

Dynamic Kinetic Resolution of Allylic Sulfoxides by Rh-Catalyzed Hydrogenation: A Combined Theoretical and Experimental Mechanistic Study

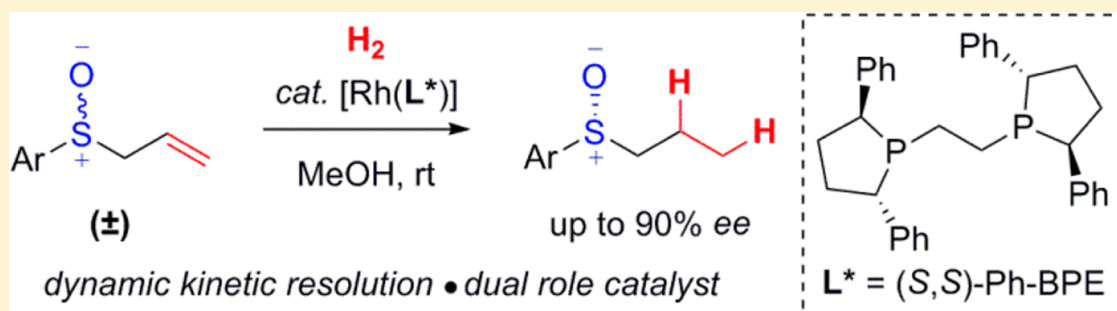
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S Supporting Information



ABSTRACT: A dynamic kinetic resolution (DKR) of allylic sulfoxides has been demonstrated by combining the Mislow [2,3]-sigmatropic rearrangement with catalytic asymmetric hydrogenation. The efficiency of our DKR was optimized by using low pressures of hydrogen gas to decrease the rate of hydrogenation relative to the rate of sigmatropic rearrangement. Kinetic studies reveal that the rhodium complex acts as a dual-role catalyst and accelerates the substrate racemization while catalyzing olefin hydrogenation. Scrambling experiments and theoretical modeling support a novel mode of sulfoxide racemization which occurs via a rhodium π -allyl intermediate in polar solvents. In nonpolar solvents, however, the substrate racemization is primarily uncatalyzed. Computational studies suggest that the sulfoxide binds to rhodium via O-coordination throughout the catalytic cycle for hydrogenation.

INTRODUCTION

Sulfoxides are valuable targets in medicinal chemistry (e.g., esomeprazole, modafinil) and useful intermediates in organic synthesis.¹ In addition, they act as both chiral auxiliaries² and as chiral ligands for asymmetric synthesis.^{3–5} As ligands, they can bind to a metal-center through O- and/or S-coordination. In contrast to other heteroatom functional groups (e.g., hydroxyl, amino), however, the use of sulfoxides to direct stereoselective transformations remains relatively unexplored. We have shown that a sulfoxide-directed hydroacylation proceeds with high diastereoselectivity.⁶ In the following article, we study the ability of sulfoxides to direct Rh-catalyzed hydrogenations and demonstrate a novel concept for dynamic kinetic resolution (DKR) of sulfoxides by the classic Mislow–Evans rearrangement.

Back in 1966, Mislow reported that enantioenriched allylic sulfoxides undergo spontaneous racemization via an achiral sulfenate ester.^{7–9} Although the equilibrium generally favors the sulfoxide, Evans subsequently showed that the sulfenate ester could be reduced *in situ* to generate alcohols.¹⁰ This Mislow–Evans transformation has been used for the stereoselective construction of allylic alcohols in many natural

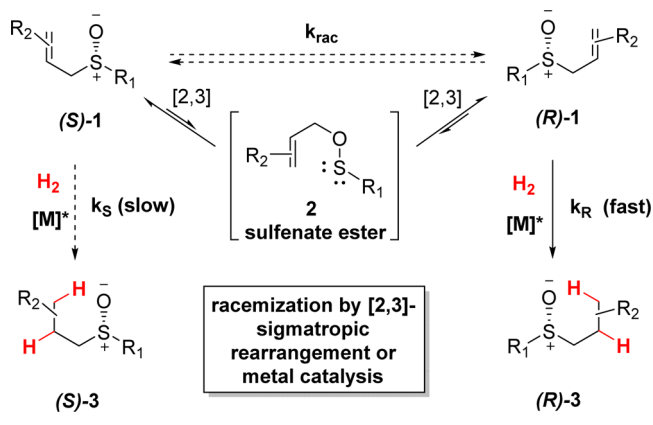
product syntheses. Considering the ability of sulfoxides to act as ligands, however, we envisioned a new use for the Mislow–Evans rearrangement (Scheme 1). Rather than trapping the sulfenate ester with stoichiometric reductants, we propose a sulfoxide-directed catalytic transformation of the olefin. This proposed DKR features the rare use of a sigmatropic rearrangement as the key mechanism for racemization of the starting reagent.^{11–13} Transforming the olefin prevents epimerization of the sulfoxide product, thus leading to enantioenriched sulfoxides.

