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Review

NHC–Ru complexes—Friendly catalytic tools for manifold chemical transformations

Valerian Dragutan [a,*], Ileana Dragutan [a], Lionel Delaude [b], Albert Demonceau [b]

[a] *Institute of Organic Chemistry, Romanian Academy, 202B Spl. Independetei, 060023 Bucharest, Romania*
[b] *Laboratory of Macromolecular Chemistry and Organic Catalysis, University of Liege, Sart-Tilman, B-4000 Liège, Belgium*

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Contents

Abstract

N-Heterocyclic carbenes are now commonly encountered in organometallic and inorganic coordination chemistry. The increasing attention they enjoy is due to their ability to act as ancillary ligands in a growing number of transition metal catalysts or even to play the role of nucleophilic reagents and catalysts in diverse organic transformations. As a fine addition to the NHC–Ru–alkylidenes, popular for their tremendous success in metathesis chemistry, an array of robust and stable Ru–NHCs has proven their utility in non-metathetical reactions. The present review surveys different classes of Ru–NHCs and their applications as efficient catalysts (or precatalysts) in several types of fundamental organic processes e.g.

* Corresponding author.
E-mail address: vdragutan@yahoo.com (V. Dragutan).

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hydrogenation, hydrogen transfer, isomerization, cycloisomerization, cyclopropanation, hydrosilylation, allylation and deallylation, enol-ester synthesis, heterocycle synthesis, C–C alkyne coupling, Kharasch addition and ATRP. A special section is devoted to tandem processes some of which include concurrent or sequential metathesis steps. Relevant mechanistic and stereochemical aspects related to NHC–Ru catalysis will be highlighted.

Keywords: *N*-Heterocyclic carbenes; Ruthenium complexes; Non-metathesis; Catalysis; Radical reactions; Tandem processes

1. Introduction

For the last two decades Ru-complexes have scored increasing numbers of productive applications in the field of organometallic chemistry and catalysis [1–3]. The newly created complexes were provided with particular ligands so as to achieve an appropriate balance between the electronic and steric environment around the metal and enable control on their activity, stability and chemoselectivity profiles [4–11]. Gratifyingly, some of the ligands manage to confer good compatibility with heteroatom-containing functional groups, air and moisture, thus widening the areas of application [12] in the direction of multiple organic transformations [13].

Shortly after the first isolation of a free *N*-heterocyclic carbene (NHC) by Arduengo et al. in 1991 [14], this family of ligands came to the forefront of coordination chemistry and organometallic catalysis [15]. NHCs are generating great interest either in their capacity of versatile nucleophilic catalysts in a variety of organic processes and as reactants in multicomponent reactions [16] or, mainly, as key ligands in numerous metal complexes that mostly turned out to be catalytic systems of broad performance [17]. These complexes pertain to practically all classes of metals, not solely transition metals in low or high oxidation states but also main group metals. The non-labile, sterically demanding NHC ligands stabilize both the pre-catalysts and the highly coordinatively unsaturated intermediates. In metal complexes NHC ligands show high propensity for acting as typical σ-donors, yet manifest only a slight π-backbonding tendency (metal-to-NHC d–π^* back-donation and ligand-to-metal-to-NHC π–d back-donation) [18]. NHCs are strong Lewis bases and, in spite of a generally similar behaviour to phosphines, bind better to the metal than their conventional congeners generating rather stable metal–carbon bonds [19]. Supposedly due to the comparatively decreased lability of the NHC ligands, the new generation of complexes bearing NHCs show improved thermal and oxidative stability, hence make long-lived and active catalysts, a feature often considered as a key asset of this type of ligands. As for the case of amines and phosphines, substituent group manipulations in NHCs and mainly sweeping through various azole rings can build a favourable steric topography and electronic environment in the immediate coordination sphere of the metal thus allowing fine-tuning of catalytic capabilities [20]. In addition to the aforementioned advantages, this class of ligands is easily accessible through well-established synthetic protocols [21], while, in synthesis, an excess of the ligand is not required in order to prevent aggregation of the catalyst. NHC ligands have very diverse structure but frequently encountered in catalytic complexes are the following prototypes: imidazol-2-ylidenes, imidazolin-2-ylidenes, thiazo-2-ylidenes and triazo-5-ylidenes.

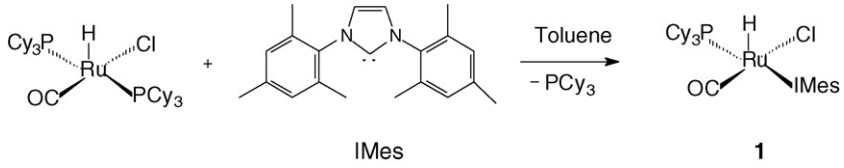
In recent years the benefits of NHC–Ru complexes as catalysts (or precatalysts) have expanded to the area of non-metathetical transformations being quickly exploited in a diversity of organic syntheses that may significantly impact modern technologies for production of advanced materials [22]. The present article gives a summary overview of important work published during the last 5 years on new NHC–Ru complexes, with a focus on their successful application in non-metathetical processes.

2. Classes of NHC–Ru complexes

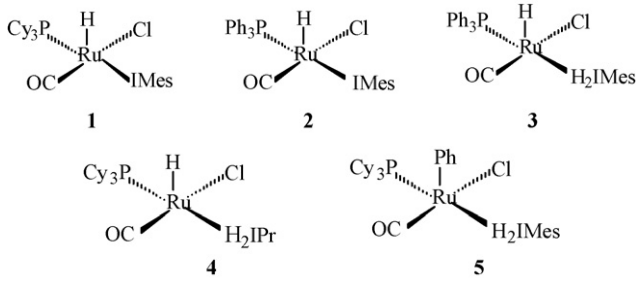
There is at present a broad range of structural motifs for the NHC–Ru complexes being applied in catalytic processes [15c,d,20d]. These complexes contain, in addition to the functional ligand (actor ligand, e.g. hydride, alkylidene), a variety of other ligands among which spectator (e.g. ancillary) or not so innocent ligands may be distinguished. Each of these ligands has its own characteristics that can be adjusted for optimal performance, and the interplay of all of them specifically modulates electronic and steric properties, reactivity and catalytic patterns. The recognized success of NHC–Ru complexes is based, among other favourable attributes, on the exceptionally wide range of oxidation states and coordination geometries available to ruthenium. The above considerations are reflected in the numerous structures reported for NHC–Ru complexes, some of them also enabling applications beyond the commonly performed metathesis reaction. Rigorous taxonomy of the multitude of structures for NHC–Ru complexes is complicated; therefore, in this review only some examples, relevant for their use in non-metathetical transformations have been highlighted, and catalogued on the basis of the activating or actor ligands accompanying the *N*-heterocyclic carbene.

2.1. NHC–Ru hydride and phenyl complexes

NHC–Ru hydride (**1**–**4**) and phenyl (**5**) complexes (IMes = *N*,*N*′-bis(mesityl)imidazol-2-ylidene, H_2IMes = *N*,*N*′-bis(mesityl)imidazolin-2-ylidene, H_2IPr = l,3-di(2,6-diisopropylphenyl)-l,3-dihydro-2H-imidazol-2-ylidene) are encountered in the hydrogenation [23] and isomerization [24] reactions of alkenes or functionalized unsaturated substrates, and as reactive intermediates arising during hydrogenations catalyzed by Ru–alkylidene complexes [25].



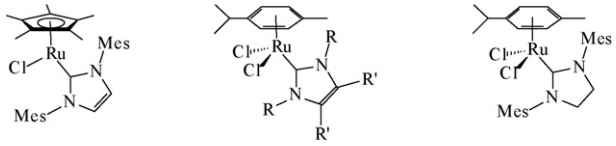
Scheme 1. Synthesis of NHC–Ru-hydride complex **1** [23a].



Their syntheses occur very easily by direct substitution of PCy_3 for NHC in the bisphosphane congeners (Scheme 1).

2.2. NHC–Ru arene complexes

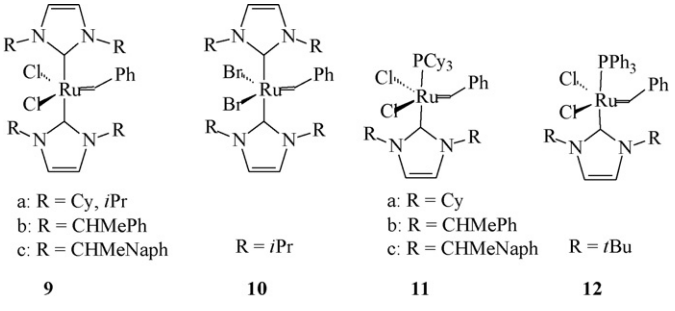
In the context of the outstanding achievements in NHC–Ru chemistry, imidazolin-2-ylidene ligands have also been employed to furnish another class of ruthenium complexes, incorporating arene moieties (e.g. **6**–**8**) that, due to easy accessibility from the commercially available ruthenium dimer $[(p\text{-cymene})RuCl_2]_2$, were directly useful in both radical and metathesis reactions [10,26].



In addition, these imidazolin-2-ylidene arene complexes have high potentiality as precursors in the synthesis of further arene ruthenium compounds showing catalytic properties in various non-metathetical organic reactions.

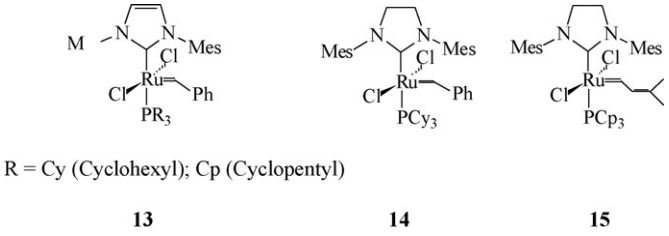
2.3. NHC–Ru alkylidene complexes

Independently and almost simultaneously, three research groups reported the synthesis of ruthenium benzylidene complexes containing nucleophilic *N*-heterocyclic carbenes (NHCs) as



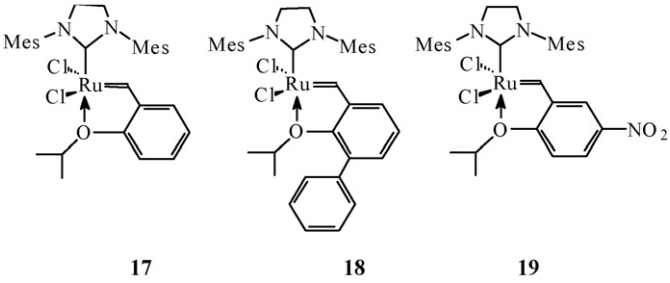
ancillary ligands [27]. Thus, Herrmann et al. [17a,27a] published the synthesis of complexes **9**–**12** from the bisphosphane ruthenium benzylidene complex $RuX_2(PR_3)_2(=CHPh)$, where R = Ph or Cy and X = Cl, Br, and the corresponding imidazolin-2-ylidenes, through ligand exchange.

At the same time, Grubbs et al. [27b] and Nolan et al. [27c] reported synthesis of complex **13** and shortly thereafter, Grubbs [27d,e], of its 4,5-dihydroimidazolin-2-ylidene analogues, **14** and **15**, that use a saturated nucleophilic *N*-heterocylic ligand of the Arduengo type [14].



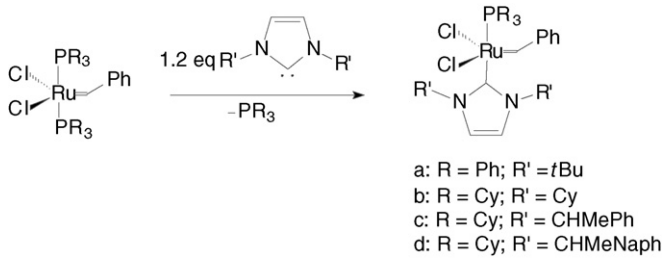
Synthesis of these Herrmann–Grubbs NHC–ruthenium complexes was effected readily in toluene or tetrahydrofuran, at room temperature, leading in high yield (80–90%) to products with either one or two imidazolin-2-ylidene ligands, depending on the molar ratio employed between the starting bisphosphane complex $RuCl_2(PR_3)_2(=CHPh)$ and the *N*,*N*-disubstituted imidazolin-2-ylidene (in practice a molar ratio of 1:1.2 or 1:2.2 is used) [27a] (Scheme 2).

The NHC–Ru class was subsequently enlarged with the group of complexes of the Hoveyda type (e.g. **17**–**19**) [27f–i] containing the isopropoxybenzylidene ligand, that proved a fine addition because of their improved catalytic activity, robustness and, in some cases (e.g. for the Hoveyda–Grubbs catalyst, **17**), recyclability not-supported by previous structures.



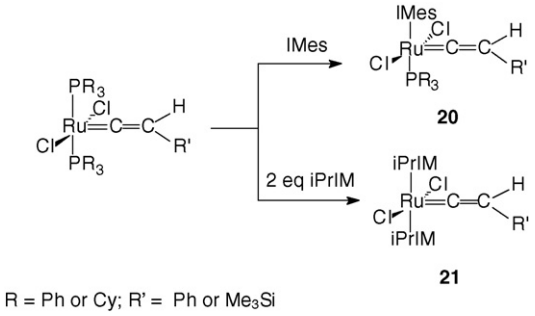
2.4. NHC–Ru vinylidene and indenylidene complexes

Endowed with enhanced activity in radical reactions and alkyne C–C coupling, NHC–Ru–vinylidene (**20** and **21**) and –indenylidene (**22** and **23**) complexes have been prepared by Verpoort starting from bisphosphane congeners and using



16

Scheme 2. Synthesis of NHC–Ru complexes **16** [27a].

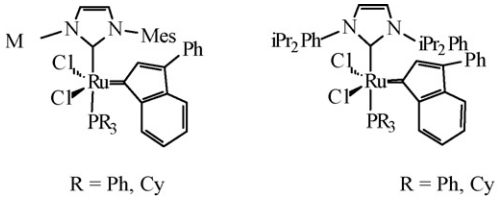


20 **21**

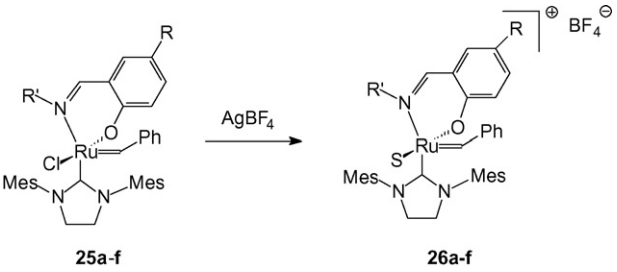
Scheme 3. Synthesis of NHC–Ru vinylidene complexes **20** and **21** [28a,b].

appropriate molar ratios of the corresponding imidazolium salt [28a,b] (Scheme 3).

In spite of their considerable steric congestion, complexes **22** and **23** unexpectedly displayed very high reactivity in certain ATRP reactions [28b].



22 **23**



Scheme 5. Synthesis of cationic NHC Schiff-base Ru complexes **26a–f** [28d].

Advancements in the rational design of active catalysts from the class of Ru–vinylidene complexes has recently been reviewed by Bruneau and Dixneuf [28c].

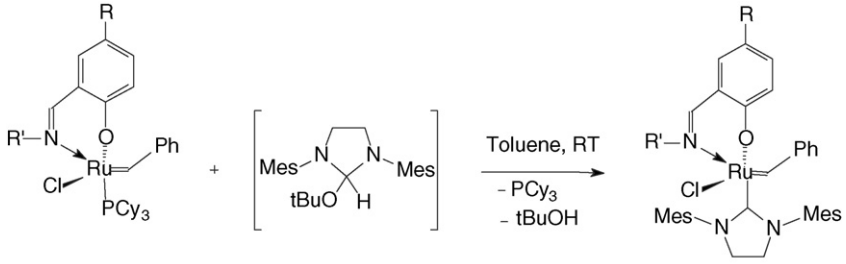
2.5. NHC–Ru Schiff-base complexes

A valuable array of NHC–ruthenium complexes, combining 1,3-dimesityl-4,5-dihydroimidazolin-2-ylidene and Schiff-base ligands, and in which the catalytic properties could be controlled through electronic and steric requirements in the metal coordination sphere, has been synthesized also by Verpoort et al. [28d,e], *via* phosphane replacement with 4,5-dihydroimidazolin-2-ylidene (Scheme 4). The protected imidazoline intermediate, was prepared *in situ*, from imidazolium tetrafluoroborate and *t*-BuOK, and directly reacted with complex **24a–f** to produce precatalysts **25a–f**.

Treatment of neutral ruthenium complexes with $AgBF_4$ afforded the corresponding cationic ruthenium benzylidene complexes, **26a–f**, employed with good results in ATRP of vinyl monomers (Scheme 5) [28d].

