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Z- and Enantioselective Ring-Opening/Cross-Metathesis with Enol Ethers Catalyzed by Stereogenic-at-Ru Carbenes: Reactivity, Selectivity, and Curtin−Hammett Kinetics

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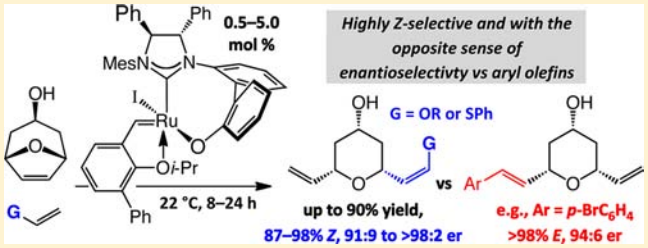
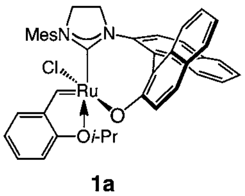
Supporting Information

ABSTRACT: The first instances of *Z*- and enantioselective Ru-catalyzed olefin metathesis are presented. Ring-opening/cross-metathesis (ROCM) reactions of oxabicyclic alkenes and enol ethers and a phenyl vinyl sulfide are promoted by 0.5−5.0 mol % of enantiomerically pure stereogenic-at-Ru complexes with an aryloxy chelate tethered to the N-heterocyclic carbene. Products are formed efficiently and with exceptional enantioselectivity (>98:2 enantiomer ratio). Surprisingly, the enantioselective ROCM reactions proceed with high *Z* selectivity (up to 98% *Z*). Moreover, reactions proceed with the opposite sense of enantioselectivity versus aryl olefins, which afford *E* isomers exclusively. Preliminary DFT calculations in support of Curtin−Hammett kinetics as well as initial models that account for the stereoselectivity levels and trends are provided.

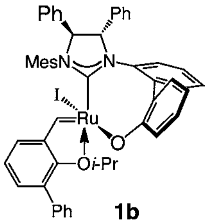


INTRODUCTION

We demonstrated a decade ago that stereogenic-at-Ru complex **1a**[1] can be prepared as a single diastereomer and used to promote enantioselective olefin metathesis;[2,3] a more active variant (**1b**) was introduced subsequently in 2005.[4] Ring-opening/cross-metathesis (ROCM) reactions can be performed with these Ru-based carbenes[1,4] with enantiomeric ratios (er's) that are generally higher than those attained with complexes bearing monodentate chiral N-heterocyclic carbene (NHC) ligands.[5] Similar levels of enantiomeric purity can be obtained with Mo-based alkylidenes that contain bidentate chiral diolates.[6] Nearly all transformations, however Ru- or Mo-catalyzed, deal with aryl-substituted alkenes and *E* isomers are formed solely or as the major products. Herein, we illustrate that stereogenic-at-Ru carbenes promote efficient ROCM of enol ethers and a vinyl sulfide. Transformations are not only exceptionally enantioselective (up to >98:2 er observed), the versatile products[7] are formed with remarkably high *Z* selectivity (up to 98%). To the best of our knowledge, there are no reported cases where enol ethers have been used in *E*- or *Z*-selective Ru-catalyzed alkene cross-metathesis; enol ethers or vinyl sulfides have not been previously utilized in any enantioselective olefin metathesis processes.[8,9]



1a
enantiomerically pure



1b
enantiomerically pure

A distinctive characteristic of **1a** and **1b** is that they contain a bidentate NHC with an aryloxy bridging ligand; this feature translates into a stereogenic metal center and two diastereomeric complexes, generated through stereochemical inversion (cf. $\mathbf{1c}_{exo}$ and $\mathbf{1c}_{endo}$, Scheme 1), which can participate in the catalytic cycle. The difference in the energetics and reactivity profiles of the aforementioned isomers is one reason why the ROCM processes carried out with such chiral carbenes proceed with minimal homocoupling and/or oligomerization.[2b] Stereogenic-at-Ru catalysts bearing a P,O-bidentate ligand that catalyze sequence-selective polymerization have been developed as well.[10] A related class of Ru carbenes with a bidentate NHC and an alkyl bridge has more recently been demonstrated to catalyze *Z*-selective olefin metathesis of unhindered terminal olefins.[11] In contrast to **1a** and **1b**, the latter two sets of complexes are used in the racemic form and thus cannot be employed in enantioselective synthesis.

