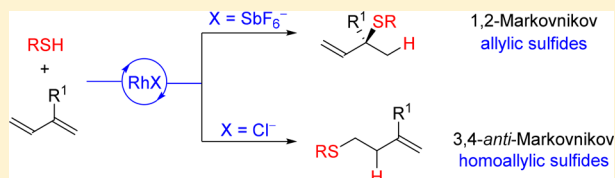


Catalytic Hydrothiolation: Counterion-Controlled Regioselectivity

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Supporting Information

ABSTRACT: In this Article, we expand upon the catalytic hydrothiolation of 1,3-dienes to afford either allylic or homoallylic sulfides with high regiocontrol. Mechanistic studies support a pathway in which regioselectivity is dictated by the choice of counterion associated with the Rh center. Non-coordinating counterions, such as SbF_6^- , allow for η^4 -diene coordination to Rh complexes and result in allylic sulfides. In contrast, coordinating counterions, such as Cl^- , favor neutral Rh complexes in which the diene binds η^2 to afford homoallylic sulfides. We propose mechanisms that rationalize a fractional dependence on thiol for the 1,2-Markovnikov hydrothiolation while accounting for an inverse dependence on thiol in the 3,4-*anti*-Markovnikov pathway. Through the hydrothiolation of an essential oil (β -farnesene), we achieve the first enantioselective synthesis of (–)-agelasidine A.



INTRODUCTION

Given the value of organosulfur compounds as metabolites and medicines,¹ synthetic chemists strive to develop versatile methods for accessing these motifs.² Both allylic and homoallylic sulfides, as well as their respective derivatives (e.g., sulfones and thioesters), comprise natural products and analogs with a wide range of bioactivities (Figure 1A).³ The hydrothiolation of olefins and dienes represents an atom-economical strategy⁴ for constructing C–S bonds.^{5,6} Despite its high atom economy, hydrothiolation remains an unexploited strategy for the synthesis of complex targets, and further development is warranted. Breit demonstrated an enantioselective hydrothiolation of allenes to generate allylic sulfides via Rh catalysis (Figure 1B).^{7a,b} Using Au catalysis, the He group achieved the hydrothiolation of 1,3-dienes to access allylic sulfides, with excellent 3,4-Markovnikov selectivity, albeit as racemic mixtures (Figure 1C).^{7c} Our laboratory recently communicated the first enantioselective 1,2-Markovnikov hydrothiolation of 1,3-dienes to generate allylic sulfides (Figure 1C).⁸ Although hydrothiolations have been developed to access allylic sulfides, selective access to the homoallylic isomer has been elusive.

In the work described in this Article, to expand the power of diene hydrothiolation, we focused on elucidating the mechanism for the 1,2-Markovnikov hydrothiolation. In theory, the addition of a thiol to an unsymmetrical diene (e.g., 2-phenyl-1,3-diene) can afford up to 11 isomers.⁹ Yet, the use of cationic Rh and a bidentate phosphine ligand afforded secondary and tertiary sulfide motifs with excellent regioselectivity and enantioselectivity. By studying the mechanism, we determined the fundamental steps that govern regiocontrol. Guided by these insights, we then focused on developing a complementary hydrothiolation to provide access to the

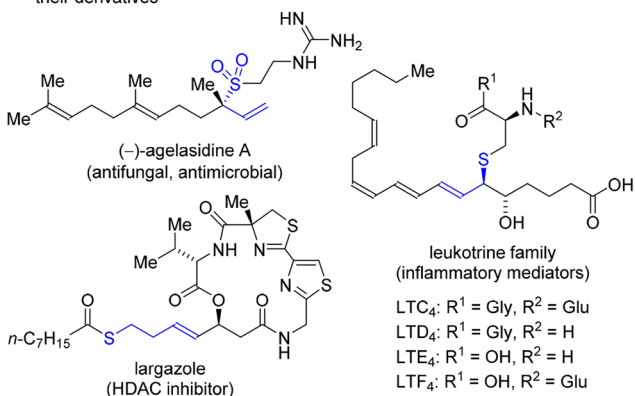
homoallylic sulfide (Figure 1C). While regiodivergent hydrothiolation of dienes has not previously been reported, Hull demonstrated regiodivergent hydrothiolations of allylic amines dictated by choice of ligand on Rh.¹⁰ Regiodivergent hydrosilylation of 1,3-dienes has been reported by Ritter, achieved through the use of an Fe versus Pt catalyst.¹¹ In this study, we enable access to homoallylic sulfides by simply changing the counterion that coordinates to Rh from non-coordinating (SbF_6^-) to coordinating (Cl^-). The scope and mechanism of this new hydrothiolation of 1,3-dienes are presented. Within this Article, we also showcase hydrothiolation in the first enantioselective synthesis of (–)-agelasidine A, a natural product that bears a chiral tertiary sulfide-derived motif (Figure 1A).

