Catalytic Asymmetric Olefin Metathesis

Amir H. Hoveyda*[a] and Richard R. Schrock*[b]

Abstract: This paper provides a survey of the first examples of efficient catalytic enantioselective olefin metathesis reactions. Mo-catalyzed asymmetric ring-closing (ARCM) and ring-opening (AROM) reactions allow access to myriad optically enriched compounds that are otherwise difficult to access.

Keywords: asymmetric catalysis · catalytic desymmetrization · enantioselectivity · kinetic resolution · metathesis · modular catalyst structures

Introduction

Rarely has a class of transformations so palpably influenced the field of organic synthesis as catalytic olefin metathesis has in the past decade.[1] In the context of the development of new methods in synthesis or as part of a complex-molecule total synthesis, Ru- and Mo-catalyzed olefin metathesis is now used routinely to prepare a wide range of compounds, including small, medium, and large rings.[2] In the first half of the nineties, an alkene metathesis step was viewed as a daring application of a relatively unknown technology in a multi-step sequence. In the past few years, on the other hand, metathesis-based approaches have been employed with such increasing frequency that they are now considered relatively routine.

With regard to the synthesis of optically pure materials, however, olefin metathesis has largely served an auxiliary role. In cases in which ring-closing metathesis (RCM) is called for,[2a–c,e,f,h] a diene substrate that is already optically pure is treated with an achiral metal catalyst to deliver a nonracemic cyclic unsaturated product. Alternatively, a racemic product obtained by metathesis may be catalytically resolved.[2b] Optically enriched cyclic alkenes are similarly employed in instances where ring-opening metathesis (ROM) is called for.[2d, g] Although such strategies have led to a number of notable and impressive accomplishments in asymmetric synthesis, some of the unique attributes of catalytic olefin metathesis can only be realized if chiral optically pure catalysts for olefin metathesis are made available. This claim is tied directly to the fact that one of the most useful characteristics of metathetic processes is their ability to promote efficient skeletal rearrangements: simple achiral or racemic substrates may be transformed into complex nonracemic organic molecules in a single stroke with an effective chiral metathesis catalyst. In numerous instances, products that are rendered readily available by a chiral metathesis catalyst would only be accessible, and often less selectively, by a longer route if alternative synthetic methods were to be used.

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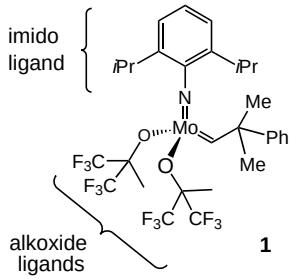
Discussion

The catalyst construct: From the outset, we judged that the makeup of Mo-based complexes, represented by **1**,[3] offers the most attractive opportunity for the design, synthesis, and



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development of effective chiral metathesis catalysts. This predilection was based on several factors: 1) Mo-based catalysts such as **1** possess a modular structure[4] involving imido and alkoxide moieties that do not disassociate from the metal center in the course of the catalytic cycle. Any structural alteration of these ligands may thus lead to a notable effect on the reaction outcome and could be employed to control both selectivity and reactivity. 2) Alkoxide moieties offer an excellent opportunity for incorporation of chirality within the catalyst structure through installment of nonracemic

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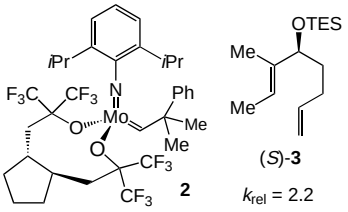
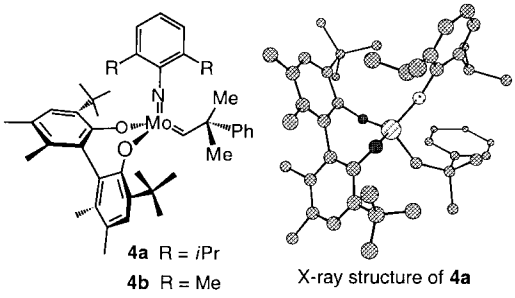
tethered chiral bis-hydroxy ligands. 3) Mo-based complexes provide appreciable levels of activity and may be utilized to prepare highly substituted alkenes.

