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Asymmetric catalysts for stereocontrolled olefin metathesis reactions

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Since the discovery of metathesis as an instrument to reorganize olefinic double bonds, substantial progress has been attained, establishing this method as a versatile and efficient tool for C–C-bond formation. In the last decade fundamental achievements were accomplished in the field of chiral Ru- and Mo-based olefin metathesis, providing an asymmetric access to structures, which are difficult to obtain by alternative routes. The reader is taken behind the scenes of catalyst development, important areas of application are described up to the current state of research; this *tutorial review* deals with the question, how metathesis is connected to enantioselective synthesis.

1. Introduction

Among the vast available methodologies in organic chemistry, the metathesis reaction has emerged as an indispensable tool for target-oriented synthesis and nowadays belongs to the standard repertoire of organic chemists. The key step of the metathesis reaction is the metal-catalyzed redistribution of two C–C double bonds by a *scission–recombination* process.[1] This revolutionary concept allows a retrosynthetic cut through a (strategically introduced) olefinic double bond within an analysis of a target molecule, a tool of immense value for synthesis.

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The development of well-defined molybdenum- and ruthenium-based alkylidene and carbene complexes by Schrock *et al.*[2] and Grubbs *et al.*[3] in 1990 and 1992, respectively, marks the beginning for enormous activities within this discipline. In the last decade impressive advances in the field of asymmetric metathesis catalysts were achieved. These complexes offer unique and efficient pathways for the synthesis of enantiomerically enriched compounds. The term "enantioselective" in connection with "metathesis" sounds confusing at the first glance, since olefin metathesis reactions include transformations of (sp^2-hybridized) carbon–carbon bonds. However, as disclosed in Scheme 1, stereocenters can be set up *indirectly* by desymmetrisation of (prochiral) *meso*-compounds. Of particular interest is the possibility to introduce heteroatoms into the backbone of the precursors, which opens access to a variety of structural motifs, *e.g. N*- and *O*-containing heterocycles. Whereby ARCM

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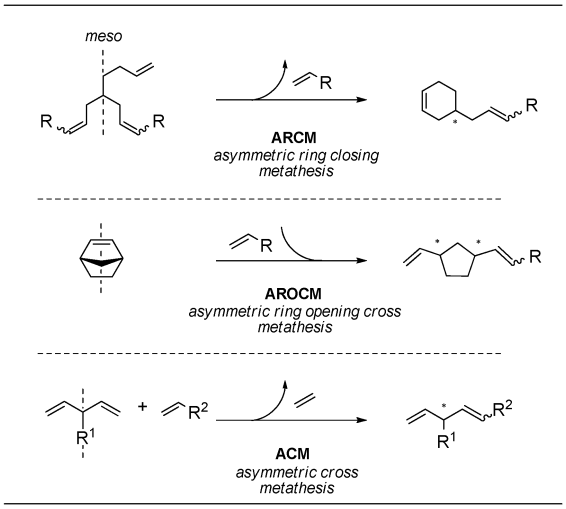
Prof. Siegfried Blechert was born in Aalborg (Denmark) in 1946. He received his PhD degree from the Universität Hannover (Germany) in 1974. After a post-doctoral period 1974–1980 in Hannover (Germany) with Prof. E. Winterfeldt and in Gif-sur-Yvette (France) with Prof. P. Potier (1981) he became a lecturer in Organic Chemistry in Hannover (1982) and a Full Professor of Organic Chemistry in 1986 at the Universität Bonn (Germany). Since 1990 he has been working at the Technische Universität Berlin (Germany). His research interests include the development of (asymmetric) catalysts for metathesis and hydroamination reactions, organocatalysis, the integration of semi-conducting materials in oxidative processes and the application of these methodologies in natural product syntheses.



Scheme 1 Representative concepts of desymmetrisation of prochiral/*meso* compounds *via* metathesis.

and AROCM are well developed disciplines, ACM is, due to the complexity of the reaction, still in its infancy. The success of metathesis is strongly correlated to the development of asymmetric catalysts, constantly improving and expanding the fields of this methodology's application. Besides the impressive results obtained so far in this research area, there still are issues, which remain to be addressed. Presently, enantioselective metathesis transformations are well elaborated and represent an efficient tool for the synthesis of useful chiral building blocks and fine chemicals; the next important level of development this methodology has to enter is its application away from selected substrates as a key step in enantioselective transformations within natural product syntheses, as it is nowadays routinely exercised with achiral metathesis catalysts.[4]

For many transformations the amount of catalyst required for an effective, cost-efficient process is too high, which prevents their wider utilization in industrial processes. Such high catalyst loadings are often the result of short catalyst lifetimes. For economical processes, current research focuses on more robust, easy-to-prepare catalysts with elongated lifetimes, high turnover frequencies (TOF) and numbers (TON), allowing more profitable transformations. Of particular interest within all the investigated fields is the efficient control of the product's *E*/*Z*-selectivity, whereby important advances were made towards the synthesis of the thermodynamically less favoured *Z*-olefins. Among all known metathetically active metal complexes, Mo- and Ru-based precatalysts still represent the privileged systems showing complementary performance in many cases, *e.g.* in terms of functional group tolerance and catalyst activity. Beyond the homogenous precatalysts known so far, immobilized systems have been developed to simplify the handling and purification of the processes.[5]

This *tutorial review* gives an insight into the field of chiral metathesis catalysts. The reader is introduced into the construction principles of asymmetric Mo- and Ru-based complexes, concepts of enantioselective metathesis reactions and the *state-of-the-art* applications thereof.

2. Construction principles of metathesis precatalysts

2.1. Molybdenum-based precatalysts

The first enantiomerically pure chiral metathesis catalysts were molybdenum-based complexes, which were synthesized to address tacticity control in ring-opening metathesis polymerisation (ROMP) processes.[6] The first suggestion that these complexes may also catalyze the enantioselective synthesis of small organic molecules appeared in 1993.[7] Henceforward, the quest for asymmetric olefin metathesis catalysts began and still goes on. However, due to their electron deficient character (14 VE-d^4) these Mo-complexes are sensitive to moisture and oxygen. Key to efficient and active high oxidation state Mo-based catalysts is a well balanced ligand sphere allowing both a sufficient Lewis acidity for olefin coordination, which is crucial for the catalyst's activity, and efficient steric protection, which still allows good access to the metal center for the coordinating substrate. In contrast to ruthenium, the attached ligands do not dissociate from the tetrahedral coordinated metal center during the catalytic cycle, therefore each ligand in particular influences the performance of the catalytically active species. This rigid construction gives access to tailor made catalysts by modularly varying the electronic and steric properties of the coordination sphere, which is important for the success of Mo-based catalysts. One can divide the ligand systems into three categories, the alkenylidene (**C**), the imido (**N**) and the oxygen based donor ligand (**O**), spanning the *CNO-face* of the complex (see also Fig. 1). A detailed discussion of each contribution to the activity and stability of the complexes is given in the literature.[8] The following will give a brief introduction:

(**C**) The alkenylidene is the metathetically active part of the complex, a Schrock-carbene, which lacks a proton in the β-position within the backbone to prevent deactivation by β-H-elimination. In most of the cases neophylidene (=CH_2CMe_2Ph) is introduced, in some cases neopentylidene (=CH_2CMe_3) can be found. For mainly stereoelectronic reasons there is an equilibrium between respective *syn*/*anti* alkenylidenes (*syn*: alkenylidene moiety points towards the imido ligand), which show different activities in metathetical transformations.

(**N**) The imido-system contributes significantly to the complex stability. The attached substituents in the 2- and 2′-position are not only shielding the sensitive metal center efficiently, but also variations at these positions allow for fine tuning of the catalyst's properties. In general aryl substituents with 2,2′-substitution (Me (**1**), *i*Pr (**2**) or Cl (**3**), Fig. 1) are employed, in some cases adamantyl is used, providing a sterical less demanding character referring to the olefin's coordination sphere (*e.g.* **4**, Fig. 1). The bonding situation of the imido ligand is best described by a triple bond (6 VE donor due to participation of the imido lone pair).

(**O**) The most significant influence can be achieved by varying the structure of the alkoxy ligands. The use of oxygen based systems has proven to be crucial for the catalytic activity, showing the essential donor–acceptor characteristics referring to a balanced Lewis acidity on the metal center. The *ortho*-substituents have shown to be most important for adjustments of the steric congestion of the complex, sterically demanding alkoxides have

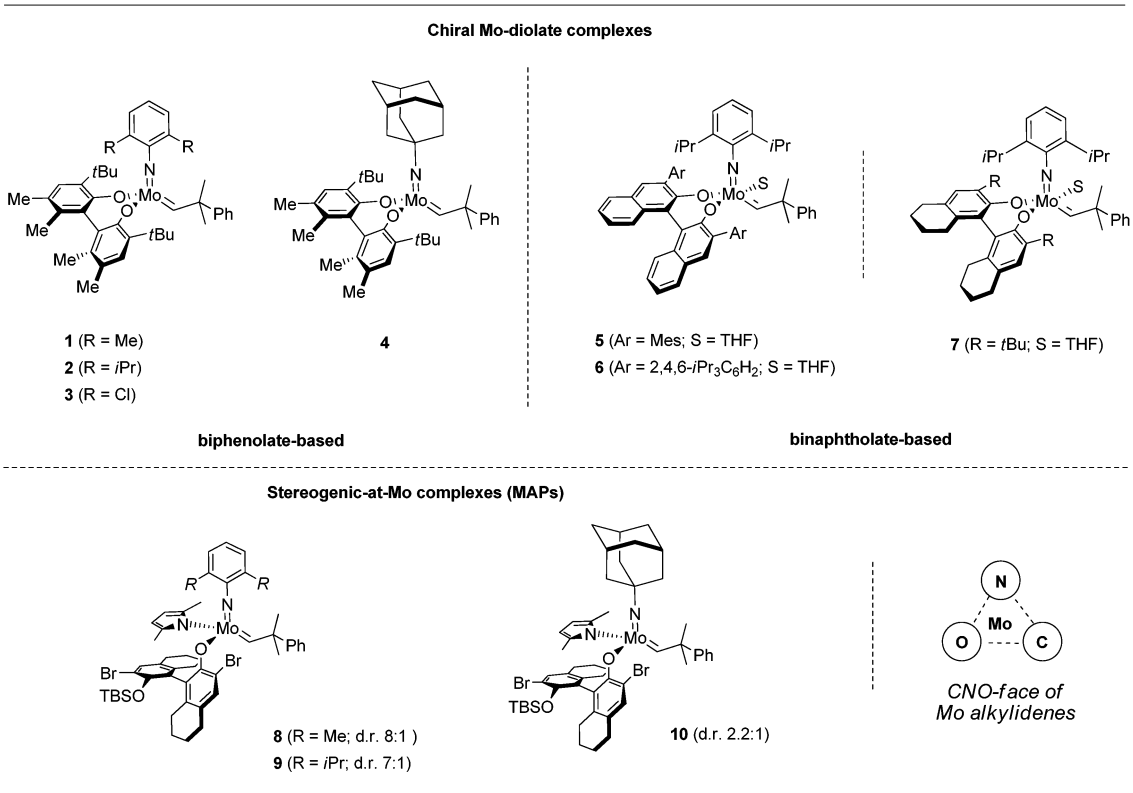
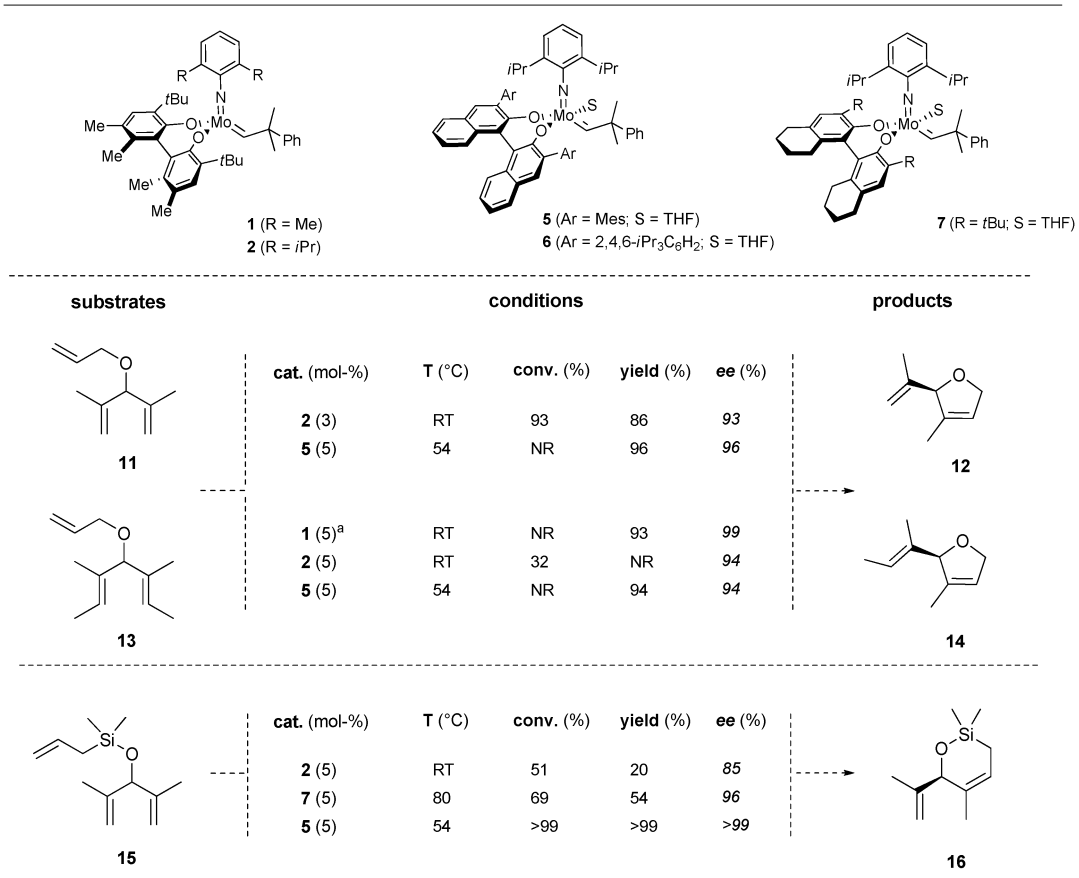


