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A mild and metal-free synthesis of chiral 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines

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ABSTRACT

Various functionalized enantiomerically pure 3-hydroxymethyl-1,4-benzoxazine derivatives, including four stereoisomers, were synthesized from chiral 2,3-epoxy-4-trityloxybutanol. The synthesis was mild and metal-free. Yields of 52%–94%, and stereoselectivities of 95% to >99% ee, were obtained. The mechanism was investigated using online Fourier-transform infrared spectroscopy. This revealed a base-promoted cyclization to form tricycle-fused benzoxazinyl-oxazolidinone intermediates in situ, followed by a hydrolysis process. The method can be easily scaled and carried out in a one-pot manner. The usefulness of the obtained chiral 3-hydroxymethyl-1,4-benzoxazine derivatives as building blocks was showcased by further derivatization to form unique tricycle-fused benzoxazines.

1. Introduction

2,3-Dihydro-1,4-benzoxazines are key structural scaffolds that are frequently found in many bioactive molecules and pharmaceutical agents [1]. Some of these compounds with the 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine motif exhibit biological activities such as antiproliferation [2], apoptotic regulation [3], adrenoceptor antagonism [4], androgen receptor modulation [5] and antitumor activity [6] (Fig. 1).

A number of methods for the synthesis of 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine analogues have been reported (Scheme 1). Chiral 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines can be obtained from 2-aminophenol and epoxides [7,8]. Enantiomerically pure 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines have been prepared from chiral aziridines via Pd-catalyzed intramolecular C–N bond formation [9]. Zhou's group reported the synthesis of 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines from 1,2-epoxy-3-(2-nitroaryloxy)propanes in the presence of Hantzsch 1,4-dihydropyridine (HEH), with Pd/C as a catalyst [10]. However, only racemic 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines could be synthesized using this procedure. Although some efforts have been devoted to the development of methods for the preparation of 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine, strategies for enantioselective synthesis are insufficient. Additionally, the reported methods suffer from limitations such as high temperatures, use of expensive metals, and limited substrate scope. Therefore, there is a need for the development of mild, efficient, and enantioselective syntheses for 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines.

The chiral β-amino alcohol motif is a useful building block with many applications, including the production of various natural products [11], medicinally active compounds [12], and chiral auxiliaries in organic synthesis [13]. In this work, we present our construction of enantiomerically pure multi-functional 2,3-dihydro-1,4-benzoxazines with the chiral 1,2-amino alcohol motif under mild conditions, starting from propyl (2-((3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamates (Scheme 2).

2. Results and discussion

Previously, we developed an efficient and mild one-pot

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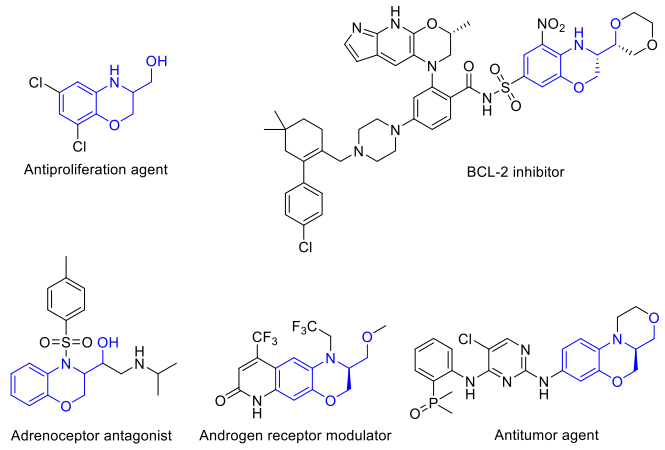
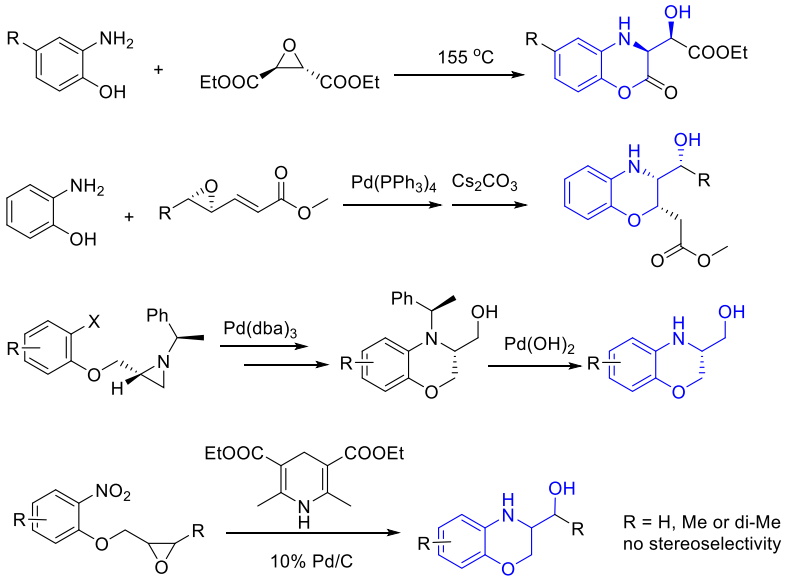
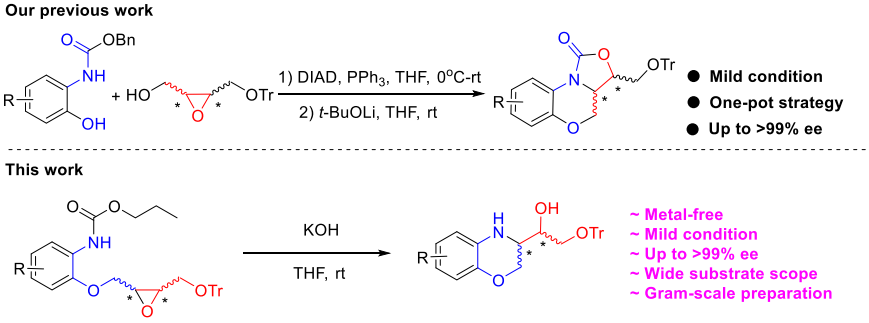


Fig. 1. Representative compounds with 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine scaffolds.

convergent synthesis for benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one derivatives [14]. We achieved the cyclization step by using *t*-BuOLi (Scheme 2). When screening bases for cyclization using benzyl carbamate as the starting material and 1.5 equiv. of KOH, we obtained a mixture of tricyclic fused benzoxazinyl-oxazolidinone and 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine. Considering the functionalized 1,4-benzoxazine skeleton, we wondered if it would be possible to obtain pure 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine from the epoxide substrate by optimizing the reaction conditions. First, to optimize the starting material, we explored the reactivity of carbamates **1a**–**c** at room temperature in the presence of KOH (2 equiv.) and in anhydrous THF under the protection of argon (Table 1, entries 1–3). We found that the desired product **2a** was isolated with a yield of 78% and 98% ee when *n*-propyl carbamate **1a** was used (entry 1), although 6% of the tricyclic compound **3** was obtained. However, when *i*-propyl carbamate **1b** and *t*-butyl carbamate **1c** were used as raw materials, much more tricyclic product **3** was observed in both reactions, and the corresponding product **2a** was obtained with a yield of about 60% (entries 2–3). These results indicate that steric hindrance has a large influence on the reactivity, and the carbamate with a small ester group benefits the desired reaction. We continued our study by choosing **1a** as the model substrate. After briefly screening the solvent in the presence of KOH (entries 4–6), a slightly improved yield of **2a** was achieved in MeCN (entry 6 vs 3). However, a large amount of solid precipitate formed in MeCN led to difficult stirring. This suggests that MeCN is not a good solvent for large-scale reaction. Next, we investigated the influence of the base on the reaction (entries 7–9). The results show that potassium alkali results

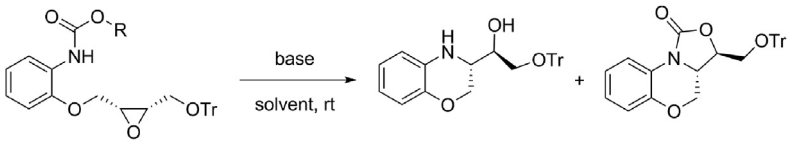


Scheme 1. Reported strategies for the construction of 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine scaffolds.



Scheme 2. Synthesis of benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-ones and 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines.

Table 1
Optimization of the reaction conditions[a].



entry	substrate	base	equiv.	solvent	ratio of 1/2a/3[b]	yield[c](%)	ee%
1	**1a**	KOH	2	THF	-/94/6	78	98
2	**1b**	KOH	2	THF	-/75/25	60	–
3	**1c**	KOH	2	THF	-/80/20	66	–
4	**1a**	KOH	2	DMF	-/84/16	70	–
5	**1a**	KOH	2	Dioxane	38/43/19	–	–
6	**1a**	KOH	2	MeCN	-/91/9	84	98
7	**1a**	NaOH	2	THF	12/51/37	–	–
8	**1a**	EtOK	2	THF	-/79/21	60	–
9	**1a**	EtONa	2	THF	15/58/27	–	–
10	**1a**	KOH	2.5	THF	-/100/-	94	98
11[d]	**1a**	KOH	2.5	THF	-/42/58	–	–

[a] Reaction conditions: **1** (0.4 mmol), anhydrous solvent (5 mL), Ar, rt, 4 h. Substrates **1a**–**c** were prepared from compounds **A1**–**3** and **B1** according to the literature [14] (Supporting Information Scheme S1).
[b] Determined by ^{1}H NMR.
[c] Isolated yields.
[d] Analytically pure THF, 11 h.

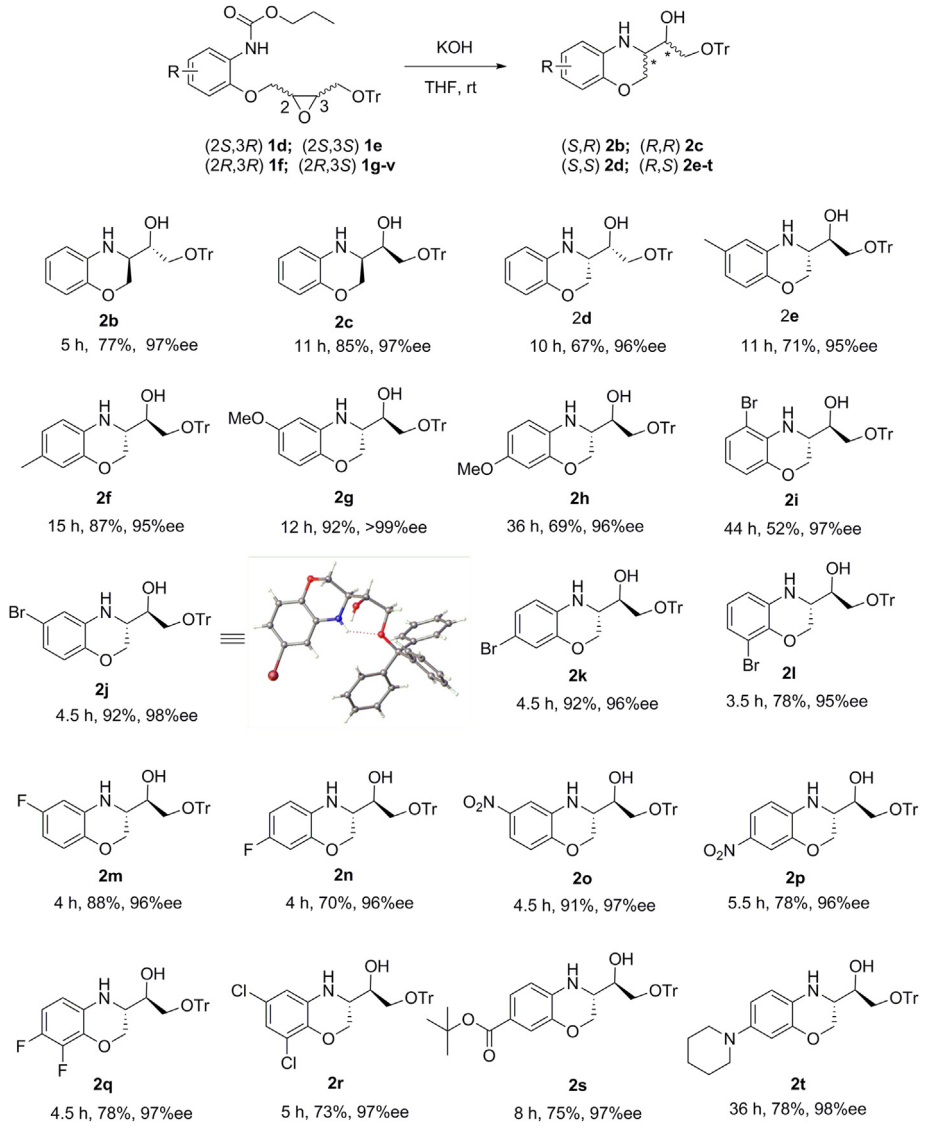
in greater conversion of starting material than sodium alkali, with KOH resulting in the greatest conversion. Upon increasing the amount of KOH to 2.5 equiv., product **2a** was obtained with a yield of 94% and 98% ee (entry 10). In addition, analytically pure THF (entry 11) was also investigated. However, it took 9 h to finish the transformation of the substrate **1a** to the intermediate **3**, and the intermediate **3** could not convert to product **2a** completely, even prolonging the reaction time to 11 h. Therefore, anhydrous THF was crucial for the reaction. On the basis of these studies, the optimal reaction conditions for the preparation of **2a** were established, as shown in entry 10.

