Olefin Metathesis

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Broadly Applicable *Z*- and Diastereoselective Ring-Opening/Cross-Metathesis Catalyzed by a Dithiolate Ru Complex**

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Abstract: *A broadly applicable Ru-catalyzed protocol for Z-selective ring-opening/cross-metathesis (ROCM) is disclosed. In addition to reactions relating to terminal alkenes of different sizes, the first examples of Z-selective ROCM processes involving heteroaryl olefins, 1,3-dienes, and O- and S-substituted alkenes as well as allylic and homoallylic alcohols are reported. Z-Selective transformations with an α-substituted allylic alcohol are shown to afford congested Z alkenes with high diastereoselectivity. Transformations are performed in the presence of 2.0–5.0 mol % of a recently disclosed Ru-based dithiolate complex that can be easily prepared in a single step from commercially available starting materials. Typically, transformations proceed at ambient temperature and are complete within eight hours; products are obtained in up to 97 % yield, >98:2 Z/E, and >98:2 diastereomeric ratio. The present investigations reveal a mechanistically significant attribute of the Ru-based dithiolates that arises from electrostatic interactions with anionic S-based ligands.*

A transformative development in olefin metathesis is the recent emergence of catalysts for efficient synthesis of *Z* alkenes.[1] The first advance was reported in 2009 in connection with a monopyrrolide-aryloxide Mo complex promoting ring-opening/cross-metathesis (ROCM) processes with a strong preference for *cis* olefin products.[2] Mo- and W-catalyzed *Z*-selective homocoupling,[3] cross-metathesis,[4] and macrocyclic ring-closing metathesis[5] were subsequently introduced. Since 2011, several Ru carbenes have also been shown to catalyze different *Z*-selective olefin metathesis reactions.[6,7] The complementary profiles of high-oxidation-state alkylidenes and later-transition-metal carbenes impart significant scope to this important set of catalytic transformations.[8] The latest progress notwithstanding, major shortcomings remain unaddressed. One limitation is the persisting lack of *Z*-selective reactions with allylic or homoallylic alcohols, processes that are in the exclusive purview of Ru-based catalysis. There are no instances of transformations that afford *cis* heteroaryl-substituted alkenes, and the lone examples of Ru-catalyzed *Z*-selective ROCM with O- and S-substituted olefins are promoted by a complex that furnishes *trans* products with other substrate types.[9] *Z*-Selective olefin metathesis with 1,3-dienes is scarce; the existing cases involve Mo-catalyzed homocoupling[10] and two cross-metathesis reactions.[4b] Instances of *Z*- and diastereoselective ROCM are unknown.

Herein, we report Ru-catalyzed *Z*-selective ROCM reactions of aliphatic as well as heteroaryl olefins, 1,3-dienes, O- and S-substituted alkenes, and allylic and homoallylic alcohols. Transformations are performed in the presence of 2.0–5.0 mol % of a readily accessible Ru dithiolate complex, typically proceed at ambient temperature, and are complete within eight hours; desired products are generated in up to 97 % yield, >98:2 *Z*/*E*, and >98:2 diastereomeric ratio (d.r.). Our findings suggest that the anionic disulfide ligand likely facilitates ROCM by forming a proton bridge with an allylic alcohol derived carbene.

We have demonstrated that Ru carbene **1**, accessed in a single step from a commercially available Ru dichlorocarbene and the disodium salt of dithiocatechol, can be used to promote efficient and exceptionally *Z*-selective ring-opening metathesis polymerization and ROCM;[11] reaction rates appear to be similar to those of processes catalyzed by commonly used (non-stereoselective) Ru-based dichlorides. Dithiolate complex **1** was conceived based on the principle that ruthenacyclobutanes would be formed exclusively *syn* to the N-heterocyclic carbene (NHC) (**I** vs. **II** or **III**, Scheme 1), and that steric repulsion between the metallacycle substituents and the sizeable NHC leads to a preference for *cis* products. We have demonstrated that, in contrast to the other *Z*-selective Ru complexes,[6] **1** can be utilized with sterically hindered alkenes (e.g., styrenes).

We have since focused on additional key questions. One is whether reactions with alkenes bearing relatively small groups would deliver high *Z*/*E* ratios, in spite of the reduced steric repulsion with mesityl moieties of the NHC ligand (cf. **II** and **III**, Scheme 1). Efficient transformations with hindered alkenes are readily catalyzed; however, there are complications associated with reactions of smaller substrates. Unhindered olefins undergo more facile homocoupling to generate ethylene and the somewhat unstable methylidene complex. Additionally, processes of the more diminutive substrates afford relatively exposed disubstituted alkenes that are more susceptible to post-metathesis isomerization.[4a,c] Another issue is whether reactions with the sparsely examined enol ethers, dienes, and heteroaryl alkenes can proceed efficiently and stereoselectively. Finally, we sought to explore the possibility of allylic or homoallylic alcohols serving as effective substrates in ROCM with the new Ru complex.

