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Synthesis of 1,1-Disubstituted Alkyl Vinyl Sulfides via Rhodium-Catalyzed Alkyne Hydrothiolation: Scope and Limitations

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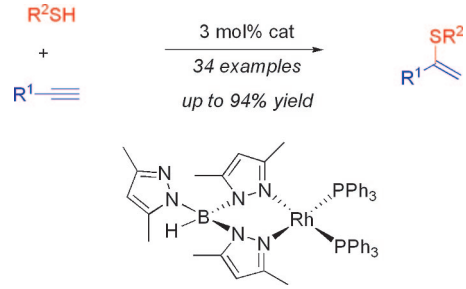
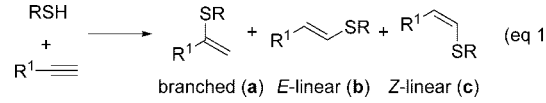


Described herein are the scope and limitations using Tp*Rh(PPh$_3$)$_2$ as a catalyst for alkyne hydrothiolation with alkyl thiols. In general, catalytic hydrothiolation proceeds in high yields and with high regioselectivity for a wide range of alkynes and thiols. A variety of functional groups were well-tolerated, including nitriles, amines, halogens, ethers, esters and silanes, although strongly coordinating groups were found to be incompatible with hydrothiolation. Both sterically encumbered alkynes and thiols were successful in hydrothiolation. Electron rich alkynes react more rapidly than electron deficient alkynes. Overall, this hydrothiolation protocol provides convenient access to a variety of functionalized branched alkyl vinyl sulfides.

Introduction

Vinyl sulfides are valuable synthetic intermediates in total synthesis[1] and are versatile building blocks[2] for many functionalized molecules. Many natural products and compounds exhibiting interesting biological properties contain an alkyl vinyl sulfide moiety.[3] For example, griseoviridin is a broad spectrum antibiotic with in vitro inhibitory activity against various pathogenic microorganisms.[4] As such, strategies for the construction of alkyl vinyl sulfides are highly desirable.

An attractive method for the formation of vinyl sulfides involves hydrothiolation, the reaction of an S−H bond across an alkynyl π-bond (eq 1). Although hydrothiolation with aryl thiols has been achieved in radical,[5] nucleophilic,[6] and metal-catalyzed[7] reactions, alkyl thiols are typically found to be unreactive.[7g] A selective method for the formation of *Z*-linear vinyl sulfides emerged in 2005,[6e] yet a general method for the stereo- and regiocontrolled synthesis of either branched and *E*-linear alkyl vinyl sulfides remained an unmet goal.



(eq 1)

We anticipated that the use of a suitable transition metal complex would overcome the substrate limitations for catalytic

(1) For examples of vinyl sulfides as intermediates in total synthesis, see: (a) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966. (b) Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648–2656. (c) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109–9122.

(2) For examples of vinyl sulfides as synthetic intermediates or precursors to functionalized molecules, see: (a) Parham, W. E.; Motter, R. F. *J. Am. Chem. Soc.* **1958**, *81*, 2146–2148. (b) Mukaiyama, T.; Kamio, K.; Kobayashi, S.; Takei, H. *Bull. Chem. Soc. Jpn.* **1972**, *4*, 193–202. (c) McClelland, R. A. *Can. J. Chem.* **1977**, *55*, 548–551. (d) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, *6*, 637–638. (e) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075–5090. (f) Sabarre, A.; Love, J. A. *Org. Lett.* **2008**, *10*, 3941–3944.

(3) For examples of vinyl sulfides as intermediates for the synthesis of bioactive molecules, see: (a) Sader, H. S.; Johnson, D. M.; Jones, R. N. *Antimicrob. Agents Chemother.* **2004**, *48*, 53–62. (b) Johannesson, P.; Lindeberg, G.; Johansson, A.; Nikiforovich, G. V.; Gogoll, A.; Synnergren, B.; Le Greves, M.; Nyberg, F.; Karlen, A.; Hallberg, A. *J. Med. Chem.* **2002**, *45*, 1767–1777. (c) Ceruti, M.; Balliano, G.; Rocco, F.; Milla, P.; Arpicco, S.; Cattel, L.; Viola, F. *Lipids* **2001**, *36*, 629–636. (d) Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553–4559. (e) Lam, H. W.; Cooke, P. A.; Pattenden, G.; Bandaranayake, W. M.; Wickramasinghe, W. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 847–848. (f) Morimoto, K.; Tsuji, K.; Iio, T.; Miyata, N.; Uchida, A.; Osawa, R.; Kitsutaka, H.; Takahashi, A. *Carcinogenesis* **1991**, *12*, 703–708.

