Title

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Journal

Journal of the American Chemical Society, 143(16)

ISSN

0002-7863

Authors

Nie, Shaozhen
Lu, Alexander
Kuker, Erin L
et al.

Publication Date

2021-04-28

DOI

10.1021/jacs.1c00939

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2022 February 14.

Published in final edited form as:

J Am Chem Soc. 2021 April 28; 143(16): 6176–6184. doi:10.1021/jacs.1c00939.

Enantioselective Hydrothiolation: Diverging Cyclopropenes Through Ligand Control

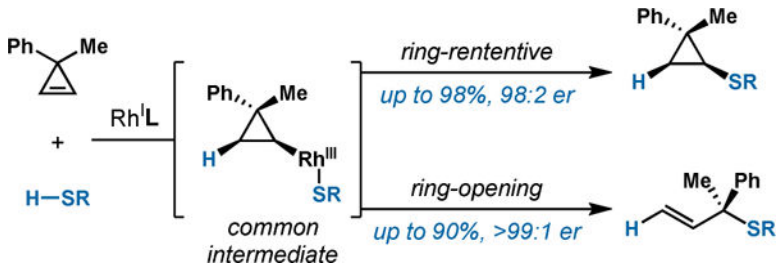
Shaozhen Nie, **Alexander Lu**, **Erin L. Kuker**, **Vy M. Dong***

Department of Chemistry, University of California, Irvine, California 92697, United States

Abstract

In this Article, we advance Rh-catalyzed hydrothiolation through the divergent reactivity of cyclopropenes. Cyclopropenes undergo hydrothiolation to provide cyclopropyl sulfides or allylic sulfides. The choice of bisphosphine ligand dictates whether the pathway involves ring-retention or ring-opening. Mechanistic studies reveal the origin for this switchable selectivity. Our results suggest the two pathways share a common cyclopropyl-Rh(III) intermediate. Electron-rich Jospiphos ligands promote direct reductive elimination from this intermediate to afford cyclopropyl sulfides in high enantio- and diastereoselectivities. Alternatively, atropoisomeric ligands (such as DTBM-BINAP) enable ring-opening from the cyclopropyl-Rh(III) intermediate to generate allylic sulfides with high enantio- and regiocontrol.

Graphical Abstract



Keywords

hydrothiolation; cyclopropenes; rhodium; catalysis

INTRODUCTION

Given the prevalence of sulfur in biologically relevant organic molecules,[1] inventing methods to forge C–S bonds remains a worthwhile pursuit.[2] Hydrothiolation, the addition of

***Corresponding Author:** dongv@uci.edu.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental Procedures and spectral data for new compounds

Crystallographic data for **3ba**

The authors declare no competing financial interest.

a thiol across a degree of unsaturation, represents a straightforward and atom economical[3] way of building molecules with sulfide functional groups.[4] In previous communications,[4c,4d] our laboratory disclosed highly regioselective hydrothiolations of conjugated dienes, where regiocontrol was achieved through careful selection of the counterion associated with the Rh-catalyst (Figure 1A). Using a non-coordinating counterion, such as SbF_6^-, allows the conjugated diene to bind the catalyst in an η^4 fashion en route to allylic sulfide products.[4c] Using a coordinating counterion, such as Cl^-, forces the conjugated diene to bind the catalyst in an η^2 fashion en route to homoallylic sulfide products.[4d] The switch in regioselectivity was achieved by having chloride occupy a coordination site on the catalyst. In this article, we focus on the hydrothiolation of cyclopropenes. In contrast to our previous study, the appropriate choice of ligand enables divergent pathways to yield either the cyclopropyl or allylic sulfide motifs, both architectures germane to natural products and biologically active molecules (Figure 1B).

Since their synthesis in 1922,[5] cyclopropenes have captivated chemists due to their strained structures and high reactivity.[6] Cyclopropene, the smallest possible unsaturated carbocycle, owes its unique reactivity to 54.1 kcal/mol of strain energy.[7] Releasing the strain energy enables cyclopropenes to undergo cycloadditions and hydrofunctionalizations that are challenging for simpler alkenes and alkynes. In contrast to less strained alkenes, however, there exists a unique challenge in controlling the diverse modes of reactivity (Figure 2A). Additions to cyclopropenes are known to occur with ring-retention to yield cyclopropyl products,[8] as well as with ring-opening to yield allylic products.[9] In general, ring-retentive hydrofunctionalizations require softer nucleophiles, such as boranes, stannanes, and carbon nucleophiles.[10,11] Ring opening hydrofunctionalizations require harder nucleophiles, such as amines, alcohols, or phosphonates.[12] However, there are exceptions to this trend, including Hou's ring-retentive hydroamination[10f] and Yamamoto's ring-opening addition of carbon nucleophiles.[12a]

Lee demonstrated that both modes of reactivity are possible for thiol nucleophiles, depending on the choice of conditions (Figure 2B).[13] The Au-catalyst opens the cyclopropene through C–C bond activation. The regioselectivity of the subsequent hydrothiolation depends on the choice of thiol or thioacid as the nucleophile. While the reactivity is novel, only racemic mixtures of the allylic sulfide are obtained when coupling unsymmetrical cyclopropenes to thiols. In the absence of a Au-catalyst, cyclopropyl sulfide products are observed.[14] Rendering either variant of Lee's cyclopropene hydrothiolation asymmetric would be difficult: the enantio-determining step of ring-opening hydrothiolation is protonation, while the ring-retentive hydrothiolation proceeds in the absence of catalyst.

To address this challenge, we hypothesized that Rh-catalysis, along with careful selection of the bisphosphine ligand, would enable access to both ring-opening and ring-retentive hydrothiolations of cyclopropenes (Figure 3A). Controlling the reactivity of the cyclopropene through ligands would enable us to select for products that are chiral, thus offering an opportunity to render the transformations enantioselective. Identifying ligands that can override the native reactivity of substrates is challenging. However, there are several examples in the literature of ligands enabling the divergent synthesis of constitutional isomers.[15,16] Ligand-control is established primarily through governing

the regioselectivity[15] or chemoselectivity[16c,16d] of the transformation. Our group has studied the reactivity of bisallylaldehydes under Rh-catalyzed hydroacylation (Figure 3B). Through the choice of bisphosphine ligand, we can alter the steps of the catalytic cycle and obtain different carbocycles from the same bisallylaldehyde starting material.[16a,16b,17] Encouraged that transition metals can catalyze reactions with thiols,[2] we focused on studying Rh-catalysts to explore how different bisphosphine ligands diverge the reactivity of cyclopropenes.

RESULTS AND DISCUSSION

Reaction Discovery, Key Parameters, and Optimization.

