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Asymmetric N-Heterocyclic Carbene Catalyzed Annulation of 2-Alkenylbenzothiazoles with α-Chloro Aldehydes

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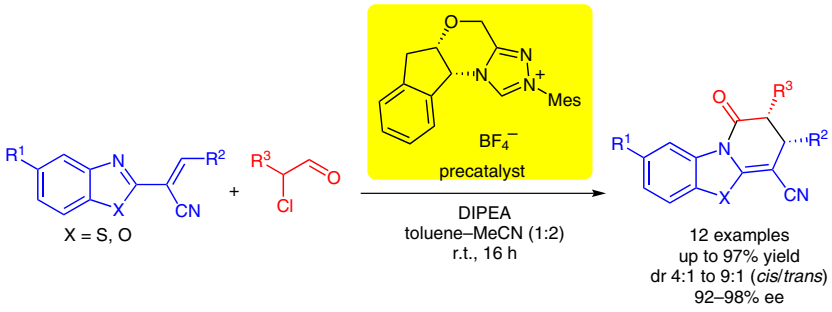
Dedicated to Professor Martin Jansen on the occasion of his 70th birthday



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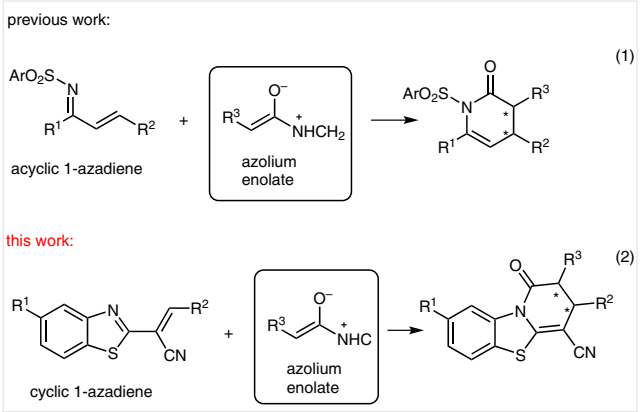
Abstract Diastereo- and enantioselective N-heterocyclic carbene catalyzed 1-azadiene Diels–Alder reactions of (*E*)-2-styrylbenzothiazoles with α-chloro aldehydes are reported. This annulation strategy provides an efficient access to medicinally important dihydrobenzothiazolopyridin-1-ones in good to excellent yields (44–97%) with very good to excellent stereoselectivities (up to 9:1 dr, 98% ee) and tolerates quite a range of substituents.

Key words N-heterocyclic carbenes, organocatalysis, asymmetric synthesis, aza-Diels–Alder reaction, annulation

The aza-Diels–Alder (aza-DA) reaction is one of the most powerful and elegant synthetic approaches to form C–C and C–N bonds, resulting in nitrogen-containing six-membered heterocycles.[1] Since Ghosez's pioneering work introducing the reaction of l-azadienes with electron-deficient dienophiles,[2] followed by Danishefsky's report on the formation of piperidine rings from imines and electron-rich dienes,[3] a great variety of aza-DA reactions under thermal conditions or catalyzed by Lewis acids[4] have been reported. With the renaissance of organocatalysis, enantioselective aza-DA reactions catalyzed by amines,[5] thioureas,[6] or chiral phosphoric acids,[7] were intensively investigated.

Over the past few decades, N-heterocyclic carbenes (NHCs), as an outstanding class of organocatalysts, have provided efficient access to various structural scaffolds through the Umpolung of aldehydes.[8] In 2004, the groups of Glorius and Bode reported the generation of homoenolates via NHC catalysis.[9] This provided an elegant way to activate the β-position of enals (conjugated Umpolung). Later, as an extended activation mode, azolium enolates were developed and acted as reactive nucleophiles in various NHC-catalyzed reactions.[10] Notably, the in situ generated azolium enolates paved the way to numerous important heterocyclic manifolds via [2+2][11] and [2+3] cycloadditions,[12] as well as [2+4] inverse-electron-demand Diels–Alder reactions.[13] In 2006, Bode and co-workers were the first to report a highly enantioselective aza-DA reaction of 1-azadienes with the enolate species generated in situ from enals.[14] Afterwards, Ye and co-workers employed ketenes[15] and α-chloro aldehydes[16] as substrates, which reacted with 1-azadienes in the presence of NHC catalysts. Then, Rovis and co-workers accessed the azolium enolate equivalents via oxidation of the Breslow intermediates, and constructed the corresponding lactams with azadienes.[17] Recently, Chi and co-workers have reported an NHC-catalyzed reaction of α-aryl esters with azadienes.[18] However, these reported studies all utilized acyclic 1-azadienes as reaction partners (Scheme 1, eq 1). To the best of our knowledge, little attention has been given to aza-DA reactions of cyclic 1-azadienes with in situ generated azolium enolate species.



