Highly Regioselective Thiocarbonylation of Allylic Alcohols with Thiols and Carbon Monoxide Catalyzed by Palladium Complexes: A New and Efficient Route to β,γ-Unsaturated Thioesters

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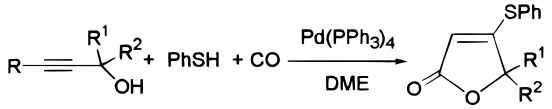
The reaction of allylic alcohols with thiols and carbon monoxide in the presence of catalytic quantities of $Pd(OAc)_2$ (3 mol %), triphenylphosphine (12 mol %), and *p*-TsOH (5 mol %) leads to a novel thiocarbonylation to afford β,γ-unsaturated thioesters in good to excellent yields. Other palladium catalyst systems such as $Pd_2(dba)_3{\cdot}CHCl_3-PPh_3-p$-TsOH, $Pd(PPh_3)_4-p$-TsOH, and $Pd(OAc)_2-$dppb−*p*-TsOH are also effective for this transformation. The thiocarbonylation reaction is believed to proceed via a allylpalladium intermediate. The reaction occurs highly regioselectively at the least hindered allylic terminal carbon of the substrate to give the products. This new carbonylation procedure was readily applied to a variety of allylic alcohols and both aromatic and aliphatic thiols.

Introduction

The palladium complex catalyzed carbonylation of allylic compounds has attracted considerable attention in recent years.[1] The reactions are considered to proceed via a π-allylpalladium complex which is formed by the oxidative addition of palladium(0) to various allylic compounds (esters, carbonates, etc.), followed by insertion of carbon monoxide into the palladium−carbon bond. Although reactions using alcohols,[2] amines,[3] carbon nucleophiles,[4] and organometallic reagents[5] to intercept allylpalladium intermediates have been well established, much less attention has been paid to reactions with organic sulfur compounds,[6] in which thiopalladation would be involved. This might be partly because chalcogen compounds often bind strongly to transition metals,[7] thus poisoning the catalysts and inhibiting catalytic reactions.[8] We and other groups have recently described a series of reactions in which chalcogen compounds are employed as the substrates along with transition metal catalysts.[6a−d] For example, thiols react with propargyl alcohols in the presence of a palladium(0) catalyst to afford β-(arylthio)-α,β-unsaturated lactones, as shown in eq 1.[6c] Following this publication, a study showed that the same products were obtained when the reaction was carried out with diaryl disulfides as substrates.[6d] In the case of allenes possessing mono- or disubstitution, the thiocarbonylation is completely regioselective, in which the thiophenyl group adds to the least-substituted double bond of the allene (eq 2).[6a] These reactions demonstrate the utility of transition metal catalysts in the reactions



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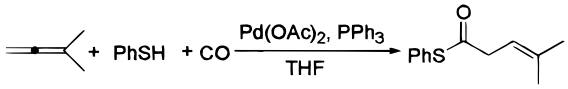

(2)

of sulfur compounds. Reported herein is the carbonylation reaction of allylic alcohols with thiols, another example of organic chalcogen compounds as reactants with a palladium catalyst. While effective methods have been

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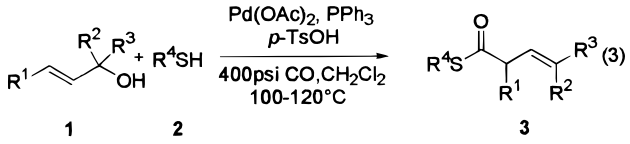
developed for the carbonylation reaction of allyl carbonates,[9] esters,[10] amines,[11] and ethers,[12] few investigations have been made using allyl alcohols as substrates.[13] The present methodology is concerned with allyl alcohols as direct starting materials under quite mild conditions.

There has been considerable interest in the preparation of thioesters.[14] The latter constitute a group of natural products[15] and are also useful building blocks in the synthesis of complex organic molecules.[16] The methodology described herein (eq 3) is a simple and direct route to β,γ-unsaturated thioesters.