To test our hypothesis, we attempted to couple cyclopropene **1a** and thiophenol **2a** using a variety of achiral bisphosphine ligands with $[Rh(cod)Cl]_2$. Gratifyingly, we observed a correlation between **3aa**:**4aa** and the bite angle of the bisphosphine ligands (Figure 4A). Bisphoshines with smaller bite angles (dppm, dppe) give exclusively cyclopropyl sulfide (±)-**4aa** (76% and 82%, >20:1 *dr*), while ligands with larger bite angles (*rac*-BINAP) form allylic sulfide (±)-**3aa** exclusively (80%, >20:1 *rr*). Bisphosphine ligands with intermediate bite angles furnish mixtures of **3aa** and **4aa**. The 1,1-dialkysubstituted cyclopropene (3,3-dihexylcycloprop-1-ene) has been shown to undergo addition with thiols in the absence of any catalysts (Figure 2B).[13] In contrast, control experiments with cyclopropene **1a** show that neither product is obtained in the absence of Rh-precursor or ligand, indicating that the selectivity is ligand-controlled. Next, we optimized for asymmetric variants of the transformation to access **3aa** or **4aa** with high enantioselectivity (Figure 4B). Ligands from the Josiphos family bearing alkyl substituents (**L5**, **L6**) afforded **3aa**. Ultimately, using **L5** with MeCN as solvent afforded the best yield and selectivity for **3aa** (90%. 95:5 *er*, >20:1 *dr*) after 6 h. Hydrothiolations promoted with axially chiral ligands bearing DTBM (3,5-di-tert-butyl-4-methoxyphenyl) substituents (**L7**, **L8**) afford allylic sulfide **4aa** with good yields (86–87%, >20:1 *rr*) when conducted at 0 °C for 30 min. The best enantioselectivity for **4aa** was achieved when using bisphosphine **L8** (96:4 *er*).[18] Given the structural differences between chiral bisphosphines **3aa** and **4aa**, both steric and electronic parameters must influence selectivity.

Ring-retentive Hydrothiolation Substrate Scope.

With these conditions in hand, we evaluated the scope of the ring-retentive hydrothiolation (Table 1). High reactivity and enantioselectivity (91:9–95:5 *er*) are observed with aromatic thiol partners (**3ab**–**3ag**). However, aliphatic thiols are unreactive under these conditions (**3ap** and **3aq**). This result most likely stems from the differences in their ability to bind Rh (vide infra). Thus, further tuning of the bisphospine ligand will be necessary to obtain reactivity using alkyl thiols. On the other hand, aromatic thiols bearing halogens transform well (**3ad**, 87%, >20:1 *dr*, 94:6 *er*). Sterically hindered thiophenols with *ortho* substituents display good reactivity and high selectivity (**3af,** 73%, >20:1 *dr*, 95:5 *er*). Withdrawing functional groups on aromatic thiols (such as 4-(trifluoromethyl)thiophenol) give mixtures of both cyclopropyl and allylic sulfide products. Aromatic thiols with extended π-systems couple to **1a** with 81% yield and 94:6 *er* (**3ag**).

Cyclopropenes bearing different aromatic groups are all suitable coupling partners for the transformation (**3ba–3da**). Cyclopropenes with electron rich aromatic groups (**3ba**) show excellent reactivity (83%) and selectivity (>20:1 *dr*, 94:6 *er*).[19] The hydrothiolation occurs even with the addition of electron withdrawing substituents on the cyclopropene (**3ca** and **3da**, 68–92%, ≥20:1 *dr*, 94:6 *er*). The methyl substituent can be replaced with a bulkier benzyl substituent (**3ea**, 61%, >20:1 *dr*, 92:8 *er*). There are many spirocyclic natural products containing quaternary carbons, and these quaternary centers are difficult to set in a stereoselective manner.[20] Through a desymmetrization of the corresponding spirocyclic cyclopropene, sulfide **3fa** is obtained in excellent yield and stereoselectivity. Cyclopropenes containing a methyl ether can also undergo hydrothiolation (**3ga**).

Ring-opened Hydrothiolation Substrate Scope.

Next, we explored the scope for obtaining allylic sulfides (Table 2). The hydrothiolation of **1a** was carried out with structurally and electronically different thiols. Both aryl (**4ab**–**4ao**) and alkyl thiols (**4ap**, **4aq**) add to cyclopropene **1a**.

In general, the ring-opened allylic sulfides are obtained with excellent regioselectivity (>20:1 *rr*).[21] Electron rich thiophenols couple to **1a** with high reactivity and good selectivities (**4ab**, **4ac**, **4ah**, 85%–90%, 92:8–96:4 *er*). Electron deficient thiophenols undergo addition with good selectivities (**4ai**–**4al**, 82%–89%, 91:9–95:5 *er*). Allylic sulfide **4al** was originally obtained as a mixture with **3al**. However, raising the reaction temperature allows for the exclusive formation of **4al**. Sterically hindered thiophenols react with high enantioselectivities (**4af** and **4ao**, >99:1 *er* and 95:5 *er*). Alkyl thiols couple, albeit with moderate yields and selectivities (**4ap** and **4aq**, 63–71%, 74:26 *er*).

Most of the cyclopropenes that react under the ring-retentive conditions also react under the ring-opened hydrothiolation conditions. Cyclopropenes with either electron rich (**4ba**) or electron poor (**4ca** and **4da**) aryl substituents can couple to **2a** (58%–83%, 85:15–97:3 *er*). Cyclopropenes bearing larger substituents, such as benzyl (**4ea**) or naphthyl (**4ha**) also show good reactivity, albeit with less selectivity (74%–88%, 85:15–88:12 *er*). Allylic sulfides **4ap**, **4aq**, **4ca**, and **4ea** are obtained as mixtures with their ring-retentive counterparts under the standard conditions. However, raising the temperature to 30 °C and switching the bisphosphine ligand from **L8** to **L7** gives exclusively the ring-opened allylic sulfide.

Mechanistic Insights for Ring-retentive Hydrothiolation.

Based on both literature precedent and our own observations, we propose the following mechanism for ring-retentive hydrothiolation of cyclopropenes (Figure 5). The catalyst resting state is an off-cycle species **III**, with multiple thiols bound. Upon dissociation of thiols to enter the catalytic cycle, the Rh-catalyst (**I**) undergoes oxidative addition to **2a** to generate **II**. Following coordination, cyclopropene **1a** inserts into the Rh–H bond to afford cyclopropyl-Rh(III) **V**. The turnover limiting step is reductive elimination to form the C–S bond, which furnishes **3aa** and regenerates the Rh-catalyst **I**. The mechanistic experiments that led to this proposed mechanism are discussed below.

