First Examples of Enantioselective Palladium-Catalyzed Thiocarbonylation of Prochiral 1,3-Conjugated Dienes with Thiols and Carbon Monoxide: Efficient Synthesis of Optically Active β,γ-Unsaturated Thiol Esters

Wen-Jing Xiao and Howard Alper*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

halper@uottawa.ca

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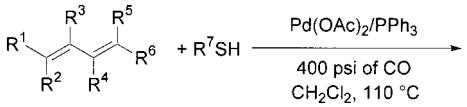
A catalyst system based on $[Pd(OAc)_2]$/(*R*,*R*)-DIOP has been found to effect asymmetric thiocarbonylation of certain prochiral 1,3-dienes to produce good yields of optically enriched β,γ-unsaturated thiol esters. The reaction was performed under an atmosphere of carbon monoxide (400 psi) at 110 °C in methylene chloride for 60 h. The asymmetric thiocarbonylation proceeded with good to excellent enanotioselectivities (up to 89% ee). The stereoselectivity is strongly influenced by the structure of the chiral phosphine ligands and substrates, as well as by the reaction conditions. The enantiodetermination step is assumed to be CO insertion to a π-allylpalladium intermediate.

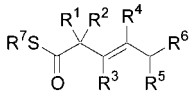
Introduction

Transition metal-catalyzed carbonylation reactions are fundamentally important organic transformations.[1] 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.[2] The search for the improvement of carbonylation technology continues, with the goal of increasing the diversity of possible substrates and reaction products. The development of transition metal-catalyzed carbonylation involving the formation of a thiocarbonyl group and using chalogen compounds as direct substrates represents a challenging goal in organic synthesis, because, in catalytic reactions, sulfur-containing compounds have been thought to act as catalyst poisons[3] because of the strong thiophilicity of transition metals.[4] The recent significant development of direct catalytic routes to thiocarbonyl-containing compounds without poisoning of the catalyst has resulted in the expanded use of catalytic carbonylation.[5] For example, in the course of our research on carbonylation processes using Pd catalysts, a substantial amount of work has been conducted on the thiocarbonylation and related reactions of functionally substituted alkenes, alkynes, allenes, and enynes.[6]

The importance and practicality of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds are well documented.[7] The outstanding synthetic utility of carbonylation has stimulated many attempts to investigate its catalytic asymmetric versions.[8] In the past few years, appreciable progress has occurred in this field;[9] however, the asymmetric version of thiocarbonylation has not been reported so far. We have recently described the novel thiocarbonylation of dienes.[6a] With the assistance of the palladium catalyst, 1,3-conjugated dienes are capable of undergoing reaction with a thiol and carbon monoxide, via η^3-allylpalladium complexes, to provide a convenient one-pot regio- and stereoselective synthesis of β,γ-unsaturated thiol esters (eq 1).[6a]



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



(1)

We reasoned that the addition of an appropriate chiral ligand could, in principle, lead to the formation of

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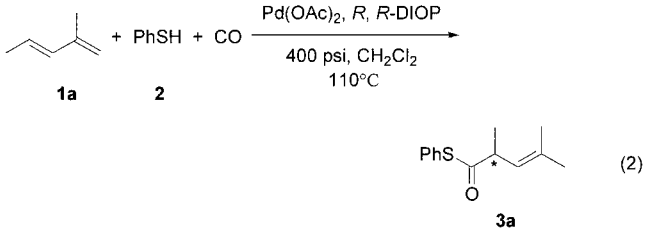
optically active thiol esters. We also recognized the challenge of having the chirality created at a center which is both allylic and alpha to the thiol ester functionality.

Enantiometrically enriched unsaturated thiol esters have been well-known as interesting synthetic building blocks.[10] Examples include the utilization of thiol esters in asymmetric cycloaddition,[11] in peptide synthesis,[12] and in natural product synthesis.[13] Herein we report the enantioselective carbonylative three-component reaction of 1,3-conjugated dienes with thiols and carbon monoxide catalyzed by Pd complexes with (*R*,*R*)-DIOP. A highlight of the present study is that these are the first examples of asymmetric thiocarbonylation, which significantly increase the scope and synthetic utility of the asymmetric carbonylation methodology. Furthermore, this method constitutes the first asymmetric synthesis of β,γ-unsaturated thiol esters by carbonylation chemistry.

