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Hydrophobic polymer-supported scandium catalyst for carbon–carbon bond-forming reactions in water

Shinya Iimura, Kei Manabe and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—It has been revealed that a hydrophobic polymer-supported scandium(III) catalyst prepared from sulfonated polystyrene resin is an effective catalyst for carbon–carbon bond-forming reactions such as Mukaiyama aldol reactions in water. According to studies on loading levels of scandium, hydrophobicity of the catalyst is a key for the efficient catalysis. The scandium catalyst was successfully recovered and reused. Several ketones instead of aldehydes were also used as substrates in the aldol reactions. Some 1,4-addition reactions also occurred using the scandium catalyst in water.

1. Introduction

Due to the increasing importance of green chemistry in organic synthesis, development of more efficient and environmentally friendly processes for chemical transformations is desired.[1] One of the ideal methodologies is the development of organic reactions using highly active, reusable solid catalysts in water.[2,3] Although use of amphiphilic polymer-supported catalysts has received much attention, we have recently found that a hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H) is an effective catalyst for several organic reactions such as formation of esters, hydrolysis of thioesters, and Mannich-type reactions in water.[4] In addition, as a result of continuous studies on the loading levels and the structures of the catalyst, it is suggested that hydrophobicity of the catalyst is a key for efficient catalysis in water.[5] We then envisaged that hydrophobic polymer-supported Lewis acids would also work effectively in water. While some solid-supported Lewis acids which work well in aqueous media have been reported so far,[2] there are still limitations in the types of reactions and substrates. It is strongly required to develop more effective, solid-supported Lewis acid catalysts for organic transformations in water. Here, we report that a novel hydrophobic polystyrene-supported scandium(III) is a powerful catalyst for carbon–carbon bond-forming reactions in pure water.

2. Results and discussion

The aldol-type reactions of silicon enolates with carbonyl compounds (Mukaiyama aldol reactions) have been recognized as one of the most important tools for carbon–carbon bond formation that afford synthetically useful β-hydroxy carbonyl compounds.[6] Thus, we performed the reaction of benzaldehyde with the thioketene silyl acetal (1.5 equiv.) derived from ethyl 2-methylthiopropionate in water. First, we tested PS-SO_3H, a polymer-supported Brønsted acid prepared by sulfonation of DVB cross-linked polystyrene with a loading level of 0.21 mmol/g (Table 1, entry 1). It was found that the desired product was obtained in a low yield due to rapid hydrolysis of the silicon enolate. Then, we tested polymer-supported Lewis acids. Among the Lewis acids, we focused on scandium(III) because we have already revealed that it is a water-compatible, strong Lewis acid.[7] While several solid-supported scandium(III) catalysts have been used for aldol reactions in water,[2a,i,j] wide substrate generality has not been demonstrated. Moreover, in the previous example of the same combination of substrates,[2a] an excess amount (3.6 equiv.) of the thioketene silyl acetal was required to obtain the desired adduct in high yield. Thus, we decided to develop a more effective polymer-supported scandium. A hydrophobic catalyst, PS-Sc **1**, was readily prepared from hydrophobic PS-SO_3H, and ICP analysis verified that 0.16 mmol/g of Sc was present in the catalyst. It was exciting to find that the reaction proceeded smoothly to give the β-hydroxy thioester in excellent yield when PS-Sc **1** was used as a catalyst (entry 6). Next, we carried out the reaction with other Lewis acids to compare the catalytic activities. $Sc(O_3SOC_{12}H_{25})_3$,[8] which we previously developed as a Lewis acid-surfactant-combined catalyst, gave the aldol product in 75% yield (entry 2). It is

Keywords: Lewis acid; Scandium; Aldol reaction; 1,4-Addition; Water.
* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail address: skobayas@mol.f.u-tokyo.ac.jp

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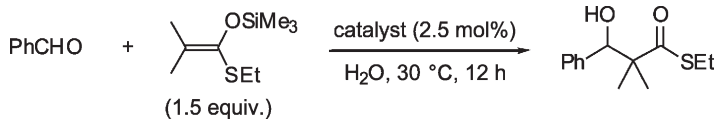
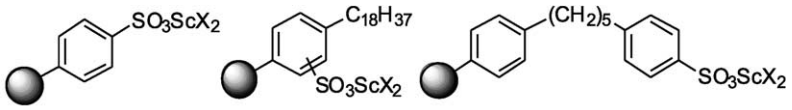
Table 1. Mukaiyama aldol reaction in water with various catalysts



