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Tandem rhodium catalysis: Exploiting sulfoxides for asymmetric transition-metal catalysis

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Sulfoxides are uncommon substrates for transition-metal catalysis due to their propensity to inhibit catalyst turnover. In a collaborative effort with Ken Houk, we developed the first dynamic kinetic resolution (DKR) of allylic sulfoxides using asymmetric rhodium-catalyzed hydrogenation. Detailed mechanistic analysis of this transformation using both experimental and theoretical methods revealed rhodium to be a tandem catalyst that promoted both hydrogenation of the alkene and racemization of the allylic sulfoxide. Using a combination of deuterium labelling and DFT studies, a novel mode of allylic sulfoxide racemization via a Rh(III)-π-allyl intermediate was identified.

Introduction

Chiral sulfoxides are structural components found in the world's top selling pharmaceutical drugs, organocatalysts, chiral auxiliaries and ligands for use in asymmetric catalysis (Figure 1).[1-6] From a synthetic standpoint, molecules containing the sulfone or sulfoxide functional handle can be exploited for carbon—carbon bond formation via the Julia olefination, an aldol-type reaction, or a Mislow-Braverman-Evans rearrangement. However, organosulfur compounds, including sulfoxides, are often challenging substrates for catalysis because they tend to poison metal catalysts by forming stable organometallic complexes.[7,8] Specifically, sulfoxides coordinate to transition metals via the sulfur and/or oxygen heteroatoms.[1,9-11] Totland and Alper showed that vinyl sulfone

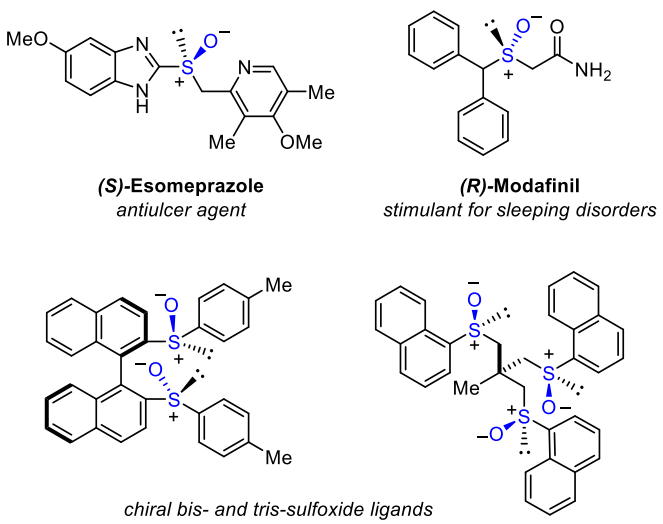
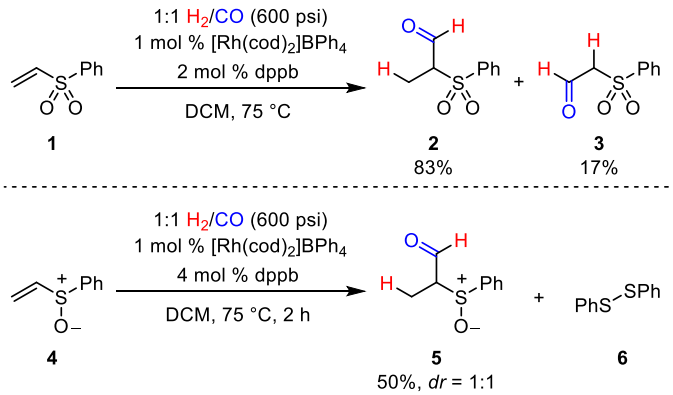
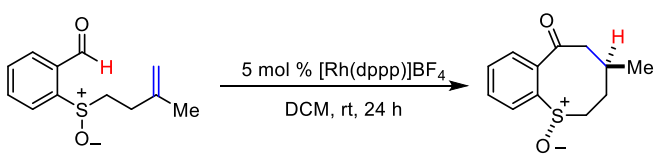


Figure 1 Select examples of drugs and ligands containing the chiral sulfoxide motif.



