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Cyclic (Alkyl)(Amino)carbenes (CAACs) in Ruthenium Olefin Metathesis

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TOC:



Abstract: Discovered in 2005, cyclic (alkyl)(amino)carbenes (CAACs) have led to numerous discoveries in the field of ruthenium olefin metathesis, until then largely dominated by the well-known *N*-heterocyclic carbenes (NHCs). Compared to the latter, CAACs are simultaneously more nucleophilic (σ -donating) and electrophilic (π -accepting), which leads to very strong metal-carbene bonds. Consequently, CAAC-ruthenium complexes are very robust, which leads to enhanced catalytic activities, as exemplified by the industrially relevant ethenolysis of unsaturated fatty acids (up to of 390,000 TON). Herein, we provide a

Revised manuscript

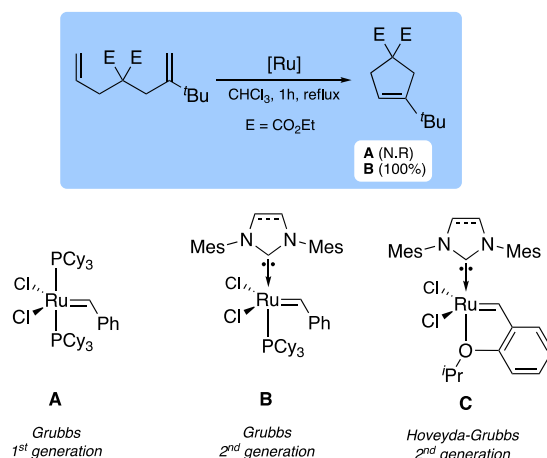
comprehensive overview of the impact of CAAC ligands in olefin metathesis, including results which are described in patents.

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1. Introduction

The discovery of stable carbenes at the end of the last century^{1,2} has unarguably triggered a profound revolution in transition metal catalysis. Until then, the field was largely dominated by phosphines as ancillary ligands.³ One of the most prominent examples is witnessed by the evolution of the first generation Grubbs ruthenium olefin metathesis catalyst **A**.⁴ The replacement of one of the two PCy₃ ligands in **A**, by the strong σ -donor and poor π -acceptor 1,3-dimesitylimidazol-2-ylidene (IMes),² (a carbene from the family of *N*-heterocyclic carbenes; *i.e.* NHCs), resulted in the extremely stable, yet very reactive second-generation Grubbs catalyst **B** (Scheme 1).^{5,6,7,8,9,10} The superior catalytic activity of **B** over **A**, originally demonstrated in the preparation of di-, tri-, and even tetra-substituted olefins,^{4,11} was later established across multiple other systems.^{5,6,7} This breakthrough, also referenced as the 00's of metathesis, paved the way for the development of hundreds of metathesis catalysts featuring *N*-heterocyclic carbene ligands,^{8,9,10} as seen with the well-known second generation Hoveyda-Grubbs catalysts **C**.¹² Recently, another class of stable singlet carbenes, named cyclic (alkyl)(amino)carbenes (CAACs), have gained considerable momentum in this field and have only briefly been discussed in a few review articles.^{13,14,15,16,17} Herein, we provide a comprehensive summary of the impact of CAACs in olefin metathesis, since the first report in 2007, including results which were only reported in patents (the latter are highlighted in pink in the schemes and figures).



Scheme 1 The debut of *N*-heterocyclic carbenes in ruthenium olefin metathesis

2. Ligand and Catalyst Design

2.1. CAACs: Properties and Preparation.

To understand the advantages and limitations of CAACs versus NHCs in ruthenium olefin metathesis, a brief comparison of their electronic properties and steric contribution is necessary.^{18,19,20,21} CAACs differ from NHCs by the presence of a σ -donating quaternary carbon α to the carbene center instead of a π -donating and σ -attracting amino group (Figure 1). As a result, CAACs are simultaneously more nucleophilic and electrophilic than traditional NHCs (HOMO: -5.35 vs. -5.82 eV and LUMO: +0.06 vs. +1.00 eV). Also contrasting with NHCs, where the steric contribution is best described as an umbrella with pendant *N*-substituents oriented towards the metal (as opposed to phosphines), the sp^3 -hybridized α carbon of CAACs provides a wall of protection. Additionally, this quaternary carbon provides a mean to introduce chirality much closer to the metal not feasible with conventional NHCs.²²

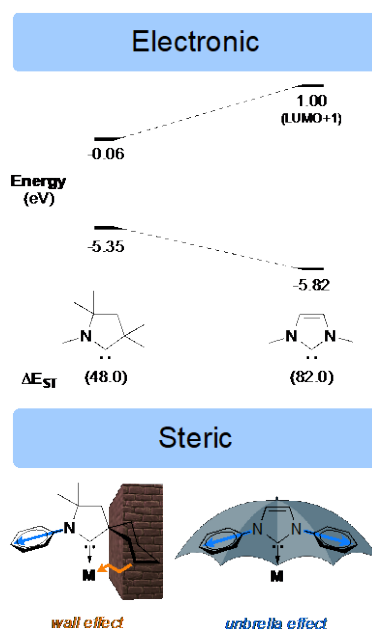
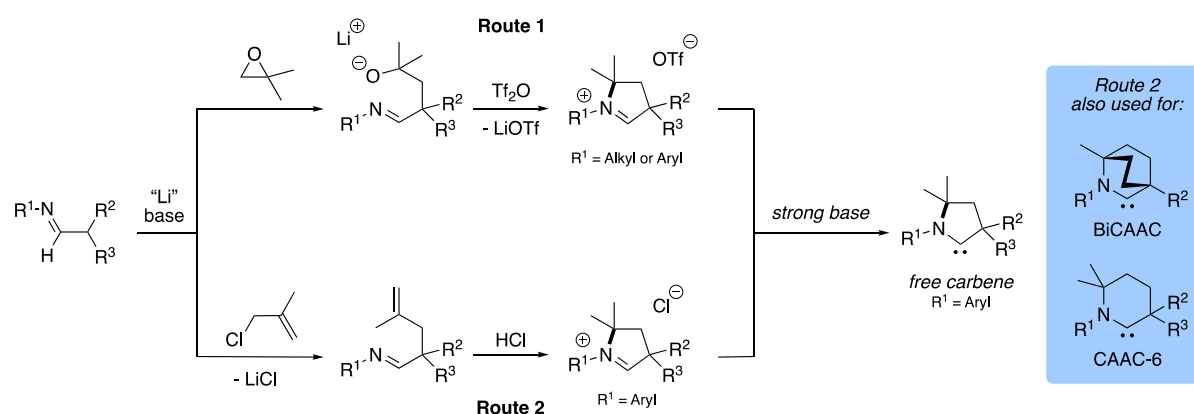


Figure 1. Electronic and steric properties of CAACs versus NHCs

The preparation of aldiminium cations, the conjugate acids of CAACs, has been achieved by two complementary synthetic routes (Scheme 2). While both methods involve the addition of electrophiles to aza-allyl anion intermediates, followed by ring closure, they differ in the nature

of the electrophile. For Route 1, the use of epoxides allows for introducing both alkyl and aryl groups at nitrogen but is somewhat restricted to relatively sterically uncongested sp^3 -hybridized carbon center.^{23,24} On the other hand, Route 2 is limited to *N*-aryl substituents, but more tolerant to steric congestion at the sp^3 carbon. It proceeds via an allylation followed by an intramolecular hydroiminium reaction.^{25,26} In recent years, Route 2 has been used for the preparation of more ambiphilic CAAC ligands such as the bicyclic (alkyl)(amino)carbenes (BiCAACs) and the 6-membered cyclic (alkyl)(amino)carbenes (CAAC-6s).^{27,28} In all cases, free CAACs were obtained from the corresponding aldiminium salts by deprotonation with a strong base such as KHMDS or LDA.



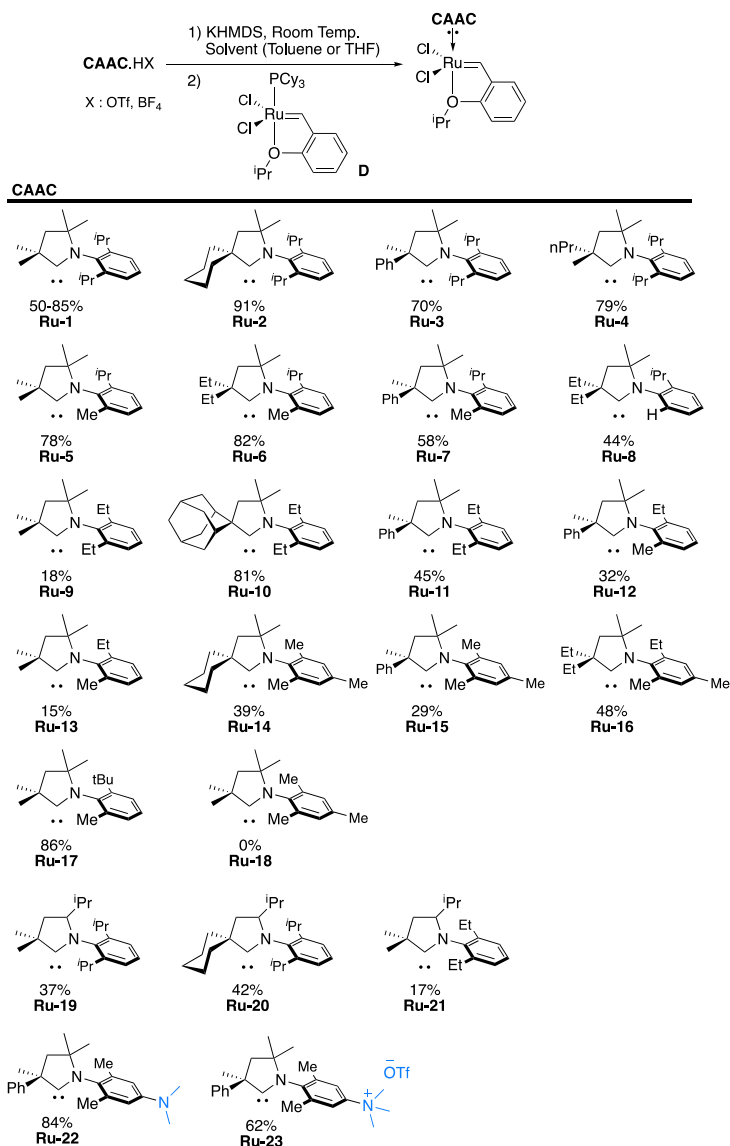
Scheme 2. Synthesis of CAACs

2.2. Heteroleptic (CAAC)Ruthenium Metathesis Complexes

2.2.1 Hoveyda-Grubbs (CAAC)Ruthenium Type Complexes

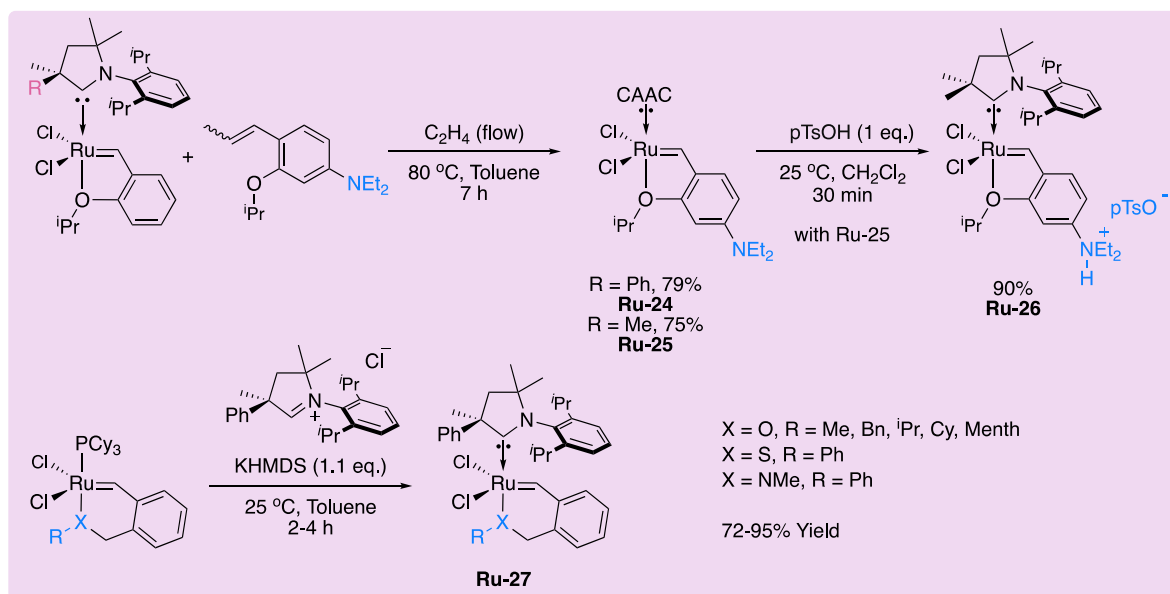
Second generation heteroleptic ruthenium metathesis complexes are typically accessed by ligand exchange, reacting the free NHC with inexpensive and readily available first-generation complexes bearing a sacrificial phosphine ligand (e.g. PCy₃). With NHC, this route classically relies on *in situ* generation of free carbenes by treatment of various imidazolium salts with a strong base.²⁹ This is also the case with CAACs which can be generated *in situ* and undergo ligand exchange at room temperature with Hoveyda-Grubbs first generation **D**³⁰ (Scheme 3).^{31,32,33} While yields appear counterintuitively higher with more sterically demanding

ligands, it is likely a consequence of the propensity of some of the metal-free CAACs to degrade via intramolecular insertion into benzylic C(sp³)-H bonds of aryl substituents.³⁴ With bulky groups, the aryl moiety is forced to be perpendicular to the CAAC skeleton, which prevents its *ortho*-substituents from approaching the carbene center. As seen with **Ru1-Ru18**, most of the modifications of the CAAC ligands in ruthenium complexes have been achieved by changing substituents on the *N*-Aryl or at the quaternary carbon adjacent to the carbene center. To investigate the influence of the backbone over the catalytic performance of these complexes, Zhang, Shi and coworkers, prepared complexes **Ru19-Ru21** bearing a bulky isopropyl group β to the carbene center.³⁵ More recently, Tóth, Tuba and coworkers extended the variety of (CAAC)Ru complexes to **Ru-22** and **Ru-23** in which the CAAC features an amino and an ammonium group on the *N*-aryl moiety.³⁶ The latter is highly polar and was shown to be soluble in environmentally benign protic media without compromising the high catalytic activity and stability.



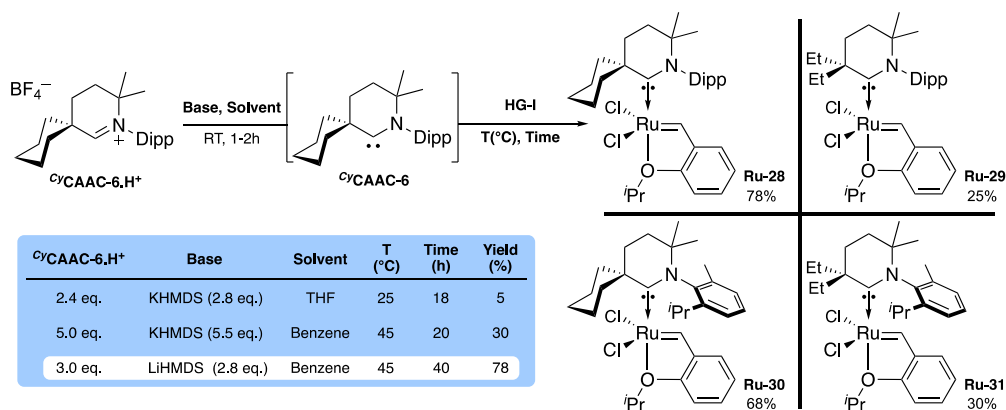
Scheme 3 Synthesis of Hoveyda-Grubbs CAACs

As shown by Olivier-Bourbigou and coworkers, the benzylidene moiety of CAAC derived Hoveyda-Grubbs complexes are readily tunable by simple addition of a chelating olefin (Scheme 4).³⁷ These authors used this pathway to introduce an amino group on the benzylidene fragment as shown by complexes **Ru-24** and **Ru-25**. In line with a report by Grela, Kirschning and coworkers,³⁸ subsequent protonation of the amino substituent of **Ru-25** with *p*TsOH afforded complex **Ru-26** which appeared to be more active, probably due to the increased lability of the benzylidene fragment. The benzylidene variants **Ru-27** have also been obtained by reacting pre-functionalized 1st generation precursors with *in situ* generated CAACs.³⁹



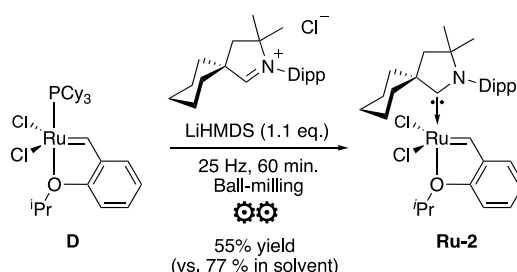
Scheme 4 Preparation of Ruthenium metathesis CAACs complexes with various benzylidene fragments

These methodologies are not limited to CAAC-5, and can be extended to other motifs of the CAAC family. Indeed, Grubbs and coworkers have recently reported the first example of CAAC-6 ruthenium metathesis complexes **Ru-28-31** (Scheme 5).⁴⁰ Here also, excellent yields were obtained with the sterically hindered cyclohexyl derivatives (>68%), whereas less hindered ethyl derivatives resulted in much lower yields (<30%). Note that the ethyl substituted CAAC-6 is less stable than the CAAC-5 analogues.²⁸ Moreover, the authors stated that decreasing sterics at nitrogen (e.g., *N*-mesityl group) or at the quaternary α -carbon (e.g., gem-dimethyl) proved challenging, because of the difficulty in preparing the CAAC conjugate acids.²⁵



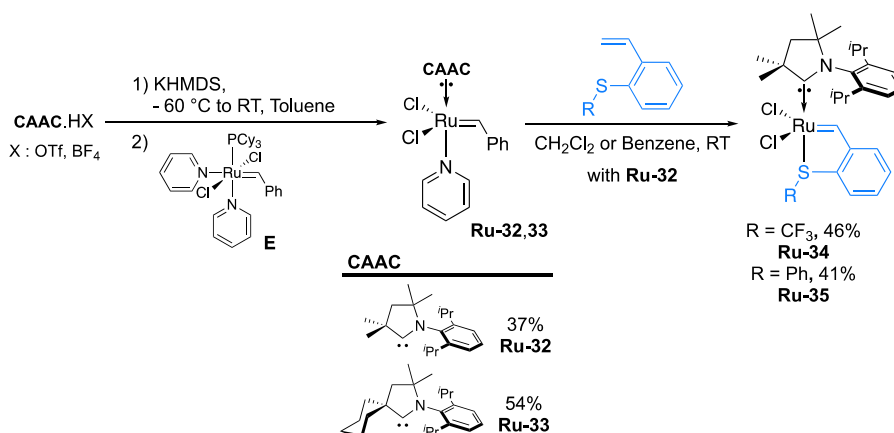
Scheme 5 Preparation of Hoveyda-Grubbs CAAC-6 complexes

As highlighted by Fogg *et al.*,⁴¹ numerous issues have been associated with the preparation of (carbene)Ru metathesis pre-catalysts by *in situ* generation of the free carbene. Looking for alternatives,^{42,43,44,45} Grela and coworkers disclosed the use of mechanochemistry (ball-milling) as a mild and solvent free method for the preparation of CAAC Hoveyda-Grubbs complexes (Scheme 6).⁴⁶ While the method compares reasonably well with the homogeneous route (55% yield vs. 77% for **Ru-2**), it arguably opens new prospects for the preparation of Hoveyda-Grubbs complexes of more challenging or low yielding CAAC motifs.



Scheme 6 Mechanochemical preparation of (CAAC)Ru metathesis pre-catalysts.

