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# Organocatalytic Asymmetric Synthesis of Benzothiazolopyrimidines via [4 + 2] Cyclization of 2-Benzothiazolimines and Aldehydes

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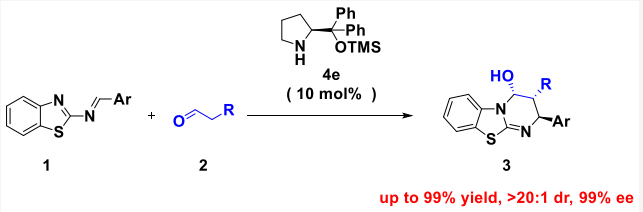
**ABSTRACT:** We report the direct asymmetric synthesis of pyrimido[2,1-*b*]benzothiazoles using a commercially available chiral amine catalyst. A variety of 2-benzothiazolimines and aldehydes were well tolerated under the reaction conditions and generated the corresponding products in 81−99% yields with excellent diastereoselectivities and enantioselectivities (up to >20:1 dr, 99% ee). Furthermore, the products could be easily converted to other useful chiral building blocks.






## INTRODUCTION

Benzothiazolopyrimidine and its derivatives are widely present in pharmacologically active molecules,[1] such as antitumor agents,[1a] antitrypanosomal agents,[1b] phosphodiesterase inhibitors,[1c] and SHP2 inhibitors (Figure 1).[1d] Moreover, Lewis

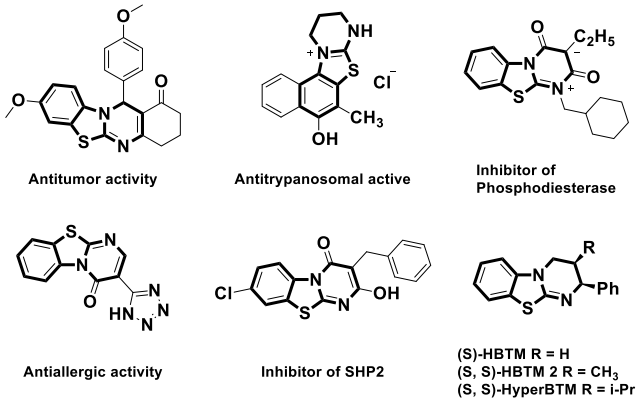
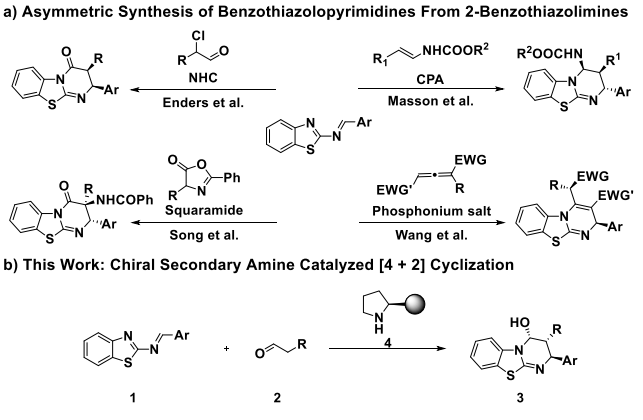



**Figure 1.** Examples of bioactive molecules and catalysts containing tricyclic pyrimido[2,1-*b*]benzothiazoles.

base isothiourea catalysts containing the tricyclic pyrimido[2,1-*b*]benzothiazole scaffold have proven to be precious catalysts applied for kinetic resolution (KR),[2] *C*-acylations,[3] *N*-acylations,[4] etc. Despite the wide distribution of this scaffold in biomolecules and organocatalysts, direct asymmetric synthesis of this scaffold has been rarely reported.[5] In 2014, the Enders group reported the asymmetric synthesis of benzothiazolopyrimidinones via chiral NHC-catalyzed Mannich/lactamization domino reaction of 2-benzothiazolimines and α-chloroaldehydes.[6] Later, a few stereoselective [4 + 2] annulations for the synthesis of benzothiazolopyrimidines were achieved by the groups of Masson, Song, and Wang, by using phosphoric acid catalysis,[7] squaramide catalysis,[8] and phosphonium salt catalysis,[9] respectively (Scheme 1a). Although

**Scheme 1. [4 + 2] Annulations for the Asymmetric Synthesis of Benzothiazolopyrimidines**




these strategies mentioned above are effective and reliable, there is still an urgent need for exploring optional methods that start from inexpensive and readily available substrates for the direct asymmetric synthesis of tricyclic pyrimido[2,1-*b*]-benzothiazole derivatives, for which products can be easily transformed to other attractive chiral molecules for further applications.

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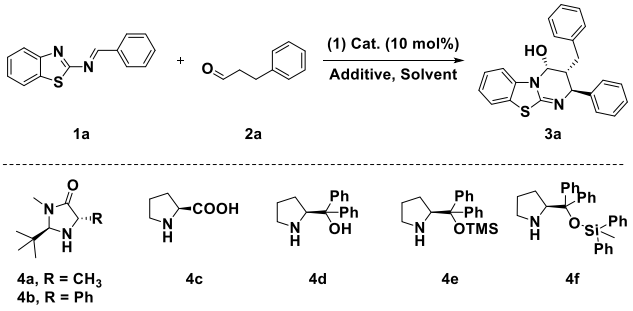
The asymmetric Mannich reactions catalyzed by chiral primary and secondary amines and bifunctional organocatalysts for new C−C bond formation have been widely used in the effective synthesis of natural products and pharmacologically active chiral compounds.[10,11] Aldehydes and $\alpha,\beta$-unsaturated aldehydes activated by secondary amines are frequently applied for the construction of multifunctional heterocycles through [2 + 2], [3 + 2], and [4 + 2] cyclization, in which the asymmetric Mannich reaction is working as the key step.[12,13] Recently, our group developed the secondary chiral amine-catalyzed three-component asymmetric Povarov reaction between anilines and aldehydes via chiral enamine intermediates which serve as electron-rich olefins.[14] As part of our research interests in developing new catalytic strategies to construct useful bioactive frameworks,[15] we herein report the direct asymmetric synthesis of benzothiazolopyrimidines via chiral secondary amine-catalyzed [4 + 2] cyclization of 2-benzothiazolimines and aldehydes (Scheme 1b). Furthermore, the products can be easily converted to other useful chiral building blocks.

## RESULTS AND DISCUSSION

We initiated our studies by examining the reaction of 2-benzothiazolimine **1a** and 3-phenylpropionaldehyde **2a** in the presence of different chiral secondary amines **4** (10 mol %) and benzoic acid (10 mol %) in DCM under room temperature (Table 1). The MacMillan's catalysts (**4a**, **4b**) could not promote the reaction (Table 1, entries 1 and 2). L-Proline **4c** could catalyze this reaction with good stereoselectivity and gave the *syn*-selective adduct **3a′** (the diastereoisomer of **3a**) with 60% yield (Table 1, entry 3). The absolute configuration of **3a′** was confirmed by X-ray crystallographic analysis (CCDC 2048709, see Supporting Information for details). To our delight, $\alpha,\alpha$-diphenylprolinol trimethylsilyl ether **4e** provided the product **3a** in 97% yield with excellent diastereoselectivity (dr 13:1) and enantioselectivity (98% ee) (Table 1, entry 5). Reducing the equivalent of aldehyde **2a** led to lower yield (Table 1, entry 7). In attempt to further improve the diastereoselectivity, we tested different solvents (DCE, PhMe, THF, and $CH_3CN$) and an acid additive ($p$-$NO_2$-PhCOOH); however, no satisfactory improvements were achieved (Table 1, entries 8−12). Fortunately, lowering the reaction temperature to 0 °C delivered the product **3a** in 94% yield, high diastereoselectivity (>20:1), and enantioselectivity (99% ee) (Table 1, entry 13). Thus, the optimized reaction conditions were established as 1.0 equiv of 2-benzothiazolimine **1a** and 1.5 equiv of 3-phenylpropionaldehyde **2a**, in the presence of chiral secondary amine **4e** (10 mol %) and benzoic acid (10 mol %) in DCM under 0 °C.

