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Enol Ethers as Substrates for Efficient *Z*- and Enantioselective Ring-Opening/Cross-Metathesis Reactions Promoted by Stereogenic-at-Mo Complexes: Utility in Chemical Synthesis and Mechanistic Attributes

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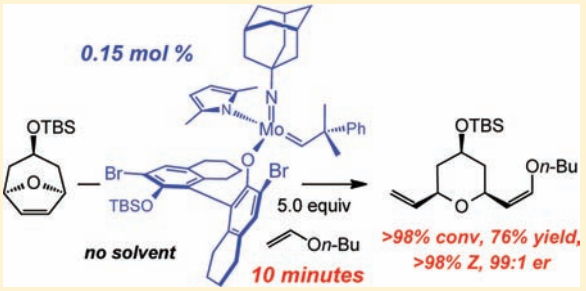
Supporting Information

ABSTRACT: The first examples of catalytic enantioselective ring-opening/cross-metathesis (EROCM) reactions that involve enol ethers are reported. Specifically, we demonstrate that catalytic EROCM of several oxa- and azabicycles, cyclobutenes and a cyclopropene with an alkyl- or aryl-substituted enol ether proceed readily in the presence of a stereogenic-at-Mo monopyrrolide-monoaryloxide. In some instances, as little as 0.15 mol % of the catalytically active alkylidene is sufficient to promote complete conversion within 10 min. The desired products are formed in up to 90% yield and >99:1 enantiomeric ratio (er) with the disubstituted enol ether generated in >90% *Z* selectivity. The enol ether of the enantiomerically enriched products can be easily differentiated from the terminal alkene through a number of functionalization procedures that lead to the formation of useful intermediates for chemical synthesis (e.g., efficient acid hydrolysis to afford the enantiomerically enriched carboxaldehyde). In certain cases, enantioselectivity is strongly dependent on enol ether concentration: larger equivalents of the cross partner leads to the formation of products of high enantiomeric purity (versus near racemic products with one equivalent). The length of reaction time can be critical to product enantiomeric purity; high enantioselectivity in reactions that proceed to >98% conversion in as brief a reaction time as 30 s can be nearly entirely eroded within 30 min. Mechanistic rationale that accounts for the above characteristics of the catalytic process is provided.



1. INTRODUCTION

Advances in catalytic olefin metathesis during the last two decades have transformed the way in which a great number of organic molecules can be prepared.[1] Cyclic structures of nearly any size and/or variety as well as a considerable number of unsaturated acyclic molecules are rendered easily accessible through this remarkable class of transformations.[2] Nonetheless, major advances remain to be achieved if catalytic olefin metathesis is to reach its true potential.[3] Discovery and development of catalysts that promote olefin metathesis efficiently and can control stereoselectivity—that is, furnish high *Z* or *E* selectivity and/or enantioselectivity—stands as a critical and challenging objective.

Since the first efficient cases of catalytic enantioselective olefin metathesis were reported in 1998 (ring-closing),[4,5] ring-opening/cross-metathesis (ROCM) processes have received significant attention.[6,7] Chiral Mo alkylidenes and Ru-based carbenes have been developed for desymmetrization of cyclic alkenes, generating carbo- or heterocyclic dienes enantioselectively. In 2007, we reported the first application of catalytic enantioselective ring-opening/cross-metathesis (EROCM) to the total synthesis of natural product baconipyrone C.[8] In spite of the above advances, a number of shortcomings remain unaddressed. One deficiency concerns the limited range of cross partners utilized: nearly all reactions have been with *aryl*-substituted alkenes. Furthermore, several problems relating to stereochemical control stand unresolved. High enantiomeric ratios are observed in a number of EROCM reactions; in most instances, however, either *E*-alkenes are formed predominantly or exclusively,[6a−d,7a−c,e] or a mixture of olefin isomers is generated with little or no stereochemical control.[7d,f] Another problem concerns the extensive reaction times (up to 120 h)[7e,f] that might be required for achieving high conversion; a more facile transformation is achievable but only at the expense of higher catalyst loadings. The issue of catalyst efficiency is a growing concern with transformations that are promoted by complexes derived from ruthenium, which is a relatively rare and increasingly precious metal.

Enol ethers are easily accessible cross partners that might be used in catalytic EROCM reactions[9] to afford versatile enantiomerically enriched products; there are, nonetheless, only a small number of cases where such O-substituted alkenes have been utilized as cross partners in intermolecular olefin metathesis

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reactions; all reported processes have been catalyzed by an achiral complex.[10] A disclosure by Ozawa in 2000 outlines a Ru-catalyzed transformation involving norbornene and phenylvinyl ether; the desired product was obtained in only 17% yield and, notably, with 85% *Z* selectivity.[11] Subsequent studies by Rainier offer five additional examples of transformations of ethylvinyl ether or enol acetate with 7-oxa- or 7-azanorbornenes, promoted by achiral Ru-based carbenes; nearly equal mixtures of *Z*- and *E*-alkenes were uniformly generated.[12] Thus, to the best of our knowledge, catalytic ROCM or EROCM reactions that involve an enol ether and which proceed with effective control of alkene stereoselectivity and/or enantioselectivity have not been disclosed.

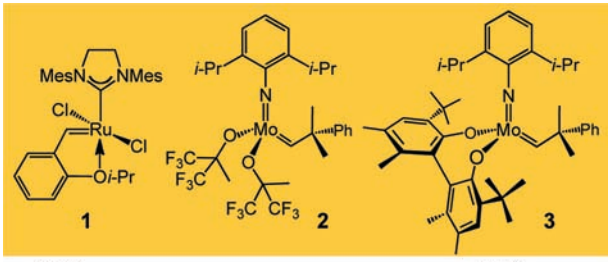
We have developed stereogenic-at-Mo and W complexes that display the unique ability to catalyze a range of olefin metathesis reactions with unique levels of efficiency and stereoselectivity.[13] We have demonstrated that the Mo- or W-based monopyrrolide-monoaryloxides promote ring-closing metathesis of dienes[14] or enynes[15] in high yield and with exceptional enantioselectivity. Subsequent investigations led us to establish that *Z*-selective EROCM[16] and homocoupling of terminal alkenes[17] as well as ethenolysis of *Z*-1,2-disubstituted olefins[18] can be performed. We have put forth the first examples of *Z*-selective cross-metathesis processes with enol ethers serving as one set of cross partners.[19] Most recently we have shown that the corresponding tungsten complexes can be used to promote *Z*-selective macrocyclic ring-closing metathesis.[20] In the case of catalytic EROCM, highly enantio- and *Z*-selective, reactions proved to be largely restricted to aryl olefins (i.e., styrenyl derivatives). Such a drawback diminishes utility, since the resulting aryl-substituted alkenes offer a limited range of possibilities for functionalization.[21]

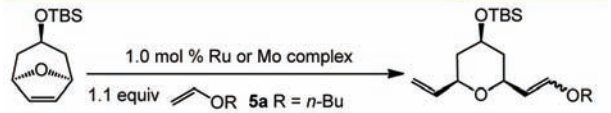
Here, we report a protocol for efficient, enantio- and *Z*-selective ROCM involving an alkyl- or aryl-substituted enol ether in combination with oxa- or azabicyclic alkenes, cyclobutenes or a cyclopropene. Transformations are promoted by 0.15−3.0 mol % of a stereogenic-at-Mo monopyrrolide-monoaryloxide and proceed to completion, typically at 22 °C, within 30 min. The desired cyclic or acyclic dienes, containing an easily differentiable terminal alkene and a vinyl ether in addition to one or more tertiary or quaternary carbon stereogenic centers, are generated in 61−90% yield, 85:15−99:1 enantiomeric ratio (er) and 84:16 to >98:2 *Z*:*E* selectivity. We show that, depending on the structure of the cyclic alkene, the amount of the terminal olefin present and the reaction time can have a significant influence on the enantioselectivity and efficiency of the EROCM (but not enol ether stereochemistry). As will be detailed below, such attributes are mechanistically important, offering valuable insights regarding the inner workings of this emerging class of olefin metathesis catalysts.[13−20]