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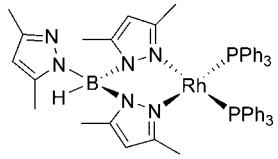


FIGURE 1. Complex **I**, Tp*Rh(PPh$_3$)$_2$.

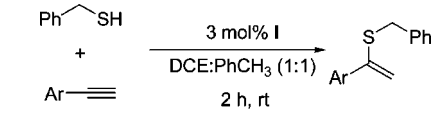
hydrothiolation. Accordingly, we recently reported that Wilkinson's catalyst[7n] and Tp*Rh(PPh$_3$)$_2$ (**I**, Figure 1)[8] are excellent catalysts for alkyne hydrothiolation using alkyl thiols to generate the *E*-linear and branched alkyl vinyl sulfides, respectively. In the latter case, the formation of the branched isomer is a significant departure from the regioselectivity obtained with other group 9 metal complexes using aryl thiols.[7] Given the apparent generality of the process, we sought to study the hydrothiolation reaction in greater detail.

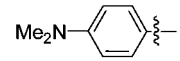
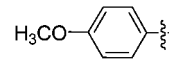
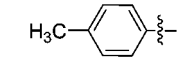
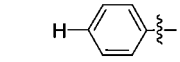
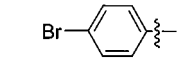
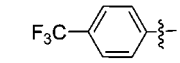
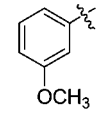
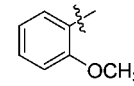
We have recently reported a detailed analysis of the ligand requirements of the pyrazolylborate ligand, along with solution and solid phase structures of the resulting rhodium complexes.[9] Both 3,5-dimethyl pyrazolylborate (Tp*) and 3-phenyl-5-methyl pyrazolylborate (Tp^{Ph,Me}) were found to be superior to other ligands studied. Given the inherent difficulties associated with the synthesis and purification of the Tp^{Ph,Me} ligand and resulting rhodium complex, we elected to use Tp*Rh(PPh$_3$)$_2$ for further study. We report herein the results of a systematic exploration of the scope and limitations of hydrothiolation using this catalyst.

Results and Discussion

Our first objective was to evaluate the range of terminal alkynes that could act as suitable substrates in hydrothiolation.

TABLE 1. Scope of Hydrothiolation of Aryl Alkynes with Benzylthiol Catalyzed by I



entry[a]	Ar	product, yield[b]
1		**1a**, 90%
2[c]		**2a**, 93%
3		**3a**, 91%
4[c]		**4a**, 90%
5[d]		**5a**, 67%
6[d]		**6a**, 40%
7		**7a**, 83%
8[e]		**8a**, 55%
9		**9a**, 85%
10		0%

[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:PhCH$_3$, and 0.3 mmol (3 mol %) catalyst, at room temperature for 2 h, unless otherwise noted. [b] Isolated yields. [c] Reference 7. [d] An additional ~5−10% of an unidentified byproduct was observed. [e] Reaction time 24 h. Yield after 2 h is 10%.

Benzylthiol, which had been previously shown to react rapidly and regioselectively with six different alkynes,[8] was selected for initial study. In a typical experiment, PhCH$_3$ (2 mL), DCE (2 mL) and Tp*Rh(PPh$_3$)$_2$ (280 mg, 0.30 mmol, 3 mol %) were combined in a 20 mL vial equipped with a magnetic stir bar and a screw cap. Benzylthiol (1.3 mL, 11 mmol, 1.1 equiv relative to alkyne) and alkyne (10 mmol, 2.5 M) were then added and the solution was stirred at room temperature for 2 h. The choice of a 2 h time limit allowed for the direct comparison of alkyne reactivity.

The effect of electronics on reactivity and selectivity was revealed by examining *para*-substituted phenylacetylenes (Table 1, entries 1−6). All reactions proceeded with high regioselectivity to provide the corresponding branched alkyl vinyl sulfides, indicating that substitution had little impact on regioselectivity. In marked contrast, both reaction efficiency and yield were

(4) (a) Paris, J. M.; Barriere, J. C.; Smith, C.; Bost, P. E. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lucas, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 183−248. (b) Di Giambattista, M.; Chinali, G.; Cocito, C. *J. Antimicrob. Chemother.* **1989**, *24*, 485–488. (c) Cocito, C. *Microbiol. Rev.* **1979**, *43*, 145–169.

