二苯基八氢吲哚醇硅醚催化 α,β -不饱和醛不对称[3+3]氮杂环化反应合成苯并呋喃衍生物

温慧玲 罗年华 欧阳露 罗人仕*

(赣南医学院药学院 江西赣州 341000)

摘要 二苯基八氢吲哚醇硅醚可高对映选择性催化 3-氨基苯并呋喃与 α,β -不饱和醛的[3+3]氮杂环化反应, 获得高收率(高达 93%)、高非对映选择性($dr > 20:1$)和高对映选择性(86%~>99% *ee*)的苯并呋喃衍生物。该方法可获得克级规模的苯并呋喃衍生物。

关键词 二苯基八氢吲哚醇硅醚; [3+3]氮杂环化; α,β -不饱和醛; 3-氨基苯并呋喃

Synthesis of Benzofuran Derivatives by Diphenylperhydroindolinol Silyl Ether-Catalyzed Asymmetric [3+3] Aza-cyclization of α,β -Unsaturated Aldehydes

Wen, Huiling Luo, Nianhua Ouyang, Lu Luo, Renshi*

(School of Pharmacy, Gannan Medical University, Ganzhou, Jiangxi 341000)

Abstract A highly enantioselective [3+3] aza-cyclization of α,β -unsaturated aldehydes with 3-aminobenzofuran promoted by diphenylperhydroindolinol silyl ether has been described, which afforded benzofuran derivatives in high yields (up to 93%), diastereoselectivities ($dr > 20:1$) and enantioselectivities (86%~>99% *ee*). This method also enabled to obtain benzofuran derivatives in gram scale-up.

Keywords diphenylperhydroindolinol silyl ether; [3+3] aza-cyclization; α,β -unsaturated aldehydes; 3-aminobenzofuran

1 Introduction

Benzofuran derivatives are an important class of compounds with broad application prospects. Many bioactive substances or important chiral drugs contain benzofuran skeleton. More than half of the top 200 drugs currently sold worldwide are chiral drugs, for example, anti-Alzheimer's drug galantamine, urinary incontinence drug darifenacin, drugs for the treatment of diseases caused by arterial occlusion beraprost, analgesics morphine, sleep agent ramelteon, antifungal drug griseofulvin (Figure 1). Therefore, an economical, effective and direct method for the preparation of chiral benzofuran would provide theoretical guidance and practical reference on the synthesis of optically active drugs.^[1]

After the efforts of chemists, there are now mature theories and techniques to synthesize benzofuran derivatives. Generally, synthesis of benzofuran derivatives can be divided into biosynthesis and chemical synthesis. Biosynthesis has been limited in its application due to its particular characteristic.^[2] Besides, benzofuran derivatives can be synthesized by chemical synthesis through chiral resolution or chiral sources and asymmetric catalysis. The methodology of asymmetric catalysis has the advantages of environmental protection, high efficiency and quickness, etc., which has become the main method for the synthesis of chiral drugs containing benzofuran skeleton. Different metal-catalyzed asymmetric reactions, such as Mg,^[3] Cu,^[4] Sc,^[5] Cr,^[6] Ir^[7] and Rh,^[8] have been reported for the synthesis of chiral benzofuran compounds recently. Mean-

* Corresponding author. E-mail: luorensi2010@163.com

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Figure 1 Chiral drugs with benzofuran skeleton

while, organocatalysts^[9] were also employed to promote asymmetric transformation to achieve such compounds. For example, Chen *et al.*^[10] exploited a chiral primary amine to construct chiral benzofuran derivatives and Şahin^[11] brought whole-cell biocatalyst for green synthesis of enantiopure (*S*)-1-(benzofuran-2-yl)ethanol. Besides, Rafinski^[12] reported *N*-heterocyclic carbene (NHC)-catalyzed organocatalytic asymmetric approach for the synthesis of functionalized benzofurans via an intramolecular Stetter reaction. Except for asymmetric desymmetrization,^[3] lactonization,^[4] bromoaminocyclization,^[5] dearomatization,^[6] and cascade^[7] strategies for the synthesis of above chiral benzofurans, enantioselective [4+2],^[13] [4+1],^[14] [3+3],^[15] and [3+2]^[16] cyclization strategies were also applied.

Although asymmetric catalytic reactions for the synthesis of benzofuran derivatives have been widely studied and achieved remarkable results, there are still many basic problems and deficiencies for asymmetric catalytic reactions, such as reactive speed, selectivity and catalysis efficiency. So new methodologies of asymmetric catalysis for the synthesis of chiral drugs are still the key to efficient, green and sustainable development.

As we all know, proline and its derivatives are kinds of important organic small molecule catalysts. Studies have shown that the catalytic activity and efficiency can be greatly changed by simply modifying proline.^[17] (2*S*,3*aS*,7*aS*)-Perhydroindoline-2-carboxylic acid is similar in structure to proline, but its steric hindrance is larger. After modifying the structure by our group, it was found that **Cat-1** and **Cat-2** employed in asymmetric Michael addition reaction showed better catalytic effect than proline (Figure 2a).^[18]

In 2018, Deng *et al.*^[15] reported the aza-[3+3] cycloaddition of *N*-tosyl-3-aminobenzofuran with α,β -unsaturated

aldehydes for the synthesis of biologically active and synthetically challenging polysubstituted fused benzofuran derivatives by sterically hindered prolinol silyl ether derivative (TBS). Aiming at further exploring the potential of perhydroindole derivatives in organocatalysis, herein we report diphenylperhydroindolinol silyl ether-mediated asymmetric [3+3] aza-cyclization of α,β -unsaturated aldehydes with 3-aminobenzofuran, in high yields (up to 93%), diastereoselectivities (*dr* > 20 : 1) and enantioselectivities (>99% *ee*) (Figure 2).

Previous asymmetric reaction reported by our group:

This work: asymmetric [3+3] aza-cyclization with **Cat-1**

Figure 2 Diphenylperhydroindolinol silyl ether-catalyzed asymmetric reactions

2 Results and discussion

According to our previous work,^[18] catalysts **Cat-1**~**Cat-5** were firstly synthesized. With this catalyst in hand, *N*-(benzofuran-3-yl)-4-methylbenzenesulfonamide (**1a**) and cinnamaldehyde (**2a**) were used as template reaction to investigate the catalytic activity (Table 1). The results showed that different catalysts had different catalytic efficiency when CH₃CN was used as solvent at 0 °C with 20 mol% catalyst loading. Using **Cat-1** as catalyst, the reaction was completely converted in 24 h with 82% *ee* (Table 1, Entry 1). Unfortunately, only 18% *ee* was obtained (Table 1, Entry 2) with **Cat-2** as the catalyst, which achieved great catalytic effect in the asymmetric Michael addition reaction. In order to prove the importance of steric hindrance in this reaction, catalysts **Cat-3**~**Cat-5** were then

used for comparison. The results showed that the size of steric hindrance of substituents attached to the catalysts had large effect on enantioselectivity of the reaction (Table 1, Entries 3~5). In order to compare the catalytic effect with the proline derivative, **Cat-6** was used to conduct a control test with **Cat-1**. The experimental results showed that **Cat-1** had better catalytic result than **Cat-6** under the same condition (Table 1, Entry 6).