Entry	Catalyst	Loading (mmol/g)[a]	Yield (%)
1	PS-SO_3H	0.21 (S)	35
2	$Sc(O_3SOC_{12}H_{25})_3$	—	75
3	$Sc(OTf)_3$	—	0
4[b]	PS-Sc	0.64 (Sc)	0
5[b]	PS-Yb	0.80 (Yb)	0
6	PS-Sc **1**	0.16 (Sc)	97 (97)[c]
7	PS-Sc **1**	0.67 (Sc)	16[c]
8	PS-Sc **2**	0.11 (Sc)	37[c]
9	PS-Sc **3**	0.11 (Sc)	21[c]

[a] The value is of the element shown in the parenthesis.
[b] Commercially available polymer-supported Lewis acid catalysts.
[c] The catalyst (1 mol%).

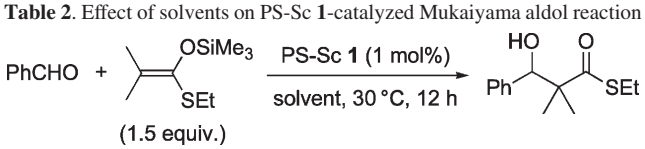


PS-Sc **1** PS-Sc **2** PS-Sc **3**

noteworthy that hydrophobic PS-Sc **1** is superior to the surfactant-type catalyst ($Sc(O_3SOC_{12}H_{25})_3$), which has been one of the best catalysts for Mukaiyama aldol reactions in water. Furthermore, only 1 mol% of the catalyst is enough to complete the reaction (entry 6). On the other hand, $Sc(OTf)_3$ and commercially available polymer-supported Lewis acid catalysts (PS-Sc and PS-Yb)[9] did not catalyze the reaction at all in every case (entries 3–5). While PS-Sc **1** did not seem to swell, these commercially available polymer-supported Lewis acids swelled significantly in water, suggesting that the hydrophobicity of the polymer-supported catalysts is a key to exhibit high activity in water. The reaction did not proceed at all in the presence of the cross-linked polystyrene which is the parent polymer of PS-Sc **1**, revealing the critical role of the scandium. We also investigated the effects of the loading levels and the polymer structures on catalytic activity (entry 7–9). It was revealed that the lower loading PS-Sc **1** (entry 6) gave better results.

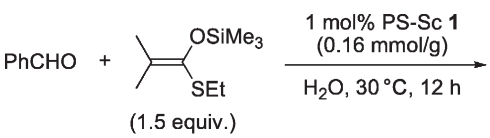
Next, we examined the effect of solvents in the PS-Sc **1**-catalyzed Mukaiyama aldol reaction (Table 2). Interestingly, it turned out that PS-Sc **1** worked well only in water (entry 6). This unique solvent effect might be mainly attributed to the following two factors: (1) hydrophobic interactions in water to concentrate the catalyst and the substrates; (2) hydration of the Sc(III) ion and counteranion by water molecules lead to dissociation of the catalyst to form a highly Lewis acidic species.[8]

Table 2. Effect of solvents on PS-Sc **1**-catalyzed Mukaiyama aldol reaction

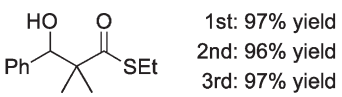


Entry	Solvent	Yield (%)
1	Neat	10
2	CH_2Cl_2	Trace
3	MeOH	9
4	THF	0
5	THF/H_2O (9/1)	23
6	H_2O	97

We then examined reusability of PS-Sc **1**, and it was found that the catalyst was easily recovered and reused without any loss of catalytic activity (Eq. 1).