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | cat. | additive | solvent | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | **4a** | PhCOOH | DCM | – | – | – |
| 2 | **4b** | PhCOOH | DCM | – | – | – |
| 3 | **4c** | PhCOOH | DCM | 60[g] | 1:20 | 97 |
| 4 | **4d** | PhCOOH | DCM | – | – | – |
| 5 | **4e** | PhCOOH | DCM | 97 | 13:1 | 98 |
| 6 | **4f** | PhCOOH | DCM | 98 | 5:1 | 88 |
| 7[e] | **4e** | PhCOOH | DCM | 88 | 13:1 | 98 |
| 8 | **4e** | PhCOOH | DCE | 95 | 4:1 | 92 |
| 9 | **4e** | PhCOOH | PhMe | 93 | 11:1 | 97 |
| 10 | **4e** | PhCOOH | THF | 96 | 6:1 | 91 |
| 11 | **4e** | PhCOOH | $CH_3CN$ | 98 | 7:1 | 96 |
| 12 | **4e** | $p$-$NO_2$-PhCOOH | DCM | 95 | 11:1 | 97 |
| 13[f] | **4e** | PhCOOH | DCM | 94 | >20:1 | 99 |

[a]Reactions conditions: **1a** (0.1 mmol), **2a** (0.15 mmol) in the presence of catalyst **4** (0.01 mmol), and acid additive (0.01 mmol) in solvent (1 mL) under room temperature for 1 h. [b]Isolated yield of both diastereomers. [c]Determined by $^1$H NMR analysis. [d]Determined by chiral HPLC analysis. [e]0.12 mmol of **2a**. [f]Reaction was performed at 0 °C. [g]Isolated yield of **3a′** (the diastereoisomer of **3a**).

With the optimized reaction conditions in hand, we then investigated the substrate scope of this protocol (Scheme 2). Initially, various 2-benzothiazolimines **1** bearing different substituents on the benzothiazole ring were reacted with 3-phenylpropionaldehyde **2a**. The electronic properties of the substituents at the C6 position of benzothiazole rings displayed negligible effects for the reactions; either electron-withdrawing groups (F, Cl) or an electron-donating group ($OCH_3$) gave the corresponding products **3b−d** with excellent yields (97−98%), diastereoselectivities (14:1−19:1), and enantioselectivities (91−98% ee). Similarly, good results were attained with the substituent at the C5 position of the benzothiazole ring (**3e**). It is worth noting that 2-benzoxazolimine was also a suitable substrate, giving the expected product **3f** in 97% ee, >20:1 dr, and 97% yield. Subsequently, 2-benzothiazolimines bearing various substituents on the phenyl ring were investigated. A wide range of substituents on the phenyl ring of 2-benzothiazolimine, including $CF_3$, Cl, F, $CH_3$, and $OCH_3$, participated well in the reactions and afforded the corresponding adducts **3g−k** in 92−99% yields with excellent enantioselectivities (95−99% ee). Furthermore, the absolute configuration of **3h** was confirmed by X-ray crystallographic analysis (CCDC 2033715, see Supporting Information for details), which turned out to be the *anti*-selective product and different from **3a′**. Notably, the 2-benzothiazolimines with furanyl, thienyl, or pyridyl groups could also participate well under the optimized reaction conditions, leading to **3l−n** in good yields (84−87%) and high enantioselectivities (94−99% ee). Moreover, the 2-benzothiazolimine with a $\beta$-naphthyl group was well tolerated and delivered the desired product **3o** with 98% yield and 98% ee.

Finally, other aliphatic aldehydes were explored in the asymmetric reaction. In general, propionaldehyde, butyraldehyde, hexanal, and decanal reacted well to give the corresponding products **3p−s** in good to high yields (83−90%) with high enantioselectivities (91−98% ee). When phenylacetaldehyde was used, the reaction proceeded slowly, which led to a slight decrease in the yield of product **3t** (81% yield, 4:1 dr, 94% ee). Furthermore, other aliphatic aldehydes with heterocycles pyrimidine and thiophene side chains were tolerated under the established reaction conditions and gave the corresponding products **3u** and **3v** with satisfactory results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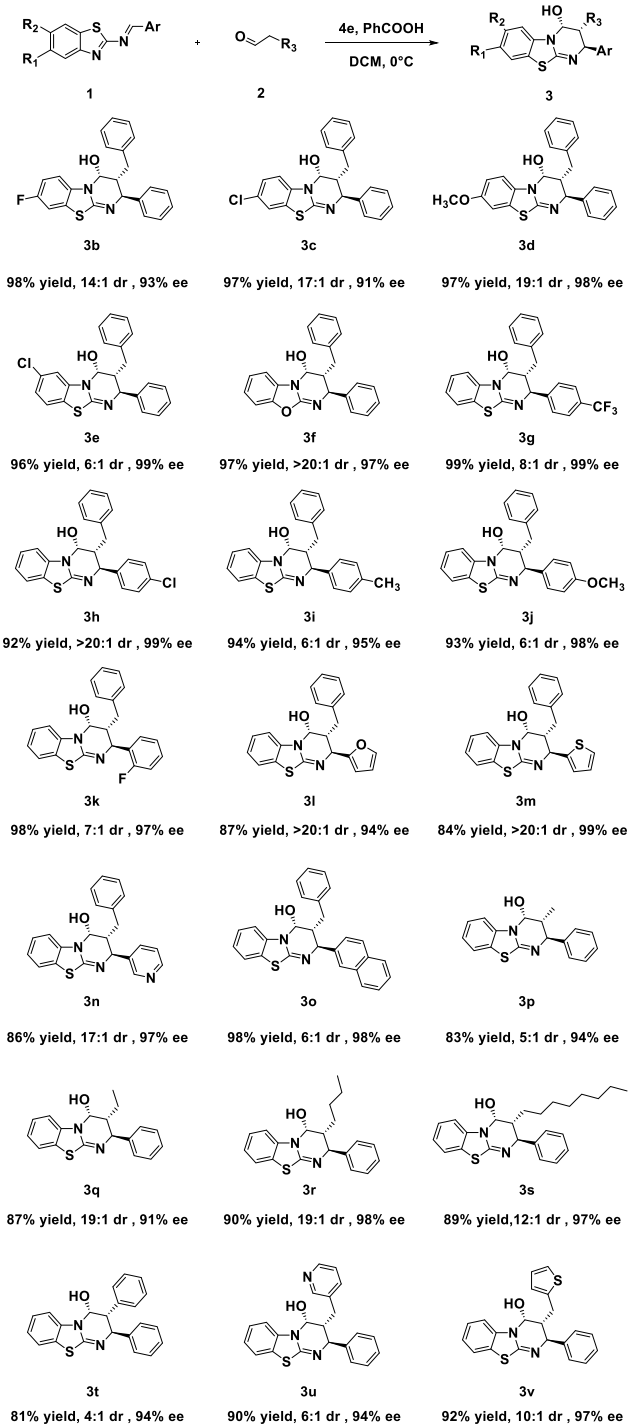
**Scheme 2. Substrate Scope of the Reactions**[a]

