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Highly *Z*- and Enantioselective Ring-Opening/Cross-Metathesis Reactions and *Z*-Selective Ring-Opening Metathesis Polymerization**

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alkenes · asymmetric catalysis · enantioselectivity · metathesis · molybdenum

The development of reactions and catalysts for the controlled and selective construction of small molecules is of utmost importance in synthetic chemistry.[1] In this context, the metal-catalyzed olefin metathesis is a groundbreaking advance that has enhanced the power of chemical synthesis.[2] The developments over the last two decades have made this remarkable transformation a fundamental reaction in both academic laboratories and in industrial applications. However, a number of challenges and issues still lie ahead. A notable challenge is the long-standing problem of controlling the olefin geometry (*E*/*Z* selectivity). The development of a catalyst to mediate highly *E*/*Z*-diastereoselective olefin metathesis would enable the efficient synthesis of either *E* or *Z* olefins, an important task in synthetic organic chemistry. In fact, olefin metathesis often furnishes the products as mixtures. In the case of ring-closing metathesis (RCM) of small or medium-sized rings, the *Z* isomers are generally formed preferably as a consequence of minimizing ring strain. However, RCM for the formation of macrocycles and cross-metathesis do not display this high degree of selectivity. Methods for the controlled synthesis of *Z* olefins have not yet been discovered.[2] In almost all cases, the Ru or Mo complexes catalyze ring-opening/cross-metathesis (ROCM) reactions with *E* selectivity.[3–5] Only in rare non-enantioselective cases when one of the olefin substrates bears an sp-hybridized substituent (enynes or acrylonitrile) may *Z* selectivity occur.[6] For example, Ru or Mo complexes catalyze the cross-metathesis between olefins and acroylonitrile with *Z*/*E* ratios ranging from 3:1 to 9:1.[6a,b] Moreover, RCM can in a few cases give either *E* or *Z* macrocyclic alkenes under kinetic or thermodynamic control, respectively, with high selectivity.[3b,c] Ring-closing alkyne metathesis followed by the stereoselective reduction of the corresponding cycloalkynes gives access to *Z* alkenes in two steps.[3c,d] To overcome the challenge of *Z* selectivity new catalysts must be developed.

The design and preparation of chiral metal-based catalysts in which the stereogenic center is at the metal are scarce. In fact, it is particularly challenging to design and synthesize enantiomerically pure catalysts stereogenic at the metal center that do not have polydentate ligands and do not readily isomerize, and can thus serve as effective chiral catalysts. The rigidity of bi- or polydentate ligation may be disadvantageous in cases were catalyst fluxionality gives rise to enhanced activity and/or enantioselectivity; however, a catalyst stereogenic at the metal center and having monodentate ligands would be beneficial. Thus, a detailed understanding of the interplay of chirality in the ligand backbone and at the metal center might give rise to novel strategies for catalyst design. In a recent study, the fruitful collaboration between the groups of Hoveyda and Schrock led to the development of novel catalysts with an asymmetrically substituted molybdenum atom for asymmetric ring-closing metathesis,[7] and based on rational design, they have now made a breakthrough in the development of highly *Z*-selective and enantioselective ROCM reactions by employing novel stereogenic-at-molybdenum complexes as catalysts.[8]

Chiral Ru and Mo complexes are employed as catalysts for the enantioselective ROCM.[5] In this context, metal complexes **1**,[5a,10] **2**,[5c,9a] and **3**[5c,9b] (Figure 1) are highly *E*-selective and produce the corresponding *trans* products in greater than 98% selectivity. For example, the chiral Ru complexes **1a** and **1b** catalyze the asymmetric ROCM of protected bicyclic compounds **4** and **4′** with olefins **5** to give the corresponding functionalized tetrahydropyrans **6** or **6′**, respectively, with high *E* selectivity and enantioselectivity (Scheme 1a,b).[5a] The synthetic applicability of this reaction was demonstrated by employing chiral Ru complex **1d** (2 mol%) as the catalyst for the asymmetric ROCM of **4b** with styrene, which gave the fully functionalized tetrahydro-