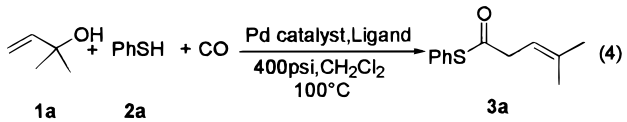
1 2 3 (3)

Results and Discussion

Reaction Conditions for Thiocarbonylation. We chose 2-methyl-3-buten-2-ol (**1a**) as a model substrate and investigated its reaction with thiophenol (**2a**), carbon monoxide, and catalytic quantities of a variety of palladium complexes under different conditions. The effect of different catalytic systems on the thiocarbonylation of **1a** is presented in Table 1.

Among the catalytic systems examined, $Pd(OAc)_2$ with PPh_3 and *p*-toluenesulfonic acid (*p*-TsOH) exhibited excellent catalytic activity to afford the thiocarbonylation product **3a** in 93% isolated yield (Table 1, entry 9). In the absence of catalyst or *p*-TsOH, **3a** was not obtained at all or was formed in very low yield (Table 1, entries 1, 2, 6, and 8). The function of *p*-TsOH is presumably to protonate the hydroxyl group of the substrate so as to eliminate H_2O to form a π-allyl palladium complex. Using HCl in place of *p*-TsOH (Table 1, entry 12), the reaction also afforded **3a**, but the yield was appreciably lower, probably because the poor solubility of HCl in CH_2Cl_2 decreases the degree of protonation of the hydroxyl group.

Table 1. Effects of Palladium Catalysts on the Thiocarbonylation of 1a with Thiophenol and CO in CH_2Cl_2[a]



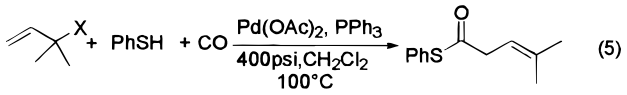
(4)

1a 2a 3a

entry	catalyst	additive	time (h)	temp (°C)	yield (%)[b]
1	none	none	48	100	0
2	$Pd(PPh_3)_4$	none	48	100	8
3	$Pd(PPh_3)_4$	*p*-TsOH	72	100	63
4	$Pd(PPh_3)_4/PPh_3$	*p*-TsOH	48	100	82
5	$Pd(PPh_3)_4$/dppb	*p*-TsOH	48	100	77
6	$Pd(OAc)_2$	none	72	120	0
7	$Pd(OAc)_2$	*p*-TsOH	72	120	0
8	$Pd(OAc)_2/PPh_3$	none	72	120	4
9	$Pd(OAc)_2/PPh_3$	*p*-TsOH	48	100	93
10	$Pd(OAc)_2$/dppb	*p*-TsOH	48	100	88
11	$Pd(OAc)_2$/dppp	*p*-TsOH	48	100	64
12	$Pd(OAc)_2/PPh_3$	HCl	48	100	47
13	$Pd(OAc)_2$/dppe	*p*-TsOH	60	100	17
14	$Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$	*p*-TsOH	60	100	84

[a] Reaction conditions: **1a** (2 mmol), **2a** (2 mmol), catalyst (0.06 mmol), ligand PPh_3 (0.24 mmol), dppb (0.12 mmol), dppp (0.12 mmol) or dppe (0.12 mmol) (if used), *p*-TsOH (0.1 mmol), or HCl (0.1 mmol) (if used), 400 psi CO and CH_2Cl_2 (10 mL). [b] Isolated yield based on thiophenol.

Thiocarbonylation of allylic carbonate **4a** and phosphonate **4b** can be carried out without *p*-TsOH or HCl (eq 5). It further demonstrates that the function of the acid is to assist the elimination of the hydroxyl group.



