

Enantioselective Hydrothiolation: Diverging Cyclopropenes through Ligand Control

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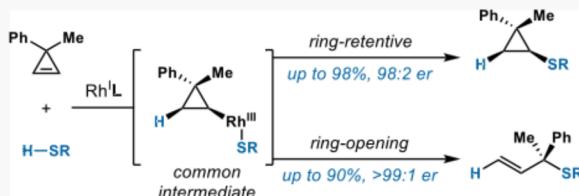
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ABSTRACT: In this article, we advance Rh-catalyzed hydrothiolation through the divergent reactivity of cyclopropenes. Cyclopropenes undergo hydrothiolation to provide cyclopropyl sulfides or allylic sulfides. The choice of bisphosphine ligand dictates 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 Josiphos ligands promote direct reductive elimination from this intermediate to afford cyclopropyl sulfides in high enantio- and diastereoselectivities. Alternatively, atropisomeric ligands (such as DTBM-BINAP) enable ring-opening from the cyclopropyl-Rh(III) intermediate to generate allylic sulfides with high enantio- and regiocontrol.



INTRODUCTION

Given the prevalence of sulfur in biologically relevant organic molecules,^{1–3} inventing methods to forge C–S bonds remains a worthwhile pursuit.^{4–11} Hydrothiolation, the addition of a thiol across a degree of unsaturation, represents a straightforward and atom economical¹² way of building molecules with sulfide functional groups.^{13–19} In previous communications,^{15,16} 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 noncoordinating counterion, such as SbF_6^- , allows the conjugated diene to bind the catalyst in an η^4 fashion en route to allylic sulfide products.¹⁵ 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.¹⁶ 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,^{20,21} cyclopropenes have captivated chemists due to their strained structures and high reactivity.^{22–31} Cyclopropene, the smallest possible unsaturated carbocycle, owes its unique reactivity to 54.1 kcal/mol of strain energy.³² 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

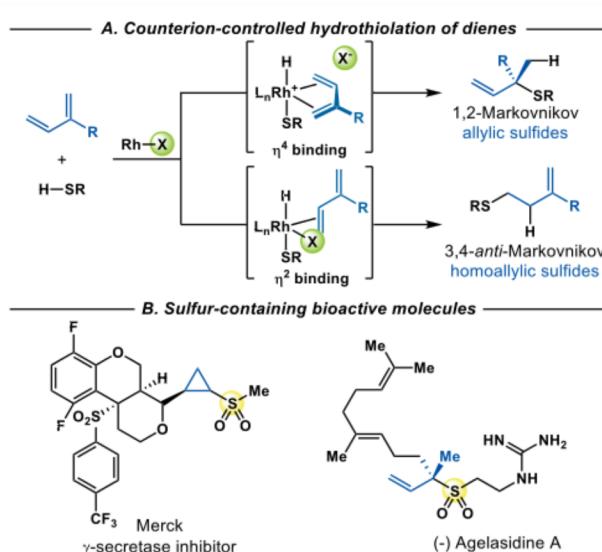
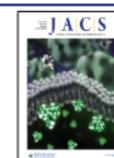


Figure 1. Extending hydrothiolations to cyclopropenes.

2A). Additions to cyclopropenes are known to occur with ring-retention to yield cyclopropyl products,³³ as well as with ring-opening to yield allylic products.^{34–39} In general, ring-retentive

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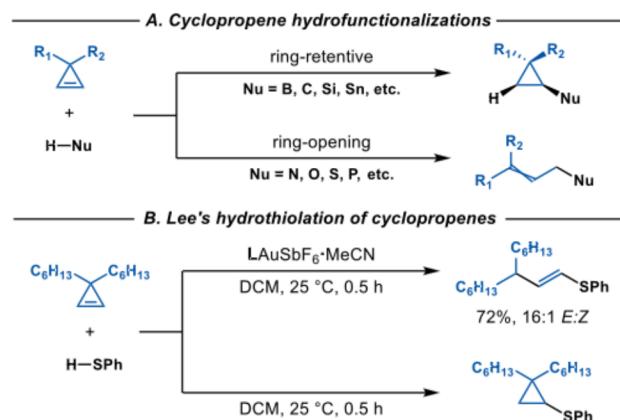


Figure 2. Diverse reactivity of cyclopropenes.

