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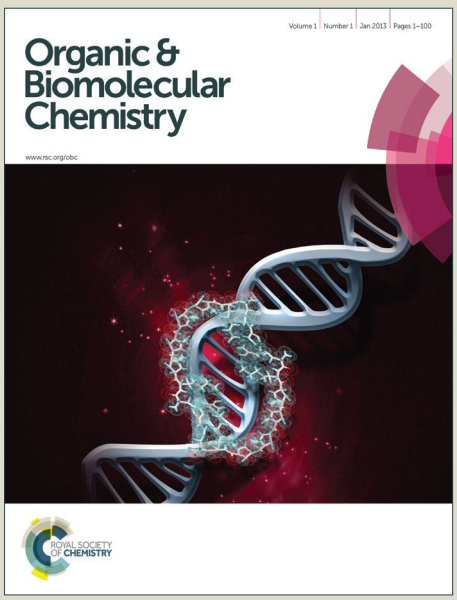





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# Enantioselective Organocatalytic Michael Addition of Isorhodanines to α, β-Unsaturated Aldehydes†

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Michael reaction of substituted isorhodanines with α, β-unsaturated aldehydes in the presence of catalytic amount of a chiral secondary amine is presented. This transformation proceeds in good to high yields furnishing the corresponding 4,5-disubstituted isorhodanine adducts in good to excellent enantioselectivities.

## Introduction

Asymmetric organocatalysis is a powerful and fruitful research area of organic chemistry by providing efficient and environmental friendly access to enantiomerically pure compounds in the synthesis of biologically active compounds and natural products.[1] In particular, asymmetric Michael reaction is a viable strategy for stereoselective formation of carbon-carbon bonds. In recent years, organocatalytic enantioselective Michael reactions has attracted wide interests and numerous synthetic approaches have been developed.[2] It is noteworthy that a variety of enolizable nucleophiles have been explored for this purpose. In these processes, generally highly active pre-enolized or readily enolizable nucleophilic species such as silyl enol ethers,[3] enamides,[4] nitroalkanes,[5] 1,3-dicarbonyls,[6] bis-sulfones,[7] active thioesters,[8] and others[9] are used.[10]

Given a broad spectrum of biological activities, such as antitumor, antitrypanosomal, antimycobacterial, and antiexudative activities and so on of isorhodanine related molecules (Figure 1),[11] synthesis of chiral isorhodanines is highly valuable for medicinal chemistry and drug discovery. In our previous work[10j], we reported a new approach to create a divergent cascade organocatalysis strategy for the facile construction of new "privileged" substructure-based DOS (pDOS) library. Diverse molecular architectures were produced facilely from readily available simple synthons thiazolidinedione and its analogues and α,β-unsaturated aldehydes. Reactions of isorhodanine via a Michael-cyclization cascade lead to structurally different fused thiopyranoid scaffolds.[10j] Inspired these results, we envision that the tautomerization of isorhodanines **2** to active enol form **2'** as new Michael donors could participate in an organocatalytic enantioselective conjugate addition reactions with enals (Scheme 1).

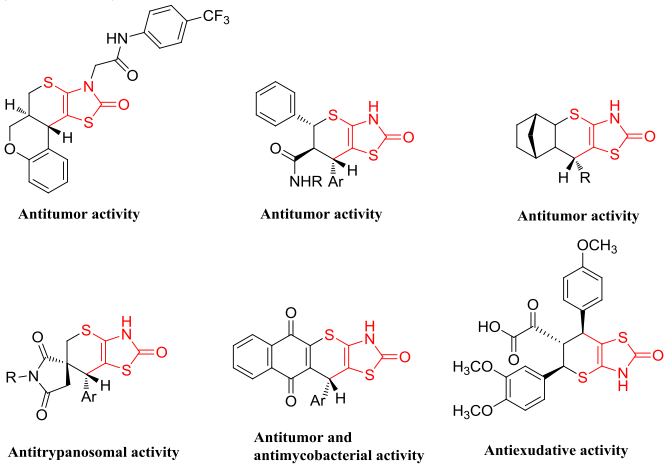
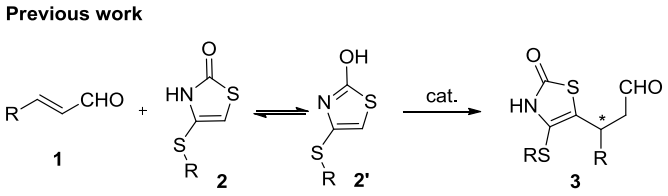



**Figure 1.** Representative bioactive molecules containing the isorhodanine unit.




**Scheme 1.** Tautomerization of substituted-isorhodanines.

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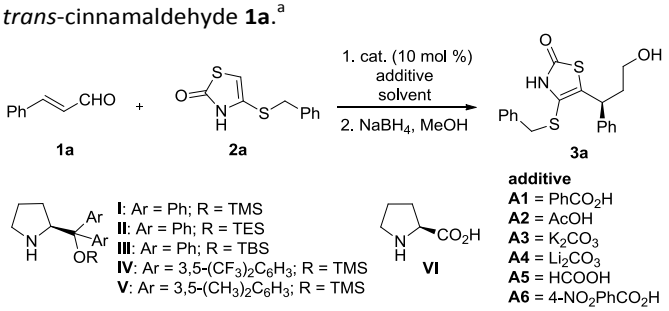
†Electronic Supplementary Information (ESI) available: Experimental procedures, NMR and HPLC spectra of new compounds. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

## Results and discussion

To probe the feasibility, we initiated the study by the reaction of 4-(benzylthio)thiazol-2(3*H*)-one (**2a**) with *trans*-cinnamaldehyde (**1a**) in toluene catalyzed by **I** (10 mol %) at room temperature (rt) (Table 1). To our delight, the desired product **3a** was obtained in 82% yield with excellent enantioselectivity (ee = 93%) (entry 1). Inspired by the outcome, catalysts **II-V** were then probed (entries 2–6). In the presence of catalyst **III,** the reaction also proceeded smoothly with high yield (83%) and excellent enantioselectivity (94% ee) (entry 3). However, catalysts **II**, **IV**, **V** and **VI** were not suitable for this reaction, giving lower ee values (9-91% ee). Moreover, larger catalyst load (20 mol% catalyst **III**) did produce better yield and enantioselectivity (entry 7). No reaction was observed between substrates **1a** and **2a** without the catalyst, suggesting the activation of the enal via an iminium ion is necessary (entry 8).

