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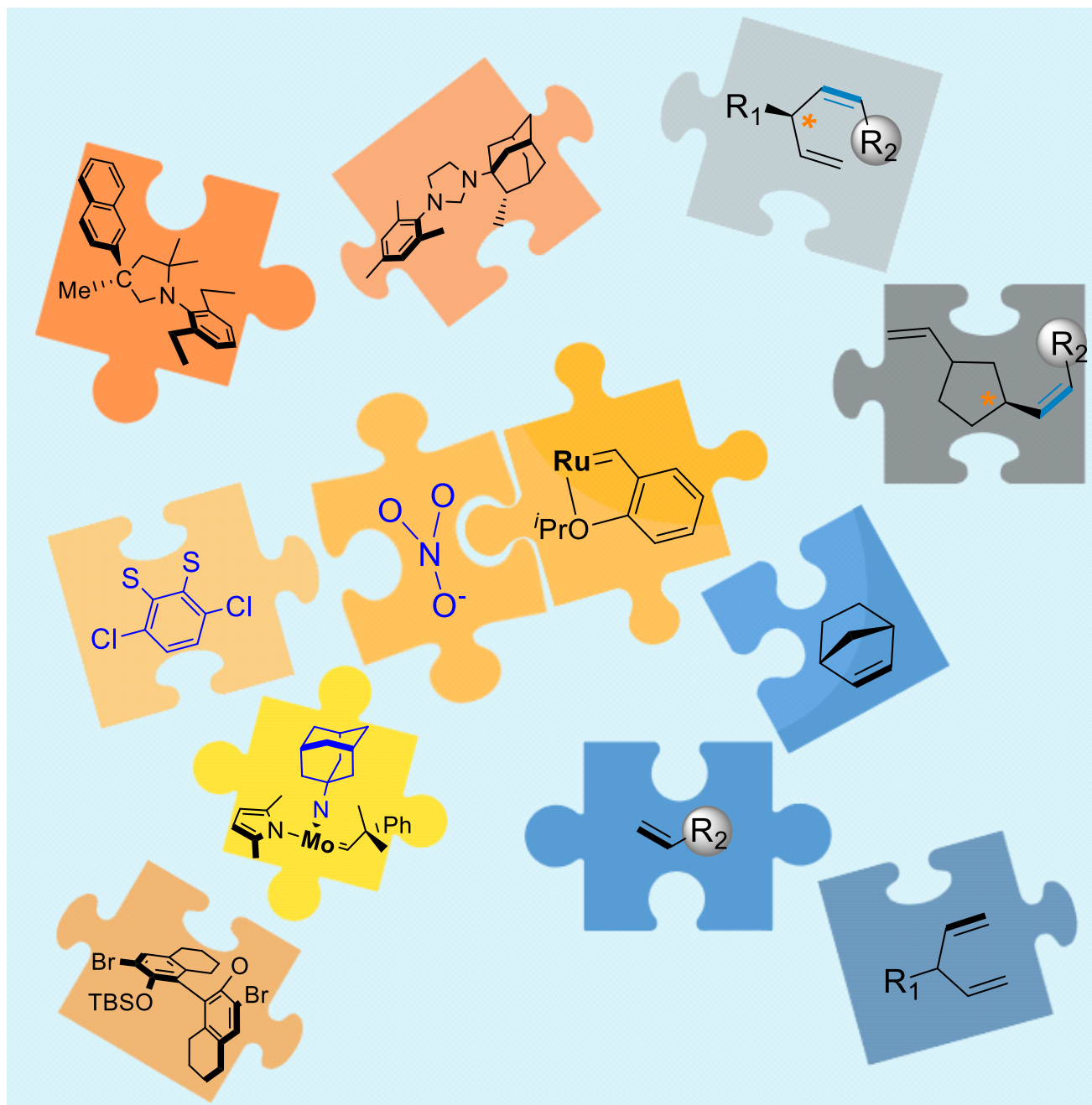


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# Challenges and Breakthroughs in Z-Enantioselective Olefin Metathesis

Jennifer Morvan,<sup>[a]</sup> Antonio Del Vecchio,<sup>[a]</sup> Jakub Talcik,<sup>[a]</sup> Dylan Bouëtard<sup>[a]</sup> and Marc Mauduit\*<sup>[a]</sup>

Dedication ((optional))



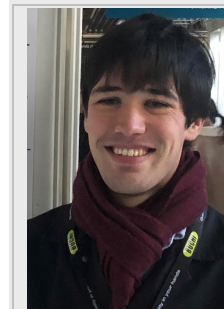
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**Abstract:** Asymmetric Olefin Metathesis (AOM) represents a highly versatile synthetic tool to lead to relevant chiral building blocks with excellent enantiopurity. As the Z-alkene moiety is ubiquitous in a wide range of natural products, the development of catalysts which are able to control both the Z-selectivity and the enantioselectivity of metathesis transformations is in high demands. This review aims to provide a comprehensive overview covering all the breakthroughs accomplished in the field of challenging Z-enantioselective olefin metathesis, which is of interest in the total synthesis of complex molecules.

Jennifer Morvan obtained her MSc and engineering degrees in Molecular chemistry in 2018 at Ecole Nationale Supérieure de Chimie de Rennes (ENSCR, France). She joined then Organometallic, Material and Catalysis department of ENSCR for her PhD supervised by Dr M. Mauduit and Dr C. Crévisy. Her work focused on the development of new Ru-based complexes for stereoselective olefin metathesis in batch and continuous flow mode. In 2022, she receives the Henri Kagan thesis award from the French Chemical Society and the René Dabard award from the ENSCR. She recently joined Janssen Pharmaceuticals (Belgium) as postdoctoral researcher to study electrochemistry in continuous flow mode.



Dylan Bouëtard studied chemistry at the Ecole Nationale Supérieure de Chimie de Rennes (ENSCR, France) where he received his MSc in Molecular Chemistry in 2021. He then joined the group of Dr. Mauduit as a Ph.D student to develop chiral metal-carbene complexes for enantioselective catalysis.



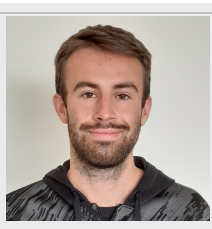
Antonio Del Vecchio obtained the MSc degree in Chemistry and Pharmaceutical Technologies at University of Ferrara (Italy). In October 2016, he joined the Service de Chimie Bioorthogonale et de Marquage (SCBM) at CEA-Saclay (French Atomic Energy Commission) under the supervision of Dr. Davide Audisio and Dr. Frédéric Taran. From 2019 to April 2023, he joined the Prof. Dr. Ackermann group at the Georg-August-Universität Göttingen (Germany, 2019-2021) and the Dr. Mauduit group (end 2021-April 2023) at the Organometallic Chemistry Department at ENSC de Rennes (France), as postdoctoral researcher. In May 2023 he joined the Department of Chemistry and Industrial Chemistry at the University of Pisa (Italy) where is currently working as Assistant Professor.



Marc Mauduit obtained his Ph.D. degree in 1999 from the University of Paris-Sud Orsay (France) under the supervision of Professor Y. Langlois. After postdoctoral studies with Professor S. Hanessian (University of Montreal, Canada, 1999-2001), he was appointed CNRS Research Fellow in 2001 at the Ecole Nationale Supérieure de Chimie de Rennes (UMR CNRS 6226 «Institut des Sciences Chimiques de Rennes»). He obtained his habilitation from the University of Rennes 1 in 2007 and was promoted CNRS Research Director in 2010. His main research interests are the development of N-heterocyclic carbene (NHC) and cyclic(amino)(alkyl)carbene (CAAC) ligands and related TM-complexes for homogeneous (asymmetric) catalysis and biomass valorization.



Jakub Talcik obtained his MSc in molecular chemistry and engineer title in 2020 at Ecole Nationale Supérieure de Chimie de Rennes (ENSCR, France). He joined then Organometallic, Material and Catalysis department of ENSCR for his PhD under the supervision of Dr M. Mauduit and Dr R. Jazzar (University of San Diego, UCSD, USA). His work focuses on the design of new CAAC-based metallic complexes for asymmetric catalysis application.



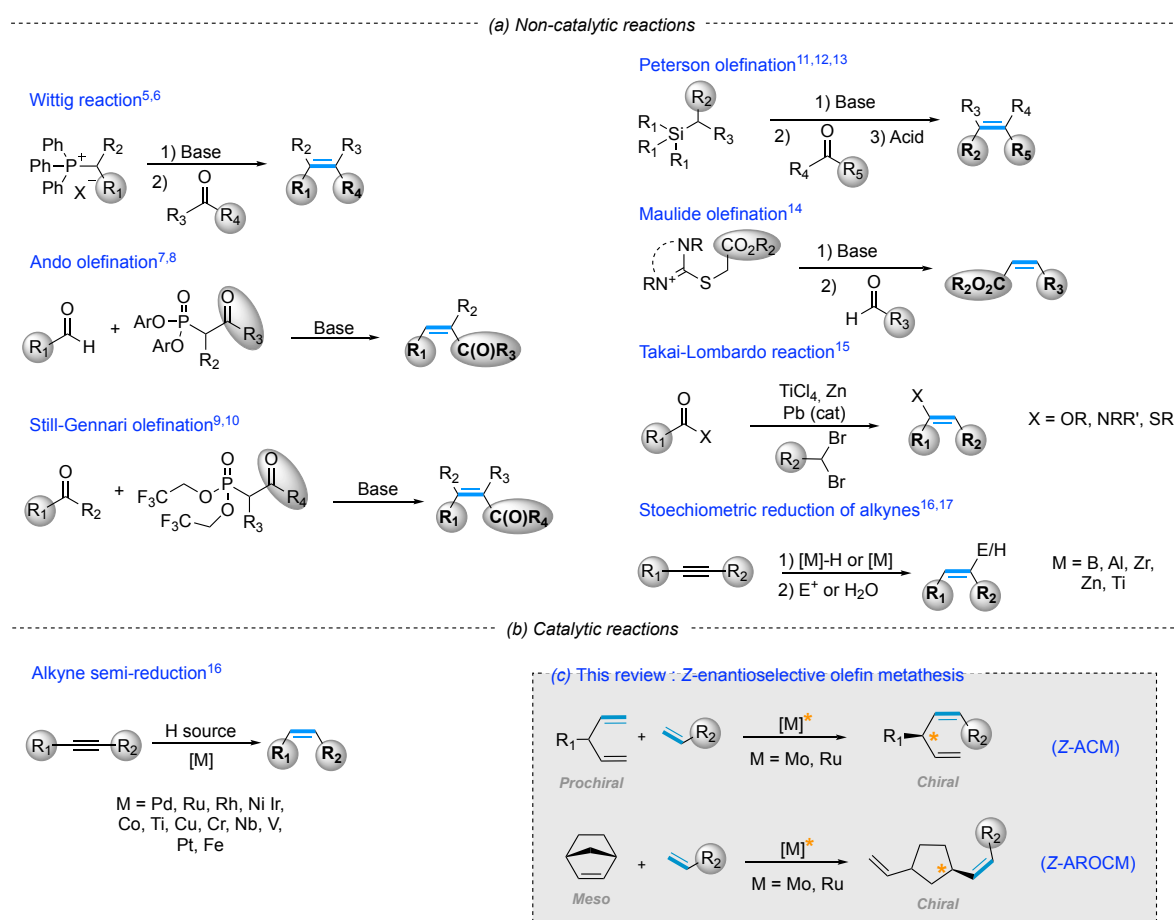
## 1. General Introduction

Csp<sup>2</sup>–Csp<sup>2</sup> double bond is an ubiquitous chemical function in organic chemistry.<sup>[1]</sup> Innumerable biologically active molecules and natural products incorporates alkenes, popular examples include carotenoids,<sup>[2]</sup> unsaturated fatty acids<sup>[3]</sup> or terpenes<sup>[4]</sup>. The sp<sup>2</sup> hybridization of the constitutive carbons restricts the rotation around the carbon-carbon bond resulting in two possible arrangements: *cis* (or *Z*) and *trans* (or *E*). These two different configurations give two distinct and stable diastereomers that display different physical, chemical and sometimes also different biological properties. In general, the less hindered *E*-isomer is thermodynamically favored and synthetic methods leading to *Z*-olefins are less explored, thus making the stereoselective synthesis highly desirable. Two categories of *Z*-selective transformations can be distinguished: those that employs stoichiometric reagents and those that operate under catalytic conditions. The long-lasting tradition of olefination is thus exploiting stoichiometric reagents such as phosphonium ylides,<sup>[5,6]</sup> phosphonates,<sup>[7-10]</sup> silyl carbanion,<sup>[11-13]</sup>

## REVIEW

sulfur ylides,<sup>[14]</sup> or a geminal di-metal species.<sup>[15]</sup> The partial reduction of alkynes is another important strategy to access Z-olefins selectively.<sup>[16,17]</sup> From a non-catalytic perspective, the reduction can be achieved by stoichiometric hydrometallation followed by reaction with an electrophile or by direct semi-reduction with an activated metal. On the other hand, catalytic processes rely on the use of stoichiometric hydride source combined with a catalytic system, Lindlar's catalyst is among the most famous examples.<sup>[18]</sup> Olefin metathesis (OM) has emerged as a powerful and versatile catalytic alternative to access *E* and *Z*-olefins. An early example of OM was firstly reported in 1931, with the formation of low amounts of but-2-ene and ethylene upon very strong heating of propene.<sup>[19]</sup> Twenty years later, DuPont, Standard Oil and Philips petroleum reproduced the same dismutation using heterogeneous molybdenum and tungsten complexes.<sup>[20]</sup> In

parallel, the polymerization experiments of norbornene were handled successfully by Eleuterio and Truett group in 1960 by using tungsten-based and titanium-based systems.<sup>[20,21]</sup> It was only in 1967 that Calderon attributed the two reactivities to the same transformation, named metathesis.<sup>[22,23]</sup> After Chauvin's mechanistic proposal,<sup>[24]</sup> Schrock and co-workers reported in 1980 the first catalytic metathesis reaction by using tantalum and tungsten complexes,<sup>[25]</sup> while Grubbs and co-workers explored preferentially the development of ruthenium-based catalysts.<sup>[26,27]</sup> Following these seminal discoveries, many efforts were made in the development of *Z*-selective and enantioselective metathesis. This mini-review aims to cover the recent developments regarding the *Z*-enantioselective OM, providing a critical overview on the different metals, ligands and substrates.