As proof of this concept, we herein demonstrate the synthesis of enantioenriched chiral sulfoxides by enantioselective reduction, rather than conventional oxidation methods.¹ Kinetic experiments point to a novel Rh-catalyzed epimerization of allylic sulfoxides. Of note, catalytic antibodies have been observed to accelerate this rearrangement,¹⁴ while metal catalysis has only been predicted theoretically.¹⁵ Complementary theoretical studies provide mechanistic insights that will more broadly impact the development of other sulfoxide-

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Scheme 1. Proposed DKR of Allylic Sulfoxides



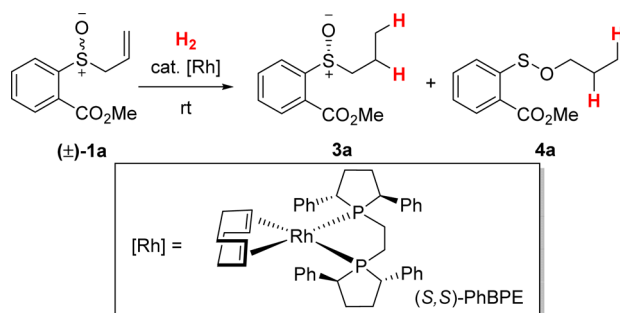
directed metal catalyzed transformations, catalytic sigmatropic methods, and DKR strategies.

RESULTS AND DISCUSSION

Initial Result. While various olefin functionalizations, including hydroacylation, can be pursued, we chose asymmetric olefin hydrogenation for initial investigation due to the wide-range of catalysts known for this reduction. To achieve an efficient DKR, the chiral catalyst must preferentially transform one enantiomer of the allylic sulfoxide (Scheme 1). In addition, the racemization of the allylic sulfoxide must be fast relative to the desired hydrogenation.¹⁶ Consequently, controlling the relative rate of hydrogenation and racemization is critical. Mislow and co-workers determined that allyl *p*-tolyl sulfoxide racemizes with a half-life of 4.4 h at 40 °C in benzene. Considering that certain metals are known to catalyze sigmatropic rearrangements, we anticipated that catalysis of the substrate racemization might be possible.

After evaluating a series of chiral bisphosphine ligands with a cationic Rh(I) source, we identified Ph-BPE¹⁷ as a promising ligand for the DKR of allylic sulfoxides (Scheme 2). The chiral sulfoxide was produced in 90% ee after complete consumption of the starting material in the presence of this ligand. Propyl sulfenate **4a** was generated as a byproduct (2.4:1 sulfoxide:-sulfenate) from hydrogenation of the transient allyl sulfenate ester **2a** that is in equilibrium with **1a**.

Scheme 2. DKR under Nonpolar and Polar Conditions



Conditions A: 1 mol % [Rh], 1 atm H₂, 19:1 PhMe : CH₂Cl₂
non-polar
> 99 % conversion; 2.4:1 **3a**:**4a**
3a: 90% ee

Conditions B: 2 mol % [Rh], 0.1 atm H₂; MeOH
polar
> 99 % conversion, 92:8 **3a**:**4a**
3a: 73% isolated yield, 88% ee

When using methanol as the solvent, we found that the undesired formation of propyl sulfenate ester significantly diminished to a 92:8 sulfoxide **3a**:sulfenate ester **4a** ratio, presumably because the equilibrium concentration of the allylic sulfenate ester **2** is lower in polar solvents.⁸ High enantioselectivity (88% ee) could be achieved at full substrate conversion and in 73% isolated yield of the sulfoxide product by lowering the H₂ pressure to 0.1 atm.

Kinetics of Racemization. To better understand the effect of reaction conditions on the rate of racemization, we performed a series of kinetic experiments. Enantioenriched phenyl allyl sulfoxide (**S**)-**1b** was synthesized using the method of Pelotier et al.^{18–20} The rate of racemization was measured by monitoring the decay of optical activity in a polarimeter or by monitoring the enantiomeric excess by SFC analysis (see Supporting Information for details).

Based on the ability of Pd(II) salts to catalyze related sigmatropic rearrangements,^{21–24} we wondered whether catalysis of the Mislow–Evans rearrangement would be possible. Pd(0) catalysis has been predicted theoretically.¹⁵ Indeed, we found that PdCl₂(PhCN)₂ accelerated the rate of racemization in 1,2-dichloroethane (DCE) by a factor of 17 (Table 1, entry 2). A dual catalyst system using both rhodium

Table 1. Racemization Rate Constants for Phenyl Allyl Sulfoxide

entry	solvent	catalyst (2 mol %)	k (h ⁻¹) ^a	t _{1/2} (h)
1 ^b	1,2-DCE	None	0.0105 (3)	66
2 ^b	1,2-DCE	Pd(PhCN) ₂ Cl ₂	0.181 (4)	3.8
3 ^c	MeOH	None	0.0022 (1)	315
4 ^c	MeOH	[Rh(L)]BF ₄	0.072 (5)	9.6
5 ^c	9:1 tol:DCM	None	0.0870 (2)	8.0
6 ^c	9:1 tol:DCM	[Rh(L)]BF ₄	0.0949(5)	7.3

^aRate constant for racemization, see Reist et al.²⁶ for definitions. All rate constants are mean values of three kinetic runs. Values in parentheses are sample standard deviations in the final decimal place.