(5)

4 2a 3a

4a: X = OCO_2CH_3 5hr 91%
4b: X = $OP(O)(OMe)_2$ 8hr 93%

Palladium(0) complexes, such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$ with added phosphine and *p*-TsOH are also excellent catalytic systems for this transformation (Table 1, entries 4, 5, and 14). However, palladium catalysts without added phosphine ligand (Table 1, entries 3 and 7) were less effective for this reaction. The bidentate phosphines, 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb), were also effective as added ligands for the $Pd(OAc)_2$-catalyzed reaction and afford **3a** in 64 and 88% yield, respectively (Table 1, entries 10 and 11), but 1,2-bis(diphenylphosphino)ethane (dppe) is almost ineffective. This can be explained by the fact that CO insertion into a Pd−C bond occurs faster for those alkylpalladium diphosphine complexes containing a more flexible metal−ligand chelate ring.[17]

Table 2 indicates some results of the effects of varying the reaction conditions on the formation of **3a**. Using the $Pd(OAc)_2-PPh_3$/*p*-TsOH catalyst system, we found that the reaction works well in CH_2Cl_2, 1,2-dimethoxyethane (DME), or THF but less so in toluene or diethyl ether (Table 2, entries 1−5). A decrease to 100 psi or increase

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Table 2. Influence of Solvent, Pressure, and Temperature on the Palladium-Catalyzed Thiocarbonylation of 1a with Thiophenol and CO[a]

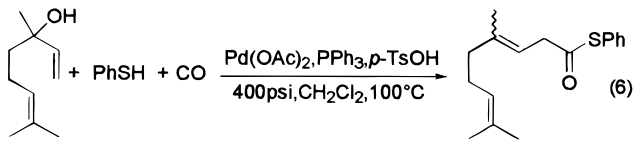
entry	solvent	temp (°C)	pressure (psi)	time (h)	yield (%)[b]
1	CH_2Cl_2	100	400	48	93
2	DME	100	400	48	90
3	THF	100	400	48	90
4	toluene	100	400	48	54
5	ether	100	400	48	47
6	CH_2Cl_2	100	100	60	53[c]
7	CH_2Cl_2	100	800	48	87[d]
8	CH_2Cl_2	50	400	48	61[e]
9	CH_2Cl_2	150	400	48	74
10	CH_2Cl_2	100	400	80	58

[a] Reaction of 2 mmol of **1a** and 2 mmol of PhSH in the presence 0.06 mmol of $Pd(OAc)_2$, 0.24 mmol of PPh_3, and 0.1 mmol of *p*-TsOH. [b] Isolated yield based on thiophenol. [c] 7% of the substitution reaction product, phenyl 3-methyl-2-butenyl sulfide, was formed. [d] 3% of dithiocarbonylation product was isolated. [e] 23% of substrate was recovered.

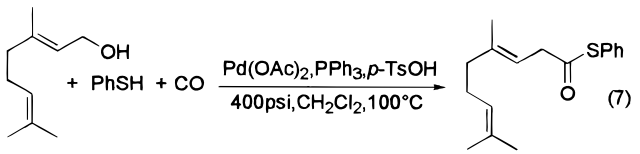
to 800 psi of CO pressures resulted in the formation of byproducts (Table 2, entries 6 and 7). Prolonged heating, 80 h versus 48 h, and increasing or decreasing reaction temperature reduced the yield of **3a** (Table 2, entries 8−10). In addition, use of an excess of **1a** did not change the yield of **3a**, but resulted in lactonization of unreacted alcohol.[18]