Having optimized the reaction conditions, we next investigated the reaction scope. There are two chiral centers in the epoxy structure of the substrate, and we first explored the influence of the configuration of these on the reactivity (Scheme 3). Substrates **1d**–**f** were prepared from compounds **A1** and **B2**–**4** according to the literature [14] (Supporting Information Scheme S2). A longer reaction time was needed to produce (1*R*, 3*R*)-**2c** or (1*S*, 3*S*)-**2d** compared with the time needed to produce (1*R*, 3*S*)-**2a** or (1*S*, 3*R*)-**2b**. The three stereoisomers **2b**–**d** were obtained with yields of 67%–85% and enantioselectivities of 96%–97% ee, providing a general approach for accessing different chiral 1,4-benzoxazine bearing *β*-amino alcohol units. Next, substrates with different substituents on the phenyl ring were examined (Scheme 3). Generally, both electron-withdrawing groups and electron-donating groups on the benzene rings were compatible with the reaction conditions, delivering the desired products (**2e**–**t**) with yields of 52%–92% and 95% to >99% ee. Although a longer reaction time was required (11–36 h), the expected products were isolated with yields of 69%–92% (**2e**–**h**) in the presence of electron-donating methoxy and methyl groups on the benzene ring. With electron-withdrawing substituents on the phenyl ring, the reaction proceeded smoothly compared to that of the substrates with electron-donating groups, which the desired benzoxazines (**2j**–**r**) were afforded in 3.5–5.5 h. Unexpectedly, for the substrate with bromine at the ortho-position to the carbamate group on the aromatic ring, a long reaction time up to 44 h was needed to produce **2i** with a yield of 52% and 97% ee. We suggest that the reactivity was mainly affected by the steric hindrance exemplified by **2i** vs **2j**–**l**. The *tert*-butoxycarbonyl group and piperidyl group were also tolerated by the reaction, giving the corresponding products **2s** and **2t** with yields of 75% and 78%, respectively. The absolute configuration of compound **2j** was confirmed by X-ray crystallography. Substrates **1g**–**v** were prepared from compounds **A4**–**19** and **B1** according to the literature [14] (Supporting Information Scheme S3).

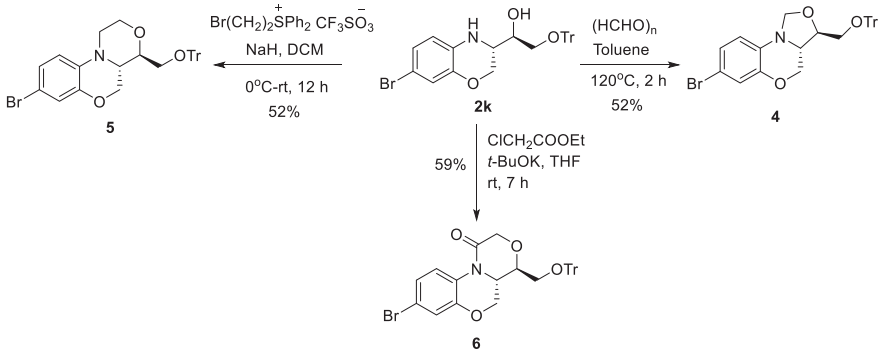
To demonstrate the usefulness of the obtained chiral functionalized 1,4-benzoxazine derivatives as building blocks, we used bromine-containing compound **2k** as a substrate to expand new three series of tricyclic fused derivatives (Scheme 4). First, **2k** was reacted with paraformaldehyde [15] to obtain benzoxazinyl-oxazolidine **4** with a yield of 52%. Second, **2k** was treated with bromoethylsulfonium salt [16], and benzoxazinyl-morpholine **5** was obtained with a yield of 52%. Compound **2k** can also react with ethyl chloroacetate [17] in the presence of *t*-BuOK to afford the desired product benzoxazinyl-morpholinone **6** with a yield of 59%. The potential of **2k** in a diverse range of synthesis applications shows that the multi-functional chiral 1,4-benzoxazine derivatives are promising building blocks which will facilitate the establishment of a diverse library of bioactive samples.

Next, the scalability of the method was explored (Scheme 5). The reaction was extended up to the gram-scale (up to 3.4 g) and the product **2k** was obtained with a yield of 97% and enantioselectivity of 98% ee. To further simplify the reaction, we investigated the possibility of carrying it out in a one-pot manner by adding KOH (5 equiv.) directly to the Mitsunobu reaction mixture of propyl (4-bromo-2-hydroxyphenyl)carbamate (**A10**) and ((2*R*,3*S*)-3-((trityloxy)methyl)oxiran-2-yl)methanol (**B1**). This reaction proceeded successfully, and **2k** was obtained with a yield of 87% without the loss of any enantiomeric excess (98% ee). This further confirms the convenience of the protocol in this study.

In the light of our experimental observations, we propose that

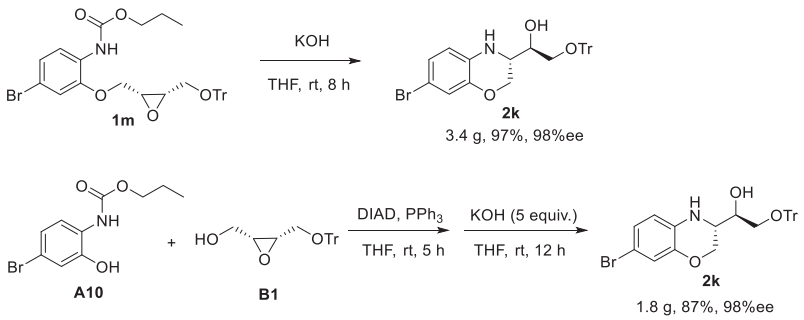


Scheme 3. Synthesis of products **2b**–**t**[a].



Scheme 4. Diverse synthesis applications of building block **2k**.

the reaction involves a cyclization followed by a hydrolysis process. To verify this, online Fourier-transform infrared spectroscopy (FTIR) was used to monitor the reaction using **1a** and KOH in anhydrous THF. First, we collected FTIR data for the starting material **1a**, the intermediate **3** and the product **2a** in THF. ConcIRT and 3D surface plot analyses were used to track changes in the absorbance profiles of **1a**, **3** and **2a** over time. These changes are shown in Figs. 2 and 3. After adding KOH, the peak height at 1737 cm^{-1} (C═O bond of **1a**,



Scheme 5. Gram-scale and one-pot preparation of **2k**.

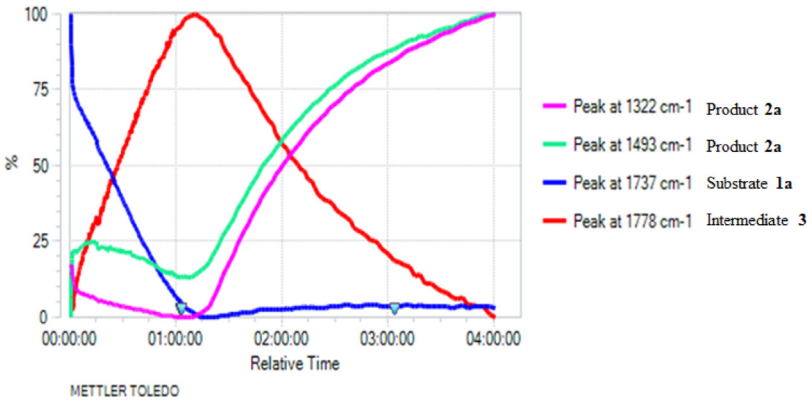


Fig. 2. ConcIRT component profiles of the reaction.

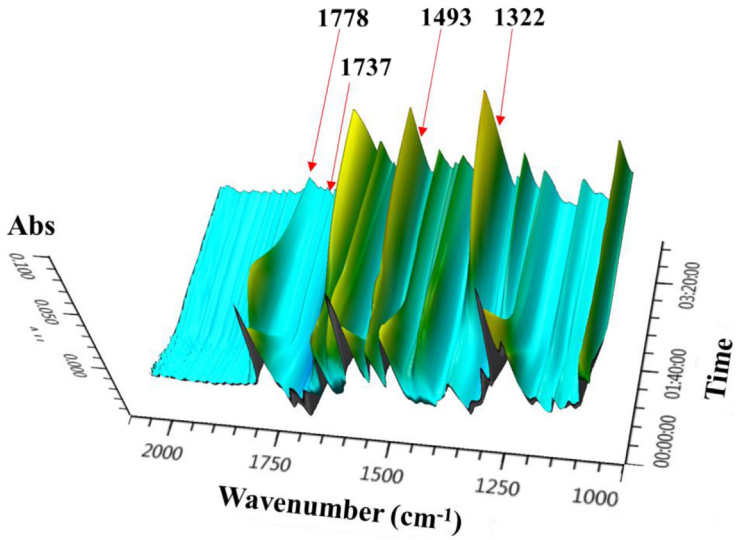


Fig. 3. In situ IR 3D surface plot of the reaction.

blue line) decreased over 1 h. Meanwhile, the peak height at 1778 cm^{-1} (C═O bond of **3**, red line) increased, reached a peak after 1 h, and then decreased. This demonstrates the formation of the intermediate **3**. The peak heights at 1322 cm^{-1} and 1493 cm^{-1} increased over this time because of the formation of product **2a**. On the basis of this experiment, we concluded that the reaction proceeds via the cyclization of **1a** to generate the intermediate **3**, and then **3** undergoes a hydrolysis process to produce the final product **2a**.

3. Conclusion

In conclusion, we have developed a simple and metal-free strategy for the synthesis of a series of chiral multi-functional 2,3-dihydro-1,4-benzoxazines containing the 1,2-amino alcohol unit. The reaction proceeds smoothly under mild conditions with yields of 52%–94% and 95% to >99% ee. The reaction has potential for the preparation of the desired product from phenol derivatives and ((2*R*,3*S*)-3-((trityloxy)methyl)oxiran-2-yl)methanol using a

one-pot convergent cyclization procedure. Furthermore, tricyclic fused benzoxazinyl-oxazolidine, benzoxazinyl-morpholine and benzoxazinyl-morpholinone have been prepared conveniently from 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine. Mechanistic investigation reveals a base-promoted cyclization to form the tricyclic fused benzoxazinyl-oxazolidinone intermediates in situ, followed by a hydrolysis process. Applications of these functionalized optically active 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines will be the subject of future investigations in our laboratory.

