Evolution and Applications of Second-Generation Ruthenium Olefin Metathesis Catalysts

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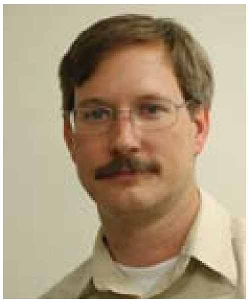

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Outline

1. Introduction

Olefin metathesis is a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds, and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The widely accepted view that olefin metathesis revolutionized the different fields of synthetic chemistry led to the awarding of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock "for the development of the metathesis method in organic synthesis".[1] While Chauvin had proposed the "carbene" mechanism to explain how the metathesis process functions[1a,2] and Schrock had prepared the first well-defined highly active metathesis catalysts,[1b,3] Grubbs provided synthetic chemists with active catalysts that could be handled in air and were tolerant of various functional groups, such as esters, amides, ketones, aldehydes, and even protic functionalities like alcohols, water, and acids.[1c,4]

The Grubbs catalysts are based on a ruthenium atom surrounded by five ligands: two neutral electron-donating entities (e.g., trialkylphosphines, N-heterocyclic carbenes), two mono-anionic groups (e.g., halides), and one alkylidene moiety (e.g., unsubstituted and substituted methylidenes). These catalysts are divided into two categories based on the nature of the neutral ligands: $L_2X_2Ru{=}CHR$ complexes (where L is a phosphine ligand) were discovered first and are referred to as the first-generation Grubbs catalysts, and $(L)(L')X_2Ru{=}CHR$ complexes (where L is a phosphine ligand and L' a saturated N-heterocyclic carbene or NHC ligand) were subsequently developed and are referred to as the second-generation Grubbs catalysts (**Figure 1**).

The first-generation Grubbs catalysts have demonstrated attractive functional-group tolerance and handling properties, and have been widely used as highly efficient promoters for ring-opening metathesis polymerizations,[5] ring-closing metathesis reactions to make disubstituted olefins,[6] ethenolysis (i.e., cleavage of the carbon–carbon double bond),[7] cross-metathesis of terminal olefins,[8] and the preparation of 1,3-dienes via enyne metathesis.[9] As such, these catalysts and analogues[10] remain very useful and are still employed in important processes, including the ethenolysis of feedstocks derived from bio-renewable seed oils[7b,c] and the manufacture of macrocyclic hepatitis C therapeutics.[11] Nonetheless, the utility of first-generation catalysts is somewhat limited, because they suffer from reduced activity as compared to the more sensitive but highly active Schrock catalysts. Examples of transformations that are poorly or simply not enabled by first-generation Grubbs catalysts include the ring-closing metathesis to form tri- and tetrasubstituted cycloalkenes and the cross-metathesis of sterically hindered or electronically deactivated olefins. Many of these limitations have been addressed through the development of the second-generation Grubbs catalysts, which possess excellent metathesis activity while retaining the handling characteristics and broad functional-group tolerance of the earlier Grubbs catalysts.

Since their discovery in 1999, second-generation Grubbs systems have rapidly evolved into a large family of catalysts with varying properties. These catalysts have been widely utilized to facilitate new transformations and to allow important applications that extend to a broad range of areas including fine chemicals, pharmaceuticals, and materials. As it is often the case in homogeneous catalysis, there does not exist a single second-generation catalyst that is best for all transformations and applications. In fact, many of the second-generation catalysts have been developed to provide systems with optimal characteristics for specific purposes. Therefore, the aim of this article is to review the evolution of this group of catalysts, point out the properties and specificity of its members, and present some of the very interesting applications enabled by them.

