JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Synthesis, Isolation, Characterization, and Reactivity of High-Energy Stereogenic-at-Ru Carbenes: Stereochemical Inversion through Olefin Metathesis and Other Pathways

R. Kashif M. Khan,† Adil R. Zhugralin,† Sebastian Torker, Robert V. O'Brien, Pamela J. Lombardi, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: The synthesis, isolation, purification (routine silica gel chromatography), and spectroscopic characterization of high-energy endo stereogenic-at-Ru complex isomers, generated by ring-opening/cross-metathesis (ROCM) reaction of the corresponding exo carbenes, are disclosed. We provide experimental evidence showing that an endo isomer can undergo thermal or Brønsted acid-catalyzed polytopal rearrangement, causing conversion to the energetically favored exo carbene.

In the course of an olefin metathesis (OM) reaction,[1] the catalyst structure undergoes numerous changes, and the metal center serves as the pivot around which these variations occur.[2] Many such alterations are unobservable in an achiral complex. The study of stereogenic-at-metal complexes, however, offers the opportunity to probe the nature of these mechanistic nuances: stereochemical inversion might be exploited to monitor structural modifications taking place during a catalytic cycle.[3] Investigations along these lines would shed light on the inner workings of stereogenic-at-Ru carbenes, represented by **1**–**3**[4−6] (Figure 1), an emerging class of

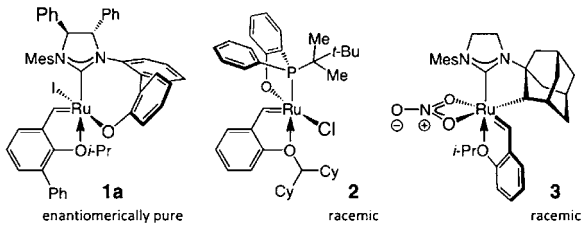
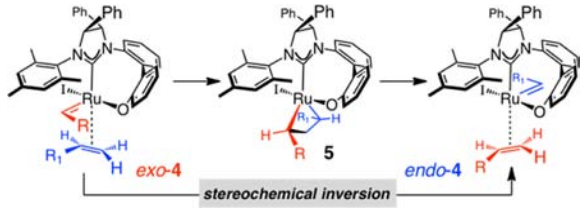


Figure 1. Stereogenic-at-Ru complexes used in olefin metathesis.

complexes used for stereo- and sequence-selective OM.[5,7,8] Herein we disclose the results of our studies regarding the fluxionality[9] of carbenes derived from **1a**. We have synthesized, isolated, and characterized the higher-energy stereogenic-at-Ru endo isomers (cf. Scheme 1) generated by a single stereochemical inversion through a ring-opening/cross-metathesis (ROCM) reaction with the exo carbene (**1a**).[10] By studying the chemistry of the endo complex, we have established that inversion can be induced thermally or catalyzed by a Brønsted acid, all of which constitute *non*-OM-based polytopal rearrangements. We briefly discuss the significance of the present findings in providing a better understanding of representative previous observations.

Ru-based complexes bearing a bidentate N-heterocyclic carbene (NHC) or phosphine ligand exist in two diastereomeric forms (Scheme 1) that are energetically distinct and can

Scheme 1. OM-Induced Stereochemical Inversion



play critical and complementary roles.[11] In the case of *exo*- and *endo*-**4** derived from *exo*-**1a**, the former represents the resting state of the complex, whereas the latter is less abundant but more reactive (ΔE = 3−4 kcal/mol).[12] We recently demonstrated that in *Z*- and enantioselective reactions involving the less active Fischer-type carbenes derived from enol ethers, the higher-energy endo complex, which is accessible by facile interconversion of the two diastereomeric forms, is likely responsible for catalyzing OM (Curtin−Hammett kinetics).[12] In instances where the catalytic cycle can commence with the lower-energy exo isomer, the endo species reacts with another substrate molecule to regenerate the more favored carbene, releasing the desired product. A more extensive understanding of the attributes of the higher-energy endo carbene and the factors that facilitate its isomerization to the alternative exo isomer is critical for an appreciation of the principles that control catalytic OM.