Table 1 Catalyst screening^a

Entry	Cat.	t/h	Yield ^b /%	ee ^c /%
1	Cat-1	24	85	82
2	Cat-2	18	84	18
3	Cat-3	36	73	38
4	Cat-4	36	71	10
5	Cat-5	36	75	50
6	Cat-6	48	75	71

^a Reactions performed using cat. (0.02 mmol), **1a** (0.1 mmol), **2a** (0.15 mmol) in MeCN (2 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis, *dr* > 20 : 1 by ¹H NMR.

The above preliminary research results showed that **Cat-1** could effectively catalyze the [3 + 3] aza-cyclization reaction of unsaturated α,β -aldehydes with 3-aminobenzofuran, which afforded fully converted product. The disadvantage was that the enantioselectivity of the reaction was just good. In order to obtain better enantioselectivity, the solvents were next screened (Table 2). The experiments showed that dichloromethane (DCM) and other commonly used solvents could obtain excellent reactivity, but the solvents had different impacts on enantioselectivity. For example, ether solvents such as tetrahydrofuran (THF) and Et₂O only obtained 51% *ee* (Table 2, Entry 5 and 6) and CH₃CN was the best reaction solvent. With the best solvent in hand, the reaction was transferred to -10 °C or -20 °C, and it was found that the temperature had little effect on the activity, while the enantioselectivity was increased to 94% and 93% *ee*, respectively (Table 2, Entries 9 and 10).

In order to obtain the best catalytic system, the effect of additive was discussed (Table 3). The results showed that additives such as aromatic acids had a greater effect on this reaction. Therefore, several acids for comparison were tried. First, 40 mol% 3,5-dinitrobenzoic acid (DNBA) was used as an additive. The enantioselectivity of the reaction did not change, but the time required for complete conversion of the reaction was doubled (Table 3, Entry 1). When PhCOOH (BA) was added as an additive, the reactivity

Table 2 Solvent screening^a

Entry	Solvent	t/h	Yield ^b /%	ee ^c /%
1	CH ₂ Cl ₂	28	89	74
2	Toluene	24	91	71
3	Hexane	24	91	60
4	Acetone	24	92	70
5	THF	28	85	51
6	Et ₂ O	24	81	51
7	MeOH	28	88	61
8	MeCN	24	95	82
9 ^d	MeCN	16	86	94
10 ^e	MeCN	18	87	93

^a Reactions performed using **Cat-1** (0.02 mmol), **1a** (0.1 mmol), **2a** (0.15 mmol) in MeCN (2 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis, *dr* > 20 : 1 by ¹H NMR. ^d -10 °C. ^e -20 °C.

Table 3 Condition optimization^a

Entry	Cat-1/mol%	Additive	t/h	Yield ^b /%	ee ^c /%
1	20	DNBA	48	83	93
2	20	BA	15	86	83
3	20	PNBA	5	95	98
4 ^d	20	PNBA	6	91	98
5 ^e	20	PNBA	5	93	98
6 ^f	20	PNBA	8	91	93
7	10	PNBA	32	63	97
8	5	PNBA	120	31	97

^a Reactions performed using **Cat-1** (0.02 mmol), **1a** (0.1 mmol), **2a** (0.15 mmol) in MeCN (2 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis, *dr* > 20 : 1 by ¹H NMR. ^d -20 °C. ^e 60 mol% additive. ^f 20 mol% additive.

was slightly improved, but the enantioselectivity of the reaction was reduced to 83% *ee* (Table 3, Entry 2). With 4-nitrobenzoic acid (PNBA) as an additive, the reaction could be completely converted within 5 h, and the enantioselectivity of the reaction was increased to 98% *ee* (Table 3, Entry 3). Further reducing the reaction temperature to -20 °C or increasing the amount of additive to 60 mol% had little effects on activity or enantioselectivity (Table 3, Entries 3 and 4). But if the loading of additives was re-

duced to 20 mol%, the enantioselectivity of the reaction was decreased to 93% *ee* (Table 3, Entry 5). On the other hand, if the catalyst loading was reduced to 10 mol% or 5 mol%, the enantioselectivity had little effect, but it had a great effect on the reaction activity (Table 3, Entries 7 and 8).

Under the above optimal catalytic conditions, the substrates to test this catalytic system had been extended (Table 4). The results showed that the reaction of different substituted cinnamaldehyde with 3-aminobenzofuran obtained good results. The reaction yields were between 87% and 93%, *dr* were greater than 20 : 1, and most reaction products obtained >99% *ee* (Table 4). Specifically, the different substituent groups on the substrate had little effect on the enantioselectivity of the reaction, but the reaction rates were slightly different. For example, 3-substituted cinnamaldehyde required the longest reaction time (Table 4, Entries 3 and 22). In addition, when unsubstituted 3-aminobenzofuran was used to react with different cinnamaldehydes, a minimum of 91% *ee* was obtained when 3-chlorophenylcinnamaldehyde and 2-methoxyphenylcinnamaldehyde were employed (Table 4, Entries 3 and 11). When cinnamaldehyde was *para*-substituted, the enantioselectivity of the reaction was up to 99% *ee* (Table 4, Entries 2, 5, 7, 8 and 12). When 6-chloro-3-aminobenzofuran was used, over 99% *ee* was obtained with any substituted cinnamaldehyde (Table 4, Entries 13~23). 98% *ee* was also obtained even when cinnamaldehyde was used as the substrate (Table 4, Entry 24). In addition, when alkyl-substituted α,β -unsaturated aldehyde such as hexenal was employed as the substrate, good *ee* and moderate yield were achieved, which indicated the limited tolerance of different substrates of this asymmetric methodology (Table 4, Entry 25).