(5) Radical reactions: (a) Oswald, A. A.; Griesbaum, K.; Hudson, B. E.; Bregman, J. M. *J. Am. Chem. Soc.* **1964**, *86*, 2877–2884. (b) Griesbaum, K. *Angew. Chem., Int. Ed.* **1970**, *9*, 270. (c) Patai, S., Ed.; In *The Chemistry of the Thiol Group*; John Wiley & Sons, Ltd.: London, 1974, *2*. (d) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J. L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647–1650. (e) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1996**, *61*, 6783–6789.

(6) Nucleophilic reactions: (a) Truce, W. E.; Simms, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2756–2759. (b) Carson, J. F.; Boggs, L. E. *J. Org. Chem.* **1966**, *31*, 2862–2864. (c) Truce, W.; Tichenor, G. J. W. *J. Organomet. Chem.* **1972**, *37*, 2391–2396. (d) Katritzky, A. R.; Ramer, W. H.; Ossana, A. *J. Org. Chem.* **1985**, *50*, 847–852. (e) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, *70*, 6468–6473.

(7) Metal-catalyzed reactions: using Mo: (a) McDonald, J. W.; Corbin, J. L.; Newton, W. E. *Inorg. Chem.* **1976**, *15*, 2056–2061using Pd: (b) Bäckvall, J. E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850–5851. (c) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351–353. (d) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y.; Timofeeva, T. V. *J. Am. Chem. Soc.* **2007**, *129*, 7252–7253. (e) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1383–1385using Pd, Rh, Ni, and Pt: (f) Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902–5903. (g) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108–5114using Rh and Ir: (h) Burling, S.; Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *J. Chem. Soc., Dalton Trans.* **2003**, 4181–4191using Ni: (i) Ananikov, V. P.; Malyshev, D. A.; Beletskaya, I. P.; Aleksandrov, G. G.; Eremenko, I. L. *Adv. Synth. Catal.* **2005**, *347*, 1993–2001. (j) Ananikov, V. P.; Zalesskiy, S. S.; Orlov, N. V.; Beletskaya, I. P. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2109–2113using Ni and Pd: (k) Malyshev, D. A.; Scott, N. M.; Marion, N.; Stevens, E. D.; Ananikov, V. P.; Beletskaya, I. P.; Nolan, S. P. *Organometallics* **2006**, *25*, 4462–4470. (l) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P. *Organometallics* **2006**, *25*, 1970–1977using Rh: (m) Misumi, Y.; Seino, H.; Yasushi, M. *J. Organomet. Chem.* **2006**, *691*, 3157–3164. (n) Shoai, S.; Bichler, P.; Kang, B.; Buckley, H.; Love, J. A. *Organometallics* **2007**, *26*, 5602–5611. (o) Silva, M.; Lara, R.; Marczewski, J.; Jacob, R.; Lenardao, E.; Perin, G. *Tetrahedron Lett.* **2008**, *49*, 1927–1930.

(8) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614–17615.

(9) Fraser, L. R.; Bird, J.; Wu, Q.; Cao, C.; Patrick, B. O.; Love, J. A. *Organometallics* **2007**, *26*, 5778–5781.

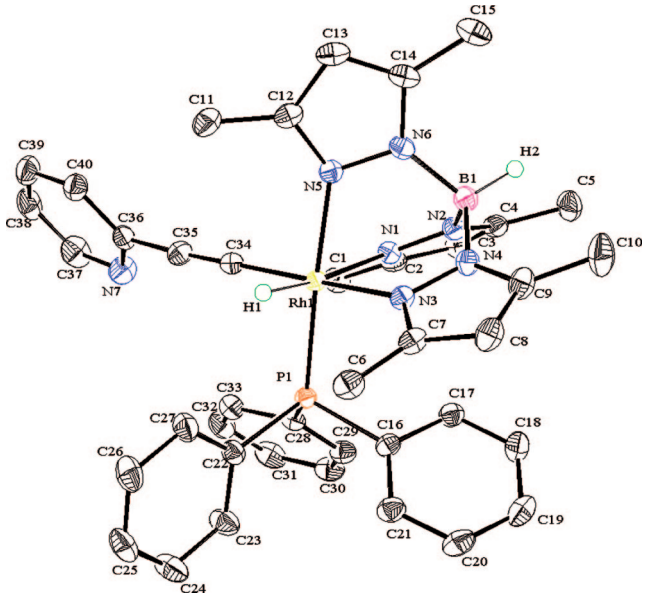


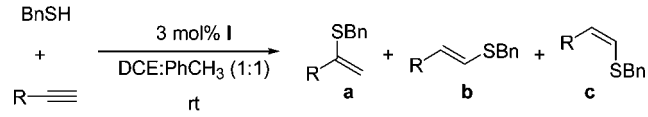
FIGURE 2. ORTEP diagram of complex **II**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms, except for the B−H hydrogen and the phenyl groups of PPh_3, are excluded for clarity. Selected bond lengths (Å), angles (deg) and crystallographic data are given in Supporting Information.

