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# Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines

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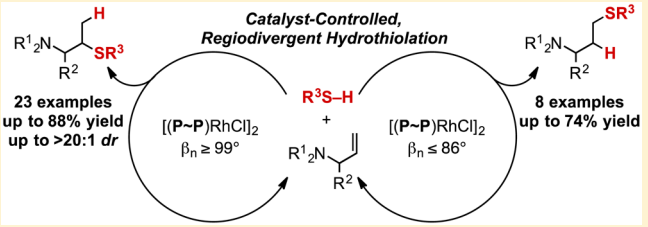
Supporting Information

**ABSTRACT:** The regiodivergent Rh-catalyzed hydrothiolation of allyl amines and imines is presented. Bidentate phosphine ligands with larger natural bite angles ($\beta_n \geq 99°$), for example, DPEphos, dpph, or **L1**, promote a Markovnikov-selective hydrothiolation in up to 88% yield and >20:1 regioselectivity. Conversely, when smaller bite angle ligands ($\beta_n \leq 86°$), for example, dppbz or dppp, are employed, the anti-Markovnikov product is formed in up to 74% yield and >20:1 regioselectivity. Initial mechanistic investigations are performed and are consistent with an oxidative addition/olefin insertion/reductive elimination mechanism for each regioisomeric pathway. We hypothesize that the change in regioselectivity is an effect of diverging coordination spheres to favor either Rh−S or Rh−H insertion to form the branched or linear isomer, respectively.




## INTRODUCTION

Hydrothiolation reactions directly couple two abundant building blocks, a thiol and an unsaturated C−C bond, to form a C−S and C−H bond with 100% atom economy.[1] This efficient strategy toward C−S bonds is highly valuable because organosulfur compounds are common synthetic intermediates[2] and composed approximately 20% of the top-selling US pharmaceutical drugs in 2012.[3] Compared to other hydrofunctionalization methods, however, transition metal-catalyzed hydrothiolation is relatively underexplored, likely due to sulfur's strong coordinating ability and ensuing catalyst deactivation.[4]

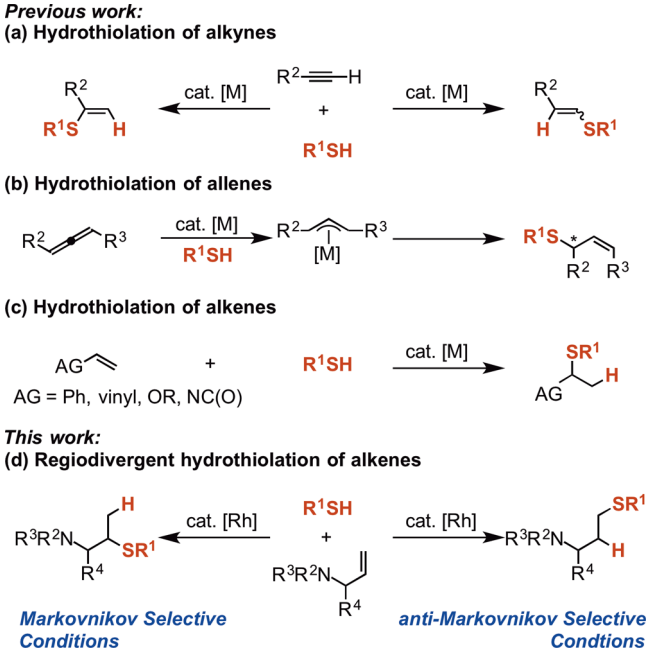
Since the first transition metal-catalyzed hydrothiolation breakthrough by Ogawa in 1992,[5] organometallic chemists have designed catalytic systems capable of selectively synthesizing both linear and branched C−S bonds from alkynes and allenes (Scheme 1a,b).[6,7] In contrast, transition metal-catalyzed hydrothiolations of alkenes is relatively underdeveloped.[8] Ogawa recently demonstrated the Au-catalyzed anti-Markovnikov hydrothiolation of terminal olefins to afford linear C−S bonds.[9] However, thus far, only electronically activated alkenes have afforded branched C−S bonds (Scheme 1c).[10]

The development of alkene functionalizations is an important challenge in modern catalysis.[11] Our group is specifically interested in using transition metal catalysis to form C−X bonds from these ubiquitous organic moieties with high degrees of regio-, chemo-, and stereoselectivity.

