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# Highly Stereoselective Palladium-Catalyzed Dithiocarbonylation of Propargylic Mesylates with Thiols and Carbon Monoxide

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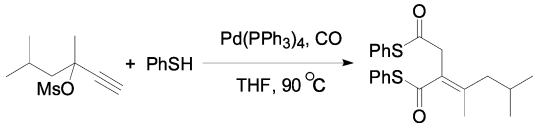


Highly stereoselective dithiocarbonylation of propargylic mesylates with thiols and carbon monoxide has been developed by the use of tetrakis(triphenylphosphine)palladium(0) as the catalyst at 90 °C in THF. The reaction affords the corresponding dithioesters in good to excellent yields. For some secondary and tertiary propargylic alcohols with a terminal or internal triple bond, the reaction stereoselectively produces *E*-dithioesters as products. The dithiocarbonylation is believed to proceed via allenylpalladium and allenyl ester intermediates, and the high stereoselectivity might be rationalized by a mechanism where nucleophilic attack of a Pd(0)$L_n$ species on the allenyl sp carbon occurs from the less hindered side of an alkyl substituent.

## Introduction

Transition-metal-catalyzed carbonylation is widely recognized as one of the most important carbonyl-forming reactions in organic synthesis.[1] Examples include the carbonylation reactions of alcohols,[2] amines,[3] carbon nucleophiles,[4] and organometallic reagents[5] with other substrates, affording esters, amides, ketones, and aldehydes, respectively. Although a large number of catalytic systems have been developed for the carbonylation of a wide range of compounds, carbonylation chemistry has still not achieved its full potential. The search for the improvement of carbonylation technology continues, with the goal of increasing the diversity of possible substrates and reaction products.[6] For example, the development of transition-metal-catalyzed carbonylation involving the formation of a thiocarbonyl unit and employing organosulfur compounds, especially thiols and thiophenols, as a direct substrate represents a challenging subject in transition-metal-catalyzed reactions, because the strong thiophilicity of transition metals[7] may make catalytic reactions ineffective.[8] As part of our continuing studies of the scope of transition-metal-catalyzed carbonylation

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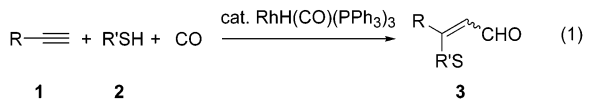
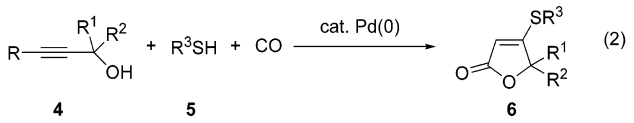
reactions, we investigated some interesting transformations employing organosulfur compounds as substrates. Thus, we developed the $Co_2(CO)_8$-catalyzed desulfurization and carbonylation of organosulfur agents,[9] demonstrating that sulfur compounds are compatible with cobalt. Subsequently, Uemura, Ohe, and co-workers reported the $Co_2(CO)_8$-catalyzed carbonylation of organic diselenides or ditellurides.[10] Remarkably, however, this reaction remained largely underdeveloped for eight years before Ogawa and co-workers were able to demonstrate the first example of $RhH(CO)(PPh_3)_3$-catalyzed "thioformylation" of acetylenes with thiols and carbon monoxide (eq 1).[11]



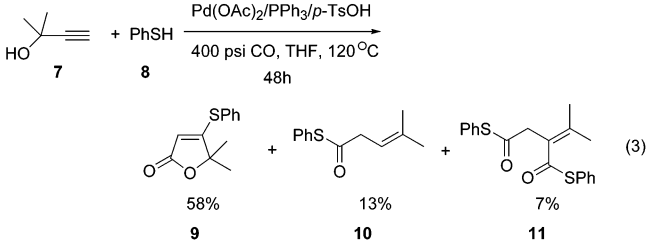

Recently, the groups of Ogama and Hirao, as well as our own, have discovered a series of carbonylation reactions of various organosulfur compounds with other substrates.[12] For example, thiols react with propargyl alcohols in the presence of a palladium(0) catalyst to afford $\beta$-(arylthio)-α, $\beta$-unsaturated lactones, as shown in eq 2.[12a]