2. RESULTS AND DISCUSSION

2.1. Preliminary Studies with Commonly Used Ru- and Mo-Based Complexes. We began by probing the ability of widely used Ru- and Mo-based complexes to catalyze a representative ROCM reaction with an enol ether. We selected silyl-protected oxabicycle **4** as the substrate and examined processes involving commercially and/or easily accessible *n*-butylvinyl ether **5a** or *p*-methoxyphenylvinyl ether **5b** (1.1 equiv vs **4**). As the data in entry 1 of Table 1 illustrate, with Ru carbene **1**, 69% disappearance of the cyclic alkene is observed after 30 min, but only 32% of the desired product (**6a**) is isolated; the remainder of the substrate is likely consumed through oligomerization. Furthermore, the resulting disubstituted

Table 1. ROCM Reactions Involving Enol Ethers Catalyzed by Some Commonly Used Ru- and Mo-Based Complexes[a]





entry	complex	enol ether	time (h)	conv (%);[b] yield (%)[c]	*Z*:*E*[b]
1	**1**	**5a**	0.5	69; 32	25:75
2	**1**	**5b**	0.5	95;<5	nd
3	**2**	**5a**	0.5	98; 10	50:50
4	**2**	**5b**	0.5	98; 14	80:20
5	**3**	**5a**	12	<2; nd	nd
6	**3**	**5b**	12	<2; nd	nd

[a]Reactions performed under N_2 atmosphere; see the Supporting Information for details. [b]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [c]Yield of products after purification by silica gel chromatography. nd = not determined.

enol ether moiety of the 2,4,6-trisubstituted pyran is generated as a 3:1 mixture of *E* and *Z* isomers. With the sterically more congested enol ether **5b** as the cross partner (entry 2, Table 1), 95% of **4a** disappears within 30 min, but oligomerization of the cyclic alkene represents the predominant pathway. In a similar fashion, with Mo-based diolate **2**, the relatively strained alkene is consumed rapidly, but the desired ROCM product is isolated in 10−14% yield (entries 3−4, Table 1), and the product enol ether is generated either nonselectively (1:1 *Z*:*E*; entry 3) or with moderate preference for the *Z* isomer (80% *Z*, entry 4). Finally, when chiral Mo diolate **3** is used, disappearance of the starting materials is not detected even after 12 h.

2.2. Stereogenic-at-Mo Monopyrrolides as Catalysts for EROCM Reactions with Enol Ethers and Utility in Chemical Synthesis. *2.2.1. Initial Examination of Various Mo-Based Monopyrrolides.* Next, we investigated whether stereogenic-at-Mo monopyrrolide-monoalkoxide or aryloxides might not only promote EROCM reactions efficiently and with high enantioselectivity, but deliver the resulting disubstituted enol ether with a high degree of *Z* selectivity as well. We thus discovered that reactions with Mo-based monopyrrolide monoalkoxide **7** and enol ethers **5a** or **5b** proceed with significantly higher efficiency than observed with the complexes shown in Table 1. As illustrated in entries 1−2 of Table 2, with 1.0 mol % catalyst in the presence of 1.1 equiv of either cross partner, there is complete consumption of oxabicycle **4a** within 30 min at 22 °C and **6a**-**b** are obtained in 48% and 75% yield, respectively, and with ∼80:20 *Z*:*E* selectivity (er is not applicable since **7** is racemic). Based on the formerly proposed models to account for *Z* selectivity observed in transformations promoted by stereogenic-at-Mo complexes,[16,19] we surmised that reactions

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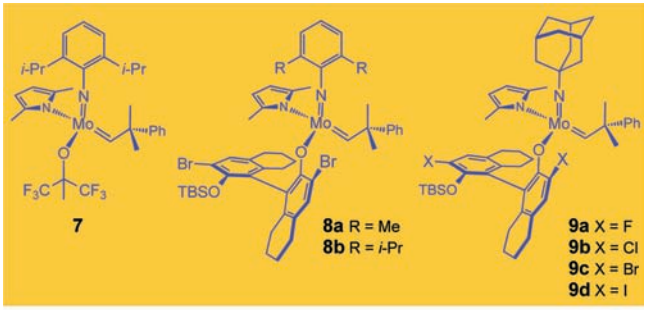
Table 2. Highly Efficient, *Z*- and Enantioselective ROCM Reactions with Various Stereogenic-at-Mo Complexes[a]



entry	complex; mol %[b]	enol ether	conv (%);[c] yield (%)[d]	*Z*:*E*[c]	er[e]
1	**7**; 1.0	**5a**	>98; 48	80:20	na
2	**7**; 1.0	**5b**	>98; 75	82:18	na
3	**8a**; 1.0	**5a**	85; 68	>98:2	99:1
4	**8a**; 1.0	**5b**	86; 47	>98:2	99:1
5	**8b**; 1.0	**5a**	<5; nd	nd	nd
6	**8b**; 1.0	**5b**	<5; nd	nd	nd
7	**9a**; 0.07	**5a**	>98; 87	>98:2	97:3
8	**9a**; 0.07	**5b**	60; 41	>98:2	88.5:11.5
9	**9b**; 0.5	**5a**	>98; 87	>98:2	98:2
10	**9b**; 0.5	**5b**	>98; 80	>98:2	92:8
11	**9c**; 0.6	**5a**	>98; 89	>98:2	99:1
12	**9c**; 0.6	**5b**	>98; 90	>98:2	98.5:1.5
13	**9d**; 0.7	**5a**	>98; 87	>98:2	98:2
14	**9d**; 0.7	**5b**	>98; 85	>98:2	98.5:1.5

[a]Reactions performed under N_2 atmosphere in C_6H_6; see the Supporting Information for details. [b]Except for alkylidene **7**, all complexes were prepared in situ from reaction of 1.0 mol % of the corresponding bispyrrolide and enantiomerically pure arylalcohol (effective catalyst loading shown). In the case of **9a**–**d** the catalyst loading shown is <1.0 mol %, since it represents the amount of monopyrrolide-monoaryloxide generated in the solution, as judged by the analysis of 400 MHz ^{1}H NMR spectra (the remainder is either unreacted bispyrrolide or bisaryloxide, which are substantially less active). [c]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [d]Yield of products after purification by silica gel chromatography (<±5%). [e]Enantiomer ratios were determined by HPLC analysis (<±2%); see the Supporting Information for details. na = not applicable; nd = not determined.

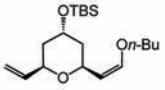
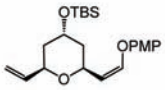
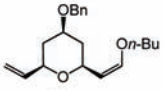
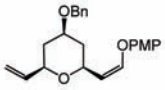
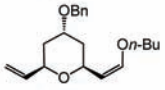
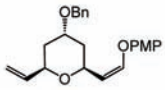
catalyzed by a related alkylidene that carries a larger aryloxide ligand might deliver improved stereoselectivity. Indeed, as the findings in entries 3–4 of Table 2 indicate, when dimethylarylimido aryloxide **8a** is employed, **6a-b** are generated exclusively as *Z* enol ethers (>98%) with exceptional enantioselectivity (99:1 er, respectively); however, efficiency is less than desirable, as the discrepancy between percent conversion and values of isolated products (cf. entries 3–4, Table 2) indicates incomplete transformation and significant oligomer formation. When the sterically more demanding di(*i*-propyl)arylimido complex **8b** is used (entries 5–6, Table 2), none of the desired EROCM products are generated within 30 min. After 12 h, under otherwise identical conditions, reactions with **5a** and **5b** result in 48% and 31% conversion, 34% and 27% yield and 96.5:3.5 and 97.5:2.5 er, respectively (>98% *Z* in both cases).