**Scheme 1.** a) non-catalytic and b) catalytic general strategies for the synthesis of *Z*-olefins; c) *Z*-enantioselective olefin metathesis (this review).

## 2. Z-selectivity in olefin metathesis

Olefin metathesis is a reversible reaction, thus the distribution of resulting products generally reflects the energetical difference existing between *E* and *Z*-isomers. As such, most of the time the *E*-isomer is observed as major product. Obtaining a pure isomer without affecting yield is more difficult: the control over the substrate approach and coordination to the active catalyst-species is primordial to develop a selective process toward the formation of the desired stereoisomer. Additionally, the frequent epimerization of products catalyzed by metal-hydride *in situ*

formed species or the reversible OM reaction on the less (thermodynamically) favored *Z*-product, results in the formation/enrichment of the *E*-isomer. All of these aspects have to be considered to build-up an efficient *Z*-selective OM process. In the late 2000's, several examples were reported where a modification on the substrate was exploited as stereo-directing group.<sup>[28]</sup> Although the methodologies were generally highly selective, scope and applications resulted limited to a few structurally similar derivatives. Therefore, more promising solutions to broaden (stereo)selectivity and applications arise from opportune structural modifications on the metal core and associated ligands. As a consequence, the challenging regulation

## REVIEW

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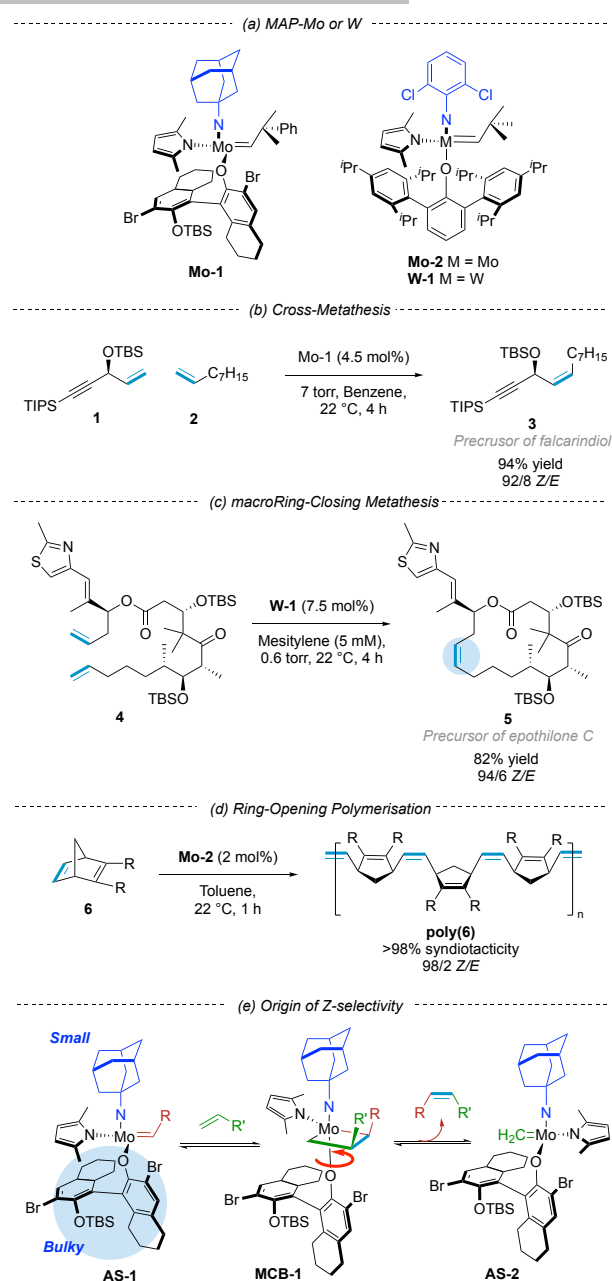
of different parameters becomes essential to reach a satisfying selectivity:

- the control over the geometry of metallacyclobutane species (MCBs) formed during the catalytic cycle, obtained by the ligand-modification in the coordination sphere.
- the control over the equilibrium and the reversibility, thus reducing the formation of competing secondary products, by using experimental engineering techniques.

## 2.1. Molybdenum and Tungsten-based complexes

### 2.1.1. Mono-Aryloxy Pyrrolide Mo- and W- based complexes

An early approach to Z-selective olefin metathesis appeared in 2009 with the work developed by Schrock and co-workers.<sup>[29]</sup> While working on Asymmetric Ring-Closing Metathesis (ARCM), the group built a series of Mo-based complexes bearing a series of mono-aryloxy, pyrrolide (MAP) and N-imido ligands (**Mo-1** and **Mo-2**, Scheme 2,a). The modification of the N-imido ligand tuned its activity, hence the presence of the N-adamantyl moiety yielded the first complex able to perform with Z-selectivity and chirality (**Mo-1**). MAP-**Mo-1**, **Mo-2** and MAP-**W-1**<sup>[30]</sup> (4.5 to 7 mol%) catalyzed Cross-Metathesis (CM),<sup>[31]</sup> macro-Ring Closing Metathesis (*macro*RCM)<sup>[32]</sup> or even Ring Opening Metathesis Polymerization (ROMP)<sup>[33]</sup> with high Z-selectivity (generally >90%, Scheme 2,b-d). In the case of MAP-Mo complexes, the Z-selectivity is due to the difference in steric hindrance between the aryloxy and imido-moieties, located in apical position and opposite to each other (Scheme 2,e). When this hindrance difference is significant, a better control of the spatial orientation of the olefin is possible, which therefore approaches in *trans* to the pyrrolide ligand (**AS-1**). The formation of **MCB-1** metallacycle whose groups point toward the small imido fragment is then favored. The cyclo-reversion step (**AS-2** to **MCB-1**) thus releases the Z-isomer exclusively.<sup>[34]</sup> More details related to the synthesis and application of these catalysts for Z-enantioselective transformations are reported in section 3.1.



**Scheme 2.** a) MAP-Mo and W catalysts; applications to b) CM, c) *macro*RCM and d) ROMP; e) origin of Z-selectivity.

### 2.1.2. Oxo W type complexes

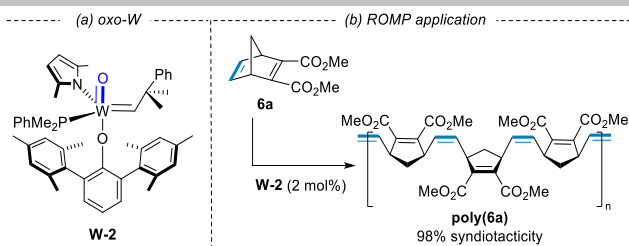
In 2011 Schrock, Hoveyda and co-workers isolated oxo-W complexes type such as **W-2** (Scheme 3,a) inspired by serendipitous observations around the unexpected reactivity of some impurities, found in the reaction mixture while performing a metathesis reaction catalysed by  $WCl_6$ .<sup>[35]</sup> Some of these complexes were indeed active in ROMP and Self Metathesis (SM), yielding desired products with high Z-selectivity and high tuneable tacticity (in case of polymerisation reactions, Scheme 3,b). Although the catalyst decomposed in less than six hours, no by-products of isomerization were formed.<sup>[36]</sup>

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## REVIEW

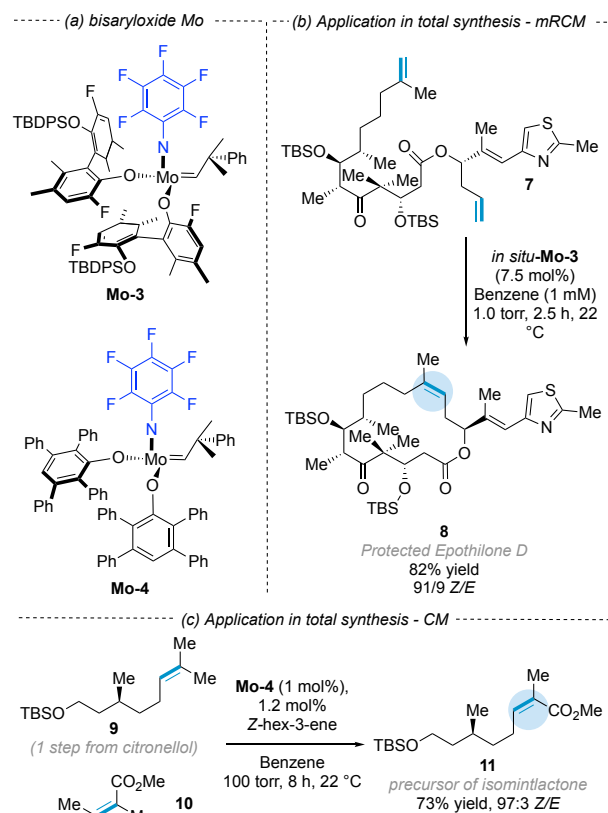
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Scheme 3. a) oxo-W complex; b) selected application to ROMP.

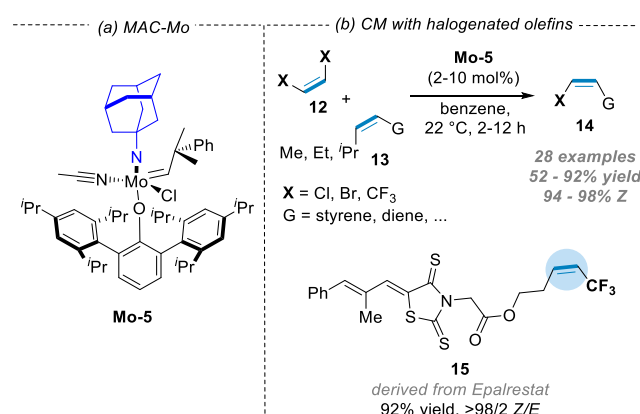
## 2.1.3. Bis-aryloxy type Mo-complexes

MAP-Mo complexes were lacking activity for the formation of trisubstituted Z-shaped double-bonds. Complexes developed for this purpose must be able to differentiate geminal substituents during the formation of metallacyclobutane in order to favor the desired Z-trisubstituted olefin. In 2013, Schrock and Hoveyda conceived a bis-aryloxy-Mo catalyst (**Mo-3** and **Mo-4**, Scheme 4, a) bearing a strongly electron-deficient imidopentafluorophenyl and two electron-withdrawing fluorinated aryloxy ligands. Catalyst **Mo-3** was efficient in *macro*RCM producing macrocycles with trisubstituted Z-olefins (Scheme 4, b).<sup>[37]</sup> Among the different applications, one of the best results was obtained for the synthesis of TBS-protected Epothilone D (**8**), isolated with 82% yield and 91:9 Z/E selectivity. Later on, catalyst **Mo-4** enabled the synthesis of Z-trisubstituted  $\alpha,\beta$ -unsaturated esters, highly valuable building blocks and precursors of natural products (Scheme 4 c).<sup>[38]</sup> The precursor of Isomint lactone **11** was isolated with 73% yield and 97:3 Z/E selectivity upon reaction between protected citronellol **9** and ester **10**.

Scheme 4. Application of (a) Z-selective bis-aryloxy Mo-catalysts in total synthesis via (b) *macro*RCM and (c) CM.

## 2.1.4. Monoaryloxy chloride (MAC) alkylidene Mo complexes

Although MAP-Mo complexes enable the formation of some halogenated olefins, the scope and the selectivity for this kind of transformation remained elusive.<sup>[39]</sup> While working on the isolation of intermediates,<sup>[40]</sup> in 2016 Schrock and Hoveyda observed the formation of **MAC-Mo-5** complexes (Scheme 5, a) bearing a chloride ligand that enhanced the Lewis acidity of the metal center. Its catalytic performance resulted therefore enhanced while the steric hindrance on the metallacyclobutane, reduced. This new family of complexes was applied for the synthesis of Z-halo- and trifluoromethyl-olefins.<sup>[41]</sup> Among the many substrates of interest prepared under the established conditions, a derivative from Epalrestat **15** was isolated with 92% yield and >98:2 Z/E (Scheme 5, b).



Scheme 5. a) MAC-Mo-5 catalysts and b) selected application for the synthesis of Epalrestat derivative.