RESULTS AND DISCUSSION

In our previous studies, we observed that different 1,3-diene substitution patterns require the use of different ligand families for optimal results (Figure 2).⁸ By using this empirical guide, one can identify either the desired product or the commodity diene of choice to functionalize. For cyclic, 1-substituted, 1,2-disubstituted, and 2,3-disubstituted dienes, we found that the BINAP ligand family is best for furnishing enantioenriched allylic sulfides, whereas 2-substituted dienes require the use of the Josiphos ligand family. The Garphos ligand scaffold provides good yields and enantioselectivities for 1,3-butadiene. In an effort to better understand the catalyst design and its effects on the hydrofunctionalizations of dienes, we interrogated the hydrothiolation mechanism to elucidate the factors that affect selectivity.

Received: October 22, 2018

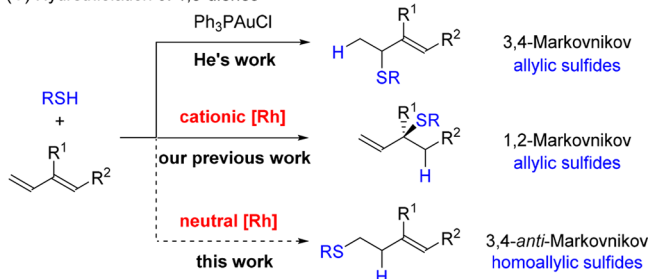
(A) Natural products and analogs containing an allylic or homoallylic sulfide and their derivatives



(B) Enantioselective hydrothiolation of allenes (Breit)

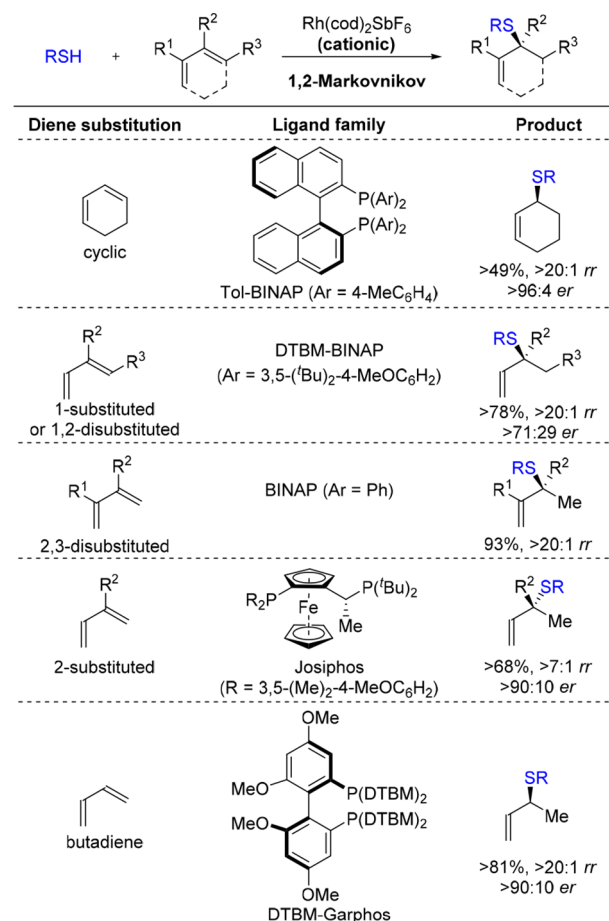
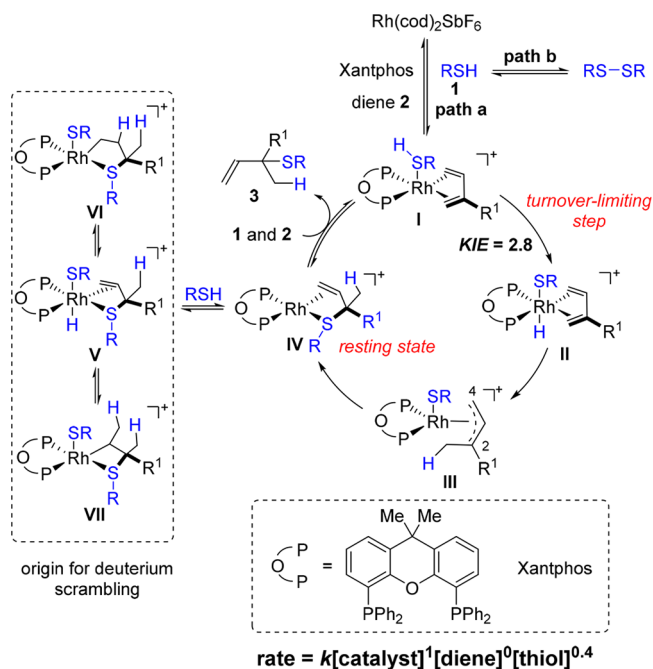