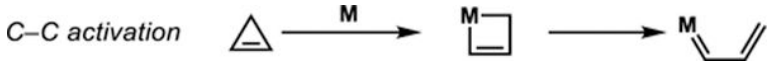
Through studies of the initial reaction rates, we determined that the hydrothiolation was first order with regards to Rh-catalyst and **1a**, and a negative fractional order with regards to thiol **2a**. A negative order in thiol has been observed in our group's previous report on the hydrothiolation of dienes,[4d] leading us to propose an off-cycle resting state where multiple thiols are coordinated through a hydrogen-bonding network (**III**).[22] The proposed resting state **III** is further supported by the presence of a metal hydride resonance at −15.9 ppm when using ^{1}H NMR spectroscopy to monitor experiments using stoichometric amounts of $[Rh(cod)Cl]_2$, dppe, and **2a**.[23]

An isotopic labelling experiment was performed with the ring-retentive conditions using deuterated thiophenol ***d*-2a** (Figure 6A). Analysis of ***d*-3aa** shows that the deuterium is incorporated exclusively *syn* relative to the sulfide. This result suggests a *syn* hydrorhodation operates in the catalytic cycle. No kinetic isotope effect (KIE) is observed when running hydrothiolations with **2a** and ***d*-2a** in parallel (Figure 6B). The empirical rate law and lack of KIE support reductive elimination as the turnover-limiting step.[24]

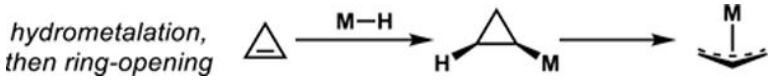
Mechanistic Insights for Ring-opened Hydrothiolation.

Based on both literature precedent and our own observations, we propose the catalytic cycle for the ring-opening hydrothiolation depicted in Figure 7. After formation of Rh-catalyst **I**, oxidative addition into **2a** occurs to form **II**, the catalyst resting state. Coordination of **1a** and its subsequent insertion into the Rh–H bond forms cyclopropyl-Rh(III) intermediate **V**. The *syn* hydrorhodation to form **V** is the turnover-limiting step. Ring-opening occurs, forming Rh-π-allyl complex **VI**. Reductive elimination forms the C–S bond of **4aa** and regenerates catalyst **I**. Reductive elimination for C–S bond formation is favored over outer-sphere attack of **2a** due to its high acidity (6.62 in H_2O).[25,26]

There are two main pathways that are proposed for cyclopropene ring opening. One pathway is through direct activation of the σ_{C-C} bond (eq. 1).[9f] However, in a few cases, it is proposed that hydrometallation occurs first to generate a cyclopropyl-metal species.[12a,12c] Ring-opening of the cyclopropyl metal species then occurs to afford a metal-π-allyl intermediate (eq. 2). Our proposed mechanism is based on the ring-opening pathway outlined in equation 2. The observations and mechanistic experiments that led to this proposed mechanism are discussed below.



eq.1



eq.2

Mixtures of **3aa** and **4aa** are obtained when certain bisphosphine ligands are used for the hydrothiolation (Figure 4A). However, in a crossover study where **3aa** is subjected to the standard ring-opening hydrothiolation conditions, only **3aa** is recovered (Figure 8A). This demonstrates that **3aa** is not converted into **4aa** during catalysis. One explanation for these results is that the ring-retentive and ring-opened pathways share a common intermediate, cyclopropyl-Rh(III) **V** (Figure 5). Allylic sulfide **4aa,** the product obtained under ring opening conditions, is similar to the products obtained from Rh-catalyzed hydrothiolation of 1,3-dienes (Figure 8B).[4c] Rh-π-allyl species generally form the branched product upon interception with a nucleophile.[27] Additionally, the correlation between the enantiomer of DTBM-BINAP and absolute configuration of the branched allylic sulfide product is in agreement between these two previous examples. The highly regioselective formation of **4aa** and its absolute configuration support the intermediacy of Rh-π-allyl **VI.**

The reactivity of cyclopropene **1g** provides additional mechanistic support for the proposed isomerization of cyclopropyl-Rh(III) **V** into Rh-π-allyl complex **VI**. While **1g** was able to couple to **2a** in a ring-retentive fashion to access **3ga** (Table 1), no reactivity was observed with **1g** under ring-opening hydrothiolation conditions (Figure 9A). One explanation for the observed reactivity could be that ring-opening requires an additional coordination site on the metal. The cyclopropyl group only occupies one coordination site, whereas the corresponding π-allyl ligand requires two. The methyl ether of **1g** could occupy the coordination site needed for ring-opening, thus halting the reaction. Similar reactivity is observed for cyclopropyl metal complexes prepared by the Puddephatt and Bergman groups.[28] For these Rh and Pt complexes, abstraction of the halide ligand is required to induce isomerization into metal-π-allyl complexes (Figure 9B).[28a–c]

Additional kinetic and isotope labelling experiments were carried out to gain further mechanistic insights. Initial rate studies show that this process is first order with regards to Rh-catalyst and cyclopropene **1a**, and zeroth order with regards to thiol **2a**. The saturation kinetics observed with **2a** support complex **II** as the catalyst resting state. The deuterium is incorporated into the terminal carbon of the olefin in ***d*-4aa**, with most of the deuterium incorporated *trans* relative to the rest of the molecule (Figure 10A). Additionally, a primary KIE of 1.6 is observed when ring opening hydrothiolations with **2a** and ***d*-2a** were carried out in parallel (Figure 10B). The first order dependence in **1a** and primary KIE of 1.6 suggest that migratory insertion to form **V** from **IV** is the turnover-limiting step.

There are a few possible explanations for the primarily *trans* incorporation of deuterium. Considering proposals from previous ring-opening hydrofunctionalizations, the ring-opening process might be through β-C elimination.[12a,12c] The *trans*-selectivity would result from a bond rotation to align the σ_{C-C} bond of the cyclopropane with the Rh–C bond in a *syn*-coplanar conformation to enable the β-elimination (Figure 10C). Studies on the isomerization of cyclopropyl metal species into metal-π-allyl complexes have also been likened to the ring-opening process to electrocyclic ring-opening.[28d] Based on Woodward-Hoffman rules, if cyclopropyl-Rh(III) **V** is treated like a cyclopropyl-anion, conrotatory electrocyclic ring-opening could also explain the *trans*-selectivity for deuterium incorporation (Figure 10D).[29]

While the reactivity of cyclopropenes has been extensively studied, there has yet to be a catalyst that takes advantage of both modes of reactivity cyclopropenes offer. Through choice of ligand on the Rh-catalyst, thiols add to cyclopropenes, resulting in cyclopropyl sulfides or allylic sulfides. This divergent reactivity allows cyclopropenes to act as versatile building blocks that enables access to a diverse chemical space. Either hydrothiolation product can be obtained with high yield and stereocontrol. Mechanistic experiments suggest that the ring opening from a cyclopropyl-Rh(III) intermediate is the key step for achieving divergent reactivity. For the ring-retentive process, the Rh-catalyst with smaller bite-angle ligands and chiral ligand **L5** promote reductive elimination to forge the C–S bond of the cyclopropyl sulfide product. For the ring-opening process, the Rh-catalyst with larger bite angle ligands and chiral ligand **L8** promote ring-opening, isomerizing the cyclopropane ring to form allylic sulfide products. Initially, the ligand bite angle effect seems contradictory, given that wider bite angle ligands are known to accelerate reductive elimination. However, given the faster reaction rate of the ring-opening hydrothiolation, the wider bite angle ligands might accelerate the ring-opening process to a greater extent than reductive elimination. These studies provide experimental support for a mechanism that has only previously been proposed. Further computational studies are warranted to provide additional insight into the more elusive aspects, such as nuances in the ring-opening of cyclopropyl-Rh(III) **V**.[30] Mechanistic insights from this study pave the way for divergent hydrofunctionalizations of cyclopropenes with a wide array of nucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Funding provided by Funding provided by UC Irvine, National Institutes of Health (R35GM127071), and National Science Foundation (CHE-1956457). A.L. is grateful for an Allergan Fellowship. We acknowledge Dr. Joseph Ziller (UC Irvine) for X-ray crystallographic analysis. We thank Solvias AG for providing the Josiphos ligands (**L5** and **L6**) used in this study.