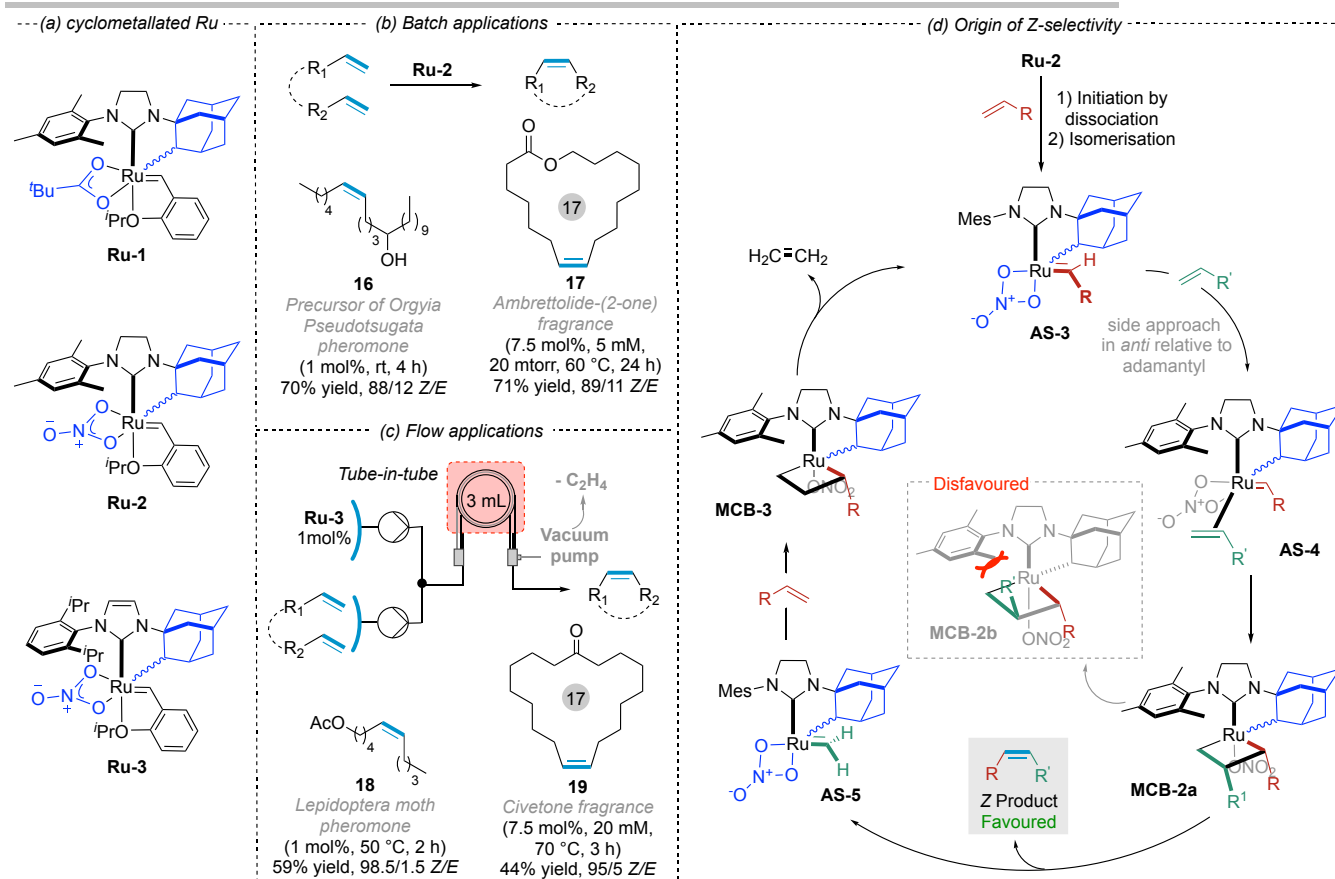
## 2.2. Ruthenium-based complexes

## 2.2.1. Grubbs cyclo-metallated Ru-complexes

In 2011, Grubbs and co-workers reported the first ruthenium-based catalyst able to perform a CM with a comparable Z-selectivity compared to the molybdenum and tungsten complexes.<sup>[42]</sup> The main feature concerns an unsymmetric N-Heterocyclic Carbene (NHC) ligand decorated with the adamantyl-group, which is directly metallated to the metal core upon an intramolecular C-H activation (**Ru-1**). Later on, in 2012, the same group demonstrated that the pivalate exchange into a nitrate-group (**Ru-2**) leading to a more efficient catalyst (Scheme 6, a).<sup>[43]</sup> This family of complexes has proven to be effective for SM and *macro*RCM of terminal alkenes<sup>[44,45,46]</sup> as shown with the synthesis of Ambrettolite fragrance **17** (71% yield, 89/11 Z/E, Scheme 6, b). Noteworthy, **Ru-2** also enabled the CM of dienes and demonstrated high *cis*-syndiotacticity in ROMP of various substituted norbornenes.<sup>[47]</sup> Moreover, their use in CM<sup>[48]</sup> to prepare valuable insect pheromones was proven to be effective (Scheme 6b) where, among those, a precursor for the synthesis of *Orgyia Pseudotsugata* pheromone **16** was obtained with 70% yield and 88:12 Z/E ratio.<sup>[49]</sup> The robustness of these metal complexes was therefore successfully exploited for continuous flow processes by Browne, Mauduit and co-workers.<sup>[50]</sup> Encouraging yields and improved selectivity were observed for both CM and *macro*RCM as highlighted in Scheme 6, c for the synthesis of *Lepidoptera* moth pheromone **18** (59% yield, 98.5/1.5 Z/E) and Civetone fragrance **19** (44% yield 95:5 Z/E).

## REVIEW

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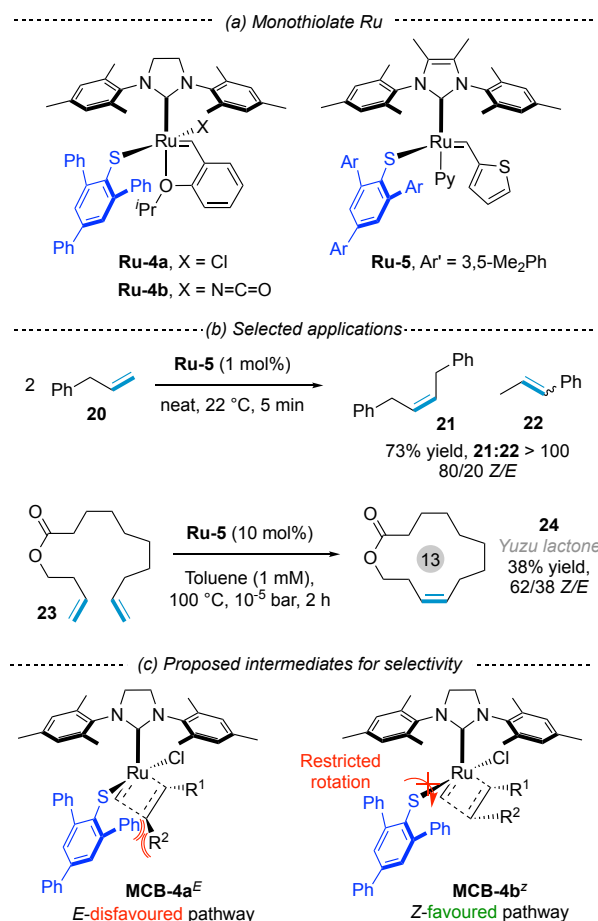
**Scheme 6.** a) C–H Activated pivalate complex **Ru-1** and nitrate-series **Ru-2** and **Ru-3**; b) applications in batch vs c) flow; d) Mechanism of Z-selectivity.

Mechanistic studies, followed by early experimental evidences were reported by Grubbs and Wang groups in 2012.<sup>[51]</sup> The main difference compared to commonly known mechanism for OM concerns the olefin approach to the active species **AS-1** from a specific position, in an *anti*-side compared to the adamantyl-moiety (**TS-1**). As the first metallacyclobutane **MCB-1** is formed, the substituent of the coupling partner is forced to place itself in *cis*, due to the steric clash that would occur with mesityl-moiety on the opposite site. This aspect leads to the favoured Z-configuration of the targeted olefin. A crucial role is played by the carboxylate/nitrate group as well, thanks to its ready switch between monodentate and bidentate form (Scheme 6,d). Cyclometalated complexes are known to be more effective with terminal olefins, however, one of the main encountered drawbacks is the drop of Z-selectivity over the reaction time, although the increase of the bulkiness on the *N*-aryl moiety helped to maintain the Z-selectivity at the expenses of the catalytic activity.<sup>[52]</sup> Aiming to solve this challenge, the group of Mauduit developed in 2018 a straightforward access to **Ru-3**, a cyclo-metallated Grubbs-type catalyst featuring an unsaturated NHC backbone and a bulky *N*-2,6-diisopropylphenyl moiety (*N*-Dipp).<sup>[47c]</sup> With this expedient, the Z-selectivity was maintained over the time, while the OM of terminal olefins resulted complete in most of the cases after six hours, especially for ROMP of norbornenes and cyclopropenes.

### 2.2.2. Z-selective monothiolated Ru-complexes

As alternative approach, Jensen and co-workers proposed in 2013 an NHC-based Ru-complex **Ru-4a** bearing a very bulky 2,4,6-triphenylbenzenethiolate ligand (Scheme 7,a).<sup>[53]</sup> The

catalyst was applied to the SM of terminal olefins, achieving moderate to good Z-selectivity, albeit lower overall yields. In 2014, the same group reported a DFT-assisted development of more robust analogue **Ru-4b** bearing an isocyanate instead of a chlorine-moiety.<sup>[54]</sup> Further developments<sup>[55]</sup> (benzylidene-moiety modification, NHC backbone substitution, increased hindrance of the thiol ligand) led to **Ru-5**, the most active and selective Ru-based complex of the series. As disclosed in Scheme 7-b, the SM on **20** provided the corresponding internal olefin **21** with 73% yield and a promising 80:20 Z/E ratio. On the other hand, the *macro*RCM on substrate **23** led to the challenging Yuzu lactone **24**. In this latter case, 11 mol% of the catalyst were required to provide the desired macrocycle with 35% yield and a 62/38 Z/E ratio.<sup>[56]</sup> The mechanism for the selectivity relates on the steric properties of the monothiolate ligand. Upon formation of the first bottom-bound metallacycle, this very bulky unit acts as “a wall” from the front side of catalyst, pushing both substituents of the incoming olefin substrate away to reduce steric hindrance. Thereby, the final configuration of the double bond in the product is forced to Z, despite being kinetically disfavoured (**MCB-4a<sup>E</sup>** and **MCB-4b<sup>Z</sup>** respectively; Scheme 7,c). Albeit improved, this Z-selective approach remains substrate dependent, being sometimes limited to homocoupling reactions only.



Scheme 7. (a) monothiolate Ru-complexes; (b) selected applications; (c) proposed mechanistic pathways for Z-selectivity.

### 2.2.3. Z-stereoretentive catechodithiolate Ru-complexes

As alternative approach to Grubbs' strategy, Hoveyda and co-workers developed in 2013 a readily accessible Z-stereoretentive ruthenium-complex **Ru-6** containing a bidentate anionic catechodithiolate ligand (Scheme 8,a), proving interesting activity in Z-selective ROMP and Z-Ring-Opening-Cross-Metathesis (Z-ROCM).<sup>[57]</sup> In 2015, the same group proposed an improved version of the previous complex by introducing electron-withdrawing chlorines on the bidentate ligand (**Ru-7a**, **7b**).<sup>[58]</sup> This second generation of Z-retentive complexes efficiently promoted various macrocyclizations<sup>[59]</sup> and demonstrated high Z-selectivity in CM transformations of challenging  $\alpha,\beta$ -unsaturated esters or acids and also Weinreb amide which facilitate *post*-functionalization.<sup>[60]</sup> Notably, a precursor of Leucascandrolide A **27** was obtained by CM between the terminal alkene **25** and the *cis*-but-2-en-1,4-diol **26**. The transformation was performed in presence of 10 mol% of **Ru-7a**, providing the desired olefin with 70% isolated yield and 98:2 Z/E ratio (Scheme 8,b).<sup>[58]</sup> DFT-studies on the mechanism showed the plausible formation of a more stabilized metallacyclobutane **MCB-5** toward the

decomposition pathways, thus proving an increased stability of the key intermediate. The experimental proof of retention, that interestingly occurs for both *E* and *Z* isomers was unambiguously shown by Grubbs and Pederson in 2015, where internal olefins were transformed in SM and CM reactions, affording respectively *E* or *Z* olefins depending on the initial configuration.<sup>[61]</sup> The year after, DFT calculation supported this experimental observation, showing once again the side-bound approach as the favored one. Moreover, the substituents at the  $\alpha$ -positions of the forming metallacycle prefer to point away from the NHC ligand, while the  $\beta$ -substituents may point in both directions to the NHC without significant steric clashes with the ligand (Scheme 8c).<sup>[62]</sup> The major drawback of the catechodithiolate Ru-based complexes is their lower efficiency toward the metathesis between two terminal olefins, due to the high instability of the methyldene-Ru species formed during this transformation. To overcome this limitation, Hoveyda and coworkers developed in 2017 a strategy based on an "in situ methylene capping".<sup>[63]</sup> Thus, both terminal olefins are pre-reacted with *Z*-2-butene in presence of **Ru-7a** to form 2 internal *Z*-double bonds. The further reaction leads to the desired cross-product (Scheme 8d). This strategy was employed for the synthesis of Prostaglandin F2 **32**, obtained with 59% isolated yield and excellent >98:2 Z/E ratio. Very recently, Bertrand, Jazzar, Mauduit and co-workers reported a new class of catechodithiolate Ru-complex **Ru-8** containing a Cyclic(Alkyl)(Amino)Carbene (CAAC) ligand (Scheme 8,a).<sup>[64,65]</sup> This variant demonstrated high Z-selectivity (ranging from 96 to >98%) in ROMP and ROCM of norbornene derivatives as well as in various CM transformations.<sup>[64]</sup>