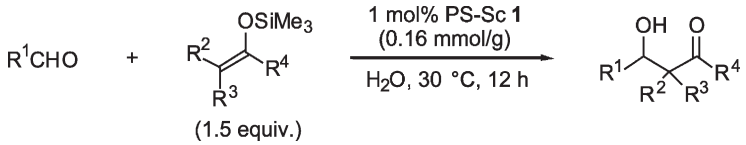


(1)



Various substrates were successfully used in the present PS-Sc **1**-catalyzed Mukaiyama aldol reactions as shown in Table 3. As for aldehydes, aromatic as well as α,β-unsaturated, and aliphatic aldehydes worked well to give the corresponding β-hydroxy thioesters in good to excellent yields (entries 1–8). While *p*-chlorobenzaldehyde is solid (mp 47–50 °C), it also reacted smoothly in water. In addition, it was revealed that silicon enolates derived from not only a thioester but also an ester and ketones reacted smoothly to afford the corresponding aldol adducts in good yields (entries 9–11). It should be noted that highly water-sensitive silicon enolates were successfully used in water under these conditions. These results suggest that a hydrophobic environment created by the catalyst in water suppresses the hydrolysis of water-sensitive silicon enolates but accelerates the desired reactions. To the best of our knowledge, there are no examples of reusable solid catalysts, which catalyze Mukaiyama aldol reactions in

Table 3. PS-Sc **1**-catalyzed Mukaiyama aldol reaction in water

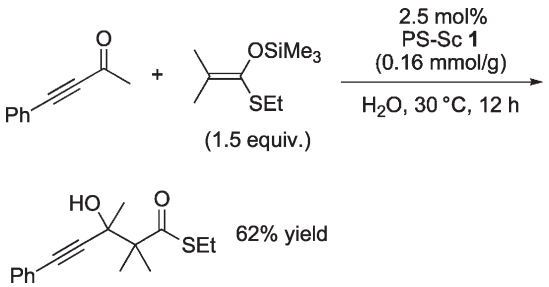


Entry	R^1	R^2	R^3	R^4	Yield (%)
1	Ph	Me	Me	SEt	97
2	4-$MeOC_6H_4$	Me	Me	SEt	96
3	4-ClC_6H_4	Me	Me	SEt	88
4	2-HOC_6H_4	Me	Me	SEt	91[a]
5	(*E*)-PhCH=CH	Me	Me	SEt	95
6	$Ph(CH_2)_2$	Me	Me	SEt	93
7[b]	*n*-C_5H_{11}	Me	Me	SEt	84
8[b]	*c*-C_6H_{11}	Me	Me	SEt	78
9[c]	Ph	Me	Me	OMe	81
10[d]	Ph	Me	H	Ph	89[e]
11[d]	Ph	H	$-(CH_2)_4-$		85[f]

[a] Yield of the cyclized, six-membered lactone which was obtained after purification.
[b] The aldehyde was slowly added to the reaction mixture over 8 h, and then the whole was stirred for 16 h.
[c] At 0 °C. The sillicon enolate was slowly added to the reaction mixture over 8 h, and then the whole was stirred for 16 h.
[d] The catalyst (2.5 mol%).
[e] *syn*/*anti*=54/46.
[f] *syn*/*anti*=68/32.

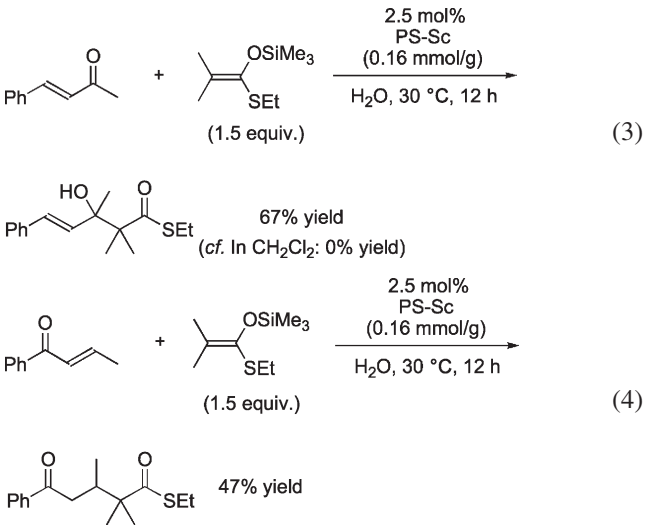
water with wide substrate generality. This reaction system would provide an ideal Mukaiyama aldol reaction with respect to efficiency and environmental friendliness for chemical transformations.

The wide substrate generality mentioned above encouraged us to investigate catalytic Mukaiyama aldol reactions of ketones in water. This type of reactions has not been reported previously. As results, it was found that the reaction of an alkynyl ketone with the thioketene silyl acetal proceeded in good yield using the present catalytic system (Eq. 2), although the yield was 36% in the case of simple acetophenone under the same conditions.



