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Rhodium-catalyzed α-methylthiolation reaction of unactivated ketones using 1,2-diphenyl-2-methylthio-1-ethanone for the methylthio transfer reagent

Mieko Arisawa [a], Fumihiko Toriyama [b], Masahiko Yamaguchi [a,c,*]

[a] Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Sendai 980-8578, Japan
[b] Process Technology Research Laboratories, Daiichi Sankyo Co., Ltd, Kanagawa, Hiratsuka 254-0014, Japan
[c] WPI Advanced Institute for Materials Research, Tohoku University, Aoba, Sendai 980-8577, Japan

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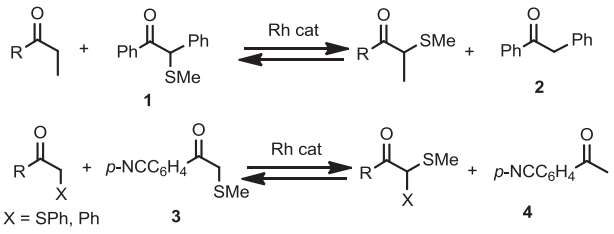
ABSTRACT

In the presence of catalytic amounts of $RhH(PPh_3)_4$, 1,2-bis(diphenylphosphino)ethane (dppe), and dimethyl disulfide, ketones without α-activating groups were α-methylthiolated with 1,2-diphenyl-2-methylthio-1-ethanone giving α-methylthio ketones. The reaction of unsymmetrical ketones proceeded at the more substituted carbons. The initial formation of kinetic α-methylthiolated products followed by their rearrangement to thermodynamic products was observed in the reaction of α-phenyl ketones. Aldehydes, phenylacetate, and phenylacetonitrile were also α-methylthiolated under these conditions.

1. Introduction

α-Organothioketones are versatile intermediates in organic synthesis and can be converted to reactive compounds, such as enones, α-sulfonyl ketones, and α-sulfoxy ketones. Their synthesis is generally accomplished by the organothiolation reaction of alkalimetal enolates, which are generated by treating ketones with amide or alkoxide bases.[1] During our investigations on the development of rhodium-catalyzed synthesis for organosulfur compounds,[2] we previously described the α-methylthiolation reaction of α-phenylthio ketones[3] and α-phenyl ketones[4] employing α-methylthio-*p*-cyanoacetophenone **3** as the methylthiolating reagent. In this equilibrium reaction, the methylthio group is transferred from **3** to the α-position of the ketone possessing the activating group with the concomitant formation of *p*-cyanoacetophenone **4** (Scheme 1). Unlike conventional methods, the α-methylthiolation reaction of ketones uses no base. For the reaction of α-phenylthio ketones, a catalyst derived from $RhH(PPh_3)_4$ and 1,2-diphenylphosphinoethane (dppe) is employed[3]; for that of α-phenyl ketones, the catalyst is activated in the presence of dimethyl disulfide.[4] Unfortunately, these methods cannot be applied to acetophenone or cyclohexanone without α-activating groups owing to the inertness of these compounds. The inertness is thought to be due to the unfavorable combination of the ketone substrate and methylthio donor. Described in this study is the use of 1,2-diphenyl-2-methylthio-1-ethanone **1**,[4] which effectively gives α-methylthio ketones from unactivated ketones with the formation of 1,2-diphenyl-1-ethanone **2** (Scheme 1).



Scheme 1.

2. Result and discussion

When propiophenone **5** (5 equiv) was reacted with **1** (1 equiv) in the presence of $RhH(PPh_3)_4$ (4 mol %), dppe (8 mol %), and dimethyl disulfide (12 mol %) in refluxing THF for 3 h, α-methylthiopropiophenone **6** was obtained in 91% yield based on **1**, which was accompanied by 1,2-diphenyl-1-ethanone **2** in 94% yield (Scheme 2). A catalytic amount of dimethyl disulfide was again

* Corresponding author. Fax: +81 22 795 6811; e-mail address: yama@mail.pharm.tohoku.ac.jp (M. Yamaguchi).

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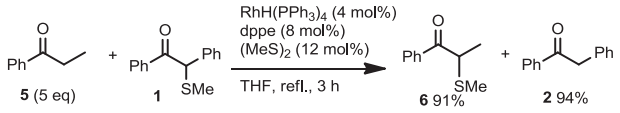
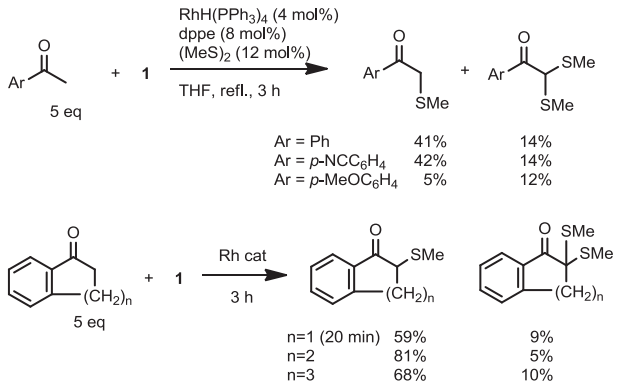
essential for this reaction, and only 24% yield of **6** was obtained in its absence. It was confirmed that no **6** was formed in the absence of either $RhH(PPh_3)_4$ or dppe. The use of **3** in place of **1** gave no detectable amount of **6** under the same conditions.



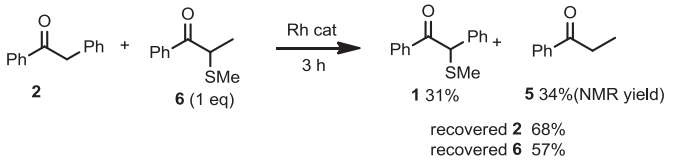
Scheme 2.

The reaction of acetophenone gave α-methylthioacetophenone (41%) and α,α-di(methylthio)acetophenone (14%) (Scheme 3). *p*-Cyanoacetophenone reacted similarly with **1**, although the yields were lower with *p*-methoxyacetophenone. The substituent effect may be ascribed to the less acidic nature of the latter with an electron-donating group. Benzocyclohexenone and benzocycloheptenone were also α-methylthiolated in 81 and 68% yields, respectively, which were accompanied by the formation of small amounts of α,α-dimethylthiolated products. The reaction of indanone proceeded rapidly giving the monomethylthio and dimethylthio products in 59 and 9% yields, respectively, after 20 min. Since the yield did not change after 3 h, this may be an equilibrium state. The higher reactivity of the five-membered ring ketone can be ascribed to the acidic nature of the substrate.[5]



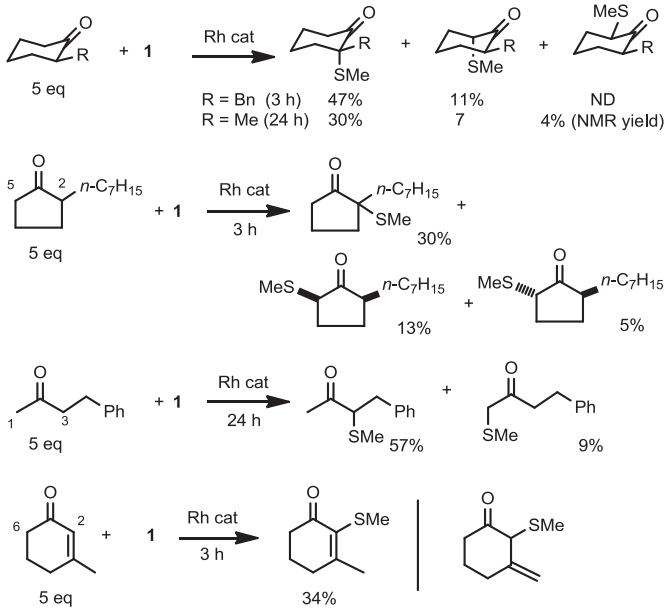
Scheme 3.