Scheme 1 Rh-catalyzed hydroformylation of vinyl sulfones and sulfoxides.



Scheme 2 A sulfoxide-directed diastereoselective Rh-catalyzed hydroacylation.

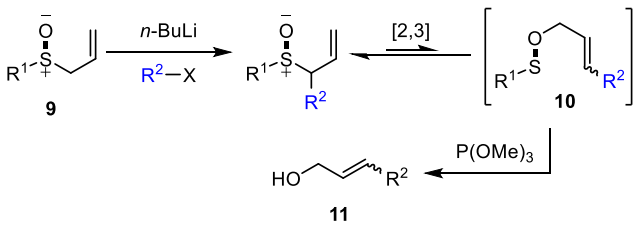
1 can be hydroformylated under rhodium catalysis to generate aldehydes **2** and **3** in high yields and good branched-to-linear selectivities (Scheme 1).[7] However, when the analogous vinyl sulfoxide **4** was subjected to similar reaction conditions, only 50% conversion of the substrate was achieved after extended reaction times, most likely due to catalyst poisoning. While the sulfoxide functionality shows promise as a directing group for formation of the branched regioisomer **5**, its strong

coordinating coordinating ability inhibits catalyst turnover.

During our own studies on heteroatom-directed Rh-catalyzed intramolecular hydroacylations, we found that sulfoxide-containing alkenal **7** can direct a highly diastereoselective cyclization to form medium ring ketone **8** (Scheme 2).[12] Thus, we became interested in studying the use of chiral sulfoxides as directing groups for stereoselective transformations.

Development of a DKR of allylic sulfoxides

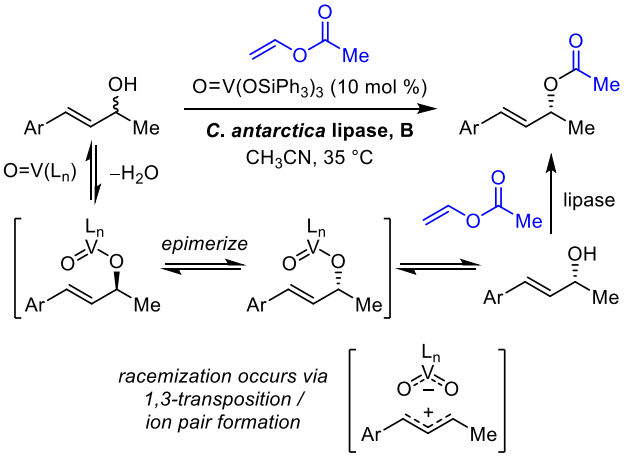
Inspired by the early reports of Mislow and coworkers,[13-15] we envisioned a DKR strategy for the functionalization of allylic sulfoxides. Unlike typical sulfoxides (*i.e.*, dialkyl, diaryl, and alkyl-aryl sulfoxides) that are configurationally stable under normal conditions,[13] (chiral) allylic sulfoxides **9** are thermolabile and can racemize rapidly at temperatures between 40−70˚C. This racemization occurs by a reversible [2,3]-sigmatropic rearrangements through the intermediacy of an achiral sulfenate ester **10**.[14] The Mislow-Braverman-Evans sequence[16,17] which furnishes substituted allyl alcohols **11**, stands as the only practical application of the [2,3]-sigmatropic rearrangement of allylic sulfoxides (Scheme 3).