Results and Discussion

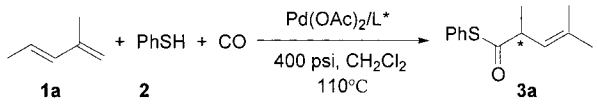
Initial studies focused on examining the feasibility of asymmetric thiocarbonylation and optimizing reaction conditions which could be applied to a variety of dienes to get high stereoselectivity. We selected 2-methyl-1,3-pentadiene (**1a**) as the model substrate for the study. The optimal reaction conditions used previously for the palladium-catalyzed thiocarbonylation of dienes[6a] were employed in the present case, with substitution of a chiral ligand for triphenylphosphine. The catalyst precursor for the asymmetric thiocarbonylation of **1a** was prepared by treatment of palladium acetate (5 mol %) with a chiral diphosphine ligand (10 mol %) under N_2 at room temperature. The resulting complex was used to effect the thiocarbonylation of **1a** with thiophenol (**2**) under 400 psi of carbon monoxide at 110 °C in CH_2Cl_2, affording the corresponding β,γ-unsaturated thiol ester (**3a**). The results are summarized in Table 1.

Among chiral ligands examined, (*R*,*R*)-(−)-*O*-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP) was found to be the chiral ligand of choice; *S*-phenyl 2,4-dimethyl-3-pentenethioate (**3a**) was isolated in 71% yield and 89% ee as determined by chiral GC (eq 2). Other commercially available chiral ligands (Chart 1) such as *R*-Tol-BINAP (72% yield, 47% ee), *R*-BINAP (56% yield, 42% ee), *R*-PROPHOS (12% yield, 17% ee), *S*,*S*-BDPP (31% yield, 76% ee), *R*,*R*-Boc-PYRPHOS (18% yield, 56% ee), and (−)-Me-DuPHOS (7% yield, 43% ee) were less effective in terms of asymmetric induction,



(2)

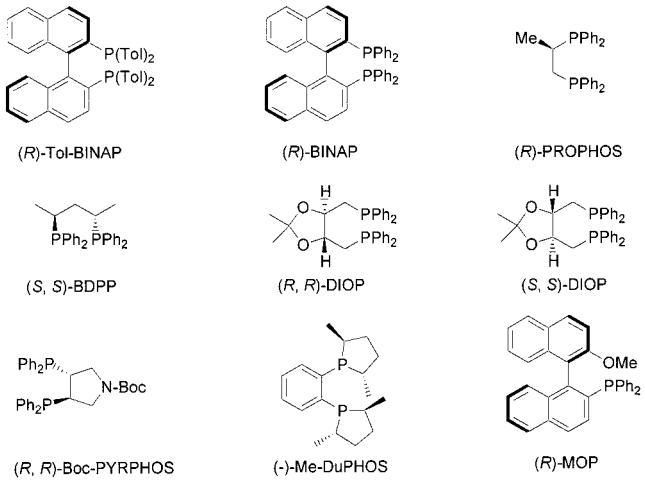
Table 1. Palladium-Catalyzed Asymmetric Thiocarbonylation of 1a with 2 and CO Using Various Chiral Phosphine Ligands[a]



entry	ligand	yield (%)	ee[b] (%)	$[\alpha]^{22}_D$ in $CHCl_3$[c]
1	*R*-Tol-BINAP	77	47	−19.8 (*c* 1.92)
2	*R*-BINAP	56	42	−18.2 (*c* 2.03)
3	*R*-PROPHOS	12	17	−14.6 (*c* 2.06)
4	*S*,*S*-BDPP	31	76	+35.7 (*c* 1.68)
5	*R*,*R*-DIOP	71	89	−48.3 (*c* 1.06)
6	*S*,*S*-DIOP	67	87	+44.4 (*c* 1.12)
7	*R*,*R*-Boc-PYRPHOS	18	56	−24.2 (*c* 2.01)
8	(−)-Me-DuPHOS	7	43	−18.7 (*c* 1.97)
9	(*R*)-MOP[d]	83	0	0

[a] Reaction conditions: thiophenol (1 mmol), 2-methyl-1,3-pentadiene (2 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), CH_2Cl_2 (5 mL), CO (400 psi), 110 °C. [b] Determined by chiral GC using a Supelco β-Dex 120 column (30 m). [c] Measured on a Perkin-Elmer polarimeter in a 10 cm cell at 22 °C. [d] 0.2 mol of the ligand was employed.