On the basis of catalysts **I** and **III**, various solvents (entries 1-14) were screened accordingly. They delivered the similar yields, but the reaction with catalyst **III** offered higher ee value than that of **I** (*e.g.* entries 9 *vs* 17, entries 10 *vs* 18, and entries 11 *vs* 19). Lower yields (33-78% yield) and enantioselectivity (80-94% ee) were observed in the presence of an additive (entries 23-28). These studies led to establishing the optimal reaction condition by using toluene as reaction medium and **III** as promoter (entry 3). The absolute configuration was determined by the X-ray crystal structure analysis of the product (**3a**) to be as (*S*), when *S*-chiral secondary amine (**III**) was used as catalyst (Figure 2).[12]

**Table 1.** Exploration and optimization of organocatalytic Michael-reduction cascade reaction of isorhodanine **2a** with *trans*-cinnamaldehyde **1a**.[a]



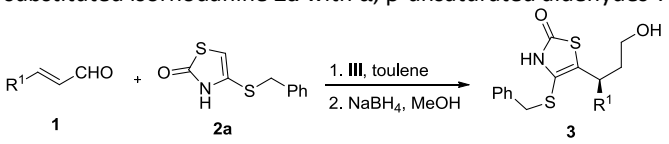

| Entry | Cat. | Additive | Solvent | t (h) | Yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|---|
| 1 | **I** | - | toluene | 11 | 82 | 93 |
| 2 | **II** | - | toluene | 11 | 80 | 80 |
| 3 | **III** | - | toluene | 12 | 83 | 94 |
| 4 | **IV** | - | toluene | 13 | 75 | 58 |
| 5 | **V** | - | toluene | 13 | 76 | 91 |
| 6 | **VI** | - | toluene | 12 | 72 | 9 |
| 7[d] | **III** | - | toluene | 13 | 78 | 95 |
| 8 | - | - | toluene | >15 | trace | nd[e] |
| 9 | **I** | - | DCM | 13 | 77 | 9 |
| 10 | **I** | - | $Cl(CH_2)_2Cl$ | 13 | 71 | 72 |
| 11 | **I** | - | MeOH | 12 | 77 | 8 |
| 12 | **I** | - | $(CH_3CH_2)_2O$ | 11 | 71 | 60 |
| 13 | **I** | - | THF | 15 | 63 | 26 |
| 14 | **I** | - | MeCN | 12 | 71 | 69 |
| 15 | **III** | - | EtOH | 12 | 74 | 36 |
| 16 | **III** | - | $CCl_4$ | 13 | 61 | 84 |
| 17 | **III** | - | DCM | 13 | 70 | 83 |
| 18 | **III** | - | $Cl(CH_2)_2Cl$ | 13 | 79 | 75 |
| 19 | **III** | - | MeOH | 12 | 78 | 7 |
| 20 | **III** | - | $(CH_3CH_2)_2O$ | 11 | 77 | 80 |
| 21 | **III** | - | THF | 15 | 60 | 39 |
| 22 | **III** | - | MeCN | 12 | 76 | 64 |
| 23 | **III** | **A1** | toluene | 15 | 78 | 84 |
| 24 | **III** | **A2** | toluene | 15 | 61 | 86 |
| 25 | **III** | **A3** | toluene | 18 | 33 | 87 |
| 26 | **III** | **A4** | toluene | 16 | 71 | 84 |
| 27 | **III** | **A5** | toluene | 15 | 66 | 94 |
| 28 | **III** | **A6** | toluene | 15 | 74 | 80 |
| 29[f] | **III** | - | toluene | 15 | 76 | 90 |

[a] Reaction conditions, unless specified, **1a** (0.16mmol, 1.2 equiv), **2a** (0.13 mmol, 1.0 equiv), and catalyst **III** (10 mol %) in solvent (1.0 mL) at rt, then methanol (1.0 mL), $NaBH_4$(0.13 mmol, 1.0 equiv) to give **3a**. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC (see the Supporting Information). [d] cat (20 mol %) was used. [e] Not determined. [f] **1a** (0.26 mmol, 3.0 equiv)

With the optimal reaction conditions in hand, the scope of the Michael reaction of isorhodanine **2a** with an array of α, β-unsaturated aldehydes **1** was probed. As shown in Table 2, a number of α, β-unsaturated aldehydes bearing electron-withdrawing, -neutral, -donating substituents and different substituted position on the benzene ring were tolerated (entries 1-9 and 13). It is found that the reaction is sensitive to

electronic effect and the position of substituted groups. It is hard to rationalize these results. Generally good to excellent enantioselectivities were obtained for enals bearing 3-substituted or 4-substituted groups (60-91% ee) (entries 3-9), and the ee value was decreased slightly. However, 4-nitro-substituted (91% ee, entry 3) substrates with strong electron-withdrawing substitutions gave the best results. In contrast, the enantioselectivities were dropped dramatically for substrates with 2-substituted groups (43% and 27% ee, entries 2 and 13). The process is also applicable for alkyl-substituted enals with good enantioselectivities (71-83% ee, entries 10-12). It is observed that the enals bearing *othro*-substituents gave poor ee (entries 2 and 13), we believed the steric effect was significantly detrimental to the enantioselectivity.

**Table 2.** Scope of the Michael-reduction cascade reaction of substituted isorhodanine **2a** with α, β-unsaturated aldehydes[a].