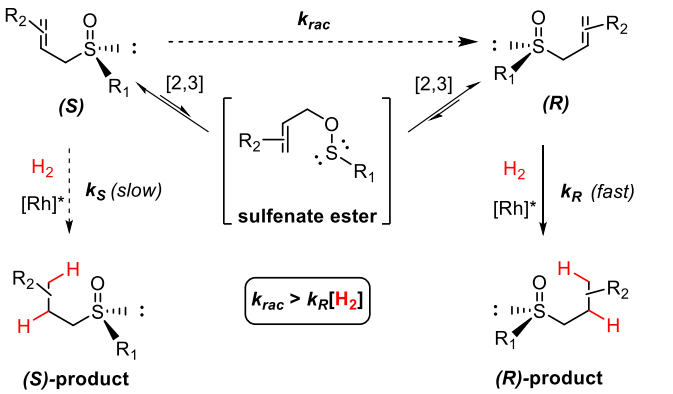
Scheme 3 Mislow-Braverman-Evans rearrangement.

In considering this limitation, rather than trapping the sulfenate ester **10** with stoichiometric reductants, we propose to use the [2,3]-sigmatropic rearrangement of allylic sulfoxides as the racemization step in a DKR. Asymmetric transformations on the olefin will halt racemization and thus enable access to configurationally stable products. This protocol would provide an alternative to standard oxidation procedures for synthesizing enantioenriched sulfoxides.[1] The use of isomerizations or sigmatropic rearrangements as the racemization element in DKRs are rare. Akai and coworkers have shown that allylic alcohols can be racemized in the presence of a vanadium oxo-reagent via 1,3-allylic transpositions, and they achieve a DKR by using lipase-catalyzed acylation (Scheme 4).[18,19]

To achieve the desired DKR, the following three criteria has to be met: 1) the chiral catalyst, [Rh]*, must react preferentially with one enantiomer, 2) the rate of racemization must be fast relative to the rate of hydrogenation,[20] and 3) the product sulfoxide must not be prone to epimerization (Scheme 5). During this study, we found that tandem catalysis[21] is operative because one rhodium complex catalyzes two distinct steps in a cascade process that involves racemization followed by hydrogenation.



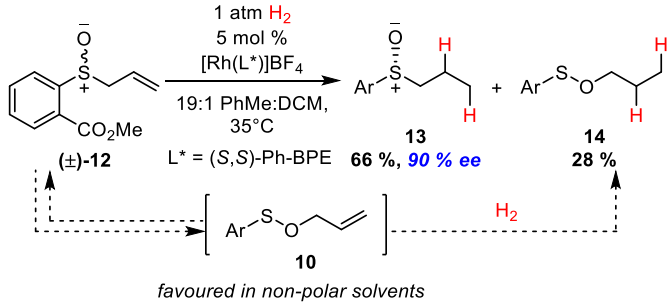
Scheme 4 Lipase and vanadium-oxo-catalyzed DKR of allyl alcohols.



Scheme 5 Proposed DKR via asymmetric hydrogenation.

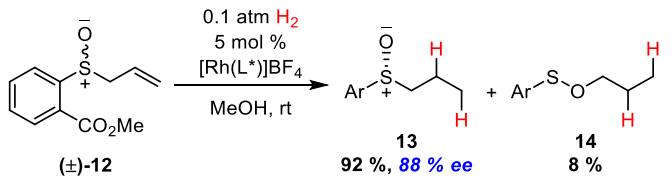
We found that [Rh((*S*,*S*)-Ph-BPE)]BF_4 catalyzes hydrogenation of racemic **12** to aryl(propyl)sulfoxide (**13**) in PhMe/DCM in 66 % yield and 90 % ee (Scheme 6). However, sulfenate ester **8** was formed in 28 % yield, presumably due to hydrogenation of allyloxy(aryl)sulfenate ester **10**. To reduce byproduct formation, the use of polar solvents (*i.e.*, methanol) that stabilize the polar sulfoxide relative to the non-polar sulfenate ester is desirable. However, polar solvents are reported to significantly lower the rates of sulfoxide epimerization.[15]