It is when Mo complex **9a**, bearing 3,3′-difluoroaryloxide and a relatively small adamantylimido (vs 2,6-dialkylarylimido), is used (entry 7, Table 2) that EROCM with *n*-butylvinyl ether **5a** proceeds with high efficiency (>98% conv, 87% yield), affording the desired pyran in high *Z*- and enantioselectivity (>98% *Z* and 97:3 er). The corresponding reaction with *p*-methoxyphenylenol ether (**5b**; entry 8, Table 2) proceeds to 60% conversion, affording **6b** in 41% yield, >98% *Z* selectivity but a lower 88.5:11.5 er (vs 97:3 with **5a**). The less efficient reaction could be the result of the larger size of the aryl substituent in **5b** (vs *n*-Bu in **5a**), exacerbated by the lower concentration of the catalytically active complex (0.07 mol % monopyrrolide-monoaryloxide generated in situ upon reaction of 1.0 mol % bispyrrolide and aryl alcohol;[22] 45–50% of the relatively less efficient bis-aryloxide[14] formed as the major component of the mixture). It follows that in the presence of the corresponding di*chloro*aryloxide **9b** (entries 9–10, Table 2), in situ formation of which is more efficient (0.5 mol % of the desired alkylidene generated), the EROCM products are isolated in higher yields (**6a** in 87% and **6b** in 80%), with enantioselectivity remaining high (98:2 and 92:8 er, respectively) and *Z* selectivity complete (>98%) in both instances. When the derived dibromide **9c** is employed (0.6 mol % generated from combination of 1.0 mol % each of the bispyrrolide and aryl alcohol; entries 11–12), further improvement in enantioselectivity is achieved and **6a-b** are generated in 99:1 and 98.5:1.5 er, respectively, without diminution in efficiency (89% and 90% yield, respectively) or control of enol ether stereochemistry (>98% *Z*). There is a nearly identical outcome when diiodoaryloxide **9d** is used (entries 13–14, Table 2). Since preparation of the requisite diiodoaryl alcohol for **9d** involves a relatively lengthy procedure,[23] we decided on dibromoaryloxide **9c** as the complex of choice for the follow-up investigations.

2.2.2. Mo-Catalyzed EROCM with Oxabicyclic Alkenes. We then turned to examining transformations of oxabicyclic alkenes of varying stereochemical identities that contain different protecting groups at their carbinol site. The results of this phase of our investigations are summarized in Table 3. When *exo* oxabicycle **10a** is subjected to 1.1 equivalents of *n*-butylvinyl ether **5a** (entry 1, Table 3) or *p*-methoxyphenylvinyl ether **5b** (entry 3, Table 3), EROCM proceeds readily to ≥97% conversion with >98% *Z* selectivity, but unexpectedly and in stark contrast to the reactions with the corresponding *endo* isomer **6a** (cf. Table 2), enantioselectivity is minimal (52:48 and 56.5:43.5 er for **11a** and **11b**, respectively). Subsequent studies, further discussed below, allowed us to establish that when larger amounts of enol ethers **5a-b** are utilized, as the data in entries 2 and 4 of Table 3 illustrate, the desired pyrans are formed in high enantioselectivity as a single enol ether isomer (>98% *Z*) and in 87–88% yield. The findings in entries 5–10 of Table 3, involving EROCM reactions of oxabicyclic benzyl ethers indicate that the requirement for excess cross partner for attaining high enantioselectivity is particular to *exo* oxabicyclic substrates (compare to entries 9–14 of Table 2). It should be noted that **12a-b** (entries 5–6, Table 3) as well as **13a-b** (entries 7–10) are generated with >98% *Z* selectivity regardless of the conditions used.

2.2.3. Mo-Catalyzed EROCM with an Azabicyclic Alkene, Two Cyclobutenes, and a Cyclopropene. *Z*-Selective Mo-catalyzed EROCM with enol ethers is not limited to reactions with oxabicyclic alkenes. As shown in entries 1–3 of Table 4, reaction with *endo* azabicycle **14** delivers 2,6-disubstituted piperidene. Although the process is significantly less efficient when lower amounts of the enol ether cross partner are employed

Table 3. *Z*- and Enantioselective ROCM Reactions Promoted by Stereogenic-at-Mo Complex 9c[a]

entry	substrate	major product	vinyl ether equiv	conv (%);[b] yield (%)[c]	*Z*:*E*[b]	er[d]
1			1.1	>98; 53[e]	>98:2	52:48
2	**10a**	**11a**	30	>98; 88	>98:2	95:5
3			1.1	97; 86	>98:2	56.5:43.5
4	**10a**	**11b**	20	>98; 87	>98:2	92:8
5			1.1	>98; 75	>98:2	96.5:3.5
	4b	**12a**				
6			1.1	>98; 80	>98:2	97:3
	4b	**12b**				
7			1.1	96; 54	>98:2	57.5:42.5
8	**10b**	**13a**	30	>98; 88	>98:2	95:5
9			1.1	94; 82	>98:2	82:18
10	**10b**	**13b**	20	>98; 87	>98:2	96.5:3.5

[a]Reactions performed under N_2 atmosphere in C_6H_6 with 0.6 mol % **9c** generated in situ from reaction of 1.0 mol % of the bispyrrolide and enantiomerically pure aryl alcohol; reaction time = 30 min; see the Supporting Information for details. [b]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [c]Yield of products after purification by silica gel chromatography (<±5%). [d]Enantiomer ratios were determined by HPLC analysis (<±2%); see the Supporting Information for details. [e]In addition, ~20% of the product from cross-metathesis of **10a** with another equivalent of **5a** is generated (based on 400 MHz ^{1}H NMR analysis).

(compare entries 1−2, Table 4), EROCM in the presence of 20 equivalents of **5b** (entry 3) generates the desired product with 92% *Z* selectivity, in 91:9 er and 90% yield. The relatively diminished preference for the *Z* isomer compared to the transformations involving oxabicyclic alkenes (cf. Tables 2−3) might be partly because to achieve high conversion with the less reactive azabicycle, elevated temperatures are needed (60 °C vs 22 °C); the reactivity differential is likely the reason for the necessity of a higher catalyst loading (3.0 vs 0.6 mol %) as well as the need for excess cross partner (20 equiv **5b**). Another attribute of the reactions with azabicycle **14**, one that is unlike the EROCM of oxabicycles (cf. Table 3), relates to lower *Z*:*E* ratios when fewer equivalents of **5a** or **5b** are employed. It is likely that such a difference arises to a degree from alkene isomerization at elevated temperatures: when the reaction in entry 1 of Table 4 is analyzed after 30 min (2.0 equiv **5b**, 60 °C), an 85:15 mixture *Z*- and *E*-**15** is observed (vs 75:25 after 3.0 h). Mechanistic factors that account for dependence of stereo- and enantioselectivity on enol ether concentration will be addressed below.