2.6. Immobilized NHC–Ru complexes

Immobilization of well-defined homogeneous complexes [29] brings several conveniences to organic synthesis such as: simpler procedures and easy separation of products, recyclability of expensive catalysts, possibility to operate in continuous flow, manageable polymer properties [30]. As typical σ-donors

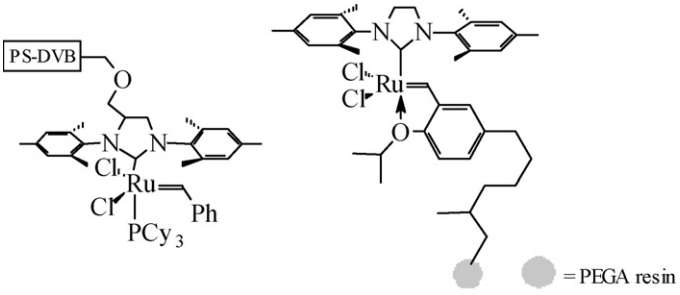


24a-f **25a-f**

a: R = H, R' = Me
b: R = NO_2, R' = Me
c: R = H, R' = 2,6-Me-4-Br C_6H_2
d: R = NO_2, R' = 2,6-Me-4-BrC_6H_2
e: R = H, R' = 2,6-iPrC_6H_3
f: R = NO_2, R' = 2,6-iPr C_6H_3

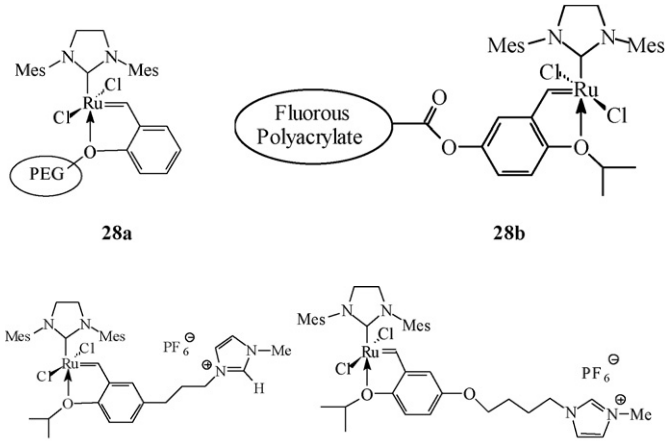
Scheme 4. Synthesis of NHC Schiff-base Ru complex **25a-f** [28d,e].

and non-dissociating ligands, *N*-heterocyclic carbenes may serve as suitable linkers for immobilizing metal complexes onto solid supports [31], a beneficial feature successfully exploited by Blechert et al. [32a] to prepare a permanently immobilized and highly active NHC–ruthenium benzylidene complex **27** and quite recently by Grubbs et al. [32b,c] to obtain water-soluble NHC–ruthenium catalysts supported by poly(ethylene glycol), catalytically active in aqueous media.



27 **28**

Immobilization can be achieved otherwise than through the NHC ligand. In this direction Blechert et al. obtained both homogeneous [33a] and heterogeneous (**28**) [33b] polymer bound catalysts of the Hoveyda–Grubbs type. The phosphine-free ruthenium alkylidene **28**, bound to a hydrophilic resin, is operative in water and methanol and its potential utility in competitive metathesis and cycloisomerization (non-metathesis) has been demonstrated. In a further variant of the above approach, Lamaty et al. [33c] prepared an interesting polymer bound NHC–ruthenium carbene catalyst (**28a**) through exchange of the benzylidene moiety from the Grubbs catalyst **14** with another PEG-supported benzylidene ligand. The poly(fluoroalkyl acrylate)-supported ruthenium carbene complex **28b**, a recyclable catalyst for olefin metathesis in minimally fluorous solvent systems ($PhCF_3/CH_2Cl_2$) should also be mentioned. This offers the practical advantage of easy separation by fluorous extraction from the reaction mixture and repeated use in sequential different metathesis reactions [33d].



28a **28b**

28c **28d**

[BMI][PF_6]/toluene (1:3 v/v) [Bmim][PF_6]/CH_2Cl_2 (1:9 v/v)

A recently developed technique for non-covalent immobilization of NHC–Ru homogeneous metathesis catalysts to soluble supports focuses on room temperature ionic liquids (RTILs). Thus, NHC–Ru complexes (e.g. **14**) [33e], and particularly the IL-tagged counterparts of the Hoveyda–Grubbs catalyst **17**, such as **28c** [33f,g] and **28d** [33h], have been used in various metathesis reactions conducted in ILs or IL/organic solvent mixtures (biphasic catalysis) with excellent results. They have a convenient recyclability combined with high reactivity and extremely low residual ruthenium levels detected in the products. Alternative entries into immobilization created heterogeneous catalysts by anchoring the NHC–Ru complexes in the pore channels of mesoporous silica [33i], or silica gel [33j] and fluorous silica gel [33k], resulted in relatively high catalytic activity in olefin metathesis reactions and reusability of five or more times.

Immobilized NHC–Ru complexes may also open future perspectives in the attractive area of non-metathetical transformations, if we take into account the diverse catalytic behaviour of IMes–Ru catalysts in the hydrogenation, isomerization or tandem and cascade reactions.

3. Non-metathetical transformations promoted by NHC–Ru complexes

Many ruthenium complexes excel in catalyzing mechanistically different processes due to the propensity of this metal for easily changing its oxidation state [34]. In their turn, *N*-heterocyclic carbenes, through their specific coordination chemistry, stabilize and at the same time activate metal centers in fundamental catalytic steps of synthetic organic chemistry, such as C–H activation, and C–C, C–H, C–O, C–N bond formation. The new generation of organometallics, i.e. the NHC–Ru precatalysts, made possible outstanding accomplishments in metathesis chemistry yet are still newcomers in the field of non-metathesis transformations. However, in the present state of the art when *N*-heterocyclic carbenes are recognized beyond dispute as versatile ligands, the extension of some catalyst classes (e.g. CpRu complexes), long employed in non-metathetical reactions [3d,34] to the NHC–Ru complexes comes as no surprise.

3.1. Hydrogenation

The hydrogenation is of major practical importance for both industrial scale processes and critical steps in organic and natural compound synthesis. Traditionally performed with homogeneous catalysts based on Rh (Wilkinson catalyst) [35], Ir (Crabtree catalyst [36], Vaska catalyst [37]) and more recently on Ru and Os [38] [e.g. $RuClH(PPh_3)_3$, $RuH(CO)(PPh_3)_3$, $RuClH(CO)(PCy_3)_2$ (**1a**), $OsClH(CO)(P\textit{i}\text{-}Pr_3)_2$], hydrogenation has again met with success when some of the above NHC catalysts have been used as mimics of phosphane ligands. The resulting catalytic species are more thermally stable and generally more active when compared to the analogous tertiary phosphane systems.

Early work on hydrogenation of unsaturated hydrocarbons in the presence of transition metal catalysts showed

that five-coordinate hydrido(carbonyl) complexes of the type $HM(CO)Cl(L)_2$ (M = Ru, Os; L = P*i*-Pr_3, P*i*-Bu_2Me) are very efficient in the hydrogenation of linear alkenes and alkynes [39]. Subsequently, Yi and Lee [40] disclosed that by replacement of P*i*-Pr_3 in $HRu(CO)Cl(Pi\text{-}Pr_3)_2$ with the sterically demanding PCy_3, the complex $HRu(CO)Cl(PCy_3)_2$ (**1a**) displayed high activity in the hydrogenation of terminal and cyclic alkenes. More recently, Nolan and Yi [23a] found that replacement of one PCy_3 with IMes in $HRu(CO)Cl(PCy_3)_2$ resulted in the NHC–hydridoruthenium complex $HRu(CO)Cl(IMes)(PCy_3)$ (**1**) which is less active for alkene hydrogenation at room temperature than the starting complex **1a** whereas at elevated temperatures comparable activities have been observed (e.g. turnover rate of 24,000 mol product/mol catalyst h and 21,500 mol product/mol catalyst h for the IMes and PCy_3 complexes, respectively, in the hydrogenation of 1-hexene to hexane, at 100 °C). The lower activity of the IMes complex *versus* PCy_3 at ambient temperature has been related to a stronger ligand coordination and steric congestion around the ruthenium center; at higher temperatures, however, ligand dissociation is facilitated.

A new hydrido(carbonyl)–Ru complex, $HRu(CO)Cl(PCy_3)(H_2IPr)$ (**4**), showing good activity in the hydrogenation and isomerization of 1-octene, was reported by Mol and coworker [23b]. Synthesis of this complex was effected from $HRu(CO)Cl(PCy_3)_2$ through the ligand exchange approach. Though species **4** was also detected by NMR in the mixture of degradation products of the Mol catalyst ($RuCl_2(PCy_3)(H_2IPr)$(=CHPh) with primary alcohols (under basic conditions), its isolation did not succeed. Experimental data indicated that at ambient temperature the hydrogenation of 1-octene to octane prevails, whereas at 100 °C, in spite of the high conversion, isomerization into 2-octene is a significant, if not major accompanying process. These results were accounted for considering the increased steric bulkiness of the NHC ligand (over the PCy_3 ligand) which impedes hydrogenation of the internal olefins resulted from isomerization of the initial terminal olefins.

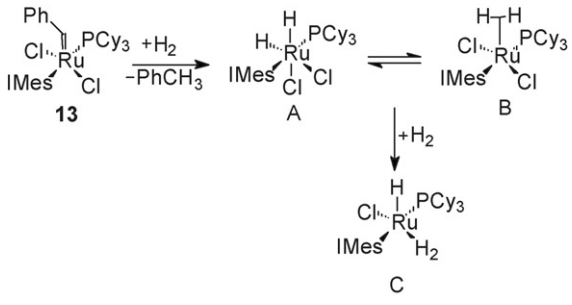
Further, exploring syntheses of new hydridoruthenium complexes of this class, Fogg and Nolan [24a] conveniently prepared $HRuCl(CO)(IMes)(PPh_3)$ (**2**) and $HRuCl(CO)(H_2IMes)(PPh_3)$ (**3**) from $HRuCl(CO)(PPh_3)_3$. In the hydrogenation of non-activated internal alkenes, these complexes exhibited more than the triple activity of the earlier complex $HRu(CO)Cl(PCy_3)_2$ and an order of magnitude greater than that of $HRu(CO)Cl(IMes)(PCy_3)$ (**1**). Moreover, these PPh_3 containing complexes displayed a broader spectrum of catalytic properties that include isomerization of terminal alkenes and polymerization of strained cycloalkenes.

Given the dissociative mechanism established for the homogeneous hydrogenation of alkenes with hydrido-carbonyl complexes [40], essential for generating the coordinatively unsaturated Ru active species able to coordinate the alkene, the poor performance of $HRu(CO)Cl(IMes)(PCy_3)$ (**1**), when compared to $HRu(CO)Cl(PCy_3)_2$, was rationalized by a decrease in the lability of the PCy_3 *trans* to the IMes, while the high activity of the parent PPh_3 complexes originates from the superior lability of the PPh_3 ligand *trans* to NHC. This mechanism found further support when addition of $HBF_4{\cdot}OEt_2$ as a cocatalyst led to a more efficient hydrogenation catalytic system (two- to five-fold increase in activity for hydrogenation of 1-hexene, allylbenzene and cyclooctene, at ambient temperature and normal hydrogen pressure). Results show that the rate enhancement induced by HBF_4 very likely implies selective entrapment of the PCy_3 ligand to give $HPCy_3{}^+BF_4{}^-$ and formation of a 14-electron species HRu(CO)Cl(IMes) that is the actual active species in the catalytic hydrogenation.

In the trend of vivid interest for single-component tandem metathesis–hydrogenation reactions [41,42], Mol and coworker [24b] investigated the efficacy of $PhRuCl(CO)(PCy_3)_2$ and $PhRuCl(CO)(PCy_3)(H_2IMes)$ (**5**) in the hydrogenation of 1-octene, in comparison to $HRuCl(CO)(PCy_3)_2$. On probing various reaction conditions it was observed that the latter had an appreciable hydrogenation activity at room temperature, while the former two complexes were considerably "activated" only at 100 °C. With these Ph-containing catalysts complete conversion into octane is attained at higher catalyst loadings whereas at lower loadings neither of the above three catalysts is selective and a significant proportion of isomerization products is obtained. It should be pointed out that the NHC complex **5** gave rise to lower contents of the direct hydrogenation product (octane), with isomerization clearly competing with hydrogenation. In the absence of solvent the Ph-containing catalysts allowed turnover frequencies of more than 100,000 h^{-1} (at 100 °C and 1 bar H_2), of practical importance for technical applications.

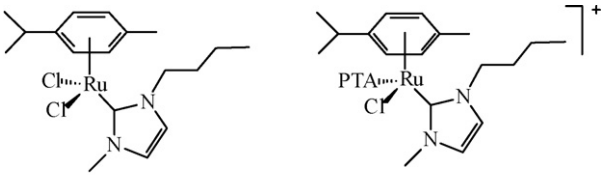
Analogously to the mechanism advanced by Fogg et al. [42b] for hydrogenolysis of the first generation Grubbs catalyst, the putative species B and C (Scheme 6) arising from the second generation Grubbs catalyst (**13** or **14**) in the presence of hydrogen, might explain the hydrogenation of unsaturated substrates induced by these catalysts. Interference of coordinatively unsaturated Ru hydride species corroborates results of Nolan and Yi [23a] in the hydrogenation promoted by complex **1**, in conjunction with HBF_4.

Catalysis in water and aqueous–organic biphasic systems by organometallic complexes soluble in these media attracts more and more attention and serves already as the basis for industrial processes [43]. Notwithstanding the strong basicity of the *N*-heterocyclic carbene ligands, some metal complexes are sta-



Scheme 6. Proposed pathway for generation of the coordinatively unsaturated NHC–Ru hydride species from second generation Grubbs catalysts [42b].

ble enough in water [44] to perform catalysis. Creating new water soluble NHC–Ru complexes is therefore a useful approach for solving environmentally sensitive catalysis problems. Along these lines, Csabai and Joo [45] synthesized complexes **29** and **30** (PTA = 1,3,5-triaza-7-phosphaadamantane). These complexes, and some derivatives *in situ* formed thereof, catalyze the homogeneous or biphasic hydrogenation of selected olefins, aldehydes and ketones, in aqueous solutions, under mild conditions, as well as the redox isomerization of allyl alcohol to propenal. The substantially higher activity and selectivity observed for complex **30** is attributable to the increased basicity (*versus* chloride) of the bulky triaza-phosphoadamantane ligand, able to better labilise *p*-cymene thus creating the active, coordinatively unsaturated Ru-species.



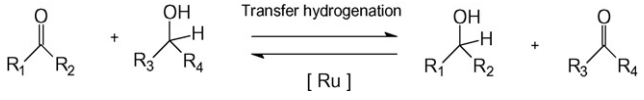
29 **30**

In addition to hydrogenation of conventional substrates, catalyst **29** can readily hydrogenate unsaturated lipid constituents in model biomembranes, with turnover numbers (e.g. 1.2) that may recommend it for biological applications such as hydrogenation of aqueous cell suspensions where the amount of substrate is very small [45].

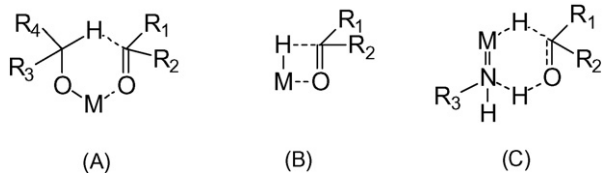
3.2. Transfer hydrogenation

Transfer hydrogenation is an attractive alternative to conventional catalytic hydrogenation, especially for the reduction of ketones (Scheme 7) [46,47]. When compared to hydride reagents and hydrogen, it offers simple and safe operation and low costs, important particularly in large scale preparations. Also, with increasing demand for "green" methods, transfer hydrogenation performed in water is now of great interest. The process involves hydrogen transfer from a donor, in most cases an organic molecule or water, to an unsaturated compound. In addition to the more traditional Pd, Rh, Ir catalysts [48], ruthenium complexes (e.g. the Noyori and Hashiguchi [49] and Grubbs' et al. [42a] catalysts, or even some recyclable ionic liquid- or polymer-supported complexes [50]) emerged as active precatalysts in this chemical transformation. Simplified catalyst systems for asymmetric transfer hydrogenation, based on Ru bearing chiral inexpensive ligands, is another issue of real challenge [51].

The reaction has been proposed to proceed through different pathways: (i) direct hydrogen transfer between the donor and acceptor molecule, in the presence of main group



Scheme 7. Transfer hydrogenation catalyzed by ruthenium [46,47].



(A) (B) (C)

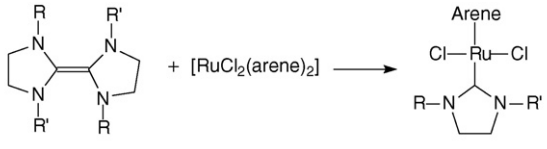
Scheme 8. Mechanisms allegedly implied in the transfer hydrogenation [52].

metal alkoxides including early transition metal alkoxides (Meerwein–Ponndorf–Verley reduction) (Scheme 8A) or (ii) a metal hydride intermediate derived from late transition metal catalysts (Scheme 8B). A different mechanism which involves concerted transfer of both H^+ and H^- (Scheme 8C) was also suggested for reactions catalyzed by late transition metal catalysts such as ruthenium or iridium complexes [52].

Although ruthenium complexes generally requiring elevated temperatures and prolonged reaction time (e.g. $RuCl_2(PPh_3)_3$) have proven to be excellent catalysts for hydrogen transfer reactions to ketones, there are until now only relatively few examples of NHC–Ru-based catalysts for this transformation [53].