The OM reaction of an exo Ru complex (e.g., *exo*-**4**) produces an endo carbene via a metallacyclobutane such as **5** (Scheme 1).[13] The higher energy of the endo isomer accounts for the fact that protocols for the preparation of stereogenic-at-Ru complexes afford exo carbenes exclusively, without detection of the endo isomers (as determined by spectroscopic studies and X-ray crystallography).[14] Several energetically favored complexes bearing a bidentate *o*-alkoxybenzylidene ligand have been isolated and characterized (including X-ray

Received: June 11, 2012
Published: July 20, 2012

 © 2012 American Chemical Society dx.doi.org/10.1021/ja3056722 | *J. Am. Chem. Soc.* 2012, 134, 12438−12441

structures);[4a,5,6,14] in contrast, data associated with a *kinetically* stable and more reactive endo species do not exist.[15] To generate a well-defined endo carbene, we chose to probe the reaction of *exo*-**1a** with *cis*-3,4-diisopropoxycyclobutene (**6**), which was selected as the substrate for two reasons: the high reactivity of the strained ring ensures facile ROCM, and additionally, an isopropoxy group, by internal chelation with the Ru center (cf. **1a**), would improve stability, facilitating isolation of the more reactive endo complex.

Treatment of *exo*-**1a** with cyclobutene **6** (22 °C, C_6D_6) led to the disappearance of the exo carbene [16.0 ppm; Figure 2, spectrum (a)] and generation of *endo*-**7a**,[16] as indicated by the appearance of a major signal at 17.07 ppm in the ^{1}H NMR spectrum [Figure 2, spectrum (b)].[17] The downfield shift of the peak is consistent with the formation of an endo complex, since in an exo isomer the carbene proton would reside below the face of the mesityl (Mes) moiety (anisotropic effect).[18] Furthermore, we were able to isolate and purify samples of *endo*-**7a** by routine silica gel chromatography (42% yield). Similarly, F-substituted *endo*-**7b** (41% yield) was accessed by the reaction of *exo*-**1b** with **6**. With a sample of pure *endo*-**7b** available, we secured additional support regarding the stereochemical identity of the product of the aforementioned ROCM reactions through ^{19}F−^{1}H heteronuclear Overhauser effect spectroscopy (HOESY) experiments (Figure 2). The same enhancement was not detected with *exo*-**1b**.

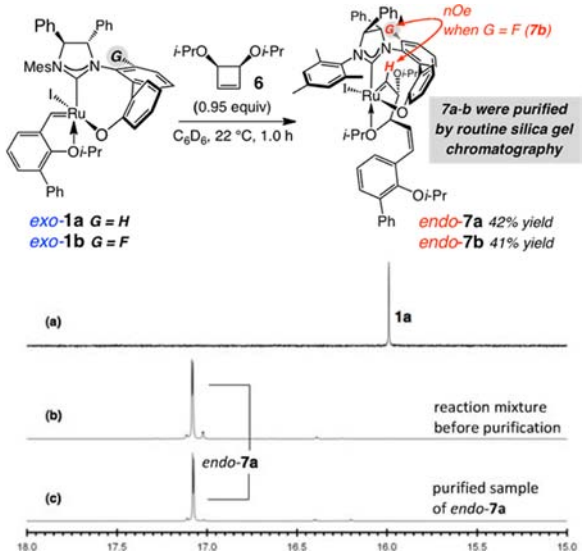


Figure 2. Syntheses of *endo*-**7a** and *endo*-**7b** by ROCM (yields are of pure products), and ^{1}H NMR spectra (C_6D_6) of (a) pure **1a**, (b) the mixture prior to purification, and (c) pure *endo*-**7a** after silica gel chromatography. See the Supporting Information (SI) for details.

An examination of the chemistry of *endo*-**7a** ensued. Treatment of pure *endo*-**7a** with 11.0 equiv of styrene (C_6D_6, 50 °C, 12 h) led to the formation of cross-metathesis product **8** (51% yield; Figure 3). The ^{1}H NMR spectrum of the mixture exhibits one carbene signal at 17.68 ppm and another, with higher intensity, at 16.41 ppm (Figure 3a). The more downfield singlet likely arises from *exo*-benzylidene **9** formed by the reaction with styrene; this contention is supported by the observation that treatment of **1a** with the aryl olefin led to the appearance of the same signal (Figure 3b). Although we were unable to isolate complex **9** because of its rapid decomposition, we did succeed in purifying and characterizing *exo*-**7a**$_{anti}$ (cf. Figure 4c), the entity responsible for the signal at 16.41 ppm [additionally, the minor carbene at 16.24 ppm is *exo*-**7a**$_{syn}$; cf. Figure 4].[16] The relatively upfield chemical shift in *exo*-**7a**$_{anti}$, similar to that in **1a** and the related complexes,[19] indicates that the *i*-PrO ligand is chelated opposite to the NHC (carbene H oriented toward Mes).