(C) Hydrothiolation of 1,3-dienes

**Figure 1.** Inspiration for the regiodivergent hydrothiolation of 1,3-dienes.

Mechanism of 1,2-Markovnikov Hydrothiolation of 1,3-Dienes. On the basis of both literature precedence and the following mechanistic studies, we propose the 1,2-Markovnikov hydrothiolation mechanism depicted in Figure 3. Ligand exchange between 1,5-cyclooctadiene (cod) with a bidentate phosphine ligand, thiol 1, and diene 2 generates intermediate I. In the turnover-limiting step, oxidative addition results in formation of an η^4 -diene-coordinated Rh–H intermediate II.¹² Subsequent 1,4-insertion of the diene into the Rh–H furnishes Rh- π -allyl intermediate III.¹³ Intermediate III undergoes reductive elimination to provide IV, where product 3 remains coordinated to Rh. Ligand exchange of product 3 with thiol 1 and diene 2 regenerates the Rh catalyst I.

For the model system, we chose to study the mechanism using an achiral ligand, Xantphos, because we previously observed that it is an effective ligand for the transformation.⁸ This bidentate ligand bears a coordinating oxygen atom that can act as a hemilabile ligand.¹⁴ Our initial mechanistic studies used thiophenol (1a) and myrcene (2a) to explore the kinetic profile of the transformation. We found a first-order dependence on the catalyst and a zeroth-order dependence on diene 2a, which is consistent with a mechanism where the Rh complex I is saturated with diene 2 or diene 2 coordination occurs after the turnover-limiting step (Figure 3). We found that thiophenol (1a) can participate in two reaction pathways: desired hydrothiolation (path a) or dimerization (path b).¹⁵ Thiophenol (1a) dimerization increases proportionally with its concentration. When adding bis(4-methoxyphenyl) disulfide to

**Figure 2.** Empirical guide for optimal ligand choice for 1,2-Markovnikov hydrothiolation. Results previously published.⁸**Figure 3.** Proposed mechanism of 1,2-Markovnikov hydrothiolation of 1,3-dienes.

a mixture of thiophenol with myrcene under the standard conditions, we observed crossover products, which suggests

that thiol dimerization (path b) is reversible (see SI, Figure S4). In accordance with these competing pathways, we observed a fractional-order dependence (0.4) on thiophenol (1a).

We also performed deuterium-labeling experiments to further probe the mechanism (Figure 4). When we subjected

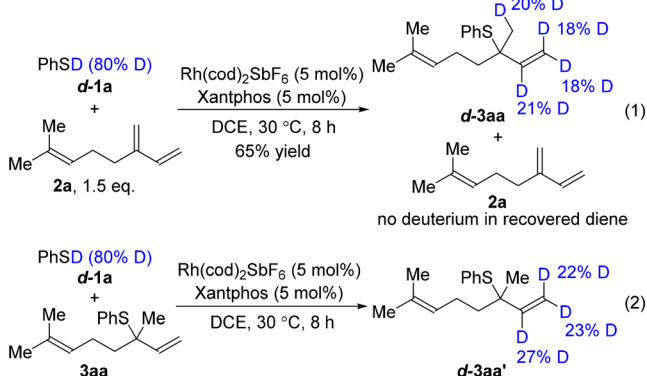


Figure 4. Deuterium-labeling studies for the 1,2-Markovnikov hydrothiolation of 1,3-dienes.

deuterated thiophenol (*d*-1a) and myrcene (2a) to the standard conditions, we found that the recovered diene starting material 2a exhibited no deuterium incorporation (eq 1 in Figure 4). This lack of scrambling supports our proposal that Rh–H insertion is an irreversible step in the catalytic cycle. However, we observed deuterium scrambling in the allylic sulfide product *d*-3aa. To examine the origin of this deuterium incorporation, we subjected a non-deuterated product 3aa to a mixture of deuterated thiophenol (*d*-1a), Rh(cod)₂SbF₆, and Xantphos (eq 2 in Figure 4). We detected similar deuterium incorporation only in the terminal olefin moiety of *d*-3aa'. Collectively, these results suggest that deuterium scrambling in product 3aa occurs from a pathway external to the catalytic cycle. We hypothesize that intermediate IV can undergo oxidative addition to an equivalent of thiol to form complex V (Figure 3). Subsequent reversible Rh–H insertion into the terminal olefin results in the deuterium scrambling observed in *d*-3aa.