4. Experimental section

Unless otherwise stated, all the solvents and reagents were purchased from commercial suppliers and were used without further purification. All melting points were measured with a micro melting point apparatus (MP-J3, Yanaco) and were uncorrected. ^{1}H NMR or ^{13}C NMR spectra were recorded on Varian 400 MHz or 500 MHz spectrometer using $CDCl_3$, DMSO-d_6 or acetone-d_6 as solvents. HR-MS spectra were obtained on a Thermo Fisher Exactive Plus mass spectrometer (ESI, ThermoFisher Scientific, Bremen, Germany). Optical rotations were measured with a Rudolph Research Analytical (Autopol IV-T).

4.1. Preparation of phenol derivatives A1–19

Propyl (2-hydroxyphenyl)carbamate (A1). A mixture of 2-aminophenol (2.7 g, 25 mmol), sodium bicarbonate (4.2 g, 50 mmol), THF (30 mL) and water (15 mL) was cooled in an ice bath under the protection of argon. Propyl chloroformate (2.9 mL, 26 mmol) was added in dropwise to the above reaction mixture. After completion monitored by TLC, ethyl acetate was added, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (25% EtOAc in PE) to give **A1** (4.5 g, 92%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.66 (s, 1 H), 8.16 (s, 1 H), 7.55 (d, J = 7.6 Hz, 1 H), 6.92–6.88 (m, 1 H), 6.83 (dd, J = 1.6, 8.0 Hz, 1 H), 6.79–6.73 (m, 1 H), 4.01 (t, J = 6.8 Hz, 2 H), 1.66–1.57 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{14}NO_3$: 196.0968; found: 196.0967.

Isopropyl (2-hydroxyphenyl)carbamate (A2). Compound **A2** was prepared from 2-aminophenol and isopropyl chloroformate following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 20% EtOAc in PE. Yellow solid (3.2 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.67 (s, 1 H), 8.03 (s, 1 H), 7.56 (d, J = 7.6 Hz, 1 H), 6.91–6.73 (m, 3 H), 4.89–4.83 (m, 1 H), 1.24 (d, J = 6.4 Hz, 6 H). HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{14}NO_3$: 196.0968; found: 196.0970.

tert-Butyl (2-hydroxyphenyl)carbamate (A3). To a suspension of 2-aminophenol (7.63 g, 70 mmol) in DCM (80 mL) was added a solution of Boc_2O (15.3 g, 70 mmol) in DCM (20 mL). The mixture was stirred at room temperature overnight. After concentration, the residue was purified by column chromatography (10–20% EtOAc in PE) to give **A3** (13.8 g, 95%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (brs, 1 H), 7.10–7.01 (m, 2 H), 6.97 (dd, J = 1.2, 8.4 Hz, 1 H), 6.89–6.81 (m, 1 H), 6.63 (brs, 1 H), 1.53 (s, 9 H).

Propyl (2-hydroxy-5-methylphenyl)carbamate (A4). Compound **A4** was prepared from 2-amino-4-methylphenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 15% EtOAc in PE. Pink solid (1.55 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.39 (s, 1 H), 8.10 (s, 1 H), 7.38 (s, 1 H), 6.70 (s, 2 H), 4.00 (t, J = 6.8 Hz, 2 H), 2.18 (s, 3 H), 1.65–1.57 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{16}NO_3$: 210.1125; found: 210.1121.

Propyl (2-hydroxy-4-methylphenyl)carbamate (A5). Compound **A5** was prepared from 2-amino-5-methylphenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 25% EtOAc in PE. White solid (1.58 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.49 (s, 1 H), 8.10 (s, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 6.64 (d, J = 1.6 Hz, 1 H), 6.56 (dd, J = 1.6, 8.4 Hz, 1 H), 3.99 (t, J = 6.8 Hz, 2 H), 2.18 (s, 3 H), 1.65–1.56 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H). HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{16}NO_3$: 210.1125; found: 210.1122.

Propyl (2-hydroxy-5-methoxyphenyl)carbamate (A6). Compound **A6** was prepared from 2-amino-4-methoxyphenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 15% EtOAc in PE. Pink solid (1.45 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.21 (s, 1 H), 8.12 (s, 1 H), 7.28 (d, J = 2.0 Hz, 1 H), 6.74 (d, J = 8.8 Hz, 1 H), 6.48 (dd, J = 3.2, 8.8 Hz, 1 H), 4.02 (t, J = 6.8 Hz, 2 H), 3.65 (s, 3 H), 1.66–1.58 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{11}H_{14}NO_4$: 224.0917; found: 224.0915.

Propyl (2-hydroxy-4-methoxyphenyl)carbamate (A7). A mixture of 5-methoxy-2-nitrophenol (1 g, 5.9 mmol), Raney nickel (0.3 g) and THF (10 mL) was hydrogenated at 20–50 psi for 5 h. The reaction mixture was filtered into a flask containing sodium bicarbonate (1 g, 11.8 mmol) and water (15 mL) under ice bath, protected by argon. Propyl chloroformate (0.69 mL, 6.2 mmol) was added dropwise, and the mixture was stirred for 2 h. Ethyl acetate was added, and then the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in PE) to give **A7** (1.03 g, 77%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.57 (s, 1 H), 8.11 (brs, 1 H), 7.26 (d, J = 6.0 Hz, 1 H), 6.41 (d, J = 2.8 Hz, 1 H), 6.34 (dd, J = 2.8, 8.4 Hz, 1 H), 3.97 (t, J = 6.8 Hz, 2 H), 3.67 (s, 3 H), 1.64–1.55 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{11}H_{14}NO_4$: 224.0917; found: 224.0917.

Propyl (2-bromo-6-hydroxyphenyl)carbamate (A8). To a mixture of 2-amino-3-bromophenol (1 g, 5.3 mmol) and calcium carbonate powder (330 mg, 3.3 mmol) in 1,4-dioxane (6 mL) was added propyl chloroformate (0.62 mL, 5.6 mmol). The reaction mixture was heated at 70 °C. After completion monitored by TLC, water was added. The resulting mixture was extracted with ethyl acetate, and then the organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in PE) to give **A8** (1.35 g, 92%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.82 (s, 1 H), 8.49 (brs, 1 H), 7.04 (dd, J = 1.6, 8.0 Hz, 1 H), 7.00 (t, J = 8.0 Hz, 1 H), 6.84 (dd, J = 2.0, 8.0 Hz, 1 H), 3.93 (t, J = 6.4 Hz, 2 H), 1.57 (brs, 2 H), 0.88 (brs, 3 H). HR-MS (ESI): m/z [M+H]$^+$ calcd for $C_{10}H_{13}BrNO_3$: 274.0073; found: 274.0064.

Propyl (5-bromo-2-hydroxyphenyl)carbamate (A9). Compound **A9** was prepared from 2-amino-4-bromophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 20% EtOAc in PE. Off-white solid (1.12 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.08 (s, 1 H), 8.33 (s, 1 H), 7.80 (d, J = 2.0 Hz, 1 H), 7.05 (dd, J = 2.4, 8.8 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 4.03 (t, J = 6.8 Hz, 2 H), 1.67–1.58 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}BrNO_3$: 271.9917; found: 271.9923.

Propyl (4-bromo-2-hydroxyphenyl)carbamate (A10). Compound **A10** was prepared from 2-amino-5-bromophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 15% EtOAc in PE. Off-white solid (1.17 g, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.22 (s, 1 H), 8.29 (s, 1 H), 7.52 (d, J = 8.4 Hz, 1 H), 6.99–6.91 (m, 2 H), 4.01 (t, J = 6.8 Hz, 2 H), 1.66–1.57 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}BrNO_3$: 271.9917; found: 271.9921.

Propyl (3-bromo-2-hydroxyphenyl)carbamate (A11).

Compound **A11** was prepared from 2-amino-6-bromophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 8–15% EtOAc in PE. Off-white solid (900 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.47 (s, 1 H), 8.72 (brs, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.27 (dd, J = 1.6, 8.0 Hz, 1 H), 6.76 (t, J = 8.0 Hz, 1 H), 4.03 (t, J = 6.8 Hz, 2 H), 1.67–1.58 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}BrNO_3$: 271.9917; found: 271.9923.

Propyl (5-fluoro-2-hydroxyphenyl)carbamate (A12). Compound **A12** was prepared from 2-amino-4-fluorophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 10–20% EtOAc in PE. Purple solid (1.25 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.75 (s, 1 H), 8.29 (s, 1 H), 7.51 (dd, J = 2.8, 10.8 Hz, 1 H), 6.80 (dd, J = 5.6, 8.8 Hz, 1 H), 6.74–6.67 (m, 1 H), 4.03 (t, J = 6.8 Hz, 2 H), 1.67–1.58 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}FNO_3$: 212.0717; found: 212.0714.

Propyl (4-fluoro-2-hydroxyphenyl)carbamate (A13). Compound **A13** was prepared from 2-amino-5-fluorophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 7–15% EtOAc in PE. Pink solid (1.44 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (brs, 1 H), 8.25 (brs, 1 H), 7.43 (brs, 1 H), 6.64–6.56 (m, 2 H), 3.99 (t, J = 6.8 Hz, 2 H), 1.65–1.58 (m, 2 H), 0.91 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}FNO_3$: 212.0717; found: 212.0716.

Propyl (2-hydroxy-5-nitrophenyl)carbamate (A14). Compound **A14** was prepared from 2-amino-4-nitrophenol following the preparation method of **A8**. Flash column chromatography was performed eluting the column with 35% EtOAc in PE. Pale yellow solid (1.15 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (s, 1 H), 8.66 (s, 1 H), 8.63 (d, J = 2.8 Hz, 1 H), 7.88 (dd, J = 2.8, 8.8 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 1 H), 4.07 (t, J = 6.8 Hz, 2 H), 1.69–1.60 (m, 2 H), 0.94 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}N_2O_5$: 239.0662; found: 239.0662.

Propyl (2-hydroxy-4-nitrophenyl)carbamate (A15). Compound **A15** was prepared from 2-amino-5-nitrophenol following the preparation method of **A8**. Flash column chromatography was performed eluting the column with 30% EtOAc in PE. Pink solid (1.3 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.96 (s, 1 H), 8.70 (brs, 1 H), 8.02 (d, J = 9.2 Hz, 1 H), 7.74 (dd, J = 2.8, 9.2 Hz, 1 H), 7.64 (d, J = 2.8 Hz, 1 H), 4.08 (t, J = 6.8 Hz, 2 H), 1.69–1.60 (m, 2 H), 0.94 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{11}N_2O_5$: 239.0662; found: 239.0663.

Propyl (3,4-difluoro-2-hydroxyphenyl)carbamate (A16). Compound **A16** was prepared from 2,3-difluoro-6-nitrophenol following the preparation method of **A7**. Flash column chromatography was performed eluting the column with 10% EtOAc in PE. Yellow solid (407 mg, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (s, 1 H), 8.60 (brs, 1 H), 7.23 (t, J = 6.8 Hz, 1 H), 6.86–6.74 (m, 1 H), 4.00 (t, J = 6.8 Hz, 2 H), 1.66–1.57 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{10}F_2NO_3$: 230.0623; found: 230.0623.

Propyl (3,5-dichloro-2-hydroxyphenyl)carbamate (A17). Compound **A17** was prepared from 2-amino-3,5-dichlorophenol following the preparation method of **A1**. Flash column chromatography was performed eluting the column with 5% EtOAc in PE. Orange solid (365 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.90 (s, 1 H), 8.80 (brs, 1 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.23 (d, J = 2.8 Hz, 1 H), 4.04 (t, J = 6.8 Hz, 2 H), 1.68–1.59 (m, 2 H), 0.92 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{10}H_{10}Cl_2NO_3$: 262.0032; found: 262.0036.

tert-Butyl 3-hydroxy-4-((propoxycarbonyl)amino)benzoate (A18). Compound **A18** was prepared from *tert*-butyl 3-hydroxy-4-nitrobenzoate following the preparation method of **A7**. Flash column chromatography was performed eluting the column with 10% EtOAc in PE. White solid (415 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.21 (s, 1 H), 8.35 (s, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.39 (d, J = 2.0 Hz, 1 H), 7.35 (dd, J = 2.0, 8.4 Hz, 1 H), 4.04 (t, J = 6.8 Hz, 2 H), 1.68–1.59 (m, 2 H), 1.52 (s, 9 H), 0.93 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M − H]$^-$ calcd for $C_{15}H_{20}NO_5$: 294.1336; found: 294.1341.