Recently, we demonstrated the Rh-catalyzed hydroamination of allylimines and homoallylamines for the selective synthesis of 1,2-diamines and 1,4-diamines, respectively.[12] We propose that the Lewis basic nitrogen binds to the catalyst and promotes the functionalization of the proximal alkene.[13] The regioselectivity is dictated by the formation of the favored five-membered metallacyclic intermediate.

We hypothesized that a similar approach may allow for the Markovnikov-selective hydrothiolation of electronically unactivated allyl amines and imines to afford 1,2-amino- and

**Scheme 1. Hydrothiolation of Unsaturated C−C Bonds**

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iminothioethers, respectively. The 1,2-*N*,*S*- moiety is commonly found in modern pharmaceuticals[14] (Figure 1a) and as

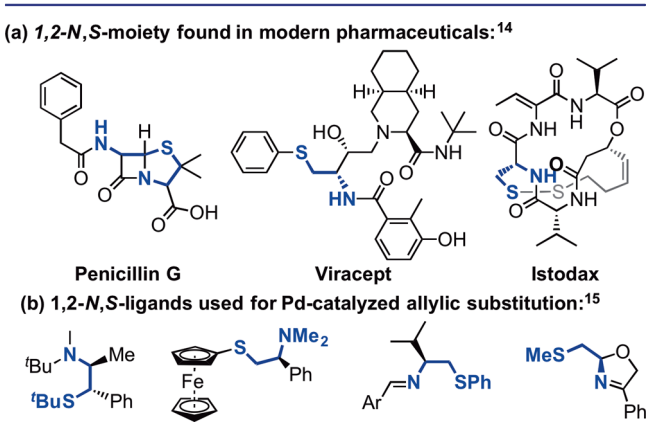


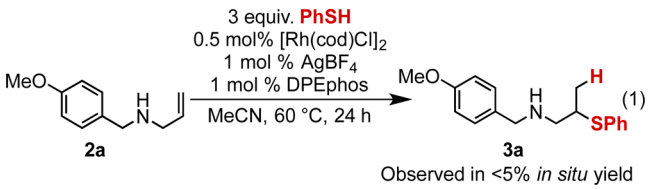

**Figure 1.** Relevant compounds containing a 1,2-aminothioether functionality.

bidentate ligands for palladium-catalyzed allylic substitution reactions[15,16] (Figure 1b). However, thus far, the incorporation of these moieties has, in many cases, depended on preinstalled functionality from ephedrine and cysteine, limiting substitution patterns for derivatization along the carbon skeleton. The development of a more general methodology for the synthesis of 1,2-aminothioethers may enable broader applicability of this moiety with increased structural diversity.

Herein we disclose an efficient synthesis of 1,2-aminothioethers via the hydrothiolation of easily accessible allyl amine derivatives. To our surprise, the regioselectivity of the olefin functionalization is ligand-controlled, allowing us to access both 1,2- and 1,3-aminothioethers from a common starting material (Scheme 1d).

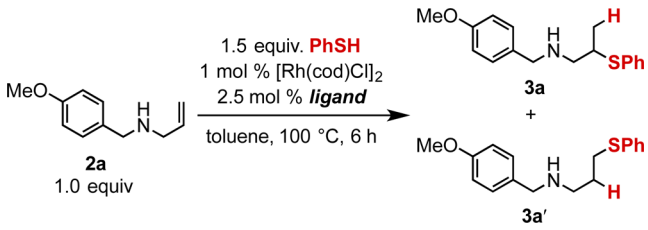
## RESULTS AND DISCUSSION

Our initial attempt at the Rh-catalyzed hydrothiolation of alkenes explored the use of thiophenol under our previously optimized conditions for the hydroamination reaction. Excitingly, we found that allyl imine **1a** and secondary allyl amine **2a** act as directing groups, affording the Markovnikov-selective hydrothiolation product, albeit in trace quantities, as detected by GC analysis (eq 1).[17]