2. Second-Generation Grubbs and Other Early NHC-Based Catalysts

2.1. Discovery of NHC-Based Olefin Metathesis Catalysts

The first examples of NHC-containing, olefin metathesis catalysts were disclosed by Herrmann and co-workers in 1998.[12] These complexes were bis-NHC ruthenium benzylidene species, **1**, where the NHC ligands were unsaturated and contained identical or different, chiral or achiral alkyl substituents on the nitrogen atoms (**Figure 2**). These systems were originally aimed at tuning the properties of the catalysts by changing the nature of the alkyl substituents on the nitrogen atoms and at producing chiral complexes.[13] Although they were first thought to be more active than the first-generation catalysts,[12] this notion turned out not to be generally true.[14] A year later, mixed NHC–phosphine ruthenium metathesis catalysts were reported: Herrmann and co-workers had focused on species containing alkyl-substituted unsaturated NHCs, **2**,[15] while the Grubbs[16] and Nolan[17] groups independently developed catalysts derived from aryl-substituted unsaturated NHCs, in particular 1,3-dimesitylimidazolin-2-ylidene or IMes, **3**. The mixed NHC–phosphine complexes **2** and **3** were found to possess greater metathesis activity and enhanced thermal stability than the first-generation Grubbs catalysts.[15a,c,16,17] In particular, compound **3**, developed by Grubbs and Nolan, proved to be an especially efficient catalyst.[18] Other IMes-based systems containing moieties such as vinylidene,[19] allenylidene,[20] or indenylidene[21] were prepared by the Grubbs, Fürstner, and Nolan groups. The allenylidene systems turned out to be inactive in metathesis, while the vinylidene complexes were active but slower than their ruthenium benzylidene analogues, and the indenylidene complexes proved to be "equipotent" to the benzylidene derivatives. Soon after developing the IMes catalyst, the Grubbs group discovered that replacing one phosphine of the first-generation systems with a *saturated* mesityl-substituted NHC (or SIMes) ligand afforded a catalyst with even greater activity than the IMes-based compounds.[22] The SIMes catalyst, **4**, commonly referred to as the second-generation Grubbs catalyst, quickly superseded the IMes species because it demonstrated superior efficiency in practically all metathesis reactions.[23,24]

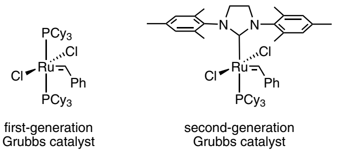


Figure 1. Most Commonly Used First- and Second-Generation Grubbs Catalysts.

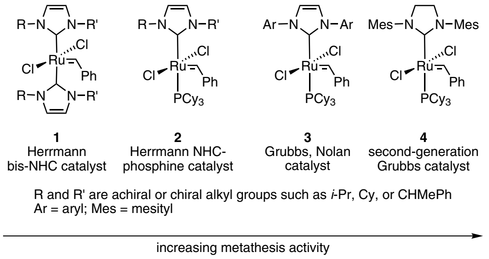
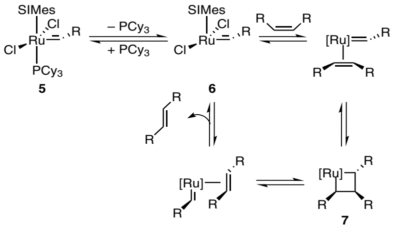


Figure 2. Evolution and Relative Activity of Early NHC-Based Metathesis Catalysts.



Ref. 25

Scheme 1. Mechanism of the Metathesis of a Symmetrical Cis Olefin to Its Trans Isomer.

2.2. Mechanistic Considerations and Development of Second-Generation Derivatives

Mechanistic studies of **4** indicated that the catalytic steps involve an initiation event where a 16-electron species, **5**, undergoes reversible phosphine dissociation to furnish a 14-electron, active catalytic complex, **6**. Complex **6** can either rebind a dissociated phosphine or proceed to reversibly coordinate an olefinic substrate to form a ruthenacyclobutane, **7**. The breaking apart of the ruthenacyclobutane follows to expel the new olefinic products (**Scheme 1**).[25] In addition, these studies showed that the second-generation catalysts initiate much more slowly than the first-generation ones, and that their enhanced activity is due to the fact that their affinity to coordinate an olefinic substrate in the presence of free phosphine is much greater than that of the first-generation systems.