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(18). The absolute configuration of allylic sulfides **4** is assigned based on the optical rotation data obtained during our synthesis of (–)-agelasidine A. See reference 4d.

(19). Deposition number 2038552 for **3ba** contains the supplementary crystallographic data for this paper. This data is provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. The absolute configurations of the remaining cyclopropyl sulfides **3** are assigned by analogy.

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(21). Some alkyl thiols (not included in this table) give mixtures of regioisomers. Isolated branched allylic thiols **4** can slowly isomerize to the achiral linear regioisomer over time. To prevent this process, the sulfides can be oxidized to the corresponding sulfones with an *m*-CPBA workup, see ref 4a.

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(24). The mechanistic experiments do not rule out the possibility of migratory insertion of the cyclopropene into the Rh–S bond. A mechanism where there is a turnover-limiting of migratory insertion of the cyclopropene into the Rh–S bond, followed by C–H forming reductive elimination also fits the kinetic data. For examples of migratory insertions into M–S bonds, see ref 14c and: (a) Ogawa A; Ikeda T; Kimura K; Hirao T Highly Regio- and Stereocontrolled Synthesis of Vinyl Sulfides via Transition-Metal-Catalyzed Hydrothiolation of Alkynes with Thiols. J. Am. Chem. Soc 1999, 121, 5108–5114.(b)Di Giuseppe A; Castarlenas R; Perez-Torrente JJ; Crucianelli M; Polo V; Sancho R; Lahoz FJ; Oro LA Ligand-Controlled Regioselectivity in the Hydrothiolation of Alkynes by Rhodium N-Heterocyclic Carbene

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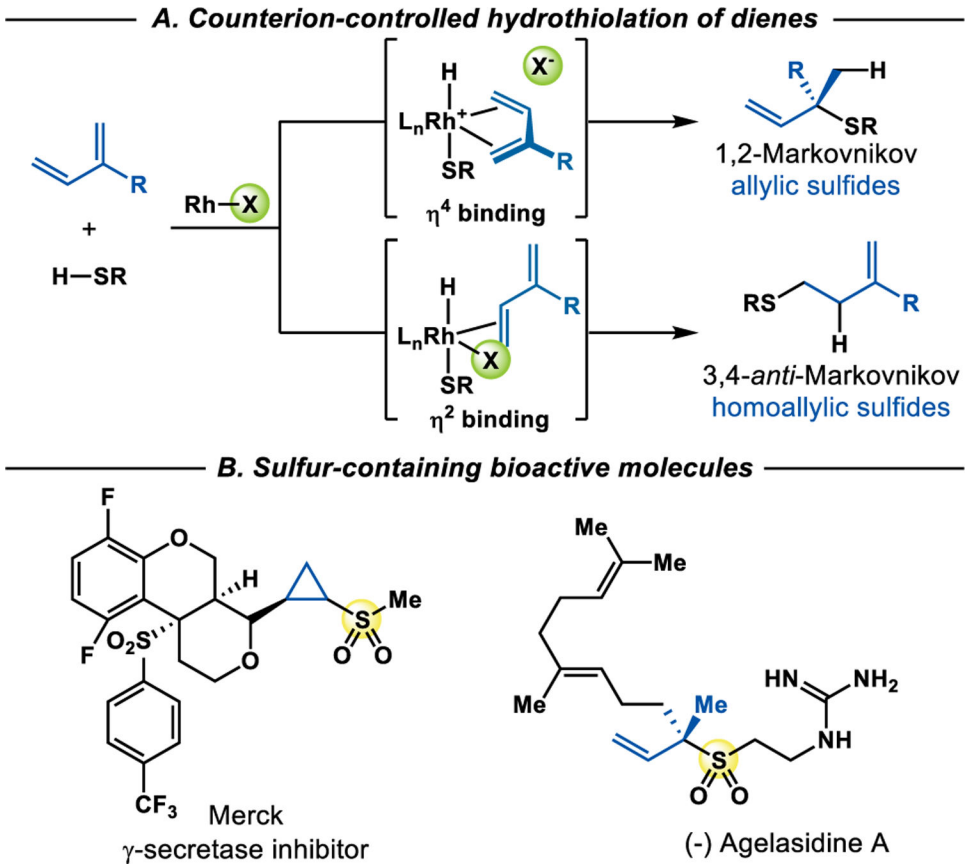


Figure 1.
Extending hydrothiolations to cyclopropenes.

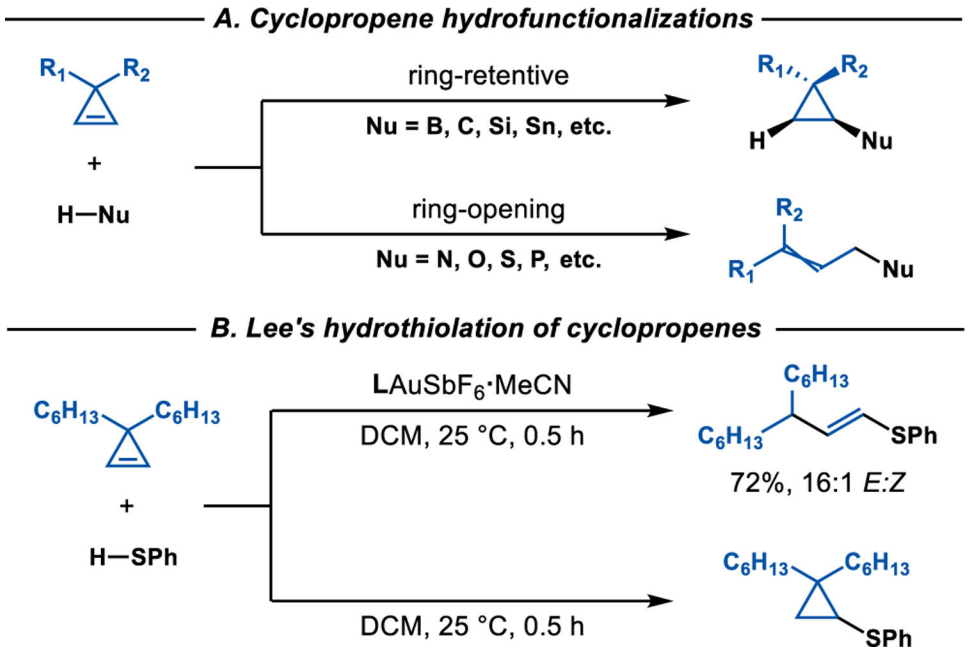


Figure 2.
Diverse reactivity of cyclopropenes.