With the above considerations in mind, in the past three years, we have prepared and examined myriad chiral Mo-based catalysts for both asymmetric RCM (ARCM) and ROM (AROM) transformations. In this article, we highlight several efficient and enantioselective reactions that are catalyzed by these chiral complexes.[5] The structural modularity inherent in the Mo-based systems allows screening of catalyst pools, so that optimal reactivity and selectivity levels are identified expeditiously.

Mo-catalyzed kinetic resolution with hexafluoro–Mo catalysts:[6] The preparation and catalytic activity of chiral complex **2**, based on the original Mo-alkylidene **1**, has been reported by Grubbs and Fujimura.[7] These workers report on the kinetic resolution of various dienes.[8] As the case regarding the resolution of **3** indicates, however, levels of enantiodifferentiation were typically low ($k_{rel} < 3$).

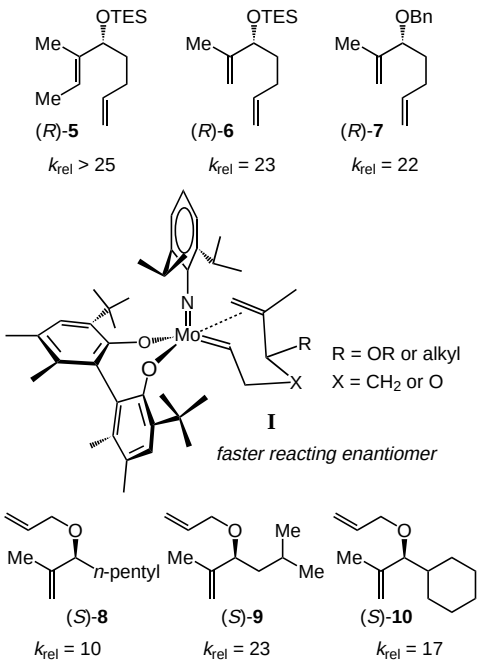


Chiral biphen–Mo catalysts: To examine the possibility of a more efficient catalytic olefin metathesis, we first prepared chiral Mo-based catalysts, **4a** and **4b**.[9] This approach was not without precedence: related chiral Mo complexes were



initially synthesized in 1993 and were used to promote polymer synthesis.[5] We judged that these biphen-based complexes would be able to initiate olefin metathesis with high levels of asymmetric induction owing to their rigidity and steric attributes. Chiral complexes **4a** and **4b** are orange solids, stable indefinitely when kept under inert atmosphere.

Catalytic kinetic resolution through ARCM: The catalytic kinetic resolution of various dienes through ARCM can be carried out in an efficient manner at 22 °C in the presence of 5 mol % of **4a**.[9] As the data in Scheme 1 illustrate, 1,6-dienes **5**–**7** are resolved with excellent levels of enantiocontrol



Scheme 1. Mo-catalyzed kinetic resolution of 1,6-dienes through ARCM.

($k_{rel} > 20$).[10] Chiral complex **4a** readily promotes the resolution of allylic ethers **8**–**10** as well.[11]

The higher levels of enantioselectivity attained through the use of **4a** (vs **2**) is likely due to a strong preference for ARCM reactions to proceed through intermediates such as **I** (Scheme 1). The intermediacy (higher reactivity) of the *anti*-Mo–alkylidene (alkylidene C–C *anti* to Mo=N) is based on previous mechanistic studies.[12] The stereochemistry of olefin–transition-metal association is based on the position of the LUMO of the chiral complex.[13, 12b] The 1,1-disubstituted olefin interacts with Mo away from the protruding *t*Bu group of the diolate and *i*Pr groups of the imido ligands (see X-ray of **4a**).

