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Enhancement of Enantioselectivity by THF in Asymmetric Mo-Catalyzed Olefin Metathesis. Catalytic Enantioselective Synthesis of Cyclic Tertiary Ethers and Spirocycles

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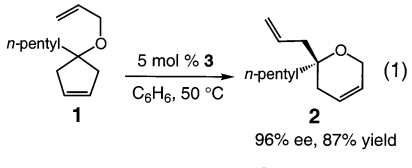
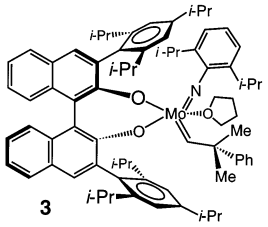
Abstract: Mo-catalyzed enantioselective rearrangement of achiral cyclopentenyl tertiary ethers to chiral cyclohexenyl tertiary ethers are reported. These olefin metathesis transformations proceed efficiently and with high levels of enantioselectivity. A noteworthy feature of these reactions is that added tetrahydrofuran exerts a remarkably positive influence on the enantioselectivity of the metathesis-based rearrangement. The first examples of catalytic asymmetric synthesis of spirocyclic structures by enantioselective olefin metathesis are also disclosed.

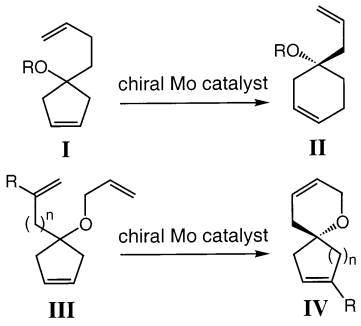
Introduction

The availability of chiral catalysts for olefin metathesis has allowed for efficient syntheses of an assortment of carbo- and heterocycles that are not otherwise readily accessible in the optically pure or enriched form.,[1−3] One recent advance involves the efficient and highly enantioselective rearrangement of achiral cyclopentenyl ethers, such as **1**, to unsaturated pyrans, represented by **2**, through asymmetric metathesis catalyzed by 1−5 mol % chiral Mo complex **3** (eq 1).[4] The utility of the catalytic asymmetric method has been demonstrated through a concise synthesis of the heterocyclic segment of the anti-HIV agent tipranavir.[4]





More recently, we have investigated another set of transformations, outlined by the conversion of **I** to **II**, where a carbocyclic tertiary ether (versus a pyran heterocycle), chiral molecules that cannot be prepared by asymmetric alkylations of ketones[5] or by kinetic resolution,[6] are the desired products. These latest studies have proved not to be a routine extension of the previously reported class of rearrangements (e.g., **1**→**2**), as they have led to the uncovering of a remarkable additive effect.[7]



In this paper, we disclose a new method for the asymmetric synthesis of tertiary carbocyclic ethers by Mo-catalyzed olefin metathesis, where the presence of tetrahydrofuran (THF) as an

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(1) For Mo-catalyzed asymmetric ring-closing metathesis (ARCM), see: (a) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4042. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720−9721. (c) Zhu, S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251−8259. (d) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553−9559. (e) Kiely, A. F.; Jernelius, J.; A.; Schrock, R.; R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868−2869. (f) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997. For an overview of chiral Mo-based olefin metathesis catalysts, see: (g) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945−950.
(2) For Mo-catalyzed asymmetric ring-opening metathesis (AROM), see: (a) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603−11604. (b) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767−7778. (c) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829.

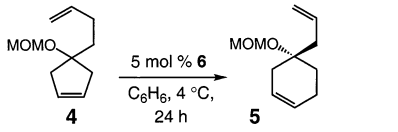
additive leads to significantly enhanced levels of enantioselectivity. In addition, we report the first examples of catalytic asymmetric synthesis of various spirocyclic structures through Mo-catalyzed tandem olefin metathesis (see **III**→**IV**).[8]

Results and Discussion

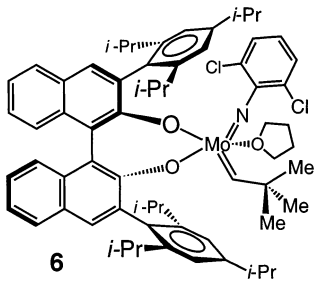
(1) Catalytic Enantioselective Synthesis of Cyclohexenyl Tertiary Ethers. We initially selected tertiary MOM (methoxymethyl) ether **4** as the substrate and examined its asymmetric rearrangement to chiral tertiary ether **5** in the presence of a variety of chiral Mo-based catalysts.[9] These studies indicated that the Lewis acidic dichloro−imido complex **6** is a desirable catalyst. Such conditions deliver the desired product in 78% ee (>98% conversion).

