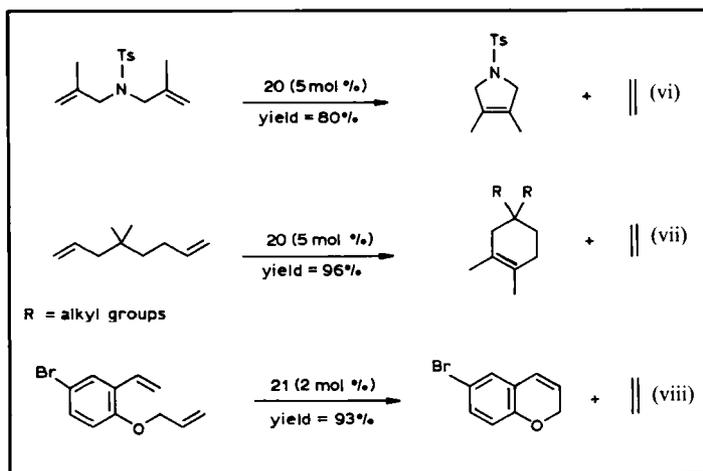


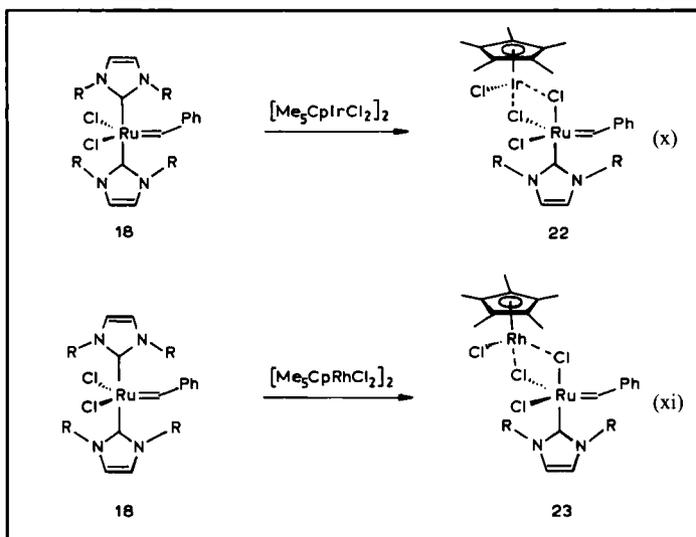
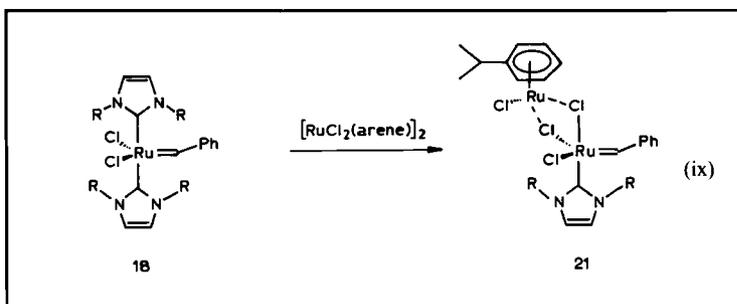
18-electron cationic allenylidene ruthenium complexes of type 17 were excellent precatalysts for alkene and enyne metathesis for the production of macrocycles, fluorinated amino acid derivatives and alkenyl dehydrofurans (20, 21). Their synthesis is accessible by the reaction of (*p*-cymene) $\text{RuCl}_2(\text{PR}_3)$ with substituted 1-propyn-2-ol derivatives, preferably with 1,1-diphenylpropyn-2-ol ($R' = \text{Ph}$) (Equation (v)).

A major advance in the chemistry of ruthenium carbene complexes occurred recently by the synthesis of a novel class of ruthenium benzylidene complexes 18, 19, 20 and 21 by Herrmann *et al.* (22, 23), *via* derivatisation of the ruthenium phosphine complex 3. For this purpose one or both PCy_3 ligands in 3

have been replaced by imidazolin-2-ylidenes, which are easily accessible and known to be more Lewis-basic than PCy_3 . These allow fine tuning of the reactivity by systematic variation of the R groups in the imidazolin-2-ylidene moiety.

Even though significant differences in their





behaviour have been observed, all these ruthenium benzylidene complexes were found to catalyse the conversion of a wide range of dienes into the corresponding cyclic compounds by ring-closing metathesis (RCM) (Equations (vi)–(viii)) (24).