An array of new $RuCl_2$(NHC)(arene) complexes, **31a–e** (arene = *p*-cymene or hexamethylbenzene), prepared by Cetinkaya et al. from electron-rich olefins and $[RuCl_2(arene)]_2$ dimers (Scheme 9) has been applied in the transfer hydrogenation of aromatic ketones to obtain the corresponding alcohols in good to excellent yields (78–95%) [54a]. Introduction of electron-withdrawing substituents (F, Cl, Br) in the *meta* position of the aryl ring of the ketone, resulted in highest activities (92–95%), while electron-donating substituents lead to somewhat diminished conversions of the ketones [54a]. This series of new NHC–Ru catalysts for transfer hydrogenation was lately further supplemented by the same research team [54b].

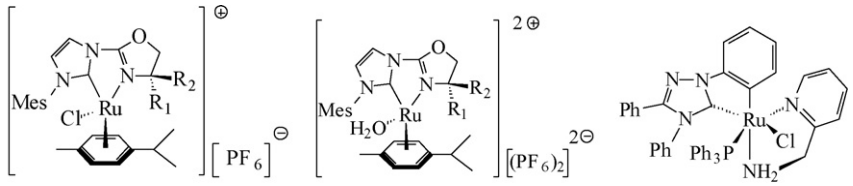
The first ruthenium complex bearing an oxazolinyl-carbene ligand, the arene–ruthenium half-sandwich **32a**, has very recently been created by coupling an *N*-heterocyclic carbene ring with a chiral oxazoline unit in a straightforward method for developing chiral catalysts based on NHC as stereodirecting units. When tested in the transfer hydrogenation of aromatic and aliphatic ketones to the corresponding secondary alcohols, from *i*PrOH/KOH, complex **32a** showed moderate activity [54c]. The formation of a dicationic species **32b** as the active catalyst, upon addition of excess $AgPF_6$, seems to be crucial since the use of complex **32a**, without further adding silver salt, gave very poor yields.



31a-e

a: R = $C_2H_5OC_2H_4$, R' = $C_2H_4C_6H_5$; **b**: R = $CH_2C_6H_2(CH_3)_3$, R' = $C_2H_4C_6H_5$
c: R = $CH_2C_6H_2(CH_3)_3$, R' = $CH_2C_{12}H_9$; **d**: R = $C_2H_5OC_2H_4$, R' = $CH_2C_{12}H_9$
e: R = $CH_3OC_2H_4$, R' = $CH_2C_{12}H_9$. Arene = *p*-cymene, hexamethylbenzene

Scheme 9. Synthesis of arene NHC–Ru complexes [54a].



32a **32b** **32c**

By combining the commercially available NHC free carbene l,3,4-triphenyl-4,5-dihydro-1*H*-l,2,4-triazol-5-ylidene with 2-(aminomethyl)pyridine (ampy) in a ruthenium complex, Baratta and Herrmann [55a] created an active and thermally stable hydrogen transfer catalyst (**32c**) with a broad application profile in the reduction of carbonyl compounds. In the synthesis of **32c** one PPh_3 is displaced by the carbene with concomitant orthometallation of a phenyl group and dihydrogen extrusion yielding a five-membered chelate ring. The orthometallated complex **32c** acts as an effective catalytic precursor in the transfer hydrogenation of a set of alkylaryl, cyclic and dialkyl ketones to give alcohols, with reactions proceeding in the presence of a base (NaOH) and with 2-propanol as hydrogen source. Almost quantitative conversions are attained within minutes, with TOF values (50,000–120,000 h^{-1}) that are among the highest reported. An asset of this new NHC–Ru precursor is that it allows a clean synthesis of unsaturated alcohols from the corresponding ketones, without intervention of hydrogenation or isomerization of the carbon-carbon double bond; thus, 5-hexen-2-one is selectively reduced only at the carbonyl group. The mechanistic pathway is suggested [55a] to involve formation of a monohydride derivative corresponding to **32c**, *via* a isopropoxide/β-elimination route in the presence of NaOH/*i*-PrOH, as reported for other ruthenium chloride catalytic precursors [55b–d]. No activity for **32c** has been observed in the absence of base. Combination of the RuH/NH_2 pattern [52] with the orthometallated heterocyclic carbene, conferring stability to the ruthenium center and avoiding facile oxidation or degradation, seems to account for the high performance of **32c**.

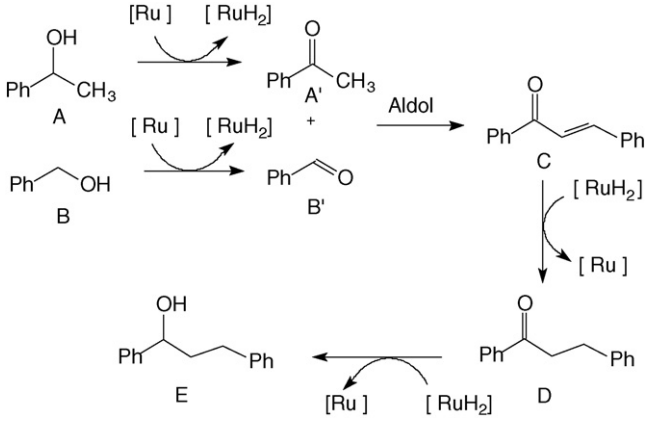
By contrast, in monodentate complexes, the *N*-heterocyclic carbene might be expected to facilitate displacement, by isopropanol, of the chlorine on Ru atom to yield $Ru(i\text{-}PrO)_2L_3$ complexes, from which the active dihydride species (RuH_2L_3) may arise by β-elimination. The dihydride complex $Ru(H_2IMes)(PPh_3)_2CO(H)_2$ performs well in both direct hydrogenation and transfer hydrogenation of ketones and imines, in the absence of base [53a].

3.3. Dehydrogenative oxidation

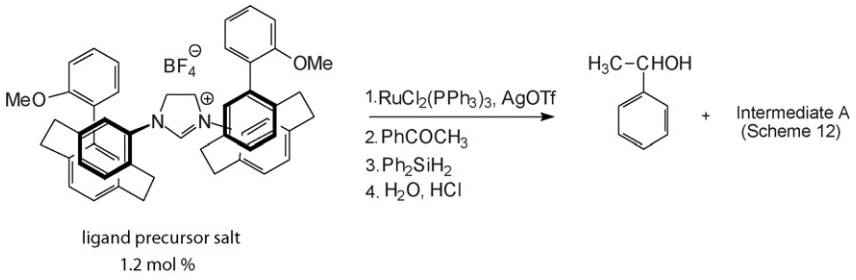
A reaction of synthetic value, the oxidation of alcohols induced by ruthenium complexes implies catalyzed dehydrogenation to ketones, with concomitant loss of hydrogen gas. The subsequent condensation of ketones with proper reaction partners may lead to *in situ* formation of the corresponding alkene or imine [56]. Actually, in the process the alcohols serve as efficient substrates for C–C and C–N bond formation [57]. In some cases, these products (alkene or imine) may undergo further hydrogenation, by return of the hydrogen "borrowed" from the dihydride catalyst, to provide the final product, an alkane or amine. In an typical experiment, Williams [58] carried our oxidation of phenylmethylcarbinol to acetophenone with either the Grubbs catalysts or the ruthenium precursor of the Noyori's transfer hydrogenation catalyst, $[(p\text{-cymene})RuCl_2]_2/PPh_3$, in high conversions (100% and 90%, respectively). It was assumed that the active species, responsible for hydrogen transfer, is a ruthenium hydride generated from the Ru precursor [59]. In the case of the second generation Grubbs catalyst, lithium hydroxide, cesium carbonate, and 1,8-diazabicyclo[5.4.0]undec-7-ene were found to be the most suitable bases. If primary and secondary alcohols are used together, e.g. benzyl alcohol and phenylmethylcarbinol, the initially formed oxidation products, i.e. benzaldehyde and acetophenone, undergo subsequent aldol condensation to form 1,3-diphenylprop-1-en-3-one; by further hydrogenation with "borrowed hydrogen" from the catalyst, the latter will give the final product, 1,3-diphenylpropan-1-ol (Scheme 10).

3.4. Hydrosilylation

The hydrosilylation of ketones using transition metal (Rh, Ru, Cu) precatalysts furnished convenient access to enantioenriched alcohols [60]. Chiral bis-paracyclophane NHC–ruthenium, *in situ* formed from $RuCl_2(PPh_3)_3$, AgOTf (1 mol%) and a ligand precursor salt (Ru/ligand = 1:2–1:3), has recently been revealed by Ma and Andrus to catalyze the asymmetric hydrosilylation of aromatic ketones with diphenylsilane [61]. The chiral *N*-heterocyclic carbene ligand (Scheme 11) provided for very selective reactions (mainly 93–97% ee) proceeding at room tem-



Scheme 10. Dehydrogenative oxidation of primary and secondary alcohols with NHC–Ru complexes [58].

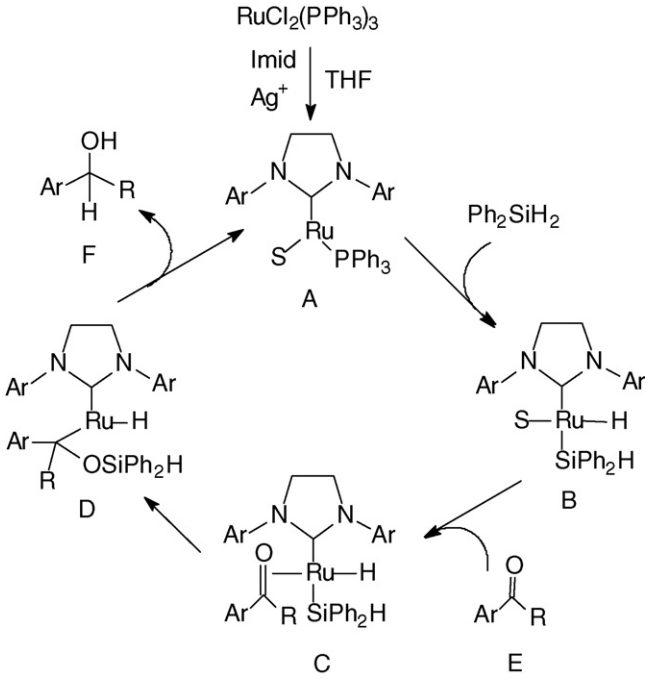


Scheme 11. Hydrosilylation of aryl ketones with NHC–Ru catalytic systems [61].

perature in high yields (80–98%, as a function of the ketone structure). Through subsequent removal of the silyl ether group (acidic hydrolysis) the corresponding aromatic alcohols could be obtained.

In agreement with the previous observations on Rh-catalyzed hydrosilylations, the authors conclude that in the case of ruthenium the reaction mechanism (Scheme 12) implies initial formation of the 14e mono-NHC complex A (favoured by excess ligand), followed by silane addition to give the metal hydride B. Silane addition was considered as the turnover-limiting step. Dissociation of ligated solvent (*S*) in B creates a vacancy allowing ketone coordination yielding intermediate C. In C a rapid transfer of silane to the carbonyl oxygen occurs resulting in the silyl ether D, from which the product F and the complex A are generated through reductive elimination. According to this mechanism, the influence of the chiral paracyclophanes is expressed by reversible formation of the distorted square planar η^2-carbonyl complex C.

The hydrosilylation of alkynes has also been described. With $Cl_2(PCy_3)_2Ru{=}CHPh$ inter- and intramolecular hydrosilylation proceeds stereoselectively, affording mainly *trans*-and *cis*-products, respectively [62].



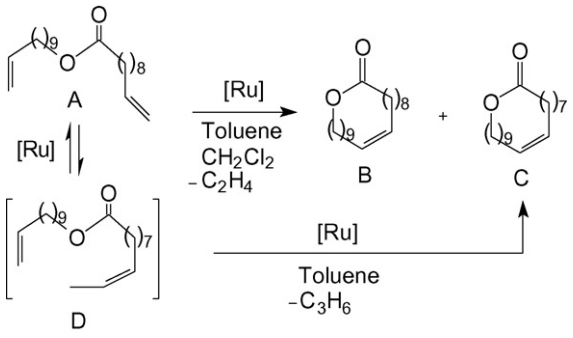
Scheme 12. Mechanism of alkyl–aryl ketone hydrosilylation [61].

3.5. Isomerization and cycloisomerization

The hydrogenation and metathesis of alkenes promoted by Ru-complexes are often accompanied by double bond migration and *cis-trans* isomerization [63]. In the hydrogenation both types of isomerization may not be observable, unless the isomer which arises is less reactive or isomerization results in other structural changes, e.g. racemization. In metathesis it is possible that isomerization occurs either, *via* double bond migration, as a concurrent side reaction, or as a result of a true metathetical pathway (i.e. self-metathesis affording a thermodynamic equilibrium of *cis–trans* isomers). An appropriate choice of reaction parameters can direct the process towards extensive isomerization. Under conditions of low catalyst loadings or hydrogen supply, isomerization may become the leading transformation.

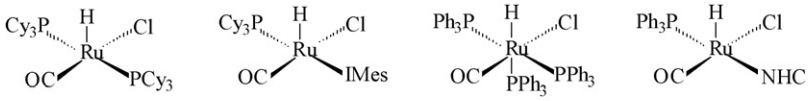
If highly selective catalysts are used, isomerization can be controlled as an independent process. Although self-standing isomerization has been effected on numerous substrates and with a variety of Ru catalysts, only a limited number of NHC–Ru applications have so far been reported. An interesting example comes from the research group of Mol who, using $Ph(CO)RuCl(H_2IMes)(PCy_3)$ (**5**) in the isomerization of 1-octene at higher temperatures (80–120 °C), obtained comparable activity (conversion 90–100%) in comparison with the parent bisphosphane complex, $H(CO)RuCl(PCy_3)_2$ (**1a**), and superior to $Ph(CO)RuCl(PCy_3)_2$ (yet at lower temperatures its performance was slightly outclassed by the hydridocarbonyl analog) [24b]. This behaviour suggests that the H_2IMes ligand in **5** counterbalances the loss in activity associated with the presence of the phenyl, instead of the hydride moiety responsible for the catalytic activity; hydride must be generated *in situ* when starting with Ph-containing complexes. Intriguingly, it was observed that at elevated temperatures and prolonged reaction times, and only in the case of the *N*-heterocyclic carbene complex, the isomerization of 1-octene to 2-octene goes along with metathesis to tridecene and dodecene.

As previously mentioned (Section 3.1), the isomerization of 1-octene to 2-octene with $HRu(CO)Cl(PCy_3)(H_2IPr)$ (**4**) occurs at 100–120 °C, with high conversions (95–96%) and TONs (95,100-96,400) [23b]. Isomerization *versus* hydrogenation of terminal olefins, with NHC–Ru complexes, was communicated in a recent paper by Fogg and Nolan [24a]. As expected, replacement of PCy_3 for PPh_3 yielding complexes **2** and **3**, increased the catalyst's propensity towards isomerization (allylbenzene to propenylbenzene). Of the two catalysts, the saturated NHC (**3**)



Scheme 13. Competing isomerization and metathesis in NHC–Ru catalysis [67].

is significantly more active in isomerization than in the hydrogenation, even at 140 psi H_2.

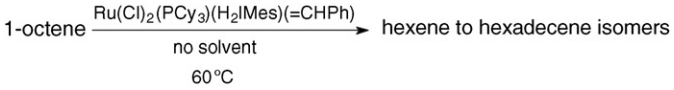


2, NHC = IMes; **3**, NHC = H_2IMes

Using $RuClH(CO)(PPh_3)_3$ (**33**), van Otterlo et al. [64] achieved allyl/propenyl isomerization on substrates containing electron-rich vinylic olefins (e.g. 1-allyl-2-allyloxybenzenes), on which Grubbs' catalysts are known to be problematic [65]. However, the *in situ* C- and O-allyl isomerization products could be cyclized (by RCM) to access benzo-fused heterocycles only by changing the catalyst to the second generation Grubbs' H_2IMes. Recently, Wagener et al. reported the isomerization of aliphatic allyl compounds occurring during metathesis condensations using Grubbs' second-generation IrklMes catalyst. This non-metathetical route particularly intervenes when heteroatoms are present at the allylic position, with isomerization becoming even the major pathway if allylic ethers contain other functional groups [66]. Isomerization can be diminished by addition of coordinating solvents such as THF or by addition of halocarbon hydride thus maximizing metathesis condensation yields.

Isomerization of alkenes in the presence of NHC–Ru metathesis precatalysts, was early signaled by Fürstner and Nolan as a minor process accompanying the RCM of oxygen-containing dienes. In toluene, RCM mainly leads to large-sized unsaturated lactones (B), with 10–12% of the isomerization product (e.g. the 20-membered ring lactone C) that cannot be suppressed by lowering the temperature [67] (Scheme 13).

However, isomerization was observed as a major process, but only in aromatic solvents, in the tandem RCM-double bond hydrogenation with Ru–H_2IMes (see Section 3.13) [42a]. In aliphatic chlorinated solvents, isomerization becomes, at most, a very minor process, if any [42,67]. In the absence of solvent (neat olefin) or in THF and toluene solutions, at 50–60 °C, Ru–H_2IMes was found to promote extensive isomerization of both internal and terminal olefins to yield a mixture of linear olefins of consecutive carbon numbers, produced concurrently with metathesis (Scheme 14) [68a,b]. Since both internal and external olefins are isomerized, the possibility that the methylidene complex is solely responsible for the olefin isomerization can be excluded.

