

Ruthenium Complexes Bearing N-Heterocyclic Carbene (NHC) Ligands

PART II: RECENT DEVELOPMENTS IN METATHESIS CHEMISTRY

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A review of recently published aspects on ruthenium complexes with nucleophilic N-heterocyclic carbene (NHC) ligands is presented here, in continuation of a paper published in the July issue of this Journal, that covered initial work and subsequent main developments in this chemistry. In Part II selected applications of these complexes as pre-catalysts in metathesis reactions are highlighted. Particular attention is paid to metathesis in room temperature ionic liquids as the solvents, asymmetric catalysis, and in situ generated, very active catalytic systems based on NHC-platinum group metals. Most NHC-platinum group metal complexes are useful as highly active and selective pre-catalysts for fundamental chemical transformations.

N-Heterocyclic carbenes (NHCs) are encountered as versatile ligands in a large variety of organometallic and coordination complexes pertaining to almost all members of the platinum group metals (pgms) (1, 2). Of these complexes, many derived from ruthenium (Ru) and palladium (Pd), are endowed with excellent catalytic properties and stability to air and functionalities. These complexes have recently seen the most striking developments (3). Commercially available and easily handled Ru-NHC pre-catalysts have made possible a wide range of transformations enabling metathesis to come to the fore (4).

A combined computational chemistry/crystallographic database analysis of bonding in NHC late transition metal complexes shows that the metal-carbon bond is approximately 4% shorter than a prototypical metal-carbon (M-C) single bond as, for example, in a metal-alkyl complex (5). Of the two hypotheses investigated for this bond shortening - multiple bond character in the M-C of the NHC complex or a change in the hybridisation of the carbenoid carbon to incorporate more *p* character - the latter hypothesis is preferred. The natural bond order analysis also suggests that in the

complex there is a substantial *trans* influence from the NHC ligands.

As with other donor ligands (for example, phosphane, amine, alkoxy, Schiff base), substituent groups in the NHC ligand allow fine-tuning of the steric and electronic effects, thus conferring better catalytic performance to the respective metal complex (6). Most of the NHC ligands were shown to be efficient in pgm complexes widely used as highly active and rather selective pre-catalysts in a range of fundamental chemical transformations, such as hydrogenation, hydrogen transfer, hydroformylation, hydrosilylation, oxidation, isomerisation, telomerisation and various C-C coupling reactions (7, 8).

Besides the ubiquitously employed imidazolin-2-ylidene and dihydroimidazolin-2-ylidene ligands, the panel of N-heterocyclic carbenes used as ligands in ruthenium complexes has recently been extended. The panel now includes other heterocyclic compounds, such as triazolin-2-ylidene, benzimidazolin-2-ylidene, tetrahydropyrimidin-2-ylidene, as well as high-membered rings and polycyclic fused ring systems (9). Derivatives of these additional ligands are also encountered.

In Situ Generated Catalysts

An important direction for research in catalysis of NHC-pgms is the *in situ* generation of very active catalytic systems (10). As an example, 1,3-diarylimidazol(in)ium chlorides react with $[\text{RuCl}_2(p\text{-cymene})]_2$ and potassium *tert*-butoxide or sodium hydride. This reaction affords the corresponding NHC ruthenium complexes, either preformed or generated *in situ*. Under visible light irradiation these ruthenium complexes, bearing NHC ligands with N,N-diaryl groups substituted on both their *ortho* positions, proved to be very active catalyst precursors for the metathesis polymerisation of a large array of high and low strained cyclic olefins, even at room temperature (11).

A thorough investigation on the influence of the NHC ligand structure on the outcome of the metathesis polymerisation of cycloolefins indicated that it was not crucial to have the C4-C5 double bond in the imidazole ring to achieve high catalytic efficiencies, and that the nature of N,N-diaryl groups was not important. On the other hand, blocking all the *ortho* positions on the phenyl ring substituents on NHC is a requisite for obtaining efficient pre-catalysts. Failure to do so probably results in *ortho*-metallation of the carbene ligand, thereby altering the coordination sphere of the active centres of the ruthenium (12). Some pre-catalysts displayed dual activity and promoted both olefin metathesis and the atom transfer radical addition reaction (ATRA).