^bMeasured by the polarimetry method. ^cMeasured by the SFC method. L = COD + (S,S)-Ph-BPE.

and palladium, however, did not prove optimal for the DKR hydrogenation. Using PdCl₂(PhCN)₂ (5 mol %) in addition to the rhodium catalyst in the hydrogenation reaction resulted in recovery of the starting material, presumably due to coordination of the benzonitrile ligands to rhodium. Use of PdCl₂(COD) resulted in formation of palladium black and substrate decomposition.

In accordance with studies by Mislow, we found racemization to be slow in polar solvents, with a racemization half-life of 315 h in methanol (Table 1, entry 3). In a less polar solvent, (9:1 toluene:DCM),²⁵ the rate of racemization was faster than in methanol by a factor of 40 (compare entries 5 and 3). Our best hydrogenation catalyst [Rh((S,S)-Ph-BPE)(COD)]BF₄ (2 mol %) accelerated the racemization in methanol by a factor of 33 (compare entries 3 and 4). On the other hand, addition of [Rh((S,S)-Ph-BPE)]BF₄ (2 mol %) in 9:1 toluene:DCM resulted in only a modest racemization rate enhancement of 10% (entries 5 and 6).

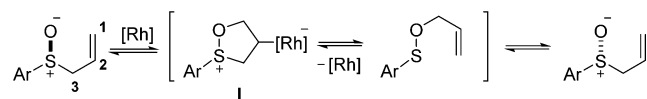
The kinetic experiments suggest that sulfoxide racemization in the DKR hydrogenation predominantly proceeds through an

uncatalyzed [2,3]-sigmatropic rearrangement under nonpolar solvent conditions (toluene:DCM mixtures). However, the allylic sulfoxide undergoes a Rh-catalyzed racemization pathway under polar solvent (MeOH) conditions. This suggests that the rhodium complex can catalyze both the hydrogenation and epimerization processes over the course of the DKR. Therefore, the catalyst concentration will impact the *relative* rates of hydrogenation versus racemization differently, depending upon the solvent choice.

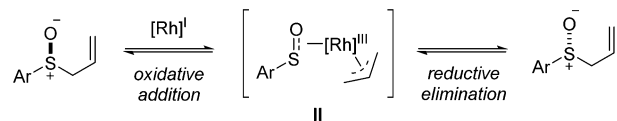
Mechanism of Rh-Catalyzed Racemization. We propose two possible mechanisms for the Rh(I)-catalyzed racemization of allylic sulfoxides. First, the metal could act as a Lewis acid and bind the olefin, thus facilitating the [2,3]-sigmatropic rearrangement by stabilizing negative charge buildup at the 2-position of the allyl group (Scheme 3a). In this case, the metal

Scheme 3. Two Proposed Mechanisms for Rh-Catalyzed Racemization in MeOH

(a) Rh(I) as a Lewis acid



(b) Rh(I) \rightleftharpoons Rh(III); π -allyl formation and sulfenate rotation



is catalyzing the reversible formation of the achiral sulfenate ester. This mechanism is analogous to soft Lewis acid (such as Pd(II) and Hg(II)) catalysis of similar sigmatropic rearrangements.^{21–24}

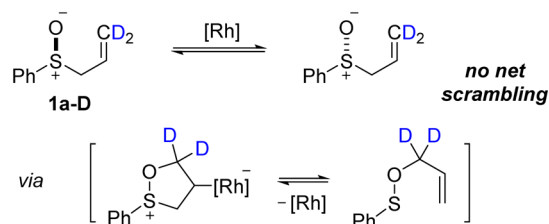
On the other hand, the metal could undergo oxidative addition to form a Rh- π -allyl intermediate II (Scheme 3b). Rotation of the sulfenate ligand followed by reductive elimination leads to overall sulfoxide epimerization. This mechanism is analogous to Pd(0) catalysis of related sigmatropic rearrangements.^{22,27}

Deuterium scrambling experiments with deuterated allylic sulfoxide **1a-D** were used to distinguish between the Lewis acid and π -allyl type mechanisms (Scheme 4). If a Lewis acid mechanism is operative, no scrambling of the deuterium should be observed since transposition of the deuterium labels in the formation of allyl sulfenate ester **2a-D** is reversed when the allylic sulfoxide is reformed. However, if a rhodium π -allyl species II is an intermediate in the racemization and rotation of the π -allyl ligand is facile, then the deuterium label should scramble to the α - and γ -positions of allylic sulfoxide **1a-D**.