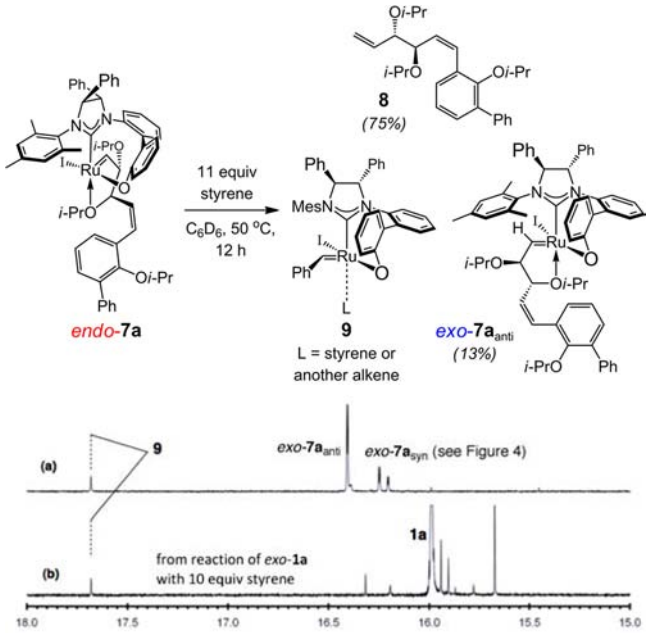


Figure 3. Reaction of *endo*-**7a** with styrene, leading to exo carbenes **9** and *exo*-**7a**$_{anti}$, and ^{1}H NMR spectra (C_6D_6) of (a) the reaction mixture prior to purification and (b) the mixture from treatment of pure **1a** with 10 equiv of styrene (50 °C, 24 h). Percent values correspond to conversion determined by analysis of 400 MHz ^{1}H NMR analysis of the unpurified mixture; 8% conv to **7a**$_{syn}$ and 4% conv to unidentified carbene. See the SI for details.

It is doubtful that *exo*-**7a**$_{anti}$ is formed through OM via *endo*-**7a**, as the two complexes differ only in the stereochemistry at the Ru center. It is likely that *exo*-**7a**$_{anti}$ is generated by non-OM-induced rearrangement of *endo*-**7a**. Another implication of the transformation in Figure 3 is that the rate of *endo*-**7a** to *exo*-**7a**$_{anti}$ isomerization can be competitive with OM. Given the central roles of stereoisomeric complexes and the significance of a possible nonmetathetic interconversion of the two carbenes, we set out to assemble additional information on non-OM-based isomerization processes.

We heated a solution of *endo*-**7a** under the conditions shown in Figure 3 (50 °C) but in the absence of styrene. After 6 h, as indicated by the ^{1}H NMR spectra in Figure 4, two major new carbene signals appeared: one at 16.41 ppm, corresponding to *exo*-**7a**$_{anti}$, and another at 16.24 ppm. The latter peak was transient: following an initial burst in intensity, it diminished and then disappeared within 18 h, concomitant with an increase in the area corresponding to the signal for *exo*-**7a**$_{anti}$. Nonetheless, we isolated and purified the less stable carbene (signal at 16.24 ppm) chromatographically, as it is considerably more polar than exo complexes *exo*-**1a** and *exo*-**7a**$_{anti}$ as well as *endo*-**7a**. By probing the identity of the relatively fleeting complex by spectroscopic analysis,[16] we established its identity as *exo*-**7a**$_{syn}$, in which the isopropoxy group is chelated syn to the NHC ligand (Figure 4); the upfield shift of the carbene proton of *exo*-**7a**$_{syn}$ relative to *exo*-**7a**$_{anti}$ is likely due to the anisotropic effect induced by the proximal anionic aryloxide

