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Enantiopure synthesis of dihydrobenzo[1,4]-oxazine-3-carboxylic acids and a route to benzoxazinyl oxazolidinones†

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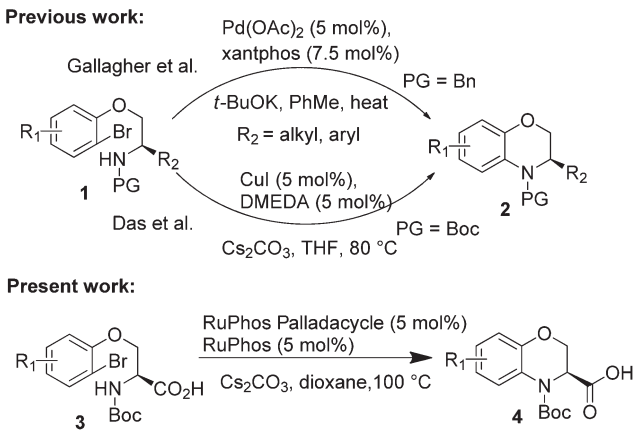
A two step protocol is developed for the efficient synthesis of enantiopure *N*-Boc-dihydrobenzo[*b*]-1,4-oxazine-3-carboxylic acids **4** from serine derived cyclic sulfamidate *via* intramolecular arylamination. The RuPhos Palladacycle along with additional RuPhos ligand is found to be an efficient catalyst for the aryl-amination of β-(2-bromoaryloxy)amino acids **3** to provide easy and direct access to a variety of dihydro-benzo[*b*]-1,4-oxazine-3-carboxylic acids **4** with complete retention of enantiopurity in moderate to high yields. Dihydrobenzo[*b*]-1,4-oxazine-3-carboxylic acids are not only important unnatural amino acids, but are key precursors for the synthesis of important compounds such as benzoxazinyl oxazolidinones. A general approach for the synthesis of benzoxazinyl oxazolidinone is presented.

Introduction

Chiral 3-substituted dihydrobenzo[*b*]-1,4-oxazines are key structural units of many bioactive natural products and pharmaceuticals.[1,2] These are also utilized as chiral catalysts in asymmetric transfer hydrogenation.[3] Thus several methods have been developed for the non-racemic synthesis of dihydrobenzoxazines.[4–6] Among these, catalytic asymmetric reduction of prochiral 1,4-benzoxazines has progressed and matured sufficiently with excellent enantioselectivity, but mostly for 3-aryl benzoxazines.[4,5] Intramolecular Buchwald–Hartwig arylamination[7] of the β-aryloxyamines is an efficient alternative protocol, as aryloxyamines can be obtained in large quantities in optically pure form. Gallagher *et al.* reported Pd-catalyzed intramolecular arylamination for the synthesis of enantiopure 1,4-dihydrobenzoxazines and the Das group has efficiently replaced the palladium with a Cu catalyst (Scheme 1).[6] Recently benz[*b*]-1,4-oxazine-3-carboxylic acids **4** and their derivatives have been found to be the fundamental moiety of many potential drugs.[8] These are also important unnatural amino acids and could be precursors in the synthesis of bio-active benzoxazinyl compounds (Fig. 1).[9,10] Intramolecular arylamination of β-(2-haloaryloxy)amino acids **3** can lead to dihydrobenzoxazine-3-carboxylic acids **4** (Scheme 1). Surprisingly, none of the above methods describe the synthesis of benzoxazine carboxylic acids or derivatives, maybe because there was no suitable method for the synthesis of β-(2-haloaryl-oxy)amino acids. To the best of our knowledge, there is no other report on the synthesis of benz[*b*]-1,4-oxazine-3-carboxylic acids in optically pure form. Recently we have developed an efficient protocol for the direct synthesis of *N*-protected



Scheme 1

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† Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C NMR spectra and LC-MS for compounds **3**, **4**, **10a**, **12a–14a**, **18a**, **20a** and **21a** and HPLC chromatograms of compounds **3a**, **3c**, **4a**, **4c**, **12a**, **14a**, **18a** and **20a**. See DOI: 10.1039/c4ob02475c

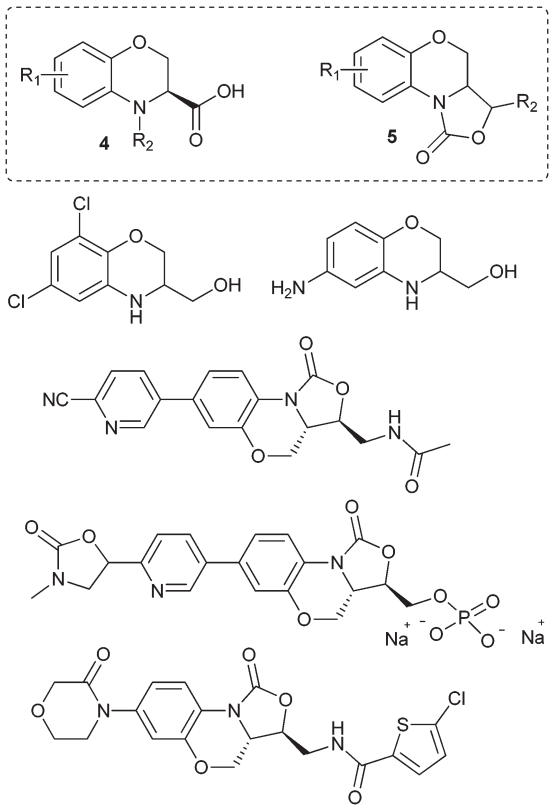


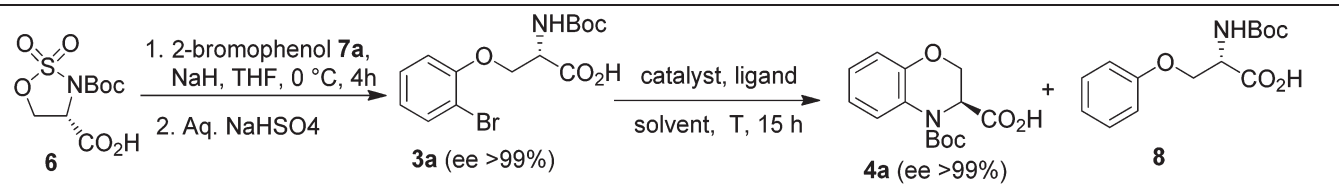
Fig. 1 Dihydrobenzoxazine-3-carboxylic acid **4** and some important bioactive benzoxazinyl compounds.

β-aryloxyamino acids from cyclic sulfamidate carboxylic acid derived from serine.[11] This prompted us to study the arylamination of β-(2-haloaryloxy)amino acids. Herein we report RuPhos Palladacycle-catalyzed efficient intramolecular arylamination of the β-(2-bromoaryloxy)amino acids for the enantiopure synthesis of *N*-Boc-benzo[*b*]-1,4-oxazine-3-carboxylic acids **4** and a general approach for the synthesis of benzoxazinyl oxazolidinones **5**.

