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Rhodium-Catalyzed Alkyne Hydrothiolation with Aromatic and Aliphatic Thiols

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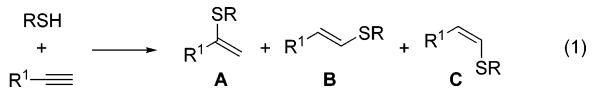
The presence of sulfur in naturally occurring compounds and synthetic materials, coupled with the utility of sulfur-based reagents in synthetic methodology, illustrates the need for efficient and versatile strategies for the construction of molecules containing sulfur.[1] However, because sulfur compounds are often considered to be incompatible with metal-catalyzed reactions, the catalytic reactivity of thiols has been explored to a much lesser extent than that of amines, alcohols, and phosphines. Nevertheless, some catalytic reactions involving thiols have been developed.[2] One such process, alkyne hydrothiolation (eq 1), is an attractive method for the formation of vinyl sulfides, which are valuable as synthetic intermediates in total synthesis[3] and as precursors to a wide range of functionalized molecules.[1,4]



(1)

Radical, nucleophilic, and metal-catalyzed hydrothiolation using aryl thiols is well-precedented,[5−8] but reactions using alkyl thiols are less common. With alkyl thiols, linear products **B** and **C** are accessible under radical[9] and nucleophilic[10] conditions. The branched product **A** can be obtained by Michael addition when the alkyne isomerizes to an allene or internal alkyne;[11] these procedures are consequently limited to certain aliphatic alkynes. Other methods to prepare isomer **A** involve the use of Hg salts or elevated reaction temperatures (>120 °C), which often results in poor regioselectivity.[12] Overall, synthetic approaches to branched alkyl vinyl sulfides (**A**, R = alkyl), which have significant potential for use in synthesis, are very limited.

Although metal catalysts are reportedly ineffective for hydrothiolation using alkyl thiols,[8,9,13,14] we postulated that highly electron-rich metal complexes, such as rhodium pyrazolylborates, would be sufficiently reactive to catalyze these reactions. Despite the efficacy of rhodium pyrazolylborate complexes in stoichiometric transformations involving bond activation,[15] catalytic reactions are comparatively rare.[16] Even so, we reasoned that rhodium pyrazolylborates offer significant promise for catalytic reactions involving bond activation (i.e., S−H activation) as a fundamental step.

Tp*Rh(PPh$_3$)$_2$ [17] (**I**, Tp* = hydrotris(3,5-dimethylpyrazolyl)-borate, Figure 1) was selected for initial study, as this complex is noted for its ability to activate C−H,[15a] Sn−H,[17b] Si−H,[17b] and S−H[15c] bonds. To our delight, a test reaction between benzylthiol and phenylacetylene revealed that **I** is a highly active catalyst, providing the branched isomer as the exclusive product within 20 min and in 90% isolated yield (Table 1, entry 1).

On the basis of this encouraging result, we selected a range of alkyl thiols to probe the influence of steric and electronic perturbations on the efficiency of hydrothiolation catalyzed by **I**. Most reactions proceeded with excellent regioselectivity and good to excellent isolated yields (63−94%), illustrating the outstanding

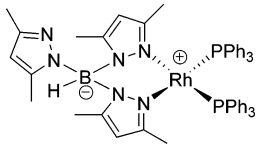


Figure 1. Complex **I**, Tp*Rh(PPh$_3$)$_2$.

reactivity of complex **I**. Notably, these reactions are conducted on 10 mmol scale of limiting reagent, suggesting that even larger scale reactions are feasible. A variety of alkyl thiols underwent hydrothiolation with both aromatic and aliphatic alkynes (entries 1−8). The lower yield with *tert*-butylacetylene is presumably due to steric hindrance of the alkyne, as well as product volatility. With *n*-octyne, selectivity for the branched product is somewhat diminished (branched:linear ratio = 12:1), and the branched product is susceptible to isomerization (entry 8). Internal alkynes also react and require heat for the reactions to proceed efficiently. For example, diphenylacetylene provided a single isomer in 94% yield (entry 9). An unsymmetrical internal alkyne proceeded with modest regioselectivity in favor of the less-hindered isomer (entry 10); Pd catalysts also give poor regioselectivity for hydrothiolation of similar unsymmetrical internal alkynes using aryl thiols.[7a,8a]

Given the high activity of **I** for alkyl thiols, we sought to explore the use of **I** for hydrothiolation reactions involving aryl thiols. The reaction of phenylacetylene with thiophenol was selected for initial study (Table 2, entry 1). A mixture of linear and branched regioisomers was obtained, although the predominant regioisomer using **I** is opposite of that obtained with other Rh complexes.[8] Consequently, **I** generates the same regioisomer that is produced using Pd catalysts. Hydrothiolation with complex **I**, however, occurs much faster and under considerably milder conditions than with the Pd complexes; the reaction using **I** proceeds at room temperature, while the Pd-catalyzed reactions require prolonged times at 80 °C.[7]