The reversibility of the methylthio transfer reaction was confirmed (Scheme 4). The treatment of equimolar amounts of **2** and **6** with the catalyst in refluxing THF for 3 h gave **1** and **5** in 31 and 34% (NMR yield) yields, which were accompanied by the quantitative recovery of the starting materials **2** and **6**, respectively.



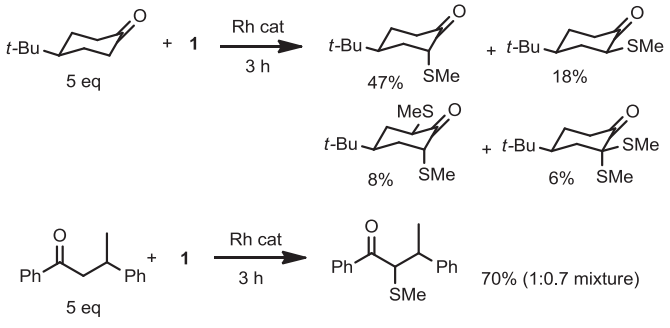
Scheme 4.

The regioselectivity of the rhodium-catalyzed α-methylthiolation reaction was examined using unsymmetrical ketones (Scheme 5). The reaction of 2-benzylcyclohexanone gave 2-benzyl-2-methylthiocyclohexanone (47%) and 6-benzyl-2-methylthiocyclohexanone (11%). The α-methylthiolation proceeded predominantly at the 2-position of 2-methylcyclohexanone and 2-heptylcyclopentanone. The reaction of 4-phenyl-2-butanone occurred predominantly at the 3-position. The α-methylthiolation at the more substituted sites was consistent with the intermediacy of thermodynamic enolates. The reaction of 3-methyl-2-cyclohexenone gave 3-methyl-2-(methylthio)-2-cyclohexenone in 34% yield. The product should be formed from the initial product 3-methylene-2-(methylthio)cyclohexanone by double-bond migration, which was formed by the 2-methylthiolation of the thermodynamic dienolate.



Scheme 5.

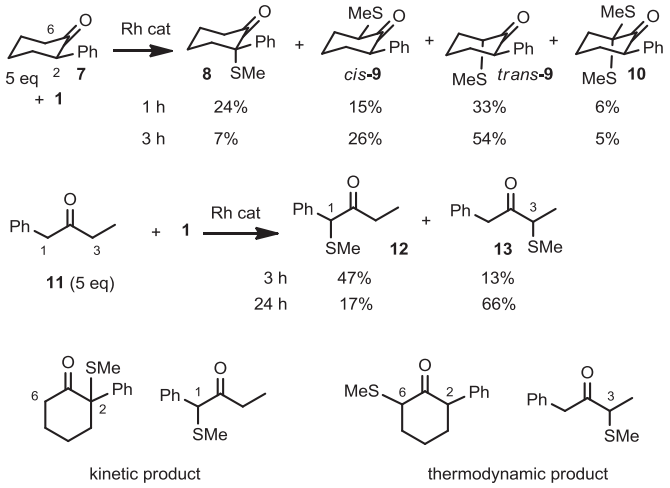
The stereochemical aspect of this reaction was also examined. When 4-(*tert*-butyl)cyclohexanone was reacted, α-methylthiolated products were obtained in 65% yield as a mixture of axial isomer (47%) and equatorial isomer (18%), together with 2,6-dimethylthiolated ketone (8%) and 2,2-dimethylthio derivative (6%) (Scheme 6). The preference for the axial-methylthiolation product was previously observed in the reaction of 2-phenylthiocyclohexanone.[3] The reaction of 1,3-diphenyl-1-butanone gave the product as a mixture of comparable amounts of diastereomers.



Scheme 6.

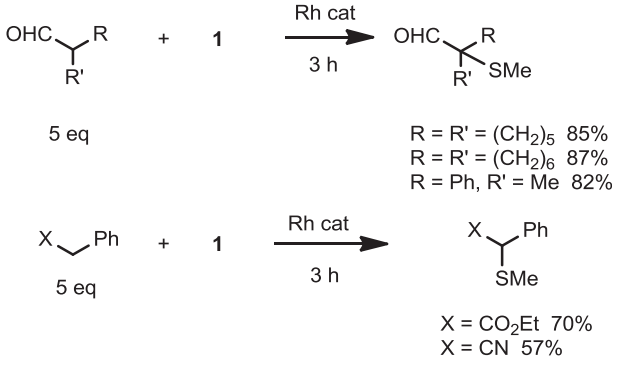
A notable reversible nature of this reaction was observed in the reaction of α-phenyl ketones (Scheme 7). The treatment of 2-phenylcyclohexanone **7** and **1** in refluxing THF for 1 h gave a mixture of 2-methylthio-2-phenylcyclohexanone **8** (24%), 6-methylthio-2-phenylcyclohexanone *cis*-**9** (15%) and *trans*-**9** (33%), and 2,2-dimethylthio-6-phenylcyclohexanone **10** (6%). When heating was continued for 3 h, the yield of **8** decreased to 7%, and that of an

isomeric mixture of **9** increased to 80%, which indicated that **8** is a kinetic product and **9** a thermodynamic product. The results are in contrast to those of the selective formation of **8** using **3**.[4] It may be likely that 1,2-diphenyl-1-ethanone **2** accepted the methylthio group from **8**, and transferred it to **7** giving **9**. That the use of **3** in place of **1** gave only **8** can be ascribed to the lack of ability of **3** to transfer the methylthio group to **7** at the 6-position. The reaction of 1-phenyl-2-butanone **11** for 3 h gave 1-methylthio derivative **12** and 3-methylthio derivative **13** in 47 and 13% yields, respectively. The amount of **12** decreased and that of **13** increased after 24 h, indicating the former to be a kinetic product and the latter a thermodynamic product.



Scheme 7.

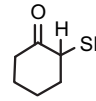
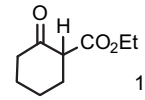
Aldehydes with α,α-disubstituents also reacted with **1** in the presence of the rhodium catalyst giving α-methylthiolated aldehydes (Scheme 8). Not only aldehydes and ketones but also phenylacetic acid derivatives were effectively converted to the products using **1**, but not **3**. The reaction of ethyl phenylacetate gave the methylthiolated compound in 70% yield and phenylacetonitrile in 57% yield.



Scheme 8.

The different reactivities of **1** and **3** in the rhodium-catalyzed reaction are summarized in Table 1, which contains pK_a values of the related acetone derivatives.[6] Using **1**, cyclohexanone and 2-phenylcyclohexanone were methylthiolated to give high yields of the product, whereas 2-(phenylthio)cyclohexanone and 2-(ethoxycarbonyl)cyclohexanone gave modest yields of the products. The reactivity of **3** was compared using the same substrates: 2-(phenylthio)cyclohexanone[3] and 2-phenylcyclohexanone[4] previously

Table 1
Reactivities of **1** and **3** in the rhodium-catalyzed methylthiolation reaction

substrate	pK_a[a]	**1**	**3**
methylthio donor			
	26.5	79%[b]	trace[b]
	19.8	92%[b]	50%[3]
	18.7	24%[b]	45%[4]
	14.2	36%[b]	7%[b]

[a] pK_a values of acetone derivatives.[6]
[b] This work.

gave the products in good yields, and cyclohexanone did not. Also it was confirmed in this work that 2-(ethoxycarbonyl)cyclohexanone gave only 7% yield of the product. It was shown here that **1** can be used to methylthiolate less acidic substrates; **3** can be used for moderately acidic substrates, and more and less acidic substrates are essentially inert. The results may be interpreted on the basis of favored combinations of compounds with stronger C–H bonds and those with stronger C–S bonds and vice versa: the stronger C–H bonds of cyclohexanone with less acidic protons were effectively converted to C–S bonds using the methylthio donor **1** with a stronger C–S bond than **3**; the weaker C–H bond of 2-(phenylthio)cyclohexanone with an acidic proton was methylthiolated using **3** with a weaker C–S bond donor **3** than **1**. Studies are now underway to develop other examples of organothio transfer equilibrium reactions and to clarify the principle, which governs the reactivity.

