Highly Regioselective Thiocarbonylation of Conjugated Dienes via Palladium-Catalyzed Three-Component Coupling Reactions

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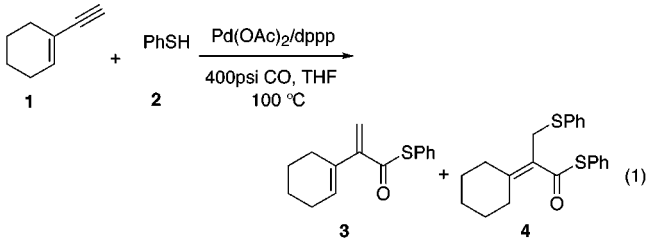
Three-component coupling reaction of conjugated dienes, thiols, and carbon monoxide affords an atom-economical thiocarbonylation of the dienes to give β,γ-unsaturated thioesters as the sole products. A catalyst system based on [$Pd(OAc)_2$] and Ph_3P showed excellent catalytic activity. The thiocarbonylation was performed under an atmosphere of carbon monoxide (400 psi) at 110 °C in CH_2Cl_2 for 60 h. A wide variety of thioesters were synthesized in good to excellent yields from easily accessible starting materials. The reaction is believed to proceed via a η^3-allylpalladium intermediate. The thiocarbonylation, which is applicable to a wide variety of conjugated dienes, occurs in high regioselectivity, the latter dependent on the steric characteristics and stability of the η^3-allylpalladium complex.

Introduction

Transition metal-catalyzed synthetic transformations employing heteroatom compounds containing silicon,[1] boron,[2] phosphorus,[3] or germanium[4] are versatile methods to the formation of heteroatom−carbon bonds in organic synthesis.[5] The use of organosulfur compounds as a direct reagent for the preparation of C−S bonds catalyzed by transition metal catalysts has had some notable successes[6] but, for the most part, it has been much less studied than its oxo and nitro analogues.[7] One possible reason is that chalcogen compounds may act as poisons for the transition metal, rendering them incompatible with catalytic species.[8] Recently, we and others have developed a series of transition metal-catalyzed reactions of organic sulfur compounds. Examples include the iridium-catalyzed group transfer reaction of 1,3-thiazanes,[9] and the rhodium(I)-catalyzed regioselective carbonyl insertion reaction of C−S bonds of α-substituted tetrahydrofuran thioethers.[10] Processes involving ruthenium[11] and palladium[12] complexes as catalysts have also been investigated. For example, thiols[13] or disulfides[14] react with propargyl alcohols in the presence of [$Pd(PPh_3)_4$] to afford β-(arylthio)-α,β-unsaturated γ-lactones as the thiolactonization products. Allylic alcohols[15] and allenes[16] react similarly with thiophenols. In 1994, Backvall and co-workers reported the regioselective addition of thiophenol to conjugated enynes,[17] and most recently, we developed the thiocarbonylation version of such a reaction.[18] In the latter case, it was found that the thiocarbonylation of enynes could afford two products (eq 1), depending on the concentrations of the reactants. It



1 + 2 → 3 + 4 (1)

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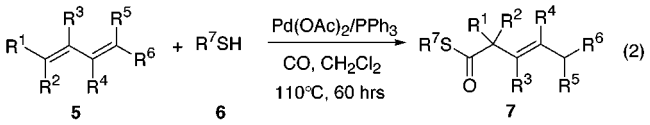
is clear that **4** might also arise by further reaction of **3**and thiophenol. Inspired by these results, we realized that the carbonylative addition of three components, conjugated dienes, thiols, and carbon monoxide, could, in principle, afford the corresponding β, γ-unsaturated thioesters.