We first probed the influence of the size of the terminal alkene cross-metathesis partners on the efficiency and

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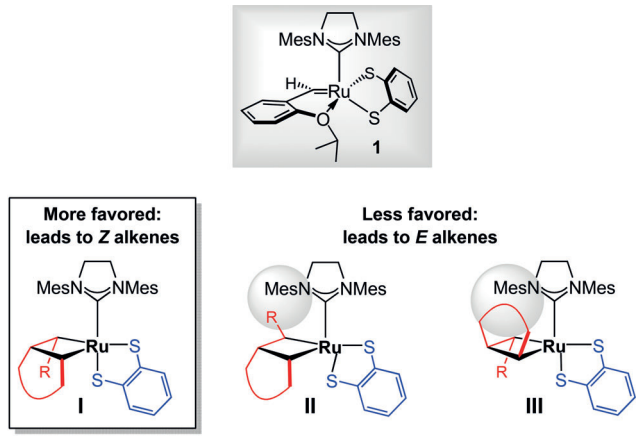
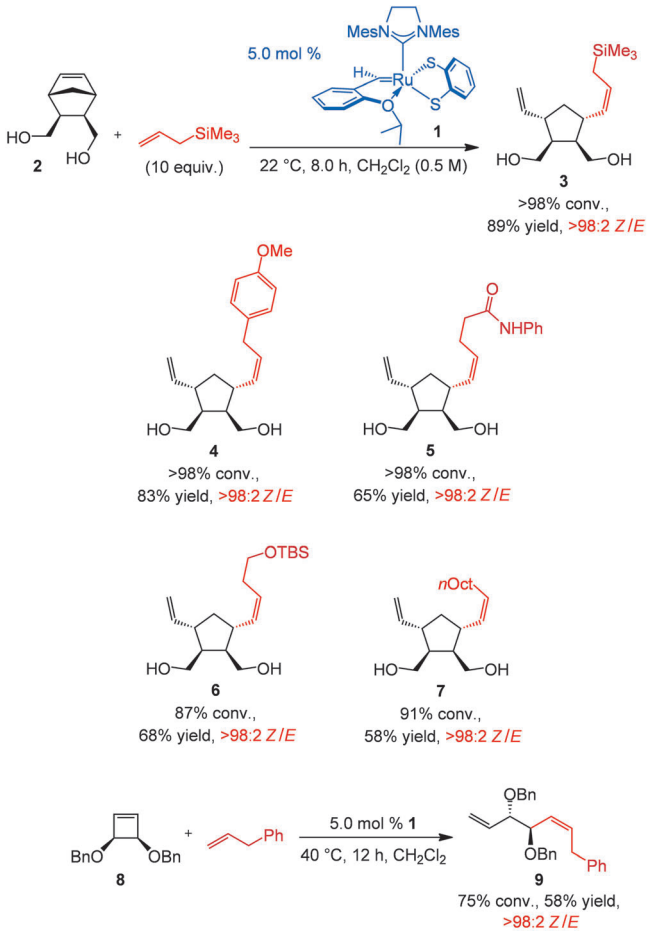


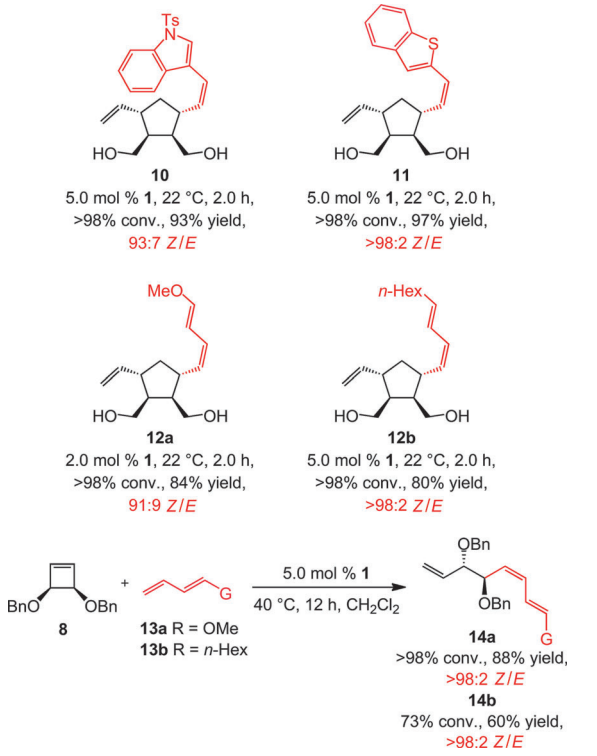
Scheme 1. Ru dithiolate **1**, the model for the origin of *Z* selectivity and potential intermediates **I**–**III** generated in reactions with alkenes.