RESULTS AND DISCUSSION

1. The Mechanistic Basis for Study of Ru-Catalyzed ROCM with Enol Ethers. The impetus for this investigation originated from the mechanistic principles outlined in Scheme 1. In ROCM with complex **1b** and aryl alkenes, several examples of which have been reported,[4] two Ru-based benzylidene diastereomers are present: $\mathbf{1c}_{exo}$ and $\mathbf{1c}_{endo}$ (G = Ar). DFT calculations point to the *exo* carbene as the favored isomer (vs *endo*; 3.9 kcal/mol).[12] The lower energy $\mathbf{1c}_{exo}$ can react with bicyclic alkene **2** to afford the higher energy $\mathbf{3}_{endo}$ in a

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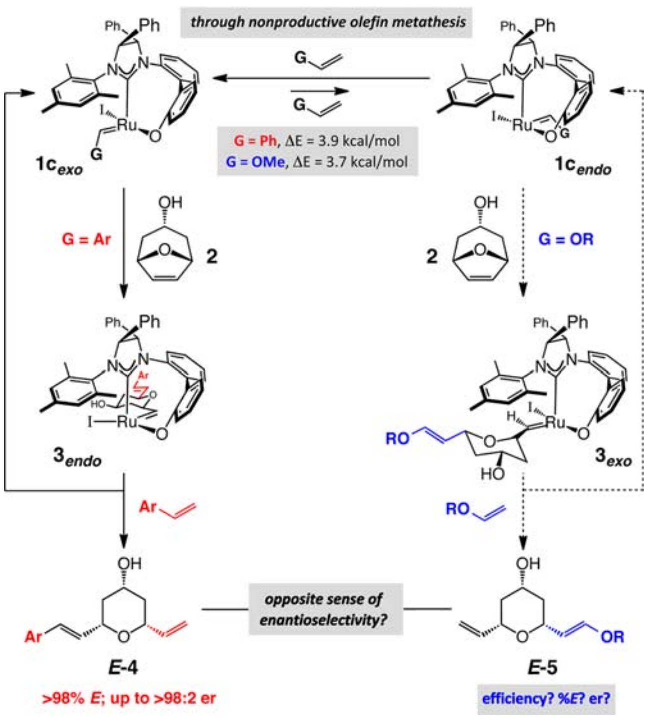
Scheme 1. Initial Hypothesis: Ru-Catalyzed ROCM of Styrenes vs Enol Ethers



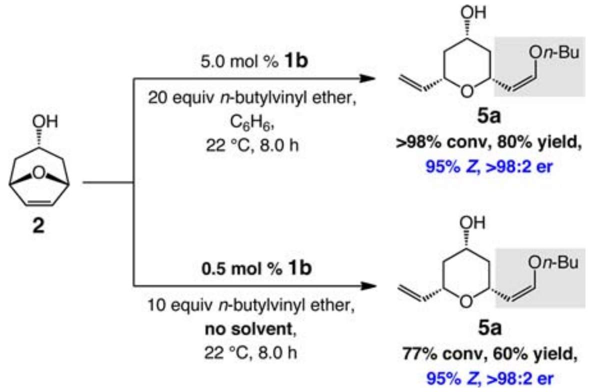
process for which strain release serves as the driving force. Ensuring cross-metathesis between **3**$_{endo}$ and an aryl alkene regenerates **1c**$_{exo}$ to furnish pyran **4** with high *E*- and enantioselectivity.

Preliminary theoretical inquiries indicated that the *exo* carbene derived from an enol ether is similarly favored (3.7 kcal/mol for complex obtained from methyl vinyl ether; Scheme 1).[12] In light of the lower activity of chiral monoaryloxides derived from a complex such as **1b** versus achiral Ru dichlorides, we surmised that reaction of an *exo* O-substituted carbene (**1c**$_{exo}$, G = OR, Scheme 1) with a cyclic alkene (e.g., **2**) would be unfavorable; such a process not only entails the conversion of a more preferred *exo* complex to its higher energy *endo* isomer, a resonance-stabilized “Fischer carbene”[13] would be converted to a less favored C-substituted variant.