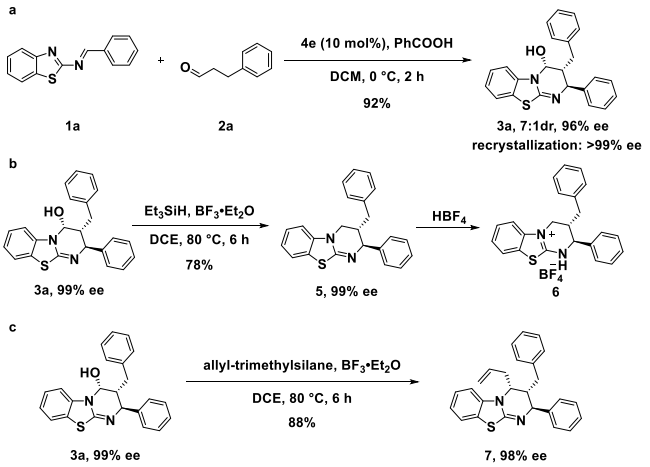



[a]Reactions conditions: **1a** (0.2 mmol), **2a** (0.3 mmol) in the presence of catalyst **4e** (0.02 mmol) and PhCOOH (0.02 mmol) in DCM (2 mL) under 0 °C for 1−12 h. Yield: isolated yield of both diastereomers. dr: determined by $^1$H NMR analysis. ee: determined by chiral HPLC analysis.

(90−92% yields, 94−97% ee). The absolute configurations of **3a−g** and **3i−v** were assigned according to **3h**. We also tested the in situ-generated 2-benzothiazolimine from 2-aminobenzothiazole and 3-phenylpropionaldehyde **2a** to react with 3-phenylpropionaldehyde **2a**; however, a mixture of byproducts was obtained. This might be due to the competitive catalytic capability of the 2-aminobenzothiazole and self-condensation of the aldehyde.[16]

To further verify the practicality of this protocol, we performed a gram-scale synthesis using 2-benzothiazolimine **1a** and 3-phenylpropionaldehyde **2a** under the standard reaction conditions. To our delight, product **3a** was isolated in excellent yield, good enantioselectivity, and good diastereoselectivity (92%, 96% ee, and 7:1 dr) (Scheme 3a). By simple

**Scheme 3. Gram-Scale Synthesis and Transformation of Product 3a**




recrystallization, **3a** could be obtained in enantiomerically pure form (>99% ee). The hydroxyl group of **3a** could be removed by reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ under 80 °C and gave the product **5** as a single diastereoisomer (Scheme 3b). **5** was then treated with fluoroboric acid to afford tetrafluoroborate **6**, and the structure was confirmed by X-ray crystallographic analysis (CCDC 2033716, see Supporting Information for details), suggesting that this synthetic strategy can be applied to quickly construct the core scaffold of Lewis base isothiourea catalysts. Additionally, the hydroxyl group of **3a** could be replaced by allyl to give the product **7** after treating with allyl-trimethylsilane/$BF_3{\cdot}Et_2O$, and the stereochemistry of the allyl substituent was confirmed by NOE analysis (Scheme 3c).

To better understand this asymmetric [4 + 2] cyclization reaction, we proposed a plausible reaction mechanism based on the results and previous studies[10b] (Scheme 4). Initially, the chiral secondary amine catalyst **4e** reacted with aldehyde **2** to give the iminium ion intermediate **I**, which rapidly tautomerized to enamine intermediate **II**. Subsequently, nucleophilic attack of the enamine intermediate **II** on 2-benzothiazolimine **1** at the *Re*-face through a Mannich reaction formed intermediate **IV**. Subsequent hydrolysis of the intermediate **IV** led to the release of catalyst **4e** and aldehyde **V**, followed by **V** tautomerization to intermediate **VI**. Finally, the intramolecular nucleophilic addition of intermediate **VI** gave the product **3**.

## CONCLUSIONS

In summary, we have developed an efficient asymmetric [4 + 2] cyclization for the direct construction of chiral benzothiazolopyrimidines with high yields and excellent stereoselectivities. A wide variety of benzothiazolimines and aldehydes were well tolerated under the mild reaction conditions. Further-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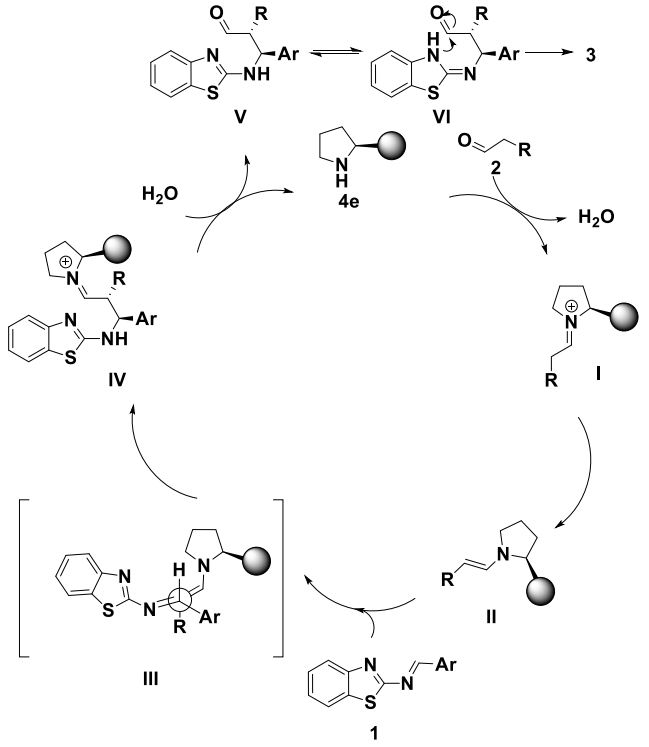
**Scheme 4. Proposed Mechanism of [4 + 2] Cyclization**




more, this synthetic strategy could be applied to quickly construct the core scaffold of Lewis base isothiourea catalysts and other precious chiral building blocks. Further applications of this protocol are currently underway in our lab.