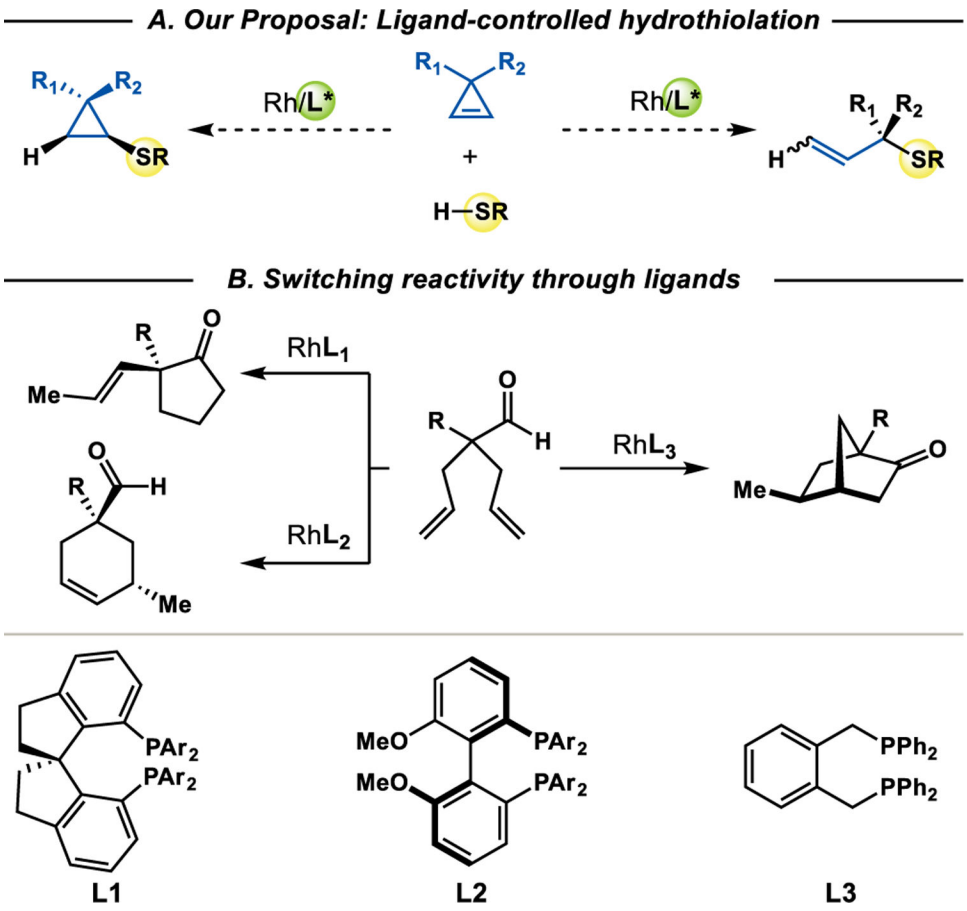


Figure 3.
Enabling divergent reactivity through ligand control.

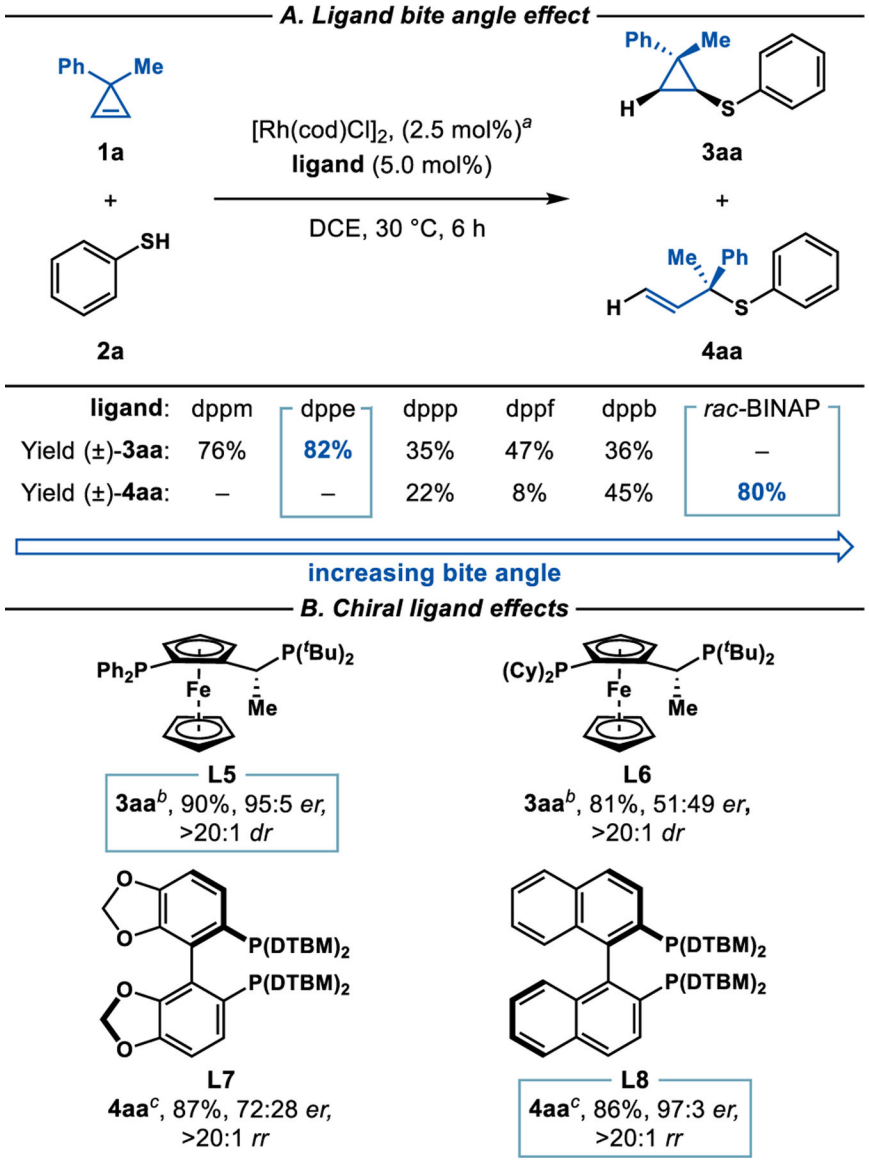


Figure 4.

Reaction optimization using various bisphosphine ligands. [a]Reaction conditions: **1** (0.12 mmol, **2** (0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), ligand (5.0 mol%), 0.6 mL DCE, 30 °C, 6 h. Yields of isolated products are given. [b]Reaction performed using MeCN for 6 h. [c]Reaction performed at 0 °C for 30 min. DTBM: 3,5-di(tert-butyl)-4-methoxyphenyl.