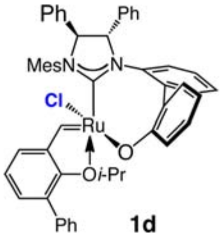
Additional calculations corroborated our concerns, indicating that *exo*−*endo* interconversion of heteroatom-substituted carbenes is less energetically demanding than the other steps in the catalytic cycle, and that Curtin−Hammett kinetics might be operative (see below for details).[12] These studies implied that the less abundant—but substantially more energetic—**1c**$_{endo}$ (G = OR, Scheme 1) might be available in sufficient quantities and reactive enough to promote opening of the cyclic alkene. The loss of resonance stabilization in the Fischer-type carbene would be compensated by ring strain release (~11 kcal/mol for **2**)[12] as well as the generation of a lower energy *exo*, albeit C-substituted, carbene. If the same mode of alkene addition were to remain favored (Scheme 1), such a pathway would reverse the sense of enantioselectivity compared to reactions with aryl olefins. We anticipated high *E* selectivity, as all previous ROCM reactions with this class of chiral Ru catalysts had uniformly afforded the lower energy disubstituted alkene isomer exclusively.[1,4]

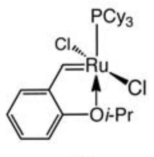
2. *Z*- and Enantioselective Ru-Catalyzed ROCM Reactions. We began by subjecting oxabicycle **2** to butyl vinyl ether (bve) and 5.0 mol % **1b** (Scheme 2). The desired process took place readily indeed, affording **5a** in 80% yield and >98:2 er. We established that the sense of enantioselectivity is opposite to that found in reactions with aryl olefins. Furthermore, and unexpectedly, we discovered that the *Z* enol ether is generated predominantly (95% *Z*-**5a**).[14] As further demonstrated in Scheme 2, the Ru-catalyzed ROCM can be performed with 0.5 mol % **1b** to afford **5a** in 60% yield, 95% *Z* selectivity, and >98:2 er. In stark contrast, in the recently disclosed version[7] of the process, catalyzed by stereogenic-at-Mo alkylidene complexes,[15] a uniform sense of enantioselectivity is observed regardless of whether an aryl olefins or an enol ether is used as the cross partner.[7] In other words, unlike stereogenic-at-Ru carbenes such as those derived from **1b**, the same Mo-based monopyrrolide alkylidene diastereomer is probably involved in the stereochemistry-determining stage of the transformation. The Mo-catalyzed ROCM reactions do not tolerate the presence of an unprotected alcohol.

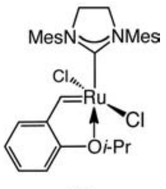
Scheme 2. *Z*- and Enantioselective Ru-Catalyzed ROCM with an Enol Ether



The outcome of reactions with different Ru complexes is shown in Table 1. Catalytic ROCM with chloride **1d** (entry 1, Table 1) furnishes **5a** in lower yield, *Z*- and enantioselectivity than when Ru iodide **1b** is employed (58% vs 80% yield, 97:3 vs >98:2 er, 92% vs 95% *Z* with **1d** and **1b**, respectively). Although achiral Ru phosphine **6a**[16] is far less effective in generating **5a**, the ROCM product is formed with 82% *Z* selectivity (entry 2, Table 1). Reaction with phosphine-free **6b**[17] (entry 3, Table 1) is slightly less facile than with **1b** or **1d**, in spite of being a more active and less conformationally constrained[18] Ru-dichloride; the major product is *E*-**5a** (77%).