## EXPERIMENTAL SECTION

**General Information.** All reagents used in the synthesis were obtained commercially and used without further purification. All experiments were monitored by analytical thin layer chromatography (TLC). UV light, $I_2$, and a solution of $KMnO_4$ were used to visualize products. NMR spectra were recorded on a Bruker (400 or 500 MHz) spectrometer. $^1H$, $^{19}F$, and $^{13}C$ NMR were recorded at 400 MHz ($^1H$ NMR), 100 MHz ($^{13}C$ {$^1H$} NMR) and 376 MHz ($^{19}F${$^1H$} NMR), or 500 MHz ($^1H$ NMR) and 125 MHz ($^{13}C$ {$^1H$} NMR), respectively. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: $\delta_H$ = 7.26 ppm, $\delta_C$ = 77.16 ppm; DMSO-$d_6$: $\delta_H$ = 2.50 ppm, $\delta_C$ = 39.52 ppm). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of (triplets). Coupling constants ($J$) are reported in hertz (Hz). High resolution mass spectrometry (HRMS) spectra were obtained on a Shimadzu LCMS-ITTOF mass spectrometer. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on a polarimeter with a sodium lamp of wavelength 589 nm and are reported as follows: $[\alpha]_\lambda^T$ ($c$ = g/100 mL, solvent). Enantiomeric excesses were determined by chiral high-performance liquid chromatography (HPLC) analysis. HPLC samples were dissolved in HPLC grade 2-propanol (IPA) unless otherwise stated. X-ray structural analysis was conducted on XtaLAB Synergy R, DW system, HyPix diffractometer. All the 0 °C reactions were controlled by magnetic agitation of the low temperature thermostat sink (EYELA, PSL-1400). 2-Benzothiazolimines were synthesized according to the literature procedures.[8] Piperidine was used as the catalyst for the preparation of the corresponding racemic products for HPLC analysis. All the chiral secondary amine organic catalysts were purchased from commercial sources such as Daicel Chiral Co.

**General Procedure for the Synthesis of 2-Benzothiazolimines.** To a 50 mL flame-dried round-bottom flask were added 2-aminobenzothiazole (1.0 mmol), benzaldehyde (1.1 mmol), and toluene (10 mL). To the above solution were added 4 Å molecular sieves (1.0 g). The mixture was refluxed for 12−20 h under an oil bath. After the complete conversion of the starting material, the mixture was filtered and the filtrate was concentrated by the evaporator. The residue was quickly purified by flash chromatography on silica gel, employing mixtures of petroleum ether and ethyl acetate as eluents to afford the desired 2-benzothiazolimines.

**General Procedure for the Asymmetric Synthesis of Products 3.** At 0 °C, aldehyde **2** (0.30 mmol, 1.5 equiv) in 2 mL of DCM was added into a mixture of 2-benzothiazolimine **1** (0.20 mmol, 1.0 equiv), catalyst **4e** (0.02 mmol, 10 mol %), and PhCOOH (0.02 mmol, 10 mol %). Then the reaction mixture was stirred at 0 °C for 1−12 h. After completion of the reaction, 2 mL of saturated $NaHCO_3$ solution was added and extracted with DCM and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The reaction mixture was purified by flash column chromatography using DCM/MeOH as the eluent to get the products.

*(2S,3R,4R)-3-Benzyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol (**3a**).* White solid (70 mg, 94% yield, DCM/MeOH = 100/1 as the eluent). mp 131.5−134.1 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (t, $J$ = 7.2 Hz, 2H), 7.49 (d, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.2 Hz, 1H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.16−7.06 (m, 2H), 7.01−6.84 (m, 4H), 6.74 (d, $J$ = 7.6 Hz, 1H), 4.84 (d, $J$ = 2.4 Hz, 1H), 4.23 (d, $J$ = 11.6 Hz, 1H), 2.13−1.97 (m, 1H), 1.88−1.80 (m, 1H), 1.59 (t, $J$ = 12.4 Hz, 1H). $^{13}C${$^1H$} NMR (100 MHz, $CDCl_3$) $\delta$ 159.1, 143.0, 139.8, 139.2, 129.3, 128.9, 128.4, 127.9, 126.1, 125.9, 123.5, 122.1, 121.2, 109.8, 74.4, 59.9, 46.4, 32.8. HRMS (ESI) $m/z$: [M + H]$^+$ Calcd for $C_{23}H_{21}N_2OS$ 373.1369; found 373.1357. $[\alpha]_{20}^D$ +66° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 8.50 min, $t_R$ (major) = 20.78 min, >20:1 dr, 99% ee.

*(2S,3R,4R)-3-Benzyl-8-fluoro-2-phenyl-3,4-dihydro-2H-benzo-[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3b**).* White solid (77 mg, 98% yield, DCM/MeOH = 100/1 as the eluent). mp 140.9−144.4 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (t, $J$ = 7.2 Hz, 2H), 7.48−7.36 (m, 3H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.15−7.10 (m, 1H), 6.93 (d, $J$ = 7.4 Hz, 2H), 6.84 (d, $J$ = 6.4 Hz, 2H), 6.58 (d, $J$ = 6.0 Hz, 1H), 4.78 (s, 1H), 4.20 (d, $J$ = 10.8 Hz, 1H), 2.05 (d, $J$ = 11.6 Hz, 1H), 1.84 (s, 1H), 1.60 (d, $J$ = 12.4 Hz, 1H). $^{13}C${$^1H$} NMR (100 MHz, $CDCl_3$) $\delta$ 158.7 (C−F, $^1J_{C-F}$ = 240.0 Hz), 158.7, 142.7, 139.0, 136.1, 129.3, 128.8, 128.5, 128.0, 126.2, 112.9(C−F, $^2J_{C-F}$ = 22.0 Hz), 110.3, 108.6 (C−F, $^2J_{C-F}$ = 26.0 Hz), 74.8, 59.7, 46.3, 32.8. $^{19}F${$^1H$} NMR (376 MHz, $CDCl_3$) $\delta$ −120.25. HRMS (ESI) $m/z$: [M + H]$^+$ Calcd for $C_{23}H_{20}FN_2OS$ 391.1275; found 391.1272. $[\alpha]_{20}^D$ +87° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 8.08 min, $t_R$ (major) = 14.07 min, 14:1 dr, 93% ee.

*(2S,3R,4R)-3-Benzyl-8-chloro-2-phenyl-3,4-dihydro-2H-benzo-[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3c**).* White solid (79 mg, 97% yield, DCM/MeOH = 100/1 as the eluent). mp 145.7−146.4 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (s, 1H), 7.60 (t, $J$ = 7.6 Hz, 2H), 7.50 (d, $J$ = 7.6 Hz, 2H), 7.41 (t, $J$ = 7.2 Hz, 1H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.15−7.05 (m, 2H), 6.91 (d, $J$ = 7.2 Hz, 2H), 6.80 (d, $J$ = 8.4 Hz, 2H), 4.76 (s, 1H), 4.20 (d, $J$ = 11.6 Hz, 1H), 2.09−1.98 (m, 1H), 1.87−1.79 (m, 1H), 1.49 (t, $J$ = 12.8 Hz, 1H). $^{13}C${$^1H$} NMR (100 MHz, $CDCl_3$) $\delta$ 158.4, 142.7, 138.9, 138.4, 129.3, 128.8, 128.6, 128.5, 128.1, 127.6, 126.3, 126.2, 124.9, 121.1, 110.6, 74.7, 59.9, 46.2, 32.8. HRMS (ESI) $m/z$: [M + H]$^+$ Calcd for $C_{23}H_{20}ClN_2OS$ 407.0979; found 407.0971. $[\alpha]_{20}^D$ +39° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 9.45 min, $t_R$ (major) = 17.47 min, 17:1 dr, 91% ee.

