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Journal
Journal of the American Chemical Society, 140(33)

ISSN
0002-7863

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Publication Date
2018-08-22

DOI
10.1021/jacs.8b06957

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2019 August 22.

Published in final edited form as:

J Am Chem Soc. 2018 August 22; 140(33): 10443–10446. doi:10.1021/jacs.8b06957.

Catalytic Hydrothiolation: Regio- and Enantioselective Coupling of Thiols and Dienes

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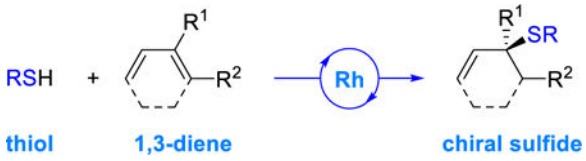
Abstract

We report a Rh-catalyzed hydrothiolation of 1,3-dienes, including petroleum feedstocks. Either secondary or tertiary allylic sulfides can be generated from the selective addition of a thiol to the more substituted double bond of a diene. The catalyst tolerates a wide range of functional groups, and the loading can be as low as 0.1 mol%. This method constitutes the first enantioselective hydrothiolation of 1,3-dienes.

Graphical Abstract



The pursuit of catalysts capable of forging carbon-sulfur linkages is a valuable goal, as molecules essential to life, from metabolites to macromolecules, contain sulfur atoms.[1] In addition, approximately 20% of all FDA approved drugs are organosulfur compounds.[2] The direct addition of a thiol to a double bond represents an attractive and atom-economical[3] approach for generating C-S bonds.[4] Inspired by this challenge, we chose to focus on the hydrothiolation of conjugated dienes, which are readily available and include commodity chemicals, like butadiene and isoprene (Figure 1).[5] One previous hydrothiolation of 1,3-dienes was reported by He, where the application of Au catalysts resulted in racemic mixtures.[6] By using Rh-catalysis, Breit pioneered an enantioselective hydrothiolation of allenes[7] and Hull achieved a regiodivergent addition to allylic amine[8]. As a complement to these strategies, we herein communicate that Rh-catalysts generate allylic sulfides from 1,3-dienes, in a regio- and enantioselective fashion, thus allowing petroleum feedstocks to be transformed into enantioenriched building blocks.[9]

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

The authors declare no competing financial interests.

While asymmetric hydroamination of dienes has been demonstrated,[10] thiols are more nucleophilic and acidic than amines, thus providing distinct challenges and opportunities for hydrofunctionalization.[11, 12] In this study, we focus on Rh complexes **I**, which we imagined could bind and activate the diene **1** by η^4-coordination (Figure 2). The resulting olefin-complex **II** undergoes oxidative addition to a thiol **2** to yield **III**. From **III**, Rh-hydride insertion can occur *via* 1,4 or 1,2-insertion, wherein rhodium adds to the less-hindered position of the diene. In **path a**, Rh-hydride insertion provides a Rh-π-allyl **IV** after 1,4-insertion. Because reductive elimination tends to favor branched products,[13] we reasoned **IV** would yield tertiary allylic sulfides **3**.[14] In **path b**, 1,2-insertion provides **V** and reductive elimination gives homoallyic sulfides **4**.

With this hypothesis in mind, we chose cyclohexadiene (**1a**) as the model substrate because its symmetric structure minimizes the number of isomers possible. We studied the coupling of **1a** and thi-ophenol (**2a**) using different bidentate phosphine ligands in the presence of $Rh(cod)_2SbF_6$ (Table 1). With the JosiPhos (**L1**), DuPhos (**L2**), and BPE (**L3**) ligands, we observed a mixture of the allylic and homoallylic sulfides. In contrast, the BINAP family afforded excellent regioselectivity for the allylic sulfide **3aa** (>20:1 *rr*) in high yields and enantioselectivity (>91% yields, and >85:15 *er*). With (*S*)-Tol-BINAP ligand (**L5**), we lowered the catalyst loading to 0.1 mol% and isolated (*S*)-sulfide **3aa**[15] on gram scale (1.2 g, 95% yield, 99:1 *er*).

Table 2 showcases the scope of this method with eighteen different thiols and **1a**, using catalyst Rh(**L5**). High reactivity (**3ab–3as**, 49–99%), enantioselectivity (96:4–>99:1 *er*), and regioselectivity (18:1 –>20:1 *rr)* are observed with both aliphatic and aromatic thiol partners. Tertiary thiols (such as *tert*-butylthiol and triphenylmethanethiol) are unreactive thus far, presumably due to steric hindrance. This method is compatible with heteroarene (**3ao**,[16] **3as**), hydroxyl (**3aq**), carboxyl (**3ar**), amino (**3ad**, **3ae**), and ester groups (**3aj**).

