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Concise Synthesis of the Isothiourea Organocatalysts Homobenzotetramisole and Derivatives

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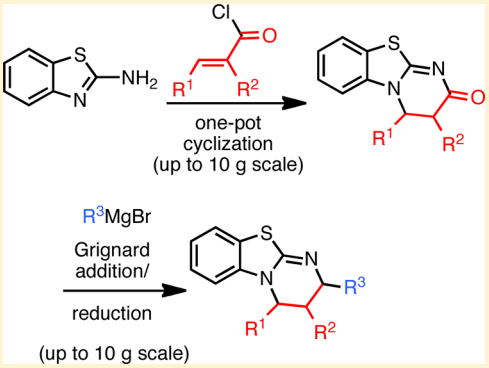
Supporting Information

ABSTRACT: A concise approach to the synthesis of homobenzotetramisole and derivatives is described. Our strategy features a one-pot acylation−cyclization of 2-aminobenzothiazole with α,β-unsaturated acid chlorides to afford annulated pyrimidones. Subsequent Grignard addition followed by acid-promoted dehydration and reduction provides good overall yields of the title compounds in three steps and in quantities up to 10 g. The synthesis employs low-cost and readily available starting materials and enables access to both optical antipodes of these increasingly useful nucleophilic catalysts following chiral separation.



Over the past decade, homobenzotetramisole (HBTM) and related amidine and isothiourea-based organocatalysts **1**−**6** have emerged as powerful tools for asymmetric organocatalysis (Figure 1).[1] These Lewis bases are capable of promoting a number of asymmetric transformations including kinetic resolution of alcohols,[2] dynamic kinetic resolution of azlactones,[3] kinetic resolution of β-lactams,[4] nucleophile-catalyzed aldol lactonization (NCAL) processes,[5] asymmetric intra- and intermolecular Michael addition lactonizations,[6] and asymmetric α-amination of carboxylic acids,[7] among others.[8] Furthermore, HBTM and derivatives have found utility for the determination of the absolute configuration of secondary alcohols, lactams, and oxazolidinones due to the large differential reaction rates observed during kinetic resolution with these catalysts.[9]

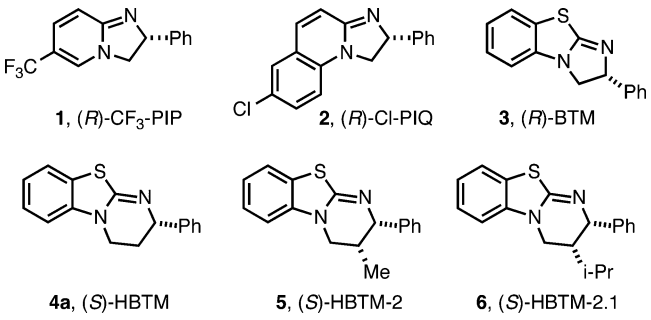
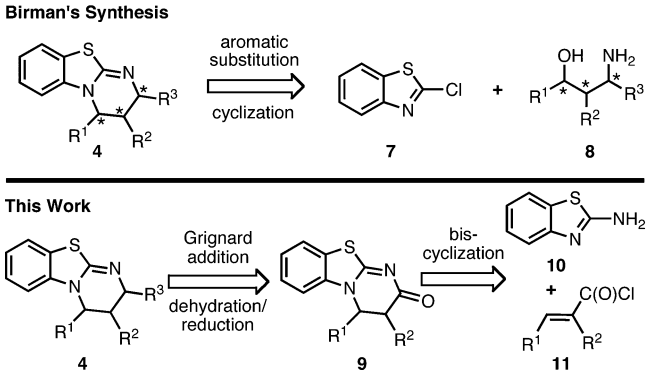


Figure 1. Amidine and isothiourea-based acyl transfer catalysts.

HBTM (**4a**) was first reported by Birman and co-workers in 2008.[2c] The synthetic approach involved an aromatic substitution of 2-chlorobenzothiazole **7** with the optically active β-amino alcohol **8** followed by cyclization to provide HBTM in serviceable yields (Scheme 1). A shortcoming of this synthesis is the cost of the enantiomeric β-amino alcohol **8**, and while a synthesis of these amino alcohols is available involving a resolution, the synthesis requires five steps and does not readily lend itself to access HBTM derivatives. Reported routes to substituted derivatives of HBTM also involve multistep syntheses of the requisite β-amino alcohols.[2f]