The applications of these ruthenium benzylidene complexes include syntheses of five-, six-, seven-, eight-, and higher-membered ring systems of *N*- and *O*-heterocyclic compounds, as well as macrocyclic products, such as the commercially important perfume ingredient Exaltolide®. Significantly, the compatibility of these ruthenium benzylidene complexes with functional groups seems to be practically identical to that of complex 3. An unex-

pected feature of this class of catalysts is their excellent performance in the formation of tri- and even tetra-substituted cycloalkene products (24).

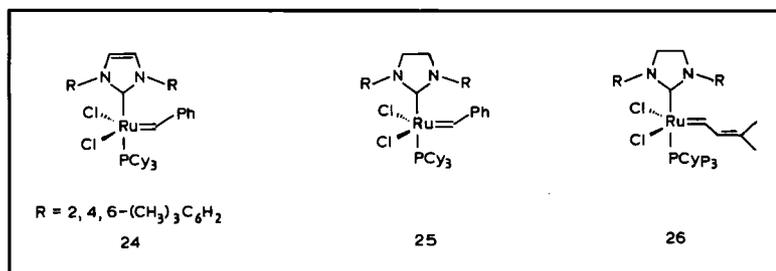
Binuclear ruthenium complexes of type 21 have been efficiently prepared from bis(imidazolin-2-ylidene) ruthenium benzylidene complex 18 by reaction with the $\text{RuCl}_2(p\text{-cymene})$ dimer (25) (Equation (ix)).

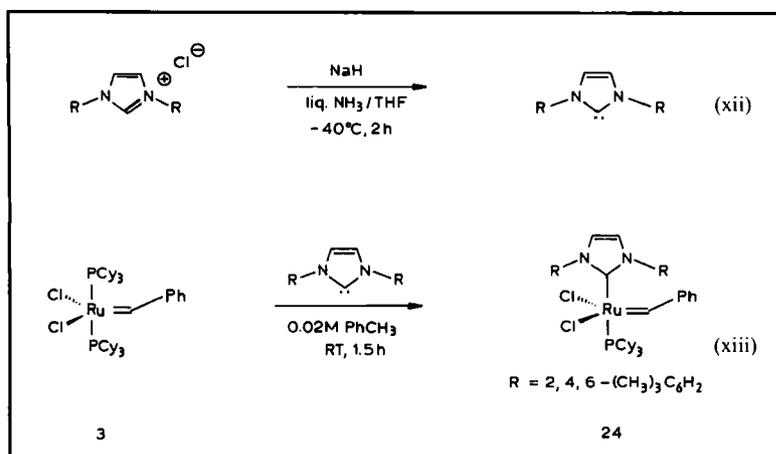
Similarly, heteronuclear ruthenium complexes 22 and 23 have been obtained starting from the bis(imidazolin-2-ylidene) ruthenium benzylidene complex 18 by reaction with the corresponding iridium and rhodium dimeric compounds, respectively, (26) (Equations (x) and (xi)).

By applying the convenient Herrmann approach for

derivatisation of ruthenium carbenes with imidazolin-2-ylidene ligands, Grubbs and coworkers (27, 28) prepared a new series, 24, 25 and 26, in this class of compounds using other members of the Arduengo imidazolinylidene ligand family (29).

From the numerous 1,3-diaryl-imidazolin-2-ylidene ligands that Grubbs investigated, only the 2,6-disubstituted aryl systems including the 1,3-dimesityl-imidazolin-2-ylidene, (which are sufficiently bulky to prevent disubstitution) gave

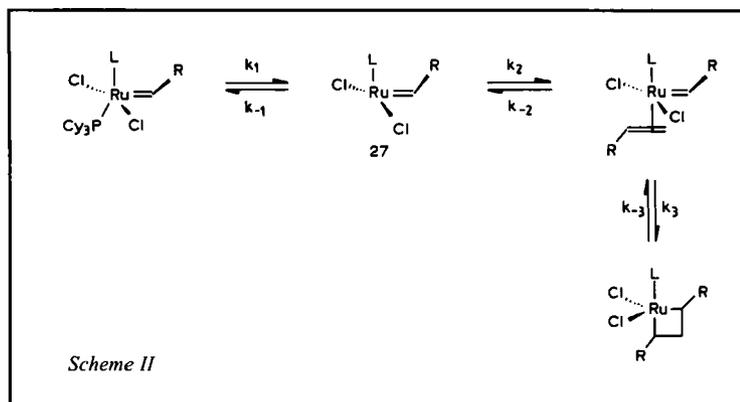




clean reaction products. Their synthesis occurs readily by a two-step procedure starting from the parent ruthenium complex 3 (Equations (xii) and (xiii)).