Next, we investigated hydrothiolation of unsymmetric 1,3-dienes (Table 3A). For 1-substituted (**1b**) and 1,2-disubstituted (**1c**) dienes, we found that a bulkier BINAP ligand (**L6**) afforded the best results (85% yield, 83:17 *er* and 78% yield 71:29 *er,* respectively). In contrast, the 2-substituted-1,3-dienes reacted poorly in the presence of BINAP ligands. In this case, the JosiPhos ligands provided a breakthrough. With **L7**, myrcene (**3d**) can be coupled with an aromatic thiol (**3da**, 68% yield, 96:4 *er,* >20:1 *rr*) and an aliphatic thiol (**3dp**, 71% yield, 90:10 *er,* >20:1 *rr*). 2-Aryl-1,3-dienes undergo hydrothiolation as well (**3ea**–**3ga**, 73–80%, 93:7–98:2 *er*); the presence of an electron-withdrawing group (**3ea**) on the phenyl ring exhibits higher regioselectivity (>20:1 *rr*) compared to electron-donating substituents (**3ga**, 7:1 *rr*).

Isoprene and butadiene are petroleum feedstocks, produced on a million metric ton scale every year and used as monomers to make plastics.[17] Hydrothiolation of isoprene (**1h**) with thiophenol and cyclohexanethiol gives the corresponding tertiary sulfides (**3ha**, **3ht**), in >89% yield and >20:1 *rr* (Table 3B). A commercial diene, 2,3-dimethyl-1,3-butadiene (**1i**), transforms into the tertiary sulfide **3ia** (93% yield, >20:1 *rr*). The construction of chiral products from butadiene remains a challenge that has inspired hydrohydroxyalkyation,[5c] cycloadditions[18] and difunctionalizations[19]. To meet this challenge, we simply switched the

ligand to DTMB-GarPhos (**L8**). With Rh(**L8**), high reactivity (81–95%) and regioselectivity (>20:1 *rr*) are achieved using both aliphatic and aromatic thiols. The products derived from aromatic thiols (**3ja**, **3jc**, **3jg**, **3ju**) are obtained in higher enantioselectivities (95:5–98:2 *er*) than those from aliphatic thiols (**3jv**, **3jw**, **3js**, 90:10–94:6 *er*)

Aside from enantioselective examples, we examined the addition of a L-cysteine ester **2x** to 1,3-cyclohexadiene (Figure 3). Either diastereomeric product, **3ax** or **3ax'**, can be generated with high diastereoselectivity (>20:1 *dr*), depending on the enantiomer of ligand **L5** employed.

In principle, the coupling of a thiol and unsymmetrical diene (e.g., 2-phenyl-1,3-diene **1f**) can result in up to eleven different isomers.[20] In addition to stereoisomers, constitutional isomers may arise due to competing 1,2 *versus* 1,4-addition, as well as *anti*-Mar-kovnikov *versus* Markovnikov type selectivity. By using a cationic rhodium precatalyst, we obtain allylic sulfides with high chemo-, regio-, and enantio-control. The catalyst loading can be lowered to 0.1 mol% and many functional groups can be tolerated, including heteroarene, hydroxyl, carboxyl, amino, and ester groups. By choosing the appropriate phosphine ligand, we can transform a wide-range of dienes into chiral sulfides. The regiocontrol observed supports a mechanism distinct from what was previously proposed for related hydroaminations.[5h10a] Further studies are warranted to elucidate the mechanism and develop access to other re-gioisomers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Funding provided by UC Irvine, the National Institutes of Health (1R35GM127071) and the National Science Foundation (CHE-1465263). We thank Alexander Lu for help with initial studies and the Jarvo Lab for help with chiral SFC analysis.