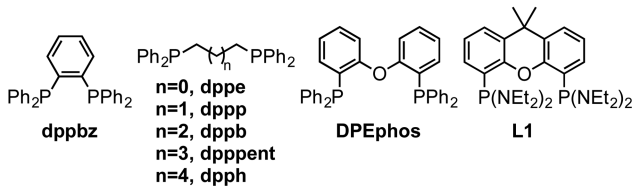



Increasing catalyst loading and temperature along with using a nonpolar solvent led to the formation of **3a** in 66% yield from amine **2a** with >20:1 selectivity for the Markovnikov isomer (Table 1, entry 7). Intriguingly, in the course of our optimization, we observed that the regioselectivity of the directed hydrothiolation of allyl amines is dictated by the ligand employed. As seen in Table 1, ligands with smaller bite angles (entries 1−3) are selective for the anti-Markovnikov hydrothiolation product. Alternatively, those with larger bite angles favor the Markovnikov isomer (entries 4−8). A similar trend is observed when allyl imines are employed. Control reactions

**Table 1. Effect of Bidentate Phosphine Ligand on the Rh-Catalyzed Hydrothiolation Reaction**




| entry | ligand | $\beta_n$[a] | yield **3a**[b] | yield **3a′**[b] |
|---|---|---|---|---|
| 1 | dppbz | 83° | <1% | 3% |
| 2 | dppe | 85° | <1% | 7% |
| 3 | dppp | 86° | <1% | 19% |
| 4 | dppb | 99° | 12% | <1% |
| 5 | dpppent | | 31% | <1% |
| 6 | dpph | | 32% | <1% |
| 7 | DPEphos | 102° | 66% | <1% |
| 8 | L1 | 168° | 21% | <1% |




[a]Natural bite angle ($\beta_n$), as defined by the preferred chelation angle based on the ligand backbone and not on the metal valence angle.[18] [b]Yield determined by comparison to an internal standard using gas chromatography.

indicate that the regioisomeric transformations are rhodium-catalyzed,[17] suggesting a change in mechanism, based on the ligand employed, that allows for a catalyst-controlled, regiodivergent hydrothiolation reaction.

Next, our efforts focused on exploring the scope of the Markovnikov-selective hydrothiolation reaction. We found that increasing catalyst loading, thiol equivalents, and time led to a more general reaction scope.[17] The addition of 0.5 equiv of LiBr increases the yield, potentially a consequence of suppressed product inhibition or an effect of a more active rhodium−bromide intermediate following salt metathesis.

As demonstrated in Table 2, secondary amines and imines are excellent directing groups for hydrothiolation, affording 1,2-aminothioethers in good yields (38−82%) with excellent regioselectivity (>20:1 in all cases). Notably, the ligand employed is dependent on the substrate, that is, with imines, higher yields are observed with **L1** (Table S8); whereas DPEphos affords higher yields when starting with a secondary amine (Table 1). The imine products are not stable to column chromatography; thus, these compounds are isolated by immediate reduction to the corresponding 1,2-aminothioether. These products can also be accessed through a three-component procedure, that is, starting with *p*-methoxybenzaldehyde and allyl amine, a one-pot imine condensation and *in situ* hydrothiolation reaction with thiophenol yielded **3a** in 58% isolated yield following reduction with $NaBH_4$.[17]

A variety of functional groups are well-tolerated, including *p*- and *o*-substituted ethers (**3a**, **3e**), a tertiary amine (**3b**), an aryl