Other examples developed in the past few years include the thioboration,[13] thiosilylation,[14] thiophosphorylation,[15] thioesterification,[16] S-propargylation,[17] and carbothiolation[18,19] of unsaturates. These findings have corrected the widely accepted concept that "sulfur compounds are poisons to transition metal catalysts". Contrary to the monocarbonylation of unsaturated substrates, catalytic dicarbonylation[20] is relatively rare due to the requirement of harsh reaction conditions. To our knowledge, the transition-metal-catalyzed dithiocarbonylation of thiols has not been realized. Herein, we report the first examples of palladium-catalyzed dithiocarbonylation of thiols with propargylic mesylates.

## Results and Discussion

Initial studies were focused on examining the feasibility of the dicarbonylation reaction, and optimizing reaction conditions that could be applied to a variety of propargylic compounds and thiols. On the basis of knowledge gained from previous findings,[12] 2-methylbut-3-yn-2-ol (**7**) and thiophenol (**8**) were first used as substrates. The reaction between **7** (1 equiv) and **8** (2 equiv) was initially carried out in THF at 120 °C for 48 h in the presence of $Pd(OAc)_2$ (3 mol %), $PPh_3$ (12 mol %), and *p*-TsOH (5 mol %) under an atmosphere of 400 psi CO, leading to complete conversion of substrate **7** (eq 3).




The reaction gave promising results, with three products, **9**, **10**, and **11**, obtained, including the dithiocarbonylation product **11**, which was isolated in 7% yield. Encouraged by this result, we pursued alternate reaction conditions and substrates in order to form **11** as the sole product. We also tried to understand how **9** and **10** were formed (eq 3) so as to minimize their formation. A possible catalytic cycle for the formation of the thiolactonization product **9** is outlined in Scheme 1.

By analogy to the hydrothiolation of rhodium[21] and platinum[22] complexes, the thiolactonization reaction may also start by oxidative addition of thiophenol to Pd(0) to form the phenylthiopalladium complex **12**, which then

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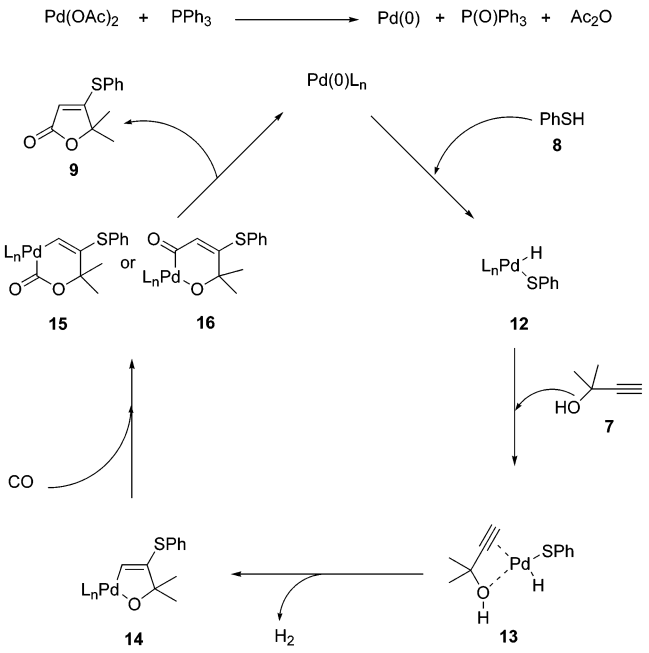
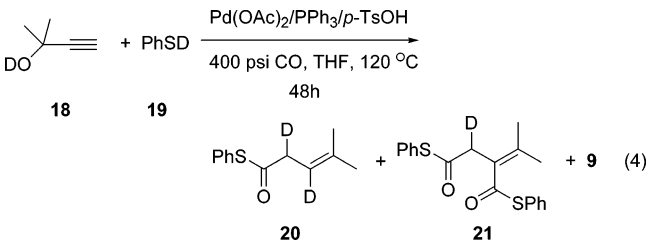
**SCHEME 1. A Possible Catalytic Cycle for the Formation of 9**