These mechanistic insights guided Grubbs and co-workers to prepare a family of second-generation catalysts with different initiation rates by varying the detachable phosphine ligands. Depending on the application, it is advantageous to employ catalysts that initiate more or less rapidly. For example, when performing ring-opening olefin metathesis polymerizations (ROMP) of strained cyclic olefinic monomers, slower-initiating catalysts are often desirable because they allow for longer handling of the monomer/catalyst resin before the polymerization starts.[26] Conversely, fast-initiating catalysts, able to promote metathesis at reduced temperatures, are useful in applications where low reaction temperatures are required to prevent catalyst decomposition and formation of undesired byproducts.[27]

Thus, analogues of **4**, such as complexes **8**–**10** containing tri(*n*-butyl)phosphine, tri(*p*-tolyl)phosphine, and triphenylphosphine, have been synthesized and their phosphine dissociation rates found to vary dramatically with the nature of the phosphine ligand (**Figure 3**).[28,29] Indeed, the phosphine dissociation rate of **10** was about *60 times greater,* and that of **8** about *170 times smaller*, than that of **4** (measured at 80 °C in toluene).[29,30]

The nature of the halide and alkylidene ligands also has an impact on the catalyst initiation rate. In particular, catalysts containing larger halide ligands initiate more rapidly, while systems with smaller alkylidene moieties (e.g., methylidene) initiate more slowly.[25b] Similarly, complex **13**, containing a large NHC ligand (i.e., 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-yl or SIDIPP) and first synthesized by Fürstner and co-workers,[31] has proved to be a fast initiator and a highly active catalyst (**Figure 4**).[23,25b,32]

2.3. Applications of Second-Generation Grubbs Catalysts

By virtue of their greatly enhanced activity vis-à-vis their first-generation counterparts, the second-generation catalysts promote the metathesis of sterically demanding or deactivated olefins. In particular, second-generation Grubbs complexes have shown increased activity in ring-closing metatheses (**eq 1–3**),[22,33,34] and in macrocyclizations.[35] They also catalyze challenging cross-metatheses[1h,36] including the coupling of olefins with α,β-unsaturated carbonyls,[37] vinylphosphonates,[38] and 1,1-disubstituted alkenes (**Scheme 2**).[39]

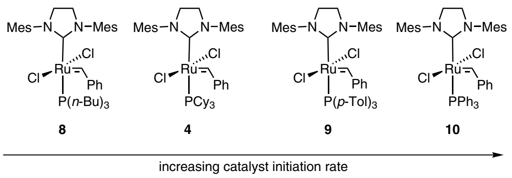
A model for the prediction of the outcome of cross-metathesis reactions has been developed based on the categorization of olefins according to their relative propensity to homodimerize via cross-metathesis and the ability of their homodimers to undergo secondary metathesis.[40] Based on this model, olefinic substrates are divided into four different types. Whether a certain olefin belongs to one type or another depends on the nature of the metathesis catalyst used (**Table 1**). Cross-metatheses between two olefins of Type I yield product mixtures that correspond to statistical distributions. Additionally, reactions between two olefins of the same type (but not of Type I) give nonselective product mixtures, while reactions between olefins of two different types are selective processes.

The ability of the second-generation catalysts to couple olefins with α,β-unsaturated carbonyls has been utilized to prepare A,B-alternating copolymers by ring-opening insertion metathesis polymerization (ROIMP).[41] Additionally, these catalysts promote the enyne metathesis of alkynes to make interesting 1,3-dienes (**eq 4,5**).[9,34,42,43] Finally, second-generation systems are often the catalysts of choice for the preparation of novel ROMP polymers, including ROMP-based immobilized reagents and scavengers.[44]

3. Phosphine-Free, SIMes-Based Second-Generation Catalysts

A phosphine-free catalyst, **14**, containing an SIMes and a chelating benzylidene ether ligand has been introduced by Hoveyda and co-workers (**Figure 5**).[45,46] This complex shows efficiencies similar to the Grubbs systems, but has slightly different substrate specificities. It is a particularly efficient catalyst for metatheses involving highly electron-deficient substrates such as acrylonitrile and fluorinated alkenes.[47]

Other phosphine-free catalysts of the Hoveyda type have been prepared by introducing different substitution patterns on the chelating benzylidene ether ligand. Thus, Blechert and co-workers have reported complexes bearing more sterically hindered chelating ligands (**15** and **16**),[48] while Grela and co-workers have disclosed benzylidene ether moieties with



Ref. 28,29

Figure 3. Effect of the Nature of the Phosphine Ligand on the Initiation Rate of the Second-Generation Catalyst.