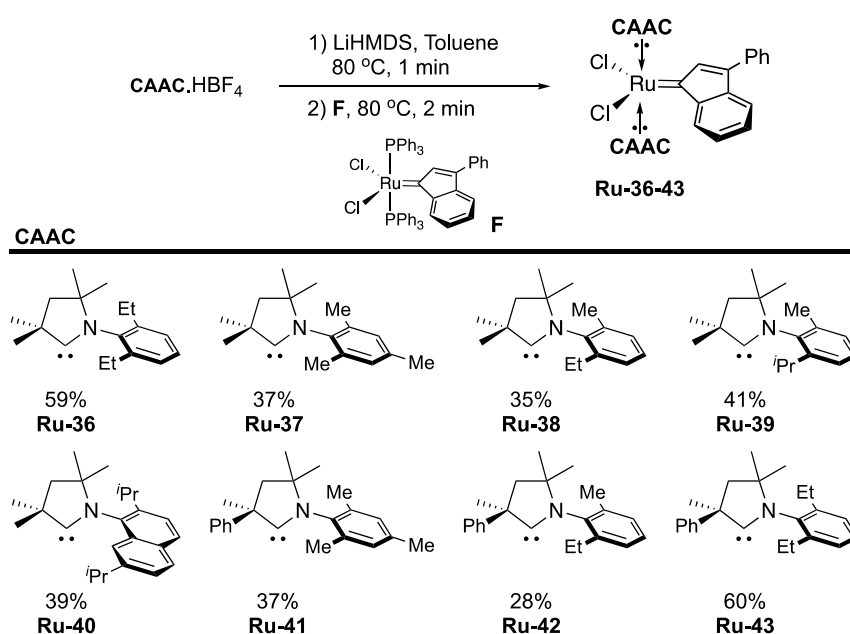
For its ability to undergo facile ligand exchange with stronger donors, pyridine complex **E** has also been used as precursor for Hoveyda-Grubbs type (CAAC)Ruthenium pre-catalysts (Scheme 7).³² As expected, treatment of **E** with CAACs, generated *in situ*, afforded the air-sensitive pyridine adducts **Ru-32** and **Ru-33**, which were isolated in modest yields. Building upon these results, Lemcoff and coworkers have shown that **Ru-32** provides a convenient route to sulfur-chelated ruthenium benzylidenes **Ru-34** and **Ru-35**.⁴⁷



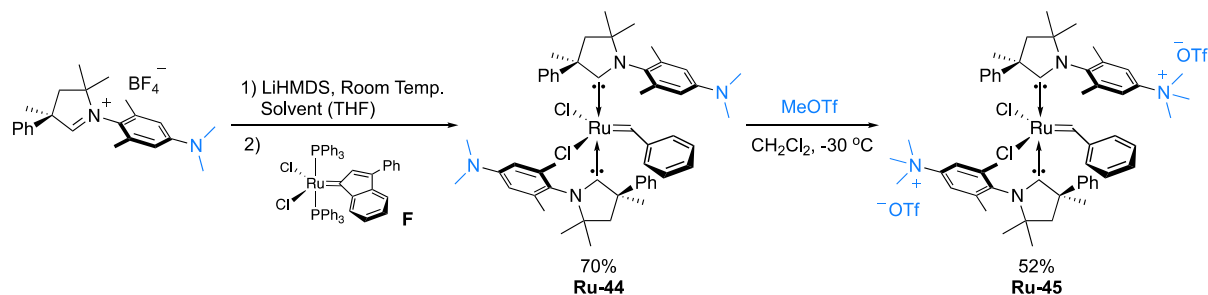
Scheme 7 Preparation of sulfur-chelated ruthenium benzylidene complexes

2.2.2 Indenylidene (CAAC)Ruthenium Type Complexes

Until recently, (CAAC)Ru complexes were mainly obtained using Hoveyda-Grubbs first-generation benzylidene complex **D** (*vide supra*), the preparation of which can be challenging.³⁰ Aiming to develop a more versatile route, Skowerski and coworkers examined the preparation of CAAC olefin metathesis ruthenium catalysts from readily accessible and patent-free precursors. They considered the indenylidene complex **F** bearing two triphenyl phosphine ligands. Excitingly, in contrast with NHCs,^{48,49} reaction of **F** with three equivalents of *in situ* generated CAACs, resulted in the formation of bis(CAAC)Ru indenylidene complexes **Ru-36-43** (Scheme 8).^{52,53} Note that higher yields were obtained with the indenylidene complex bearing two tricyclohexyl phosphines, albeit with longer reaction times. Tóth, Tuba and coworkers extended this methodology to CAAC bearing NMe₂ **Ru-44** and *N*-Me₃⁺ ammonium **Ru-45** groups on the *N*-aryl moiety (Scheme 9).³⁶

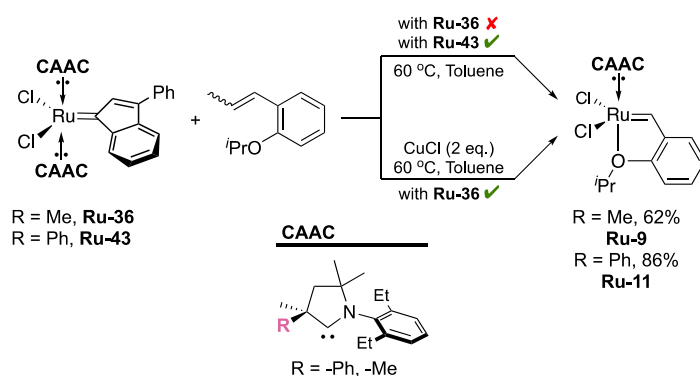


Scheme 8 Preparation of bis(CAAC)Ru indenylidene complexes



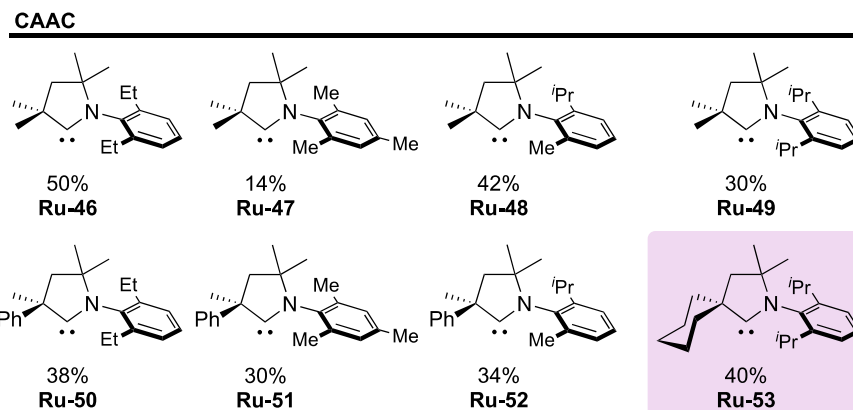
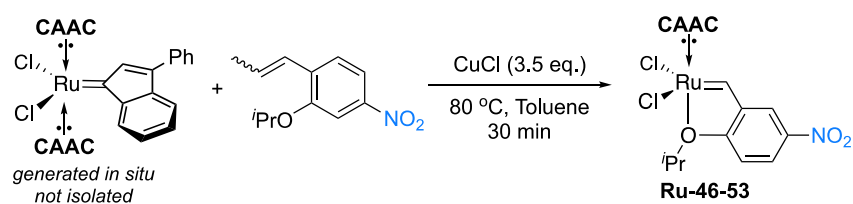
Scheme 9 Preparation of bis(CAAC)Ru complexes bearing polar amino substituents

The propensity of ruthenium bis-NHCs alkylidenes to generate active catalytic species has been discussed.^{43,51,54,55} To determine whether strongly σ -donating and π -accepting CAACs could impede or facilitate the activation of bis-CAAC-Ru-indenylidene complexes, Skowerski and coworkers next examined their reaction with a doubly chelating olefin.⁵² As shown in Scheme 10, reaction of **Ru-43** with 1-isopropoxy-2-(propenyl)benzene at 60 °C in toluene led to the clean formation of the Hoveyda-Grubbs derivative **Ru-11**, which was isolated in 86% yield. Interestingly, the authors also noted that under the same conditions no conversion was observed with the less sterically hindered **Ru-36** even after 48h. However, it was shown that simple addition of CuCl (2 eq.), likely acting as a carbene scavenger, is sufficient to drive the reaction forward, thus affording complex **Ru-9** in good yield.

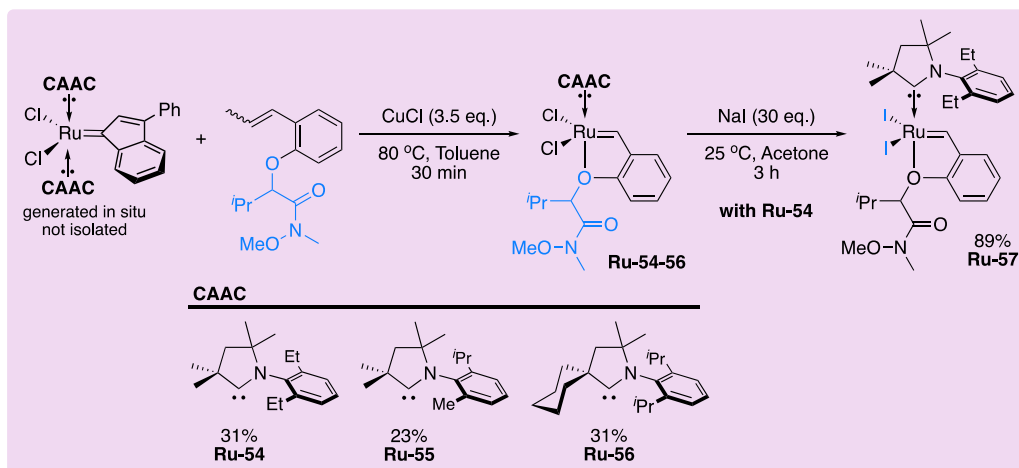


Scheme 10 Accessing Hoveyda-Grubbs type complexes from bis(CAAC)Ru indenylidenes

Capitalizing on these results the same group extended the methodology to other Grela type⁵⁶ Hoveya-Grubbs CAAC-ruthenium metathesis complexes **Ru-46-52** (Scheme 11),^{57,58} as well as **Ru-53** and **Ru-54-57** which were only reported in a patent (Scheme 12).⁵⁹

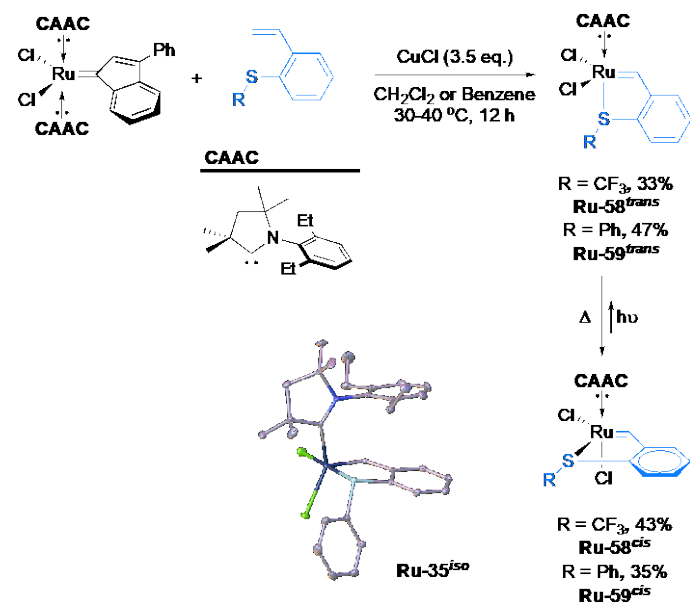


Scheme 11 Accessing nitro-Grela type complexes from bis(CAAC)Ru indenylidenes



Scheme 12 Bis(CAAC)Ru indenylidenes a convenient route to mono-CAAC ruthenium metathesis complexes

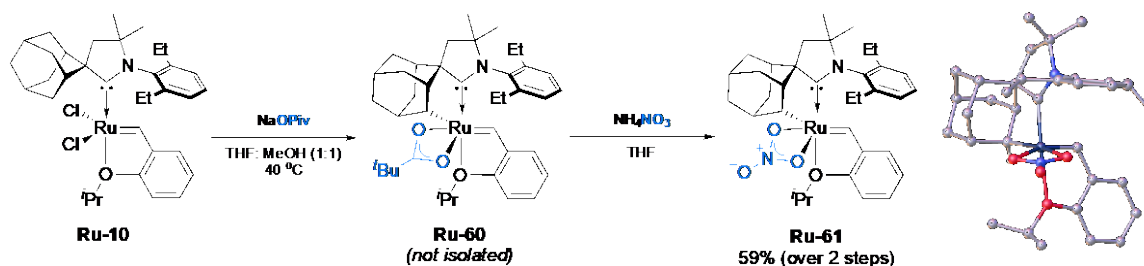
Similarly, Lemcoff and coworkers showed that sulfur-chelated ruthenium benzylidenes **Ru-58** and **Ru-59** are also accessible by this route as a mixture of *trans*- and *cis*- isomers (Scheme 13).⁴⁷ The *cis/trans* ratio could readily be tuned by solvent polarity and temperature, and UV-irradiation was sufficient to revert from *cis* to *trans*.



Scheme 13 Preparation and configurational behavior of sulfur-chelated ruthenium benzylidenes

2.2.3. Other Types of (CAAC)Ruthenium Complexes

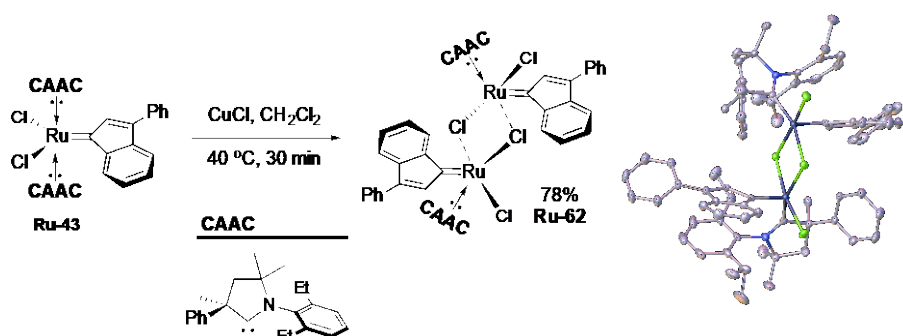
The development of Z-selective ruthenium-based catalysts bearing cyclometalated NHC ligands^{60,61} has been expanded to CAAC derivatives.⁶² As shown in Scheme 14, the general synthetic strategy used to access the adamantyl variant **Ru-60**, involves the exchange of the chlorines of Hoveyda-Grubbs CAAC complex **Ru-10** with sodium-pivalate. With NHCs, cyclometalated-nitrato catalyst have been shown to afford more stable and more selective catalysts.⁶³ The CAAC analogue **Ru-61** is readily available in 59% yield by simple treatment of **Ru-60** with ammonium nitrate.



Scheme 14 Preparation of CAAC-Ru cyclometalated complexes

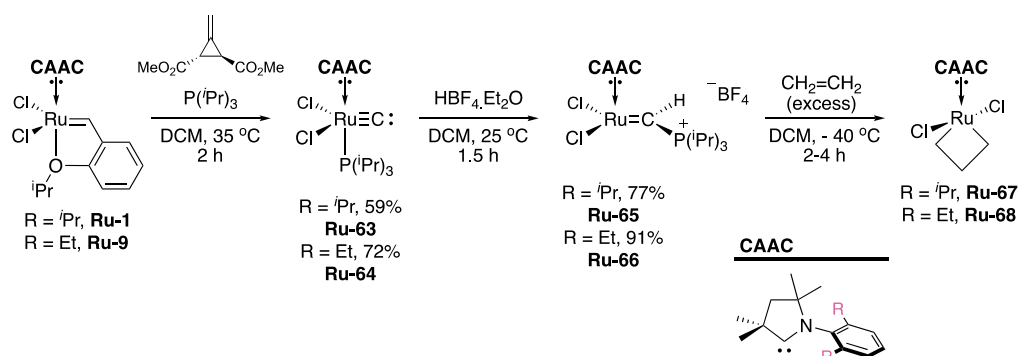
As previously mentioned, bis(CAAC)Ru-indenylidene pre-catalysts are rather difficult to initiate, requiring high temperatures or the use of additives such as copper chloride. This

arguably impedes their catalytic activity under mild conditions, because of catalyst degradation.^{64,65} To circumvent these limitations, Fogg and coworkers reported a novel (CAAC)Ru-indenylidene dimer **Ru-62**,⁶⁶ bridged by dative Cl interactions.⁶⁷ To access this species, the bis(CAAC)Ru indenylidene **Ru-43** was treated with CuCl in the absence of additional donors in CH₂Cl₂ (Scheme 15). Under these conditions, trapping of one of the two CAAC ligands afforded **Ru-62** in 78% isolated yield.



Scheme 15 Preparation of Fogg's (CAAC)Ru-indenylidene dimer **Ru-62**

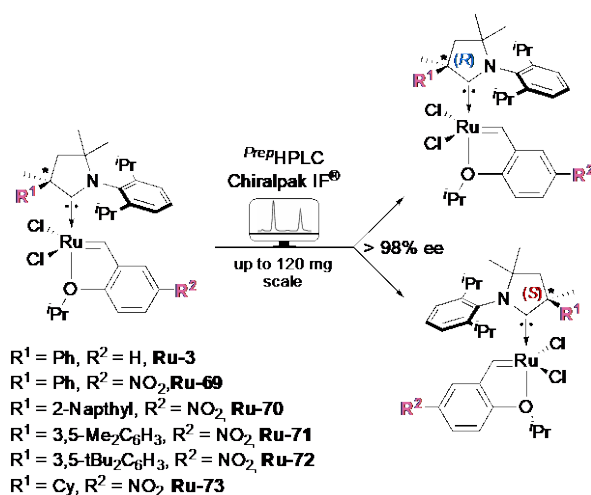
Grubbs and coworkers sought to better understand the influence of CAACs versus NHCs on elementary steps of the RCM catalytic cycle, correlating these effects with the selectivity for either degenerate or productive olefin metathesis.⁶⁸ For this purpose, they prepared CAAC ethylene ruthenacycles **Ru-67,68** via a three-step procedure involving the reaction of Hoveyda-Grubbs type complexes **Ru-1,9** with P^iPr_3 , which afforded carbides **Ru-63,64** (Scheme 16). Following protonation with HBF₄, the reactivity of the ensuing Piers type phosphonium alkylidene **Ru-65,66** complexes was evaluated under ethene atmosphere to afford **Ru-67,68**.⁶⁹ It is worth mentioning that these results show that phosphonium alkylidenes are accessible from Hoveyda-type complexes. Note that ethylene ruthenacycles can also be obtained starting from Fogg's (CAAC)Ru-indenylidene dimer **Ru-62**.⁷⁰



Scheme 16 Preparative sequence for accessing ethylene ruthenacycles **Ru-67,68**

2.2.4 Optically pure (CAAC)Ruthenium Complexes

Owing to their simple accessibility, optically pure NHCs have fostered numerous asymmetric applications in olefin metathesis.^{71,72,73} Recently, it was shown that the highly modular steric environment of CAACs could also provide potent optically pure ligands for asymmetric catalysis.²² Eager to streamline the discovery of optically pure CAAC-ruthenium metathesis catalysts, we have shown that preparative high-performance liquid chromatography (^{Prep}HPLC),⁷⁴ provides means for bypassing problems typically associated with the synthesis of chiral catalysts (i.e. multisteps, low yielding, single enantiomers).⁷⁵ Of the several columns evaluated, only amylose chiral stationary phases substituted with chloro-phenylcarbamate allowed for separations with good enantioselectivity and excellent resolution. Using Chiralpak IF® for its antipode's separation, shorter elution time and good loading capacity, (+)-**Ru-3** and (–)-**Ru-3** enantiomers were isolated in excellent yields (46 and 45%, respectively) and excellent enantiomeric purities (>98% ee) (Scheme 17). This method was successfully extended to Grela type complexes **Ru-53** and **Ru-69-73**.⁷⁶



Scheme 17 Preparation of optically pure (CAAC)Ruthenium complexes

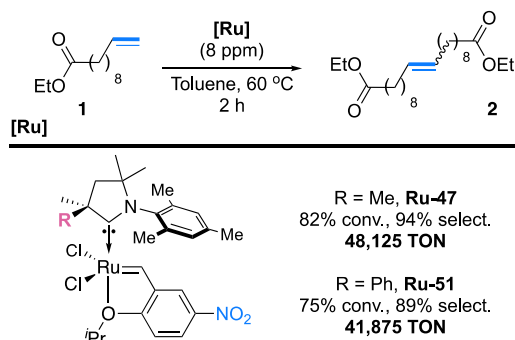
3. (CAAC)Ruthenium catalysts in Olefin Metathesis

3.1. Application to Self- and Cross metathesis

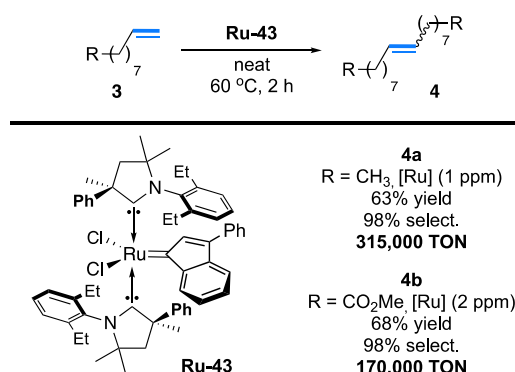
The cross metathesis (CM) between two different olefins or between the same olefin, known as self-metathesis (SM), offers a straightforward access to higher value, multifunctional compounds. Of course, the latter (SM) competes with the former (CM), thus both processes are often considered in parallel across the literature. To better delineate the specificities of these processes we have chosen to present them separately.

3.1.1. Self-metathesis

In contrast with NHC ruthenium catalysts which are generally known to be very active in self-metathesis processes reaching up to 640,000 TONs with 1-octene,⁷⁷ CAACs variants are comparatively less efficient. This is apparent in the self-metathesis of type 1 olefins⁷⁸ such as olefin **1** which results in lower TONs in the presence of Hoveyda-Grubbs **Ru-47**, **Ru-51** complexes (Scheme 18).⁵⁷ Contrasting with this statement are bis(CAAC)-indenylidene type complexes such as **Ru-43** yielding up to 315,000 (Scheme 19).⁵² Such differences likely results from the different initiation modes between these two families of complexes.