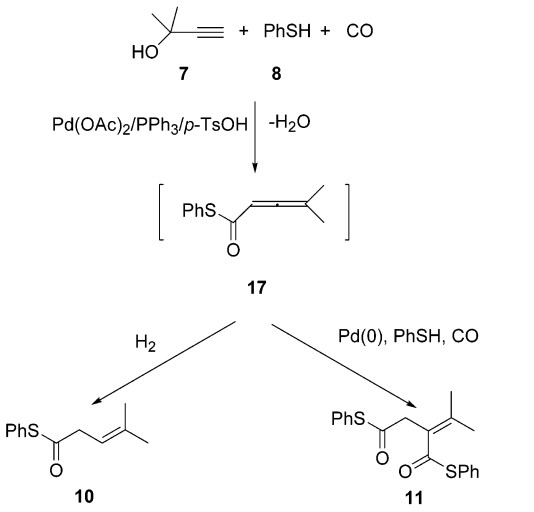

coordinates with the electron-rich carbon−carbon triple bond and the hydroxyl group of the propargylic alcohol to form complex **13**. Subsequent insertion of the triple bond into the Pd−S bond (intramolecular cyclization) and elimination of hydrogen would form the palladocycle **14**. The introduction of carbon monoxide into either the palladium−carbon bond or the palladium−oxygen bond could give the acylpalladium intermediate **15** or **16**, and then reductive elimination would afford the $\beta$-phenylthio-$\gamma$-lactone **9** as well as regenerate the active catalyst species. Note that the generation of $H_2$ is probably the key to the formation of the monothiocarbonylation product **10**. We believe that both **10** and **11** may arise from intermediate **17**, which reacts further with either thiophenol and carbon monoxide to form the dithiocarbonylation product **11**, or hydrogen to afford the reduction product **10** (Scheme 2).

Although we did not study the possible mechanisms in detail, we did find that the yield of **10** could be dramatically increased if we employed a mixture of CO and $H_2$ (1:1, 800 psi) for the reaction. Furthermore, the reaction of deuterated thiophenol and 2-methylbut-3-yn-2-ol under the same conditions afforded the deuterated product **20** (eq 4).




(4)

**SCHEME 2. Thiocarbonylation of Propargylic Alcohol to Mono- and Dithioesters**




According to these experimental results and the mechanistic analysis, we believed that propargylic alcohols were not the ideal substrates for the dithiocarbonylation and we envisioned that the dithiocarbonylation of propargylic mesylates with thiols and carbon monoxide should be carried out instead.

All propargylic mesylates were prepared from the corresponding alcohols by modification of a published procedure.[23] Using n-BuLi as the base, in place of triethylamine, greatly improved the yields of the mesylates. The reaction of 1,1-dimethyl-prop-2-ynyl mesylate (**22a**) and thiophenol (**8**) with carbon monoxide was chosen as the model reaction, and we then examined the effect of varying the catalyst, ligand, solvent, base, and reaction temperature on this reaction.

Table 1 shows the results of the reaction using several palladium catalysts and mono- or bis-phosphine ligands, with or without $Et_3N$. Among the catalytic systems examined, palladium(0) complexes, such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$, exhibit high activity for the dithiocarbonylation reaction (Table 1, entries 9−12). In particular, the use of 3 mol % $Pd(PPh_3)_4$ (relative to 1,1-dimethyl prop-2-ynyl mesylate) was the most effective catalyst, resulting in the formation of **11** in 88% yield (Table 1, entry 10). Palladium acetate with mono- or bidentate phosphine ligands can also catalyze the dithiocarbonylation; however, it catalyzes the reaction at a slower rate with lower efficiency (Table 1, entries 1−8). The base, triethylamine, does not affect the reaction (Table 1, entries 1, 3, and 9). Therefore, it was decided to use $Pd(PPh_3)_4$ as the catalyst and to examine the effect of different solvents, reaction pressures, and temperatures on the dithiocarbonylation reaction.