*(2S,3R,4R)-3-Benzyl-8-methoxy-2-phenyl-3,4-dihydro-2H-benzo-[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3d**).* White solid (78 mg, 97% yield, DCM/MeOH = 100/1 as the eluent). mp 122.8−123.9 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (t, $J$ = 7.2 Hz, 2H), 7.48 (d, $J$ = 7.2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Hz, 2H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.12 (t, $J$ = 7.2 Hz, 1H), 6.95 (d, $J$ = 7.2 Hz, 2H), 6.81 (d, $J$ = 8.8 Hz, 1H), 6.67 (dd, $J$ = 8.8, 0.8 Hz, 1H), 6.40 (s, 1H), 4.79 (s, 1H), 4.22 (d, $J$ = 11.2 Hz, 1H), 3.74 (s, 3H), 2.07 (d, $J$ = 12.0 Hz, 1H), 1.83 (t, $J$ = 10.0 Hz, 1H), 1.62 (t, $J$ = 12.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 155.6, 143.1, 139.3, 134.0, 129.3, 128.9, 128.4, 127.9, 126.1, 124.8, 111.1, 110.1, 107.6, 100.1, 74.5, 59.7, 56.0, 46.3, 32.9. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O_2S$ 403.1475; found 403.1461. $[\alpha]_{20}^{D}$ +47° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 11.66 min, $t_R$ (major) = 25.22 min, 19:1 dr, 98% ee.

*(2S,3R,4R)-3-Benzyl-7-chloro-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3e**). White solid (78 mg, 96% yield, DCM/MeOH = 100/1 as the eluent). mp 115.6−116.6 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (t, $J$ = 7.2 Hz, 2H), 7.50 (d, $J$ = 7.2 Hz, 2H), 7.41 (t, $J$ = 7.2 Hz, 1H), 7.21 (t, $J$ = 7.2 Hz, 2H), 7.18−7.10 (m, 1H), 6.85−6.75 (m, 4H), 6.69 (d, $J$ = 8.8 Hz, 1H), 4.78 (d, $J$ = 1.6 Hz, 1H), 4.21 (d, $J$ = 11.2 Hz, 1H), 2.07 (d, $J$ = 12.4 Hz, 1H), 1.85 (t, $J$ = 11.6 Hz, 1H), 1.53 (t, $J$ = 12.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.7, 142.6, 140.8, 138.8, 132.3, 129.3, 128.8, 128.6, 128.2, 126.3, 122.2, 121.9, 121.6, 110.3, 74.7, 60.0, 46.3, 32.8. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{20}ClN_2OS$ 407.0979; found 407.0965. $[\alpha]_{20}^{D}$ +43° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.62 min, $t_R$ (major) = 23.17 min, 6:1 dr, 99% ee.

*(2S,3R,4R)-3-Benzyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]-oxazolo[3,2-a]pyrimidin-4-ol* (**3f**). White solid (69 mg, 97% yield, DCM/MeOH = 100/1 as the eluent). mp 91.3−94.3 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (s, 1H), 7.56 (t, $J$ = 7.2 Hz, 2H), 7.45−7.37 (m, 3H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.15−7.08 (m, 1H), 7.03 (t, $J$ = 7.6 Hz, 1H), 6.96 (d, $J$ = 7.4 Hz, 2H), 6.91 (d, $J$ = 7.6 Hz, 1H), 6.81 (t, $J$ = 7.6 Hz, 1H), 5.53 (d, $J$ = 7.6 Hz, 1H), 4.84 (s, 1H), 4.30 (d, $J$ = 10.8 Hz, 1H), 2.04 (d, $J$ = 12.4 Hz, 1H), 1.79 (t, $J$ = 11.2 Hz, 1H), 1.72−1.59 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.4, 144.2, 142.9, 139.4, 131.8, 129.5, 128.9, 128.3, 127.9, 126.1, 123.3, 121.0, 109.3, 107.4, 74.4, 58.6, 47.1, 32.9. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_2$ 357.1598; found 357.1595. $[\alpha]_{20}^{D}$ +71° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 10.87 min, $t_R$ (major) = 30.00 min, >20:1 dr, 97% ee.

*(2S,3R,4R)-3-Benzyl-2-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3g**). White solid (87 mg, 99% yield, DCM/MeOH = 100/1 as the eluent). mp 123.0−123.7 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 8.0 Hz, 2H), 7.21 (t, $J$ = 7.8 Hz, 2H), 7.17−7.13 (m, 2H), 6.97 (t, $J$ = 7.6 Hz, 1H), 6.90 (t, $J$ = 6.8 Hz, 3H), 6.82 (d, $J$ = 7.6 Hz, 1H), 4.91 (d, $J$ = 2.8 Hz, 1H), 4.25 (d, $J$ = 11.2 Hz, 1H), 2.07 (d, $J$ = 12.8 Hz, 1H), 1.91 (t, $J$ = 11.6 Hz, 1H), 1.74 (t, $J$ = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.5, 147.1, 139.5, 138.1, 130.5 (C−F, $^2J_{C-F}$ = 32.0 Hz), 129.1, 129.1, 129.0, 128.6, 126.5, 126.2, 125.6,124.4 (C−F, $^1J_{C-F}$ = 242.0 Hz), 122.6, 121.4, 109.8, 74.3, 59.8, 45.9, 33.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta$ −62.37. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{24}H_{20}F_3N_2OS$ 441.1243; found 441.1224. $[\alpha]_{20}^{D}$ +56° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.20 min, $t_R$ (major) = 25.51 min, 8:1 dr, 99% ee.

*(2S,3R,4R)-3-Benzyl-2-(4-chlorophenyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3h**). White solid (75 mg, 92% yield, DCM/MeOH = 100/1 as the eluent). mp 136.6−137.6 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.4 Hz, 2H), 7.38 (d, $J$ = 8.0 Hz, 2H), 7.23 (t, $J$ = 7.2 Hz, 2H), 7.20−7.08 (m, 2H), 6.95 (t, $J$ = 7.6 Hz, 3H), 6.90 (d, $J$ = 8.0 Hz, 1H), 6.78 (d, $J$ = 7.6 Hz, 1H), 4.88 (d, $J$ = 2.0 Hz, 1H), 4.19 (d, $J$ = 11.2 Hz, 1H), 2.13 (d, $J$ = 10.4 Hz, 1H), 1.85 (t, $J$ = 11.6 Hz, 1H), 1.73 (t, $J$ = 12.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.3, 141.5, 139.6, 138.5, 133.8, 130.0, 129.1, 128.7, 128.6, 126.4, 126.1, 123.3, 122.4, 121.4, 109.8, 74.3, 59.4, 46.0, 33.0. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{20}ClN_2OS$ 407.0979; found 407.0961. $[\alpha]_{20}^{D}$ +66° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 10.07 min, $t_R$ (major) = 30.17 min, >20:1 dr, 99% ee.