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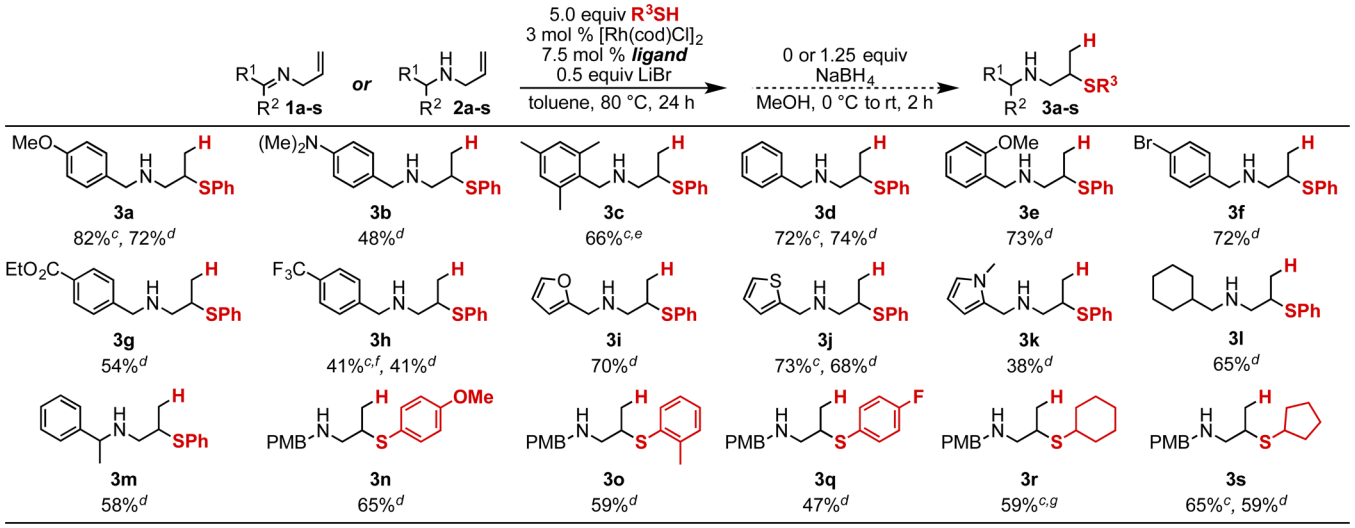
**Table 2. Markovnikov-Selective Hydrothiolation of Allyl Imines and Secondary Allyl Amines**[a,b]




[a]Isolated yields are reported as an average of two runs. [b]Regioselectivity > 20:1 is observed, as determined by NMR or GC analysis of the crude reaction mixtures. [c]Reaction conditions: (i) $[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), **L1** (0.03 mmol, 7.5 mol %), LiBr (0.2 mmol, 0.5 equiv), toluene (2 M), allyl imine **1** (0.4 mmol, 1 equiv), and thiol (2.0 mmol, 5.0 equiv) at 80 °C for 24 h. (ii) $NaBH_4$ (0.6 mmol, 1.5 equiv), MeOH, 0 °C to rt for 2 h. [d]Reaction conditions: $[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), DPEphos (0.03 mmol, 7.5 mol %), LiBr (0.2 mmol, 0.5 equiv), toluene (2 M), allyl amine **2** (0.4 mmol, 1 equiv), and thiol (2.0 mmol, 5.0 equiv) at 80 °C for 24 h. [e]100 °C. [f]48 h, 7.0 equiv of PhSH. [g]48 h.