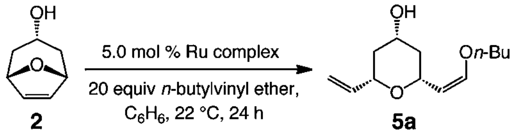

1d


6a


6b

Next, we analyzed the influence of alterations in the structure of the enol ether. Catalytic ROCM with the more sterically demanding cyclohexylvinyl ether affords **5b** in 64% yield, 98% *Z* selectivity (vs **5a** in 95% *Z*), and >98:2 er (entry 1, Table 2). With an aryl-substituted vinyl ether (entry 2), **5c** is obtained

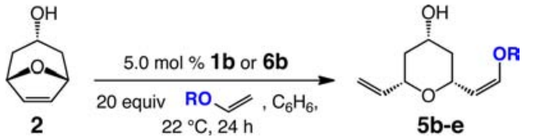
Table 1. *Z*- and Enantioselective ROCM with Other Ru-Based Complexes[a]



entry	Ru complex	conv (%)[b]	yield (%)[c]	*Z*:*E*[b]	er[d]
1	**1d**	85	58	92:8	97:3
2	**6a**	07	nd[e]	82:18	na[f]
3	**6b**	79	41	23:77	na[f]

[a] Reactions performed under N_2 atm. [b] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures and refers to consumption of the substrate. [c] Yield of isolated and purified products. [d] Determined by HPLC analysis; for determination of the absolute configuration of the major enantiomer, see the SI. [e] nd = not determined. [f] na = not applicable.

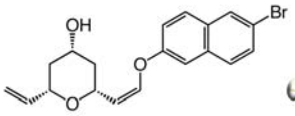
Table 2. ROCM with Ru Complexes 1b and 6b and Various Enol Ethers[a]



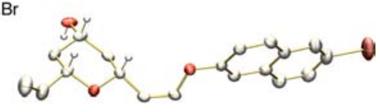
			with chiral complex **1b**			with achiral complex **6b**	
entry	R		conv (%);[b] yield (%)[c]	*Z*:*E*[b]	er[d]	conv (%);[b] yield (%)[c]	*Z*:*E*[b]
1	Cy	**b**	>98; 64	98:2	>98:2	>98; 58	37:63
2	PMP	**c**	>98; 67	95:5	97:3	>98; 41	43:57
3	CH_2CF_3	**d**	>98; 65	94:6	96:4	>98; 59	27:73
4	$(CH_2)_2Cl$	**e**	>98; 63	95:5	>98:2	>98; 31	24:76

[a] Reactions performed under N_2 atm. [b] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures and refers to consumption of the substrate. [c] Yield of isolated and purified products. [d] Determined by HPLC analysis; for determination of the absolute configuration of the major enantiomer, see the SI.

with the same *Z* selectivity as **5a** and in 97:3 er. The findings in entries 3–4 of Table 2 illustrate that enantiomerically enriched pyrans with an electron-withdrawing trifluoromethyl (**5d**) or a chloro ethyl ether substituent (**5e**) can be accessed with high *Z*- and enantioselectivity. The stereochemical identity of products from ROCM reactions with enol ethers was ascertained through the X-ray structure of **5f**, obtained in 90% yield, 89% *Z* selectivity, and 96:4 er (with 10 equiv of the corresponding enol ether).[12] As before (cf. Table 1), diminished yields (i.e., more significant oligomerization) and low *Z*:*E* values are observed with achiral dichloro-Ru **6b** as the catalyst precursor (Table 2, right column, entries 1–4).



5f
98% conv, 90% yield,
89% *Z*, 96:4 er

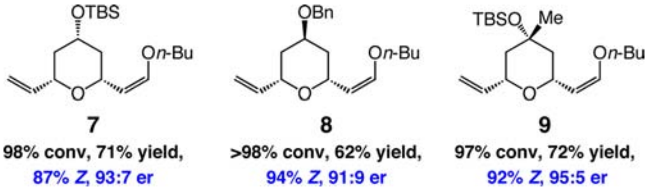


X-ray of **5f**

Treatment of **5a** with 5.0 mol % **6b** and 20 equiv of bve (C_6H_6, 22 °C, 12 h) leads to significant conversion to the corresponding *E* isomer (32% vs 95% *Z*; there is no detectable change in er). The latter finding, together with the 82% *Z* selectivity observed in the ROCM with **6a** (entry 2, Table 1),[19] imply that reactions with Ru-based dichlorides, such as **6a**,**b**, might be kinetically *Z*-selective. While the more active achiral carbene **6b** gives higher conversion, extensive postmetathesis isomerization might be taking place. The above observations point to a principal attribute of any *Z*-selective olefin metathesis process:[20] catalysts must efficiently promote ROCM without being too active to engender significant erosion of kinetic selectivity (see below for further discussion).