When bis-silylether cyclobutene **16** is used (entries 4−7, Table 4), similar to *endo* oxabicycles (Table 3), lower amounts of the catalyst (0.6 mol %) are sufficient for achieving >98% conversion; however, the requirement for excess enol ether for achieving higher enantioselectivity (cf. entries 4 vs 5 and 6 vs 7, Table 4) is reminiscent of the *exo* oxabicyclic alkenes (Table 3; see below for mechanistic rationale). With bis-benzyl ether cyclobutene **18** as the cyclic alkene (entries 8 and 9, Table 4), reactions are significantly more sluggish, in spite of the smaller size of the alkoxy groups (vs OTBS in **16**, entries 4−7 of Table 4). Such a difference in efficiency might be the result of internal chelation between the Mo center and the sterically accessible and Lewis basic benzyloxy, leading to the lowering of reaction rate.[24] Accordingly, as shown in entries 8 and 9 of Table 4, elevated temperatures (60 vs 22 °C in reaction of 16) are required for achieving complete conversion to bis-benzyloxy dienes **19a**,**b**, which are formed in 85:15 er and isolated in 61 and 73% yield, respectively. It is noteworthy that the *Z*:*E* value for synthesis of **19a** is lower than all other examples; this might partly arise from the elevated temperatures required for efficient EROCM, which could cause Mo-catalyzed isomerization of the kinetically preferred *Z*-enol ether. Isomerization of the sterically more hindered 1,2-disubstituted alkene in **19b** likely occurs less readily (98% *Z*; entry 9, Table 4). Catalytic EROCM of cyclopropene **20** (entries 10−11, Table 4) proceeds to >98% conversion in 30 min, affording 1,4-dienes **21a**,**b**, bearing a quaternary carbon stereogenic center, with complete *Z* selectivity, in 79 and 71% yield and 94.5:5.5 and 96.5:3.5 er, respectively. The lower enantioselectivities observed with cyclobutenes **16** and **18** (entries **4**−**9**, Table 4 vs cyclopropene **20**) is likely due to the lower degree of steric differentiation between the two faces of the cyclic alkene (i.e., the oxygen atom of the substituent reduces the effective size of the silyl and benzyl ether units).

2.2.4. Utility in Chemical Synthesis; Representative Functionalization of the Enantiomerically Enriched Z-Enol Ethers. A hallmark of the present class of catalytic reactions is

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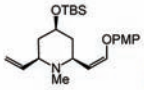
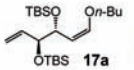
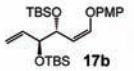
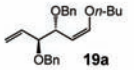
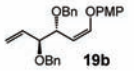
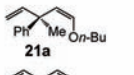
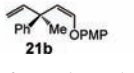
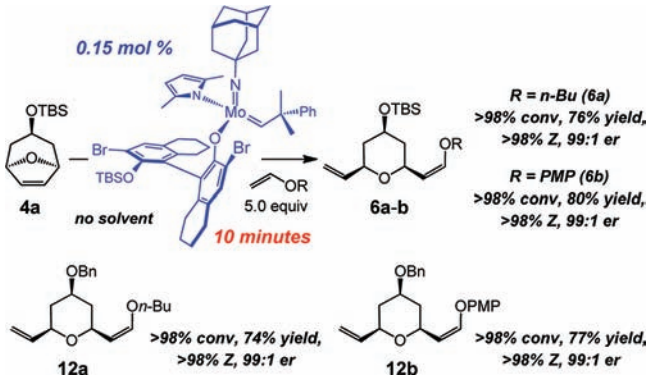
Table 4. Z- and Enantioselective ROCM Reactions of Enol Ethers with an Azabicycle, Cyclobutenes, and a Cyclopropene Promoted by Stereogenic-at-Mo Complex 9c[a]

entry	substrate	major product	mol % 9c[b]	temp (°C); time (h)	vinyl ether; equiv	conv (%);[c] yield (%)[d]	Z:E[c]	er[e]
1	 14	 15	3.0	60; 3.0	**5b**; 2.0	28; 25	75:25	72:28
2			3.0	60; 3.0	**5b**; 10	69; 50	80:20	75:25
3			3.0	60; 3.0	**5b**; 20	98; 90	92:8	91:9
4	 16	 17a	0.6	22; 0.5	**5a**; 1.1	60; 52	97:3	79.5:20.5
5			0.6	22; 0.5	**5a**; 10	>98; 90	96:4	86:14
6		 17b	0.6	22; 0.5	**5b**; 1.1	57; 34	95:5	68:32
7			0.6	22; 0.5	**5b**; 10	>98; 90	94:6	85:15
8	 18	 19a	0.6	60; 0.5	**5a**; 20	>98; 61	84:16	85:15
9		 19b	0.6	60; 0.5	**5b**; 20	>98; 73	98:2	85:15
10	 20	 21a	3.0	22; 0.5	**5a**; 10	93; 79	>98:2	94.5:5.5
11		 21b	3.0	22; 0.5	**5b**; 2	95; 71	>98:2	96.5:3.5

[a]Reactions performed under N_2 atmosphere in C_6H_6; see the Supporting Information for details. [b]All complexes were prepared in situ from reaction of 5.0 mol % (entries 1 and 8–9; effective catalyst loading = 3.0 mol %) or 1.0 mol % of the corresponding bispyrrolide and enantiomerically pure aryl alcohol (effective catalyst loading = 0.6 mol %). [c]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [d]Yield of products after purification by silica gel chromatography (<±5%). [e]Enantiomer ratios were determined by HPLC analysis (< ± 2%); see the Supporting Information for details. PMP = *p*-methoxyphenyl.

the degree of efficiency with which these highly Z- and enantioselective processes proceed. As further demonstration of the exceptional facility of the Mo-catalyzed transformations and as the representative cases in Scheme 1 illustrate, we have been able

Scheme 1. Highly Efficient Mo-Catalyzed Z-Selective EROCM Reactions[a]

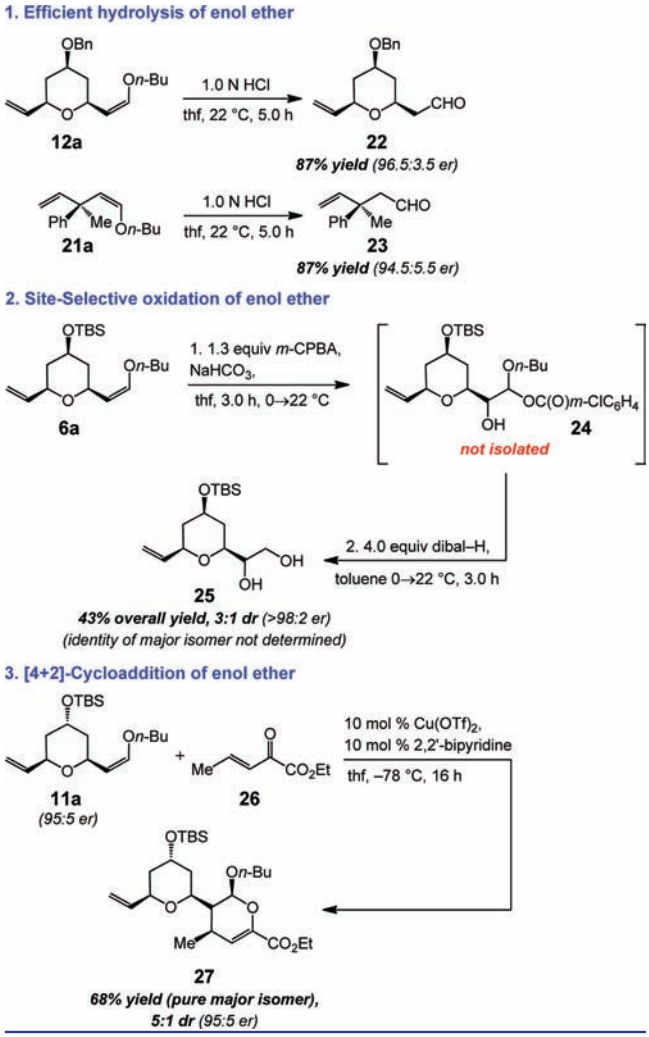


[a]All reactions performed under the conditions shown for formation of **6a,b**; for details on yields and er values, refer to Tables 2 and 3. See the Supporting Information for details.

to establish that reactions can be performed in minimal solvent[25] in the presence of only 0.15 mol % of the monopyrrolide-monoaryloxide, leading to complete consumption of starting materials within 10 min to afford the desired heterocyclic Z-enol ethers in >70% yield and with exceptional stereoselectivity.