In searching for conditions that lead to improved enantioselectivity, we examined the effect of various additives. This approach was based on the assumption that association of a Lewis base to the Lewis acidic Mo complex might alter the equilibrium between syn and anti Mo−alkylidenes, each of which may exhibit substantially different levels of reactivity and give rise to varying degrees of enantioselectivity.[10] Moreover, association of the Lewis base with the Mo center may alter the steric environment of the catalyst's chiral pocket, which may in turn exert a positive influence on asymmetric induction. The expectation that the transition metal system would efficiently associate with a Lewis basic additive is supported by the fact that all binaphtholate-derived chiral Mo catalysts are isolated as THF-bound complexes (see **3** and **6** in eq 1 and Scheme 1).[1c,9e] Within this context, as illustrated in Scheme 1, we have established that in the presence of 2 equiv of THF (relative to **4**), under otherwise identical conditions, tertiary ether **5** can be obtained in 85% ee (versus 78% ee).[11] When the amount of THF additive is increased to 10 equiv, **5** is isolated in 92% ee and 93% yield after silica gel chromatography (Scheme 1).[12] Although reactions are faster and additive effects are observed when the above transformation is performed at 22 and 50 °C, enantioselectivity levels are lower than that obtained at 4 °C.[13] Two important points merit mention: (1) Rates of formation of tertiary cyclohexenyl ethers are not significantly altered by the presence of THF. There is, however, <5% conversion when reaction of **4** is attempted in pure THF (even at 50 °C). (2) Similar additive effects are *not* observed in the related processes represented by the transformation shown in eq 1. This difference in the effect of added THF, the mechanistic basis of which is not clear at the present time, underlines the notion that formation of carbocyclic tertiary ethers (e.g., **5**) is not a simple extension of the earlier processes affording chiral nonracemic dihydropyrans (e.g., eq 1).

Scheme 1. Mo-Catalyzed Rearrangement of Achiral **4** to Chiral Tertiary Ether **5**



[a] Equivalents are relative to the amount of the substrate.



Screening of other additives suggests that the influence of THF is likely due to its coordinative ability rather than alteration of the polarity of the reaction medium. For example, **5** is obtained in 80% ee in the presence of 10 equiv of Et_2O or dichloroethane. When catalyst **3** is used in the reaction of **4**, carbocycle **5** is formed in 45% ee. Consistent with the argument that the high Lewis acidity of **6** is critical to the additive effect, the addition of 10 equiv of THF does not increase the enantioselectivity of the process catalyzed by **3**. Remarkably, when 5 equiv of 2,5-dimethyl THF is used (5 mol % **6**), only 23% conversion is observed after 24 h and **5** is obtained in only 38% ee. With 10 equiv of 2,5-dimethyl THF, conversion is reduced to <10% and the desired carbocycle is obtained in 27% ee. It is plausible that coordination of the sterically bulky additive inhibits substrate association to the Mo center, signifi-

(3) For reports on asymmetric Ru-catalyzed olefin metathesis, see the following. (a) Ru-catalyzed ARCM: Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228. (b) Ru-catalyzed AROM: Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955.

(4) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139−3140.

(5) For examples of catalytic enantioselective addition of carbon nucleophiles to ketones, see: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (b) Casolari, S.; D_Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061−1063.

(6) For recent reviews of metal-catalyzed kinetic resolutions, see: (a) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537−574. (b) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869−885. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5−26.

(7) For a review on the effect of additives on asymmetric catalytic processes, see: (a) Vogel, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577. For additional recent examples, see: (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186. (d) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256−1257. (e) Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861−866. (f) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299−307, and references therein. (g) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012.

(8) For reports on synthesis of spirocycles by tandem olefin metathesis (with achiral catalysts), see: (a) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247−3250. (b) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A.J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *Org. Lett.* **2001**, *3*, 671−674. (c) Wallace, D. J.; Bulger, P. G.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Synlett.* **2001**, 357−360.