Results and discussion

For the screening of the arylamination catalysts (Table 1), β-(2-bromophenyloxy)amino acid **3a** was taken as a model substrate, and was prepared by the regioselective ring opening of cyclic sulfamidate **6** with 2-bromophenol **7a** at 0 °C following our previously-developed method.[11] Substrate **3a** was heated in the presence of $Pd(OAc)_2$ under the conditions reported by the Gallagher group. It showed >90% disappearance of substrate **3a** but only traces of product **4a** (<5%) detected by LC-MS (Table 1; entry 1) and there was no improvement by changing the solvent to dioxane (entry 2). The CuI-mediated reaction of substrate **3a** showed 40% conversion after 15 h giving a 1 : 1 mixture of the desired cyclized product **4a** and des-bromo product **8** along with other unidentified compounds (entry 3). PEPPSI-IPr was also found to be ineffective towards arylamination of **3a** (entry 4). We then screened the commonly-used Buchwald–Hartwig arylamination catalyst $Pd_2(dba)_3$ in the

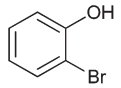
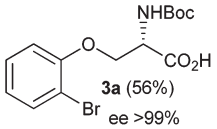
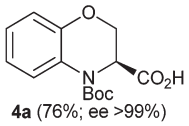
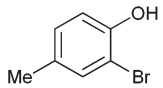
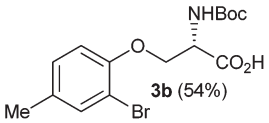
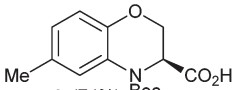
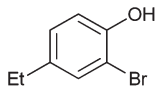
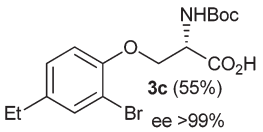
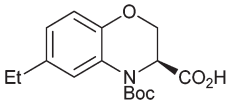
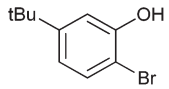
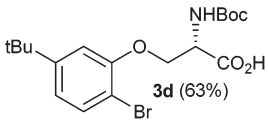
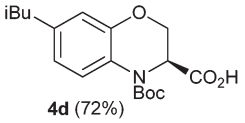
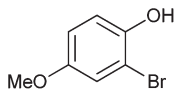
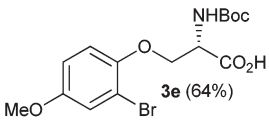
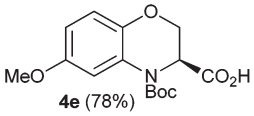
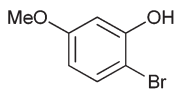
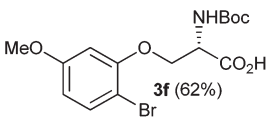
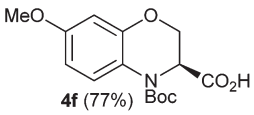
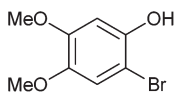
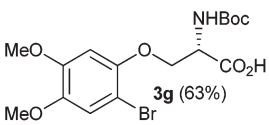
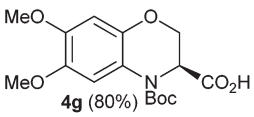
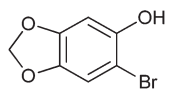
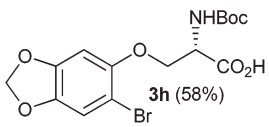
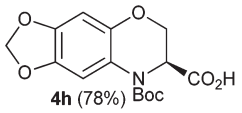
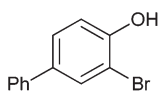
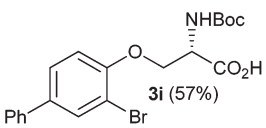
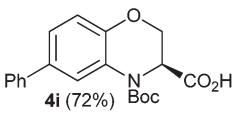
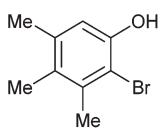
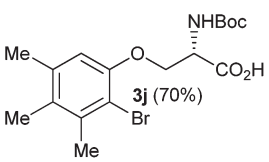
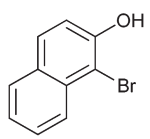
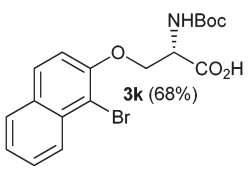
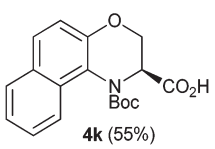
Table 1 Screening of catalysts and reaction conditions for the intramolecular Buchwald–Hartwig coupling of **3a**



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	*T* (°C)	Conv.[a] (%)	**4a** : **8**[b]	Yield[c] of **4a**
1	$Pd(OAc)_2$ (5)	Xantphos (7.5)	Toluene	100	>90	ND	<5[a]
2	$Pd(OAc)_2$ (5)	Xantphos (7.5)	Dioxane	100	>90	ND	<5[a]
3	CuI (5)	DMEDA (5)	THF	80	40	1 : 1[a]	<10[a]
4	PEPPSI-IPr (2)	—	Dioxane	100	30	6 : 1[a]	—
5	$Pd_2(dba)_3$ (15)	BINAPH (15)	Dioxane	100	60	54 : 46	—
6	$Pd_2(dba)_3$ (15)	SPhos	Dioxane	100	100	80 : 20	85
7	$Pd_2(dba)_3$ (15)	XPhos	Dioxane	100	100	83 : 17	79
8	$Pd_2(dba)_3$ (15)	BrettPhos	Dioxane	100	100	95 : 5	73
9	$Pd_2(dba)_3$ (15)	RuPhos	Dioxane	100	100	96 : 4	76
10	$Pd_2(dba)_3$ (15)	BrettPhos	Dioxane	60	70	85 : 15	74
11	RuPhos Palladacycle (15)	—	Dioxane	100	100	98 : 2	72
12	RuPhos Palladacycle (15)	RuPhos (15)	Dioxane	60	60	97 : 3	—
13	RuPhos Palladacycle (15)	RuPhos (15)	Dioxane	100	100	>99 : 1	76
14	RuPhos Palladacycle (10)	RuPhos (10)	Dioxane	100	100	>99 : 1	76
15	**RuPhos Palladacycle (5)**	**RuPhos (5)**	Dioxane	**100**	**100**	**>99 : 1**	**76**
16	RuPhos Palladacycle (2)	RuPhos (2)	Dioxane	100	75	98 : 2	60
17	RuPhos Palladacycle (1)	RuPhos (1)	Dioxane	100	<25	10 : 1	—

[a] Determined by LC-MS. [b] Determined by ^{1}H NMR of crude reaction mixture unless otherwise noted. [c] Combined isolated yield of **4a** and **8** unless otherwise noted.