Scheme 1 NHC-catalyzed aza-Diels–Alder reactions

Herein, we describe an enantioselective NHC-catalyzed cycloaddition of (*E*)-2-styrylbenzothiazoles with α-chloro aldehydes (Scheme 1, eq 2). The resulting dihydro-1*H*-benzothiazolopyridine core is an important structural motif existing in various biologically active products and numerous pharmaceuticals, such as antitumor[19] and antibacterial drugs.[20]

Initially, we investigated the reaction of (*E*)-2-(benzothiazol-2-yl)-3-phenylacrylonitrile (**1a**) with 2-chloro-3-phenylpropanal (**2a**) at room temperature in toluene in the presence of triethylamine and triazolium precatalyst **A**. The reaction was finished within 16 hours and gave the aza-DA adduct **3a** in a good *cis*/*trans* diastereoselectivity (dr = 6:1) and an excellent ee value (95%) of the major *cis*-diastereomer, albeit in a low yield (29%) (Table 1, entry 1). Other triazolium precatalysts **B**–**D** were also tested, but only traces (Table 1, entries 2 and 3) or even no product at all (Table 1, entry 4) was obtained under the same conditions. In an attempt to increase the yield of the desired **3a**, we elevated the reaction temperature to 40 °C, leading to no improvement (Table 1, entry 5). Next, base screening showed that organic bases (such as TMEDA, DIPEA, or DABCO) gave better or similar yields as well as excellent stereoselectivities (Table 1, entries 6–8); however, inorganic bases (such as NaOAc or K_2CO_3) furnished only traces or no product at all (Table 1, entries 9 and 10). We then focused on optimizing a series of reaction solvents in the presence of precatalyst **A** and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine at room temperature (Table 1, entries 11–14). Interestingly, an excellent yield (96%) and enantioselectivity (96% ee) was obtained in acetonitrile (Table 1, entry 14); however, the dr was inversed (*cis*/*trans*, 1:2.5) relative to the other solvents tested. In order to improve the dr, we retested the organic bases in acetonitrile and obtained a better dr (3.5:1) when *N*,*N*-diisopropylethylamine was used as base (Table 1, entry 16). Finally, we sought to adjust the solvent ratio of toluene and acetonitrile. Fortunately, the product was obtained with excellent yield and ee, as well as good dr (7:1), in a mixed solvent of toluene–acetonitrile (1:2) (Table 1, entry 20).

Under the optimized conditions, the scope of the reaction was evaluated on a 0.5-mmol scale (Table 2). Initially, a variety of (*E*)-2-styrylbenzothiazoles **1** with different electronic properties were examined. Obviously, the electron-donating effect influenced the reaction reactivity and decreased yields of the desired products were obtained, while good dr and excellent ee values were observed (R^2 = 4-Tol, 4-$MeOC_6H_4$; Table 2, **3b** and **3c**). In the case of electron-withdrawing groups (such as 3-OMe, 4-Cl, 3-Cl, or 4-F), the reactions were finished within 16 hours and gave the desired lactam adducts in good to excellent yields, good diastereoselectivities and excellent enantioselectivities (Table 2, **3d**–**g**). If R^2 is a 2-furyl group, a relatively low yield was obtained in 40 hours (Table 2, **3h**). This may be due to the electron-donating effect of the furan ring. The variation of R^1 on the benzothiazole motif **1** to a chloro substituent afforded the corresponding product **3i** in 97% yield and excellent stereoselectivity (dr = 9:1, 98% ee). Notably, this protocol could also be extended to (*E*)-2-(benzoxazol-2-yl)-3-phenylacrylonitrile (**1j**), which produced product **3j** in 97% yield, 4:1 dr, and 95% ee. With regard to the α-chloro aldehydes **2**, aliphatic linear aldehydes are also tolerated, leading to the corresponding products **3k** and **3l** in moderate yields. The relative configuration of the major diastereomer of **3** was assigned by NOE measurements on **3d** (see Supporting Information). It was clear that H^a and H^b are in a *cis* relationship, which is in accordance with the absolute configuration of compound **3d** determined by X-ray crystal structure analysis (Figure 1).[21]