Fig. 1 Representative chiral Mo-based metathesis precatalysts.

to be used for the formation of stable complexes. The structure of these ligands gives rise to a classification of Mo-based systems, the *diolate*- and the *stereogenic-at-Mo* complexes. Fig. 1 shows the most important representatives for these two catalyst classes. Privileged ligands for the former class are mainly based on C_2-symmetric bidentate binol and biphenol derivatives; biphenol-systems can generally be considered as less bulky in comparison to binol-based complexes. Both diol-systems promote the formation of enantioenriched carbon- and heterocycles through ARCM and AROCM (*vide infra*). The biphenolate-based catalysts are very versatile and perform good to excellent in different disciplines of metathesis, but from a practical point of view these systems have one disadvantage. The synthesis of optically pure biphenolates is usually achieved by resolution through fractional crystallisation of mentholates,[9] whereas binaphthols are readily accessible starting from commercially available *R*- and *S*-binols. To circumvent this shortcoming, the groups of Hoveyda and Schrock developed a new biphenolate system (compare catalyst **7**) derived by partial hydrogenation of binol-derivatives.[10] These tetrahydrobinaphtholates share structural features with both the binol and the biphenol based systems in terms of selectivity and reactivity profiles. Additionally, protocols have been developed for *in situ* use of these catalysts, which allow for more convenient handling. Since all Mo-complexes show a distinct substrate–catalyst dependency, a vast library of metathetically active catalysts based on these classes has been developed to address different challenges. In this sense a systematic screen for the optimal catalyst and conditions is always needed in Mo-based metathesis, however, the excellent activity and enantioselectivity in many cases justify these expenses. By comparing the structurally different diolate-based catalysts in ARCM of benchmark substrates as disclosed in Scheme 2, some trends in the catalyst's activities are becoming evident. Less bulky substrates are transformed in high efficiency by sterically demanding catalysts. In this sense, binol based catalyst **5** shows superior enantioinduction and yields within the transformation of **11** and **15**,[11] compared to the less bulky biphenol-analogue **2**.[12,13] Concerning the transformation of substrate **13**, catalyst **1** shows superior results.[11–13] This example indicates, how slight variations in the catalyst's structure can fundamentally influence the outcome of the reaction; the variation in **1** in comparison to **2** (Me-imido *vs.* *i*Pr-imido) leads to a significant decrease in activity (conversion $>93\%$ *vs.* 32%, respectively). Apart from that, **1** is exceedingly active performing the reaction without solvent (5 min for full conversion); additionally a beneficial effect is observed on the yield of the process. Although catalyst **5** still shows similar results, the more bulky catalyst **6** does not promote any reaction. Beyond that, the transformation of substrate **15** clearly demonstrates that **7** not only shares structural features of biphenol and binol systems, but also the performance bridges the properties of both systems with respect to conversion, yield and enantioinduction.[10] It is worth mentioning that ruthenium cannot achieve this efficiency within the transformation of **11** and **15**.

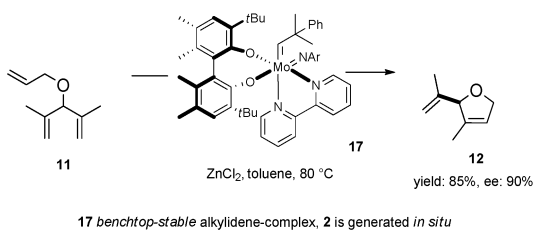
One important step towards a more user-friendly handling of Mo-based biphenol catalysts was recently published by Fürstner and Heppekausen.[14] As disclosed in Scheme 3, the introduction of a chelating bidentate 2,2′-bipyridine into precatalyst **2** gives an 18 VE complex **17**, which can be *stored on the benchtop* without decomposition. These complexes are activated



Scheme 2 Performance of Mo-based metathesis catalysts in ARCM of benchmark substrates; (a) the reaction was performed without solvent; NR: not reported.

by $ZnCl_2$, which, subsequent to a thermal dissociation, complexes the bipyridine and generates the desired 14 VE metathesis precatalyst **2** *in situ*. This work demonstrates that one major drawback of Mo-based catalysts, the difficult handling due to their sensitivity to moisture and oxygen, can be overcome with a suitable set of ligands. In comparison to the transformation with catalyst **2** (Scheme 2), **17** shows just a slightly diminished selectivity under more forcing conditions within the transformation of **11**.

A model that accounts for the sense and levels of enantioselectivity in ARCM concerning the biphenol class has been suggested by Hoveyda (Fig. 2).[15] Subsequent to the formation of the substrate–catalyst complex, ARCM might proceed through the more reactive *anti*-alkylidene. The resulting complex may



Scheme 3 2,2′-Bipyridine-adduct of catalyst **2** (benchtop-stable); Ar = 2,2′-diisopropylphenyl.

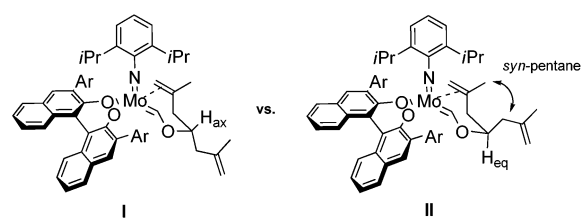
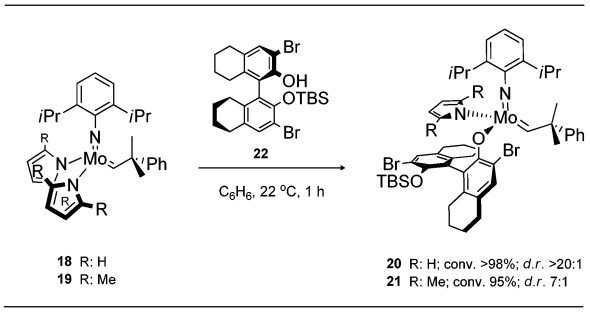


Fig. 2 Model for the origin of asymmetry in ARCM of Mo diolate-complexes.

then coordinate with one of the enantiotopic olefins (**I** *vs.* **II**) from the sterically more accessible *CNO-face*. Consequently, the remaining butenyl group arranges in a pseudo-equatorial position, thereby avoiding a *syn*-pentane interaction as can be seen in **II**.

Recently, in the context of efforts towards the total synthesis of *Aspidosperma* alkaloid quebrachamine (see Section 3.1), the groups of Schrock and Hoveyda reported a new type of olefin metathesis catalyst with an unprecedented structural motif.[16,17] Until then, all existing diolate-based Mo-complexes were unable to perform the desired ARCM. Based on theoretical works by the group of Eisenstein, a new catalyst system was designed bearing an electron donating and an electron withdrawing ligand. Instead of a bidentate ligand employed in the former systems, pyrrole and axially chiral alkoxides, both monodentate systems,



Scheme 4 Representative synthesis of MAP complexes by diastereoselective protonation.

have been used here. Importantly, the employment of this ligand set generates a stereocenter at the metal, which was assumed to have a significant impact on enantioselectivity. As disclosed in Scheme 4, the establishment of the stereogenic center at Mo is achieved by diastereoselective protonation of a universal prochiral bispyrrolide precursor (see **18** and **19**). Moreover these *stereogenic-at-Mo* complexes, also called *MAPs* (*monoaryloxide monopyrrolides*), are not only easy to prepare, much more importantly they can be generated *in situ,* performing enantioselective transformations without additional steps of purification–crystallisation. Their unique properties make them important candidates even for transformations beyond enantioselective synthesis, *e.g.* *Z*-selective CM (cross metathesis, Section 3.3.2).

2.2. Ruthenium-based precatalysts

Summarising the main representatives of Ru-based precatalysts in Fig. 3 it becomes evident that so far solely NHCs are employed for the implementation of chirality. These ligands offer excellent opportunity for this purpose; due to the strong Ru–NHC bond they do not dissociate from the metal during the catalytic cycle. The first report of a chiral Ru-based metathesis precatalyst (**23**) was published in 2001 by Grubbs and co-workers.[18] Pioneering attempts to install chirality near the metal by asymmetric *N*-substituents did not provide promising results (see also ref. 19), therefore the NHC's backbone was targeted for the installation of stereoinformation. Since the stereocenters at these positions are remote from the metal, aromatic *N*-substituents were used to transfer the chirality to the olefin's coordination sphere by a well defined twist around the *N*-aryl bond. In this regard, the *ortho*-substituents within the aromatic rings are forced to reside on the NHC-face opposite to the bulky groups within the NHC's backbone ("*gearing effect*",[20] see also Fig. 4). Beyond that important role, the employment of *N*-aryls proved to contribute significantly to the stability of the respective complexes. An important structural property of this class of catalysts is the use of C_2-symmetric NHCs; according to this, the rotation around the Ru–NHC axis has not to be considered. Within this first generation the impact of structural modifications of the NHC was evaluated for the desymmetrisation of standard prochiral trienes in ARCM (Scheme 5). These investigations revealed that the employment of phenyl groups within the NHC's backbone provides the best enantioinduction, furthermore *ortho*-substituents at the *N*-aryl have shown to be beneficial for the enantioselectivity of the transformations. These early investigations led to the development of catalyst **23a** (Fig. 3). As presented in Scheme 5, this complex showed good conversions under optimized reaction conditions, but only moderate enantioinduction for ARCM of substrate **13** was achieved; no temperature and solvent effects were observed on enantioselectivity. It has been shown for catalysts of this class that the addition of iodides improves the enantioinduction considerably. Referring to this, the diiodoruthenium methylene species **23b** is generated *in situ* (Scheme 5), showing a better enantiodiscrimination, albeit at the cost of shorter lifetimes and need for higher catalyst loadings. However, high levels of enantioinduction were achieved only for selected substrates (**13**, **36**) using **23b**, further developments were focussed on more general applications. By varying the substituents and the substitution pattern of the *N*-aryls the stability and the activity could be improved.[20] Especially ring sizes >6 are challenging in asymmetric Ru-based metathesis; in this regard, the next generation of Grubbs-type catalyst **24** (Fig. 3) exhibits an enhanced performance for this purpose. In comparison to **23b**, **37** is obtained readily by employing **24a** (cat.-load.: 2 mol%) yielding 92% of the desired product (Scheme 5). Even silicon containing 7-membered rings are feasible with complex **24a** (Scheme 7). Beyond that, catalyst **C** promotes the AROCM of norbornene derivatives (see Section 3.2). A first impression is given in Scheme 6, demonstrating the excellent yields and high enantioinduction for this process including benchmark substrate **38**. The first attempts to catalyse the ACM, the most challenging discipline, were conducted using this class of precatalysts with promising results (see Section 3.3).[21] Despite this being a ground breaking achievement, there was still room for improvement. High enantioselectivity in ARCM could only be obtained by addition of iodides with twice the amount of catalyst needed to reach comparable conversions to the chloride containing complex. Especially in AROCM no *E*/*Z*-selectivity was observed, yielding 1 : 1 mixtures of respective products; moreover high amounts of cross partner (styrene, 10 eq.) were employed for this transformation.