3. Conclusion

In summary, unactivated ketones were effectively α-methylthiolated using 2-methylthio-1,2-diphenyl-1-ethanone **1** under rhodium-catalyzed conditions. The higher efficiency of **1** than of α-methylthio-*p*-cyanoacetophenone **3** may be ascribed to the equilibrium shift, probably due to the stronger C–S bond energy of **1** than of **3**, which favors α-methylthiolated ketones over unactivated ketones possessing less acidic α-protons. It is likely that the rhodium complex can activate various carbonyl α-protons, and that the use of appropriate methylthio donors is critical for organothiolation.

4. Experimental section

4.1. General

^{1}H NMR, ^{13}C NMR spectra were recorded on a Varian Mercury (400 MHz, 300 MHz), a JEOL JNM-ECA600 (600 MHz), and a JNM-ECA500 (500 MHz). IR spectra were measured on a JASCO FT/IR-410 spectrophotometer (neat/KBr), a FT/IR-8900 spectrophotometer

(neat/KBr), a FT/IR-6100 spectrometer (ATR), or a FT/IR-6300 spectrometer (ATR). Melting points were determined with a Yanagimoto micro melting point apparatus without correction. High- and low-resolution mass spectra were measured on a JEOL JMS-DX-303, a JEOL JMS-700, a JEOL JMS-T100GC, a JEOL GCmate, or a JMS-T100LC.

4.2. Typical procedures for α-methylthiolation reaction

In a two-necked flask equipped with a reflux condenser were placed $RhH(PPh_3)_4$ (4 mol %, 11.5 mg), 1,2-bis(diphenylphosphino) ethane (8 mol %, 8.0 mg), propiophenone **5** (1.25 mmol, 166 μL), 2-methylthio-2-phenylacetophenone **1**[4] (0.25 mmol, 60.6 mg), and dimethyl disulfide (12 mol %, 2.7 μL) in THF (0.25 mL) under an argon atmosphere, and the solution was heated at 90 °C for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving **6** (41.1 mg, 91%) and 1,2-diphenyl-1-ethanone **2** (46.0 mg, 94%) with the recovery of **5** (86.8 mg, 52%) and **1** (3.6 mg, 6%).

Their structures were determined by comparing the spectral data with references: 2-(Methylthio)-1-phenyl-1-ethanone,[3] 2,2-di(methylthio)-1-phenyl-1-ethanone,[7] 2-(methylthio)-1-(4-cyanophenyl)-1-ethanone,[3] 2,2-di(methylthio)-1-(4-cyanophenyl)-1-ethanone,[3] 2-(methylthio)-1-(4-methoxyphenyl)-1-ethanone,[3] 2,2-di(methylthio)-1-(4-methoxyphenyl)-1-ethanone,[8] 2-(methylthio)-2-phenylcyclohexanone (**8**),[4] and 1-(methylthio)-1-phenyl-2-butanone (**12**).[4]

*4.2.1. 2-(Methylthio)-1-phenyl-1-propanone (**6**)*[7]. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, *J*=6.9 Hz, 3H), 1.96 (s, 3H), 4.33 (q, *J*=6.8 Hz, 1H), 7.46 (tt, *J*=7.5, 1.5 Hz, 2H), 7.56 (tt, *J*=7.4, 1.7 Hz, 1H), 8.01 (d, *J*=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 15.0, 40.7, 128.4, 128.4, 132.9, 135.5, 194.9. IR (neat) 3060, 2973, 2924, 1674, 1447, 1334, 1235, 950, 726, 703 cm^{-1}. MS (EI) *m*/*z* 180 (M^+, 26%), 134 (M^+-CH_2S, 59%), 105 (M^+−MeSCHMe, 100%). HRMS (EI) calcd for $C_{10}H_{12}OS$: 180.0609. Found: 180.0598.

4.2.2. 2-(Methylthio)-1-indanone[9]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.95–3.02 (m, 1H), 3.57–3.64 (m, 2H), 7.40 (t, *J*=7.5 Hz, 1H), 7.44 (d, *J*=7.7 Hz, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 7.80 (d, *J*=7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 34.2, 46.8, 124.5, 126.3, 127.8, 135.1, 135.3, 152.0, 202.9. IR (ATR) 2918, 2843, 1701, 1607, 1463, 1431, 1274, 743 cm^{-1}. MS (EI) *m*/*z* 178 (M^+, 36%), 132 (M^+-CH_2S, 100%). HRMS (ESI) calcd for $C_{10}H_{11}OS$ $[M+H]^+$: 179.0531. Found: 179.0523.

4.2.3. 2,2-Di(methylthio)-1-indanone. Colorless solid. Mp 65 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 6H), 3.47 (s, 2H), 7.38 (d, *J*=7.5 Hz, 1H), 7.42 (t, *J*=7.3 Hz, 1H), 7.62 (td, *J*=7.6, 0.9 Hz, 1H), 7.83 (d, *J*=7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 43.9, 62.1, 125.6, 126.0, 128.2, 133.7, 135.3, 149.1, 197.1. IR (ATR) 2916, 2852, 1694, 1432, 851, 757, 647 cm^{-1}. MS (EI) *m*/*z* 224 (M^+, 20%), 177 (M^+−MeS, 100%). HRMS (ESI) calcd for $C_{11}H_{13}OS_2$ $[M+H]^+$: 225.0408. Found: 225.0402.

4.2.4. 2-(Methylthio)-3,4-dihydro-1(2H)-naphthalenone. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.33 (dq, *J*=13.9, 4.2 Hz, 1H), 2.53 (ddt, *J*=13.8, 11.8, 4.4 Hz, 1H), 2.84 (dt, *J*=17.0, 4.2 Hz, 1H), 3.22 (ddd, *J*=16.9, 12.0, 4.8 Hz, 1H), 3.50 (t, *J*=4.2 Hz, 1H), 7.22 (d, *J*=7.7 Hz, 1H), 7.33 (t, *J*=7.6 Hz, 1H), 7.72 (td, *J*=7.5, 1.3 Hz, 1H), 8.10 (dd, *J*=7.8, 0.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 25.8, 28.6, 50.0, 126.8, 128.1, 128.5, 130.7, 133.3, 142.7, 192.3. IR (ATR) 2919, 2854, 1674, 1600, 1454, 1301, 1282, 1241, 741 cm^{-1}. MS (EI) *m*/*z* 192 (M^+, 45%), 146 (M^+-CH_2S, 100%). HRMS (ESI) calcd for $C_{11}H_{13}OS$ $[M+H]^+$: 193.0687. Found: 193.0687.

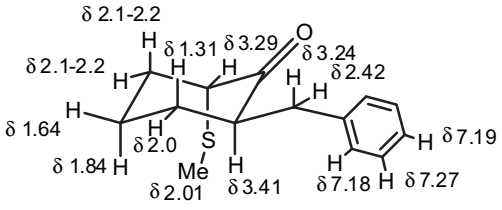
4.2.5. 2,2-Di(methylthio)-3,4-dihydro-1(2H)-naphthalenone[10]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (s, 6H), 2.61 (t, *J*=6.3 Hz, 2H), 3.09 (t, *J*=6.3 Hz, 2H), 7.21 (d, *J*=7.5 Hz, 1H), 7.34 (t, *J*=7.6 Hz, 1H), 7.48 (td, *J*=7.5, 1.3 Hz, 1H), 8.13 (dd, *J*=7.8, 0.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 26.5, 35.4, 64.7, 127.0, 128.4, 128.8, 130.3, 133.4, 142.0, 188.4. IR (ATR) 2917, 2852, 1670, 1598, 1424, 1290, 1217, 813, 744 cm^{-1}. MS (EI) *m*/*z* 238 (M^+, 21%), 191 (M^+−MeS, 100%). HRMS (ESI) calcd for $C_{12}H_{14}NaOS_2$ $[M+Na]^+$: 261.0384. Found: 261.0376.