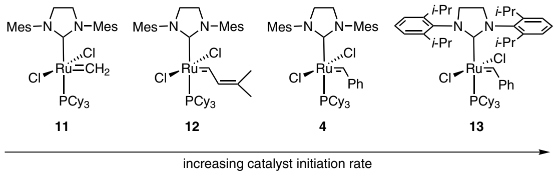


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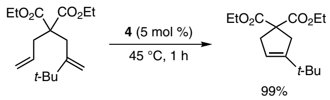
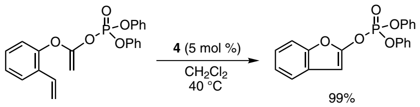
Figure 4. Influence of the Nature of the Alkylidene and NHC Ligands on the Initiation Rate of the Second-Generation Catalyst.



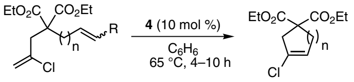
Ref. 22

eq 1



Ref. 34b

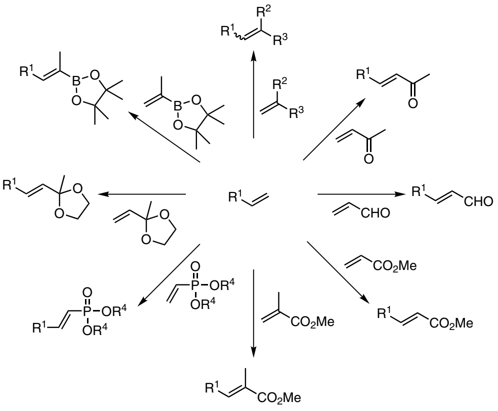
eq 2



n	R	Yield
1	H	85%
1	Me	96%
2	H	99%
2	Me	98%
3	H	92%

Ref. 34c

eq 3

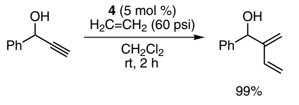


Ref. 37–39

Scheme 2. Cross-Metatheses Catalyzed by Second-Generation Grubbs Catalysts.

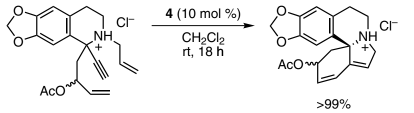
Table 1. Olefin Categories Based on Their Metathesis Reactivity

Olefin Type	First-Generation Grubbs Catalysts	Second-Generation Grubbs Catalysts
Type I (facile homodimerization; homodimers are readily consumable)	terminal olefins; allyl silanes; 1° allylic alcohols, ethers, and esters; allyl boronate esters; allyl halides	terminal olefins, 1° allylic alcohols and esters; allyl boronate esters; allyl halides; styrenes (without large ortho substituents); allyl phosphonates; allyl silanes; allyl phosphine oxides; allyl sulfides; protected allylic amines
Type II (more difficult homodimerization; homodimers sparingly consumable)	styrenes; 2° allylic alcohols; vinyl dioxolanes; vinyl boronates	styrenes (with large ortho substituents); acrylates; acrylamides; acrylic acid; acrolein; vinyl ketones; unprotected 3° allylic alcohols; vinyl epoxides; 2° allylic alcohols; perfluorinated alkane olefins
Type III (no homodimerization)	vinyl siloxanes	1,1-disubstituted olefins; nonbulky trisubstituted olefins; vinyl phosphonates; phenyl vinyl sulfone; 4° allylic hydrocarbons; protected 3° allylic alcohols
Type IV (spectator substrates: do not undergo cross-metathesis)	1,1-disubstituted olefins; disubstituted α,β-unsaturated carbonyls; 4° allylic carbon-containing olefins; perfluorinated alkane olefins; protected 3° allylic amines	olefins with vinylic nitro group; protected trisubstituted allylic alcohols