In 2002, Hoveyda and co-workers came up with the alternative concept of installing chirality within the Ru-based metathesis precatalyst, using axial chiral C_1-symmetric *bidentate* NHCs lacking a backbone substitution (Fig. 3). The introduction of a chelating NHC prevents a free rotation of the ligand. The chiral information, installed within the *N*-substituent, is efficiently transferred *via* diastereoselective complexation with the ruthenium, generating a stereocenter *at the metal* (*stereogenic-at-Ru* catalysts).[22] However, this ligand exchange (chloride against alkoxy) diminishes the reactivity by means of decreased Lewis acidity at the metal; additionally this cumbersome system causes a significant steric congestion, making high catalyst loadings necessary. This class found wide applications in AROCM processes; a sufficient level of activity was obtained by structural variations within the *N*-binaphthyl and styrene etherate moiety in **29**.[23] As shown in Scheme 6, catalyst **30a** promoted the transformation of **38** under ambient conditions with a pronounced *E*/*Z*-selectivity (see also Section 3.2) The installation of an *ortho*-phenyl group introduced at the chelating etherate (precatalyst **30**, Fig. 3) is a well established method to enhance the initiation rate leading to a higher concentration of the active species.[24] Besides this important improvement, the activity of **30** was additionally enhanced significantly by employing an electron withdrawing CF_3-group

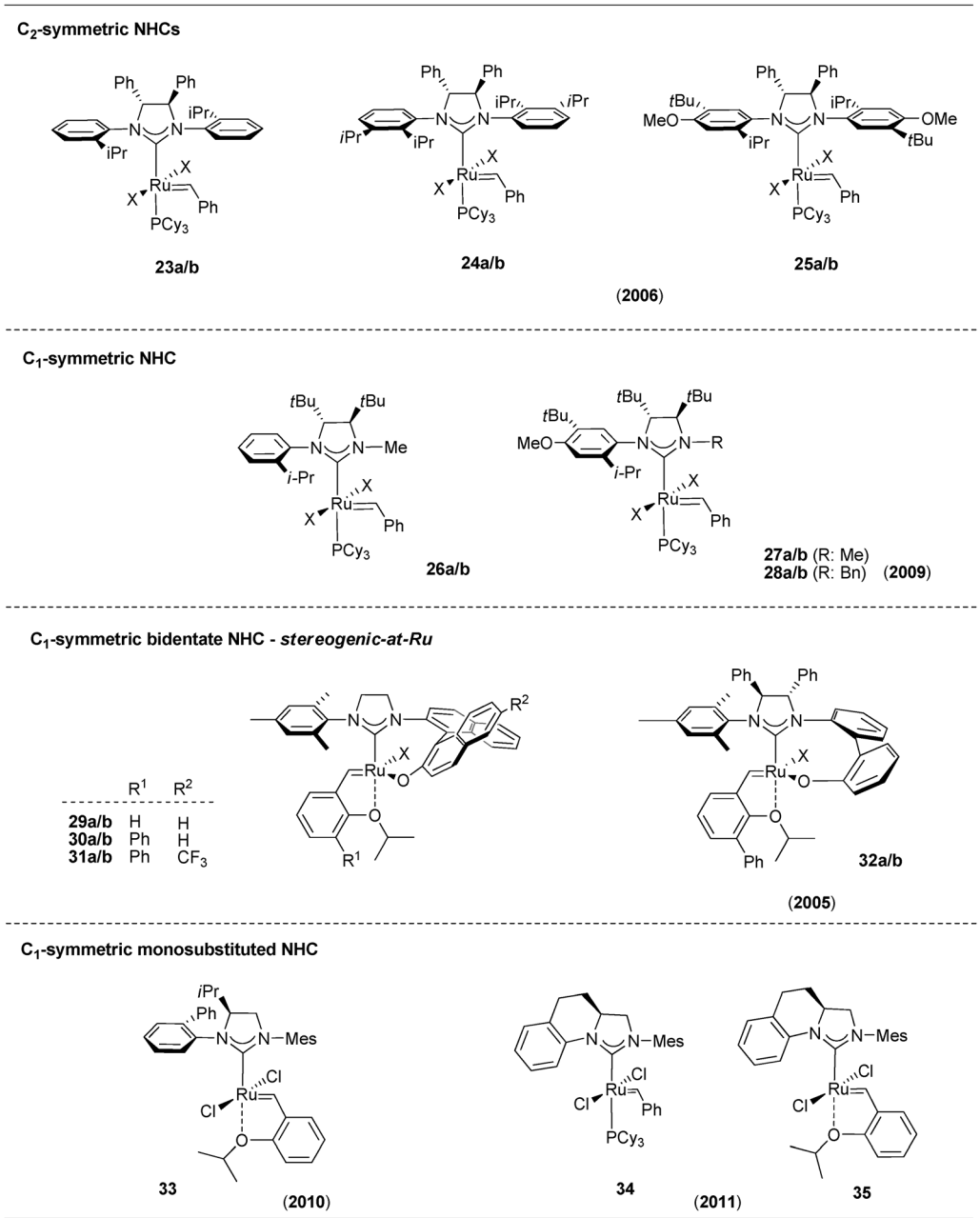
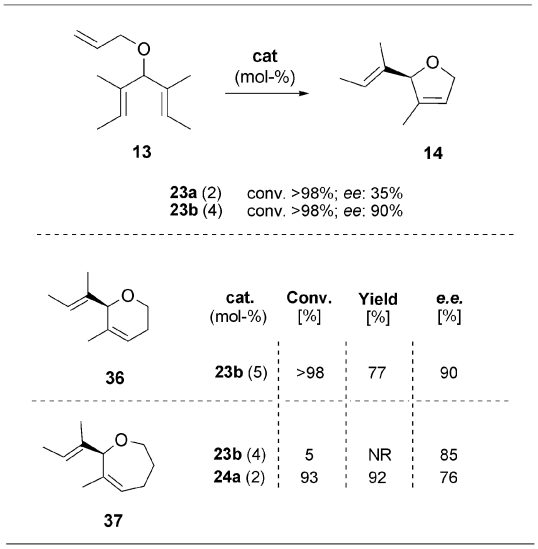


Fig. 3 Important representatives of chiral Ru-based metathesis precatalysts; a: X = Cl; b: X = I.

within the binaphthyl backbone (see **31**, Fig. 3), partly compensating for the decreased Lewis acidity at the metal. It is worth mentioning that the lack of backbone substitution leads to a gain of space, the mesityl substituent is no longer forced into the equatorial coordination sphere of the ruthenium; presumably this enables the installation of the chelating etherate moiety in **29–31** (Fig. 3), which is one key factor for the outstanding stability of this class of catalysts. Reactions with catalysts **29** and **30** can be conducted in undistilled solvents under air without appreciable loss of selectivity. Additionally, the high stability allows the recycling of the catalysts by column chromatography subsequent to the reaction. The major drawbacks of these systems are the auxiliary-directed multi-step synthesis of the chiral NHC and the high catalyst loadings in metathetical transformations. To circumvent these shortcomings a second generation of *stereogenic-at-Ru* complexes was developed. The above mentioned construction principles for catalysts containing mono- (*gearing effect*) and bidentate NHCs (*stereogenic-at-metal*) coalesce in the second generation of chiral Ru-chelates, the biphenyl-based complexes **32** (Fig. 3), published by the same group in 2005.[25] Within these systems, the chiral information within the NHC's backbone has an effect on the orientation of the achiral biphenyl moiety, which, under this influence, coordinates diastereoselectively to the Ru-center. In this way, the chirality is efficiently transferred to the metal, circumventing the synthesis of optical pure amino alcohols used in complexes **29–31** (Fig. 3) and generally reduces the steric demand of the ligand for higher activity. Albeit the chromatographic isolation of chloride containing **32** is no longer possible, these systems can be used *in situ,* rendering a more

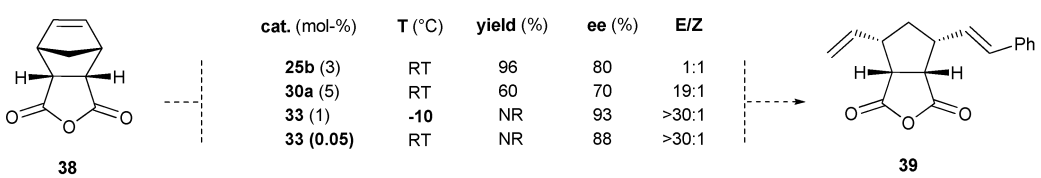


Scheme 5 ARCM employing Grubbs-type catalysts; Ru–Cl (a), Ru–I (b).

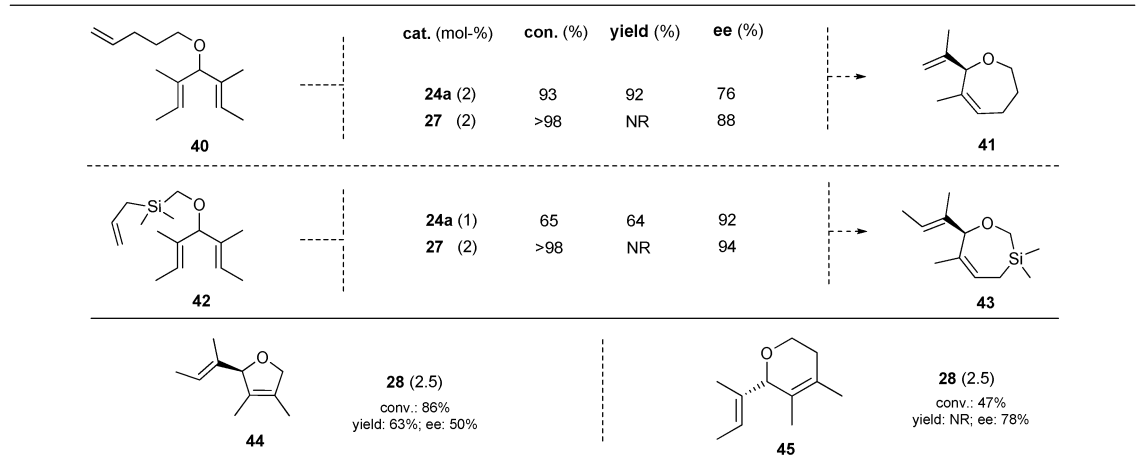
practical handling with comparable levels of enantioinduction in AROCM with respect to the binaphthyl based catalysts. Especially the iodide-containing catalyst **32b** proved to be efficient in AROCM transformations of low strained oxa- and azabicycles.[25] The need for halogen-additives and the high catalyst loadings in AROCM were remaining drawbacks, leaving room for further developments.

Inspired by the latest results in the area of Ru-based metathesis catalysts using unsymmetrical NHCs,[26] Collins and Fournier presented a new development in the field of chiral Grubbs-type catalysts.[27] Conceptually, an increase in steric bulk within the C_1-symmetric monodentate NHC using *tert*-butyl groups was meant to enforce the influence of the chiral backbone. Due to this increase in steric demand it was necessary to employ a smaller *N*-substituent for complex synthesis; within the first generation an aliphatic Me-group was introduced (**26**, Fig. 3). Due to the lack of C_2-symmetry or a chelating group within the NHC, in this class of catalysts *syn*/*anti* rotamers in ratios depending on the introduced aliphatic substituent are observed. Of great importance is the Me derivative **26**, surprisingly, showing only the *syn* rotamer (Me-group resides above the Ru–carbene, Fig. 3). This catalyst class was exclusively investigated in ARCM. This first generation provided inferior results compared to its counterparts **23–25**, but structural variations within the aryl rings proved once again as beneficial for catalytic performance.[27] In this regard, catalyst **27** (Fig. 3) showed comparable efficiency within the transformation of benchmark substrates **11** and **13**;[28] furthermore an improved activity for the generation of 7-membered ether **41** and silane-ether **43** could be achieved.[28] (Scheme 7). Since the coordination sphere is less encumbered, this catalyst shows a high activity, albeit only short lifetimes have been reported so far. Recently, the desymmetrisation of prochiral trienes, providing tetrasubstituted olefins, was published employing the benzyl-analogue **28** (Fig. 3), demonstrating the high activity of this class.[29] As disclosed in Scheme 7, for this challenging substrates satisfactory results were obtained for **44** and **45**, showing an enantiomeric excess of 50% and 78%, respectively. The disclosed systems confirmed the important role of sterically less crowded cavities for high activity within the metathesis catalysts; unfortunately the introduction of aliphatic groups significantly diminishes the stability of the active species. The outstanding performance in ARCM without the need for halide additives providing equal or superior results in ARCM, and additionally the ability to provide enantioenriched products containing tetrasubstituted double bonds, marks an important step towards efficient asymmetric metathesis.

In 2010, a new chiral precatalyst of unprecedented structure was published by Blechert and co-workers.[30] In contrast to the known Ru-based systems (*vide supra*) this complex class bears a backbone-*mono*substituted and monodentate NHC of C_1-symmetry. Since *N*-aryl substituted complexes are generally more stable than *N*-alkyl ones, two different aromatic systems are employed herein. Depending on their location relative to the stereocenter they fulfil two different tasks. The *ortho*-substituted aryl ring next to the stereocenter efficiently transfers the chirality to the equatorial coordination sphere (*gearing effect*). On the other side a mesityl-moiety is installed, which, due to the lack of backbone substituent, gains space to adopt a planar arrangement; in this effect the cavity for metathesis transformations is significantly increased. This combination leads to a new class of highly stable and highly active catalysts, showing both excellent enantioselectivity and outstanding *E*-selectivity in AROCM (for details see Section 3.2). Remarkably, stability-tests have shown that even after 12 days in DCM at 40 °C no decomposition is observed. This exceptional stability can be attributed to the introduction of a chelating etherate and the (aromatic) mesityl moieties, which has already proved valuable in the development of achiral catalysts. Within the transformation of **38** (Scheme 6), catalysts **33** (see Fig. 3) outperforms catalysts **25b** and **30a** with respect to catalyst loadings and enantioinduction, additionally showing an improved *E*-selectivity. The high activity of complex **33** allows for reactions to be conducted below 0 °C. Amazingly, transformation of **38** can be performed with a catalyst loading of only 0.05 mol%, a magnitude that has not been reported in asymmetric metathesis chemistry of small molecules so far. It has to be underlined that no halide additives were necessary for these results.



Scheme 6 AROCM of benchmark substrate **38**; Ru–Cl (a), Ru–I (b).



Scheme 7 Comparison of Grubbs-type catalysts with the unsymmetrical variation of Collins and co-workers; NR = not reported, Ru–Cl (a), Ru–I (b).

Remarkably, stability-tests have shown that even after 12 days in DCM at 40 °C no decomposition is observed.