In order to verify the practicality of **Cat-1**, gram-scale experiment was tried with the template reaction. Based on the above optimal standard conditions, a fully converted addition product was obtained in yield of 93% and enantioselectivity of 98% after reacting for 18 h with 5 mmol of **1a** and 7.5 mmol of **2a** (Figure 3).

Figure 3 Gram-scale experiment

3 Conclusion

In conclusion, a diphenylperhydroindolinol silyl ether-catalyzed [3+3] aza-cyclization of α,β -unsaturated aldehydes with 3-aminobenzofuran has been developed for the preparation of functionalized benzofuran derivatives in

Table 4 Screening of substrate scope^a

Entry	R ¹	R ²	t/h	Yield ^b / % (3)	ee ^c / %
1	H	Ph	5	93 (3aa)	98
2	H	4-ClC ₆ H ₄	14	92 (3ab)	>99
3	H	3-ClC ₆ H ₄	72	90 (3ac)	91
4	H	2-ClC ₆ H ₄	17	89 (3ad)	97
5	H	4-NO ₂ C ₆ H ₄	8	90 (3ae)	>99
6	H	2-NO ₂ C ₆ H ₄	12	87 (3af)	95
7	H	4-BrC ₆ H ₄	14	93 (3ag)	>99
8	H	4-FC ₆ H ₄	13	93 (3ah)	>99
9	H	4-CH ₃ C ₆ H ₄	24	92 (3ai)	96
10	H	4-OCH ₃ C ₆ H ₄	18	93 (3aj)	97
11	H	2-OCH ₃ C ₆ H ₄	24	92 (3ak)	91
12	H	2,6-F ₂ C ₆ H ₃	18	93 (3al)	>99
13	6-Cl	4-BrC ₆ H ₄	15	92 (3ba)	>99
14	6-Cl	4-ClC ₆ H ₄	15	91 (3bb)	>99
15	6-Cl	4-FC ₆ H ₄	13	92 (3bc)	>99
16	6-Cl	4-CH ₃ C ₆ H ₄	18	92 (3bd)	>99
17	6-Cl	2-OCH ₃ C ₆ H ₄	24	93 (3be)	>99
18	6-Cl	4-OCH ₃ C ₆ H ₄	18	91 (3bf)	>99
19	6-Cl	2-ClC ₆ H ₄	15	90 (3bg)	>99
20	6-Cl	4-NO ₂ C ₆ H ₄	13	90 (3bh)	>99
21	6-Cl	2-NO ₂ C ₆ H ₄	18	92 (3bi)	>99
22	6-Cl	3-ClC ₆ H ₄	72	92 (3bj)	>99
23	6-Cl	2,6-F ₂ C ₆ H ₃	18	93 (3bk)	>99
24	6-Cl	Ph	8	93 (3bl)	97
25	H	Propyl	72	43 (3bm)	86 ^d

^a Reactions performed using **Cat-1** (0.02 mmol), **1** (0.1 mmol), **2** (0.15 mmol) in MeCN (2 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis, *dr* > 20 : 1 by ¹H NMR. ^d Determined by the acetylated compound.

high yields (up to 93%), diastereoselectivities (*dr* > 20 : 1) and enantioselectivities (up to >99% *ee*). The experimental results show that **Cat-1** has better catalytic result than **Cat-6**. Moreover, this simple and readily method also enables to obtain chiral benzofuran compound in gram scale-up. Even more important, this protocol gives a new viewpoint on classical [3+3] aza-cyclization. Ongoing studies are focused on exploring the **Cat-1**-catalyzed organic methodology on different reactions and the applications.

4 Experimental section

4.1 General information

Reagents were purchased from commercial sources and were used as received. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AVANCE NEO 400 MHz NMR spectrometers. Chemical shifts (δ) are reported from internal tetramethylsilane for ¹H NMR and relative to the

central CDCl_3 resonance ($\delta=77.16$ for ^{13}C NMR). The melting points were determined on a WRR melting point apparatus and were uncorrected. Optical rotations were recorded on a PerkinElmer PE-341 instrument. Single-crystal X-ray diffraction experiments were carried out with a Bruker APEX DUO diffractometer using graphite-monochromated $\text{Cu K}\alpha$ radiation. HPLC separations were performed on an Agilent 1100 system. Conversion was monitored by thin layer chromatography (TLC). Flash column chromatography was performed over silica gel (200~300 mesh).

4.2 General procedures for the synthesis of products (3aa~3bm)

A round-bottom flask was charged with **Cat-1** (0.02 mmol), **1** (0.1 mmol), **2** (0.15 mmol) and additive 4- $\text{O}_2\text{N}-\text{C}_6\text{H}_4\text{COOH}$ (0.04 mmol) in MeCN (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C until the reaction was completely converted to **1**. The residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc ($V:V=5:1$) to afford the desired products. Analogues **3aa**~**3bm** were synthesized by using similar procedures. The racemic products of **3aa**~**3bm** were prepared with racemic **Cat-6** under the same conditions.

(2*R*,4*S*)-4-Phenyl-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3aa**): Light yellow solid, 38.9 mg, 93% yield, m.p. 183~184 °C (Lit.^[15a] 182~184 °C); $[\alpha]_{\text{D}}^{20} + 56$ (CH_2Cl_2 , c 0.24); ^1H NMR (400 MHz, Chloroform-*d*) δ : 8.24~8.21 (m, 1H), 7.58~7.53 (m, 2H), 7.38~7.27 (m, 5H), 7.24~7.17 (m, 3H), 6.70~6.66 (m, 2H), 5.87 (d, $J=2.0$ Hz, 1H), 4.22 (dd, $J=11.7$, 7.1 Hz, 1H), 2.99 (s, 1H), 2.43 (s, 3H), 2.22 (ddd, $J=14.2$, 7.1, 2.6 Hz, 1H), 1.26~1.20 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 148.2, 144.6, 140.2, 133.6, 130.0 (2C), 128.7 (2C), 128.0 (2C), 127.8 (2C), 127.4, 124.8, 124.7, 123.2, 122.5, 116.3, 111.4, 80.5, 36.2, 35.4, 21.7; HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=12.35$ min (major), 17.95 min (minor).

