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The Significance of Degenerate Processes to Enantioselective Olefin Metathesis Reactions Promoted by Stereogenic-at-Mo Complexes

Simon J. Meek,[†] Steven J. Malcolmson,[†] Bo Li,[†] Richard R. Schrock,[‡] and Amir H. Hoveyda*[,†]

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received September 14, 2009; E-mail: amir.hoveyda@bc.edu

We recently disclosed a class of chiral Mo-based complexes (e.g., *S*-**1** and *S*-**2**, Figure 1) that are prepared diastereoselectively (7.0:1 and 2.2:1, respectively) and used *in situ* to promote olefin metathesis[1,2] with high reactivity and enantioselectivity.[3] A notable feature of the new catalysts is the presence of a donor (pyrrolide) and an acceptor (aryloxide or alkoxide) ligand (vs two acceptor ligands as utilized previously),[2a] which, on the basis of initial theoretical studies,[4] is likely critical to achieving high efficiency. The fluxional pyrrolide−aryloxides bear only monodentate ligands and a stereogenic metal center, which undergoes inversion with every sequence that involves formation of a metallacyclobutane (Mo_R=C + substrate olefin → metallacyclobutane → C=Mo_S + product olefin).[5] In the simplest analysis, each olefin metathesis catalytic cycle includes two inversion processes: cross-metathesis leading to a substrate-derived alkylidene and a subsequent ring-closing, ring-opening, or cross-metathesis. Under such a regime, a stereogenic-at-metal complex emerges from a reaction as the same stereoisomer that begins the process (net retention). Inversion at the metal, however, might occur beyond the boundaries of a productive catalytic cycle as a result of degenerate metathesis; such isomerizations can have significant consequences on reaction efficiency as well as enantioselectivity. Herein, we provide evidence demonstrating that degenerate metathesis, which is prevalent in transformations catalyzed by stereogenic-at-metal complexes, is critical to the effectiveness of enantioselective ring-closing metathesis (RCM) processes.

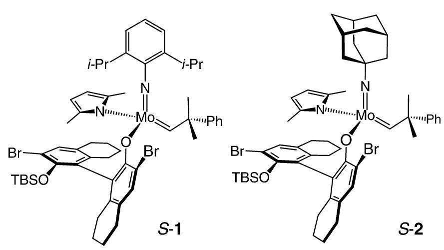


Figure 1. Stereogenic-at-Mo complexes (major diastereomers).

We began with the determination of the structure of *R*-**1**, generated as the minor diastereomer (7:1 *S*/*R*). In spite of being the less predominant component, *R*-**1** was isolated in sufficient quantities to allow us to secure its X-ray structure (Scheme 1; the X-ray structure of *S*-**1**[3a] is also shown).[6] Earlier studies had indicated that ≥95% of *R*-**1** remains intact in an RCM reaction (Table 1) that proceeds to completion in 30 min with a 7:1 *S*-**1**/*R*-**1** mixture.[3a] A comparison of the structures of *S*-**1** and *R*-**1**

Scheme 1. Isolation and X-ray Crystal Structure of *R*-**1**

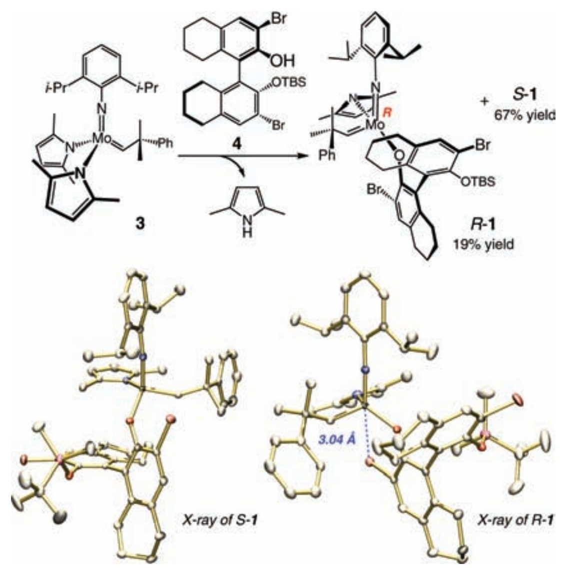
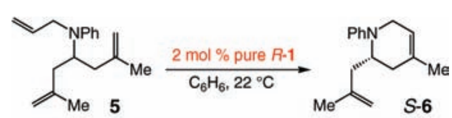


Table 1. Time Dependence of Conversion and Selectivity in Catalytic RCM with Pure *R*-**1** (Minor Diastereomer)[a]



entry	time (min)	conv (%)[b]	er (*S*:*R*)[c]
1	30	5	85.5:14.5
2	45	15	94:6
3	60	23	95:5
4	180	>98	96:4