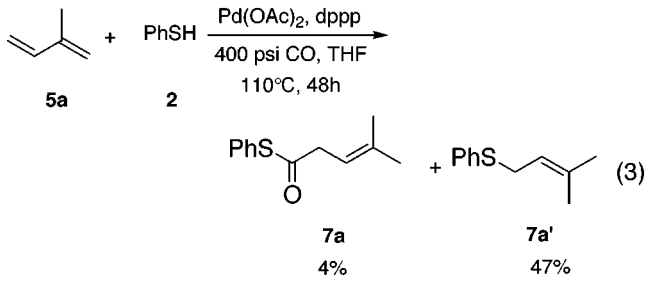
The synthesis of thioesters is an important subject in organic synthesis,[19] with selectivity[20] and atom economy[21] as key issues. The present methodology (shown in eq 2) represents a highly regioselective and atom-economical route to β,γ-unsaturated thioesters.



R^1, R^2, R^3, R^4, R^5, R^6, and R^7 = H, alkyl, aryl, or cycloalkyl

Results and Discussion

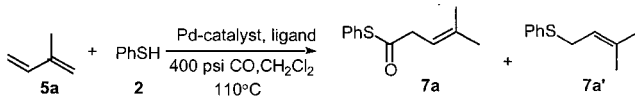
Reaction Conditions for the Thiocarbonylation of 2-Methyl-1,3-butadiene. Influence of the Catalyst System on the Reaction. Initially, the reaction of 2-methyl-1, 3-butadiene (**5a**) with thiophenol and carbon monoxide was investigated. The optimal reaction conditions [5 equiv of diene, 1 equiv of thiophenol, 3 mol % [$Pd(OAc)_2$], 6 mol % 1,3-bis(diphenylphosphino)propane (dppp), 400 psi of carbon monoxide, and THF (15 mL per mmol of thiophenol)], employed previously for the thiocarbonylation of conjugated enynes[18] were used to check the feasibility of the process (eq 3).



The reaction gave two products **7a** and **7a′** in yields of 4% and 47%, respectively, with 16% recovery of unreacted thiophenol after 48 h. Although the yield of the desired product **7a** was low, we were nevertheless encouraged and examined the reaction in detail under a variety of conditions in an attempt to increase the yield. Several palladium complexes and phosphine ligands were examined as catalytic systems, and the results are summarized in Table 1.

Among the catalysts examined, [$Pd(OAc)_2$], with 4 equiv of PPh_3 showed high activity for the catalytic thiocarbonylation reaction (Table 1, entry 5), while [$Pd(OAc)_2$] with dppf (2 equiv) as the added ligand resulted in the 1,4-addition of thiophenol to 2-methyl-1,3-butadiene (Table 1, entry 4). Palladium(0) complexes, such as [$Pd(PPh_3)_4$] and $Pd_2(dba)_3{\cdot}CHCl_3$, with added triphenylphosphine, were also good catalysts for the thiocarbonylation reaction (Table 1, entries 8 and 9). It was observed that the ligands employed played an important role in the selectivity of the reaction (Table 1, entries 1−7 and 10). For example, using [$Pd(OAc)_2$] as the catalyst precursor in the presence of bidentate phosphines gave 1,4-addition as the sole or major pathway (Table 1, entries 1−4), while only carbonylative 1,4-adducts were isolated in the case of monodentate phosphines (Table 1, entries 5−7). Under the same conditions, the yield of **7a** increased by changing the ligand from dppe to dppp or dppb. These results are in accord with the observation by Van Leeuwen and co-workers that the rate of carbon monoxide insertion into a Pd−C bond is faster for alkylpalladium bisphosphine complexes containing a flexible metal ligand chelate ring.[23] In addition to triphenylphosphine, PCy_3 and PBu_3 can also be used for this reaction, but they are inferior to PPh_3 (Table 1, entries 5−7). When the reaction was performed without any ligand, a deep red precipitate was formed, and there was 68% and 47% recovery of 2-methylbutadiene and thiophenol, respectively.[22]