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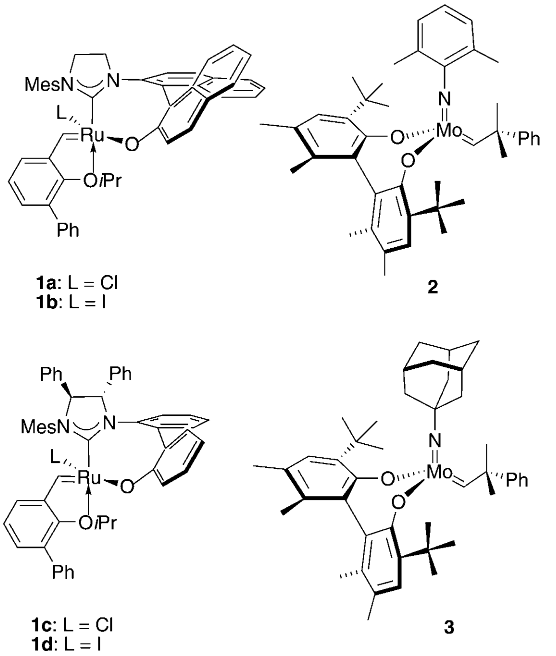
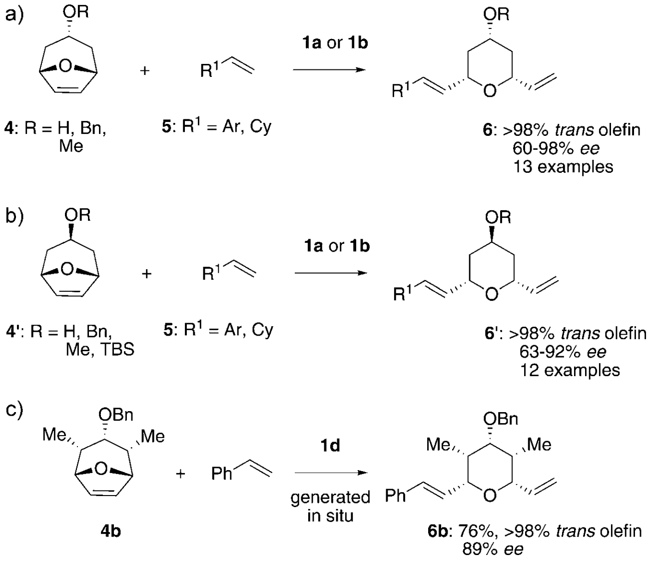


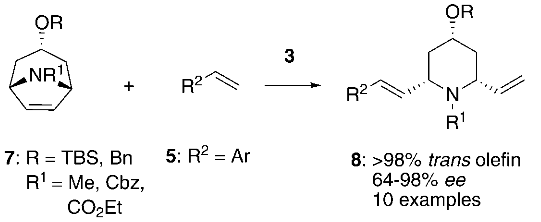
Figure 1. Examples of Ru and Mo complexes for ROCM. Mes = mesityl.



Scheme 1. a) ROCM of **4** catalyzed by Ru complexes **1 a** or **1 b**. b) ROCM of **4′** catalyzed by Ru complexes **1 a** or **1 b**. c) ROCM of **4 b** catalyzed by Ru complex **1 d**. Bn = benzyl, Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl.

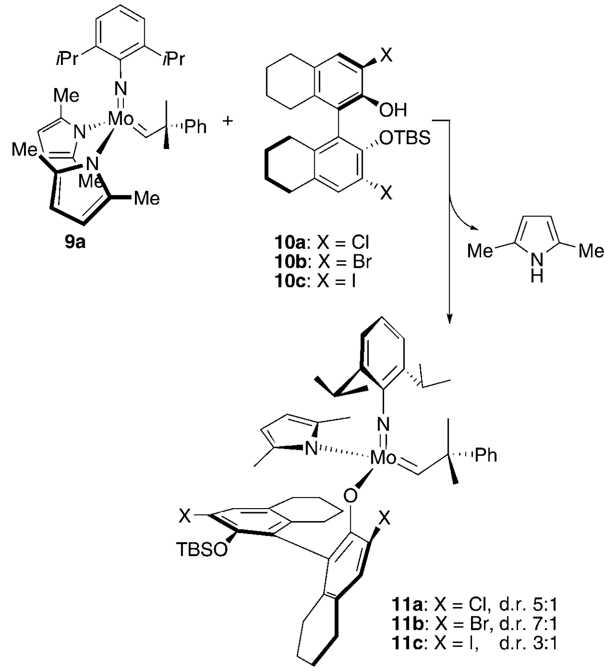
pyran **6b** (> 98 % *trans* olefin) in 76 % yield with 89 % *ee* (Scheme 1 c). The reaction was then used as the key step in the elegant total synthesis of baconipyrone C.[10]