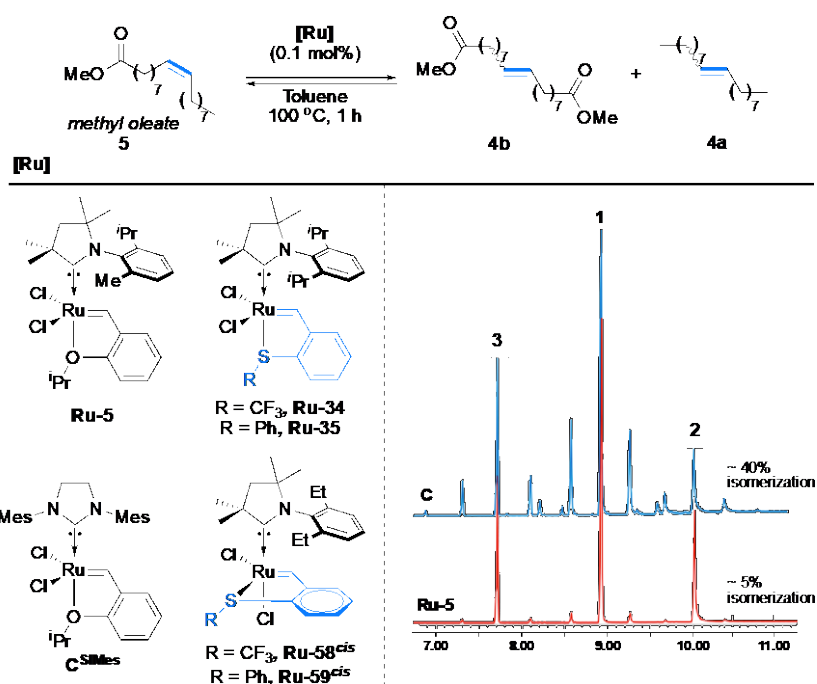
Scheme 18. Activity of CAAC-Ru Grela type complexes in self-metathesis



Scheme 19. Activity of bis(CAAC)Ru indenylidenes catalysts in self-metathesis

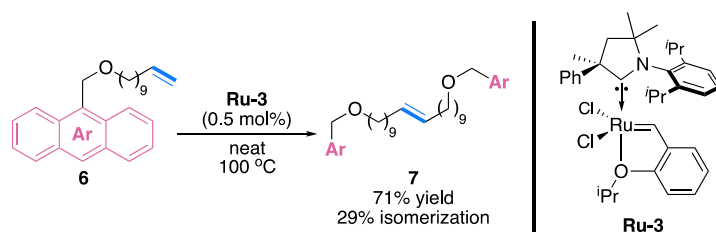
Despite the moderate activity of CAAC catalysts in the homo-dimerization of olefin, their inherent reactivity provides a convenient tool for reducing isomerization pathways. This was unambiguously established by Lemcoff and coworkers by comparing the Hoveyda-Grubbs 2nd generation **C** to the CAAC **Ru-5** in the self-metathesis of methyl oleate **5** at 100 °C in the presence of 0.1 mol% catalyst loading (Scheme 20).⁷⁹ These authors showed that after 1 h, up to 40% isomerization was observed with **C**, whereas it was suppressed almost completely with **Ru-5**. Interestingly, a similar study performed with thioether chelated precatalysts **Ru-34,35**, **Ru-58,59^{cis}** supported these findings.⁴⁷ Supported by DFT, this selectivity was proposed to originate from the greater difficulty of CAAC ruthenium complexes to form the ruthenium-hydride- π -allyl intermediate compulsory to the isomerization mechanism. These results also suggest that the conformation of the catalyst and the nature of the benzylidene moiety should be accounted for when predicting the reactivity of these species. Indeed, marked differences were observed between **Ru-58^{cis}** and **Ru-59^{cis}** upon performing the reaction at either 100°C

to 120°C, the former yielding up to 47% increase in isomerization products. Moreover, it was shown to also impact the stability of the catalyst as seen with the lack of reactivity of **Ru-35**.



Scheme 20 CAACs catalysts appear to be more selective than their NHC variant in olefin self-metathesis

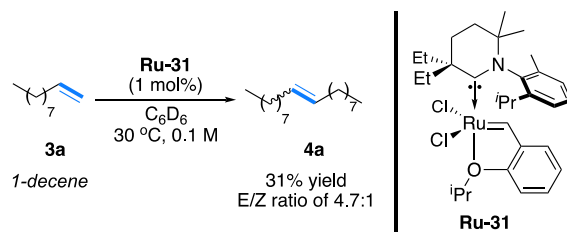
As expected, and as highlighted by Wagener and coworkers,⁸⁰ the propensity of CAAC ruthenium catalysts to completely inhibit isomerization processes remains contingent on the nature of the olefin. This was demonstrated in the homodimerization of an anthracene substituted olefin **6** in the presence of **Ru-3** at 100 °C, which afforded up to 29% of the isomerization product **7** (Scheme 21).



Scheme 21 CAAC catalyst selectivity is likely contingent to the nature of the olefin

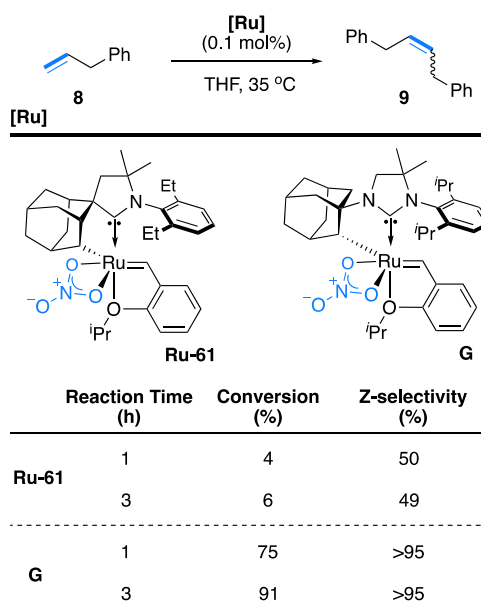
The homo-dimerization of olefins by a CAAC-6 ruthenium complex has also been reported using 1-decene **3a** and **Ru-31**, albeit with moderate (31% conversion after 2h; **4a**: E/Z ratio:

4.7/1) (Scheme 22).⁴⁰ The reduced catalytic activity and selectivity were proposed to originate from the increased steric bulk of the CAAC-6 ligand.²⁸ It is worth noting that allylbenzene resulted in significant olefin migration under the same conditions.



Scheme 22 Activity of CAAC-6 Hoveyda-Grubbs type complexes in self-metathesis

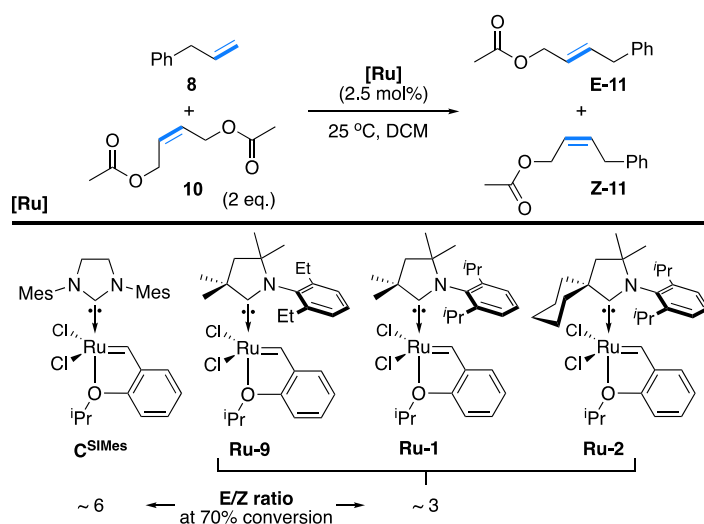
To improve the Z-selectivity of the self-metathesis reaction, Grubbs and coworkers compared the activity of several cyclometalated carbene ruthenium complexes. As illustrated by selected examples in Scheme 23, NHC complexes (such as **G**) were found to outcompete the CAAC ruthenium variant **Ru-61** in the self-metathesis of allylbenzene **8**. While the lack of reactivity was attributed to the instability of **Ru-61**, the diminished Z-selectivity was proposed to originate from conformational differences with NHCs variants.



Scheme 23. Activity of cyclometalated CAAC complexes in self-metathesis

3.1.2. Cross metathesis

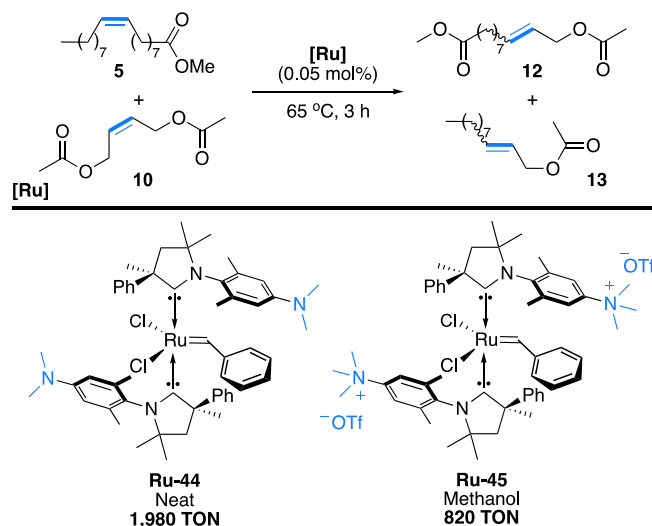
The development of E/Z-diastereoselective olefin metathesis catalysts is an area of substantial interest in organic chemistry.^{81,82} Typically, the E/Z diastereoselectivity of an olefin metathesis reaction is controlled by the thermodynamic stability of the olefin isomers rather than the selectivity of the catalyst. Looking to further investigate the influence of CAACs on this predicament, Grubbs and coworkers reported that CAAC-substituted catalysts exhibit lower E/Z ratio of **11** (2:1 at 70% conversion) in the cross metathesis of cis-1,4-diacetoxy-2-butene **10** with allylbenzene **8** (Scheme 24).³³ As highlighted by the selectivity of **C^{Si}Mes**, NHC-catalysts are typically more selective towards the most thermodynamically stable E-olefins, whereas CAACs afford higher ratio of Z-olefins. Interestingly, the shorter reaction times observed with the less hindered **Ru-9** (at ~60% conversion after 1 h at 22 °C; vs. 32 h for **Ru-1** and 48 h for **Ru-2** at 60 °C) indicate that the higher Z selectivity observed with CAACs is a result of the inherent catalyst selectivity, rather than an artefact of a less active catalyst unable to isomerize olefins.



Scheme 24. Cross metathesis with CAAC ruthenium catalysts appears to be more E-selective than with NHC variants

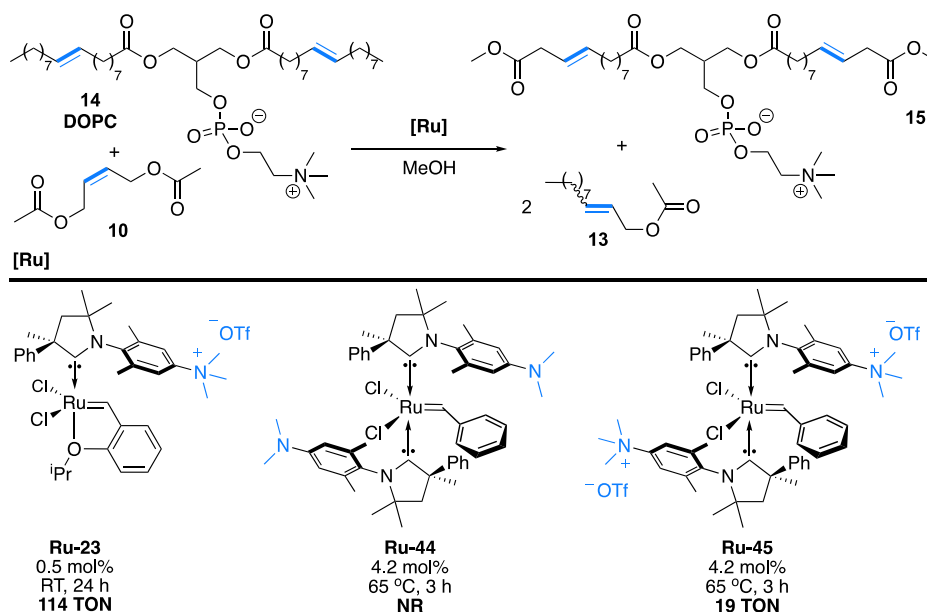
The activity of the CAAC ruthenium catalysts in cross metathesis of methyl oleate **5** has also been achieved with 1,4-diacetoxy-2-butene **10**. It was found to be quite straightforward,

achieving up to 99 % yield of the corresponding olefins **12** and **13** under solvent free conditions with catalyst **Ru-44** at 0.05 mol % loading and 65°C (Scheme 25). Note that the reaction can also be achieved under protic conditions in methanol using the more polar **Ru-45**.³⁶



Scheme 25 Cross metathesis of methyl oleate with Bis-CAAC-Ru complexes **Ru-44** and **Ru-45**

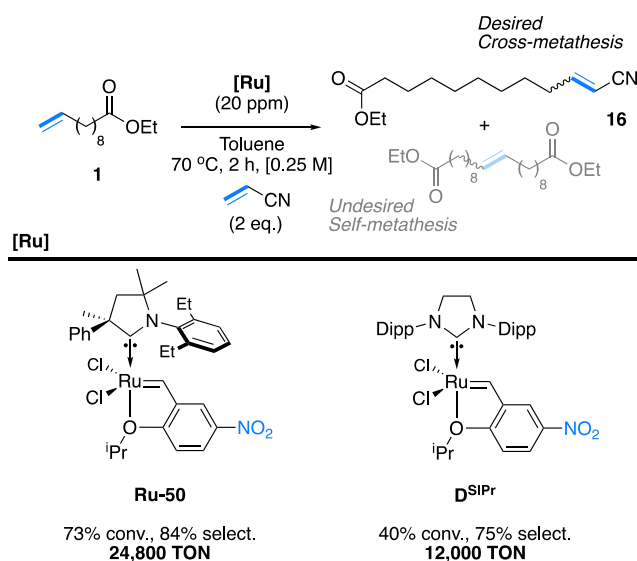
In recent years, the production of value-added molecules from microalgae including pigments, vitamins, proteins and lipids has shown significant potential. Specifically,⁸³ for polyunsaturated fatty acids, a class of lipids which are of particular interest given their range of applications in cosmeceuticals, nutraceuticals, fine chemicals, pharmaceuticals, and biodiesel.⁸⁴ Despite the difficulty of transforming such complex molecules, Tuba, Tóth and coworkers have shown that Hoveyda-Grubbs **Ru-23** and indenylidene Bis(CAAC)Ruthenium **Ru-45** were active in the cross metathesis of 1,4-diacetoxy-2-butene **10** with 1,2-dioleoyl-sn-glycero-3-phosphocholine **14** (DOPC) (Scheme 26),³⁶ a glycerophospholipid obtained from low value algae.



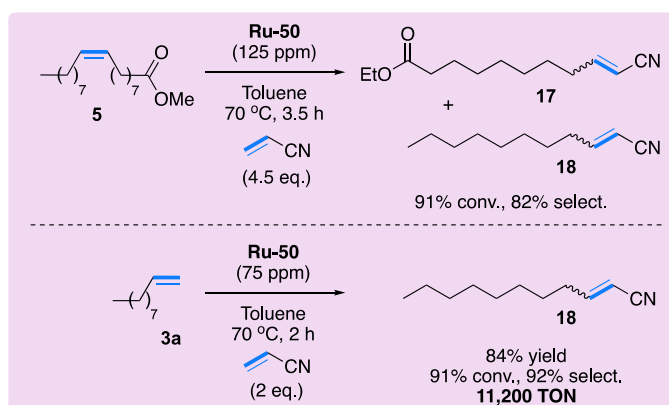
Scheme 26 Cross metathesis of polyunsaturated fatty acids

The use of nitriles in olefin metathesis is quite attractive as it offers a convenient access to value-added chemicals such as the Rilsan® Nylon 11 precursor “10-cyanodec-9-enoate” **16**, which is obtained by reaction of methyl 9-decenoate **1** with acrylonitrile. Yet, as noted by Fogg and others,^{85,86} traditional NHC ruthenium metathesis catalysts (**B**, **C**) are susceptible to decomposition in the presence of nitriles (*e.g.* acrylonitrile). Looking to improve upon the best NHC catalytic systems in the field,^{87,88} Skowerski and coworkers envisaged capitalizing on the enhanced activity and stability of Grela-type catalysts bearing CAAC ligands.⁵⁷ As highlighted in Scheme 27, despite the proficiency of the NHC Grela-type **D^{SIPr}**, CAAC derived **Ru-50** was found to be much more reactive leading up to 24,800 TON. Performing the same reaction with 20 ppm of **Ru-50** and at 85 °C led to 30,000 TON and 82% selectivity. In line with previous comments,³¹ the authors proposed that this improved performance originates from higher stability of the active species rather than from better kinetics. This postulate was later supported by a DFT study by Trzaskowski and coworkers, who demonstrated that in marked contrast with NHCs, CAAC-derived ruthenium catalysts were less susceptible to undergo acrylonitrile-assisted degradation.⁸⁹ The superior activity of CAAC catalysts in cross metathesis processes

with acrylonitrile was successfully extended to methyl oleate **5** and 1-decene **3a** affording the corresponding olefins **17** and **18** (Scheme 28).⁹⁰



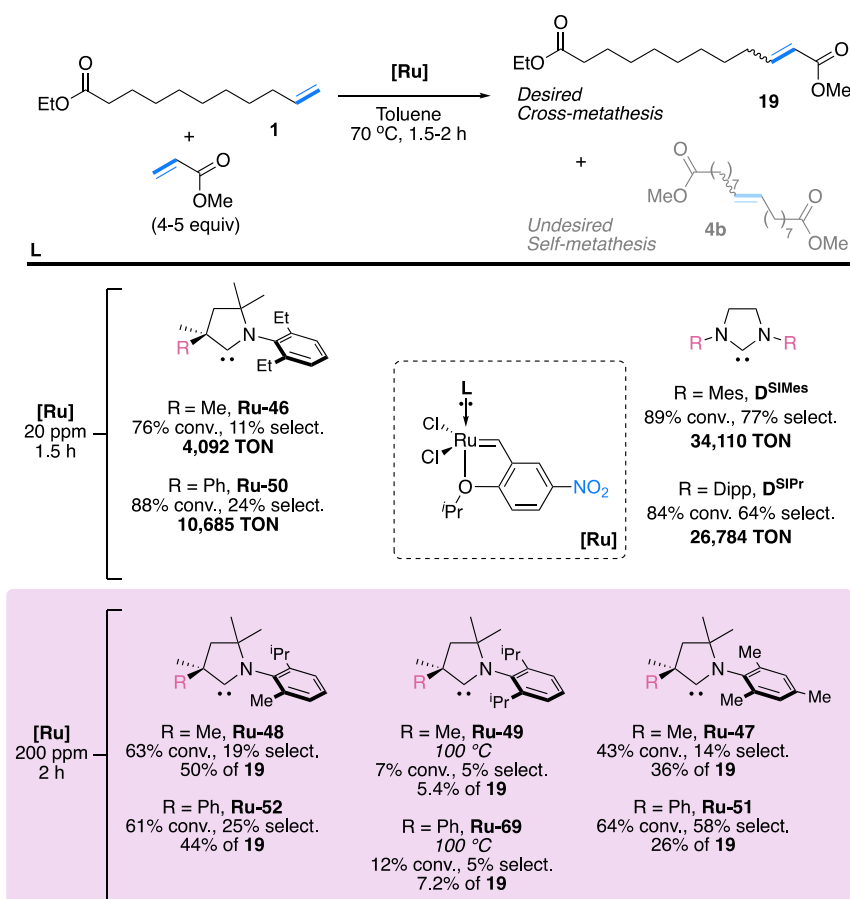
Scheme 27 CAAC ruthenium catalysts remain very efficient in Cross metathesis in the presence of nitriles



Scheme 28 Cross metathesis of methyl oleate or 1-decene with acrylonitrile using Grela CAAC-Ru catalyst Ru-50.

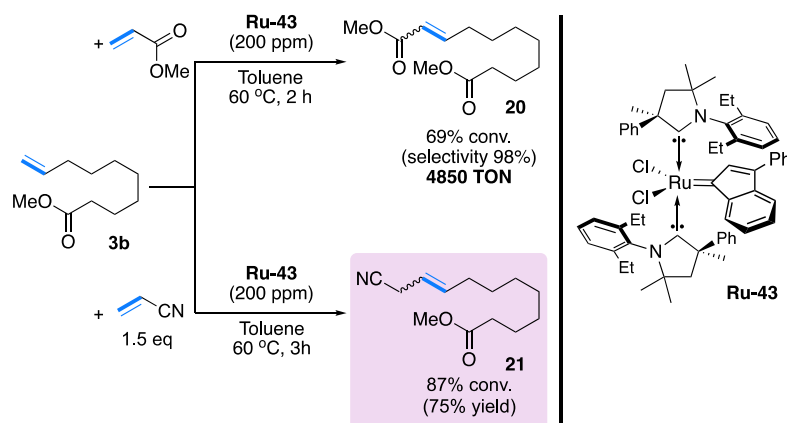
Acrylates (type II olefins⁷⁸) have a significant number of applications,⁹¹ but have poor reactivity in metathesis transformations as shown with Grubbs 2nd generation catalysts which require activation by a copper additive.^{92,93} Having found that CAAC catalysts allowed for improved catalytic activities in the cross metathesis of ethyl 10-undecenoate **1** with acrylonitrile,⁵⁷ Skowerski and coworkers naturally extended their study to acrylates.^{94,90} Using ethyl 10-undecenoate **1** in the presence of methyl acrylate, these authors compared the activity

of CAACs **Ru-46,50** to NHCs **D^{SiMe₃}** and **D^{SiPr}** (Scheme 29). However, with turnovers as high as 34,110, NHC-based catalysts were found to be more selective than CAAC catalysts, which are more prone to undergo self-metathesis. The authors could confirm these results across a larger range of CAAC complexes **Ru47-49,51,52,69**.⁹⁰



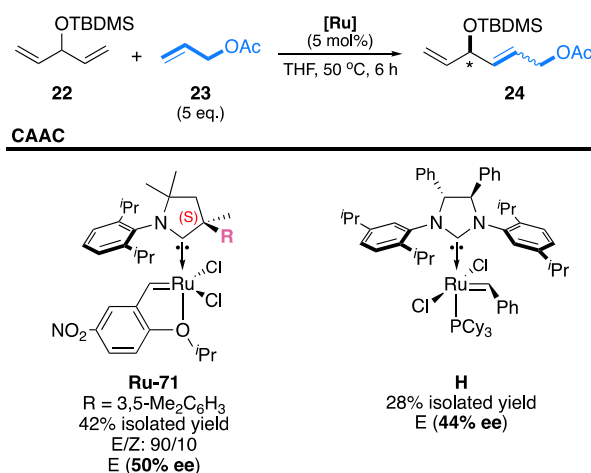
Scheme 29 Cross metathesis with methyl acrylate and CAAC-Ru Grela type complexes

As shown in Scheme 30, these challenging cross metathesis reactions between electron-deficient methyl acrylate and acrylonitrile with methyl 9-undecenoate **3b** was readily extended to bis(CAAC)Ru-indenylidene pre-catalysts.⁵² Note that in this case the use of the more reactive **Ru-43** without the necessity of adding CuCl to activate the catalyst.