Next, we studied key steps of the hydrothiolation by NMR spectroscopy. First, we monitored a mixture of thiophenol (1a), Rh(cod)₂SbF₆ (10 mol%), and Xantphos (10 mol%) in DCE-*d*₄ by ¹H NMR analysis. A resonance at –13.5 ppm was observed in less than 10 min at room temperature in the ¹H NMR spectrum, which is consistent with previously reported values for Rh–H complexes.¹⁶ This observation suggests that a Rh–H is rapidly generated from the catalyst precursor Rh(cod)₂SbF₆ in the presence of Xantphos and thiophenol (1a). While observation of a Rh–hydride does not necessitate its involvement in catalysis, we found that this hydride species is consumed when treated with an equivalent of diene (myrcene, 2a). In this stoichiometric experiment, we observed formation of a new Rh complex with non-equivalent phosphine resonances in the ³¹P NMR spectrum at –40 °C [a pair of doublet of doublet signals (δ = 26.6 ppm, $J_{\text{Rh-P}}$ = 174 Hz, $J_{\text{P-P}}$ = 8 Hz; δ = 16.0 ppm, $J_{\text{Rh-P}}$ = 115 Hz, $J_{\text{P-P}}$ = 8 Hz)]. When we subjected the product 3aa to a mixture of Rh(cod)₂SbF₆ and Xantphos in DCE-*d*₄, we observed the same species by ³¹P NMR spectroscopy. Based on these results, we label Rh

intermediate IV as the resting state in the catalytic cycle (Figure 3).

To investigate the turnover-limiting step, we carried out several kinetic experiments. First, a H/D kinetic isotope effect (KIE) experiment with thiophenol (1a) and deuterated thiophenol (*d*-1a) was performed. The initial rate constants were determined in parallel, and we observed a primary KIE ($k_{\text{H}}/k_{\text{D}}$ = 2.8, Figure 5). Second, a Hammett plot was

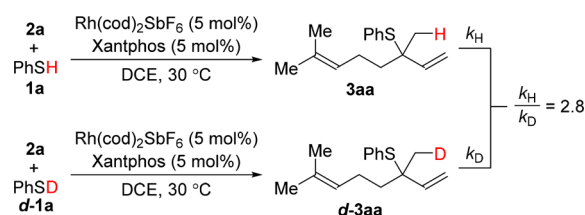


Figure 5. KIE from two parallel reactions using initial rates (1,2-Markovnikov).

constructed, using various *para*-substituted thiophenols, to determine if there was a rate dependence on the electronic character of the thiol 1 partner (Figure 6). A relatively small ρ

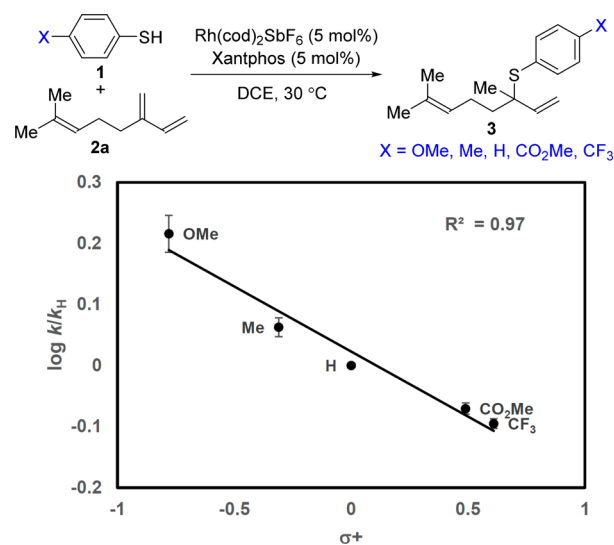


Figure 6. Hammett plot ($\log k/k_{\text{H}} = m\sigma^+ + b$ ($m = -0.22 \pm 0.02$; $b = 0.03 \pm 0.01$)).

value (-0.22 ± 0.02) is observed with more electron-rich thiophenols undergoing hydrothiolation slightly faster. We hypothesize that the thiol initially coordinates to Rh to provide a transient species (see I, Figure 3), which then undergoes insertion of the Rh into the S–H bond to form the Rh–H species (see II). Electron-rich thiols can accelerate this process by stabilizing positive charge build up on the Rh-center during the transition state for oxidative addition.

Based on these mechanistic studies, we reason that the elementary steps from intermediate II to IV account for the observed regioselectivity (Figure 3). Hydrometalation occurs with the bulky Rh center preferentially adding to the less sterically encumbered terminal position (C4). This net 1,4-insertion ultimately yields the Rh- π -allyl intermediate III. Reductive elimination of III at the more-substituted position to form the branched product is preferred, which is consistent

with other Rh-catalyzed alkyne, allene, and diene hydrofunctionalizations.¹⁷

When intermediate **II** bears a chiral thiolate ligand, the configuration appears to have little/no influence on the stereochemical outcome. Our initial report included an example of a chiral cysteine-derived thiol undergoing hydrothiolation to selectively give one diastereomer, depending on which enantiomer of the bisphosphine ligand was used (Figure 7, entry A).⁸ To elaborate on this observation, we investigated