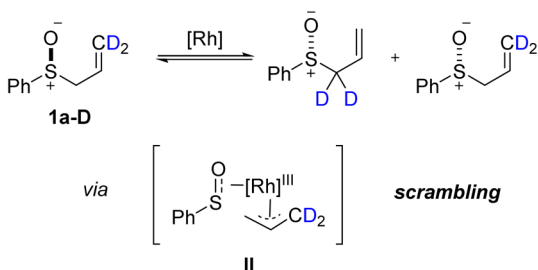
Exposure of **1a-D** to hydrogenation under polar solvent conditions in methanol led to scrambling of the deuterium label in both the recovered starting material and the product (Scheme 5). This result suggests the intermediacy of a rhodium π -allyl species in the mechanism of racemization. Note that complete (1:1 α : γ) scrambling in the product would not be expected because the starting material is labeled exclusively at the outset of the reaction and only scrambles as the reaction proceeds. The extent of deuterium scrambling in the product (40:60 α : γ) is consistent with a racemization occurring exclusively through a rhodium π -allyl intermediate. On the other hand, when the reaction is performed in 9:1

Scheme 4. Possible Deuterium Scrambling Scenarios during Allylic Sulfoxide Racemization

(a) Deuterium scrambling scenario for Lewis acid mechanism



(b) Deuterium scrambling scenario for π -allyl rotation



toluene:DCM, only 12% deuterium scrambling was observed in the propyl sulfoxide product **3a-D**. The extent of scrambling is intimately related to the product ee because these two quantities result from the same pathway. Based on kinetic modeling, approximately 20% scrambling is expected given 50% product ee. Since the observed scrambling is less than this prediction, we conclude that the Rh-catalyzed racemization is only partially responsible for the substrate racemization in non-polar solvents and that uncatalyzed substrate racemization is also occurring. This proposal is consistent with our racemization kinetics results (*vide supra*).

To better understand the racemization process in MeOH, we conducted theoretical studies on the π -allyl mechanism. In a study of metal catalyzed aza-Claisen rearrangements, Bosnich proposed that cationic Rh(I) bisphosphine catalysts could undergo oxidative addition to generate a rhodium π -allyl intermediate with the amide anion still bound to rhodium.²² Analogously, we considered oxidative addition of the allylic sulfoxide to generate a rhodium π -allyl sulfenate complex. A relevant model system was designed to minimize computational cost while maintaining relevance to the experimental system. Dimethylphosphinoethane was modeled as the ligand to match the electronic and geometrical parameters of Ph-BPE. All calculations were performed with Gaussian 09.²⁸ Structures were optimized in the gas phase with M06²⁹ and a mixed basis set of SDD for rhodium and 6-311+G** for all other atoms. The need for a large basis set to accurately calculate the thermodynamics of the 2,3-rearrangement of allylic sulfoxides has previously been noted in several studies,^{15,30–32} and we confirmed this in our own benchmarking studies. Frequency calculations were performed to check the nature of the stationary points and obtain free energies. A solvation energy correction was added using the SMD³³ method with methanol as solvent. In cases where multiple conformations of the substrate or ligand were stable minima, the lowest-energy conformer is shown.

The energy profile for this racemization pathway is illustrated in Figure 1. Oxidative addition of the allylic sulfoxide occurs