profoundly influenced by electronic modifications. Hydrothiolation of both electron-rich (entries 1−3) and unsubstituted (entry 4) phenylacetylenes proceeded in excellent yields, whereas electron-deficient alkynes (entry 5 and 6) provided inferior yields.

Having established that *para*-substitution plays a crucial role in reactivity but not selectivity, the effect of substitution at both the *meta*- and *ortho*- positions was next addressed. As anticipated, only the branched isomer was observed in each reaction (entries 7−9). The incorporation of a methoxy group in the *meta*-position was well-tolerated (entry 7), whereas the use of 2-methoxyphenylacetylene provided a mere 55% yield after 24 h (entry 8). The lower yield in the latter case could be a consequence of greater steric hindrance at the ortho position. Alternatively, coordination of the methoxy oxygen to rhodium could impede catalysis. To differentiate between these scenarios, *ortho*-methylphenylacetylene was examined, as the methyl substituent has a greater steric demand than methoxy, but a substantially lower propensity for coordination to rhodium. The methyl-substituted alkyne (entry 9) reacted with benzylthiol with considerably higher efficiency and in higher yield than did *ortho*-methoxyphenylacetylene (entry 8). As such, we concluded that oxygen coordination was responsible for both the lower yield and turnover rate with *ortho*-methoxyphenylacetylene.

Consistent with this analysis, 2-pyridylacetylene was unreactive in hydrothiolation (entry 10). Further insight was obtained from the stoichiometric reaction of $Tp^*Rh(PPh_3)_2$ (93 mg, 0.1 mmol) and 2-pyridylacetylene (0.1 mL, 1.0 mmol) in d_8-toluene (1 mL). The reaction was monitored by both ^1H and ^{31}P NMR spectroscopy. Within 30 min, the PPh_3 resonance of $Tp^*Rh(PPh_3)_2$ (δ 42.92, d, J = 175.6 Hz) disappeared and a new doublet emerged (δ 45.90, J_{Rh-P} = 124.7 Hz). The ^1H NMR spectrum indicated the appearance of a rhodium hydride species (δ −14.68, J_{Rh-H} = 20.5 Hz, J_{P-H} = 17.6 Hz). This phenomenon was also observed in the attempted catalytic reaction. Transfer of the d_8-toluene solution to a 5 mL vial, followed by layering with 2 mL hexanes, provided, after 2 days at room temperature,

TABLE 2. Scope of Hydrothiolation of Aliphatic Alkynes with Benzylthiol Catalyzed by I



entry[a]	R	time (h)	product, yield[b]
1	Ph	24	**10a**, 85%
2	NC	48	**11a**, 88%
3	Cl	24	**12a**, 90%
4	n-C_6H_{13}	16	**13a**, 92%
5	PhO	24	**14a**, 33%
6[c]		10	**15a**, 81%
7[c]	t-Bu	24	**16a**, 63%
8	TMS	2	**17a:17b:17c** = 6:3:2, 88%
9	EtO_2C	2	**18b:18c** = 2:1, 68%

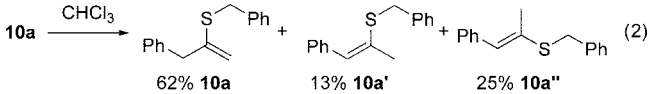
[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:$PhCH_3$, and 0.3 mmol (3 mol %) catalyst, rt. [b] Isolated yields. [c] Reference 7.