Scheme 30 Activity of Bis(CAAC)Ru-indenylidene **Ru-43** in the Cross metathesis with methyl acrylate and acrylonitrile

Extending the field to asymmetric transformations, we recently examined the activity of optically pure CAACs in challenging asymmetric cross metathesis (ACM).⁹⁵ As shown in Scheme 31, we found that Grela type enantiopure (CAAC)Ru-(S) **Ru-71** afforded **24** with up to 50% ee in the cross metathesis of diene **22** with allyl acetate **23**.⁷⁵ Note that these preliminary results surpass state of the art chiral NHC ligands, which suggest that further investigations should be performed to delineate the impact of CAACs in ACM.⁹⁶



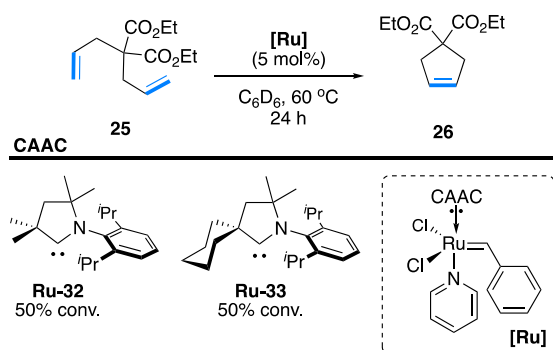
Scheme 31 First application of an optically pure CAAC in asymmetric cross metathesis

3.2. Application to Ring-Closing Metathesis

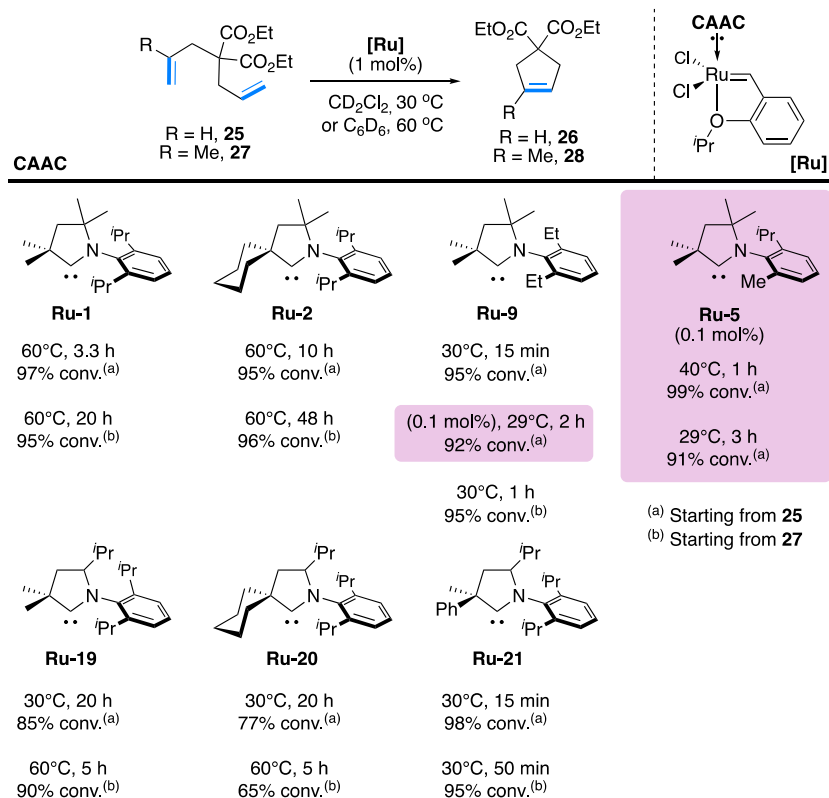
3.2.1. Small molecules

The catalytic performance of CAAC-based ruthenium catalysts in ring-closing metathesis (RCM) was first established by Grubbs and coworkers in the RCM of diallylmalonate **25**.³² As

shown in Scheme 32, pyridine-based CAAC-complexes **Ru-32,33** showed moderate reactivities (50% conv. over 24 h), which was attributed to premature catalyst decomposition occurring even at room temperature. As expected, improved efficiencies were observed with the more stable Hoveyda-type derivatives **Ru-1,2**, reaching almost full conversions with trisubstituted olefin **27**, even at 1 mol% catalyst loading, albeit with longer reaction times. (Scheme 33). As observed between **Ru-1,2** and **Ru-9** the catalytic activity of CAAC catalysts is largely influenced by sterics. Improving upon these results, Skowerski and coworkers obtained higher activities with the least sterically hindered **Ru-9** and **Ru-5**.⁹⁰ However, CAAC catalysts could not efficiently perform the RCM of dimethyl diallylmalonate to yield the cyclic tetra-substituted olefin (not shown). Examining the influence of the substitution of the backbone, Zhang, Shi and coworkers obtained higher reactivity with **Ru-19-21** featuring an isopropyl instead of their gem-dimethyl analogues (Scheme 33).³⁵ While these results clearly highlight the importance of sterics in this process, they also indicate that steric decongestion at the *N*-aryl *ortho*-substituent is more critical than on the backbone of the CAAC ligand.



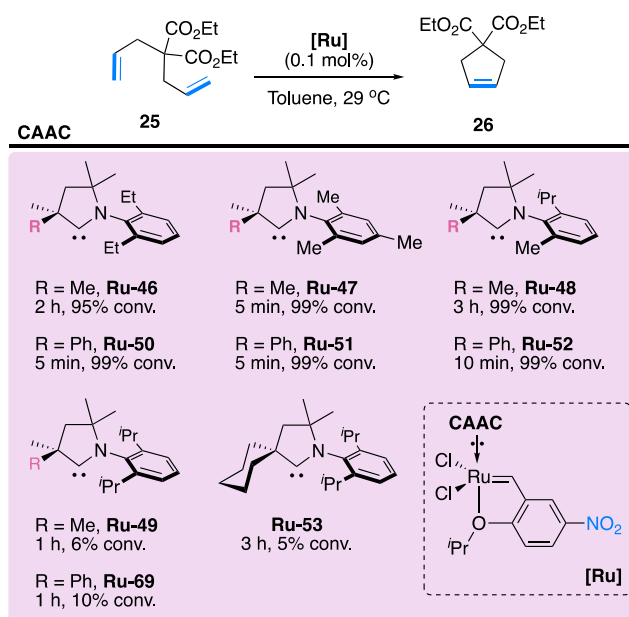
Scheme 32 Ring Closing-Metathesis using pyridine-based CAAC-complexes **Ru-32**



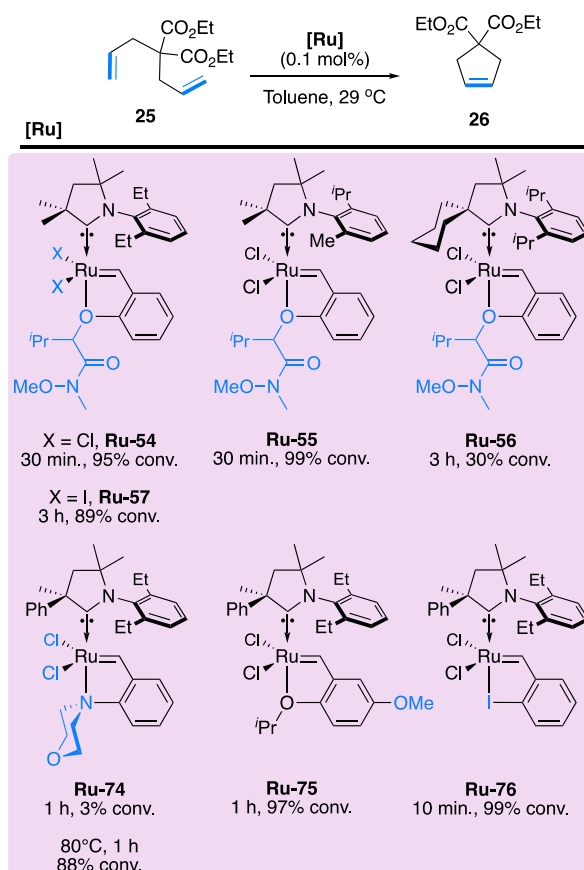
Scheme 33 Activity of Hoveyda-Grubbs CAAC catalysts in Ring Closing-Metathesis of diallyl malonate

Investigating the structure/activity relationship of Grell-type catalysts, Skowerski and coworkers further highlighted the importance of sterics as shown by the very efficient **Ru-47** (scheme 34).⁵⁹ Note that replacing a methyl by a phenyl on the quaternary carbon next to the carbene center also led to a faster RCM (**Ru-50,52**). Going further, these authors considered the nature of the styrenyl motif (Scheme 35).^{59,90} Notably, introduction of a modified styrenyl ether ligand, containing the Weinreb-amide functionality, drastically improved the initiation rate of **Ru-54-56**. Per comparison, *N*-chelating morpholine moiety (**Ru-74**) was less efficient, requiring a thermal activation to initiate the RCM. Note that the replacement of chloride by iodide in **Ru-55** appeared to be detrimental, while addition of an electron donating methoxy group in **Ru-75** led to a severe drop of reactivity in marked contrast with **Ru-50** bearing an electron withdrawing group. Such behavior has also been observed with NHC-based

catalysts.⁹⁷ A remarkable initiation rate was also observed with iodine-chelated catalyst **Ru-76** reaching full conversion within 10 min.

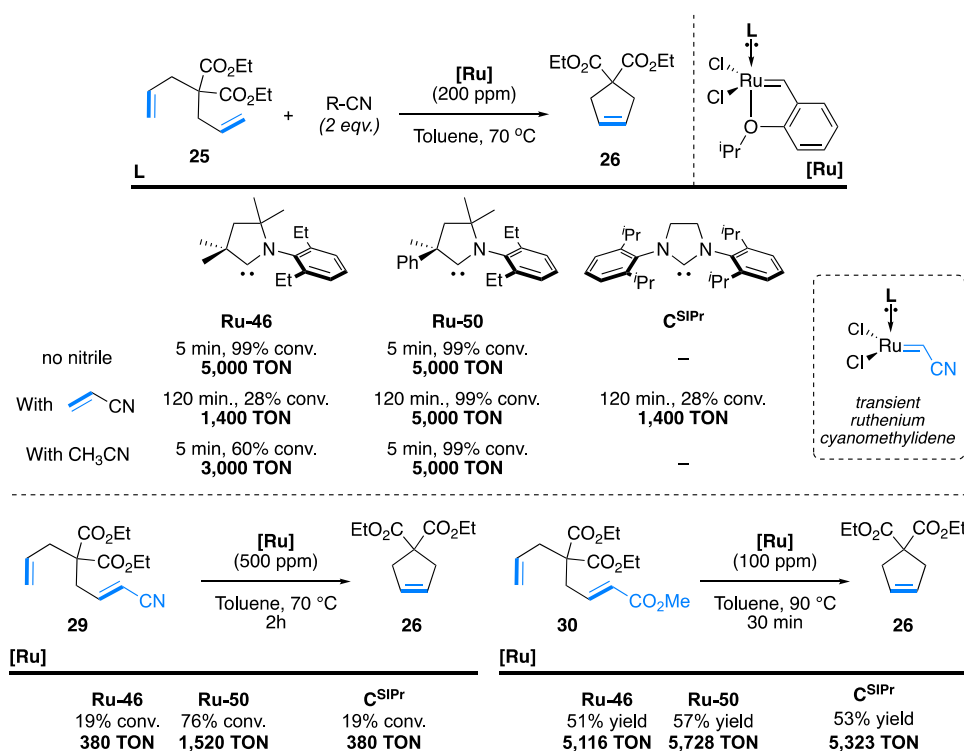


Scheme 34 Activity of nitro-Grela CAAC catalysts in Ring Closing-Metathesis of diallyl malonate



Scheme 35 Impact of the styrenyl ether ligand on the Ring Closing-Metathesis of diallyl malonate

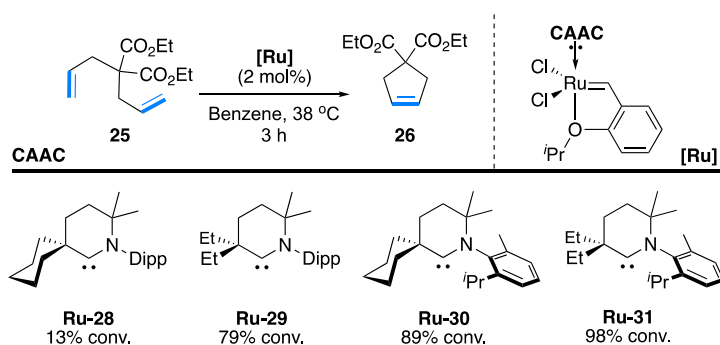
As already mentioned, nitriles are known to poison many Ru-based olefin metathesis catalysts.^{85,86} However, Skowerski and coworkers examined the RCM of diallyl malonate **25** in the presence of nitrile additives. They reported that CAAC-Ru-**50** was only slightly impacted, maintaining high reactivity at low catalyst loading (0.02 mol%), in marked contrast with Ru-**46** NHC-based catalyst **C^{SI}Pr** (Scheme 36).⁵⁷ Additional experiments and DFT calculations highlighted that some CAAC-Ru catalysts impede the formation of transient ruthenium cyanomethylidenes that are more prone to undergo acrylonitrile-assisted decomposition.⁸⁹ In another report, it was also shown that CAAC-catalysts are tolerant to methyl acrylates (as in **30**) another well-known poison for metathesis catalysts.⁹⁴



Scheme 36 CAAC ruthenium catalysts remain very efficient in Ring Closing Metathesis in the presence of nitriles or acrylates

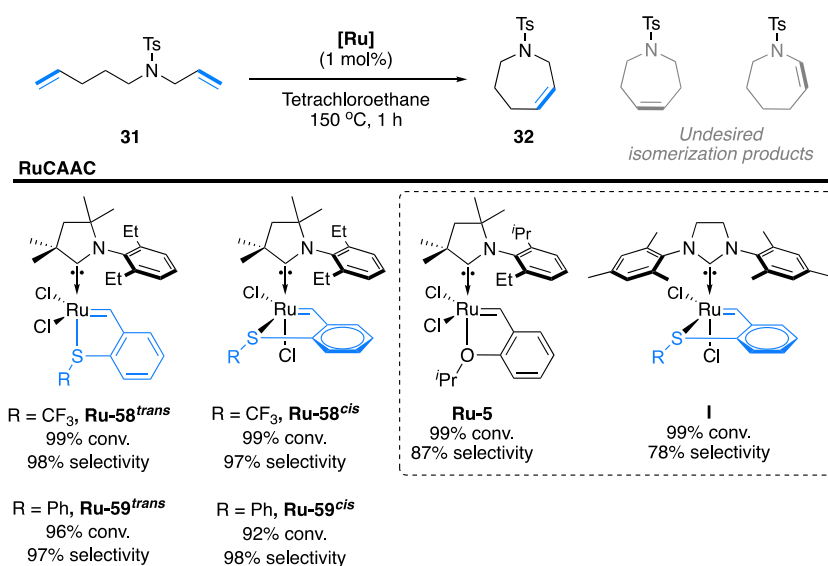
Recently, Grubbs and coworkers extended these studies to six-membered CAAC-Hoveyda catalysts **Ru-28-31** (Scheme 37).⁴⁰ As with their 5-membered counterparts, some important structure/activity insights were identified through an initiation study involving butyl vinyl ether (not shown), combined with reactive profiles of the benchmark RCM of diallylmalonate **25**.

As expected from more donating ligands, faster catalyst initiation was observed with CAAC-6 complexes (vs. CAAC-5), likely due to a weaker Ru-O bond. For now, CAAC-6 catalysts do not meet the catalytic activities of CAAC-5 motifs. However, given the small range of CAAC-6 studied and the critical influence of subtle steric modifications of the ligand structure in these systems, it seems premature to critically assess the impact of CAAC-6 in olefin metathesis.



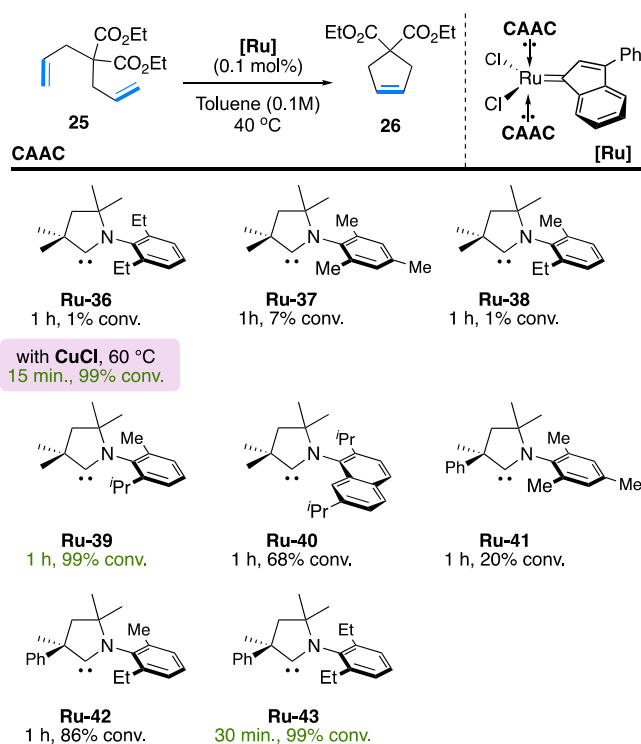
Scheme 37 Activity of CAAC-6 Hoveyda-Grubbs catalysts in Ring Closing Metathesis

Lemcoff and coworkers have investigated the reactivity of latent sulfur-chelated Ru-benzylidenes containing CAACs in the RCM of tosylsulfonamide **31** (scheme 38).⁴⁷ Under drastic thermal conditions (150 °C), *cis* and *trans* **Ru-58,59** afforded excellent conversions to 7-membered **32**, with extremely low isomerization of the double bond (97% selectivity). This is in marked contrast with the CAAC Hoveyda-type **Ru-5** and NHC SIMes *cis*-variant **I**, which give significant amounts of isomerized by-products.⁷⁹



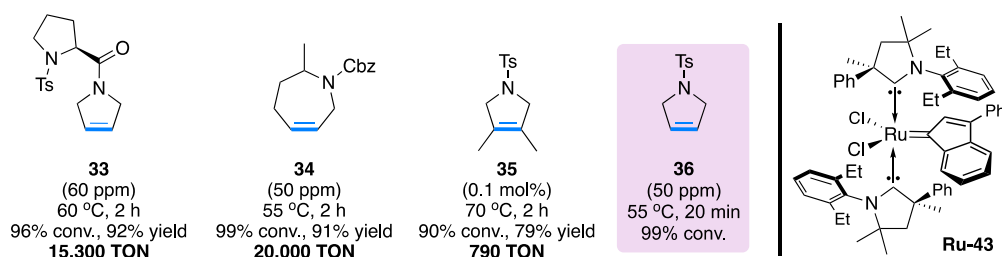
Scheme 38 Activity of sulfur-chelated (CAAC)Ru-benzylidenes in the RCM of tosylsulfonamide

Looking for even more efficient catalysts, Skowerski and coworkers disclosed the remarkable activity of bis(CAAC)Ru indenylidene complexes **Ru-36-43** (Scheme 39).^{52,59} Compared to traditional Hoveyda-Grubbs CAAC ruthenium complexes, bis(CAAC)Ru indenylidene complexes were shown to be more difficult to activate (**Ru-36**: 1% in 1 h versus **Ru-9**: 95% in 15 min). However, this could be overcome by promoting ligand to ligand steric repulsion through the CAAC motifs (**Ru-36** vs. **Ru-39** or **Ru-43**), or by simple addition of a CuCl additive.