The chiral Mo complexes **2** and **3** catalyze the ROCM of azabicycles **7**.[5c] Notably, complex **3** is able to catalyze the asymmetric ROCM of azabicycles **7** with styrenes **5** to give the corresponding piperidines **8** in high yields and high *E* selectivity and enantioselectivity [Eq. (1); Cbz = benzyloxycarbonyl].[5c] The Mo- and Ru-based catalysts are complementary with regards to functional-group tolerance.[5a,c,11] As will be discussed later in this article, Ru carbenes promote reactions of substrates that bear a hydroxy group, whereas Mo-based catalysts retain their high activity in the presence of tertiary amines.[11]



(1)

Catalysts **1**–**3** have bidentate ligands, which had been believed to be necessary to achieve high selectivity. However, the structural rigidity of the bidentate ligands was proven to give poor activities in the catalytic RCM that was required for the asymmetric synthesis of (+)-quebrachamine.[7a] Based on this, the groups of Hoveyda and Schrock conjectured that structural fluxionality of the catalyst complex could help it meet the variable steric requirements in the catalytic cycle. To achieve this, monodentate alkoxides were selected as ligands. Thus, a new class of olefin metathesis catalysts were introduced that are stereogenic at the metal center.[7,12] The catalysts were synthesized by treatment of the bispyrrolide Mo complex **9 a** with mono-TBS-protected diols **10** to give the corresponding diasteromerically enriched aryl oxide pyrrolidine complexes **11**, which are formed and used in situ (Scheme 2). These new Mo alkylidenes **11** are excellent catalysts for asymmetric ring-closing metathesis transformations. For example, an impressive expeditious enantioselec-



Scheme 2. Preparation of Mo complexes **11**.

tive synthesis of (+)-quebrachamine was executed by using Mo complex **11a** as the catalyst for the RCM key step.[7a]

With these results in hand, Hoveyda, Schrock, and coworkers embarked on the challenging project of developing a *Z*-selective enantioselective ROCM reaction.[8] In the mechanistic model used to develop this process, it was envisioned that the flexibility of the Mo monoaryloxides is crucial (Figure 2). Hence, a catalyst was proposed in which a bulky aryloxide ligand freely rotates about the Mo–O bond and the substituent on the imide ligand is smaller than the aryloxide ligand. It was thought that the reaction should start with the *syn* alkylidene isomer **A** and proceed via the all-*cis* metallacyclobutane **B** to give the *cis* olefin and complex **C**. In comparison, the rigid bidentate aryloxide ligands of Mo complexes **2** and **3** (Figure 1) present a lower steric barrier, the *trans*-substituted metallacyclobutane is formed, and the reaction is *E*-selective.

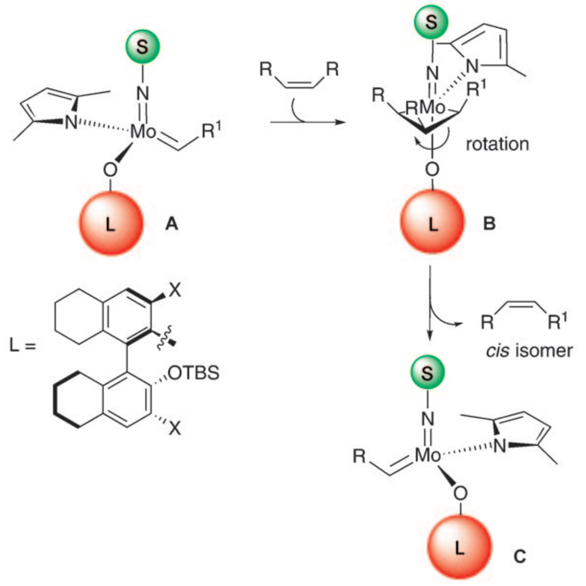
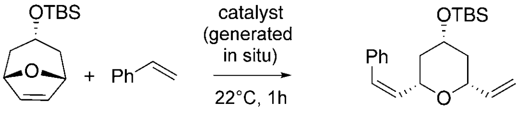