hydrofunctionalizations require softer nucleophiles, such as boranes, stannanes, and carbon nucleophiles.^{40–55} Ring-opening hydrofunctionalizations require harder nucleophiles, such as amines, alcohols, or phosphonates.^{56–59} However, there are exceptions to this trend, including Hou's ring-retentive hydroamination⁴⁵ and Yamamoto's ring-opening addition of carbon nucleophiles.⁵⁶

Lee demonstrated that both modes of reactivity are possible for thiol nucleophiles, depending on the choice of conditions (Figure 2B).⁶⁰ 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.⁶¹ Rendering either variant of Lee's cyclopropene hydrothiolation asymmetric would be difficult: the enantiodetermining 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.^{62–71} Ligand control is established primarily through governing the regioselectivity^{62–67} or chemoselectivity^{70,71} 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.^{68,69,72} Encouraged that transition metals can catalyze reactions with thiols,^{4–11} we focused on studying Rh-catalysts to explore how different bisphosphine ligands diverge the reactivity of cyclopropenes.

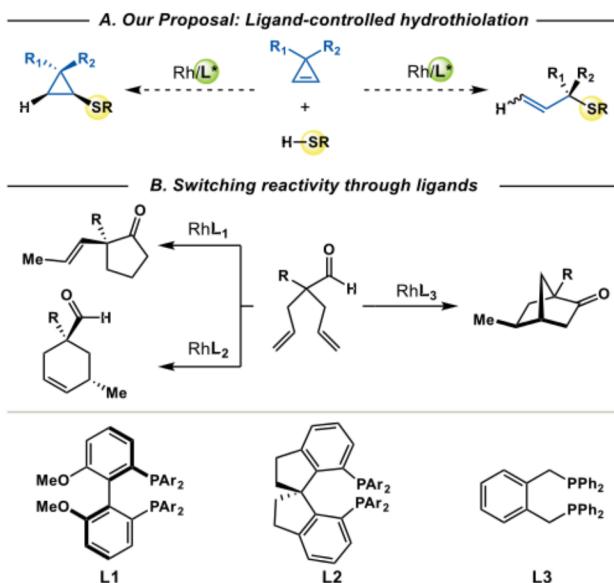


Figure 3. Enabling divergent reactivity through ligand control.

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 $[\text{Rh}(\text{cod})\text{Cl}]_2$. Gratifyingly, we observed a correlation between **3aa**:**4aa** and the bite angle of the bisphosphine ligands (Figure 4A). Bisphosphines with smaller bite angles (dpmm, dppe) give exclusively cyclopropyl sulfide (\pm)-**4aa** (76% and 82%, $>20:1$ dr), while ligands with larger bite angles (*rac*-BINAP) form allylic sulfide (\pm)-**3aa** exclusively (80%, $>20:1$ rr). Bisphosphine ligands with intermediate bite angles furnish mixtures of **3aa** and **4aa**. The 1,1-dialkylsubstituted cyclopropene (3,3-dihexylcycloprop-1-ene) has been shown to undergo addition with thiols in the absence of any catalysts (Figure 2B).⁶⁰ 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).⁷³ Given the structural differences between chiral bisphosphines **L5** and **L8**, 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 bisphosphine