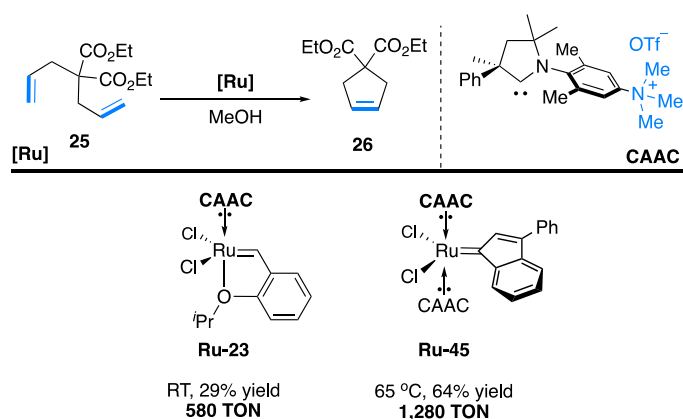
Scheme 39 Activity of Bis(CAAC)Ru-indenylidene complexes in Ring Closing Metathesis

The most performant catalyst **Ru-43** was found to outperform the traditional Grubbs II catalyst (50% yield and 8,300 TON, not shown) in the RCM leading to proline derivative **33** (TON 15,300) (Scheme 40). Seven-membered ring azepine derivative **34** and challenging (sterically hindered) tetra-substituted olefin **35** were also efficiently transformed, as well as diallyltosylamine **36**.⁹⁰



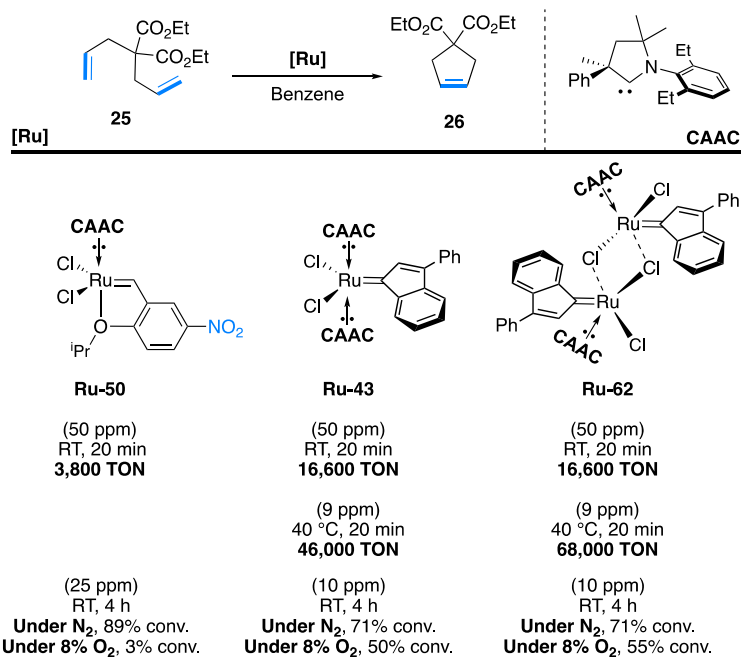
Scheme 40 Bis(CAAC)Ru-indenylidene Ru-43, a powerful catalyst for RCM of azo-dienes

Tuba, Tóth and coworkers examined the catalytic performances of Ru-complexes containing polar tags in protic media such as methanol (Scheme 41).³⁶ It is worth mentioning that both complexes were highly robust toward air and moisture.



Scheme 41 Ring-Closing-Metathesis catalyzed by ammonium-tagged CAAC Ru-complexes

In the case of the indenylidene chloro-bridge dimer complex **Ru-62**, the high lability of the bridging anionic ligand considerably increased the initiation rate as well as the productivity in the RCM of diallyl malonate **25** (Scheme 41).⁶⁶ At extremely low catalyst loading (0.005 mol%), it could outperform bis(CAAC)Ru indenylidene complexes **Ru-43** and the state of the art NHC-based catalysts (*e.g.* nitro-Grela, Umicore M2; not shown). Note however that the activity of dimer **Ru-62** was comparable (or slightly higher at 9 ppm) than nitro CAAC-catalyst **Ru-50**. Interestingly, both catalysts remained active in presence of oxygen, even at 1 ppm, attesting of their remarkable robustness.⁹⁸

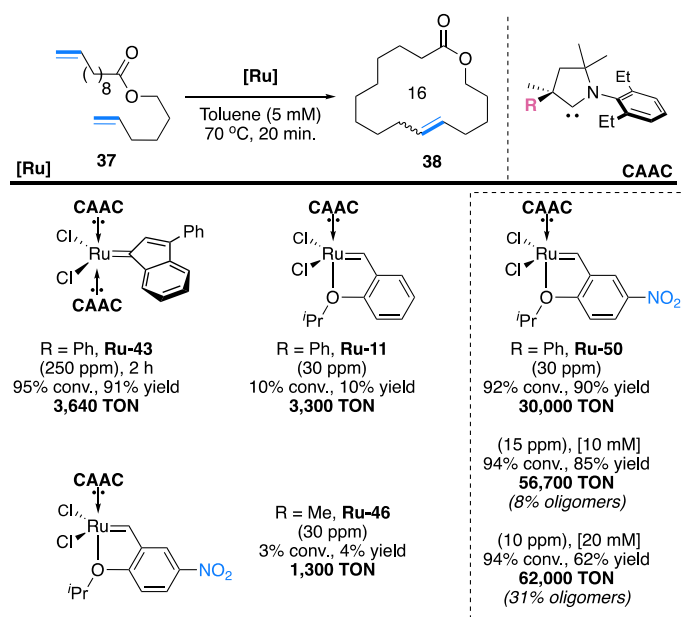


Scheme 42 Fogg's indenylidene chloro-bridge dimer complex **Ru-62**, a very active RCM catalyst

3.2.2. Macrocycles

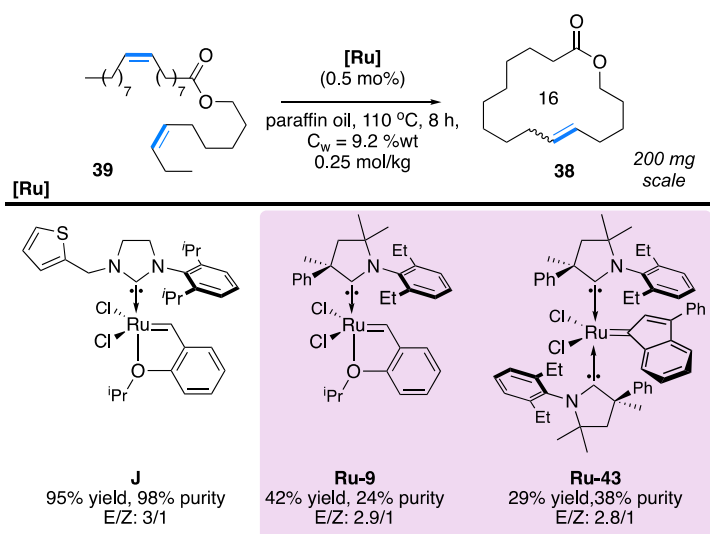
Macrocycle cores are ubiquitous in numerous natural molecules, notably in pharmaceutical drugs and cosmetics. In this context, olefin metathesis represents a clean and highly competitive synthetic tool to form macrocycle scaffolds (*e.g.* ketone, lactone, lactam) even those containing various organic functions. Nevertheless, the high dilutions and catalyst loadings required in these processes remains a major drawback. This limits the usefulness of macro-RCM for any practical industrial developments, especially in the area of macrocyclic fragrance molecules. To confront these challenges, Skowerski and coworkers demonstrated that BisCAAC **Ru-43** could efficiently convert diene **37** into 16-membered macrocycle **38**, a precursor of highly desirable exaltolide, a musk known for its odorant property (Scheme 43).⁵² However, a much more impressive 62,000 TON (TOF 3,000 min⁻¹) was achieved with the nitro CAAC-catalyst **Ru-50**, enabling fast metathetic macrocyclizations at extremely low catalyst loadings (as low as 10 ppm).⁵⁷ It is worth mentioning that these TONs are the highest reported so far in macro-RCM, outperforming classical NHC-containing catalysts such as Grubbs **B**, Hoveyda-Grubbs **C** or nitro-Grela **D**, as well as other CAAC-complexes (**Ru-11,46**). At higher

concentrations, excellent conversions were observed, however at the expense of substantial oligomer formation (up to 31%).



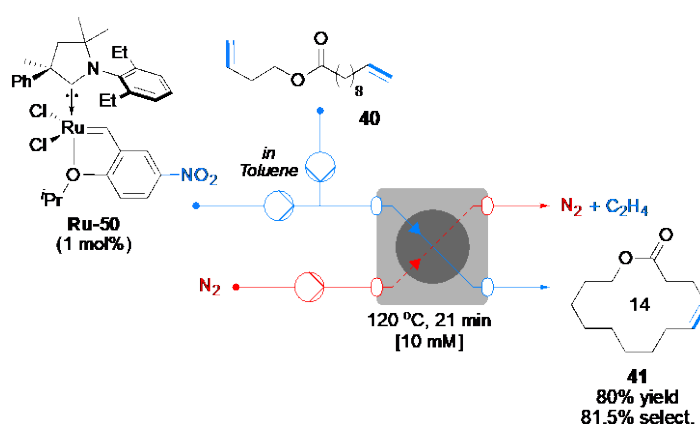
Scheme 43 Activity of nitro-Grela CAAC complexes in Macro-Ring-Closing Metathesis

Using high substrate concentration (*i.e.* 200 mM; 0.25 mol/kg), reduced pressure and paraffin oil as a solvent, Grela and coworkers investigated the macro-RCM of oleyl derived diene **39** (Scheme 44). Surprisingly compared to NHC **J**, CAAC-catalysts appeared to be quite inefficient under these specific conditions, both in productivity and selectivity.^{99,100}



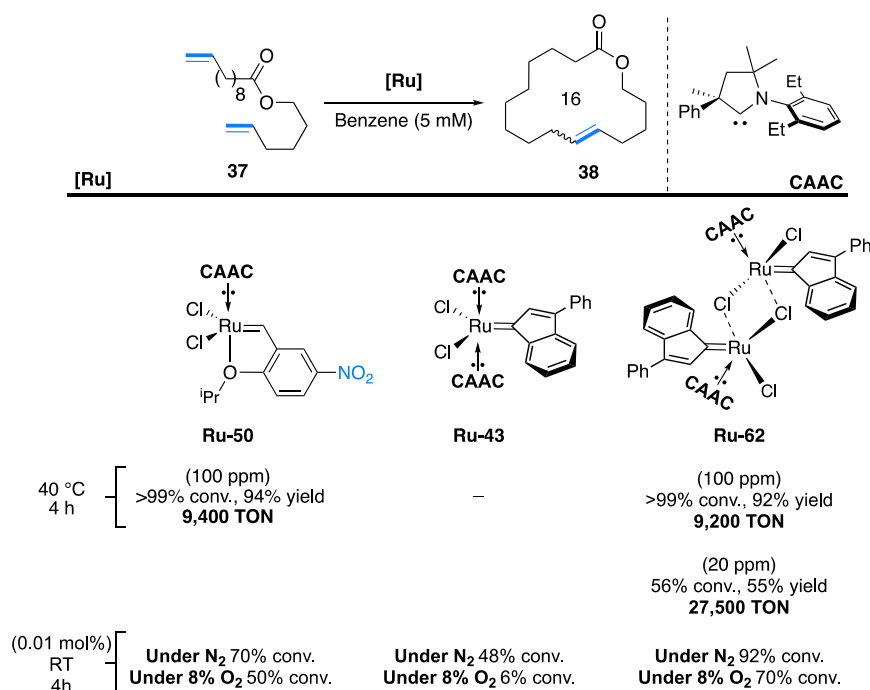
Scheme 44 The activity of CAAC complexes in Macro-Ring-Closing Metathesis

Recently, Jamison, Bio and coworkers described the macro-RCM of diene **40** using a continuous flow olefin metathesis process (Scheme 45).¹⁰¹ Thanks to a selective membrane allowing a high flux ethylene gas permeation, nitro-CAAC **Ru-50** efficiently catalyzed the production of 14-membered macrocyclic lactone **41**, a relevant molecule of the fragrance industry. Despite its excellent performance, significant amounts of oligomers were also formed due to high substrate concentration (*i.e.* 10 mM). Note that similar catalytic performances were also obtained using the a bis-iodo-SIMes nitro-Grela catalyst (not shown).



Scheme 45 Macro-RCM of diene **40 in continuous flow using **Ru-50****

Fogg's chloro-bridge dimer **Ru-62** compared well with nitro CAAC-**Ru-50** in the selective formation of exaltolide precursor **37** (*i.e.* without traces of oligomer) (Scheme 46).⁶⁶ As an added feature, **Ru-62** was shown to be more oxygen tolerant than Hoveyda-Grubbs **Ru-50**. In marked contrast, bis(CAAC)Ru indenylidene **Ru-43** displayed an acute sensitivity to oxygen,⁹⁸ possibly resulting from O₂ binding to its sixth vacant coordination site. Factors favoring this degradation pathway have been proposed to result from several factors such as the inherent π -acidity of the CAAC ligands, the low ligand lability, and the reduced steric crowding of the indenylidene unit.



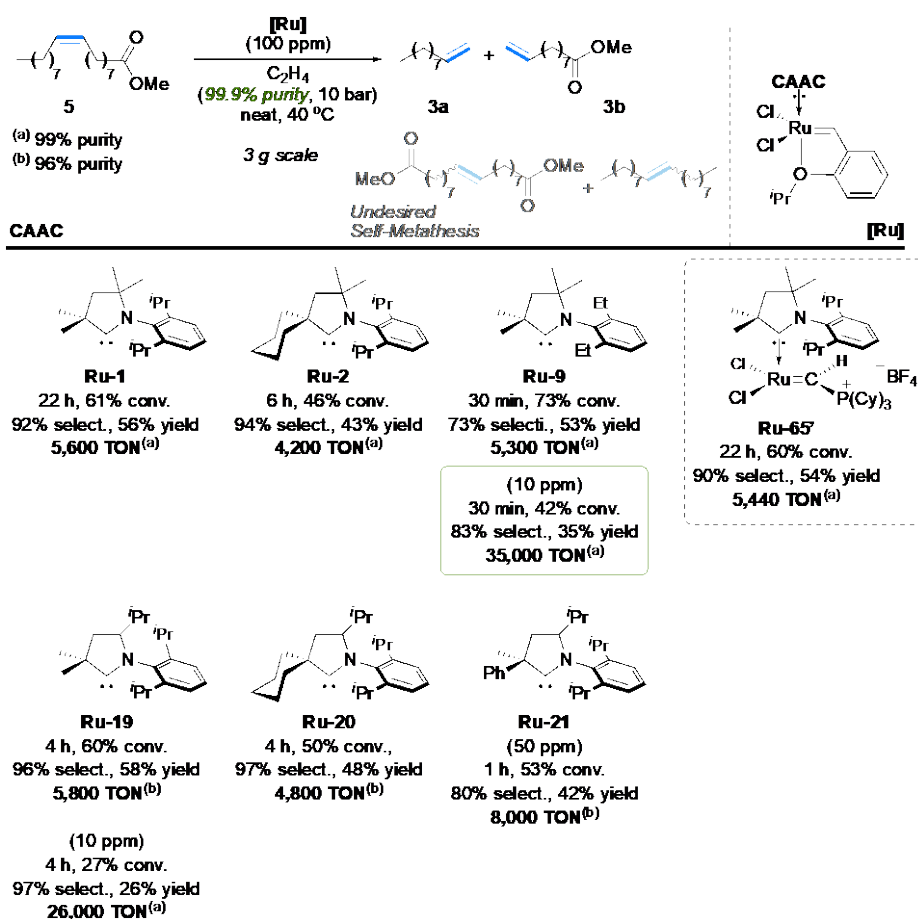
Scheme 46 Fogg's chloro-bridge dimer **Ru-62** a competitive catalyst for macro-RCM

3.3. Applications in Ethenolysis

3.3.1. Methyl and ethyl Oleate

Cross metathesis involving ethylene, the so-called ethenolysis, has received tremendous attention as means to produce alpha-olefins in high demands for many industrial applications (materials, lubricants, surfactants, plasticizers, antimicrobials, etc...). In the context of biomass fuel production (biorefinery), the ethenolysis of unsaturated fatty acids/esters derived from natural vegetable oils (preferentially nonedible ones) provides bio-sourced alpha-olefins. Among the transition-metals able to promote ethenolysis of the biomass, robust and air stable ruthenium alkylidenes complexes rapidly emerged as promising catalyst candidates. However, the instability of propagating methylene species and concurrent inhibition by ethenolysis products only resulted in modest productivity (ca. TON <14,000).¹⁰² Complicating the matter further, second generation NHC-based catalysts were shown to favor undesirable self-metathesis pathways. In that respect, the discovery of CAAC-based catalysts undeniably contributed to overcome these fundamental issues. In 2008, Schrodi and colleagues examined

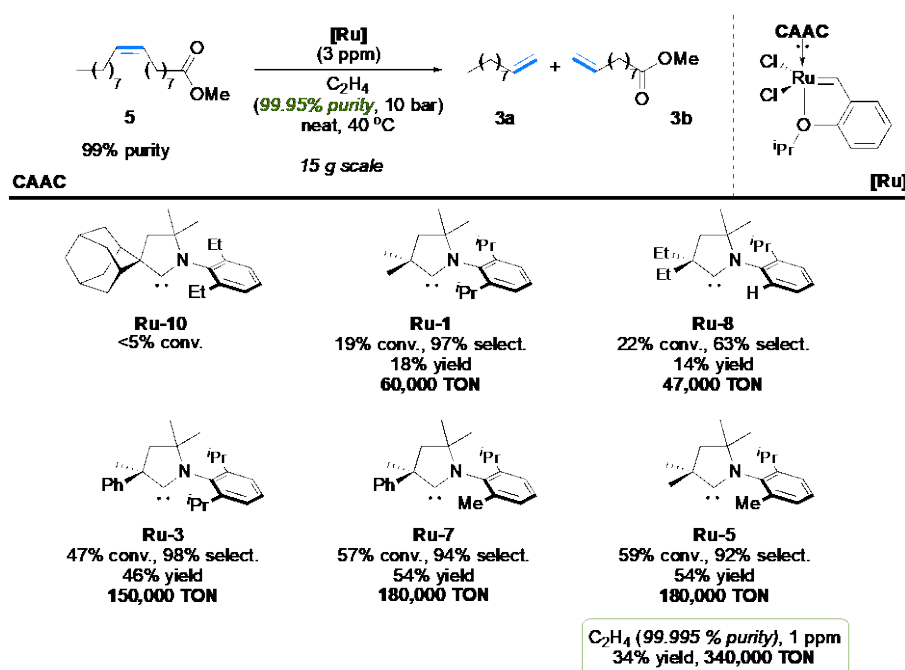
for the first time the reactivity of CAAC-Ru Hoveyda-type complexes in the ethenolysis of methyl oleate **5** (Scheme 47).³³ At low catalyst loading (*i.e.* 100 ppm) and under 10 bar of ethylene, in solvent-free conditions, **Ru-1**, **Ru-2** and **Ru-9** exhibited good conversions and selectivity toward the desired terminal olefins **3a** and **3b**. Reduction of the catalyst loading to 10 ppm even allowed up to 35,000 TON with **Ru-9**, one of the highest reported at that time. Under similar conditions, Piers-type CAAC-**Ru-65'** performed as efficiently, whereas the monosubstituted *i*Pr-CAACs **Ru-19-21** gave excellent performances despite a lower purity (96%) of the methyl oleate and ambient conditions.^{35,103} Comparatively, the Hoveyda catalyst **C^{SIMes}** gave lower yield and selectivity (20 and 33%, resp.; TON 2,000; not shown).³³



Scheme 47 CAAC Ruthenium catalysts as powerful tools for ethenolysis

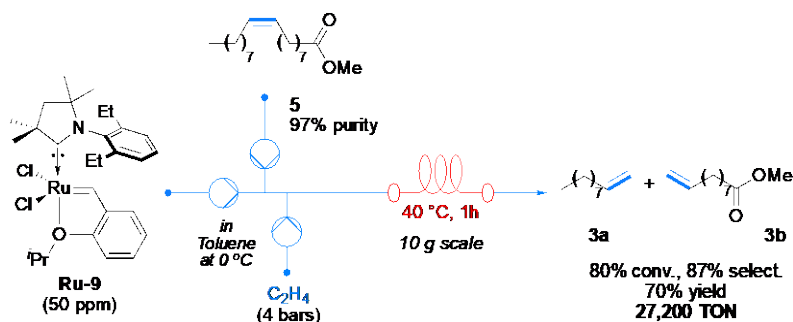
Grubbs and coworkers reported an extensive study of the ethenolysis of neat methyl oleate (Scheme 48).³¹ The use of high purity ethylene (99.95%) considerably improved the performance of catalysts reaching 180,000 TONs with **Ru-5** and **Ru-7**. Pushing the system

even further, with even higher ethylene purity (up to 99.995%), allowed reaching 340,000 TON with **Ru-5**, one of the highest reported to date.



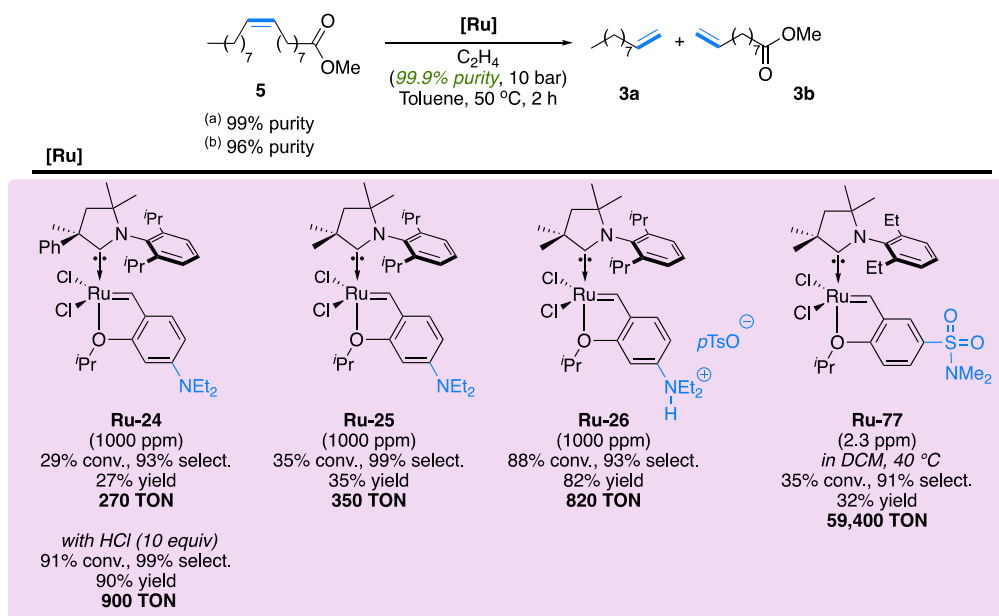
Scheme 48 Importance of the purity of ethylene for improving TON in ethenolysis

This impressive productivity/selectivity was attributed to i) CAAC induced increased electron density at the ruthenium leading to more stable methylidene propagating species and ii) large *N*-aryl substituents limiting the formation of ruthenium hydrides thereby limiting secondary reaction pathways. Comparison of initiation rates and TONs support this hypothesis, suggesting that an optimal balance must be found to achieve stability and reactivity. Grubbs and coworkers later achieved the low pressure ethenolysis of methyl oleate **5**, using continuous flow condition with **Ru-9** (Scheme 49).¹⁰⁴ At 50 ppm catalyst loading, **Ru-9** surpassed its NHC-counterparts (*i.e.* Grubbs and Hoveyda-Grubbs) by affording the highest yield (*ca.* 70%) and a TON of 27,200. Note that this high catalytic performance was achieved using lower purity material (97%).