Table 2 Enantiopure synthesis of dihydrobenzo[*b*]-1,4-oxazine-3-carboxylic acids **4**[a]

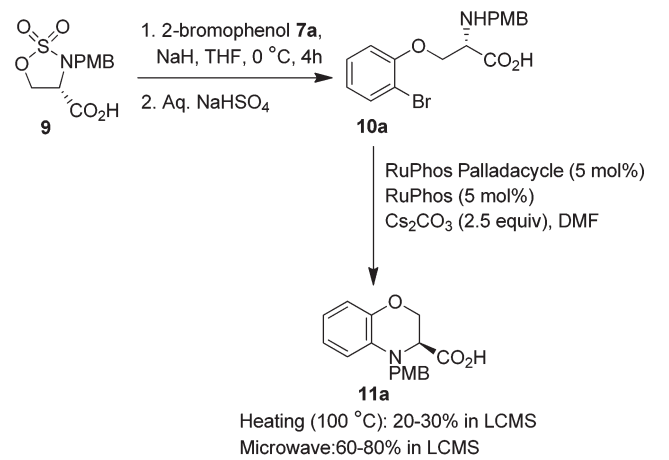
Entry	ArOH	7	Amino acid **3**	Dihydrobenzoxazine **4**
1		**7a**	 **3a** (56%) ee >99%	 **4a** (76%; ee >99%)
2		**7b**	 **3b** (54%)	 **4b** (74%)
3		**7c**	 **3c** (55%) ee >99%	 **4c** (73%; ee>99%)
4		**7d**	 **3d** (63%)	 **4d** (72%)
5		**7e**	 **3e** (64%)	 **4e** (78%)
6		**7f**	 **3f** (62%)	 **4f** (77%)
7		**7g**	 **3g** (63%)	 **4g** (80%)
8		**7h**	 **3h** (58%)	 **4h** (78%)
9		**7i**	 **3i** (57%)	 **4i** (72%)
10		**7j**	 **3j** (70%)	NR
11		**7k**	 **3k** (68%)	 **4k** (55%)

[a] For the synthesis of dihydrobenzo[*b*]-1,4-oxazine-3-carboxylic acids **4**, intramolecular arylamination (Buchwald–Hartwig coupling) of **3** was carried out using RuPhos Palladacycle (5 mol%) and RuPhos (5 mol%) as a catalyst with Cs_2CO_3 in dioxane at 100 °C.

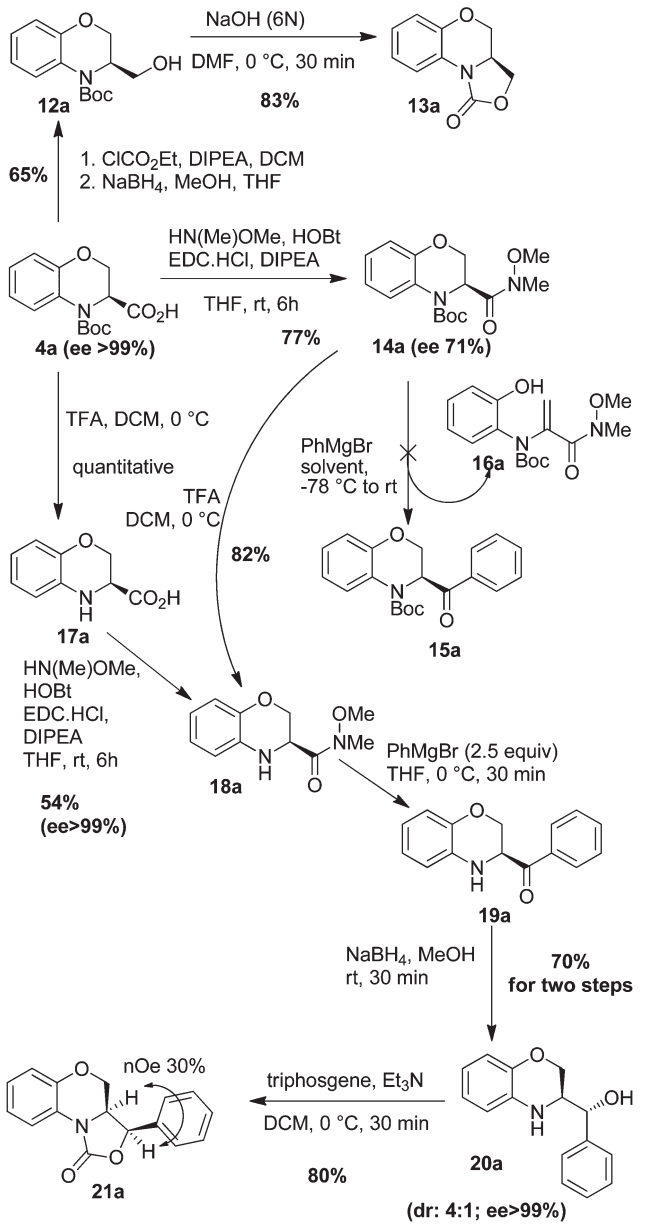
presence of different commercially available ligands (entries 5–10). Among these, BrettPhos and RuPhos were found to be efficient systems providing high selectivity and yields towards arylamination over the des-bromo product (entries 8 and 9). Difficulties in the removal of minor des-bromo by-product **8** led us to look for a more efficient catalyst. We are delighted to report that RuPhos Palladacycle was found to be a very efficient catalyst and provided very high selectivity towards arylamination over the des-bromo by-product (98 : 2; entry 11). Further optimization using additional RuPhos ligand gave rise to excellent selectivity (>99 : 1) towards cyclized product **4a** with very good isolated yield (76%; entry 13). The optimum catalyst loading was found to be 5 mol% without any loss of yield and selectivity with complete retention of enantiopurity (entry 15). Further lowering the catalyst loading (entries 16 and 17) and the reaction temperature (entries 10 and 12) led to poor conversion and selectivity.

After standardization of the intramolecular arylamination conditions, the method was generalized with different substrates. For this purpose, a number of 2-bromophenols were reacted with *N*-Boc-cyclic sulfamidate **6** providing moderate to good yields of β-aryloxyamino acids **3**, which were heated in dioxane in the presence of RuPhos Palladacycle along with the RuPhos ligand under standardized conditions (Table 2). All the substrates **3** except substrates **3j** and **3k** underwent smooth arylamination and gave very good yields of the desired dihydrobenzoxazin-3-carboxylic acids **4** with complete preservation of enantiopurity (*e.g.* Table 2; entries 1 and 3). The moderate yield of dihydronaphthoxazin-2-carboxylic acid **3k** (entry 11), might be due to the steric effect of the *peri*-hydrogen and the lack of reaction with substrate **3j** (entry 10), might be due to the *ortho*-steric effect.

Similarly *N*-PMB protected serine sulfamidate carboxylic acid **9** can provide *N*-PMB protected benzoxazine carboxylic acid **11** in two steps (Scheme 2). In the first step, the regioselective ring opening of **9** afforded a very good yield of *N*-PMB-β-(2-bromophenyloxy)amino acid **10a**. However, intramolecular aminoarylation of **10a** under the above optimized conditions gave traces of desired product **11a.** The poor solubility of the amino acid **10a** in dioxane could be the cause of the failure of the reaction. Other solvents such as DMF, *t*-BuOH and a combination of mixed solvents were screened for the aminoarylation of **10a**. DMF was found to be a suitable solvent for aminoarylation of **10a** in the presence of RuPhos Palladacycle and RuPhos at 100 °C and showed 20–30% of the desired cyclized product mass (*m*/*z*) **11a** in LC-MS. When the reaction was carried out under microwave conditions, it showed 60–80% of *N*-PMB-benzoxazine **11a** in LC-MS. Surprisingly, the compound **11a** could not be isolated in pure form by silica-gel column chromatography and was found to be decomposed on the silica gel, leading to a complex mixture of products.



