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Divergent Reactions of 2-Aminophenol with α-Bromoacetate: Asymmetric Synthesis of Two Regioisomeric 1,4-Benzoxazinones

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2-Aminophenol displays a diverse pattern of reactivity in the substitution reaction of α-bromoacetate. The substitution under neutral or basic conditions results in the formation of 1,4-benzoxazinones, whereas Lewis acid-promoted substitution leads to Friedel–Crafts alkylation of 2-aminophenol. Asymmetric synthesis of two regioisomeric 1,4-benzoxazinones is accomplished from the nucleophilic substitution of highly diastereoenriched α-aryl-α-bromoacetates with *N*-alkyl-2-aminophenols under varied reaction conditions.

Keywords: Nucleophilic substitution, Asymmetric synthesis, Dynamic resolution, Heterocycles, Chiral auxiliary

Introduction

Condition-based divergence in organic synthesis can generate more than one molecular scaffold in a selective manner from one set of starting materials. As 2-aminophenol has three nonequivalent nucleophilic sites such as amino, hydroxyl, and aromatic groups, it can display a diverse pattern of reactivity in the reactions with an electrophile under varied reaction conditions. In the nucleophilic substitution reaction of α-aryl-α-bromoacetate **1** with 2-aminophenol shown in Figure 1, the displacement with the amino group at the α-bromo carbon and following lactonization with the hydroxy group (Path A) can provide 1,4-benzoxazin-2-one **2**. Next, appropriate tuning of 2-aminophenol reactivity with a base can lead to the nucleophilic substitution with the phenoxide group at the α-bromo carbon and following lactamization with the amino group (Path B) affords regioisomeric 1,4-benzoxazin-3-one **3**. In addition, Lewis acid-promoted reaction of the highly nucleophilic aromatic ring of 2-aminophenol with α-aryl-α-bromoacetate (Path C) leads to Friedel–Crafts alkylation to produce trisubstituted aromatic compound **4**.

Both 1,4-benzoxazin-2-one and 1,4-benzoxazin-3-one structures are frequently found in important pharmaceuticals and natural compounds.[1] Accordingly, an efficient protocol for the asymmetric synthesis of these systems has become a topic of high interest in organic synthesis. While promising advances have recently been made in developing asymmetric synthetic methods for these frameworks,[2,3] the studies for asymmetric synthesis of *N*-alkyl-1,4-benzoxazinones have rarely been reported. We have formerly reported on the *N*-benzoyl-L-threonine-mediated crystallization induced dynamic resolution (CIDR) of configurationally labile α-aryl-α-bromoacetate.[4a] Continuous interest has been focused on developing α-aryl-α-bromoacetate **1** as generally useful platforms for asymmetric organic synthesis.[4b–d] It is recently envisaged that a divergent asymmetric synthesis of two regioisomeric *N*-alkyl-1,4-benzoxazinones would be possible through the nucleophilic substitution reaction of nearly diastereomerically pure α-aryl-α-bromoacetate **1** with *N*-alkyl-2-aminophenols and subsequent spontaneous cyclization. We report herein the convenient divergent asymmetric synthesis of two regioisomeric 1,4-benzoxazinones such as 4-alkyl-3-aryl-1,4-benzoxazin-2-one **2** and 4-alkyl-2-aryl-1,-4-benzoxazin-3-one **3** through the nucleophilic substitution of the configurationally labile α-aryl-α-bromoacetate **1** with various *N*-alkyl-2-aminophenol nucleophiles.

Results and Discussion

Initial studies were carried out with isopropyl *N*-benzoyl L-threoninate-derived α-bromo-α-phenylacetate (**1a**) and *N*-methyl-2-aminophenol as shown in Table 1. When **1a** of 50:50 diastereomeric ratio (dr) was treated with *N*-methyl-2-aminophenol (2.0 equiv), diisopropylethylamine (1.1 equiv., DIEA) and tetrabutylammonium iodide (1.1 equiv., TBAI) in $CHCl_3$ at ambient temperature for 1.5 h, the substitution with the amino group and spontaneous lactonization produced **2a** in 81% yield with 59:41 enantiomeric ratio (er) along with a small amount of regioisomer **3a** as shown in entry 1. The result suggests that the dynamic kinetic resolution of two diastereomers of α-bromo-α-phenylacetate **1a** is not considerably operating in the substitution reaction. The same reaction with highly diastereoenriched (*αR*)-**1a** (99:1 dr) provided **2a** in 95% yield with 89:11 er (entry 2). To obtain the highly enantioenriched **2a** from the substitution of (*αR*)-**1a**, it is essential to perform the substitution under the reaction conditions