Scheme 49 Low pressure ethenolysis of methyl oleate **5** in continuous flow using **Ru-9**

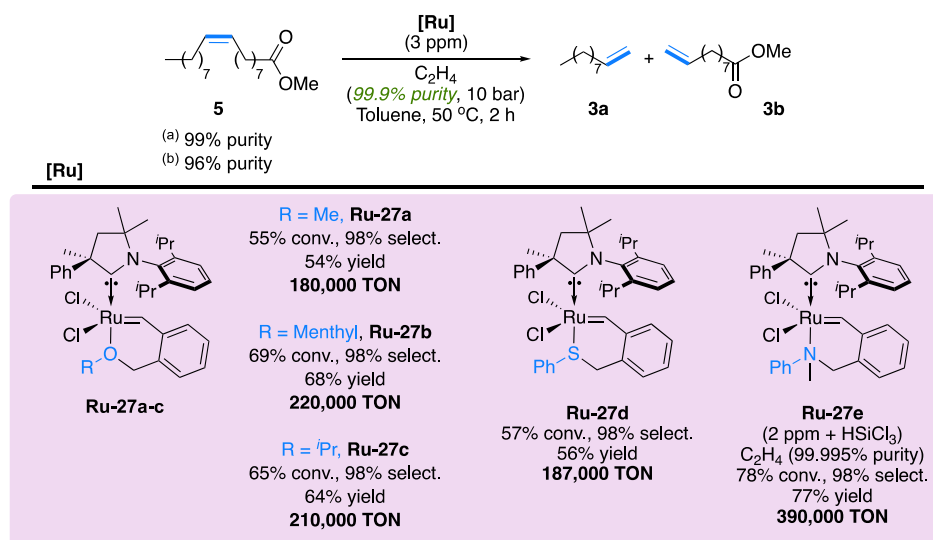
Modulating the nature of the styrenyl ether ligand, Mignagni, Vallée and coworkers investigated the reactivity of CAAC-catalysts **Ru-24,25** (Scheme 49).^{37,105} Addition of electron donating amino groups was shown to be detrimental to the catalytic activities, even at 1000 ppm catalytic loading. Attempts to activate the catalysts under acidic conditions only resulted in a marginal improvement. More interestingly, activation of **Ru-77** with a dimethyl sulfonamide EWG (Zhan type catalyst¹⁰⁶) afforded a very efficient catalyst reaching 59,400 TON.¹⁰⁷



Scheme 50 Impact of the nature of the styrenyl ether ligand in ethenolysis

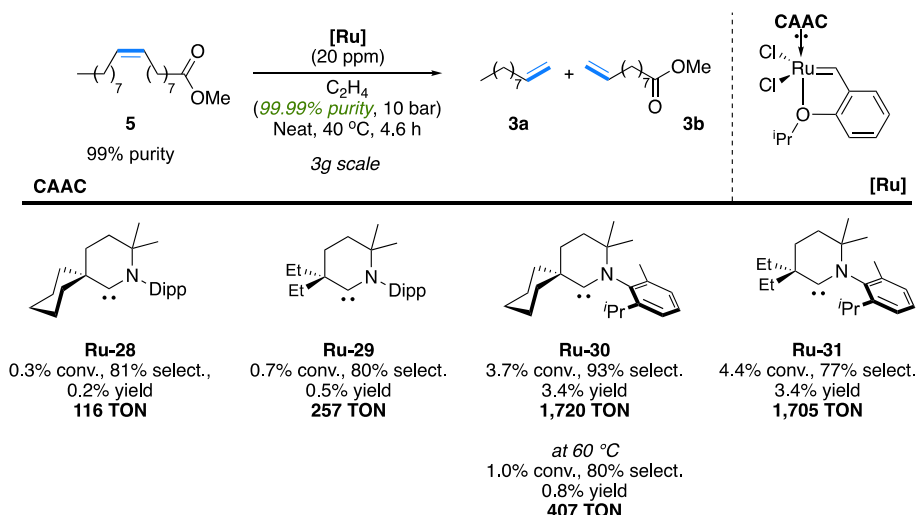
Similarly, Verpoort and coworkers examined the influence of labile benzylether, benzylthioether and benzylamine chelating groups.³⁹ As shown in Scheme 51, all **Ru-27** catalysts converted methyl oleate **5** (neat) with excellent selectivity (98%) and impressive

TONs (from 180,000 to 210,000), outperforming the Hoveyda complex **Ru-3** (150,000, see Scheme 48). The reaction carried out with high purity ethylene gas (99.995%), in the presence of benzylamine-chelated **Ru-27e** and a Brønsted acid activator (HSiCl_3), afforded the highest TON value reported so far (390,000), slightly surpassing the state of art **Ru-5** (340,000).



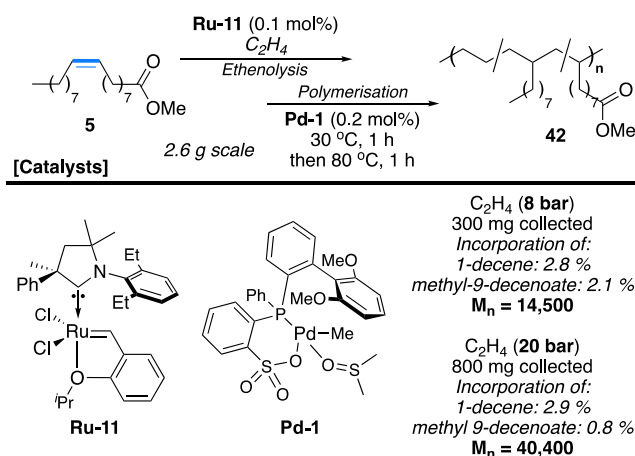
Scheme 51 Benzylether, benzylthioether and benzylamine substituted CAAC-Ru catalysts display very reactivities

As depicted in Scheme 52, six-membered CAAC-ligated Ru-catalysts **Ru-28-31** displayed much poorer reactivities than their five-membered counterparts in the ethenolysis of neat methyl oleate **5**.⁴⁰ Given a significant drop of activity at elevated temperature, it is likely that the poor catalytic behavior of these complexes could be imparted to their lower stability. Nevertheless, the authors also noted that CAAC-6 catalysts outperformed CAAC-5 in term of selectivity.



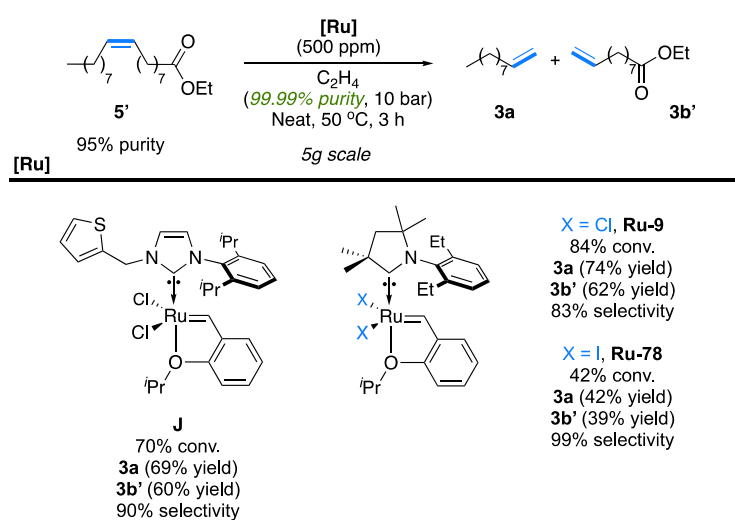
Scheme 52 Activity of CAAC-6 Hoveyda-Grubbs catalysts in Ethenolysis

Capitalizing on these results, Chen and coworker envisaged combining the Ru-ethenolysis and Pd-copolymerization of internal olefins to generate highly desirable polar functionalized linear low density polyethylene materials.¹⁰⁸ Using neat methyl oleate, and thanks to the high selectivity of CAAC-catalyst in ethenolysis, this tandem catalytic process involving CAAC **Ru-11/Pd-1** was able to produce valuable copolymers with high molecular weight and a tunable incorporation of 1-decenoate/1-decene (Scheme 53). It is worth noting that the direct copolymerization route failed due to the steric mismatch between the 1,2-disubstituted olefin and the palladium catalyst.

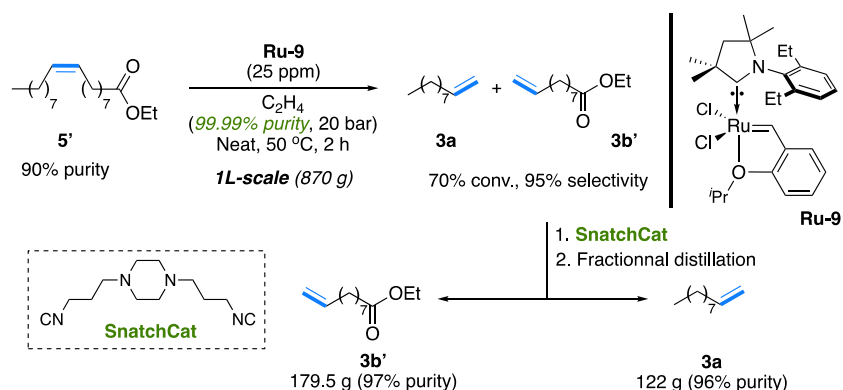


Scheme 53 Tandem Ru-ethenolysis and Pd-copolymerization of internal olefins towards polyethylene materials

CAAC-catalysts were also investigated in the ethenolysis of ethyl oleate **5'**. The later takes the advantage of a higher boiling point allowing for an easier separation of the corresponding products.¹⁰⁹ In an extensive study, Grela and coworkers reported on the catalytic activity of sixty-five NHC and CAAC Ru-complexes in the ethenolysis of **5'** (95% purity; 15 mmol scale) under ambient conditions (Scheme 54).¹⁰⁹ Amongst all the catalysts screened, CAAC **Ru-9** and NHC **J** were shown to be the most efficient (*i.e.* combining high reactivity and high selectivity). Note that a lower activity was observed with iodine derived CAAC **Ru-78** albeit a higher selectivity (99%). Expanding upon their work, these authors could perform large scale production using **Ru-9** as a catalyst (Scheme 55).¹¹⁰ Note that in this case they relied on SnatchCat as a metal scavenger to facilitate the purification.

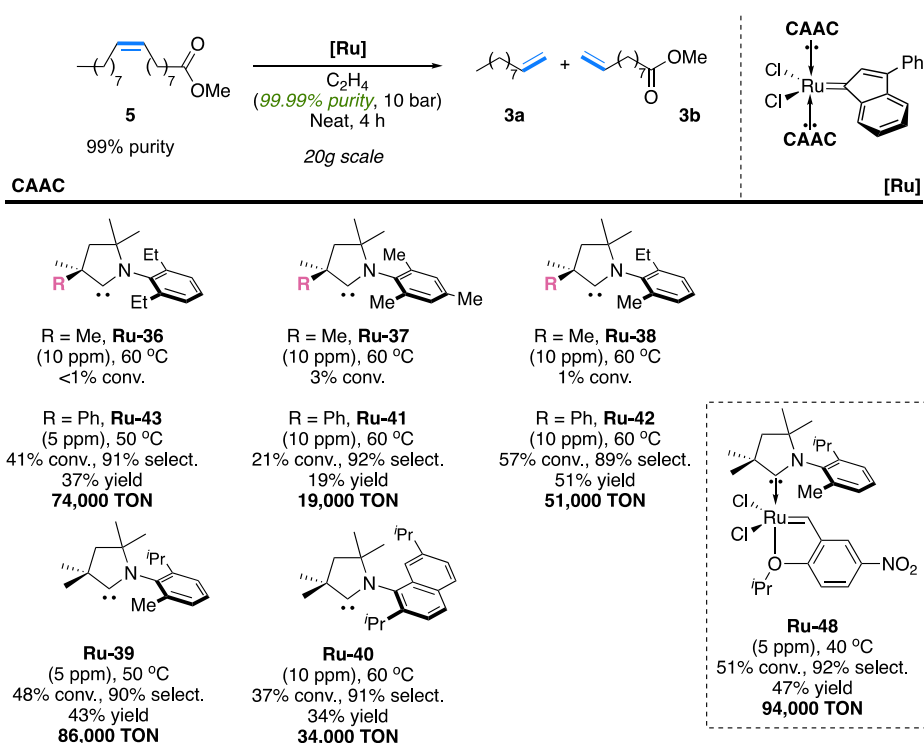


Scheme 54 CAAC-Ru catalysts in the ethenolysis of ethyl oleate



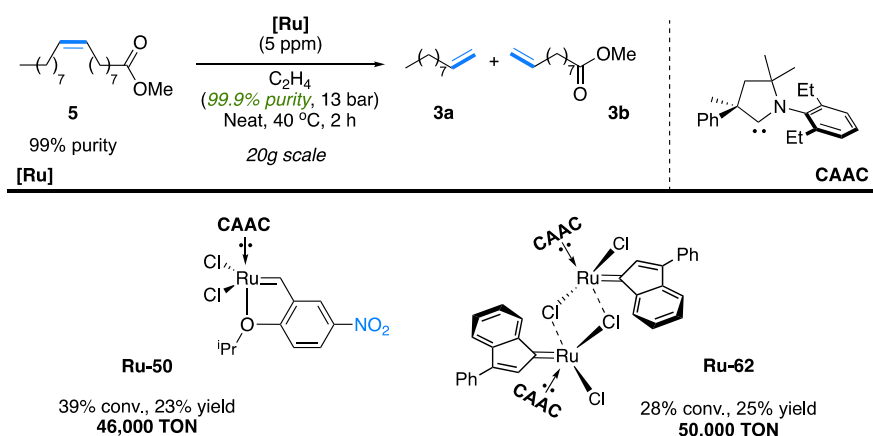
Scheme 55 Large scale ethenolysis of ethyl oleate under ambient conditions using **Ru-9**

Bis(CAAC)Ru indenylidene complexes developed by Skowerski and workers also proved to be efficient in the ethenolysis of neat methyl oleate **5** affording up to 86,000 TONs (Scheme 56).⁵² As expected, higher activities were obtained with the more sterically demanding phenyl substituted CAAC catalysts **Ru-41-43** and sterically unbalanced *N*-aryl **Ru-39** and **Ru40** reaching 86,000 TONs. Despite such exceptional reactivities, these catalysts remained slightly less reactive than nitro-Grela **Ru-48** (TON 94,000).



Scheme 56 Catalytic performances of bis(CAAC)Ru-indenylidene complexes in ethenolysis

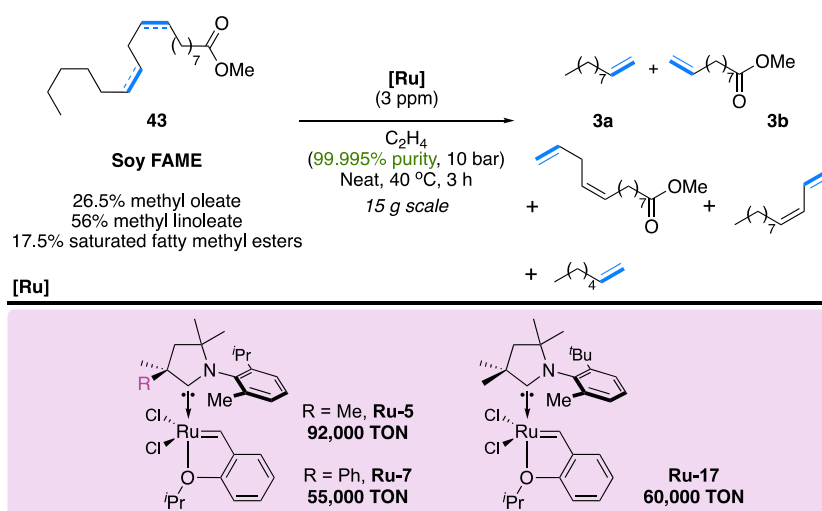
With up to 50,000 TON, Fogg's chloro-bridge dimer **Ru-62** was also shown to be a very potent catalyst for this transformation, even outperforming the Grela type catalyst **Ru-50** (Scheme 57).⁶⁶ Note however, that with this dimer, the catalytic activity was shown to be largely impacted by ethylene pressures.



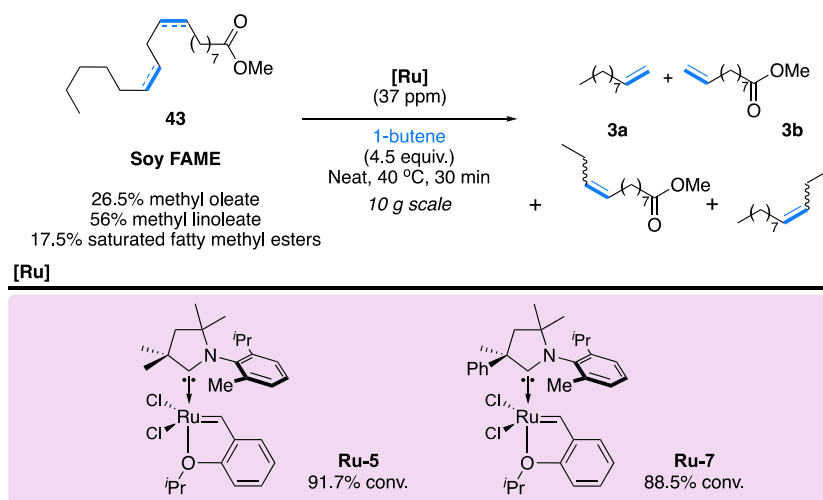
Scheme 57 Fogg's chloro-bridge dimer **Ru-62** a competitive catalyst for ethenolysis

3.3.2. Fatty acid methyl esters (FAME) mixture

Given the excellent catalytic performance of CAAC-catalysts in the ethenolysis of oleic esters, the methodology was applied to more valuable raw materials, such as FAME mixtures derived from transesterification of seed oils. The ethenolysis of soy FAME was first studied by Grubbs and coworkers using CAAC-Ru catalysts **Ru-5,7** and **Ru-17** (Scheme 58).¹¹¹ At 3 ppm catalyst loading and 10 bar of extremely pure ethylene (99.995%), the corresponding terminal olefins were produced with high TONs, up to 92,000 with **Ru-5**. Note that these complexes were also shown to efficiently catalyze the butenolysis of soy FAME **43**, delivering terminal and internal olefins in high conversions within 30 min (Scheme 59).

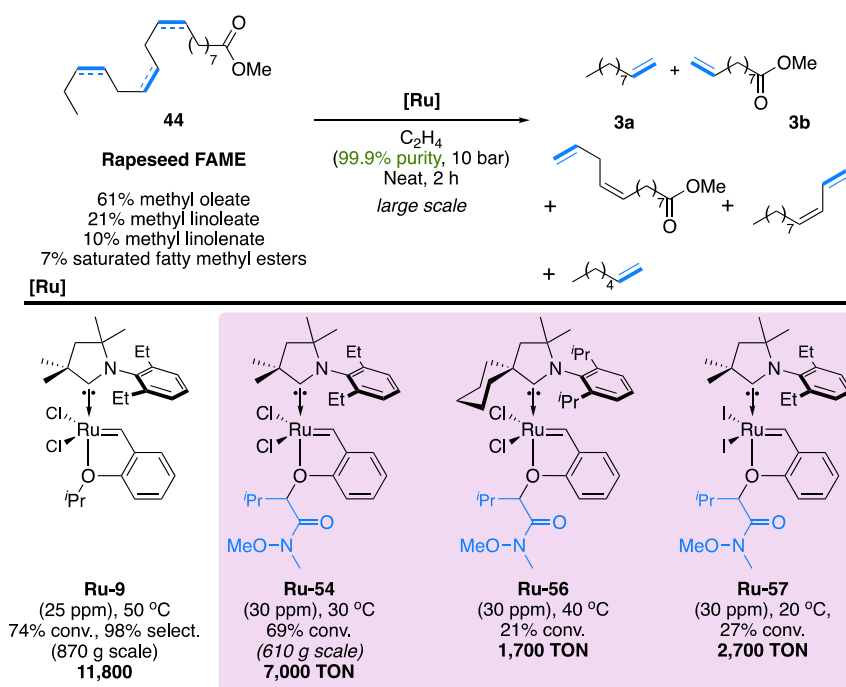


Scheme 58 CAAC-Ru complexes in the ethenolysis of soy FAME



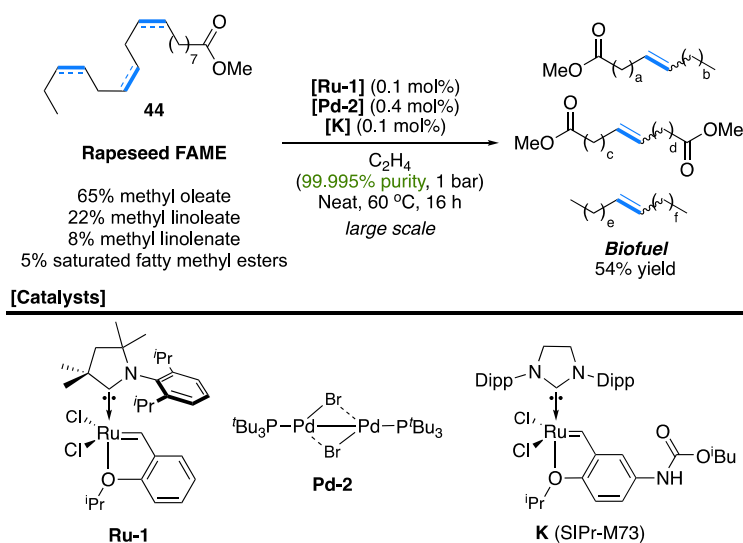
Scheme 59 CAAC-Ru complexes in the butenolysis of soy FAME

More recently, Grela and coworkers reported the catalytic activity of CAAC **Ru-9** in the ethenolysis of rapeseed FAME, performed at a 1 liter-scale, under industrially relevant conditions (*i.e.* ambient conditions, technical grade of oleic raw materials and ethylene).¹¹⁰ Despite these unfavorable settings, **Ru-9** remained very active at 25 ppm loading, affording terminal olefins with high conversion and excellent selectivity (Scheme 60). Weinreb-amide containing CAAC-catalysts **Ru-54-56** were used by Skowerski for large-scale transformation of rapeseed FAME but in this case lower productivities were obtained.⁵⁹



Scheme 60 CAAC-Ru complexes in the ethenolysis of rapeseed FAME

In 2017, Goossen and coworkers described the effective conversion of rapeseed FAME into biofuel via a catalytic process taking advantage of three specific catalysts: CAAC-Ru-1 (for ethenolysis), [Pd(I)(μ -Br)(t Bu₃P)]₂ **Pd-2** (for isomerization) and state of the art SIPr-M73 ruthenium catalyst **K**¹¹² (for cross- and self-metathesis) (Scheme 61).¹¹³ Used in a 1:4:1 ratio, these three mutually compatible catalysts performed the large scale transformation of rapeseed FAME to produce a mixture of C₁₂-C₁₄ linear internal olefins (monoesters, diesters and hydrocarbons), thus affording an end-product with boiling specifications expected for biodiesel fuels. Advantageously, this eco-friendly and practical process produces no wastes, involves soft conditions (60 °C), and requires no solvent. Note that the use of the highly active ethenolysis catalyst CAAC-Ru-1 was shown to be critical in promoting high ethylene incorporation into the product mixture.