(2)

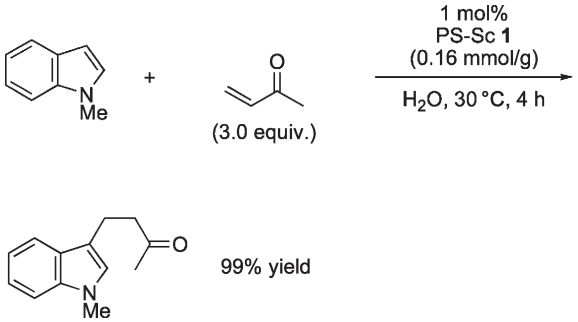
Furthermore, the reaction of benzalacetone gave the desired 1,2-adduct (Eq. 3). This result is remarkable, not only because the aldol reaction with the ketone proceeded smoothly but also because the 1,2-adduct was obtained without the 1,4-adduct.[10] This regioselectivity is contrary to that of $Sc(OTf)_3$-catalyzed reaction performed in organic solvents where the corresponding 1,4-adduct was obtained as the sole product.[11] On the other hand, the corresponding 1,4-adduct was obtained in 47% yield without the 1,2-adduct when phenyl 1-propenyl ketone was used as a substrate (Eq. 4). While the yield was still unsatisfactory, this is the first example of Mukaiyama–Michael reaction[12] in water. Although the origin of this unique regioselectivity is not clear at this stage, these results suggest that both 1,2- and 1,4-adducts could be obtained by simply switching the reaction systems.[13]



(3)

(4)

Finally, Michael addition of an indole in water using this catalytic system was carried out (Eq. 5).[14] It was found that the reaction proceeded smoothly in the presence of only 1 mol% of the catalyst to give the product in excellent yield.



(5)

In summary, we have developed a novel hydrophobic

polystyrene-supported scandium catalyst for carbon–carbon bond-forming reactions in water. This work will not only expand our concept related to hydrophobic Brønsted acid catalysts but also provide new possibilities for organic reactions in water. Detailed mechanistic studies of the unique regioselective reaction in Mukaiyama–Michael reaction in water and application of the concept of hydrophobic polymer-supported catalysts to other Lewis acid catalysis are now in progress.

3. Experimental

3.1. General

Melting points were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-610 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-LA300 or JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (δ=0) was used as an internal standard for ^1H NMR and $CDCl_3$ (δ=77.0) for ^{13}C NMR. Mass spectra (MS) were measured with a JEOL JMS-MS700V or Burker BIO TOF-II spectrometer. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography (TLC) was carried out using Wakogel B-5F. Distilled water was used as a solvent for aqueous reactions. Polystyrene resin (1% DVB cross-linked) was purchased from Advanced ChemTech Co., Inc. All other reagents were purified based on standard procedures unless otherwise noted. Starting materials are commercially available or were synthesized by the reported procedure. The structures of the known compounds were confirmed by comparison with published data.

3.2. Preparation of polymer-supported sulfonic acid catalysts

Various types of polystyrene-supported sulfonic acid catalysts (PS-SO_3H, ALPS-SO_3H, PS-spacer-SO_3H) were prepared according to the our previous report.[5a]

3.3. Preparation of polymer-supported scandium catalyst

To a suspension of hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H **1**, 0.20 mmol/g, 2.00 g, 0.41 mmol) in THF/H_2O (3/1, 25 mL) was slowly added 1 N aq. NaOH (2.0 mL, 2.00 mmol) at rt, and stirred for 24 h at the temperature. The resin was collected on a glass filter, rinsed with water, water/THF, THF, and dichloromethane, and dried in vacuo to give the sodium salt of PS-SO_3H. Scandium triflate was immobilized into the resin in the following step. $Sc(OTf)_3$ (536 mg, 1.01 mmol) was added to a suspension of PS-SO_3Na (1.82 g, ca. 0.37 mmol) in THF (35 mL) at rt. After being stirred for 72 h at the same temperature, the resin was collected on a glass filter, rinsed with water, water/THF, THF, and dichloromethane, and dried in vacuo to give the hydrophobic polymer-supported scandium catalysts (PS-Sc). From a result of ICP analysis (found: Sc, 0.74%; Na, 0.01%), the scandium content was estimated as 0.16 mmol/g. PS-Sc **1** with another loading level was similarly prepared by changing the loading of the starting PS-SO_3H (1.55 mmol/g). PS-Sc **2** was also similarly prepared from ALPS-SO_3H (0.37 mmol/g). PS-Sc **3** was also similarly prepared from PS-spacer-SO_3H (0.57 mmol/g).