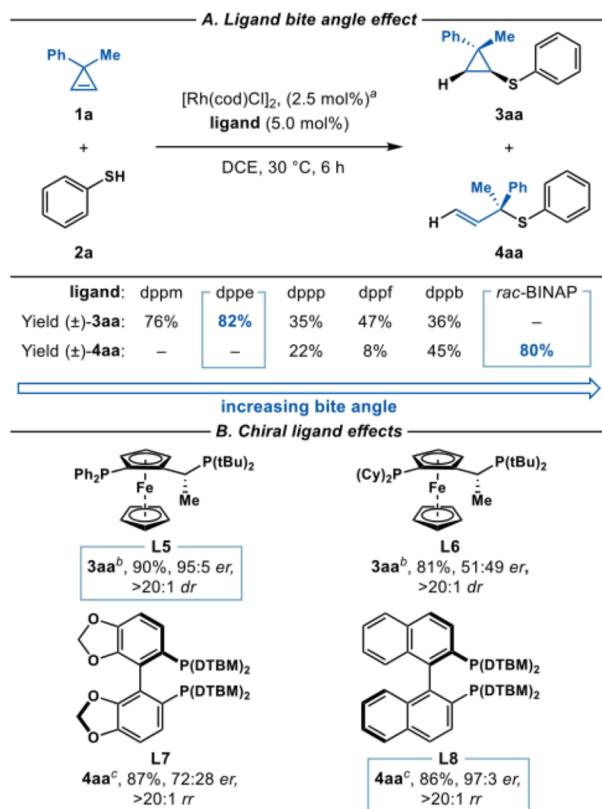


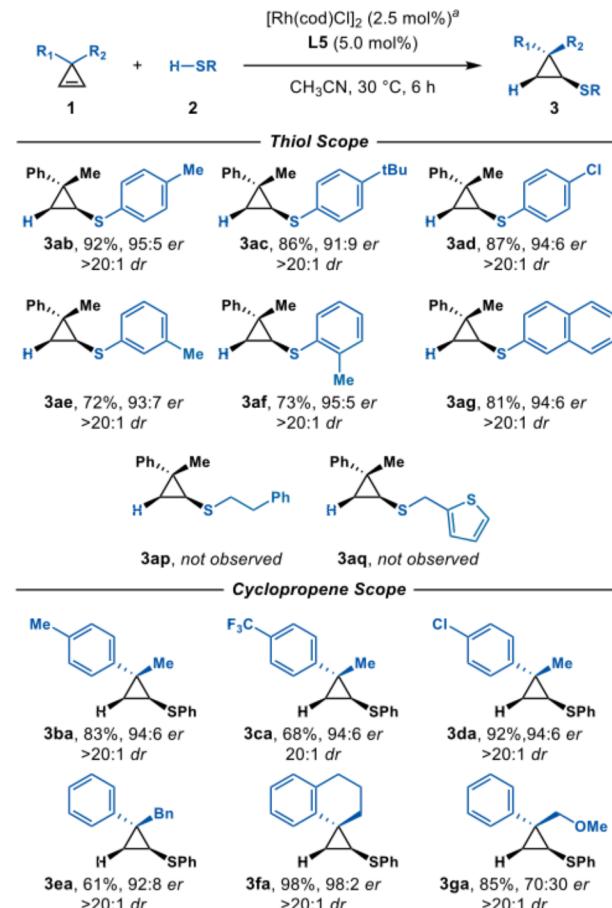
Figure 4. Reaction optimization using various bisphosphine ligands.
“Reaction conditions: 1 (0.12 mmol), 2 (0.10 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %), ligand (5.0 mol %), 0.6 mL of DCE, 30 °C, 6 h. Yields of isolated products are given. ^bReaction performed using MeCN for 6 h. ^cReaction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

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).⁷⁴ 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.^{75,76} 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).

Table 1. Ring-Selective Hydrothiolation of Cyclopropenes



“Reaction conditions: 1 (0.12 mmol), 2 (0.10 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %), L5 (5.0 mol %), 0.6 mL of 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.

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). 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).⁷⁷

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

Table 2. Ring-Opened Hydrothiolation of Cyclopropenes

^aReaction conditions: 1 (0.12 mmol), 2 (0.1 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %), L8 (5.0 mol %), 0.4 mL of 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. ^bReaction performed at 30 °C. ^cReaction performed with L7 at 30 °C.

(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. On the basis of 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

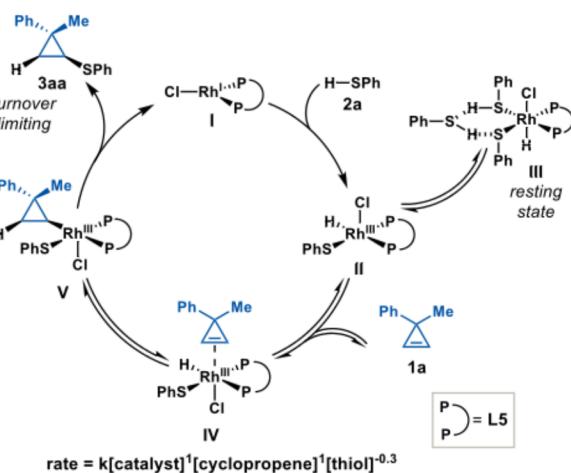


Figure 5. Proposed catalytic cycle for ring-retentive hydrothiolation.