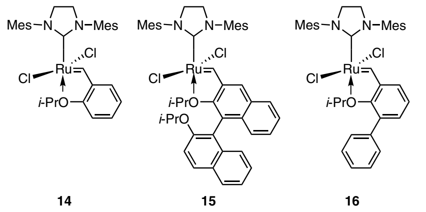
Ref. 42

eq 4



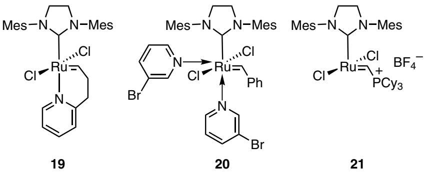
Ref. 43

eq 5



Ref. 45,48,49

Figure 5. Phosphine-Free, SIMes-Based Second-Generation Catalysts.



Ref. 50,52,55

Figure 6. Very Slow and Very Fast Initiating, Second-Generation Catalysts.

electron-withdrawing substituents in the position para to the alkoxy group to make catalysts such as compounds **17** and **18**.[49] Both of these steric and electronic alterations of the original ligand have resulted in faster-initiating catalysts than the parent Hoveyda complex **14**, presumably because the ether ligands in species **15–18** dissociate faster from the ruthenium than the ether ligand in catalyst **14**.

4. Slow- and Fast-Initiating NHC-Based Catalysts

Additional tuning of the initiation rates led to the development of exceptionally slow- and exceptionally fast-initiating metathesis catalysts. Thus, complex **19** (**Figure 6**) is a latent phosphine-free initiator, but a highly active catalyst once it has initiated.[50,51] As such, complex **19** is a useful promoter for the ROMP of strained cyclic olefinic monomers such as dicyclopentadiene.[26] On the other hand, catalyst **20** is a very fast phosphine-free initiator,[52] which has proved useful for the production of polymers with narrow polydispersities and for the synthesis of block copolymers.[53,54]

Catalysts such as compound **21**, developed by Piers and co-workers, are extremely fast initiators and are capable of catalyzing the ring-closing metathesis of terminal dienes at 0 °C.[55] The ability of Piers's systems to turn over at very low temperatures has proved useful in very elegant mechanistic studies resulting in the direct observation of olefin metathesis metallacyclobutane intermediates,[56] and has made them ideal candidates for low-temperature applications.

5. Other Recent Developments in the Design of Second-Generation Catalysts

5.1. Second-Generation Catalysts Based on Unsymmetrical Alkyl,Aryl-NHC Ligands

Second-Generation-type systems bearing unsymmetrical saturated NHC ligands, substituted with an alkyl group on one nitrogen atom and an aryl group on the other, were initially investigated by Mol and co-workers, who prepared the mixed 1-adamantyl,mesityl complex **22** (**Figure 7**).[57] This compound turned out to be an extremely poor metathesis catalyst, presumably because of the large steric hindrance resulting from the adamantyl substituent.[57]

More recently, Blechert's research group reported the preparation of mixed methyl,mesityl and ethyl,mesityl systems of the Grubbs and Hoveyda–Grubbs types (**23** and **24**).[58] These complexes demonstrated activities comparable to the Grubbs and Hoveyda–Grubbs analogues **4** and **14** in the metathesis of several common substrates. However, catalyst **24** performed much more poorly than **14** in a challenging cross-metathesis with acrylonitrile.[58] Additionally, complex **23** gave lower *E/Z* ratios than **4** and **14** in various cross-metatheses. While this specificity may prove useful in certain applications, it is also an additional hint that mixed alkyl,aryl systems tend to be less active than bisaryl ones.[59]