Table 1. Optimization of Catalyst Systems for the Palladium-Catalyzed Thiocarbonylation of Conjugated Dienes[a]



entry	catalyst	ligand	time(h)	yield(%)[b] 7a	7a′
1	$Pd(OAc)_2$	dppb	60	12	66
2	$Pd(OAc)_2$	dppp	60	8	74
3	$Pd(OAc)_2$	dppe	72	trace[c]	52
4	$Pd(OAc)_2$	dppf	60	trace[c]	90
5	$Pd(OAc)_2$	PPh_3	60	83	0
6	$Pd(OAc)_2$	PCy_3	48	70	0
7	$Pd(OAc)_2$	PBu_3	48	72	0
8	$Pd(PPh_3)_4$	PPh_3	48	58	0
9	$Pd_2(dba)_2{\cdot}CHCl_3$	PPh_3	48	64	0
10[d]	$Pd(OAc)_2$	none	48	0	0

[a] Reaction conditions: thiophenol (1 mmol), 2-methyl-1,3-butadiene (5 mmol), catalyst (0.05 mmol), Ph_3P, PCy_3, or PBu_3 (0.2 mmol, if used), 1,4-bis(diphenylphosphino)butane (dppb), 1,3-bis(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)ethane (dppe), or 1,1′-bis(diphenylphosphino)ferrocene (dppf) (0.1 mmol, if used), CH_2Cl_2 (5 mL), 110 °C. [b] Isolated yield. [c] The presence of the phenylthiocarbonyl group was indicated by an IR of the crude product, but attempts to isolate the carbonylation product were unsuccessful. [d] The reaction gave a deep red and very insoluble solid, which might be a polymer.[22]

Solvent Optimization. The reaction is sensitive to the solvent as shown by the results in Table 2. As noted

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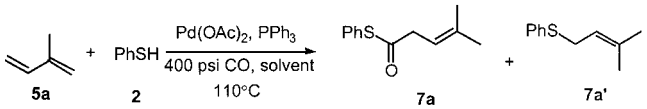
Table 2. Solvent Effects on the Palladium-Catalyzed Reaction of 2-Methylbutadiene with Thiophenol and Carbon Monoxide[a]



entry	solvent	time(h)	isolated yield(%) 7a	7a'
1	THF	48	27	52
2	CH_3CN	60	0	78
3	Benzene	60	trace[b]	64[c]
4	DME	48	47	18
5	Et_2O	48	64	20
6	CH_2Cl_2	60	83	0

[a] Reaction conditions: 2-Methyl-1,3-butadiene (5 mmol). Thiophenol (1 mmol), $[Pd(OAc)_2]$ (0.05 mmol), PPh_3 (0.2 mmol), 400 psi of carbon monoxide, solvent (5 mL), 110 °C. [b] Phenylcarbonyl group was identificated by IR of the crude product, but attempts to isolate the carbonylation product were unsuccessful. [c] 15% of thiophenol was recovered.

already, THF was not an ideal solvent for the thiocarbonylation of **5a** (eq 3).

When $[Pd(OAc)_2]$ with PPh_3 was used as the catalyst precursor, the reaction in THF gave the thioester (**7a**) and sulfide (**7a′**) in 27% and 52% yield, respectively (Table 2, entry 1). The reaction worked very well in CH_2Cl_2 and afforded **7a** as the sole product in 83% isolated yield (Table 2, entry 6); however, under the same conditions, using CH_3CN or benzene as the solvent, **7a′** was formed as the major or the sole product (Table 2, entries 2 and 3). Reactions in 1,2-dimethoxyethane (DME) and diethyl ether gave a mixture of **7a** and **7a′** (Table 2, entries 4 and 5).

On the basis of these results, the reaction of a variety of conjugated dienes and thiols were performed, and the results are summarized in Tables 3−5.