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 regard to Rh-catalyst and cyclopropene 1a and a negative fractional order with regard to thiol 2a. A negative order in thiol has been observed in our group's previous report on the hydrothiolation of dienes,¹⁶ leading us to propose an off-cycle resting state where multiple thiols are coordinated through a hydrogen-bonding network (III).⁷⁸ The proposed resting state III is further supported by the presence of a metal hydride resonance at -15.9 ppm when using ^1H NMR spectroscopy to monitor experiments using stoichiometric amounts of $[\text{Rh}(\text{cod})\text{Cl}]_2$, dppe, and 2a.⁷⁹

An isotopic labeling 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* hydrothiolation operates in the catalytic cycle.

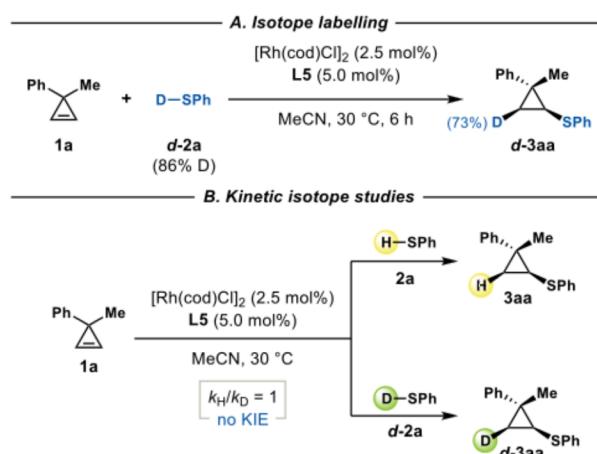


Figure 6. Mechanistic experiments for ring-retentive hydrothiolation using d-2a.

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.^{80–83}

Mechanistic Insights for Ring-Opened Hydrothiolation. On the basis of both literature precedent and our own observations, we propose the catalytic cycle for the ring-opening hydrothiolation depicted in Figure 7. After formation

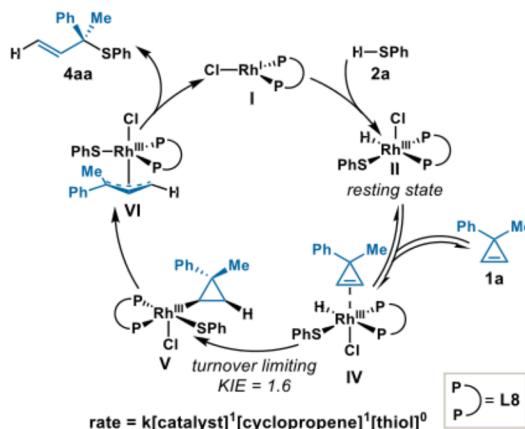
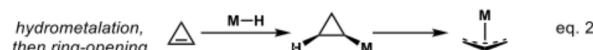


Figure 7. Proposed catalytic cycle for ring-opening hydrothiolation of cyclopropenes.

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**. While trends in Tsuji–Trost allylation would suggest outer-sphere attack of **2a** due to its high acidity ($pK_a = 6.62$ in H_2O),^{84,85} the thiolate should already be coordinated to the Rh atom in intermediate Rh–H **II**, thus reductive elimination for C–S bond formation is favored.

There are two main pathways that are proposed for cyclopropene ring-opening. One pathway is through direct activation of the $\sigma_{C–C}$ bond (eq 1).³⁹ However, in a few cases,



it is proposed that hydrometalation occurs first to generate a cyclopropyl–metal species.^{56,58} 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 eq 2. The observations and mechanistic experiments that led to this proposed mechanism are discussed below.

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

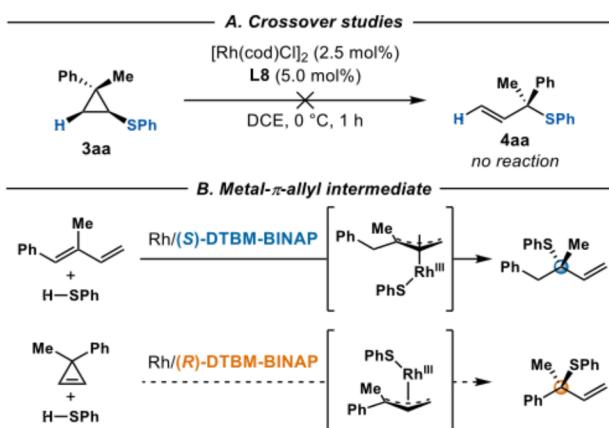


Figure 8. Determining the operative pathway for ring-opening.