Thiocarbonylation of Thiols with Various Acyclic Allylic Alcohols. The carbonylative coupling reaction of a series of acyclic allylic alcohols (**1a**−**n**) was effected using 1 equiv of thiols or mercaptans, 3 mol % of $Pd(OAc)_2$, 12 mol % of PPh_3, and 5 mol % of *p*-TsOH, in CH_2Cl_2 at 400 psi CO for 48 h at 100 °C, affording β,γ-unsaturated thioesters in isolated yields of 56−93% (Table 3). Arenethiols and alkanethiols can be successfully employed in the reaction (Table 3, entries 1−7) together with primary, secondary, and tertiary acyclic allylic alcohols (Table 3, entries 8, 11, and 16). It is noteworthy that allylic alcohols containing terminal or internal C=C bonds with alkyl or phenyl substituents reacted with similar efficiency. The reaction exhibits high regioselectivity, with insertion of carbon monoxide occurring at the least-substituted terminal allylic carbon to give linear rather than branched thioesters (Table 3, entries 8−10, 16, and 20). α,β-Unsaturated thioesters were not formed in these reactions despite the facile known isomerization of β,γ-unsaturated to α,β-unsaturated esters.[19] An isomeric mixture of β,γ-unsaturated thioesters were obtained when some alcohols were employed as substrates. To consider the question of double bond integrity of the product, the thiocarbonylation reactions of (*E*)- and (*Z*)-2-hexen-1-ol ((*E*)-**1g** and (*Z*)-**1g**) were examined under the standard conditions (Table 3, entries 13 and 14). (*E*)-**1g** and (*Z*)-**1g** were converted into a 4:1 mixture of (*E*)- and (*Z*)-phenyl-3-heptenethioate (**3j**), irrespective of the stereochemistry of the starting alcohol. The stereochemistry of the carbon−carbon double bond in **3j** may be due to $\pi-\sigma-\pi$-isomerization of intermediate π,π-allylpalladium complexes **5** and **7** (Scheme 1),[20] with some selectivity for the thermodynamically more stable (*E*)-isomers. As Murahashi[20a] observed in the alkoxycarbonylation of diethyl cinnamyl phosphate and diethyl geranyl phosphate, cinnamyl alcohol (**1h**) and geraniol (**1l**) undergo the thiocarbonylation to afford stereoselectively (*E*)-phenyl-4-phenyl-3-butenethioate (**3k**) and (*E*)-phenyl-4,8-dimethyl-3-nonenethioate ((*E*)-**3l**), respectively (Table 3, entries 15 and 19).

The regioselectivity of the reaction was further investigated using linalool (**1i**) and geraniol (**1l**) as reactants. While linalool afforded a 3:1 mixture of *E*/*Z* **3l**, only (*E*)-**3l** was isolated when geraniol was the substrate (eqs 6 and 7).

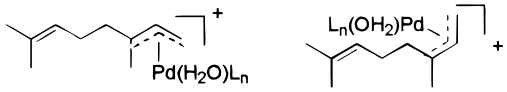


1i (*E*)- and (*Z*)-**3l**



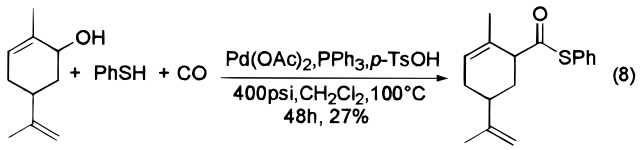
1l (*E*)- **3l**

It is conceivable that **8** is favored over **9** on steric grounds and the ease of generation of **8**/**9** from **1i** and **1l** governs the isomer distribution.



8 **9**

Thiocarbonylation of Thiophenol to Cyclic Allylic Alcohols. Although acyclic allylic alcohols undergo thiocarbonylation readily under mild conditions, cyclic allylic alcohols show quite low reactivity toward the carbonylative coupling reactions with thiophenol and carbon monoxide. When carveol (**10**) was treated under the optimized conditions for the thiocarbonylation of acyclic substrates, the corresponding thioester **11** was obtained only in 27% yield, with recovery of 52% of the substrate (eq 8).



10 **11**

Optimization of the reaction conditions resulted in the thiocarbonylation reaction proceeding to afford thioesters in higher yield at 120 °C for 3 to 7 days (other conditions being the same as those for acyclic substrates).[21]

The scope and limitations of the palladium-catalyzed carbonylative coupling reaction of cyclic allylic alcohols with thiophenol and CO are summarized in Table 4. When 2-cyclohexen-1-ol (**12**) was allowed to react under the optimal conditions, phenyl 2-cyclohexenyl formthioate (**13**) was formed in 84% yield (Table 4, entry 2); but under