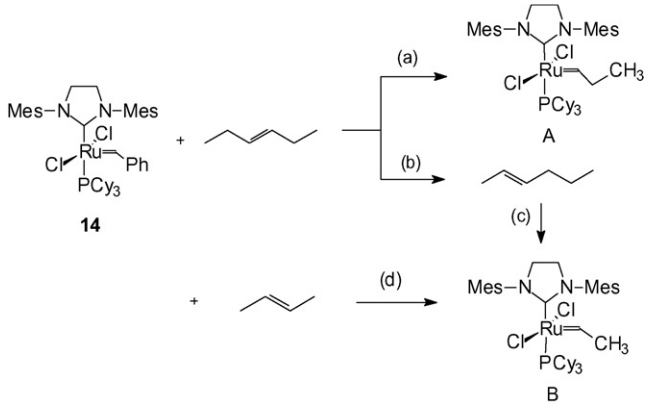


Scheme 14. Isomerization of 1-octene in the presence of catalyst **14** [68a,b].

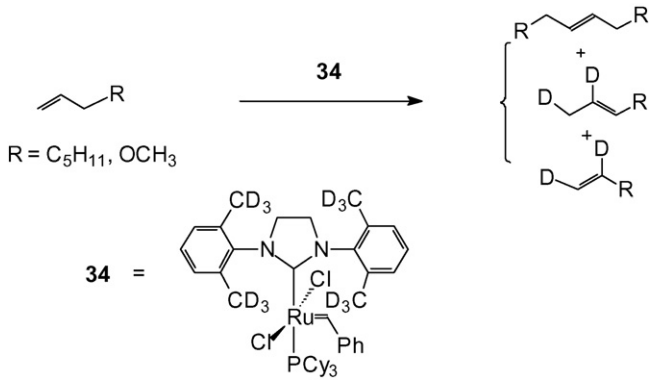
The occurrence of isomerization as a process parallel to metathesis during the synthesis of ruthenium metathesis catalysts bearing linear alkyl carbene groups has been demonstrated by Wagener by means of the NMR spectroscopic technique [68c]. Thus, reaction of complex **14** with *trans*-3-hexene results in the formation of the expected propylidene complex (A), in addition to the ethylidene complex (B) resulting from isomerization of 3-hexene to 2-hexene followed by metathesis (Scheme 15).

Noteworthy, the ethylidene complex was the major product indicating a greater stability of this complex compared to the higher alkyl homologue. Most importantly, the reaction of **14** with 2-butene results in a single product (B); in this case, it was assumed that the rate of isomerization of the double bond to an external position is much slower than the rate of metathesis of 2-butene with catalyst **14**. That the Ru-hydride might intervene as a transient species in olefin isomerization has been demonstrated beyond doubt by Wagener et al. [68d] in α-olefin metathesis/isomerization induced by deuterated Grubbs catalyst **34** (Scheme 16).

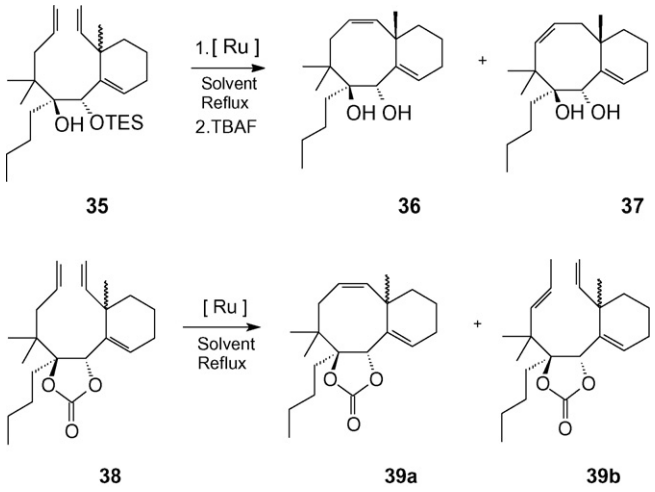
Thus, incorporation of deuterium at various positions of the olefin product backbone after interaction with complex **34** indicated the formation of a ruthenium deuteride and the involvement of the *N*-heterocyclic carbene ligand in the isomerization reaction [68e]. This particular feature of NHC presumably originates from the C–H activation process which might be responsible for the occurrence of a ruthenium hydride species into this process [68f,g]. Isomerization, appearing as an important



Scheme 15. Olefin isomerization during synthesis of alkenyl Ru complexes [68c].



Scheme 16. Metathesis *vs*. isomerization of α-olefin with deuterated NHC–Ru **34** [68d].



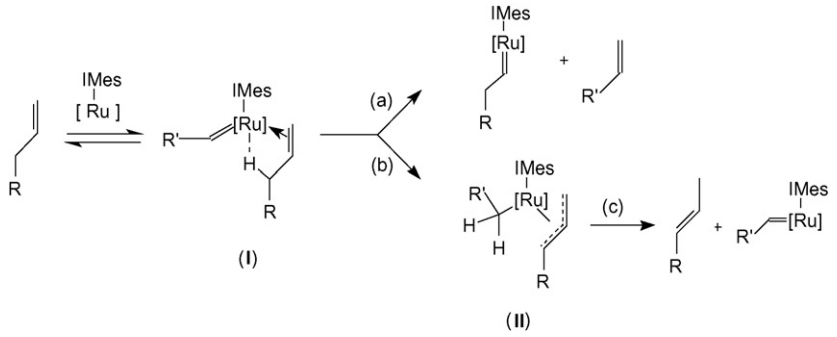
Scheme 17. Competing isomerization/RCM with complex **14** [69].

drawback of the RuIMes catalyst in RCM at elevated temperatures and extended reaction times, was also observed by Nolan and Prunet [69] who suspected that this particular reactivity is attributable to the RuIMes catalyst **14** itself. Yet, such demanding reaction conditions resulting in isomerization as a major competitor to RCM, are needed only in the case of slow-reacting substrates, in order to overcome the high energy of activation for the RCM reaction. Whereas, compound **35** gave small amounts of the two cyclized products, **36** and **37** (6% and 7%, respectively), with the first generation Grubbs catalyst [69b], significant isomerization of one of the double bonds in diene **38**, *versus* RCM, was observed with the NHC–Ru complex, but the choice of the solvent proved crucially important in the last case (isomerization product augments from 30% in benzene to 100% in dimethoxy ethane and 10% in dichloroethane) (Scheme 17). A judicious selection of the substrate, catalyst and solvent/additive can strongly influence and completely eliminate isomerization.

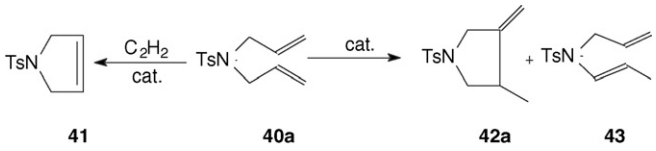
Dienes leading to 'easy' RCM, in which coordination to the second double bond occurs rapidly enough to avoid the slower isomerization process, afford cyclic products irrespective of the solvent. Competition between isomerization and RCM with pre-catalyst **14** is demonstrated by the two possible pathways for the intermediate complex (**I**) coordinating the less crowded double bond of the diene (Scheme 18) [22a]. Path (b) leads to a π-allyl complex (**II**), responsible for the double bond migration, through deprotonation. The allylic proton is trapped by the carbene carbon, with an increased basicity induced by the IMes ligand, also receiving help from the agostic interaction between the 16-electron transition metal complex and the allylic hydrogen. The more coordinating solvents will prevent the second double bond from coordinating to the ruthenium center, which is necessary to achieve the RCM process, so isomerization will prevail.

Concurrent isomerization processes in certain olefin metathesis reactions can result from the decomposition products of the ruthenium catalysts observed especially at long reaction times. In the case of the carbene species $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CH_2$ isomerization has been rationalized by involvement of a dinuclear ruthenium complex, with a bridging carbide and a hydride ligand, resulting from thermal decomposition of the olefin metathesis catalyst [70].

A three-component catalytic system, generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$, 1,3-bismesitylimidazolinium chloride (as precursor of *N*-heterocyclic carbene ligand), and cesium carbonate was found by Dixneuf et al. [71] to exhibit dual activity for promoting either cycloisomerization and isomerization of dienes (e.g. **40a**) to **42a** and **43**, respectively, or, in the presence of acetylene, exclusive metathesis to **41** (Scheme 19). However, bulkier alkynes such as (fert-butyl)acetylene favoured formation of **42a** and **43** (ratio 4:1), whereas trimethylsilylacetylene non-selectively led to **42a**, **41**, and **43** (in the ratio 3:12:5). The activity and selectivity of the catalytic system also depend on the nature of the precursor



Scheme 18. Mechanistic pathways for isomerization *vs*. metathesis with IMesRu [22a].



Scheme 19. Cycloisomerization *vs.* RCM and isomerization of dienes [71].

salt (1,3-bismesitylimidazolinium, 1,3-bismesitylimidazolium, or 1,3-bis(2,6-diisopropyl-phenyl)imidazolinium), with 1,3-bismesitylimidazolinium chloride making the most efficient catalyst for cycloisomerization.

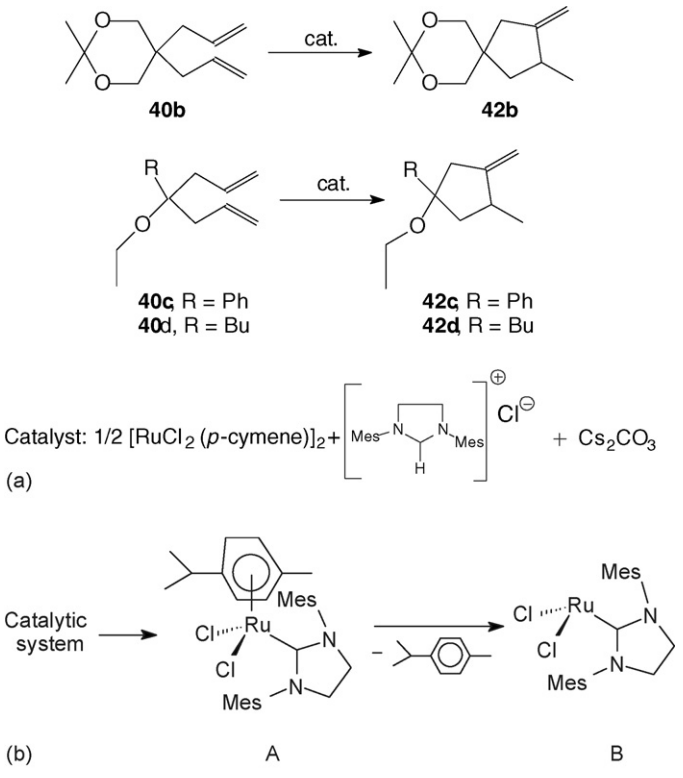
With the catalytic system $[RuCl_2(p\text{-cymene})]_2$, 1,3-bismesitylimidazolinium chloride, Cs_2CO_3, under N_2, dienes **40b–d** were completely transformed in the corresponding methylene–cyclopentanes **42b–d** (Scheme 20a).

The dual behaviour of the above catalytic system was rationalized by formation of a highly coordinatively unsaturated species B through decoordination of *p*-cymene from A, stabilized by the bulkiness of the carbene ligand (Scheme 20b).

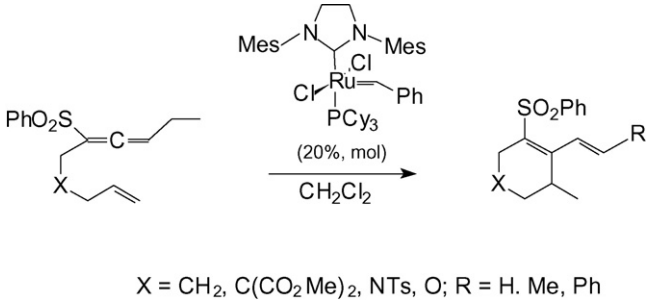
This highly unsaturated species is common to both cycloisomerization and metathesis but the fact that the former reaction is inhibited by acetylene hints at a different fate for B in the two processes. In cycloisomerization species B further coordinates the diene, by oxidative addition favoured by the electron-donating NHC ancillary ligand, and through successive eliminations gives the final product **42**. Support for this assertion comes from the observation that slower and less-selective cycloisomerization occurs when using a catalytic system based on 1,3-bismesitylimidazolium chloride, which affords a less-electron-rich carbene ligand than the 1,3-bisimidazolinium chloride. Alternatively, the metathesis route also involving B takes place through the ubiquitous coordination and ruthenium–carbene mechanism. Cycloisomerization, competing with RCM in tandem catalysis, provides relevant circumstances for illustrating advantages offered by a completely different promoter, the polymer bound complex **28**. Along these lines, Connon and Blechert [33b] prepared immobilized the NHC–Ru complex **28** and applied it in reactions of the model diene diallyl tosylamide, **40a**, while monitoring the two competing processes. The utility for olefin metathesis in protic solvents of the phosphine-free ruthenium alkylidene bound to a hydrophilic solid support (catalyst **28**) has been eloquently demonstrated.

Through an ingenious combination of vinyloxytrimethylsilane and the Grubbs' NHC catalyst, Nishida et al. managed the isomerization of functionalized terminal olefins to internal olefins which, under the action of the latter catalyst, undergo ring-closing metathesis to useful scaffolds (e.g. indole derivatives) [72a–d]. Under similar conditions but at a higher molar ratio of the Grubbs' catalyst, direct cycloisomerization of appropriate diene structures to the corresponding 2,3-dihydroindole derivatives could be performed. In addition to catalyst loading, the solvent and temperature also influence the shift from isomerization/RCM to cycloisomerization: the latter is favoured in refluxing xylene whereas quantitative isomerization occurs in refluxing methylene chloride [72d]. The synthesized indoles belong to a class of alkaloids reputed for their pharmacological activity; a relevant example is fistulosin whose first total synthesis was accomplished taking advantage of the above cycloisomerization protocol [72d]. Under the influence of the Grubbs catalyst **14** cycloisomerization of allenenes, having an alkyl appendage at the allenic terminus, succeeds towards the construction of the cyclohexene, tetrahydropyran, and tetrahydropyridine ring-systems [72e]; best yields (92–98%) have been reported for substituents on the allenene moiety R = H, Me, Ph (Scheme 21).

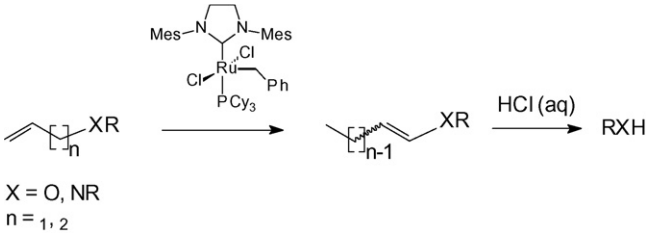
Ruthenium–carbenoid catalysts such as Grubbs' complex **14** promote isomerization of β,γ-unsaturated ethers and amines to the corresponding vinyl ethers and enamines (Scheme 22) [73]; this reaction can be useful in the deprotection of allyl and homoallyl ethers or amines.



Scheme 20. (a) Cycloisomerization of dienes with NHC–Ru systems [71]. (b) Generation of coordinatively unsaturated Ru-species from arene NHC–Ru complexes [71].



Scheme 21. Cycloisomerization of allenenes mediated by Grubbs' catalyst **14** [72e].



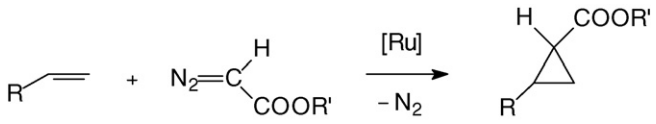
Scheme 22. Isomerization of allylic ethers and amines with NHC–Ru catalysts [73].

3.6. Allylation and deallylation

Allylic substitution induced by metal complexes, and specifically by Pd- and Ru-complexes, is an important catalytic reaction for C–C and C–O bond formation in organic chemistry. Of the most efficient catalysts employed in this process, $[Cp^*(MeCN)_3Ru][PF_6]$ bearing labile ligands was recently shown by Bruneau and coworkers [74] to be convenient for synthesizing aryl allyl ethers starting from allylic halides and phenols. Moreover, the same authors proved that another catalyst precursor, Cp^*(bipy)Ru, displays substantial catalytic activity enabling neutral soft carbon pronucleophiles to be directly involved in this process [75]. An important issue in this reaction is to control the regioselectivity when unsymmetrical allylic derivatives are used as substrates and this can be achieved by an appropriate selection of the catalyst.

Recently, Bruneau et al. [76] used a set of NHC ligands, in association with Cp^*Ru-complexes, for the regioselective allylic alkylation of soft nucleophiles and etherification of phenols obtaining in all cases a very good activity and regioselectivity. The benzimidazolium halides employed in this study as ligand precursors in the Cp^*(NHC)Ru-catalyzed substitution of allylic carbonates and halides with carbon nucleophiles and phenols exhibited enhanced catalytic activity and regioselectivity when compared with Cp^*(bipy)Ru and $[Cp^*(MeCN)_3Ru][PF_6]$ complexes (Scheme 23). This procedure seems to be a suitable strategy for the protection of phenolic groups.