It can be concluded from the results summarized in Table 2 that the reaction is significantly influenced by the solvent, temperature and pressure. For example, the dithiocarbonylation works very well in THF and $CH_2Cl_2$ and gives the dithioester **11** in 88 and 86% isolated yields, respectively (Table 2, entries 1 and 3); however, under the same conditions, using $CH_3CN$ as the solvent, the

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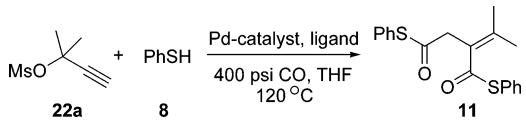
**TABLE 1. Optimization of Catalyst Systems for the Palladium-Catalyzed Dithiocarbonylation[a]**

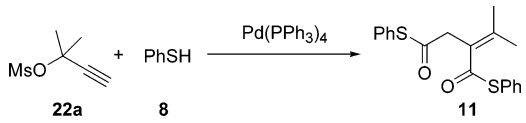



22a 8 11

| entry | catalyst | ligand | base | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$ | $Et_3$ | 48 | 57 |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | none | 48 | 53 |
| 3 | $Pd(OAc)_2$ | $PCy_3$ | $Et_3N$ | 48 | 42 |
| 4 | $Pd(OAc)_2$ | $PCy_3$ | none | 48 | 41 |
| 5 | $Pd(OAc)_2$ | $PBu_3$ | none | 36 | 52 |
| 6 | $Pd(OAc)_2$ | dppb | none | 30 | 58 |
| 7 | $Pd(OAc)_2$ | dppp | none | 36 | 60 |
| 8 | $Pd(OAc)_2$ | dppe | none | 48 | 55 |
| 9 | $Pd(PPh_3)_4$ | $PPh_3$ | $Et_3$ | 24 | 86 |
| 10 | $Pd(PPh_3)_4$ | none | none | 24 | 85 |
| 11 | $Pd(PPh_3)_4$ | $PPh_3$ | none | 24 | 85 |
| 12 | $Pd_2(dba)_3CHCl_3$ | none | none | 24 | 75 |

[a] Reaction conditions: thiophenol (4 mmol), 1-1-dimethyl prop-2-ynyl mesylate (2 mmol), Pd catalyst (0.06 mmol), $PPh_3$, $PCy_3$, or $PBu_3$ (0.24 mmol, in the case of $Pd(OAc)_2$ (if used), or 0.06 mmol in the case of $Pd(PPh_3)_4$ (if used)), 1,4-Bis(diphenylphosphino)butane (dppb), 1,3-bis(diphenylphosphino)propane (dppp), or 1,2-bis(diphenylphosphino)ethane (dppe) (0.12 mmol, if used), CO (400 psi), THF (10 mL) 120 °C. [b] Isolated yield.