To enhance the rates of sulfoxide racemization, we investigated the possibility of catalysing the [2,3]-sigmatropic rearrangement. Palladium(II) salts have been reported to catalyse the [2,3]-sigmatropic rearrangement of allylic amine *N*-oxides,[22] and [3,3]-sigmatropic rearrangements, including the Overman,[23] Claisen,[24] and aza-phospha-oxa-Cope[25] processes. On the contrary, metal catalyzed [2,3]-sigmatropic rearrangements of allylic sulfoxides are unprecedented. As part of an effort to elicit antibodies that catalyze pericyclic reactions, the Hilvert group has reported two antibodies that catalyse sulfoxide-sulfenate rearrangements.[26] We performed a series of kinetics experiments and found that [Rh((*S*,*S*)-Ph-BPE)]BF_4] enhances the rate of racemization in methanol by a factor of 33 ($t_{1/2}$ = 9.6 h).[11]



Scheme 6 Rh-catalyzed hydrogenation of allylic sulfoxides in a non-polar solvent.

With the discovery that the rhodium complex behaves as a tandem catalyst for both sulfoxide racemization and olefin hydrogenation, it became evident that the relative rates of racemization and hydrogenation could not be controlled simply by changing the catalyst loading. Therefore, we subjected sulfoxide (±)-**12** to Rh-catalyzed DKR hydrogenation in methanol at lower pressures of H_2 (Scheme 7). By lowering the hydrogen pressure to 0.1 atm, the rate of racemization relative to the rate of hydrogenation is increased. Under these conditions, DKR of allylic sulfoxide **12** occurs to generate enantioenriched sulfoxide **13** in 92 % yield and 88 % ee. Performing the reaction in methanol suppresses undesired byproduct formation, and sulfenate ester **14** is formed in only 8 % yield.

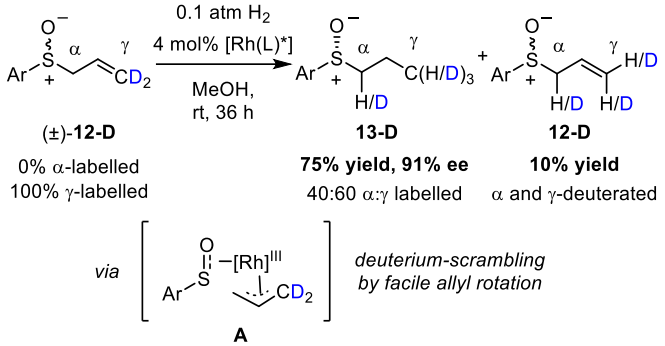


Scheme 7. DKR of allylic sulfoxide by tandem Rh-catalysis.

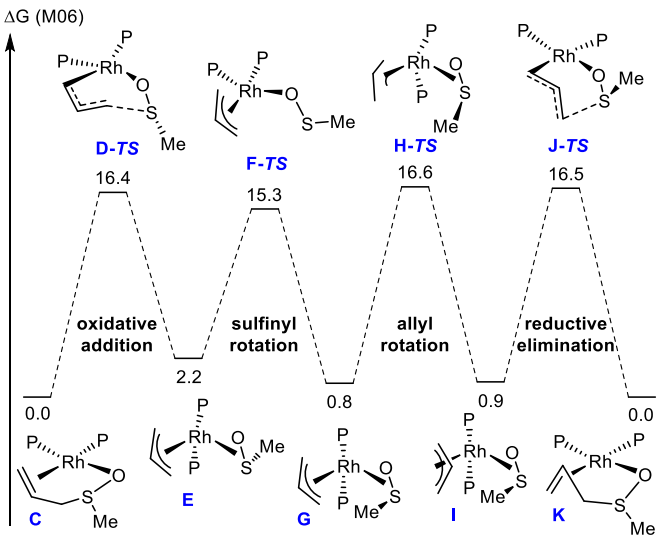
A new mode of allylic sulfoxide racemization by rhodium catalysis

To understand the Rh-catalyzed racemization of allylic sulfoxides, γ-deuterated allylic sulfoxide (±)-**12-D** was prepared and subjected to hydrogenation in methanol (Scheme 8). After 36 h, deuterated product **13-D** was isolated in 75 % yield and 91 % ee. Importantly, a significant amount of deuterium had been scrambled to the α-position. Complete scrambling of the deuterium label was also observed in the recovered starting material. These results support a mechanism involving a Rh(III)-π-allyl intermediate **A**. Rate acceleration in methanol is consistent with the relatively polar nature of the Rh(III) intermediate.