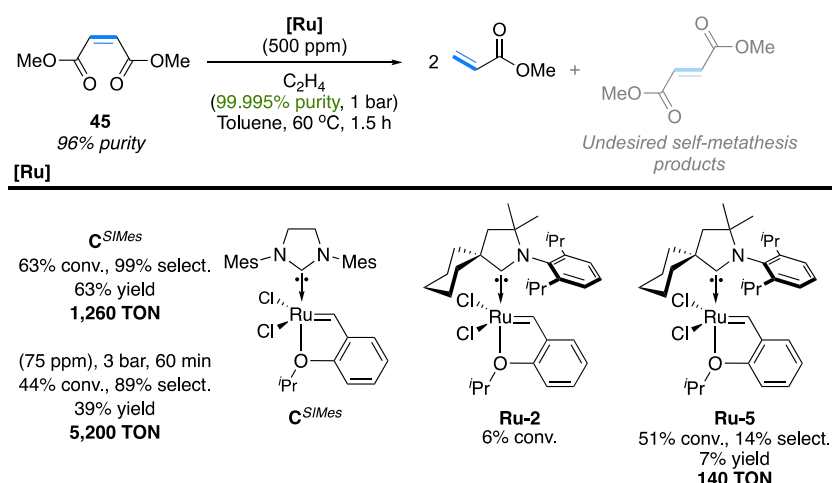


Scheme 61 One-pot, three-catalysts transformation of rapeseed FAME into biofuel

3.3.3. Other substrates

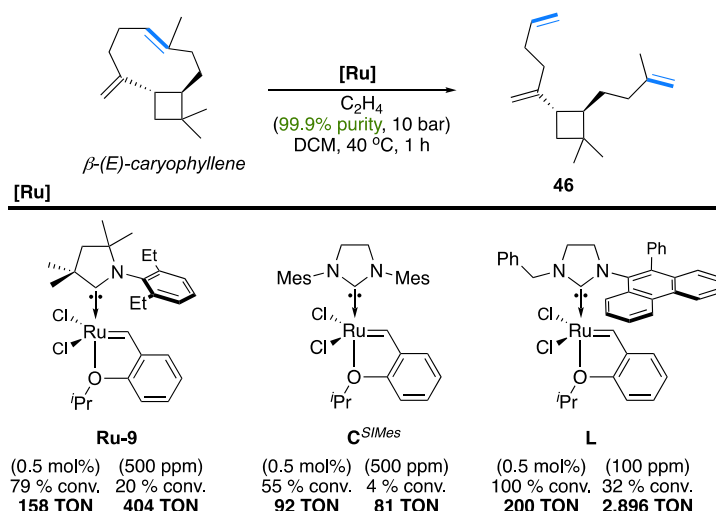
Aside from the transformation of bio-sourced unsaturated fatty esters, the ethenolysis reaction remains widely underexplored. In 2020, Fedorov, Togni and coworkers examined the catalytic activity of a number of ruthenium catalysts in the ethenolysis of inexpensive maleate esters,

competitive alternatives to industrially relevant acrylates.^{114,115} In contrast with the promising productivity (up to 5,200 TON) and good selectivity (up to 99%) obtained with Hoveyda-Grubbs catalyst **C**^{SIMes} in ethenolysis of dimethyl maleate **45**, CAAC complexes **Ru-2,5** proved to be much less efficient (Scheme 62). Although not discussed by the authors, this unexpected inefficiency, which severely contrasts with high TONs exhibited with fatty esters, could be the result of the rapid deactivation of the transient CAAC-Ru=CHCO₂Me.¹¹⁶



Scheme 62 Carbene-Ru complexes in the ethenolysis of acrylates

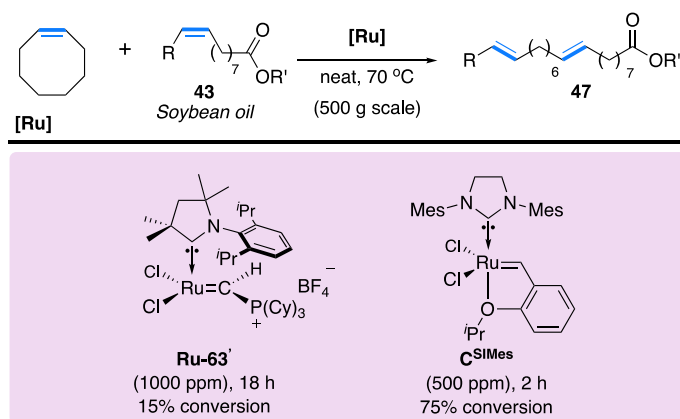
Recently, Grela and coworkers reported the ethenolysis of *β*-caryophyllene **E**, a bicyclic sesquiterpene, ubiquitous in various essential oils, that is largely used as an additive in food industry and as a fragrance ingredient (Scheme 63).¹¹⁷ CAAC-**Ru-9** showed promising catalytic performance, leading to the expected triene **46** with a TON of 404 (*ca.* 20% conversion at 0.05 mol%). Note that a lower 4% conversion (TON of 81) was observed with standard Hoveyda **C**^{SIMes}, while higher TONs (up to 2,876) were reached with a newly designed Ru-catalyst **L**, containing an unsymmetrical phenanthrene-based NHC.



Scheme 63 Comparing the activities of Carbene-Ru complexes in the ethenolysis of β -caryophyllene

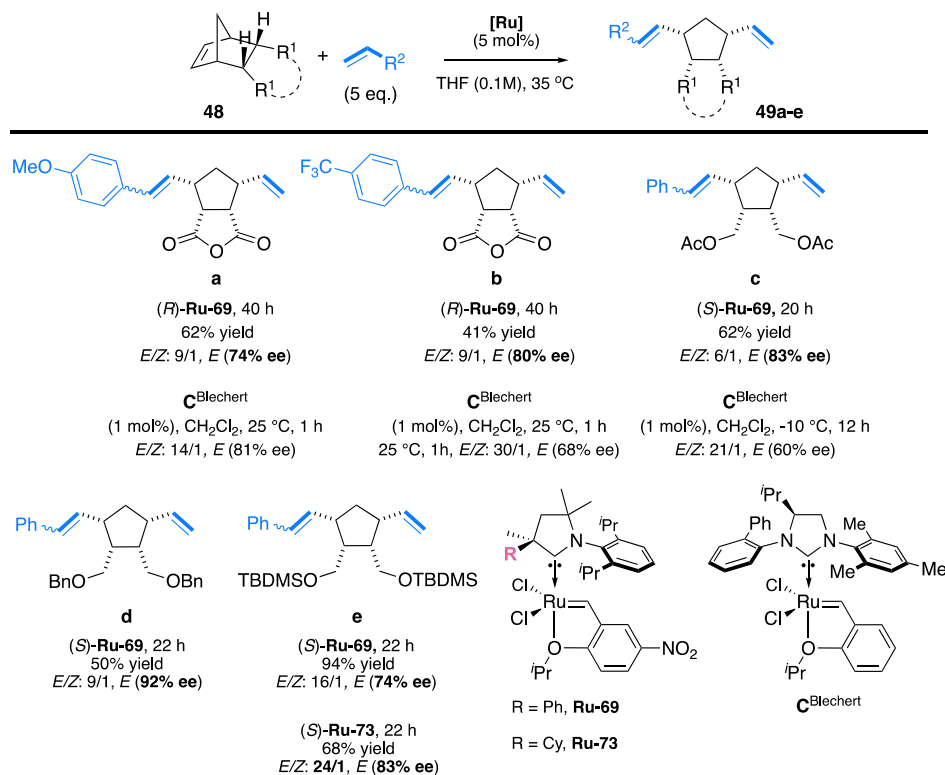
3.4. Application to ROCM

The two-directional desymmetrisation of chains is a popular strategy for the synthesis of complex molecules. Using ring-opening metathesis polymerisation (ROMP) or asymmetric ring-opening cross metathesis (AROCM), cyclic alkenes have been exploited as potential chain precursors. Interestingly, there are much fewer examples involving ring-opening metathesis and double cross metathesis (ROCM). Capitalizing on this approach, Lee and coworkers described a large scale two-directional desymmetrisation of cyclooctene using Soybean oil (Scheme 64).¹¹⁸ Comparing the catalytic activities of CAAC **Ru-63'** to the NHC catalyst **C^{SiMes}**, these authors demonstrated that NHCs perform much more efficiently. However, given the lack of more comprehensive studies, it seems premature to draw some conclusion.

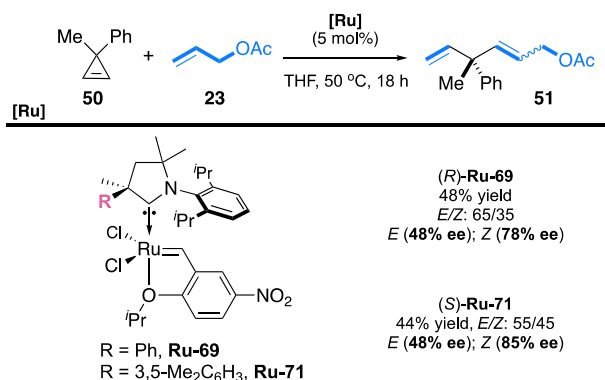


Scheme 64 Tandem ring-opening cross metathesis with CAAC-Ru Piers type catalyst

Owing to their unique and highly modular steric environment, chiral NHCs have attracted considerable interests for the development of AROCM transformations.^{119,120} Having developed an efficient access to optically pure CAAC ruthenium metathesis catalysts, we evaluated their activity in AROCM.⁷⁵ So far, chiral CAACs catalysts are less reactive and E/Z selective than Hoveyda-Grubbs type chiral catalysts, such as the one developed by Blechert and coworkers **C^{Blechert}** (Scheme 65).¹²¹ However, they have been shown to trigger asymmetric induction in AROCM up to 92% ee. While the specifics of the chiral induction phenomenon in these C1-symmetric chiral CAAC ligands are still unclear, DFT studies indicate that it likely originates from steric clashing between substituents at the quaternary position to the carbene center and the incoming substrate. Taking advantage of the CAAC framework, the remarkable asymmetric induction is clearly illustrated upon comparing the enantio- and E/Z selectivity obtained with the cyclohexyl derived **Ru-73**, in comparison to the phenyl derived **Ru-69** (Entry e). These catalysts were also evaluated in the challenging AROCM of cyclopropenes for which moderate yields but good Z-selectivity were observed (Scheme 66). It can be expected that further modifications of the CAAC motif will permit more competitive asymmetric inductions.



Scheme 65 First example of CAAC ruthenium catalysts in asymmetric ring-opening cross metathesis of norbornenes



Scheme 66 First example of CAAC ruthenium catalysts in asymmetric ring-opening cross metathesis of cyclopropenes

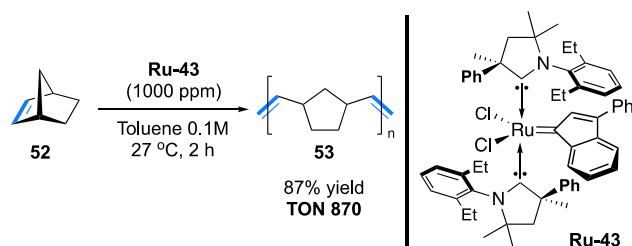
3.5. Application to Olefin Polymerization

NHC ruthenium catalysts have shined in the preparation of polymers via ring-opening metathesis polymerization (ROMP) or acyclic diene metathesis (ADMET) polycondensation.^{122,123,124,125,126} The former, which converts cyclic olefins into linear highly unsaturated polymers via chain polymerization, provides a wide range of unique architectures.

The latter, involving a step-growth polymerization mechanism is advantageous for the synthesis of polymeric materials containing in-chain functionalities.

3.5.1. Ring Opening Metathesis Polymerization (ROMP)

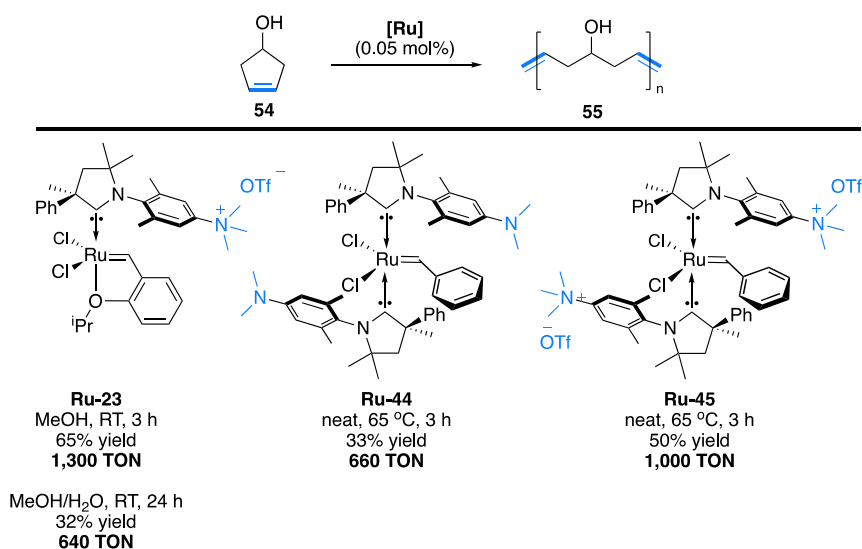
There are surprisingly very few examples of CAAC metathesis ruthenium complexes applied to ring opening metathesis polymerization. Using bis(CAAC)Ru indenylidene **Ru-43**, Skowerski and coworkers investigated the formation of polynorbornene (PNB), an elastomer used in the production of a wide variety of rubber goods which is also known as a super absorbent oil binding polymer (up to 30 times its own weight).⁵² Under mild conditions and using 1000 ppm of catalyst, up to 87% yield of PNB was obtained (Scheme 67).



Scheme 67 Activity of Bis(CAAC)Ru-indenylidene in Ring-Opening Metathesis Polymerization of Norbornene.

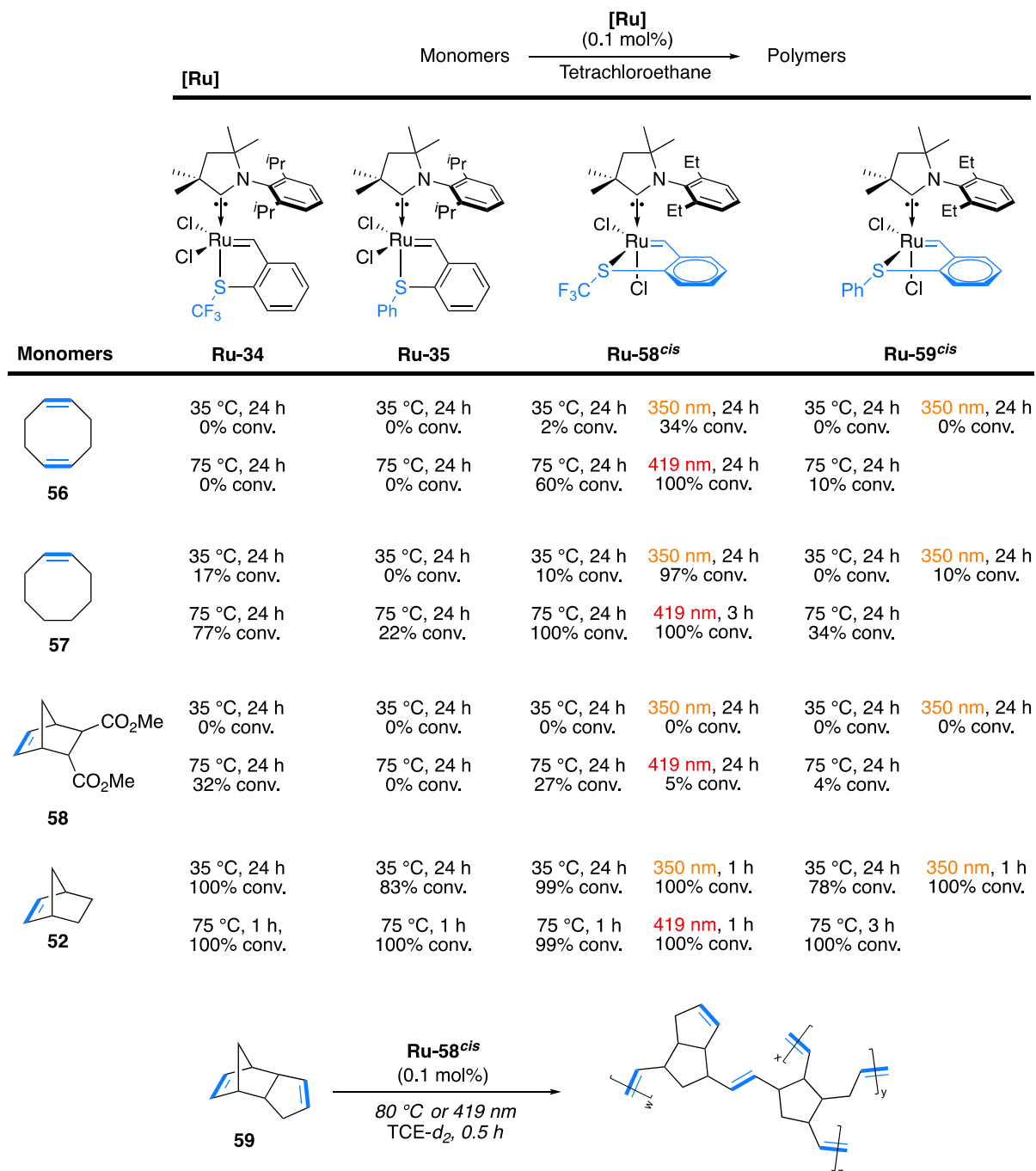
Compared to norbornene derivatives, there are much fewer examples of ROMP involving low-strain cyclic olefins such as hydroxyl functionalized cycloalkenes.¹²⁷ Recently, Tuba and coworkers extended the application of CAAC ruthenium catalysts to the polymerization of cyclopent-3-en-1-ol **54**, using the more polar **Ru-23** and **Ru-44,45**.³⁶ As shown in Scheme 68, second generation type catalyst **Ru-23** performs efficiently in methanol, affording biopolymer **55** in good yields and TONs. Despite the increased solubility of this catalyst, it was shown to be less efficient in a 50/50 mixture of MeOH/H₂O. As expected, bis(CAAC)Ru indenylidene **Ru-44,45** required higher temperature to catalyze this transformation reaching 1,000 TONs with **Ru-45**. Attempts to obtain the same polymer through acyclic diene metathesis

polymerization (ADMET) of hepta-1,6-dien-4-ol only led to a mixture of products despite higher catalyst loading (0.5 mol %).



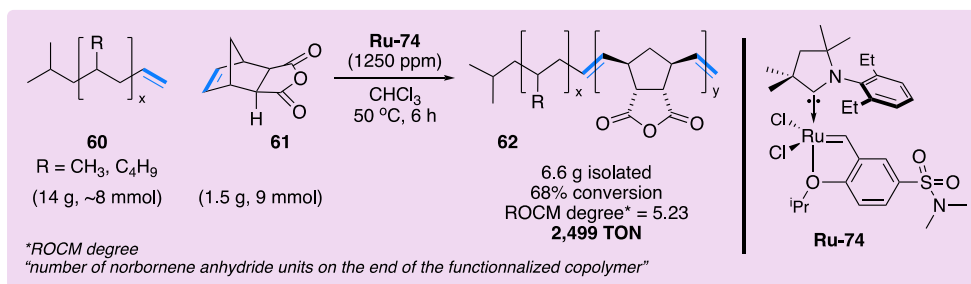
Scheme 68 Activity of polar Bis(CAAC)Ru-benzylidene in Ring-Opening Metathesis Polymerization of cyclopent-3-en-1-ol.