3.4. A typical experimental procedure for PS-Sc-catalyzed Mukaiyama aldol reactions in water (Table 1, entry 6)

Benzaldehyde (26.5 mg, 0.25 mmol) and the thioketene silyl acetal (76.4 mg, 0.374 mmol) derived from ethyl 2-methylthiopropionate were successively added to a mixture of PS-Sc (0.16 mmol/g, 38.8 mg, 0.0064 mmol) in degassed water (1.5 mL) at 30 °C. The reaction mixture was stirred for 12 h at the same temperature. The polymer was filtered and washed with water and ethyl acetate. After extraction with ethyl acetate, the organic layer was dried over anhydrous Na_2SO_4, and evaporated. The mixture was purified by preparative TLC on silica gel to give the desired product (57.8 mg, 97%).

3.4.1. Ethyl 3-hydroxy-2,2-dimethyl-3-phenylthiopropionate.[15] Colorless oil; ^1H NMR ($CDCl_3$) δ 1.12 (3H, s), 1.22 (3H, s), 1.26 (3H, t, J=7.4 Hz), 2.89 (2H, q, J=7.4 Hz), 2.96 (1H, br s), 4.94 (1H, s), 7.27–7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.0, 23.3, 23.7, 54.3, 78.9, 127.78, 127.80, 139.9, 208.0.

3.4.2. *S*-Ethyl 3-hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropanethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.09 (3H, s), 1.20 (3H, s), 1.25 (3H, t, J=7.4 Hz), 2.88 (2H, q, J=7.4 Hz), 2.94 (1H, br d, J=3.7 Hz), 3.79 (3H, s), 6.81–6.88 (2H, m), 7.20–7.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.9, 23.3, 23.6, 54.5, 55.2, 78.5, 113.1, 128.8, 132.0, 159.1, 208.0; IR (neat) 3502, 2974, 1670, 1512, 1248, 1038, 945 cm^{-1}; MS (ESI-TOF) m/z 291 (M^++Na). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 62.40; H, 7.50.

3.4.3. *S*-Ethyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.11 (3H, s), 1.19 (3H, s), 1.25 (3H, t, J=7.4 Hz), 2.88 (2H, q, J=7.4 Hz), 3.10 (1H, br s), 4.90 (1H, s), 7.20–7.31 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.1, 23.3, 23.4, 54.2, 78.2, 127.9, 129.1, 133.5, 138.4, 207.9.

3.4.4. 4-Hydroxy-3,3-dimethyl-2-chromanone.[16] Colorless needles. Mp 101.6–101.9 °C; ^1H NMR ($CDCl_3$) δ 1.19 (3H, s), 1.39 (3H, s), 2.16 (1H, br s), 4.49 (1H, s), 7.06 (5H, d, J=7.7 Hz), 7.14–7.20 (1H, m), 7.31–7.39 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.7, 22.5, 43.5, 74.0, 116.6, 124.4, 124.7, 127.9, 130.2, 150.5, 172.7.

3.4.5. (*E*)-*S*-Ethyl 3-hydroxy-2,2-dimethyl-5-phenylpent-4-enethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, J=7.5 Hz), 1.27 (3H, s), 1.30 (3H, s), 2.72 (1H, d, J=5.4 Hz), 2.88 (2H, q, J=7.4 Hz), 4.38–4.43 (1H, m), 6.19 (1H, dd, J=15.9, 7.1 Hz), 6.63 (1H, d, J=15.8 Hz), 7.22–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.2, 23.2, 54.0, 78.1, 126.6, 127.3, 127.8, 128.6, 132.9, 136.6, 207.4; IR (neat) 3485, 2972, 2931, 1668, 1462, 945 cm^{-1}; MS (FAB) m/z 265 (M^++1). Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.62. Found: C, 68.13; H, 7.63.