4.2.6. 6-(Methylthio)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89–2.02 (m, 3H), 2.13 (s, 3H), 2.21–2.27 (m, 1H), 2.94 (ddd, *J*=15.4, 9.1, 3.7 Hz, 1H), 3.05 (ddd, *J*=15.6, 7.3, 4.0 Hz, 1H), 3.74 (dd, *J*=8.0, 5.0 Hz, 1H), 7.19 (d, *J*=7.7 Hz, 1H), 7.29 (t, *J*=7.3 Hz, 1H), 7.40 (td, *J*=7.4, 1.5 Hz, 1H), 7.62 (dd, *J*=7.7, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 24.1, 29.9, 34.2, 55.4, 126.5, 128.9, 129.6, 131.5, 138.7, 139.9, 203.0. IR (ATR) 2921, 2861, 1668, 1597, 1446, 1287, 1267, 771, 735 cm^{-1}. MS (EI) *m*/*z* 206 (M^+, 11%), 158 (M^+−MeSH, 100%). HRMS (ESI) calcd for $C_{12}H_{14}NaOS$ $[M+Na]^+$: 229.0663. Found: 229.0668.

4.2.7. 6,6-Di(methylthio)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one[11]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88 (t, *J*=6.1 Hz, 2H), 1.99 (quint, *J*=6.6 Hz, 2H), 2.08 (s, 6H), 2.86 (t, *J*=6.9 Hz, 2H), 7.12 (d, *J*=7.5 Hz, 1H), 7.28 (td, *J*=7.5, 0.9 Hz, 1H), 7.36 (d, *J*=6.5 Hz, 1H), 7.38 (td, *J*=7.4, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 22.7, 31.1, 31.5, 68.4, 126.5, 127.8, 128.2, 130.9, 136.7, 138.7, 199.0. IR (ATR) 2916, 2855, 1677, 1244, 958, 759, 674, 633 cm^{-1}. MS (EI) *m*/*z* 252 (M^+, 36%), 205 (M^+−MeS, 100%). HRMS (ESI) calcd for $C_{13}H_{16}NaOS_2$ $[M+Na]^+$: 275.0540. Found: 275.0531.

4.2.8. 2-Benzyl-2-(methylthio)cyclohexanone[11]. Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.51 (qt, *J*=13.5, 4.3 Hz, 1H), 1.56–1.59 (m, 1H), 1.75 (dq, *J*=14.5, 3.2 Hz, 1H), 1.82 (ddd, *J*=14.5, 13.1, 4.1 Hz, 1H), 1.91–2.00 (m, 2H), 1.96 (s, 3H), 2.25 (dquint, *J*=15.1, 2.1 Hz, 1H), 2.94 (d, *J*=14.1 Hz, 1H), 3.11 (ddd, *J*=15.1, 14.0, 6.2 Hz, 1H), 3.19 (d, *J*=14.0 Hz, 1H), 7.19 (d, *J*=7.5 Hz, 2H), 7.21 (tt, *J*=7.4, 1.7 Hz, 1H), 7.26 (tt, *J*=7.3, 1.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 20.6, 26.1, 35.7, 37.0, 39.3, 57.0, 126.4, 127.8, 131.0, 137.0, 206.1. IR (neat) 3028, 2937, 2862, 1699, 1496, 1447, 1417, 1124, 700 cm^{-1}. MS (EI) *m*/*z* 234 (M^+, 46%), 188 (M^+-CH_2S, 32%), 187 (M^+−MeS, 38%), 143 (M^+−Bn, 100%). HRMS (EI) calcd for $C_{14}H_{18}OS$: 234.1078. Found: 234.1065.

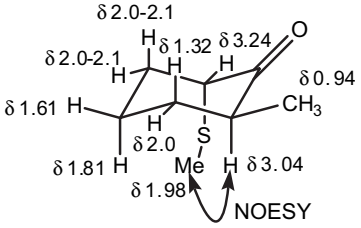
4.2.9. (2R,6S*)-2-Benzyl-6-(methylthio)cyclohexanone.* Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (qd, *J*=13.0, 3.6 Hz, 1H), 1.64 (dquint, *J*=13.9, 3.5 Hz, 1H), 1.84 (qt, *J*=13.1, 4.0 Hz, 1H), 1.95–2.00 (m, 1H), 2.01 (s, 3H), 2.07–2.17 (m, 2H), 2.42 (dd, *J*=14.1, 8.9 Hz, 1H), 3.24 (dd, *J*=14.1, 4.8 Hz, 1H), 3.29 (dd, *J*=4.6, 2.6 Hz, 1H), 3.41 (ddd, *J*=12.9, 8.8, 5.2 Hz, 1H), 7.18 (d, *J*=7.6 Hz, 2H), 7.19 (t, *J*=7.6 Hz, 1H), 7.27 (t, *J*=7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.2, 21.2, 32.9, 33.1, 35.3, 45.9, 53.9, 126.0, 128.3, 129.1, 140.2, 209.5. IR (neat) 3060, 3027, 2933, 2860, 1699, 1496, 1453, 1441, 754, 703 cm^{-1}. MS (EI) *m*/*z* 234 (M^+, 40%), 191 ($M^+-C_3H_7$, 40%), 186 (M^+−MeSH, 100%). HRMS (EI) calcd for $C_{14}H_{18}OS$: 234.1078. Found: 234.1062. The configuration of the 2-benzyl group was determined by the coupling constant *J*=12.9 Hz of the 2-axial proton (δ 3.41). The configuration of the 6-methylthio group was determined by the coupling constant *J*=4.6 Hz of the 6-equatorial proton (δ 3.29).



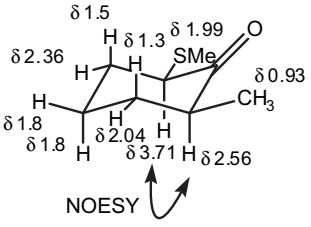
4.2.10. 2-Methyl-2-(methylthio)cyclohexanone[11]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.57–1.67 (m, 2H), 1.85 (td, *J*=13.4,

3.7 Hz, 1H), 1.88 (s, 3H), 1.98–2.13 (m, 3H), 2.20–2.23 (m, 1H), 3.13 (td, J=14.3, 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 21.1, 22.7, 26.9, 36.6, 40.1, 53.2, 207.8. IR (ATR) 2926, 2863, 1698, 1444, 1423, 1282, 1125, 1088, 991, 821 cm^{-1}. MS (EI) m/z 158 (M^+, 86%), 115 ($M^+-C_3H_7$, 51%), 112 (M^+-CH_2S, 100%). HRMS (ESI) calcd for $C_8H_{14}NaOS$ $[M+Na]^+$: 181.0663. Found: 181.0658.

4.2.11. (2S,6S*)-2-Methyl-6-(methylthio)cyclohexanone*[12]. Colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 40 °C) δ 0.94 (d, J=6.7 Hz, 3H), 1.32 (qd, J=12.7, 3.8 Hz, 1H), 1.61 (dquint, J=13.7, 3.7 Hz, 1H), 1.81 (qt, J=9.2, 3.7 Hz, 1H), 1.98 (s, 3H), 1.96–2.12 (m, 3H), 3.04 (dquint, J=12.5, 6.3 Hz, 1H), 3.24 (dd, J=4.5, 2.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 40 °C) δ 14.4, 14.4, 20.6, 32.1, 34.9, 38.7, 52.7, 208.9. IR (ATR) 2931, 2854, 1702, 1443, 1224, 1173, 1124, 1006, 868 cm^{-1}. MS (EI) m/z 158 (M^+, 100%), 115 ($M^+-C_3H_7$, 81%), 112 (M^+-CH_2S, 86%). HRMS (ESI) calcd for $C_8H_{14}NaOS$ $[M+Na]^+$: 181.0663. Found: 181.0673. Their configurations of the 2-methyl group and the 6-methylthio group were determined by observing NOE between the 2-axial proton (δ 3.04) and the 6-methylthio proton (δ 1.98).