Catalyst modularity and optimization of ARCM efficiency and selectivity: In spite of the high asymmetric induction observed in the Mo-catalyzed ARCM of 1,6-dienes, when complexes **4a** and **4b** are used in reactions involving 1,7-dienes, inferior asymmetric induction is obtained. For example, as illustrated in Scheme 2, dienes **12** and **13** are not resolved with useful selectivity ($k_{rel} < 5$) when **4a** is employed as the catalyst. To address this shortcoming, we took advantage of the modular character of the Mo complexes and prepared a range of other chiral complexes as potentially effective catalysts. Accordingly, as depicted in Scheme 2, we discovered that binol-based catalyst **11a** promotes the RCM of dienes **12** and **13** with outstanding levels of selectivity ($k_{rel} = 24$ and > 25, respectively).[14] Binol-based complex **11b**, bearing the (dimethyl)phenylimido ligand (vs [di(isopropyl)]-phenylimido of **11a**), is not an efficient catalyst for the kinetic resolution of the dienes **12** and **13**. These observations underline the importance of catalyst modularity and substrate specficity in asymmetric catalysis.

The data in Scheme 3 illustrate that a wide range of 1,7-dienes can be resolved with excellent levels of selectivity and

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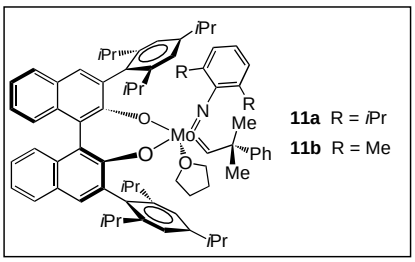
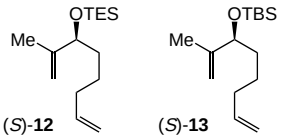
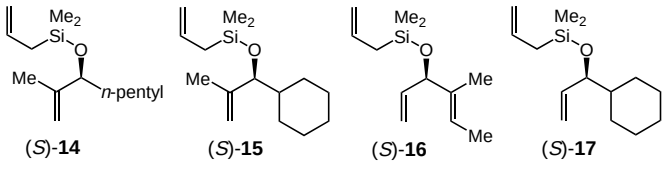




	(S)-12	(S)-13
with **4a**	k_{rel} = <5	k_{rel} = <5
with **11a**	**k_{rel} = 24**	**k_{rel} = >25**
with **11b**	k_{rel} = <5	k_{rel} = <5

Scheme 2. Mo-catalyzed kinetic resolution of 1,7-dienes and the importance of subtle structural modification of the chiral catalysts.



	(S)-14	(S)-15	(S)-16	(S)-17
with **4a**	k_{rel} = <5	k_{rel} = <5	**k_{rel} = 21**	**k_{rel} = >25**
with **4b**	k_{rel} = 10	k_{rel} = 14	k_{rel} = <5	k_{rel} = <5
with **11a**	**k_{rel} = >25**	**k_{rel} = >25**	k_{rel} = <5	k_{rel} = <5

Scheme 3. Small changes within the substrate structure can alter the identity of the optimum chiral metathesis catalyst.

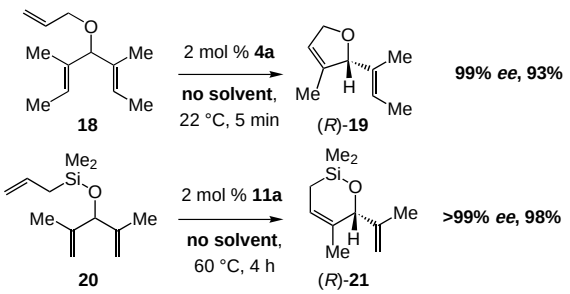
efficiency. These findings provide further evidence regarding the importance of the availability of a diverse set of chiral catalysts: Although binol-based complexes (e.g., **11a**) typically promote ARCM of 1,7-dienes with higher selectivity than the biphen-based catalysts (e.g., **4a**), such a generalization is not always true. As expected, **11a** catalyzes the kinetic resolution of 1,7-dienes **14** and **15** with $k_{rel} > 25$. Unlike biphen complex **4a**, however, the closely related catalyst **4b** also provides appreciable enantioselection, albeit less effectively than **11a**. With substrates **16** and **17**, in which two terminal alkenes are involved, the situation is completely reversed: now, it is the biphen-based complex **4a** that is the only efficient catalyst. Although each catalyst is not optimal in every instance, efficient kinetic resolution of a wide range of chiral, oxygenated 1,6- and 1,7-dienes can be achieved by various chiral Mo complexes.