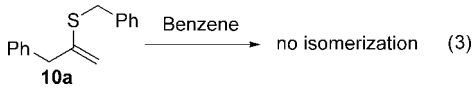
crystals suitable for X-ray-analysis. The ORTEP diagram, shown in Figure 2, indicates that the alkyne underwent activation of the alkynyl C−H bond to generate a rhodium hydrido acetylide (**II**). We[10] and others[11] have found this process to be quite facile for a number of alkynes in the presence of $Tp^*Rh(PPh_3)_2$. With respect to the hydrothiolation reaction, we hypothesize that coordination of pyridine precludes the reaction of thiol, thereby presenting an opportunity for the rhodium species to activate the alkynyl C−H bond. Further evidence for this suggestion was obtained by evaluating the effect of 2-pyridylacetylene as a catalyst poison. Addition of 1 equiv of 2-pyridylacetylene to a typical reaction of benzylthiol and phenylacetylene precluded catalysis. This result suggests that the reaction of 2-pyridylacetylene with $Tp^*Rh(PPh_3)_2$ is more rapid than hydrothiolation and that the C−H activation is irreversible. In comparison, C−H activation of the alkynyl C−H bond of o-methoxyphenylacetylene is considerably slower than with 2-pyridylacetylene. Thus, we conclude that the methoxy group slows productive hydrothiolation but does not completely shut down catalysis. A possible explanation for the lower yield with o-methyoxyphenylacetylene as compared with the para-isomer is that the catalyst is slowly depleted from the reaction by C−H activation.

Given the importance of electronic and steric effects in the reactivity of substituted arylacetylenes, we were eager to evaluate the reactivity of nonaromatic alkynes (Table 2). In general, aliphatic alkynes required longer reaction times to reach completion than aryl alkynes. Importantly, a variety of potentially reactive functional groups were well-tolerated in this reaction, including nitriles, halogens, ethers, esters and silanes.

Good-to-excellent yields of product were obtained for all alkynes studied, with the exception of phenyl propargyl ether (entry 5). The lower yield in this case may result from slower turnover due to coordination of the ether moiety to rhodium.

We had previously disclosed that vinyl sulfides containing propargylic protons are prone to isomerization to the corresponding internal vinyl sulfide. For example, benzyl(1-benzylvinyl)sulfane (**10a**), the product of entry 1, was found to isomerize to the internal alkyl vinyl sulfides upon standing in a chloroform solution overnight (eq 2), presumably due to trace amounts of HCl.[8] This isomerization is suppressed by avoiding chloroform as a solvent for either chromatography or NMR spectroscopic studies (eq 3). Purification of chloroform prior to use also precludes isomerization.





The product indicated in entry 6 and its oxidized derivatives are potential Diels−Alder substrates. Although rhodium catalysts have been reported to promote the [4 + 2] cycloaddition of dienes,[12] the cycloaddition of the product of 1-ethynylcyclohexene with either remaining alkyne or vinyl sulfide product was not observed under the reaction conditions. The effect of sterically bulky groups on hydrothiolation efficiency was also investigated (entries 7 and 8). Both *tert*-butylacetylene and trimethylsilylacetylene reacted efficiently, although high regioselectivity was achieved only in the former case. Nevertheless, the vinyl silane products (entry 8) can potentially be further functionalized in Hiyama[13] cross-coupling or deprotected to yield the monosubstituted vinyl sulfide. Of additional interest, the regioselectivity of the reaction reverses when electronically activated alkynes, such as ethyl propiolate, are used (entry 9). In this case, a 2:1 ratio of *E*- and *Z*-linear isomers was formed.[14]

Having established that a broad range of terminal alkynes could undergo efficient hydrothiolation with high regioselectivity, we were poised to investigate the scope of thiols that could participate in the reaction (Table 3). Both sterically undemanding (entries 1 and 2) and bulky thiols (entry 3) provide the corresponding branched vinyl sulfide in good yields. Consistent with our findings regarding alkynyl substituents, a variety of functional groups are tolerated in the reaction,

TABLE 3. Scope of Hydrothiolation of Phenylacetylene with Different Thiols Catalyzed by I

entry[a]	R	product, yield[b]
1[c]	Ph	**1a**, 90%
2[d]		**19a**, 74%
3[c]		**20a**, 78%
4		**21a**, 75%
5	PhO	**22a**, 70%
6	BuO	**23a**, 80%
7[e]	Me_2N	**24a**, 65%
8[e]	HO_2C	0%
9[e]		0%

[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:$PhCH_3$, and 0.3 mmol (3 mol %) catalyst, at rt for 2 h, unless otherwise noted. [b] Isolated yields. [c] Reference 7. [d] Reference 2f. [e] Reaction time: 24 h.

including heteroaromatic groups, ethers, esters and unprotected amines (entries 4−7, respectively). In contrast, the use of a thiol bearing either a carboxylic acid moiety (entry 8) or an allyl group (entry 9) was not tolerated. In the latter case, the olefin must play some role in suppressing catalysis, as *n*-propylthiol reacts uneventfully (entry 2). Had the allyl-substituted thiol successfully reacted, the product could be susceptible to a number of possible subsequent transformations, including thio-Cope[15] and Mislow-Evans[16] rearrangements (upon oxidation to the sulfoxide). As such, we sought an explanation for the lack of reactivity of allyl mercaptan under these reaction conditions.