[a] See the Supporting Information for all experimental details, including spectroscopic data for *R*-**1**. [b] Based on 400 MHz ^{1}H NMR analysis of unpurified mixtures. [c] Based on HPLC analysis (see the Supporting Information for details).

points to a rationale for such reactivity differences. Approach of an alkene to *S*-**1** *trans* to the pyrrolide[7] is hindered by a Br, which can be moved out of the way by a slight rotation about the Mo−O bond. In *R*-**1**, however, olefin coordination is blocked by the larger (vs Br) tetrahydronaphthyl ring of the aryloxide. Furthermore, a bromide substituent of the aryloxide ligand resides within 3.04 Å of the Mo in *R*-**1**, suggesting a Mo−Br interaction.[8] Such association discourages rotation around the Mo−O bond, which is required if the metal center is to be accessible to a substrate molecule.

With a pure sample of *R*-**1** available, we examined the ability of this diastereomer to promote enantioselective RCM. As the

[†] Boston College.
[‡] Massachusetts Institute of Technology.

Table 2. Time Dependence of Conversion and Selectivity in Catalytic RCM with Pure *S*-**1** (Major Diastereomer)[a]

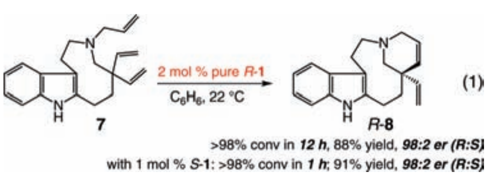
5 → S-6 (2 mol % pure S-1; C_6H_6, 22 °C)

entry	time (min)	conv (%)[b]	er (S:R)[c]
1	2	4	76:24
2	2.5	7	87.5:12.5
3	3	13	93.5:6.5
4	20	>98	96.5:3.5

[a−c] See Table 1, footnotes *a*−*c*.

data summarized in Table 1 indicate, *R*-**1** does promote RCM of triene **5**, but at a lower rate than when *S*-**1** is used (180 vs 20 min for >98% conv; Tables 1 and 2). Surprisingly, however, the RCM with *R*-**1** delivers the *same* major product enantiomer (*S*-**6**) as obtained when *S*-**1** is employed, with nearly the same enantioselectivity (96:4 vs 96.5:3.5 er; see Tables 1 and 2).

The observations in eq 1 regarding RCM of **7**, a key intermediate in the recent enantioselective total synthesis of quebrachamine,[3a,b] offer an additional example: triene **7** reacts with *R*-**1** significantly more slowly (12 h vs 1 h with *S*-**1**), but as with *S*-**1**, *R*-**8** is generated with precisely the same level of enantioselectivity (98:2 er) and sense of absolute stereochemistry (*R*-**8** major).[9] The above data imply that the stereochemical identity of the stereogenic-at-metal complex is significant vis-à-vis the rate of initiation of the initial neophylidene but has no bearing on the eventual stereochemical outcome. Isomerization of the two diastereomers of the chiral complex is therefore likely to be more facile than ring closure; that is, Curtin−Hammett conditions[10] apply for a significant duration of the catalytic cycle. Another set of mechanistically critical observations, depicted in Tables 1 and 2, shows that irrespective of whether pure *R*-**1** or *S*-**1** is used, the initial enantioselectivity is lower than that of the final product (see entries 1). A rationale for such findings will be provided below.

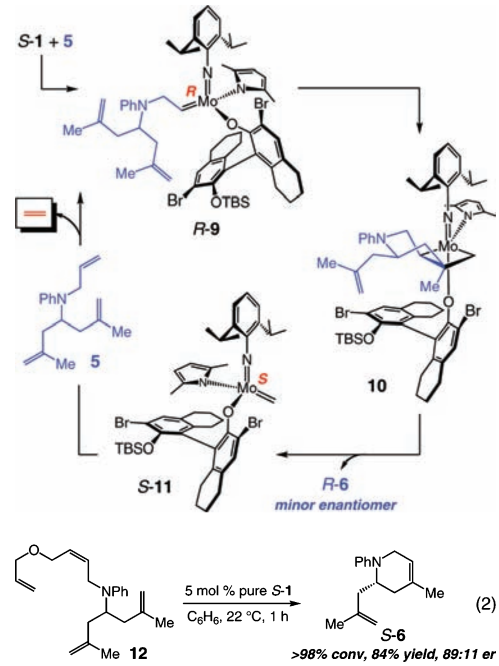


The observations described above undermine the validity of the simplest form of the catalytic cycle involving two inversions at the metal center. Two other issues detract from the pathway in Scheme 2: (1) The lower activity of alkylidenes bearing an *R* Mo center should apply to *R*-**9** as well; *S*-**9** is expected to be more reactive. (2) RCM through *R*-**9** would likely afford *R*-**6**, the minor enantiomer observed in the reactions shown in Tables 1 and 2.