Intrigued by the regioselectivity change using Tp* as a ligand for Rh, we examined a series of arylacetylene and aryl thiol substrates (Table 2). Isolated yields were excellent (83−90%), but regioselectivities were modest (6:1 to 1.4:1). In all cases, the major isomer was the branched isomer, which is separable from the minor isomer using column chromatography. The presence of any substituent on the aromatic ring of the alkyne or thiol substrates was detrimental to the regioselectivity of the reaction. This lowered regioselectivity could be indicative of a reversible reaction or change in mechanism. Mechanistic studies are underway to address these possibilities. Monitoring the reactions indicated in entries 1 and 4 revealed that the product ratio remained constant over the course of both reactions. In addition, exposure of the major (branched) product of entry 5 to the catalyst resulted in minimal equilibration (<5%) over 48 h, suggesting that the low regioselectivity is not due to reversibility.

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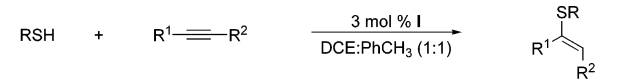
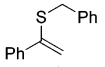
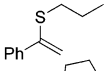
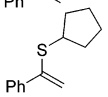
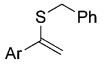
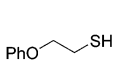
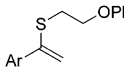
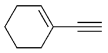
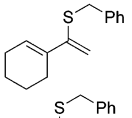
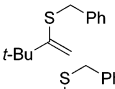
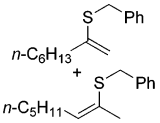
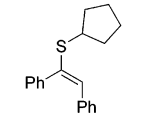
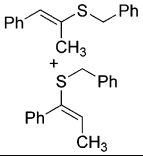
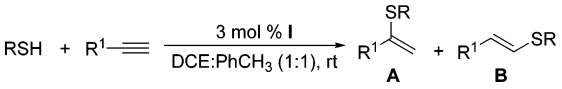
Table 1. Alkyne Hydrothiolation with Alkyl Thiols Using **I**



Entry[a]	Thiol	Alkyne	Product	Cond, Time, Yield[b,c]
1	$PhCH_2SH$	Ph—≡		A, 20 min, 90%
2	*n*-PrSH	Ph—≡		B, 80 min, 87%
3		Ph—≡		A, 2 h, 78%
4	$PhCH_2SH$	*p*-$CH_3OC_6H_4$—≡		B, 80 min, 93%[d,e]
5		*p*-$CH_3OC_6H_4$—≡		A, 2 h, 83%[d]
6	$PhCH_2SH$			A, 10 h, 81%
7	$PhCH_2SH$	*t*-Bu—≡		A, 24 h, 63%
8	$PhCH_2SH$	*n*-C_6H_{13}—≡		A, 16 h, 70% (2:1)[f]
9		Ph—≡—Ph		C, 24 h, 94%
10	$PhCH_2SH$	Ph—≡—CH_3		D, 4 h, 70%[g] (3.5:1)

[a] Reaction conditions: 10 mmol alkyne, 11 mmol thiol, 4 mL of 1:1 DCE:$PhCH_3$, and 0.3 mmol (3 mol %) catalyst, unless otherwise noted. [b] Conditions: A = rt; B = 20 min at 0 °C, warmed to 20 °C over 1 h; C = 80 °C, D = 50 °C. [c] Isolated yields. [d] Ar = $CH_3OC_6H_4$. [e] Branched:linear ratio 19:1. [f] Branched:linear ratio 12:1. [g] Yield based on ^1H NMR analysis.

Table 2. Hydrothiolation of Aryl Alkynes with Aryl Thiols Using **I**



Entry[a]	RSH	R^1	Time (h)	Yield (%)[b]	A:B[c]
1	Ph	Ph	2	84	6:1
2	Ph	*p*-$CH_3OC_6H_4$	10	89	3.2:1
3	Ph	*o*,*p*-$F_2C_6H_3$	2	90	2.6:1
4	*p*-$CH_3C_6H_4$	Ph	1.5	83	1.4:1
5	*p*-BrC_6H_4	Ph	23	85	1.7:1

[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] Trace amounts of **C** observed.

In summary, we have found that Tp*Rh(PPh_3)$_2$ (**I**) catalyzes the hydrothiolation of a range of alkynes with both aryl and alkyl thiols. The reactions with alkyl thiols proceeded with excellent regioselectivity, providing convenient access to branched alkyl vinyl sulfides, which are difficult to synthesize by other means. Hydrothiolation reactions with aryl thiols were less selective, providing a mixture of branched and linear products. Although no trend is apparent with aryl thiols, we anticipate that mechanistic studies will provide insight into the regioselectivity of this process. In addition, we are currently exploring the origin of the typically high selectivity with alkyl thiols relative to aryl thiols. We are also exploring the use of **I** in other catalytic processes involving X−H activation.

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Supporting Information Available: Complete experimental details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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