Scheme 5. Hydrogenation of Deuterium-Labeled Allylic Sulfoxide

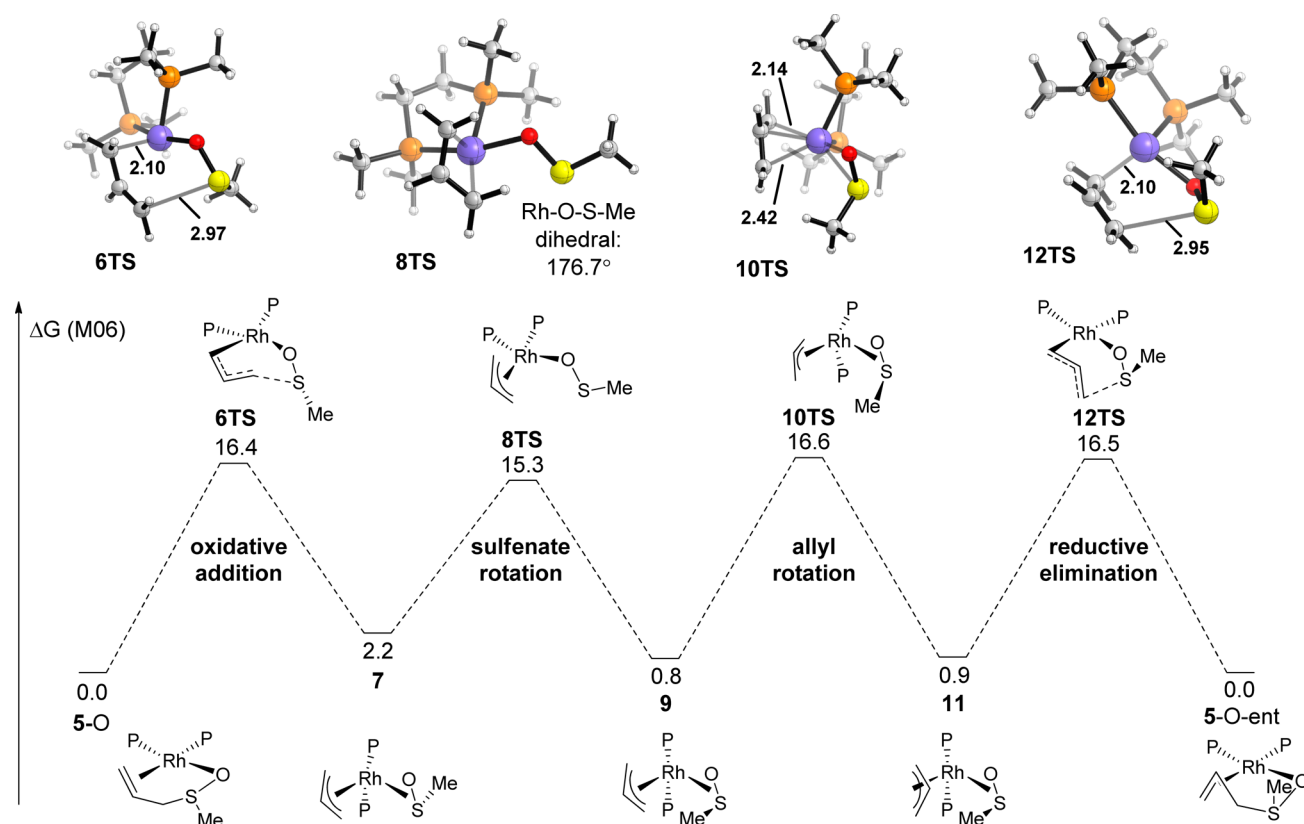
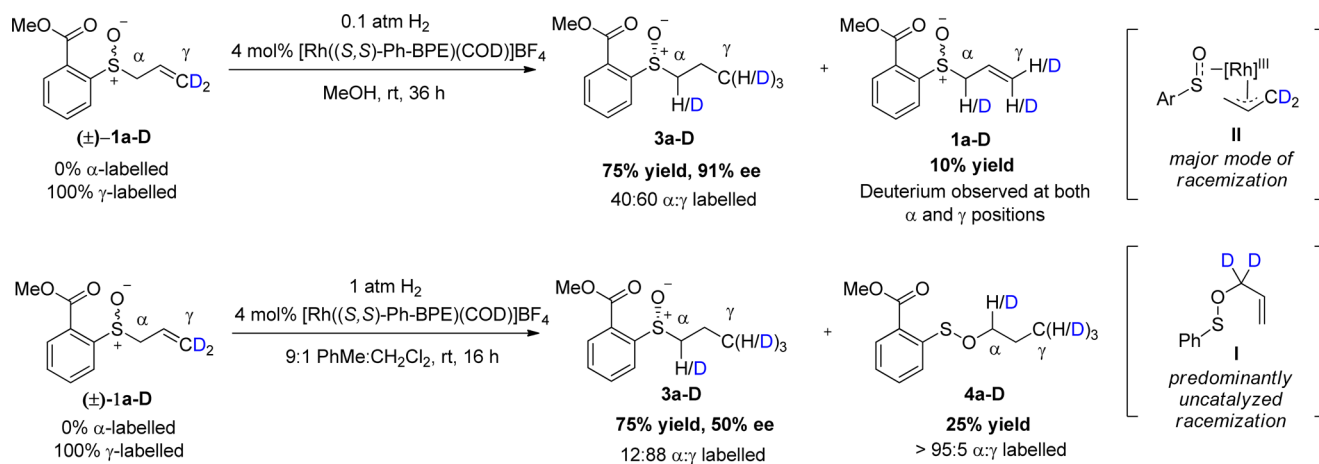


Figure 1. The free energy (kcal/mol) profile for the Rh-catalyzed racemization of allylic sulfoxides.

through a six-membered transition state where the sulfoxide is bound to rhodium through oxygen (6TS), with an energy of 16.4 kcal/mol. The resulting rhodium π -allyl intermediate contains an η -2 bound sulfenate ligand (7). Overall racemization requires rotation of the sulfenate ligand, which occurs through an η -1 O-bound isomerization transition state (8TS). A transition state for inversion of the allyl group (10TS) was located which involves rotation of the allyl group by 180°, with a transition-state energy of 16.6 kcal/mol. The transition structure for this isomerization was found to be a simple rotation with a slight lengthening of one of the Rh–C bonds (2.42 versus 2.14 Å), indicating a small degree of π -allyl to σ -allyl interconversion in the transition state.³⁴ Reductive elimination from intermediate 11 results in the enantiomer of

5.³⁵ This model system with an achiral ligand provides a useful description of the overall process. The true system contains a chiral ligand, however, and thus the binding affinity of either enantiomer of substrate to the catalyst will not be equal in energy.