(9) For details of catalyst screening, see the Supporting Information.

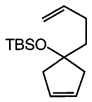
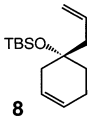
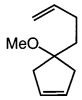
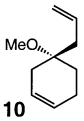
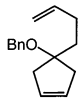
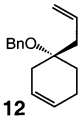
(10) (a) Schrock, R. R.; Crowe, W. E.; Bazan, G. C.; DiMare, M.; O'Regan, M. B.; Schofield, M. H. *Organometallics* **1991**, *10*, 1832−1843. (b) Oskam, J. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11831−11845. (c) Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700−3715. (d) Tsang, W. C.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2001**, *20*, 5658−5669. (e) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409−417.

(11) For proof of absolute stereochemistry of the products reported herein, see the Supporting Information.

(12) Levels of enantioselectivity are not further improved in the presence of 20 equiv of THF.

(13) At 22 °C, under otherwise identical conditions as shown in Scheme 1, reaction of **4** is complete (>95% conversion) within 2 h and **5** is obtained in 90% ee (2 h and 77% ee without THF). At 50 °C, the desired carbocycle is obtained in 85% ee within 2 h (80% ee in the absence of THF).

Table 1. Mo-Catalyzed Enantioselective Rearrangement of Protected Achiral Cyclopentenol to Cyclohexenyl Tertiary Ethers[a]

entry	substrate	product	THF (equiv)	conv (%)[b]; yield (%)[c]	ee (%)[d]
1			0	>98; nd	58
2			***10***	***>98; 94***	***96***
	7	**8**			
3			0	>98; nd	80
4			***10***	***>98; 88***	***90***
	9	**10**			
5			0	>98; nd	78
6			***10***	***>98; 92***	***85***
	11	**12**			

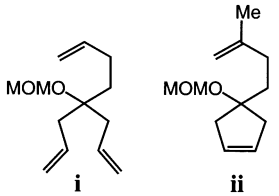
[a] Conditions: 5 mol % **6**, C_6H_6, 4 °C, 24 h. [b] Conversions determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified mixtures. [c] Isolated yields after silica gel chromatography. [d] Determined by chiral GLC (Betadex column for entries 1−2, CDGTA column for entries 3−6); see the Supporting Information for details. nd = not determined.

cantly reducing reactivity; the diminution in selectivity is more difficult to explain.[14]

As the data in Table 1 illustrate, various carbocyclic tertiary ethers can be synthesized by the Mo-catalyzed method efficiently and in 85−96% ee. In all cases, enhancement in enantioselectivity is effected in the presence of 10 equiv of THF. Particularly noteworthy is the reaction of silyl ether **7**: whereas **8** is obtained in 58% ee in the absence of an additive (entry 1), addition of THF (10 equiv) leads to the formation of the desired product in 96% ee (94% isolated yield).

The present method puts forth an effective catalytic approach to the synthesis of tertiary ethers (and the derived alcohols after deprotection) that cannot be accessed by alkylations of the corresponding ketones[5] or through other catalytic or stoichiometric protocols.[15] Another attractive feature of the method is that the requisite catalyst can be prepared in situ[16] without isolation and characterization of the Lewis acidic chiral complex **6**. Thus, as shown in Scheme 2, treatment of **13** with 1 equiv of (*R*)-**14** in THF at −40 °C and stirring at 22 °C for 24 h affords a solution of chiral catalyst **6** that can be used directly

(14) It should be noted that all attempts to effect Mo-catalyzed ARCM of **i** to **5** (at 4, 22, 50, and 80 °C) proved unsuccessful (<20% ee); this is in contrast to the related studies reported in ref 4 (see eq 1). In addition, <5% conversion was observed in attempts to effect a similar reaction of the more highly substituted diene **ii**. These findings, collectively, suggest that reactions of **4** and related derivatives proceed through initial formation of a terminal Mo alkylidene followed by an ARCM (versus AROM and a subsequent RCM).