5.2. Chiral, Second-Generation Ruthenium Metathesis Catalysts[60]

Although the syntheses of the first ruthenium metathesis catalysts with chiral, saturated NHC ligands (e.g., complex **25**) go back to the time of the discovery of the second-generation catalysts,[22] asymmetric metatheses affording appreciable enantiomeric excesses were not achieved until chiral complexes such as **26** and **27** were developed by the Grubbs and Hoveyda groups, respectively (**Figure 8**).[61,62] Complex **26** effectively catalyzed the desymmetrizing RCM of prochiral trienes to afford enantiomeric excesses ranging from 13% to 90%.[61] Catalyst **27** led to high enantioselectivities in the asymmetric, tandem, ring-opening metatheses–cross-metatheses of tricyclic norbornene derivatives.[62] However, complex **27** is altogether a less active catalyst and requires elevated reaction temperatures and prolonged reaction times. Hoveyda and co-workers have subsequently reported analogs of **27** with enhanced catalytic activity using lower catalyst loadings.[63] More recently, Grubbs and collaborators developed highly active analogues of catalyst **25** (e.g., **28**) that can induce chirality with greater efficiency than **25**.[64]

5.3. Immobilized, Second-Generation Catalysts and Related Developments

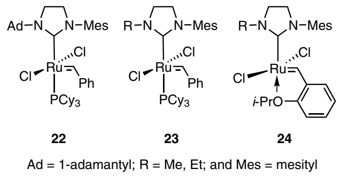
Considerable research efforts have been applied to immobilizing second-generation catalysts on various supports.[65] Many of the systems prepared involve the attachment of the ruthenium complex via its alkylidene moiety.[45,66] This approach, by its nature, does not lead to a permanent anchoring of the system on the support, but rather to a controlled release of the catalytic species into the reaction solution. Depending on the specific systems employed, the released metal species have been observed to partially return and reattach themselves to the support.[45] Other approaches consist of attaching the ruthenium catalysts via the NHC or the anionic ligands.[66c,67] The most noteworthy examples of this approach are the catalysts immobilized on silica, polymers, or monolithic supports developed by Buchmeiser and co-workers.[68] Using similar strategies, Grubbs and co-workers have prepared an active, water-soluble catalyst by connecting the NHC ligand to a poly(ethylene glycol) chain.[69] A related development was recently reported by the Gladysz group, who prepared a second-generation Grubbs catalyst bearing a fluorinated phosphine ligand and used it in biphasic reactions.[70]

5.4. Second-Generation Catalysts for the Metathesis of Hindered Olefins

The most exciting recent additions to the family of second-generation catalysts concern the metathesis of hindered olefins and, in particular, RCM to form tetrasubstituted cycloalkenes. While catalysts **2**, **3**, **4,** and **14** have enabled several such transformations,[15c,16,23,24] RCM to make tetrasubstituted, five-membered-ring olefins (e.g., RCM of dimethallylmalonates) had remained especially challenging until very recently. Indeed, catalysts **4** and **14** gave a 6% and a 17% conversion, respectively, in the RCM of diethyl dimethallylmalonate *after 4 days* at 30 °C.[23] The best catalyst systems for making tetrasubstituted, five-membered cycloalkenes, the unsaturated NHC-based catalysts (e.g., complexes **2** and **3**), gave *a modest 31% conversion after 4 days* at 30 °C.[23] As a result, an extensive search for improved catalysts for the metathesis of hindered olefins was undertaken. Complexes **29**–**31**, prepared by Grubbs and co-workers (**Figure 9**),[71–73] are more efficient catalysts for such transformations than **2**–**4** and **14**. For example, **29**–**31** all afford high conversions (~ 90%) in the RCM of diethyl dimethallylmalonate after 24 hours at 60 °C.[72,73] However, attempts to optimize and scale up the preparation of these catalysts revealed that they would be relatively difficult and expensive to produce at scale.[74] Most recently, catalysts **32** and **33** were developed and the scope of their utility investigated. These complexes proved to be the most efficient catalysts in the benchmark RCM of dimethallylmalonates, affording *greater than 95% conversion in less than 1 hour* (**eq 6**).[75]

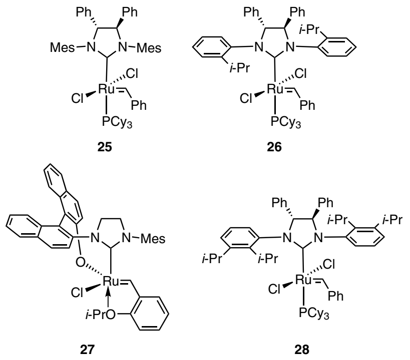
6. Practical Considerations for Using Olefin Metathesis Catalysts