Thiocarbonylation of 2-Methyl-1,3-butadiene(5a) Using Various Thiols. The results in Table 3 indicate the scope and limitations of the palladium-catalyzed carbonylative coupling reaction of **5a** and representative thiols. In most cases, thiophenols were found to work more effectively than alkanethiols. For example, **5a** reacted with thiophenol (**2**), *p*-nitrobenzenethiol (**6b**), and *p*-bromobenzenethiol (**6c**) affording only the carbonylative 1,4-addition products **7a**, **7c**, and **7d** in similar yields (Table 3, entries 1, 3, and 4), while the corresponding reaction with alkanethiols always gave mixtures of thiocarbonylation and simple 1,4-addition products (Table 3, entries 6−9). Reactions involving alkanethiols took longer to complete than those with arenethiols. The reaction was rather sensitive to both the acidity (electronic factor) and the effective bulk (steric factors) of the thiols. For example, **6a** (*p*-methoxybenzenethiol), an arenethiol with an electron-donating *p*-methoxy group, and **6b** (*p*-nitrobenzenethiol), an arenethiol with an electron-withdrawing group, show somewhat different behavior in this reaction. Using **6a** as the substrate gives a mixture of **7b** (60%yield) and **7b′** (18% yield) after a period of 72 h (Table 3, entry 2), whereas **6b** gives only the carbonylative 1,4-addition product in 80% yield (Table 3, entry 3) after a period of 48 h. Reactions with arenethiols, such as 2-naphthalenethiol (**6d**), gave an approximately 1:1 mixture of the carbonylation **7e** and 1,4-addition products (**7e′**) (Table 3, entry 5). In the case of alkanethiols, it was observed that increasing the length of the alkyl group caused the thiols to become less reactive, with a mixture of addition and carbonylative addition products formed in all the cases (Table 3, entries 7−9). When cyclohexyl mercaptan was employed as the substrate, no products were obtained at all.

Thiocarbonylation of Acyclic Conjugated Dienes Using Thiophenol (2). A series of acyclic conjugated dienes were thiocarbonylated smoothly, by $[Pd(OAc)_2]$ and PPh_3, to give the corresponding β,γ-unsaturated thioesters in good to excellent yields (Table 4).

α,β-Unsaturated thioesters were not detected among the products either before or after purification, although it is well-known that isomerizations of β,γ-unsaturated thioesters to α,β-unsaturated isomers might occur.[24] Importantly, the reaction exhibits excellent regioselectivity in all cases. Depending on the structural characteristics of the dienes employed, the reaction could selectively afford carbonylative 1,4- or 1,2-addition products. Usually, the monosubstituted and 2,3-substituted dienes reacted with **2** and CO to afford carbonylative 1,4-addition products (Table 4, entries 1−5, 7, 10, and 11), while 1,1-disubstituted dienes such as **5f** and **5i,** as well as *tert*-butyl-substituted butadiene (**5h**), underwent thiocarbonylation to form products of carbonylative 1,2-addition (Table 4, entries 6, 8, and 9). A substitutent at the C-2 position of the dienes was found to direct the H of **2** exclusively to the C-1 position, and the phenylthiocarbonyl group to the C-4 position of the molecule, although the reaction might give two isomeric carbonylative 1,4-adducts. The regioselectivity can be explained by the nature of the diene and the stability of the η^3-allylpalladium complex. For example, in the case of **5a** (Scheme 1), the H of **2** can attack either at C-1 or C-4 to form two isomeric π-allylpalladium complexes **8** or **9**, which would then give thioester **7a** or **10**, respectively. With an electron-donating group in the C-2 position, C-1 is more protophilic than C-4.[25] Furthermore, η^3-allylpalladium complex **8** is known to be more stable than **9**.[26] Therefore, it can be envisaged that the reaction of **5a** with **2** and CO can only occur by path (a) to give the thioester **7a** as the sole product.

It was observed that the regioselectivity decreased when a substrate with a substituent at C-1 of the diene was employed in this reaction (Table 4, entries 3−5). It is probable, therefore, that during the reaction, two isomeric η^3-allylpalladium complexes were formed (Scheme 2, illustrated for piperylene). The ratio of the two products (**7k** and **7l**) may depend on steric factors.