Propyl (2-hydroxy-4-(piperidin-1-yl)phenyl)carbamate (A19). Compound **A19** was prepared from 2-nitro-5-(piperidin-1-yl) phenol following the preparation method of **A7**. Flash column chromatography was performed eluting the column with 15% EtOAc in PE. Lilac solid (1.75 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.24 (s, 1 H), 8.05 (brs, 1 H), 7.16 (brs, 1 H), 6.39 (d, J = 2.8 Hz, 1 H), 6.34 (dd, J = 2.4, 8.8 Hz, 1 H), 3.96 (t, J = 6.8 Hz, 2 H), 3.01 (t, J = 5.6 Hz, 4 H), 1.64–1.47 (m, 8 H), 0.91 (t, J = 7.6 Hz, 3 H). HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_3$: 279.1703; found: 279.1700.

4.2. *Preparation of alcohol derivatives B1–4*

Compounds **B1–4** were prepared in accordance with the procedures in our previous work [14].

(2R,3S)-(3-((Trityloxy)methyl)oxiran-2-yl)methanol (B1). (*Z*)-4-(trityloxy)but-2-en-1-ol and *D*-(−)-diethyl tartrate were used to undergo the Sharpless oxidation reaction. After solution workup, the title compound **B1** was obtained as an off-white solid by trituration with a mixture of hexane and ethyl acetate. The corresponding alcohol was analyzed by Chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1 mL/min; λ = 220 nm; T = 17 °C): t_R = 12.82 min (97.86%), 14.74 min (2.14%). The enantiomeric purity of **B1** was determined to be 96% *ee*. $[\alpha]_D^{20}$ = +32.3 (*c* 1, $CHCl_3$).

(2S,3R)-(3-((Trityloxy)methyl)oxiran-2-yl)methanol (B2). Compound **B2** was prepared from (*Z*)-4-(trityloxy)but-2-en-1-ol and *L*-(+)-diethyl tartrate. The enantiomeric purity of **B2** was determined to be 97% *ee*. $[\alpha]_D^{24}$ = −31.1 (*c* 1, $CHCl_3$).

((2S,3S)-3-((Trityloxy)methyl)oxiran-2-yl)methanol (B3). Compound **B3** was prepared from (*E*)-4-(trityloxy)but-2-en-1-ol and *L*-(+)-diethyl tartrate. The corresponding alcohol was analyzed by Chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250mm; eluent: hexane/isopropanol, 97/3; flow rate: 1 mL/min; λ = 220 nm; T = 20 °C): t_R = 18.62 min (1.72%), 21.26 min (98.28%).The enantiomeric purity of **B3** was determined to be 97% *ee*. $[\alpha]_D^{25}$ = −10.5 (*c* 1, EtOAc).

((2R,3R)-3-((Trityloxy)methyl)oxiran-2-yl)methanol (B4). Compound **B4** was prepared from (*E*)-4-(trityloxy)but-2-en-1-ol and *D*-(−)-diethyl tartrate. The enantiomeric purity of **B4** was determined to be 98% *ee*. $[\alpha]_D^{25}$ = +9.4 (*c* 1, EtOAc).

4.3. *Preparation of ether derivatives 1a–v*

General procedure for the synthesis of compounds 1a–v. To a solution of phenol **A1–19** (1 mmol), alcohol **B1–4** (1.35 mmol), PPh_3 (1.5 mmol) in anhydrous THF (5 mL) at 0 °C was added dropwise a solution of DIAD (1.5 mmol) in anhydrous THF (0.3 mL). The reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature. After the reaction was completed, the reaction mixture was purified by column chromatography (10–25% EtOAc in PE) to give the desired product **1a–v**.

Propyl (2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy) phenyl)carbamate (1a). White solid (7.6 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J = 6.0 Hz, 1 H), 7.50–7.42 (m, 6 H), 7.34–7.21 (m, 9 H), 7.18 (s, 1 H), 7.00–6.89 (m, 2 H), 6.72 (dd, J = 1.6, 7.6 Hz, 1 H), 4.18–4.08 (m, 3 H), 3.84 (dd, J = 6.8, 11.2 Hz, 1 H), 3.48 (dd, J = 5.6, 10.8 Hz, 1 H), 3.42–3.39 (m, 1 H), 3.34 (q, J = 5.2 Hz, 1 H), 3.16 (dd, J = 5.2, 10.8 Hz, 1 H), 1.75–1.66 (m, 2 H), 0.97 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 154.2, 148.0, 144.7, 129.4, 129.2,

128.7, 128.0, 123.5, 122.0, 119.5, 112.8, 87.8, 68.4, 67.0, 63.1, 55.1, 54.5, 23.0, 10.5. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}NNaO_5$: 546.2251; found: 546.2226.

Isopropyl (2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1b). White solid (1.1 g, 70%).^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 7.2 Hz, 1 H), 7.50–7.42 (m, 6 H), 7.35–7.20 (m, 9 H), 7.12 (s, 1 H), 6.98–6.90 (m, 2 H), 6.72 (dd, *J* = 1.6, 7.6 Hz, 1 H), 5.05–4.99 (m, 1 H), 4.15 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.84 (dd, *J* = 7.2, 11.6 Hz, 1 H), 3.49 (dd, *J* = 5.6, 10.8 Hz, 1 H), 3.43–3.39 (m, 1 H), 3.34 (q, *J* = 5.2 Hz, 1 H), 3.17 (dd, *J* = 5.2, 10.4 Hz, 1 H), 1.31 (d, *J* = 1.6 Hz, 3 H), 1.29 (d, *J* = 1.2 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 153.7, 147.8, 144.7, 129.4, 129.2, 128.7, 128.0, 123.4, 122.0, 119.3, 112.7, 87.7, 68.8, 68.3, 63.1, 55.1, 54.5, 22.23, 22.22. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}NNaO_5$: 546.2251; found: 546.2247.

tert-Butyl (2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1c). White solid (2.5 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 7.6 Hz, 1 H), 7.50–7.17 (m, 15 H), 7.04 (brs, 1 H), 6.99–6.85 (m, 2 H), 6.71 (dd, *J* = 1.2, 7.6 Hz, 1 H), 4.15 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.83 (dd, *J* = 6.8, 11.2 Hz, 1 H), 3.48 (dd, *J* = 5.6, 10.8 Hz, 1 H), 3.45–3.38 (m, 1 H), 3.38–3.29 (m, 1 H), 3.17 (dd, *J* = 5.2, 10.8 Hz, 1 H), 1.52 (s, 9 H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 153.3, 147.7, 144.7, 129.4, 129.3, 128.7, 128.0, 123.2, 121.9, 119.2, 112.5, 87.7, 80.3, 68.2, 63.0, 55.0, 54.5, 28.4. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_5$: 560.2407; found: 560.2425.

Propyl (2-(((2S,3R)-3-((trityloxy)methyl)oxiran-2-yl)methoxy) phenyl)carbamate (1d). White solid (350 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 6.4 Hz, 1 H), 7.48–7.42 (m, 6 H), 7.34–7.21 (m, 9 H), 7.18 (s, 1 H), 7.00–6.90 (m, 2 H), 6.72 (dd, *J* = 2.0, 8.0 Hz, 1 H), 4.17–4.08 (m, 3 H), 3.85 (dd, *J* = 6.8, 11.2 Hz, 1 H), 3.48 (dd, *J* = 5.6, 10.8 Hz, 1 H), 3.43–3.38 (m, 1 H), 3.34 (q, *J* = 5.2 Hz, 1 H), 3.16 (dd, *J* = 5.6, 10.8 Hz, 1 H), 1.75–1.66 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 154.2, 148.0, 144.7, 129.4, 129.1, 128.7, 128.0, 123.5, 122.0, 119.5, 112.8, 87.7, 68.4, 66.97, 63.1, 55.1, 54.5, 23.0, 10.5. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}NNaO_5$: 546.2251; found: 546.2229.

Propyl (2-(((2S,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy) phenyl)carbamate (1e). White solid (475 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (brs, 1 H), 7.49–7.42 (m, 6 H), 7.33–7.30 (m, 6 H), 7.27–7.22 (m, 4 H), 7.00–6.94 (m, 2 H), 6.85 (dd, *J* = 1.5, 7.5 Hz, 1 H), 4.31 (dd, *J* = 2.5, 11.5 Hz, 1 H), 4.13 (t, *J* = 7.0 Hz, 2 H), 3.97 (dd, *J* = 6.0, 11.5 Hz, 1 H), 3.40 (dd, *J* = 3.5, 10.5 Hz, 1 H), 3.35–3.31 (m, 1 H), 3.25 (dd, *J* = 5.0, 11.0 Hz, 1 H), 3.18–3.16 (m, 1 H), 1.74–1.67 (m, 2 H), 0.98 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.6, 146.4, 143.6, 128.6, 128.1, 127.9, 127.1, 122.6, 121.9, 118.5, 111.6, 86.9, 69.1, 66.8, 63.5, 54.9, 53.7, 22.2, 10.4. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}NNaO_5$: 546.2251; found: 546.2233.

Propyl (2-(((2R,3R)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1f). White solid (349 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (brs, 1 H), 7.49–7.42 (m, 6 H), 7.33–7.28 (m, 6 H), 7.27–7.23 (m, 4 H), 7.01–6.92 (m, 2 H), 6.85 (dd, *J* = 2.0, 7.5 Hz, 1 H), 4.31 (dd, *J* = 2.5, 11.5 Hz, 1 H), 4.12 (t, *J* = 6.5 Hz, 2 H), 3.97 (dd, *J* = 6.0, 11.5 Hz, 1 H), 3.40 (dd, *J* = 3.0, 11.0 Hz, 1 H), 3.33–3.31 (m, 1 H), 3.25 (dd, *J* = 5.0, 11.0 Hz, 1 H), 3.18–3.16 (m, 1 H), 1.74–1.67 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.6, 146.4, 143.6, 128.6, 128.1, 127.9, 127.1, 122.6, 121.9, 118.5, 111.6, 86.9, 69.1, 66.8, 63.5, 54.9, 53.7, 22.2, 10.4. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}NNaO_5$: 546.2251; found: 546.2240.

Propyl (5-methyl-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1g). White solid (1.47 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (brs, 1 H), 7.47–7.43 (m, 6 H), 7.31–7.28 (m, 6 H), 7.27–7.22 (m, 3 H), 7.15 (brs, 1 H), 6.72 (dd, *J* = 1.5, 8.5 Hz, 1 H), 6.61 (d, *J* = 8.5 Hz, 1 H), 4.14–4.08 (m, 3 H), 3.80 (dd, *J* = 6.5, 11.0 Hz, 1 H), 3.46 (dd, *J* = 5.5, 10.5 Hz, 1 H), 3.40–3.37 (m, 1 H), 3.33 (q, *J* = 5.5 Hz, 1 H), 3.15 (dd, *J* = 5.5, 10.5 Hz, 1 H), 2.28 (s, 3 H), 1.73–1.66 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.6, 144.2, 143.4, 131.3, 128.5, 127.9, 127.6, 127.2, 122.7, 119.0, 111.2, 87.1, 67.3, 66.7, 61.9, 54.5, 54.2, 22.3, 21.0, 10.4. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_5$: 560.2407; found: 560.2397.