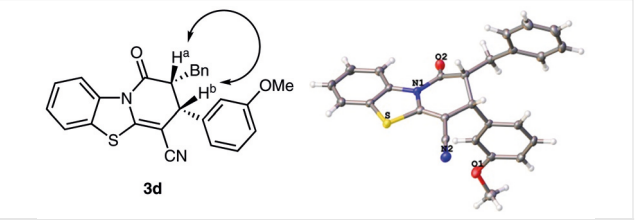
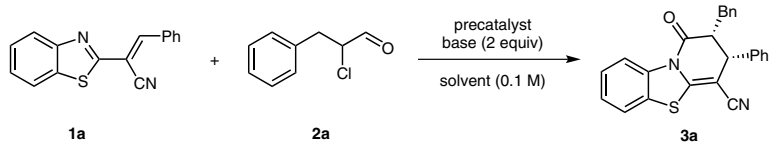


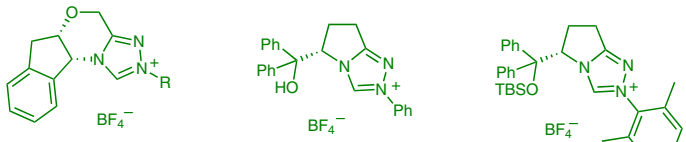
Figure 1 The relative (NOE) and absolute configuration [X-ray, χ_{abs} = 0.049(18)] of **3d**

A possible mechanism explaining the *cis* configuration of the major diastereomer is shown in Scheme 2. Initially, nucleophilic addition of the free carbene **A′** to the α-chloro aldehyde **2** affords the adduct **I**, followed by the removal of hydrogen chloride to form the enolate species **II**. Since the *Re* face of the azolium enolate is blocked by the indane backbone of the NHC, the enolate undergoes an aza-DA reaction on the *Si* face with the (*E*)-2-styrylbenzothiazole **1**, via the favored *endo* transition state ***endo*-TS**.[13i,22] Subsequent α-elimination leads to the final product **3** and liberates the NHC catalyst for further cycles. In a more asynchronous manner, the annulation can be seen as a Michael–lactamization sequence. The rather low ee values of the minor *trans*-diastereomer may be explained by the presence of an *E*/*Z*-azolium enolate mixture (see Supporting Information).

In summary, we have developed an efficient NHC-catalyzed asymmetric reverse-electron-demand 1-azadiene Diels–Alder reaction of (*E*)-2-styrylbenzothiazoles with α-chloro aldehydes, resulting in the desired *cis*-dihydrobenzothiazolopyridin-1-ones in good to excellent yields, good diastereomeric ratios and excellent ee values. This annulation protocol tolerates quite a range of substrates, leading to medicinally interesting tricyclic dihydrobenzothiazolopyridines bearing a synthetically useful cyano group at the 4-position.

Table 1 Optimization of the Reaction Conditions[a]





A R = Mes
B R = C_6F_5

C

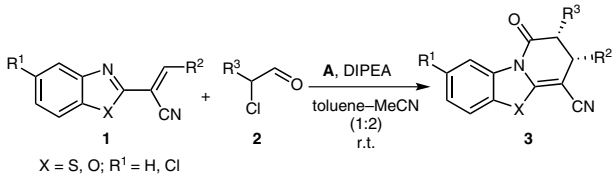
D

Entry	Precatalyst	Base	Solvent	Yield[b] (%)	dr[c] (*cis*/*trans*)	ee[d] (%) (*cis*)
1	**A**	Et_3N	toluene	29	6:1	95
2	**B**	Et_3N	toluene	trace	–	–
3	**C**	Et_3N	toluene	trace	–	–
4	**D**	Et_3N	toluene	n.r.	–	–
5[e]	**A**	Et_3N	toluene	29	6:1	93
6	**A**	TMEDA	toluene	40	5:1	95
7	**A**	DIPEA	toluene	37	7:1	94
8	**A**	DABCO	toluene	30	3:1	94
9	**A**	NaOAc	toluene	trace	–	–
10	**A**	K_2CO_3	toluene	n.r.	–	–
11	**A**	TMEDA	THF	41	3:1	94
12	**A**	TMEDA	mesitylene	29	3.5:1	94
13	**A**	TMEDA	CH_2Cl_2	46	3:1	97
14	**A**	TMEDA	MeCN	96	1:2.5	96
15	**A**	DABCO	MeCN	58	1:13	87
16	**A**	DIPEA	MeCN	99	3.5:1	97
17	**A**	DIPEA	toluene–MeCN, 4:1	76	7.5:1	97
18	**A**	DIPEA	toluene–MeCN, 1:4	97	5:1	97
19	**A**	DIPEA	toluene–MeCN, 2:1	94	7:1	97
20	**A**	**DIPEA**	**toluene–MeCN, 1:2**	**95**	**7:1**	**98**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), precatalyst (0.02 mmol), base (0.4 mmol), solvent (v/v, 2 mL in total), r.t., under argon, 16 h.
[b] Yield of isolated product **3a** after column chromatography; n.r. = no reaction.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC on a chiral stationary phase.
[e] Performed at 40 °C.