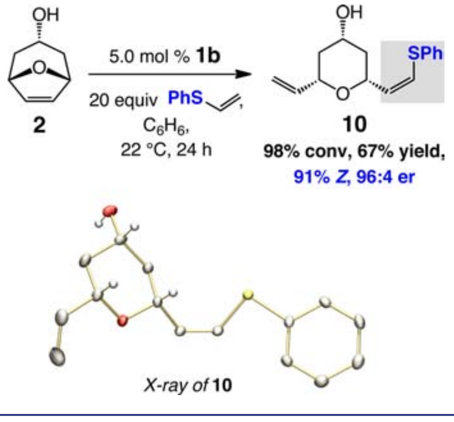
Enantioselective synthesis of *Z*-disubstituted alkenes **7–9** through ROCM of a silyl ether, the benzyl ether derived from the corresponding diastereomer of **2** (**8**), and a more sterically demanding tertiary ether (**9**), respectively, are presented in Scheme 3. The catalytic protocol can be applied to *Z*- and enantioselective synthesis of a range of trisubstituted pyrans.

Scheme 3. Enantioselective Ru-Catalyzed ROCM with Various Oxabicycles



We have investigated the reaction of cyclic olefin **2** with a S-substituted alkene, a member of a family of cross partners formerly shown to behave similarly to enol ethers in Ru-catalyzed olefin metathesis.[21] Vinyl sulfide **10** is obtained in 67% yield, 96:4 er, and with 91% *Z* selectivity (Scheme 4). As indicated by the X-ray structure (Scheme 4), the ROCM proceeds with the same sense of enantioselectivity as enol ethers—opposite to what is observed with aryl olefins. Consistent with the aforementioned significance of postmetathesis isomerization, when the reaction to generate **10** is analyzed after 75% conversion (14 h), complete *Z* selectivity is detected (>98% vs 91% at >98% conv in 24 h). The stereogenic-at-Ru complex therefore appears to possess some ability—albeit minimal—to promote *Z*-to-*E* conversion.