Allyl deprotection of functional groups is another subject of interest for synthetic practitioners. Ruthenium catalyzed *N*-allyl deprotection, a selective protocol applicable to deallylation of allylic ethers, amines, amides, lactams, imides, pyrazolidones, hydantoins, oxazolidinones, etc., is emerging as a further application of the Grubbs alkylidenes in organic synthesis thereby extending the utility of allyl as protective groups [77]. The methodology capitalizes on the Ru catalyst's compatibility with various functionalities to perform sequential isomerization to *N*-enamides, *via* ruthenium hydride species, followed by deprotection through oxidative (RuO_4) cleavage of the *N*-substituent [77a,b]. Such Ru-hydride dinuclear species usually arise from the thermal decomposition of NHC–Ru carbene and as by-products during the preparation of the second generation Grubbs catalyst, and are responsible for concurrent isomerization reactions [70].



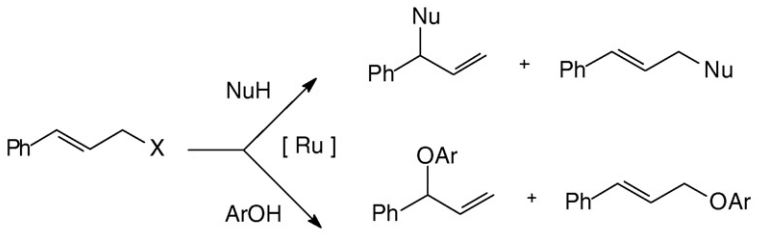
Scheme 24. Carbenoid cyclopropanation of alkenes [3c].

3.7. Cyclopropanation

Cyclopropanation of alkenes using diazo compounds as a carbene source in the presence of transition metal catalysts (carbenoid cyclopropanation) is one of the most productive methods for synthesis of cyclopropane derivatives. These carbocyclic ring systems are important synthetic building blocks, widely encountered in a diversity of natural compounds and biologically active products. For this reason, highly effective and stereocontrolled synthesis of cyclopropanes has been since long a topic of concern for organic chemists. Excellent reviews on various aspects of intra- and intermolecular cyclopropanation reactions have recently been published [3c,78,79].

Beside the traditional cyclopropanation precatalysts based on copper, rhodium and palladium, largely applied in the carbenoid cyclopropanation of alkenes, ruthenium complexes gained recognition as practical catalysts for this reaction (Scheme 24) during the last decade [3c].

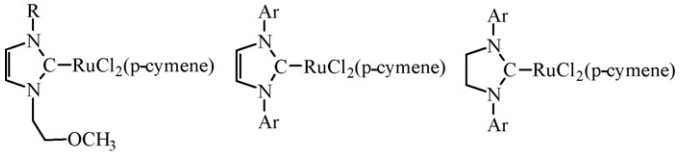
By virtue of the flexible coordination ability of ruthenium and the large number of oxidation states it can assume, with easy redox transitions between them in catalytic cycles, a diversity of mononuclear and dinuclear ruthenium complexes could be designed and intended for a variety of targeted applications [80]. Stimulated by valuable results from the early, pioneering work of Hubert and Noels [81] on cyclopropanation of alkenes with the dinuclear Ru(II)/Ru(III) complex $Ru_2(OAc_4)Cl$, Demonceau et al. [82] continued to create Ru/ligands combinations leading to improved catalytic systems for cyclopropanation. They particu-



X = Cl, O_2COEt; NuH = $H_2C(CO_2Me)_2$, $H_2C(COPh)_2$, $H_2C(COMe)_2$; Ar = Ph, 4-Cl-C_6H_4

Scheme 23. Allylation of soft nucleophiles and phenols [76].

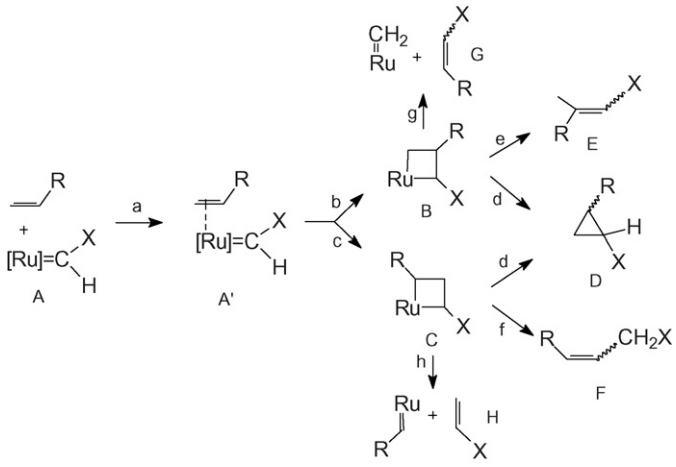
larly focused on introducing new Ru complexes bearing arene ligands [83] or bulky, multidentate carborane moieties [84]. Several other research groups reported numerous Ru(II) complexes with multidentate nitrogen ligands (e.g. porphyrin) [85,86] or N,O ligands (e.g. pybox, salen) [87,88]. More recently, with the advent of *N*-heterocyclic carbenes having tremendous potential for tailoring quite robust and highly active transition metal catalysts (or precatalysts) [15], to apply the novel NHC–Ru complexes in the carbenoid cyclopropanation reaction became a challenging task.



44 **45** **46**

In this context, Dixneuf et al. [89] prepared an NHC–Ru (*p*-cymene) complex containing the imidazolin-2-ylidene ligand tethered with a hemilabile ether group (**44**), that turned out to be a successful precatalyst in cyclopropanation of various alkenes. Very recently, Delaude et al. synthesized a broad array of imidazolium and imidazolinium salts [90] and carboxylates [91] and tested their ability as NHC ligand precursors in the ruthenium catalyzed cyclopropanation of terminal alkenes and cyclic olefins. Thus, l,3-diarylimidazol(in)ium chlorides (aryl = phenyl, 1-naphthyl, 4-biphenyl, 3,5-dimethylphenyl, 2-tolyl, 2,6-dimethylphenyl, 2,4,6-trimethylphenyl and 2,6-diisopropylphenyl) react with the $[RuCl_2(p\text{-cymene})]_2$ dimer and potassium *tert*-butoxide or sodium hydride to generate, *in situ*, the corresponding NHC–ruthenium complexes, used as such in the cyclopropanation of styrene and cyclooctene with ethyl diazoacetate [90,91]. With these NHC–Ru complexes, cyclopropanation (in chlorobenzene, at 60 °C) of the styrene double bond proceeded in high yield (80–85%) but with some competition from homologation (10–15%) and metathesis (2–3%) reactions. The activity of imidazol(in)ium-2-carboxylates in the ruthenium-promoted cyclopropanation of styrene with ethyl diazoacetate at room temperature [91] paralleled that obtained with 2-imidazol(in)ium salts. The method used to generate the NHC ligands, *in situ*, had no significant impact on the yield of cyclopropanation nor on its stereoselectivity [91].

The homologation side-products result from a formal carbene insertion in either of the vinyl C–H bonds of styrene, a process for which the ruthenacycobutane intermediate (Scheme 24) has been proposed [92,82b,c]. The metathesis side-products obtained in cyclopropanation with these catalysts provide further support for the intervention of a transient ruthenacarbene species [93]. Replacing an unsaturated imidazolium salt with its saturated analogue did not significantly affect the cyclopropanation yield, nor the diastereoselectivity of this reaction, except for a decrease in the *cis*/*trans* ratio. Under the same conditions, yields in the cyclopropanation of cyclooctene (a more reluctant cycloalkene) were far from being quantitative; formation of ethyl fumarate and maleate prevailed (up to 60%, based on ethyl



Scheme 25. Coordination mechanism for carbenoid cyclopropanation [3c].

diazoacetate), being accompanied by some homologation (3%) and metathesis (ROMP, 3–7% polyoctenamer) side reactions. Catalytic screenings showed that the nature of the *N*,*N*′-diaryl substituents on the carbene ligand had very little influence on the cyclopropanation outcome.

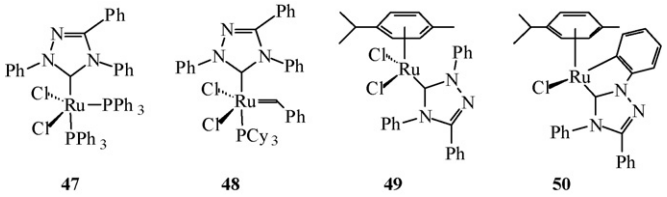
It is now beyond dispute that in carbenoid cyclopropanation with transition metal complexes the main active species is a metal carbene [79c]. Two principal pathways have been postulated for carbene transfer from the metal carbene complex to an alkene: a carbenoid, and a coordination mechanism [3c,81]. The above results obtained in cyclopropanations catalyzed by the systems **45** and **46** formed *in situ* [90,91], are consistent with the latter mechanism [81]. We may consider that intermediate A′ (Scheme 25), arising by coordination of the olefin at the ruthenacarbene A, further leads to the ruthenacyclobutanes B and C, *via* [2 + 2] cycloaddition. Intermediates B and C may embark upon several reaction channels responsible for the products: (i) first, route d will give the cyclopropanation products by reductive elimination of the metal fragment; (ii) cleavage of one Ru–C bond, followed by metal elimination and H shift (routes e and f) will yield the homologation products; (iii) and then, routes g and h will provide the metathesis products by [2 + 2] cycloreversion.

3.8. Enol-ester synthesis

Enol-esters are useful intermediates for carbon–carbon and carbon–heteroatom bond formation. They have been used for the selective generation of enolates, acylation of carbonyl compounds and *O*- and *N*-acylation under mild conditions. This class of compounds can be produced through the regiospecific and stereoselective nucleophilic addition of carboxylic acids to terminal alkynes, known also as a vinylation reaction. Low valent ruthenium complexes catalyze the addition of carboxylic acids to acetylenes giving alkenyl-esters (enol-esters), *via* transient transition metal vinylidenes. The addition may proceed through a Markovnikov and *anti*-Markovnikov mode (Scheme 26). The selectivity of the addition to alkynes is dependent on the acidity of the carboxylic acid added. With decreasing pK_a, a change in

regioselectivity from Markovnikov to *anti*-Markovnikov addition is observed.

The reaction, an eloquent case of non-metathetical transformation, was shown by Verpoort et al. to readily occur in the presence of a broad array of NHC–Ru complexes in spite of their known catalytic activity in metathesis [28e,94,95]. As *N*-heterocyclic carbene some of these complexes contain SIMes (e.g. **25a–f**), others 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene (e.g. **47–50**). With octadiyne as a substrate, the addition of both formic and acetic acids, induced by Ru-complexes with *O*,*N*-bidentate Schiff-base **25a–f**, led selectively to (*E*)-alk-1-en-1-yl esters (71–83%, for all the catalytic systems) [95a,b]. Besides the *anti*-Markovnikov (*E*)-alk-1-en-1-yl ester, small amounts of the Markovnikov product, (*Z*)-alk-1-en-1-yl ester and disubstituted enol-ester were also formed. The total yield depended on the type of catalyst precursor and carboxylic acid. Complexes **25a–f** are, to the best of our knowledge, among the most active ruthenium catalytic systems introduced so far for the selective synthesis of (*E*)-alk-1-enyl esters starting from acetylenes and saturated carboxylic acids. These precatalysts represent an illustrative example for a concerted activating effect of the bidentate Schiff-base and the *N*-heterocyclic carbene coordinated by ruthenium.



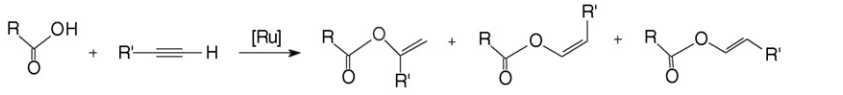
47 **48** **49** **50**

In the class of triazol-5-ylidene containing complexes, the addition of carboxylic acids to terminal alkynes occurs very fast and quantitatively with precatalyst **47** [95d]. With **48**, the nucleophilic addition of acetic acid on terminal alkynes proceeds smoothly and regioselectively towards Markovnikov addition; the enol-ester synthesis can be controlled through the acidity of the carboxylic acid. With increasing acidity, a higher conversion of the alkyne is obtained while the vinylation/dimerization ratio augments (see Scheme 27) [95e]. Vinylation catalyzed by **49** and **50** (in refluxing toluene) affords almost quantitative yields in enol-esters after reaction times of 4–24 h, markedly depending on the alkyne [95c].

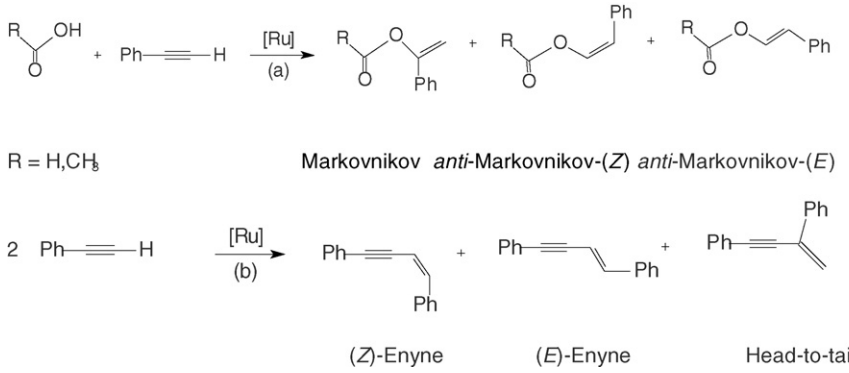
3.9. Alkyne C–C coupling

Herrmann and Baratta [96] disclosed a very productive C–C coupling reaction of alkynes to give dimeric enyne products in the presence of arene NHC–Ru complexes, $Cp^*RuCl(NHC)$, where NHC = 1,3-dicyclohexyl- or 1,3-dimesitylimidazol-2-ylidene. Quantitative conversions have been readily attained within 5–10 min starting from phenylacetylene, tolylacetylene or trimethylsilylacetylene (TOF = 10,320 and TON = 860). In the case of phenylacetylene and tolylacetylene, of the two stereoisomeric internal olefin products formed, the *trans*-coupling product prevailed. However, trimethylsilylacetylene gave predominantly α-olefin (92%). It was inferred that the above Ru complexes associate 2e ligands, L = CO, PCy_3, NC_5H_5 or $CH(CO_2Et)$, to form the tetracoordinate adducts $Cp^*RuCl(L)(NHC)$ which, *via* π-addition of alkynes, effectively promote consecutive C–C coupling reactions.

More recently, Verpoort et al. [94,95a] found that when a specific acetylene, phenylacetylene, is used as the starting material in conjunction with carboxylic acids and in the presence of NHC–Ru complexes containing Schiff bases as additional ligands (**25a–f**), alkyne dimerization (pathway b) becomes an important competitive route to enol-ester synthesis (pathway a) (Scheme 27). Remarkably, with the very active NHC–Ru complexes **25a–f** dimerization of phenylacetylene turns out to be the major reaction pathway, leading predominantly to (*E*)-*enyne*



Scheme 26. Enol-ester synthesis from carboxylic acids and acetylenes [94].



Scheme 27. Competitive enol-ester formation and phenylacetylene dimerization in the presence of NHC–Ru complexes [94].

with selectivities in the range of 73–81% and yields in excess of 90%.

When changing the catalyst to RuCl*x* (*p*-cymene) (triazol-5-ylidene) (**49** or **50**) the dimerization of terminal alkynes gives preferentially tail-to-tail coupling reactions [95c]. Systematic investigation on the direct coupling between two 1-alkynes (pathway b) promoted by **48** indicated a decreasing reactivity order from 1-octyne > 1,7-octadiyne > phenylacetylene > 3,3-dimethyl-1-butyne; the nature of the terminal alkyne had a strong influence on the reaction regioselectivity [95d].

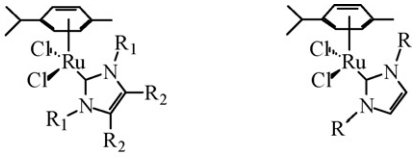
3.10. Kharasch addition (ATRA)

Kharasch addition or atom transfer radical addition (ATRA) is a synthetically useful process for functionalizing organic compounds by means of halogen derivatives. The first active ruthenium-based catalyst investigated for ATRA was $RuCl_2(PPh_3)_3$. The fact that Ru benzylidene complexes, $(PR_3)_2Cl_2Ru{=}CHPh$ (R = phenyl, cyclopentyl, cyclohexyl), catalyze the chemo- and regioselective Kharasch addition of chloroform or carbon tetrachloride across alkenes has been known from earlier work on metathesis of alkenes under the influence of the above catalysts [97a,b]. The subject has been reviewed by Demonceau and Noels presenting all the Ru-based catalysts applied in ATRA [97c,d]. The striking outcome obtained with the Grubbs' metathesis catalyst not only extended the use of Ru complexes to this well-known, fundamental transformation of alkenes but unveiled the mild conditions under which the process might occur with the new type of catalyst (low temperature, short reaction time), in contrast to the traditional $Cl_2Ru(PPh_3)_3$ requiring more severe reaction conditions (higher temperatures and longer reaction times). Moreover, with readily metathesisable alkene substrates, Kharasch addition concurrent with metathesis has been observed; this unexpected observation raises questions regarding the reaction mechanism of the two processes.