Scheme 1. Synthetic Strategies to HBTM and Derivatives



We envisioned that HBTM (**4a**) and derivatives (*e.g.*, **5**, **6**) could be accessed in a convergent manner through addition of organometallic reagents to 4-dihydropyrimidones **9** followed by dehydration and reduction of the resulting hemiaminals. The required 4-dihydropyrimidones **9** could be accessed by a one-pot bis-cyclization of 2-aminobenzothiazole (**10**) with a variety of α,β-unsaturated acid chlorides or related synthons (Scheme

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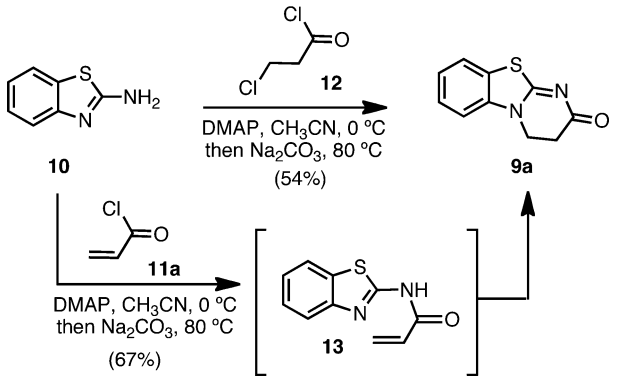
1). Herein we describe the implementation of this concise strategy to HBTM and derivatives that is easily scalable and utilizes inexpensive, commercially available materials.

We first sought reaction conditions to promote the bis-cyclization of 2-aminobenzothiazole with α,β-unsaturated acid chlorides or β-chloro acid chlorides with 2-aminobenzothiazole to provide the desired 4-dihydropyrimidone **9a** in a single reaction vessel. In our initial studies, we treated 2-amino-benzothiazole with 3-chloropropanoyl chloride (**12**) in acetonitrile with catalytic dimethylaminopyridine (DMAP) at 0 °C which initially provided the corresponding *N*-acylated product. Subsequent heating to reflux following addition of solid Na_2CO_3 afforded the desired 4-dihydropyrimidone **9a** in 54% yield (Scheme 2). We then sought to explore the potential

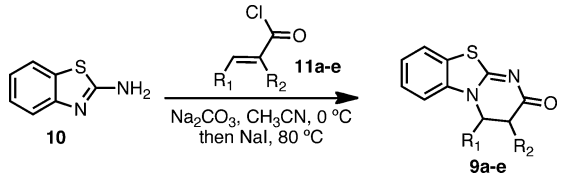
Scheme 2. Initial Routes to the Pyrimidone 9a via a Single-Pot, Bis-Cyclization



use of α,β-unsaturated acid chlorides, given their greater availability, lower cost, and the possibility that *in situ* β-elimination was occurring to give the same intermediate **13** from chloride **12**. In the case of acryloyl chloride, identical reaction conditions also provided the desired pyrimidone **9a** in an improved 67% yield (Scheme 2). However, when we attempted to apply these reaction conditions to other unsaturated acid chlorides, low yields were obtained. This prompted us to optimize this cyclization process for other unsaturated acid chlorides.

After some experimentation, we found that use of NaI, as an additive (1.0 equiv), dramatically improved the overall yields of the bis-cyclization. Initial *N*-acylation of 2-aminobenzothiazole with acryloyl chloride could be achieved with Na_2CO_3 in acetonitrile at 0 °C and provided the corresponding acylated product in nearly quantitative yields. Heating the initial acylated adduct **13** to reflux in the presence of NaI afforded the desired dihydropyrimidone **9a** in 86% yield (Table 1, entry 1). Based on our hypothesis that the iodide ion was promoting the cyclization step through a transient alkyl iodide, formed by conjugate addition of iodide to the unsaturated amide, and subsequent intramolecular S_N2 reaction, we briefly explored other additives. These included DMAP and imidazole; however, NaI provided the best yields.[10] Substituted α,β-unsaturated acid chlorides were also good substrates for this reaction. Methacryloyl chloride and crotonyl chloride provided the substituted dihydropyrimidones **9b** and **9c** in serviceable yields (entries 2 and 3, respectively). Cinnamoyl chloride, however, afforded only low yields of the desired cyclized product **9d** (entry 4). The bis-substituted acid chloride **11e** also provided a low yield of the cycloadduct **9e** (entry 5). In these

Table 1. Scope of the One-Pot Cyclization



entry	acid chloride	dihydropyrimidone	yield[a]
1	**11a**	**9a**	86%
2	**11b**	(±)-**9b**	70%
3	**11c**	(±)-**9c**	62%
4	**11d**	(±)-**9d**	10%
5	**11e**	(±)-**9e**	19% 5:1 dr[b]

[a]Values refer to isolated yields. [b]Ratios were determined by analysis of the crude reaction mixture by ^{1}H NMR (500 MHz).

latter examples, a major byproduct isolated was the *N*-acylated intermediate (*cf.* **13**) that had not undergone cyclization.