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).¹⁵ Rh- π -allyl species generally form the branched product upon interception with a nucleophile.^{86–88} 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

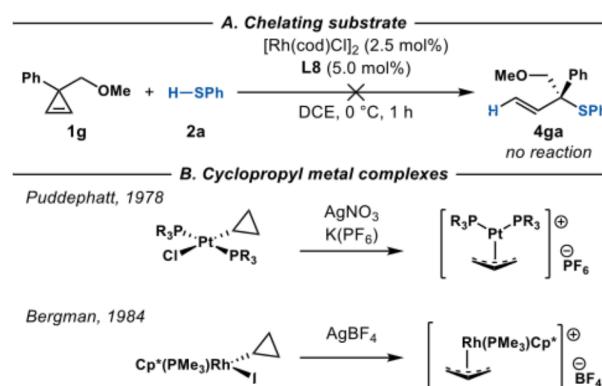


Figure 9. Ring-opening of prepared cyclopropyl metal complexes.

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.^{89–92} For these Rh and Pt complexes, abstraction of the halide ligand is required to

induce isomerization into metal- π -allyl complexes (Figure 9B).^{89–91}

Additional kinetic and isotope labeling experiments were carried out to gain further mechanistic insights. Initial rate studies show that this process is first order with regard to Rh-catalyst and cyclopropene **1a** and zeroth order with regard to thiol **2a**. The saturation kinetics observed with **2a** support complex **II** as the catalyst resting state. The deuterium atom of **d-2a** 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

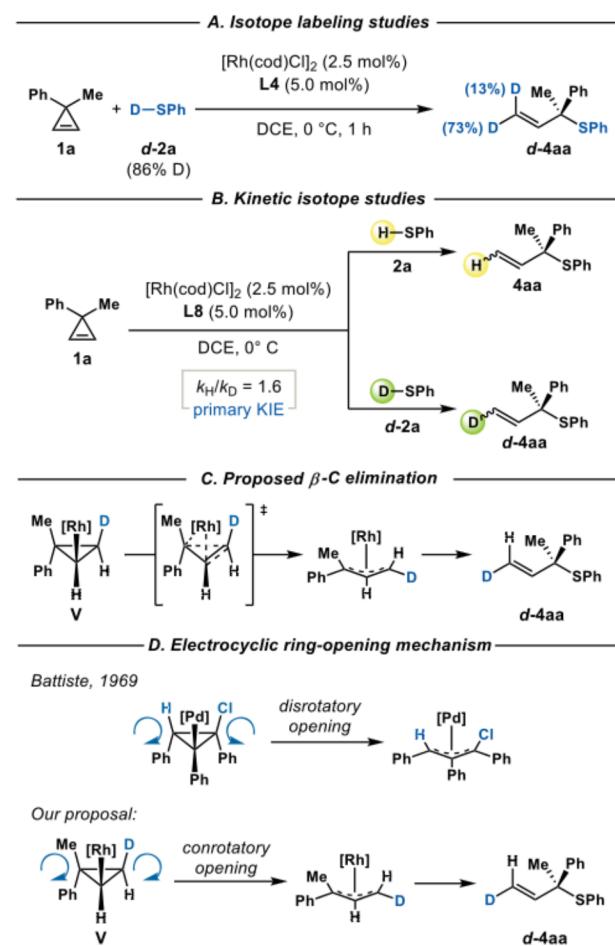


Figure 10. Deuterium labeling studies for ring-opening hydrothiolation.

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.^{56,58} 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 -C elimination (Figure 10C). Studies on the isomerization of cyclopropyl metal species into metal- π -allyl complexes have also likened the ring-

opening process to electrocyclic ring-opening.⁹² Based on Woodward–Hoffmann 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).⁹³

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 to form cyclopropyl sulfides or allylic sulfides. This divergent reactivity allows cyclopropenes to act as versatile building blocks, which 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 previously has only 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**.⁹⁴ Mechanistic insights from this study pave the way for divergent hydrofunctionalizations of cyclopropenes with a wide array of nucleophiles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c00939>.

Experimental procedures and spectral data for new compounds; crystallographic data for **3ba** (PDF)

Accession Codes

CCDC 2038552 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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