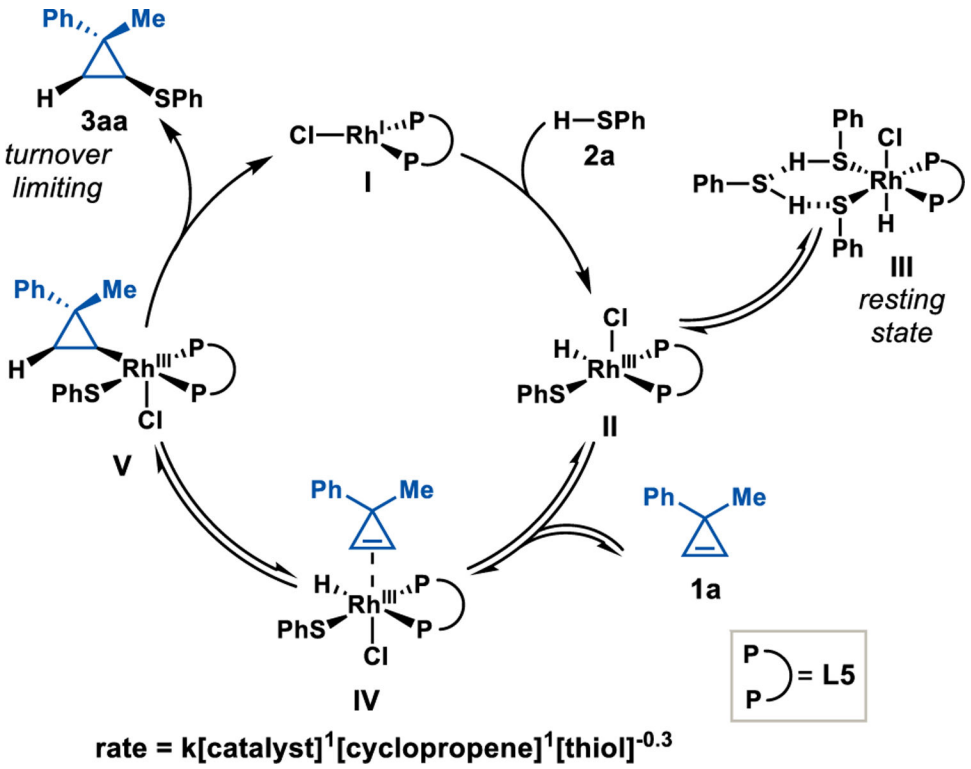


Figure 5.
Proposed catalytic cycle for ring-retentive hydrothiolation.

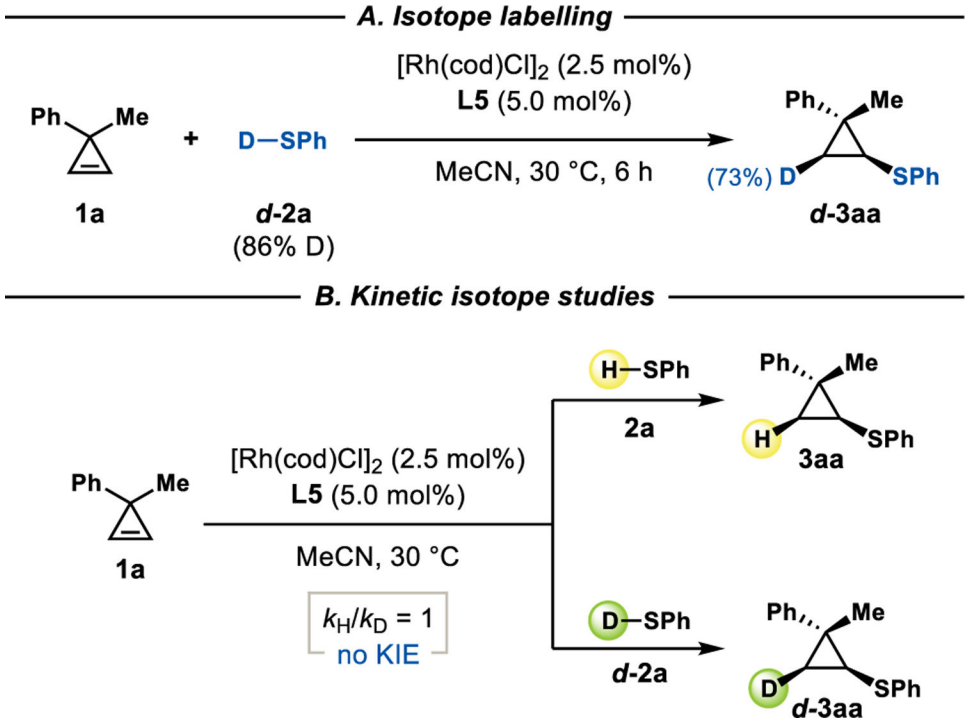


Figure 6.
Mechanistic experiments for ring-retentive hydrothiolation using ***d*-2a.**

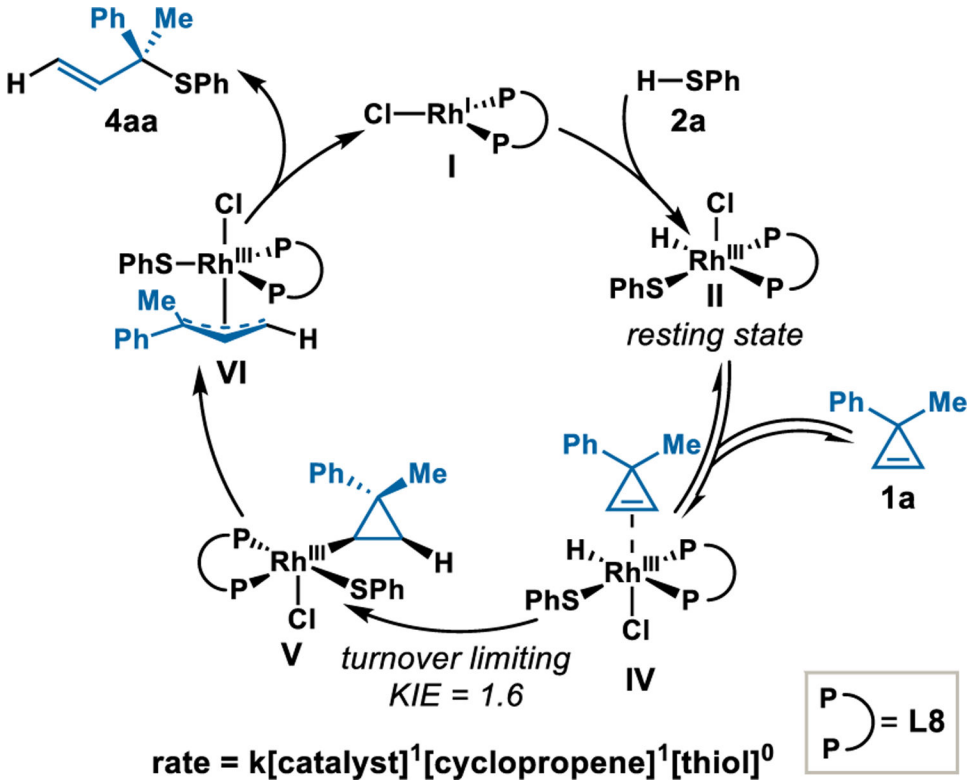


Figure 7.
Proposed catalytic cycle for ring-opening hydrothiolation of cyclopropenes.