Chart 1



whereas *S*,*S*-DIOP (67% yield, 87% ee) gave almost the same yield and % ee as those obtained by using *R*,*R*-DIOP but, as anticipated, for the other enantiomer (entries 1−8 in Table 1). When a chiral monodentate phosphine ligand, (*R*)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP), was employed, the thiocarbonylation occurred in high yield, but no asymmetric induction was observed (entry 9 in Table 1). van Leeuwen studied the rate of CO insertion and found that the rate decreases in the order 1,4- > 1,3- ≫ 1,2-bisphosphine.[14] Thus, little thiocarbonylation took place using a palladium catalyst and a 1,2-bisphosphine ligand (e.g., (*R*)-PROPHOS and

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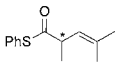
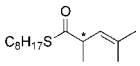
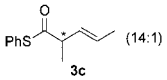
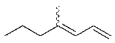
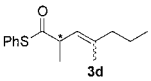
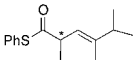
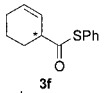
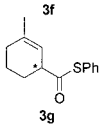
Table 2. Asymmetric Thiocarbonylation of Various 1,3-Conjugated Dienes with Thiophenol and CO in the Presence of $Pd(OAc)_2$−(*R*,*R*)-DIOP[a]

entry	diene	product (*E*/*Z*)	yield (%)	ee (%)	$[a]^{22}_D$ in $CHCl_3$
1	 1a	 3a	71	89	-48.4 (c 1.06)
2[b]	1a	 3b	24	85	-41.7 (c 1.20)
3	 1b	 (14:1) 3c	38	6	-3.78 (c 1.38)
4	 1c	 (19:1) 3d	72	82	-53.3 (c 1.42)
5	 1d	 (16:1) 3e	46	84	-53.1 (c 1.18)
6	 1e	 3f	64	10	-12.2 (c 1.52)
7	 1f	 3g	57	48	-23.6 (c 1.45)

[a] Reaction conditions: thiophenol (1 mmol), diene (2 mmol), $Pd(OAc)_2$ (0.05 mmol), (*R*,*R*)-DIOP (0.1 mmol), carbon monoxide (400 psi), CH_2Cl_2 (5 mL), 110 °C, 60 h. [b] $C_8H_{17}SH$ (1 mmol) was used instead of thiophenol, and the reaction time was 72 h.

(−)-Me-DuPHOS), and this might be associated with a small ligand−metal ring chelate.[14]

The effect of varying solvents was also examined. The reaction works well in CH_2Cl_2 (71% yield, 89% ee) and THF (63% yield, 85% ee), but less so in benzene (34% yield, 67% ee) and diethyl ether (47% yield, 54% ee).

The thiocarbonylation of various acyclic and cyclic 1,3-conjugated dienes, catalyzed by $[Pd(OAc)_2]$/(*R*,*R*)-DIOP, was effected under the optimal conditions. The results are presented in Table 2.