An array of NHC–Ru complexes containing benzylidene (**25a**–**f**), vinylidene (**20**), indenylidene (**22**) moieties, envisaged by Verpoort et al. [28,98], proved active in ATRA of vinyl substrates. Complexes **25**, in which the H_2IMes and Schiff-base ancillary ligands are associated, were employed in Kharasch addition. A comparative study with the parent phosphane Ru-complexes indicated that methyl methacrylate and styrene readily underwent addition of carbon tetrachloride, at 65 °C, in the presence of **25** giving chlorinated products in high yield (85–98%). On performing Kharasch addition with the more sluggish methyl acrylate, butyl acrylate and acrylonitrile, reaction proceeded slower and a differentiation between the catalytic systems was observed. Two aspects concerning the interdependence between the Schiff-base and the NHC ligand are relevant. First, the steric influence played by the bulky *O*,*N*-bidentate Schiff-base on the activity in ATRA is more significant in the case of the NHC-containing systems than in that of the related catalysts without NHC. Secondly, the electronic properties of the Schiff-base ligands decisively influence the activity of the NHC–Ru complexes. Along these lines, it has been concluded that complexes exhibiting the optimal catalytic performance with all olefinic substrates have a maximized interplay of the steric and electronic effects.

NHC–Ru–vinylidene complexes (**20**) and –indenylidene complexes (**22**) proved to be versatile catalysts for the Kharasch addition of polyhalogenated alkanes to olefins, such as methylmethacrylate, styrene and 1-octene, proceeding along with other non-metathetical reactions (e.g. vinylation). While catalysts **20** have enhanced activity in the ATRA of the above olefins, when compared to their phosphane congeners, reaction with **22** slowed down [28b], as expected, because of the higher steric congestion created by the large NHC and indenylidene co-ligands. Surprisingly, cationic complexes corresponding to the neutral **20** perform poorer than the latter, hinting that the counteranion suppresses the beneficial activation of the NHC ligand [98b]; this behaviour is opposed to that observed in metathesis where cationic complexes generally increase activity [28].

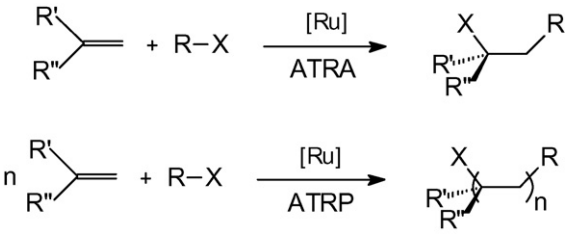
In recent work, Demonceau et al. [99,100] revealed interesting data on the Kharasch reaction of a set of common vinylic monomers (styrene, methyl methacrylate, *n*-butyl acrylate) promoted by several NHC–$RuCl_2$(*p*-cymene) complexes (**51**).



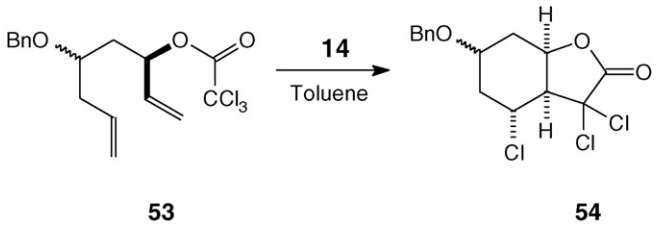
51 **52**

R_1 = Mes, Cy; R_2 = H, Cl, Me

On varying the substituent on the NHC ligand, and also the molar ratio between the olefin and the halogen derivative, it was observed that both the Kharasch addition and the atom transfer radical polymerization (ATRP) surpassed olefin metathesis. Attempts were made to rationalize the dual activity of these complexes in radical reactions and olefin metathesis [100]. Lately, a detailed study on ATRA of styrene with carbon tetrachloride (in toluene at 85 °C) using arene NHC–Ru complexes **52**, generated *in situ* from *N*,*N*-substituted imidazolium salts (R = 4-biphenyl, 2-tolyl, 2,6-dimethylphenyl, 2,4,6-trimethylphenyl and 2,6-diisopropylphenyl) and the ruthenium dimer $[Cl_2Ru(p\text{-cymene})]_2$, unveiled interesting new data on the activity and selectivity in Kharasch addition [90]. First, the reaction selectivity and yield were severely influenced by the nature of the substituents, in contrast to the cyclopropanation of styrene with ethyl diazoacetate under the action of the same catalytic systems. The highest conversion of styrene (94%) and selectivity (71%) in addition product, 1,3,3,3-tetrachloroethylbenzene, were obtained for the mesityl substituted NHC ligand, whereas the 4-biphenyl, the poorest substituent, afforded only a 50% styrene conversion and 3% addition product. Secondly, two other competitive processes, namely metathesis of styrene to *cis*- and *trans*-stilbene and multiple insertion of styrene into the activated C–Cl bond, were found to occur along with the Kharasch addition. The last concurrent process often accompanies ATRA and can be suppressed under certain experimental conditions. Evidence for the occurrence of multiple insertion of olefin into the



Scheme 28. ATRA *vs*. ATRP reactions of vinyl monomers [90].



Scheme 29. ATRC reaction of unsaturated haloesters with complex **14** [104a].

activated C–Cl bond during ATRA is an important observation lending support to the concept that ATRA corresponds to an early stage of ATRP (Scheme 28).

3.11. ATRC of haloalkenes

Transition metal-catalyzed atom transfer radical cyclization (ATRC) is one of the most important carbon–carbon bond-forming reactions and a powerful method for synthesis of a large variety of heterocyclic compounds including macrolide and alkaloid skeletons. A high reaction temperature is a prerequisite in ATRC, especially in reactions involving activation of less reactive carbon–halogen bonds, which from a synthetic point-of-view is a general disadvantage of this procedure. Combination of appropriate substrates with vigorous catalytic systems is recommended.

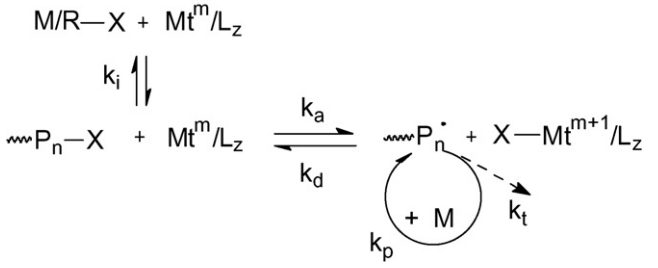
ATRC has lately enjoyed considerable attention, mainly after the reports of Snapper et al. [97a] and Demonceau et al. [97b,c] that the ruthenium metathesis catalyst $RuCl_2(PCy_3)_2(=CHPh)$ acts as a promoter for intra- and intermolecular Kharasch addition, and of Demonceau et al. [101] and Grubbs et al. [102] that this same metathesis catalyst is also effective in ATRP of vinyl monomers. Subsequently, Quayle et al. [103] exploited the latter Ru catalyst in the synthesis of γ-lactones and γ-lactams by intramolecular Kharasch addition of haloalkenes.

Quite recently, Schmidt and Pohler [104a] and again Quayle et al. [104b] managed ATRC of unsaturated haloesters in a tandem ring closing metathesis–atom transfer radical cyclization process using the IMes Grubbs' catalyst **14**. Contrary to previous conclusions that the second generation Grubbs' catalyst was less reactive in ATRA and ATRC than the first generation catalyst, it was found that **14** mediated both steps, metathesis and ATRC, in good preparative yields and rates of conversion [104a]. Conversion of both diastereomeric precursors **53** to the bicyclic product **54** proceeds equally efficiently in sequential RCM and ATRC, indicating that orientation of the additional benzyloxy group does not influence the efficiency of either cyclization step. Complete conversion of the intermediate RCM product was observed (Scheme 29). Since catalyst **14** effects ATRC in a sequence of reactions, further comments on ATRC can be found in Section 3.14.

3.12. ATRP of vinyl monomers

The synthesis of well-defined polymers with controlled topology and functionality is nowadays a fully developed methodology for producing advanced materials with complex molecular architectures and well-defined properties [105]. Along with copper catalysts, ruthenium complexes showed an excellent application profile in obtaining such polymers using the ATRP protocol [105a–d] (Scheme 30).

A detailed examination by Demonceau et al. of controlled ATRP of vinyl monomers with $RuCl_2$(*p*-cymene)(PCy_3) and $RuCl_2(=CHPh)(PCy_3)_2$ proved the two Ru complexes to be active in initiating this radical reaction [106]. Replacing PCy_3 for one or two *N*-heterocyclic carbene ligands, L and L′, in the Herrmann–Grubbs air-stable benzylidene complexes $RuCl_2(=CHPh)(L)(L')$ enabled new insight into the ATRP domain and involvement of ruthenium alkylidenes in radical reactions [107]. The ligands L (PCy_3 and/or *N*-heterocyclic carbene) turned out to play a particularly important role in determining the rate of the polymerizations. Experiments with methyl methacrylate or styrene using the new complexes demonstrated a significant decrease in the catalytic activity with respect to the PCy_3 counterparts. Polymerization proceeded in a controlled manner as indicated by the first-order kinetics in MMA and the number-average molecular weight which increased linearly with monomer conversion. Notably, M_w/M_n were broader upon substitution of *N*-heterocyclic carbenes for one or both PCy_3. A similarly pronounced influence of the substituents of the *N*-heterocyclic carbene was observed. With butyl acrylate and vinyl acetate the polymerizations were not controlled and most probably took place through a redox-initiated free-radical process. Importantly, these results indicate that the catalysts decompose quickly under ATRP conditions, and polymerizations are mediated by both $[RuCl_2(=CHPh)(L)(L')]$ complexes and ruthenium species deprived of the benzylidene moiety, through a pathway in which both tricyclohexylphosphine and/or *N*-heterocyclic carbene ligands remain bound to the metal center [100,107].



Scheme 30. Dynamic equilibrium in ATRP of vinylic monomers (M = vinyl monomer; R-X = co-initiator; Mt = metal; L = ligand) [98c,105].

Aiming at developing novel catalytic systems for ATRP, Demonceau et al. [99a,108] embarked on an in-depth investigation of the activity of $RuCl_2$(*p*-cymene)(NHC) complexes (**51**) (preformed or generated *in situ*) in ATRP of methyl methacrylate (MMA) and styrene. The preformed complexes were prepared from the Ru dimer and NHC carbenes deriving from a set of imidazolium salts in the presence of a base, such as potassium *tert*-butoxide, cesium carbonate or aluminium isopropoxide. Polymerization of methyl methacrylate occurred readily (94% yield) with pseudo-first-order kinetics and good control of M_n. Polydispersities (M_w/M_n) were quite low (typically ca. 1.3) and decreased with monomer conversion. Polymerization of styrene also gave good yields (ca. 89%) and exhibited an acceptable control of M_n. When the NHC ligand had specific substituents (e.g. Mes or Cy in the 1 and 3 positions and Me in positions 4 and 5), a poor and uncontrolled reaction was manifest thus clearly illustrating the importance of fine-tuning the stereoelectronic parameters in the catalyst for every monomer. Despite the good overall results, the applicability of this class of preformed Ru precatalysts in ATRP reactions was hampered by the fact that the synthesis and isolation of the pure $RuCl_2$(*p*-cymene)(NHC) complexes were sometimes strenuous. To avoid these drawbacks, an alternate strategy was developed i.e. generating the active catalytic species *in situ* by mixing together $[RuCl_2(p\text{-cymene})]_2$, the imidazolium salt and a base. The protocol offered significant advantages since it requires only stable and readily available commercial reagents, thus leading to straightforward and economical polymerization processes. ATRP of MMA or styrene using the latter technique provided mostly polymerization profiles similar to those obtained with preformed complexes; however, with certain *in situ* generated catalytic systems the resulting M_n were lower and polydispersities (M_w/M_n) slightly higher. Experimental M_n were close to theoretical values, an observation indicative of an almost quantitative yield in the initiation step.

In elaborate research on the ATRP reactions of several vinyl monomers with catalyst precursors **24a–f** and **25a–f**, Verpoort et al. [109] recorded yields and polymer characteristics (number-average molecular weight, polydispersity index and initiator efficiency) that depend substantially on the nature of both the precatalyst and monomer. Only complexes **24c**,**d** and **25c**,**d** could conveniently promote polymerization of acrylates and methacrylates. By contrast, all precatalysts were able to convert styrene, though significant differences in performance were observed: with systems exhibiting the lowest activity (**24a**,**b** and **25a**) only 10% and 8% conversion of styrene was reached, respectively, whereas most active systems (**24d** and **25d**) efficiently converted styrene (88% and 75% yields, respectively). Also the PMMA obtained with the latter two precatalysts displayed the lowest polydispersity (1.22 and 1.18, respectively).

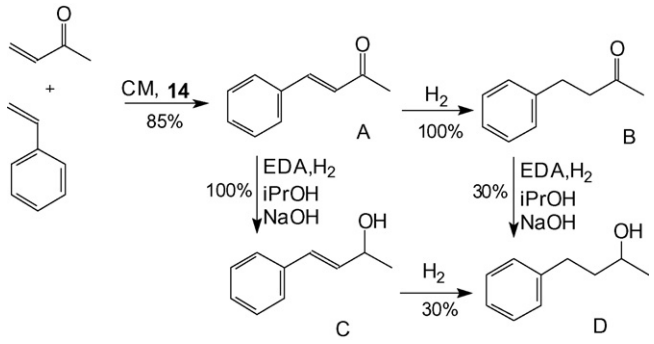
Intriguingly, the ATRP of the above set of vinyl monomers occurred in a different way in the presence of the cationic Schiff-base ruthenium complexes **26a–f** [109b]. The following remarks are relevant: (i) polymer yields varied widely as a function of the monomer and catalyst precursor; (ii) superior activity of the cationic complexes was systematically recorded when compared with the corresponding neutral complexes (**25a–f** or **24a–f**), regardless of the solvent; (iii) yields are considerably higher in a toluene–water mixture than in toluene alone, reaching nearly quantitative conversions for styrene (99% with **26d**); (iv) the polymer characteristics vary with the solvent, the polymerization being less controlled in toluene than in a water–toluene mixture.

When carrying out ATRP of MMA with the complex **47**, in the presence of a primary or secondary amine and in conjunction with a bromide initiator (ethyl 2-bromoisobutyrate), a controlled polymerization leading to narrow molecular weight distributions was observed [109d]. However, the molecular weight distribution is strikingly dependent on the nature of the amine, varying from 1.08 for primary amines to 1.43 for secondary amines. Optimal initiation efficacy was recorded with the combination **47**/ethyl 2-bromoisobutyrate/nBu_2NH (1:1:4) giving 93% yield of polymer with 1.24 polydispersity. Interaction of **47** with the amine gave a highly active catalytic species as inferred from monitoring the reaction by NMR spectroscopy. The syndiotactic microstructure of the PMMA once again supports a radical pathway for the polymerization.

3.13. Tandem, sequential and cascade reactions

Syntheses of complex carbon frameworks, in particular of natural compounds, imply a multitude of related or totally different reaction steps occurring successively or concomitantly. By offering new opportunities for simple and expeditious preparation of intricate targets, ruthenium complexes endowed with non-dissociating *N*-heterocyclic carbene ligands abruptly rose to the rank of valuable catalysts. In the quest for atom economy and environmentally friendly protocols, desirable in the currently diversity oriented synthetic repertoire, chemists found that combining metathetical with non-metathetical procedures, as tandem and cascade reactions mainly proceeding *via* mechanistically distinct pathways, leads to gratifying results. A substantial number of papers based on the tandem/cascade approach has lately been published thus broadening the synthetic utility of the NHC–Ru catalysts to a level unthinkable before [110]. Quite recently tandem and stepwise metathesis/non-metathesis processes, catalyzed by a broader range of ruthenium catalysts than just the NHC–Ru, have been also reviewed [111].

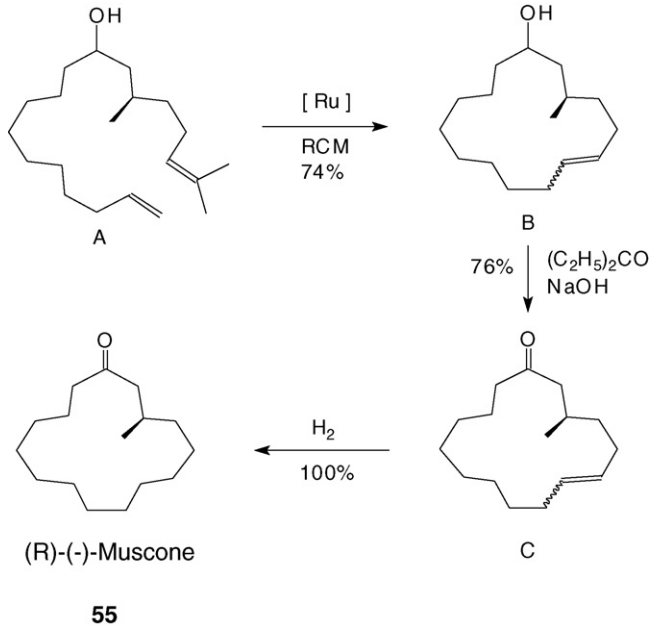
The field of NHC–Ru catalyzed tandem and cascade reactions is vast comprising mostly combinations of: (i) different types of metathesis reactions (CM, RCM, ROM, RCEYM, ROMP, etc.) [112]; (ii) metathetical/non-metathetical transformations (this chapter; see also: Morita–Baylis–Hillman reaction/RCM for synthesis of functionalized hetero- and carbocyclic alkenols [113], allylation/RCM on reaction products from a Ugi four-component coupling towards cyclized peptidomimetics with various appendages [114], and sequential or tandem metathesis/Diels–Alder [115]; (iii) various non-metathetical steps (e.g. tandem isomerization/Claisen rearrangement [116a], diastereo- and enantioselective cyclization [116b], etc.) Some representative examples covering mainly the largest category, tandem metathesis/non-metathesis reactions promoted by Ru–NHC, are discussed henceforth.