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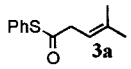
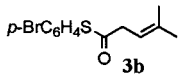
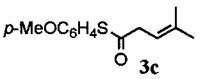
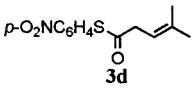
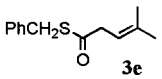
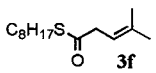
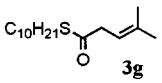
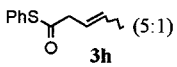
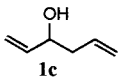
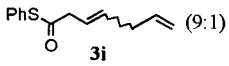
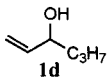
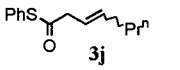
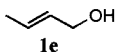
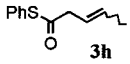
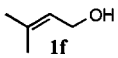
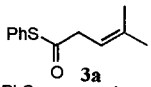
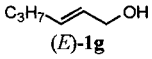
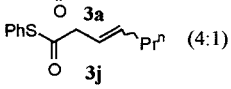
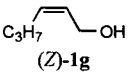
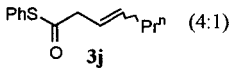
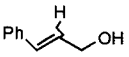
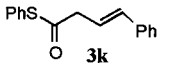
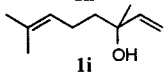
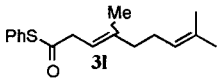
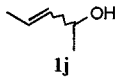
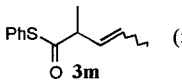
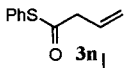
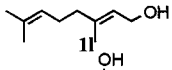
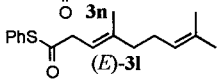
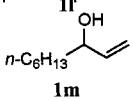
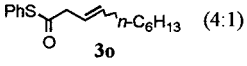
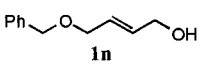
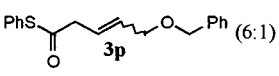
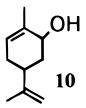
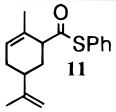
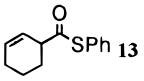
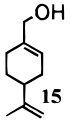
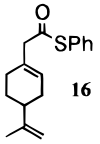
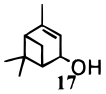
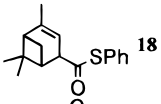
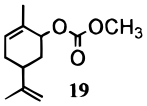
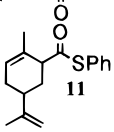
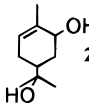
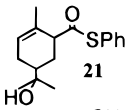
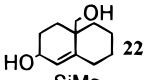
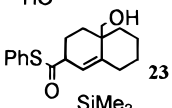
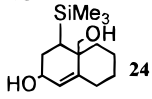
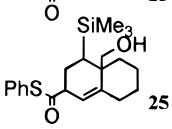
(21) The reaction was monitored by TLC (SiO_2, EtOAc−hexane 1:10).

Table 3. Palladium-Catalyzed Thiocarbonylation of Acyclic Allyl Alcohols with Thiols and Carbon Monoxide[a]

entry	alcohol	thiol	product(E/Z)[b]	yield(%)[c]
1	 **1a**	PhSH **2a**	 **3a**	93
2	**1a**	*p*-BrC_6H_4SH **2b**	 **3b**	88
3	**1a**	*p*-$MeOC_6H_4SH$ **2c**	 **3c**	90
4	**1a**	*p*-$NO_2C_6H_4SH$ **2d**	 **3d**	92
5	**1a**	$PhCH_2SH$ **2e**	 **3e**	84
6	**1a**	$C_8H_{17}SH$ **2f**	 **3f**	87
7	**1a**	$C_{10}H_{21}SH$ **2g**	 **3g**	86
8	 **1b**	**2a**	 (5:1) **3h**	94
9	 **1c**	**2a**	 (9:1) **3i**	78
10	 **1d**	**2a**	 (4:1) **3j**	92
11	 **1e**	**2a**	 (2:1) **3h**	89
12	 **1f**	**2a**	 **3a**	93
13	 (*E*)-**1g**	**2a**	 (4:1) **3j**	87
14	 (*Z*)-**1g**	**2a**	 (4:1) **3j**	85
15	 **1h**	**2a**	 (100:0) **3k**	76
16	 **1i**	**2a**	 (3:1) **3l**	91
17	 **1j**	**2a**	 (5:1) **3m**	92
18	 **1k**	**2a**	 **3n**	56
19	 **1l**	**2a**	 (100:0) (*E*)-**3l**	84
20	 **1m**	**2a**	 (4:1) **3o**	86
21	 **1n**	**2a**	 (6:1) **3p**	87

[a]Reaction conditions: alcohol (2 mmol), thiol (2 mmol), CO (400 psi), $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.24 mmol), *p*-TsOH (0.1mmol), CH_2Cl_2 (10 mL), 100°C, 48 h. [b]The ratio of E to Z was determined by ^1H NMR. [c]Isolated yield based on the reactant thiol.