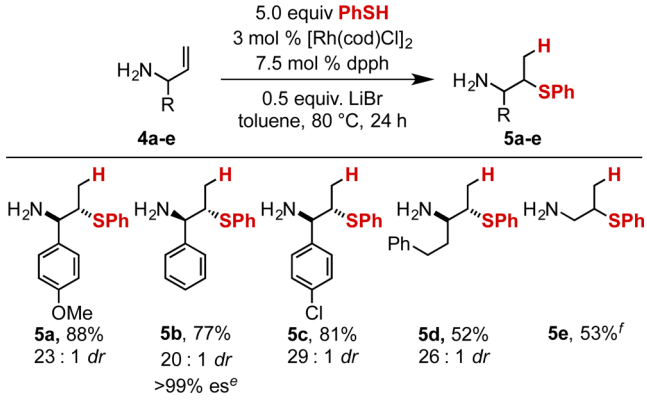
bromide (**3f**), and an ester (**3g**). Heterocycles, including thiophene, furan, and *N*-methyl pyrrole, afforded good yields of the Markovnikov hydrothiolation products **3i**-**3k**. Aliphatic amine **2l** is also readily hydrothiolated in 65% yield. In general, decreasing the electron density on benzyl-substituted allyl amines decreases reactivity but not selectivity (**3g**, **3h**), likely due to reduction of Lewis basicity of the directing group. Similarly, increasing the steric hindrance proximal to the secondary amine moderately reduces the yield of **3m** to 58%. Likewise, substitution at the $\alpha$-position of the secondary allyl amine consequently results in poor conversion to the hydrothiolation product (<5%). Unfortunately, this reaction is also limited to terminal alkenes, as both 1,1- and 1,2-disubstitued alkenes afforded <5% of the desired product.

A variety of thiophenol derivatives are tolerated under the reaction conditions, including electron-rich (**3n**), sterically encumbered (**3o**), and electron-poor (**3q**) thiophenols. Additionally, this methodology proved general for both cyclic aryl and alkyl thiols, as cyclopentane and cyclohexanethiol are effective nucleophiles for the hydrothiolation reaction (**3r**, **3s**). However, linear thiols (ethanethiol or octanethiol) do not participate in the reaction.

To our delight, primary amines are also effective directing groups for the Rh-catalyzed hydrothiolation reaction. In addition to simple allyl amine, as seen in Table 3, both aromatic and aliphatic substituted allyl amines proceed to afford *anti*-1,2-aminothioethers in good to excellent yields as a single diastereomer (>20:1 in all cases).[19] When enantiomerically enriched **4b** was employed, the stereochemical information remained with >99% enantiospecificity, suggesting that the Rh-catalyst does not isomerize to the allylic position.[17]

We next explored the anti-Markovnikov hydrothiolation of allyl amine derivatives as a demonstration of the catalyst-controlled regiodivergent reaction. Although the regioselective synthesis of linear C−S bonds from olefins has been demonstrated for over a century with both activated and unactivated substrates via the thiol−ene reaction,[20] the synthetic versatility and mechanistic implications of a regiodivergent pathway is both advantageous and intriguing. Gratifyingly, both secondary and primary amines afford 1,3-aminothioethers in fair to very good yields (37−74%) when dppbz is employed as the ligand (Table 4). Secondary and substituted primary allyl amine substrates afforded the anti-Markovnikov product as a single constitutional isomer (>20:1 a-M:M). Notably, when allyl amine is subjected to the reaction conditions both isomers are observed in a 5.5:1 of **5e′**/**5e**. Unlike the Markovnikov-selective conditions, these reactions are limited to thiophenol nucleophiles.

**Table 3. Markovnikov-Selective Hydrothiolation of Primary Allyl Amines**[a,b,c,d]




[a]Isolated yields are reported as an average of two runs. [b]Regioselectivity > 20:1 is observed, as determined by NMR or GC analysis of the crude reaction mixtures. [c]Diastereoselectivities were determined by GC analysis of the crude reaction mixtures. [d]Reaction conditions: $[Rh(cod)Cl]_2$ (0.009 mmol, 3.0 mol %), **dpph** (0.023 mmol, 7.5 mol %), LiBr (0.15 mmol, 0.5 equiv), toluene (2 M), allyl amine **4** (0.3 mmol, 1 equiv), and thiol (1.5 mmol, 5.0 equiv). [e]When starting with enantiomerically enriched **4a**. [f]Isolated following boc-protection.