Scheme 4. *Z*- and Enantioselective Ru-Catalyzed ROCM with a Vinyl Sulfide



3. Preliminary Theoretical and Experimental Studies Regarding the Involvement of Curtin–Hammett Ki-

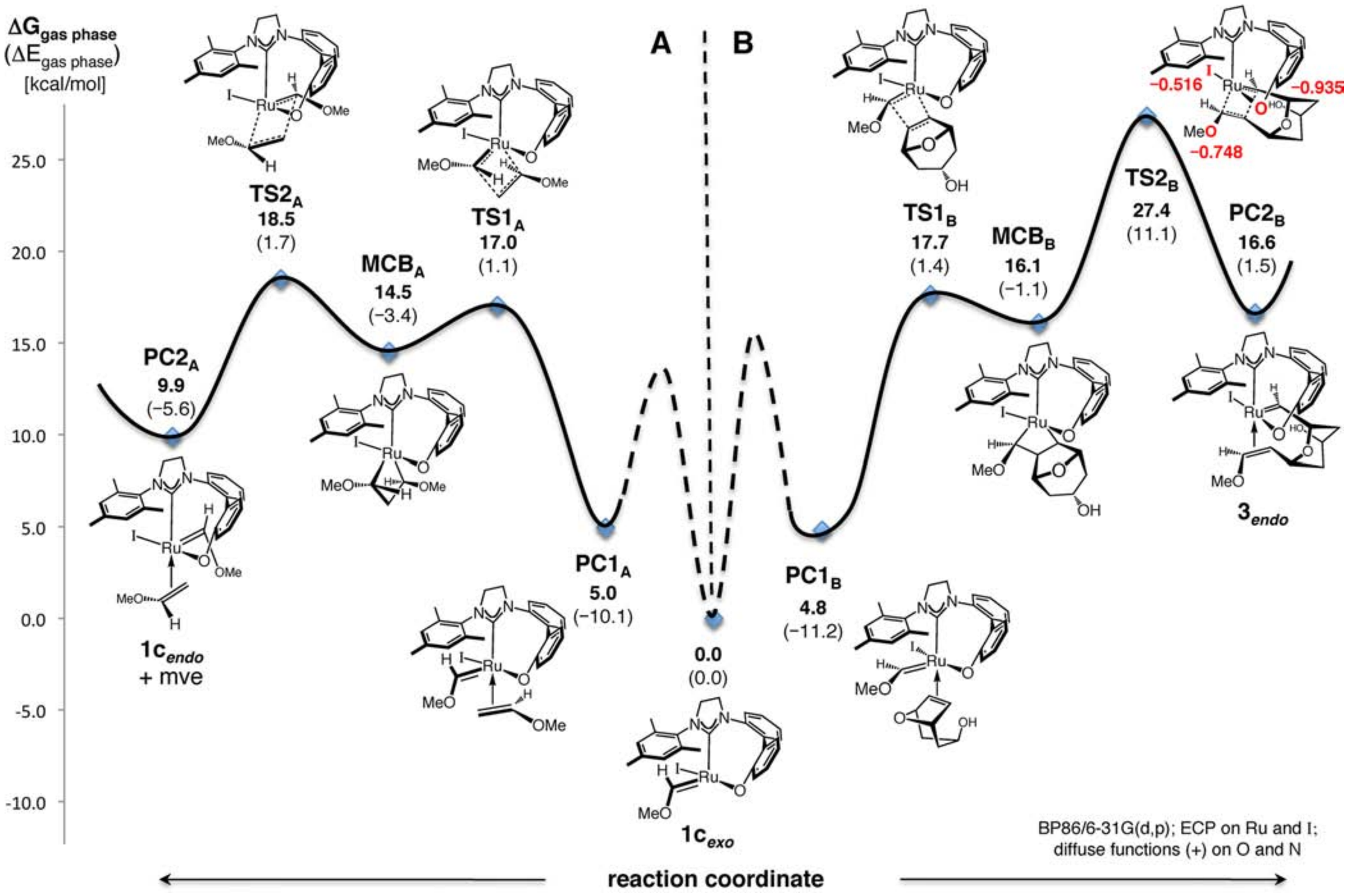


Figure 1. Computed energy barriers (ΔG in kcal/mol; bold values) for nonproductive olefin metathesis reactions of methylvinyl ether (A, $\mathbf{1c}_{exo} \rightarrow \mathbf{1c}_{endo}$ + mve) and productive ring-opening/cross-metathesis (ROCM) of the *exo* carbene derived from the same enol ether with oxabicyclic alkene **2** (B, $\mathbf{1c}_{exo} \rightarrow \mathbf{3}_{endo}$; non-Curtin−Hammett pathway). ΔE values (gas phase) are provided in parentheses. mve = methyl vinyl ether; PC = π complex, TS = transition state; MCB = metallacyclobutane.

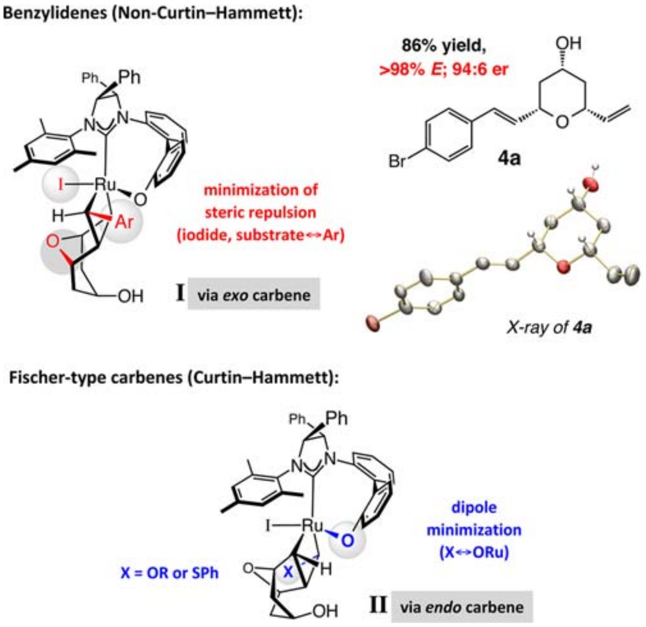
netics. To gain insight in connection with the aforementioned mechanistic nuances, we carried out additional theoretical studies, the results of which are illustrated in Figure 1.[22] In order to minimize the computational cost, the phenyl groups of the NHC moiety were omitted.[12] The relative difference in energy between the two diastereomeric 14-electron carbenes of the truncated model system (ΔE = 4.1 and 4.2 kcal/mol for G = Ph and OMe, respectively) proves to be only slightly larger compared to the full system presented in Scheme 1. Hence, we saw it fit to consider the model Ru complex as an appropriate approximation for further computational analysis (Figure 1).