Table 4. Palladium-Catalyzed Thiocarbonylation of Cyclic Allylic Alcohols with Thiophenol and Carbon Monoxide[a]

entry	alcohol	reaction time(day)	product	yield (%)[b]
1	 **10**	5	 **11**	72
2	 **12**	3	 **13**	84
3	 **14**	7	No reaction	0
4	 **15**	5	 **16**	64
5	 **17**	7	 **18**	18[c]
6	 **19**	2	 **11**	86
7	 **20**	7	 **21**	27
8	 **22**	7	 **23**	63
9	 **24**	7	 **25**	54

[a]Reaction conditions: alcohol (2 mmol), **2a** (2 mmol), CO (400psi), $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.24 mmol), *p*-TsOH (0.1mmol), CH_2Cl_2 (10 mL),120°C. [b]Isolated yield based on reactant thiophenol. [c]The decarbonylated sulfide was also obtained in 14% yield.

the same reaction conditions, thiocarbonylation of myrtenol (**14**) was inactive (Table 4, entry 3). In most cases, the reactions were clean and no byproduct was formed (except entry 5). Carvyl carbonate (**19**) was smoothly thiocarbonylated to give the corresponding β,γ-unsaturated thioester in excellent yield (Table 4, entry 6), while the same reaction of carveol (**10**) needed a longer reaction time (five vs two days, Table 4, entry 1). Some functional groups, such as hydroxyl (Table 4, entries 7 to 9), trimethylsilyl (Table 4, entry 9), and vinyl (Table 4, entries 1, 4, and 6) groups, did not affect the thiocarbonylation reactions. The reaction proceeded regioselectively. Substituted cyclic alcohols with unsymmetrical allylic species, such as **15**, **17**, **22**, and **24**, undergo thiocarbonylation exclusively at the less-substituted end of the allylic group (Table 4, entries 4, 5, 8, and 9), while substrates with symmetrical allylic units can, of course, only afford one product (Table 4, entries 1, 2, 6, and 7).

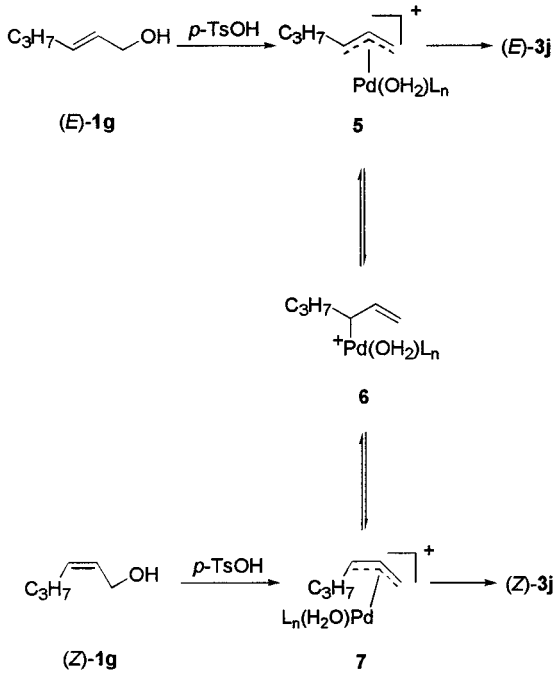
Mechanistic Aspects. A probable mechanism for the thiocarbonylation of allylic alcohols is outlined in Scheme 2 (illustrated for allyl alcohol). It is well-known that $Pd(OAc)_2$ is easily reduced to Pd(0) in situ in the presence of phosphine ligands and carbon monoxide.[22] Oxidative addition of protonated allylic alcohol to Pd(0) gives the π-allylpalladium complex **26**,[23] which may undergo substitution of H_2O by SPh to form the π-allylpalladium sulfide complex **27**. Insertion of CO to **27** affords the acylpalladium complex **28**.[6a] Reductive elimination of Pd(0) would form β,γ-unsaturated thioesters.