Catalytic asymmetric synthesis through ARCM: Undoubtedly, the arena in which catalytic asymmetric olefin metathesis can have the largest impact on organic synthesis is the desymmetrization of readily accessible achiral molecules. Two examples are illustrated in Scheme 4. Treatment of achiral triene **18** with 5 mol% of **4a** leads to the formation of (*R*)-**19** in 99% *ee* and 93% yield.[10] The reaction is complete within five minutes at 22 °C and, importantly, does not require a solvent. Another example is illustrated in Scheme 4 as well; here, binol complex **11a** is used to promote the formation of optically pure (*R*)-**21** from siloxy triene **20** in nearly quantitative yield. Once again, no solvents are needed.[15] Readily accessible substrates are rapidly transformed to nonracemic, optically enriched molecules that are otherwise significantly more difficult to access without generating solvent waste.

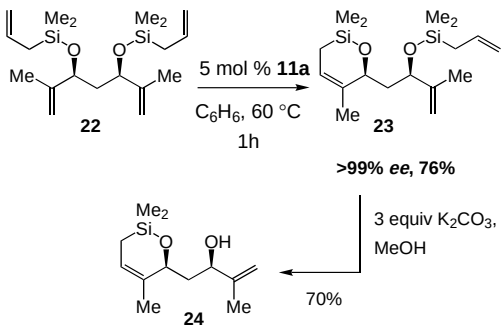
In connection with reactions for which a solvent is required, it must be noted that all transformations promoted by chiral Mo catalysts may be carried out in toluene (in addition to benzene) or various alkanes (e.g., *n*-pentane) with equal efficiency (see below for specific examples). Moreover, although 5 mol% catalyst is typically used in our studies, 1–2 mol% loading often delivers equally efficient and selective transformations.

As the above studies predicate, reaction of **18** is significantly less efficient with **11a** (<5% conversion in 18 h) and that of **20** proceeds only to 50% conversion in 24 h in the presence of **4a** (65% *ee*). Remarkably, in the latter transformation, even in a 0.1 M solution, the major product is the "dimer" formed through homometathesis of the terminal alkenes. The absence of dimer generation when **11a** is used as the catalyst, particularly in the absence of any solvent, bears testimony to the high degree of catalyst–substrate specificity in these catalytic C–C bond-forming reactions.

The catalytic desymmetrization shown in Scheme 5 involves a *meso*-tetraene substrate: optically pure unsaturated siloxane **23** is obtained in >99% *ee* and 76% yield.[15] The unreacted siloxy ether moiety is removed to deliver optically pure **24**. Mo–alkylidenes derived from both enantiotopic



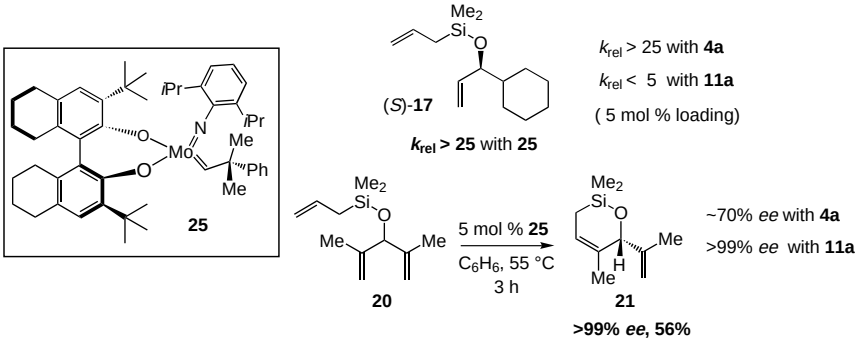
Scheme 4. Mo-catalyzed ARCM of achiral trienes can be effected efficiently, enantioselectively, and in the absence of solvent.