**TABLE 2. Influence of Solvents, Reaction Pressure, and Temperature on the Dithiocarbonylation Reaction[a]**




22a 8 11

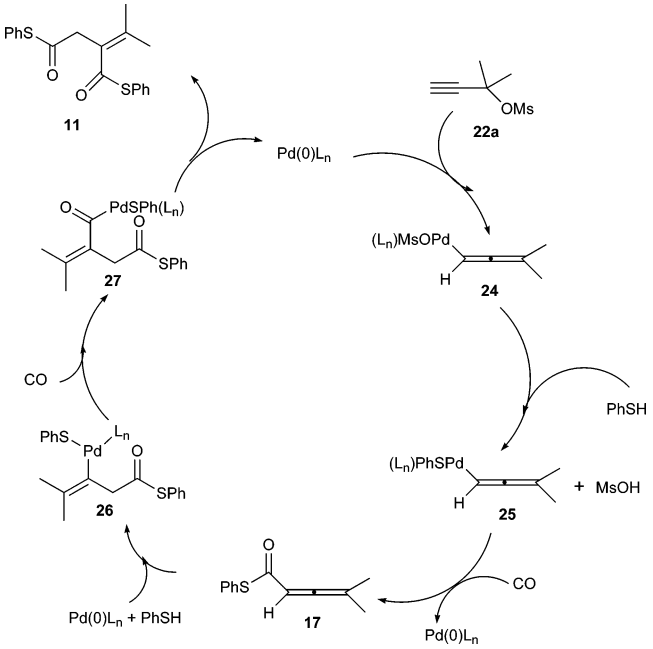
| entry | solvent | pressure (psi) | *T* (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | THF | 400 | 120 | 48 | 88 |
| 2 | benzene | 400 | 120 | 48 | 79 |
| 3 | $CH_2Cl_2$ | 400 | 120 | 48 | 86 |
| 4 | toluene | 400 | 120 | 48 | 67 |
| 5 | $Et_2O$ | 400 | 120 | 48 | 73 |
| 6 | $CH_3CN$ | 400 | 120 | 48 | 58 |
| 7 | THF | 600 | 120 | 36 | 87 |
| 8 | THF | 800 | 120 | 30 | 82 |
| 9 | THF | 200 | 120 | 48 | 37 |
| 10 | THF | 400 | 120 | 48 | 88 |
| 11 | THF | 400 | 100 | 48 | 85 |
| 12 | THF | 400 | 90 | 48 | 88 |
| 13 | THF | 400 | 80 | 55 | 34 |

[a] Reaction conditions: thiophenol (4 mmol), 1,1-dimethyl prop-2-ynyl mesylate (2 mmol), $Pd(PPh_3)_4$ (0.06 mmol), CO (400−800 psi) solvent (10 mL), 80−120 °C. [b] Isolated yield.

yield of **11** decreased to 58% (Table 2, entry 6). Other solvents, such as benzene, toluene, and diethyl ether, can be employed as the solvent for the dithiocarbonylation, but none of them appears to be as effective as THF (Table 2, entries 2, 4, and 5).

We did not rigorously examine the effect of CO pressure on the dithiocarbonylation; however, we found that the reaction proceeded well when the pressure of CO was 400−600 psi (Table 2, entries 1 and 7). When the pressure of CO was reduced to 200 psi, only 37% of **11** was isolated (Table 2, entry 9). Increasing the pressure of CO to 800 psi did increase the reaction rate, but the yield of **11** decreased to 82% (Table 2, entry 8). Thus, in subsequent studies, 400 psi of carbon monoxide was usually used, consistent with our previous experience with other thiocarbonylation reactions.[12a−g]

**SCHEME 3. Possible Mechanism for the Dithiocarbonylation of Propargylic Mesylates**



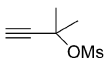
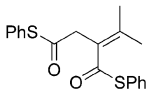
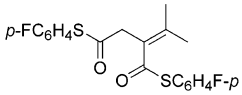
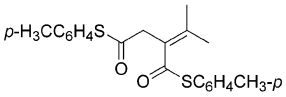
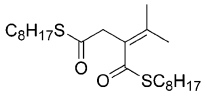
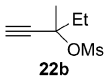
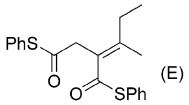
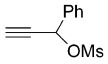
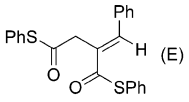
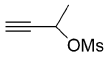
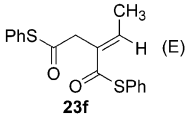
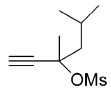
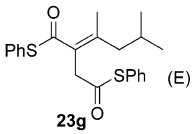
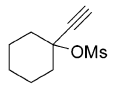
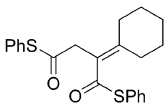
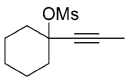
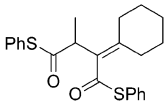
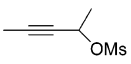
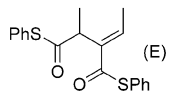
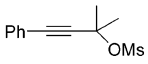
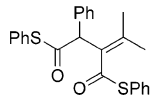
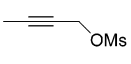
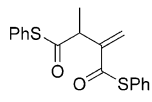