dx.doi.org/10.1021/ja3056722 | J. Am. Chem. Soc. 2012, 134, 12438−12441

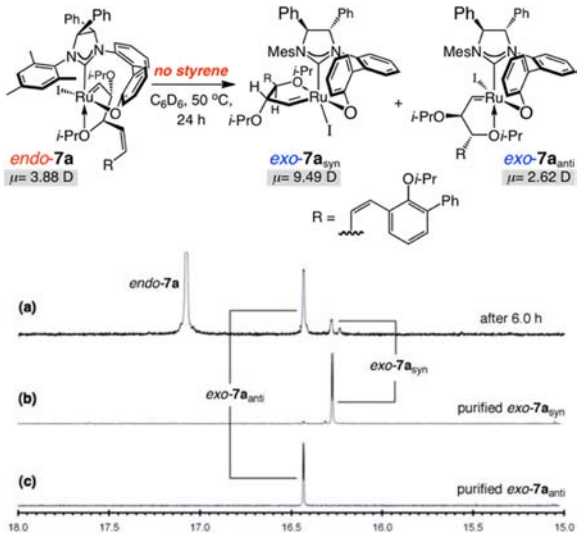
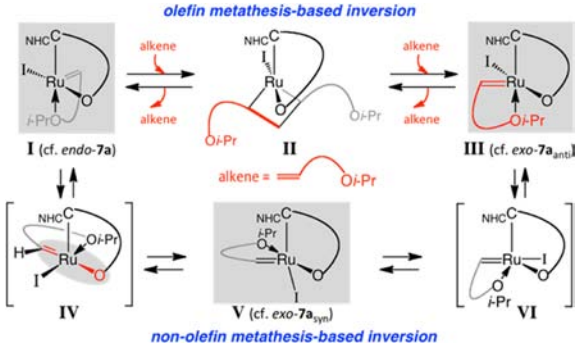


Figure 4. Thermal rearrangement of *endo*-**7a**, leading to *exo*-**7a**$_{syn}$ and *exo*-**7a**$_{anti}$, and ^{1}H NMR spectra (C_6D_6) of (a) the reaction mixture after 6.0 h, (b) isolated and purified *exo*-**7a**$_{syn}$, and (c) isolated *exo*-**7a**$_{anti}$. See the SI for details.

ligand.[20] The higher polarity of *exo*-**7a**$_{syn}$ probably results from the syn orientation of the anionic iodide and aryloxide ligands (anti in *exo*-**1a**, *endo*-**7a**, and *exo*-**7a**$_{anti}$; isopropyl ether is a neutral ligand).[21] The calculated structure of *exo*-**7a**$_{syn}$ exhibits a larger dipole moment than the other complexes (9.49 D for *exo*-**7a**$_{syn}$ vs 2.76, 3.88, and 2.62 D for *exo*-**1a**, *endo*-**7a**, and *exo*-**7a**$_{anti}$, respectively). When pure *exo*-**7a**$_{syn}$ was heated for several hours, it was transformed to *exo*-**7a**$_{anti}$, showing that the conversion of *endo*-**7a** to *exo*-**7a**$_{anti}$ can proceed via *exo*-**7a**$_{syn}$. Kinetic studies confirmed that the formation of *exo*-**7a**$_{anti}$ is first-order in *endo*-**7a** and occurs by a unimolecular process.[14]

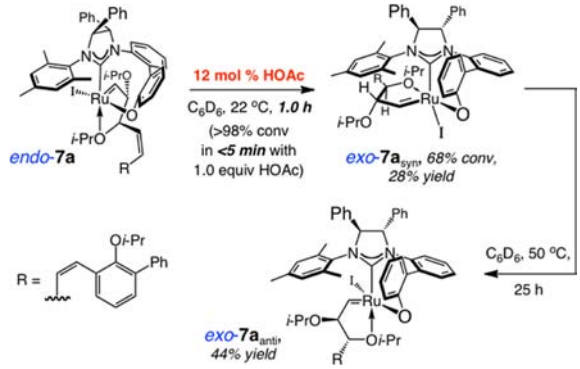
An OM reaction, as outlined in Scheme 2 (top), converts a Ru–alkene complex, such as that derived from **I** (cf. *endo*-**7a**), to a Ru carbene exemplified by **III** (cf. *exo*-**7a**$_{anti}$) via metallacyclobutane **II** (cf. **5** in Scheme 1); such a transformation can be regarded as a series of polytopal rearrangements[22] that involve bond cleavage and formation and lead to stereochemical inversion. As depicted in Scheme 2, *endo*-**7a** (cf. **I**) can also be converted to *exo*-**7a**$_{anti}$ via **IV**–**VI** by a *non*-OM-based process consisting of polytopal rearrangements.[22] A key conclusion of the present study is that in competition with metathesis-based polytopal rearrangements, isomerizations by nonmetathetic pathways can occur, impacting the efficiency and selectivity of the overall process.