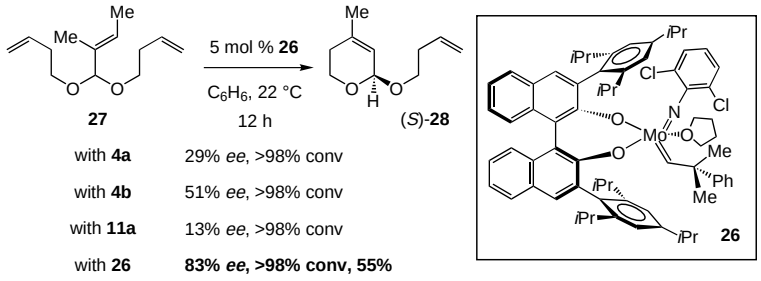
Scheme 5. Mo-catalyzed desymmetrization of *meso*-tetraenes proceeds to afford optically pure heterocycles.

terminal alkenes in **22** are likely formed. Since the initial metal–alkylidene generation is rapidly reversible, however, the major product arises from the rapid RCM of the "matched" segment of the tetraene. If any of the "mismatched" RCM takes place, a subsequent and more facile-matched RCM leads to the formation of *meso*-bicyclized product. Such a byproduct is absent from the unpurified mixture containing **23**, indicating the exceptionally high degree of stereodifferentiation induced by the chiral Mo complex in this transformation. As before, catalyst **4a** is not effective in promoting ARCM of **22**.

Additional examples, in which modification of the chiral alkoxide ligand leads to substantial improvement of selectivity, are found in connection with the chemistry of chiral catalyst **25** (Scheme 6). Complex **25**[16] shares structural features with both the biphen- (**4**) and binol-based (**11**) systems and represents an intriguing possibility regarding the



Scheme 6. Chiral complex **25** represents a hybrid between biphen- and binol-based catalysts and provides a unique selectivity profile that is often not seen with these two classes individually.



Scheme 7. Chiral complex **26**, bearing a 2,6-dichloro imido ligand is the catalyst of choice for asymmetric synthesis of acetals.

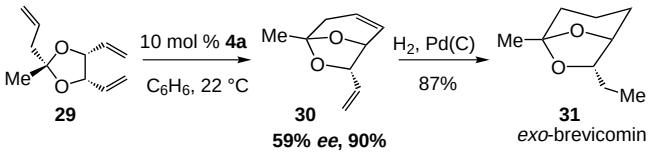
range of starting materials for which it may be a suitable catalyst. Two examples are depicted in Scheme 6: catalyst **25** delivers compounds of high optical purity where either biphen- or binol-based complexes are ineffective. It is not in all instances that **25** operates as well as **4a** and **11a**. As an example, in the presence of 5 mol% of **25**, triene **18** (Scheme 4) is converted to furan **19** in 77% *ee* and 73% yield (vs 99% *ee* and 93% yield with **4a**).

Incorporation of electron-withdrawing groups within either the imido or diolate segments of Mo complexes might result in higher levels of catalytic activity, since the Lewis acidity of the transition metal center is enhanced. As the representative examples in Scheme 7 depicts, such structural modifications can have a profound effect on the levels of enantioselectivity as well. In the desymmetrization of acetal **27**, dichlorophenylimido complex **26** provides substantially higher levels of asymmetric induction than biphen- or binol-based catalysts that carry 2,6-dialkylphenylimido moieties (e.g., **11a**).[16] Acetals of the type represented by **28** in Scheme 7 retain their stereochemical integrity through various routine operations, such as silica gel chromatography, and can be readily functionalized to deliver a range of chiral nonracemic heterocyclic compounds.[14]

The emerging Mo-catalyzed ARCM technology summarized above has been utilized in a brief and enantioselective total synthesis of *exo*-brevicomin (**31**) by Burke. The key step, as illustrated in Scheme 8, is the desymmetrization of achiral triene **29**.[17]

Catalytic asymmetric synthesis through tandem AROM/RCM: The appreciable levels of asymmetric induction observed in the catalytic ARCM reactions mentioned above suggest a high degree of enantiodifferentiation in the association of olefinic substrates and chiral complexes. Such stereochemical induction may also be exploited in asymmetric ring-opening metathesis (AROM). Catalytic ROM transformations[18]—although less exploited than the related RCM processes—offer unique and powerful methods for the preparation of complex molecules in a single step.[2d, g] The chiral Mo–alkylidenes that are products of AROM reactions can then be trapped either intramolecularly (RCM) or intermolecularly (cross-metathesis, CM) to afford a range of optically enriched adducts.