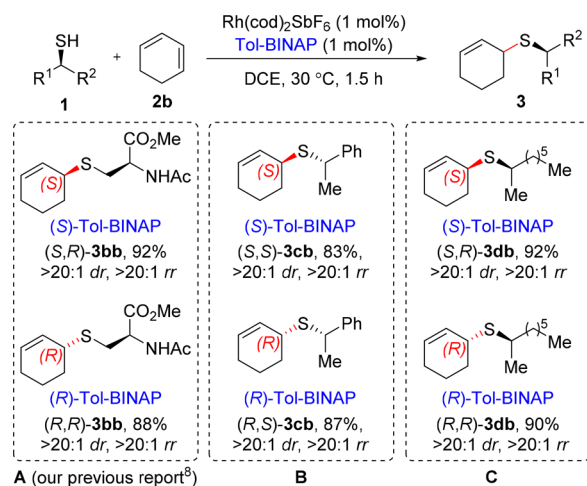


Figure 7. Catalyst-controlled diastereoselective 1,2-Markovnikov hydrothiolation.

chiral secondary thiols, where the chiral information is closer to the Rh-center. Hydrothiolation occurs with high reactivity (**3cb** and **3db**, 83–92% yield, entries **B** and **C**), regioselectivity (>20:1 *rr*), and diastereoselectivity (>20:1 *dr*) when using chiral secondary thiols (**1c** and **1d**). These results demonstrate complete catalyst control when forging the C–S bond. Thus, chiral secondary thiols can be transformed to sulfides in a diastereodivergent fashion. With a better understanding of the 1,2-Markovnikov hydrothiolation mechanism, we set out to apply this asymmetric hydrothiolation methodology to the total synthesis of a natural product.

Total Synthesis of (–)-Agelasidine A. (–)-Agelasidine A (**4**), an antifungal and antimicrobial agent isolated from marine sponges of the genus *Agelas*,^{3b} has previously been synthesized as a racemate from farnesol. Ichikawa reported two different methods for the installation of the key tertiary sulfide moiety of (±)-agelasidine A; a [2,3]-sigmatropic rearrangement or hetero-Claisen rearrangement has been used to construct the C–S bond and access (±)-**4** in three and eight steps, respectively.¹⁸

We focused on intercepting an enantioenriched variant of sulfone **5**, which was previously elaborated to (±)-**4** in Ichikawa's synthesis (Figure 8). To achieve this goal, we focused on coupling β-farnesene (**2c**), which is a renewable feedstock found in many essential oils,¹⁹ and 2-mercaptoethyl acetate (**1e**). Referencing our hydrothiolation guide (Figure 2), the Josiphos ligand scaffold is the most promising choice for achieving high reactivity and selectivity because **2c** is a 2-substituted 1,3-diene. In line with this guide, we found that β-farnesene (**2c**) can be coupled with **1e** to give the tertiary sulfide **3ec** in 78% yield with high enantioselectivity (>99:1 *er*) when using a Josiphos ligand (R = Cy, Figure 2). Various methods have been developed to chemoselectively oxidize

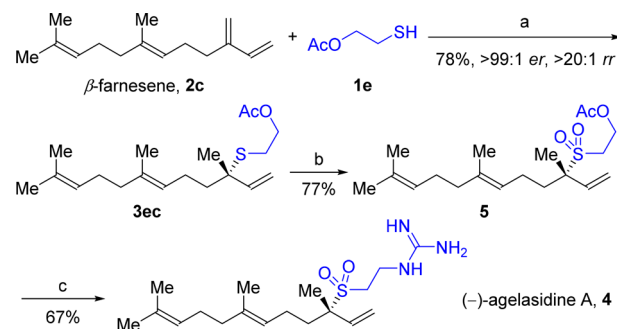


Figure 8. Enantioselective synthesis of (–)-agelasidine A. Reagents and conditions: (a) Rh(cod)₂SbF₆ (5 mol%), Josiphos (5 mol%, R = Cy, Figure 2), DCE, 30 °C, 15 h. (b) (NH₄)₆Mo₇O₂₄·4H₂O (10 mol %), H₂O₂, MeOH, rt, 4 h. (c) NaH, EtOH, NH₂C(=NH)NH₂·HCl, 1,4-dioxane, rt, 12 h.

sulfides to the corresponding sulfones.²⁰ We observed high reactivity (77% yield) when using catalytic (NH₄)₆Mo₇O₂₄·4H₂O and H₂O₂ to oxidize sulfide **3ec** to sulfone **5**.²⁰ⁱ Following Ichikawa's report, we found that enantioenriched sulfone **5** could be transformed to (–)-agelasidine A (**4**, 67% yield) in the presence of excess guanidine.^{18c} Collectively, our approach requires only three steps from commercially available β-farnesene (**2c**) to afford enantioenriched (–)-**4** in 40% overall yield. We anticipate that this methodology will be applicable to other natural products and synthetic targets bearing C–S bonds.²¹