The reaction temperature is another critical factor for the successful dithiocarbonylation, with the best result being reached at 90 °C (Table 2, entry 12). Increasing the temperature from 90 to 120 °C did not change the reaction yield (Table 2, entries 1, 10, 11, and 12); however, decreasing the temperature to 80 °C gave only the dithiocarbonylation product in 34% yield after 55 h (Table 2, entry 13).

The dithiocarbonylation reaction of a series of propargylic mesylates (**22a**−**j**) was effected using 2 equiv of various thiols and 3 mol % of $Pd(PPh_3)_4$ in THF at 400 psi CO for 48 h at 90 °C, and representative results are summarized in Table 3. Under these conditions, the reaction proved to be general for substrates containing different substituents. Arenethiols and alkanethiols can be successfully employed in the reaction (Table 3, entries 1−5) together with primary, secondary, and tertiary propargylic mesylates (Table 3, entries 5−13). It is noteworthy that propargylic mesylates containing terminal or internal carbon−carbon triple bonds with alkyl, cycloalkyl, or phenyl substituents reacted with similar efficiency (Table 3, entries 5−13). For some secondary and tertiary propargylic mesylates, with a terminal or internal triple bond, the reaction stereoselectively afforded *E*-dithioesters as the products (Table 3, entries 5−8 and 11). The *E* configuration for the double bond of these compounds was assigned on the basis of NOESY experiments.

The reaction may proceed by the mechanism proposed in Scheme 3. The first step of the catalytic reaction may be oxidative addition of the propargylic mesylate (**22a**) to the Pd(0) species to form a coordinatively unsaturated Pd(II) intermediate **24**.[24] Ligand exchange would afford a thiopalladium complex **25**, followed by CO insertion and reductive elimination to generate **17**. It is expected that

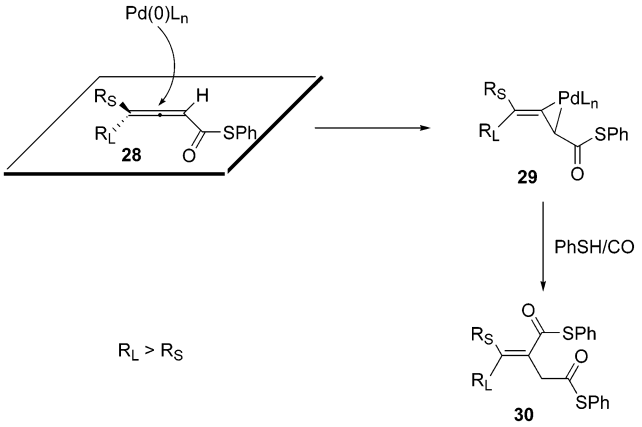
(24) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 81.

**TABLE 3. Palladium-Catalyzed Dithiocarbonylation of Propargylic Mesylates**[a]

| entry | alcohol | thiol | product | yield(%)[b] |
|---|---|---|---|---|
| 1 |  **22a** | PhSH **8** |  **11** | 88 |
| 2 | **22a** | *p*-$FC_6H_4SH$ **9a** |  **23a** | 91 |
| 3 | **22a** | *p*-$CH_3C_6H_4SH$ **9b** |  **23b** | 73 |
| 4 | **22a** | $C_8H_{17}SH$ **9c** |  **23c** | 74 |
| 5[c] |  **22b** | **8** |  **23d** | 72 |
| 6[c] |  **22c** | **8** |  **23e** | 63 |
| 7[c] |  **22d** | **8** |  **23f** | 88 |
| 8 |  **22e** | **8** |  **23g** | 76 |
| 9 |  **22f** | **8** |  **23h** | 57 |
| 10 |  **22g** | **8** |  **23i** | 64 |
| 11 |  **22h** | **8** |  **23j** | 70 |
| 12 |  **22i** | **8** |  **23k** | 67 |
| 13 |  **22j** | **8** |  **23l** | 62 |