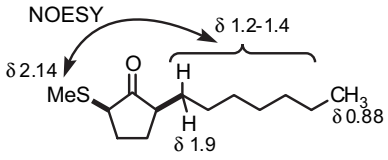


4.2.12. (2S,6R*)-2-Methyl-6-(methylthio)cyclohexanone*[12]. Colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6, 40 °C) δ 0.93 (d, J=6.5 Hz, 3H), 1.26–1.34 (m, 1H), 1.47–1.56 (m, 1H), 1.76–1.81 (m, 2H), 1.99 (s, 3H), 2.04 (ddq, J=13.0, 5.9, 3.0 Hz, 1H), 2.36 (ddq, J=12.7, 5.9, 2.9 Hz, 1H), 2.56 (dquintd, J=13.0, 6.5, 1.2 Hz, 1H), 3.71 (ddd, J=12.9, 5.7, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.7, 14.6, 24.7, 35.0, 36.0, 44.5, 55.2, 208.1. IR (ATR) 2930, 2858, 1713, 1446, 1124, 1039, 772 cm^{-1}. MS (EI) m/z 158 (M^+, 100%), 115 ($M^+-C_3H_7$, 82%), 112 (M^+-CH_2S, 88%). HRMS (ESI) calcd for $C_8H_{14}NaOS$ $[M+Na]^+$: 181.06631. Found: 181.06668. Their configurations of the 2-methyl group and the 6-methylthio group were determined by observing NOE between the 2-axial proton (δ 2.56) and the 6-axial proton (δ 3.71).

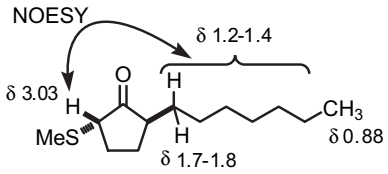


4.2.13. 2-Heptyl-2-(methylthio)cyclopentanone. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.13–1.22 (m, 1H), 1.23–1.35 (m, 8H), 1.42 (ddd, J=14.0, 11.7, 4.4 Hz, 1H), 1.48–1.55 (m, 1H), 1.76 (td, J=13.1, 3.9 Hz, 1H), 1.84–1.99 (m, 3H), 1.89 (s, 3H), 2.01–2.17 (m, 2H), 2.59–2.65 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 14.1, 18.2, 22.6, 24.3, 29.2, 29.9, 31.0, 31.8, 35.0, 35.7, 55.3, 211.0. IR (ATR) 2954, 2923, 2855, 1724, 1462, 1163 cm^{-1}. MS (EI) m/z 228 (M^+, 35%), 185 ($M^+-C_3H_7$, 100%), 182 (M^+-CH_2S, 55%). HRMS (ESI) calcd for $C_{13}H_{25}OS$ $[M+H]^+$: 229.1626. Found: 229.1625.

4.2.14. (2S,5R*)-2-Heptyl-5-(methylthio)cyclopentanone.* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.21–1.43 (m, 11H), 1.76–1.82 (m, 1H), 1.86–1.92 (m, 2H), 2.07–2.14 (m, 3H), 2.14 (s, 3H), 3.07 (d, J=5.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.4, 22.6, 27.1, 27.7, 28.2, 29.1, 29.5, 31.8, 32.1, 47.9, 48.6, 213.9. IR (ATR) 2954, 2923, 2854, 1726, 1458, 1027, 804, 723 cm^{-1}. MS (EI) m/z 228 (M^+, 50%), 185 ($M^+-C_3H_7$, 45%), 181 (M^+-MeS, 41%), 74 ($MeSC_2H_3$, 100%). HRMS (ESI) calcd for $C_{13}H_{25}OS$ $[M+H]^+$: 229.1626. Found: 229.1618. Their configurations of the 2-heptyl group and the 5-methylthio group were determined by observing NOE between the 2-heptyl methylene proton (δ 1.21–1.43) and the 5-methylthio proton (δ 2.14).



4.2.15. (2S,5S*)-2-Heptyl-5-(methylthio)cyclopentanone.* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 1.21–1.36 (m, 11H), 1.52 (dtd, J=12.2, 9.0, 7.0 Hz, 1H), 1.69–1.78 (m, 2H), 2.17 (s, 3H), 2.21–2.36 (m, 3H), 3.03 (t, J=8.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.2, 22.6, 27.0, 27.4, 27.8, 29.1, 29.5, 30.0, 31.8, 47.0, 49.4, 216.2. IR (ATR) 2955, 2923, 2854, 1731, 1458, 1022, 803, 722 cm^{-1}. MS (EI) m/z 228 (M^+, 20%), 185 ($M^+-C_3H_7$, 35%), 181 (M^+-MeS, 21%), 74 ($MeSC_2H_3$, 100%). HRMS (ESI) calcd for $C_{13}H_{25}OS$ $[M+H]^+$: 229.1626. Found: 229.1624. Their configurations of the 2-heptyl group and the 5-methylthio group were determined by observing NOE between the 2-heptyl methylene proton (δ 1.21–1.43) and the 5-proton (δ 3.03).



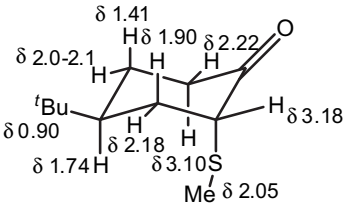
4.2.16. 3-(Methylthio)-4-phenyl-2-butanone[13]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.24 (s, 3H), 2.90 (dd, J=14.1, 6.7 Hz, 1H), 3.20 (dd, J=14.1, 8.5 Hz, 1H), 3.49 (dd, J=8.5, 6.7 Hz, 1H), 7.18–7.23 (m, 3H), 7.29 (t, J=7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.2, 27.2, 35.2, 54.6, 126.6, 128.5, 128.9, 138.3, 203.1. IR (ATR) 3029, 2921, 1703, 1497, 1424, 1354, 1234, 1154, 751, 700 cm^{-1}. MS (EI) m/z 194 (M^+, 10%), 151 (M^+-MeCO, 100%), 147 (M^+-MeS, 73%). HRMS (ESI) calcd for $C_{11}H_{15}OS$ $[M+H]^+$: 195.0844. Found: 195.0837.

4.2.17. 1-(Methylthio)-4-phenyl-2-butanone[14]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.92–2.97 (m, 4H), 3.14 (s, 2H), 7.17–7.21 (m, 3H), 7.28 (t, J=7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 29.9, 41.5, 43.1, 126.2, 128.4, 128.5, 140.8, 204.5. IR (ATR) 3027, 2919, 1704, 1497, 1453, 1087, 745, 698 cm^{-1}. MS (EI) m/z 194 (M^+, 75%), 105 ($M^+-MeSCH_2CO$, 100%). HRMS (ESI) calcd for $C_{11}H_{14}NaOS$ $[M+Na]^+$: 217.0663. Found: 217.0667.

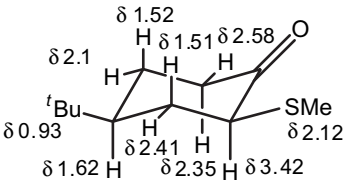
4.2.18. 3-Methyl-2-(methylthio)-2-cyclohexenone. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (quint, J=6.4 Hz, 2H), 2.21 (s, 3H), 2.26 (s, 3H), 2.49 (t, J=6.0 Hz, 2H), 2.50 (t, J=6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 21.8, 24.1, 33.9, 38.4, 132.2, 165.0, 195.0. IR (ATR) 2923, 1668, 1583, 1424, 1272, 808, 584 cm^{-1}. MS (EI) m/z 156 (M^+, 100%). HRMS (ESI) calcd for $C_8H_{13}OS$ $[M+H]^+$: 157.0687. Found: 157.0683.