## 3. Z-enantioselectivity in olefin metathesis

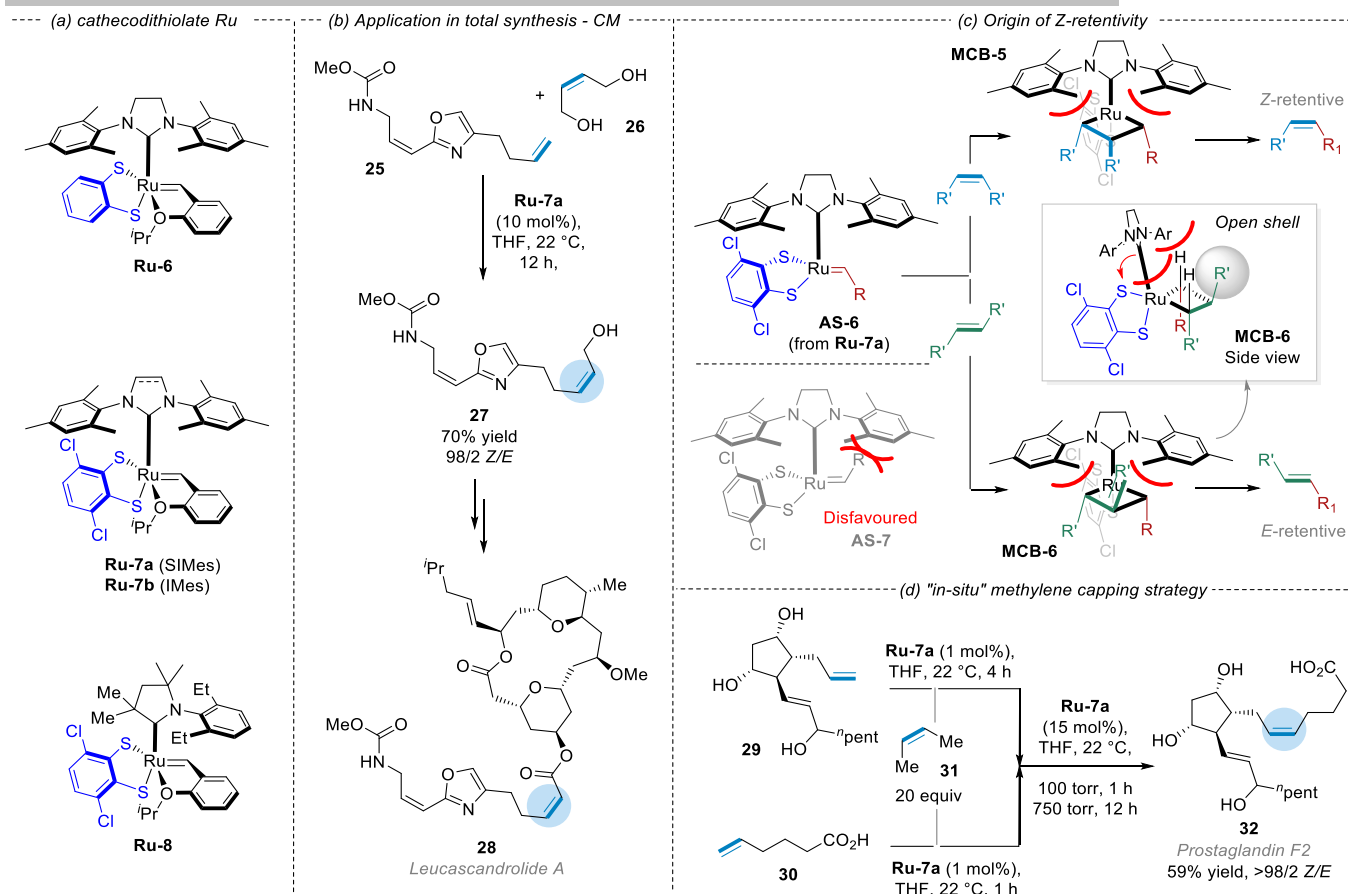
### 3.1. Chiral Mo-based complexes

The history of Z-enantioselective metathesis begins with the work of Hoveyda and Schrock who reported the first chiral molybdenum complexes featuring a chiral mono-aryloxy ligand and a pyrrolide ligand around the metal, known as "MAP". Firstly used in various ARCM with high enantio-induction, chiral catalyst **Mo-6** was then successfully applied in the total synthesis of Tetrahydro-(+)-quebrachamine, which was isolated in 83% yield and an excellent 95% ee (Scheme 9).<sup>[29]</sup> After these seminal works, Schrock and Hoveyda brought some modifications on the ligands surrounding the complex allowing a fine tuning of Z-selectivity. Thus, by replacing the *N*-Dipp of the **Mo-6** complex with a less bulky *N*-adamantylimido group, the authors observed relevant performances in Z-selective asymmetric Ring-Opening Cross Metathesis (AROCM) reactions (Scheme 10, b).<sup>[66]</sup> The chosen ligand **38** was prepared over 3 steps from the enantiopure (*R*)-binol **35**. On the other side, complex **Mo-7** was reacted with 2,5-dimethylpyrrol-1-ide **39** thus providing the proto-catalyst **Mo-8**, which bears two labile pyrrolide ligands, ready for the exchange.<sup>[67]</sup> The desired catalyst **Mo-1** complex could be generated *in situ* upon reaction between **38** and **Mo-8**, thus avoiding the manipulation of enantiomerically pure air-sensitive species.

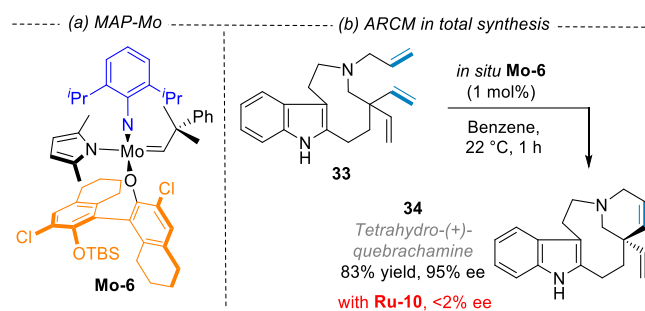


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**Scheme 8.** a) catechodithiolate NHC-Ru-6, Ru-7a, Ru-7b vs CAAC-Ru-8; b) applications in total synthesis; c) mechanism of Z-retentivity; d) "in-situ" methylenide capping strategy for the synthesis of Prostaglandin F2 $\alpha$ .

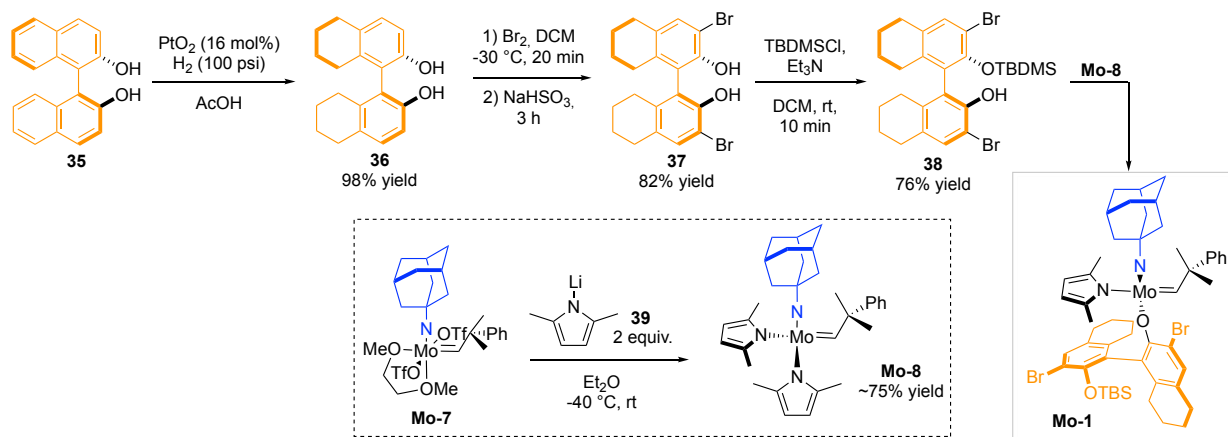


**Scheme 9.** First application of chiral MAP-Mo-6 in total synthesis of Tetrahydro-(+)-quebrachamine **34**.

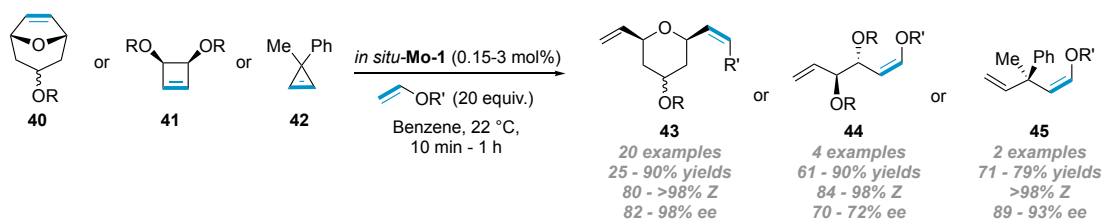
As briefly introduced in the previous section, AROCM reactions involving highly strained olefin rings such as oxabicycles, cyclobutenes and cyclopropenes were deeply investigated. Among the four ligands studied, bearing different halogenated derivatives, the presence of bromine in **Mo-1** (1 mol%), allowed to combine, as general trend, high reactivity, high Z-stereoselectivity and good to high enantioselectivity (Scheme 10,b).<sup>[66-68]</sup> Oxabicycles **40** could be successfully reacted in presence of different styrene-derivatives. The resulting dienes

**43** were obtained with isolated yields ranging from 25 to 90% depending on the stability of the product toward the usual purification methods, while good Z-selectivity (80 to >98%) and high enantioselectivity (92-98%) were reached (Scheme 10,c). Enol ethers have also been engaged as a crossover partner in various Z-AROCM for the formation of linear dienes. Differently substituted dienes **44** were produced from cyclobutenes **41** with good yields (61 to 90%), moderate enantio-induction (70 to 72% ee) and good to high Z-selectivity (84 to 98% Z; Scheme 10,c). Increasing the catalytic loading of **Mo-1** complex to 3 mol% allowed the transformation of cyclopropenes **42** to 1,4-dienes **45** with excellent Z-selectivity >98% and excellent enantioselectivity (89-93% ee; Scheme 10,c). This efficient methodology was then successfully applied to the total synthesis of (+)-Neopeltolide **46**, an anti-tumor agent (Scheme 10,d).<sup>[69]</sup> Described by Schrock and Hoveyda in 2015, this multi-step synthesis relies on the Z-AROCM step catalyzed by **Mo-1** at low catalyst loading (0.6 mol%), furnishing **43d** in 88% yield (1.2 g scale) with high Z-selectivity (>98/2 Z/E) and excellent 98% ee (Scheme 10, d). Three additional Z-selective metathesis reactions completed the total synthesis of **46**, which was isolated in high 20.9 % yield over 11 steps.<sup>[70]</sup>

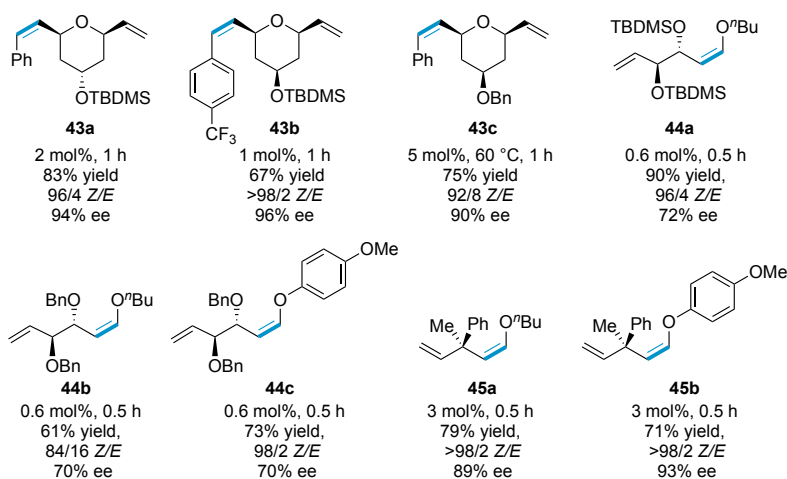
## (a) Ligand and complex synthesis



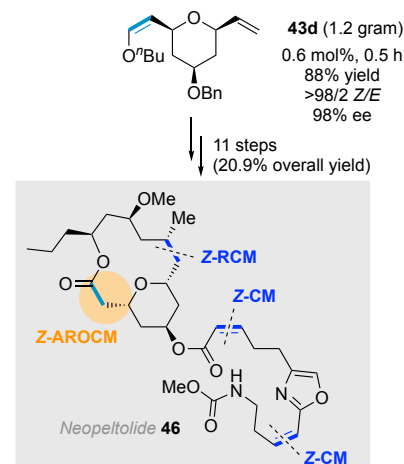
## (b) AROCM applications



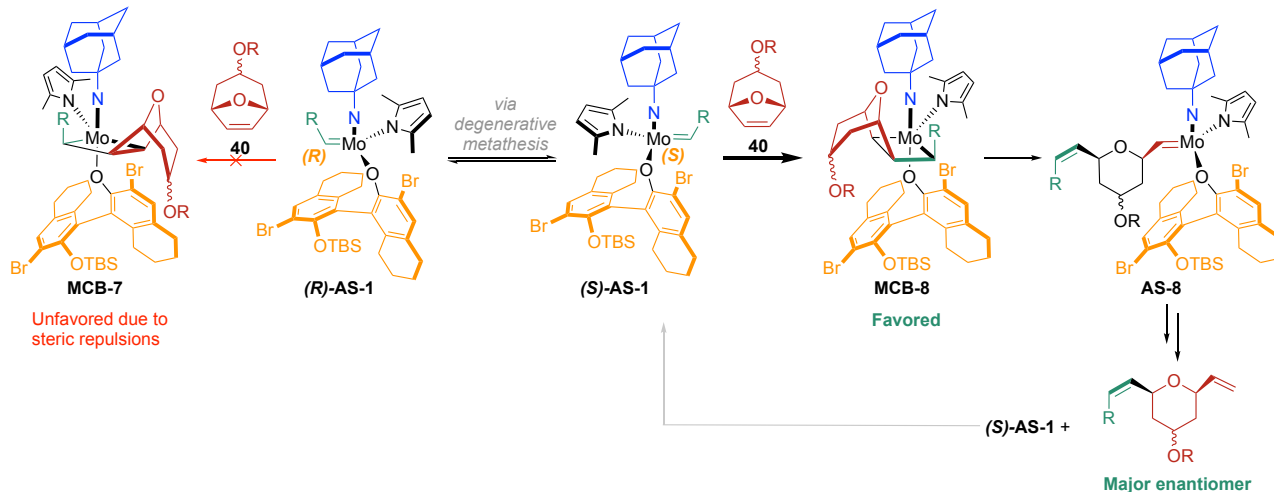
## (c) Selected examples



## (d) Application to total synthesis



## (e) Mechanistic insights



**Scheme 10.** a) synthesis of MAP-Mo-1; b) application to AROCM; c) selected examples; d) application in total enantioselective synthesis of Neopeltolide; e) mechanistic insights.