In this pathway, due to rotation of the allyl group, a net transposition of the allylic termini has occurred. This theoretical prediction is consistent with the deuterium scrambling observed experimentally. Scrambling occurs as a direct result of the formation of a rhodium π -allyl sulfenate intermediate and would not be expected to occur in a simple uncatalyzed [2,3]-sigmatropic rearrangement.

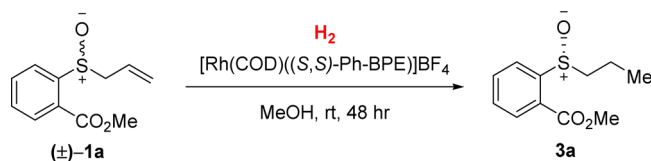
The highest barrier in this Rh-catalyzed racemization pathway has an energy of 16.6 kcal/mol, which is significantly

lower than the uncatalyzed [2,3]-sigmatropic rearrangement transition-state energy of 23.5 kcal/mol (See SI for details). Therefore this rhodium π -allyl type mechanism^{22,36} is consistent with the observed racemization rate enhancement as well as the deuterium labeling study. However, the calculated barrier for hydrogenation (18.4 kcal/mol, *vide infra*) is higher than that for racemization (16.6 kcal/mol). Taking into account the concentration of dissolved hydrogen (~ 0.004 M for 1 atm),³⁷ this predicts that racemization should be faster than hydrogenation. The truncation of the ligand (chiral Ph-BPE to achiral bis-dimethylphosphinoethane) and substrate (aryl allyl sulfoxide to methyl allyl sulfoxide) may play a role in altering these rates. Additionally, the difficulty in obtaining accurate energies for reactions involving change in oxidation states at sulfur has been noted previously.^{15,30–32,38}

Hydrogen Pressure Effects on Enantioselectivity.

Given this mechanistic insight, we examined the effect of H₂ pressure and catalyst concentration on enantioselectivity (Table 2). Using 1 atm H₂ and methanol as solvent, the product was

Table 2. Effect of Catalyst Loading and Hydrogen Pressure



entry	loading (mol %)	p(H ₂) (atm)	conv (%) ^a	ee 3a (%)	yield 4b (%) ^a
1	2	1.0	100	27	1
2	2	0.44	100	53	1
3	4	0.44	100	48	1
4	2	0.29	100	74	6
5	2	0.10	100 (73)	88	8
6	8	0.10	100	88	3
7	3	0.06	100	89	10
8 ^b	1	1.0	6	93	–
9 ^c	1	0.1	7	94	–

^aNMR yield (isolated yield in parentheses). ^bReaction time = 5 min. ^cReaction time = 1 h.

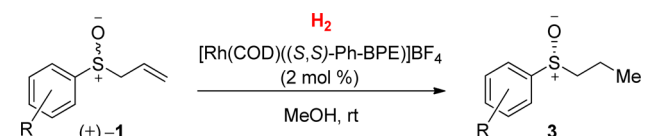
obtained in only 27% ee at full conversion. This poor enantioselectivity reflects the slow rate of racemization in methanol relative to the rate of olefin hydrogenation. Reducing the H₂ pressure resulted in an increase in the enantiomeric excess of the product at full conversion. By simply decreasing the pressure of H₂ to 0.1 atm, 88% ee was achieved at full conversion (73% isolated yield). A more efficient DKR is possible because lowering the pressure of H₂ decreases the rate of hydrogenation, while not affecting the rate of racemization. Furthermore, the catalyst loading did not significantly impact the ee (compare entries 2, 3 and 5, 6). These results support the idea that rhodium catalyzes both hydrogenation and racemization. The sulfenate ester byproduct **4** was formed in only 1–10% under these conditions.³⁹

In our DKR, the H₂ pressure effect is related to the relative rates of interconversion of enantiomeric substrates versus productive hydrogenation. We observe lower enantioselectivities at higher pressures of H₂ because hydrogenation is relatively fast compared to racemization of the substrate. As shown in Table 2 (entries 8 and 9), the H₂ pressure does not affect the ee at low conversion. In a classic study, Halpern observed lower enantioselectivities at higher pressures in his

study of the hydrogenation of α -acylaminoacrylic acid derivatives. However this inverse relationship occurred for a different reason: the interconversion of diastereomeric catalyst-substrate complexes was slow relative to hydrogenation.⁴⁰

Substrate Scope. With this protocol for the DKR of **1a**, we investigated the effect of substituents on the aromatic ring (Table 3). Electron-neutral **1b** resulted in only 50% ee at full