With dihydropyrimidones **9** in hand, we next explored the planned Grignard addition−dehydration−reduction sequence. Following optimization, monoaddition of phenyl Grignard to dihydropyrimidone **9a** was achieved at −15 °C in THF to deliver hemiaminal **14**. Dehydration *in situ* gave the corresponding enamines **15** by careful quenching with TFA. This acid-promoted dehydration also facilitated isolation of the products by simple extraction of the corresponding enamines, enabling direct reduction without the need for further purification. Reduction to the isothiourea was readily achieved by treatment of the enamine intermediates with Et_3SiH in TFA at −15 °C. In this manner, HBTM (**4a**) was obtained in 71% on 1 g scale and was reliably scaled up to 10 g scale in comparable yield (68%, Table 2, entry 1).

We explored the scope of this sequence with other Grignard reagents. Both electron-deficient and -rich *p*-substituted phenyl Grignard reagents provided the corresponding HBTM derivatives **4b−c** in good yields (entries 2−3). 3-Methyl-thiophen-2-yl magnesium bromide also afforded the expected thiophene HBTM derivative **4d** in modest yield (entry 4).

The use of 2-naphthyl and 9-phenanthryl Grignard reagents gave access to HBTM derivatives **4e−f** bearing bulkier substituents in moderate yields (entries 5−6). This transformation was then extended to substituted dihydropyrimidones **9b** and **9c** with phenyl magnesium bromide to provide bis-substituted HBTM congeners **5** and **4g** in modest yields but good diastereoselectivities (entries 7−8).[11]

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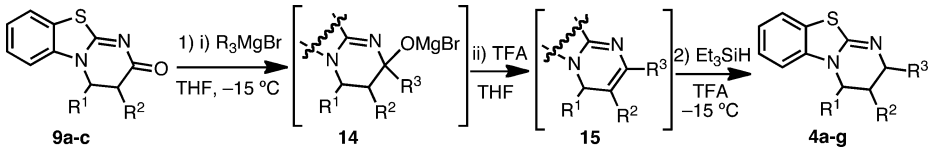
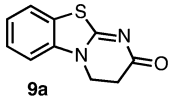
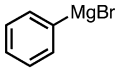
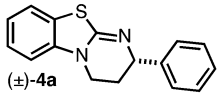
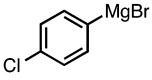
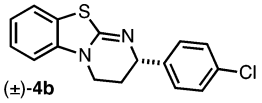
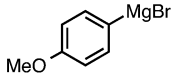
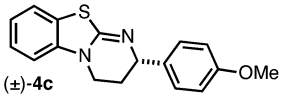
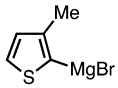
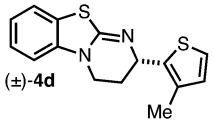
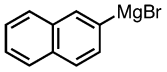
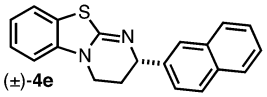
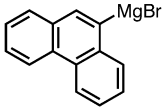
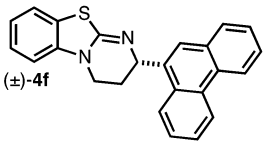
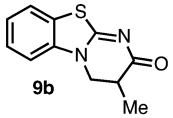
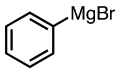
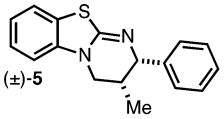
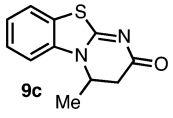
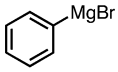
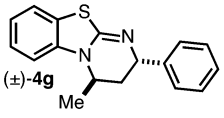
Table 2. Scope of the Grignard Addition/Reduction Sequence



entry	substrate	Grignard reagent	product	yield[a]
1	 9a		 (±)-4a	71%[b] 68%[c]
2	"		 (±)-4b	60%
3	"		 (±)-4c	51%
4	"		 (±)-4d	32%
5	"		 (±)-4e	50%
6	"		 (±)-4f	40%
7	 9b		 (±)-5	41% ≥19:1 dr[d]
8	 9c		 (±)-4g	44% 10:1 dr[d]

[a]Values refer to isolated yields. [b]Reaction performed on a 1 g scale. [c]Reaction performed on a 10 g scale. [d]The reduction was performed at −40 °C. Diastereomeric ratios (dr) were determined by analysis of crude reaction mixtures by ^{1}H NMR (500 MHz).