3.4.6. *S*-Ethyl 3-hydroxy-2,2-dimethyl-5-phenylpentanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, s), 1.225 (3H, s), 1.231 (3H, t, J=7.5 Hz), 1.56–1.67 (1H, m), 1.73–1.81 (1H, m), 2.50 (1H, d, J=6.6 Hz), 2.59–2.68 (1H, m), 2.85 (2H, q, J=7.4 Hz), 2.90–2.98 (1H, m), 3.67 (1H, ddd, J=10.6, 6.7, 2.0 Hz), 7.16–7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.9, 22.7, 23.1, 32.9, 33.7, 54.1, 76.6, 125.9, 128.4, 128.5, 142.0, 207.8; IR (neat) 3492, 2974, 1672, 1456, 1076, 937 cm^{-1}; MS (FAB) m/z 267 (M^++1). Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.37; H, 8.27.

3.4.7. *S*-Ethyl 3-hydroxy-2,2-dimethyloctanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J=6.8 Hz), 1.21–1.35 (15H, m), 1.40–1.47 (1H, m), 1.54–1.63 (1H, m), 2.27 (1H, d, J=6.6 Hz), 2.86 (2H, q, J=7.5 Hz), 3.62–3.68 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.5, 20.9, 22.5, 22.6, 23.1, 26.4, 31.7, 31.8, 54.2, 77.2, 207.8; IR (neat) 3477, 2929, 1672, 1464, 939 cm^{-1}; MS (FAB) m/z 233 (M^++1). Anal. Calcd for $C_{12}H_{24}O_2S$: C, 62.02; H, 10.41. Found: C, 61.75; H, 10.26.

3.4.8. *S*-Ethyl 3-cyclohexyl-3-hydroxy-2,2-dimethylpropanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.11–1.71 (20H, m), 2.84 (2H, d, J=7.3 Hz), 2.85 (1H, br s), 3.40 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.7, 23.0, 24.1, 26.2, 26.3, 26.7, 27.4, 32.1, 40.4, 53.2, 82.6, 208.6; IR (neat) 3465, 2933, 2852, 1674, 1450, 943 cm^{-1}; MS (FAB) m/z 245 (M^++1). Anal. Calcd for $C_{13}H_{24}O_2S$: C, 63.89; H, 9.90. Found: C, 63.70; H, 9.99.

3.4.9. Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate.[17] Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, s), 1.15 (3H, s), 3.05 (1H, br s), 3.73 (3H, s), 4.90 (1H, s), 7.27–7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 23.1, 47.8, 52.2, 78.8, 127.4, 127.7, 127.8, 140.0, 178.3.

3.4.10. 3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one.[18] Colorless oil; (*syn*/*anti*=54/46): ^{1}H NMR ($CDCl_3$) δ 1.06 (1.38H, d, J=7.1 Hz), 1.19 (1.62H, d, J=7.1 Hz), 3.03 (0.46H, br s), 3.64–3.75 (1.08H, m), 3.83 (0.46H, quint, J=7.3 Hz), 4.99 (0.46H, br d, J=8.1 Hz), 5.23 (0.54H, br d, J=3.1 Hz), 7.23–7.62 (8H, m), 7.90–7.99 (2H, m); ^{13}C NMR ($CDCl_3$) δ 11.2, 15.7, 47.1, 48.0, 73.1, 76.8, 126.0, 126.7, 127.3, 127.9, 128.2, 128.45, 128.48, 128.54, 128.6, 128.8, 128.9, 133.3, 133.6, 135.7, 136.8, 141.8, 142.2, 204.9, 205.7.

3.4.11. 2-(Hydroxy(phenyl)methyl)cyclohexanone.[18] Colorless crystals; (*syn*/*anti*=68/32): ^{1}H NMR ($CDCl_3$) δ 1.23–1.38 (0.32H, m), 1.43–1.89 (4.68H, m), 2.01–2.14 (1H, m), 2.31–2.68 (3H, m), 3.02 (0.68H, br s), 3.98 (0.32H, br s), 4.78 (0.32H, d, J=8.8 Hz), 5.39 (0.68H, m), 7.21–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 24.7, 24.9, 26.0, 27.8, 28.0, 30.9, 42.7, 57.2, 57.5, 70.6, 74.8, 125.8, 126.98, 127.03, 127.9, 128.2, 128.4, 141.0, 141.5, 214.8, 215.6.