Scheme 2. Two Pathways for Stereochemical Inversion



We then considered what other commonly encountered conditions, in addition to elevated temperatures, might promote non-metathesis-based interconversions of stereogenic-at-Ru complexes. Since a hallmark of Ru catalysts is their constitutional (vs stereochemical) stability toward functional groups that carry an acidic proton, we set out to establish whether polytopal isomerization can occur in the presence of a Brønsted acid. Such a possibility was founded on the hypothesis that rearrangement of an endo carbene such as *endo*-**7a** to the exo carbenes *exo*-**7a**$_{anti}$ and *exo*-**7a**$_{syn}$ likely proceeds via complexes in which the carbene and the aryloxide ligand—both strong donor groups—are situated in an anti orientation (cf. **IV** in Scheme 2). We envisioned that diminution of the aryloxide's donor ability, achieved through its interaction with an appropriate Lewis acid, might lower the barrier needed for the isomerization. The above deliberations led us to discover that, as illustrated in Scheme 3, treatment of *endo*-**7a** with 12

Scheme 3. Acid-Catalyzed Polytopal Rearrangement



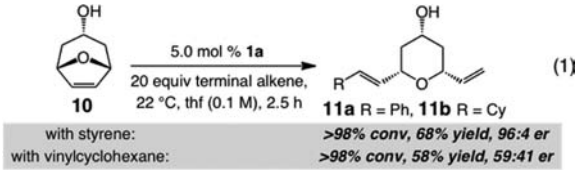
mol % HOAc at 22 °C (C_6D_6) resulted in 68% conversion to *exo*-**7a**$_{syn}$ (cf. **V** in Scheme 2) within only 1 h (vs >98% conv to *exo*-**7a**$_{anti}$ in 24 h by heating);[22] with 1.0 equiv of HOAc, isomerization was complete in less than 5 min. To ascertain that conversion to *exo*-**7a**$_{syn}$ was not induced by coordination of the Lewis basic[23] carbonyl of acetic acid with the Ru center, we treated *endo*-**7a** with acetone, dimethyl sulfoxide, and MeOH, none of which led to any detectable change (<2%).

Unlike the conversion of *endo*-**7a** to *exo*-**7a**$_{syn}$, the isomerization of *exo*-**7a**$_{syn}$ to *exo*-**7a**$_{anti}$ is not facilitated by acetic acid (Scheme 3). The latter rearrangement does not involve the intermediacy of Ru complexes in which the aryloxide ligand is positioned trans to the carbene (cf. **VI** in Scheme 2); the presence of HOAc therefore does not impact the rearrangement. In principle, generation of *exo*-**7a**$_{anti}$ via *exo*-**7a**$_{syn}$ can occur by an isopropoxy group dissociation/carbene bond rotation/reassociation pathway. Theoretical studies of quinoline-chelated nonstereogenic-at-Ru complexes have revealed that the aforementioned route and the polytopal rearrangement pathway might be energetically similar.[24] Nonetheless, it is unlikely that loss of chelation/rechelation is facile; otherwise, isolation of *exo*-**7a**$_{syn}$ would not be feasible.

The knowledge that Ru carbenes undergo competitive stereoisomerizations that are not induced by OM provides insight regarding the origin of some of the existing reactivity and selectivity profiles. The present systems involve association of oxygen-based chelates with the Ru center in place of an alkene. It is thus likely that the less structurally rigid complexes with a monodentate NHC and/or a carbene more readily undergo polytopal isomerizations, including OM reactions.[7a]

dx.doi.org/10.1021/ja3056722 | J. Am. Chem. Soc. 2012, 134, 12438–12441

The nonmetathetic interconversions of higher-energy carbenes can account for errors in copolymerization of alkene substrates performed with complexes such as **2** (Figure 1).[5] Another example pertains to catalytic ROCM performed with **1a**; high enantioselectivity likely demands that only one of the two forms participate in the stereochemistry-determining RO step; the less energetic exo species participates in RO of the strained alkene, and the endo carbene is involved in product-releasing CM.[11b] Conditions that promote out-of-sequence non-OM-based isomerization of the higher-energy endo carbene engender diminished enantioselectivities. Such considerations provide a rationale for the enantioselectivity differences in enantiomeric ratio (er) values in Ru-catalyzed ROCM of oxabicyclic alkenes such as **10** with aryl- versus alkyl-substituted terminal olefins (eq 1).[25] Since there is minimal non-OM-based



(1)

isomerization with the faster-forming benzylidene intermediates, **11a** is obtained in higher enantioselectivity than **11b** (i.e., less out-of-sequence interconversion with the aryl olefin).