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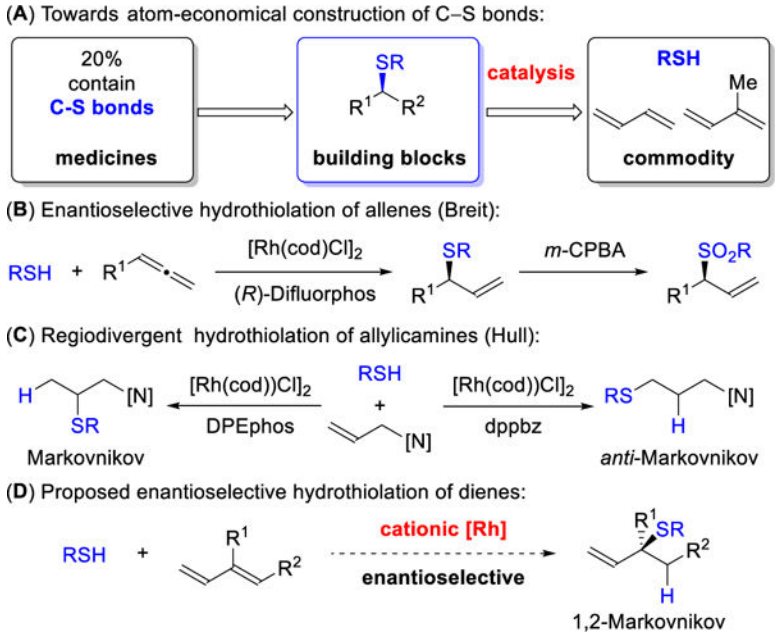


Figure 1.
Inspiration for hydrothiolation of 1,3-dienes.

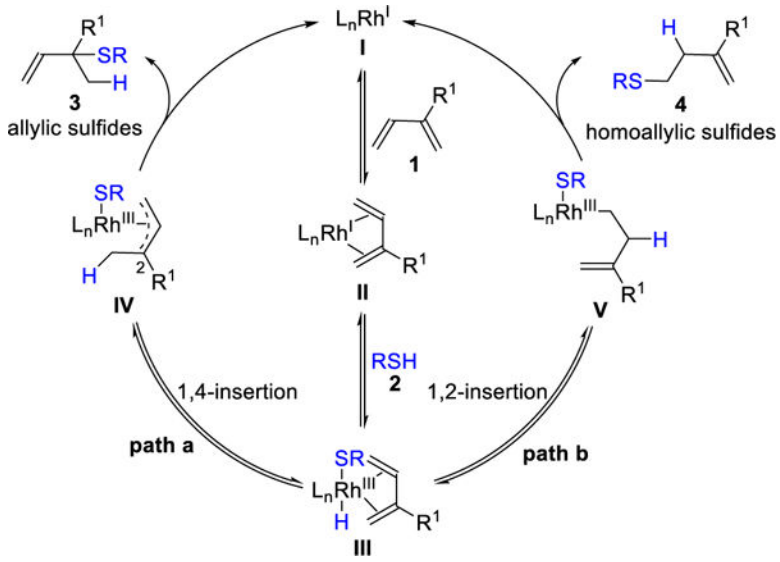


Figure 2.
Proposed Rh-catalyzed hydrothiolation of 1,3-dienes.

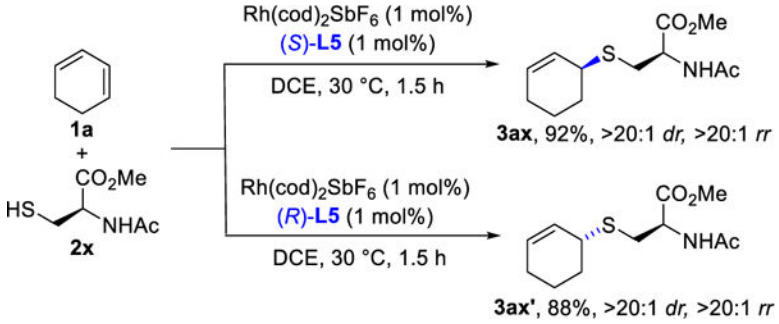
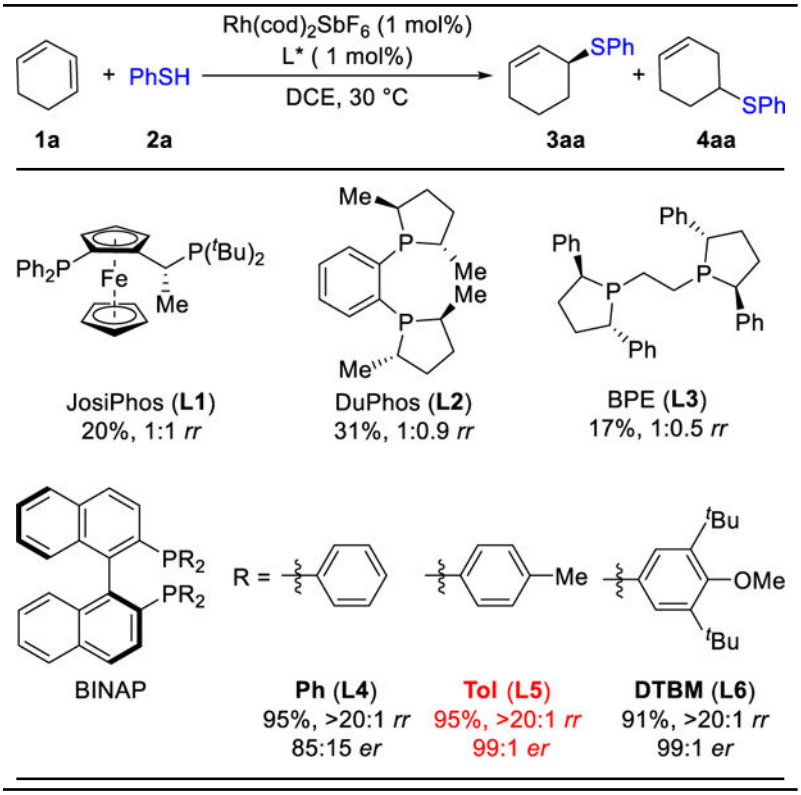