The described synthetic approach provides practical access to racemic HBTM and derivatives in a highly concise manner. Importantly, enantiomer separation would enable facile access to both optical antipodes of HBTM. This was accomplished on preparative scale (a 5 g batch) using supercritical fluid chromatography (SFC), providing both (*R*)-HBTM (2.4 g, >99% ee) and (*S*)-HBTM (2.3 g, >99% ee) in high optical purity and mass recovery.[12]

In summary, we developed a concise and convenient approach for the synthesis of racemic HBTM and derivatives. Our strategy features a single-pot acylation−cyclization of 2-aminobenzothiazole with α,β-unsaturated acid chlorides to afford the corresponding dihydropyrimidones. Subsequent Grignard addition followed by dehydration and reduction of the corresponding enamines provides the desired isothioureas in three steps from commercially available reagents. The described approach is scalable as demonstrated for the synthesis of up to 10 g of racemic HBTM and uses low-cost and readily available starting materials. The strategy will enable access to both optical antipodes of HBTM and derivatives on scale and should facilitate access to these increasingly useful chiral, nucleophilic organocatalysts.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under a nitrogen atmosphere in oven-dried or flame-dried glassware using dry solvents under anhydrous conditions. All anhydrous solvents were dried with activated molecular sieves (3 Å or 4 Å beads) and tested for trace water content with a coulometric Karl Fischer titrator. All solvents used for extraction and chromatography procedures were used as received from commercial suppliers without further purification. All reagents were purchased and used as received unless otherwise noted. ^{1}H and ^{13}C NMR spectra were measured in deuterated chloroform ($CDCl_3$) at 500 MHz/125 MHz, respectively. All proton NMR spectra were recorded at 500 MHz and were referenced with residual chloroform (7.27 ppm) and reported in parts per million (ppm). Coupling constants (J) are reported in hertz (Hz).

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Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; m, multiplet; bs, broad singlet. All carbon NMR spectra were measured at 125 MHz and were referenced with residual chloroform (77.23 ppm) and reported in parts per million (ppm). All FT-IR spectra were recorded on sodium chloride discs. High-resolution mass spectra (ESI or MALDI) were obtained using a quadruple time-of-flight mass spectrometer (QTOF). Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel $60F_{254}$; 0.25 mm thickness). Flash chromatography was carried out with silica gel 60 Å (230−400 mesh ASTM) and basic alumina 60 Å (50−200 μm).

Representative Procedure for the One-Pot Cyclization. The 2-aminobenzothiazole (1.0 equiv, 0.5−10 g) and Na_2CO_3 (2.2 equiv) were suspended in dry acetonitrile, and then the suspension was cooled to 0 °C. The corresponding acid chloride (1.2 equiv) was then added dropwise, and the resulting reaction mixture was stirred at 0 °C for 2 h. NaI (1.0 equiv) was then added, and the reaction mixture was heated to 80 °C with stirring until TLC analysis indicated completion of the reaction (8−48 h). The reaction was concentrated under reduced pressure, diluted with water, and extracted with dichloromethane (3×). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the crude was purified by MPLC on silica gel using a gradient of dichloromethane and acetone as eluent.

3,4-Dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-2-one (9a). Dihydropyrimidone **9a** was prepared according to the representative procedure from 2-aminobenzothiazole (1.0 g, 6.66 mmol), Na_2CO_3 (1.55 g, 14.65 mmol) in acetonitrile (40 mL) and acryloyl chloride (0.646 mL, 7.99 mmol), and NaI (0.998 g, 6.66 mmol) after a reaction time of 8 h. Purification was performed by MPLC on silica gel using a gradient of dichloromethane and acetone (9:1 → 1:1) as eluent to afford the desired product (1.165 g, 86%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.0, 1.0 Hz 1H), 7.44 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.27 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.23 (t, J = 7.5, 2H), 2.86 (t, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.66, 173.20, 138.43, 127.40, 124.33, 123.43, 122.81, 110.81, 41.12, 28.44. FT-IR (neat, cm^{-1}): 1655, 1509, 1471, 1369. HRMS (ESI+): Calcd for $C_{10}H_9N_2OS$ ($[M+H]^+$), 205.0436. Found: 205.0441.