*(2S,3R,4R)-3-Benzyl-2-(p-tolyl)-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol* (**3i**). White solid (72 mg, 94% yield, DCM/MeOH = 100/1 as the eluent). mp 168.9−170.5 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (dd, $J$ = 15.6, 7.6 Hz, 4H), 7.20 (t, $J$ = 7.2 Hz, 2H), 7.11 (dd, $J$ = 15.2, 7.2 Hz, 2H), 7.00−6.86 (m, 4H), 6.76 (d, $J$ = 7.6 Hz, 1H), 4.83 (s, 1H), 4.22 (d, $J$ = 11.2 Hz, 1H), 2.38 (s, 3H), 2.12 (d, $J$ = 11.6 Hz, 1H), 1.86 (t, $J$ = 11.6 Hz, 1H), 1.61 (t, $J$ = 12.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.7, 140.1, 139.8, 139.4, 137.4, 129.2, 129.1, 128.8, 128.4, 126.0, 125.8, 123.5, 122.1, 121.2, 109.8, 74.5, 59.6, 46.2, 32.9, 21.4. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2OS$ 387.1526; found 387.1522. $[\alpha]_{20}^{D}$ +52° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 9.10 min, $t_R$ (major) = 21.71 min, 6:1 dr, 95% ee.

*(2S,3R,4R)-3-Benzyl-2-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3j**). White solid (75 mg, 93% yield, DCM/MeOH = 100/1 as the eluent). mp 152.8−154.1 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41 (d, $J$ = 8.4 Hz, 2H), 7.20 (t, $J$ = 7.2 Hz, 2H), 7.15−7.05 (m, 4H), 7.01−6.87 (m, 4H), 6.76 (d, $J$ = 7.2 Hz, 1H), 4.84 (s, 1H), 4.22 (d, $J$ = 11.2 Hz, 1H), 3.81 (s, 3H), 2.14 (d, $J$ = 12.0 Hz, 1H), 1.82 (t, $J$ = 11.2 Hz, 1H), 1.68 (t, $J$ = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.4, 158.8, 139.9, 139.3, 135.2, 129.8, 129.3, 128.4, 126.1, 125.9, 123.6, 122.1, 121.2, 113.8, 109.8, 74.5, 59.2, 55.6, 46.5, 33.0. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O_2S$ 403.1475; found 403.1471. $[\alpha]_{20}^{D}$ +53° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 12.55 min, $t_R$ (major) = 33.21 min, 6:1 dr, 98% ee.

*(2S,3R,4R)-3-Benzyl-2-(2-fluorophenyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3k**). White solid (77 mg, 98% yield, DCM/MeOH = 100/1 as the eluent). mp 125.2−131.5 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (s, 1H), 7.40−7.30 (m, 2H), 7.23−7.17 (m, 3H), 7.16−7.08 (m, 2H), 7.00−6.92 (m, 3H), 6.91−6.81 (m, 2H), 4.94 (s, 1H), 4.68 (s, 1H), 2.28 (d, $J$ = 10.4 Hz, 1H), 2.21−1.98 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.0 (C−F, $^1J_{C-F}$ = 245.0 Hz), 158.7, 139.6, 138.9, 130.6, 130.0, 129.3, 129.2, 128.4, 126.2, 125.9, 124.5, 123.4, 122.2, 121.3, 115.6 (C−F, $^2J_{C-F}$ = 23.0 Hz), 109.7, 74.1, 54.6, 45.4, 33.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) $\delta$ −114.42. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{20}FN_2OS$ 391.1275; found 391.1279. $[\alpha]_{20}^{D}$ +33° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 8.10 min, $t_R$ (major) = 15.27 min, 7:1 dr, 97% ee.

*(2S,3R,4R)-3-Benzyl-2-(furan-2-yl)-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol* (**3l**). White solid (63 mg, 87% yield, DCM/MeOH = 100/1 as the eluent). mp 99.4−100.8 °C. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.60 (d, $J$ = 0.8 Hz, 1H), 7.46 (dd, $J$ = 7.6, 0.8 Hz, 1H), 7.28 (t, $J$ = 7.2 Hz, 2H), 7.21−7.15 (m, 4H), 7.20−6.95 (m, 2H), 6.91 (d, $J$ = 8.0 Hz, 1H), 6.45−6.37 (m, 2H), 5.15 (dd, $J$ = 6.4, 2.4 Hz, 1H), 4.58 (d, $J$ = 11.6 Hz, 1H), 2.71−2.62 (m, 1H), 2.40−2.25 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 156.1, 155.3, 142.5, 139.5, 139.3, 129.3, 128.8, 126.5, 126.4, 122.6, 122.5, 122.0, 110.7, 109.1, 107.8, 73.3, 54.1, 42.0, 33.7. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2O_2S$ 363.1162; found 363.1161. $[\alpha]_{20}^{D}$ +90° ($c$ 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, $n$-hexane/$i$-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.35 min, $t_R$ (major) = 16.69 min, >20:1 dr, 94% ee.

*(2S,3R,4R)-3-Benzyl-2-(thiophen-2-yl)-3,4-dihydro-2H-benzo-[4,5]thiazolo[3,2-a]pyrimidin-4-ol* (**3m**). White solid (63 mg, 84% yield, DCM/MeOH = 100/1 as the eluent). mp 92.3−96.7 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (d, $J$ = 5.2 Hz, 1H), 7.35 (d, $J$ = 2.8 Hz, 1H), 7.22 (d, $J$ = 7.6 Hz, 2H), 7.19−7.09 (m, 3H), 7.06 (d, $J$ = 7.2 Hz, 2H), 6.94 (t, $J$ = 7.6 Hz, 2H), 6.75 (d, $J$ = 8.0 Hz, 1H), 4.91 (d, $J$ = 2.0 Hz, 1H), 4.72 (d, $J$ = 11.2 Hz, 1H), 2.33 (d, $J$ = 11.2 Hz, 1H), 2.01 (t, $J$ = 11.6 Hz, 1H), 1.90 (t, $J$ = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 147.3, 139.7, 139.1, 129.4, 128.5, 126.6, 126.2, 126.1, 126.0, 125.2, 123.4, 122.3, 121.2, 110.0, 74.5, 56.3, 46.9, 33.2. HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2OS_2$


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379.0933; found 379.0926. $[\alpha]_{20}^{D}$ +30° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 8.15 min, $t_R$ (major) = 22.74 min, >20:1 dr, 99% ee.

*(2S,3R,4R)-3-Benzyl-2-(pyridin-3-yl)-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol (**3n**).* White solid (64 mg, 86% yield, DCM/MeOH = 100/2 as the eluent). mp 185.2−186.5 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.59 (d, *J* = 1.6 Hz, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.26−7.21 (m, 2H), 7.20−7.13 (m, 2H), 7.12−7.05 (m, 3H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.12 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 2.69 (dd, *J* = 13.6, 11.2 Hz, 1H), 2.35−2.25 (m, 1H), 2.21 (dd, *J* = 13.6, 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.6, 150.0, 148.8, 139.6, 139.4, 139.2, 136.1, 129.3, 128.8, 126.5, 126.5, 123.9, 122.6, 122.5, 122.1, 109.1, 73.5, 58.2, 43.7, 33.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_3OS$ 374.1322; found 374.1319. $[\alpha]_{20}^{D}$ +102° (*c* 1.0, MeOH). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 13.37 min, $t_R$ (major) = 22.84 min, 17:1 dr, 97% ee.