More detailed computational and mechanistic studies and utilization of the concepts described above in the design of more efficient catalysts and stereoselective OM protocols are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

amir.hoveyda@bc.edu

Author Contributions

†R.K.M.K. and A.R.Z. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NSF (CHE-0715138 and 1111074). A.R.Z. and R.V.O. were LaMattina Graduate Fellows and S.T. was a Swiss NSF Postdoctoral Fellow.

■ REFERENCES

(1) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.
(2) For the mechanism of Ru-catalyzed OM, see: (a) Sanford, M. S.; Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. *1*, p 112. (b) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496.
(3) Meek, S. J.; Malcolmson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407.
(4) (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502. (c) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.
(5) (a) Bornand, M.; Chen, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7909. (b) Bornand, M.; Torker, S.; Chen, P. *Organometallics* **2007**, *26*, 3585. (c) Torker, S.; Muller, A.; Sigrist, R.; Chen, P. *Organometallics* **2010**, *29*, 2735.
(6) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693 and references cited therein.
(7) For stereogenic-at-Mo catalysts, see: (a) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933. (b) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.
(8) For stereogenic-at-W catalysts, see: Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88.
(9) (a) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933. (b) Muetterties, E. L. *J. Am. Chem. Soc.* **1969**, *91*, 1636. (c) Gillespie, P.; Hoffman, P.; Klusacek, H.; Marquarding, D.; Pfohl, S.; Ramirez, F.; Tsolis, E. A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 687.
(10) The designation is used according to whether the Ru=C bond is exo or endo with respect to the azaoxaruthenacycle.
(11) (a) Reference 5a. (b) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 34.
(12) Khan, R. K. M.; O'Brien, R. V.; Torker, S.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, DOI: 10.1021/ja304827a.
(13) For studies regarding structures of Ru-based metallacyclobutanes, see: (a) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032. (b) Wenzel, A. G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 16048. (c) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485. (d) Van der Eide, E. F.; Piers, W. E. *Nat. Chem.* **2010**, *2*, 571.
(14) See the Supporting Information (SI) for details.
(15) One endo isomer of a phosphine complex related to **2** (vs bidentate benzylidenes as in **1**–**3**) that is thermodynamically stabilized by a C–H agostic interaction has been isolated and characterized (see ref 5b).
(16) For detailed spectroscopic analyses to establish the identity of Ru complexes, see the SI.
(17) The calculated shift for the signal corresponding to *endo*-**7a** is similar in value to that measured experimentally (in $CDCl_3$, calcd 17.01 ppm, exptl 16.82 ppm). See the SI for details.
(18) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.
(19) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(20) Similar characteristics have been disclosed for a Ru-based bidentate carbene with a sulfide bridge syn to the NHC complex. See: Ben-Asuly, A.; Tzur, E.; Diesendruck, C. E.; Sigalov, M.; Goldberg, I.; Lemcoff, N. G. *Organometallics* **2008**, *27*, 811.
(21) A Ru complex is more polar when a bidentate carbene is chelated syn to the NHC than when associated anti to the same ligand. See: (a) Benitez, E.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 12218. (b) Correa, A.; Cavallo, L. *J. Am. Chem. Soc.* **2006**, *128*, 13352.
(22) For mechanistic aspects of polytopal rearrangements, see: (a) Couzijn, E. P. A.; Slootweg, J. C.; Ehlers, A. W.; Lammertsma, K. *J. Am. Chem. Soc.* **2010**, *132*, 18127 and references cited therein. (b) Moberg, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10290. For related isomerizations involving Ru complexes, see: (c) Hoffman, P. R.; Caulton, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 4221. (d) Krassowski, D. W.; Nelson, J. H.; Brower, K. R.; Hauenstein, D.; Jaconson, R. A. *Inorg. Chem.* **1988**, *27*, 4294.
(23) Marinescu, S. C.; Schrock, R. R.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 58.
(24) Poater, A.; Ragone, F.; Correa, A.; Szadkowska, A.; Barbasiewicz, M.; Grela, K.; Cavallo, L. *Chem.—Eur. J.* **2010**, *16*, 14354.
(25) In regard to the slower reaction of alkyl- vs aryl-substituted terminal olefins with Ru-based carbenes, see: Lane, D. R.; Beavers, C. M.; Olmstead, M. M.; Schore, N. E. *Organometallics* **2009**, *28*, 6789.