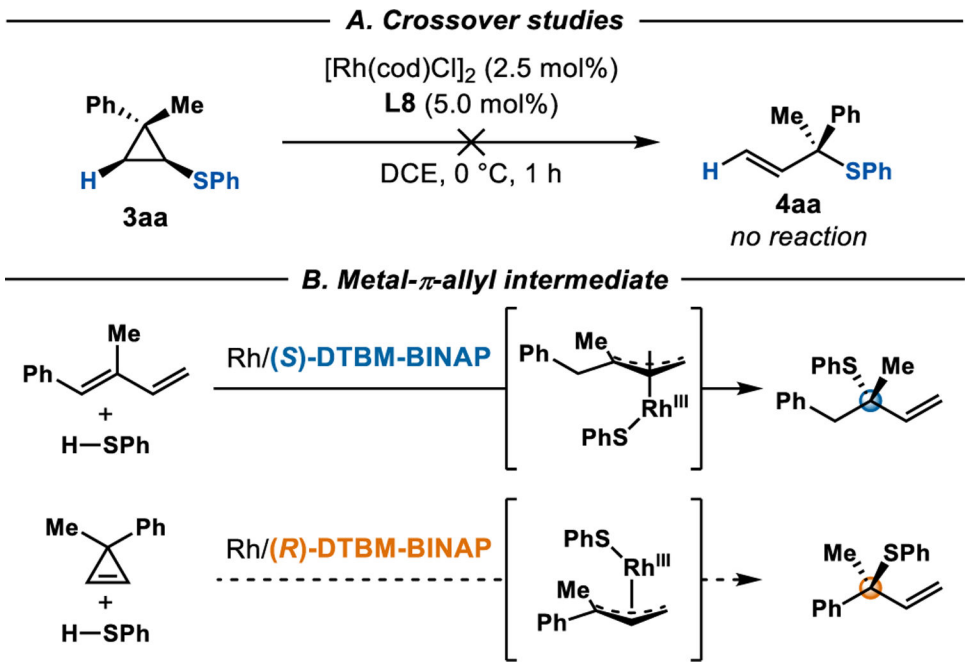


Figure 8.
Determining the operative pathway for ring-opening.

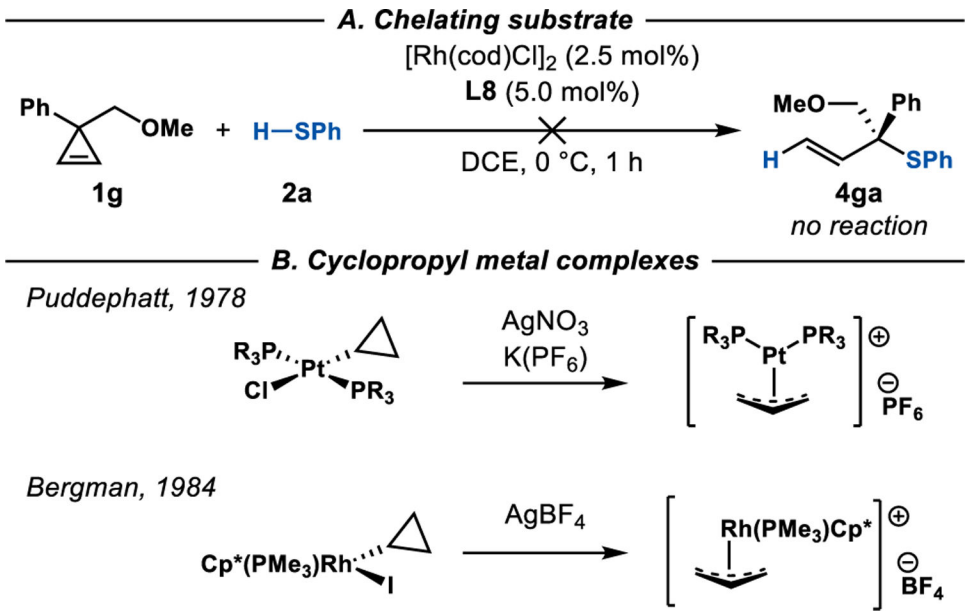


Figure 9.
Ring-opening of prepared cyclopropyl metal complexes.