All reactions were carried out under argon. THF and toluene were distilled over Solvona®. CH_2Cl_2 was distilled over CaH_2. All other chemicals were used without further purification. Triazolium salts, chiral triazolium-derived carbene catalysts **A**–**D** and the achiral triazolium-derived carbene catalyst 2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (which was used to synthesize the racemic products) were prepared according to known literature procedures.[23] (*E*)-2-(Benzothiazol-2-yl)-3-phenylacrylonitriles were prepared from benzothiazol-2-ylacetonitriles.[24] α-Chloro aldehydes were prepared from aldehydes.[25] Chromatographic purification of the products was performed on Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC was performed on SIL G-25 UV254 plates (MACHEREY-NAGEL). The developed TLC plates were visualized with ultraviolet irradiation (254 nm). Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed with a Vario EL elemental analyzer. Mass spectra and high-resolution mass spectra were acquired on a Finnigan MAT 95 (EI/CI) or on a Thermo Fisher Scientific LTQ Orbitrap XL (ESI) mass spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 spectrometer using a Diamant/KRS5 ATR attachment. Evaluation was undertaken using the supplementary software. The absorption bands are given in wavenumbers

Table 2 Asymmetric Synthesis of Dihydrobenzothiazolopyridin-1-ones **3**[a]



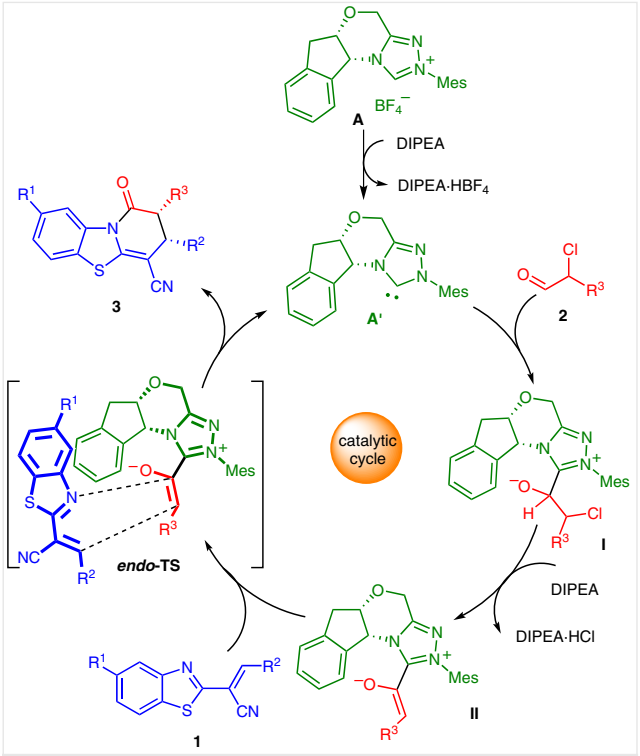
3	R^2	R^3	Yield[b] (%)	dr[c]	ee[d] (%)
a	Ph	Bn	93	7:1	96
b	4-Tol	Bn	74	9:1	96
c[e]	4-$MeOC_6H_4$	Bn	72	8:1	94
d	3-$MeOC_6H_4$	Bn	94	6:1	98
e	4-ClC_6H_4	Bn	84	6:1	97
f	3-ClC_6H_4	Bn	97	4:1	98
g	4-FC_6H_4	Bn	97	4:1	97
h[f]	2-furyl	Bn	68	6:1	92
i[g]	Ph	Bn	97	9:1	98
j[h]	Ph	Bn	97	4:1	95
k	Ph	*n*-Bu	71	8:1	98
l	Ph	*n*-Hex	44	5:1	96

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), precatalyst **A** (0.05 mmol), DIPEA (1.0 mmol), toluene–MeCN (1:2, v/v; 5 mL in total), r.t., under argon, 16 h; R^1 = H, X = S, unless otherwise noted.
[b] Yield of isolated product **3** as a mixture of diastereomers after column chromatography.
[c] Determined by ^1H NMR spectroscopy.
[d] Determined by HPLC on a chiral stationary phase.
[e] Reaction time was 43 h.
[f] Reaction time was 40 h.
[g] R^1 = Cl; reaction time was 18 h.
[h] X = O.

(cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at ambient temperature on Varian VNMRS 600 and Inova 400 instruments. The chemical shifts are reported in ppm downfield from TMS and referenced to residual solvent peak resonances as internal standard. The order of citation of data in parentheses is a) multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet), b) coupling constants, and c) number of protons. Coupling constants (*J*) are reported in hertz (Hz). Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases (Daicel AD, Daicel IA, Daicel IC).

Compounds 3a–l; General Procedure

To a dried and argon-filled Schlenk flask was added an (*E*)-2-styrylbenzothiazole **1** (0.5 mmol, 1.0 equiv), an α-chloro aldehyde **2** (0.75 mmol, 1.5 equiv), triazolium salt **A** (0.05 mmol, 10 mol%), and DIPEA (1.0 mmol, 2.0 equiv) in a mixed solvent of toluene–MeCN (1:2, v/v; 5 mL). The mixture was stirred at r.t. and monitored by TLC until completion of the reaction. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (pentane–Et_2O, 10:1) to afford the product **3a–l** as a colorless or light yellow solid.



Scheme 2 Proposed reaction mechanism

(2*R*,3*R*)-2-Benzyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3a)

The ee (96%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 9:1, 0.5 mL/min; t_R = 11.01 min (minor), 13.47 min (major)].

Yield: 183.2 mg (93%); colorless solid; mp 140–142 °C.

$[\alpha]_D^{21}$ –501.5 (*c* 1.0, $CHCl_3$).

IR (ATR): 3446, 3026, 2938, 2321, 2196, 2103, 1948, 1719, 1605, 1493, 1455, 1364, 1314, 1223, 1135, 1065, 1027, 983, 919, 849, 748, 697 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.4 Hz, 1 H), 7.38–7.24 (m, 9 H), 7.07 (d, *J* = 7.2 Hz, 4 H), 3.66–3.63 (m, 1 H), 3.55–3.52 (m, 1 H), 3.46 (dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz, 1 H), 2.49 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3, 152.3, 138.1, 137.5, 136.5, 129.3 (2 C), 128.9 (2 C), 128.7 (2 C), 128.5, 127.7 (2 C), 127.1, 126.8, 126.0, 123.8, 121.9, 117.9, 117.3, 83.5, 48.0, 43.1, 31.5.

MS (ESI): *m*/*z* = 395.1215 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{18}N_2OS$: 417.1032; found: 417.1030.

(2*R*,3*R*)-2-Benzyl-1-oxo-3-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3b)

The ee (96%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–*i*-PrOH, 97:3, 1.0 mL/min; t_R = 16.05 min (minor), 27.22 min (major)].

Yield: 151.8 mg (74%); colorless solid; mp 133–135 °C.

$[\alpha]_D^{21}$ –509.4 (*c* 1.0, $CHCl_3$).

IR (ATR): 3441, 3024, 2928, 2324, 2196, 2100, 1978, 1718, 1606, 1508, 1456, 1364, 1313, 1223, 1134, 1029, 982, 934, 813, 748, 702 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1 H), 7.38–7.22 (m, 6 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 7.07 (d, *J* = 7.2 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 3.60 (d, *J* = 6.6 Hz, 1 H), 3.52–3.48 (m, 1 H), 3.44 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1 H), 2.49 (dd, J_1 = 14.4 Hz, J_2 = 9.0 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4, 152.0, 138.2, 138.2, 137.5, 133.4, 129.9 (2 C), 128.9 (2 C), 128.7 (2 C), 127.5 (2 C), 127.1, 126.8, 125.9, 123.8, 121.8, 117.9, 117.3, 83.7, 48.1, 42.7, 31.5, 21.1.

MS (ESI): *m*/*z* = 409.1373 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_2OS$: 431.1189; found: 431.1188.

(2*R*,3*R*)-2-Benzyl-3-(4-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3c)

The ee (94%) was measured by HPLC using a chiral stationary phase [Chiralpak AD; *n*-heptane–EtOH, 7:3, 0.5 mL/min; t_R = 18.94 min (minor), 25.78 min (major)].

Yield: 152.0 mg (72%); colorless solid; mp 96–98 °C.

$[\alpha]_D^{21}$ –500.9 (*c* 2.89, $CHCl_3$).