*(2S,3R,4R)-3-Benzyl-2-(naphthalen-2-yl)-3,4-dihydro-2H-benzo-[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3o**).* White solid (82 mg, 98% yield, DCM/MeOH = 100/1 as the eluent). mp 119.8−122.0 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.95−7.83 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.19−7.02 (m, 4H), 7.00−6.90 (m, 2H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 6.4 Hz, 2H), 4.88 (s, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 1.96−1.80 (m, 2H), 1.47 (t, *J* = 15.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.2, 140.3, 139.9, 138.9, 133.3, 129.1, 128.3, 128.1, 128.0, 127.8, 126.7, 126.5, 126.2, 126.0, 126.0, 123.5, 122.2, 121.3, 109.8, 74.5, 60.0, 46.0, 32.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{27}H_{23}N_2OS$ 423.1526; found 423.1529. $[\alpha]_{20}^{D}$ +60° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 11.56 min, $t_R$ (major) = 36.48 min, 6:1 dr, 98% ee.

*(2S,3R,4R)-3-Methyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol (**3p**).* White solid (49 mg, 83% yield, DCM/MeOH = 100/1 as the eluent). mp 123.6−127.7 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.25−7.15 (m, 4H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 5.19 (s, 1H), 4.01 (d, *J* = 10.4 Hz, 1H), 1.64 (s, 1H), 0.38 (d, *J* = 4.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.7, 142.9, 140.0, 128.5, 128.1, 127.4, 126.0, 123.5, 122.1, 121.4, 109.6, 100.1, 60.3, 38.8, 13.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2OS$ 297.1056; found 297.1057. $[\alpha]_{20}^{D}$ +35° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.97 min, $t_R$ (major) = 14.84 min, 5:1 dr, 94% ee.

*(2S,3R,4R)-3-Ethyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo-[3,2-a]pyrimidin-4-ol (**3q**).* White solid (53 mg, 87% yield, DCM/MeOH = 100/1 as the eluent). mp 151.4−153.1 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.25−7.20 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 7.0 Hz, 1H), 5.31 (s, 1H), 3.99 (d, *J* = 11.5 Hz, 1H), 1.45−1.35 (m, 1H), 0.84−0.57 (m, 4H), 0.46 (dd, *J* = 11.0, 6.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 158.5, 143.1, 140.1, 128.7, 128.0, 127.3, 125.9, 123.6, 122.0, 121.3, 109.7, 74.8, 60.0, 45.0, 19.7, 10.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2OS$ 311.1213; found 311.1206. $[\alpha]_{20}^{D}$ +20° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 10.40 min, $t_R$ (major) = 19.27 min, 19:1 dr, 91% ee.

*(2S,3R,4R)-3-Butyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo-[3,2-a]pyrimidin-4-ol (**3r**).* White solid (60 mg, 90% yield, DCM/MeOH = 100/1 as the eluent). mp 88.9−91.1 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.26−7.20 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 5.28 (s, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 1.45 (t, *J* = 10.8 Hz, 1H), 1.31−1.20 (m, 1H), 1.06−0.94 (m, 2H), 0.85−0.74 (m, 1H), 0.71 (t, *J* = 7.2 Hz, 3H), 0.52−0.63 (m, 1H), 0.52−0.40 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.5, 143.1, 140.2, 128.7, 128.0, 127.4, 125.9, 123.7, 122.0, 121.3, 109.8, 75.2, 60.0, 43.4, 28.5, 26.5, 22.8, 14.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2OS$ 339.1526; found 339.1522. $[\alpha]_{20}^{D}$ +31° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.76 min, $t_R$ (major) = 15.12 min, 19:1 dr, 98% ee.

*(2S,3R,4R)-3-Octyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo-[3,2-a]pyrimidin-4-ol (**3s**).* White solid (70 mg, 89% yield, DCM/MeOH = 100/1 as the eluent). mp 112.8−113.9 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (t, *J* = 7.6 Hz, 2H), 7.34−7.25 (m, 3H), 7.19 (dd, *J* = 15.2, 7.6 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 2.4 Hz, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 1.45 (t, *J* = 10.8 Hz, 1H), 1.31−1.22 (m, 4H), 1.21−1.11 (m, 3H), 1.10−1.00 (m, 2H), 0.90−1.00 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.85−0.75 (m, 1H), 0.56 (t, *J* = 11.9 Hz, 1H), 0.48−0.35 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.6, 143.1, 140.2, 128.8, 128.0, 127.4, 125.9, 123.7, 122.0, 121.2, 109.8, 75.2, 59.9, 43.4, 31.9, 29.8, 29.5, 29.4, 26.7, 26.3, 22.8, 14.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2OS$ 395.2152; found 395.2147. $[\alpha]_{20}^{D}$ +37° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 5.42 min, $t_R$ (major) = 8.35 min, 12:1 dr, 97% ee.

*(2S,3R,4R)-2,3-Diphenyl-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3t**).* White solid (58 mg, 81% yield, DCM/MeOH = 100/1 as the eluent). mp 126.8−127.4 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.50 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.26−7.20 (m, 2H), 7.19−7.13 (m, 4H), 7.13−7.08 (m, 3H), 7.08−7.01 (m, 3H), 6.89 (d, *J* = 6.4 Hz, 1H), 5.58 (dd, *J* = 6.4, 2.8 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 3.37 (dd, *J* = 12.4, 2.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 154.5, 144.1, 139.8, 138.9, 130.7, 128.6, 128.1, 128.1, 126.9, 126.8, 126.4, 122.6, 122.4, 122.1, 109.4, 76.2, 59.1, 49.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2OS$ 359.1213; found 359.1197. $[\alpha]_{20}^{D}$ +59° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 17.16 min, $t_R$ (major) = 19.70 min, 4:1 dr, 94% ee.

*(2S,3R,4R)-2-Phenyl-3-(pyridin-3-ylmethyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3u**).* White solid (67 mg, 90% yield, DCM/MeOH = 100/2 as the eluent). mp 95.6−108.6 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.36 (d, *J* = 3.6 Hz, 1H), 8.20 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.18−7.06 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.86 (dd, *J* = 16.4, 8.0 Hz, 2H), 4.85 (s, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 2.15−2.04 (m, 1H), 1.95−1.84 (m, 1H), 1.83−1.72 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.8, 150.5, 147.6, 142.8, 139.6, 137.1 134.7 128.7, 128.6, 128.1 126.0, 123.5, 123.3, 122.4, 121.4, 109.6, 74.1, 60.0, 45.7, 30.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{20}N_3OS$ 374.1322; found 374.1320. $[\alpha]_{20}^{D}$ +50° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 9.97 min, $t_R$ (major) = 31.30 min, 6:1 dr, 94% ee.

*(2S,3R,4R)-2-Phenyl-3-(thiophen-2-ylmethyl)-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ol (**3v**).* White solid (70 mg, 92% yield, DCM/MeOH = 100/1 as the eluent). mp 96.6−100.3 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (t, *J* = 7.2 Hz, 2H), 7.48−7.35 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 5.2 Hz, 1H), 7.02−6.92 (m, 2H), 6.86 (dd, *J* = 4.8, 3.2 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 5.06 (s, 1H), 4.18 (d, *J* = 10.4 Hz, 1H), 2.21 (t, *J* = 11.2 Hz, 1H), 1.99−1.81 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 142.5 141.2, 139.8 128.8 128.5, 128.0, 127.0, 126.1, 126.0, 123.7, 122.3 121.3, 109.8, 100.1, 74.5 59.6, 46.3 27.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2OS_2$ 379.0933; found 379.0928. $[\alpha]_{20}^{D}$ +72° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 7.63 min, $t_R$ (major) = 19.16 min, 10:1 dr, 97% ee.