1 2a 3

| Entry | Product | $R^1$ | t (h) | Yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|
| 1 | **3a** | Ph | 12 | 83 | 94 |
| 2 | **3b** | 2-$NO_2C_6H_4$ | 16 | 79 | 43 |
| 3 | **3c** | 4-$NO_2C_6H_4$ | 12 | 70 | 91 |
| 4 | **3d** | 4-$CH_3OC_6H_4$ | 12 | 68 | 78 |
| 5 | **3e** | 3-$CH_3C_6H_4$ | 12 | 71 | 65 |
| 6 | **3f** | 4-$CH_3C_6H_4$ | 12 | 72 | 63 |
| 7 | **3g** | 4-$CF_3C_6H_4$ | 12 | 77 | 79 |
| 8 | **3h** | 3-$ClC_6H_4$ | 12 | 71 | 70 |
| 9 | **3i** | 4-$BrC_6H_4$ | 12 | 75 | 70 |
| 10 | **3j** | $CH_3$ | 13 | 55 | 71 |
| 11 | **3k** | $CH_2CH_3$ | 13 | 51 | 83 |
| 12 | **3l** | $CH(CH_3)_2$ | 13 | 56 | 74 |
| 13 | **3m** | 2-$CH_3OC_6H_4$ | 12 | 70 | 27 |

[a] Reaction conditions, unless specified, **1** (0.16mmol, 1.2 equiv), **2a** (0.13 mmol, 1.0 equiv), and catalyst **III** (10 mol %) in solvent (1.0 mL) at rt, then methanol (1.0 mL), $NaBH_4$ (0.13 mmol, 1.0 equiv) to give **3a-m**. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC (see the Supporting Information).

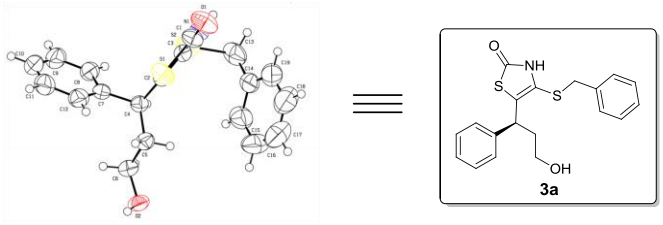
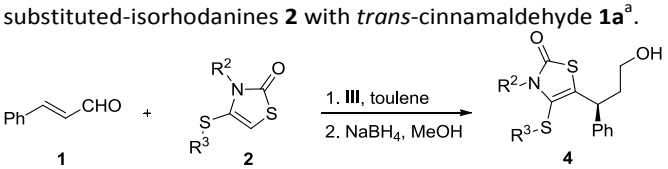



**Figure 2** X-ray crystal structure of the product **3a**

Furthermore, we explored the substrate scope by the variation of isorhodanines **2** (Table 3). To our delight, under the same conditions, the processes between different substituted isorhodanines **2** and α, β-unsaturated aldehyde **1a** proceeded smoothly with good enantioelectivity (61-> 99% ee) and yields (50-83%). Excellent entioselectivity was obtained for the methyl- (> 99% ee, entry 2) and ethyl-substituted (92% ee, entry 3) isorhodanines, whereas their yields were relatively low (50% and 56%, respectively). For 2-naphthylmethylene-substituted isorhodanines, the enantioselectivity was decreased (88% ee) but with high yields (83% yield, entry 4). It is suggested that the size of substituted group was one of the crucial factors to improve the enantioselectivity. The substituted benzyl isorhodanines (entries 5-11) gave high yields (68-81% yield) and good to excellent ee values (61-97% ee). For the 3-substituted or 4-substituted substrate, the enantioselectivity was decreased (entries 5, 7, and 9-11), however, 3-substituted or 4-substituted substrates bearing strong electron-withdrawing groups benefit the enantioselectivity (such as 93% ee, entry 9). For the 2-substituted substrates, excellent enantioselectivities maintained (97% and 94% ee, entries 6 and 8). For the substrate bearing acetonitrile substitution (entry 12), the yield was good (71% yield), but the enantioselectivity was decreased (76% ee). It appears that steric demanding is beneficial to the enantioselectivty (entries 4, 6 and 8), while less hindered ones deliver relatively poor outcomes (entries 5, 7 and 12). When the *N*-substitued substrates were reacted with compound **1a**, no desired products were obtained (entry 13). It is suggested that the enol form in isorhodanines is critical for the reaction process (Scheme 1). It is difficult for *N*-substituted isorhodanines to produce the active species via tautomerization (Scheme 2).

**Table 3.** Scope of the Michael-reduction cascade reaction of substituted-isorhodanines **2** with *trans*-cinnamaldehyde **1a**[a].

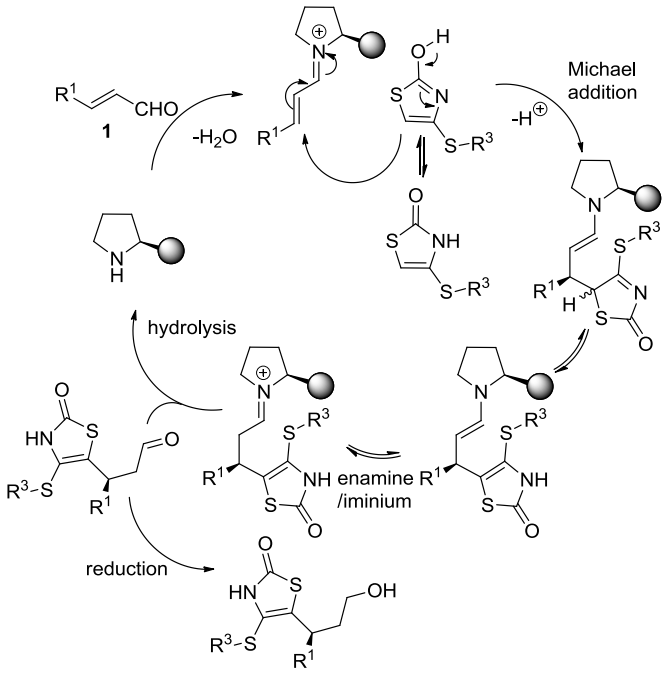



1 2 4

| Entry | Product | $R^2$, $R^3$ | t (h) | Yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|
| 1 | **3a** | H, Ph | 12 | 83 | 94 |
| 2 | **4a** | H, $CH_3$ | 13 | 50 | >99 |
| 3 | **4b** | H, $CH_3CH_2$ | 13 | 56 | 92 |

| | | | | | |
|---|---|---|---|---|---|
| 4 | **4c** | H, 2-naphthyl$CH_2$ | 13 | 83 | 88 |
| 5 | **4d** | H, 3-F$C_6H_4CH_2$ | 12 | 71 | 78 |
| 6 | **4e** | H, 2-$CH_3C_6H_4CH_2$ | 12 | 76 | 97 |
| 7 | **4f** | H, 4-$CH_3C_6H_4CH_2$ | 12 | 81 | 61 |
| 8 | **4g** | H, 2-$NO_2C_6H_4CH_2$ | 12 | 70 | 94 |
| 9 | **4h** | H, 4-$NO_2C_6H_4CH_2$ | 12 | 68 | 93 |
| 10 | **4i** | H, 4-$CNC_6H_4CH_2$ | 12 | 80 | 83 |
| 11 | **4j** | H,4-*tert*-butyl$C_6H_4CH_2$ | 12 | 78 | 83 |
| 12 | **4k** | H, $CH_2CN$ | 18 | 71 | 76 |
| 13 | **4l** | $CH_3$, $CH_3$ | 36 | NR[d] | - |

[a] Reaction conditions, unless specified, **1** (0.16mmol, 1.2 equiv), **2a** (0.13 mmol, 1.0 equiv), and catalyst **III** (10 mol %) in toluene (1.0 mL) at rt, then methanol (1.0 mL), $NaBH_4$ (0.13 mmol, 1.0 equiv) to give **4a-l**. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC (see the Supporting Information). [d] No reaction.