Many of the first- and second-generation Grubbs and Hoveyda–Grubbs catalysts discussed so far are commercially available. Olefin metathesis reactions catalyzed by these ruthenium-based catalysts can be conducted in neat olefinic substrates or in solvents of varied polarities. Toluene and dichloromethane are most commonly used, but 1,2-dichloroethane, chlorinated benzenes, diethyl ether, tetrahydrofuran, ethyl acetate, acetone, and methanol may also be employed. Of further utility,



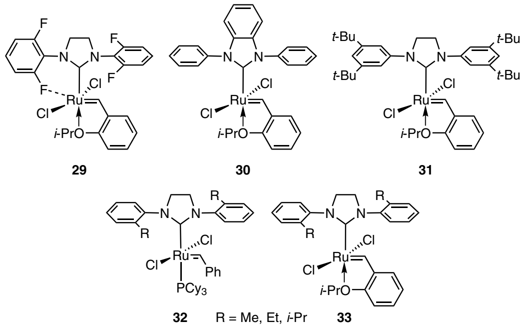
Ref. 57,58

Figure 7. Second-Generation Catalysts Based on Unsymmetrical Alkyl,Aryl-Substituted NHCs.



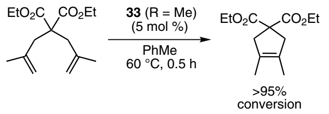
Ref. 22,61,62,64

Figure 8. Examples of Chiral Ruthenium Olefin Metathesis Catalysts.



Ref. 71,72,73,75

Figure 9. Highly Efficient Catalysts for the Metathesis of Hindered Olefins.



Ref. 75

eq 6

solvents and substrates do not need to be anhydrous. Although ruthenium-based catalysts are relatively robust to oxygen, degassing the reaction solvents and olefinic substrates before adding the catalysts is recommended. Additionally, improved efficiencies may be obtained upon further purification of the olefinic substrates by filtration through silica gel or activated alumina.

Reaction temperatures of about 30 to 50 °C are typical for second-generation Grubbs and Hoveyda–Grubbs catalysts (i.e., complexes **4** and **14**, respectively). Catalysts **8**, **12**, and **19** will usually require higher temperatures (e.g., about 50 to 60 °C for **12**, and about 60 to 80 °C for **8** and **19**) to perform adequately, while catalysts **10** and **20** may be used at lower temperatures (e.g., about 10 °C for **10**, and about 0 °C for **20**). **Table 2** summarizes the specificities of different catalysts. Optimal catalyst and substrate loadings may vary depending on the metathesis reaction, the catalyst, and the reaction conditions, but typical loadings are in the range of 0.1–5 mol %. Finally, upon completion of the metathesis reaction, the catalyst can be removed from the products or from the organic phase by employing published methods.[76]

7. Conclusions

Although first-generation olefin metathesis catalysts such as the first-generation Grubbs and Hoveyda–Grubbs systems remain extremely useful tools in synthetic chemistry, the introduction and evolution of the second-generation catalysts have greatly widened the scope of chemical transformations enabled by metathesis reactions. The second-generation Grubbs (e.g., **4** and **12**) and Hoveyda–Grubbs (e.g., **14**) catalysts have opened the way to new metathesis applications including the formation of trisubstituted cycloalkenes via RCM and the polymerization and cross-metathesis of sterically hindered or electronically deactivated olefins. Moreover, many second-generation catalysts have been developed to address additional needs of synthetic chemists. Slow-initiating, phosphine-containing (e.g., **8**) and phosphine-free (e.g., **19**) catalysts were designed for the controlled ROMP of strained cyclic olefins, while fast-initiating phosphine-containing (e.g., **10**) and extremely fast-initiating phosphine-free (e.g., **20**) systems may be used in low-temperature metathesis processes or in the production of polymers with narrow polydispersities. Additionally, recently developed systems that contain small, saturated NHC ligands (e.g., **32** and **33**) are very efficient at promoting the metathesis of hindered alkenes, even RCM to form tetrasubstituted, five-membered-ring cyclic olefins. By opening these new avenues, catalysts **32** and **33** promise to lead to new exciting applications.