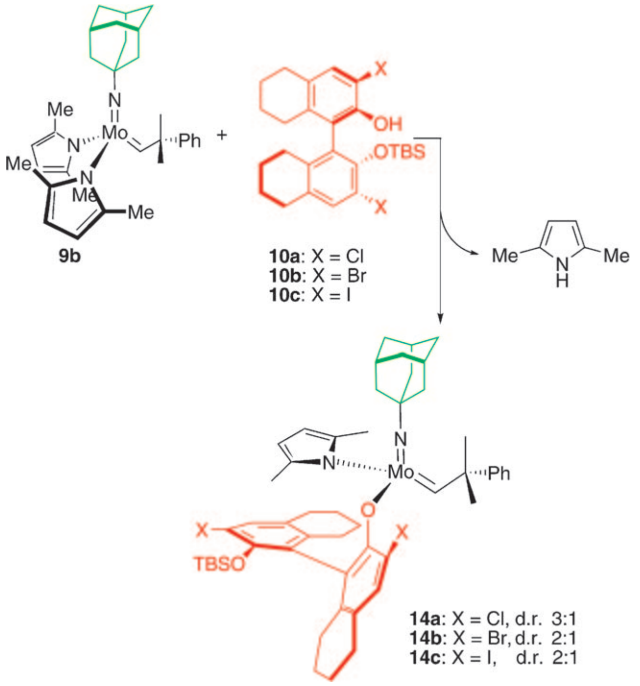
Figure 2. The proposed model catalyst for obtaining *Z* selectivity.

To test this hypothesis, the ROCM reaction of bicyclic compound **4a** and styrene in the presence of Mo complex **11b** was investigated [Eq. (2)]. The conversion was very low (< 2% in 1 h, minimal formation of benzylidene) as a result of the bulky ligands of **11b**, which made the formation of the requisite *syn* or *anti* alkylidene **A** and subsequent cross-metathesis difficult. To overcome this steric effect, Mo complexes **14** with an adamantylimido group were prepared in situ by mixing the bispyrrolido Mo complex **9b** with mono-TBS-protected diols **10** (Scheme 3). It should be mentioned that significant amounts of **9b** are consumed in this procedure and inactive bisaryloxide complexes are formed; this implies that the actual amount of active catalyst is less than the values for the corresponding precursors indicate. The Mo complexes **14** were highly active for the reaction between oxabicycle **4a** and styrene giving the corresponding product **15a** in high yields and enantioselectivity [Eq. (2)]. It is important to note that when the Mo alkylidene complexes **14a** and **14b** were employed, the *Z* selectivity was excellent (> 98:2 *Z*/*E*). The enantioselectivity was higher with Mo complex **14c** but the *Z* selectivity was slightly lower (95:5 *Z*/*E*). Thus, complex **14b** generated in situ was applied as the catalyst for several enantioselective ROCM transformations of oxabicycles **4** and **4′** with various styrenes **5** to furnish the corresponding pyrans **15** and **15′**, respectively, with high *Z* selectivity (Scheme 4).[8]



4a **5a** **15a** (2)

cat. **11b** (5 mol%): <2% conversion
cat. **14a** (1 mol%): 80% yield, 90% *ee*, >98:2 *Z*/*E*
cat. **14b** (1 mol%): 85% yield, 97% *ee*, >98:2 *Z*/*E*
cat. **14c** (1 mol%): 60% yield, >96% *ee*, 95:5 *Z*/*E*



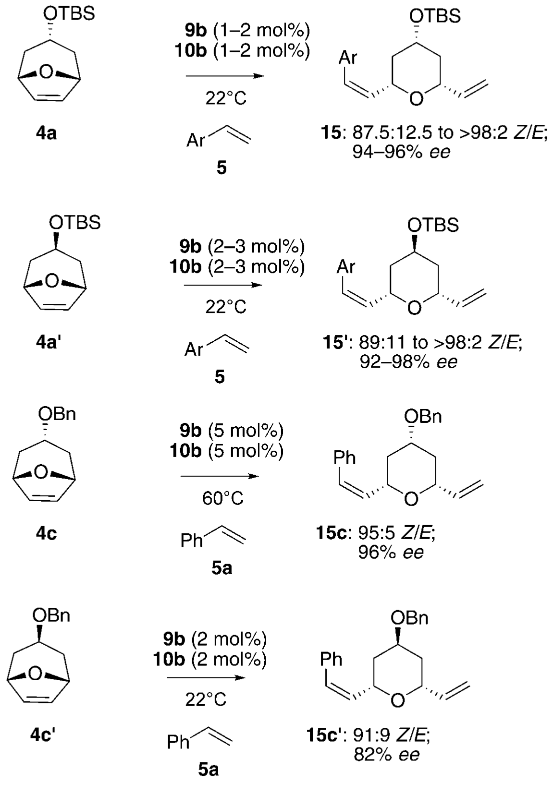
9b

10a: X = Cl
10b: X = Br
10c: X = I

14a: X = Cl, d.r. 3:1
14b: X = Br, d.r. 2:1
14c: X = I, d.r. 2:1

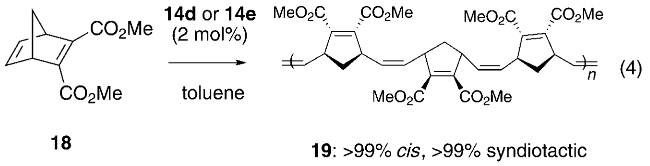
Scheme 3. Preparation of Mo complexes **14**.