4.2.19. (2R,4S*)-4-(tert-Butyl)-2-(methylthio)cyclohexanone*[3]. Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (s, 9H),

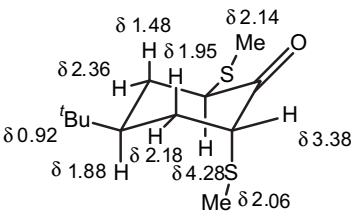
1.41 (qd, J=13.2, 4.1 Hz, 1H), 1.74 (tt, J=12.4, 2.9 Hz, 1H), 1.90 (td, J=13.4, 5.2 Hz, 1H), 2.02–2.07 (m, 1H), 2.05 (s, 3H), 2.18 (dq, J=13.9, 2.8 Hz, 1H), 2.22 (dquint, J=15.0, 2.0 Hz, 1H), 3.10 (td, J=14.6, 6.2 Hz, 1H), 3.17–3.18 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.4, 27.4, 27.5, 32.1, 33.1, 35.8, 41.5, 52.9, 208.3. IR (neat) 2960, 2920, 2869, 1709, 1479, 1439, 1421, 1367 cm^{-1}. MS (EI) m/z 200 (M^+, 100%), 154 (M^+-CH_2S, 40%). HRMS (EI) calcd for $C_{11}H_{20}OS$: 200.1235. Found: 200.1221. The configuration of the 2-methylthio group was determined by observing the coupling constant J=5.2 Hz of the 2-equatorial proton (δ 3.18).



4.2.20. (2S,4S*)-4-(tert-Butyl)-2-(methylthio)cyclohexanone*[3]. Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.51 (q, J=12.5 Hz, 1H), 1.52 (qd, J=12.6, 4.9 Hz, 1H), 1.62 (tt, J=12.0, 3.1 Hz, 1H), 2.08–2.13 (m, 1H), 2.12 (s, 3H), 2.35 (tdd, J=13.6, 6.2, 1.0 Hz, 1H), 2.41 (ddt, J=12.8, 5.8, 3.0 Hz, 1H), 2.58 (ddd, J=14.1, 4.5, 3.1 Hz, 1H), 3.42 (ddd, J=12.7, 5.9, 1.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 27.5, 27.8, 32.6, 35.2, 40.7, 47.3, 54.9, 207.3. IR (neat) 2960, 2870, 1716, 1445, 1367, 1260, 1228, 1132, 1071, 806 cm^{-1}. MS (EI) m/z 200 (M^+, 100%), 154 (M^+-CH_2S, 77%). HRMS (EI) calcd for $C_{11}H_{20}OS$: 200.1235. Found: 200.1232. The configuration of the 2-methylthio group was determined by the coupling constant J=12.7 Hz of the 2-axial proton (δ 3.42).



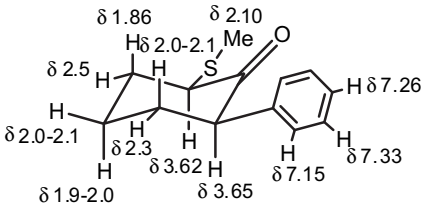
4.2.21. (2R,6R*)-4-(tert-Butyl)-2,6-di(methylthio)cyclohexanone.* Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.48 (q, J=12.7 Hz, 1H), 1.88 (tt, J=12.2, 2.8 Hz, 1H), 1.95 (td, J=13.2, 5.0 Hz, 1H), 2.06 (s, 3H), 2.14 (s, 3H), 2.18 (dq, J=13.6, 2.6 Hz, 1H), 2.36 (ddt, J=12.7, 5.2, 2.6 Hz, 1H), 3.38 (dd, J=5.0, 2.2 Hz, 1H), 4.28 (dd, J=13.1, 5.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 15.4, 27.4, 32.3, 33.5, 35.3, 42.7, 50.1, 53.0, 204.1. IR (neat) 2961, 2920, 2869, 1713, 1439, 1367, 1261, 1233, 1105 cm^{-1}. MS (EI) m/z 246 (M^+, 26%), 199 (M^+–SMe, 100%). HRMS (EI) calcd for $C_{12}H_{22}OS_2$: 246.1112. Found: 246.1107. The configuration of the 2-methylthio group was determined by the coupling constant J=5.0 Hz of the 2-equatorial proton (δ 3.38). The configuration of the 6-methylthio group was determined by the coupling constant J=13.1 Hz of the 6-axial proton (δ 4.28).



4.2.22. 4-(tert-Butyl)-2,2-di(methylthio)cyclohexanone. Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.48 (qd, J=12.9, 4.7 Hz, 1H), 1.90 (tt, J=12.4, 3.1 Hz, 1H), 1.95 (s, 3H), 2.02 (s, 3H), 2.01–2.08 (m, 2H), 2.38 (dt, J=13.7, 3.1 Hz, 1H), 2.41 (ddd, J=15.1, 4.7, 3.0 Hz, 1H), 3.10 (td, J=14.3, 6.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.7, 12.4, 27.1, 27.4, 32.4, 36.5, 40.6, 42.5, 67.5, 203.9. IR (neat) 2960, 2920, 2871, 1704, 1418, 1367, 1260, 1150, 798 cm^{-1}. MS (EI) m/z 246 (M^+, 31%), 199 (M^+–MeS, 100%). HRMS (EI) calcd for $C_{12}H_{22}OS_2$: 246.1112. Found: 246.1113.

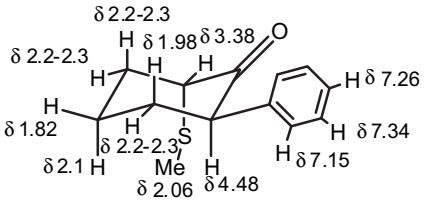
4.2.23. 2-(Methylthio)-1,3-diphenyl-1-butanone (1:0.7 diastereomixture). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (major) 1.53 (d, J=7.0 Hz, 3H), 2.01 (s, 3H), 3.45 (dq, J=11.0, 7.0 Hz, 1H), 4.34 (d, J=10.9 Hz, 1H), 7.09 (t, J=7.1 Hz, 1H), 7.17–7.23 (m, 4H), 7.31–7.38 (m, 2H), 7.45 (t, J=7.3 Hz, 1H), 7.77 (d, J=7.5 Hz, 2H). δ (minor) 1.27 (d, J=6.7 Hz, 3H), 1.83 (s, 3H), 3.49 (dq, J=11.2, 6.9 Hz, 1H), 4.27 (d, J=10.9 Hz, 1H), 7.26–7.38 (m, 5H), 7.48 (t, J=7.36 Hz, 2H), 7.57 (t, J=7.3 Hz, 1H), 8.04 (d, J=7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 11.1, 20.0, 37.1, 52.7, 126.5, 127.4, 128.0, 128.4, 128.5, 132.6, 136.5, 144.5, 193.0. δ (minor) 11.7, 21.4, 38.7, 52.6, 126.8, 127.5, 128.3, 128.5, 128.6, 133.0, 136.6, 143.9, 193.7. IR (ATR) 2964, 2926, 1667, 1445, 1284, 1271, 743, 690, 660, 539 cm^{-1}. MS (EI) m/z 270 (M^+, 4%), 166 ($M^+-PhC_2H_3$, 100%). HRMS (ESI) calcd for $C_{17}H_{18}NaOS$ $[M+Na]^+$: 293.0976. Found: 293.0966.