As described previously, this thiocarbonylation reaction is highly regioselective.[6a] Depending on the structural characteristics of substrates employed, the reaction could afford carbonylative 1,4- or 1,2-addition products. In general, the reaction gave good to excellent enantioselectivity. The reaction of 2-methyl-1,3-pentadiene (**1a**) with thiophenol and CO under optimal reaction conditions affords the carbonylative 1,4-addition product **3a** in 89% ee (entry 1 in Table 2). When an aliphatic thiol ($C_8H_{17}SH$) was used instead of thiophenol, the reaction also gave the corresponding carbonylative 1,4-addition product with a similar ee value, but the yield was appreciably lower (entry 2 in Table 2). Such behavior was also observed for the nonasymmetric version of palladium-catalyzed thiocarbonylation of 1,3-dienes.[6a] The ee values of the corresponding β,γ-unsaturated thiol esters (**3a**−**3f**) varied greatly, depending on the structures of the reactant 1,3-dienes **1**. Substantially lower enantioselectivities were observed when the substrate structure was changed from **1a** (entry 1 in Table 2) to **1b** (entry 2 in Table 2). Similarly, the ee was also lowered when 1-methyl-1,3-cyclohexadiene (**1f**) (entry 7 in Table 2) was replaced by cyclohexadiene (**1e**) (entry 6 in Table 2). With the increase of the bulkiness of substrates from **1b** to **1c** and to **1d**, the enantioselectivity increased significantly to give **3c**, **3d**, and **3e** in 6, 82, and 84% ee, respectively. Although the asymmetric thiocarbonylation of acyclic dienes works well, extension of the reaction to the cyclic substrate **1e** gives poor results (e.g., 10% ee, entry 6 in Table 2). When 1,3-cyclohexadiene with a methyl group at C-1 of the diene was used as the substrate, the ee of the product increased to 48%. Attempts to improve the stereoselectivity of the reaction of cyclohexadiene by changing the chiral ligands met with no success (eq 3).

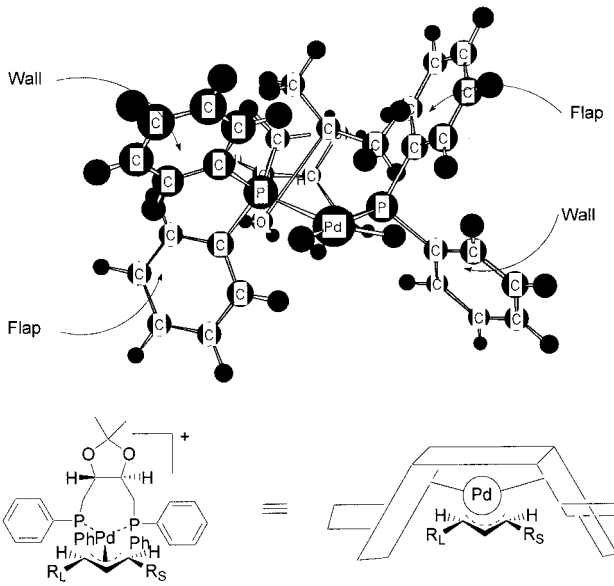
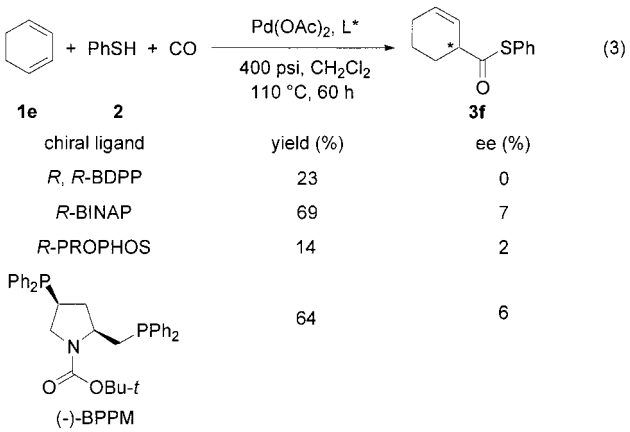


Figure 1. Trost's model of chiral pocket and cartoon representation of complex derived from *R*,*R*-DIOP.