**Procedure for the Synthesis of Product 3a′.** To a 5 mL flame-dried tube was added 3-phenylpropionaldehyde **2a** (0.15 mmol, 1.5 equiv) in 1 mL of DCM into a mixture of 2-benzothiazolimine **1a** (0.10 mmol, 1.0 equiv), catalyst **4c** (0.01 mmol, 10 mol %), and


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PhCOOH (0.01 mmol, 10 mol %). Then the reaction mixture was stirred at room temperature. After completion of the reaction, 2 mL of saturated $NaHCO_3$ solution was added and extracted with DCM and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The reaction mixture was purified by flash column chromatography using DCM/MeOH as the eluent to get the products.

*(2S,3S,4R)-3-Benzyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidin-4-ol (**3a′**).* White solid (22 mg, 60% yield, DCM/MeOH = 100/1 as the eluent). mp 130.1−135.2 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.31 (m, 1H), 7.29−7.23 (m, 3H), 7.15−7.06 (m, 3H), 7.04 (t, J = 7.0 Hz, 2H), 6.86−6.81 (m, 1H), 6.69 (s, 2H), 6.51 (s, 2H), 5.13 (s, 1H), 4.67 (s, 1H), 2.24 (d, J = 13.5 Hz, 1H), 2.05 (d, J = 8.5 Hz, 1H), 2.01−1.85 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.1, 141.0, 140.2, 139.4, 129.0, 128.5, 128.4, 127.9, 126.7, 126.3, 126.1, 123.4, 122.4, 121.4, 109.8, 76.6, 56.9, 45.5, 30.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2OS$ 373.1369; found 373.1357. $[\alpha]_{20}^{D}$ +30° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 11.27 min, $t_R$ (major) = 12.97 min, 1:20 dr, 97% ee.

**Procedure for the Synthesis of Product 5.** To a 5 mL flame-dried tube were added **3a** (37 mg, 0.1 mmol) and $Et_3SiH$ (160 $\mu$L, 1.0 mmol) in DCE (1 mL), and then $BF_3{\cdot}Et_2O$ (253 $\mu$L, 2.0 mmol) was slowly added at room temperature. Then the reaction mixture was stirred at 80 °C in an oil bath for 6 h. After completion of the reaction, saturated $NaHCO_3$ solution was added until pH > 7 and extracted with DCM and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude products were purified by flash column chromatography (DCM/MeOH = 100/1) to give the product **5**.

*(2S,3S)-3-Benzyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo-[3,2-a]pyrimidine (**5**).* White solid (28 mg, 78% yield, DCM/MeOH = 100/1 as the eluent). mp 158.1−160.1 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.30 (m, 3H), 7.30−7.25 (m, 4H), 7.25−7.18 (m, 2H), 7.15 (td, *J* = 8.0, 1.2 Hz, 1H), 7.11−7.06 (m, 2H), 7.00 (td, *J* = 7.6, 0.8 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.54 (d, *J* = 5.6 Hz, 1H), 3.49−3.34 (m, 2H), 2.88 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.52 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.34−2.25 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.8, 143.8, 140.6, 139.2, 129.1, 128.8, 128.7, 127.2, 127.2, 126.6, 126.0, 122.8, 122.0, 122.0, 107.6, 64.0, 43.0, 38.9, 38.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2S$ 357.1420; found 357.1406. $[\alpha]_{20}^{D}$ +74° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 20.62 min, $t_R$ (major) = 34.48 min, 99% ee.

**Procedure for the Synthesis of Product 6.** To a 5 mL flame-dried tube was added **5** (35 mg, 0.1 mmol) in DCE (1 mL), and fluoroboric acid (18 mg, 0.2 mmol) was slowly added at room temperature for 2 h. After completion of the reaction. The crude products were purified by flash column chromatography (DCM/MeOH = 100/2) to give the product **6**.

*(2S,3S)-3-Benzyl-2-phenyl-1,2,3,4-tetrahydrobenzo[4,5]thiazolo-[3,2-a]pyrimidin-5-ium Tetrafluoroborate (**6**).* White solid (40 mg, 91% yield, DCM/MeOH = 100/2 as the eluent). mp 160.2−162.1 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, *J* = 7.2 Hz, 1H), 7.43−7.37 (m, 1H), 7.35−7.27 (m, 4H), 7.25−7.16 (m, 6H), 7.09 (d, *J* = 6.8 Hz, 2H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.77 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.75−2.65 (m, 1H), 2.65−2.48 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.0, 138.0, 137.5, 137.2, 129.3, 129.1, 129.0, 129.0, 128.2, 127.1, 126.8, 126.0, 123.0, 122.2, 112.2, 59.5, 45.0, 38.1, 35.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2S$ 357.1420; found 357.1424.

**Procedure for the Synthesis of Product 7.** To a 5 mL flame-dried tube were added **3a** (37 mg, 0.1 mmol) and allyl-trimethylsilane (158 $\mu$L, 1.0 mmol) in DCE (1 mL), and then $BF_3{\cdot}Et_2O$ (253 $\mu$L, 2.0 mmol) was slowly added at room temperature. Then the reaction mixture was stirred at 80 °C in an oil bath for 6 h. After completion of the reaction, saturated $NaHCO_3$ solution was added until pH > 7 and extracted with DCM and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude products were purified by flash column chromatography (DCM/MeOH = 100/1) to give the product **7**.

*(2S,3S,4R)-4-Allyl-3-benzyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]-thiazolo[3,2-a]pyrimidine (**7**).* White solid (35 mg, 88% yield, DCM/MeOH = 100/1 as the eluent). mp 132.8−134.9 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35 (d, *J* = 7.6 Hz, 1H), 7.33−7.28 (m, 4H), 7.26−7.20 (m, 3H), 7.20−7.13 (m, 4H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.30−5.18 (m, 1H), 4.84−4.81 (m, 2H), 4.26 (d, *J* = 17.2 Hz, 1H), 3.79 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.00−2.86 (m, 1H), 2.77−2.70 (m, 2H), 2.16−2.06 (m, 1H), 2.14−1.60 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3) $\delta$ 156.7, 144.2, 140.2, 139.6, 132.8, 129.4, 128.8, 128.4, 126.7, 126.7, 126.6, 126.0, 122.9, 122.1, 122.0, 118.9, 107.8, 60.8, 54.8, 41.3, 39.4, 35.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2S$ 397.1733; found 397.1723. $[\alpha]_{20}^{D}$ − 4° (*c* 1.0, $CH_2Cl_2$). HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 88/12, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 11.27 min, $t_R$ (major) = 20.93 min, 98% ee.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02499.

HPLC and NMR spectra and crystallographic data for **3h**, **6**, and **3a′** (PDF)

### Accession Codes

CCDC 2033715−2033716 and 2048709 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.



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