Metathesis in Ionic Liquids

Catalysis in room temperature ionic liquids is now receiving growing attention due to the acknowledged advantages they offer:

- low vapour pressure, making them environmentally benign media and suitable to replace traditional organic solvents;
- ability to dissolve both polar and non-polar species, including organometallic catalysts: this is important for efficient homogeneous catalysis;
- ease of reuse, based on their immiscibility with organic solvents, enabling facile extraction of the reaction products; and,
- as promoters of many organic transformations they allow eco-friendly protocols (13).

When applied to Ru-catalysed metathesis, ionic liquids act to minimise the critical limitations associated with even the best second generation catalysts of the NHC type. The limitations include: low level recyclability and difficulty in removing all traces of Ru from the reaction products.

Imidazolium-tagged ruthenium catalysts can perform efficient ring-closing metathesis (RCM) of a variety of di- and tri-substituted dienes or oxygen-containing dienes, in room temperature ionic liquids, and have afforded an extremely low Ru content (7.3 ppm/run) in the RCM products (14).

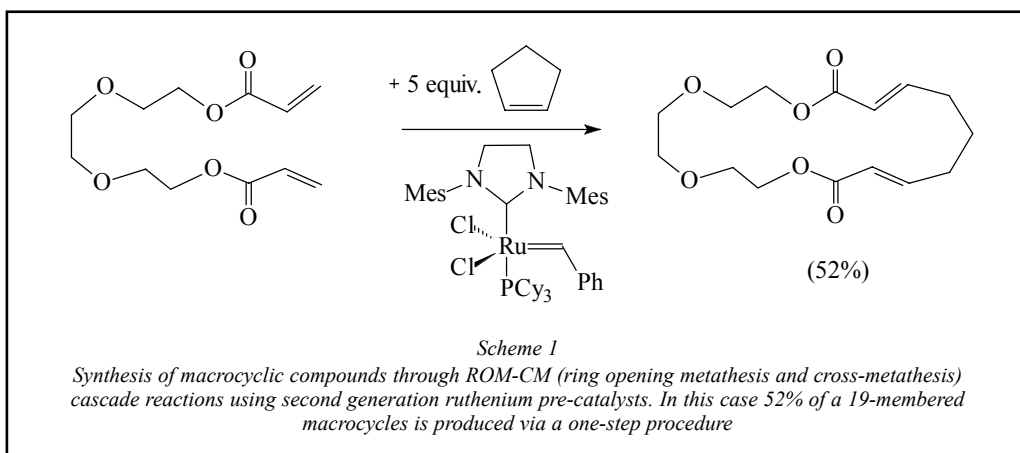
Also, RCM of substituted diene and enyne substrates, in the presence of a second generation Hoveyda-Grubbs Ru complex bearing an ionic liquid tag, afforded excellent results and permitted convenient recycling and reuse (up to 17 cycles) of the pre-catalyst, with only a slight loss in activity. The authors proved that the ionic liquid tag is crucial for recycling ability, as the untagged parent pre-catalyst rapidly loses its activity when recycled in the ionic liquid layer (15).

Asymmetric Catalysis

Interesting applications of chiral NHC Ru complexes in asymmetric catalysis are presently evolving, but elaborate electronic and steric variations on NHCs will still be necessary for further progress in this field. Chiral N-heterocyclic carbene modules open convenient ways of creating catalytic systems of high synthetic utility in organic synthesis. In this connection, structures involving chiral NHCs ligated to ruthenium are interesting for asymmetric catalysis. Of the new variants, oxazolines appear to be powerful structural building blocks and have been incorporated into many chiral NHC ligands. They lead to rigid architectures that have been successfully applied in asymmetric catalysis (16). We cite here oxazolines arising from optically active amino acids, binaphthyl systems generating atropisomerism, and ferrocene affording planar chirality (17, 18).