Conclusion. Palladium complexes such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3{\cdot}CHCl_3$ with added phosphine ligands and *p*-TsOH are effective for the thiocarbonylation of acyclic and cyclic allyl alcohols with thiols and carbon monoxide. These reactions occur in a highly regioselective manner, at the less-hindered allylic terminal carbon of the substrate, to give the corresponding thioesters. Not only is this methodology attractive for the preparation of thioesters and the direct carbonylation of allyl alcohols, but it also further demonstrates the utility of transition metal catalysts in the synthesis of chalcogen compounds.

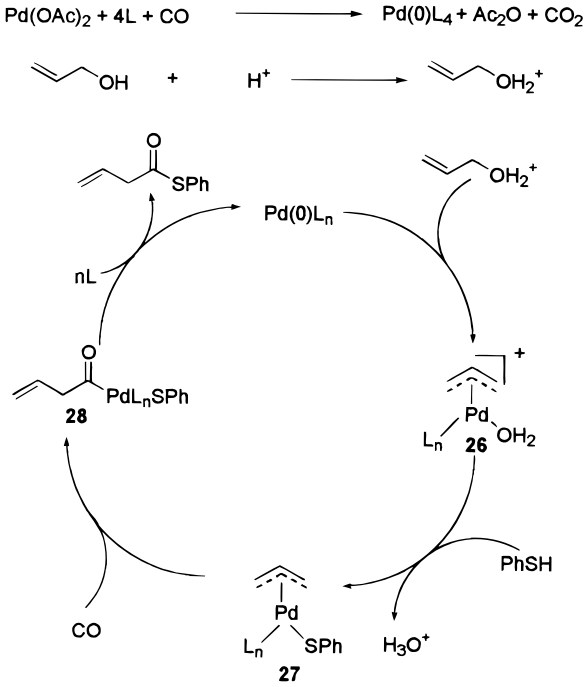
(22) Amatore, C.; Jutand, A.; M'Barki, M. *Organometallics* **1992**, *11*, 3009. (b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818.

(23) Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559.

Scheme 1



Scheme 2



Experimental Section

General Methods.[6a] Prior to use, THF, DME, and ether were distilled from sodium benzophenone ketyl while CH_2Cl_2 and toluene were distilled from CaH_2 under N_2. All thiols and allylic alcohols were purchased from Aldrich and were used as received. Allyl carbonates (**4a**[24] and **19**[25]) and phosphate (**4b**)[26] and $Pd_2(dba)_3{\cdot}CHCl_3$[27] were prepared according to the reported procedure.

General Procedure for the Palladium-Catalyzed Thiocarbonylation of Allylic Alcohols with Thiols. To a 45 mL Parr autoclave fitted with a glass liner and stirring bar was added $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.24 mmol), *p*-TsOH (0.1 mmol), allylic alcohol (2.0 mmol), thiol (2.0 mmol), and dry CH_2Cl_2 (10 mL). The CO line was flushed three times with CO, the autoclave was filled and vented three times with CO to displace the air, and subsequently the pressure was increased to 400 psi. The mixture was stirred in the autoclave at 100−120 °C (oil bath temperature) for 2 to 7 days. After cooling, excess CO was released, the reaction mixture was filtered through Florisil, and the solvent was removed by rotary evaporation. The residue was separated by preparative TLC (silica gel, eluant: *n*-hexane/ethyl acetate 10:1).

Phenyl 4-methyl-3-pentenethioate (3a): oil; IR (neat) 1708 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.78 (s, 3H), 3.35 (d, 2H, J = 7.4 Hz), 5.36 (t, 1H, J = 7.4 Hz), 7.30−7.49 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.10, 25.76, 43.10, 115.10, 127.76, 128.68, 129.07, 133.27, 137.82, 196.36; MS (EI) *m*/*z* 206 (M^+); HRMS calcd for $C_{12}H_{14}OS$ 206.0765, found 206.0790. Anal. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84. Found: C, 69.82; H, 6.90.

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Supporting Information Available: Characterization data for all products (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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