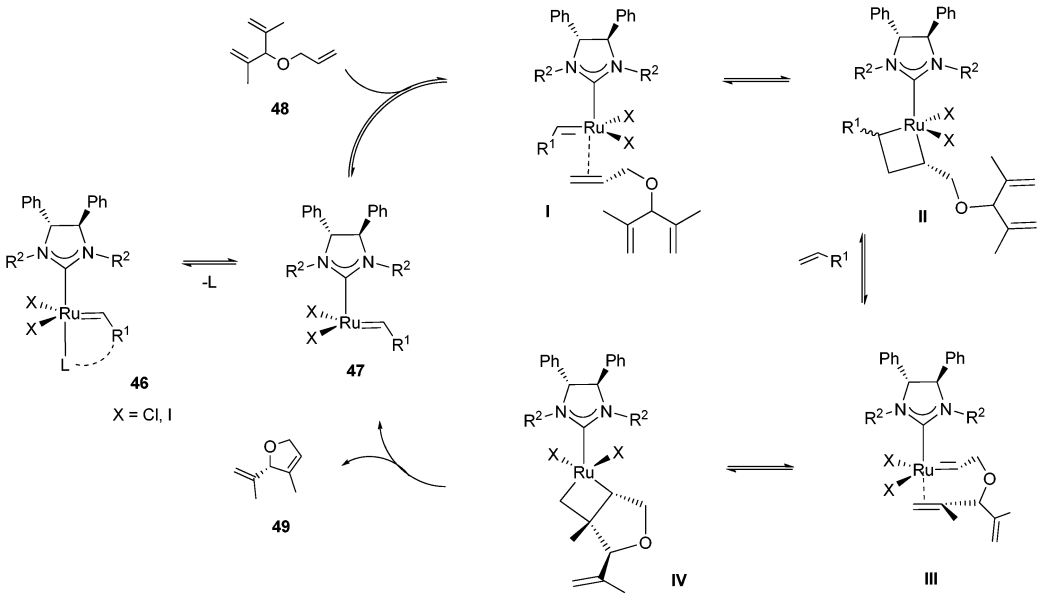
Based on the concept of monosubstitution, complexes **34** and **35** were developed in 2011 by the same group.[31] This innovation bears an intramolecular linkage between the *N*-aryl and the NHC's backbone, which causes a rigid chiral environment around the Ru-center. A crystal structure of **34** provided an insight into the steric influence of the ligand, which revealed some important characteristics and unique structural features. The ethylene-bridge, which connects the stereocenter with the *N*-aryl moiety, causes a large twist of 45° around the *N*-aryl bond and forces the carbon atom at C-13 into the equatorial coordination sphere of the ruthenium center. This orientation gives rise to an agostic interaction (Ru–C–H), which could even be observed through NMR spectroscopy. The resulting catalysts were employed in AROCM with excellent results (Section 3.2), showing the same outstanding stability as discussed for **33**. With a closer look to the choice of cross partners including the catalysts mentioned so far, it becomes evident that almost exclusively styrene and its derivatives have been employed for AROCM. Of course this happened deliberately, since the metathesis adduct (a benzylidene species, *dormant species*) is particularly stable, giving rise to low catalyst loadings. Catalyst **34**, however, is capable of transforming allylsilanes, offering a higher flexibility for further transformations.

There is an ongoing debate regarding the mechanism and the origin of asymmetric induction, a detailed discussion for ARCM is provided in the following section. A well accepted mechanistic model proposed for Ru-catalyzed ARCM employing C_2-symmetric NHCs is briefly accounted in Scheme 8.[32] A 14 VE species (**47**) is formed by the dissociation of a ligand in **46** (L = phosphine or chelating etherate moiety). The subsequent coordination of substrate **48** takes place regioselectively at the least substituted olefin within the triene affording intermediate **I**, which furnishes **III** upon [2+2] cycloaddition (**II**) and cycloreversion. At this stage the installed chirality within complex **III** leads to a selective reaction with one of the prochiral enantiofaces of the olefin, setting up the desired stereocenter. A following cycloreversion releases the enantiomerically enriched product and regenerates the active 14-VE species (analogue to **47** a methylene species with R_1 = H is formed after the first catalytic cycle).

One important point discussing the mechanism of metathesis reactions is the formal reversibility of every particular step within the catalytic cycle. It is assumed that any intermediate, which involves the substrate covalently bound to Ru, can be enantiodetermining. With the confinement, that the coordination of the olefin to the metal center is approximately barrier-free and product formation is irreversible (driving the equilibrium to the desired side), the attention is focussed on the steps including [2+2] cycloaddition/reversion (formation of **II**, **III** and **IV**). Based on a quantum-mechanistic/molecular mechanistic study (QM/MM), Costabile and Cavallo revealed valuable details concerning the origin of enantioinduction in the ARCM using C_2-symmetric NHCs:[33]

The Newman projection in Fig. 4 shows the influence of the chiral backbone (*) on the orientation of the *N*-aryl group, the interaction of the phenyl with the *i*Pr-group within the *N*-substituent is minimized in this way. The unsubstituted side of the aromatic ring is bent down to the equatorial plane (leaning black bar in the Newman projection) narrowing one of the enantiofaces within the complexes coordination sphere. Two energetically different stereoisomers concerning the catalyst-substrate complex **III** can be obtained, which differ in their orientation of the bound substrate (**III-a** and **III-b**, Fig. 4). Due to the twisted *N*-aryl moiety there is a significant steric interaction in **III-b**, leading to a kinetically favoured formation of intermediate **III-a**. The theoretical studies suggest that this chiral orientation in turn selects the prochiral enantiofaces of the olefins through a well-defined folding of the complex.

In this regard, initiated by a *trans* coordination (regarding the NHC) of the olefin, a five membered ring (relaxed pseudo-envelope) is set up on the enantioface of the complex, which is not hindered by the bent-down *N*-aryl ring (Fig. 4). For this *trans* coordination the two remaining olefins are capable, leading to energetically different structures, in which the unbound olefin moiety is located in the equatorial or axial position of the five membered ring. Due to steric interactions within the catalyst's backbone in the transition state



Scheme 8 General mechanism for the ARCM including chiral Ru-based metathesis catalysts.

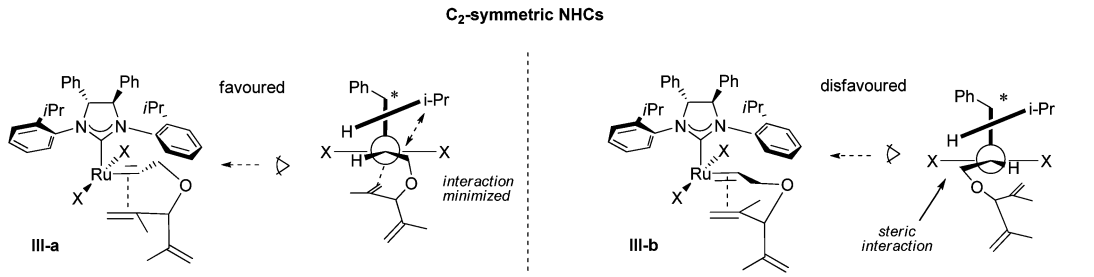


Fig. 4 Determination of the ligand's orientation within the catalyst–substrate complex **III**.

(Me-group and halogen depicted in Fig. 5) the product **IV**-equatorial, in which the uncoordinated olefin occupies the equatorial position, is favoured. This working model depicts the crucial role of the Me-group within the olefin's substitution pattern referring the choice of adequate substrates for ARCM. Furthermore, an increase of the steric demand, for example by employing iodides instead of chlorides in the equatorial position of the Ru, amplifies these steric effects; this explains the superior performance of the diiodoruthenium derivatives within this catalytic system.

Inasmuch as rotamers of C_2-symmetric ligands are structurally/energetically identical, this fact has not to be considered at this position. The situation changes dramatically if C_1-symmetric (*e.g.* **26–28**) or bidentate NHCs (*e.g.* **29–32**) are employed. In the former case rotamers play an important role, in the latter the bidentate nature of the ligand influences the energetics of the intermediates fundamentally, leading to modified mechanistic proposals. Even though this working model explains the observed enantiomers very well, it has to be underlined that it refers solely to this special example; nevertheless it provides an impression of the origin of enantioselectivity in Ru-based metathesis reactions.

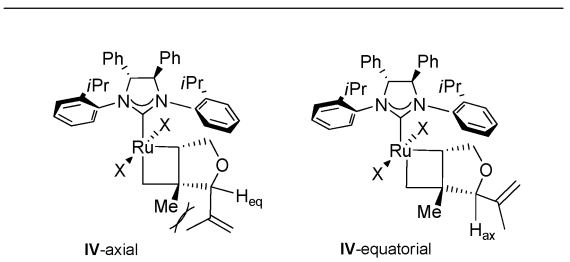
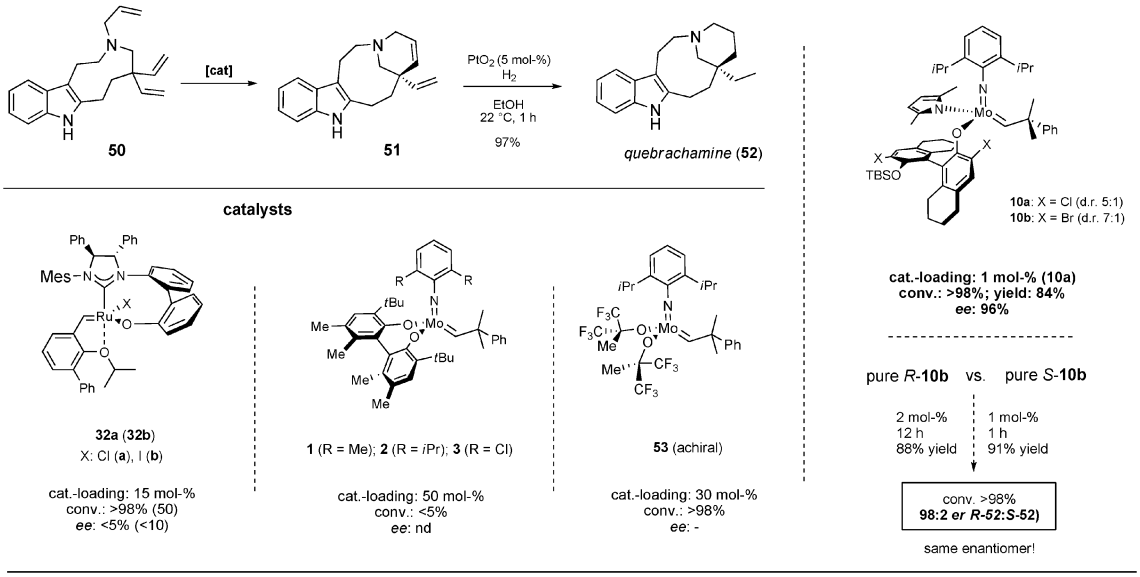


Fig. 5 Folding of the catalyst–substrate complex.

3. Applications of chiral metathesis precatalysts

3.1. ARCM—asymmetric ring-closing metathesis

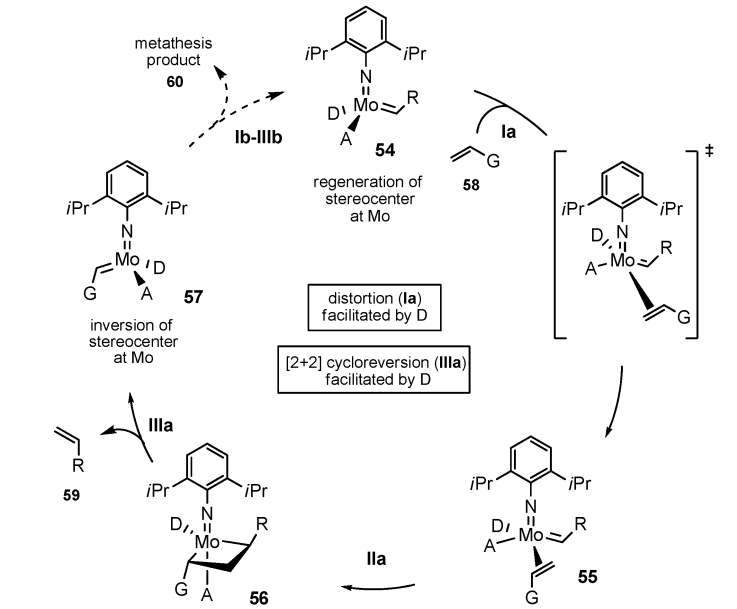
The desymmetrisation of prochiral trienes through ARCM processes is a powerful tool for the construction of small, medium and large carbon- and heterocycles. Since the first metathesis transformation takes places regioselectively at the least congested olefin, the propagating species is controlled efficiently by the nature of the olefins within the substrates; there is only one propagating species, which generally simplifies



Scheme 9 Representative catalysts employed for the ARCM of **50** (for experimental details see references, nd: not determined).

the course of the reaction. The crucial role of the catalyst is limited to an efficient selection of the enantiofaces during ring closing metathesis (second transformation).