Propyl (4-methyl-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1h). White solid (1.37 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (brs, 1 H), 7.49–7.43 (m, 6 H), 7.32–7.29 (m, 6 H), 7.26–7.23 (m, 3 H), 7.08 (brs, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.52 (d, *J* = 1.0 Hz, 1 H), 4.14–4.08 (m, 3 H), 3.81 (dd, *J* = 7.0, 11.0 Hz, 1 H), 3.48 (dd, *J* = 5.5, 10.5 Hz, 1 H), 3.43–3.38 (m, 1 H), 3.34 (q, *J* = 5.0 Hz, 1 H), 3.17 (dd, *J* = 5.5, 11.0 Hz, 1 H), 2.28 (s, 3 H), 1.73–1.66 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 154.2, 148.0, 144.7, 133.2, 129.4, 128.7, 128.0, 126.5, 122.3, 119.5, 113.5, 87.7, 68.3, 66.9, 63.0, 55.1, 54.5, 23.0, 21.1, 10.6. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_5$: 560.2407; found: 560.2380.

Propyl (5-methoxy-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1i). Colorless oil (1.4 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (s, 1 H), 7.51–7.44 (m, 6 H), 7.32–7.34 (m,6 H), 7.30–7.23 (m, 4 H), 6.68 (d, *J* = 9.0 Hz, 1 H), 6.48 (dd, *J* = 3.0, 8.5 Hz, 1 H), 4.17–4.10 (m, 3 H), 3.83–3.77 (m, 4 H), 3.49 (dd, *J* = 6.0, 10.5 Hz, 1 H), 3.43–3.38 (m, 1 H), 3.36 (q, *J* = 5.0 Hz, 1 H), 3.17 (dd, *J* = 5.0, 10.5 Hz, 1 H), 1.75–1.70 (m, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.5, 153.5, 143.4, 140.4, 129.7, 128.9, 128.5, 127.9, 127.2, 112.6, 107.4, 87.1, 67.9, 66.8, 61.9, 55.7, 54.6, 54.2, 22.2, 10.3. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_6$: 576.2357; found: 576.2344.

Propyl (4-methoxy-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1j). Pale-yellow solid (1.45 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (brs, 1 H), 7.48–7.43 (m, 6 H), 7.34–7.27 (m, 6 H), 7.27–7.20 (m, 3 H), 6.93 (brs, 1 H), 6.48 (dd, *J* = 2.5, 9.0 Hz, 1 H), 6.34 (d, *J* = 2.5 Hz, 1 H), 4.15–4.06 (m, 3 H), 3.82–3.73 (m, 4 H), 3.47 (dd, *J* = 5.5, 10.5 Hz, 1 H), 3.41–3.38 (m, 1 H), 3.34 (q, *J* = 5.0 Hz, 1 H), 3.15 (dd, *J* = 5.0, 10.5 Hz, 1 H), 1.72–1.65 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 156.9, 154.5, 149.5, 144.7, 129.4, 128.7, 128.0, 122.2, 121.0, 105.5, 100.7, 87.7, 68.4, 66.8, 63.1, 55.7, 55.1, 54.5, 23.0, 10.6. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_6$: 576.2357; found: 576.2338.

Propyl (2-bromo-6-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1k). White solid (1.31 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47–7.43 (m, 6 H), 7.32–7.29 (m, 6 H), 7.27–7.20 (m, 4 H), 7.03 (t, *J* = 8.5 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.02 (s, 1 H), 4.12–4.06 (m, 3 H), 3.88 (dd, *J* = 6.0, 11.0 Hz, 1 H), 3.44 (dd, *J* = 6.0, 11.0 Hz, 1 H), 3.37–3.35 (m, 1 H), 3.31 (q, *J* = 5.5 Hz, 1 H), 3.16 (dd, *J* = 5.0, 10.5 Hz, 1 H), 1.70–1.63 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.9, 154.3, 143.5, 128.5, 128.3, 127.9, 127.2, 125.4, 125.3, 123.3, 112.0, 87.0, 67.5, 67.2, 61.9, 54.5, 54.1, 22.3, 10.3. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{32}BrNNaO_5$: 624.1356; found: 624.1333.

Propyl (5-bromo-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1l). White solid (1.8 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (brs, 1 H), 7.47–7.42 (s, 6 H), 7.35–7.22 (m, 9 H), 7.15 (brs, 1 H), 7.02 (dd, *J* = 2.4, 8.4 Hz, 1 H), 6.57 (d, *J* = 8.8 Hz, 1 H), 4.19–4.08 (m, 3 H), 3.80 (dd, *J* = 6.8, 11.2 Hz, 1 H), 3.50 (dd, *J* = 5.2, 10.4 Hz, 1 H), 3.41–3.30 (m, 2 H), 3.15 (dd, *J* = 5.6, 10.8 Hz, 1 H), 1.75–1.66 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.2, 145.3, 143.4, 129.2, 128.5, 128.0, 127.3, 125.0, 121.1, 114.2, 112.5, 87.1, 67.5, 67.1, 61.8, 54.5, 54.0, 22.2, 10.3. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{32}BrNNaO_5$: 624.1356; found: 624.1326.

Propyl (4-bromo-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl) methoxy)phenyl)carbamate (1 m). White solid (1.7 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 8.8 Hz, 1 H), 7.48–7.42 (m, 6 H), 7.35–7.23 (m, 9 H), 7.10–7.08 (m, 2 H), 6.81 (d, *J* = 2.0 Hz, 1 H),

4.15–4.08 (m, 3 H), 3.72 (dd, J = 7.2, 11.2 Hz, 1 H), 3.55 (dd, J = 5.2, 10.8 Hz, 1 H), 3.42–3.33 (m, 2 H), 3.12 (dd, J = 5.6, 10.4 Hz, 1 H), 1.76–1.64 (m, 2 H), 0.97 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 146.9, 143.4, 128.5, 128.0, 127.3, 127.1, 124.5, 119.5, 114.6, 114.5, 87.1, 67.6, 67.0, 61.6, 54.4, 53.9, 22.2, 10.4. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}BrNNaO_5$: 624.1356; found: 624.1327.

Propyl (3-bromo-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1n). White solid (1.3 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.0 Hz, 1 H), 7.48 (s, 1 H), 7.44–7.38 (m, 6 H), 7.29–7.24 (m, 6 H), 7.23–7.18 (m, 3 H), 7.14 (dd, J = 1.5, 8.0 Hz, 1 H), 6.96 (t, J = 8.0 Hz, 1 H), 4.31 (dd, J = 3.5, 11.5 Hz, 1 H), 4.11 (t, J = 7.0 Hz, 2 H), 3.56 (dd, J = 7.5, 11.0 Hz, 1 H), 3.46–3.40 (m, 2 H), 3.38–3.34 (m, 1 H), 3.12 (dd, J = 4.5, 10.5 Hz, 1 H), 1.71–1.64 (m, 2 H), 0.95 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.5, 144.0, 143.4, 133.6, 128.5, 127.9, 127.2, 126.5, 126.1, 118.1, 116.2, 87.0, 71.6, 67.0, 61.8, 55.5, 54.0, 22.2, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}BrNNaO_5$: 624.1356; found: 624.1329.

Propyl (5-fluoro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1o). White solid (1.39 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, J = 6.5 Hz, 1 H), 7.49–7.41 (m, 6 H), 7.32–7.28 (m, 6 H), 7.27–7.21 (m, 4 H), 6.66–6.56 (m, 2 H), 4.15–4.11 (m, 3 H), 3.80 (dd, J = 6.5, 11.0 Hz, 1 H), 3.48 (dd, J = 5.5, 11.0 Hz, 1 H), 3.40–3.37 (m, 1 H), 3.35 (q, J = 5.0 Hz, 1 H), 3.15 (dd, J = 5.5, 10.5 Hz, 1 H), 1.74–1.67 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.6 (d, J = 236.3 Hz), 153.3, 143.4, 142.3 (d, J = 2.5 Hz), 129.1 (d, J = 11.3 Hz), 128.5, 128.0, 127.3, 111.9 (d, J = 8.8 Hz), 107.9 (d, J = 23.8 Hz), 106.1 (d, J = 28.8 Hz), 87.1, 67.9, 67.0, 61.8, 54.6, 54.1, 22.2, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}FNNaO_5$: 564.2157; found: 564.2140.

Propyl (4-fluoro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1p). White solid (1.27 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (s, 1 H), 7.51–7.42 (m, 6 H), 7.33–7.30 (m, 6 H), 7.30–7.22 (m, 3 H), 7.00 (s, 1 H), 6.69–6.65 (m, 1 H), 6.47 (dd, J = 3.0, 10.0 Hz, 1 H), 4.14–4.10 (m, 3 H), 3.76 (dd, J = 7.0, 11.0 Hz, 1 H), 3.53 (dd, J = 5.5, 10.5 Hz, 1 H), 3.41–3.34 (m, 2 H), 3.14 (dd, J = 5.5, 11.0 Hz, 1 H), 1.73–1.66 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 159.3 (d, J = 238.8 Hz), 154.4, 149.3 (d, J = 7.5 Hz), 144.7, 129.4, 128.7, 128.0, 125.3 (d, J = 2.5 Hz), 120.7, 107.4 (d, J = 22.5 Hz), 101.1 (d, J = 27.5 Hz), 87.7, 68.8, 67.0, 63.0, 55.1, 54.3, 22.9, 10.5. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}FNNaO_5$: 564.2157; found: 564.2140.

Propyl (5-nitro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1q). Yellow solid (1.25 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.03 (s, 1 H), 7.86 (dd, J = 2.5, 9.0 Hz, 1 H), 7.48–7.42 (m, 6 H), 7.33–7.30 (m, 6 H), 7.27–7.23 (m, 4 H), 6.77 (d, J = 9.0 Hz, 1 H), 4.31 (dd, J = 3.0, 11.5 Hz, 1 H), 4.20–4.13 (m, 2 H), 3.95 (dd, J = 7.5, 11.5 Hz, 1 H), 3.56 (dd, J = 5.0, 10.5 Hz, 1 H), 3.45–3.40 (m, 1 H), 3.36 (q, J = 5.5 Hz, 1 H), 3.19 (dd, J = 5.5, 10.5 Hz, 1 H), 1.76–1.69 (m, 2 H), 0.99 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.1, 150.7, 143.3, 142.1, 128.5, 128.3, 128.0, 127.3, 118.6, 113.6, 110.3, 87.2, 68.1, 67.4, 61.7, 54.5, 53.7, 22.2, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}N_2NaO_7$: 591.2102; found: 591.2078.

Propyl (4-nitro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1r). Yellow solid (1.2 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.31 (d, J = 9.0 Hz, 1 H), 7.93 (dd, J = 2.5, 9.0 Hz, 1 H), 7.59 (d, J = 2.5 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 7 H), 7.34–7.24 (m, 9 H), 4.29 (dd, J = 2.5, 11.0 Hz, 1 H), 4.20–4.12 (m, 2 H), 3.83 (dd, J = 7.5, 11.0 Hz, 1 H), 3.59 (dd, J = 5.5, 10.5 Hz, 1 H), 3.46–3.43 (m, 1 H), 3.37 (q, J = 5.0 Hz, 1 H), 3.16 (dd, J = 5.5, 11.0 Hz, 1 H), 1.76–1.69 (m, 2 H), 0.99 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.9, 145.6, 143.3, 142.2, 134.3, 128.5, 128.0, 127.3, 118.3, 116.8, 106.2, 87.2, 68.0, 67.5, 61.6, 54.4, 53.7, 22.1, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{32}N_2NaO_7$: 591.2102; found: 591.2075.

Propyl (3,4-difluoro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1s). Colorless oil (720 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (brs, 1 H), 7.45–7.38 (m, 6 H), 7.33–7.15 (m, 10 H), 6.89–6.82 (m, 1 H), 4.38–4.34 (m, 1 H), 4.10 (t, J = 6.8 Hz, 2 H), 3.84–3.79 (m, 1 H), 3.46–3.30 (m, 3 H), 3.11 (dd, J = 4.8, 10.4 Hz, 1 H), 1.74–1.63 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.6, 146.6 (dd, J = 11.0, 243.0 Hz), 143.7 (dd, J = 14.0, 245.0 Hz), 143.4, 136.0 (d, J = 9.0 Hz), 128.5, 127.9, 127.2, 112.9 (d, J = 5.0 Hz), 111.3 (d, J = 17.0 Hz), 87.1, 72.7, 67.1, 61.8, 55.0, 54.0, 22.2, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{31}F_2NNaO_5$: 582.2063; found: 582.2053.