To gain further insight into this issue, we conducted the following stoichiometric reaction. Tp*Rh(PPh_3)$_2$ (93 mg, 0.1 mmol) was dissolved in d_8-toluene (1 mL). The resulting solution was added by pipet to an NMR tube, and allyl mercaptan (0.08 mL, 1.0 mmol) was added by syringe. The reaction was monitored by both ^{1}H and ^{31}P NMR spectroscopy. Within 30 min, the PPh_3 resonance of Tp*Rh(PPh_3)$_2$ (δ 42.92, d, J = 175.6 Hz) disappeared and a new singlet emerged at δ −4.56, indicating complete dissociation of PPh_3. The thiol methylene signal changed from doublet of doublets (δ 3.16, J = 7.0 Hz, J = 7.0 Hz) to a doublet (δ 2.78, J = 6.9 Hz) with concomitant loss of the thiol S−H signal. No rhodium hydride species were observed in the ^{1}H NMR spectrum. Although we were unable to isolate this new species, the data are consistent

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with the formation of a rhodium dithiolate that is inactive in hydrothiolation. Such a species has been identified by Mizobe and co-workers in related hydrothiolation studies.[17] Consistent with this analysis, a small amount of diallyldisulfide was formed, as evidenced by comparison of the ^{1}H NMR spectrum with an authentic sample. Our hypothesis is that the presence of the olefin of allyl mercaptan, in comparison to *n*-propanethiol, which undergoes productive hydrothiolation, provides additional stability to the resulting rhodium species, precluding catalysis. Alternatively, the olefin may result in the rhodium complex following an entirely different pathway than other thiols. We are currently investigating the detailed reaction mechanism to provide additional information about this surprising result.

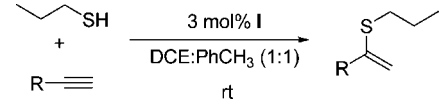
We have also found that addition of 1 equiv of allyl mercaptan to a typical reaction of benzylthiol, phenylacetylene and Tp*Rh(PPh$_3$)$_2$ completely shuts down catalysis. This result indicates that the reaction of allyl mercaptan with Tp*Rh(PPh$_3$)$_2$ is more rapid than hydrothiolation and is also irreversible. This is consistent with poisoning of the catalyst by allyl mercaptan. We therefore considered the possibility that the carboxylic acid (entry 8) could also be poisoning the catalyst. However, addition of 1 equiv of acetic acid to a typical reaction of benzylthiol, phenylacetylene and Tp*Rh(PPh$_3$)$_2$ had no effect on catalysis; it is worth noting that we have previously found that neither organic nor mineral acids catalyze hydrothiolation.[8] Thus, our hypothesis is that the lack of reactivity of is due to coordination of the carboxylic acid.

The catalytic hydrothiolation of *n*-propanethiol and various alkynes was also investigated.[2f] Consistent with expectation, all reactions proceeded with high selectivity. Likewise, the reaction of *para*-substituted phenylacetylenes followed the same trends observed for benzyl thiol, with electron-rich alkynes reacting rapidly and electron-deficient alkynes proceeding more slowly and in lower yields (Table 4, entries 1−4). Both aliphatic alkynes examined reacted in high isolated yields and with high selectivity (entries 5−7). The resulting *n*-propyl vinyl sulfides have proven to be suitable substrates for Kumada-type cross-coupling to generate 1,1-disubstituted olefins.[2f,18]

We next explored the catalytic hydrothiolation of internal alkynes. Unlike terminal alkynes, which react rapidly within 2 h at rt, hydrothiolation of internal alkynes typically requires elevated temperatures and/or extended reaction times (Table 5). For example, cyclopentylthiol reacted with diphenylacetylene to provide the corresponding vinyl sulfide as a single isomer in 94% yield (entry 1). In contrast, the reaction of benzylthiol only produced trace amounts of the expected product (entry 2). When 3-hexyne was used as the alkyne, an additional complication arose. The desired vinyl sulfide was obtained in only 32% yield (entry 3); hexaethylbenzene, was formed by cyclotrimerization in 20% yield.[19] Elevated temperatures did not facilitate the reactions shown in either entries 2 or 3. The reaction of an unsymmetrical internal alkyne proceeded with modest regioselectivity in favor of the less-hindered isomer (entry 4).