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(25) Ab initio calculations showed that the electron distribution of 2-methyl-1,3-butadiene (**5a**) (after 6-31G geometry optimization) is as follows:

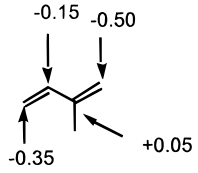

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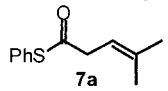
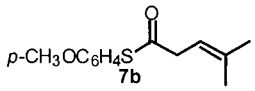
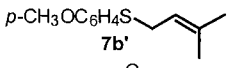
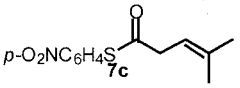
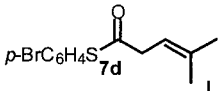
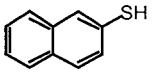
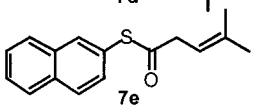
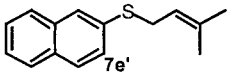
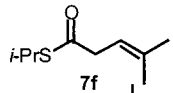
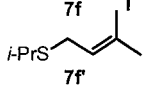
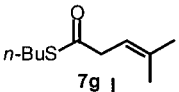
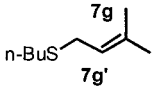
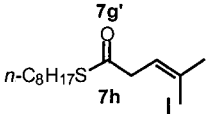
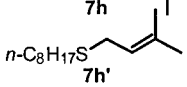
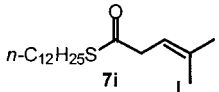
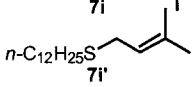
Table 3. Palladium-Catalyzed Reaction of 5a with Thiols and CO[a]

entry	thiol	time(h)	product	isolated yield(%)
1	PhSH, **2**	60	 **7a**	83
2	*p*-CH_3O-C_6H_4SH **6a**	72	 **7b**	60
			 **7b'**	18
3	*p*-O_2N-C_6H_4SH **6b**	48	 **7c**	84
4	*p*-Br-C_6H_4SH **6c**	60	 **7d**	80
5	 **6d**	60	 **7e**	18
			 **7e'**	20
6	*i*-PrSH, **6e**	84	 **7f**	42
			 **7f'**	36
7	*n*-BuSH, **6g**	84	 **7g**	45
			 **7g'**	23
8	*n*-$C_8H_{17}SH$, **6g**	120	 **7h**	17
			 **7h'**	54
9	*n*-$C_{12}H_{25}SH$, **6h**	128	 **7i**	trace
			 **7i'**	58

[a] Reaction conditions: 2-Methyl-1,3-butadiene (10 mmol), thiol (2 mmol), [$Pd(OAc)_2$] (0.1 mmol), PPh_3 (0.4 mmol), 400 psi of carbon monoxide, CH_2Cl_2 (10 mL).

For 1,1-disubstituted dienes, the phenylthiocarbonyl group exclusively attacked the least substituted terminal allylic carbon of the η^3-allylpalladium complexes, affording the carbonylative 1,2-addition products (Scheme 3).

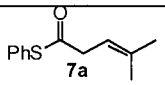
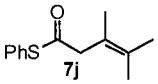
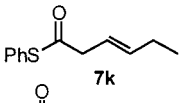
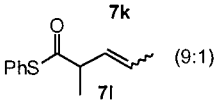
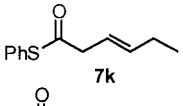
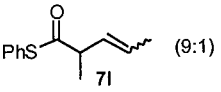
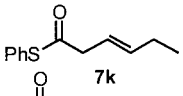
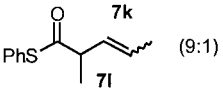
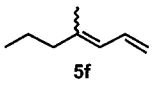
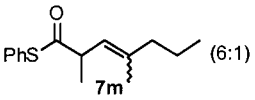
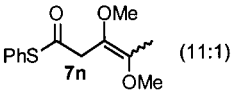
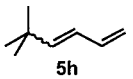
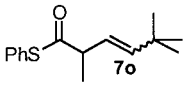
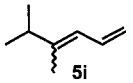
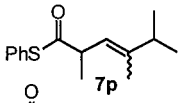
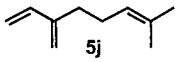
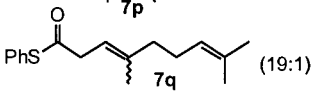
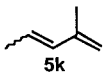
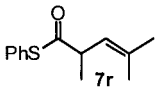
Fine stereoselectivity for the β,γ-unsaturated thioesters resulted using some dienes as substrates. The thermodynamically more stable (*E*)-isomers were obtained preferentially, irrespective of the stereochemistry of the starting reactants (Table 4, entries 3−10). For example, homogeranic acid, which is a precursor of tetrahydroastinidiolides,[27] can be obtained stereoselectively (*E*/*Z* = 19/1) from myrcene (**5j**) (Table 4, entry 10). Noth that double thiocarbonylation of the triene did not occur. It is interesting to note that the thiocarbonylation reactions of (*E*)- and (*Z*)-piperylene (**5d** and **5e**) afford a 9:1 mixture of (*E*)- and (*Z*)-phenyl 2-methyl-3-pentenethioate (**7l**), independent of the stereochemistry of the starting dienes (Table 4, entries 4 and 5). It is likely that the variation of the stereochemistry is due to the η^3-η^1-η^3 isomerization of the intermediate π-allylpalladium complexes **10** and **12** (Scheme 4),[28] with preference for the thermodynamically more stable (*E*)-isomer product.