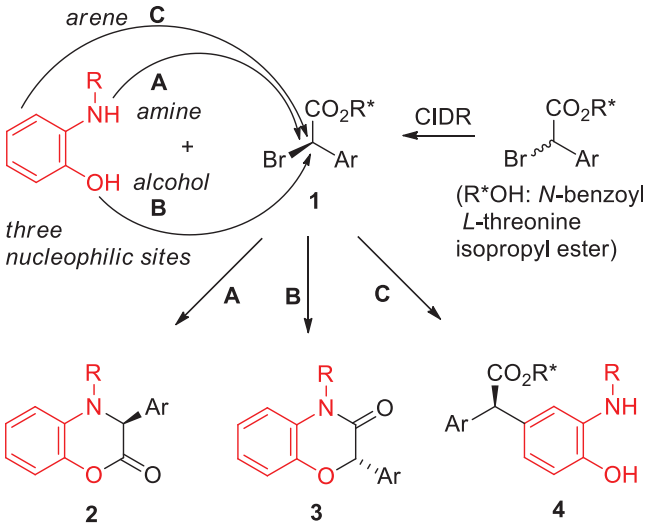
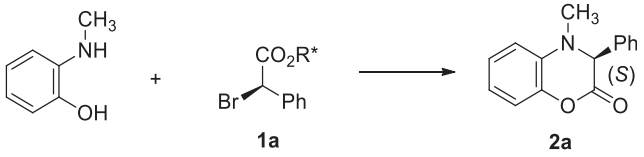


Figure 1. Divergent pathways for the substitution of α-bromoacetate with 2-aminophenol.

that avoid or at least minimize the unfavorable epimerization of (*αR*)-**1a**, when exposed to the basic reaction conditions. Without both DIEA and TBAI, under which conditions the epimerization is not activated, the reaction afforded **2a** as an only product with an improved er of 94:6, while the reaction was slower to provide **2a** in 53% yield after 1.5 h (entry 3). We have thus examined to use more excess amounts of *N*-methyl-2-aminophenol nucleophiles to accelerate the substitution rate with respect to the rate of epimerization of (*αR*)-**1a**. The use of 10 equiv. of *N*-methyl-2-aminophenol successfully produced (*S*)-**2a** in 90% yield with a satisfactory er of 99:1 (entry 4).[5]

The highly efficient asymmetric synthesis of *N*-methyl-1,4-benzoxazin-2-one (**2a**) under the conditions shown in Table 1 (entry 4) encouraged us to investigate the stereoselective syntheses of 4-alkyl-3-aryl-1,4-benzoxazin-2-ones **2b-j** as shown in Scheme 1. When (α*R*)-**1a** of 99:1 dr was treated with seven different *N*-alkyl-2-aminophenols (10 equiv) under the reaction conditions optimized in Table 1, the substitution-lactonizations provided (*S*)-1,-4-benzoxazin-2-ones **2b–h** in yields of 94–63% with high ers ranging from 99:1 to 96:4. The *N*-substituted alkyl groups such as the allyl, *n*-propyl, *n*-pentyl, and benzyl groups influenced both yield and er of products. The reactions with three different *N*-benzyl-2-aminophenols produced **2e**, **2g**, and **2h** with a lowest er of 96:4 among the seven *N*-alkyl-2-aminophenol nucleophiles examined (Scheme 1). Also, the substitution-lactonization of α-bromo-α-(*p*-chlorophenyl)acetate **1b** and α-bromo-α-(*p*-bromophenyl) acetate **1c** with *N*-methyl 2-aminophenol afforded 3-(*p*-chlorophenyl) and 3-(*p*-bromophenyl) substituted 1,4-benzoxazin-2-ones **2i** and **2j** with 99:1 er. The limited results show that the variation of the α-aryl substituent of α-bromoacetate did not affect the er of 1,4-benzoxazin-2-one products. The present er values of

Table 1. Reactions of α-bromo-α-phenylacetate (α*R*)-**1a** with *N*-methyl-2-aminophenol.

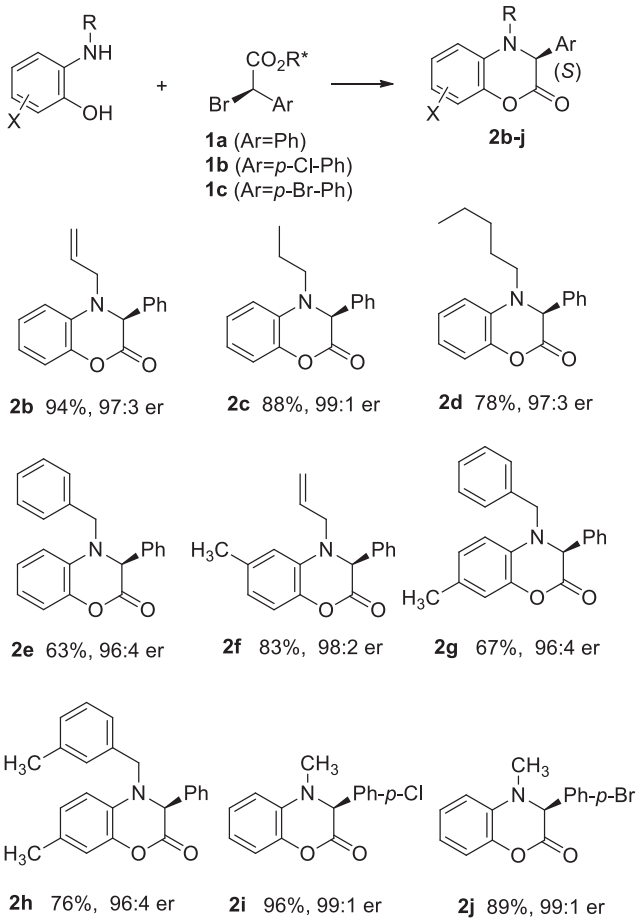


(R*OH: *N*-benzoyl *L*-threonine isopropyl ester)