This reaction was also carried out on 10 g scale (2-amino-benzothiazole), and the product was recrystallized from ethanol (two crops from 550 and 250 mL sequentially) to give the desired product (11.4 g, 84%) without further purification.

(±)-3-Methyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidin-2-one (9b). Dihydropyrimidone **9b** was prepared according to the representative procedure from 2-amino-benzothiazole (1.0 g, 6.66 mmol), Na_2CO_3 (1.55 g, 14.65 mmol) in acetonitrile (40 mL) and methacryloyl chloride (0.773 mL, 7.99 mmol), and NaI (0.998 g, 6.66 mmol) after a reaction time of 24 h. Purification was performed by MPLC on silica gel using a gradient of dichloromethane and acetone (9:1 → 1:1) as eluent to afford the desired product (1.010 g, 70%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 1.0 Hz 1H), 7.45 (ddd, J = 8.5, 8.0, 1.0 Hz, 1H), 7.28 (ddd, J = 8.5, 8.0, 1.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.32 (dd, J = 12.0, 7.0 Hz, 1H), 3.76 (t, J = 12.0 Hz, 1H), 2.92−2.84 (m, 1H), 1.38 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.03, 172.46, 138.54, 127.40, 124.32, 123.68, 122.94, 110.72, 47.33, 32.62, 14.03. FT-IR (neat, cm^{-1}): 2930, 1673, 1504, 1470, 1368. HRMS (ESI+): Calcd for $C_{11}H_{11}N_2OS$ ($[M+H]^+$), 219.0592. Found: 219.0588.

(±)-4-Methyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidin-2-one (9c). Dihydropyrimidone **9c** was prepared according to the representative procedure from 2-aminobenzothiazole (1.0 g, 6.66 mmol), Na_2CO_3 (1.55 g, 14.65 mmol) in acetonitrile (40 mL) and crotonoyl chloride (0.765 mL, 7.99 mmol), and NaI (0.998 g, 6.66 mmol) after a reaction time of 36 h. Purification was performed by MPLC on silica gel using a gradient of dichloromethane and acetone (9:1 → 1:1) as eluent to afford the desired product (0.896 g, 62%) as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 0.5 Hz 1H), 7.45 (ddd, J = 8.0, 7.0, 0.5 Hz, 1H), 7.27 (ddd, J = 8.0, 7.0, 0.5 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 4.72 (p, J = 7.0 Hz, 1H), 3.01 (dd, J = 16.0, 7.0 Hz, 1H), 2.66 (d, J = 16.0 Hz, 1H), 1.43 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.46, 171.97, 137.64, 127.45, 124.28, 123.94, 123.04, 110.74, 48.83, 35.58, 17.97. FT-IR (neat, cm^{-1}): 2976, 1671, 1505, 1468, 1360. HRMS (ESI+): Calcd for $C_{11}H_{11}N_2OS$ ($[M+H]^+$), 219.0592. Found: 219.0584.

(±)-4-Phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidin-2-one (9d). Dihydropyrimidone **9d** was prepared according to the representative procedure from 2-aminobenzothiazole (1.0 g, 6.66 mmol), Na_2CO_3 (1.55 g, 14.65 mmol) in acetonitrile (40 mL) and cinnamoyl chloride (1.33 mL, 7.99 mmol), and NaI (0.998 g, 6.66 mmol) after a reaction time of 48 h. Purification was performed by MPLC on silica gel using a gradient of dichloromethane and acetone (9:1 → 1:1) as eluent to afford the desired product (0.190 g, 10%) as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 1.0 Hz 1H), 7.33−7.28 (m, 5H), 7.23 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 3.29 (dd, J = 16.0, 8.0 Hz, 1H), 2.91 (dd, J = 16.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.21, 172.49, 138.05, 137.20, 129.72, 129.10, 127.43, 125.55, 124.47, 123.52, 122.87, 111.56, 56.37, 36.98. FT-IR (neat, cm^{-1}): 3043, 1668, 1537, 1467, 1362. HRMS (ESI+): Calcd for $C_{16}H_{13}N_2OS$ ($[M+H]^+$), 281.0749. Found: 281.0738.