## REVIEW

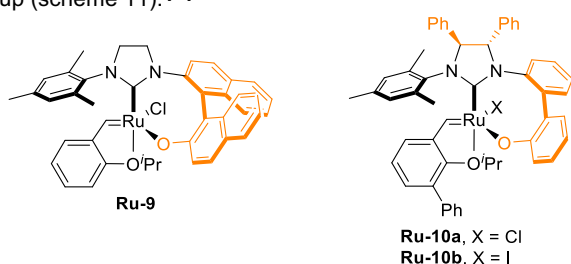
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## 3.2. Chiral Ru-based complexes

## 3.2.1. Chiral Cyclometallated Complexes

## a) Chiral Phenoxy-cyclometallated Hoveyda's complexes

In 2002 Hoveyda and co-workers described a new class of enantiomerically pure Ru-based complexes containing a chiral bidentate NHC ligand derived from enantiopure 2-Amino-2'-hydroxy-1,1'-dinaphthalene (Scheme 11).<sup>[71]</sup> The chiral **Ru-9** catalyst was efficient in AROCM between norbornenes and vinyl aryls with excellent enantioselectivity (up to >98% ee) and full *E*-selectivity (>98%). Few years later, the same group described a more accessible catalyst **Ru-10** bearing a NHC ligand that combines a chiral diamine backbone and an achiral biphenol group (scheme 11).<sup>[72]</sup>

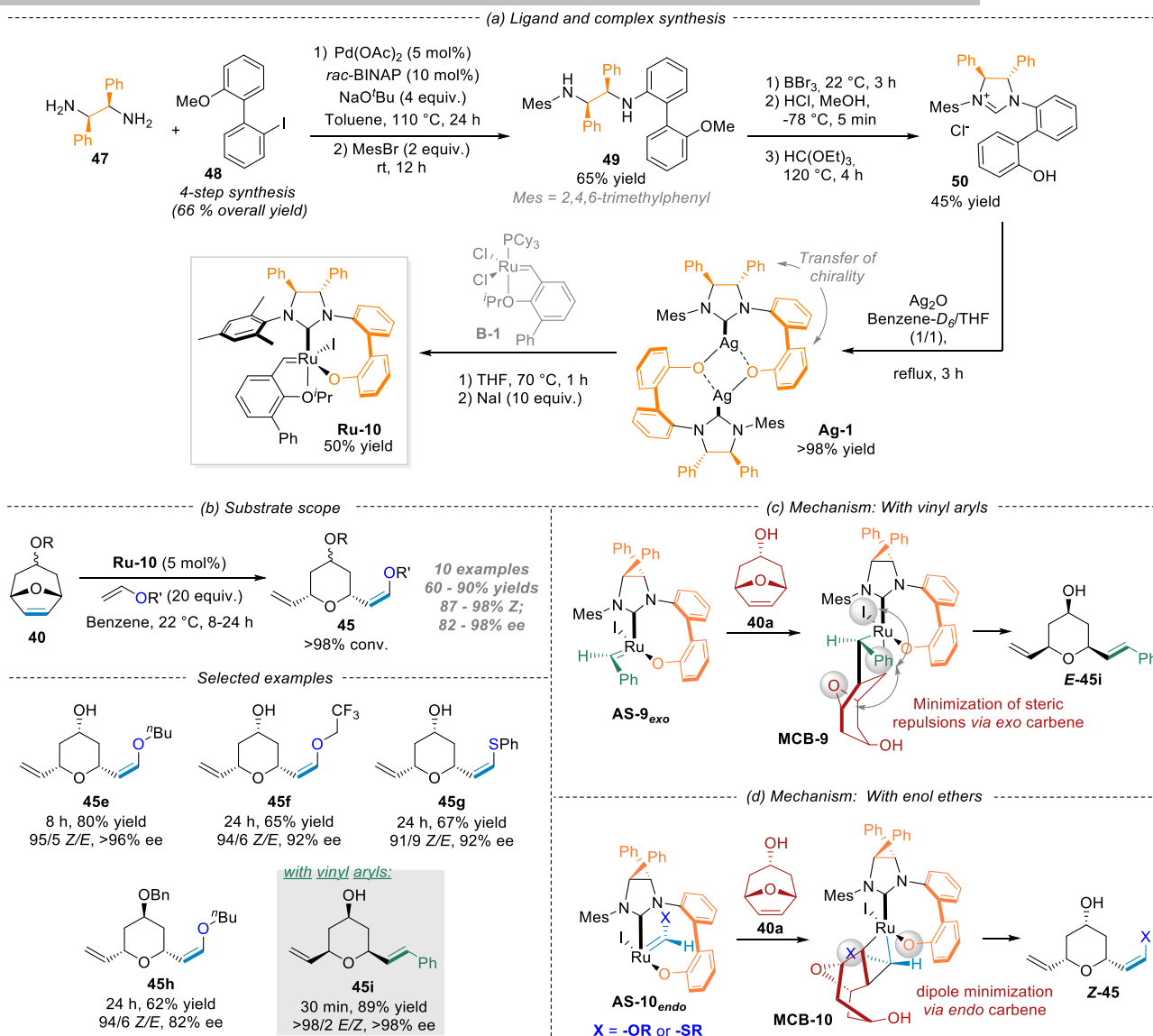


**Scheme 11** two generations of optically pure chiral-at-Ru complexes.

Starting from commercially available enantiopure Corey's diamine **47**, the NHC ligand precursor **50** was obtained *via* a Buchwald-Hartwig amination followed by cyclisation of the resulting diamine **49** with a 29% overall yield (Scheme 12, a).<sup>[72]</sup> An enantiomerically pure silver dimer **Ag-1** was then obtained thanks

to a successful transfer of chirality<sup>[73]</sup> from the backbone to the biphenyl chelating substituent. The *trans*-metalation from the silver-complex intermediate **Ag-1** to a Blechert-type complex **B-1** led to the desired complex **Ru-10a**.<sup>[74]</sup> Surprisingly **Ru-10a** appeared to be sensitive toward air and moisture. The replacement of the anionic chloride ligand by iodine afforded a more stable complex (**Ru-10b**), which could be purified by column chromatography (50% yield, Scheme 12, a). Albeit complex **Ru-10b** was mostly employed for *E*-selective asymmetric olefin metathesis, Hoveyda and co-workers reported in 2012 that the use of enol ethers for the AROCM of oxabicycles **40** (instead of the usual vinyl aryls cross-partners) led to an inversion of stereoselectivity in favor of the *Z*-isomer **45** (Scheme 12, b).<sup>[75]</sup> Various vinyl-ethers and vinyl-sulfides were successfully screened, providing the desired ring-opening product with good yields (ranging from 60 to 90%), high *Z*-selectivity (87-98%) and excellent enantioselectivity (82-98% ee) even in presence of the free alcohol (**45e-g**). Curiously, an inversion of the absolute configuration of all stereogenic centers is observed when using vinyl-aryls instead (**45i**). However, other types of strained cyclic olefins were not subjected to this study, while the high *Z*-selectivity reported was strictly limited to the use of enol ethers or thioethers. The *E*-stereoselectivity observed in the presence of vinyl-aryls can be attributed to the minimization of steric repulsions between the phenyl group of the cross partner and the iodine ligand of the complex on the **MCB-9** leading to **E-45i** (Scheme 12c). The difference in stereoselectivity toward the *Z*-product in the presence of enol-ethers can be attributed to the minimization of electronic repulsions between the aryloxy arm and the *O/S* of the coupling partner on the transition state. These steric repulsions justify the reactivity of the *endo*-carbene active species **AS-10** toward the formation of metallacyclobutane **MCB-10** leading to **Z-45** as major isomer.

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**Scheme 12.** Synthesis of ligand and its related complex **Ru-10**; b) selected substrate scope; proposed mechanism with c) vinyl aryls and d) enol ethers.

### b) Chiral Adamantyl-cyclometallated Grubbs' complexes

In 2013 Grubbs and coworkers reported an enantiomerically-pure version of the cyclometallated **Ru-2**. The latter was obtained from the racemic mixture *via* a anionic ligand exchange involving a chiral silver carboxylate **Ag-2**.<sup>[76]</sup> The resulting two diastereomers **Ru-12** were separated on silica gel chromatography under inert atmosphere. A subsequent anionic ligand exchange afforded the desired enantiomerically pure (*R*)-**Ru-2** with 12% overall yield (4 steps; Scheme 13,a). Complex (*R*)-**Ru-2** was initially used for Z-AROCM between bicyclic *endo*-norbornene derivatives *endo*-**51** and several cross-partners to produce the corresponding Z-olefins.<sup>[76]</sup> In presence of 1 mol% of catalyst at room temperature, desired tri- or tetra-substituted cyclopentanes *cis*-**52** were formed with yields ranging from 40 to 65%, low to high Z-selectivity (15 to 98%) and moderate to excellent ee's (60-98%, Scheme 13,b), with a wide functional group tolerance (esters, protected amines, anhydride, succinimide). However, without hindered substituents in position 2,3 on the norbornene scaffold, a significant drop in the Z-selectivity was observed (15-70%) for trisubstituted

cyclopentanes **52d** and **52e**, although the enantio-induction remained very high for both stereoisomers (93-95% ee). AROCM of *meso*-dioxycyclobutenes **41** was also investigated under the established conditions to furnish expected 1,2-*anti*-diols **44** (Scheme 13,b). Despite lower Z-selectivity (from 75 to 90%), all Z-products were formed with high enantioselectivity (from 89% to 99% ee).<sup>[77]</sup> This system tolerates a wide variety of functional groups such as free alcohols, boronic esters, acetate, amines and esters.

The origin of the enantioselectivity was investigated by Grubbs and co-workers who suggested two catalytic pathways depending on the ee's of each Z/E-stereoisomers (Scheme 13,c). If both stereoisomers are formed with the same level of enantio-induction (e.g. **52d** and **52e**), the enantio-determining step may occur prior to the cross-metathesis, which drives the Z-stereoselectivity of the reaction,<sup>[78]</sup> *via* Ru-methylidene active species **AS-5/AS-12**. On the other hand, if a significant difference of ees is observed for Z- and E-isomers, another mechanistic pathway may occur that would imply both enantio- and Z-determining steps during the ring-opening promoted by the Ru-alkylidene active species **AS-3** (Scheme 13,c).

## REVIEW

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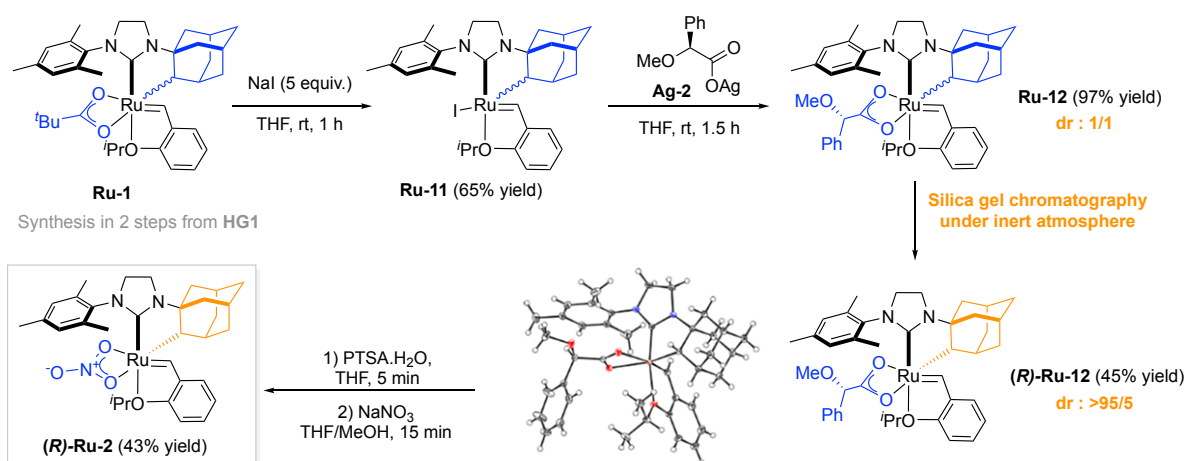
Noteworthy, this efficient methodology was illustrated in the total synthesis of (+)-*endo*-brevicommin **55**, a tree-killing insect's pheromone useful for biocontrol (Scheme 13,d). AROCM between **41** and **53** led to the key synthon **44g**, which was isolated in 85% yield, 91:9 *Z/E* ratio and 95% ee. The latter was then converted into the desired natural product in 59% yield over two steps. By analogy, the *meso*-dioxycyclobutenes was reacted with

the cross-partner **54** affording **44h** in 61% yield, a 88:12 *Z/E* ratio and high 97% ee. From this key synthon, the *L*-Ribose derivative **56** was obtained in 31% yield over three subsequent steps. Although both alkenes are reduced during this process, the *Z*-stereoisomer was beneficial for the cyclisation step, ensuring the exclusive formation of **56** with high ee.