Propyl (3,5-dichloro-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1t). Colorless oil (368 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 2.0 Hz, 1 H), 7.52 (brs, 1 H), 7.46–7.37 (m, 6 H), 7.33–7.18 (m, 9 H), 6.98 (d, J = 2.8 Hz, 1 H), 4.31 (dd, J = 2.8, 11.2 Hz, 1 H), 4.11 (t, J = 6.8 Hz, 2 H), 3.55 (dd, J = 7.2, 11.2 Hz, 1 H), 3.45 (dd, J = 6.0, 10.8 Hz, 1 H), 3.41–3.33 (m, 2 H), 3.10 (dd, J = 4.8, 10.8 Hz, 1 H), 1.73–1.64 (m, 2 H), 0.95 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.2, 143.4, 141.6, 134.2, 130.5, 128.5, 127.9, 127.5, 127.2, 123.0, 117.4, 87.1, 71.9, 67.2, 61.7, 55.5, 53.9, 22.2, 10.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{31}Cl_2NNaO_5$: 614.1471; found: 614.1461.

tert-Butyl 4-((propoxycarbonyl)amino)-3-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)benzoate (1u). White solid (510 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (d, J = 8.0 Hz, 1 H), 7.63 (dd, J = 1.5, 8.5 Hz, 1 H), 7.48–7.43 (m, 6 H), 7.38–7.35 (m, 2 H), 7.33–7.29 (m, 6 H), 7.27–7.21 (m, 3 H), 4.22 (dd, J = 3.5, 11.0 Hz, 1 H), 4.16–4.11 (m, 2 H), 3.84 (dd, J = 7.5, 11.0 Hz, 1 H), 3.49 (dd, J = 6.0, 11.0 Hz, 1 H), 3.45–3.41 (m, 1 H), 3.35 (q, J = 5.0 Hz, 1 H), 3.17 (dd, J = 5.0, 10.5 Hz, 1 H), 1.75–1.68 (m, 2 H), 1.57 (s, 9 H), 0.98 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 153.2, 145.6, 143.4, 131.9, 128.5, 128.0, 127.2, 125.9, 123.7, 117.0, 111.6, 87.1, 80.9, 67.4, 67.1, 61.9, 54.6, 53.8, 28.2, 22.2, 10.4. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{38}H_{41}NNaO_7$: 646.2775; found: 646.2760.

Propyl (4-(piperidin-1-yl)-2-(((2R,3S)-3-((trityloxy)methyl)oxiran-2-yl)methoxy)phenyl)carbamate (1v). White solid (2.8 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (s, 1 H), 7.50–7.41 (m, 6 H), 7.34–7.22 (m, 9 H), 6.91 (s, 1 H), 6.54 (dd, J = 2.0, 9.2 Hz, 1 H), 6.40 (d, J = 2.0 Hz, 1 H), 4.20–4.04 (m, 3 H), 3.83 (dd, J = 6.8, 11.8 Hz, 1 H), 3.47–3.31 (m, 3 H), 3.17 (dd, J = 5.2, 10.8 Hz, 1 H), 3.02 (t, J = 5.2 Hz, 4 H), 1.73–1.66 (m, 6 H), 1.58–1.55 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 148.8, 147.3, 143.5, 128.5, 128.0, 127.2, 120.5, 119.4, 109.6, 102.1, 87.1, 67.2, 66.6, 61.9, 54.6, 54.2, 51.6, 26.0, 24.2, 22.3, 10.4. HR-MS (ESI): m/z [M + H]$^+$ calcd for $C_{38}H_{43}N_2O_5$: 607.3166; found: 607.3152.

4.4. Preparation of target compounds 2a–k

General procedure for the synthesis of target compounds. To a solution of **1** (1.0 equiv.) in anhydrous THF (5 mL) under argon was added KOH (2.5 equiv.). The reaction mixture was stirred at room temperature for 3.5–44 h. Water (10 mL) and brine (10 mL) was added, the mixture was extracted with EtOAc (15 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The residue was purified by column chromatography eluting with 10–20% EtOAc in PE or triturated to give the corresponding products **2a**–**k**.

(R)-1-((S)-3,4-Dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2a). White solid (156 mg, 94%); mp: 55–57 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 10.02 min (99.32%), 14.57 min (0.68%). The enantiomeric purity of **2a** was determined to be 98% ee. $[\alpha]_D^{20}$ = +3.2 (c 1, EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.54–7.51 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.24 (m, 3 H), 6.69–6.59 (m, 3 H), 6.53–6.48 (m, 1 H), 4.97 (brs, 1 H), 4.37 (d,

J = 6.0 Hz, 1 H), 4.11–4.08 (m, 1 H), 3.86 (dd, J = 6.8, 10.8 Hz, 1 H), 3.81–3.76 (m, 1 H), 3.56–3.52 (m, 1 H), 3.36 (dd, J = 4.0, 10.0 Hz, 1 H), 3.20 (dd, J = 4.8, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.0, 144.6, 134.9, 129.6, 128.7, 127.9, 122.0, 118.4, 116.8, 116.3, 87.5, 71.1, 66.9, 66.6, 53.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{27}NNaO_3$: 460.1883; found: 460.1866.

(S)-1-((R)-3,4-Dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2b). White solid (135 mg, 77%); mp: 50–52 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 10.06 min (1.34%), 14.52 min (98.66%). The enantiomeric purity of **2b** was determined to be 97% ee. $[\alpha]_D^{22}$ = −4.7 (c 1, EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.56–7.49 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.23 (m, 3 H), 6.69–6.59 (m, 3 H), 6.52–6.48 (m, 1 H), 4.97 (brs, 1 H), 4.38 (d, J = 6.0 Hz, 1 H), 4.09 (dd, J = 3.2, 10.8 Hz, 1 H), 3.86 (dd, J = 6.8, 10.8 Hz, 1 H), 3.81–3.76 (m, 1 H), 3.56–3.52 (m, 1 H), 3.36 (dd, J = 4.0, 9.6 Hz, 1 H), 3.20 (dd, J = 4.8, 9.6 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.0, 144.5, 134.9, 129.5, 128.7, 127.9, 122.0, 118.3, 116.7, 116.3, 87.5, 71.0, 66.8, 66.6, 53.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{27}NNaO_3$: 460.1883; found: 460.1862.

(R)-1-((R)-3,4-Dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2c). White solid (149 mg, 85%); mp: 55–57 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1.0 mL/min; λ = 220 nm; T = 11 °C): t_R = 9.36 min (98.46%), 12.21 min (1.54%). The enantiomeric purity of **2c** was determined to be 97% ee. $[\alpha]_D^{22}$ = −6.2 (c 1, EtOAc). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.55–7.50 (m, 6 H), 7.36–7.33 (m, 6 H), 7.29–7.26 (m, 3 H), 6.65–6.59 (m, 2 H), 6.50–6.46 (m, 1 H), 6.39 (dd, J = 1.5, 8.0 Hz, 1 H), 4.52 (brs, 1 H), 4.38 (d, J = 5.5 Hz, 1 H), 4.24 (dd, J = 5.0, 10.5 Hz, 1 H), 4.09 (dd, J = 2.5, 10.5 Hz, 1 H), 3.83–3.76 (m, 1 H), 3.55–3.51 (m, 1 H), 3.47 (dd, J = 3.5, 9.5 Hz, 1 H), 3.22 (dd, J = 5.0, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 145.0, 144.5, 134.5, 129.5, 128.7, 127.9, 122.0, 118.1, 116.8, 115.7, 87.4, 70.4, 66.4, 66.0, 53.1. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{27}NNaO_3$: 460.1883; found: 460.1865.

(S)-1-((S)-3,4-Dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2d). White solid (117 mg, 67%); mp: 60–62 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1.0 mL/min; λ = 220 nm; T = 11 °C): t_R = 9.45 min (2.09%), 12.17 min (97.91%). The enantiomeric purity of **2d** was determined to be 96% ee. $[\alpha]_D^{21}$ = +4.4 (c 1, EtOAc). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.55–7.49 (m, 6 H), 7.36–7.33 (m, 6 H), 7.30–7.25 (m, 3 H), 6.63–6.60 (m, 2 H), 6.50–6.45 (m, 1 H), 6.39 (d, J = 10.0 Hz, 1 H), 4.52 (brs, 1 H), 4.37 (d, J = 5.5 Hz, 1 H), 4.23 (dd, J = 5.0, 10.5 Hz, 1 H), 4.09 (dd, J = 2.5, 10.5 Hz, 1 H), 3.81–3.77 (m, 1 H), 3.54–3.50 (m, 1 H), 3.47 (dd, J = 4.0, 10.0 Hz, 1 H), 3.22 (dd, J = 5.0, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 145.0, 144.5, 134.5, 129.5, 128.7, 127.9, 122.0, 118.1, 116.8, 115.7, 87.4, 70.4, 66.4, 66.0, 53.1. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{27}NNaO_3$: 460.1883; found: 460.1862.

(R)-1-((S)-6-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2e). Off-white solid (127 mg, 71%); mp: 152–154 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 0.7 mL/min; λ = 220 nm; T = 17 °C): t_R = 14.32 min (97.29%), 16.67 min (2.71%). The enantiomeric purity of **2e** was determined to be 95% ee. $[\alpha]_D^{22}$ = +3.2 (c 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.56–7.50 (m, 6 H), 7.36–7.33 (m, 6 H), 7.29–7.24 (m, 3 H), 6.50 (d, J = 8.0 Hz, 1 H), 6.44 (d, J = 1.5 Hz, 1 H), 6.31 (dd, J = 1.5, 8.5 Hz, 1 H), 4.89 (brs, 1 H), 4.39 (d, J = 6.0 Hz, 1 H), 4.05 (dd, J = 2.5, 10.5 Hz, 1 H), 3.83 (dd, J = 7.0, 10.5 Hz, 1 H), 3.80–3.75 (m, 1 H), 3.55–3.49 (m, 1 H), 3.35 (dd, J = 4.5, 10.0 Hz, 1 H), 3.18 (dd, J = 4.5, 10.0 Hz, 1 H), 2.12 (s, 3 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 145.0, 142.4, 134.5, 130.9, 129.5, 128.6, 127.9, 118.8, 116.7, 116.5, 87.4, 71.0, 66.7, 66.5, 53.3, 20.8. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{30}H_{29}NNaO_3$: 474.2040; found: 474.2025.

(R)-1-((S)-7-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2f). Off-white solid (157 mg, 87%); mp: 58–60 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 10.02 min (97.78%), 16.75 min (2.22%). The enantiomeric purity of **2f** was determined to be 96% ee. $[\alpha]_D^{22}$ = +6.8 (c 1, EtOAc). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.55–7.51 (m, 6 H), 7.36–7.31 (m, 6 H), 7.29–7.24 (m, 3 H), 6.54–6.45 (m, 3 H), 4.78 (brs, 1 H), 4.37 (d, J = 6.0 Hz, 1 H), 4.08 (dd, J = 3.0, 10.5 Hz, 1 H), 3.85 (dd, J = 7.0, 10.5 Hz, 1 H), 3.80–3.75 (m, 1 H), 3.52–3.48 (m, 1 H), 3.35 (dd, J = 4.0, 10.0 Hz, 1 H), 3.18 (dd, J = 4.5, 10.0 Hz, 1 H), 2.13 (s, 3 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 144.2, 143.7, 131.4, 128.7, 127.8, 127.0, 126.9, 121.5, 116.5, 115.6, 86.6, 70.1, 66.1, 65.7, 52.5, 19.7. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{30}H_{29}NNaO_3$: 474.2040; found: 474.2025.