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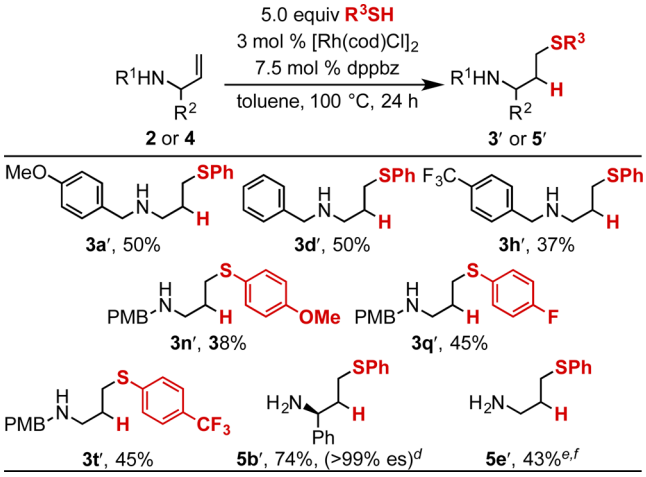
**Table 4. Anti-Markovnikov-Selective Hydrothiolation of Allyl Amines**[a,b,c]

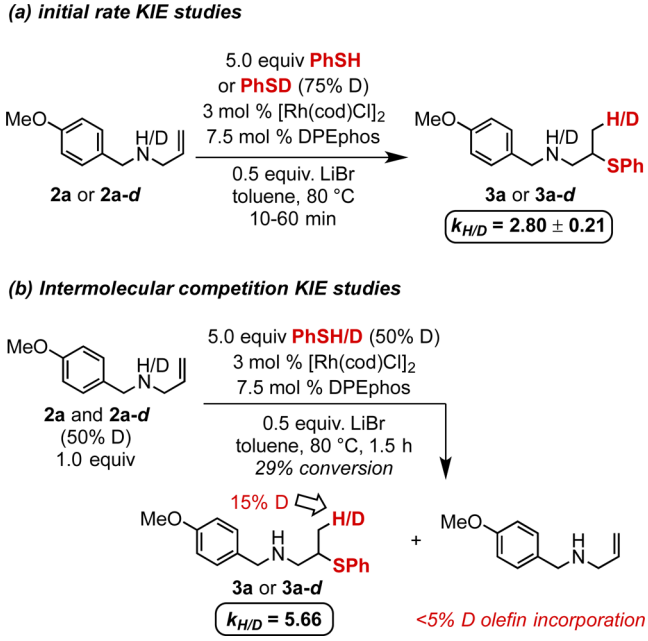



[a]Isolated yields are reported as an average of two runs. [b]Regioselectivity > 20:1 is observed, as determined by NMR or GC analysis of the crude reaction mixtures. [c]Reaction conditions: $[Rh(cod)Cl]_2$ (0.012 mmol, 3.0 mol %), **dppbz** (0.030 mmol, 7.5 mol %), toluene (2.0 M), allyl amine **2** or **4** (0.40 mmol, 1.0 equiv), and thiol (2.0 mmol, 5.0 equiv). [d]Starting with enantiomerically enriched **4a.** [e]Isolated following boc-protection. [f]A regioselectivity of 5.5:1 **5e′**/**5e** was observed by $^1$H NMR analysis of the crude reaction mixture.[17]

We hypothesize that the change in regioselectivity is an effect of diverging coordination spheres and, consequently, preferential Rh−S or Rh−H insertion to afford branched or linear isomers, respectively. We are currently investigating the coordination mode of the complexes formed with small and large bite-angle ligands and how those factors might affect the mechanistic divergence;[17,21] however, we have performed several experiments that offer key insight into each catalytic cycle.