Thiocarbonylation of Cyclic Dienes Using Thiophenol (2). Table 5 shows the results of the [$Pd(OAc)_2$]/PPh_3-catalyzed thiocarbonylation of PhSH with several cyclic conjugated dienes. Consistent with the pattern

(27) (a) Kato, T.; Kumazawa, S.; Kitahara, Y. *Synthesis* **1972**, 573. (b) Hoye, T. R.; Caruso, A. J.; Kurth, M. J. *J. Org. Chem.* **1981**, *46*, 3550. (c) Gnonlonfoun, N.; Zamarlik, H. *Tetrahedron Lett.* **1987**, *28*, 4035.

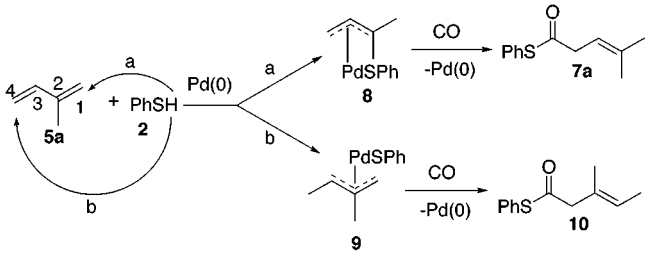
(28) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

Table 4. Palladium-Catalyzed Thiocarbonylation of Acyclic Conjugated Dienes Using Thiophenol and CO[a]

entry	diene	product (E/Z)[b]	isolated yield(%)
1	 5a	 7a	83
2	 5b	 7j	94
3	 5c	 7k	15
		 (9:1) 7l	64
4	 5d	 7k	22
		 (9:1) 7l	59
5	 5e	 7k	17
		 (9:1) 7l	65
6	 5f	 (6:1) 7m	69
7	 5g	 (11:1) 7n	58
8	 5h	 (9:1) 7o	89
9	 5i	 (10:1) 7p	70
10	 5j	 (19:1) 7q	91
11	 5k	 7r	86

[a] Reaction conditions: Diene (10 mmol), thiophenol (2 mmol), $[Pd(OAc)_2]$ (0.1 mmol), PPh_3 (0.4 mmol), CO (400 psi), CH_2Cl_2 (10 mL), reaction time (60 h), reaction temperature (110 °C). [b] The ratio of *E* to *Z* was determined by ^1H NMR.