IR (ATR): 3455, 3017, 2956, 2841, 2631, 2321, 2195, 2102, 2063, 2008, 1908, 1727, 1605, 1509, 1455, 1366, 1224, 1132, 1029, 930, 826, 747, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1 H), 7.41–7.22 (m, 6 H), 7.08 (d, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.59 (d, *J* = 7.2 Hz, 1 H), 3.52–3.49 (m, 1 H), 3.44 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1 H), 2.49 (dd, J_1 = 15.0 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4, 159.6, 151.8, 138.1, 137.4, 128.9 (2 C), 128.8 (2 C), 128.7 (2 C), 128.4, 127.1, 126.8, 126.0, 123.8, 121.9, 118.0, 117.2, 114.6 (2 C), 83.9, 55.3, 48.2, 42.4, 31.5.

MS (ESI): *m*/*z* = 425.1315 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{20}N_2O_2S$: 447.1138; found: 447.1137.

(2*R*,3*R*)-2-Benzyl-3-(3-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3d)

The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–*i*-PrOH, 9:1, 1.0 mL/min; t_R = 11.62 min (minor), 14.60 min (major)].

Yield: 200.6 mg (94%); light yellow solid; mp 134–135 °C.

$[\alpha]_D^{21}$ –491.0 (*c* 1.0, $CHCl_3$).

IR (ATR): 3425, 3023, 2937, 2839, 2641, 2322, 2195, 2088, 1989, 1922, 1715, 1599, 1454, 1312, 1255, 1140, 1039, 932, 862, 748, 702 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 7.8 Hz, 1 H), 7.42–7.19 (m, 7 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 6.86 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 6.57 (s, 1 H), 3.76 (s, 3 H), 3.59 (d, *J* = 7.2 Hz, 1 H), 3.53–3.45 (m, 2 H), 2.51 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3, 160.0, 152.3, 138.1, 137.9, 137.4, 130.4, 128.9 (2 C), 128.7 (2 C), 127.1, 126.8, 126.0, 123.7, 121.8, 119.6, 117.9, 117.3, 113.9, 113.4, 83.3, 55.2, 48.0, 43.1, 31.5.

MS (ESI): *m*/*z* = 423.1194 $[M - H]^-$.

Anal. Calcd for $C_{26}H_{20}N_2O_2S$ (424.12): C, 73.56; H, 4.75; N, 6.60. Found: C, 73.15; H, 5.00; N, 6.35.

(2*R*,3*R*)-2-Benzyl-3-(4-chlorophenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3e)

The ee (97%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 0.7 mL/min; t_R = 13.11 min (minor), 17.74 min (major)].

Yield: 180.3 mg (84%); colorless solid; mp 97–98 °C.

$[\alpha]_D^{21}$ –596.0 (*c* 1.0, $CHCl_3$).

IR (ATR): 3450, 3025, 2937, 2639, 2323, 2195, 2104, 1985, 1905, 1721, 1605, 1491, 1458, 1365, 1318, 1222, 1134, 1094, 1015, 934, 825, 747, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1 H), 7.43–7.22 (m, 8 H), 7.05 (d, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 3.61 (d, *J* = 7.2 Hz, 1 H), 3.56–3.52 (m, 1 H), 3.46 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1 H), 2.44 (dd, J_1 = 15.0 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.0, 152.6, 137.6, 137.3, 134.9, 134.4, 129.5 (2 C), 129.0 (2 C), 128.8 (2 C), 128.8 (2 C), 127.2, 127.0, 126.1, 123.7, 121.9, 117.7, 117.3, 82.8, 47.7, 42.4, 31.5.

MS (ESI): *m*/*z* = 429.0825 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{17}ClN_2OS$: 429.0823; found: 429.0823.

(2*R*,3*R*)-2-Benzyl-3-(3-chlorophenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3f)

The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 1.0 mL/min; t_R = 9.42 min (minor), 13.16 min (major)].

Yield: 208.5 mg (97%); colorless solid; mp 85–86 °C.

$[\alpha]_D^{21}$ –506.3 (*c* 1.0, $CHCl_3$).

IR (ATR): 3441, 3025, 2929, 2640, 2322, 2195, 2101, 1979, 1718, 1601, 1458, 1362, 1315, 1221, 1135, 1081, 870, 747, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 7.8 Hz, 1 H), 7.43–7.22 (m, 8 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 7.00–6.99 (m, 1 H), 6.95 (d, *J* = 7.2 Hz, 1 H), 3.61 (d, *J* = 7.2 Hz, 1 H), 3.57–3.53 (m, 1 H), 3.47 (dd, J_1 = 15.0 Hz, J_2 = 4.8 Hz, 1 H), 2.45 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 152.9, 138.4, 137.6, 137.3, 134.9, 130.6, 129.1, 129.1, 128.8 (2 C), 128.8 (2 C), 128.7, 128.1, 127.2, 127.0, 126.1, 125.6, 121.9, 117.3, 82.5, 47.7, 42.7, 31.5.