Transformations shown in Schemes 9–11 constitute the first examples of catalytic AROM reactions ever reported.



Scheme 8. Application of Mo-catalyzed ARCM to the synthesis of brevicomin.

meso-Triene **32** is converted to chiral heterocyclic triene **33** in 92% *ee* and 68% yield in the presence of 5 mol% of **4a** (Scheme 9).[19] Presumably, stereoselective approach of the more reactive cyclobutenyl alkene in the manner shown in Scheme 9 (**II**) leads to the enantioselective formation of Mo–alkylidene **III**, which in turns reacts with an adjacent terminal

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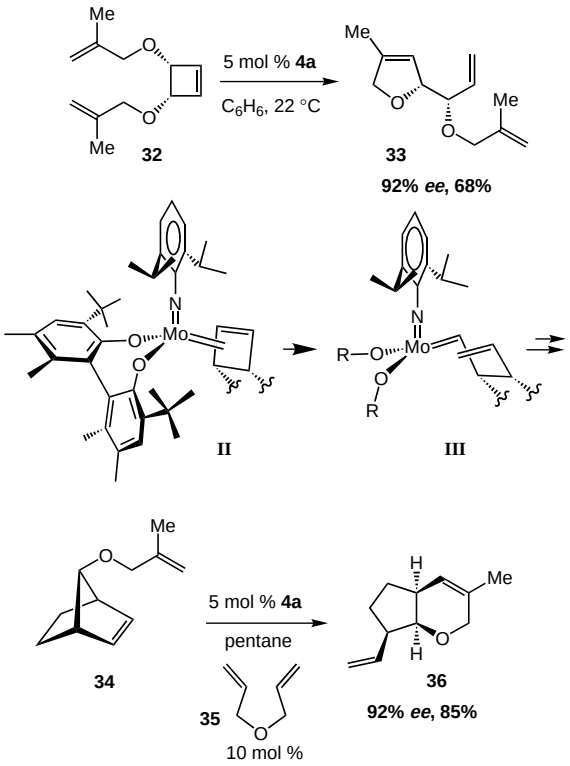
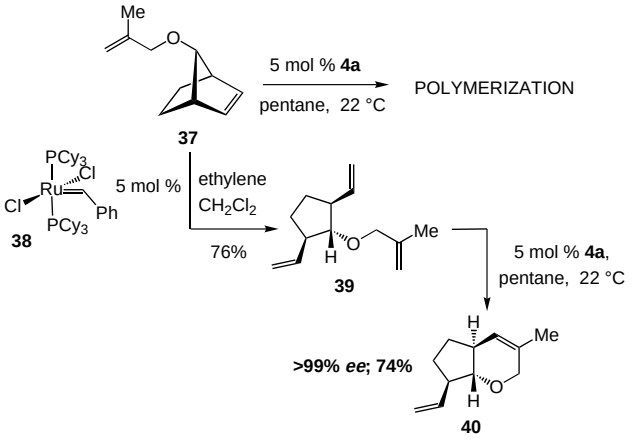


Scheme 9. Mo-catalyzed tandem AROM/RCM allows access to complex heterocyclic structures efficiently and in optically enriched form.

olefin to deliver **33**. Another example in Scheme 9 involves the net rearrangement of *meso*-bicycle **34** to bicyclic structure **36** in 92% *ee* and 85% yield. The reaction is promoted by 5 mol% of **4a** and requires the presence of diallyl ether **35**.[20] Mechanistic studies suggest that initial reaction of **35** with **4a** leads to the formation of the substantially more reactive chiral Mo=CH_2 complex (vs neophylidene **4a**), which then can react with the sterically hindered norbornyl alkene to initiate the catalytic cycle.