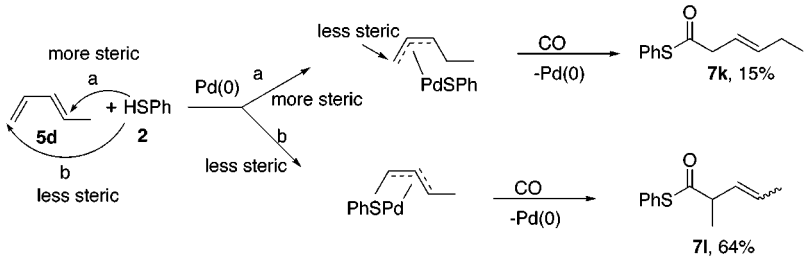
Scheme 1



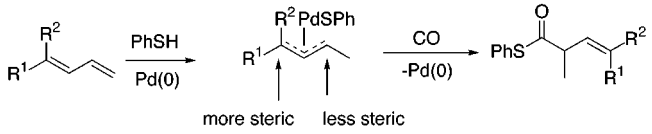
found for acyclic analogues, the regioselectivity of the reaction employing cyclic dienes was quite high. While 1,4- and 1,2-thiocarbonylative adducts are structurally identical when unsubstituted cyclic dienes were used as substrates (Table 5, entries 1−3), the substituted cyclic dienes afford 1,4- or 1,2-products, depending on the substrates. For example, only the 1,4-product was formed when *exo*-methylene cyclohexene (**5o**) was the reactant (Table 5, entry 4). In contrast, the 1,2-product was obtained in the case of 1-methyl-1,3-cyclohexadiene (**5p**) (Table 5, entry 5). It is conceivable that the reactions of **5o** and **5p** proceed through the same intermediate (Scheme 5), and this could be the reason both reactions gave identical products.

Mechanistic Aspects. A possible pathway for the palladium-catalyzed thiocarbonylation of **5** (using **5b** as the example) with thiophenol (**2**) is outlined in Scheme 6. It is well-known that Pd(0) is readily formed in situ by the reduction of $[Pd(OAc)_2]$ in the presence of phos-

Scheme 2



Scheme 3



Scheme 4

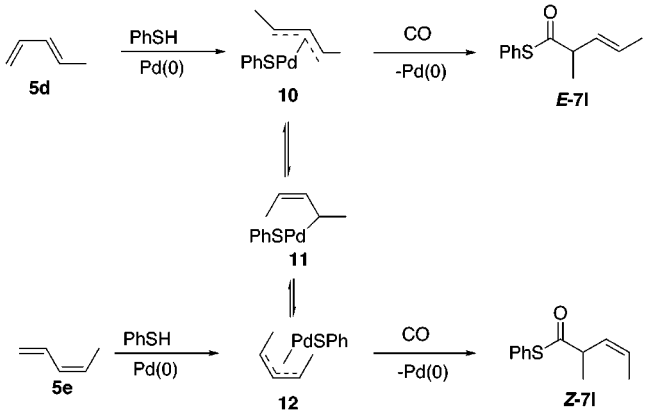
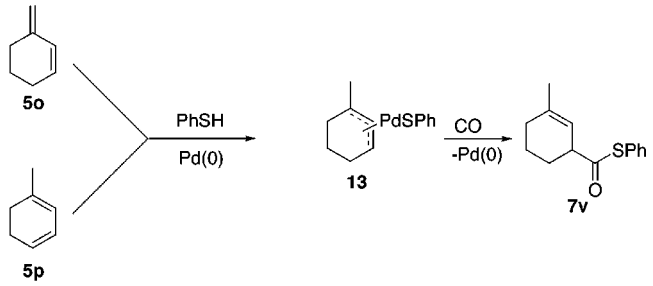


Table 5. Palladium-Catalyzed Thiocarbonylation of Cyclic Conjugated Dienes[a]

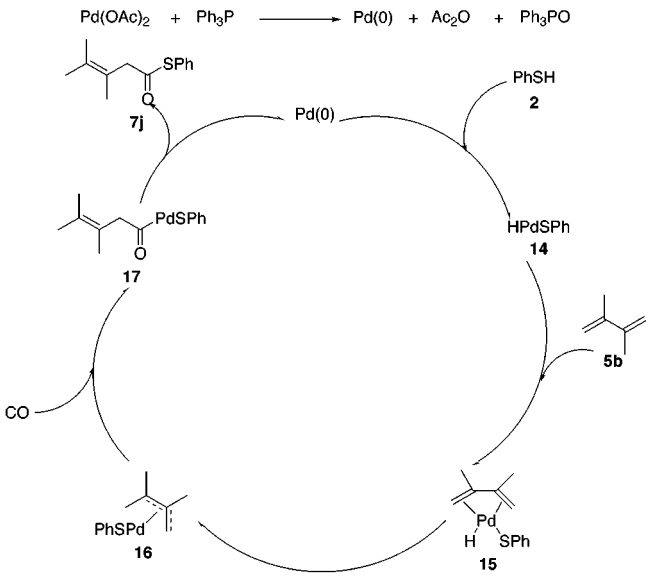
entry	diene	reaction time(h)	product	isolated yield(%)
1	5l	48	7s	84
2	5m	72	7t	86
3	5n	144	7u	61
4	5o	48	7v	75
5	5p	48	7v	67