The enantiomerically enriched dienes available through Mo-catalyzed EROCM can be functionalized in a variety of manners; several preliminary examples are provided in Scheme 2.

Scheme 2. Representative Functionalization Procedures with Enantiomerically Enriched Enol Ethers Obtained through Mo-Catalyzed ROCM Reactions



A noteworthy aspect of the present approach, in contrast to the related previously reported protocols involving styrenyl cross partners, is that the two alkenes of the products are electronically distinct and can be readily differentiated. Thus, as the formation of **22** and **23** illustrates, the enol ether moiety can be efficiently hydrolyzed to afford the desired aldehyde in 87% yield. Aldehydes such as **22** and **23** are versatile intermediates, allowing access to a range of additional enantiomerically enriched molecules. γ–δ-Unsaturated aldehyde **23**, bearing an all-carbon quaternary stereogenic center[26] at its β carbon constitutes the product of a conjugate addition, which does not have a catalytic enantioselective variant available.[27]

The Z-enol ether of the EROCM products can participate in stereoselective transformations; two examples are shown in

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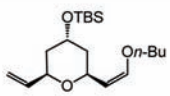
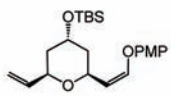
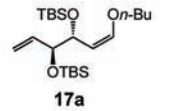
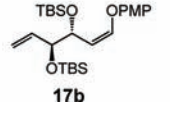
Scheme 2. Preliminary studies indicate that diastereoselective epoxidation/hydrolysis of **6a** affords **24**, which upon treatment with diisobutylaluminum hydride is converted to diol **25** as a 3:1 mixture of diastereomers in 43% overall yield.[28] Equally noteworthy is the Cu-catalyzed diastereoselective cycloaddition[29] that converts **10a** to bispyran **27** in 5:1 diastereoselectivity and 68% yield. Future development of more efficient strategies, reagents, and catalysts for functionalization of enol ethers is expected to enhance the utility of the enantiomerically enriched *Z*-enol ethers accessed through catalytic EROCM.

2.3. Mechanistic Analysis. The Significance of Stereogenicity at the Mo Center. *2.3.1. Influence of Post-EROCM Ring Closure on Product Enantiopurity; Rationale for the Effect of Larger Equivalents of Enol Ether Cross Partner.* As described above, in the case of certain cyclic alkene substrates, larger equivalents of the enol ether cross partner lead to higher enantioselectivity (cf. Tables 3 and 4). Specifically, EROCM reactions with oxabicyclic alkenes that contain an *exo*-siloxy or -benzyloxy group (entries 1−4 and 7−10 in Table 3) otherwise furnish 2,4,6-trisubstituted pyrans with relatively low enantiomeric purity (52:48−82:18 er vs 92:8−96.5:3.5 er with excess enol ether); this is in contrast to the corresponding *endo* derivatives (cf. Table 2 and entries 5−6, Table 3). Another set of transformations where enantioselectivity improves with excess enol ether, albeit to a lesser degree, relates to reactions with cyclobutenes **16** and **18** (cf. entries 4−9, Table 4). A systematic investigation with different amounts of **5a** or **5b**, summarized in Table 5, further underlines the strong dependence of enantioselectivity in Mo-catalyzed EROCM of the aforementioned selected cyclic alkenes. The level of *Z* selectivity, however, is unaltered by enol ether concentration in the above cases.

Table 5. Influence of the Amount of Enol Ether Cross Partner on the Efficiency and Enantioselectivity of EROCM Reactions[a,b]

entry	product	vinyl ether equiv	conv (%);[c] yield (%)[d]	*Z*:*E*[c]	er[e]
1		1.1	>98; 53	>98:2	52:48
2		5.0	>98; 80	>98:2	62.5:37.5
3		10	>98; 80	>98:2	73:27
4		20	>98; 85	>98:2	84.5:15.5
5	**11a**	30	>98; 88	>98:2	95:5
6		1.1	97; 86	>98:2	56.5:13.5
7		5.0	>98; 87	>98:2	84.5:15.5
8		10	>98; 90	>98:2	91.5:8.5
9		20	>98; 87	>98:2	92:8
10	**11b**	30	>98; 82	>98:2	91.5:8.5
11		1.1	60; 52	97:3	79.5:20.5
12		2.0	65; 53	97:3	80:20
13		5.0	97; 89	97:3	82.5:17.5
14	**17a**	10	>98; 90	96:4	86:14
11		1.1	57; 34	95:5	68:32
12		2.0	68; 58	94:6	75:25
13		5.0	98; 90	94:6	81:19
14	**17b**	10	>98; 90	94:6	85:15

[a]Reactions performed under N_2 atmosphere in C_6H_6 at 22 °C; see the Supporting Information for details. [b]The requisite complexes were prepared in situ from reaction of 1.0 mol % of the corresponding bispyrrolide and enantiomerically pure aryl alcohol (effective loading of **9c** = 0.6 mol %); reaction time = 30 min in all cases. [c]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [d]Yield of products after purification by silica gel chromatography (<±5%). [e]Enantiomer ratios were determined by HPLC analysis (<±2%); see the Supporting Information for details.

One likely reason for the dependence of enantioselectivity in EROCM of *exo*- (but not *endo*-) oxabicyclic substrates is related to the higher tendency of the corresponding products or the derived alkylidenes to undergo ring closure; reformation of the cyclic substrates leads to sequences of ring-opening/ring-closing reactions that can result in diminution of kinetically derived er values.[30] As illustrated in Scheme 3, the pyran ring within Mo alkylidene **II** is able to undergo ring-closing metathesis (RCM) to regenerate **10a**; although **II** can be converted to the conformational isomer **III**, the energetic difference is not such that the latter exists in solution exclusively. Such a chain of events allows the overall transformation to occur under more thermodynamically controlled (reversible) conditions, leading to diminution of enantioselectivity. In contrast, the alkylidene that is formed through reaction of the *endo*-oxabicycle (**IV**, Scheme 3) is unlikely to participate in a similarly facile RCM to regenerate the relatively more strained **4a** (vs *exo*-isomer **10a**), since the relatively high-energy all-axial pyran likely isomerizes rapidly to all-equatorial **V**, which cannot undergo RCM (Scheme 3). In the presence of excess amounts of enol ether, reaction with intermediate complexes **II** or **III** takes place more readily, minimizing the degree to which enantioselectivity-reducing equilibration takes place; therefore, higher er values are obtained with an increase in enol ether concentration.

The validity of the above scenario is supported by the substantial variations in enantiomeric purity of EROCM products as a function of reaction time; representative observations are presented in Table 6. Whereas within 30 s, pyrans **11a** and **11b** are obtained in 95:5 and 90:10 er (entries 1 and 2, Table 6), after only 3 min, enantioselectivity is decreased (84.5:14.5 and 86:14, respectively; entries 3 and 7); particularly in the case of **11a**, diminution of enantiomeric purity continues after 30 min (entries 4 and 8, Table 6). Facile rates of RCM/ROM can therefore lead to highly efficient erosion of er values.