The potential energy surfaces depicted in Figure 1, calculated for the reaction of the *exo* Fischer carbene $\mathbf{1c}_{exo}$ with either methyl vinyl ether or oxabicycle **2**, indicate that *exo*−*endo* interconversion of heteroatom-substituted carbenes is energetically less demanding than the other steps in the catalytic cycle, and that Curtin−Hammett kinetics can be operative.[12] Specifically, the low barrier ($\mathbf{TS2_A}$ = 18.5 kcal/mol; TS = transition state) to access the higher energy *endo* Fischer carbene $\mathbf{1c}_{endo}$ ($\mathbf{PC2_A}$; PC = π complex) through nonproductive olefin metathesis supports *fast* equilibration between the two diastereomeric carbenes, a requirement for Curtin−Hammett kinetics. In contrast, the barrier for the productive ring-opening metathesis step involving the cyclic alkene **2** through the lower energy Fischer carbene $\mathbf{1c}_{exo}$ to generate the product with the observed Z alkene stereochemistry (via intermediate $\mathbf{3}_{endo}$ ($\mathbf{PC2_B}$)) is found to be higher ($\mathbf{TS2_B}$ = 27.4 kcal/mol).

To explore the role of the diastereomeric carbenes yet further, we probed the identity of the complex formed by reaction of **1b** with bve. As forecasted by theory (Scheme 1 and Figure 1), spectroscopic analysis (NOE)[12] indicates the exclusive presence of an *exo* carbene (>98%; $\mathbf{1c}_{exo}$, G = O*n*-Bu, Scheme 1). The latter complex likely forms via the higher energy *endo* species (cf. $\mathbf{1c}_{endo}$), which undergoes isomerization by nonproductive cross-metathesis with another molecule of vinyl ether (cf. interconversion represented in section A, Figure 1). The proposed scenario is confirmed by facile deuterium scrambling when a mixture of bve and d_3-*p*-methoxyphenyl vinyl ether is subjected to 0.5 mol % **1b** (C_6D_6, 22 °C, 2.0 h): 30% of monodeuterio-*p*-methoxyphenyl vinyl ether is detected (^{1}H NMR analysis).[12] The above experiments lend credence to the notion that nonproductive olefin metathesis with enol ethers is relatively fast and Curtin−Hammett kinetics can be applied to the present class of transformations.[23]

4. Preliminary Stereochemical Models. Rationales for the observed selectivities are presented in Scheme 5. With aryl alkenes, the stereochemical identity of which has been established through extensive chemical correlation[1,4,7a] as well as X-ray crystallography (e.g., **4a**, Scheme 5), *exo* benzylidenes are probably sufficiently reactive (vs Fischer-type carbenes) to serve as intermediates in ROCM.[24] Unfavorable propinquity

Scheme 5. Factors Leading to Different Stereochemical Outcomes



between the large aryl and the iodide ligand as well as the oxabicycle moiety is therefore avoided in metallacyclobutane **I**.