Table 3. Substrate Scope for the Asymmetric Hydrogenation of Allylic Sulfoxides

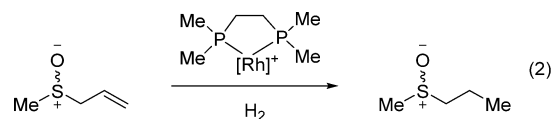


entry ^a	R	P _{H₂} (atm)	t (h)	yield 3 (%)	ee 3 (%)
1	2-CO ₂ Me (1a)	0.1	48	73	88
2	H (1b)	0.1	48	65	50
3	2-CO ₂ tBu (1c)	0.1	48	69	84
4	2-CO ₂ <i>n</i> C ₆ H ₁₃ (1d)	0.1	48	84	86
5	2-NO ₂ (1e)	1	24	55	72
6 ^b	2-CF ₃ (1f)	0.1	48	53	88

^aFull substrate conversion was achieved in all cases. ^b4 mol % Rh-catalyst used.

conversion of starting material (entry 2). Having electron-withdrawing groups at the *ortho*-position of the aromatic ring was necessary to achieve high enantioselectivity, presumably since they increase the rate of allylic sulfoxide racemization. Nitro (**1e**, entry 5) and trifluoromethyl (**1f**, entry 6) groups were tolerated; however the best enantioselectivities were obtained with ester substituents (entries 1, 3, and 4). The steric effect of the *ortho*-substituent may also contribute to enantioinduction.⁴¹ Reduced sulfenate ester **4** and the corresponding disulfide were observed as byproducts in these reactions, accounting for most of the mass balance.

Mechanism of Hydrogenation. The mechanism of the Rh-catalyzed hydrogenation was investigated with DFT calculations to study sulfoxide coordination. Sulfoxides are known to bind to transition metals through either oxygen or sulfur, and low-valent Rh(I) complexes with both S- and O-bound sulfoxides have been isolated.^{1,42,43} Coordination through oxygen is generally favored for hard metals, while coordination through sulfur is favored for soft metals. However, these preferences can be overridden if one binding mode is strained or otherwise geometrically unfavorable. In our system, S-coordination would likely produce more strain in the relevant hydrogenation intermediates than O-coordination. In this model study (eq 2), the ligand is achiral,⁴⁴ while the substrate



contains a chiral center. Considering the facial approach of H₂ to the square planar Rh-substrate complex, and two possible orientations of H₂ oxidative addition, there are eight diastereomeric pathways each for O- and S-coordination. Landis previously modeled a similarly complex set of pathways for the [Rh(DuPHOS)]⁺ catalyzed hydrogenation of enamides.^{45,46}