Scheme 2 Synthesis of *N*-PMB-benzoxazine carboxylic acid **11a**.



Scheme 3 Asymmetric synthesis of benzoxazinyl oxazolidinone **21**.

Functional modifications of the carboxylic acid group of benzoxazine-3-carboxylic acids **4** can lead to the synthesis of a wide variety of important bioactive compounds; for example, benzoxazinyl oxazolidinones **5**. Reduction of compound **4a** and subsequent cyclization gave a very good yield of benzoxazinyl oxazolidinone **13a** (Scheme 3). To get other substituted oxazolidinone compounds, acid **4a** was converted to Weinreb amide **14a**, which could be a versatile building block. However, to our surprise, it did not undergo any reaction with a Grignard reagent under different conditions; in some cases ring-opening product **16a** was obtained as a minor side product. It was presumed that the bulky *tert*-butyl group in the less flexible benzoxazine moiety might be inhibiting the approach of the Grignard reagent. Also to note is that the synthesis of the Weinreb amide led to 10–15% epimerization. Amide coupling with other amines also shows similar findings (not shown in the scheme). Boc-deprotection of the Weinreb amide **14a** with TFA gave unprotected amide **18a**. To obtain enantiopure Weinreb amide **18a**, the reaction sequence was reversed and this was successful in obtaining amide **18a** without any loss of ee. Weinreb amide **18a** was treated with PhMgBr at 0 °C and gave desired amino ketone **19a**. Without any purification, it was reduced with $NaBH_4$ at 0 °C and afforded amino alcohol **20a** as a diastereomeric mixture (dr 4 : 1) in good yield with preservation of enantiopurity. The amino alcohol **20a** was treated with triphosgene and Et_3N and gave benzoxazinyl oxazolidinone **21a** in 80% yield. Hydride transfer was expected to be from the less hindered side *via* a chelated transition state and led to the *anti*-product as the major diastereomer. The *cis*-stereochemistry of benzoxazinyl oxazolidinone **21a** (major isomer) was assigned from the coupling constant of the benzylic proton [J_{cis} = 9.0 Hz (major isomer) and J_{trans} = 7.6 Hz (minor isomer)] and by NOE experiment. Thus the reaction of different nucleophiles with the Weinreb amide **18** can lead to a wide variety of benzoxazinyl oxazolidinones by following this reaction sequence.

Conclusion

In summary, we have developed an efficient and general protocol for the enantiopure synthesis of *N*-Boc-dihydrobenzo-1,4-oxazine-3-carboxylic acids from β-(2-bromoaryloxy)amino acids *via* intramolecular aminoarylation. RuPhos Palladacycle along with additional RuPhos ligand was found to be an efficient catalyst for the aminoarylation. The method is generalized with a variety of substrates and provides easy and direct access to *N*-Boc dihydrobenzo-1,4-oxazine-3-carboxylic acids in moderate to very good yields with complete preservation of enantiopurity. Benzoxazine-3-carboxylic acid is not only the fundamental moiety of potential drugs but could be a key precursor for the synthesis of important bioactive compounds. This is exemplified with the synthesis of benzoxazinyl oxazolidinones from a benzoxazine carboxylic acid-derived Weinreb amide. The developed protocol is a general approach for the synthesis of enantiopure dihydrobenzoxazine-3-carboxylic acids and benzoxazinyl oxazolidinones.

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Experimental

General

All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar) or nitrogen (N_2). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (100–200 mesh). TLC was performed on aluminium-backed plates coated with Silica gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz using $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) and DMSO-d_6 (δ = 2.49); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0) and DMSO-d_6 (δ = 39.7). High resolution mass spectra (HRMS) were measured with a QTOF I (quadrupole–hexapole TOF) mass spectrometer with an orthogonal Z-spray–electro-spray interface. Sulfamidates **6** and **9** were prepared by following the literature procedure.[11]

General procedure for the synthesis of *N*-Boc-β-(2-bromoaryloxy)-amino acid 3

To a suspended solution of NaH (60% in oil; 0.105 g, 2.6 mmol) in THF (3.0 mL), 2-bromophenol (0.152 g, 0.88 mmol) was added at 0 °C. The reaction mixture was stirred for 10 min and then it was brought to 0 °C. Serine sulfamidate acid **6** (0.224 g, 0.84 mmol) in dry THF (1.0 mL) was slowly added to it at 0 °C. After 6 h, the reaction mixture was acidified (pH 2; monitored by pH paper) by addition of $NaHSO_4$. It was then extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with brine (100 mL), dried over sodium sulfate and purified by column chromatography to get the β-(2-bromophenoxy)-α-amino acid **3a** (0.17 g, 56%).

(*S*)-3-(2-Bromophenoxy)-2-((*tert*-butoxycarbonyl)amino)-propanoic acid (3a). Yield 56%; light yellow semi-solid, ^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (br s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 4.41–4.38 (m, 1H), 4.32–4.29 (m, 1H), 4.25–4.20 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.2, 154.3, 132.9, 128.9, 122.4, 114.0, 111.1, 78.3, 68.3, 53.1, 28.1(3C). LC-MS (ESI): 358.0 $[M - H]^-$. HRMS (ESI): calcd for $C_{14}H_{18}BrNNaO_5$ 382.0266 m/z $[M + Na]^+$, found 382.0266. HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 275 nm, tr (major) 7.73, tr (minor) 6.63, ee > 99%, $[\alpha]_D^{25}$ = +33.4 (c 0.52, MeOH). HPLC for the D-isomer: HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 275 nm, tr (major) 6.66, tr (minor) 7.77, ee > 99%, $[\alpha]_D^{25}$ = −33.2 (c 0.52, MeOH).

(*S*)-3-(2-Bromo-4-methylphenoxy)-2-((*tert*-butoxycarbonyl)-amino)propanoic acid (3b). Yield 54%; light yellow sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 7.38 (s, 1H), 7.12–7.10 (m, 1H), 6.99–6.97 (m, 1H), 6.88–6.86 (m, 1H), 6.79 (d, J = 7.2 Hz, 1H), 4.33–4.19 (m, 3H), 2.22 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.1, 152.3, 133.1, 131.6, 129.1, 114.0, 110.9, 78.1, 68.8, 53.4, 28.1 (3C), 19.5. LC-MS (ESI): 374.3 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{20}BrNNaO_5$ 396.0423 m/z $[M + Na]^+$, found 396.0423; $[\alpha]_D^{25}$ = +33.9 (c 0.50, MeOH).

(*S*)-3-(2-Bromo-4-ethylphenoxy)-2-((*tert*-butoxycarbonyl)-amino)propanoic acid (3c). Yield 55%; colourless sticky liquid, ^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 1H), 7.40 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 4.38–4.35 (m, 1H), 4.28–4.25 (m, 1H), 4.21–4.17 (m, 1H), 2.56–2.50 (m, 2H), 1.39 (s, 9H), 1.13 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.1, 152.3, 138.1, 132.0, 127.9, 114.1, 110.9, 78.2, 68.5, 53.1, 28.0 (3C), 26.8, 15.6. LC-MS (ESI): 388.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{16}H_{22}BrNNaO_5$ 410.0579 m/z $[M + Na]^+$, found 410.0579. HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 280 nm, tr (major) 6.81, tr (minor) 5.99, ee > 99%, $[\alpha]_D^{25}$ = +33.0 (c 0.20, MeOH). HPLC for the D-isomer: HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 280 nm, tr (major) 6.00, tr (minor) 6.75, ee > 99%; $[\alpha]_D^{25}$ = −33.1 (c 0.52, MeOH).