Scheme 31. Tandem CM/hydrogenation/hydrogen transfer using NHC–Ru catalysts [42a].

An early case in point is the metathesis reaction, followed by addition of a reducing agent (*p*-toluenehydrazide as hydrogen source), where Grubbs and Bielawski achieved hydrogenation of the ROMP product of a sterically hindered, trisubstituted cyclic alkene, 1,5-dimethyl-1,5-cyclooctadiene, through a short cut sequential process catalyzed by the prototypical catalyst **14**; the final product is an ethylene–propylene copolymer [117]. Further work from the same group concentrated on assisted tandem RCM- or CM-hydrogenation reactions involving regiospecific ketone and olefin reduction, transfer hydrogenation of ketones and dehydrogenative oxidation of alcohols, all of which are mediated by the above highly active NHC–Ru catalyst **14**, in good to excellent overall yields [42a]; this broad spectrum of catalytic activity is demonstrated hereinafter for the tandem CM-hydrogenation and -transfer hydrogenation (Schemes 31 and 32).

The first sequence in Scheme 31 (A → B → D) comprises the cross-metathesis (CM) of styrene with methyl vinyl ketone to the unsaturated ketone A, followed by hydrogenation (H_2) to B, likely promoted by a Ru-hydride species generated from **14** and H_2, and transfer hydrogenation to D (with ethylenediamine, NaOH, *i*-PrOH and H_2) suggested to occur under the action of a Noyori type catalyst, RuHCl(EDA)(PCy_3)(H_2IMes). In the second sequence (A → C → D) the allyl alcohol C, obtained quantitatively by transfer hydrogenation with no trace of C=C reduction, was hydrogenated to the final product, the saturated alcohol D.

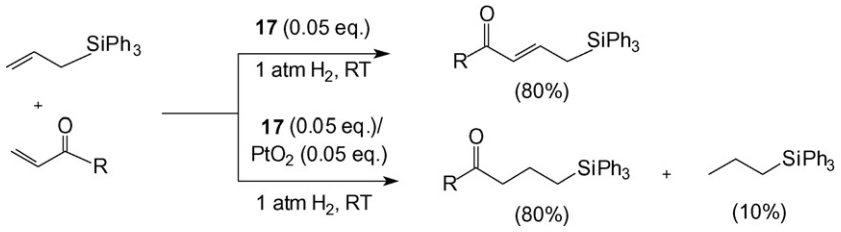


Scheme 32. Synthesis of (*R*)-(−)-Muscone by tandem RCM/hydrogen transfer/hydrogenation with Ru catalysts [42a].

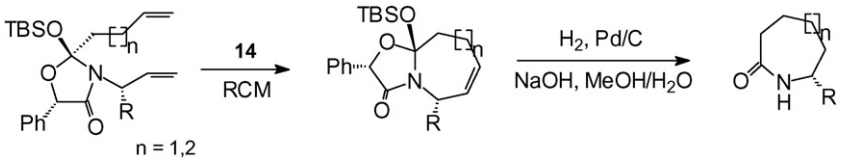
Another example illustrative of productive cascade catalysis with **14** is the "one-pot" enantioselective synthesis of (*R*)-(−)-muscone (**55**), a natural product with valuable fragrance properties (Scheme 32) [42a]. Thus, diene substrate A, bearing an unprotected secondary hydroxyl group, was cyclized (RCM) to a macrocyclic alkenol B (mixture of geometrical isomers), followed by its dehydrogenative oxidation to C (*via* hydrogen transfer to 3-pentanone in the presence of NaOH), and chemoselective hydrogenation (H_2 gas) at the olefinic double bond of the suitable stereoisomer in C, to the targeted saturated macrocyclic ketone **55** in the desired stereoconfiguration (56% overall yield).

With the aim of reaching high performance in all pathways of the tandem process, conditions have to be found that allow for controlling reactivity and selectivity in each step. A first concept is developing catalytic systems able to catalyze distinct reactions by just simple modifications [118]. Another strategy for efficacy is to devise reactions making use of catalysts that are compatible and perform reactions with different rates. Thus, rapid construction of small molecules has been accomplished in a sequential CM-hydrogenation employing the second generation Grubbs catalyst **14** [42a].

The issue of compatibility of two catalysts was further addressed by Cossy et al. [119a] in a relevant example of orthogonal catalysis, a one-pot CM-hydrogenation tandem procedure employing a Ru–NHC metathesis catalyst resistant to hydrogenolysis, namely **17**. With the Hoveyda–Grubbs catalyst (**17**) alone, under hydrogen at room temperature, the cross-metathesis of allyltriphenyl silane and an α,β-unsaturated carbonyl compound gave the metathesis product (80% yield) and only traces of the corresponding saturated derivative. Nevertheless, in orthogonal catalysis, when the hydrogenation catalyst PtO_2 was used in conjunction with the metathesis promoting catalyst **17**, the tandem procedure was shifted drastically towards the saturated derivative which now became the major product (80%). With Pd/C, instead of PtO_2, the hydrogenation products prevailed, hence hydrogenation was faster than metathesis. The results convincingly demonstrated that by ingenious interplay between two compatible catalysts, reaction rates can be manipulated towards the desired product. The high yield in the metathesis (over hydrogenation) product obtained in the presence of **17** subtly proved that, in contrast to the traditional NHC–Ru **14**, the Hoveyda–Grubbs catalyst **17** is not converted to a Ru–H species to act as a promoter in the hydrogenation of the double bond of the CM product. This is not surprising if we take into consideration that **17** has an *O*,*C*-bidentate ligand preventing formation of the Ru-hydride species (Scheme 33).



Scheme 33. Orthogonal tandem metathesis CM/hydrogenation with **17**/PtO_2 system [119a].



Scheme 34. Synthesis of saturated lactams through sequential RCM/hydrogenation [119b].

The reversed sequence, RCM/hydrogenation (with the catalyst couple **14**/Pd-C), is the basis of a convenient synthesis of saturated, unsubstituted medium-sized lactams (Scheme 34) [119b].

The starting oxyoxazolidinones, prepared from secondary *O*-acylmandelamides by treatment with TBSOTf, underwent RCM in the presence of Grubbs catalyst **14** to give either oxazoloazepines or oxazoloazecines.

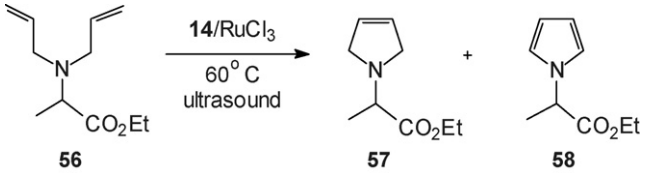
Unprecedented RCM/oxidation sequences have quite recently been developed for the straightforward one-pot synthesis of pyrrole derivatives based on orthogonal catalysis employing Grubbs' second generation catalyst (**14**) associated with a dehydrogenation agent. In the first methodology, diallylamines (e.g. **56**) were converted to the corresponding pyrroles (e.g. **58**) in more than 90% yield by using the second generation Grubbs' catalyst (10%) with 2% $RuCl_3{\cdot}H_2O$, in 1,2-dichloroethane at 60 °C and under ultrasonic irradiation to form a fine dispersion of the $RuCl_3{\cdot}H_2O$ in the reaction mixture (Scheme 35) [119c].

To establish if role of the catalyst **14**, in the two mechanistically different yet simultaneously occurring reactions, is limited to just RCM, a comparative study was performed with or without addition of $RuCl_2{\cdot}H_2O$. In both cases the formation of the corresponding pyrroline **57** and pyrrole **58** was observed, but the pyrrole formation was greatly favoured in the presence of $RuCl_3{\cdot}H_2O$ (2%). When second generation Grubbs' is used at lower temperatures, no pyrrole formation is observed. This might suggest that at higher temperatures, some other Ru-species are formed, due to the decomposition of the catalyst, which catalyze the dehydrogenation. The general applicability of these tandem reactions was demonstrated on a number of substrates producing a variety of pyrroles in good to excellent yields. Taking advantage of a somewhat modified technique (dehydrogenating agent: TCQ), the same authors succeeded in synthesizing 2-phosphonopyrroles starting from the suitable precursors, under mild conditions (Scheme 36) [119d].

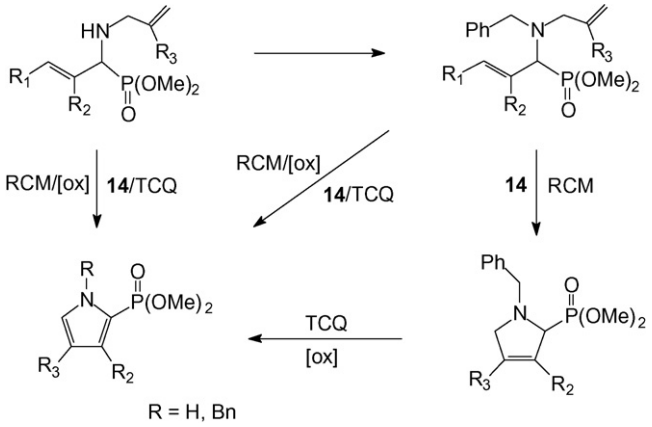
The key step involves a one-pot ring-closing metathesis/oxidation sequence of a functionalized α-aminoalkenyl phosphonate using catalyst **14** (5 mol%)/TCQ. A synergism was observed between the RCM catalyst and the oxidizing agent, causing higher oxidation rates and allowing reaction for substrates that normally fail to ring close under standard RCM conditions.

An innovative, controlled tandem protocol consisting of olefin isomerization-RCM, introduced by the Snapper group provided direct access to medium-sized *O*-heterocycles, starting from various, readily available oxygen-containing dienes such as **59a–61a** (Scheme 37) [120]. The reaction products (e.g. **59–61**) pertain to the class of cyclic enol ethers reputed as versatile subunits in the synthesis of bioactive compounds (glycals, polyether or nucleoside antibiotics, natural products).

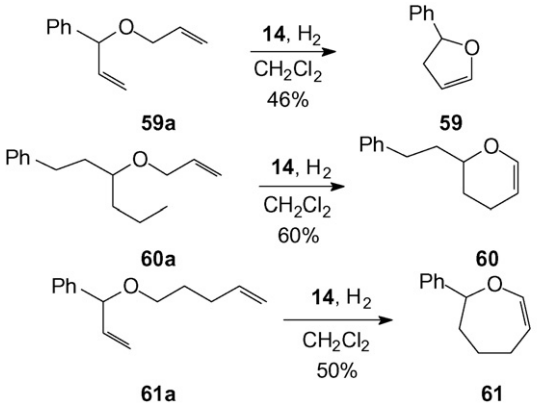
Of note is the observation that treatment of NHC–Ru complex **14** in CH_2Cl_2 with small amounts of H_2 (95:5 of mixture N_2:H_2) led reproducibly to an isomerization Ru-catalyst, while keeping down the competitive olefin hydrogenation (<10%). However,



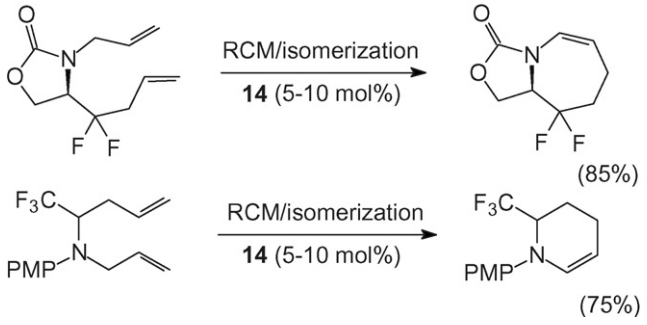
Scheme 35. Tandem RCM/oxidation with **14**/$RuCl_3$ catalysts [119c].



Scheme 36. Multiple reaction pathways in tandem RCM/oxidation [119d].



Scheme 37. Tandem isomerization/RCM reactions with Ru complex **14** [120].



Scheme 38. Tandem RCM/isomerization to unsaturated fluorinated lactams and tetrahydropyridines [122a].

total absence of hydrogen suppresses isomerization reaction, irrefutable evidence that a Ru-hydride species is involved. An array of solvents was screened for their ability to enhance the isomerization activity, with methylene chloride giving the best results. In all cases examined, the regiochemistry furthered the less substituted enol ether. As a bonus, when enantiomerically enriched dienes were subjected to this tandem protocol, the resulting cyclic enol ethers were generated without loss of enantiomeric purity, indicating that the isomerization does not proceed *via* the respective achiral enol ether. As an alternative to the above method, in a related synthesis of cyclic enol ethers through tandem metathesis–isomerization of allyl ethers, Schmidt activated the Ru carbene complex **14** to catalyze double bond isomerization by addition of conventional hydride sources (NaH or $NaBH_4$) [121a–d]. *In situ* formation of Ru-H species in isomerization of allyl ethers using Grubbs catalyst has been demonstrated spectroscopically in recent work by Schmidt [121e]. Other studies have availed themselves of a similar hydride transfer from $NaBH_4$, performed on a pincer $PC^{NHC}P$–Ru complex to generate *mer*-$RuHCl(CO)PC^{NHC}P$ [121f].

An original tandem RCM/isomerization gave access to fluorinated or nonfluorinated unsaturated lactams in a regioselective synthesis from the corresponding amide precursors (Scheme 38) [122a].

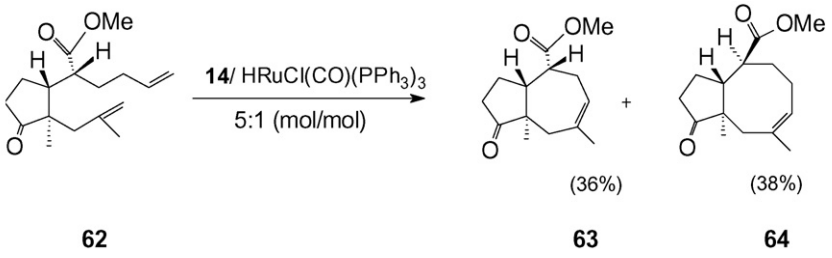
The regioselective course of the overall tandem transformation is determined by the presence of the *gem*-difluoro moiety in the starting material, which is crucially important for a controlled isomerization, and also by the heteroatom. The process is most productive for synthesis of five- to eight-membered lactams for which the RCM step, because of auspicious ring size formation, is very fast and surpasses isomerization; nevertheless, the opposite is true for the case of nine-membered ring lactam when isomerization takes place first resulting in formation of several ring sized lactams. The same tandem afforded CF_3-substituted tetrahydropyridines in good yield.

Another interesting example of tandem double bond isomerization-RCM was recently described by Wicha for sterically congested 1,9-dienes as substrates, capitalizing on a binary system consisting of the first or second generation Grubbs catalyst associated with $HRuCl(CO)(PPh_3)_3$ (Scheme 39) [122b].

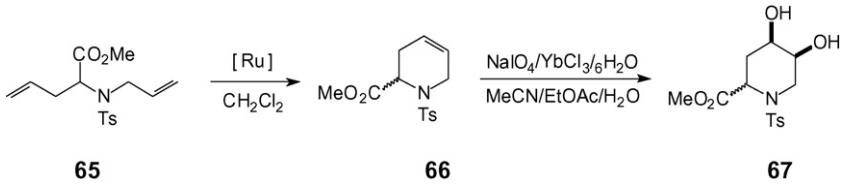
The two catalysts were compatible and their mixture allowed good conversion of the starting dienes. Non-bonding interactions within the reaction products and intermediates were invoked to rationalize the outcome of each reaction step.

The sequential metathesis/dihydroxylation of a variety of dienes involving RCM (or CM) followed by *cis*-dihydroxylation of the resulting C=C double bond, utilizing the same ruthenium source, was reported this year by Blechert et al. [123a] to efficiently lead to vicinal diols under mild conditions. The creative idea was to promote metathesis with a NHC–Ru precatalyst and then oxidize this ruthenium source to conduct *cis*-dihydroxylation of the newly formed disubstituted olefin in a one-pot procedure. This seems to be the first reference for a *N*-heterocyclic carbene application as Ru catalyst in dihydroxylation of olefins.

Since the authors had found that even small amounts of dichloromethane resulted in low yields in the dihydroxylation step, the solvent was totally removed after completion of RCM and replaced, for dihydroxylation, with the solvent mixture indicated in Scheme 40. Dihydroxylation proceeded rapidly at 0 °C



Scheme 39. Tandem isomerization/RCM using Grubbs catalysts/$HRuCl(CO)(PPh_3)_3$ [122b].