(R)-1-((S)-6-Methoxy-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2g). Off-white solid (173 mg, 92%); mp: 200–202 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 16.77 min (100.0%). The enantiomeric purity of **2g** was determined to be >99% ee. $[\alpha]_D^{21}$ = +6.2 (c 1, EtOAc). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.54–7.49 (m, 6 H), 7.36–7.33 (m, 6 H), 7.29–7.26 (m, 3 H), 6.52 (d, J = 8.5 Hz, 1 H), 6.25 (d, J = 2.5 Hz, 1 H), 6.08 (dd, J = 3.0, 8.5 Hz, 1 H), 5.07 (brs, 1 H), 4.40 (d, J = 4.8 Hz, 1 H), 4.03 (dd, J = 2.4, 8.8 Hz, 1 H), 3.83–3.74 (m, 2 H), 3.64 (s, 3 H), 3.54–3.51 (m, 1 H), 3.35 (dd, J = 3.6, 8.0 Hz, 1 H), 3.18 (dd, J = 3.6, 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 155.5, 145.0, 138.5, 135.4, 129.5, 128.6, 127.9, 116.8, 103.2, 101.7, 87.4, 71.1, 66.63, 66.59, 55.5, 53.4. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{30}H_{29}NNaO_4$: 490.1989; found: 490.1974.

(R)-1-((S)-7-Methoxy-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2h). White solid (129 mg, 69%); mp: 65–67 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 13.65 min (98.06%), 16.70 min (1.94%). The enantiomeric purity of **2h** was determined to be 96% ee. $[\alpha]_D^{22}$ = +8.0 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.53–7.50 (m, 6 H), 7.37–7.31 (m, 6 H), 7.30–7.23 (m, 3 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.31 (dd, J = 2.8, 8.8 Hz, 1 H), 6.28 (d, J = 2.4 Hz, 1 H), 4.58 (brs, 1 H), 4.34 (d, J = 6.4 Hz, 1 H), 4.10 (dd, J = 2.8, 10.4 Hz, 1 H), 3.86 (dd, J = 7.2, 10.8 Hz, 1 H), 3.81–3.74 (m, 1 H), 3.65 (s, 3 H), 3.51–3.43 (m, 1 H), 3.35 (dd, J = 4.4, 10.0 Hz, 1 H), 3.19 (dd, J = 4.8, 9.6 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 153.7, 145.4, 145.0, 129.5, 128.6, 128.2, 127.9, 117.3, 107.6, 103.1, 87.5, 70.8, 67.3, 66.5, 55.7, 53.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{30}H_{29}NNaO_4$: 490.1989; found: 490.1975.

(R)-1-((S)-5-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2i). White solid (107 mg, 52%); mp: 113–114 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 97/3; flow rate: 0.6 mL/min; λ = 220 nm; T = 11 °C): t_R = 26.62 min (98.39%), 31.39 min (1.61%). The enantiomeric purity of **2i** was determined to be 97% ee. $[\alpha]_D^{21}$ = −6.5 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.55–7.50 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.24 (m, 3 H), 6.98 (dd, J = 1.2, 8.0 Hz, 1 H), 6.67 (dd, J = 1.2, 8.0 Hz, 1 H), 6.50–6.46 (m, 1 H), 5.02 (brs, 1 H), 4.62 (d, J = 6.0 Hz, 1 H), 4.15–4.11 (m, 1 H), 3.90–3.80 (m, 2 H), 3.67–3.62 (m, 1 H), 3.37 (dd, J = 4.4, 10.0 Hz, 1 H), 3.21 (dd, J = 4.4, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.2, 144.9, 132.8, 129.5, 128.7, 127.9, 125.3, 118.6, 116.1, 109.3, 87.6, 70.9, 66.7, 66.4, 53.3. HR-MS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{26}BrNNaO_3$: 538.0988; found: 538.0965.

(R)-1-((S)-6-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2j). White solid (190 mg, 92%); mp: 75–77 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 16 °C): t_R = 10.20 min (98.75%), 11.84 min (1.25%). The enantiomeric purity of **2j** was determined to be 98% ee. $[\alpha]_D^{22}$ = +22.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.55–7.48 (m, 6 H), 7.36–7.32 (m, 6 H), 7.30–7.23 (m, 3 H), 6.82 (d, J = 2.0 Hz, 1 H), 6.61 (dd, J = 2.0, 8.4 Hz, 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 5.37 (brs, 1 H), 4.46 (d, J = 6.0 Hz, 1 H), 4.08 (dd, J = 2.8, 10.8 Hz, 1 H), 3.90–3.84 (m, 1 H), 3.81–3.74 (m, 1 H), 3.58–3.51 (m, 1 H), 3.34 (dd, J = 4.0, 10.0 Hz, 1 H), 3.19 (dd, J = 4.4, 9.6 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.0, 143.6, 136.8, 129.5, 128.7, 127.9, 120.2, 118.3, 118.0, 113.7, 87.6, 71.1, 66.60, 66.55, 53.0. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}BrNNaO_3$: 538.0988; found: 538.0978.

(R)-1-((S)-7-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2k). White solid (190 mg, 92%); mp: 57–59 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 97/3; flow rate: 0.6 mL/min; λ = 220 nm; T = 15 °C): t_R = 17.57 min (97.86%), 25.10 min (2.14%). The enantiomeric purity of **2k** was determined to be 96% ee. $[\alpha]_D^{21}$ = +19.1 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.53–7.48 (m, 6 H), 7.37–7.30 (m, 6 H), 7.30–7.23 (m, 3 H), 6.82–6.76 (m, 2 H), 6.60 (d, J = 8.4 Hz, 1 H), 5.22 (brs, 1 H), 4.44 (d, J = 6.4 Hz, 1 H), 4.10 (dd, J = 2.8, 10.4 Hz, 1 H), 3.89 (dd, J = 6.8, 10.4 Hz, 1 H), 3.82–3.75 (m, 1 H), 3.56–3.52 (m, 1 H), 3.33 (dd, J = 4.0, 10.0 Hz, 1 H), 3.20 (dd, J = 4.8, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.2, 145.0, 134.6, 129.5, 128.7, 127.9, 124.7, 119.4, 117.3, 108.4, 87.6, 71.1, 66.8, 66.6, 53.1. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}BrNNaO_3$: 538.0988; found: 538.0984.

(R)-1-((S)-8-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2l). Off-white solid (161 mg, 78%); mp: 60–62 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 11.04 min (97.67%), 14.01 min (2.33%). The enantiomeric purity of **2l** was determined to be 95% ee. $[\alpha]_D^{22}$ = +6.1 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.53–7.51 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.24 (m, 3 H), 6.75 (dd, J = 1.5, 8.0 Hz, 1 H), 6.64 (d, J = 1.5, 8.0 Hz, 1 H), 6.59 (t, J = 8.0 Hz, 1 H), 5.32 (brs, 1 H), 4.49 (d, J = 6.5 Hz, 1 H), 4.21–4.18 (m, 1 H), 3.98 (dd, J = 7.0, 11.0 Hz, 1 H), 3.84–3.77 (m, 1 H), 3.59–3.55 (m, 1 H), 3.33 (dd, J = 4.5, 10.0 Hz, 1 H), 3.22 (dd, J = 4.5, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 144.9, 141.0, 136.4, 129.5, 128.7, 127.9, 122.8, 121.4, 115.1, 110.5, 87.5, 71.0, 67.2, 66.6, 53.2. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}BrNNaO_3$: 538.0988; found: 538.0967.

(R)-1-((S)-6-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2 m). White solid (160 mg, 88%); mp: 59–61 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 17 °C): t_R = 10.59 min (97.80%), 12.76 min (2.20%). The enantiomeric purity of **2m** was determined to be 96% ee. $[\alpha]_D^{22}$ = +6.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.54–7.49 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.24 (m, 3 H), 6.58 (dd, J = 5.6, 8.8 Hz, 1 H), 6.43 (dd, J = 2.8, 10.4 Hz,1 H), 6.23–6.18 (m,1 H), 5.36 (brs, 1 H), 4.43 (d, J = 6.4 Hz, 1 H), 4.07–4.04 (m, 1 H), 3.86–3.75 (m, 2 H), 3.57–3.53 (m, 1 H), 3.34 (dd, J = 4.0, 9.6 Hz, 1 H), 3.20 (dd, J = 4.8, 9.6 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 158.7 (d, J = 233.0 Hz), 145.0, 140.4 (d, J = 2.0 Hz), 136.1 (d, J = 11.0 Hz), 129.5, 128.6, 127.9, 117.0 (d, J = 10.0 Hz), 103.2 (d, J = 24.0 Hz), 102.0 (d, J = 27.0 Hz), 87.5, 71.1, 66.51, 66.49, 53.1. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}FNNaO_3$: 478.1789; found: 478.1773.

(R)-1-((S)-7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2n). White solid (128 mg, 70%); mp: 49–51 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 17 °C): t_R = 10.61 min (98.04%), 14.81 min (1.96%). The enantiomeric purity of **2n** was determined to be 96% ee. $[\alpha]_D^{21}$ = +6.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.55–7.48 (m, 6 H), 7.36–7.32 (m, 6 H), 7.30–7.23 (m, 3 H), 6.63 (dd, J = 6.0, 8.4 Hz, 1 H), 6.50–6.41 (m, 2 H), 4.92 (brs, 1 H), 4.40 (d, J = 6.0 Hz, 1 H), 4.12 (dd, J = 2.8, 10.8 Hz, 1 H), 3.89 (dd, J = 3.2, 10.4 Hz, 1 H), 3.81–3.76 (m, 1 H), 3.52–3.49 (m, 1 H), 3.35 (dd, J = 4.8, 10.0 Hz, 1 H), 3.20 (dd, J = 4.8, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 156.3 (d, J = 232.0 Hz), 145.0, 144.9 (d, J = 11.0 Hz), 131.3 (d, J = 2.0 Hz), 129.5, 128.7, 127.9, 116.5 (d, J = 9.0 Hz), 107.9 (d, J = 22.0 Hz), 104.0 (d, J = 26.0 Hz), 87.5, 70.9, 67.2, 66.5, 53.1. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}FNNaO_3$: 478.1789; found: 478.1780.

(R)-1-((S)-6-Nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2o). Yellow solid (176 mg, 91%); mp: 78–80 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 85/15; flow rate: 1.0 mL/min; λ = 220 nm; T = 17 °C): t_R = 12.47 min (98.41%), 15.61 min (1.59%). The enantiomeric purity of **2o** was determined to be 97% ee. $[\alpha]_D^{22}$ = +63.7 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.60 (d, J = 2.5 Hz, 1 H), 7.54–7.49 (m, 6 H), 7.45 (dd, J = 3.0, 9.0 Hz, 1 H), 7.36–7.33 (m, 6 H), 7.30–7.23 (m, 3 H), 6.79 (d, J = 8.5 Hz, 1 H), 5.82 (brs, 1 H), 4.61 (d, J = 6.5 Hz, 1 H), 4.25–4.20 (m, 1 H), 4.03 (dd, J = 6.5, 11.0 Hz, 1 H), 3.85–3.81 (m, 1 H), 3.66–3.60 (m, 1 H), 3.34 (dd, J = 4.0, 10.0 Hz, 1 H), 3.23 (dd, J = 5.0, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 149.6, 144.9, 143.0, 135.5, 129.5, 128.7, 127.9, 116.6, 113.8, 110.2, 87.5, 71.1, 67.1, 66.5, 52.6. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}N_2NaO_5$: 505.1734; found: 505.1709.

(R)-1-((S)-7-Nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2p). Yellow solid (150 mg, 78%); mp: 90–91 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 85/15; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 16.00 min (98.07%), 19.57 min (1.93%). The enantiomeric purity of **2p** was determined to be 96% ee. $[\alpha]_D^{20}$ = +64.6 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.68 (dd, J = 2.5, 9.0 Hz, 1 H), 7.52–7.50 (m, 7 H), 7.36–7.32 (m, 6 H), 7.29–7.24 (m, 3 H), 6.76 (d, J = 9.0 Hz, 1 H), 6.59 (brs, 1 H), 4.66 (d, J = 6.0 Hz, 1 H), 4.14 (dd, J = 3.0, 11.0 Hz, 1 H), 3.98 (dd, J = 6.0, 11.0 Hz, 1 H), 3.89–3.84 (m, 1 H), 3.76–3.70 (m, 1 H), 3.32 (dd, J = 4.0, 10.0 Hz, 1 H), 3.23 (dd, J = 4.5, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 144.9, 142.32, 142.29, 137.9, 129.5, 128.7, 127.9, 119.7, 113.4, 112.3, 87.6, 71.2, 66.5, 66.0, 53.3. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}N_2NaO_5$: 505.1734; found: 505.1715.