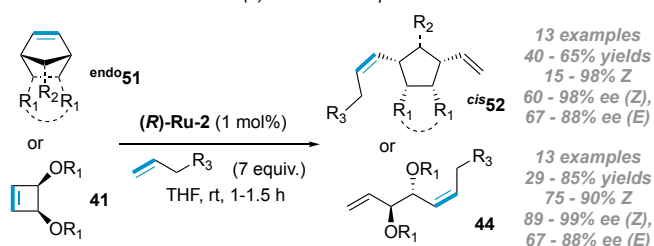
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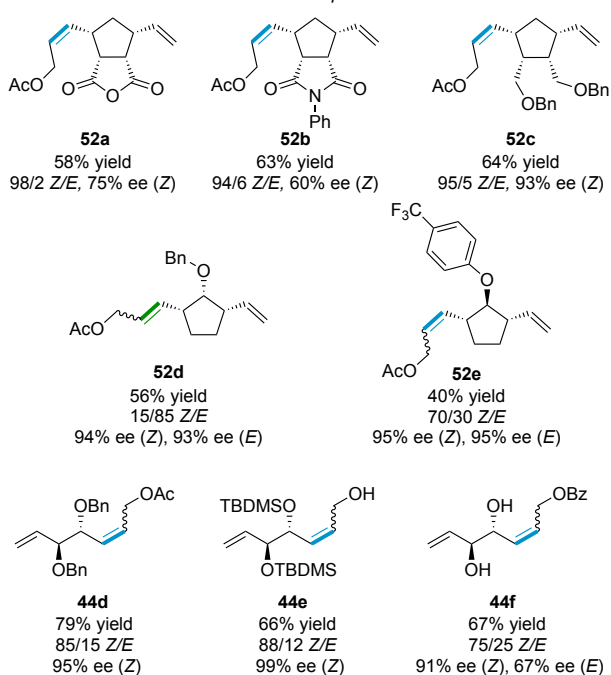
## (a) Enantiomerically pure catalyst synthesis



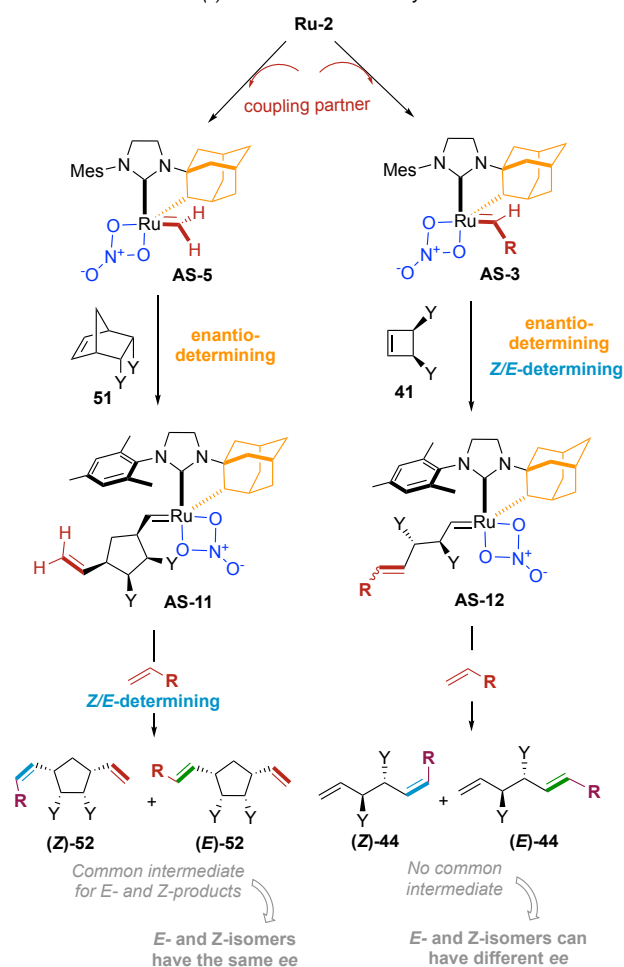
## (b) Substrate scope



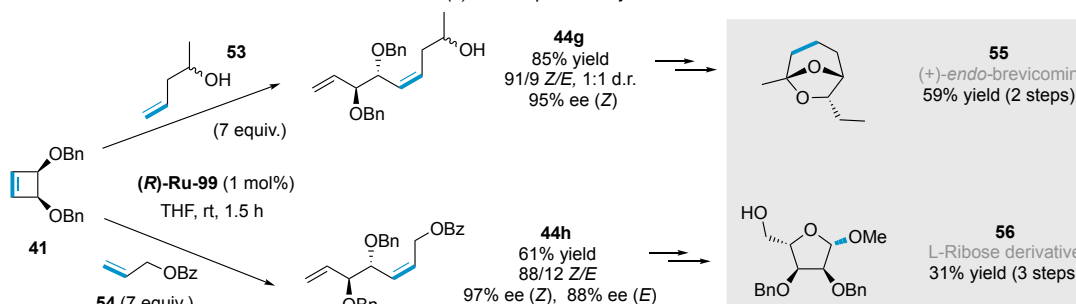
## Selected examples



## (c) Mechanism of selectivity



## (d) Natural products synthesis

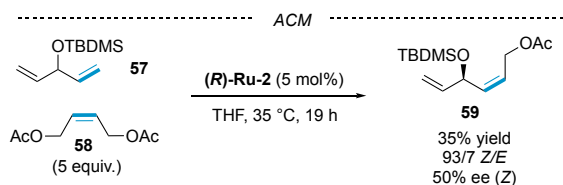


Scheme 13. a) synthesis of (R)-Ru-2; b) selected scope; c) proposed mechanism for selectivity; d) application to natural product synthesis.

## REVIEW

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Grubbs and co-workers also investigated the challenging Z-Asymmetric-Cross-Metathesis (ACM) with chiral Z-selective (*R*)-**Ru-2**.<sup>[79]</sup> Despite a higher catalyst loading (5 mol%), the CM between the *meso* skipped 1,4-diene **57** and the *cis*-diacetate **58** afforded the desired product **59** in 35% yield, 93% Z/E and 50% ee (Z) (Scheme 14).



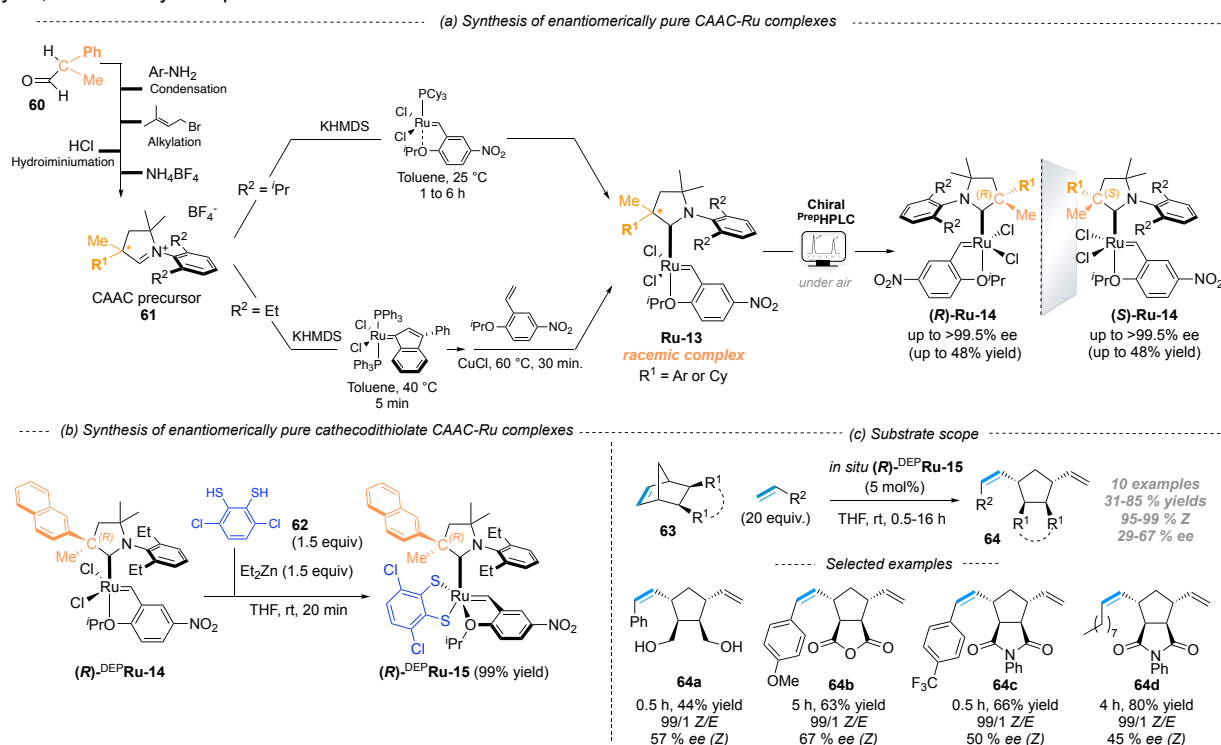
Scheme 14. Z-selective Asymmetric-Cross-Metathesis catalyzed by (*R*)-**Ru-2**

### 3.2.2. Chiral catechodithiolated complexes

#### a) with chiral CAAC ligands

In recent years, the development of CAACs and their corresponding ruthenium-complexes enabled remarkable breakthroughs in the field of olefin metathesis, and notably the highest TON in ethenolysis process (up to 340 000).<sup>[80]</sup> Reported in 2005 by Bertrand and co-workers,<sup>[81]</sup> CAAC ligands are readily accessible from commercially available aldehydes **60** via a 4-step process involving first the aniline condensation followed by a methallyl-alkylation. The resulting imine is then cyclised via an hydroiminium process leading to the corresponding cyclic iminium salts **61** as CAAC precursors (Scheme 15,a). In 2019, Mauduit, Jazzar, Bertrand and co-workers proposed the first application of chiral CAACs issued from chiral pool in asymmetric copper-catalysis, reaching moderate enantio-induction (up to 55% ee).<sup>[82]</sup> Further on, in 2020, a different approach has been explored by coordinating chiral racemic CAAC ligands **61** on Ru-catalysts, followed by a separation of the two enantiomers via a

preparative high-performance liquid chromatography resolution (HPLC) using a chiral stationary phase (Scheme 15,a). This efficient and rapid protocol led to the first enantiomerically pure CAAC-Ru complexes **Ru-14** containing *N*-2,6-diisopropylphenyl) moiety (DIPP), which demonstrated high enantioselectivity in AROCM (up to 92% ee) and a promising 50% ee in ACM.<sup>[83a]</sup> The strategy was then applied to Ru-complexes bearing a less bulky *N*-2,6-diethylphenyl (DEP) unit, however, lower enantioselectivities were observed (up to 80% ee).<sup>[83b]</sup> As disclosed in section 2.2.3., the successful synthesis of achiral catechodithiolate <sup>DEP</sup>CAAC-Ru complex **Ru-8** was logically extended to its enantiopure congeners.<sup>[64]</sup> Reaction between enantiomerically-pure (*R*)-CAAC-**Ru-14** and catechodithiol **62** afforded to (*R*)-**Ru-15** within 20 minutes in nearly quantitative yield (Scheme 15,b). The latter demonstrated excellent Z-selectivity (>98%) in AROCM of *exo*-norbornene **63a** affording the expected *trans*-cyclopentane **64a** with a promising 57% ee (Scheme 15,c). Thanks to a previously described “*in situ*” protocol for the Z-stereoretentive cross-metathesis, which avoids the use of a glove-box,<sup>[84]</sup> a series of Z-AROCM transformations were efficiently catalyzed by the *in situ* generated (*R*)-**Ru-15** showing good tolerance for norbornene derivatives and olefin cross-partners (Scheme 15,c). The corresponding *trans*-tetrasubstituted cyclopentanes **64b-d** were isolated with moderate to good yields (31-85%), excellent Z-selectivity (95 to 99%) and up to 67% ee. It is worth to note that the presence of free alcohol, acid, halide and aldehyde on the scaffold is tolerated by this class of complexes. At the same time, while the enantioselectivity was moderate, Z-AROCM of *exo*-norbornenes remains scarce and have been reported with similar or lower ee's. Nevertheless, as a limitation, the chiral catechodithiolate <sup>DEP</sup>CAAC-Ru complex was unable to promote the Z-AROCM of *endo*-norbornene derivatives **51** nor cyclopropane **42**.