NHC-Ru Synthetic Applications

NHC ruthenium pre-catalysts were proved to have a “high tolerance towards many organic functionalities”. As suggested by one referee of our

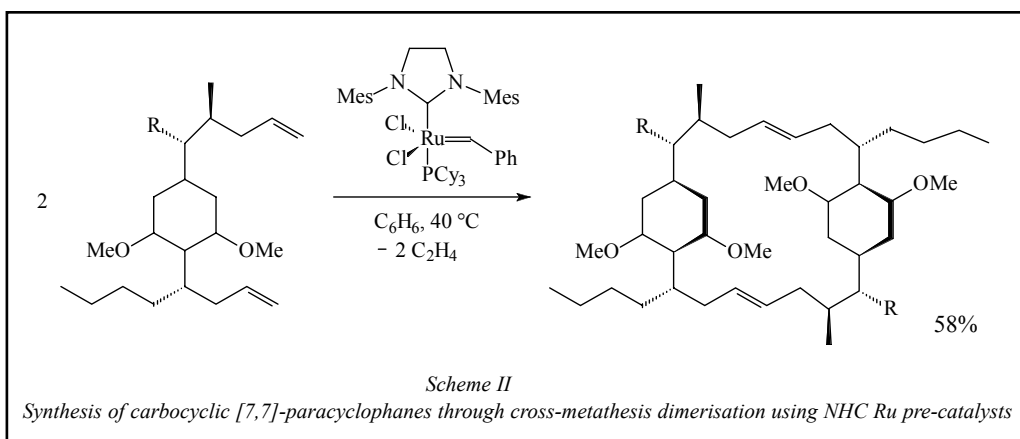


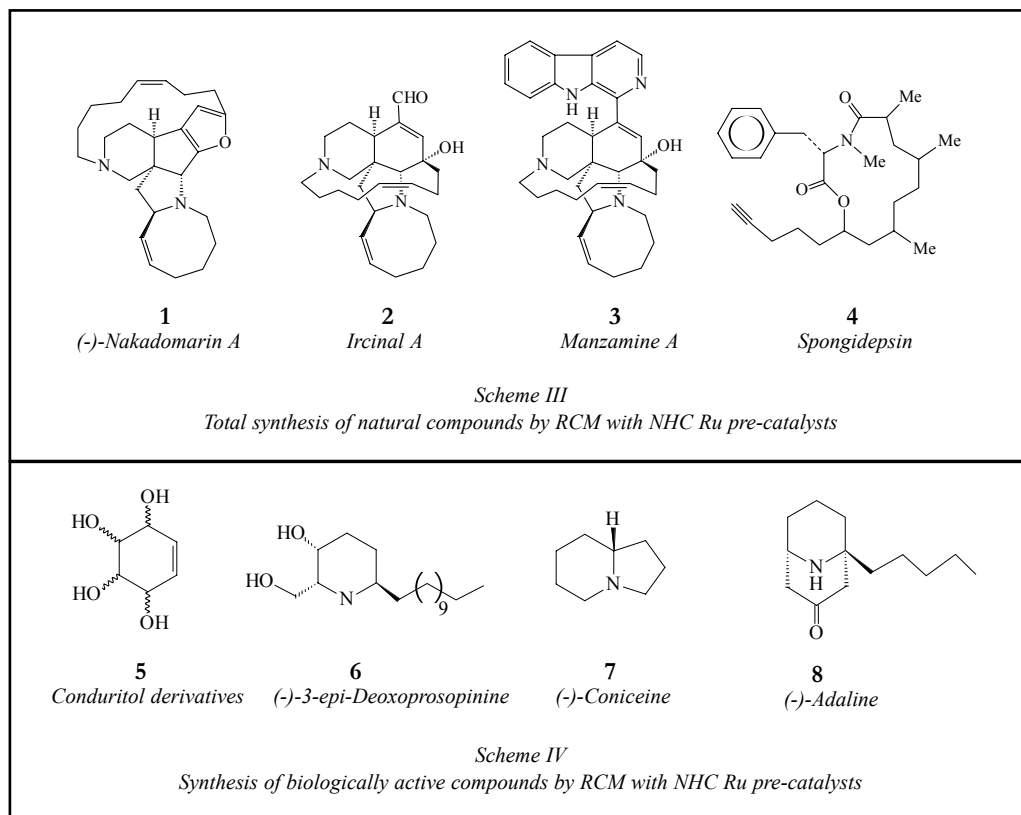
earlier paper (1a), this important asset of NHC ruthenium complexes opens possibilities, previously unthinkable, for taking advantage of unusual substrates. Of the numerous examples reported in the literature (19), we will mention first the ring-expansion of unstrained cycloalkenes using highly functionalised diene substrates as a promising method for the synthesis, in moderate yield, of specialty macrocycles. Synthesis occurs *via* ring-opening metathesis and cross-metathesis (ROM-CM) cascade reactions (20) (Scheme I).