To substantiate further the proposed mechanistic scenario, we resubjected several enantiomerically enriched pyrans to the reaction conditions to confirm that the aforementioned equilibration through RCM of pyran products is indeed detrimental. As the findings summarized in Table 7 indicate, loss of enantioselectivity by post-EROCM isomerization afflicts the reactions of *exo* bicyclic substrates (entries 3−4, Table 7) but, as predicted by the model illustrated in Scheme 3, significantly less erosion is observed with products derived from reactions of the *endo* diastereomers (entries 1−2).

2.3.2. Mo Alkylidene Isomerization through Nonproductive Olefin Metathesis and Variations in Enantioselectivity; Rationale for Enhanced Enantioselectivity Due to Increased Enol Ether Concentration. Another key factor to be considered is the identity of the alkylidene diastereomer (i.e., *S* or *R* at the Mo center) that reacts with the cyclic alkene. As outlined in Scheme 4, such principles can dictate which pyran-containing alkylidene stereoisomer is involved (**V** vs **X**, Scheme 4) and how critical is the facility with which the two oxygen-substituted alkylidene diastereomers isomerize (i.e., *S*-**I** vs *R*-**I** leading to **VII** vs **IX**, respectively, in Scheme 4).

Previous investigations performed in these laboratories involving examination of various kinetic parameters, and labeling studies as well as X-ray structures corresponding to the two diastereomeric forms of the stereogenic-at-Mo complexes,[31]

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Scheme 3. Relative RCM Rate of ROCM Products as a Function of Stereochemical Identity of the Intermediate Alkylidene

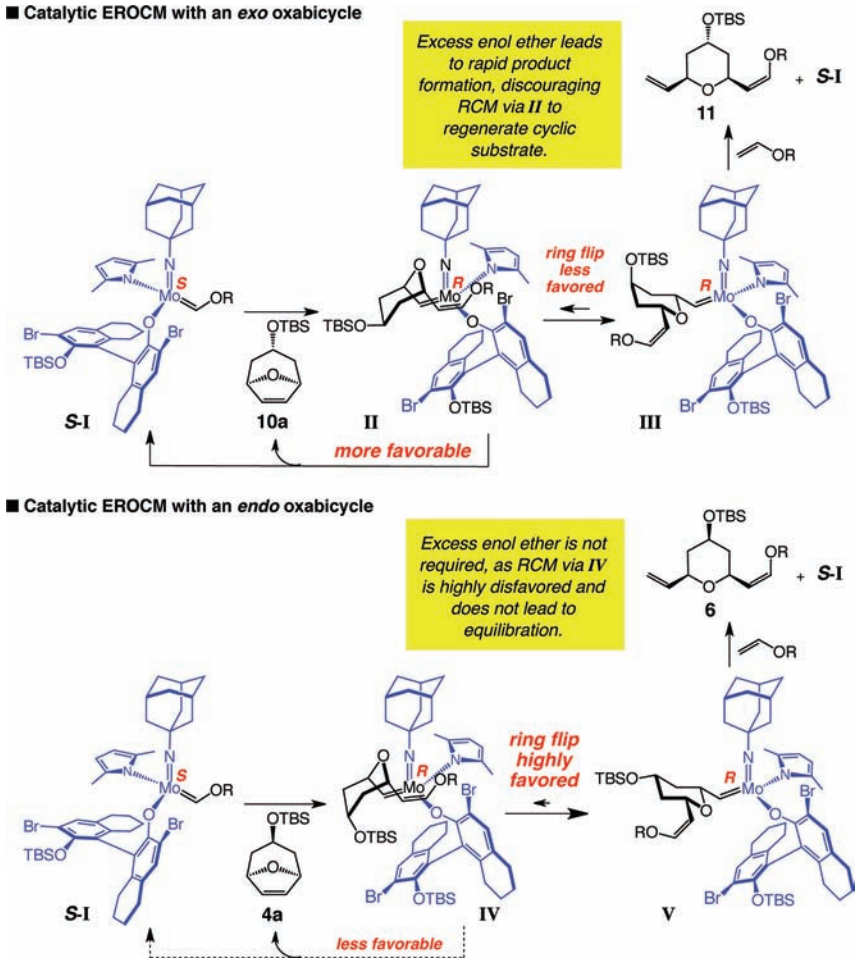
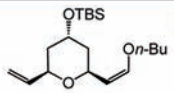
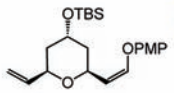


Table 6. Influence of Reaction Time on the Eficiency and Enantioselectivity of ROCM Reactions[a,b]

entry	product	time (min)	conv (%);[c] yield (%)[d]	Z:E[c]	er[e]
1		0.5	97; 83	>98:2	95:5
2		1.0	>98; 89	>98:2	90:10
3		3.0	>98; 86	>98:2	85.5:14.5
4	11a	30	>98; 80	>98:2	62.5:37.5
5		0.5	97; 86	>98:2	90:10
6		1.0	97; 82	>98:2	87:13
7		3.0	>98; 83	>98:2	86:14
8	11b	30	>98; 87	>98:2	84.5:15.5

[a]Reactions performed under N_2 atmosphere in the presence of 5.0 equiv of enol ether cross partner at 22 °C; see the Supporting Information for details. [b]The requisite were prepared in situ from reaction of 1.0 mol % of the corresponding bispyrrolide and enantiomerically pure aryl alcohol (effective loading of **9c** = 0.6 mol %). [c]Conversion and alkene stereoselectivity were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [d]Yield of products after purification by silica gel chromatography (<±5%). [e]Enantiomer ratios were determined by HPLC analysis (<±2%); see the Supporting Information for details.

point to one isomer as substantially more reactive (i.e., the *S* isomer of complexes shown in Schemes 3 and 4 is more active). The primary reason for such a difference appears to be the blocking of the approach of the incoming alkene, which likely occurs *anti* to the pyrrolide, by the large aryloxide ligand. As shown in Figure 1, the X-ray structure of the related *R*-neophylidene isomer shows that the oxygen-based ligand is held in a particularly unfavorable orientation for alkene substrate approach, partly due to association of one of its halides with the Lewis acidic metal center.

If one alkylidene diastereomer (e.g., *S*-**I**) reacts preferentially with the cyclic alkene substrate, then two noteworthy issues arise:

(1). How the rate with which the two diastereomeric oxygen-substituted alkylidenes (*S*-**I** and *R*-**I**) isomerize influences the overall reaction rate and enantioselectivity. At higher enol ether concentration, alkylidene diastereomers interconvert more readily as a result of an increasingly facile nonproductive ("degenerate") olefin metathesis, as illustrated in Scheme 5. When alkylidene isomerization proceeds rapidly, the more reactive isomer remains more available, allowing EROCM to proceed rapidly and enantioselectively through the intermediacy of *S*-**I**. Both isomeric forms likely promote highly *Z*-selective processes, since the size differential between the adamantylimido and aryloxide ligands, the purported roots of high alkene stereoselectivity, remains unaltered. The *R* alkylidene (*R*-**I**) diastereomer can promote EROCM via **VIII**, **IX**, and **X** (Scheme 4) to cause diminution of enantioselectivity, unless it is quickly isomerized to the *S* isomer. Rapid conversion