(±)-4-Methyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidin-2-one (9e). Dihydropyrimidone **9e** was prepared according to the representative procedure from 2-aminobenzothiazole (0.5 g, 3.33 mmol), Na_2CO_3 (0.776 g, 7.32 mmol) in acetonitrile (20 mL) and tigloyl chloride (0.439 mL, 3.99 mmol), and NaI (0.499 g, 3.33 mmol) after a reaction time of 36 h. Purification was performed by MPLC on silica gel using a gradient of dichloromethane and acetone (9:1 → 1:1) as eluent to afford the desired product (0.149 g, 19%, 5:1 dr) as a light orange solid. Data for the major diastereomer (*anti*) **9e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz 1H), 7.43 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.25 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 4.72 (p, J = 7.0 Hz, 1H), 3.03 (p, J = 7.0 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.66, 171.28, 137.61, 127.34, 124.10, 124.06, 122.99, 110.61, 53.43, 37.43, 12.47, 11.28. FT-IR (neat, cm^{-1}): 2929, 1681, 1504, 1468, 1360. HRMS (ESI+): Calcd for $C_{12}H_{13}N_2OS$ ($[M+H]^+$), 233.0749. Found: 233.0756.

Data for the minor diastereomer (*cis*) **9e′**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.0, 1.0 Hz 1H), 7.46 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.29 (ddd, J = 8.5, 8.0, 1.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 4.30 (q, J = 7.0 Hz, 1H), 2.71 (q, J = 7.0 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.98, 170.73, 138.21, 127.45, 124.32, 124.26, 123.13, 110.59, 55.51, 40.81, 18.14, 17.44. FT-IR (neat, cm^{-1}): 2930, 1681, 1504, 1468, 1360. HRMS (ESI+): Calcd for $C_{12}H_{13}N_2OS$ ($[M+H]^+$), 233.0749. Found: 233.0754.

Representative Procedure for the Grignard Addition−Dehydration−Reduction Sequence As Described for (±)-HBTM. The corresponding pyrimidin-2-one (1.0 equiv, 0.5−10 g) was suspended in dry THF and then cooled −15 °C. The corresponding Grignard reagent (1.2 equiv) was then added dropwise, and the reaction mixture was stirred at −15 °C for 5 h. Trifluoroacetic acid (3.0 equiv) was then carefully added, and the reaction was stirred at −15 °C for 30 min. The mixture was concentrated under reduced pressure, diluted with water, and extracted with EtOAc (4×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Et_3SiH was added (15 equiv) to the crude mixture, and the mixture was cooled to −15 °C. Trifluoroacetic acid was added, and the reaction was stirred vigorously at −15 °C for 6 h. The reaction was then concentrated under reduced pressure, washed with hexanes (3×), diluted with EtOAc, and washed with NaOH 1.5 M (3×, pH of the aqueous phases was 10−11). The combined aqueous fractions were extracted with EtOAc (4×), and the combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by aluminum oxide flash chromatography using hexanes and ethyl acetate as eluent.

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(±)-2-Phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]-pyrimidine, HBTM (4a). HBTM (**4a**) was prepared according to the representative procedure from pyrimidin-2-one **9a** (1.0 g, 4.90 mmol) in THF (50 mL) and PhMgBr (5.88 mL, 1.0 M in THF, 5.88 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (1.11 mL, 14.70 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (12 mL, 73.50 mmol) and trifluoroacetic acid (50 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (95:5 → 60:40) as eluent to provide (±)-HBTM (**4a**) as an off-white solid (0.931 g, 71%). All spectroscopic and physical data for this compound were identical to data reported by Birman.[2c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.32 (m, 5H), 7.28−7.25 (m, 1H), 7.21 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 4.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.86−3.81 (m, 1H), 3.72−3.68 (m, 1H), 2.35−2.29 (m, 1H), 2.04−1.97 (m, 1H). HRMS (ESI +): Calcd for $C_{16}H_{15}N_2S$ ($[M+H]^+$), 267.0956. Found: 267.0952.

This reaction was also performed on 10 g scale (10 g of pyrimidin-2-one, **9a**), and the product was purified by filtration on an aluminum oxide plug using hexanes and ethyl acetate (95:5 → 60:40) as eluent to provide (±)-HBTM (**4a**) as an off-white solid (8.75 g, 68%). Separation of 5 g of HBTM was accomplished by Lotus Separations, Ltd. by supercritical fluid chromatography to provide 2.4 g of the *R* enantiomer (>99% ee) and 2.3 g of the *S* enantiomer (>99% ee).