phine ligands.[29] Oxidative addition of **2** to palladium(0) can then give the thiopalladium complex (**14**),[30] which can coordinate with the diene to form a Pd-η^4-diene complex **15**.[31] Intramolecular hydropalladation would

Scheme 5



Scheme 6



afford the η^3-allylpalladium complex **16**. Insertion of CO into the Pd−S bond of **16** or into the Pd−C bond of the σ-allyl analogue of **16,** followed by regioselective intramolecular transfer would afford the acylpalladium complex **17**.[32] Reductive elimination of **17** would afford the thioester (**7j**), with regeneration of the palladium catalyst.

Conclusions

In summary, a highly effective catalytic system ([Pd(OAc)$_2$]−PPh$_3$) has been developed for the carbonylative coupling reaction of conjugated dienes, thiols, and carbon

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(31) Lukas, J.; Kramer, P. A. *J. Organomet. Chem.* **1971**, *31*, 111.

(32) A similar mechanism for the insertion of acetylene into the Pd−CO σ bond has been reported. See: Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505.

monoxide to form the corresponding β,γ-unsaturated thioesters. These reactions take place in a highly regioselective manner, depending on the steric characteristics and stability of the proposed η^3-allylpalladium complex. Furthermore, the reactions exhibit good to excellent stereoselectivity.

Experimental Section

Materials. Benzene, THF, 1,2-dimethoxyethane, and diethyl ether were dried and distilled from sodium/benzophenone ketyl under nitrogen before use. Dichloromethane was freshly distilled from CaH_2 under nitrogen. CH_3CN was dried by storing over molecular sieves (4A) and distilled under nitrogen. All other common solvents and chemicals were used as received. 3-Methylenecyclohexene (**5o**),[33] 1-methyl-1,3-cyclohexadiene (**5p**),[34] and $Pd_2(dba)_3{\cdot}CHCl_3$[35] were prepared according to literature procedures.

General Procedure for the Palladium-Catalyzed Thiocarbonylation of Conjugated Dienes. To a 45-mL Parr autoclave fitted with a glass liner and stirring bar were added [$Pd(OAc)_2$] (0.1 mmol), PPh_3 (0.4 mmol), diene (10 mmol), thiol (0.2 mmol), and dry CH_2Cl_2 (10 mL). The CO line was flushed three times with CO, the autoclave was fill-vented three times with CO to displace the air, and the pressure was subsequently increased to 400 psi. The mixture was stirred in the autoclave at 110 °C (oil bath temperature) for 48−144 h. After cooling, the 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 GF_{254}, eluant: *n*-hexane/ethyl acetate 10:1).

Phenyl 4-Methyl-3-pentenethioate (7a). Colorless oil; IR (neat): $\upsilon = 1708$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.70$ (s, 3H), 1.78 (s, 3H), 3.35 (d, 2H, $J = 7.4$ Hz), 5.36 (t, 1H, $J = 7.4$ Hz), 7.40 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.10$, 25.76, 43.10, 115.10, 127.76, 128.68, 129.07, 133.27, 137.82, 196.36; MS (70 eV, EI): 206.1 [M^+]; HRMS (70 eV, EI): calcd for $C_{12}H_{14}OS$ 206.0765, found 206.0790. Anal. Calcd for $C_{12}H_{14}OS$: C 69.80, H 6.84. Found: C 69.88, H 6.92.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Council of Canada for the support of this research. We are indebted to Dr. David Butler and Ms. Helen Clark for helpful discussions and valuable comments.

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

JO000231O

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