Additional insight into this unique mode of racemization was gathered by computing the free energy profile (Scheme 8). We find that oxidative insertion occurs via a concerted 6-membered transition state (**D-*TS***) with a barrier of 16.4 kcal/mol to generate Rh(III)-π-allyl intermediate **E**. Sulfoxide epimerization occurs by rotation of the sulfinyl unit, and this has a barrier of 15.3 kcal/mol (**F-*TS***). Consistent with our deuterium scrambling results, allyl group rotation via **H-*TS*** is



Scheme 8 Deuterium-labelling experiment consistent with a mechanism invoking a Rh-π-allyl species. Ar = 2-CO_2Me-C_6H_4



Scheme 9 Free energy profile (M06/6-311G+**, SDD for Rh) for the Rh-catalyzed racemization of allylic sulfoxides.

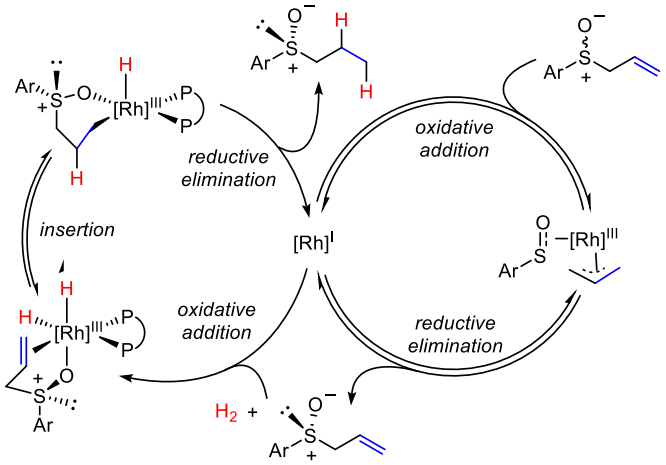
facile and exhibits a barrier of 16.6 kcal/mol. A final C—S reductive elimination regenerates the epimerized allylic sulfoxide. The highest barrier (16.6 kcal/mol) within this pathway is significantly lower in energy than the transition-state energy of the uncatalyzed pathway, which is computed to be 23.5 kcal/mol. Throughout the catalytic cycle for sulfoxide-directed hydrogenation, DFT calculations[11] support a mechanism where the oxygen atom of the sulfoxide is bound in all of the lowest energy ground states and transition states (Scheme 9).

Conclusions and Future Outlook

This study contributes to our emerging interest in using tandem catalysis to address challenges in organic synthesis, including tandem Ru-catalyzed hydroacylations[27,28] and tandem Ru-catalyzed aminations.[29] The first demonstration of a catalytic asymmetric transformation of racemic allylic sulfoxides is achieved through Rh-catalyzed hydrogenation.

This reaction is made possible by a tandem rhodium catalyst, [Rh((*S*,*S*)-Ph-BPE)]BF_4, that plays a dual role in accelerating the rate of allylic sulfoxide epimerization and catalyzing olefin hydrogenation (Scheme 10). It is also the first small molecule that catalyzes allylic sulfoxide racemization. A new mechanism for allylic sulfoxide racemization is proposed to occur through the intermediacy of a Rh(III)-π-allyl complex.