Figure 3.
Catalyst-controlled diastereoselective hydrothiolation.

Table 1.

Ligand Effects on Asymmetric Hydrothiolation of 1a[a]

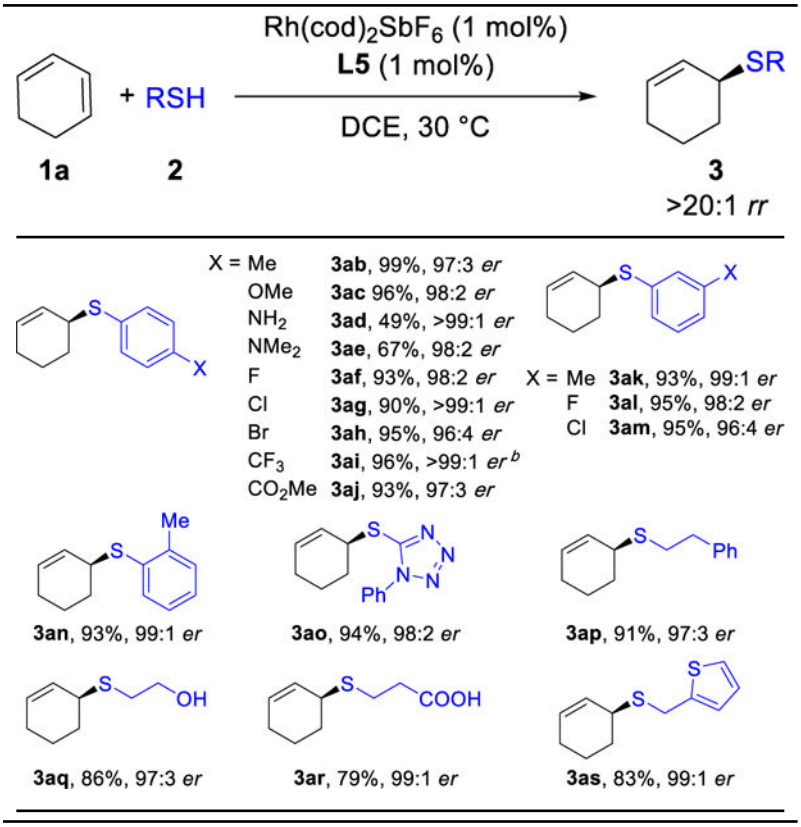


[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), $Rh(cod)_2SbF_6$ (1 mol%), ligand (1 mol%), DCE (0.2 mL), 3 h. Isolated yield.

Regioselectivity ratio (*rr*) is the ratio of **3aa** to **4aa**, which is determined by ^1H NMR analysis of reaction mixture. Enantioselectivity determined by chiral SFC.

Table 2.

Hydrothiolation of 1a with Various Thiols[a]