(2*R*,4*S*)-4-(4-Chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ab**): Light yellow solid, 40.5 mg, 92% yield, m.p. 182~183 °C (Lit.^[15a] 182~184 °C); $[\alpha]_{\text{D}}^{20} + 372$ (CH_2Cl_2 , c 0.13); ^1H NMR (400 MHz, Chloroform-*d*) δ : 8.27~8.15 (m, 1H), 7.55 (d, $J=8.1$ Hz, 2H), 7.39~7.25 (m, 5H), 7.16 (d, $J=8.2$ Hz, 2H), 6.60 (d, $J=8.3$ Hz, 2H), 5.85 (s, 1H), 4.19 (dd, $J=11.7$, 7.1 Hz, 1H), 3.42 (s, 1H), 2.45 (s, 3H), 2.17 (ddd, $J=13.9$, 7.1, 2.1 Hz, 1H), 1.16 (t, $J=12.8$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 147.6, 144.7, 138.7, 133.5, 133.1, 130.0 (2C), 129.1 (2C), 128.8 (2C), 128.0 (2C), 124.9, 124.5, 123.3, 122.5, 116.5, 111.4, 80.3, 35.6, 35.2, 21.7. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=13.67$ min (major), 18.61 min (minor).

(2*R*,4*S*)-4-(3-Chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ac**): Light yellow solid, 41.0 mg, 90% yield, m.p. 183~184 °C (Lit.^[15a] 183~184 °C); $[\alpha]_{\text{D}}^{20} + 310$ (CH_2Cl_2 , c 0.16); ^1H NMR (400

MHz, Chloroform-*d*) δ : 8.26~8.20 (m, 1H), 7.55 (d, $J=7.9$ Hz, 2H), 7.40~7.30 (m, 5H), 7.24~7.14 (m, 2H), 6.79 (d, $J=7.2$ Hz, 1H), 6.54 (s, 1H), 5.86 (s, 1H), 4.20 (dd, $J=11.7$, 7.1 Hz, 1H), 2.90 (s, 1H), 2.44 (s, 3H), 2.19 (dd, $J=13.8$, 7.0 Hz, 1H), 1.11 (t, $J=13.0$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 154.3, 147.4, 145.0, 142.2, 134.7, 133.4, 130.2 (2C), 130.0, 127.9 (2C), 127.7, 127.3, 126.6, 125.0, 124.6, 123.4, 122.7, 116.7, 111.5, 80.3, 35.9, 35.0, 21.8. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=11.02$ min (major), 15.28 min (minor).

(2*R*,4*S*)-4-(2-Chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ad**): Light yellow solid, 39.9 mg, 89% yield, m.p. 188~189 °C (Lit.^[15a] 188~189 °C); $[\alpha]_{\text{D}}^{20} + 363$ (CH_2Cl_2 , c 0.1); ^1H NMR (400 MHz, Chloroform-*d*) δ : 8.28~8.17 (m, 1H), 7.59~7.51 (m, 2H), 7.41~7.29 (m, 4H), 7.26~7.21 (m, 2H), 7.20~7.11 (m, 1H), 7.02~6.94 (m, 1H), 6.27 (d, $J=7.3$ Hz, 1H), 5.89 (s, 1H), 4.78 (dd, $J=11.0$, 7.2 Hz, 1H), 3.28 (s, 1H), 2.43~2.31 (m, 4H), 1.14~0.97 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 147.3, 144.5, 138.0, 134.0, 133.7, 129.9 (2C), 129.8, 128.5, 128.5, 128.0 (2C), 126.9, 124.8, 124.7, 123.3, 122.5, 117.3, 111.4, 80.4, 33.2, 33.2, 21.6. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=14.40$ min (major), 18.10 min (minor).

(2*R*,4*S*)-4-(4-Nitrophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ae**): Light yellow solid, 40.7 mg, 90% yield, m.p. 185~186 °C (Lit.^[15a] 185~186 °C); $[\alpha]_{\text{D}}^{20} + 197$ (CH_2Cl_2 , c 0.1); ^1H NMR (400 MHz, Chloroform-*d*) δ : 8.07~8.02 (m, 2H), 7.58~7.53 (m, 2H), 7.37~7.27 (m, 5H), 6.85 (d, $J=8.6$ Hz, 2H), 5.90 (s, 1H), 4.35 (dd, $J=11.6$, 7.1 Hz, 1H), 3.21 (brs, 1H), 2.45 (s, 3H), 2.23 (ddd, $J=14.1$, 7.2, 2.6 Hz, 1H), 1.23~1.14 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 153.3, 147.0, 146.3, 145.4, 143.9, 132.5, 129.0 (2C), 127.6 (2C), 127.0 (2C), 124.2, 123.3, 123.0 (2C), 122.5, 121.7, 116.0, 110.4, 79.1, 35.1, 34.0, 20.8. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=22.88$ min (major), 27.52 min (minor).

(2*R*,4*S*)-4-(2-Nitrophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3af**): Light yellow solid, 40.0 mg, 87% yield, m.p. 175~176 °C; $[\alpha]_{\text{D}}^{20} + 224$ (CH_2Cl_2 , c 0.1); ^1H NMR (400 MHz, Chloroform-*d*) δ : 8.24~8.18 (m, 1H), 7.90 (d, $J=8.2$ Hz, 1H), 7.62~7.55 (m, 2H), 7.42~7.22 (m, 7H), 6.31 (d, $J=7.8$ Hz, 1H), 5.91 (s, 1H), 4.85 (dd, $J=11.2$, 7.0 Hz, 1H), 3.21 (brs, 1H), 2.63 (dd, $J=12.8$, 7.2 Hz, 1H), 2.40 (s, 3H), 1.22~1.13 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 149.8, 146.8, 144.6, 135.6, 133.8, 132.9, 130.0 (2C), 129.5, 128.2, 128.0 (2C), 125.1, 124.8, 124.5, 123.4, 122.6, 117.7, 111.4, 80.4, 34.6, 32.3, 21.7. HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$ 487.0940; found 487.0939. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=25.75$ min (major), 29.48 min (minor).

(2*R*,4*S*)-4-(4-Bromophenyl)-1-tosyl-1,2,3,4-tetrahydro-

benzofuro[3,2-*b*]pyridin-2-ol (**3ag**): Light yellow solid, 45.7 mg, 93% yield, m.p. 186~187 °C (Lit.^[15a] 186~187 °C); $[\alpha]_D^{20} + 233.3$ (CH₂Cl₂, *c* 0.20); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.23~8.19 (m, 1H), 7.54 (d, *J*=8.3 Hz, 2H), 7.36~7.26 (m, 7H), 6.55 (d, *J*=8.4 Hz, 2H), 5.85 (t, *J*=2.4 Hz, 1H), 4.18 (dd, *J*=11.6, 7.1 Hz, 1H), 3.23 (brs, 1H), 2.45 (s, 3H), 2.18 (ddd, *J*=14.1, 7.1, 2.5 Hz, 1H), 1.16 (ddd, *J*=14.1, 11.9, 2.5 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 147.5, 144.7, 139.2, 133.6, 131.8 (2C), 130.0 (2C), 129.5 (2C), 128.0 (2C), 124.9, 124.5, 123.3, 122.6, 121.2, 116.6, 111.4, 80.3, 35.7, 35.1, 21.7. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=15.51 min (major), 21.46 min (minor).