(±)-2-(4-Chlorophenyl)-3,4-dihydro-2*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidine (4b). Compound **4b** was prepared according to the representative procedure from pyrimidin-2-one **9a** (0.5100 g, 2.50 mmol) in THF (50 mL) and 4-Cl-PhMgBr (3.7 mL, 1.0 M in THF, 3.70 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.6 mL, 7.50 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (6 mL, 37.4 mmol) and trifluoroacetic acid (50 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (8:2 → 1:1) as eluent to provide compound **4b** as a light yellow solid (0.457 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 7.22 (ddd, *J* = 7.5, 7.5, 1.0 1H), 7.03 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.69 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.86−3.80 (m, 1H), 3.73−3.69 (m, 1H), 2.33−2.27 (m, 1H), 1.97−1.89 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.31, 142.93, 140.56, 132.46, 128.52, 128.07, 125.96, 122.36, 121.86, 107.58, 57.83, 40.61, 27.92. FT-IR (neat, cm^{-1}): 2959, 2922, 2881, 1632, 1582. HRMS (ESI +): Calcd for $C_{16}H_{14}ClN_2S$ ($[M+H]^+$), 301.0566. Found: 301.0561.

(±)-2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine (4c). Compound **4c** was prepared according to the representative procedure from pyrimidin-2-one **9a** (55 mg, 0.27 mmol) in THF (5 mL) and 4-MeO-PhMgBr (808 μL, 0.5 M in THF, 0.404 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.6 mL, 7.50 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (652 μL, 4.0 mmol) and trifluoroacetic acid (5 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (7:3 → 1:1) as eluent to provide compound **4c** as a light yellow solid (40 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.5, 1.0, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.21 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 7.5 Hz, 1H), 4.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.84−3.79 (m, 1H), 3.80 (s, 3H), 3.71−3.66 (m, 1H), 2.31−2.25 (m, 1H), 2.00−1.93 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.63, 158.03, 140.84, 136.56, 127.75, 125.96, 122.65, 121.94, 121.81, 113.93, 107.53, 57.98, 55.44, 40.60, 28.03. FT-IR (neat, cm^{-1}): 2956, 2925, 1626, 1581. HRMS (ESI+): Calcd for $C_{17}H_{17}N_2OS$ ($[M+H]^+$), 297.1062. Found: 297.1065.

(±)-2-(3-Methylthiophen-2-yl)-3,4-dihydro-2*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine (4d). Compound **4d** was prepared according to the representative procedure from pyrimidin-2-one **9a** (200 mg, 0.98 mmol) in THF (10 mL) and 3-methyl-2-thienylmagnesium bromide (2.9 mL, 0.5 M in THF, 1.47 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.6 mL, 7.50 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (2.4 mL, 14.69 mmol) and trifluoroacetic acid (10 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes/ethyl acetate (8:2) as eluent to provide compound **4d** as a light brown viscous oil (90 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.5, 1H), 7.21 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 7.03 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.82 (d, *J* = 5.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.87−3.78 (m, 2H), 2.34−2.29 (m, 1H), 2.26 (s, 3H), 2.06−1.99 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.99, 141.61, 140.50, 131.91, 130.37, 126.12, 122.70, 122.59, 122.22, 122.05, 107.91, 53.12, 40.68, 26.89, 14.00. FT-IR (neat, cm^{-1}): 1619. HRMS (ESI+): Calcd for $C_{15}H_{15}N_2S_2$ ($[M+H]^+$), 287.0677. Found: 287.0668.

(±)-2-(Naphthalen-2-yl)-3,4-dihydro-2*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidine (4e). Compound **4e** was prepared according to the representative procedure from pyrimidin-2-one **9a** (0.5 g, 2.40 mmol) in THF (50 mL) and 2-naphthylmagnesium bromide (14.7 mL, 0.25 M in Me-THF, 3.7 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.6 mL, 7.50 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (5.9 mL, 36.70 mmol) and trifluoroacetic acid (50 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (95:5 → 60:40) as eluent to provide compound **4e** as a light yellow solid (0.400 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.83 (m, 4H), 7.49−7.44 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.04 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.90 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.87−3.82 (m, 1H), 3.72−3.67 (m, 1H), 2.41−2.35 (m, 1H), 2.10−204 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.42, 141.71, 140.78, 133.58, 132.73, 128.31, 128.10, 127.72, 126.08, 126.01, 125.65, 125.28, 125.16, 122.64, 121.98, 121.90, 107.63, 58.56, 40.62, 27.91. FT-IR (neat, cm^{-1}): 3055, 2956, 2925, 2872, 1619, 1588. HRMS (ESI +): Calcd for $C_{20}H_{17}N_2S$ ($[M+H]^+$), 317.1112. Found: 317.1106.