**Scheme2.** Proposed mechanism for the designed Michael addition of isorhodanines to α, β-unsaturated aldehydes.

## Conclusions

In summary, we have developed an efficient organocatalytic enantioselective Michael addition of isorhodanines derivatives to α,β-unsaturated aldehydes. Under the optimal reaction conditions, good yields and good to excellent enantioselectivities are achieved with broad substrate scope. The synthetic application of the resulting 4,5-disubstituted isorhodanines as versatile building blocks for the rapid synthesis of chiral isorhodanines is demonstrated. Moreover, due to diverse bioactivity of isorhodanines, the new derivatives reported herein will inspire medicinal chemists to investigate their pharmacological activity and discover drug leads. Such chemical and medicinal investigations are currently ongoing in our laboratories.

## Experimental

### General Information

Commercial reagents were used as received, unless otherwise stated. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker AVANCE II 300, AVANCE II 500 or AVANCE II 600 MHz nuclear magnetic resonance spectrometer ($CDCl_3$ or DMSO-$d_6$ as solvent) and teramethylsilane (TMS) was used as reference. Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (double of doublet) or m (multiplets). Coupling constants were reported in Hertz (Hz). High resolution mass spectrometry (HRMS) was recorded on an Agilent 6538 UHD Accurate-Mass Q-TOF LC/MS spectrometer. Analytical thin layer chromatography (TLC) was performed on silica gel GF254 (Qingdao Haiyang Chemical China) and compounds were visualized with a UV light at 254 nm. Flash chromatography was performed on silica gel 100-200 mesh with freshly distilled solvents. Enantioselectivities were determined by High performance liquid chromatography (HPLC) analysis employing a Daicel Chiralpak AS-H, OZ-H, AD-H. Optical rotations were measured in $CH_2Cl_2$ or Ethyl Acetate (EtOAc) on a SGW-1 automatic polarimeter (Shanghai Precision Scientific Instrument CO., LTD) with a 0.8 mL cell (c given in g/100 mL). Absolute configuration of the products was determined by X-ray.

### General reaction procedure and characterization for 3

Catalyst **III** (22.0 mg, 0.06 mmol, 0.1 equiv) was added to a solution of α,β-unsaturated aldehyde **1** (21.3 mg, 0.16 mmol, 1.2 equiv) and S-benzyl-substituted isorhodanine **2a** (30.0 mg, 0.13 mmol, 1.0 equiv) in toluene (1.0 mL). The mixture was stirred for 12 h at room temperature. Then, methanol (1.0 mL) and $NaBH_4$ (5.1 mg, 0.13 mmol, 1.0 equiv) were added. After stirring for 0.5 h, the solvent was evaporated and the crude product was purified though column chromatography over silica gel with hexane/EtOAc (5:1-3:1) as the eluent to yield **3a** (38.5 mg, 83% yield) as a white solid. Compounds **3b**-**m** were prepared with the same procedure.

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-phenylpropyl)thiazol-2(3*H*)-one (3a).** $^1H$ NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.84 (s, 1H), 7.31-7.36 (m, 4H), 7.29-7.30 (m, 1H), 7.21-7.25 (m, 3H), 7.13-7.16 (m, 2H), 4.41 (t, $J$ = 8.1 Hz, 1H), 3.87-3.98 (m, 2H), 3.38-3.53 (m, 2H), 2.05-2.16 (m, 1H), 1.80-1.92 (m, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.92, 141.93, 137.23, 131.14, 128.96, 128.84, 128.78, 127.65, 127.32, 127.03, 118.78, 60.15, 40.25, 39.45, 37.93, 29.71; HRMS (ESI) calcd for $C_{19}H_{18}NO_2S_2$ $[M-H]^-$ =