(2*R*,4*S*)-4-(4-Fluorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ah**): Light yellow solid, 40.2 mg, 93% yield, m.p. 186~187 °C; $[\alpha]_D^{20} + 231.8$ (CH₂Cl₂, *c* 0.88); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.23~8.19 (m, 1H), 7.55 (d, *J*=8.3 Hz, 2H), 7.36~7.27 (m, 5H), 6.88 (dd, *J*=12.0, 5.3 Hz, 2H), 6.68~6.60 (m, 2H), 5.86 (t, *J*=2.5 Hz, 1H), 4.21 (dd, *J*=11.6, 7.1 Hz, 1H), 3.13 (brs, 1H), 2.44 (s, 3H), 2.19 (ddd, *J*=14.1, 7.1, 2.5 Hz, 1H), 1.23~1.14 (m, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 147.9, 144.7, 135.8, 135.8, 133.6, 130.0 (2C), 129.3, 129.2, 128.0 (2C), 124.9, 124.6, 123.3, 122.5, 116.4, 115.7, 115.5, 111.4, 80.4, 35.4, 35.4, 21.7. HRMS (ESI-TOF) calcd for C₂₄H₂₀FN₄SO₂Na [M+Na]⁺: 460.0995; found 460.0994. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=13.52 min (major), 19.48 min (minor).

(2*R*,4*S*)-4-(*p*-Tolyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ai**): Light yellow solid, 39.4 mg, 92% yield, m.p. 142~143 °C; $[\alpha]_D^{20} + 223$ (CH₂Cl₂, *c* 0.15); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.26~8.20 (m, 1H), 7.57 (d, *J*=8.2 Hz, 2H), 7.38~7.27 (m, 5H), 7.02 (d, *J*=7.9 Hz, 2H), 6.59 (d, *J*=8.0 Hz, 2H), 5.87 (t, *J*=2.4 Hz, 1H), 4.19 (dd, *J*=11.5, 7.0 Hz, 1H), 3.07 (brs, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 2.18 (ddd, *J*=14.1, 7.1, 2.5 Hz, 1H), 1.23~1.19 (m, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 148.5, 144.6, 137.0, 137.0, 133.6, 130.0 (2C), 129.4 (2C), 128.0 (2C), 127.7 (2C), 124.7, 124.6, 123.1, 122.4, 116.1, 111.4, 80.5, 35.8, 35.3, 21.7, 21.2. HRMS (ESI-TOF) calcd for C₂₅H₂₄NO₄S [M+H]⁺: 434.1426; found 434.1426. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=13.22 min (major), 17.93 min (minor).

(2*R*,4*S*)-4-(4-Methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3aj**): Light yellow solid, 41.3 mg, 93% yield, m.p. 175~176 °C (Lit.^[15a] 175~176 °C); $[\alpha]_D^{20} + 488$ (CH₂Cl₂, *c* 0.1); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.25~8.15 (m, 1H), 7.58~7.52 (m, 2H), 7.39~7.24 (m, 5H), 6.76~6.69 (m, 2H), 6.63~6.55 (m, 2H), 5.85 (s, 1H), 4.17 (dd, *J*=12.0, 7.1 Hz, 1H), 3.80 (s, 3H), 3.14 (s, 1H), 2.45 (s, 3H), 2.26~2.11 (m, 1H), 1.19 (t, *J*=12.9 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 158.8, 154.2, 148.6, 144.6, 133.6, 132.0, 130.0 (2C), 128.7 (2C), 128.0 (2C), 124.7, 124.7, 123.2, 122.4, 116.1,

114.1 (2C), 111.4, 80.5, 55.4, 35.4, 35.3, 21.7. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=15.58 min (major), 19.48 min (minor).

(2*R*,4*S*)-4-(2-Methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ak**): Light yellow solid, 40.9 mg, 92% yield, m.p. 184~185 °C (Lit.^[15a] 183~185 °C); $[\alpha]_D^{20} + 252$ (CH₂Cl₂, *c* 0.1); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.22 (d, *J*=7.5 Hz, 1H), 7.54 (d, *J*=7.7 Hz, 2H), 7.40~7.15 (m, 6H), 6.86 (d, *J*=8.3 Hz, 1H), 6.68 (t, *J*=7.5 Hz, 1H), 6.16 (d, *J*=7.5 Hz, 1H), 5.87~5.83 (m, 1H), 4.75 (dd, *J*=11.3, 7.1 Hz, 1H), 3.80 (s, 3H), 2.88 (s, 1H), 2.38 (s, 3H), 2.36~2.28 (m, 1H), 1.07 (t, *J*=12.6 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 157.2, 154.0, 148.7, 144.5, 133.6, 129.9 (2C), 128.4, 128.3, 127.9 (2C), 127.7, 124.9, 124.5, 123.1, 122.3, 120.5, 116.8, 111.4, 110.6, 80.6, 55.5, 33.6, 29.2, 21.7. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=15.17 min (major), 17.46 min (minor).

(2*R*,4*S*)-4-(2,6-Difluorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3al**): Light yellow solid, 42.1 mg, 93% yield, m.p. 175~176 °C; $[\alpha]_D^{20} + 194$ (CH₂Cl₂, *c* 0.4); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.26 (d, *J*=7.8 Hz, 1H), 7.58 (d, *J*=8.0 Hz, 2H), 7.38~7.18 (m, 6H), 6.81 (t, *J*=8.8 Hz, 1H), 5.89 (s, 1H), 4.72 (dd, *J*=12.1, 6.3 Hz, 1H), 3.12 (s, 1H), 2.40 (s, 3H), 2.13 (ddd, *J*=13.4, 6.2, 2.2 Hz, 1H), 1.30~1.24 (m, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 162.8 (d, *J*=7.6 Hz, 1C), 160.4 (d, *J*=7.8 Hz, 1C), 153.8, 145.9, 144.3, 134.3, 130.0 (2C), 129.1 (t, *J*=10.4 Hz, 1C), 127.8 (2C), 124.5, 124.5, 123.1, 122.6, 115.2, 114.8 (t, *J*=16.6 Hz, 1C), 111.8 (d, *J*=3.3 Hz, 1C), 111.6 (d, *J*=3.3 Hz, 1C), 111.3, 79.9, 30.9, 25.4, 21.7. HRMS (ESI-TOF) calcd for C₂₄H₁₉F₂NO₄Na [M+Na]⁺: 478.0901; found 478.0898. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=12.58 min (major), 15.57 min (minor).