The sulfoxide has great potential for stereoselective transition-metal-catalyzed transformations due to its strong coordinating ability and inherent chirality. While there is concern for sulfoxides to undergo undesired side-reactions or poison catalysts, both of these undesirable processes can be minimized under the appropriate reaction conditions (*i.e.*, solvent, pressure). In demonstrating a successful DKR of allylic sulfoxides, we reveal mechanistic insights that could enable the development of other sulfoxide-directed metal processes. Future studies from our laboratory will focus on complexity-forming reactions, such as hydroacylation.



Scheme 10 Proposed mechanism for tandem Rh-catalyzed racemization/hydrogenation for the DKR of allylic sulfoxides.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 I. Fernández, N. Khiar, *Chem. Rev.* 2003, **103**, 3651.
2. P. K. Dornan, P. L. Leung, V. M. Dong, *Tetrahedron* 2011, **67**, 4378.
3. M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.* 2005, **127**, 6970.
4. R. Mariz, X. Luan, M. Gatti, A. Linden, R. Dorta, *J. Am. Chem. Soc.* 2008, **130**, 2172.
5. J. J. Bürgi, R. Mariz, M. Gatti, E. Drinkel, X. Luan, S. Blumentritt, A. Linden, R. Dorta, *Angew. Chem. Int. Ed.* 2009, **48**, 2768.
6. Trost, B. M.; Rao, M. *Angew. Chem. Int. Ed.* 2015, **54**, 5026.
7. K. Totland, H. Alper, *J. Org. Chem.* 1993, **58**, 3326.
8. A. Müller, E. Diemann, In *Comprehensive Coordination Chemistry*; G. Wilkinson, Ed.; Pergamon Press: Oxford, 1987, Vol. 2, Chapter 16.1, 515−689.
9. M. Calligaris, O. Carugo, *Coord. Chem. Rev.* 1996, **153**, 83.
10. R. Dorta, H. Rozenberg, D. Milstein, *Chem. Commun.* **2002**, 710.
11. P. K. Dornan, K. G. M. Kou, K. N. Houk, V. M. Dong, *J. Am. Chem. Soc.* 2014, **136**, 291.
12. M. M. Coulter, P. K. Dornan, V. M. Dong, *J. Am. Chem. Soc.* 2009, **131**, 6932.
13. D. R. Rayner, A. J. Gordon, K. Mislow, *J. Am. Chem. Soc.* 1968, **90**, 4854.
14. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* 1968, **90**, 4869.
15. R. Tang, K. Mislow, *J. Am. Chem. Soc.* 1970, **92**, 2100.
16. D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* 1974, **7**, 147.
17. S. Braverman, Y. Stabinsky, *Chem. Commun. (London)*, 1967, 270.
18. S. Akai, K. Tanimoto, Y. Kanao, M. Egi, T. Yamamoto, Y. Kita, *Angew. Chem., Int. Ed.* 2006, **45**, 2592.
19. S. Akai, R. Hanada, N. Fujiwara, Y. Kita, M. Egi, *Org. Lett.* 2010, **12**, 4900.
20. M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* 1993, **115**, 144.
21. D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* 2004, **248**, 2365.
22. H. Bao, X. Qi, U. K. Tambar, *J. Am. Chem. Soc.* 2011, **133**, 1206.
23. L. E. Overman, *Angew. Chem., Int. Ed. Engl.* 1984, **23**, 579.
24. T. G. Schenck, B. Bosnich, *J. Am. Chem. Soc.* 1985, **107**, 2058.
25. E. E. Lee, R. A. Batey, *J. Am .Chem. Soc.* 2005, **127**, 14887.
26. Z. S. Zhou, A. Flohr, D. Hilvert, *J. Org. Chem.* 1999, **64**, 8334.
27. S. K. Murphy, V. M. Dong, *J. Am. Chem. Soc.* 2013, **135**, 5553.
28. Q. A. Chen, F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc.* 2015, **137**. 3157.
29. N. J. Oldenhuis, V. M. Dong, Z. Guan, *J. Am. Chem. Soc.* 2014, **136**, 12548.