(*S*)-3-(2-Bromo-5-(*tert*-butyl)phenoxy)-2-((*tert*-butoxy-carbonyl)amino)propanoic acid (3d). Yield 63%; colourless sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 12.96 (br s, 1H), 7.45 (d, J = 6.7 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.93 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H), 4.36–4.24 (m, 3H), 1.39 (s, 9H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.2, 155.2, 153.9, 152.1, 132.2, 119.5, 111.9, 108.2, 78.3, 68.6, 53.2, 34.6, 30.8 (3C), 28.1 (3C). LC-MS (ESI): 414.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{18}H_{26}BrNNaO_5$ 438.0892 m/z $[M + Na]^+$, found 438.0892; $[\alpha]_D^{25}$ = +25.0 (c 0.23, MeOH).

(*S*)-3-(2-Bromo-4-methoxyphenoxy)-2-((*tert*-butoxycarbonyl)-amino)propanoic acid (3e). Yield 64%; brown sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 7.15 (d, J = 2.8, 1H), 7.06 (d, J = 9.0 Hz, 1H), 6.96–6.89 (m, 2H), 4.31 (m, 1H), 4.23–4.19 (m, 1H), 4.17–4.13 (m, 1H), 3.71 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.2, 155.2, 154.1, 148.5, 118.2, 115.6, 114.0, 111.9, 78.2, 69.3, 55.6, 53.3, 28.1 (3C), LC-MS (ESI): 390.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{20}BrNNaO_6$ 412.0372 m/z $[M + Na]^+$, found 412.0372; $[\alpha]_D^{25}$ = +27.7 (c 0.51, MeOH).

(*S*)-3-(2-Bromo-5-methoxyphenoxy)-2-((*tert*-butoxycarbonyl)-amino)propanoic acid (3f). Yield 62%; colourless sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 12.95 (br s, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.52 (dd, J = 8.7 Hz, J = 2.3 Hz, 1H), 4.39–4.36 (m, 1H), 4.31–4.28 (m, 1H), 4.24–4.20 (m, 1H), 3.75 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 159.9, 155.2, 154.9, 132.8, 127.6, 121.6, 101.2, 78.3, 68.4, 55.4, 53.1, 28.1 (3C). LC-MS (ESI): 389.9 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{20}BrNNaO_6$ 412.0372 m/z $[M + Na]^+$, found 412.0372; $[\alpha]_D^{25}$ = +33.0 (c 0.23, MeOH).

(*S*)-3-(2-Bromo-4,5-dimethoxyphenoxy)-2-((*tert*-butoxy-carbonyl)amino)propanoic acid (3g). Yield 63%; brown solid, m.p. 138–140 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 12.9 (br s, 1H), 7.10 (s, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.84 (s, 1H), 4.35 (m, 1H), 4.25–4.19 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.2, 155.2, 148.9, 148.6, 144.1, 116.0, 101.7, 100.8, 78.3, 69.7, 56.2, 55.8, 53.3, 28.1 (3C). HRMS (ESI): calcd for $C_{16}H_{22}BrNNaO_7$ 442.0477 m/z $[M + Na]^+$, found 442.0477; $[\alpha]_D^{25}$ = + 24.0 (c 0.20, MeOH).

(*S*)-3-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)oxy)-2-((*tert*-butoxy-carbonyl)amino)propanoic acid (3h). Yield 58%; brown sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 12.92 (br s, 1H), 7.16 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.93 (s, 1H), 6.02 (s, 2H), 4.34–4.31 (m, 1H), 4.23–4.20 (m, 1H), 4.18–4.13 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.1, 149.5, 147.5, 142.1, 111.8, 101.8, 101.3, 98.3, 78.3, 69.7, 53.2, 28.1(3C). LC-MS (ESI): 403.8 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{18}BrNNaO_7$ 426.0164 m/z $[M + Na]^+$, found 426.0164; $[\alpha]_D^{25}$ = +24.0 (c 0.20, MeOH).

(*S*)-3-((3-Bromo-[1,1′-biphenyl]-4-yl)oxy)-2-((*tert*-butoxy-carbonyl)amino)propanoic acid (3i). Yield 57%; white solid, m.p. 112–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 12.98 (br s, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.64–7.63 (m, 3H), 7.44 (t, J = 7.5 Hz, 2H), 7.36–7.32 (m, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 4.42–4.41 (m, 1H), 4.38–4.35 (m, 1H), 4.30–4.26 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.2, 153.8, 138.2, 134.4, 130.7, 128.8 (2C), 127.2, 127.0, 126.3 (2C), 114.3, 111.7, 78.3, 68.5, 53.1, 28.1 (3C). LC-MS (ESI): 436.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{20}H_{22}BrNNaO_5$ 458.0579 m/z $[M + Na]^+$, found 458.0579; $[\alpha]_D^{25}$ = +34.0 (c 0.22, MeOH).

(*S*)-3-(2-Bromo-3,4,5-trimethylphenoxy)-2-((*tert*-butoxy-carbonyl)amino)propanoic acid (3j). Yield 70%; white solid, m. p. 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6):12.9 (s, 1H), 6.98 (d, J = 8.32 Hz, 1H), 6.81 (s, 1H), 4.50–4.35 (m, 1H), 4.25–4.15 (m, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.2, 155.1, 151.8, 136.3, 135.9, 128.7, 113.3, 111.8, 78.2, 68.6, 53.2, 28.1(3C), 20.3, 19.9, 15.8. LC-MS (ESI): 400.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{17}H_{24}BrNNaO_5$ 424.0736 m/z $[M + Na]^+$, found 424.0736; $[\alpha]_D^{25}$ = +36.0 (c 0.21, MeOH).

(*S*)-3-((1-Bromonaphthalen-2-yl)oxy)-2-((*tert*-butoxy-carbonyl) amino)propanoic acid (3k). Yield 68%; white solid, m.p. 106–108 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 13.0 (br s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.52–7.45 (m, 2H), 7.11 (d, J = 7.6 Hz, 1H), 4.50–4.38 (m, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.1, 155.2, 152.6, 132.1, 129.6, 129.2, 128.2, 128.0, 125.2, 124.5, 115.7, 108.0, 78.3, 69.2, 53.3, 28.0 (3C). LC-MS (ESI): 410.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{18}H_{20}BrNNaO_5$ 432.0423 m/z $[M + Na]^+$, found 432.0423; $[\alpha]_D^{25}$ = +45.0 (c 0.20, MeOH).