In the first step, the imidazol-2-ylidene carbene ligand has been conveniently synthesised from the corresponding salt with sodium hydride in liquid ammonia/THF, and could be isolated and used without purification in the subsequent step involving a ligand exchange reaction in toluene. The latter reaction is rapid at room temperature yielding product 24, which is isolated as a pinkish-brown microcrystalline solid that could be purified by recrystallisation from pentane at -78°C.

This ruthenium catalyst, 24, allows many of the desirable RCM reactions to be carried out, resulting in good yields and product selectivity. Numerous examples are reported for reactions of various dienes leading to substituted cycloalkenes and heteroatom-containing cycloalkenes (27). Although at room temperature the new complex 24 is normally less reactive for RCM than the parent compound 3, at slightly higher temperatures its reactivity increases dramatically.

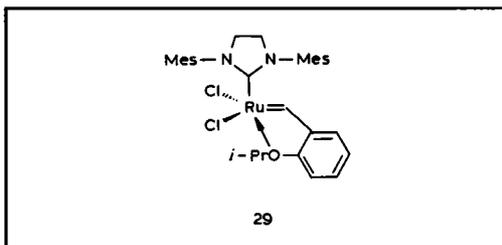
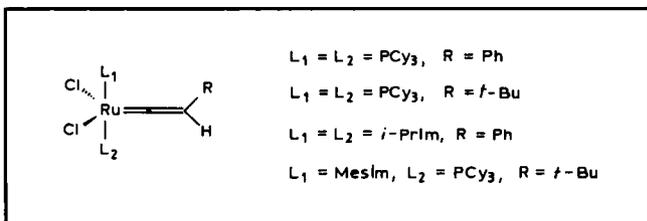


Substantially elevated activity was gained by the saturation of the imidazol-2-ylidene ligand – as in the ruthenium complex 25. The higher basicity of the saturated ligand results in a ruthenium catalyst of unprecedented activity in this class. In many cases the activity exceeds that of the molybdenum complex 2, while

maintaining the environmental stability of the parent benzylidene ruthenium complex 3.

Interesting mechanistic studies, carried out by Grubbs and coworkers (30), of the metathesis reaction with ethyl vinyl ether, induced by ruthenium catalysts 3 and 25, indicated that the initial substitution of a phosphine ligand by the olefinic substrate proceeded in a dissociative fashion and involved a 14-electron shell intermediate 27, see Scheme II.

As illustrated in Scheme II, this intermediate can be either trapped by free PCy₃ to regenerate the starting ruthenium alkylidene (k₁/k₋₁) or can bind substrate (k₂/k₋₂) and undergo metathesis *via* the metallacyclobutane pathway (k₃/k₋₃). The dramatic increase in activity of the *N*-heterocyclic carbene-coordinated catalyst 25, which had previously been attributed to its ability to promote



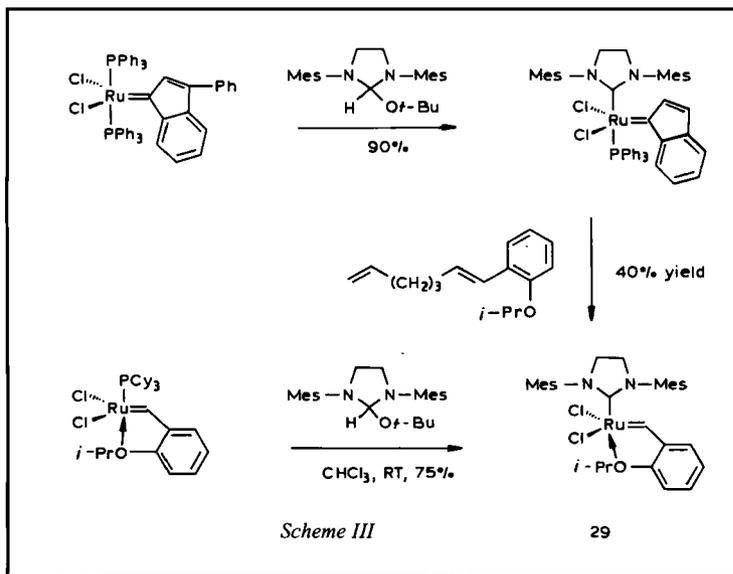
phosphine dissociation, appears instead to be due to an improved selectivity for binding π -acidic olefinic substrates, in the presence of σ -donating free phosphine.

Grubbs and coworkers have also reported a large series of ruthenium vinylidene complexes, 28, (31). Some of these complexes, particularly those bearing both phosphine and imidazolylidene ligands, display a substantial activity in olefin metathesis and ROMP of cycloolefins. In 28, the ligands $i\text{-PrIm} = 1,3$ -diisopropyl-4,5-dimethylimidazol-2-ylidene and $\text{MesIm} = 1,3$ -dimesityl-

imidazol-2-ylidene. The generation of complexes *in situ* from $[(p\text{-cymene})\text{RuCl}_2]_2$ and substituted acetylenes, and their subsequent application in RCM reactions of dienes, has also been demonstrated.