356.4897, found 356.2246; HPLC (Chiralpak AS-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 30/70, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 12.8 min, $t_{major}$ = 30.6 min, ee = 94.1%; $[\alpha]^{25}_{D}$ = -12.5 (*c* = 0.32 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(2-nitrophenyl)propyl)thiazol-2(3*H*)-one (3b).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 8.99 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.23-7.24 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 4.94 (t, *J* = 7.3 Hz, 1H), 3.83 (d, *J* = 12.9 Hz, 1H), 3.78 (d, *J* = 12.9 Hz, 1H), 3.41-3.50 (m, 2H), 2.04-2.10 (m, 1H), 1.83-1.89 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, TMS): $\delta$ = 171.11, 149.09, 136.29, 135.99, 132.54, 128.43, 128.37, 127.39, 127.31, 124.13, 120.16, 59.47, 39.11, 38.40, 34.07; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4S_2$ $[M-H]^-$ = 401.4872, found 401.2043; HPLC (Chiralpak AS-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 25/75, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 50.3 min, $t_{major}$ = 81.7 min, ee = 43.1%; $[\alpha]^{25}_{D}$ = 2.9 (*c* = 0.19 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(4-nitrophenyl)propyl)thiazol-2(3*H*)-one (3c).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.87 (s, 1H), 8.08 (d, *J* = 7.7 Hz, 2H), 7.29-7.30 (m, 2H), 7.25-7.26 (m, 1H), 7.19 (s, 1H), 7.16-7.18 (m, 3H), 4.47 (t, *J* = 7.6 Hz, 1H), 3.93 (s, 2H), 3.36-3.46 (m, 2H), 2.01-2.06 (m, 1H), 1.82-1.87 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.02, 148.83, 146.37, 136.61, 128.43, 128.40, 128.25, 127.70, 127.32, 123.47, 119.56, 59.08, 39.45, 38.82, 37.04; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4S_2$ $[M-H]^-$ = 401.4872, found 401.2130; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 38.6 min, $t_{major}$ = 43.8 min, ee = 91.1%; $[\alpha]^{25}_{D}$ = -40.0 (*c* = 0.20 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(4-methoxyphenyl)propyl) thiazol-2(3*H*)-one (3d).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 8.72 (s,1H), 7.26-7.31 (m, 3H), 7.18 (d, *J* = 7.4, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.36 (t, *J* = 7.8 Hz, 1H), 3.86 (s, 2H), 3.77 (s, 3H), 3.40-3.49 (m, 2H), 2.01-2.07 (m, 1H), 1.80-1.86 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$, TMS): $\delta$ = 171.46, 158.06, 136.75, 133.51, 131.39, 128.40, 127.82, 127.24, 117.55, 113.67, 59.73, 54.76, 39.25, 39.08, 37.66; HRMS (ESI) calcd for $C_{20}H_{20}NO_3S_2$ $[M-H]^-$ = 386.5156, found 386.4143; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 14.1 min, $t_{major}$ = 23.6 min, ee = 77.5%; $[\alpha]^{25}_{D}$ = 46.7 (*c* = 0.09 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(m-tolyl)propyl)thiazol-2(3*H*)-one (3e).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.71 (s, 1H), 7.31 (m, 2H), 7.14-7.29 (m, 4H), 7.05-7.12 (m, 1H), 6.96-7.00 (m, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.96 (d, *J* = 13.4 Hz, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.37-3.52 (m, 2H), 2.35 (s, 3H), 2.20-2.14 (m, 1H), 1.78-1.89 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.82, 141.87, 138.43, 137.23, 131.30, 128.05, 128.94, 128.81, 128.67, 128.06, 127.81, 127.65, 124.32, 118.61, 60.21, 40.24, 39.47, 38.08, 29.70, 21.53; HRMS (ESI) calcd for $C_{20}H_{22}NO_2S_2$ $[M+H]^+$ = 372.5162, found 372.1102; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 37.4 min, $t_{major}$ = 46.8 min, ee = 65.3%; $[\alpha]^{25}_{D}$ = 31.2 (*c* = 0.16 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(p-tolyl)propyl)thiazol-2(3*H*)-one (3f).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.53 (s, 1H), 7.26-7.30 (m, 3H), 7.17-7.18 (m, 2H), 7.06-7.09 (m, 2H), 6.99-7.00 (m, 2H), 4.34 (t, *J* = 7.6 Hz, 1H), 3.90 (d, *J* = 13.0 Hz, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.37-3.46 (m, 1H), 2.29 (s, 3H), 2.01-2.07 (m, 1H), 1.78-1.83 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.02, 148.83, 146.37, 136.61, 128.43, 128.40, 12825, 127.70, 127.32, 123.47, 119.56, 59.08, 39.45, 38.82, 37.04; HRMS (ESI) calcd for $C_{20}H_{22}NO_2S_2$ $[M+H]^+$ = 372.5162, found 372.2172; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 9.8 min, $t_{major}$ = 16.7 min, ee = 63.3%; $[\alpha]^{25}_{D}$ = 32.5 (*c* = 0.16 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(4-(trifluoromethyl)phenyl)propyl)thiazol-2(3*H*)-one (3g).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.51 (s, 1H), 7.51-7.52 (m, 1H), 7.47 (s, 1H), 7.41-7.44 (m, 1H), 7.32-7.34 (m, 2H), 7.30-7.32 (m, 2H), 7.20-7.23 (m, 2H), 4.49-4.51 (m, 1H), 3.93 (dd, *J* = 13.1, 23.0 Hz, 2H), 3.47-3.51 (m, 1H), 3.41-3.44 (m, 1H), 2.06-2.12 (m, 1H), 1.86-1.92 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.40, 143.06, 137.07, 130.97, 130.79, 129.91, 129.82, 129.29, 129.14, 128.88, 127.79, 124.03, 124.01, 123.95, 119.47, 59.77, 39.99, 39.47, 37.90, 29.70; HRMS (ESI) calcd for $C_{20}H_{17}F_3NO_2S_2$ $[M-H]^-$ = 424.4876, found 424.4721; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 24.8 min, $t_{major}$ = 30.3 min, ee = 79.3%; $[\alpha]^{25}_{D}$ = 26.9 (*c* = 0.23 in EtOAc).

**(*S*)-4-(Benzylthio)-5-(1-(3-chlorophenyl)-3-hydroxypropyl)thiazol-2(3*H*)-one (3h).** $^1$H NMR (600 MHz, DMSO-$d_6$, TMS): $\delta$ =11.45 (s, 1H), 7.27-7.29 (m, 2H), 7.22-7.25 (m, 3H), 7.19-7.20 (m, 2H), 7.04 (s, 1H), 6.91 (d, *J* = 7.1 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.24 (t, *J* = 7.6 Hz, 1H), 4.00-4.05 (m, 2H), 3.12-3.16 (m, 2H), 1.85-1.90 (m, 1H), 1.65-1.71 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, TMS): $\delta$ = 170.04, 144.89, 137.03, 133.07, 130.40, 128.72, 128.48, 127.44, 126.83, 126.61, 125.87, 119.31, 58.20, 40.07, 37.87, 37.60; HRMS (ESI) calcd for $C_{19}H_{19}ClNO_2S_2$ $[M+H]^+$ = 392.9347, found 392.4198; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 11.2 min, $t_{major}$ = 14.2 min, ee = 70.3%; $[\alpha]^{25}_{D}$ = -135.5 (*c* = 0.09 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(1-(4-bromophenyl)-3-hydroxypropyl)thiazol-2(3*H*)-one (3i).** $^1$H NMR (600 MHz, DMSO-$d_6$, TMS): $\delta$ = 11.44 (s, 1H), 7.37-7.39 (m, 2H), 7.26-7.30 (m, 3H), 7.19-7.20 (m, 2H), 6.86-6.88 (m, 2H), 4.44 (t, *J* = 4.6 Hz, 1H), 4.20 (t, *J* = 7.7 Hz, 1H), 4.06 (d, *J* = 12.9 Hz, 1H), 4.00 (d, *J* = 12.9 Hz, 1H), 3.13-3.17 (m, 2H), 1.84-1.89 (m, 1H), 1.64-1.70 (m, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$, TMS): $\delta$ = 170.08, 141.79, 137.16, 131.30, 129.28, 128.77, 128.54, 127.73, 127.29, 119.55, 119.09, 58.24, 39.12, 37.84, 37.41; HRMS (ESI) calcd for $C_{19}H_{17}BrNO_2S_2$ $[M-H]^-$ = 435.3857, found 434.9761; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle

size: 5 μm, 25 °C, *i*-propanol/hexane = 10/90, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 13.6 min, $t_{major}$ = 16.6 min, ee = 70.5%; $[\alpha]^{25}_D$ = 36.6 (*c* = 0.18 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(4-hydroxybutan-2-yl)thiazol-2(3*H*)-one (3j).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.46 (s, 1H), 7.29-7.32 (m, 2H), 7.24-7.25 (m, 1H), 7.20-7.21 (m, 2H), 3.92 (dd, *J* = 13.2, 19.4 Hz, 2H), 3.45-3.48 (m, 1H), 3.34-3.38 (m, 1H), 3.09-3.15 (m, 1H), 1.70 (s, 1H), 1.60-1.66 (m, 1H), 1.37-1.43 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H); HRMS (ESI) calcd for $C_{14}H_{16}NO_2S_2$ $[M-H]^-$ = 294.4203, found 294.1168; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{major}$ = 10.0 min, $t_{minor}$ = 12.3 min, ee = 71.3%; $[\alpha]^{25}_D$ = 44.3 (*c* = 0.11 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(1-hydroxypentan-3-yl)thiazol-2(3*H*)-one (3k).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.45 (s, 1H), 7.30-7.32 (m, 2H), 7.26-7.27 (m, 1H), 7.22-7.25 (m, 2H), 3.94 (dd, *J* = 13.0, 23.0 Hz, 2H), 3.44-3.48 (m, 1H), 3.28-3.33 (m, 1H), 2.95-3.00 (m, 1H), 1.71-1.77 (m, 1H), 1.35-1.54 (m, 3H), 0.75 (t, *J* = 0.75 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.99, 137.28, 131.44, 128.92, 128.58, 127.70, 119.08, 60.20, 39.75, 38.50, 37.01, 29.32, 11.83; HRMS (ESI) calcd for $C_{15}H_{18}NO_2S_2$ $[M-H]^-$ = 308.4469, found 3708.4225; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 15/85, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{major}$ = 17.0 min, $t_{minor}$ = 21.0 min, ee = 82.9%; $[\alpha]^{25}_D$ = 25.5 (*c* = 0.18 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(1-hydroxy-4-methylpentan-3-yl)thiazol-2(3*H*)-one (3l).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.67 (s, 1H), 7.27-7.34 (m, 5H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 4.43 (m, 1H), 3.20 (m, 1H), 2.89 (m, 1H), 1.90 (m, 1H), 1.59 (m, 1H), 1.40 (m, 1H), 0.94 (d, *J* = 6.2 Hz, 3H), 0.79 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.59, 136.77, 129.12, 128.42, 128.34, 127.19, 119.38, 59.95, 41.31, 39.00, 35.14, 32.81, 20.08, 19.88; HRMS (ESI) calcd for $C_{16}H_{20}NO_2S_2$ $[M-H]^-$ = 322.4734, found 322.4475; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 15/85, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{major}$ = 14.1 min, $t_{minor}$= 22.2 min, ee = 73.5%; $[\alpha]^{25}_D$ = 28.7 (*c* = 0.16 in $CH_2Cl_2$).

**(*S*)-4-(Benzylthio)-5-(3-hydroxy-1-(2-methoxyphenyl)propyl) thiazol-2(3*H*)-one (3m).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.24 (s, 1H), 7.28-7.31 (m, 2H), 7.18-7.26 (m, 5H), 6.93-6.95 (m, 1H), 6.85-6.88 (m, 1H), 4.80 (t, *J* = 8.3 Hz, 1H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.85 (s, 3H), 3.42 (t, *J* = 6.3 Hz, 2H), 2.08-2.03 (m, 1H), 1.87-1.93 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 182.53, 155384, 137.30, 130.54, 130.07, 128.87, 128.82, 128.27, 128.14, 127.68, 121.02, 118.96, 110.91, 60.32, 55.39, 39.59, 37.56, 34.67; HRMS (ESI) calcd for $C_{20}H_{20}NO_3S_2$ $[M-H]^-$ = 386.5156, found 386.4575; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 23.2 min, $t_{major}$ = 35.3 min, ee = 25.7%; $[\alpha]^{25}_D$ = 144.4 (*c* = 0.90 in EtOAc).

**Reaction procedure and characterization for 4**

Catalyst **III** (7.5 mg, 0.02 mmol, 0.1 equiv) was added to a solution of α,β-unsaturated aldehyde **1a** (32.3 mg, 0.24 mmol, 1.2 equiv) and S-methyl-substituted isorhodanine **2a** (30.0 mg, 0.2 mmol, 1.0 equiv) in toluene (1.0 mL). The resulted solution was stirred for 12 h at room temperature. Then, methanol (1.0 mL) and $NaBH_4$ (7.7 mg, 0.2 mmol, 1.0 equiv) were added. After stirring for 0.5 h, the solvent was evaporated and the crude product was purified though column chromatography over silica gel with hexane/EtOAc (3:1-1:1) as the eluent to yield **4a** (28.2 mg, 50% yield) as a white solid. Compounds **4b**-**l** were prepared with the same procedure.

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-(methylthio)thiazol-2(3*H*)-one (4a).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 10.11 (s, 1H), 7.30-7.32 (m, 2H), 7.27-7.28 (m, 2H), 7.21-7.24 (m, 1H), 4.63 (dd, *J* = 6.8, 9.0 Hz, 1H), 3.58-3.66 (m, 2H), 2.27 (s, 3H), 2.15-2.21 (m, 1H), 2.08-2.14 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 173.46, 142.15, 128.86, 128.77, 127.33, 127.11, 121.18, 60.25, 40.35, 37.94, 18.37; HRMS (ESI) calcd for $C_{13}H_{16}NO_2S_2$ $[M+H]^+$ = 282.3937, found 282.4685; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 12.6 min, $t_{major}$ = 20.0 min, ee > 99%; $[\alpha]^{25}_D$ = -28.4 (*c* = 0.26 in $CH_2Cl_2$).