(*S*)-3-(2-Bromophenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10a). Yield 72%; white solid, m.p. 166–168 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.60 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.44 Hz, 2H), 7.36 (t, J = 8.24 Hz, 1H), 7.15 (d, J = 8.12 Hz, 1H), 6.96–6.92 (m, 3H), 4.49–4.46 (m, 1H), 4.40–4.35 (m, 1H), 4.17

(s, 2H), 3.87 (m, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6):167.8, 159.4, 154.1, 133.1, 131.2 (2C), 129.2, 125.4, 122.8, 114.1, 114.0 (2C), 111.1, 68.3, 58.5, 55.2, 49.6. LC-MS (ESI): 382.1 $[M - H]^-$. HRMS (ESI): calcd for $C_{17}H_{18}BrNNaO_4$ 402.0317 *m/z* $[M + Na]^+$, found 402.0317; $[\alpha]_D^{25}$ = +8.0 (*c* 0.17, MeOH).

General procedure for intramolecular arylamination (Buchwald–Hartwig coupling)

To compound **3a** (0.1 g, 0.28 mmol) in dioxane (5 ml) was added RuPhos Palladacycle (0.01 g, 0.014 mmol), RuPhos (0.085 g, 0.014 mmol) and Cs_2CO_3 (0.217 g, 0.67 mmol). The reaction mixture was degassed with argon for 15 min, and then heated at 100 °C in a preheated oil bath for 15 h. Dioxane was then evaporated under reduced pressure. To the crude mass, water (10 ml) was added and the mixture was extracted with ethyl acetate (3 × 10 ml). The aqueous portion was acidified with aqueous $NaHSO_4$ to maintain pH 3–4 and then extracted with ethylacetate (3 × 10 ml); the organic layer was then washed with brine, dried over sodium sulphate and the solvent was evaporated to obtain the product **4a** which was purified by column chromatography. Yield: 0.059 g (76%).

(*S*)-4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine-3-carboxylic acid (4a). Yield 76%; light brown sticky solid, ^{1}H NMR (400 MHz, DMSO-d_6): 13.16 (br s, 1H), 8.15 (br s, 1H), 6.92–6.85 (m, 3H), 5.06 (m, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.13 (d, *J* = 11.1 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.3, 151.6, 145.0, 126.2, 122.9, 121.3, 120.9, 116.7, 81.5, 65.4, 55.3, 27.6 (3C). LC-MS (ESI): 278.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{14}H_{17}NNaO_5$ 302.1004 *m/z* $[M + Na]^+$, found 302.1004; HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 240 nm, tr (major) 5.88, tr (minor) 5.45, ee > 99%, $[\alpha]_D^{25}$ = −40.8 (*c* 0.49, MeOH). HPLC for the D-isomer: HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 240 nm, tr (major) 5.49, tr (minor) 5.88, ee > 99%; $[\alpha]_D^{25}$ = +40.6 (*c* 0.50, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-6-methyl-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine-3-carboxylic acid (4b). Yield 74%; off-white solid, m.p. 132–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (br s, 1H), 8.02 (br s, 1H), 6.72–6.70 (m, 2H), 5.02 (m, 1H), 4.55 (d, *J* = 11.2, 1H), 4.08 (dd, *J* = 11.6 Hz, *J* = 2.8 Hz, 1H), 2.22 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.3, 151.5, 142.8, 129.7, 125.8, 123.4, 121.2, 116.4, 81.3, 65.3, 55.3, 27.6 (3C), 20.6. LC-MS (ESI): 292.4 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{19}NNaO_5$ 316.1161 *m/z* $[M + Na]^+$, found 316.1161; $[\alpha]_D^{25}$ = −56.0 (*c* 0.20, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-6-ethyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylic acid (4c). Yield 73%; grey solid, m.p. 112–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 13.13 (br s, 1H), 8.02 (br s, 1H), 6.78–6.73 (m, 2H), 5.04 (m, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.08 (dd, *J* = 11.3 Hz, *J* = 2.9 Hz, 1H), 2.55–2.50 (m, 2H), 1.48 (s, 9H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.4, 151.6, 143.0, 136.2, 125.8, 122.3, 120.3, 116.4, 81.4, 65.3, 55.2, 27.8, 27.7 (3C), 15.8. LC-MS (ESI): 306.0 $[M - H]^-$. HRMS (ESI): calcd for $C_{16}H_{21}NNaO_5$ 330.1317 *m/z* $[M + Na]^+$, found 330.1317, HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 240 nm, tr (major) 5.08, tr (minor) 4.59, ee > 99%, $[\alpha]_D^{25}$ = −72.0 (*c* 0.20, MeOH). HPLC for the D-isomer: HPLC analysis: Chiralpak IA (4.6 × 250 mm) 5μ, (MeOH) 1.0 mL min^{-1}, 240 nm, tr (major) 4.59, tr (minor) 5.08, ee > 99%; $[\alpha]_D^{25}$ = +71.7 (*c* 0.20, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-7-isobutyl-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine-3-carboxylic acid (4d). Yield 72%; off-white solid, m.p. 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.07 (br s, 1H), 6.89 (dd, *J* = 8.8 Hz, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 1.6 Hz, 1H), 4.89 (m, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.02 (dd, *J* = 11.1 Hz, *J* = 2.5 Hz, 1H), 1.46 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.5, 151.7, 145.3, 144.6, 123.9, 120.6, 117.4, 113.3, 80.7, 65.7, 55.8, 33.6, 30.9 (3C), 27.7 (3C). LC-MS (ESI): 334.3 $[M - H]^-$. HRMS (ESI): calcd for $C_{18}H_{25}NNaO_5$ 358.1630 *m/z* $[M + Na]^+$, found 358.1634; $[\alpha]_D^{25}$ = −50 (*c* 0.21, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-6-methoxy-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine-3-carboxylic acid (4e). Yield 78%; light yellow solid, m.p. 110–112 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 13.15 (br s, 1H), 7.85 (br s, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8 Hz, *J* = 2.6 Hz, 1H), 5.00 (m, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.05 (dd, *J* = 11.5 Hz, *J* = 2.7 Hz, 1H), 3.69 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, MeOD): 172.7, 155.5, 153.9, 141.3, 128.1, 118.4, 110.5, 108.3, 83.6, 66.9, 57.8, 56.3, 28.6 (3C). LC-MS (ESI): 307.8 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{19}NNaO_6$ 332.1110 *m/z* $[M + Na]^+$, found 332.1110; $[\alpha]_D^{25}$ = −59.7 (*c* 0.52, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-7-methoxy-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine-3-carboxylic acid (4f). Yield 77%; grey solid, m.p. 120–122 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 13.12 (br s, 1H), 8.12 (br s, 1H), 6.50 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.05 (m, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.12 (dd, *J* = 11.3 Hz, *J* = 2.7 Hz, 1H), 3.68 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.3, 155.0, 151.5, 145.7, 121.9, 119.3, 106.9, 101.8, 81.1, 65.7, 55.1, 54.9, 28.1 (3C). LC-MS (ESI): 308.2 $[M - H]^-$. HRMS (ESI): calcd for $C_{15}H_{19}NNaO_6$ 332.1110 *m/z* $[M + Na]^+$, found 332.1110; $[\alpha]_D^{25}$ = −51 (*c* 0.23, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylic acid (4g). Yield 80%; light yellow solid, m.p. 148–150 °C. ^{1}H NMR (400 MHz, MeOD): 7.94 (br s, 1H), 6.48 (s, 1H), 5.07 (m, 1H), 4.65 (d, *J* = 10.4, 1H), 4.08 (dd, *J* = 11.2 Hz, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.3, 151.7, 144.7, 142.3, 138.8, 118.2, 106.4, 101.5, 81.3, 65.6, 56.0, 55.6, 54.9, 27.7 (3C). LC-MS (ESI): 338.0 $[M - H]^-$. HRMS (ESI): calcd for $C_{16}H_{21}NNaO_7$ 362.1216 *m/z* $[M + Na]^+$, found 362.1216; $[\alpha]_D^{25}$ = −61.0 (*c* 0.22, MeOH).