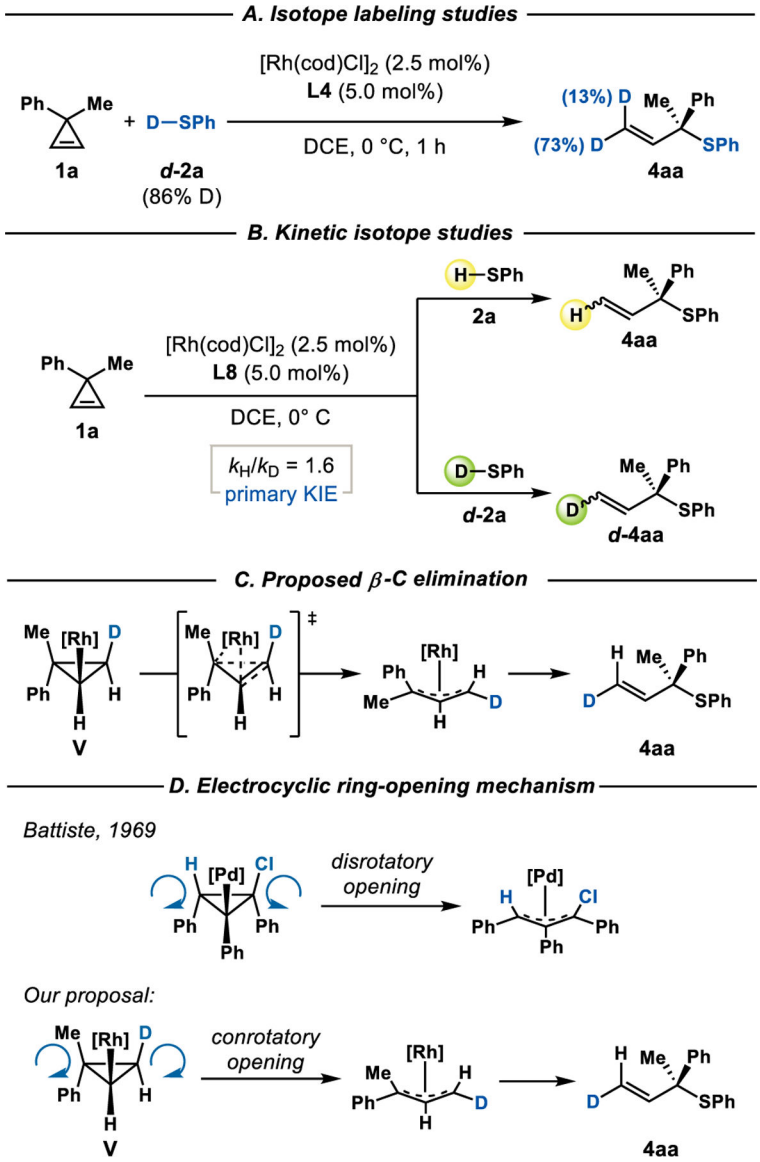
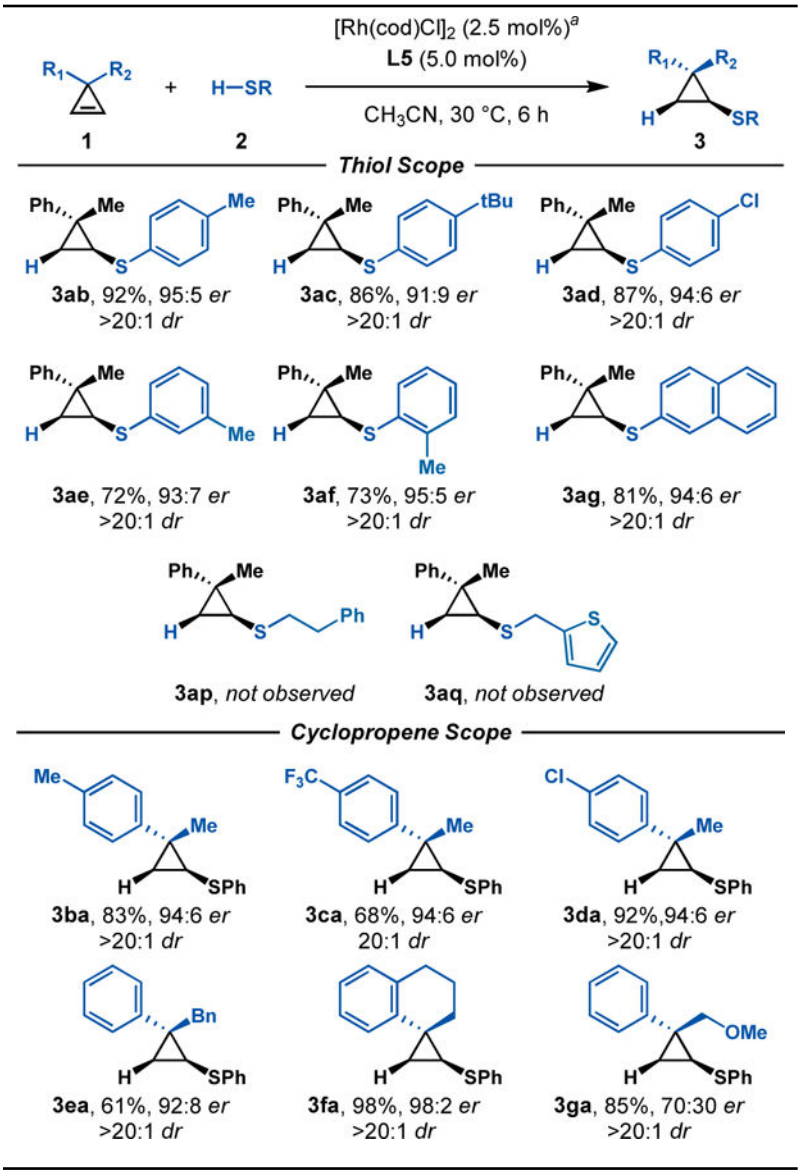


Figure 10.
Deuterium labeling studies for ring-opening hydrothiolation.

Table 1.

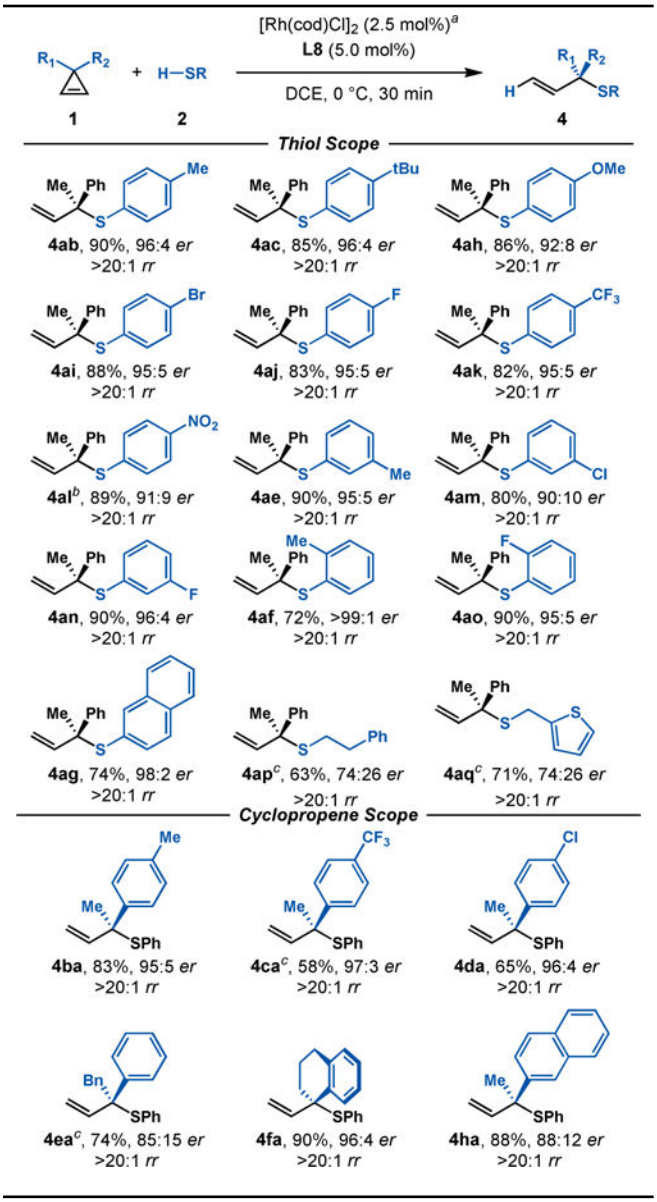
Ring-Retentive Hydrothiolation of Cyclopropenes



[a]**Reaction conditions: 1** (0.12 mmol, **2** (0.10 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), **L5** (5.0 mol%), 0.6 mL MeCN, 30 °C, 6 h. Yields of isolated products are given. Diastereomeric ratios (*dr*) were determined from ^1H NMR analysis of the unpurified reaction mixture. Enantiomeric ratios (*er*) were determined by SFC analysis on a chiral stationary phase.

Table 2.

Ring-opened Hydrothiolation of Cyclopropenes



[a]**Reaction conditions: 1** (0.12 mmol), **2** (0.1 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), **L8** (5.0 mol%), 0.4 mL DCE, 0 °C, 30 min. Yields of isolated products are given. Regioisomeric ratios (*rr*) were determined from ^1H NMR analysis of the unpurified reaction mixture. Enantiomeric ratios (*er*) were determined by SFC analysis on a chiral stationary phase.

[b]Reaction performed at 30 °C.

[c]Reaction performed with **L7** at 30 °C.