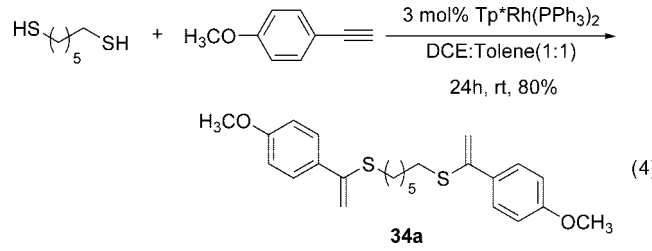
Our final goal was to demonstrate the viability of a bis-thiol to undergo hydrothiolation. 1,6-Hexanedithiol reacted with 2.2 equiv of 4-ethynylanisole in the presence of 3 mol % of Tp*Rh(PPh$_3$)$_2$ to generate the desired product in 80% isolated yield after 24 h at rt (eq 4). No evidence for formation of the monofunctionalized vinyl sulfide was detected.

TABLE 4. Scope of Hydrothiolation of Different Alkynes with *n*-Propanethiol Catalyzed by I



entry[a,b]	R	time (h)	product, yield[c]
1	Ph-	2	**19a**, 74%
2	H$_3$CO-	2	**25a**, 72%
3	Br-	16	**26a**, 69%
4	F$_3$C-	16	**27a**, 15%
5	NC-	16	**28a**, 86%
6		2	**29a**, 83%
7	*n*-C$_6$H$_{13}$-	16	**30a**, 86%

[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:PhCH$_3$, and 0.3 mmol (3 mol %) catalyst, rt. [b] Reference 2f. [c] Isolated yields.



(4)

In conclusion, Tp*Rh(PPh$_3$)$_2$ successfully catalyzes the hydrothiolation a wide variety of thiols and alkynes, including both terminal and internal alkynes. In general, the reactions proceed in good to excellent yields, and the branched isomer is predominates in most cases. A broad range of functional groups are tolerated, including halides, amines, nitriles, amines, ethers, esters and silanes. Strongly coordinating groups, such as pyridine, hinder catalysis. Our current efforts are focused on delineating the reaction mechanism, exploring the use of this methodology in the synthesis of bioactive molecules and generating catalysts capable to promoting hydrothiolation of recalcitrant substrates.

Experimental Section

Materials and Methods. Hexanes (boiling range 68.3−69.6 °C), CH_2Cl_2, benzene, DCE (1,2-dichloroethane), Et_2O, THF and $PhCH_3$ were dried by passage through solvent purification columns.[20]

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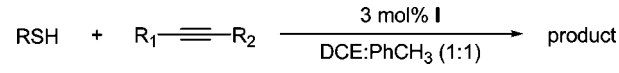
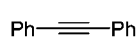
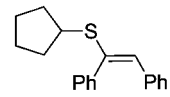
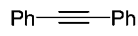
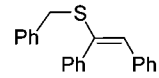
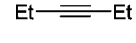
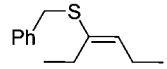
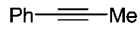
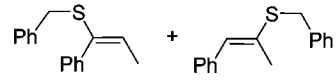
TABLE 5. Scope of Hydrothiolation of Internal Alkynes Catalyzed by I



entry[a]	R	alkyne	temperature, time	product	yield[b]
1[c]			80 °C, 24 h		**31a**, 94%
2			rt, 24 h		trace
3			rt, 24 h		**32a**, 32%[d]
4[c]			50 °C, 4 h		**33a:33b**[e]= 1:3.5,70%[d]

[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:$PhCH_3$, and 0.3 mmol (3 mol %) catalyst. [b] Isolated yields. [c] Reference 7. [d] Yield based on ^1H NMR analysis. [e] Note that **33b** is identical to **10a″** (eq 3).