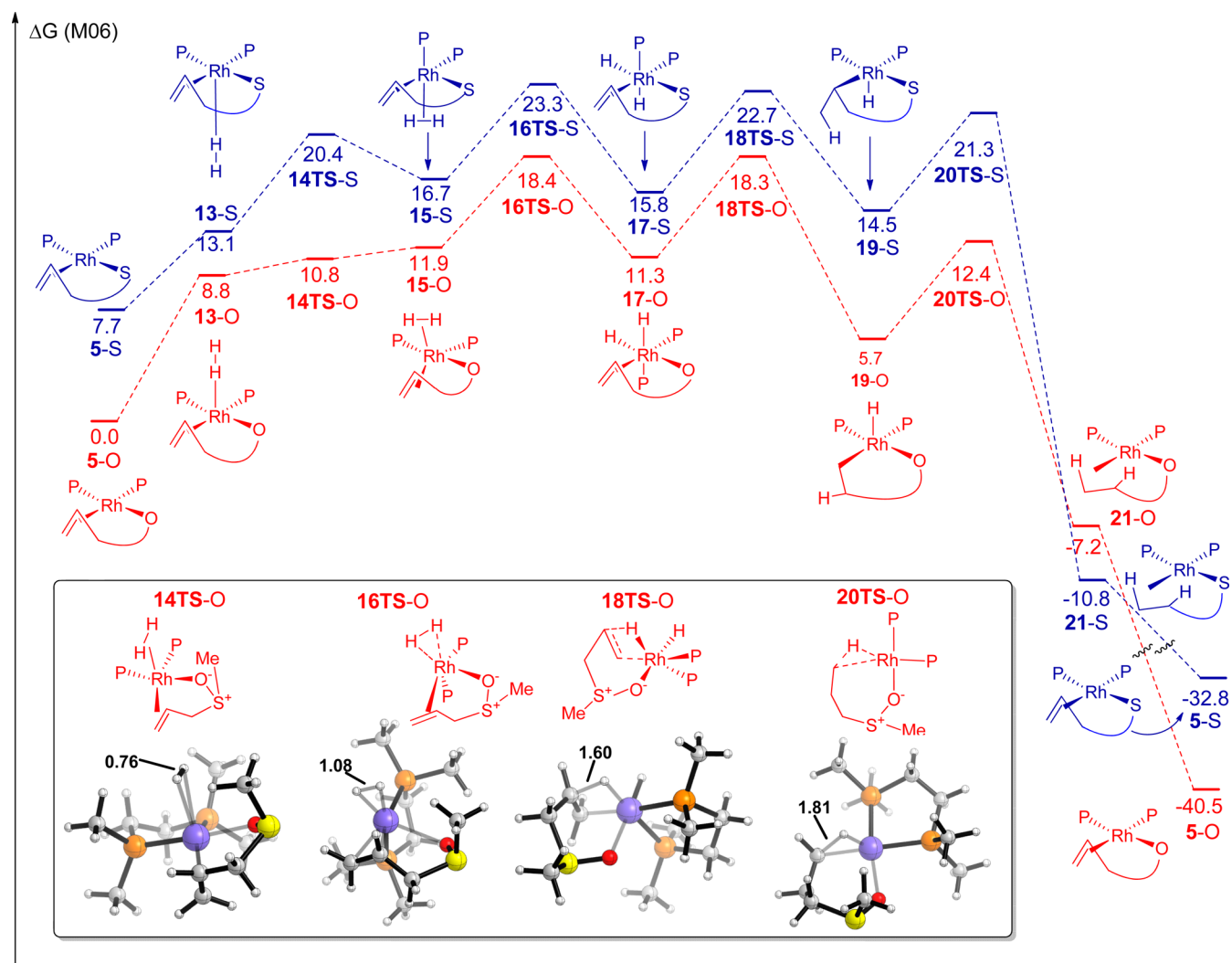


Figure 2. Free energy profile for the most favorable O- and S-bound pathways in the Rh-catalyzed hydrogenation of methyl allyl sulfoxide. S = starting material; 13 = ion-induced dipole complex; 14TS = ion-induced dipole transition state;⁴⁸ 15 = molecular hydrogen complex; 16TS = oxidative addition transition state; 17 = dihydride complex; 18TS = insertion transition state; 19 = alkyl hydride complex, 20TS = reductive elimination transition state; 21 = product.

The lowest-energy O- and S-bound pathways are shown in Figure 2.⁴⁷ Molecular H₂ first binds to the catalyst-substrate complex (S) with a weak ion-induced dipole interaction (13). The dihydrogen molecule then isomerizes (14TS) to a η -2 complex 15, followed by oxidative addition (16TS) to generate the octahedral dihydride complex 17. After olefin insertion (18TS), a square pyramidal alkyl hydride complex 19 is formed. Reductive elimination (20TS) furnishes the hydrogenated product. Pathways where the phosphine is *trans* to the olefin were generally more favorable than pathways where a hydride is *trans* to the olefin, presumably due to the high *trans* effect of the olefin and hydride ligands. The product is predicted to bind to the Rh-complex preferentially through sulfur, as has been observed experimentally for most Rh-sulfoxide complexes.^{1,42} All catalytic intermediates and transition states, however, are higher in energy for the S-bound pathways versus the O-bound pathways, presumably due to strain in the S-bound chelated intermediates. The most favorable S-bound pathway had a rate-determining transition-state energy of 23.3 kcal/mol, while the most favorable O-bound pathway was 18.4 kcal/mol. Therefore, we conclude that the hydrogenation is directed by O-coordination.

CONCLUSION

We have demonstrated a DKR of allylic sulfoxides by asymmetric hydrogenation using a dual role catalyst. The chiral rhodium complex catalyzes both the sulfoxide-directed olefin hydrogenation and sulfoxide racemization in methanol. A deuterium scrambling experiment supports a rhodium π -allyl species as an intermediate in the substrate racemization. Modeling of the Rh-catalyzed racemization suggests allylic sulfoxide oxidative addition generates a rhodium π -allyl sulfenate intermediate, which can undergo sulfenate rotation followed by reductive elimination to obtain the epimerized sulfoxide. This catalysis of racemization was further supported by deuterium labeling experiments. In nonpolar solvents, however, racemization is primarily uncatalyzed. Computational studies of the hydrogenation pathway implicate the sulfoxide as a directing group through O-coordination. The mechanistic insights gained from this study will enable the development of other sulfoxide-directed metal processes⁴⁹ that are amenable to DKR and dual role catalysts. These new transformations will add molecular complexity to the alkene while setting the sulfoxide stereocenter. In addition, future work will focus on

developing new catalysts and strategies for promoting allylic sulfoxide racemization.

■ ASSOCIATED CONTENT

Supporting Information

Full synthetic and characterization details, energies, and optimized geometries of all calculated species. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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sulfenate ester **2** from (*R*)-**1** or (*S*)-**1** will also be slow. As the hydrogenation proceeds and the initial equilibrium concentration of **2** is consumed, the regeneration of **2** is slow, and therefore the concentration of **2** will be lower than expected based on equilibrium constants. Consequently propyl sulfenate ester **4** will be formed to a lesser extent over the course of the reaction. This scenario is relevant for entry 1, where low ee and only 1% sulfenate ester was observed.

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(49) 25% yield, 25% ee was achieved in the linear-selective hydroacylation of phenyl allyl sulfoxide with salicylaldehyde.