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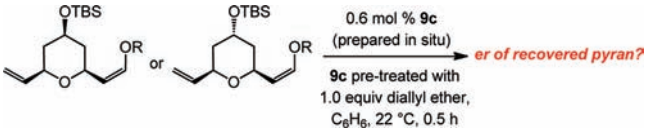
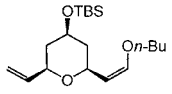
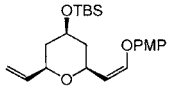
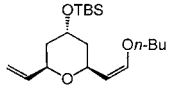
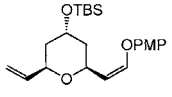
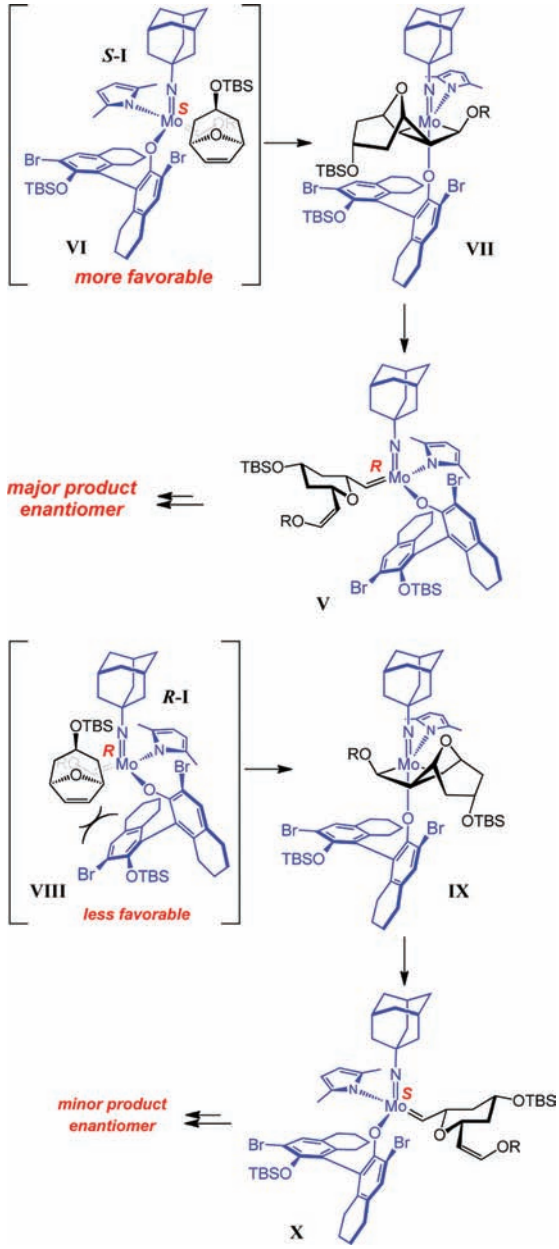
Table 7. Tendency of Diastereomeric ROCM Products to Undergo Racemization[a,b]



entry	ROCM product	recovered yield (%)[c]	initial er[b]	recovered er[b]
1	 **6a**	45	98:2	95:5
2	 **6b**	80	98.5:1.5	97.5:2.5
3	 **11a**	22	95:5	55:45
4	 **11b**	72	92:8	62.5:37.5

[a]Reactions performed under N_2 atmosphere; see the Supporting Information for details. [b]Enantiomer ratios were determined by HPLC analysis (<±2%); see the Supporting Information for details. [d]Yield of products after purification by silica gel chromatography (<±5%). [c]Enantiomer ratios were determined by HPLC analysis; see the Supporting Information for details.

Scheme 4. Reaction through the *S* Mo Complex Diastereomers is Likely More Facile. A Plausible Mechanistic Model



of *R*-**I** to *S*-**I** ensures a faster rate of formation and yield of the desired EROCM product as well as higher enantioselectivity. This proposal is in line with previous mechanistic investigations[31] and is further supported by the deuterium scrambling observed when a mixture of **5b** and d_3-**5b** are subjected to 1.2 mol % **9c** (C_6D_6, 22 °C; Scheme 5); facile scrambling of the atomic labels takes place within 30 min, generating significant amounts of d_1-**5b** and d_2-**5b** (detected through high resolution mass spectrometry). Similarly, when an equal mixture of **5a** and d_3-**5b** is treated with 1.2 mol % **9c**, after 30 min all the volatiles (including **5a** and d_2-**5a**) are removed and the remaining residue is analyzed by 400 MHz ^{1}H NMR spectroscopy, a 45:55 mixture of d_1-**5b** and d_2-**5b** is detected (Scheme 5).[32] Such exchange of deuterium likely proceeds through a nonproductive olefin metathesis process via the symmetric metallacyclobutane **XI** (Scheme 5). The significance of the rate of isomerization of alkylidene diastereomers is especially relevant to EROCM reactions with cyclobutene substrates, where substantially higher ring strain renders post-metathesis RCM unlikely (in contrast to oxabicycles). The higher enantioselectivity observed with increasing concentration of enol ether, as shown in entries 11−14 of Table 5, is probably due to an increase in the rate of nonproductive olefin metathesis of the enol ether cross partner, leading to a steady concentration of the more active and stereochemically discriminating *S*-**I**. Similar principles can be used to explain why in reactions of *exo*-oxabicyclic alkenes (e.g., entries 1 vs 2, Table 3), lower enol ether concentration leads to formation of significant amounts of achiral bis-cross products. Such a complication concerns EROCM with *exo* isomers only because, as detailed above (Scheme 3), unlike *endo* variants (cf. Table 2 and entries 5−6, Table 3) they can undergo facile ring closure, allowing increasing amounts of initially generated chiral pyran to be converted to the achiral bis-cross product through the pathway shown below (via **XIII** in Scheme 6). The above considerations suggest that the less reactive[31] *R*-**III** (Scheme 6), derived from *S*-**I**, reacts preferably through the sterically less congested, symmetrically substituted metallacyclobutane **XII** to produce the corresponding chiral pyran in high enantioselectivity. In contrast, alkylidene **X**, a more reactive and less discriminating *S*-Mo complex, can give rise to the formation of the *meso*-bis-enol ether through metallacyclobutane **XIII**, while generation of the alternative product enantiomer occurs through **XV** (Scheme 6). High yields and enantioselectivities might thus depend on the fast rate of alkylidene isomerization not only because the appropriate alkylidene

dx.doi.org/10.1021/ja210946z | *J. Am. Chem.Soc.* 2012, 134, 2788−2799

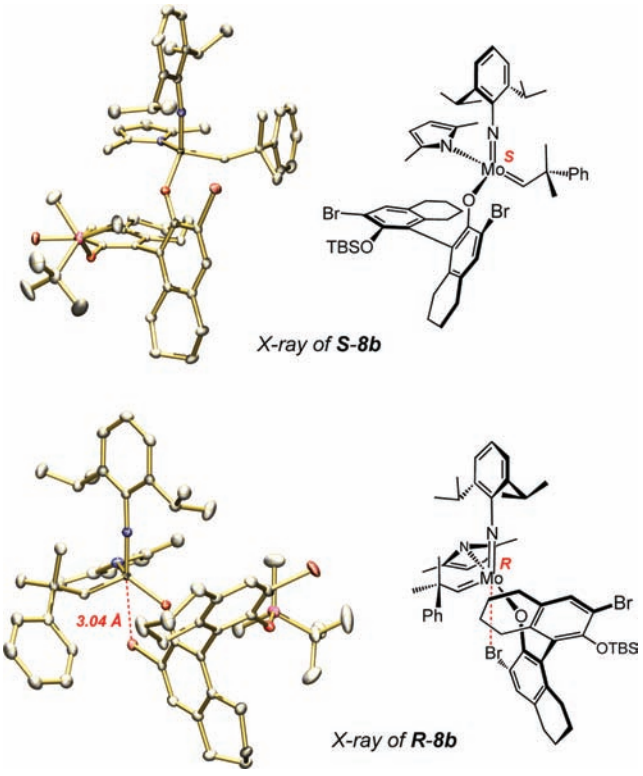


Figure 1. X-ray structures of two diastereomers of a stereogenic-at-Mo monopyrrolide monoaryloxide.