stereoselectivity of ROCM reactions with diol **2**. With allyltrimethylsilane, where the alkene and the sizeable moiety are linked by a methylene unit (vs. styrenes or vinylcyclohexane), reaction proceeds to >98% conversion, affording *Z*-**3** in 89% yield as the sole isomer (<2% *E*); when the β-substituent is the smaller *p*-methoxyphenyl group, ROCM remains efficient and exceptionally *Z* selective (cf. **4**, Scheme 2). γ,δ-Unsaturated amide **5**, in which an additional methylene unit separates the C=C bond and the carbonyl-containing moiety, is formed with complete *Z* selectivity and in 65% yield. ROCM is likely less efficient owing to more competitive homocoupling of the terminal olefins and generation of the less robust methylidene. In further support of this hypothesis, under identical conditions, ROCM of **2** with a homoallylic silyl ether proceeds to 87% conversion, affording **6** in 68% yield and >98:2 *Z*/*E*. When the least hindered 1-decene is used, there is 91% conversion (disappearance of **2**) and diene **7** is isolated in 58% yield, yet the corresponding *E* alkene remains undetected. Transformation of cyclobutene **8** to diene **9** (58% yield, >98:2 *Z*/*E*) provides an additional example with a different cyclic olefin. The above findings indicate that exceptional *Z* selectivity persists despite the diminishing size of the substituent of a cross-metathesis partner. The steric repulsion between a mesityl moiety of the NHC and the substituents of a ruthenacyclobutane appears to be sufficient for the intermediacy of **II** or **III** to remain non-competitive with **I** even when R is relatively small.

Ru-catalyzed ROCM reactions can be used to produce heterocycle-substituted *Z* alkenes. As represented by synthesis of **10** and **11** (Scheme 3), products are obtained in 93–97% yield and 93:7 to >98:2 *Z*/*E* in no more than two hours at ambient temperature. We then examined the corresponding transformations with 1,3-dienes. In the presence of 2.0–



Scheme 2. Ru-catalyzed ROCM of **2** with different cross-metathesis partners indicates that exceptionally high *Z* selectivity can be isolated with diminishing substituent size. TBS = *tert*-butyl(dimethyl)silyl.

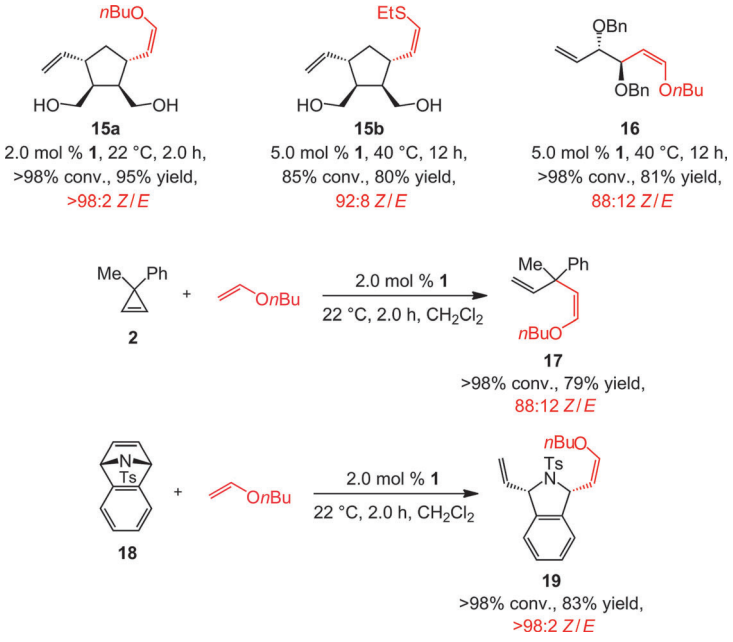


Scheme 3. *Z*-selective ROCM with heterocyclic alkenes and linear 1,3-dienes; same conditions used as shown in Scheme 2.