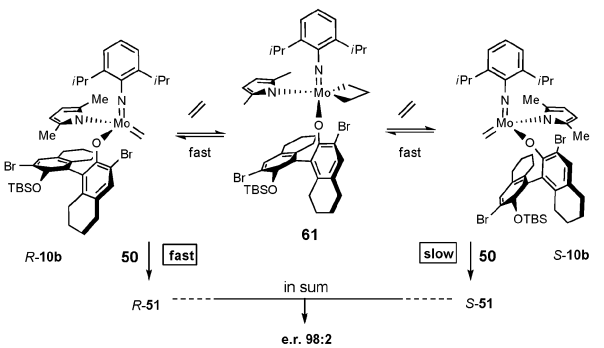
An excellent example of ARCM involving the natural product synthesis of the *Aspidosperma* alkaloid quebrachamine (**52**) was reported by Hoveyda.[17,34] As disclosed in Scheme 9, the strategy envisaged an ARCM process of **50** in the late stage of the total synthesis. The sterically hindered vinyl groups at a congested all-carbon quaternary center and the presence of a Lewis basic tertiary amine made this transformation very challenging. None of the known chiral biphenol- and binol-based Mo-complexes promoted any reaction, even under forcing conditions and catalyst loadings of up to 50 mol% (*e.g.* **1–3** in Scheme 9, conv. $<5\%$). It merits mention that Ru based catalysts (*e.g.* **32a**, **32b**) performed well in this defiant example (conversion up to 98%, catalyst loading 15 mol%), however, enantioinduction was not satisfactory (up to 10% ee). In an intensive screening for suitable *achiral* Mo-based catalysts, **53**, which is not a chelate complex, was principally applicable for the transformation of **50**, albeit a catalyst loading of 30 mol% was necessary for a conversion of 98%. Based on these results it was concluded that the lack of activity in Mo-based chelate-complexes is an effect of strains within the transition states of the catalytic cycle caused by the rigid architecture, whereas systems bearing monodentate ligands allow for a more flexible adaption of conformational changes. With the aim of overcoming these difficulties and to optimize this critical step within the synthesis of the desired alkaloid **52**, a new catalyst concept was targeted, which involves the use of chiral monodentate ligands. Based on computational studies the group of Eisenstein reported in 2007[16] that Mo-based catalysts, bearing two electronically distinct monodentate ligands, should be effective promoters of metathesis transformations. The use of monodentate ligands sets up a stereocenter at the metal, which was assumed to be beneficial for enantioinduction. Based on these facts, a new catalyst was designed: instead of the chelating diolate, a chiral monodentate alkoxide (electron withdrawing ligand) as well as pyrrole (electron donating system) were employed. It was suggested that the alkoxy ligand (A: acceptor ligand) in these complexes ensures a sufficient Lewis acidity, which is critical for olefin coordination. In addition the calculations revealed that pyrrole exerts a stereoelectronic influence within the catalytic cycle. As disclosed in Scheme 10 the donor ligand causes a distortion of the tetrahedral complex geometry in **54**, which opens the coordination sphere and lowers the barrier for olefin coordination (**Ia**). A subsequent [2 + 2] cycloaddition (**IIa**) provides metallacyclobutane **56**. A second beneficial effect is proposed for the cycloreversion step in **IIIa**, which is based on the *trans*-position of the donor ligand to the metallacyclobutane, facilitating the [2 + 2] cycloreversion process; after decomplexation of the side-product (**59**) the substrate–catalyst complex **57** is formed. It is worth highlighting that at this stage, after one complete metathesis transformation, the stereocenter at Mo is inverted; subsequently, a second metathesis process (**Ib–IIIb**) generates the desired product and regenerates the catalyst and the stereocenter at Mo.[35] However, complex **10a** (dr 5 : 1) was prepared from the corresponding achiral Mo-bispyrrolide and the respective chiral aryl alcohol by a diastereoselective Mo–*N* bond protonation (*vide supra* Section 2.1) and subsequently used *in situ*. Among others, this complex promoted the difficult ARCM reaction with outstanding selectivity, so that tetracyclic compound **51** was obtained efficiently in 84% yield and with an enantiomeric ratio of 98 : 2 using a catalyst loading of only 1 mol%. With a closer look, an important phenomenon becomes evident. The enantiomeric ratio of the product exceeds the diastereomeric ratio of the employed chiral complexes, which at the glance contradicts the principles of chiral catalysis. To get a deeper insight, both diastereomers were isolated and investigated separately.[36] It turned out that *R*-**1** and *S*-**1** catalyse the reaction with different efficiency (12 h, 2 mol% *R*-**1** *vs.* 1 h; 1 mol% von *S*-**1**, see Scheme 9), but surprisingly



Scheme 10 Catalytic cycle of metathesis using MAP complexes with focus on the electronic influences of donor ligand D based on the calculations of Eisenstein. All steps are formally reversible.

and fortunately, both diastereomers produce *the same* main enantiomer with *the same* level of enantioinduction. A crystal structure obtained for complex *R*-**10b** denotes a hindered rotation of the alkoxy-ligand by a Mo–halogen interaction, causing a diminished activity. Assuming that one diastereomer catalyzes the reaction substantially inefficiently, a fast equilibrium between both structures could explain the observation that both complexes efficiently yield the same enantiomer. As presented in Scheme 10, a single metathetical reaction inverts the stereocenter at the Mo-center. Since a successful cycle of a metathesis consists in two transformations (formation of a substrate–catalyst complex and reaction with a second olefin), the stereocenter is regenerated after every cycle. For this reason the transformations of the employed substrates do not participate in a stereomutation at the metal. However, the observation that the ees in the early stage of the metathesis (starting with the less reactive diastereomer) are inferior gave a hint that a product of the catalytic cycle may influence an inversion of the stereocenter. Experiments have shown that in the presence of ethylene, which is generated as a by-product after every cycle, the ees are significantly improved. Based on these observations, a degenerative equilibrium between both diastereomers is suggested, which is faster than product formation, interconverting the two structures during a non-productive metathesis reaction (regeneration of the substrate and catalyst after a single transformation of ethylene, Scheme 11).

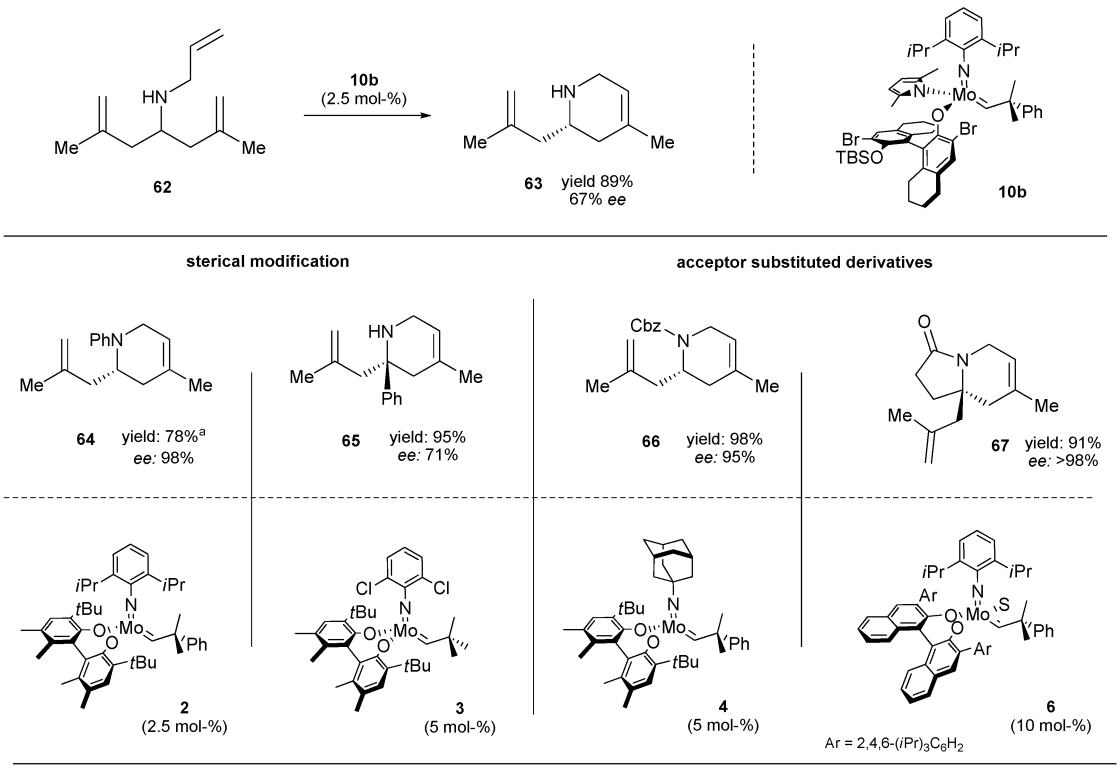
A key intermediate of this model is structure **61**, which upon cycloreversion potentially provides both diastereomers. This working model gives an explanation for the initially discussed different rates of product formation of the separated diastereomers, as the more reactive catalyst *S*-**10b** has to be generated first, as well as the observed low ees in the early stage of the transformation.



Scheme 11 In the presence of ethylene both diastereomers of catalyst **10b** are proposed to be interconvertable; both diastereomers show different kinetics in the formation of **51**.

It appears from these results that a stereoselective synthesis of the catalysts in this class is not necessary; even in the case of employing the diastereomer, which does not lead to the desired enantiomer, the same levels of enantioinduction for the same enantiomer have been observed in the presence of ethylene. But unfortunately, this is only found for selected *stereogenic-at-Mo* catalysts.

Nitrogen-containing heterocycles are found in a myriad of biologically active compounds. In this regard, metathesis opens access to enantioenriched heterocycles, which are difficult to obtain *via* alternative routes. *N*-containing compounds are difficult substrates for metathesis, since their Lewis basic character often diminishes the activity of the Lewis acidic catalysts. As depicted in Scheme 12, two main strategies have evolved for circumventing these problems, the use of sterically hindered amines as well as the transformation of acceptor-substituted

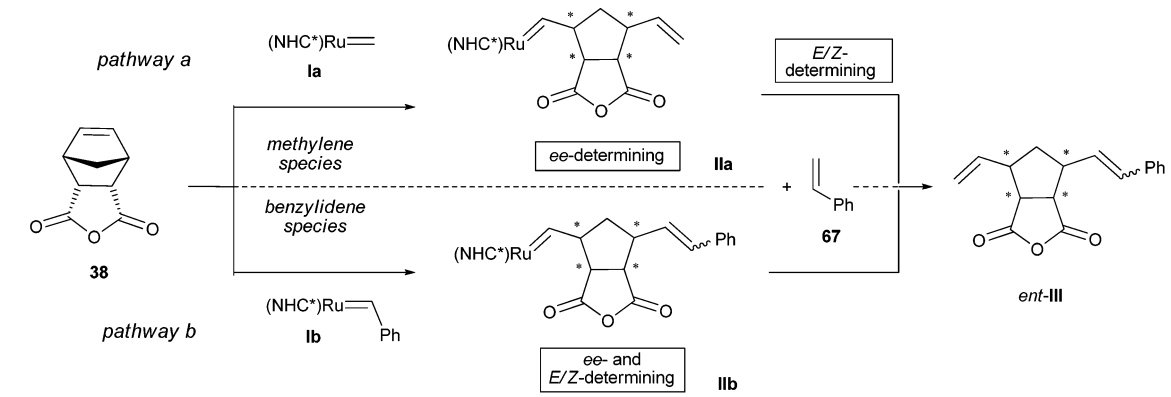


Scheme 12 Representative catalysts employed for the ARCM of representative amines; (a): reaction was performed neat.

amines (*e.g.* amides).[37–39] The first ARCM including acyclic amines obtaining small and medium sized heterocycles could already be demonstrated in 2002, employing substrates of type **64**, which are sterically protected by a phenyl group at the tertiary nitrogen.[37] Noteworthy is the ability to close seven- and eight-membered rings, even under solvent-free conditions, since oxygen containing analogues, as well as the generation of carbon cycles, have proven to be very challenging substrates. However, since *N*-phenyl groups are troublesome to cleave, alternative strategies were targeted. Product **65** bears a phenyl group in the α-position to the amine, which reduces the tendency of both, substrate and product, for coordination to the catalyst and, importantly, allows the transformation of a secondary amine. As this additional concept of enhanced sterics around the nitrogen is structurally limited and the enantioinduction moderate (71% ee), the use of different *N*-protecting groups was focused.[38] In this regard the Cbz-group in **66**, which usually can be removed with ease, proved to be suitable. **4** efficiently promoted the ARCM in 98% yield and 95% ee with a catalyst loading of 5 mol%. A variant is the intramolecular protection *via* amide formation in **67**, opening the access to enantiomerically enriched hexahydroindolizinones. As the use of protecting groups is always associated with at least two additional synthetic steps, the search for active catalysts circumventing these manipulations, transforming secondary amines, is still continuing. The development of MAPs in 2008 had a significant impact on this field. As disclosed in Scheme 12, catalyst **10b** (2.5 mol%) showed to be optimal among the known MAP systems promoting the ring closure of the *secondary* amine **62** (2.5 mol%) with 89% yield and 67% ee.[34] Even though this is a remarkable development, the moderate enantioselectivity is an issue that remains to be addressed.