(2*R*,4*S*)-4-(4-Bromophenyl)-7-chloro-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3ba**): Light yellow solid, 48.4 mg, 92% yield, m.p. 188~189 °C; $[\alpha]_D^{20} + 212$ (CH₂Cl₂, *c* 0.2); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.13 (d, *J*=8.6 Hz, 1H), 7.52 (d, *J*=8.2 Hz, 2H), 7.38~7.27 (m, 6H), 6.53 (d, *J*=8.4 Hz, 2H), 5.85 (s, 1H), 4.20~4.13 (m, 1H), 2.92 (s, 1H), 2.46 (s, 3H), 2.20 (ddd, *J*=14.1, 7.1, 2.5 Hz, 1H), 1.22~1.09 (m, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 148.2, 144.9, 138.8, 133.4, 131.9 (2C), 130.8, 130.1 (2C), 129.4 (2C), 128.0 (2C), 124.1, 123.2, 123.2, 121.4, 116.5, 112.0, 80.3, 35.6, 35.0, 21.8; HRMS (ESI-TOF) calcd for C₂₄H₁₈BrClNO₄S [M-H]⁻: 529.9828; found 529.9819; HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=13.74 min (major), 34.55 min (minor).

(2*R*,4*S*)-7-Chloro-4-(4-chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bb**): Light yellow solid, 44.4 mg, 91% yield, m.p. 165~166 °C; $[\alpha]_D^{20} + 70$ (CH₂Cl₂, *c* 0.3); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.10 (d, *J*=8.6 Hz, 1H), 7.50 (d, *J*=8.1 Hz, 2H), 7.37~

7.23 (m, 4H), 7.14 (d, $J=8.2$ Hz, 2H), 6.56 (d, $J=8.3$ Hz, 2H), 5.83 (s, 1H), 4.16 (dd, $J=11.6, 7.1$ Hz, 1H), 3.08 (s, 1H), 2.43 (s, 3H), 2.17 (ddd, $J=14.1, 7.1, 2.2$ Hz, 1H), 1.18~1.05 (m, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 154.2, 148.3, 144.9, 138.3, 133.4, 133.3, 130.8, 130.1 (2C), 129.0 (2C), 129.0 (2C), 128.0 (2C), 124.1, 123.2 (2C), 116.4, 112.0, 80.3, 35.5, 35.1, 21.8. HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{19}\text{Cl}_2\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 510.0310; found 510.0307. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=13.16$ min (major), 33.35 min (minor).

(2*R*,4*S*)-7-Chloro-4-(4-fluorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bc**): Light yellow solid, 42.9 mg, 92% yield, m.p. 189~190 °C; $[\alpha]_{\text{D}}^{20}+242$ (CH_2Cl_2 , c 0.3); ^1H NMR (400 MHz, Chloroform- d) δ : 8.10 (d, $J=8.6$ Hz, 1H), 7.50 (d, $J=8.2$ Hz, 2H), 7.35~7.32 (m, 1H), 7.31~7.24 (m, 3H), 6.86 (t, $J=8.5$ Hz, 2H), 6.64~6.57 (m, 2H), 5.82 (s, 1H), 4.16 (dd, $J=11.5, 7.1$ Hz, 1H), 3.17 (s, 1H), 2.42 (s, 3H), 2.17 (ddd, $J=14.1, 7.1, 2.3$ Hz, 1H), 1.13 (t, $J=12.9$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 163.4, 160.8, 154.2, 148.6, 144.9, 135.4 (d, $J=3.1$ Hz, 1C), 133.4, 130.8, 130.1 (2C), 129.2 (d, $J=8.0$ Hz, 1C), 128.0 (2C), 124.0, 123.3, 123.2, 116.3, 115.8, 115.6, 112.0, 80.4, 35.4, 35.3, 21.7. HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{19}\text{FCINO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 494.0605; found 494.0600. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=11.90$ min (major), 30.60 min (minor).

(2*R*,4*S*)-7-Chloro-4-(*p*-tolyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bd**): Light yellow solid, 42.5 mg, 92% yield, m.p. 142~143 °C; $[\alpha]_{\text{D}}^{20}+319$ (CH_2Cl_2 , c 0.17); ^1H NMR (400 MHz, Chloroform- d) δ : 8.12 (d, $J=8.6$ Hz, 1H), 7.54 (d, $J=8.2$ Hz, 2H), 7.54 (d, $J=8.2$ Hz, 1H), 7.32~7.27 (m, 3H), 7.01 (d, $J=7.8$ Hz, 2H), 6.55 (d, $J=8.0$ Hz, 2H), 5.87~5.83 (m, 1H), 4.17 (dd, $J=11.2, 6.8$ Hz, 1H), 3.32 (s, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 2.18 (ddd, $J=14.1, 7.1, 2.5$ Hz, 1H), 1.20 (ddd, $J=14.1, 11.9, 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 154.2, 149.2, 144.8, 137.2, 136.6, 133.4, 130.5, 130.0 (2C), 129.5 (2C), 128.0 (2C), 127.6 (2C), 123.9, 123.4, 123.1, 116.1, 111.9, 80.5, 35.7, 35.2, 21.7, 21.2. HRMS (ESI-TOF) calcd for $\text{C}_{25}\text{H}_{22}\text{ClNO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 490.0856; found 490.0847. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=11.42$ min (major), 27.36 min (minor).