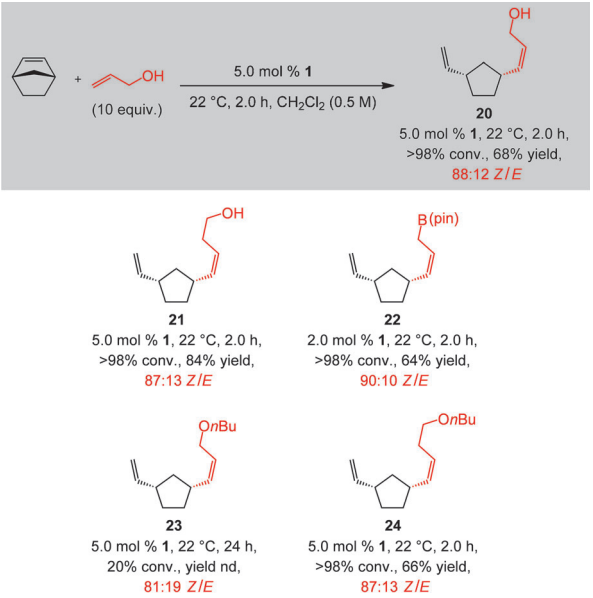
5.0 mol% **1**, use of (*E*)-1-methoxy-1,3-butadiene generates **12a** in 84% yield and 91:9 *Z*/*E*, and **12b** is isolated in 80% yield and >98% *Z* selectivity when (*E*)-deca-1,3-diene is employed; the latter processes proceed to completion in two hours at 22°C. Two other examples involving cyclobutene **8**, delivering **14a** and **14b** (88% and 60% yield, respectively) without a trace of the *E*,*E*-diene isomer (<2%), are shown in Scheme 3.[12] Thus, reactions with 1,3-dienes, such as **13a**,**b**, proceed with high *Z* selectivity despite the involvement of acyclic substrates that are smaller than the aryl-substituted alkenes (cf. **10**,**11**).

There is only one report of *Z*-selective Ru-catalyzed ROCM reactions of enol ethers or vinyl sulfides.[11] In the said study, a stereogenic-at-Ru carbene bearing a bidentate N-heterocyclic ligand was used, and it was the higher energy carbene diastereomer[13] that promoted the desired transformation. However, the ability of the iodoaryloxide Ru complex to catalyze *Z*-selective ROCM processes does not extend to other classes of alkenes (e.g., aryl or aliphatic olefins), where usually *E* isomers are obtained exclusively. In contrast, dithiolate complex **1** can be employed to generate *Z* enol ethers (Scheme 4). Transformations are efficient: with 2.0–5.0 mol% **1**, the desired O- or S-substituted carbo- or heterocyclic (**15a**,**b** and **19**, Scheme 4) as well as acyclic products (**16** and **17**) are obtained in 79–95% yield and 88:12 to >98:2 *Z*/*E*.

A recent investigation regarding Ru-catalyzed *Z*-selective ROCM entailed transformations of norbornene-derived bis-benzyl ether or bis-acetate with allyl acetate;[14] reactions with either or both of the parent alcohols were not mentioned. We therefore turned to the possibility of using allylic or homoallylic alcohols as cross-metathesis partners. ROCM of norbornene and allyl alcohol in the presence of 5.0 mol% **1** is complete in two hours (22°C), affording **20** in 68% yield and 88:12 *Z*/*E* (Scheme 5). Likewise, homoallylic alcohol **21** is formed in 84% yield and 87% *Z* selectivity. *Z*-Allylboron compounds, precursors to useful organic molecules (e.g., allylic amines[15]) can be readily accessed: ROCM with (pinacolato)allylboron generates **22** in 64% yield and 90:10 *Z*/*E*.



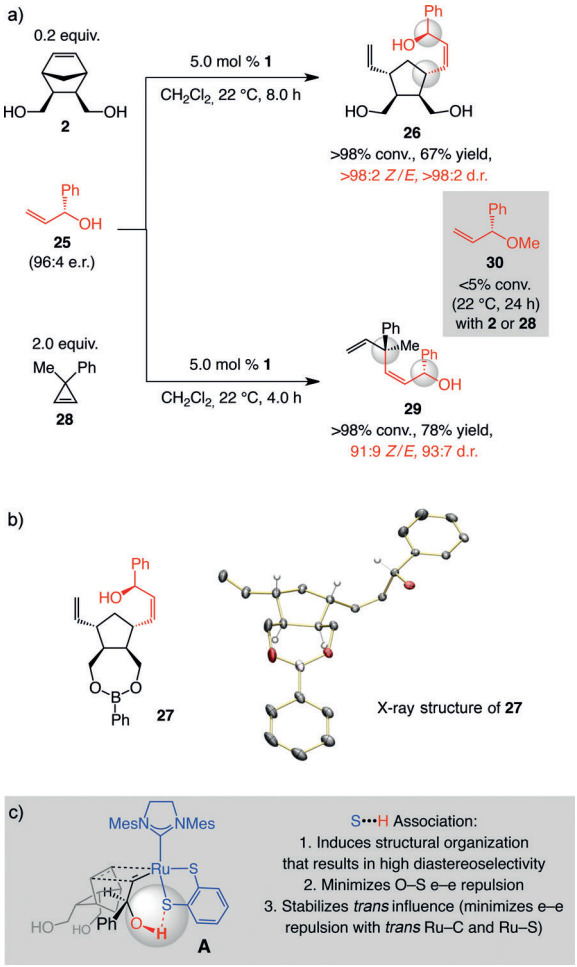
Scheme 4. ROCM reactions with O- or S-substituted alkenyl ethers proceed efficiently and with high *Z* selectivity.