(±)-2-(Phenanthren-9-yl)-3,4-dihydro-2*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine (4f). Compound **4f** was prepared according to the representative procedure from pyrimidin-2-one **9a** (400 mg, 2.00 mmol) in THF (50 mL) and 9-phenanthrenylmagnesium bromide (5.9 mL, 0.5 M in THF, 2.9 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.6 mL, 7.50 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (4.7 mL, 29.4 mmol) and trifluoroacetic acid (50 mL) at −15 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes/ethyl acetate (8:2) as eluent to provide compound **4f** as a light orange solid (118 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 7.5, 2.0 Hz, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.11 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.90 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.83 (s, 1H), 7.69 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.63 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 1.0 1H), 7.21 (ddd, *J* = 8.0, 8.0, 1.0 1H), 7.05 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.52 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.84−3.79 (m, 1H), 3.61−3.57 (m, 1H), 2.53−2.47 (m, 1H), 2.12−2.05 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.73, 140.81, 137.31, 131.79, 131.14, 129.98, 129.88, 129.08, 126.81, 126.79, 126.54, 126.27, 126.05, 125.50, 123.70, 123.56, 122.74, 122.48, 122.02, 121.92, 107.66, 55.21, 40.51, 26.66. FT-IR (neat, cm^{-1}): 3064, 2932, 2874, 1614, 1587. HRMS (ESI+): Calcd for $C_{24}H_{20}N_2S$ ($[M+H]^+$), 367.1269. Found: 367.1253.

(±)-3-Methyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidine (5). Compound **5** was prepared according to the representative procedure from pyrimidin-2-one **9b** (200 mg, 0.916 mmol) in THF (10 mL) and PhMgBr (1.10 mL, 1.0 M in THF, 1.10 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.5 mL, 7.35 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (2.4 mL, 14.69 mmol) and trifluoroacetic acid (10 mL) at −40 °C and slowly warmed up to 0 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (95:5 → 60:40) as eluent to provide compound **5** as a light orange solid (0.106 g, 41%), as a single diastereomer. All spectroscopic and physical data for this compound matched those reported by Birman.[2f] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.19 (m, 7H), 6.94 (dd, *J* = 7.5, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.0

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Hz, 1H), 4.65 (d, J = 4.0 Hz, 1H), 3.76 (dd, J = 11.5, 4.5 Hz, 1H), 3.28 (dd, J = 11.5, 7.5 Hz, 1H), 2.37−2.30 (m, 1H), 0.73 (d, J = 7.0 Hz, 3H). HRMS (ESI+): Calcd for $C_{17}H_{17}N_2S$ ($[M+H]^+$), 281.1112. Found: 281.1106.

(±)-3-Methyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo-[3,2-*a*]pyrimidine (4g). Compound **4g** was prepared according to the representative procedure from pyrimidin-2-one **9c** (200 mg, 0.916 mmol) in THF (10 mL) and PhMgBr (1.10 mL, 1.0 M in THF, 1.10 mmol) at −15 °C for 5 h and then quenched with trifluoroacetic acid (0.5 mL, 7.35 mmol) at −15 °C for 30 min. The reduction step was carried out with Et_3SiH (2.4 mL, 14.69 mmol) and trifluoroacetic acid (10 mL) at −40 °C and slowly warmed up to 0 °C for 6 h. The crude residue was purified by flash chromatography on aluminum oxide using hexanes and ethyl acetate (95:5 → 60:40) as eluent to provide compound **4g** as a light orange solid (0.112 g, 44%, 10:1 dr). All spectroscopic and physical data for this compound matched those reported by Birman.[2f] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.17 (m, 7H), 7.01 (dd, J = 13.0, J = 5.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.70 (dd, J = 8.0, 4.0 Hz, 1H), 4.33−4.28 (m, 1H), 2.06 (ddd, J = 13.0, 4.0, 1.5 Hz, 1H), 1.94 (ddd, J = 13.0, 12.0, 5.0 Hz, 1H), 1.56 (d, J = 6.5 Hz, 3H). HRMS (ESI+): Calcd for $C_{17}H_{17}N_2S$ ($[M+H]^+$), 281.1112. Found: 281.1118.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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