(3)

In addition to the enantioselectivity, fine *E*/*Z* selectivity for the β,γ-unsaturated thiol esters resulted when some dienes were used as substrates. Using (*R*,*R*)-DIOP as the ligand, the *E*/*Z* selectivity is higher than that using PPh_3[6a] as the ligand. The thermodynamically more stable (*E*)-isomers were obtained in both cases. Although the source of the enantioselectivity is complicated by the possibility that one or more steps in the catalytic cycle may be enantiodiscriminating,[15] it is generally accepted that, in the attack of CO on the intermediate cationic

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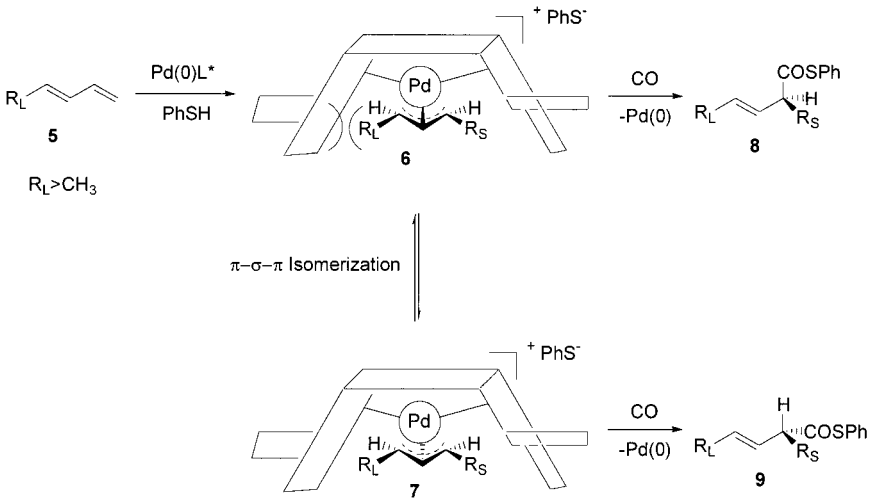

Figure 2. Predicted path for asymmetric thiocarbonylation for the reaction using *R*,*R*-DIOP.

(η^3-allyl)Pd(II) complex,[16] the steric interactions in the transition states[17] between the chiral ligand and the organic entity bound to the Pd center are an important factor which can largely determine the selectivity.

Mechanical and cartoon models for *R*,*R*-DIOP utilized herein are depicted in Figure 1, which are derived from the ground-state structure of the ligand−palladium−π-allyl complex and Trost's hypothesis regarding the structural features required for creating chiral space and molecular modeling.[18] In this model, the walls represent the chiral space created by the propeller-like array of the phenyl rings; the raised flaps represent the phenyls which lie in a plane approximately perpendicular to the allyl, while the lowered flaps represent phenyls which are somewhat parallel to the allyl.[18e]

When a prochiral diene was employed, intermediates **6** and **7** could be formed, which could rapidly racemize via a $\pi-\sigma-\pi$ mechanism.[19] Insertion of CO into **6** and **7** can result in the formation of **8** and **9**, respectively (Figure 2). The enantiodifferentiation step in this asymmetric thiocarbonylation is presumed to be the CO insertion step. The fine enantioselectivity is attributed to the differentiation of allyl complexes. Molecular modeling calculations indicate that the difference between the two π-allyl complexes, **6** and **7**, is approximately 2.73 kcal/mol.[18e,20] The difference might be due, at least in part, to greater steric interaction between the "wall" and the substituent, R_L, of **6**. To the extent that the transition-state energy for the insertion of CO into **7** is lower than that for CO insertion into **6**, one of the intermediates may react significantly faster than the other and consequently give the major enantiomer. The magnitude of the % ee might depend on the relative rate of the CO insertion and $\pi-\sigma-\pi$ isomerization.

In the case of cyclohexadiene as the substrate, the stereoselectivity of the reaction was much lower, presumably because of the quite symmetric structure of the possible intermediate. In this case, R_L and R_S are the same, and carbon monoxide can insert from both sides, resulting in lower enantioselectivity of the reaction.

Conclusions

In summary, we have developed the *first* asymmetric thiocarbonylation of prochiral 1,3-conjugated dienes with thiophenol and CO for the synthesis of optically active thiol esters. The asymmetric thiocarbonylation occurs in up to 89% ee. Although the stereoselectivity is only partially interpreted at this moment, the ability to carry out enantioselective carbonylation markedly enhances the synthetic utility of the reaction and constitutes a simple method to prepare chiral β,γ-unsaturated thiol esters.