Development of 3,4-anti-Markovnikov Hydrothiolation of 1,3-Dienes. Based on the 1,2-Markovnikov mechanism depicted in Figure 3, we reasoned that it would be possible to access other hydrothiolation regioisomers by tuning the ligands²² and/or counterions on Rh. Previous reports have demonstrated that coordination modes of 1,3-dienes to a metal center can switch the observed regioselectivity of transition-metal-catalyzed hydrofunctionalizations. For example, Ritter and co-workers found that η⁴-diene coordination provides 1,4-addition products,^{11a} whereas η²-diene coordination gives 3,4-anti-Markovnikov hydrosilylation products.^{11b} We envisioned using this concept to design a regiodivergent hydrothiolation of 1,3-dienes by switching from η⁴- to η²-diene binding. As shown in Figure 9, cationic Rh

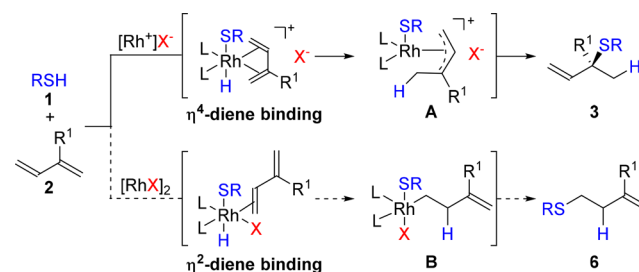


Figure 9. Proposed counterion-controlled regiodivergent hydrothiolations.

precatalysts prefer η⁴-diene binding due to the presence of two open coordination sites. In contrast, a neutral Rh species would prefer η²-diene binding due to the availability of only one coordination site. Subsequent 1,2-insertion would lead to an intermediate **B** in which Rh adds to the less sterically hindered terminal position. Reductive elimination of this Rh-alkyl species **B** would yield homoallylic sulfides **6**.

To begin our study, we chose isoprene (**2d**), a petroleum feedstock, and thiophenol (**1a**) as model substrates (Figure 10). Since **6ad** is achiral, we focused on identifying an achiral

<p>1a + 2d $\xrightarrow[\text{DCE, 30 } ^\circ\text{C}]{[\text{Rh}] (5 \text{ mol } \%), \text{ Xantphos } (5 \text{ mol } \%)}$ 3ad or 6ad</p>					
<p>cationic rhodium 1,2-Markovnikov</p>		<p>neutral rhodium 3,4-anti-Markovnikov</p>			
Entry	1	2	3	4	5
[Rh]	Rh(cod) ₂ SbF ₆	Rh(cod)Cl] ₂	Rh(cod)I] ₂	Rh(cod)OMe] ₂	[Rh(C ₂ H ₄) ₂ Cl] ₂ ^b
Yield	83%	74%	18%	49%	94%
rr	>20:1	1:>20	1:>20	1:>20	1:>20

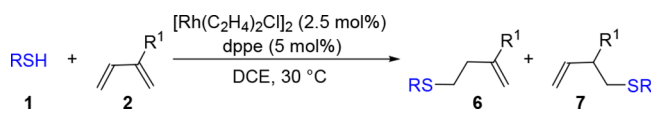
Figure 10. Rh precatalyst leads to a switch in regioselectivity. Reaction conditions: **1a** (0.1 mmol), **2d** (0.5 mmol), [Rh] (5 mol%), ligand (5 mol%), DCE (0.2 mL), 15 h. Isolated yield. Regioselectivity ratio (rr) is the ratio of **3ad** to **6ad**, which is determined by ¹H NMR analysis of reaction mixture. ^bUsing dppe as ligand, 3 h.

ligand for the 3,4-*anti*-Markovnikov hydrothiolation. In the early stages of 1,2-Markovnikov hydrothiolation development, we found that Xantphos is a viable choice for the ligand. Indeed, with a combination of Rh(cod)₂SbF₆ and Xantphos, the expected tertiary allylic sulfide **3ad** could be synthesized in 83% yield and >20:1 rr (entry 1). In stark contrast, when using the neutral [Rh(cod)Cl]₂ as a catalyst precursor, the homoallylic sulfide **6ad** was obtained in 74% yield and 1:>20 rr (entry 2). These results suggest that regioselectivity is controlled by the counterion on Rh (SbF₆[−] vs Cl[−]), which is in line with our proposal (η^4 - vs η^2 -diene coordination).²³ Switching the counterion to I[−] or MeO[−] lowers the reactivity (18% and 49% yield, respectively, entries 3 and 4) while maintaining high regioselectivity (1:>20 rr). With further tuning, we found that [Rh(C₂H₄)₂Cl]₂ and bidentate phosphine ligand dppe furnish **6ad** in 94% yield with 1:>20 rr in 3 h (entry 5). Furthermore, with this catalyst, we can lower the loading to 0.1 mol% and synthesize **6ad** on gram scale (1.3 g) in 74% yield with 1:>20 rr.