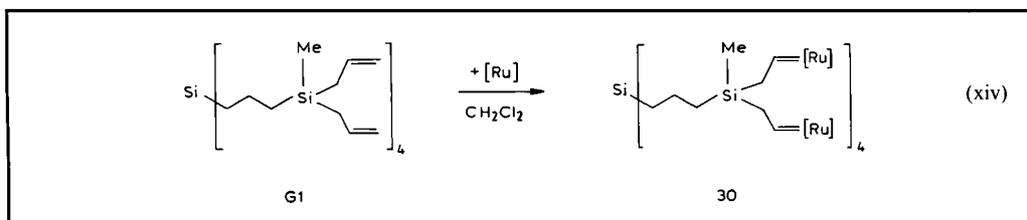
A very stable and highly active catalyst, selective for cross-metathesis (CM) and RCM, namely the ruthenium benzylidene complex 29, which has a 1,3-dimesitylimidazolylidene ligand, has recently been prepared by Hoveyda and colleagues (32). Blechert and coworkers reported two other convenient synthetic routes to the ruthenium benzylidene complex 29, starting from different ruthenium alkylidene complexes as precursors, see Scheme III (33).

Nguyen and Grubbs (34) introduced a new class of polymer-supported ruthenium complexes by using cross-linked polystyrene-divinylbenzene as the solid support. Verdonck and his team (35) immobilised ruthenium alkylidene complexes on a dendrimeric carbosilane core. The latter catalysts were manufactured by attaching the ruthenium complexes to the boundary of the zeroth generation (G0) or first generation (G1) of the carbosilane dendrimers (Equation (xiv) where [Ru] denotes the ruthenium catalyst).



The catalytic activity of the dendrimeric ruthenium catalyst 30 has been tested in the ROMP of norbornene. Using these complexes, multi-arm star polymers could be produced in a controlled manner.

More recently, a range of improved immobilised $[\text{RuCl}_2(p\text{-cymene})]_2$ complexes (36) and Schiff base modified ruthenium alkylidene catalysts (37) have been successfully designed and prepared by Verpoort and his coworkers. These have been applied in the



polymerisation of strained cycloolefins with both high and low steric strain. It is noteworthy that Verpoort's type of heterogenised catalysts combines higher thermal stability with increased metathesis activity and stereoselectivity, and can play an important role in chiral processes.

Conclusions

The number of single-site ruthenium metathesis catalysts has increased rapidly during the last few years due to their easy accessibility, remarkable activity and selectivity, and good tolerance toward organic functionalities, air and moisture. Most of them can be conveniently prepared starting from the classical Grubbs' ruthenium benzylidene cata-

lyst. A significant advancement was further achieved by the introduction of imidazolin-2-ylidene ligands into the conventional ruthenium alkylidene complexes. New trends in process development are currently being opened by design and synthesis of immobilised ruthenium catalysts. These novel single-site ruthenium metathesis catalysts lead to high performances in various reactions of this type, particularly in cross-metathesis (CM), enyne metathesis, ring-closing metathesis (RCM), ring-opening metathesis (ROM) and ring-opening metathesis polymerisation (ROMP). Indeed, the stable singlet carbenes recently described by Bertrand and coworkers (38) offer hopes for yet better catalysis in the future.

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Microwave-Assisted Homogeneous Sonogashira Coupling Reactions

Arylalkynes are intermediates for the synthesis of a variety of compounds: heterocycles, cyclophanes, enediyne antibiotics, etc. Sonogashira coupling has provided these compounds via the palladium(0)-catalysed coupling of terminal alkynes and aryl iodides in the presence of copper(I) and a base. Weaknesses of this reaction include long reaction times and the limited choice of reaction medium.

In recent years, microwave heating has emerged as a technique to speed up organic reactions. Now, a microwave-enhanced, rapid and efficient homogeneous-phase version of the Sonogashira coupling reaction of aryl iodides, bromides, triflates and an aryl chloride with trimethylsilylacetylene has been established by scientists from Sweden (M. Erdélyi and A. Gogoll, *J. Org. Chem.*, 2001, 66, (12), 4165–4169). Pd(PPh₃)₂Cl₂ and copper(I) iodide were used as the catalyst system, in the presence of diethylamine. Excellent yields (80 to 95%) were obtained in 5 to 25 minutes.