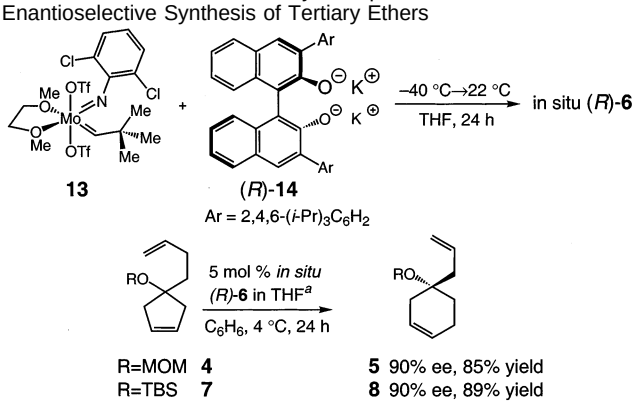


i **ii**

(15) For enantioselective synthesis of tertiary ethers and alcohols through Mo-catalyzed olefin metathesis, see: (a) Hultzsch, K. C.; Jernelius, J. A.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 589−593. (b) References 1e and 4.

(16) For in situ preparation of another chiral Mo-based metathesis catalyst, see: Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J., Jr.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452−1456.

Scheme 2. Use of Chiral Catalyst Prepared in Situ in the Enantioselective Synthesis of Tertiary Ethers

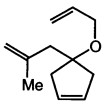
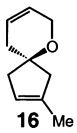
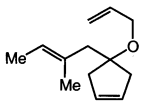
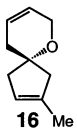
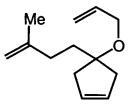
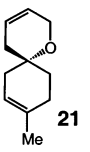
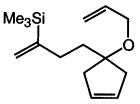
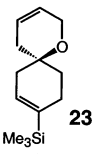
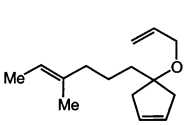
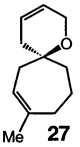


[a] THF present is equal to 12 equiv relative to the substrates.

to catalyze the enantioselective syntheses of MOM and *tert*-butyldimethylsilyl (TBS) ethers **5** and **8**, respectively. Levels of selectivity are comparable to those attained by the isolated complex (in the presence of THF additive).

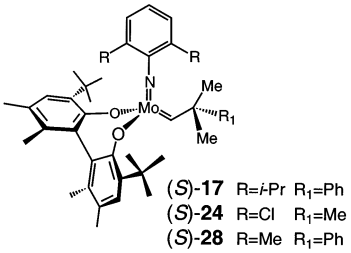
(2) Catalytic Enantioselective Synthesis of Spirocycles. Replacement of the ether protecting groups (e.g., MOM and TBS ethers of substrates **5** and **8**) with an alkenyl unit allows for two tandem olefin metathesis reactions and generation of nonracemic spirocyclic structures. As the results in Table 2 illustrate, depending on the olefin substitution and the size of the unsaturated rings formed, various achiral cyclopentenyl

Table 2. Mo-Catalyzed Enantioselective Synthesis of Spirobicyclic Ethers[a]

entry	substrate	product	catalyst; mol %	conv (%)[b]; yield (%)[c]	ee (%)[d]
1			(*S*)-**17**; 5	>98; 45[e]	88
	15	**16** Me			
2			(*R*)-**3**; 9	>98; 75	80
	19	**16** Me			
3			(*R*)-**6**; 9	>98; 80	83
	20	**21** Me			
4			(*S*)-**24**; 5	>98; 70	85
	22	**23** Me_3Si			
5			(*S*)-**28**; 5	>98; 90	62
	26	Me **27**			

[a] Conditions: indicated mol % chiral Mo catalyst, 24 h. All reactions carried out in C_6H_6, except that in entry 2 (in isooctane). All reactions carried out at 22 °C, except entry 1 (50 °C). [b]Conversions determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified mixtures. [c]Isolated yields after silica gel chromatography. [d]Determined by chiral GLC (CDGTA column for all entries). [e]The product mixture contains 55% of achiral **18**.

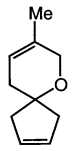
trienes can be catalytically converted to spiro-bicyclic ethers efficiently and enantioselectively (62−88% ee). Catalytic reactions afford optically enriched products with the same absolute stereochemical sense as those observed in processes shown in Scheme 1 and Table 1.



(*S*)-**17** R=*i*-Pr R_1=Ph
(*S*)-**24** R=Cl R_1=Me
(*S*)-**28** R=Me R_1=Ph

Several issues with regard to the data in Table 2 merit mention:

(1) Enantioselective formation of spirocycle **16** (88% ee) is accompanied by the generation of achiral **18** (55%). To circumvent this complication, the related trisubstituted alkene **19** (92% *E*) was prepared and its asymmetric conversion to **16** was examined. These studies indicate that, with **19** as the substrate, **16** can be obtained in 80% ee and 75% isolated yield, with <10% of byproduct **18** formed.