Experimental Section

General Methods. All NMR spectra were recorded in $CDCl_3$, with TMS as an internal standard on Bruker AMX 500, Varian XL-300, or Gemini 200 spectrometers. Infrared spectra were recorded on a Bomem MB 100-C15 Fourier transform spectrometer and were reported in wavenumbers (cm^{-1}). Mass spectra were obtained on a VG 7070E spectrometer. Optical rotations were measured on a Perkin-Elmer polarimeter in a 10 cm cell at 22 °C. Chiral chromatographic analyses were performed on a Varian 3300 gas chromatograph installed with a Supelco β-Dex 120 30-m permethylated β-cyclodextrin fused silica capillary column 0.25 mm i.d. × 0.25 μm d_f, using helium as the carrier gas. Elemental analyses were performed by the elemental analysis service of the Department of Chemistry at the University of Ottawa, Canada.

Materials. 1-Methyl-1,3-cyclohexadiene (**1f**),[21] (−)-BPPM,[22] and (*R*,*R*)-Boc-PYRPHOS[23] were prepared according to literature procedures.

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General Procedure for the Asymmetric Palladium-Catalyzed Thiocarbonylation of Prochiral 1,3-Conjugated Dienes. A mixture of $Pd(OAc)_2$ (0.05 mmol), chiral phosphine ligand (0.1 mmol), and dichloromethane (10 mL) in a 45-mL autoclave was stirred at room temperature under nitrogen for 30 min. Prochiral 1,3-conjugated diene (2 mmol) and thiophenol (1 mmol) were then added. The reactor was flushed three times with CO and pressurized to 400 psi of CO. The mixture was stirred at 110 °C (oil bath temperature) for 60 h. After cooling, the excess CO was released. The mixture was filtered through Florisil, and the solvent was removed by rotary evaporation. The residue was purified by preparative silica gel TLC. The purified product was rechromatographed on preparative HPLC in order to eliminate the rest of the chiral phosphine ligand. The enantiomeric excess was determined by chiral GC equipped with a Superlco β-Dex 120 column.

Phenyl 2,4-Dimethyl-3-pentenethioate (3a). Colorless oil. IR (neat): υ 1710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (dd, 3H, J = 7.0 and 1.5 Hz), 1.80 (s, 3H), 1.86 (s, 3H), 3.47 (m, 1H), 5.53 (d, 1H, J = 9.2 Hz), 7.44 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.43, 18.24, 24.20, 45.78, 121.46, 129.04, 129.40, 131.04, 133.19, 134.28, 199.12. MS (70 eV, EI): M^+ 220.1. HRMS (70 eV, EI): calcd for $C_{13}H_{16}OS$, 220.0922; found, 220.0924. Anal. Calcd for $C_{13}H_{16}OS$: C, 70.88; H, 7.33. Found: C, 70.80; H, 7.44.

***n*-Octyl 2,4-Dimethyl-3-pentenethioate (3b).** Colorless oil. IR (neat): υ 1711 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.8 Hz), 1.22−1.35 (m, 11H), 1.43−1.60 (m, 4H), 1.68 (s, 3H), 1.73 (s, 3H), 2.74 (t, 2H, J = 7.2 Hz), 3.29−3.43 (m, 1H), 5.23 (d, 1H, J = 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.07, 16.52, 22.72, 23.59, 28.16, 28.98, 29.05, 29.20, 29.22, 32.40, 43.91, 125.78, 132.80, 199.73. MS (70 eV, EI): M^+ 256.2. HRMS (70 eV, EI): calcd for $C_{15}H_{28}OS$, 256.1861; found, 256.1868. Anal. Calcd for $C_{15}H_{28}OS$: C, 70.26; H, 11.02. Found: C, 70.34; H, 11.18.

Phenyl 2-Methyl-3-pentenethioate (3c). Colorless oil. IR (neat): υ 1706 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (d, 3H, J = 7.0 Hz), 1.74 (d, 1/15 × 3H, J = 6.0 Hz,), 1.78 (d, 14/15 × 3H, J = 6.8 Hz,), 3.32−3.48 (m, 1H), 5.57−5.71 (m, 2H), 7.42 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.24, 17.55, 17.77, 18.00, 25.55, 47.16, 51.65, 119.80, 127.71, 128.01, 128.85, 129.01, 129.11, 129.23, 131.47, 199.61. MS (70 eV, EI): M^+ 206.1. HRMS (70 eV, EI): calcd for $C_{12}H_{14}OS$, 206.0765; found, 206.0758. Anal. Calcd for $C_{12}H_{14}OS$: C, 69.88; H, 6.85. Found: C, 69.92; H, 6.90.