Extending this study to five typical cyclic olefins (**52**, **56-59**) (Scheme 69), Lemcoff and coworkers looked at the reactivity of sulfur-chelated ruthenium benzylidenes **Ru-34,35**.⁴⁷ Apart from the most reactive ROMP monomer, norbornene **52**, both catalysts showed latency at 35 °C. As expected, performing the reaction at higher temperature (75 °C) resulted in full polymerization of **52**, meanwhile other monomers remained poorly reactive. Similar results were obtained with sulfur-chelated cis-ruthenium benzylidenes **Ru-58^{cis}** and **Ru-59^{cis}** under thermal conditions. However, taking advantage of the photoactivity of these complexes, the authors could trigger significant catalytic activity under irradiation at 350 nm, as illustrated with **Ru-58^{cis}** and cyclooctene. Screening additional wavelengths with **Ru-58^{cis}** (254 and 419 nm), it was found that visible light at 419 nm resulted in excellent reactivity. The activation of **Ru-58^{cis}** with UV-A and visible light arguably marks a new method for the activation of CAAC containing olefin metathesis catalysts. The polymerization of dicyclopentadiene **57**, a diene of significant industrial importance was also considered, and complete polymerization was observed with **Ru-58^{cis}** upon irradiation at 419 nm or by heating to 80°C.



Scheme 69 Polymerization scope for sulfur-chelated CAAC Ru-benzylidenes

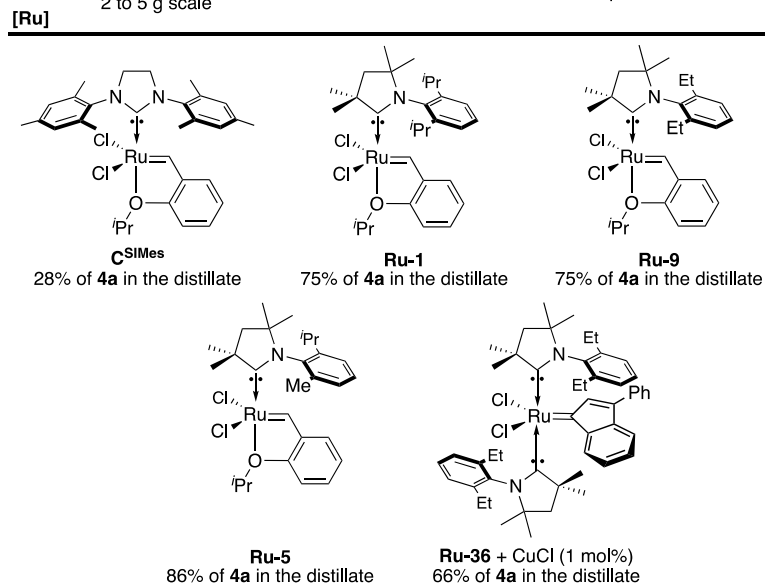
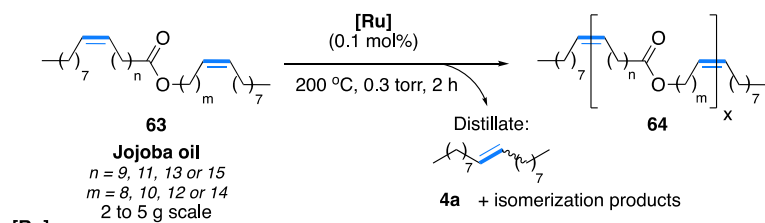
Although the subject of fewer studies, a variation of ROMP is the ring-opening cross metathesis (ROCM). It involves a tandem reaction sequence between a ring-opened cyclic-olefin and an acyclic olefin crossed onto the newly formed termini. Probing the activity of CAAC ruthenium catalysts in this process, Holtcamp *et al.* disclosed that **Ru-74** afforded up to 68 % of the desired functionalized hexene-propylene copolymer **62** (Scheme 70).¹²⁸



Scheme 70 ROCM with vinyl terminated polymers and Ru-CAAC functionalized Hoveyda type catalyst

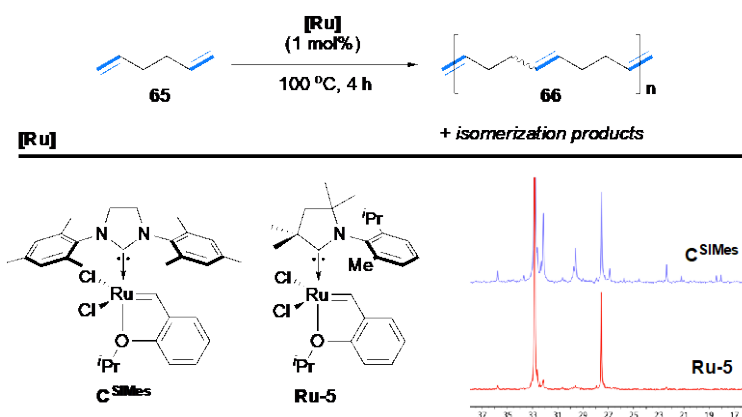
3.5.2. Acyclic Diene Metathesis (ADMET) Polycondensation

The propensity of CAAC ruthenium catalysts to promote the polymerization of dienes has also been used as a mean to improve the acyclic diene metathesis (ADMET) polymerization of Jojoba oil **65**. Traditionally this process requires rather high temperatures (*i.e.* 200 °C) to separate the polyester polymer **66** from the octadec-9-ene (**4a**) biofuel side product. However, under these demanding conditions traditional NHC ruthenium catalysts are prone to decompose and thus promote undesirable isomerizations.¹²⁹ This is well illustrated with Hoveyda-Grubbs **C^{SiMes}** which only provides up to 28% of **4a** (Scheme 71). In marked contrast, under the same conditions, CAAC catalysts **Ru-1,5,9** and **Ru-36** were shown to suppress the isomerization reaching up to 86% of hydrocarbon **4a**.⁷⁹



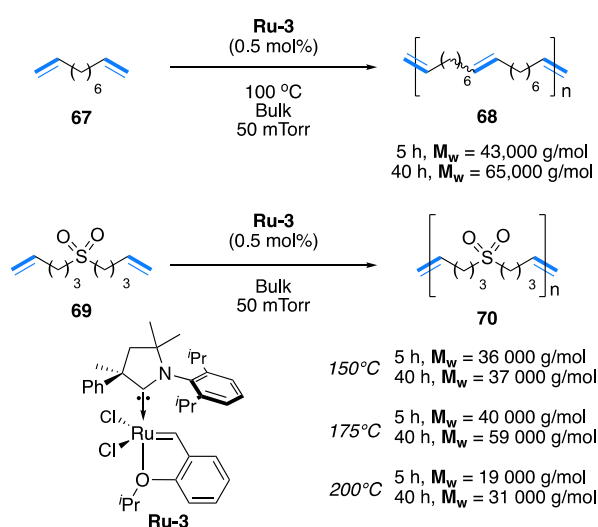
Scheme 71 Highly selective ADMET of Jojoba oil catalyzed by CAAC Ru-complexes

The advantage of using CAAC catalysts in the ADMET was also evidenced with 1,5-hexadiene **65**, a precursor to polybutadiene **66**. As shown in Scheme 72, a more pronounced isomerization can be seen in the C^{SIMes} derived polymer, whereas much fewer defects are observed with **Ru-5**.⁷⁹ The authors proposed that CAACs afford more stable ruthenium complexes less prone to form the ruthenium-hydride- π -allyl intermediates necessary to promote the double migration.



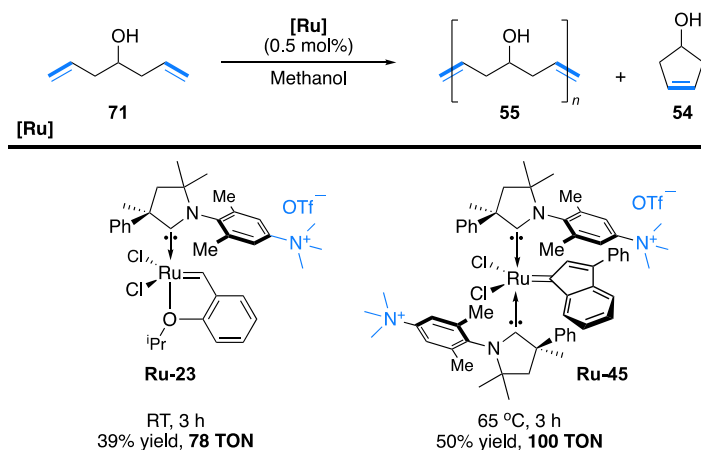
Scheme 72 ADMET of 1,5-hexadiene illustrating the selectivity of Ru-5 versus C^{SIMes}.

Capitalizing on these results Wagener and coworkers extended the study to the bulk polymerization of 1-9 decadiene **67** and bis(pent-4-en-1-yl)sulfone **69** (Scheme 73).⁸⁰ While excellent polycondensation results were obtained in both cases, the authors demonstrated the stability of CAAC ruthenium catalyst **Ru-3** up to 175 °C, with a slight loss of reactivity at 200 °C. While this later result is presumably due to slow catalyst degradation, it clearly shows that CAAC complexes can retain their activities despite the very high working temperatures necessary to maintain liquid state in high crystallinity polymers.



Scheme 73 Ru-3 catalyzed Bulk Acyclic Diene Metathesis Polycondensation

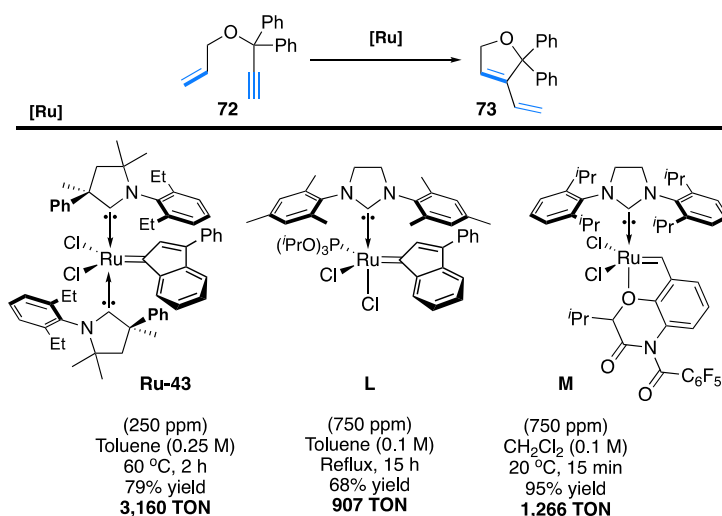
More recently, Tuba and coworkers have shown that ADMET polymerization of heptadiene-4-ol **71** could be achieved under protic conditions using the very polar CAAC ruthenium Hoveyda-Grubbs **Ru-23** and the bis(CAAC)Ru indenylidene **Ru-45** (Scheme 74).³⁶ Note that polymer **55** was obtained selectively by ROMP of cyclopent-3-en-1-ol **54** (Scheme 68).



Scheme 74 ADMET of heptadiene-4-ol **71** using polar ammonium tagged CAAC-based catalysts.

3.6. Application to En-Yne Metathesis

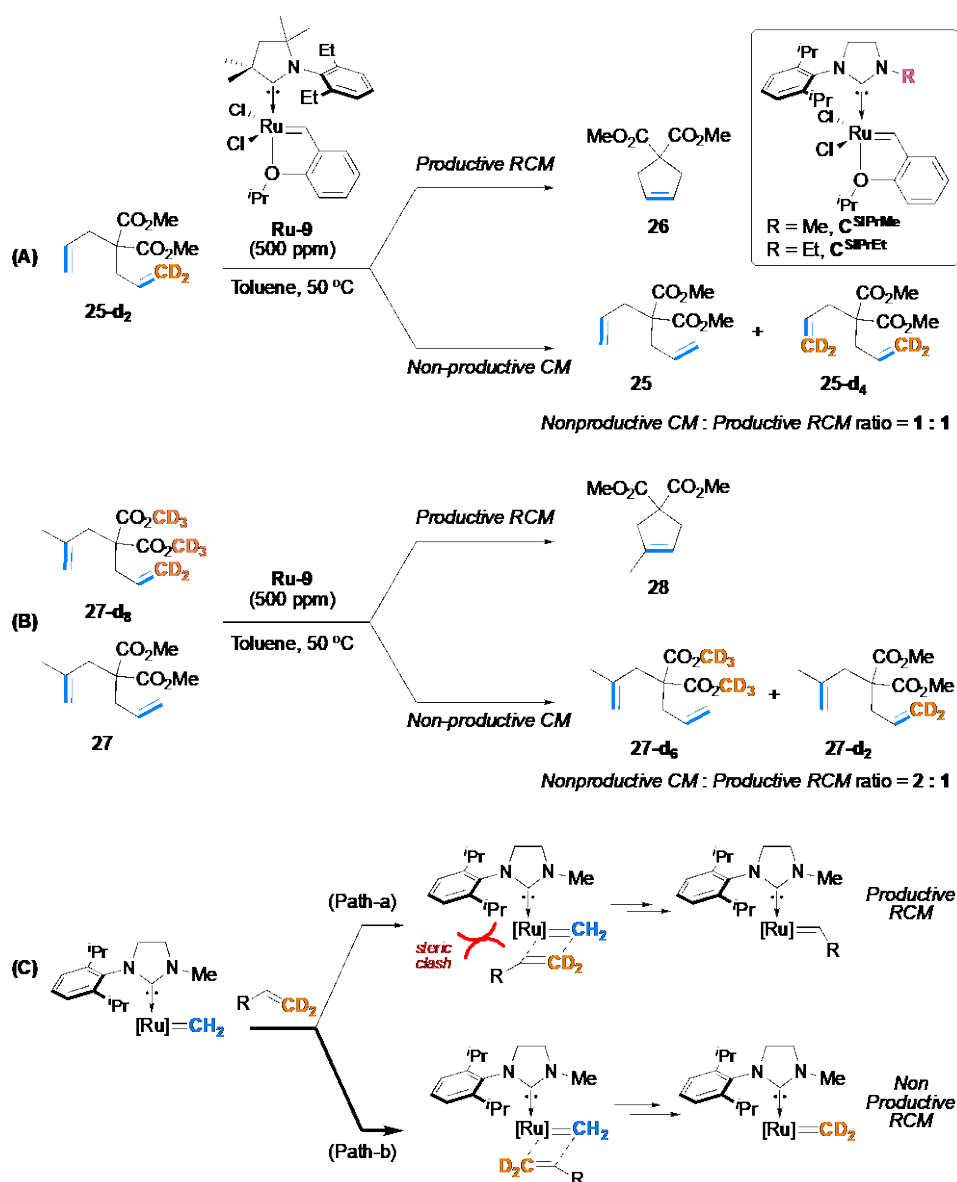
The en-yne metathesis is a fundamental chemical transformation involving an alkene and an alkyne to generate a diene.^{130,131} Skowerski and coworkers were the first to show that the reactivity of CAACs ruthenium catalysts extends to the intramolecular Ring-Closing En-Yne Metathesis (RCEYM¹³²).⁵² In the presence of 250 ppm of the bis(CAAC)Ru indenylidene complex **Ru-43**, up to 3160 TONs of 1,3-diene **73** were obtained starting from en-yne **72** (Scheme 75). Contrasting with other catalysts, such as Cazin's ruthenium phosphite indenylidene **L** (907 TON)¹³³ or benzylidene-oxazinone catalysts **M** (1,266 TON),¹³⁴ these results prompt further investigations on the use of (CAAC)Ru catalysts in en-yne metathesis.



Scheme 75 Comparing the activities of carbene-Ru catalysts in Ring-Closing En-Yne Metathesis

3.7. Activity in Degenerate (Nonproductive) Metathesis

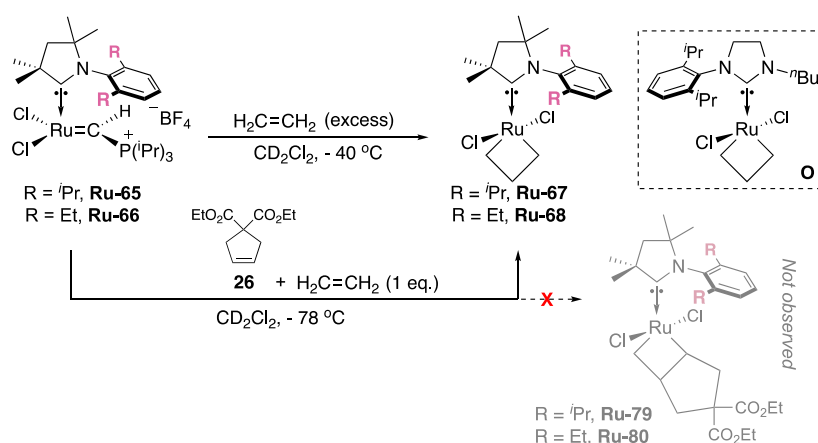
As mentioned previously, CAAC-Ru-complexes have largely outperformed their diamino-NHC counterparts in ethenolysis by remaining highly active at extremely low catalyst loadings (as low as 1 ppm), thus affording the highest TONs reported so far. To explain these remarkable catalytic performance, Grubbs and coworkers compared several catalysts in non-productive (*i.e.* degenerative) metathesis events occurring during RCM.¹³⁵ Investigating the RCM of deuterated diethyl diallyl malonate **25-d2** (Scheme 76-A), they showed that **Ru-9** and Hoveyda-type NHC ruthenium complexes **C^{SiPrMe}** and **C^{SiPrEt}** displayed almost equal amounts of degenerative vs productive metathesis events (1:1), whereas bulkier **C^{SiMes}** or **C^{SiTol}** complexes gave a 1:10 ratio (not shown). These contrasting behaviors were also confirmed during the RCM of deuterated dimethyl allylmethyl malonate **27-d8** (Scheme 76-B), in which a higher amount of non-productive cross metathesis was observed with **Ru-9**, **C^{SiPrMe}** and **C^{SiPrEt}**. To explain these results, the authors proposed that steric interactions in catalysts bearing unsymmetrical carbene ligands (*i.e.* **Ru-9**, **C^{SiPrMe}**, **C^{SiPrEt}**) could favor the formation of the less sterically hindered β -substituted metallacycle (Path b) over the more productive α -substituted metallacycle (Path a) (Scheme 76-C).



Scheme 76 Nonproductive events in RCM using CAAC catalysts

Later, the same authors reported the clean formation of CAAC-based ruthenacyclobutanes **Ru-67,68** resulting from the reaction of Piers catalysts **Ru-65,66** with an excess of ethylene (Scheme 77).⁶⁸ Unexpectedly, relatively low exchange rate of α and β methylene protons in ethylene ruthenacycles was found for **Ru-67,68** compared to their NHC variant **O**. Moreover, substituting DEP at nitrogen with DIPP resulted in a remarkable 2.6-fold increase in the exchange rate, suggesting that subtle changes in ligand architecture is sufficient to alter the reactivity and the selectivity of CAAC catalysts. As pointed by the authors, the relatively low exchange rate observed with **Ru-67** suggests that CAAC derived metathesis-relevant

ruthenacycles may be viable targets for crystallographic characterization. Additionally, the reaction of Piers catalysts **Ru-65,66** with cyclopentene **26** in the presence of one equivalent of ethylene did not lead to the expected substituted ruthenacycle **Ru-79,80** (as observed with NHC congeners),⁶⁸ but to the ethylene ruthenacycles **Ru-67,68**. The authors noted that this peculiarity, although surprising, could be related to the preferential ability of CAAC-catalysts to propagate as methylenide species in metathesis reactions.



Scheme 77 Probing the origin of degenerate metathesis for CAAC-based Ru complexes via the generation of ethylene ruthenacycles

4. Conclusions and Future Directions

Since stable *N*-heterocyclic carbenes were discovered in 1991, whereas CAACs were only isolated in 2005, it is not surprising that NHCs are dominant ligands in many transition metal catalyzed reactions. However, the advent of CAACs in olefin metathesis has resulted in numerous achievements and breakthroughs, including in industry, as illustrated by the number of patents. Compared to NHCs, they reveal enhanced metathesis performances in several reactions, in particular in ethenolysis processes (up to of 390,000 TON). In a recent study, Fogg and Nascimato noted that such a breakthrough can likely be attributed to the remarkable stability of CAAC-ruthenacycles toward β -elimination, and CAAC-ruthenium-methylidenes toward bimolecular decomposition at extremely low catalyst loading.¹³⁶ As illustrated by the diversity of complexes obtained so far (>70), with some of them already prepared industrially,

the high structural modularity of the CAAC framework is particularly attractive for olefin metathesis applications. Undoubtedly, we expect the number CAAC-ruthenium catalysts and their ensuing applications to increase significantly with other motifs such as the 6-membered CAAC-6s²⁸, the bicyclic BiCAACs²⁷, the multifunctional FunCAACs^{22,137}, and their chiral variant ChiCAACs^{22,75}, which have recently been used in asymmetric olefin metathesis. Thanks to the stability of CAAC ruthenium complexes, we are confident that they will prove invaluable for the solid-state characterization of metathesis-relevant ruthenacycles (achiral and chiral).⁶⁸ For the same reason, it can be expected that their enantioselective version might shine as *air-stable* Z-selective^{138,139} and stereoretentive¹⁴⁰ catalysts. Finally, much remain to be done in their development as new thermo- and photo-switchable latent catalysts for a highly-controlled polymerization,^{141,142} a growing area of research interest.

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