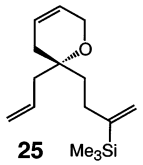


18

(2) Screening studies indicate that depending on the substrate, different Mo complexes serve as the optimal chiral catalyst. Such variations can arise from either a change in alkene substitution (entries 1 and 2), the olefin substituent (entries 3 and 4), or the size of the ring formed (entries 2, 3, and 5). Since it is not unusual that the identity of the optimal chiral catalyst varies as a function of structural modification within a substrate,[17] the results in Table 2 further underline the importance of the modular character of this class of chiral catalysts.

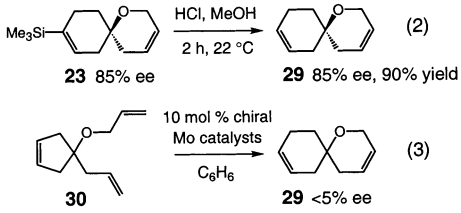
(3) Although complex **6** is used in the formation of spirocycle **21**, added THF does not improve the level of enantioselectivity. This observation suggests that the above-mentioned additive effect depends on subtle mechanistic factors and its validity should be determined on a case-by-case basis.

(4) When reactions of **22** and **26** are analyzed early, a mixture of chiral monocyclic and bicyclic products are detected, where the spircocycles are of higher enantiomeric purity than after complete conversion. As an example, in the reaction of vinylsilane **22** (entry 4, Table 2), after 30 min, the product mixture contains equal amounts of spirocycle **23** and dihydropyran **25** (versus 80% **23** and 20% **25** after 5 and 24 h). Furthermore, this sample of **23** (after 30 min of reaction) is of higher optical purity (92% ee versus 85% ee after 5 h). These results imply that levels of enantioselectivity can be altered in the course of the second RCM.[18] That is, one enantiomer of the initially formed monocyclic **25** is converted more rapidly to **23** (partial kinetic resolution).[6] Thus, as the reaction proceeds, a larger fraction of the initial minor enantiomer undergoes a second RCM, resulting in improved yield of the spirocycle but diminished optical purity.



25 Me_3Si

(5) The nonracemic vinylsilane **23** can be further functionalized to a variety of compounds that are not otherwise easily accessible. Conversion to spircocycle **29**, shown in eq 2, is illustrative. It should be noted that catalytic metathesis of triene **30** (eq 3) in the presence of a range of chiral Mo complexes leads to the formation of **29** in <5% ee.



Conclusions

The catalytic asymmetric reactions outlined herein should prove to be of utility, as they deliver optically enriched products that can be further functionalized but cannot be readily prepared by alternative methods. The effect of added THF on the levels of asymmetric induction is mechanistically and synthetically intriguing and might be beneficial in a number of other Mo-catalyzed enantioselective olefin metatheses.

Future studies will be directed toward the development of additional Mo-catalyzed protocols for asymmetric synthesis of synthetically versatile organic molecules, a comprehensive examination of various additives, elucidation of the corresponding mechanistic principles, and related applications in target-oriented synthesis.

Experimental Section

(1) General Methods. Infrared (IR) spectra are recorded on a ThermoNicolet Avatar 210 spectrophotometer, υ_{max} (cm^{-1}). Bands were characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra are recorded on a Varian Unity INOVA 400 (400 MHz) or Varian Gemini 2000 (400 MHz). Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra are recorded on a Varian Unity INOVA 400 (100 MHz) or Varian Gemini 2000 (100 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associates Chiraldex GTA column (30 m × 0.25 mm)) or BETADEX 120 column (30 m × 0.25 mm)) in comparison with authentic materials. Elemental analyses are performed

(17) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885−1889.

(18) For other examples where enantioselectivity is proposed to be influenced in two steps (in a reaction after the irreversible step) of the catalytic cycle, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417−1419. (b) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425−426, and references therein.

by Robertson Microlit Laboratories (Madison, NJ). High-resolution mass spectrometry is performed by the University of Illinois Mass Spectrometry Laboratories (Urbana, IL). Absolute stereochemistry is determined by optical rotation on a Rudolph Research Analytical Autopol IV polarimeter.