3.2. AROCM–asymmetric ring-opening cross metathesis

3.2.1. Norbornene derivatives. AROCM processes can be classified as a variant of ACM (Section 3.3), since an intermolecular coupling of two olefins is performed. It can be statistically rationalized that without exercising any control, two olefins A (*meso*) and B (cross partner) can provide 8 different products: desired enantiomers of the cross products AB and their respective *E*/*Z*-isomers (4), as well as the *E*/*Z*-isomers of the homodimerisation products AA and BB (4). This fact alone clearly suggests that within this type of metathesis more factors have to be considered in detail for the selective and efficient generation of the desired product. It has to be ensured that both introduced olefins A and B are providing the desired cross product (AB) selectively, whereby homodimerisation processes (AA/BB) are reduced to a minimum. In this regard, strained olefins (A) and terminal olefins (B) are employed. If the more reactive olefin A is opened by a respective catalyst, the ring closure (back-reaction) is disfavoured thermodynamically and the homodimerisation (AA) process is reduced due to the sterically demanding nature of olefin A. This leads to a favourable reaction with the cross partner, which is usually enforced by an excess of olefin B. It merits mention that the amount of cross partner is critical for efficient transformations. There is a minimum required for selective metathesis; nevertheless, excessively high concentrations facilitate the homodimerisation process (BB). As can be rationalized, the dimerization of the cross partner is less favoured due to steric interactions

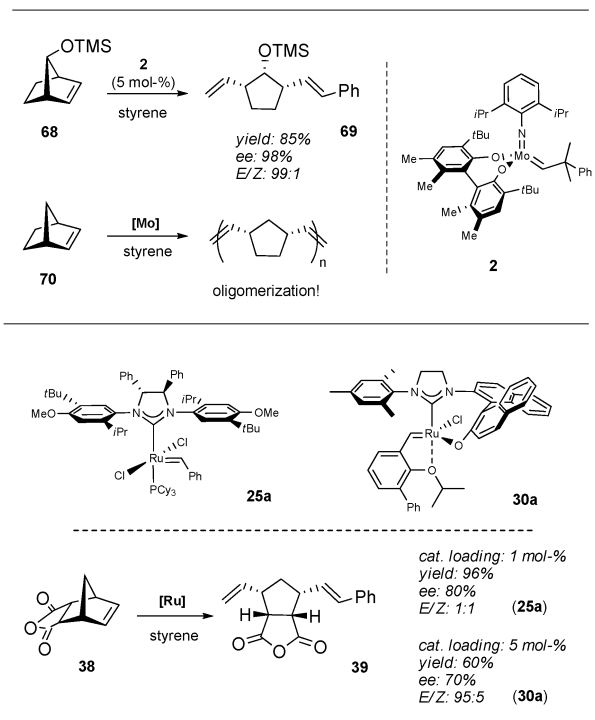


Scheme 13 Course of the AROCM including **Ia** (methylene) and **Ib** (benzylidene) as propagating species.

in the metallacyclobutane within the second metathesis transformation; the cross partner is regenerated as the main product. Due to this non-productive reaction the catalyst may be consumed, leading to the necessity of high catalyst loadings. However, as disclosed in Scheme 13 for the example of Ru-based AROCM of norbornene derivative **38** (olefin A) with styrene (olefin B), two pathways including different propagating species (**I**) are, in principle, feasible.[21]

Pathway a is initiated by a methylene species (**Ia**), which provides intermediate **IIa** after the reaction with substrate **38**. Importantly, during the formation of **IIa** the ee is determined, the subsequent cross metathesis with the cross partner defines the *E*/*Z* ratio of the respective reaction and regenerates the propagating species. As a result of this pathway, the ee values for the *E*- and *Z*-isomer of the generated products *are the same*. In a second scenario (*pathway b*), the metathesis is initiated by a benzylidene complex **Ib**, a subsequent reaction with the substrate leads to intermediate **IIb**. In this step both the ee and the *E*/*Z* selectivity are determined independently and following this route, the ee-values for *E* and *Z* may, but does not have to be same. This mechanistic fact gives a hint, if the reaction proceeded either through *pathway a*, *pathway b* or even both, unselectively. It is assumed that AROCM reactions, which proceed uncontrolled through both pathways, may provide opposite enantiomers, thus diminishing the overall enantioselectivity of the respective reactions. In this regard, a selective catalyst should initiate the reaction *via* one of the *pathways a* or *b*, whereby efficient enantiodiscrimination, as well as a selective formation of either *E*- or *Z*-isomers, needs to be accomplished. If all these factors are sufficiently controlled, this process opens access to a variety of useful carbon and heterocycles as building blocks for target oriented synthesis.

The first examples of Mo-catalyzed AROCM included *meso*-norbornene derivatives. Detailed studies with respect to structural modifications within the starting materials (A and B) were carried out.[40] It was demonstrated that a substituent at the 7-position, pointing to the olefin's *exoface* within the norbornene-scaffold, is crucial for the success of the reaction using Mo-based catalysts, circumventing oligomerisation by means of the enhanced sterics (compare **68** and **70**, Scheme 14). Biphenol-based catalysts of type **2** have turned out to be optimal within these transformations. The AROCM of 7-*O*-substituted norbornyl systems with terminal olefins as cross partner proved to be quite general; this allows a flexible access to products of type **69** with outstanding selectivities for the thermodynamically favored *E*-isomer (>98% *trans*). Although this is a remarkably efficient process, the substrate scope is limited by the necessity of a shielding substituent at the 7-position and the use of styrene as cross partner. The predominant formation of oligomers with substrates lacking a 7-substituent can be rationalized with the high reactivity of Mo-based systems, predominantly forming the products of a ROMP (ring opening metathesis polymerisation) process. This gap could be closed by ruthenium-based systems, which exhibit a balanced reactivity for norbornenes of this structural motif. In this regard, substrates of type **38** (Scheme 14) have the greatest impact in this field, since a desymmetrisation process generates



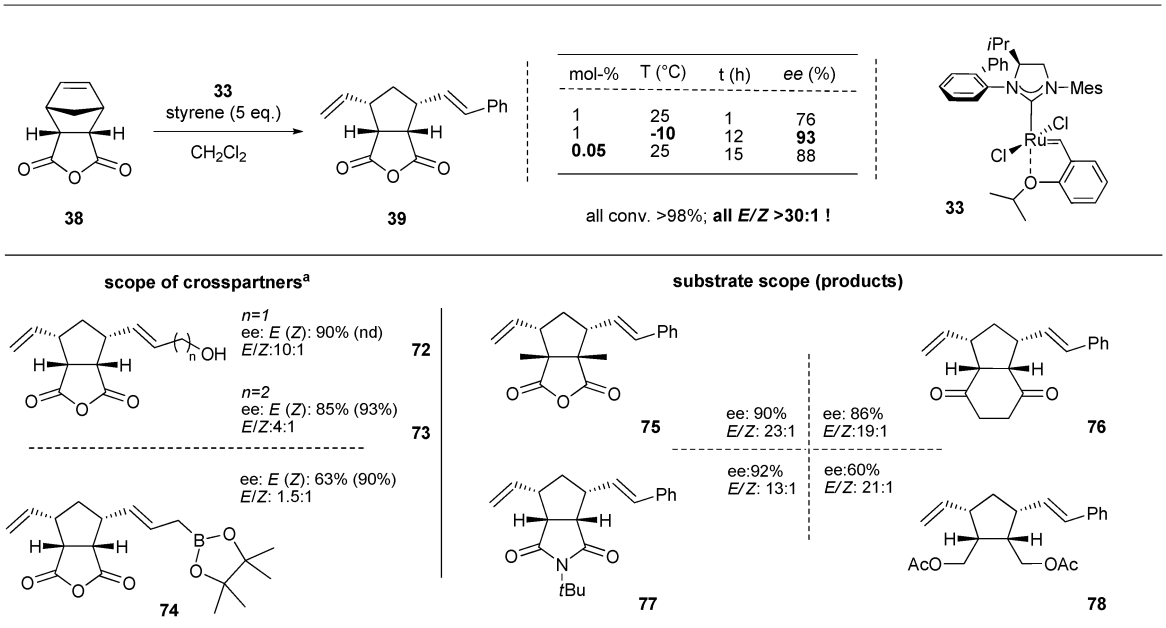
Scheme 14 Representative transformation of norbornene derivatives regarding the substrate scope of Mo and Ru-based catalysts.

four stereocenters in a single transformation. Beyond that, the synthesis of norbornene derivatives is a well developed discipline and allows very efficient access to a diverse library of substrates. For the transformation of benchmark substrate **38**, catalyst **25a** provides **39** in excellent yields of 96%, using a catalyst loading of just 1 mol%, however, the enantioinduction is moderate (80% ee) and no differentiation between *E* and *Z* isomers is observed (Scheme 14);[20] this and the fact that 10 eq. of cross partner had to be used are issues that remained to be addressed. It is worth underlining that no improvements upon adding iodides were achieved with this catalyst. However, *stereogenic-at-metal* complexes of type **30** were an important development regarding this type of reaction. As presented in Scheme 14, the chloride derivative **25a** shows excellent *E*-selectivity (*E*/*Z*: 95 : 5), whereby the enantioinduction is only moderate (70% ee). With NaI as additive, forming **25b** *in situ,* the enantioinduction was significantly improved (98% ee) providing **39** with a yield of 72%, though, the value for *E*/*Z*-selectivity was not reported for this case.[25] As discussed in Section 2.2 the stability of these chelate complexes is outstanding and the catalysts can be recycled subsequent to the reaction; transformations with this type of complexes are usually conducted employing 5 eq. of cross partner (compare **25a**, 10 eq.). However, the improvement of stability was accompanied with a loss of activity, high temperatures and high catalyst loadings are necessary for the transformations including chelates of type **30**.

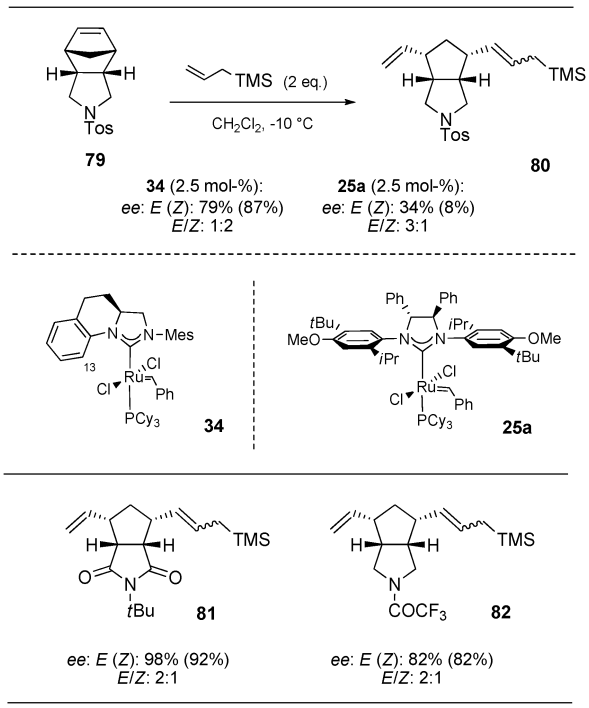
As disclosed in Scheme 15, in the presence of catalyst **33** substrate **38** could be obtained as the *E*-isomer exclusively (*E*/*Z*: >30 : 1) under a variety of reaction conditions. This catalyst class combines high stability with superior activity. Stability-tests have shown that even after 12 days in DCM at 40 °C no decomposition is observed, generally rendering low catalyst loadings; furthermore, reactions can be conducted at temperatures down to −10 °C, without losing the catalytic activity. Amazingly, the transformation of **38** can be performed with a catalyst loading of only 0.05 mol%, providing full conversion after 15 h.[30]

A catalyst loading of this magnitude has not been reported before in asymmetric metathesis chemistry of small molecules. As discussed in Section 2.2, the high stability and activity are effects of the NHC's mono-substitution and the installation of solely aromatic systems as *N*-substituents therein. Due to a gain in space, the mesityl-systems (Mes) adopt a planar arrangement; in this effect the cavity for metathesis transformations is significantly increased and a chelating etherate moiety within the carbene ligand can be installed, which enhances the stability dramatically. In this regard, the shown system allows for economical processes, marking a fundamental step towards efficient metathesis. Of great importance is the scope of cross partners, which can be employed (Scheme 15). Allyl alcohol and homoallyl alcohol were introduced successfully, leading to products **72** and **73** (Scheme 15) with high ees up to 93%.[41] It is worth underlining that these cross partners cannot be used with Mo-based catalysts. Furthermore, boronic esters were coupled effectively, opening efficient access to building blocks for palladium catalyzed cross-couplings. The employment of different cross partners is a key feature of this new catalyst class, as in the former cases styrene and its derivatives were essential for the stability of the propagating benzylidene species (*pathway b*, Scheme 13). The scope of substrates showed to be quite general referring to substitution patterns within the backbone of the norbornene derivatives. Anhydrides (*e.g.* **75**), as well as succinimide derivatives (*e.g.* **77**), were transformed efficiently, and functionalized six membered rings (**76**) and aliphatic functionalized side chains (**78**) are applicable to this reaction, broadening the horizon of the AROCM process.

Based on the concept of NHC mono-substitution, complex **34** was developed in 2011 by the same group.[31] This special architecture renders a rigid reaction pocket, which has significant impact on enantiodiscrimination. Hence, this new catalyst was investigated in AROCM metathesis showing very good results;



Scheme 15 Performance of **33** in AROCM processes, scope of cross partners and substrates; all conv. >98%; nd: not determined.

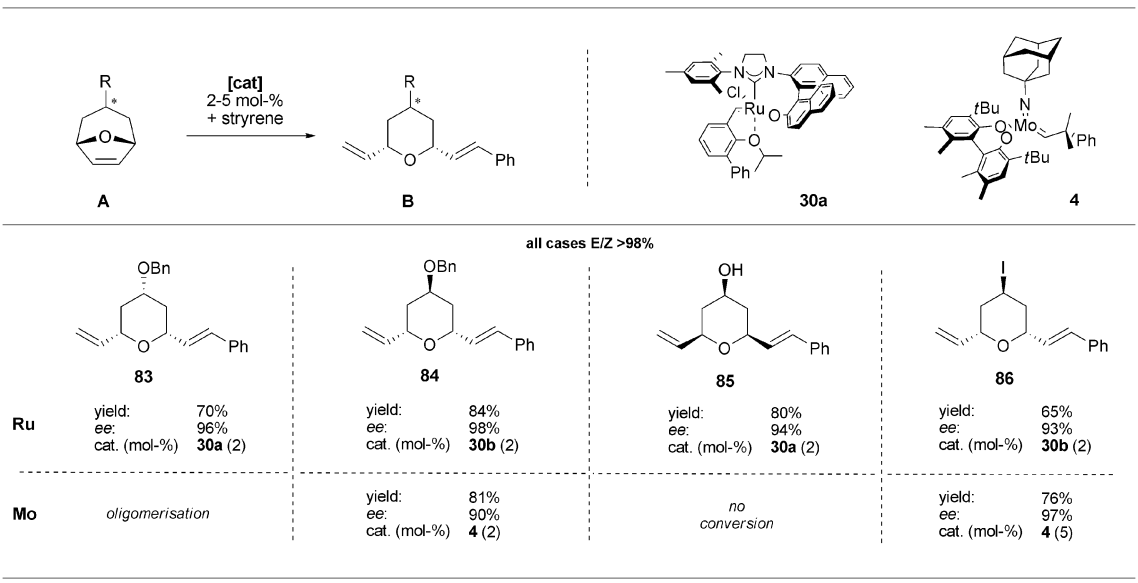


Scheme 16 AROCM of norbornene derivatives with trimethylallylsilane in the presence of **34**.