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Phenyl 2,4-Dimethyl-3-heptenethioate (3d). Colorless oil. IR (neat): υ 1707 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 6.8 Hz), 1.25 (d, 3H, J = 6.8 Hz), 1.43−1.50 (m, 2H), 1.73 (d, 19/20 × 3H, J = 1.4 Hz), 1.75 (d, 1/20 × 3H, J = 1.4 Hz), 2.02−2.15 (m, 2H), 3.55−3.63 (m, 1H), 5.14−5.22 (m, 19/20 × 1H), 5.44−5.55 (m, 1/20 × 1H), 7.40 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.60, 14.03, 17.99, 18.39, 20.70, 21.05, 23.44, 40.59, 41.69, 47.37, 47.60, 123.08, 123.59, 127.09, 128.37, 128.98, 129.47, 134.49, 139.83, 200.02. MS (70 eV, EI): M^+ 248.1. HRMS (70 eV, EI): calcd for $C_{15}H_{20}OS$, 248.1235; found, 248.1235. Anal. Calcd for $C_{15}H_{20}OS$: C, 72.54; H, 8.12. Found: C, 72.56; H, 8.20.

Phenyl 2,4,5-Trimethyl-3-hexenethioate (3e). Colorless oil. IR (neat): υ 1708 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (d, 6H, J = 6.8 Hz), 1.22 (d, 3H, J = 6.8 Hz), 1.67 (s, 3H), 2.56 (q, 1H, J = 6.8 Hz), 3.34 (dq, 1/17 × 1H, J = 6.8 and 9.2 Hz), 3.38 (dq, 16/17 × 1H, J = 7.0 and 9.2 Hz), 5.31 (d, 1H, J = 9.2 Hz), 7.40 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.84, 19.97, 22.50, 38.78, 45.78, 47.32, 121.90, 124.84, 128.84, 130.07, 134.19, 137.48, 199.96. MS (70 eV, EI): M^+ 248.1. HRMS (70 eV, EI): calcd for $C_{15}H_{20}OS$, 248.1235; found, 248.1241. Anal. Calcd for $C_{15}H_{20}OS$: C, 72.54; H, 8.12. Found: C, 72.58; H, 8.07.

Phenyl 2-Cyclohexene-1-carbothioate (3f). Colorless oil. IR (neat): υ 1701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.92−2.08 (m, 6H), 3.30−3.38 (m, 1H), 5.78−5.84 (m, 1H), 5.94−6.02 (m, 1H), 7.38 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.44, 24.70, 26.27, 49.92, 123.36, 127.98, 129.09, 129.18, 131.50, 134.55, 199.77. MS (70 eV, EI): M^+ 218.1. HRMS (70 eV, EI): calcd for $C_{13}H_{14}OS$, 218.0782; found, 218.0764. Anal. Calcd for $C_{13}H_{14}OS$: C, 71.52; H, 6.46. Found: C, 71.44; H, 6.50.

Phenyl 3-Methyl-2-cyclohexene-1-carbothioate (3g). Colorless oil. IR (neat): υ 1704 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.58−1.78 (m with a singlet at δ 1.76, 5H), 1.90−2.08 (m, 2H), 2.50−2.67 (m, 2H), 3.26−3.33 (m, 1H), 5.84−5.86 (m, 1H), 7.43 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.04, 22.13, 29.46, 32.04, 53.25, 122.32, 124.18, 129.02, 131.00, 133.29, 136.56, 198.84. MS (70 eV, EI): M^+ 232.1. HRMS (70 eV, EI): calcd for $C_{14}H_{16}OS$, 232.0922; found, 232.0918. Anal. Calcd for $C_{14}H_{16}OS$: C, 72.39; H, 6.95. Found: C, 72.46; H, 7.04.

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