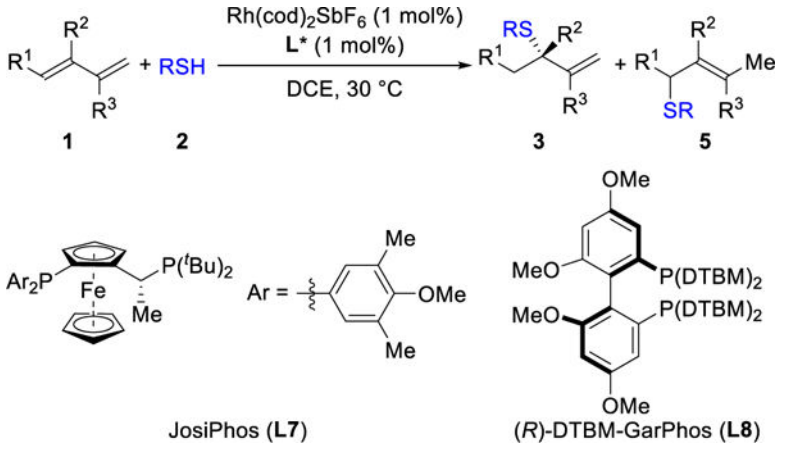


[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $Rh(cod)_2SbF_6$ (1 mol%), **L5** (1 mol%), DCE (0.4 mL), 30 °C, 5 h. Isolated yields. Regioselectivity ratio (*rr*) is the ratio of **3** to **4**, which is determined by ^1H NMR analysis of reaction mixture. Enantioselectivity determined by chiral SFC.

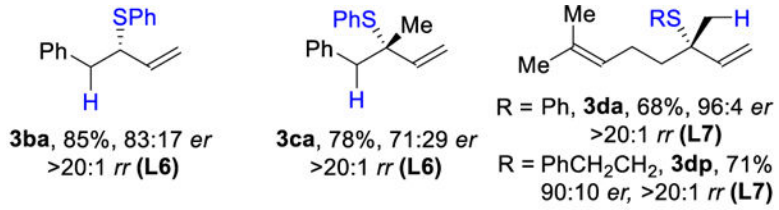
[b]18:1 *rr*.

Table 3.

Hydrothiolation of Various 1,3-Dienes[a]



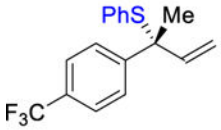
(A) Hydrothiolation of unsymmetric dienes[b]



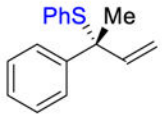
3ba, 85%, 83:17 *er* >20:1 *rr* **(L6)**

3ca, 78%, 71:29 *er* >20:1 *rr* **(L6)**

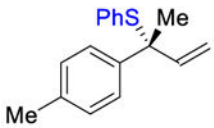
R = Ph, **3da**, 68%, 96:4 *er* >20:1 *rr* **(L7)**
R = $PhCH_2CH_2$, **3dp**, 71% 90:10 *er*, >20:1 *rr* **(L7)**



3ea, 80%, 98:2 *er* >20:1 *rr* **(L1)**

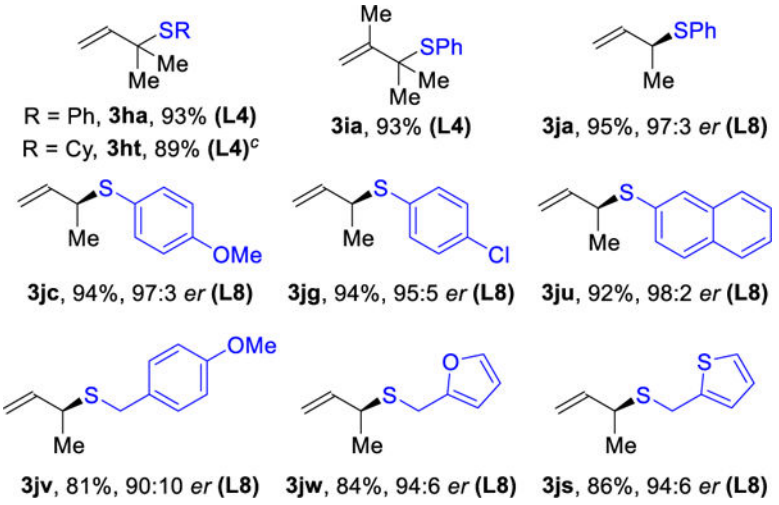


3fa, 73%, 96:4 *er* 12:1 *rr* **(L1)**



3ga, 77%, 93:7 *er* 7:1 *rr* **(L1)**

(B) Hydrothiolation of feedstock dienes(> 20:1 *rr*)



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), $Rh(cod)_2SbF_6$ (1 mol%), **L** (1 mol%), DCE (0.4 mL), 30 °C, 5 h. Isolated yields. Ligand used in parentheses. Regioselectivity ratio (*rr*) is the ratio of **3** to **5**, which is determined by ^1H NMR analysis of reaction mixture. Enantioselectivity determined by chiral SFC.

[b]Using $Rh(cod)_2SbF_6$ (5 mol%), **L** (5 mol%), 15 h.

[c]13:1 *rr*