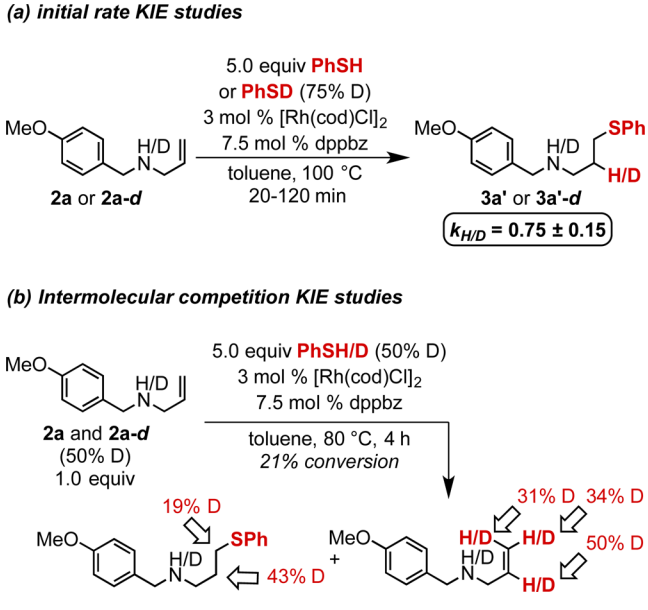
**Mechanistic Investigations.** Our initial mechanistic studies focused on the Markovnikov-selective hydrothiolation reaction. Stoichiometric investigations of $[Rh(cod)Cl]_2$, DPEphos, and 4-methoxythiophenol in THF-$d_8$ show a Rh−H resonance at −17.2 ppm (dt, $J$ = 19.4, 18.1) in the $^1$H NMR. This observation indicates that the Rh complex can undergo oxidative addition into the PhS−H bond to afford a Rh(III) intermediate with the hydride cis to both phosphines. We next explored kinetic isotope effects (KIE) under the Markovnikov-selective hydrothiolation conditions. Initial rate KIE experiments performed with deuterated thiophenol (75%-$d_1$) are consistent with a primary KIE ($k_H/k_D$ = 2.8; Scheme 2a), whereas competition experiments afford a KIE = 5.7 (Scheme 2b).[22] The KIE experiments are consistent with X−H bond breaking/forming at or before the turnover limiting step. Further, the new C−D bond is formed exclusively at the terminal carbon, indicating that $\beta$-hydride elimination is not occurring after olefin insertion. Combined, this data is consistent with (i) reversible oxidative addition into the PhS−H/D bond followed by (ii) olefin coordination and a subsequent (iii) slow olefin insertion into the Rh−S bond and (iv) fast reductive elimination to form the C−H/D bond (Scheme 4, cycle A). Transition metal-catalyzed hydrothiolations of alkynes and allenes with group 9 metals are thought to occur through similar oxidative addition/insertion/reductive elimination steps.[6a,g,h,7b]

**Scheme 2. Markovnikov-Selective Hydrothiolation KIE Studies**




We next performed similar investigations on the anti-Markovnikov-selective reaction. When $[Rh(cod)Cl]_2$, dppp (employed for its increased solubility relative to dppbz), and 4-methoxythiophenol are combined in THF-$d_8$ in the presence of $Bn_2NH$ (added to act as a surrogate for the allylic amine substrate), a Rh−H resonance is observed at −13.63 ppm (dt, $J$ = 16.1, 11.2 Hz, 1H) in the $^1$H NMR spectrum. Again, this demonstrates that oxidative addition can occur and that the Rh(III) hydride generated is cis to both phosphines. Additionally, under anti-Markovnikov conditions, when PhS−D is employed in intermolecular competition studies, extensive deuterium incorporation into each olefinic position of the recovered starting material is observed (Scheme 3b). While this