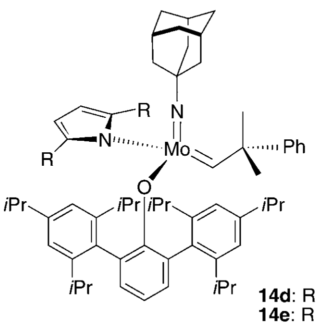
Despite the steric and stereoelectronic effects caused by the substituents of styrene **5**, the olefin formation remains strongly *Z*-selective. Even for the sterically more demanding *ortho*-substituted styrenes, the *Z* selectivity is only slightly diminished (87.5:12.5 *Z*/*E*). The enantioselective ROCM reactions with TBS-protected **4a** and **4a′** give the corresponding products **15** and 15′ with 92–98% *ee*. The use of a benzyl protecting group slightly decreases the enantioselectivity of the transformation. Notably, the ROCM reaction catalyzed by the Mo complex **14b** is not limited to styrenes as cross-metathesis partners. In this context, it was shown that Mo alkylidene **14b** catalyzed the asymmetric ROCM of bicycle **4c** with TBS-protected allyl alcohol **16** to give the corresponding enantiomerically enriched pyran **17** in moderate yield with 72% *ee* and a *Z*/*E* ratio of 95:5 [Eq. (3)].[8]



Scheme 4. Catalytic Z- and enantioselective ROCM. Ar = 4-MeOC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-BrC$_6$H$_4$, 2-MeC$_6$H$_4$.

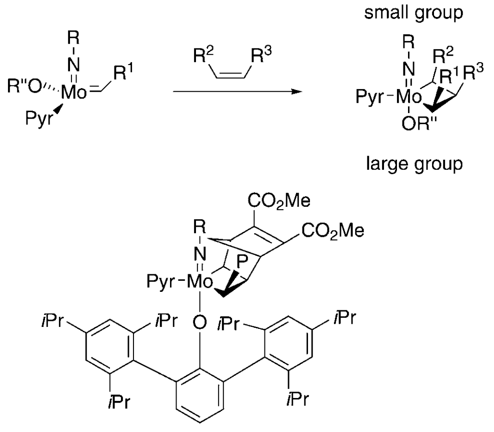
The collaboration between Schrock, Hoveyda and co-workers has recently led to the development of a new Z-selective ring-opening olefin metathesis polymerization catalyzed by molybdenum hexaisopropylterphenoxide monopyrrolide complexes **14d** and **14e**.[13] The highly Z-selective ring-opening metathesis polymerization of dimethoxycarbonylnorbornadiene **18** using a catalyst loading of 2% in toluene followed by quenching with benzaldehyde gave polymer **19** [Eq. (4)].[14]





14d: R = H
14e: R = Me

This microstructure has not been possible to prepare in pure form until now.[14] As highlighted above, the high Z selectivity is possible owing to the attack at the metal *trans* to the pyrrolide in a *syn* complex to yield metallacyclobutane intermediates in which all the substituents point toward the "small" axial amide ligand and away from the "large" axial OR″ group (Scheme 5). Thus, the fluxionality at the metal center is very important to achieve high Z selectivity, and the polymer can propagate via intermediate **20**.



20: R = 1-adamantyl; P = polymer chain

Scheme 5. Model for the high Z selectivity in the polymerization reaction.

In conclusion, Hoveyda and Schrock and their co-workers have made a breakthrough in the area of olefin metathesis by demonstrating that highly Z-selective ring-opening cross-metathesis can be achieved by employing novel Mo complexes as chiral catalysts. The most important characteristic for the high Z selectivity is the use of large alkoxy groups and small imido substituents in the axial positions of the metallacyclobutane intermediate. This forces all of the substituents on the metallacyclobutane to point toward the "small" imido group, affording the Z olefin. Up until now, the Z-selective reaction has been demonstrated for the enantioselective ROCM of oxabicycles with styrenes or allyl ethers, but it is reasonable to expect the reaction to be successful with azabicycles and other cross-metathesis partners as well. It should also be possible to apply metal complexes that are stereogenic at the metal center for enantioselective Z-selective cross-metathesis transformations that do not include bicyclic substrates.

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