All reactions are conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry nitrogen. Solvents are purified under a positive pressure of dry Ar by a modified Advanced Chem Tech Purification system. Benzene and toluene were sparged with argon and passed through activated copper and alumina columns. Tetrahydrofuran and diethyl ether are also sparged with argon and passed through activated alumina columns. Olefin-free pentane was generated by stirring commercial grade pentane over concentrated sulfuric acid for 24 h. The pentane is then poured over fresh concentrated sulfuric acid. This process was repeated until the acid layer remained colorless for 48 h. The pentane was subsequently separated, washed with water, dried over Na_2SO_4, filtered, sparged with nitrogen, and then passed through activated alumina and activated copper columns, respectively. All handling of the Mo catalysts was performed in a glovebox under inert atmosphere. All substrates were vigorously dried by azeotropic distillation with anhydrous benzene (3×) prior to use.

(2) Representative Procedure for Mo-Catalyzed Enantioselective Synthesis of Cyclohexenyl Tertiary Ethers. To a solution of diene **7** (36.0 mg, 0.143 mmol) in benzene (1.44 mL) and THF (117 μL, 1.43 mmol) precooled at 4 °C was added Mo catalyst **6** (7.82 mg, 7.20 ìmol) (in one portion). The reaction vessel was sealed with a Teflon cap, and the solution was allowed to stir at 4 °C for 24 h. At this point, the mixture was exposed to air and was then charged with MeOH (140 μL). Removal of the volatiles in vacuo followed by silica gel chromatography (pentanes:diethyl ether, 50:1) afforded (*S*)-**8** (34.0 mg, 0.137 mmol, 96% yield) as a colorless oil. Optical purity of the product was established to be 96% ee by chiral GLC.

(a) (*S*)-4-Allyl-4-(methoxymethoxy)cyclohexene (5). IR (neat): 3068(w), 3024(m), 2923(s), 2848(m), 1640(w), 1451(m), 1155(w), 1105(m), 1036(s), 916(m), 658(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (ddt, J = 17.6, 10.4, 7.2 Hz, 1H, CH_2=C*H*), 5.70−5.54 (m, 2H, C*H*=C*H*), 5.11−5.00 (m, 2H, CH_2=CH), 4.78 (d, J = 7.2 Hz, 1H, OCH_2O), 4.72 (d, J = 7.6 Hz, 1H, OCH_2O), 3.37 (s, 3H, OCH_3), 2.44−1.96 (m, 6H, allylic-H), 1.80 (ddt, J = 13.2, 1.2, 6.0 Hz, 1H, CH=CHCH$_2$C***H***$_2$), 1.64 (dddd, J = 12.8, 6.8, 6.0, 1.2 Hz, 1H, CH=CHCH$_2$CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 126.3, 124.4, 117.6, 90.8, 76.0, 55.5, 42.0, 34.9, 30.9, 23.0. Anal. Calcd for $C_{11}H_{16}O_2$: C, 72.49; H, 9.95. Found: C, 72.38; H, 10.02. GLC (CDGTA: column temperature = 70 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 52.0 min; t_r(minor) = 54.9 min.

(b) (*S*)−(1-Allyl-cyclohex-3-enyloxy)-*tert*-butyldimethylsilane (8). IR (neat): 3068(w), 3018(m), 2936(s), 2854(m), 1640(w), 1476(m), 1256(m), 1098(m), 922(m), 834(m), 771(m), 671(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (ddt, J = 16.8, 10.4, 7.2 Hz, 1H, CH_2=C*H*), 5.66−5.51 (m, 2H, C*H*=C*H*), 5.08−4.99 (m, 2H, CH_2=CH), 2.31−1.92 (m, 6H, allylic-H), 1.70−1.55 (m, 2H, CH=CHCH$_2$CH_2), 0.86 (s, 9H, C(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 126.3, 124.9, 117.0, 73.4, 45.0, 38.4, 33.9, 25.9, 23.8, 18.3, −2.0, −2.1. Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 71.61; H, 10.96. GLC (BETADEX: column temperature = 70 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 197.6 min; t_r(minor) = 193.5 min.