Table 2. Specificities of Olefin Metathesis Catalysts

Catalyst	Comments
First-generation Grubbs	Useful in the ROMP of strained cyclic olefins, in the ethenolysis of internal olefins, as well as in the ADMET, CM, and RCM of terminal olefins.
First-generation Hoveyda–Grubbs	Possesses reactivity similar to that of first-generation Grubbs. Especially useful in the industrial production of macrocycles via RCM.
4	Known as the second-generation Grubbs catalyst and is considerably more active than the first-generation catalysts. Has shown increased activity in RCM and has been employed in challenging CMs of sterically demanding or deactivated olefins, including 1,1-disubstituted olefins and α,β-unsaturated carbonyls. Typically used at 30–50 °C.
8	A much slower initiator than **4** and requires higher reaction temperatures (e.g., 60–80 °C).
10	A faster initiator than **4** and can therefore be used at lower temperatures than **4** (e.g., 10–30 °C).
12	Slower to initiate than **4**, but faster than **8**. Requires reaction temperatures of typically 50 to 60 °C.
14	Known as the second-generation Hoveyda–Grubbs catalyst and possesses reactivity comparable to that of **4**. However, it initiates more readily at lower temperatures (e.g., 5–30 °C), depending on the other reaction conditions such as catalyst loading and substrate concentration. Is also an efficient catalyst for the metathesis of highly electron-deficient substrates such as acrylonitrile.
19	A latent initiator that possesses the high activity of second-generation catalysts once it has initiated. Was developed mainly for industrial ROMP applications, in which longer monomer or catalyst resin handling times are desired. Its latency could also prove useful in other applications.
20	A much faster initiator than **4** and can therefore be used at lower temperatures (e.g., ~0 °C), depending on the other reaction conditions. It tends to be less soluble than **4** in nonpolar solvents, and is generally less stable than **4** in solution. Has been employed in the production of block copolymers and polymers with narrow polydispersities.
32 (R = Me)	A highly efficient catalyst for the metathesis of hindered olefins. Is particularly useful in the preparation of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins.
33 (R = Me)	This is the Hoveyda–Grubbs analogue of **32** (R = Me). Is also useful in the synthesis of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins. Depending on the substrate and reaction conditions, it may prove more efficient than **32** (R = Me).

Together, compounds **4**, **8**, **10**, **12**, **14**, **19**, **20**, **32,** and **33**, along with the first-generation Grubbs and Hoveyda–Grubbs complexes, constitute a powerful tool kit that allows synthetic chemists to perform most metathesis transformations currently facilitated by the class of ruthenium-based olefin metathesis catalysts. These catalysts have enabled and will continue to enable the preparation of previously unattainable molecules and materials in all fields of chemistry and materials science.

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Richard L. Pederson was born in 1962 in Albert Lea, Minnesota. He earned his B.S. degree in chemistry in 1985 from the University of Wisconsin-River Falls, where he did research under Professor John Hill. He worked under the supervision of Professor Chi-Huey Wong at Texas A&M University, earning his Ph.D. degree in organic chemistry in 1990. He joined Bend Research, Inc. in Bend, Oregon, where, in 1997, he and Professor Robert H. Grubbs patented the production of insect pheromones using ruthenium metathesis catalysts. Dr. Pederson has spent the last twelve years in entrepreneurial start-ups using olefin metathesis to develop new routes to insect pheromones and pharmaceutical intermediates, while also managing numerous projects and technical personnel. In 2000, he joined Materia, Inc., to start up the Fine Chemicals Group, where he is the Director of Fine Chemicals R&D. Dr. Pederson is the author of numerous patents and publications, including key patents related to the production of chelating metathesis ligands and the use of metathesis in the production of insect pheromones.