With enol ethers or the vinyl sulfide, transformations can occur via **II**, originating from the higher energy *endo* complex ("Curtin−Hammett pathway"). Consequently, heterocyclic product bearing a *Z* enol ether is formed with the opposite sense of enantioselectivity versus aryl olefins (cf. **I**). In **II**, the heteroatomic substituent might prefer to be anti to the Ru-aryloxide in order to minimize dipole. Since the substituent of an enol ether is relatively small (vs Ar),[25] steric repulsion between an OR unit or SPh in **II** and the iodide ligand would incur little energetic cost. The calculated charge density for the key heteroatoms provides the basis for the hypothesis involving dipole minimization. Thus, the atomic polar tensor (APT) charges for complex $\mathbf{TS2_B}$ (Figure 1) on the phenoxide oxygen (ORu), the iodide (I), and the methyl ether oxygen (OMe) are −0.935, −0.516, and −0.748, respectively.[12]

The stronger influence of steric factors in reactions with aryl olefins is supported by the calculations indicating that phenyl-substituted *E*-**4** is preferred by 2.8 kcal/mol, whereas enol ether *Z*-**5a** is only slightly higher in energy than its *E* isomer (0.36 kcal/mol).[12] As such, the high *E* selectivity in ROCM of aryl olefins can be expected to arise from a pathway that reflects the favorability of the corresponding trans products.[24] In contrast, enol ether *Z* selectivity is more catalyst-induced; there would otherwise be little selectivity or only a negligible preference for the *E* products. It is nevertheless difficult to decipher at the present time precisely what electronic or steric principles cause the oxabicyclic moiety in **II** to be oriented syn to the iodide ligand. Additional selectivity data and more detailed computational and mechanistic investigations are needed for a more extensive elucidation of factors that give rise to *Z* selectivities. The results of these investigations will be reported in due course.

■ CONCLUSIONS

The present study underscores a unique attribute of stereogenic-at-Ru catalysts: While substantial reactivity can be accessed by the higher energy diastereomeric *endo* form, the more prevalent but less active *exo* isomer (catalyst's "resting state") does not cause significant erosion of the kinetically generated stereoselectivity. As a result, appreciable efficiency and high *Z*- and enantioselectivity can be attained. The results of the investigation described here highlight the ability of enantiomerically pure complexes to provide insight that would remain undetected if an achiral or a racemic mixture of a chiral catalyst were used[23] (i.e., enantioselectivity with enol ethers vs aryl alkenes); such characteristics might be relevant to other *Z*-selective stereogenic-at-Ru carbenes.[11] The above findings constitute the first cases of efficient Ru-catalyzed stereo- and/or enantioselective olefin metathesis reactions with enol ethers, and lend further credence to the emerging role of chiral catalysts in controlling alkene stereochemistry in olefin metathesis.[2b,7,10d,11a]

In addition to more in-depth mechanistic investigations, design and development of new Ru-based catalysts and stereoselective olefin metathesis protocols based on the findings described in this report, as well as applications to synthesis of complex molecules, are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for substrates and products and theoretical studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Another noteworthy example can be found in ref 8a, where an ROCM reaction catalyzed by a first-generation Ru-dichloride is reported to afford 85% *Z*-alkene product in 17% yield.

(20) For the importance of interplay between kinetic *Z* selectivity and postmetathesis isomerization in Mo- and W-catalyzed processes, see: (a) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461. (b) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88.

(21) For relative reactivity of O- and S-substituted Fischer-type carbenes, see: (a) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153. (b) Katayama, H.; Urushima, H.; Ozawa, F. *Chem. Lett.* **1999**, 369.

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(23) For the role of Curtin−Hammett kinetics in enantioselective reactions with enantiomerically pure stereogenic-at-Mo alkylidene complexes, see: Meek, S. J.; Malcolmson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407.

(24) Control experiments indicate that the high *E* selectivity in ROCM reactions with aryl olefins is not due to facile postmetathesis isomerization. For example, subjection of a mixture of oxabicycle **2** and styrene (20 equiv) to 0.1 mol % **1b** at 22 °C leads to 63% conversion after 30 min and the desired product exclusively as the *E* isomer (<2% *Z* as judged by ^{1}H NMR analysis).

(25) For *Z*-selective Ru-catalyzed cross-metathesis between vinyl sulfides and 1,2-dichloroethylene, see: (a) Macnaughtan, M. L.; Gray, J. B.; Gerlach, D. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2009**, *28*, 2880. (b) Sashuk, V.; Samojlowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468.