(c) (*S*)-4-But-3-enyl-4-methoxycyclopentene (10). IR (neat): 3068-(w), 3031(m), 2974(m), 2930(s), 2829(m), 1640(w), 1451(m), 1180-(w), 1080(m), 910(m), 740(w), 658(m) cm−^{1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (ddt, J = 16.8, 10.8, 7.2 Hz, 1H, CH_2=C*H*), 5.72−5.64 (m, 1H, C*H*=CH), 5.61−5.53 (m, 1H, CH=C*H*), 5.09 (ddt, J = 10.0, 2.4, 1.2 Hz, 1H, CH_2=CH), 5.08 (ddt, J = 17.2, 2.0, 1.6 Hz, 1H, CH_2=CH), 3.24 (s, 3H, CH_3O), 2.32 (ddt, J = 14.8, 7.6, 1.6 Hz, 1H, CH_2CH=CH$_2$), 2.25 (ddt, J = 14.4, 7.2, 1.6 Hz, 1H, CH_2CH=CH$_2$), 2.20−1.92 (m, 4H, CH_2CH=CHCH_2), 1.76 (m, 1H, CH=CHCH$_2$CH_2), 1.64−1.55 (m, 1H, CH_2CH$_2$CH=CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 126.5, 124.2, 117.4, 74.2, 48.6, 39.4, 34.5, 29.7, 22.9. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.69; H, 10.22. HRMS: Cacld for $C_{10}H_{17}O$ (M + 1): 153.1279. Found: 153.1281. GLC (CDGTA: column temperature = 80 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 13.1 min; t_r(minor) = 13.9 min.

(d) (*S*)−(1-Allylcyclohex-3-enyloxymethyl)benzene (12). IR (neat): 3068(w), 3031(m), 2930(m), 2842(m), 1640(w), 1451(m), 1281-(w), 1092(m), 1067(m), 922(m), 740(m), 702(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H, C_6H_5), 5.94 (ddt, J = 16.8, 9.6, 7.2 Hz, 1H, CH_2=C*H*), 5.73−5.55 (m, 1H, C*H*=C*H*), 5.14−5.06 (m, 2H, CH_2=CH), 4.50 (d, J = 11.2 Hz, 1H, CH_2O), 4.47 (d, J = 11.2 Hz, 1H, CH_2O), 2.42−1.96 (m, 6H, allylic-H), 1.86 (dt, J = 13.2, 6.0 Hz, 1H, CH=CHCH$_2$CH_2), 1.69 (dt, J = 13.2, 6.0 Hz, 1H, CH=CHCH$_2$CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 134.0, 128.2, 127.3, 127.1, 126.5, 124.2, 117.4, 74.8, 63.1, 40.2, 34.7, 30.4, 23.1. Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.44; H, 8.59. HRMS. Cacld for $C_{16}H_{20}O$: 228.1514. Found: 228.1515.

(3) Representative Procedure for Mo-Catalyzed Enantioselective Synthesis of Spirocycles. A 10 mL round-bottom flask was charged with triene **20** (20.0 mg, 0.10 mmol) and benzene (1 mL) in a glovebox under an atmosphere of nitrogen. Chiral Mo catalyst **6** (10.2 mg, 9.37 μmol) was added in one portion at 22 °C. The flask was capped with a septum and an 18 gauge needle inserted to vent the reaction to the glovebox atmosphere. After 24 h, the solution was exposed to air and MeOH (180 μL) was added. Removal of the volatiles in vacuo followed by silica gel chromatography on silica gel (pentanes: diethyl ether 50: 1) afforded (*R*)-**21** (13.6 mg, 0.083 mmol, 80% yield). Optical purity of the product was established to be 83% ee by chiral GLC.

(a) (*S*)-2-Methyl-6-oxaspiro[4.5]deca-2,8-diene (16). IR (neat): 3035(m), 2914(s), 2831(m), 1645(w), 1435(m), 1338(w), 1179(m), 1091(s), 1012(m), 833(m), 650(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83−5.75 (m, 1H, C*H*=CH), 5.72−5.65 (m, 1H, CH=C*H*), 5.28−5.20 (m, 1H, C*H*=CCH$_3$), 4.30−4.20 (m, 2H, CH_2O), 2.64−2.45 (m, 2H, allylic-*H*), 2.30−2.15 (m, 4H, allylic-*H*), 1.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 125.6, 123.6, 121.7, 81.1, 62.0, 48.2, 44.1, 35.9, 16.9. HRMS. Calcd for $C_{10}H_{14}O$: 150.1045. Found: 150.1049. GLC (CDGTA: column temperature = 80 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 23.2 min; t_r(minor) = 22.5 min.