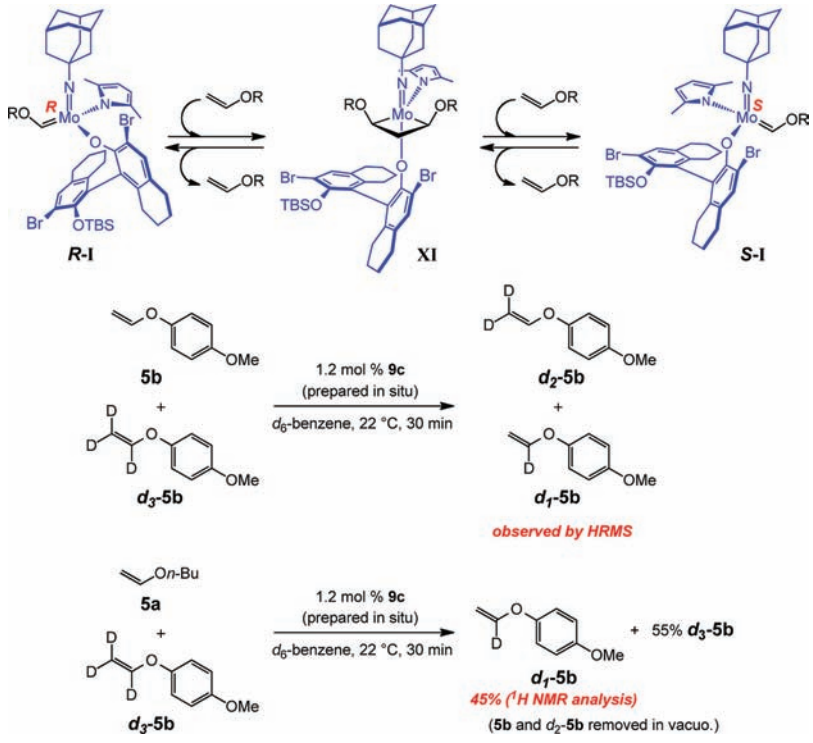
isomer can then efficiently participate in the ring-opening process but also since the latter pathway delivers a diastereomer (**XII**, Scheme 6) that reacts more readily with an enol ether in such a way that leads to the chiral product (vs *meso*). The improved enantioselectivity in reactions of azabicycle **14** (entries 1−3, Table 4) can be accounted for through similar reasoning. Moreover, the effect of enol ether concentration on *Z*−*E* selectivity is probably due to minimization of RCM of the piperidene product to regenerate the starting azabicycle, which undergoes ring closure faster than the more strained oxabicycles.[6c]

(2). The predominant involvement of **S-I** as the initiating alkylidene suggests the intermediacy of **III** (Scheme 3), which possesses an *R* stereogenic Mo center—an isomeric form that, as was described above, is relatively hesitant to react intermolecularly with another alkene substrate. Accordingly, higher concentrations of enol ether could be required to enhance the rate of intermolecular transformation with the cross partner, minimizing the potentially more facile intramolecular RCM that leads to loss of enantiomeric purity.

3. CONCLUSIONS

Examples of efficient and highly stereoselective olefin metathesis reactions that involve enol ethers are uncommon; the first cases of cross-metathesis reactions with this electronically distinct class of alkenes were developed in these laboratories only recently.[19] In this disclosure, we put forward the first instances of catalytic EROCM processes that proceed readily and with exceptional *Z* selectivity, delivering the desired products in high enantiomeric purity. The products obtained from reactions of oxa- or azabicycles, cyclobutenes or cyclopropenes cannot be readily accessed by alternative protocols and are amenable to site-selective functionalization of the enol ether moiety and should thus prove to be of value in chemical synthesis. As detailed above, enantioselectivity levels can vary, dictated by various mechanistic aspects of the process.

Scheme 5. Interconversion of Diastereomeric Mo Complexes through Nonproductive Olefin Metathesis[a]



[a]See the Supporting Information for experimental details.

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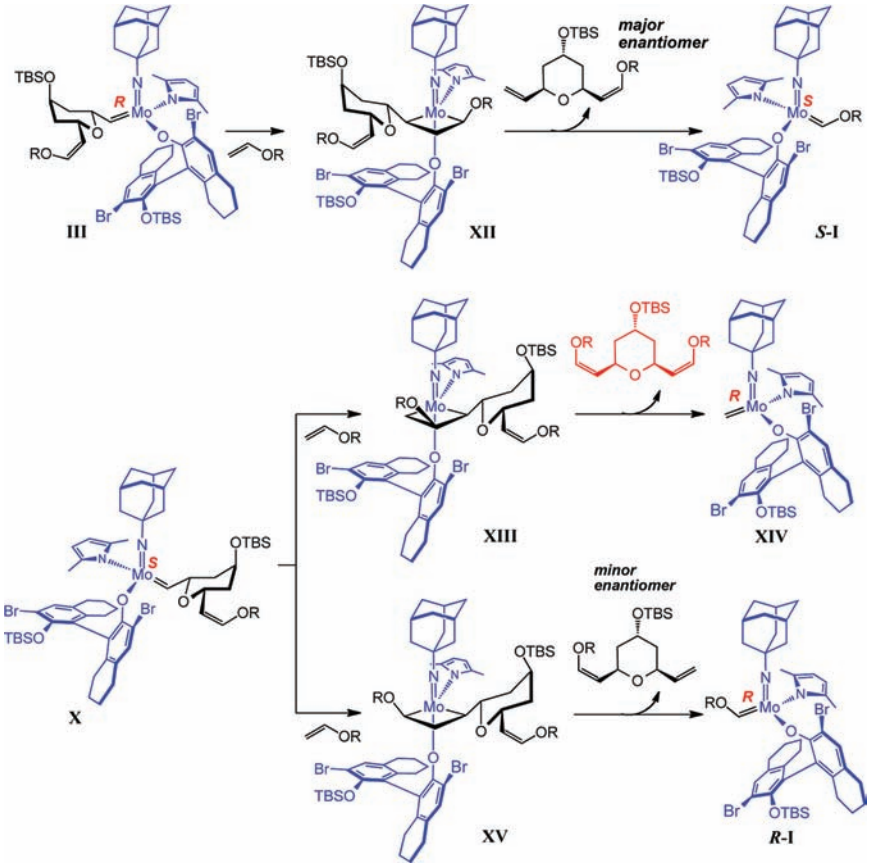
Scheme 6. Reaction through Different Alkylidene Diastereomers Can Afford Entirely Different Products



Additionally, an aspect that is particular to the class of stereogenic-at-metal catalysts used in these studies is the facility with which the complex diastereomers interconvert, strongly impacting the stereochemical outcome of the reaction. That is, conditions that accelerate the rate of isomerization between the diastereomeric forms of such complexes (e.g., excess cross partner) by nonproductive olefin metathesis pathways can be used to impact the reaction outcome.

The catalytic transformations described in this report bear further testimony to the unique ability of monopyrrolide stereogenic-at-metal complexes to promote highly efficient and stereoselective olefin metathesis reactions. Design and development of additional catalysts and methods for stereo- and enantioselective olefin metathesis reactions involving enol ethers, as well as application of catalytic EROCM processes described herein to efficient preparation of biologically active complex molecules[19,20] are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for substrates and products; crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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formation and reversion of the minor isomer is higher) requires a longer time to achieve equilibration, since with every reverse/forward sequence, less of the minor enantiomer, which less readily participates in the reverse reaction, is generated. The larger the amount of the minor enantiomer generated with each cycle, the less time it takes to accumulate 50% of that isomer (i.e., reach complete equilibration between the two enantiomers).

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