(2*R*,4*S*)-7-Chloro-4-(2-methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3be**): Light yellow solid, 44.5 mg, 93% yield, m.p. 162~163 °C; $[\alpha]_{\text{D}}^{20}+173$ (CH_2Cl_2 , c 0.3); ^1H NMR (400 MHz, Chloroform- d) δ : 8.11 (d, $J=8.6$ Hz, 1H), 7.52 (d, $J=8.2$ Hz, 2H), 7.37~7.35 (m, 1H), 7.30~7.17 (m, 4H), 6.86 (d, $J=8.2$ Hz, 1H), 6.68 (t, $J=7.4$ Hz, 1H), 6.14 (d, $J=6.9$ Hz, 1H), 5.84 (s, 1H), 4.73 (dd, $J=11.4, 7.0$ Hz, 1H), 3.79 (s, 3H), 3.31 (brs, 1H), 2.39 (s, 3H), 2.30 (ddd, $J=13.9, 7.0, 2.4$ Hz, 1H), 1.12~0.98 (m, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 157.2, 154.1, 149.5, 144.6, 133.4, 130.3, 130.0 (2C), 128.4, 128.1, 127.9 (2C), 127.7, 123.8, 123.6, 123.0,

120.5, 116.7, 111.9, 110.7, 80.5, 55.5, 33.6, 29.2, 21.7. HRMS (ESI-TOF) calcd for $\text{C}_{25}\text{H}_{22}\text{ClNO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 506.0805; found 506.0808. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=75/25$, 1.0 mL/min, 220 nm], $t_{\text{R}}=13.57$ min (major), 23.96 min (minor).

(2*R*,4*S*)-7-Chloro-4-(4-methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bf**): Light yellow solid, 43.5 mg, 91% yield, m.p. 161~162 °C; $[\alpha]_{\text{D}}^{20}+245$ (CH_2Cl_2 , c 0.1); ^1H NMR (400 MHz, Chloroform- d) δ : 8.11 (d, $J=8.5$ Hz, 1H), 7.51 (d, $J=7.7$ Hz, 2H), 7.35~7.32 (m, 1H), 7.31~7.25 (m, 3H), 6.71 (d, $J=8.0$ Hz, 2H), 6.54 (d, $J=7.9$ Hz, 2H), 5.83 (s, 1H), 4.13 (dd, $J=11.5, 7.1$ Hz, 1H), 3.77 (s, 3H), 2.84 (s, 1H), 2.43 (s, 3H), 2.17 (dd, $J=14.1, 7.1$ Hz, 1H), 1.17 (t, $J=12.8$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 159.0, 154.2, 149.3, 144.8, 133.5, 131.6, 130.6, 130.1 (2C), 128.7 (2C), 128.0 (2C), 123.9, 123.4, 123.1, 116.1, 114.2 (2C), 112.0, 80.5, 55.4, 35.3, 35.3, 21.8. HRMS (ESI-TOF) calcd for $\text{C}_{25}\text{H}_{22}\text{ClNO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 506.0805; found 506.0797. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=75/25$, 1.0 mL/min, 220 nm], $t_{\text{R}}=11.94$ min (major), 28.22 min (minor).

(2*R*,4*S*)-7-Chloro-4-(2-chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bg**): Light yellow solid, 43.8 mg, 90% yield, m.p. 186~187 °C; $[\alpha]_{\text{D}}^{20}+251$ (CH_2Cl_2 , c 0.2); ^1H NMR (400 MHz, Chloroform- d) δ : 8.12 (d, $J=8.6$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 2H), 7.37~7.34 (m, 1H), 7.34~7.27 (m, 2H), 7.26~7.21 (m, 2H), 7.15 (t, $J=7.7$ Hz, 1H), 6.96 (t, $J=7.5$ Hz, 1H), 6.20 (d, $J=7.6$ Hz, 1H), 5.85 (d, $J=2.1$ Hz, 1H), 4.73 (dd, $J=11.4, 7.0$ Hz, 1H), 3.02 (s, 1H), 2.37 (s, 3H), 2.36~2.30 (m, 1H), 1.04 (t, $J=12.8$ Hz, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 154.2, 148.0, 144.8, 137.6, 134.0, 133.5, 130.8, 130.0 (2C), 130.0, 128.7, 128.4, 127.9 (2C), 127.0, 124.0, 123.3, 123.2, 117.1, 112.0, 80.4, 33.2, 33.1, 21.7. HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{19}\text{Cl}_2\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 510.0310; found 510.0300. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=75/25$, 1.0 mL/min, 220 nm], $t_{\text{R}}=11.59$ min (major), 24.25 min (minor).

(2*R*,4*S*)-7-Chloro-4-(4-nitrophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bh**): Light yellow solid, 44.6 mg, 90% yield, m.p. 190~191 °C; $[\alpha]_{\text{D}}^{20}+250$ (CH_2Cl_2 , c 0.16); ^1H NMR (400 MHz, Chloroform- d) δ : 8.12 (d, $J=8.6$ Hz, 1H), 8.03 (d, $J=8.8$ Hz, 2H), 7.52 (d, $J=8.3$ Hz, 2H), 7.35~7.27 (m, 4H), 6.81 (d, $J=8.7$ Hz, 2H), 5.87~5.84 (m, 1H), 4.31 (dd, $J=11.6, 7.1$ Hz, 1H), 3.19 (s, 1H), 2.44 (s, 3H), 2.23 (ddd, $J=14.0, 7.1, 2.6$ Hz, 1H), 1.18~1.08 (m, 1H); ^{13}C NMR (100 MHz, Chloroform- d) δ : 154.3, 147.6, 147.4, 147.1, 145.1, 133.4, 131.2, 130.1 (2C), 128.6 (2C), 128.0 (2C), 124.3, 124.0 (2C), 123.4, 123.0, 117.0, 112.0, 80.1, 36.0, 34.9, 21.8. HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{20}\text{ClN}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 499.0731; found 499.0703. HPLC [Chiralpak IF, $V(n\text{-hexane})/V(i\text{-propanol})=80/20$, 1.0 mL/min, 254 nm], $t_{\text{R}}=21.77$ min (major), 51.22 min (minor).

(2*R*,4*S*)-7-Chloro-4-(2-nitrophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bi**): Light yellow

solid, 42.6 mg, 86% yield, m.p. 157~158 °C; $[\alpha]_D^{20} + 370$ (CH₂Cl₂, *c* 0.1); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.11 (d, *J*=8.5 Hz, 1H), 7.88 (d, *J*=8.1 Hz, 1H), 7.54 (d, *J*=8.0 Hz, 2H), 7.34~7.25 (m, 6H), 6.25 (d, *J*=7.7 Hz, 1H), 5.89 (s, 1H), 4.82 (dd, *J*=11.2, 6.9 Hz, 1H), 3.04 (s, 1H), 2.62 (dd, *J*=13.7, 6.9 Hz, 1H), 2.39 (s, 3H), 1.14 (t, *J*=12.3 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 149.8, 147.5, 144.8, 135.2, 133.7, 132.9, 131.0, 130.1 (2C), 129.4, 128.4, 128.0 (2C), 124.9, 124.2, 123.3, 123.2, 117.7, 112.0, 80.3, 34.5, 32.3, 21.7. HRMS (ESI-TOF) calcd for C₂₄H₁₉ClN₂O₆Na [M+H]⁺: 521.0550; found 521.0550. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=80/20, 1.0 mL/min, 254 nm], *t*_R=29.52 min (major), 49.55 min (minor).