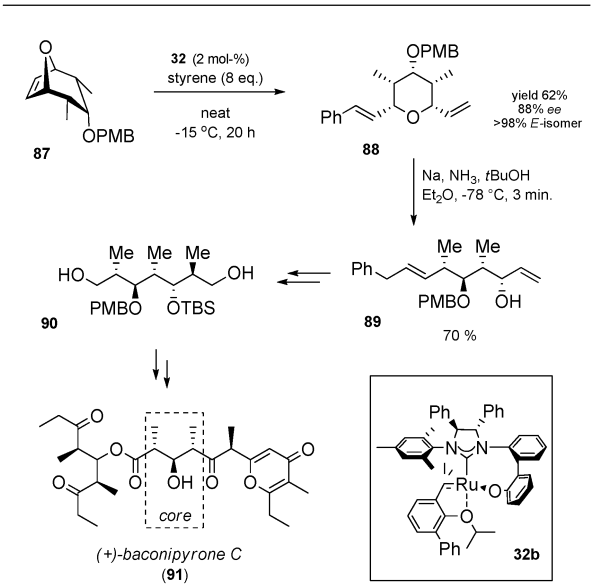
of special interest in this regard is the use of trimethylallylsilane as cross partner, which till today has not been achieved employing Mo-based catalysts. As disclosed in Scheme 16, substrate **79** was transformed efficiently into the desired product, whereby low temperatures (−10 °C), again, had a beneficial effect on the ee and *E*/*Z*-selectivity; catalyst **25a** does not provide any noteworthy enantiomeric excess. Regarding the high activity and high enantioinduction the same arguments mentioned for **33** can be applied here. It merits mention that in some cases, *e.g.* transformation of **79**, the *Z*-isomer was obtained predominantly. That this outcome is caused by catalyst control has been demonstrated by the transformation of **79** in the presence of catalyst **25a**, providing the *E*-isomer predominantly. The efficient enantioinduction of **34** in comparison to **25a** may be attributed to the hindered rotation which results in a well-defined environment within the coordination sphere of the Ru-center. The efficient enantioinduction applying rigid Ru-based catalysts could also be demonstrated for substrates **81** and **82** as disclosed in Scheme 16.

3.2.2. Oxa- and azacycles. The desymmetrisation of oxabicycles (type **A**, Scheme 16) *via* AROCM processes is a powerful tool for the construction of oxygen containing *cis*-substituted pyranes **B**. In comparison to norbornenes, these systems are less strained, what places different demands on the catalysts. Generally, biphen-based complex **4** (Scheme 17) is the only Mo-based system capable of these transformations, yielding *E*-selective AROCM products. The synthesis of oxacycles is a strong discipline of Ru, especially chelate-complex **30** (Scheme 17) shows a well-balanced reactivity for these reactions. As disclosed in Scheme 17,[42,43] *endo*-compound **83** is transformed by **30a** in good yield (70%) and high enantioselectivity (96% ee), whereby the reaction with complex **4** only generates oligomeric products. Converting the less reactive *exo*-system **84** in the presence of catalyst **4** shows good activity, but complex **30a** still provides superior results in terms of yield (81% *vs.* 84%) and ee (90% *vs.* 98% ee). Typically, Mo-based complexes are not capable of performing the transformation of substrates containing hydroxyl groups like **85**, whereby Ru–carbenes show superior results, circumventing the use of protection groups. As disclosed for substrate **86**, in some instances Mo-alkylidenes can compete with Ru-based catalysts. It is worth mentioning that reaction with **30a** or **30b** is conducted under solvent free conditions, generally reducing the waste of the process.

This method renders access to enantiomerically enriched pyrans, which are versatile building blocks for target oriented synthesis. As disclosed in Scheme 18, highly substituted intermediate **88**, formed through a AROCM process of *meso*-**87** in



Scheme 17 Synthesis of pyranes using Mo and Ru-based complexes, Ru-catalyzed reactions run in the absence of solvent (neat); Ru–Cl (a), Ru–I (b).

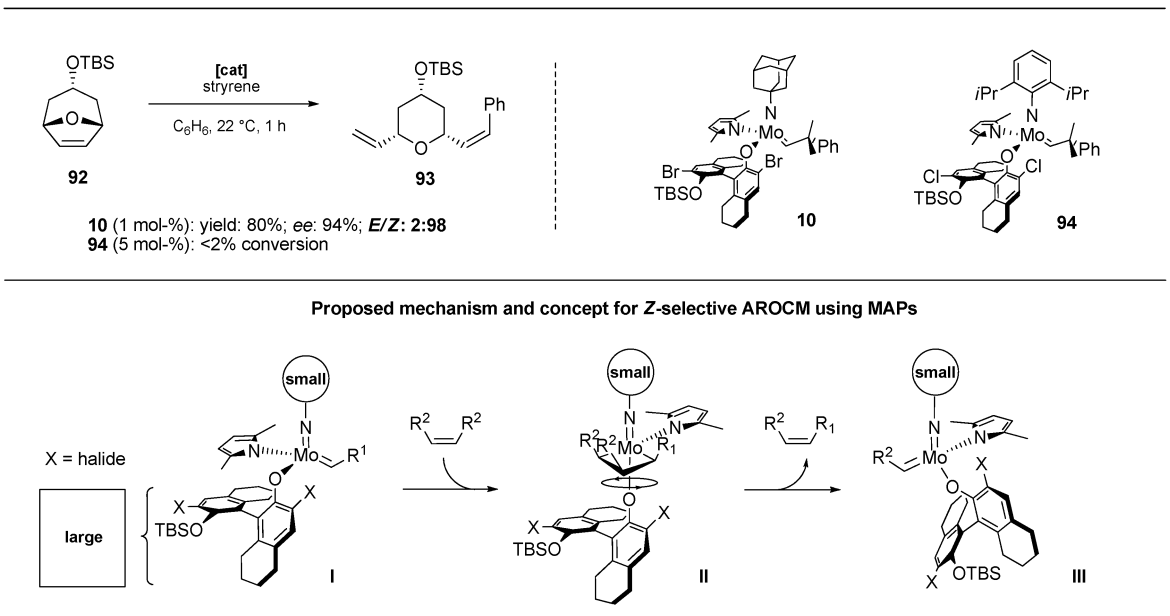


Scheme 18 Concept of the total synthesis of (+)-*baconipyrone C* (**91**).

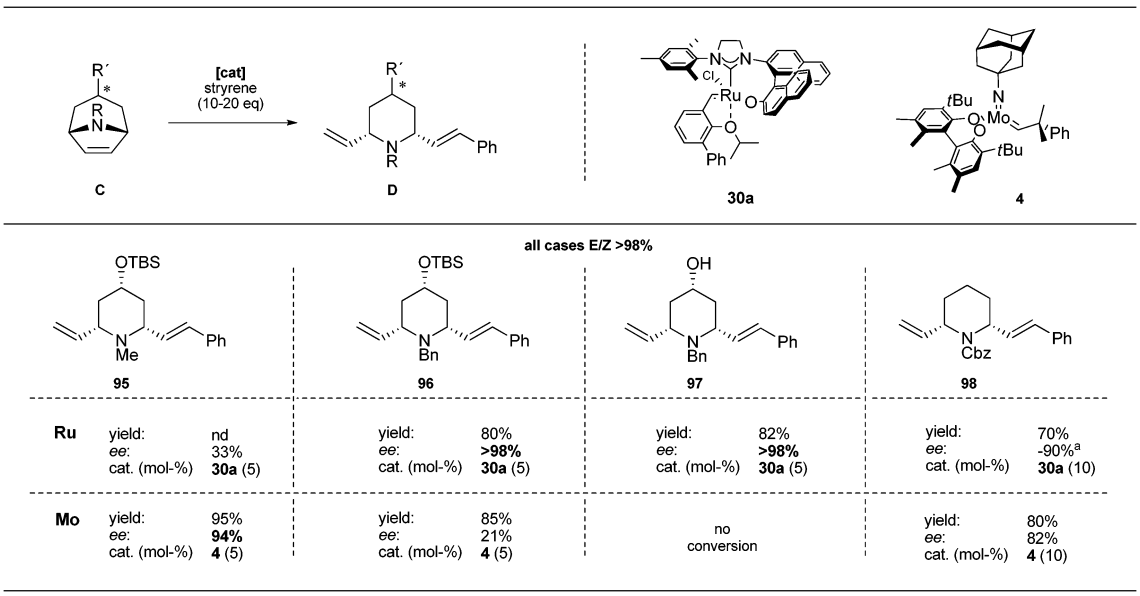
good yield (62%) and enantioinduction (88% ee), was the key intermediate in the total synthesis of (+)-*baconipyrone C* (Scheme 18).[44] This desymmetrisation step provided the stereocenters within the core fragment of the target structure **91**. The reductive ring opening of **88** led to intermediate **89**, which upon further manipulations provided the desired highly functionalized product **91**. The reductive opening of the pyrans to a chiral aliphatic system demonstrates the flexibility for further transformations of the products obtained through AROCM.

In 2009, the groups of Schrock and Hoveyda reported the utilization of MAP complexes for AROCM of oxabicycles.[45] As disclosed in Scheme 19, these transformations render products with an excellent *Z*-selectivity, which have not been described before. It is generally accepted that the formation of *Z*-olefins is caused by an all-*cis* metallacyclobutane (**II**), its formation was rationalized as depicted in Scheme 19 (**I–III**). Within this proposal, the formation of intermediate **II** upon reaction of catalyst **I** with a respective *cis*-olefin is favored by a combination of a large alkoxy-ligand with a sufficiently smaller imido-system. The free rotation of the alkoxy-ligand sets up a steric barrier on the bottom side of the MAP, forcing the residues in a *cis*-configuration, whereby the use of a small substituent leaves enough room for this arrangement at the metallacyclobutane. Cycloreversion of intermediate **II** leads to the formation of the desired product and regenerates the catalytically active species (**III**). In this regard substrate **92** (Scheme 19) was transformed using catalyst **10** with high enantioinduction (94% ee) and good yield (80%), providing the *Z*-olefin predominantly (*E*/*Z*: 2 : 98). It has been demonstrated that the introduction of an adamantyl-imido system is crucial for the success of the system, since the usually employed 2,6-diisopropylphenylimido (in complex **94**) did not lead to any conversion, even at a high catalyst loading of 5 mol%. This *Z*-selectivity is a breakthrough in the field of metathesis, this concept also proved to be applicable in different metathesis disciplines.

A simple modification in the structure of *meso*-**A** (Scheme 20), replacing oxygen by nitrogen, opens the access to 2,6-*cis*-substituted piperidines (**D**).[39,43] *N*-containing heterocycles have a significant impact on target oriented synthesis, since this structural motif is present in a vast number of biologically active products. As discussed within ARCM (Section 3.1) the transformation of amines is troublesome, since their Lewis basic character often diminishes the activity of the Lewis acidic catalysts; no transformation through an AROCM process including secondary amines has been reported until now. Chelate-complexes like **30** and **4** have proven to be active for the transformation of substrates of type **C** (Scheme 20), providing products with excellent *E*-selectivity in all mentioned cases (>98% *E*-isomer).



Scheme 19 Z-selective AROCM of oxabicycles using MAPs.

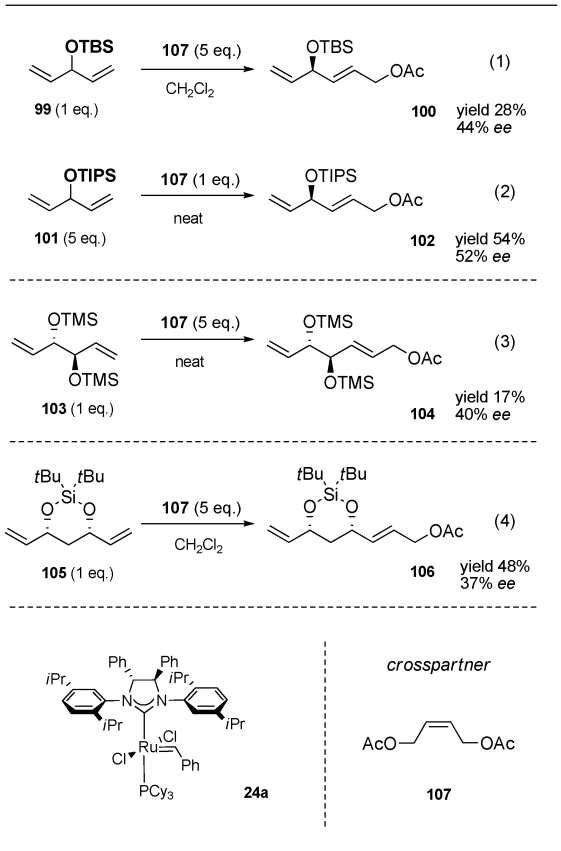


Scheme 20 Synthesis of piperidines *via* AROCM using chiral Mo and Ru-based complexes; (a) the opposite enantiomer was obtained; nd: not determined.