(R)-1-((S)-7,8-Difluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2q). White solid (147 mg, 78%); mp: 54–56 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 0.7 mL/min; λ = 220 nm; T = 15 °C): t_R = 12.39 min (98.54%), 14.15 min (1.46%). The enantiomeric purity of **2q** was determined to be 97% ee. $[\alpha]_D^{21}$ = +7.1 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.54–7.49 (m, 6 H), 7.34 (t, J = 8.0 Hz, 6 H), 7.27 (t, J = 7.5 Hz, 3 H), 6.64–6.56 (m, 1 H), 6.45–6.42 (m, 1 H), 5.20 (brs, 1 H), 4.50 (d, J = 6.0 Hz, 1 H), 4.20 (dd, J = 2.0, 11.0 Hz, 1 H), 3.95(dd, J = 7.0, 11.0 Hz, 1 H), 3.85–3.77 (m, 1 H), 3.57–3.53 (m, 1 H), 3.34 (dd, J = 4.0, 9.5 Hz, 1 H), 3.21 (dd, J = 4.5, 9.5 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 144.9, 144.3 (dd, J = 10.0, 231.2 Hz), 141.0 (dd, J = 15.0, 240.0 Hz), 133.6 (dd, J = 2.5, 10.0 Hz), 132.9, 129.5, 128.7, 127.9, 109.4 (dd, J = 3.8, 7.5 Hz), 108.3 (d, J = 17.5 Hz), 87.5, 70.9, 67.2, 66.5, 52.9. HR-MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{25}F_2NNaO_3$: 496.1695; found: 496.1671.

(R)-1-((S)-6,8-Dichloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-

3-yl)-2-(trityloxy)ethan-1-ol (2r). White solid (149 mg, 73%); mp: 154–156 °C. The product was analyzed by chiral HPLC (OZ-H, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1.0 mL/min; λ = 220 nm; T = 15 °C): t_R = 8.84 min (98.29%), 11.93 min (1.71%). The enantiomeric purity of **2r** was determined to be 97% ee. $[\alpha]_D^{22}$ = +27.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.54–7.48 (m, 6 H), 7.38–7.31 (m, 6 H), 7.30–7.24 (m, 3 H), 6.66 (d, *J* = 2.4 Hz, 1 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 5.70 (brs, 1 H), 4.53 (d, *J* = 6.0 Hz, 1 H), 4.19 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.99 (dd, *J* = 6.4, 10.8 Hz, 1 H), 3.84–3.78 (m, 1 H), 3.62–3.57 (m, 1 H), 3.32 (dd, *J* = 4.4, 10.0 Hz, 1 H), 3.22 (dd, *J* = 4.8, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 144.9, 138.8, 137.4, 129.5, 128.7, 127.9, 126.1, 121.9, 117.1, 113.5, 87.6, 71.1, 66.9, 66.5, 53.0. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{25}Cl_2NNaO_3$: 528.1104; found: 528.1094.

***tert*-Butyl (S)-3-((R)-1-hydroxy-2-(trityloxy)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylate (2s).** White solid (161 mg, 75%); mp: 78–80 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 0.8 mL/min; λ = 220 nm; T = 15 °C): t_R = 18.56 min (1.60%), 21.84 min (98.40%). The enantiomeric purity of **2s** was determined to be 97% ee. $[\alpha]_D^{21}$ = +24.8 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.54–7.49 (m, 6 H), 7.37–7.31 (m, 7 H), 7.29–7.21 (m, 4 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 5.79 (brs, 1 H), 4.53 (d, *J* = 6.0 Hz, 1 H), 4.09 (dd, *J* = 3.0, 10.5 Hz, 1 H), 3.90 (dd, *J* = 6.5, 11.0 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.67–3.59 (m, 1 H), 3.33 (dd, *J* = 4.0, 10.0 Hz, 1 H), 3.21 (dd, *J* = 4.5, 10.0 Hz, 1 H), 1.53 (s, 9 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 166.1, 144.9, 142.9, 139.5, 129.5, 128.7, 127.9, 124.4, 121.0, 117.8, 114.3, 87.5, 79.8, 71.2, 66.6, 66.3, 53.3, 28.4. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_5$: 560.2407; found: 560.2389.

***(R)*-1-((*S*)-7-(Piperidin-1-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2t).** Pale yellow solid (162 mg, 78%); mp: 73–75 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 85/15; flow rate: 1.0 mL/min; λ = 220 nm; T = 16 °C): t_R = 9.52 min (98.78%), 13.30 min (1.22%). The enantiomeric purity of **2t** was determined to be 98% ee. $[\alpha]_D^{22}$ = +12.8 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.54–7.48 (m, 6 H), 7.37–7.32 (m, 6 H), 7.29–7.24 (m, 3 H), 6.53 (d, *J* = 8.4 Hz, 1 H), 6.37 (d, *J* = 7.6 Hz, 1 H), 6.31 (s, 1 H), 4.52 (brs, 1 H), 4.30 (d, *J* = 6.4 Hz, 1 H), 4.08 (dd, *J* = 2.8, 10.4 Hz, 1 H), 3.85 (dd, *J* = 7.2, 10.8 Hz, 1 H), 3.80–3.73 (m, 1 H), 3.47 (brs, 1 H), 3.35 (dd, *J* = 4.4, 10.0 Hz, 1 H), 3.18 (dd, *J* = 4.8, 10.0 Hz, 1 H), 2.92 (t, *J* = 5.6 Hz, 4 H), 1.66–1.61 (m, 4 H), 1.52–1.47 (m, 2 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 146.7, 145.1, 145.0, 129.5, 128.6, 127.9, 117.2, 111.9, 106.7, 87.4, 70.8, 67.2, 66.5, 53.4, 52.8, 26.9, 25.0. HR-MS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}N_2O_3$: 521.2799; found: 521.2787.

***Gram*-scale synthesis of (R)-1-((S)-7-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2k).** A mixture of **1m** (4.1 g, 6.8 mmol) and KOH (0.96 g, 17 mmol) in anhydrous THF (40 mL) was stirred at room temperature under argon for 8 h. After solution workup and purification by chromatography (15–20% EtOAc in PE), the title compound **2k** was obtained as a white solid (3.4 g, 97%). The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 97/3; flow rate: 0.6 mL/min; λ = 220 nm; T = 15 °C): t_R = 17.53 min (99.15%), 25.04 min (0.85%). The enantiomeric purity of **2k** was determined to be 98% ee.

***One*-pot synthesis of (R)-1-((S)-7-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-(trityloxy)ethan-1-ol (2k).** To an ice cooled mixture of propyl (4-bromo-2-hydroxyphenyl)carbamate (1.1 g, 4 mmol), ((2*R*,3*S*)-3-((trityloxy)methyl)oxiran-2-yl)methanol (1.9 g, 5.4 mmol) and PPh_3 (1.6 g, 6 mmol) was added DIAD (1.2 mL, 6 mmol) under argon. The reaction mixture was allowed to warm to room temperature and stirred for 5 h, then KOH (1.1 g, 20 mmol) was added and stirred overnight. After standard workup, **2k** was obtained as a white solid (1.8 g, 87%). The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 97/3; flow rate: 0.6 mL/min; λ = 220 nm; T = 15 °C): t_R = 17.60 min (99.14%), 25.15 min (0.86%). The enantiomeric purity of **2k** was determined to be 98% ee.

***(3R,3aS)*-7-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazine (4).** To a solution of **2k** (200 mg, 0.39 mmol) in toluene (5 mL) in a sealed tube was added paraformaldehyde (120 mg). The sealed tube was heated for 2 h at 120 °C. After cooling to room temperature, the mixture was purified by column chromatography eluting with 10–15% EtOAc in PE to give **4** (106 mg, 52%) as a white solid. mp: 108–110 °C. $[\alpha]_D^{21}$ = +6.36 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.41 (m, 6 H), 7.35–7.28 (m, 6 H), 7.27–7.22 (m, 3 H), 7.02 (d, *J* = 2.4 Hz, 1 H), 6.99 (dd, *J* = 2.0, 8.4 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 4.99 (d, *J* = 3.6 Hz, 1 H), 4.80 (d, *J* = 3.6 Hz, 1 H), 4.39 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.93–3.87 (m, 1 H), 3.65 (dd, *J* = 7.2, 10.8 Hz, 1 H), 3.56–3.51 (m, 1 H), 3.48 (dd, *J* = 4.8, 9.6 Hz, 1 H), 3.31 (dd, *J* = 6.0, 10.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 143.5, 132.3, 128.6, 128.0, 127.2, 125.1, 119.8, 117.2, 111.3, 87.1, 84.1, 77.5, 64.7, 64.0, 57.5. HR-MS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{30}H_{26}BrNNaO_3$: 550.0988; found: 550.0969.

***(4R,4aS)*-8-Bromo-4-((trityloxy)methyl)-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine (5).** The title compound **5** was prepared referring to the literature method [16]. A solution of **2k** (515 mg, 1 mmol) in anhydrous DCM (30 mL) was treated with NaH (60%, 200 mg, 5 mmol) at 0 °C under argon. After 5 min, (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (1.1 g, 2.5 mmol) was added and the mixture was stirred for 3 h at 0 °C, followed by 12 h at room temperature. The reaction was then quenched with water (10 mL), extracted with DCM, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum. After chromatography eluting with 5–10% EtOAc in PE, compound **5** was obtained as an off-white solid (284 mg, 52%). mp: 205–206 °C. $[\alpha]_D^{20}$ = +8.28 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44–7.32 (m, 12 H), 7.28 (t, *J* = 6.8 Hz, 3 H), 6.95 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.87–6.81 (m, 2 H), 4.06 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.91 (dd, *J* = 2.8, 10.8 Hz, 1 H), 3.83 (dd, *J* = 8.4, 10.4 Hz, 1 H), 3.68–3.59 (m, 2 H), 3.36–3.26 (m, 2 H), 3.23–3.16 (m, 1 H), 2.94 (dd, *J* = 3.2, 10.8 Hz, 1 H), 2.81–2.71 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.0, 143.4, 134.6, 128.1, 128.0, 127.2, 123.7, 118.1, 114.9, 109.5, 86.0, 74.9, 65.6, 65.0, 63.4, 52.9, 45.0. HR-MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}BrNO_4$: 542.1325; found: 542.1302.

***(4R,4aS)*-8-Bromo-4-((trityloxy)methyl)-4a,5-dihydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-1(2H)-one (6).** Compound **6** was prepared referring to the literature method [17]. A solution of **2k** (515 mg, 1 mmol) in anhydrous THF (8 mL) under argon was treated with *t*-BuOK (168 mg, 1.5 mmol) at room temperature. After 5 min, ethyl chloroacetate (0.16 mL, 1.5 mmol) was added, and the reaction mixture was stirred for 7 h. Brine was added, the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by chromatography (18% EtOAc in PE) to give the title compound **6** as a white solid (330 mg, 59%). mp: 161–162 °C. $[\alpha]_D^{19}$ = +45.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.22 (d, *J* = 8.8 Hz, 1 H), 7.54–7.49 (m, 6 H), 7.40–7.33 (m, 6 H), 7.32–7.26 (m, 3 H), 7.08–7.02 (m, 2 H), 4.44 (d, *J* = 16.4 Hz, 1 H), 4.25–4.11 (m, 3 H), 4.04–3.96 (m, 1 H), 3.86–3.82 (m, 1 H), 3.56 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.37 (dd, *J* = 4.4, 10.8 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ 165.1, 147.7, 144.6, 129.4, 128.8, 128.1, 125.6, 124.7, 124.0, 120.4, 117.6, 87.8, 74.3, 69.0, 67.3, 64.5, 54.4. HR-MS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}BrNO_4$: 556.1118; found: 556.1101.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132304.

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