65 66 67

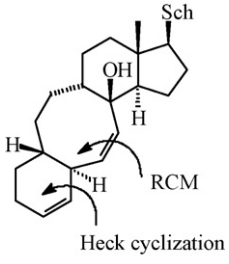
Scheme 40. Tandem metathesis/dihydroxylation of dienes [123a].

when an optimal order of addition of reagents to the solution of crude ring-closed product ($YbCl_3{\cdot}6H_2O$ before $NaIO_4$) was observed and stirring of the heterogeneous reaction mixture was vigorous. Of a series of catalysts tested, the Grubbs II (**14**) and Hoveyda–Grubbs (**17**) gave lower yields even at longer reaction times (ca. 50% for the latter in CM/dihydroxylation sequences), supposedly as a consequence of the strong binding between the *N*-heterocyclic carbene (NHC) ligand and the ruthenium in these complexes which slows down the formation of the oxidating species [123b].

Related versatile heterocyclic compounds, namely substituted quinoline derivatives, were readily prepared in excellent yield by a sequence involving first allylation (allyl bromide, K_2CO_3) of anthranilic acid derived enol ethers, followed by RCM with Grubbs catalyst **14** [123c]. This is the first report on the synthesis of a heterocyclic enol silyl ether (4-TBDMSO-1-Ts-quinoline) *via* enol silyl ether-ene metathesis and the utility of enol TBDMS ethers as substrates in RCM. Simultaneously, the highly regioselective cascade synthesis of carbocyclic enol ethers, in almost quantitative yields, starting from readily accessible acyclic alkenyl ketones or acyclic alkenyl silyl esters, was reported to necessitate first carbonyl olefination (Tebbe reagent) and secondly RCM (catalyst **14**) (Scheme 41); advantages of, this time, OTMS ethers as RCM substrates were highlighted [123d].

The tandem allyl transfer/CM of linear homoallylic alcohols with terminal ester functionality has been achieved by Lee and Loh, in a highly enantioselective synthesis proceeding in single reaction vessel [123e]; the homoallyl reaction partner, to be cross-metathesized (catalyst **14**) with acrylic or methacrylic esters, was first obtained by enantioselective allyl transfer to phenylpropenal (or other aldehydes) using a camphor-derived homoallylic alcohol. Asymmetric allyl transfer followed by olefin cross-metathesis provided easy access to a wide variety of linear enantiomerically enriched and geometrically defined homoallylic alcohols. Ordered addition of reagents and catalysts enabled a controlled reaction ensuring complete consumption of the starting aldehyde.

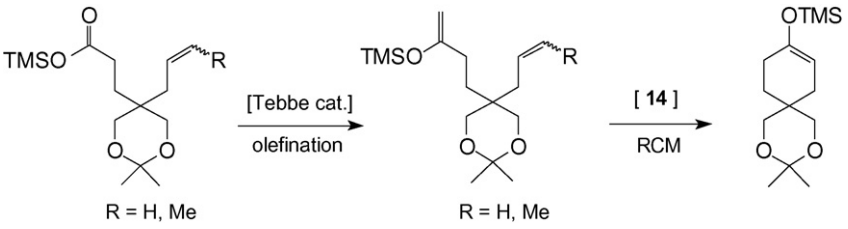
A new strategy to access polycyclic systems containing eight-membered carbocycles, a large class of compounds of importance in organic chemistry, biology, and medicine has been published for construction of steroid-like systems on the CD framework using a combination of RCM and Heck cyclizations. The stereoselective synthesis of the 6-8-6-5 fused carbocyclic system that mimics the putative transition structure of isomerization of pre-Vitamin D_3 to Vitamin D_3 is exemplified in **68** [123f].



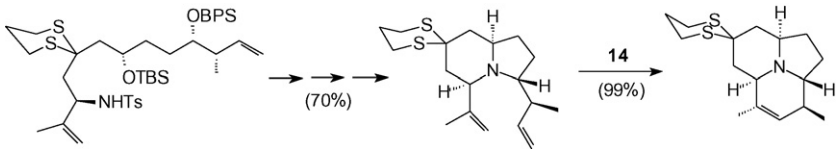
68

RCM in conjunction with sequential ring closures enable essential steps in the highly efficient and enantioselective total synthesis of the alkaloid (−)-**205B**, a natural compound with potential biological activity, and of related alkaloids. The two rings that comprise the 3,5-disubstituted indolizidine ring, embedded in the 8b-azaacenaphthylene tricyclic scaffold of the alkaloid (−)-**205B**, were constructed prior to RCM through successive, in one flask cyclizations proceeding in 70% yield [123g]. In turn, the last RCM step to the tricyclic framework furnished nearly quantitative yield (Scheme 42).

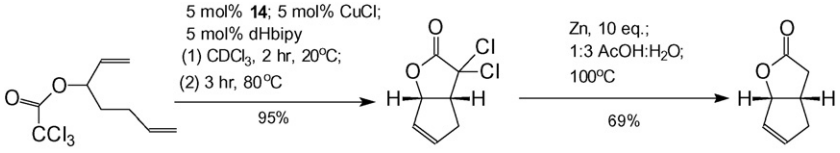
Reference to a different matched pair of tandem reactions, Kharasch addition/RCM, comes again from Snapper et al. who revealed the ability of the bisphosphane Grubbs catalyst, $RuCl_2(PCy_3)_2(=CHPh)$ to perform facile construction of the bicyclic[3.3.0], [4.3.0] and [5.3.0] ring systems, in one step, from the appropriate acyclic precursors [124]. Remarkably, these authors found that by combining the intra-and intermolecular Kharasch additions with RCM, three new contiguous C–C bonds with multiple stereocenters can be generated by the Ru-catalyst



Scheme 41. Tandem olefination/RCM in synthesis of carbocyclic enol ethers [123d].



Scheme 42. Sequential steps in synthesis of the tricyclic framework of the alkaloid (−)-**205B** [123g].

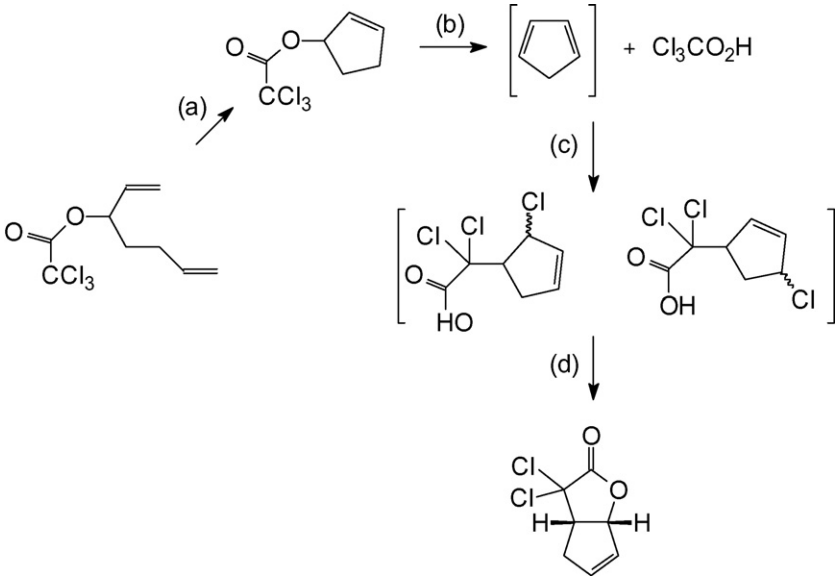


Scheme 43. RCM/ATRC of dienes with Grubbs' catalyst **14** [104b].

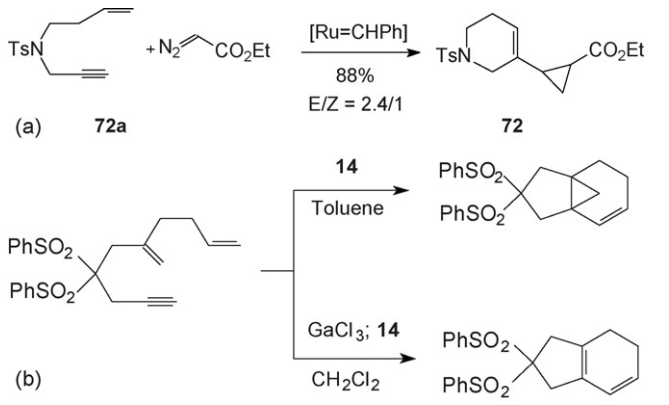
in a controlled fashion, in one operation but *via* two mechanistically distinct pathways. Almost simultaneously, Schmidt and Pohler discovered that the NHC–Ru Grubbs catalyst is also able to mediate both RCM and Kharasch addition sequences of α,ω-dienes, bearing a pendant trichloroacetoxy groups, to bicyclic γ-butyrolactones [104a]. The activity and selectivity of the catalyst were rather high. Surprisingly, cyclization occurring during the second, ATRC step also showed excellent diastereoselectivity indicating that the different orientations of the additional substituents do not influence either of the cyclization steps. Quite recently it was demonstrated that the sequential RCM–ATRC reactions of halo dienes **69** proceed with either of the Grubbs metathesis catalysts (bisphosphane– or NHC–Ru) to afford bicyclic lactones (**70** and **71**) (Schemes 43 and 44) or lactams [103b,104b].

Intriguingly, attempts by Snapper et al. to prepare alkenyl cyclopropanes, e.g. **72**, through a NHC–Ru catalyzed tandem enyne metathesis–cyclopropanation sequence failed, the sole product, a triene dimer, resulting through an enyne metathesis–cross-metathesis sequence [125a]; the tandem procedure occurred successfully only in the presence of the bisphosphane–Ru congener (Scheme 45a). In this case, cyclopropanation took place almost exclusively on the less hindered double bond with moderate *E*/*Z* stereoselectivity.

However, Peppers and Diver [125b] found that certain dienynes give tandem cyclopropanation/ring-closing alkene metathesis, triggered by either a ruthenium carbene (**14**) or noncarbene ruthenium(II) species, (dihydroIMes)(Cy_3P)$RuCl_2$, formed *in situ*. In toluene (80 °C), the presumed cyclopropyl carbene intermediate further undergoes ring-closing metathe-



Scheme 44. Cascade reactions in RCM/ATRC of dienes with Grubbs' catalysts [104b].



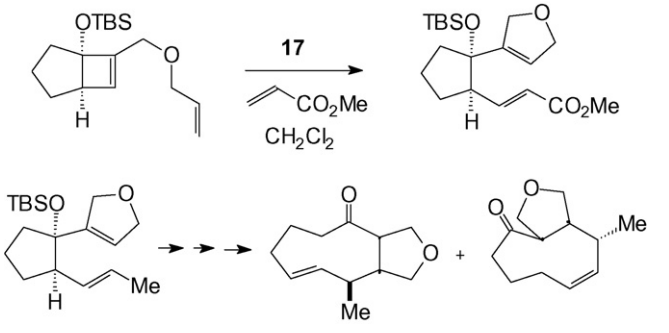
Scheme 45. (a) Tandem enyne metathesis/cyclopropanation with Ru complexes [125a]. (b) Tandem cyclopropanation/ring-closing metathesis of dienynes [125b].

sis to a cyclorearranged tricyclic product (Scheme 45b). With a sequential use of catalysts ($GaCl_3$, **14**), in CH_2Cl_2 (r.t.) a tandem ring-closing enyne/alkene metathesis was responsible for the bicyclic product obtained.

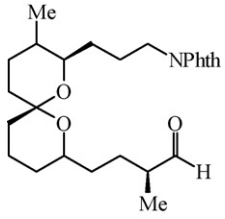
Of great utility for the rapid access to building blocks and polycyclic units in natural compounds, a ring-opening metathesis/ring-closing metathesis/oxy-Cope rearrangement strategy developed by Snapper et al. (Scheme 46) [125c] benefits from the high activity and selectivity that the second generation Grubbs and Hoveyda–Grubbs catalysts display in metathesis reactions. Metathesis steps are high yielding (82–95%) ensuring good overall yields in the final products.

The process occurs neatly and, under the reaction conditions employed, side reactions such as dimerization of cyclobutene substrates or secondary metathesis intermediates, were not detected. By this reaction sequence, a stereocontrolled preparation of a variety of medium ring-containing bicyclic systems was accessible.

Sometimes the coupling of non-metathetical with metathetical reactions gets really sophisticated. This is the case of the remarkable atom economical ring-opening/cross-metathesis cascade, associated with hydrogenation and Dess–Martin oxidation, by which Kozmin et al. [126] prepared the key spiroketal fragment **73**. From **73** they were able, in a refined way, to complete the enantioselective total synthesis of (+)-bistramide A, a protein kinase C activator.



Scheme 46. Cascade reactions ring-opening metathesis/ring-closing metathesis/oxy-Cope rearrangement [125c].



73

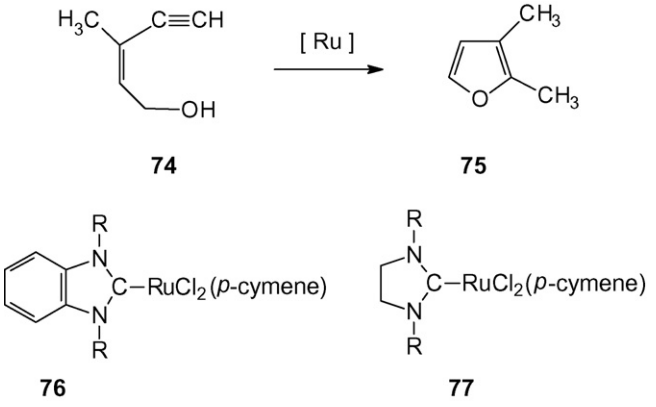
3.14. Miscellaneous processes

A quite interesting intramolecular cyclization of (*Z*)-3-methylpent-2-en-4-yn-1-ol (**74**) to 2,3-dimethylfuran (**75**), proceeding under the action of an array of neutral arene-ruthenium-carbenes precursors, **76** and **77**, bearing benzoimidazolin-2-ylidene or imidazolidin-2-ylidene ligands was described by Dixneuf et al. [127a] to afford very good yields (>90%) in cyclic product (Scheme 47).

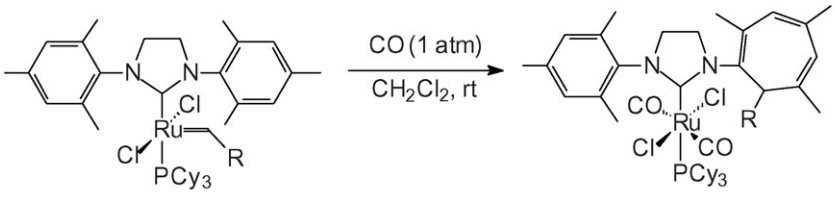
Of the two NHC ligands employed, imidazolin-2-ylidene ensured an improved activity of the catalyst precursor. The mononuclear complexes afforded the furan in 90% yield, at 80 °C, whereas related binuclear catalysts, having a linked bis-carbene bridge, operate even at room temperature initiating an exothermic reaction to produce the furan in 90–97% yield [127b]. The ability of the precatalyst to bring about stereoselective electrophilic activation of the C≡C bond of *Z*-enynols is responsible for the cyclization yet the actual mechanism of the cyclization pathway needs more clarification.

A Buchner reaction of the Grubbs' second generation complex was identified by Diver et al. [128] to proceed by interaction of the Ru complex **14a** or **14b** with carbon monoxide. It has been proved spectroscopically that one of the mesityl groups of NHC turns into a substituted cycloheptatrienyl, with carbon monoxide concomitant binding to ruthenium to form **78** (Scheme 48).

This unprecedented transformation of a metathesis–active ruthenium carbene complex has been rationalized by a cyclopropanation of the closest "double bond" of the mesityl group by the CHR (R = Ph or H) carbene fragment, followed by electrocyclic ring-opening of the transient cyclopropane to provide the cycloheptatriene structure. The absence of regioisomers indicated that the carbene CHR was still encumbered to the ruthe-



Scheme 47. Furan synthesis using Ru complexes **76** and **77** [127a].



Scheme 48. Buchner reaction of Ru complex **14** [128].

nium center and was not reacting as a free carbene with the remote aromatic π-bonds. This pathway may be facilitated in the case of **14a** because of the π-π stacking occurring between the benzylidene moiety and the aromatic ring of mesitylene. It was assumed that CO binding may weaken π-backbonding between the ruthenium atom and the CHR carbene ligand, making it more electrophilic and disengaging it from the metal center. This remarkable observation sheds some light on the mechanism of carbenoid cyclopropanation promoted by ruthenium carbene species.

4. Conclusions

The review amply documents non-metathetical chemical transformations catalyzed by *N*-heterocyclic carbene ruthenium complexes as successful tactics for furthering short and economical synthesis of a variety of compounds. Rightfully a matter of great current interest, Ru–NHC promoted non-metathetical reactions constitute, especially in comparison with metathesis, a new and relatively unexplored field as reflected by the references cited in this review, mostly spanning the last 5 years. Combining metathetical with non-metathetical reactions in tandem and cascade procedures, sometimes occurring in a single operation balancing different preconditions for the catalysts employed, is in the spotlight right now. The methodology, outperforming more conventional approaches, has already yielded previously unexpected accomplishments in key areas of catalysis and still holds genuine promise for atom- or catalyst-economy oriented practical applications.

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