In another interesting procedure, carbocyclic [7,7]-paracyclophanes have been prepared *via* olefin cross-metathesis dimerisation as the key step, in the presence of NHC Ru pre-catalysts (21) (Scheme II).

Due to the combination of high activity and

good tolerance towards organic functionalities displayed by the NHC ruthenium complexes, a very broad panel of total syntheses of natural products and biologically active complex molecules has been reported. Most of them use the versatile RCM process as the key synthetic step. Thus, asymmetric total synthesis (Scheme III) of (-)-nakadomarin A, **1**, a natural compound related to ircinal A, **2**, a biogenetic precursor of the manzamine A alkaloid, **3**, have been effectively performed by RCM of diene precursors using NHC Ru complexes in the key steps (22). Compounds **2** and **3** have cytotoxic activity against murine lymphoma cells as well as antimicrobial activity. The difference in reactivity of bisphosphane and NHC/phosphane pre-catalysts has been shown to be significant (23). When using the





former, the 15-membered azacycle in 26% yield was produced, while using the latter led to the 8-membered azacycle in 83% yield. Spongidepsin, **4**, a remarkable natural compound with cytotoxic and antiproliferative activities against several cancer cell lines, has also been synthesised through a stereodivergent ring-closing strategy (23). The corresponding diene amide precursors were cyclised under the action of the second generation Grubbs pre-catalyst, and after the separation of stereoisomers by flash column chromatography and hydrogenation over Pd/C, saturated macrolides were obtained. Structural assignment was performed using advanced spectroscopic studies.

Using the same strategy, the synthesis of conduritol derivatives, **5**, starting from galactitol, D-mannitol and D-glucitol, by Tebbe olefination followed by RCM in the presence of a NHC-based ruthenium complex, was successfully achieved (24) (Scheme IV). High yields of polyhydroxylated compounds (70–90%, from the corresponding

dienes) were readily attained in the presence of the second generation Grubbs pre-catalyst, with activity sometimes comparable to that obtained using the very active and sensitive Schrock imido alkoxide molybdenum alkylidene complex.

Also, the total synthesis of a trisubstituted piperidine, (-)-3-*epi*-deoxoprosopinine, **6**, has been carried out in 8 steps starting from the Garner aldehyde (overall yield 27%) involving RCM of an intermediate diene (induced by the dihydroimidazolidin-2-ylidene ruthenium complex) as the key step to construct the piperidine moiety (25).

Furthermore, (-)-coniceine, **7**, the simplest indolizidine alkaloid with pronounced biological activity, has been prepared by several routes from different sources. The dihydroimidazolidin-2-ylidene ruthenium complex was used for the RCM of the intermediate diene to give the indolizidine unit (26). The same ruthenium complex also proved to be highly efficient in building bridged bicyclic alkaloids containing a nitrogen atom in the one-atom

bridge, as illustrated by the synthesis of (-)-adalin, 8, a major alkaloid from the chemical defence secretion of the European two-spotted ladybird *Adalia bipunctata* (27).

Cyclic Polymer Synthesis

In a recent protocol, “cyclic” NHC ruthenium initiators permitted the synthesis of interesting cyclic polymers by a novel approach that circumvents the need for linear polymeric precursors (28). Applying this attractive approach afforded the synthesis of cyclic polyoctenamer by the ring-opening metathesis polymerisation (ROMP) of *cis*-cyclooctene, and then further production of cyclic polyethylene by the hydrogenation of the cyclic polyoctenamer. Additionally, cyclic polybutadiene was synthesised by the ROMP of 1,5-cyclooctadiene (29).

In this respect, it should be emphasised that the topological restrictions imposed upon cyclic polymers result in a variety of physical properties that distinguish them from their linear counterparts. For instance, cyclic polymers are less viscous, exhibit higher glass transition temperatures, and have smaller hydrodynamic volumes and radii (R_h) than their respective linear analogues. These properties render them suitable for specialty applications (30).

Conclusions

The literature continues to report interesting work on ruthenium catalysed metathesis reactions, demonstrating the advantages of this chemistry. Recent advances into biological areas indicate there is still work to be done with ruthenium complexes bearing NHC ligands.

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