(2*R*,4*S*)-7-Chloro-4-(3-chlorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bj**): Light yellow solid, 41.6 mg, 85% yield, m.p. 193~194 °C; $[\alpha]_D^{20} + 289$ (CH₂Cl₂, *c* 0.2); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.12 (d, *J*=8.6 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 2H), 7.38~7.28 (m, 4H), 7.22~7.12 (m, 2H), 6.75 (d, *J*=7.2 Hz, 1H), 6.48 (s, 1H), 5.83 (s, 1H), 4.16 (dd, *J*=11.7, 7.0 Hz, 1H), 2.88 (s, 1H), 2.42 (s, 3H), 2.17 (dd, *J*=12.2, 7.0 Hz, 1H), 1.06 (t, *J*=12.9 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.3, 148.1, 145.2, 141.8, 134.7, 133.3, 130.9, 130.3 (2C), 130.1, 127.8, 127.8 (2C), 127.2, 126.6, 124.1, 123.3, 123.2, 116.6, 112.0, 80.3, 35.9, 35.0, 21.9. HRMS (ESI-TOF) calcd for C₂₄H₁₉Cl₂NO₄Na [M+Na]⁺: 510.0310; found 510.0306. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=75/25, 1.0 mL/min, 220 nm], *t*_R=8.90 min (major), 24.27 min (minor).

(2*R*,4*S*)-7-Chloro-4-(2,6-difluorophenyl)-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bk**): Light yellow solid, 45.0 mg, 93% yield, m.p. 161~162 °C; $[\alpha]_D^{20} + 148$ (CH₂Cl₂, *c* 0.4); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.10 (dd, *J*=7.9, 1.2 Hz, 1H), 7.51 (d, *J*=8.2 Hz, 2H), 7.33~7.12 (m, 7H), 6.69~6.60 (m, 2H), 5.86~5.80 (m, 1H), 4.22 (dd, *J*=11.6, 7.1 Hz, 1H), 3.02 (brs, 1H), 2.41 (s, 3H), 2.20 (ddd, *J*=14.2, 7.2, 2.6 Hz, 1H), 1.20 (ddd, *J*=14.2, 11.6, 2.6 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 162.8 (d, *J*=7.6 Hz, 1C), 160.3 (d, *J*=7.7 Hz, 1C), 153.8, 146.6, 144.5, 134.1, 130.3, 130.0 (2C), 129.2 (t, *J*=10.46 Hz, 1C), 127.7 (2C), 123.8, 123.3, 123.2, 115.1, 114.5 (t, *J*=16.61 Hz, 1C), 111.8, 111.8, 111.6 (d, *J*=16.61 Hz, 1C), 79.9, 30.8, 25.4, 21.7. HRMS (ESI-TOF) calcd for [C₂₄H₁₈ClF₂NO₄Na [M+Na]⁺ 512.0511; found 512.0509; HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=75/25, 1.0 mL/min, 220 nm], *t*_R=10.84 min (major), 22.81 min (minor).

(2*R*,4*S*)-7-Chloro-4-phenyl-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-ol (**3bl**): Light yellow solid, 41.5 mg, 93% yield, m.p. 190~191 °C [Lit.^[15a] 204~206 °C]; $[\alpha]_D^{20} + 336$ (CH₂Cl₂, *c* 0.2); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.11 (d, *J*=8.6 Hz, 1H), 7.51 (d, *J*=8.2 Hz, 2H), 7.35~7.33 (m, 1H), 7.31~7.26 (m, 3H), 7.23~7.15 (m, 3H), 6.63 (d, *J*=6.9 Hz, 2H), 5.84 (d, *J*=2.5 Hz, 1H), 4.17 (dd, *J*=11.7, 7.1 Hz, 1H), 2.93 (t, *J*=2.4 Hz, 1H), 2.42 (s, 3H), 2.20 (ddd, *J*=14.2, 7.1, 2.5 Hz, 1H),

1.19 (ddd, *J*=14.0, 11.8, 2.4 Hz, 1H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 154.2, 149.0, 144.8, 139.8, 133.4, 130.6, 130.1 (2C), 128.8 (2C), 128.0 (2C), 127.7 (2C), 127.5, 124.0, 123.3, 123.2, 116.2, 112.0, 80.4, 36.1, 35.2, 21.7. HPLC [Chiralpak IF, *V*(*n*-hexane)/*V*(*i*-propanol)=75/25, 1.0 mL/min, 220 nm], *t*_R=10.66 min (major), 32.78 min (minor).

(2*S*,4*S*)-4-Propyl-1-tosyl-1,2,3,4-tetrahydrobenzofuro[3,2-*b*]pyridin-2-yl acetate (**3bm**): Oil, 37.5 mg, 43% yield; $[\alpha]_D^{20} + 67$ (MeOH, *c* 0.07); ¹H NMR (400 MHz, Chloroform-*d*) δ : 8.16~8.05 (m, 1H), 7.54 (d, *J*=8.1 Hz, 2H), 7.50~7.41 (m, 1H), 7.36~7.28 (m, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 6.75 (t, *J*=2.8 Hz, 1H), 3.01~2.90 (m, 1H), 2.41 (s, 3H), 2.07~2.01 (m, 1H), 1.99 (s, 3H), 1.70~1.56 (m, 1H), 1.31~1.18 (m, 1H), 1.13~0.95 (m, 3H), 0.84 (t, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, Chloroform-*d*) δ : 169.0, 153.8, 149.6, 144.5, 133.9, 129.8, 127.9, 124.4, 124.4, 123.1, 122.4, 115.8, 111.1, 79.1, 33.7, 30.4, 28.9, 21.6, 21.1, 19.0, 14.2; HRMS (ESI-TOF) calcd for C₂₄H₁₈ClF₂NO₄Na [M+Na]⁺: 450.1360; found 450.1346; HPLC [Chiralpak AS, *V*(*n*-hexane)/*V*(*i*-propanol)=98/2, 1.0 mL/min, 254 nm], *t*_R=18.9 min (minor), 21.1 min (major).

Supporting Information ¹H NMR and ¹³C NMR spectra of **3aa**~**3bm**, X-ray crystallographic data of **3bc**. The Supporting Information is available free of charge via the Internet at <http://siooc-journal.cn/>.

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(Li, L.; Fan, Y.)