[a] Reaction conditions: propargylic mesylates (2 mmol), thiol (4 mmol), $Pd(PPH_3)_4$ (0.06 mmol), 400 psi of CO, THF (10 mL), 90 °C. [b] Isolated yield. [c] The stereochemistry was assigned as *E* by NOE experiments.

**SCHEME 4. Possible Mechanism for the Formation of *E*-Dithioesters**




compound **17** would be susceptible to Michael type addition of Pd(0)$L_n$ to the allenyl *sp* carbon[25] followed by reaction with thiophenol in the presence of Pd (0), resulting in the formation of **26**. Finally, the dithiocarbonylation product (**11**) resulted by a second CO insertion into **26**, and subsequent reductive elimination of Pd(0) from the acyl palladium complex **27**.

The formation of **17**, although not detected directly, could be supported by the observation that the *E* geometry was obtained for the dithioesters as shown in entries 5−8 and 11 of Table 3, respectively. Such high stereoselectivity might be rationalized by a mechanism where nucleophilic attack of a Pd(0)$L_n$ species on the allenyl sp carbon occurred from the less hindered side of an alkyl-substituted ($R_s$) (Scheme 4).

## Conclusions

In summary, this research has resulted in the stereoselective carbonylation reaction of propargylic mesylates with thiols and carbon monoxide catalyzed by a palladium complex, to form dithioesters in good to excellent yields. To our knowledge, this is the first example of a dithiocarbonylation employing thiols as direct reactants. Not only is this methodology attractive for the one-pot synthesis of dithioesters, but it also further demonstrates the utility of transition-metal catalysts for the synthesis of sulfur compounds.

(25) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

## Experimental Section

**Typical Procedure for the Palladium-Catalyzed Dithiocarbonylation of Propargylic Mesylates with Thiols.** An autoclave, its glass liner, and a magnetic stirring bar were dried in an oven and cooled in a drybox. The liner was charged with $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol). The propargylic mesylate (2 mmol), thiol (4 mmol), and 10 mL of THF were then added to the liner. An additional amount of THF (1−2 mL) was placed in the autoclave prior to insertion of the liner. The gauge and gauge block assembly were attached. The CO line was flushed three times with CO, and the system was also pressurized and flushed three times with CO, gradually increasing the pressure to 400 psi. The autoclave was then placed in the center of an oil bath on a heater stirrer preset to 90 °C. After 48 h, the autoclave was removed from the oil bath and allowed to cool to room temperature. The excess gas was discharged and the system disassembled. The reaction mixture was filtered through Florisil and washed with diethyl ether. The solvent was removed by rotary evaporation under reduced pressure. The residue was separated by preparative TLC (silica gel, eluant: *n*-hexane/ethyl acetate 9:1).

**2-Isopropylidenedithiosuccinic acid di-*S*-phenyl ester (11):** oil; IR (neat) 1703, 1676 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.92 (s, 3H), 2.14 (s, 3H), 3.81 (s, 2H), 7.40−7.55 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 23.8, 23.9, 45.3, 118.4, 129.7, 129.8, 130.0, 130.1, 132.6, 133.7, 134.8, 134.9, 135.4, 138.45, 148.6, 192.5, 195.2; MS (EI) *m/z* 342 ($M^+$); HRMS calcd for $C_{19}H_{18}O_2S_2$ 342.0748, found 342.0741. Anal. Calcd for $C_{19}H_{18}O_2S_2$: C, 66.65; H, 5.30. Found: C, 66.72; H, 5.48.

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**Supporting Information Available:** Analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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