3.4.12. *S*-Ethyl 3-hydroxy-2,2-dimethyl-3-phenylbutanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, s), 1.22 (3H, s), 1.22 (3H, t, J=7.3 Hz), 1.61 (3H, s), 2.84 (2H, q, J=7.3 Hz), 4.57 (1H, br s), 7.19–7.35 (3H, m), 7.42–7.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.8, 21.9, 23.5, 25.0, 56.1, 77.8, 126.9, 127.3, 127.4, 143.4, 210.9; IR (neat) 3481, 2976, 2933, 1641, 1450, 1375, 962, 704 cm^{-1}; MS (FAB) m/z 253 (M^++1). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.65; H, 7.97.

3.4.13. *S*-Ethyl 3-hydroxy-2,2,3-trimethyl-5-phenylpent-4-ynethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ1.24 (3H, t, J=7.4 Hz), 1.39 (3H, s), 1.51 (3H, s), 1.53 (3H, s), 2.79–2.97 (2H, m), 4.50 (1H, br s), 7.25–7.43 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.9, 22.1, 23.5, 24.8, 56.2, 72.9, 83.9, 91.2, 122.7, 128.2, 128.3, 131.7, 209.8; IR (neat) 3469, 2978, 2933, 1645, 1387, 960 cm^{-1}; MS (FAB) m/z 277 (M^++1). Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.27; H, 7.44.

3.4.14. *S*-Ethyl 2,2,3-trimethyl-5-oxo-5-phenylpentanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d, J=6.3 Hz), 1.18–1.27 (9H, m), 2.62–2.75 (2H, m), 2.87 (2H, q, J=7.4 Hz), 3.02 (1H, br d, J=14.6 Hz), 7.42–7.59 (3H, m), 7.91–7.98 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.6, 14.9, 21.2, 23.1, 23.5, 36.8, 41.4, 52.7, 128.2, 128.6, 133.0, 137.1, 199.5, 206.8; IR (neat) 2972, 1680, 1450, 1292, 957 cm^{-1}; MS (FAB) m/z 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 68.93; H, 8.13.

3.4.15. (*E*)-*S*-Ethyl 3-hydroxy-2,2,3-trimethyl-5-phenylpent-4-enethioate. Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, J=7.3 Hz), 1.34 (9H, s), 2.73–2.88 (2H, m), 4.09 (1H, br s), 6.29 (1H, d, J=15.9 Hz), 6.66 (1H, d, J=15.9 Hz), 7.18–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.4, 23.4, 23.7, 56.1, 76.4, 126.5, 127.4, 128.5, 129.4, 132.4, 137.1, 210.1; IR (neat) 3486, 2973, 1642, 961 cm^{-1}; MS (FAB) m/z 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 69.09; H, 8.12.

3.4.16. *S*-Ethyl 2,2-dimethyl-5-oxo-3-phenylhexanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, s), 1.19 (3H, s), 1.23 (3H, t, J=7.3 Hz), 1.98 (3H, s), 2.68 (1H, dd, J=16.3, 3.6 Hz), 2.84 (2H, q, J=7.3 Hz), 3.01 (1H, dd, J=16.3, 11.2 Hz), 3.64 (1H, dd, J=11.2, 3.6 Hz), 7.17–7.29 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.5, 23.3, 25.6, 30.2, 44.8, 48.2, 52.7, 127.0, 128.0, 129.6, 139.2, 206.6, 206.8; IR (neat) 2972, 1718, 1668, 1456, 1360, 958 cm^{-1}; MS (FAB) m/z 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 68.73; H, 7.96.

3.4.17. 4-(1-Methyl-1*H*-indol-3-yl)butan-2-one. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.12 (3H, s), 2.82 (2H, t, J=7.3 Hz), 3.03 (2H, t, J=7.3 Hz) 3.71 (3H, s), 6.83 (1H, s), 7.07–7.12 (1H, m), 7.19–7.28 (2H, m), 7.6 (1H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.2, 30.0, 32.5, 44.3, 109.2, 113.6, 118.69, 118.73, 121.6, 126.3, 127.5, 137.0, 208.7; IR (neat) 3055, 2925, 1714, 1475, 1159, 741 cm^{-1}; MS (FAB) m/z 202 (M^++1). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.54; H, 7.72; N, 6.96.

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