(*S*)-8-(*tert*-Butoxycarbonyl)-7,8-dihydro-6*H*-[1,3]dioxolo-[4′,5′:4,5]benzo[1,2-*b*][1,4]oxazine-7-carboxylic acid (4h). Yield 78%; brown sticky solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.69 (br s, 1H), 6.43 (s, 1H), 5.89 (d, *J* = 8.0 Hz, 2H), 4.74 (m, 1H), 4.56 (d, *J* = 10.3 Hz, 1H), 3.94 (dd, *J* = 10.5 Hz, *J* = 2.7 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.2, 151.5, 142.4, 140.9, 139.8, 118.9, 101.9, 100.8, 98.2, 81.3, 65.7, 55.0, 27.6 (3C). LC-MS (ESI): 322.0, $[M - H]^-$. HRMS (ESI): calcd for

$C_{15}H_{17}NNaO_7$ 346.0903 *m/z* $[M + Na]^+$, found 346.0903; $[\alpha]_D^{25}$ = −65.0 (*c* 0.15, MeOH).

(*S*)-4-(*tert*-Butoxycarbonyl)-6-phenyl-3,4-dihydro-2*H*-benzo[*b*]-[1,4]oxazine-3-carboxylic acid (4i). Yield 72%; light yellow solid, m.p. 130–132 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.49 (br s, 1H), 7.56–7.55 (m, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.34–7.30 (m, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.01 (m, 1H), 4.65 (d, *J* = 10.8, 1H), 4.12 (d, *J* = 10.6 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.3, 151.8, 144.8, 140.3, 132.9, 128.8 (2C), 126.7, 126.1 (2C), 121.1, 119.3, 117.1 (2C), 81.2, 65.8, 55.8, 27.7 (3C). LC-MS (ESI): 354.4 $[M - H]^-$. HRMS (ESI): calcd for $C_{20}H_{21}NNaO_5$ 378.1317 *m/z* $[M + Na]^+$, found 378.1317; $[\alpha]_D^{25}$ = −113 (*c* 0.21, MeOH).

(*S*)-1-(*tert*-Butoxycarbonyl)-2,3-dihydro-1*H*-naphtho[2,1-*b*]-[1,4]oxazine-2-carboxylic acid (4k). Yield 55%; off-white sticky solid, ^{1}H NMR (400 MHz, MeOD): 7.81 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 5.45 (m, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 4.33 (dd, *J* = 10.9 Hz, *J* = 4.0, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 169.4, 152.9, 144.3, 129.6, 128.5, 127.4, 126.5, 125.0, 123.6, 123.2, 118.0, 117.6, 81.2, 67.0, 53.9, 27.5 (3C). LC-MS (ESI): 328.2, $[M - H]^-$. HRMS (ESI): calcd for $C_{18}H_{19}NNaO_5$ 352.1161 *m/z* $[M + Na]^+$, found 352.1160; $[\alpha]_D^{25}$ = +7 (*c* 0.10, MeOH).

(*R*)-*tert*-Butyl 3-(hydroxymethyl)-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (12a). To the acid compound (**4a**) (0.6 g, 2.1 mmol) in dry THF (13 ml) was added diisopropyl amine (0.94 ml, 5.4 mmol). Ethylchloroformate (0.23 ml, 2.3 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 20 min. $NaBH_4$ (0.327 g, 8.6 mmol) was added followed by MeOH (2.2 ml) at 0 °C. The reaction mixture stirred at rt for 1 h. THF and MeOH were evaporated under reduced pressure. To the crude mass, water (15 ml) was added and the solution was then extracted with ethylacetate (3 × 15 ml), dried over sodium sulphate, evaporated and purified by column chromatography to obtain the desired product. Yield: 0.37 g, (65%); yellow sticky liquid, ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (d, *J* = 8.04 Hz, 1H), 6.97–6.93 (m, 1H), 6.89–6.84 (m, 2H), 4.64–4.61 (m, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.09 (dd, *J* = 11.2 Hz, *J* = 2.7 Hz, 1H), 3.67–3.63 (m, 2H), 1.76 (t, *J* = 5.8 Hz, 1H), 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 152.8, 144.9, 124.3, 124.1, 123.4, 120.7, 116.9, 82.1, 64.4, 59.9, 51.9, 28.3 (3C). LC-MS (ESI): 266.3 $[M + H]^+$. HRMS (ESI): calcd for $C_{14}H_{19}NNaO_4$, 288.1212 *m/z* $[M + Na]^+$, found 288.1212. HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (EtOH) 0.5 mL min^{-1}, 242 nm, tr (major) 6.78, tr (minor) 7.28; >98% ee; $[\alpha]_D^{25}$ = −27 (*c* 0.2, MeOH). From D-serine: yellow sticky liquid, HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (EtOH), 0.5 mL min^{-1}, 242 nm, tr (major) 7.26, tr (minor) 6.78, >99% ee, $[\alpha]_D^{25}$ = +26 (*c* 0.22, MeOH).

(*S*)-3a,4-Dihydrobenzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1(3*H*)-one (13a). To the alcohol **12a** (0.081 g, 0.3 mmol) in DMF (1 ml) was slowly added aqueous (6 N) NaOH solution (0.07 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Water (5 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 5 ml). The organic layer was washed with brine, dried over sodium sulphate and purified by column chromatography. Yield: 0.048 g (83%); off white solid, m.p. 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (dd, *J* = 7.7 Hz, *J* = 1.2 Hz, 1H), 7.06–7.01 (m, 2H), 6.99–6.93 (m, 1H), 4.63 (t, *J* = 8.8 Hz, 1H), 4.47 (dd, *J* = 10.6 Hz, *J* = 3.1 Hz, 1H), 4.31–4.23 (m, 1H), 4.11–4.07 (m, 1H), 3.88 (t, *J* = 10.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 154.2, 144.3, 124.8, 123.1, 121.8, 119.6, 116.9, 66.7, 63.5, 50.5. LC-MS (ESI): 192.0 $[M + H]^+$. HRMS (ESI): calcd for $C_{10}H_9NO_3$, 192.0661 *m/z* $[M + H]^+$, found 192.0655; $[\alpha]_D^{25}$ = −51 (*c* 0.26, $CHCl_3$).