MS (ESI): *m*/*z* = 429.0825 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{17}ClN_2OS$ (428.08): C, 70.00; H, 3.99; N, 6.53. Found: C, 69.85; H, 3.82; N, 6.65.

(2*R*,3*R*)-2-Benzyl-3-(4-fluorophenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3g)

The ee (97%) was measured by HPLC using a chiral stationary phase [Daicel IA; *n*-heptane–EtOH, 9:1, 1.0 mL/min; t_R = 11.42 min (minor), 17.83 min (major)].

Yield: 201.3 mg (97%); light yellow solid; mp 64–66 °C.

$[\alpha]_D^{21}$ –486.3 (*c* 1.0, $CHCl_3$).

IR (ATR): 3448, 3025, 2939, 2651, 2323, 2196, 2106, 1894, 1720, 1603, 1506, 1457, 1363, 1315, 1223, 1138, 1026, 911, 831, 743 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1 H), 7.42–7.22 (m, 7 H), 7.05–6.96 (m, 5 H), 3.63 (d, *J* = 7.2 Hz, 1 H), 3.56–3.52 (m, 1 H), 3.45 (dd, J_1 = 15.0 Hz, J_2 = 4.8 Hz, 1 H), 2.45 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 162.6 (d, J_{F-C} = 246 Hz), 152.4, 137.7, 137.3, 132.3 (d, J_{F-C} = 4 Hz), 129.4 (d, J_{F-C} = 8 Hz, 2 C), 128.8 (2

C), 128.7 (2 C), 127.2, 126.9, 126.1, 123.7, 121.9, 117.7, 117.3, 116.2 (d, J_{F-C} = 22 Hz, 2 C), 83.2, 47.9, 42.3, 31.5.

MS (ESI): *m*/*z* = 413.1121 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{17}FN_2OS$: 413.1118; found: 413.1119.

(2*R*,3*S*)-2-Benzyl-3-(furan-2-yl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3h)

The ee (92%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 1.0 mL/min; t_R = 11.21 min (minor), 13.72 min (major)].

Yield: 129.8 mg (68%); colorless solid; mp 76–78 °C.

$[\alpha]_D^{21}$ –444.6 (*c* 1.0, $CHCl_3$).

IR (ATR): 3781, 3118, 3065, 3027, 2933, 2719, 2345, 2197, 2040, 1990, 1963, 1790, 1719, 1606, 1579, 1497, 1458, 1361, 1318, 1256, 1227, 1135, 1066, 1012, 922, 865, 814, 789, 743, 702 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.4 Hz, 1 H), 7.40–7.22 (m, 7 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 6.35–6.34 (m, 1 H), 6.19 (d, *J* = 3.0 Hz, 1 H), 3.67 (d, *J* = 6.6 Hz, 1 H), 3.54 (dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz, 1 H), 3.36–3.32 (m, 1 H), 2.41 (dd, J_1 = 14.4 Hz, J_2 = 10.8 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 153.7, 149.7, 143.1, 138.0, 137.7, 129.0 (2 C), 128.8 (2 C), 127.1, 126.9, 125.8, 123.7, 121.8, 117.8, 117.4, 110.4, 109.0, 79.9, 47.4, 36.2, 31.7.

MS (ESI): *m*/*z* = 383.0845 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}N_2O_2S$: 385.1005; found: 385.1005.

(2*R*,3*R*)-2-Benzyl-8-chloro-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3i)

The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 0.5 mL/min; t_R = 19.67 min (minor), 27.51 min (major)].

Yield: 208.3 mg (97%); colorless solid; mp 240–242 °C.

$[\alpha]_D^{21}$ –597.3 (*c* 1.0, $CHCl_3$).

IR (ATR): 3413, 3124, 3084, 3029, 2920, 2877, 2318, 2190, 2037, 1993, 1955, 1825, 1714, 1602, 1573, 1493, 1457, 1418, 1368, 1297, 1267, 1221, 1135, 1080, 1052, 996, 939, 896, 865, 805, 752, 698, 663 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 2.0 Hz, 1 H), 7.34–7.20 (m, 8 H), 7.05–7.02 (m, 4 H), 3.63 (d, *J* = 6.8 Hz, 1 H), 3.54–3.49 (m, 1 H), 3.41 (dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz, 1 H), 2.48 (dd, J_1 = 14.8 Hz, J_2 = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 152.0, 138.2, 137.9, 136.2, 133.2, 129.3 (2 C), 128.8 (2 C), 128.7 (2 C), 128.6, 127.6 (2 C), 126.9, 126.0, 122.3, 122.2, 117.7, 117.5, 84.3, 48.0, 43.1, 31.5.