In this field of AROCM, Mo-based systems are more efficient compared to those of Ru. Due to the high affinity of amines to Ru, the reaction times are significantly longer. Especially in cases of less steric congestion, *e.g.* Me-substituted **95**, Ru-based catalysts cannot be used due to rapid deactivation of the catalytic species, however, in the presence of **4**, the product is obtained in high yield of 95% and high enantiomeric excess (94% ee). Interestingly, the situation turns in cases including Bn-substituted amines (*e.g.* **96**), Ru complex **30a** outperforms **4**, showing excellent enantioinduction providing >98% ee with a yield of 80%. Following the same trend compared to the synthesis of pyrans, substrates containing a free hydroxyl-group (**97**) are still reserved to a Ru-based system. In this regard, neither the yield nor the excellent enantioinduction is diminished conducting the reaction without a protecting group at the hydroxyl-moiety (*e.g.* **97**, >98% ee, yield 82%; compare **96**, >98% ee, yield 80%). The conversion of amides proceeds with comparable results for both systems, as disclosed for product **98**. The synthesis of piperidines through AROCM processes is still in its infancy. With respect to the use of 10–20 equivalents of cross partner and usually 5 mol% of catalyst, there is still room for improvements. What still remains to be addressed is the development of a catalyst, providing the product with favour for the *Z*-olefin.

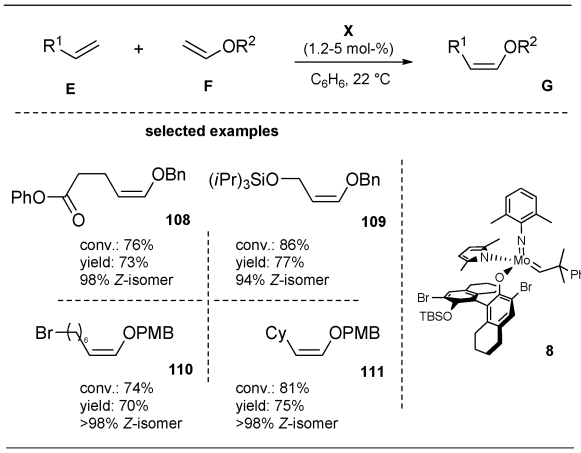
3.3. (A)CM—(asymmetric) cross metathesis

3.3.1. ACM–asymmetric cross metathesis. In contrast to catalytic ARCM and AROCM reactions, catalytic ACM processes are the most difficult and, compared to the other types, relatively underdeveloped; the search for efficient catalysts for ACM is an ongoing challenge. An ideal catalyst would differentiate efficiently between the two employed olefins, leading to a well-defined propagating species. This species in turn has to react with the cross partner selectively, providing excellent enantioface-selection, whereby homodimerisation processes are suppressed and the resulting products are not attacked for further transformations. Another important point is the control of the *E*/*Z*-selectivity within the desired product. Developments in the research field of ACM would have an enormous impact on the area of target oriented synthesis; it is one of the last great challenges, which have to be faced in metathesis chemistry. Besides the catalyst's control, a sophisticated set of substrates and conditions has a key role in ACM, as discussed for AROCM, as well. The general feasibility of ACM processes was proved by the group of Grubbs in 2006.[21] In this work acyclic *meso*-dienes are employed in a desymmetrisation process in the presence of *cis*-substituted cross partner **107** (Scheme 21). Some important facts within these substrate systems merit mention. For steric reasons *Z*-olefins (**107**) are more reactive than their *E*-analogues; employed in excess the propagating species can be controlled sufficiently. Only terminal olefins can be introduced for transformations including **24a**. Furthermore, the diene compounds tested in this study are incapable of undergoing RCM due to ring strains within the corresponding products. Large protecting groups seem to be beneficial for ee and yield (compare eqn (1) and (2), Scheme 21); it has to be underlined that in the transformation in eqn (2) olefin **101** was employed in excess. *Meso*-substrates based on 1,2- and 1,3-diols were reacted showing promising results (see eqn (3) (**103**) and eqn (4) (**105**), Scheme 21). No *E*/*Z* ratios for the disclosed reactions have been reported. However, based on the isolation of *bis*-cross-product (15%) for the reaction of **99**, the moderate yields, generally obtained for the disclosed ACM (17–54%), were explained by further metathesis processes. Since the structures of starting material and product are very similar, it is difficult to suppress further conversion of the product. Even though, the *state of the art* is still far away from a general use in synthesis, this pioneering work points in a positive direction. No doubt that these results are very valuable for the design of new catalysts, which have to be developed to overcome these difficulties.



Scheme 21 Structural studies on the feasibility of ACM processes by Grubbs; (a) conditions: 5 mol% catalyst **24a**, 40 °C, 6 h. *E*/*Z* values are not reported.

3.3.2. *Z*-selective CM metathesis. In most of the known metathesis reactions high selectivities are achieved by employing substrates with specific substitution patterns and well-designed steric demands. If the sterics are not sufficient enough for an efficient control of the reaction, an electronic differentiation may be a potential solution. For example the use of enolether substrates presents an attractive option in this regard, as the homodimerisation process for electron-rich systems is strongly disfavored. Following this concept, the groups of Hoveyda and Schrock reported a *Z*-selective CM of enolethers with different backbone substituted terminal olefins employing chiral MAP systems of type **10** (Fig. 1).[46] It is worth underlining that Ru-based catalysts are not capable of converting enolethers in cross metathesis transformations; in fact adding an enolether to a solution containing Ru-based metathesis catalysts is a convenient method of stopping the reaction by forming a stable metathetically inactive Fischer carbene complex. It should be noted at this point that selected substrates containing enolethers are capable of undergoing RCM (ring closing metathesis) employing achiral Ru–carbene complexes, but examples remain rare.[47] However, Scheme 22 highlights several important results for Mo-based systems. As can be seen therein, a synthetically useful scope of substrates can be introduced, whereby in these cases catalyst **8** has proven to be superior. Besides unfunctionalised hydrocarbons (**111**), the feasibility of employing unsaturated esters (**108**), halides (**110**) and silylethers (**109**) has been shown, obtaining good results

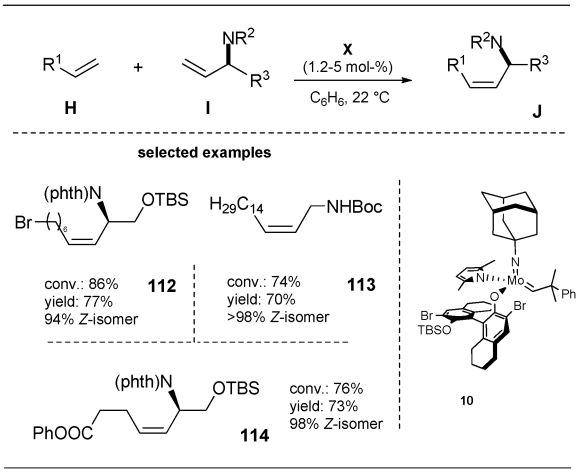


Scheme 22 CM in the presence of MAP **8** employing enolethers.

and high *Z*-selectivities. Generally low catalyst loadings are required (1.2–5 mol%), which is attributed to the stability of the alkylidene derived from an enolether. The formation of this stable intermediate as propagating species is enforced by an excess of **F** (10 eq.), as it has been described for the other ACM variants (*vide supra*). A more efficient process is rendered conducting the reactions under reduced pressure (1 Torr), allowing for the employment of a 1 : 1 mixture of the respective cross partners. This is presumed to reduce the concentration of ethylene in the reaction solution, which develops during the process, and in this context minimizing the amount of unstable Mo-methylidene to be formed.

The substrate scope was extended to amides, which are generally compatible with metathesis catalysts (see Sections 3.1 and 3.2). The control of the propagating species was achieved by the use of steric demanding amines, disfavoring homodimerisation processes by steric means. This CM was successfully conducted even under weaker vacuum of 7 Torr (compared to the previously mentioned system), which broadens the substrate scope referring to volatile cross partners. Until now, no transformations of free amines have been reported, however, the strategy of acceptor substituted systems showed to work well for the disclosed examples (Scheme 23). Phthalimide- and Boc-groups, commonly used protecting groups for amines, can be reliably cleaved with ease in most cases. It merits mention that the conversions reported for the latter examples (enolethers and amides) do not correlate with the maximum TON of the catalysts, in fact the reactions were stopped at an advantageous balance between stereoselectivity and efficiency regarding *Z*-selectivity, yield, the amount of homodimerisation and further metathesis processes of the highly reactive *Z*-olefins. These results mark an important step towards the control of the propagating species in CM. It has been shown that sufficient control regarding the propagating species can be obtained by electronic (enolether) and steric variations (including amides) using chiral MAP complexes. It will be interesting to see, if these concepts can be applied even in ACM processes.

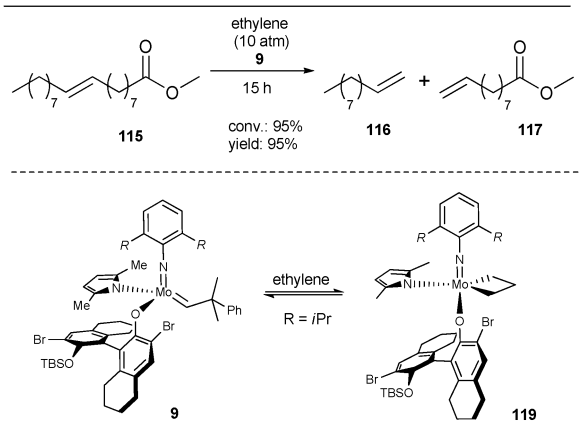
Recently, the development of Ru-based catalysts for Z-selective CM reactions has made significant progress (for further reading see ref. 48). Since the employed catalysts are achiral, they will not be discussed within this article.



Scheme 23 CM in the presence of MAP **8** employing amides.

3.3.3. Ethenolysis reaction. In 2009, Hoveyda and co-workers demonstrated the use of MAP-systems for ethenolysis, another field, in which one would not presume the use of chiral metathesis catalysts.[49,50] Here again, it is not the chirality which leads to the superior performance, rather the well balanced electronics and sterics are the reason for the success in this specific area of metathesis. The fact that some methylidene-MAP species have shown to be unusually stable in the presence of ethylene makes these systems promising candidates for reactions in the presence of the latter and has led to detailed investigations.

In an intensive screening of catalysts for the transformation of methyl oleate (**115**, Scheme 24), complex **9** turned out to be superior, cleaving the substrate at a pressure of 10 bar of ethylene at room temperature showing outstanding selectivity (>99%) so that the products could be obtained in a yield of 95% (conv. 95%). In this case a TON of 4750 for catalyst **9** was reported, demonstrating the efficiency of this catalyst. For intermediate **119** a crystal structure of the unsubstituted metallacyclobutane could be obtained at −30 °C, which indicates the outstanding stability of this intermediate; the origin of this exceptional behavior is not known, so far. However, chemical modifications of methyl oleate (**115**) are of particular interest, since it is a resource obtained from biomass.



Scheme 24 Ethenolysis of methyl oleate using MAPs.

4. Conclusion

During the last decade catalytic enantioselective olefin metathesis emerged as a valuable tool in asymmetric synthesis. The protocols disclosed in this *tutorial review* provide access to numerous carbon- and heterocycles, which in many cases are difficult to obtain *via* alternative routes and proved to be valuable key intermediates in natural product syntheses.

In the beginning, the crucial concepts and principles behind the development of metathetically active catalysts were elucidated. A vast number of chiral catalysts have been developed so far and their activity in various metathesis disciplines were evaluated; in this regard Mo and Ru have arisen as the privileged metals. A highlight among recent achievements in the area of Mo-based complexes is the development of MAP complexes, which exhibit a breakthrough in modern catalyst design and enter a growing field of applications, even beyond enantioselective synthesis (*e.g.* CM and ethenolysis, Section 3.3.2 and 3.3.3, respectively). Besides their high activity and high enantioinduction, the pronounced *Z*-selectivity marks an important solution for a long standing problem in this specific field of chemistry. Also in the area of Ru-based systems fundamental progress could be achieved. In this regard, the performance and stability of the catalytically active species were significantly improved and render transformations with catalyst loadings of 0.05 mol%, which is a remarkable step towards more effective and cost-efficient transformations. A ground-breaking achievement is the employment of cross partners beyond styrene derivatives. Referring to this, allyl-silanes and ally-alcohols were transformed with high efficiency, extending the scope for subsequent manipulations of the obtained products.

Besides all these striking results, there are still issues, which remain to be addressed to realise the full potential of this synthetic tool. The high catalyst loadings, generally applied for homogeneous metathesis transformations, are still a common drawback with respect to a wider utilization, especially on an industrial scale. It is a desirable goal to develop more functional-group tolerant systems with respect to substrates containing Lewis basic heteroatoms within their scaffold (*e.g.* amines). In addition to this, in most of the transformations starting materials with specific substitution patterns are required. The distinct substrate-to-catalyst dependency calls for more universal catalysts to prevent intensive catalyst screenings. Furthermore, most examples of asymmetric olefin metathesis deal with RCM, ROCM processes, several other important types of catalytic metathesis reactions remain underdeveloped. Among them, ACM and enyne metathesis are of particular interest, especially in the field of ACM efficient protocols would be highly desirable.

New innovations in this field will be based on the development of new catalysts and catalyst concepts with the aim of reaching higher activities and improved selectivities for target oriented synthesis. No doubt that enantioselective olefin metathesis will remain as an exciting and challenging research field for the next decade.

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