The results of RCM of tetraene **12** performed with pure *S*-**1** (eq 2), which affords *S*-**6** as the predominant enantiomer (90:10 er), further substantiate that additional inversions at the metal center, outside the confines of a catalytic cycle that involves only a double inversion, play a crucial role. The simplest catalytic cycle for conversion of **12** to **6** would include three olefin metathesis reactions (vs two for **5** or **7**). In the absence of any additional isomerizations at Mo, the catalyst would have undergone net inversion after formation of every molecule of **6** (from **12**), leading to generation of **6** in low enantiomeric purity.

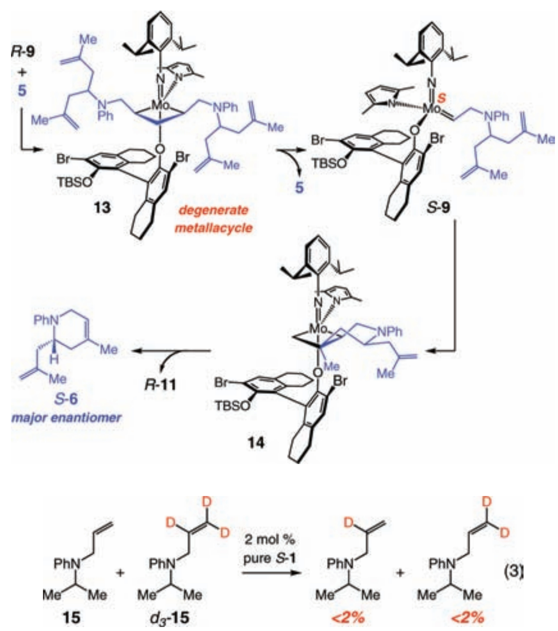
Inversion at the Mo center can also occur through degenerate olefin metathesis. Thus, as illustrated in Scheme 3, reaction of alkylidene *R*-**9** (Scheme 2) with another molecule of **5** might afford the

Scheme 2. Initial Mechanism without Mo-Center Isomerization Outside the Main Catalytic Cycle



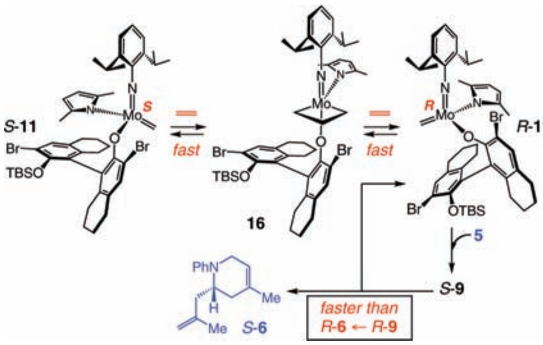
symmetrically substituted metallacyclobutane **13**; such a process might furnish *S*-**9**, an alkylidene that can deliver the observed major enantiomer *S*-**6** via metallacyclobutane **14**. However, an experiment involving the reaction of a 1:1 mixture of allylamines **15** and d_3-**15** in the presence of pure *S*-**1** (eq 3), which did not lead to any detectable amounts of deuterium scrambling, serves as evidence against inversion at Mo through a substrate-induced degenerate process.

Scheme 3. Mo Isomerization by Substrate-Induced Degenerate Metathesis



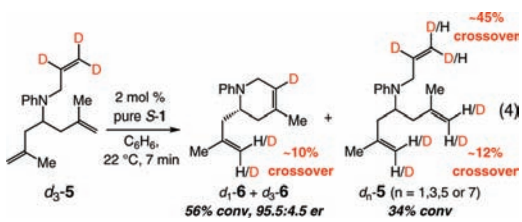
Ethylene, although not present at the earliest stages of the RCM process, can promote degenerate olefin metathesis as well. As shown in Scheme 2, through the first RCM, *S*-**1** sheds the neophylidene unit of the initial complex, leading to methylidene *S*-**11**,[11] which may proceed through cross-metathesis with substrate **5** to produce ethylene

Scheme 4. Mo Isomerization by Ethylene-Induced Degenerate Metathesis



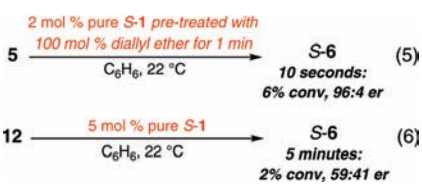
(and regenerate *R*-**9**). Degenerate metathesis and inversion at the Mo center can thus occur by rapid interconversion of *S*-**11** and *R*-**11** via unsubstituted metallacyclobutane **16** (Scheme 4).[3e] Cross-metathesis of *R*-**11** with **5** would give *S*-**9**, which would readily undergo RCM to afford *S*-**6**.

Three additional findings support the proposal that ethylene initiates degenerate metathesis and promotes high enantioselectivity: (1) Treatment of d_3-**5** with 2 mol % pure *S*-**1** leads to deuterium scrambling within 7 min (eq 4).