4.2.24. (2R,6R*)-2-(Methylthio)-6-phenylcyclohexanone (cis-**9**).* Colorless crystals. Mp 89–91 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.86 (qd, J=12.6, 3.7 Hz, 1H), 1.90–1.98 (m, 1H), 2.02–2.10 (m, 2H), 2.10 (s, 3H), 2.27–2.31 (m, 1H), 2.49–2.54 (m, 1H), 3.62 (ddd, J=12.4, 5.5, 1.0 Hz, 1H), 3.65 (dd, J=12.7, 5.5 Hz, 1H), 7.15 (d, J=7.9 Hz, 2H), 7.26 (tt, J=7.4, 1.4 Hz, 1H), 7.33 (t, J=7.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 25.4, 34.9, 35.6, 56.2, 57.5, 127.0, 128.3, 128.6, 138.1, 205.1. IR (KBr) 3028, 2941, 2861, 1700, 1497, 1452, 1300, 1051, 743, 696, 591 cm^{-1}. MS (EI) m/z 220 (M^+, 100%), 177 ($M^+-C_3H_7$, 38%), 173 (M^+–MeS, 51%), 144 ($M^+-MeSC_2H_5$, 63%). HRMS (EI) calcd for $C_{13}H_{16}OS$: 220.0922. Found: 220.0921. The configuration of the 2-methylthio group was determined by the coupling constant J=12.4 Hz of the 2-axial proton (δ 3.62). The configuration of the 6-phenyl group was determined by the coupling constant J=12.7 Hz of the 6-axial proton (δ 3.65).



4.2.25. (2S,6R*)-2-(Methylthio)-6-phenylcyclohexanone (trans-**9**).* Colorless crystals. Mp 74–75 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.82 (dquint, J=13.5, 3.3 Hz, 1H), 1.98 (qd, J=12.8, 3.3 Hz, 1H), 2.05–2.12 (m, 1H), 2.06 (s, 3H), 2.22–2.30 (m, 3H), 3.38 (t, J=3.6 Hz, 1H), 4.48 (dd, J=12.9, 5.3 Hz, 1H), 7.15 (d, J=7.5 Hz, 2H), 7.26 (t, J=7.2 Hz, 1H), 7.34 (t, J=7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.2, 21.5, 32.9, 35.0, 51.0, 53.8, 126.9, 128.3, 128.7, 138.6, 207.2. IR (KBr) 3029, 2922, 2855, 1695, 1496, 1454, 1445, 1155, 1078, 754, 703, 548 cm^{-1}. MS (EI) m/z 220 (M^+, 57%), 173 (M^+–MeS, 100%), 144 ($M^+-MeSC_2H_5$, 45%). HRMS (EI) calcd for $C_{13}H_{16}OS$: 220.0922. Found: 220.0923. The configuration of the 2-methylthio group was determined by the coupling constant J=3.6 Hz of the 2-equatorial proton (δ 3.38). The configuration of the 6-phenyl group was

determined by observing the coupling constant J=12.9 Hz of the 6-axial proton (δ 4.48).



*4.2.26. 2,2-Di(methylthio)-6-phenylcyclohexanone (**10**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (dquint, J=13.6, 3.4 Hz, 1H), 1.98 (s, 3H), 2.03 (s, 3H), 2.00–2.09 (m, 1H), 2.16–2.31 (m, 2H), 2.41 (td, J=13.6, 4.3 Hz, 1H), 2.52 (dq, J=14.3, 3.2 Hz, 1H), 4.57 (dd, J=8.1, 5.0 Hz, 1H), 7.14 (d, J=7.4 Hz, 2H), 7.27 (t, J=7.4 Hz, 1H), 7.34 (t, J=7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.8, 12.5, 22.3, 34.8, 40.3, 51.8, 69.0, 127.1, 128.3, 128.8, 138.5, 203.4. IR (ATR) 2917, 2859, 1706, 1441, 1094, 750, 698, 660 cm^{-1}. MS (EI) m/z 266 (M^+, 19%), 218 (M^+−MeSH, 41%), 191 (M^+−$MeSC_2H_4$, 100%). HRMS (ESI) calcd for $C_{14}H_{19}OS_2$ $[M+H]^+$: 267.0877. Found: 267.0881.

*4.2.27. 3-(Methylthio)-1-phenyl-2-butanone (**13**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, J=7.0 Hz, 3H), 1.91 (s, 3H), 3.44 (q, J=6.9 Hz, 1H), 3.90 (d, J=15.4 Hz, 1H), 3.96 (d, J=15.2 Hz, 1H), 7.23–7.27 (m, 3H), 7.32 (t, J=7.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 14.6, 45.7, 46.5, 126.9, 128.6, 129.5, 134.5, 203.2. IR (ATR) 2973, 2922, 1704, 1496, 1453, 1031, 743, 697 cm^{-1}. MS (EI) m/z 194 (M^+, 100%), 147 (M^+−MeS, 66%). HRMS (ESI) calcd for $C_{11}H_{15}OS$ $[M+H]^+$: 195.0844. Found: 195.0850.

4.2.28. 1-(Methylthio)cyclohexanecarbaldehyde[15]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29–1.43 (m, 3H), 1.54–1.60 (m, 3H), 1.71–1.77 (m, 2H), 1.79 (s, 3H), 1.93–1.99 (m, 2H), 8.95 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9, 23.0, 25.5, 29.8, 55.3, 191.9. IR (ATR) 2929, 2855, 2800, 2708, 1709, 1448 cm^{-1}. MS (EI) m/z 158 (M^+, 17%), 129 (M^+−CHO, 100%). HRMS (EI) calcd for $C_8H_{14}OS$: 158.0765. Found: 158.0750.

4.2.29. 1-(Methylthio)cycloheptanecarbaldehyde. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.50 (m, 2H), 1.58 (quint, J=3.4 Hz, 4H), 1.68 (ddd, J=14.8, 9.6, 1.5 Hz, 2H), 1.67–1.74 (m, 2H), 1.78 (s, 3H), 2.00 (ddd, J=14.8, 9.2, 1.6 Hz, 2H), 8.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 22.9, 29.5, 31.6, 58.7, 192.4. IR (ATR) 2922, 2854, 2803, 2705, 1707, 1459, 1444, 905 cm^{-1}. MS (EI) m/z 172 (M^+, 13%), 143 (M^+−CHO, 100%). HRMS (EI) calcd for $C_9H_{16}OS$: 172.0922. Found: 172.0932.

4.2.30. 2-(Methylthio)-2-phenylpropanal[16]. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.91 (s, 3H), 7.33 (t, J=7.2 Hz, 1H), 7.40 (t, J=7.7 Hz, 2H), 7.45 (d, J=7.7 Hz, 2H), 9.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 21.2, 58.7, 127.2, 128.0, 128.9, 138.2, 190.1. IR (ATR) 2978, 2923, 2819, 2712, 1706, 1492, 1444, 1066, 889, 761, 697, 532 cm^{-1}. MS (EI) m/z 180 (M^+, 2%), 151 (M^+−CHO, 100%). HRMS (ESI) calcd for $C_{10}H_{12}NaOS$ $[M+Na]^+$: 203.0507. Found: 203.0508.

4.2.31. Ethyl 1-(methylthio)-1-phenylacetate[18]. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.2 Hz, 3H), 2.09 (s, 3H), 4.19 (dq, J=10.8, 7.2 Hz, 1H), 4.23 (dq, J=10.9, 7.1 Hz, 1H), 4.50 (s, 1H), 7.30 (t, J=7.0 Hz, 1H), 7.35 (t, J=7.2 Hz, 2H), 7.46 (d, J=6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.9, 53.5, 61.6, 128.0, 128.4, 128.6, 135.8, 170.6. IR (neat) 2981, 2919, 1733, 1284, 1215, 1148, 1027, 697 cm^{-1}. MS (EI) m/z 210 (M^+, 24%), 137 (M^+−CO_2Et, 100%). HRMS (EI) calcd for $C_{11}H_{14}O_2S$: 210.0715. Found: 210.0711.

4.2.32. 1-(Methylthio)-1-phenyl-acetonitrile[17]. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 4.78 (s, 1H), 7.37 (t, J=7.0 Hz, 1H), 7.41 (tt, J=7.4, 2.0 Hz, 2H), 7.48 (d, J=7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 38.1, 117.3, 127.6, 128.9, 129.1, 132.4. IR (neat) 3033, 2920, 2238, 1494, 1454, 774, 720, 697 cm^{-1}. MS (EI) m/z 163 (M^+, 52%), 116 (M^+−MeS, 100%). HRMS (EI) calcd for C_9H_9NS: 163.0456. Found: 163.0430.