**(*S*)-4-(Ethylthio)-5-(3-hydroxy-1-phenylpropyl)thiazol-2(3*H*)-one (4b).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 10.07 (s, 1H), 7.30-7.32 (m, 2H), 7.27-7.29 (m, 2H), 4.62 (dd, *J* = 7.1, 8.7 Hz, 2H), 3.59-3.66 (m, 2H), 2.72 (dd, *J* = 7.1, 15.0 Hz, 2H), 2.16-2.21 (m, 1H), 2.08-2.14 (m, 1H), 2.00 (s, 1H), 1.20 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 173.28, 142.20, 129.82, 128.82, 127.37, 127.08, 119.77, 60.27, 40.37, 38.25, 25.43, 14.99; HRMS (ESI) calcd for $C_{14}H_{18}NO_2S_2$ $[M+H]^+$ = 296.4203, found 296.3168; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 10/90, flow rate: 0.6 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 49.6 min, $t_{major}$ = 79.7 min, ee = 92.7%; $[\alpha]^{25}_D$ = -26.6 (*c* = 0.18 in $CH_2Cl_2$).

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-((naphthalen-2-ylmethyl)thio)thiazol-2(3*H*)-one (4c).** $^1$H NMR (600 MHz, DMSO-$d_6$, TMS): $\delta$ = 11.46 (s, 1H), 7.81-7.91 (m, 2H), 7.82-7.84 (m, 1H), 7.66 (s, 1H), 7.48-7.53 (m, 2H), 7.43 (dd, *J* = 1.7, 8.4 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.76 (d, *J* = 7.3 Hz, 2H), 4.41 (t, *J* = 4.8 Hz, 1H), 4.17-4.27 (m, 3H), 3.15-3.16 (m, 2H), 1.85-1.92 (m, 1H), 1.64-1.71 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 170.64, 142.71, 135.29, 133.39, 132.71, 129.20, 128.77, 128.70, 128.07, 127.63, 127.53, 127.39, 126.84, 126.77, 126.45, 119.14, 58.83, 38.69, 37.98; HRMS (ESI) calcd for $C_{23}H_{20}NO_2S_2$ $[M-H]^-$ = 406.5483, found 406.6723; HPLC (Chiralpak AD-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 29.4 min, $t_{major}$ = 43.2 min, ee = 88.3%; $[\alpha]^{25}_D$ = 46.2 (*c* = 0.16 in EtOAc).

**(*S*)-4-((3-Fluorobenzyl)thio)-5-(3-hydroxy-1-phenylpropyl)thiazol-2(3*H*)-one (4d).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 10.03 (s, 1H), 7.26-7.31 (m, 1H), 7.18-7.23 (m, 2H), 7.11-7.14 (m, 2H), 6.90-6.94 (m, 3H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.86 (s, 2H), 3.41-3.54 (m, 2H), 2.05-2.16 (m, 1H), 1.83-1.95 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 173.10, 164.47, 161.20, 141.86, 139.43, 131.30, 130.32, 130.21, 128.81, 127.28, 127.09, 124.63, 124.60, 118.61, 115.96, 115.67, 114.78,

114.50, 60.14, 40.35, 38.87, 38.85, 38.09; HRMS (ESI) calcd for $C_{19}H_{17}FNO_2S_2$ $[M-H]^-$ = 374.4801, found 374.3347; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 18.9 min, $t_{major}$ = 22.3 min, ee = 78.7%; $[\alpha]^{25}_D$ = 78.6 (*c* = 0.14 in $CH_2Cl_2$).

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-((2-methylbenzyl)thio) thiazol-2(3*H*)-one (4e).** $^1$H NMR (300 MHz, $CDCl_3$, TMS): $\delta$ = 11.45 (s, 1H), 7.19-7.24 (m, 3H), 7.09-7.18 (m, 3H), 7.02-7.04 (m, 1H), 6.93-6.95 (m, 2H), 4.41-4.45 (m, 1H), 4.20 (t, *J* = 7.7 Hz, 1H), 4.05 (s, 2H), 3.13 (s, 2H), 2.36 (s, 3H), 1.83-2.00 (m, 1H), 1.60-1.72 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): $\delta$ = 170.62, 142.89, 136.95, 135.27, 130.93, 130.13, 129.35, 128.97, 128.12, 127.47, 126.98, 126.39, 119.24, 58.89, 38.07, 36.83, 19.14; HRMS (ESI) calcd for $C_{20}H_{20}NO_2S_2$ $[M-H]^-$ = 370.5162, found 370.3602; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 30/70, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 29.4 min, $t_{major}$ = 43.2 min, ee = 97.5%; $[\alpha]^{25}_D$ = 57.8 (*c* = 0.09 in $CH_2Cl_2$).

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-((4-methylbenzyl)thio) thiazol-2(3*H*)-one (4f).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.66 (s, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 7.19-7.22 (m, 1H), 7.09-7.11 (m, 4H), 7.06-7.07 (m, 2H), 4.38 (t, *J* = 7.9 Hz, 1H), 3.86 (dd, *J* = 9.4, 13.1 Hz, 2H), 3.37-3.49 (m, 2H), 2.31 (s, 3H), 2.05-2.10 (m,1H), 1.81-1.88 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.67, 141.97, 137.53, 134.11, 131.03, 129.50, 128.85, 128.75, 127.35, 137.01, 118.88, 60.20, 40.26, 39.32, 37.99, 21.14; HRMS (ESI) calcd for $C_{20}H_{20}NO_2S_2$ $[M-H]^-$ = 370.5162, found 370.5243; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 30/70, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 7.9 min, $t_{major}$ = 9.4 min, ee = 77.1%; $[\alpha]^{25}_D$ = -50.6 (*c* = 0.17 in $CH_2Cl_2$).