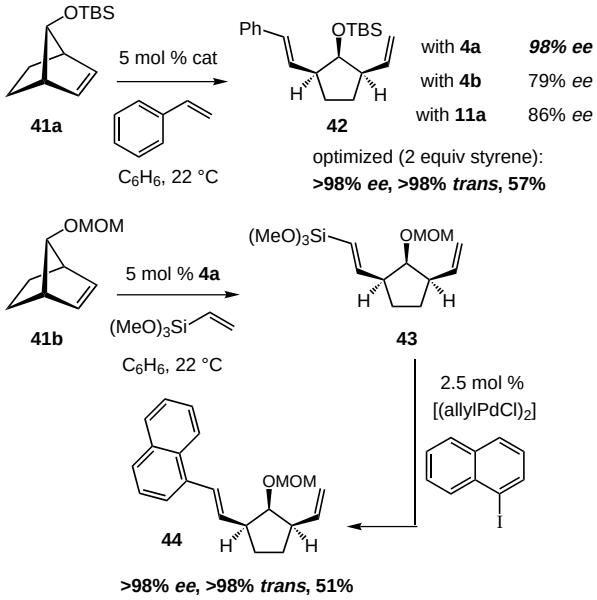
In contrast to **34** (Scheme 9), diastereomer **37** (Scheme 10), because of its more exposed and highly reactive strained olefin, undergoes rapid polymerization in the presence of **4a**. The less reactive Ru complex **38**[21] can, however, be used



Scheme 10. Grubb's Ru complex **38** (ROM) is used in conjunction with chiral catalyst **4a** (ARCM) to obtain **40** in the optically pure form.

under an atmosphere of ethylene to effect a tandem ROM/CM to generate **39**. The resulting triene is then induced to undergo Mo-catalyzed ARCM (5 mol% **4a**) to afford optically pure **40**, the AROM/RCM product that would be obtained from **37**.

Catalytic asymmetric synthesis through tandem AROM/CM: The chiral Mo–alkylidene complex derived from AROM of a cyclic olefin may also participate in an *inter*molecular cross-metathesis reaction. As depicted in Scheme 11, treatment of



Scheme 11. Mo-catalyzed tandem AROM/RCM delivers highly functionalized cxclopentanes in the optically pure form.

meso-**41** with a solution of 5 mol% **4a** and two equivalents of styrene leads to the formation of optically pure **42** in 57% isolated yield and >98% *trans* olefin selectivity.[22] The Mo-catalyzed AROM/CM reaction can be carried out in the presence of vinylsilanes: the derived optically pure **43** (Scheme 11) may subsequently be subjected to Pd-catalyzed cross-coupling reactions, allowing access to a wider range of optically pure cyclopentanes.

Conclusion

The above studies clearly indicate that the modular Mo-based construct initially reported for catalyst **1** can be exploited to generate a range of highly efficient and selective chiral catalysts for olefin metathesis. Both ARCM and AROM reactions can be promoted by these chiral catalysts to obtain optically enriched or pure products that are typically unavailable by other methods or can only be accessed by significantly longer routes. Substantial variations in reactivity and selectivity, arising from subtle changes in catalyst structures, support the notion that synthetic generality is more likely if a range of catalysts are available.

The chiral Mo-based catalysts discussed herein are more senstive to moisture and air than the related Ru-based

catalysts.[1] These complexes, however, are the only effective asymmetric metathesis catalysts reported so far and are significantly more robust than the original hexafluoro–Mo complex **1**. Furthermore, chiral Mo-based catalysts **4**, **11**, **25**, and **26** can be easily handled on a large scale. In the majority of cases, reactions proceed readily to completion in the presence of only 1 mol% of catalyst and, in certain cases, optically pure materials can be accessed within minutes or hours in the absence of solvents; little or no waste products need to be dealt with upon obtaining optically pure materials. It also merits mention that complex **4a** is commercially available from Strem (both antipodes and racemic). The above attributes collectively render this new and unique class of chiral catalysts extremely attractive for future applications in efficient, catalytic, enantioselective, and environmentally conscious protocols in organic synthesis.

Acknowledgements

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