**Scheme 3. Anti-Markovnikov-Selective Hydrothiolation KIE Studies**



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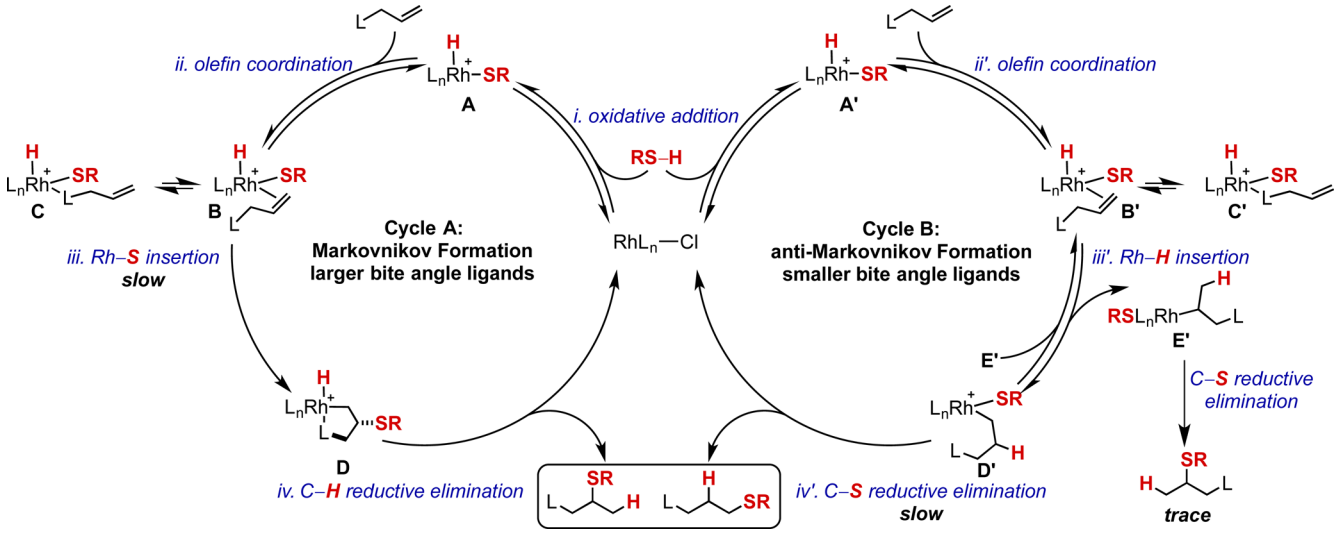
**Scheme 4. Proposed Mechanistic Divergence for the Selective Synthesis of 1,2- and 1,3-Aminothioethers**




precluded us from determining a competition KIE, the extensive deuterium incorporation indicates a reversible insertion of the Rh−H/D into the olefin (Scheme 4, step iii′).[17] Deuterium incorporation at the terminal position of the olefin can be rationalized by a reversible Rh−H/D migratory insertion to form **E′**, followed by *β*-hydride elimination to form deuterated starting material.

To measure a KIE under anti-Markovnikov conditions, we performed initial rate KIE experiments comparing the reactivity of thiophenol to deuterated thiophenol (75%-$d_1$). Under these conditions, an inverse KIE was observed ($k_H/k_D$ = 0.75 ± 0.15) (Scheme 3a), suggesting that X−H bond making or breaking does not influence the rate of the reaction. Rather, an equilibrium isotope effect explains the observed inverse KIE, an effect of the reversible olefin insertion of the Rh−H/D bond. Under pre-equilibrium conditions, the rate of product formation is affected by the equilibrium between the [$L_n$RhCl] and **B′**. The stronger C−D bond, relative to the C−H bond, will increase the concentration of the **D′**-*d* intermediate by decreasing the Δ*G*, thereby increasing the rate of reductive elimination from **D′**-*d* compared to **D′**.[17] Combined, these observations are consistent with (i) oxidative addition into the PhS−H/D, (ii′) olefin coordination, and (iii′) rapid, reversible migratory insertion into the Rh−H/D bond, followed by (iv′) slow reductive elimination to form the C−S bond (Scheme 4, cycle B).

## CONCLUSIONS

We have demonstrated the first catalyst-controlled regiodivergent hydrothiolation of electronically unactivated alkenes for the selective synthesis of 1,2- and 1,3-aminothioethers. The reactions are chemo-, regio-, and stereoselective. Initial mechanistic investigations suggest that the two catalytic cycles are both occurring via oxidative addition into the RS−H bond but that large bite angle ligands favor insertion into the Rh−SR bond while small bite angle ligands favor insertion into the Rh−H bond. The mechanism of both transformations and source for the observed regiodivergence is currently under investigation. Additionally, future studies will focus on expanding to alkenes lacking a directing group and rendering the Markovnikov-selective reaction asymmetric.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07142.

Crystallographic information for **5c** (CIF)
Optimization tables, detailed reaction protocols, and full characterization (PDF)

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

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