$CDCl_3$ was distilled from P_2O_5 and was degassed prior to use. C_6D_6 was purified by vacuum transfer from Na/benzophenone. All organic reagents were obtained from commercial sources and used as received. Wilkinson Catalyst was purchased from Strem Chemicals and was used without further purification. $Tp^*Rh(PPh_3)_2$ (**I**)[21] was prepared as previously reported.[9]

General Experimental Procedure for Hydrothiolation. $Tp^*Rh(PPh_3)_2$ (280 mg, 0.30 mmol, 3 mol %), $PhCH_3$ (2 mL), DCE (2 mL) were combined in the glovebox in a 20 mL vial equipped with a magnetic stir bar and a screw cap. Thiol (11 mmol) and alkyne (10 mmol) were added sequentially. The vial was removed from the glovebox. The vial was then wrapped in aluminum foil and the solution was stirred at room temperature and monitored by TLC. After the reaction was completed, the resulting mixture was filtered through silica gel, washed by hexanes, concentrated under vacuum. Flash chromatography (SiO_2, hexanes or a mixture of hexanes: EtOAc as eluent) provided the product. Note: The reactions proceed very slowly in the absence of the catalyst, indicating that background reactions are minimal. The addition of a non-nucleophilic base (2,2-lutidine) does not impede or improve the reaction.[8] Analytical data for **2a**, **4a**, **13a**, **15a**, **16a**, **19a**, **20a**, **31a**, and **33a,b** were previously reported.[8] Representative examples of data for new compounds are given below.

Benzyl(1-(4-*N*,*N*-dimethyphenylvinyl)sulfane (1a). Yellow oil. Column chromatography conditions: 20:1 hexanes:EtOAc and 3% Et_3N. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, 2H, J = 8.7 Hz), 7.31−7.23 (m, 5H), 6.71 (d, 2H, J = 9.1 Hz), 5.36 (s, 1H), 5.08 (s, 1H), 3.90 (s, 2H), 2.99 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 149.3, 145.7, 138.5, 129.9, 129.4, 129.1, 128.2, 128.0, 113.0, 110.1, 41.5, 38.2. HRMS (EI) *m*/*z* calcd for $C_{17}H_{19}SN$: 269.1238; found: 269.1236. Anal. calcd for $C_{17}H_{19}SN$: C, 75.79; H, 7.11; N, 5.20; found: C, 75.72; H, 7.16; N, 5.53.

2-((1-Phenylvinylthio)methyl)furan (21a). Yellow oil. Column chromatography conditions: 20:1 hexanes:EtOAc. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56−7.53 (m, 2H), 7.39−7.33 (m, 4H), 6.29−6.27 (m, 1H), 6.10 − 6.09 (m, 1H), 5.49 (s, 1H), 5.31 (s, 1H), 3.88 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 150.8, 144.4, 142.2, 139.2, 128.6, 128.5, 127.5, 113.5, 110.6, 107.8, 31.1. HRMS (EI) *m*/*z* calcd for $C_{13}H_{12}SO$: 216.0609; found: 216.0606. Anal. calcd for $C_{13}H_{12}SO$: C, 72.19; H, 5.59; found: C, 72.45; H, 5.60.

Synthesis of Complex II. In glovebox, a solution of $Tp^*Rh(PPh_3)_2$ (93 mg, 0.1 mmol) in toluene (1 mL) were combined in the glovebox in a 5 mL vial equipped with a screw cap and a magnetic stir bar. 2-pyridylacetylene (0.1 mL, 1.0 mmol) was added by syringe to the solution. The mixture was stirred for 2 h at room temperature, followed by layering with 2 mL hexanes. After 2 days, brown crystals formed. The solution was decanted, and the crystals were washed with 2 × 1 mL of hexanes. The product was dried under reduced pressure to give 50 mg (65%) of an brown crystalline solid. ^1H NMR (CD_2Cl_2, 400 MHz) at 25 °C: δ 8.19 (d, 1H, J = 3.9 Hz) 7.60 (m, 6H),7.42−7.33 (m, 4H), 7.24−7.20 (m, 6H), 7.70−6.90 (m, 2H), 5.71 (d, 2H, J = 8.8 Hz), 5.17 (s, 1H), 2.72 (s, 3H), 2.50 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), δ −14.68 (q, 1H, J_{Rh-H} = 20.5 Hz, J_{P-H} = 17.6 Hz), B−H not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100 MHz): δ 154.5, 150.8, 149.8, 147.8, 145.5, 144.5, 135.9, 135.8, 135.6, 133.8, 133.4, 130.5, 128.2, 128.1, 126.1, 119.7, 107.5, 106.3, 106.1, 16.5, 13.2, 12.9, 12.1. $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 121 MHz): δ 37.69 (J_{Rh-P} = 130.8 Hz). HRMS (EI) *m*/*z* calcd for $C_{40}H_{42}BN_7PRh$: 765.2387; found: 765.2389.

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Supporting Information Available: Analytical data, NMR spectra for all new compounds, and X-ray report for complex **II**. This material is available free of charge via the Internet at http://pubs.acs.org.

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