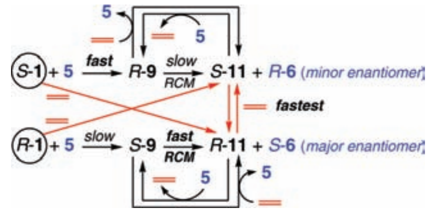
(2) As shown in eq 5, when RCM of **5** is performed with 100 mol % diallyl ether (to generate ethylene and promote rapid methylidene generation), high enantioselectivity is observed early in the reaction (95:5 er vs entries 1, Tables 1 and 2). The more rapid initiation (vs Table 2) points to a more facile formation of **11**.

(3) RCM of tetraene **12** with 5 mol % pure *S*-**1** delivers **6** in only 60.5:39.5 *S*/*R* after ∼2% conversion (eq 6; compare to eq 2). Thus, without sufficient ethylene, the catalytic cycle in its simplest form is largely operative (triple inversion at Mo).



The proposed mechanism, summarized in Scheme 5, offers a rationale for low enantioselectivity at the nascent stages of RCM with *S*-**1** or *R*-**1** (Tables 1 and 2). In reactions that commence with *S*-**1**, little or no ethylene is initially present; thus, RCM likely proceeds via *R*-**9** to afford a significant amount of *R*-**6** (minor product enantiomer). When the catalytic cycle is initiated by *R*-**1**, the faster-reacting *S*-**9** is formed, and the major product isomer *S*-**6** can be generated. If ethylene is available only at low concentration, however, maximum enantioselectivity (∼96:4 er) cannot be achieved, since ethylene can convert *R*-**1** to *S*-**11**, which reacts with **5** to form *R*-**9**, leading to the minor product enantiomer (*R*-**6**). Only when sufficient ethylene is present, allowing inversion at Mo to occur at an appropriately high rate, can *S*-**9** become easily accessible, leading to high enantioselectivity. The stereochemical outcome of the RCM

Scheme 5. Equilibria Promoted by Ethylene Critical to Efficiency and Enantioselectivity



reaction is thus independent of the identity of the initiating alkylidene *S*-**1** or *R*-**1** (Curtin−Hammett kinetics).[10]

An important feature of metal-catalyzed olefin metathesis promoted by stereogenic-at-metal complexes is that with each reaction the metal center is inverted. We have demonstrated that at steady state, such inversions are faster than product formation. The absence of multidentate ligands, which can raise the barrier to inversion at the metal and reduce catalyst activity, is therefore a significant attribute of the present class of catalysts. Our study highlights the principle that diastereomeric—not enantiomeric—chiral catalysts might be preferable to those that contain a C_2-symmetric bidentate ligand[2a] (and thus a nonstereogenic metal center). In diastereomeric complexes that undergo rapid interconversion of metal center configuration by degenerate metathesis, stereomutation at the metal becomes inconsequential and, as a result, stereoselective synthesis of a chiral catalyst candidate is not required.

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Supporting Information Available: Experimental procedures, spectral and analytical data for all reaction products, and crystallographic data for *R*-**1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews of catalytic olefin metathesis, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.

(2) For reviews of high-oxidation-state complexes used in catalytic olefin metathesis, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (b) Schrock, R. R. *Chem. Rev.* **2009**, *109*, 3211.

(3) (a) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933. (b) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943. (c) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844. (d) Lee, Y.-J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10652. (e) Marinescu, S. C.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10840.

(4) (a) Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2005**, *127*, 14015. (b) Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207.

(5) For applications of stereogenic-at-Ru complexes to enantio- or product-selective olefin metathesis reactions, see: (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502. (b) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288. (c) Bornand, M.; Chen, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7909.

(6) See the Supporting Information for details of the crystal structure of *R*-**1**.

(7) For crystallographic evidence that a Lewis basic PMe_3 associates *trans* to the pyrrolide, see: Marinescu, S. C.; Schrock, R. R.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 58.

(8) The observed Mo−Br distance (3.04 Å) is significantly less than the sum of the van der Waals radii for Mo and Br (1.85 and 2.00 Å, respectively).

(9) For additional examples, see the Supporting Information.

(10) For selected instances where Curtin−Hammett conditions have been illustrated for metal-catalyzed enantioselective reactions, see: (a) Halpern, J. *Science* **1982**, *217*, 401. (b) Hughes, D. L.; Lloyd-Jones, G. C.; Krska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5379. For additional cases, see the Supporting Information.

(11) For an X-ray structure of a monoaryloxide−monopyrrolide W-based methylidene complex, see: Jiang, A. J.; Simpson, J. H.; Müller, P.; Schrock, R. R. *J. Am. Chem. Soc.* **2009**, *131*, 7770.

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