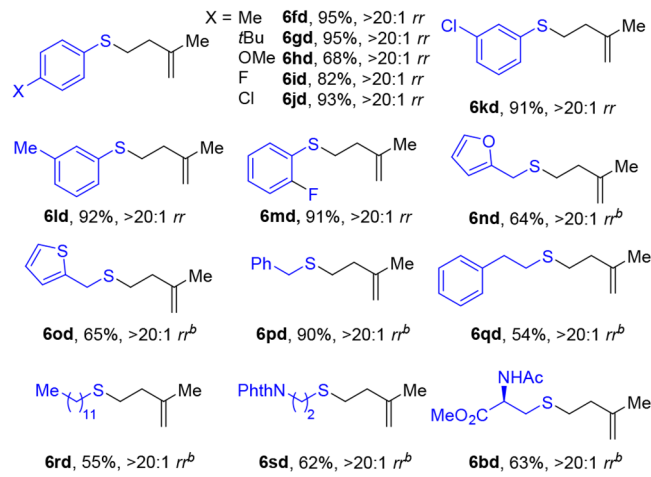
With these optimal conditions, we examined the coupling of 15 different thiols with isoprene (**2d**) to generate the corresponding homoallylic sulfides (Table 1A). High reactivity (**6bd**–**6sd**, 54–95% yield) and regioselectivity (>20:1 rr) are obtained with both aromatic and aliphatic thiol partners. This method is also compatible with heteroarene (**6nd**, **6od**), imide (**6sd**), amide (**6bd**), and ester (**6bd**) functionalities.

Next, we investigated the scope of the 1,3-diene partner in the 3,4-*anti*-Markovnikov hydrothiolation using thiophenol (**1a**) as a model thiol partner (Table 1B). Both aromatic and aliphatic 2-substituted 1,3-dienes are converted to the sulfide products (**6aa**–**6aj**) in high yields (60–95%). The electronics of the 2-aryl ring on the 1,3-diene has a noticeable effect on the regioselectivity of the transformation. Electron-rich 1,3-dienes (**6af**, **6ag**, >20:1 rr) yield higher regioselectivity than electron-poor 1,3-dienes (**6ah**, **6ai**, 13:1 and 8:1 rr, respectively). 3,4-*Anti*-Markovnikov hydrothiolation of butadiene (**2k**) provides the corresponding homoallylic sulfide (**6ak**) in 28% yield. A 2,3-disubstituted diene **2l** also transforms well to the homoallylic sulfide **6al** (73% yield). Moreover, myrcene (**2a**) could be converted to the corresponding homoallylic thiol **8** via a formal addition of H₂S, which consisted of 3,4-*anti*-Markovnikov hydrothiolation followed by deprotection (Table 1C).²⁴

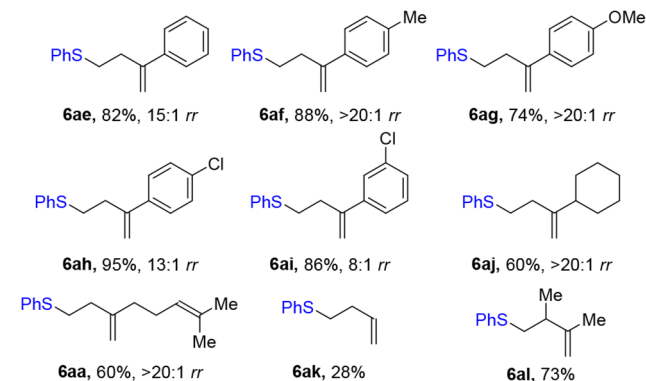
Table 1. 3,4-*Anti*-Markovnikov Hydrothiolation of 1,3-Dienes^a



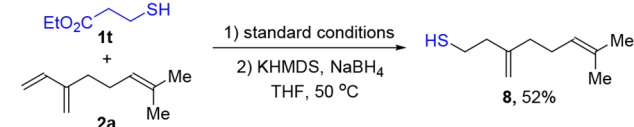
A. Thiol scope of the 3,4-*anti*-Markovnikov hydrothiolation



B. Diene scope of the 3,4-*anti*-Markovnikov hydrothiolation



C. Synthesis of homoallylic thiol



^aReaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), [Rh(C₂H₄)₂Cl]₂ (2.5 mol%), dppe (5 mol%), DCE (0.4 mL), 3 h. Isolated yield. Regioselectivity ratio (rr) is the ratio of **6** to **7**, which is determined by ¹H NMR analysis of reaction mixture. ^bUsing [Rh(cod)Cl]₂ (2.5 mol %), Xantphos (5 mol%), and 3,5-dimethylbenzoic acid (50 mol%), 12 h.