MS (ESI): *m*/*z* = 427.0682 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{17}ClN_2OS$: 429.0823; found: 429.0817.

(2*R*,3*R*)-2-Benzyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carbonitrile (3j)

The ee (95%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 0.7 mL/min; t_R = 19.07 min (minor), 26.35 min (major)].

Yield: 183.8 mg (97%); colorless solid; mp 138–140 °C.

$[\alpha]_D^{21}$ –445.9 (*c* 1.0, $CHCl_3$).

IR (ATR): 3448, 3028, 2942, 2320, 2204, 2103, 1967, 1893, 1692, 1621, 1471, 1368, 1263, 1225, 1192, 1128, 1089, 1006, 923, 843, 745, 697 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01–7.98 (m, 1 H), 7.34–7.24 (m, 9 H), 7.07–7.06 (m, 2 H), 7.03 (d, *J* = 7.2 Hz, 2 H), 3.68–3.67 (m, 1 H), 3.51–3.46 (m, 2 H), 2.50–2.46 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.6, 156.9, 146.9, 137.9, 137.2, 129.3 (2 C), 128.8 (2 C), 128.7 (2 C), 128.4, 127.4 (2 C), 127.1, 126.9, 125.8, 125.0, 116.0, 114.4, 110.4, 66.0, 47.9, 41.3, 31.2.

MS (ESI): *m*/*z* = 401.1860 [M + Na]$^+$.

Anal. Calcd for $C_{25}H_{18}N_2O_2$ (378.14): C, 79.35; H, 4.79; N, 7.40. Found: C, 79.06; H, 4.94; N, 7.29.

(2*R*,3*R*)-2-Butyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3k)

The ee (98%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 0.5 mL/min; t_R = 15.59 min (minor), 19.09 min (major)].

Yield: 128.1 mg (71%); colorless solid; mp 100–102 °C.

$[\alpha]_D^{21}$ –511.7 (*c* 0.96, $CHCl_3$).

IR (ATR): 3423, 3029, 2948, 2865, 2196, 1947, 1717, 1606, 1457, 1310, 1226, 1135, 1060, 1028, 908, 846, 740 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 7.8 Hz, 1 H), 7.40–7.23 (m, 6 H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 2 H), 3.84 (d, *J* = 7.2 Hz, 1 H), 3.09 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1 H), 1.94–1.88 (m, 1 H), 1.42–1.21 (m, 5 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8, 152.5, 137.6, 136.5, 129.2 (2 C), 128.3, 127.4 (2 C), 127.1, 125.9, 123.8, 121.8, 118.1, 117.2, 83.0, 46.5, 43.9, 29.5, 25.4, 22.5, 13.9.

MS (ESI): *m*/*z* = 359.1202 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{20}N_2OS$: 383.1196; found: 383.1187.

(2*R*,3*R*)-2-Hexyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carbonitrile (3l)

The ee (96%) was measured by HPLC using a chiral stationary phase [Daicel IC; *n*-heptane–EtOH, 97:3, 0.7 mL/min; t_R = 12.62 min (minor), 14.81 min (major)].

Yield: 85.5 mg (44%); colorless solid; mp 123–125 °C.

$[\alpha]_D^{21}$ –448.6 (*c* 1.0, $CHCl_3$).

IR (ATR): 3427, 3029, 2927, 2858, 2645, 2321, 2196, 2104, 1993, 1804, 1717, 1607, 1457, 1309, 1225, 1135, 1062, 1028, 908, 850, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.32–7.23 (m, 5 H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 2 H), 3.84 (d, *J* = 7.2 Hz, 1 H), 3.09 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1 H), 1.93–1.87 (m, 1 H), 1.43–1.38 (m, 2 H), 1.31–1.20 (m, 7 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8, 152.5, 137.6, 136.5, 129.2 (2 C), 128.3, 127.4 (2 C), 127.1, 125.9, 123.7, 121.8, 118.1, 117.2, 83.0, 46.5, 43.9, 31.5, 29.1, 27.3, 25.7, 22.5, 14.0.

MS (ESI): *m*/*z* = 387.1536 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{24}N_2OS$: 411.1504; found: 411.1502.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379369. Included are copies of the ^{1}H and ^{13}C NMR spectra of products **3a**–**l**, HPLC measurements of products **3a**–**l**, and the NOESY spectrum of **3d**.

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