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-((2-nitrobenzyl)thio)thiazol-2(3*H*)-one (4g).** $^1$H NMR (300 MHz, $CDCl_3$, TMS): $\delta$ = 9.76 (s, 1H), 8.01 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.47 (td, *J* = 1.1, 7.3, 14.8 Hz, 1H), 7.39 (td, *J* = 1.5, 7.9, 15.9 Hz, 1H), 7.27-7.29 (m, 1H), 7.19-7.23 (m, 2H), 7.13-7.16 (m, 1H), 7.09-7.11 (m, 2H), 4.29-4.35 (m, 2H), 4.18-4.22 (m, 1H), 3.43 (t, *J* = 6.3 Hz, 2H),1.99-2.11 (m, 2H), 1.76-1.88 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): $\delta$ = 172.63, 147.93, 141.72, 133.58, 132.75, 132.19, 132.12, 128.96, 128.85, 127.26, 127.11, 125.74, 118.17, 60.13, 40.46, 38.28, 36.91; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4S_2$ $[M-H]^-$ = 401.4872, found 401.2156; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 29.4 min, $t_{major}$ = 43.2 min, ee = 94.1%; $[\alpha]^{25}_D$ = 25.5 (*c* = 0.22 in $CH_2Cl_2$).

**(*S*)-5-(3-Hydroxy-1-phenylpropyl)-4-((4-nitrobenzyl)thio)thiaz-ol-2(3*H*)-one (4h).** $^1$H NMR (300 MHz, $CDCl_3$, TMS): $\delta$ = 10.26 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.31-7.37 (m, 2H), 7.18-7.23 (m, 3H), 7.04-7.07 (m, 2H), 4.40 (t, *J* = 7.8 Hz, 1H), 3.93 (dd, *J* = 13.1, 31.5 Hz, 2H), 3.47-3.51 (m, 2H), 2.05-2.13 (m, 1H), 2.02 (s, 2H), 1.84-1.96 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): $\delta$ = 173.19, 147.23, 144.42, 141.64, 131.90, 129.71, 128.80, 127.18, 123.98, 118.14, 59.95, 40.32, 38.54, 31.60, 25.35; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4S_2$ $[M-H]^-$ = 401.4872, found 401.3219; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 30/70, flow rate: 0.8 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 20.6 min, $t_{major}$ = 24.9 min, ee = 93.3%; $[\alpha]^{25}_D$ = -46.0 (*c* = 0.20 in $CH_2Cl_2$).

**(*S*)-4-(((5-(3-Hydroxy-1-phenylpropyl)-2-oxo-2,3-dihydrothiazol-4-yl)thio)methyl)benzonitrile (4i).** $^1$H NMR (300 MHz, $CDCl_3$, TMS): $\delta$ = 10.22 (s, 1H), 7.44-7.54 (m, 2H), 7.28-7.31 (m,2H), 7.14-7.22 (m, 3H), 7.04-7.08 (m, 2H), 4.17 (t, *J* = 8.0 Hz, 1H), 3.90 (dd, *J* = 13.0, 29.7 Hz, 2H), 3.44-3.57 (m, 2H), 2.06-2.16 (m, 1H), 1.86-1.97 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): $\delta$ = 173.21, 142.40, 141.70, 132.52, 131.72, 129.63, 128.86, 127.24, 127.21, 118.58, 118.27, 111.37, 59.96, 40.28, 38.88, 38.28; HRMS (ESI) calcd for $C_{20}H_{18}N_2O_2S_2$ $[M-H]^-$ = 381.4991, found 381.5132; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 25/75, flow rate: 0.7 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 33.8 min, $t_{major}$ = 40.7 min, ee = 82.5%; $[\alpha]^{25}_D$ = 35.0 (*c* = 0.12 in EtOAc).

**(*S*)-4-((4-(Tert-butyl)benzyl)thio)-5-(3-hydroxy-1-phenylpropyl)thiazol-2(3*H*)-one (4j).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 9.78 (s,1H), 7.34-7.35 (m, 2H), 7.28-7.31 (m, 2H), 7.22-7.23 (m, 1H), 7.19-7.21 (m, 2H), 7.14-7.16 (m, 2H), 4.43 (t, *J* = 7.6 Hz, 1H), 4.14 (dd, *J* = 7.0, 14.4 Hz, 2H), 3.96 (d, *J* = 12.9 Hz, 1H), 3.84 (d, *J* = 12.9 Hz, 1H), 3.43-3.46 (m, 1H), 3.33-3.37 (m, 1H), 2.03-2.10 (m, 1H), 1.78-1.84 (m, 1H), 1.32 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.35, 150.35, 141.56, 133.60, 130.31, 128.29, 128.19, 128.10, 127.58, 126.86, 126.67, 126.52, 125.22, 125.01, 124.95, 118.55, 59.54, 39.71, 38.54, 37.48, 34.09, 30.81; HRMS (ESI) calcd for $C_{23}H_{26}NO_2S_2$ $[M-H]^-$ = 412.5960, found 412.6328; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 10/90, flow rate: 0.7 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 40.6 min, $t_{major}$ = 50.0 min, ee = 82.5%; $[\alpha]^{25}_D$ = -26.7 (*c* = 0.15 in EtOAc).

**(*S*)-2-((5-(3-Hydroxy-1-phenylpropyl)-2-oxo-2,3-dihydrothiazol-4-yl)thio)acetonitrile (4k).** $^1$H NMR (600 MHz, $CDCl_3$, TMS): $\delta$ = 10.32 (s, 1H), 7.28-7.32 (m, 4H), 7.22-7.24 (m, 1H), 4.71 (t, *J* = 7.7 Hz, 1H), 3.64-3.66 (m, 2H), 3.55 (d, *J* = 17.2 Hz, 2H), 3.41 (d, *J* = 17.0 Hz, 2H), 2.12-2.14 (m, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$, TMS): $\delta$ = 172.32, 141.20, 135.06, 135.06, 128.53, 128.53, 126.82, 115.81, 115.31, 59.22, 39.95, 37.98, 29.20, 19.75; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_2S_2$ $[M-H]^-$ = 305.4032, found 305.3396; HPLC (Chiralpak OZ-H, column size: 0.46 cmI.D. × 25 cmL, particle size: 5 μm, 25 °C, *i*-propanol/hexane = 20/80, flow rate: 1.0 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 22.4 min, $t_{major}$ = 27.6 min, ee = 76.1%; $[\alpha]^{25}_D$ = -24.8 (*c* = 0.29 in EtOAc).

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12 The structure of compound derived from molecule **3a** was determined by X-ray crystal analysis. CCDC-1432606 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.