Mechanism of 3,4-*anti*-Markovnikov hydrothiolation of 1,3-dienes. Based on kinetic studies and NMR experiments, we propose the mechanism shown in Figure 11A for the 3,4-*anti*-Markovnikov hydrothiolation of 1,3-dienes. Oxidative addition of thiol **1** with Rh provides intermediate II'. Two equivalents of thiol **1** can then associate to furnish the resting state III'. A similar off-cycle resting state with an Ir(III)–H complex bearing a six-membered ring formed from two hydrogen bonds to ethanol has been reported.²⁵ Intermediate III' displays a hydride resonance at −15.8 ppm with symmetrical phosphines [doublet (δ = 52.2 ppm, J_{Rh–P} = 94

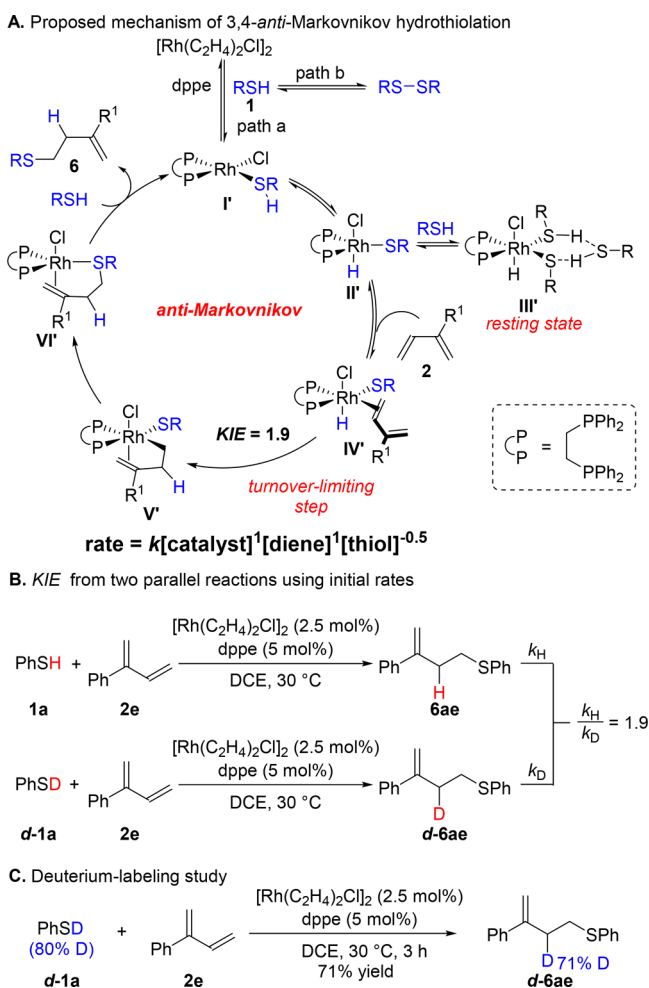


Figure 11. Mechanistic studies of 3,4-*anti*-Markovnikov hydrothiolation of 1,3-dienes.

Hz)]. Moreover, a negative half-order dependence on thiol **1** supports the proposed side pathway.

In contrast to the η^1 -diene binding exhibited in **II** (Figure 3), we propose that the less substituted olefin coordinates to intermediate **II'** to form η^2 -diene coordinated Rh complex **IV'**. This diene binding mode is due to the presence of one coordination site and could be the foundation for the switch in regioselectivity. Insertion of the 1,3-diene into the Rh–H bond then provides the less sterically encumbered intermediate **V'**. The observed primary KIE ($k_H/k_D = 1.9$, Figure 11B) supports that either oxidative addition to the S–H bond or diene insertion into the Rh–H is turnover-limiting. Given the first-order rate dependence on diene **2e** and catalyst (Figure 11A), as well as the results of deuterium incorporation into the allylic position of **d-6ae** (Figure 11C), we postulate diene insertion is the turnover-limiting step. Rh- π -allyl **V'** then undergoes reductive elimination to yield intermediate **VI'**, which can perform a ligand exchange of product **6** with thiol **1** to regenerate Rh catalyst **I'**.

CONCLUSION

Hydrothiolation of 1,3-dienes provides an efficient and straightforward way to construct primary, secondary, and tertiary C–S centers. A concise total synthesis of (–)-agelasidine **4** exemplifies the facile use of this methodology in a synthetic setting. Allylic and homoallylic sulfides can be

synthesized in a regiodivergent manner with the choice of the Rh precatalyst. Mechanistic investigations shed light on the origin of the high regioselectivity observed for both hydrothiolations. Future efforts will focus on the development of a unified mechanistic approach for accessing different regioisomers of 1,3-diene hydrofunctionalizations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11395.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Funding was provided by UC Irvine, the National Institutes of Health (R35GM127071), and the National Science Foundation (CHE-1465263). S.-Z.N. thanks Liaocheng University for a scholarship. F.A.C. is grateful for an NSF Graduate Research Fellowship. We thank Dr. Peter Dornan (Amgen) and Jan Riedel for helpful discussions.

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