(*S*)-*tert*-Butyl-3-(methoxy(methyl)carbamoyl)-2*H*-benzo[*b*]-[1,4]oxazine-4(3*H*)-carboxylate (14a). To the acid **4a** (0.050 g, 0.18 mmol) in dry THF (2 ml) was added EDC·HCl (0.052 g, 0.26 mmol), HOBT (0.036 g, 0.26 mmol), diisopropylethylamine (0.1 ml, 0.55 mmol) and hydrochloride salt of Weinreb amine (0.021 g, 0.21 mmol) successively. The reaction mixture was stirred at rt overnight. THF was evaporated under reduced pressure and water (5 ml) was added to the crude mixture, which was extracted with ethyl acetate (3 × 5 ml). The organic layer was washed with brine, dried over sodium sulphate, evaporated and purified by column chromatography to obtain the desired product. Yield: 0.045 g (77%); off white solid, m.p. 118–120 °C, ^{1}H NMR (400 MHz, DMSO-d_6): 8.20 (bs, 1H), 6.91–6.88 (m, 2H), 6.82–6.79 (m, 1H), 5.29 (m, 1H), 4.47 (dd, *J* = 11.7 Hz, *J* = 1.68 Hz, 1H), 4.19 (dd, *J* = 11.7 Hz, *J* = 3.44 Hz, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 168.3, 151.5, 145.5, 127.4, 122.5, 121.1, 120.6, 116.6, 81.5, 64.7, 61.2, 54.4, 32.0, 27.7 (3C). LC-MS (ESI): 323.1 $[M + H]^+$, 340.1 $[M + NH_4]^+$, HRMS (ESI): calcd for $C_{16}H_{22}N_2NaO_5$ 345.1426 *m/z* $[M + Na]^+$, found 345.1426.

(*S*)-3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylic acid (18a). To the acid **4a** (0.1 g, 0.36 mmol) in DCM (4 ml) was added TFA (0.3 ml, 3.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. DCM and TFA were then evaporated under reduced pressure. To the crude Boc-deprotected acid in dry THF (4 ml) was added EDC·HCl (0.104 g, 0.54 mmol), HOBT (0.073 g, 0.54 mmol), diisopropylethylamine (0.23 ml, 1.3 mmol) and Weinreb amine (0.043 g, 0.44 mmol). The reaction mixture was stirred at rt overnight. THF was evaporated under reduced pressure and water (6 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 6 ml). The organic layer was washed with brine, dried over sodium sulphate and purified by column chromatography. Yield: 0.043 g (54%); yellowish liquid, ^{1}H NMR (400 MHz, DMSO-d_6): 6.70–6.65 (m, 2H), 6.62–6.60 (m, 1H), 6.48–6.44 (m, 1H), 5.87 (s, 1H), 4.37–4.36 (m, 1H), 4.22 (dd, *J* = 10.8 Hz, *J* = 2.9 Hz, 1H), 4.10 (dd, *J* = 10.6 Hz, *J* = 4.1 Hz, 1H), 3.73 (s, 3H), 3.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 143.7, 131.9, 121.9, 119.3, 117.5, 116.7, 64.8, 61.6, 51.8, 32.5. LC-MS (ESI): 223.2 $[M + H]^+$, 245.1 $[M + Na]^+$, HPLC analysis: Cellulose-1 (4.6 × 250 mm) 5μ, (MeOH) Containing 75% CO_2, 2 mL min^{-1}, 210 nm, tr (major) 3.75, tr (minor) 4.35; >99% ee; $[\alpha]_D^{25}$ = −33.4 (*c* 0.5, DCM). HRMS (ESI): calcd for $C_{11}H_{14}N_2NaO_3$, 245.0902 *m/z* $[M + Na]^+$, found 245.0902. From D-serine: yellowish liquid, HPLC analysis: Cellulose-1 (4.6 × 250 mm) 5μ, (MeOH) containing 75% CO_2, 2 mL min^{-1}, 210 nm, tr (major) 4.35, tr (minor) 3.76; >99% ee; $[\alpha]_D^{25}$ = +33.5 (*c* 0.5, DCM).

(*R*)-((*S*)-3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)(phenyl)-methanol (20a). To the Boc-deprotected Weinreb amide **18a** (0.167 g, 0.75 mmol) in dry THF (2 ml) was added phenylmagnesium bromide (1 M, in THF, 2 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was then quenched with saturated NH_4Cl (4 ml) and extracted with ether (3 × 6 ml). The organic layer was dried over sodium sulphate and evaporated under reduced pressure at room temperature. The crude compound was immediately used for the next step without further purification.

To the crude compound **19a** (0.180 g, 0.75 mmol) in MeOH (4 ml) was added $NaBH_4$ (0.029 g, 0.75 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. MeOH was then evaporated under reduced pressure. To the crude product was added NH_4Cl (5 ml) and the mixture was then extracted with ethyl acetate (3 × 6 ml). The organic layer was washed with brine, dried over sodium sulphate, evaporated under reduced pressure, and purified by column chromatography to afford the desired product **20a**. Yield: 0.128 g (70%); sticky liquid, ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.35 (m, 5H), 6.81–6.78 (m, 1H), 6.75–6.63 (m, 2H), 6.46 (d, J = 7.2 Hz, 1H), 4.71–4.67 (m, 1H), 4.33 (d, J = 4.1 Hz, 2H), 3.57–3.45 (m, 1H), 3.39 (bs, 1H), 2.21 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer: 143.6, 140.3, 132.3, 128.5 (2C), 128.2, 126.4 (2C), 121.2, 118.5, 116.2, 115, 73.2, 65.5, 54.4. LC-MS (ESI): 242.2 $[M + H]^+$. HRMS (ESI): calcd for $C_{15}H_{15}NNaO_2$, 264.1000 m/z $[M + Na]^+$, found 264.1000. HPLC analysis: YMC Amylose-C (4.6 × 250 mm) 5μ, (EtOH) 0.5 mL min^{-1}, 220 nm, major diastereomer tr (major) 16.68, tr (minor) 10.16, ee > 99%, minor diastereomer, tr (major) 13.66, tr (minor) 14.86; ee > 99%.

(3*R*,3a*S*)-3-Phenyl-3a,4-dihydrobenzo[*b*]oxazolo[3,4-*d*][1,4]-oxazin-1(3*H*)-one (21a). To the amino alcohol **20a** (0.062 g, 0.26 mmol) in dry DCM (4 ml) was added Et_3N (0.09 ml, 0.64 mmol) and then triphosgene (0.08 g, 0.27 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. Water (6 ml) was added to the reaction mixture, which was then extracted with DCM (3 × 8 ml). The organic layer was washed with brine, dried over sodium sulphate, evaporated and purified by column chromatography to obtain the desired product. Yield: 0.055 g (80%); white solid, m.p. 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): major isomer of **21a** 8.08–8.05 (m, 1H), 7.48–7.38 (m, 4H), 7.30 (d, J = 6.3 Hz, 2H), 7.02–6.99 (m, 2H), 6.89–6.87 (m, 1H), 5.86 (d, J = 9.0, 1H), 4.41 (dt, J = 10.4 Hz, J = 2.8 Hz, 1H), 3.87 (dd, J = 11.0 Hz, J = 2.8 Hz, 1H), 3.24 (t, J = 10.7 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): major isomer: 153.7, 143.8, 133.4, 129.2, 128.6 (2C), 124.9 (2C), 124.5, 123.2, 121.4, 119.4, 116.5, 75.1, 64.7, 53.4. LC-MS (ESI): 268.0 $[M + H]^+$. HRMS (ESI): calcd for $C_{16}H_{13}NNaO_3$, 290.0793 m/z $[M + Na]^+$, found 290.0793.

Notes and references

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