4.3. Reverse reaction

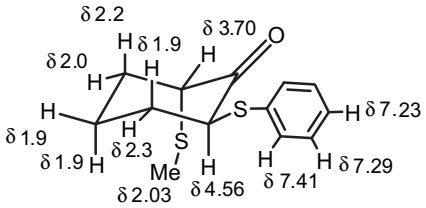
In a two-necked flask equipped with a reflux condenser were placed $RhH(PPh_3)_4$ (4 mol %, 11.5 mg), 1,2-bis(diphenylphosphino) ethane (8 mol %, 8.0 mg), **6** (0.25 mmol, 45.1 mg), **2** (0.25 mmol, 49.1 mg), and dimethyl disulfide (12 mol %, 2.7 μL) in THF (0.25 mL) under an argon atmosphere, and the solution was heated at 90 °C for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving **1** (18.9 mg, 31%) as well as the recovery of **2** (33.4 mg, 68%), and **6** (25.6 mg, 57%). The yield of **5** (34%) was determined by ^{1}H NMR using 1,1,2-tricholoroethane as an internal standard.

4.4. α-Methylthiolation reaction of 2-(phenylthio) cyclohexanone using 1

In a two-necked flask equipped with a reflux condenser were placed $RhH(PPh_3)_4$ (4 mol %, 11.5 mg), 1,2-bis(diphenylphosphino) ethane (8 mol %, 8.0 mg), 2-(phenylthio)cyclohexanone (1.25 mmol, 258 mg), **1** (0.25 mmol, 60.6 mg), and dimethyl disulfide **2** (12 mol %, 2.7 μL) in THF (0.25 mL) under an argon atmosphere, and the solution was heated at 90 °C for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving 2-(methylthio)-2-(phenylthio)cyclohexanone (3.1 mg, 5%), (2*S**,6*S**)-2-(methylthio)-6-(phenylthio)cyclohexanone (9.5 mg, 15%), and (2*R**,6*S**)-2-(methylthio)-6-(phenylthio)cyclohexanone (2.3 mg, 4%).

4.4.1. 2-(Methylthio)-2-(phenylthio)cyclohexanone. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71–1.78 (m, 2H), 1.83–1.91 (m, 1H), 1.93–1.99 (m, 2H), 2.14 (s, 3H), 2.29 (ddd, J=14.5, 11.0, 3.7 Hz, 1H), 2.54 (ddd, J=14.9, 4.6, 1.4 Hz, 1H), 2.98 (ddd, J=14.9, 11.6, 5.8 Hz, 1H), 7.32 (t, J=7.2 Hz, 2H), 7.37 (t, J=6.6 Hz, 1H), 7.51 (d, J=8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 21.9, 26.3, 37.3, 40.3, 70.7, 128.5, 129.2, 130.3, 137.0, 203.2. IR (neat) 3058, 2940, 2863, 1696, 1474, 1439, 1226, 1118, 751, 692 cm^{-1}. MS (EI) m/z 252 (M^+, 20%), 143 (M^+−PhS, 100%). HRMS (ESI) calcd for $C_{13}H_{17}OS_2$ $[M+H]^+$: 253.0721. Found: 253.0715.

4.4.2. (2S,6S*)-2-(Methylthio)-6-(phenylthio)cyclohexanone.* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84–1.93 (m, 3H), 2.00–2.05 (m, 1H), 2.03 (s, 3H), 2.20–2.29 (m, 2H), 3.70 (t, J=5.5 Hz, 1H), 4.56 (dd, J=9.3, 5.6 Hz, 1H), 7.23 (t, J=7.3 Hz, 1H), 7.29 (t, J=7.3 Hz, 2H), 7.41 (d, J=7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 21.6, 33.2, 34.4, 53.1, 53.7, 127.4, 129.0, 132.0, 133.7, 203.7. IR (ATR) 2935, 2858, 1705, 1438, 1091, 740, 689 cm^{-1}. MS (EI) m/z 252 (M^+, 59%), 205 (M^+−MeS, 95%), 143 (M^+−PhS, 100%). HRMS (ESI) calcd for $C_{13}H_{17}OS_2$ $[M+H]^+$: 253.0721. Found: 253.0724. The configuration of the 2-methylthio group was determined by the coupling constant J=5.5 Hz of the 2-equatorial proton (δ 3.70). The configuration of the 6-phenylthio group was determined by observing the coupling constant J=9.3 Hz of the 6-axial proton (δ 4.56).



4.4.3. (2R,6S*)-2-(Methylthio)-6-(phenylthio)cyclohexanone.* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (dtt, J=13.9, 10.3, 3.7 Hz, 1H), 1.82–1.93 (m, 2H), 2.02–2.08 (m, 1H), 2.11 (s, 3H), 2.25–2.37 (m, 2H), 3.46 (ddd, J=9.9, 5.5, 1.0 Hz, 1H), 3.89 (ddd, J=9.9, 5.5, 0.9 Hz, 1H), 7.26 (t, J=7.2 Hz, 1H), 7.30 (t, J=7.2 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 23.1, 33.8, 34.8, 54.8, 57.3, 127.6, 129.0, 132.7, 134.3, 202.0. IR (neat) 3056, 2921, 2855, 1713, 1583, 1479, 1444, 1295, 1046, 747, 692 cm^{-1}. MS (EI) m/z 252 (M^+, 100%), 205 (M^+–MeS, 27%). HRMS (ESI) calcd for $C_{13}H_{17}OS_2$ $[M+H]^+$: 253.0721. Found: 253.0714. Their configurations of the 2-methylthio group and the 6-phenylthio group were determined by observing their coupling constants J=9.9 Hz of their axial protons (δ 3.46, 3.89).

4.5. α-Methylthiolation reaction of 2-(ethoxycarbonyl) cyclohexanone using 1

In a two-necked flask equipped with a reflux condenser were placed $RhH(PPh_3)_4$ (4 mol %, 11.5 mg), 1,2-bis(diphenylphosphino) ethane (8 mol %, 8.0 mg), 2-(ethoxycarbonyl)cyclohexanone (1.25 mmol, 226 μL), **1** (0.25 mmol, 60.6 mg), and dimethyl disulfide (12 mol %, 2.7 μL) in THF (0.25 mL) under an argon atmosphere, and the solution was heated at 90 °C for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving 2-(ethoxycarbonyl)-2-(methylthio)cyclohexanone (19.4 mg, 36%), and **2** (26.1 mg, 53%) with the recovery of 2-(ethoxycarbonyl)cyclohexanone (209.1 mg, 91%) and **1** (24.5 mg, 40%). When **3** was used in place of **1**, 7% yield of 2-(ethoxycarbonyl)-2-(methylthio)cyclohexanone was obtained.

4.5.1. 2-(Ethoxycarbonyl)-2-(methylthio)cyclohexanone. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, J=7.1 Hz, 3H), 1.63–1.70 (m, 1H), 1.81–1.88 (m, 2H), 1.90–1.96 (m, 2H), 2.08 (s, 3H), 2.42 (ddd, J=14.3, 9.1, 5.2 Hz, 1H), 2.65–2.71 (m, 1H), 2.73–2.78 (m, 1H), 4.25 (dq, J=10.8, 7.1 Hz, 1H), 4.28 (dq, J=10.8, 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 14.0, 22.1, 26.8, 36.0, 39.4, 61.9, 63.5, 169.2, 203.1. IR (ATR) 2938, 2866, 1711, 1444, 1235, 1202, 1125, 1021, 561 cm^{-1}. MS (EI) m/z 216 (M^+, 1%), 170 (M^+-CH_2S, 100%). HRMS (EI) calcd for $C_{10}H_{16}O_3S$: 216.0820. Found: 216.0817.

Acknowledgements

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