(b) (*S*)-9-Methyl-1-oxaspiro[5.5]undeca-3,8-diene (21). IR (neat): 2919(m), 2930(m), 2827(m), 1446(m), 1180(w), 1090(m), 840-(m), 658(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80−5.62 (m, 2H, C*H*=C*H*), 5.30−5.22 (m, 1H, CH$_3$C=C*H*), 4.24−4.08 (m, 2H, CH_2O), 2.20−1.82 (m, 7H, allylic-*H*, CH$_3$CCH$_2$CH_2) 1.67 (s, 3H, CH_3), 1.60−1.48 (m, 1H, CH$_3$CCH$_2$CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 125.4, 122.8, 118.1, 69.6, 60.8, 36.0, 34.0, 30.9, 27.5, 23.3. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.62; H, 9.85. GLC (CDGTA: column temperature = 80 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 39.2 min; t_r(minor) = 41.0 min.

(c) (*R*)-Trimethyl(1-oxaspiro[5.5]undeca-3,8-dien-9-yl)silane (23). IR (neat): 3031(w), 2949(s), 2899(s), 2829(m), 1627(m), 1426(w), 1250(s), 1180(m), 1092(s), 1016(w), 941(w), 840(s), 752(m), 651(m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89−5.84 (m, 1H, olefin-*H*), 5.78−5.68 (m, 2H, olefin-*H*), 4.24−4.12 (m, 2H, CH_2O), 2.28−1.80 (m, 7H, allylic-*H*, CH$_2$CH_2CO), 1.57−1.49 (m, 1H, CH$_2$CH_2CO), 0.04 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 132.4, 125.5, 122.7, 69.7, 60.7, 37.4, 33.7, 31.2, 24.5, −2.2. Anal. Calcd for $C_{13}H_{22}$-OSi: C, 70.21; H, 9.79. Found: C, 69.99; H, 9.69. HRMS. Cacld for $C_{13}H_{22}OSi$: 222.1440. Found: 222.1442. GLC (CDGTA: column

temperature = 70 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 25 psi): t_r(major) = 143.8 min; t_r(minor) = 141.4 min.

(d) (*R*)-9-Methyl-1-oxaspiro[5.6]dodeca-3,8-diene (27). IR (neat): 3032(m), 2926(m), 2852(m), 1650(w), 1446(m), 1388(w), 1180(w), 1092(m), 1015(w), 850(m), 828(w), 656(m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.76−5.66 (m, 2H, C*H*═C*H*), 5.33 (t, J = 6.8 Hz, 1H, CH_3C═C*H*), 4.13−4.05 (m, 2H, CH_2O), 2.32 (dd, J = 14.8, 6.8 Hz, 1H, CH_3CH═CHCH_2), 2.22 (dd, J = 14.8, 6.8 Hz, 1H, CH_3CH═CHCH_2), 2.15 (ddd, J = 15.2, 8.8, 2.8 Hz, 1H, allylic-*H*), 2.08 (ddd, J = 15.2, 8.4, 2.8 Hz, 1H, allylic-*H*), 2.00−1.94 (m, 2H, CH_2(CH_3)C═CHCH_2), 1.81 (t, J = 6.0 Hz, 2H, C$H_2CH_2CCH_3$), 1.73 (s, 3H, CH_3), 1.75−1.58 (m, 1H, $CH_3CCH_2CH_2CH_2$), 1.48−1.37 (m, 1H, CH_3CCH_2-CH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 125.3, 122.9, 118.8, 71.8, 60.8, 41.7, 35.6, 34.4, 34.2, 26.0, 21.6. HRMS. Calcd for $C_{12}H_{18}O$: 178.1359. Found: 178.1358. GLC (CDGTA: column temperature = 90 °C (isothermal); injector and detector temperature = 250 °C; inlet pressure = 15 psi): t_r(major) = 38.6 min; t_r(minor) = 40.3 min.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all substrates and proof of stereochemistry (PDF). This material is available free of charge via the Internet at http://www.acs.pubs.org.

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