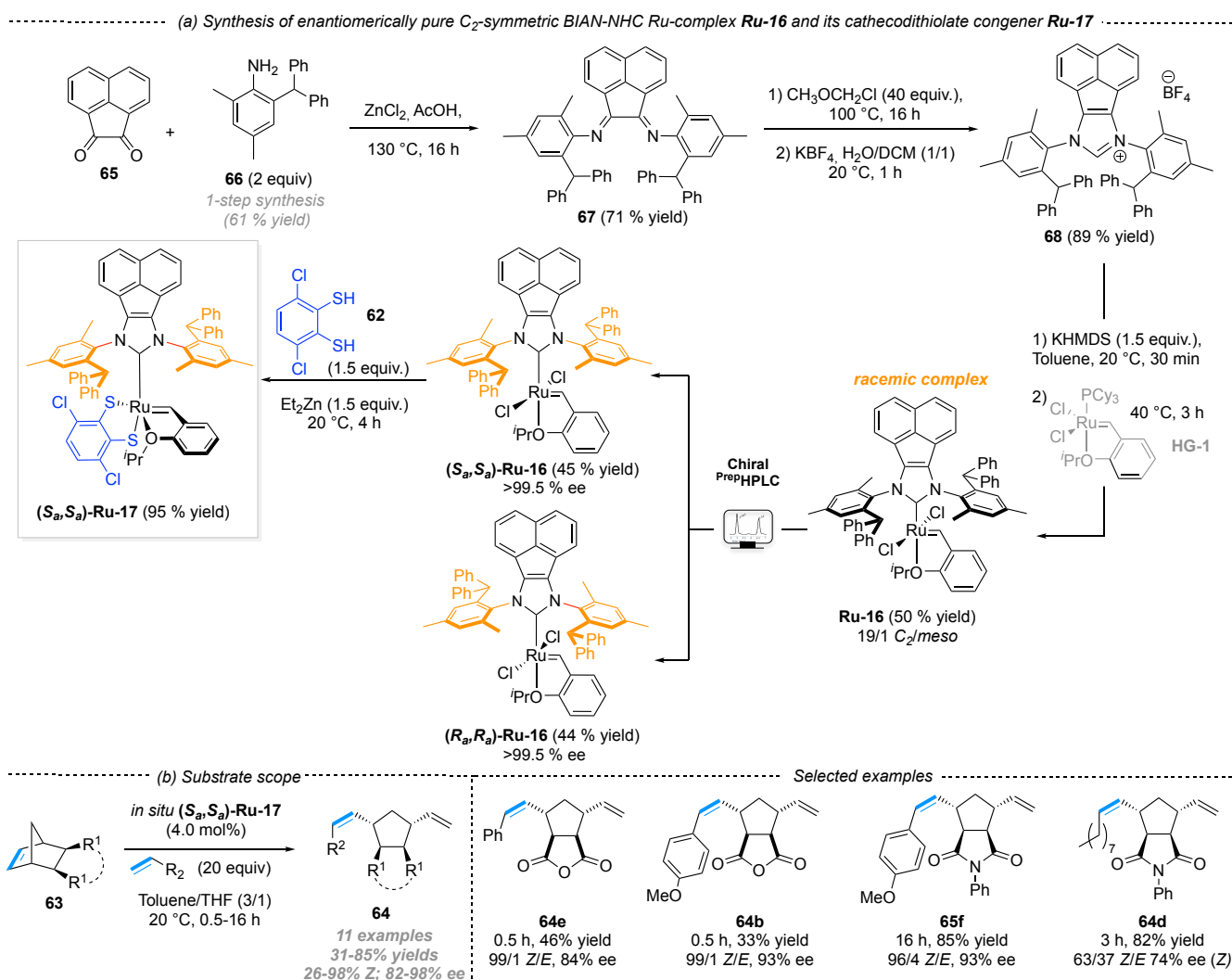


Scheme 15. a) general access to enantiomerically pure CAAC-Ru complexes, (b) synthesis of chiral Z-catechodithiolated Ru-catalyst and c) application in Z-selective AROCM

## b) with chiral atropisomeric NHC ligands

In 2020, Clavier and Mauduit groups reported the synthesis of enantiopure  $C_1$ - and  $C_2$ -symmetric atropisomeric NHC-metal complexes from prochiral NHC precursors.<sup>[85]</sup> This original concept is based on the formation of an axis of chirality across the metal-carbene bond. The resulting configurationally stable atropisomers of palladium, gold and copper complexes were isolated by resolution on a preparative chiral HPLC in high yield and excellent enantiopurity (up to 99.5% ee). Copper and palladium complexes were successfully used in asymmetric allylic alkylation (AAA) and intramolecular  $\alpha$ -arylation (AIA), respectively, with excellent enantio-inductions (up to 95% ee).<sup>[85a]</sup> In 2023, the methodology was extended to the synthesis of a set of various  $C_1$ - and  $C_2$ -symmetric atropisomeric NHC-Ru complexes. Among them, the Ru-complex **Ru-16** containing a bis(imino)acenaphthene (BIAN) backbone was the most efficient for the AROCM of *exo*-

norbornenes with styrene derivatives as cross-partners (up to 94% ee).<sup>[86]</sup> The synthesis of the BIAN-NHC precursor **68** was achieved upon a two-step process, consisting of diimination of acenaphthoquinone **65** followed by cyclisation (Scheme 16,a). Coordination of the BIAN-NHC ligand to **HG-1** complex led to the corresponding  $C_2$ -symmetric (racemic)**Ru-16** in respectable 50% yield. The subsequent chiral resolution *via* preparative HPLC afforded both enantiomers of **Ru-16** in high yield and excellent enantiopurity. The (**S<sub>a</sub>,S<sub>a</sub>**)-(+)-**Ru-16** was further successfully converted into its *Z*-selective catechodithiolate congener (**S<sub>a</sub>,S<sub>a</sub>**)-**Ru-17** in 95% yield.<sup>[86]</sup> When generated *in situ*, the latter showed impressive *Z*-selectivity and enantioselectivity (99/1 *Z/E*, up to 93% ee) for the AROCM of *exo*-norbornenes **63** with styrene derivatives as cross-partners (Scheme 16,b). However, a drop of *Z*-selectivity occurred upon reaction with aliphatic cross-partner. Furthermore, lower ee's (30-45% ee) were observed for *exo*-norbornenes containing diols and protected diols.



Scheme 16. a) synthesis of ligand and the corresponding metal complex **Ru-17** and *Z*-enantioselective (**S<sub>a</sub>,S<sub>a</sub>**)-**Ru-18**; b) selected examples.

## REVIEW

## 4. Conclusion and perspectives

Z-enantioselective OM is a promising tool for the synthesis of molecules of interest, enabling a straightforward approach for the obtainment of building blocks with high stereoselectivity, thus shortening the traditional synthetic pathways. However, as general trend, the Z-selective and Z-enantioselective catalysts introduced since the last 15 years remain highly sensitive toward air and moisture, often requiring harsh conditions or manipulation in glove-box. With the discovery of *in-situ* assembled metal-catalysts (MAP-Mo and dithiolate-Ru complexes) these drawbacks are overcome, however, at the expenses of broader applications. Industrial applications are known but currently poorly investigated. The price of catalysts,<sup>[87]</sup> their scarce commercial availability, or their time-consuming synthesis might also be the reason for the moderate development of this strategy to industrial scale. Moreover, each catalytic system allows nowadays the transformation of one or two geometries of substrate only (e.g. pyrans for MAP-Mo and cyclo-metalated-Ru-complexes, exo-norbornenes for catechodithiolate-Ru-complexes), with a limited family of cross-partners (styrene derivatives or ether enols mainly), thus sometimes requiring very high catalyst loading and impacting dramatically on the overall costs for eventual plant production. In these cases, a consistent variation on the reacting substrate leads to a dramatic drop either in terms of enantio-induction either Z-selectivity or even reactivity. Note also that a high excess of cross partner (from 5 to 20 equiv.) is often required to increase the yields. The emergence for the development of more robust and broadly applicable manifolds remains one of the major challenges of this field. With the advent of new technologies, some problems related to the catalyst manipulation may be avoided with the use of *in situ*-generated catalysts as well as continuous flow chemistry<sup>[88]</sup> while the development of bench stable Z-(enantio)selective catalysts may offer new perspectives of (chiral) applications.

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## References

- [1] W.-Y. Siau, Y. Zhang, Y. Zhao, *Top Curr Chem* **2012**, 327, 33–58.
- [2] A. V. Rao, L. G. Rao, *Pharmacol. Res.* **2007**, 55, 207–216
- [3] H. M. Roche, H. Roche, *Proc. Nutr. Soc.* **1990**, 58, 397–401.
- [4] C. C. C. R. De Carvalho, M. M. R. Da Fonseca, *Biotechnol. Adv.* **2006**, 24, 134–142.
- [5] G. Wittig, G. Geissler, *Justus Liebig's Ann. Chem.* **1953**, 580, 44–57.
- [6] P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, 42, 6670–6696.
- [7] K. Ando, *Tetrahedron Lett.* **1995**, 36, 4105–4108.
- [8] K. Ando, *J. Synth. Org. Chem. Japan* **2000**, 58, 869–876.
- [9] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, 24, 4405–4408.
- [10] I. Janicki, P. Kielbasiński, *Adv. Synth. Catal.* **2020**, 362, 2552–2596.
- [11] D. J. Peterson, *J. Org. Chem.* **1968**, 33, 780–784.
- [12] D. J. Ager, *Org. React.* **1990**, 1–223.
- [13] L. F. Van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, 31, 195–200.
- [14] J. Mérad, P. S. Grant, T. Stopka, J. Sabbatini, R. Meyrelles, A. Preinfalk, J. Matyasovskiy, B. Maryasin, L. González, N. Maulide *J. Am. Chem. Soc.* **2022**, 144, 12536–12543.
- [15] (a) T. Okazoe, K. Takai, K. Oshima, K. Utimoto, *J. Org. Chem.* **1987**, 52, 4410–4412. (b) R. C. Hartley, G. J. McKiernan, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2, 2763–2793.
- [16] C. Oger, L. Balas, T. Durand, J. M. Galano, *Chem. Rev.* **2013**, 113, 1313–1350.
- [17] X. Lei, H. Li *Top Curr Chem* **2012**, 327, 163–196.
- [18] H. Lindlar, *Helv. Chim. Acta* **1952**, 35, 446–450.
- [19] V. Schneider, P. K. Frolich, *Ind. Eng. Chem.* **1931**, 23, 1405–1410.
- [20] H. S. Eleuterio, *J. Mol. Catal.* **1991**, 65, 55–6.
- [21] W. L. Truett, D. R. Johnson, I. M. Robinson, B. A. Montague, *J. Am. Chem. Soc.* **1960**, 82, 2337–2340.
- [22] N. Calderon, H. Y. Chen, K. W. Scott, *Tetrahedron Lett.* **1967**, 8, 3327–3329.
- [23] N. Calderon, *Acc. Chem. Res.* **1972**, 5, 127–132.
- [24] P. J.-L. Hérisson, Y. Chauvin, *Die Makromol. Chemie* **1971**, 141, 161–176.
- [25] R. Schrock, S. Rocklage, J. Wengrovius, G. Rupprecht, J. Fellmann, *J. Mol. Catal.* **1980**, 8, 73–83.
- [26] S. B. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, 114, 3974–3975.
- [27] S. B. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, 115, 9858–9859.
- [28] (a) Y. Wang, M. Jimenez, A. S. Hanse, E.-A. Raiber, S. L. Schreiber, D. W. Young. *J. Am. Chem. Soc.* **2011**, 133, 9196–9199. (b) Y. Wang, M. Jimenez, P. Sheehan, A. W. Hung, C. P. Tam, D. W. Young. *Org. Lett.* **2013**, 15, 1218–1221. (c) D. Gallenkamp, A. Fürstner. *J. Am. Chem. Soc.* **2011**, 133, 9232–9235.
- [29] S. J. Malcolmson, S. J. Meek, E. S. Sattely, R. R. Schrock, A. H. Hoveyda. *Nature* **2008**, 456, 933–937.
- [30] (a) A. J. Jiang, Y. Zhao, R. R. Schrock, A. H. Hoveyda. *J. Am. Chem. Soc.* **2009**, 131, 16630–16631. (b) S. C. Marinescu, R. R. Schrock, P. Müller, M. K. Takase, A. H. Hoveyda. *Organometallics*, **2011**, 30, 1780–1782. (c) E. M. Townsend, R. R. Schrock, A. H. Hoveyda. *J. Am. Chem. Soc.* **2012**, 134, 11334–11337.
- [31] (a) S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock, A. H. Hoveyda. *Nature* **2011**, 471, 461–466. (b) T. J. Mann, A. W. H. Speed, R. R. Schrock, A. H. Hoveyda. *Angew. Chem. Int. Ed.* **2013**, 52, 8395–8400. (c) E. T. Kiesewetter, R. V. O'Brien, E. C. Yu, S. J. Meek, R. R. Schrock, A. H. Hoveyda. *J. Am. Chem. Soc.* **2013**, 135, 6026–6029. (d) A. W. H. Speed, T. J. Mann, R. V. O'Brien, R. R. Schrock, A. H. Hoveyda. *J. Am. Chem. Soc.* **2014**, 136, 16136–16139..
- [32] (e) T. Koengeter, C. Qin, B. Khanh Mai, Q. Liu, Y. Mu, P. Liu, A. H. Hoveyda. *J. Am. Chem. Soc.* **2023**, 145, 3774–3785. (f) Q. Liu, Y. Mu, T. Koengeter, R. R. Schrock, A. H. Hoveyda. *Nat. Chem.* **2022**, 14, 463–473. (g) Y. Mu, T. T. Nguyen, M. J. Koh, R. R. Schrock, A. H. Hoveyda. *Nat. Chem.* **2019**, 11, 478–487.
- [32] (a) M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda. *Nature*, **2011**, 479, 88–93. (b) C. Wang, M. Yu, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda. *Chem. Eur. J.* **2013**, 19, 2726–2740.