Scheme 5. *Z*-selective ROCM with allyl alcohol and homoallyl alcohol; reaction with an allyl ether is inefficient but (pinacolato)allylboron and homoallyl ether are suitable substrates. B(pin) = (pinacolato)boron.

Contrary to the parent alcohol, ROCM of norbornene with allyl *n*-butyl ether gives rise to only 20% conversion to **23** even after 24 h (vs. >98% conv. in 2.0 h with allyl alcohol); such a difference in reactivity does not apply to homoallyl alcohol and its alkyl ether (cf. **21** and **24**). In view of the efficiency of reactions with linear alkenes (cf. Scheme 2), it appears that insertion of an ether oxygen at the allylic position (cf. **23**) induces an unfavorable effect, one that is no longer present when allyl alcohol is used (cf. **20**). To gain further insight, we examined the reaction of an enantiomerically enriched secondary allylic alcohol, since the ease with which the sterically congested *Z*-alkene is generated could further substantiate the positive impact of the hydroxyl group. Moreover, whether the latter ROCM proceeds diastereoselectively would shed additional light on the nature of the positive influence of the alcohol unit.

Subjection of commercially available allylic alcohol **25** (96:4 enantiomeric ratio) with cyclic alkene **2** (5:1) in the presence of 5.0 mol% **1** affords triol **26** in 67% yield as a single diastereomer (>98:2 *Z*/*E* and >98:2 d.r.; Scheme 6a). The identity of the major isomer was established by the X-ray structure of the phenylboronate derivative **27** (Scheme 6b). When **25** is treated with cyclopropene **28** (1:2), under otherwise the same conditions, the congested *cis* alkene **29** is obtained in 78% yield, 91% *Z* selectivity and 93:7 d.r.



Scheme 6. a) Ru-catalyzed ROCM with enantiomerically enriched allylic alcohol **25** bears significant mechanistic implications and demonstrates that congested *Z* alkenes can be accessed. b) X-ray structure of the phenylboronate derivative **27**. c) Intermedate **A**. e.r. = enantiomeric ratio; d.r. = diastereomeric ratio.

There is < 5% conversion after 24 h (22 °C) when methyl ether **30** is used with either **2** or **28**.

The observations depicted in Scheme 6 underscore a key mechanistic factor. We have previously shown that allylic alcohols react significantly faster and with higher diastereoselectively than their protected variants in transformations catalyzed by Ru dichloride complexes.[16] Electrostatic attraction ("H-bonding") between the hydroxyl unit and the anionic halides was put forth as the principal reason for the rate acceleration and elevated d.r. values. The data in Scheme 6 indicate that similar principles are likely operative here (see **A**, Scheme 6c).[17] The resulting structural organization leads to high diastereofacial differentiation; additionally, it stabilizes the ruthenacyclobutane and the preceding transition state by minimizing the *trans* influence that arises from the placement of the NHC and sulfide groups. What is more, the proton bridge dispenses with the electron–electron repulsion that otherwise exists between the heteroatom-containing carbene substituent and the nearby sulfide (cf. **23**, Scheme 5).[18] The collective consequence is the distinctive ability of a Ru dithiolate to catalyze reactions with alkenes containing a proximal hydroxy group, likely because the sulfide group positioned opposite to the donor NHC ligand participates in favorable electrostatic interactions.

Development of more efficient catalysts and other types of stereoselective olefin metathesis reactions are in progress.

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[18] Similar unfavorable repulsive forces between the oxygen subsituent and the sulfide ligand are not likely in effect for vinyl (Scheme 4) and homoallylic ethers (cf. **6** in Scheme 2 and **24** in Scheme 5); it appears that it is the heteroatom within an allylic ether that engenders repulsive electronic interactions.