## REVIEW

WILEY-VCH

- [33] M. M. Flook, A. J. Jiang, R. R. Schrock, P. Müller, A. H. Hoveyda. *J. Am. Chem. Soc.* **2009**, *131*, 7962–7963.
- [34] A. J. Jiang, J. H. Simpson, P. Müller, R. R. Schrock. *J. Am. Chem. Soc.* **2009**, *131*, 7770–7780.
- [35] (a) J.-M. Basset, G. Coudurier, R. Mutin, H. Pralaud. *J. Catal.* **1974**, *34*, 152–155. (b) J. R. Kress, M. J. M. Russel, M. G. Wesolek, J. A. Osborn. *J. Chem. Soc. Chem. Commun.* **1980**, 431–432.
- [36] (a) D. V. Peryshkov, R. R. Schrock, M. L. Takase, P. Müller, A. H. Hoveyda. *J. Am. Chem. Soc.* **2011**, *133*, 20754–20757 (b). W. P. Forrest, J. C. Axtell, R. R. Schrock *Organometallics* **2014**, *33*, 2313–2325.
- [37] C. Wang, F. Haeflner, R. R. Schrock, A. H. Hoveyda. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.
- [38] C. Qin, T. Koenigter, F. Zhao, Y. Mu, K. N. Houk, A. H. Hoveyda. *J. Am. Chem. Soc.* **2023**, *145*, 3748–3762.
- [39] M. J. Koh, T. T. Nguyen, H. Zhang, R. R. Schrock, A. H. Hoveyda. *Nature*. **2016**, *531*, 459–465.
- [40] J. K. Lam, C. Zhu, K. V. Bukhryakov, P. Müller, A. H. Hoveyda, R. R. Schrock. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.
- [41] M. J. Koh, T. T. Nguyen, J. K. Lam, S. Torker, J. Hyvl, R. R. Schrock, A. H. Hoveyda. *Nature*. **2017**, *542*, 80–85.
- [42] K. Endo, R. H. Grubbs. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527.
- [43] B. K. Keitz, K. Endo, P. R. Patel, M. B. Herbert, R. H. Grubbs. *J. Am. Chem. Soc.* **2012**, *134*, 693–699.
- [44] (a) P. Liu, X. Xu, X. Dong, B. K. Keitz, M. B. Herbert, R. H. Grubbs, K. N. Houk. *J. Am. Chem. Soc.* **2012**, *134*, 1464–1467. (b) Y. Dang, Z. X. Wang, X. Wang, *Organometallics* **2012**, *31*, 8654–8657. (c) Y. Dang, Z. X. Wang, X. Wang, *Organometallics* **2012**, *31*, 7222–7234.
- [45] V. M. Marx, M. B. Herbert, B. K. Keitz, R. H. Grubbs. *J. Am. Chem. Soc.* **2013**, *135*, 94–97.
- [46] S.-X. Luo, J. S. Cannon, B. L. H. Taylor, K. M. Engle, K. N. Houk, R. H. Grubbs. *J. Am. Chem. Soc.* **2016**, *138*, 14039–14046.
- [47] a) B. K. Keitz, A. Fedorov, R. H. Grubbs. *J. Am. Chem. Soc.* **2012**, *134*, 2040–2043. b) L. E. Rosebrugh, R. S. Ahmed, V. M. Marx, J. Hartung, P. Liu, J. G. Lopez, K. N. Houk, R. H. Grubbs. *J. Am. Chem. Soc.* **2016**, *138*, 1394–1405. c) A. Dumas, R. Tarrieu, T. Vives, T. Roisnel, V. Dorcet, O. Baslé, M. Mauduit, *ACS Catal.* **2018**, *8*, 3257–3262.
- [48] B. L. Quigley, R. H. Grubbs. *Chem. Sci.* **2014**, *5*, 501–506.
- [49] M. B. Herbert, V. M. Marx, R. L. Pederson, R. H. Grubbs. *Angew. Chem. Int. Ed.* **2013**, *52*, 310–314.
- [50] J. Morvan, T., McBride, I. Curbet, S. Colombel-Rouen, T. Roisnel, C. Crévisy, D. L. Browne, M. Mauduit, *Angew. Chem. Int. Ed.* **2021**, *60*, 19685–19690.
- [51] a) L. E. Rosebrugh, M. B. Herbert, V. M. Marx, B. K. Keitz, R. H. Grubbs. *J. Am. Chem. Soc.* **2013**, *135*, 1276–1279. b) J. S. Cannon, R. H. Grubbs. *Angew. Chem. Int. Ed.* **2013**, *52*, 9001–9004. c) S. L. Mangold, D. J. O'Leary, R. H. Grubbs. *J. Am. Chem. Soc.* **2014**, *136*, 12469–12478.
- [52] a) S. M. Bronner, M. B. Herbert, P. R. Patel, V. M. Marx, R. H. Grubbs. *Chem. Sci.* **2014**, *5*, 4091–4098. b) Y. Xu, Q. Gan, A. E. Samkian, J. H. Ko, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2022**, *61*, e2021130.
- [53] G. Occhipinti, F. R. Hansen, K. W. Törnroos, V. R. Jensen, *J. Am. Chem. Soc.* **2013**, *135*, 3331–3334.
- [54] G. Occhipinti, V. Koudriavtsev, K. W. Törnroos V. R. Jensen, *Dalt. Trans.*, **2014**, *43*, 11106–11117.
- [55] (a) W. Smit, J. B. Ekeli, G. Occhipinti, B. Woźniak, K. W. Törnroos V. R. Jensen, *Organometallics* **2020**, *39*, 397–407. (b) W. Smit, V. Koudriavtsev, G. Occhipinti, K. W. Törnroos, V. R. Jensen. *Organometallics*. **2016**, *35*, 1825–1837.
- [56] G. Occhipinti, K. W. Törnroos, V. R. Jensen. *Organometallics* **2017**, *36*, 3284–3292
- [57] (a) R. K. M. Khan, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261. (b) M. J. Koh, R. K. M. Khan, S. Torker, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2014**, *53*, 1968–1972.
- [58] M. J. Koh, R. K. M. Khan, S. Torker, M. Yu, M. S. Mikus, A. H. Hoveyda, *Nature* **2015**, *517*, 181–186.
- [59] T. S. Ahmed, R. H. Grubbs. *Angew. Chem. Int. Ed.* **2017**, *56*, 11213–11216.
- [60] Z. Liu, C. Xu, J. del Pozo, S. Torker, A. H. Hoveyda. *J. Am. Chem. Soc.* **2019**, *141*, 7137–7146.
- [61] A. M. Johns, T. S. Ahmed, B. W. Jackson, R. H. Grubbs, R. L. Pederson, *Org. Lett.* **2016**, *18*, 772–775.
- [62] J. M. Grandner, H. Shao, R. H. Grubbs, P. Liu, K. N. Houk, *J. Org. Chem.* **2017**, *82*, 10595–10600.
- [63] C. Xu, X. Schen, A. H. Hoveyda *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928
- [64] J. Morvan, F. Vermersch, J. Lorkowski, J. Talcik, T. Vives, T. Roisnel, C. Crévisy, L. Cavallo, N. Vanthuyne, G. Bertrand, R. Jazzar, M. Mauduit, *Catal. Sci. Technol.* **2023**, *13*, 381–388.
- [65] A similar work was reported in the meantime by Grela and co-workers, see: Ł. Grzesiński, M. Milewski, M. Nadirova, A. Kajetanowicz, K. Grela, *Organometallics* **2022**, in press, <https://pubs.acs.org/doi/full/10.1021/acs.organomet.2c00428>
- [66] I. Ibrahim, M. Yu, R. R. Schrock, A. H. Hoveyda. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.
- [67] A. S. Hock, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 16373–16375.
- [68] M. Yu, I. Ibrahim, M. Hasegawa, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 2788–2799.
- [69] A. E. Wright, J. C. Botelho, E. Guzmán, D. Harmody, P. Linley, P. J. McCarthy, T. P. Pitts, S. A. Pomponi, J. K. Reed, *J. Nat. Prod.* **2007**, *70*, 412–416
- [70] M. Yu, R. R. Schrock, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2015**, *54*, 215–220.
- [71] (a) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (b) J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Kataoka, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508. (c) D. G. Gillingham, O. Kataoka, S. B. Garber, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (d) G. A. Cotez, C. A. Baxter, R. R. Schrock, A. H. Hoveyda, *Org. Lett.* **2007**, *9*, 2871–2874. (e) D. G. Gillingham, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2007**, *46*, 3860–3864. (f) R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825.
- [72] J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.
- [73] T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225–3228.
- [74] H. Wakamatsu, S. Blechert, *Angew. Chem. Int. Ed.* **2002**, *114*, 2509–2511.
- [75] R. K. M. Khan, R. V. O'Brien, S. Torker, B. Li, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 12774–12779.
- [76] J. Hartung, R. H. Grubbs, *J. Am. Chem. Soc.* **2013**, *135*, 10183–10185.

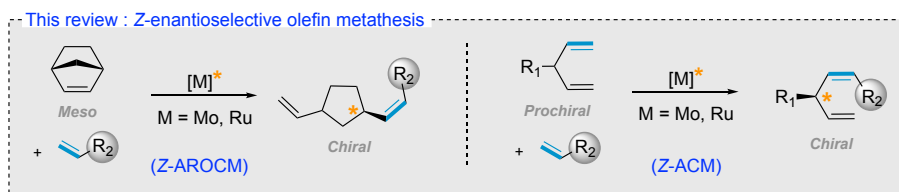


## REVIEW

WILEY-VCH

- [77] J. Hartung, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2014**, *53*, 3885–3888.
- [78] J. M. Berlin, S. D. Goldberg, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2006**, *45*, 7591–7595.
- [79] J. Hartung, P. K. Dornan, R. H. Grubbs, *J. Am. Chem. Soc.* **2014**, *136*, 13029–13037.
- [80] J. Morvan, M. Mauduit, G. Bertrand, R. Jazzar, *ACS Catal.*, **2021**, *11*, 1714–1748.
- [81] (a) V. Lavallo, Y. Canac, C. Präsang, B. Donnadiou, G. Bertrand *Angew. Chem. Int. Ed.* **2005**, *44*, 5705–5709 (b) R. Jazzar, R. D. Dewhurst, J.-B. Bourg, B. Donnadiou, Y. Canac, G. Bertrand *Angew. Chem. Int. Ed.* **2007**, *46*, 2899–2902. (c) F. Vermersch, L. Oliveira, J. Hunter, M. Soleilhavoup, R. Jazzar, G. Bertrand. *J. Org. Chem.* **2022**, *87*, 3511–3518.
- [82] D. Pichon, M. Soleilhavoup, J. Morvan, G. P. Junor, T. Vives, C. Crévisy, V. Lavallo, J. M. Campagne, M. Mauduit, R. Jazzar, G. Bertrand, *Chem. Sci.* **2019**, *10*, 7807–7811.
- [83] (a) J. Morvan, F. Vermersch, Z. Zhang, L. Falivene, T. Vives, V. Dorcet, T. Roisnel, C. Crévisy, L. Cavallo, N. Vanthuyne, G. Bertrand, R. Jazzar, M. Mauduit, *J. Am. Chem. Soc.* **2020**, *142*, 19895–19901. (b) J. Morvan, F. Vermersch, Z. Zhang, T. Vives, T. Roisnel, C. Crévisy, L. Falivene, L. Cavallo, N. Vanthuyne, G. Bertrand, R. Jazzar, M. Mauduit, *Organometallics* **2023**, *42*, 495–504. (c) for more active CAAC-catalysts ; see : A. Del Vecchio, J. Talcik, S. Colombel-Rouen, J. Lorkowski, M. R. Serrato, T. Roisnel, N. Vanthuyne, G. Bertrand, R. Jazzar, M. Mauduit *ACS Catal.* **2023**, *13*, 6195–6202.
- [84] D. S. Müller, I. Curbet, Y. Raoul, J. Le Nôtre, O. Baslé, M. Mauduit *Org. Lett.* **2018**, *20*, 6822–6826.
- [85] (a) Kong, J. Morvan, D. Pichon, M. Jean, M. Albalat, T. Vives, S. Colombel-Rouen, M. Giorgi, V. Dorcet, T. Roisnel, C. Crévisy, D. Nuel, P. Nava, S. Humbel, N. Vanthuyne, M. Mauduit, H. Clavier, *J. Am. Chem. Soc.* **2020**, *142*, 93–98. (b) L. Kong, Y. Chou, M. Jean, M. Albalat, N. Vanthuyne, P. Nava, S. Humbel, H. Clavier, *Adv. Synth. Catal.* **2021**, *363*, 4229–4238. (c) M. Savchuk, L. Bocquin, M. Albalat, M. Jean, N. Vanthuyne, P. Nava, S. Humbel, D. Hérault, H. Clavier, *Chirality* **2022**, *34*, 13–26.
- [86] J. Morvan, D. Bouétard, L. Kong, Y. Chou, T. Vives, M. Albalat, T. Roisnel, C. Crévisy, P. Nava, S. Humbel, N. Vanthuyne, H. Clavier, M. Mauduit, *Chem. – A Eur. J.* **2023**, e202300341.
- [87] Prices of (*rac*)-**Ru-2** (Aldrich, august 2023): 500€/500 mg.
- [88] A. Del Vecchio, H. R. Smallman, J. Morvan, T. McBride, D. L. Browne, M. Mauduit, *Angew. Chem. Int. Ed.* **2022**, *61*, e202209564.

## Entry for the Table of Contents



This review aims to provide a comprehensive overview covering all the breakthroughs accomplished in the field of challenging Z-enantioselective olefin metathesis, which is of interest in the total synthesis of complex molecules.

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