Entry[a]	Dr of **1a**	Conditions	**2a**:**3a**	Yield	Er[b]
1	50:50	Nuc (2.0 euqiv), TBAI, DIEA	96:4	81	59:41
2	99:1	Nuc (2.0 equiv), TBAI, DIEA	94:6	95	89:11
3	99:1	Nuc (2.0 equiv)	99:1	53	94:6
4	99:1	Nuc (10.0 equiv)	99:1	90	99:1

[a] All the reactions were carried out in $CHCl_3$ (0.1 M) at ambient temp. For 1.5 h.

[b] The enantiomeric ratios were determined by chiral stationary phases (CSP) HPLC using a racemic mixture as a standard.



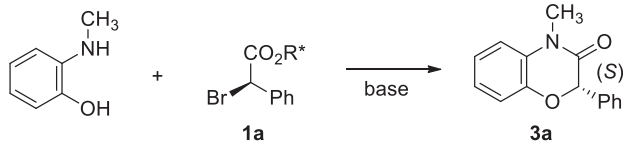
Scheme 1. Asymmetric synthesis of 4-alkyl-3-aryl-1,-4-benzoxazin-2-ones.

3-aryl-1,4-benzoxazin-2-ones **2a-j** obtained from α-aryl-α-bromoacetates (*αR*)-**1a-c** are much higher than the er values (about 90:10 er) obtained from our previous work using the (*R*)-pantolactone-mediated dynamic kinetic resolution of α-aryl-α-bromoacetates.[2h]

Having successfully established a convenient synthetic method in the asymmetric synthesis of 3-aryl-1,4-benzoxazin-2-ones **2a-j**, we next investigated the stereoselective synthesis of their regioisomeric 1,4-benzoxazin-3-ones using phenoxide as a nucleophile. However, the existence of the potentially unstable stereocenter at 2-position of 2-aryl-1,4-benzoxazin-3-one makes it particularly challenging to obtain high optical purity of the product under basic conditions. Our strategy to minimize both the epimerization of (*αR*)-α-aryl-α-bromoacetate and the racemization of 2-aryl-1,4-benzoxazin-3-one is to run the substitution with preformed phenoxide in shortest possible reaction time. Preliminary investigations were performed with the nucleophilic substitution of (*αR*)-**1a** of 99:1 dr with *N*-methyl-2-aminophenol under basic conditions as shown in Table 2. The addition of (*αR*)-**1a** to the premixed solution of *N*-methyl-2-aminophenol (1.5 equiv) and K_2CO_3 (1.3 equiv) in DMF produced two regioisomeric benzoxazinones **3a** and **2a** at a ratio of 67:33 in 85% yield. The substitution of α-bromo-α-phenylacetate **1a** with the preformed phenoxide and spontaneous lactamization afforded 2-phenyl-1,4-benzoxazin-3-one (**3a**) as a major product with 84:16 er and a regioisomer **2a** as a minor product (entry 1). The use of *t*-BuO^-Na^+ as a base improved both the regioisomeric ratio to 86:14 and the er of **3a** to 93:7 (entry 2). No further significant improvement in stereoselectivities was achieved in the reaction using *t*-BuO^-K^+ or NaH (entries 3–4). The use of 2.0 equiv. of base improved the regioselectivity of the reaction to give **3a** as an only product, but the er of **3a** was significantly diminished. We next studied the scope of this asymmetric synthetic strategy with four different *N*-alkyl-2-aminophenols to produce enantio-enriched 2-aryl-1,4-benzoxazin-3-ones as shown in Scheme 2. The treatment of (*αR*)-α-bromo-α-phenylacetate **1a** of 99:1 dr with *N*-alkyl-2-aminophenols and *t*-BuO^-Na^+ under the same reaction conditions shown in Table 2 (entry 2) successfully provided *N*-alkyl-2-phenyl-1,4-benzoxazin-3-ones **3b-e** with er values that ranged from 90:10 to 87:13 in isolated yields of 72–43%.[5]

We have previously studied that both arenes and alcohols can act as a nucleophile for AgOTf-promoted nucleophilic substitution of α-aryl-α-bromoacetates.[4c,d] In order to investigate the competing reactivity between arene and hydroxyl group of 2-aminophenol, the reaction of α-bromoacetate with *N*-Boc-2-aminophenol was investigated in the presence of AgOTf as shown in Scheme 3. The substitution of (*αR*)-α-bromo-α-phenylacetate **1a** (99:1 dr) gave 4-alkyl substituted 2-aminophenol **4a** exclusively in 80% yield with 99:1 dr through the Friedel-Crafts alkylation at the *para*-position to the strong electron donating OH group. When 4-methyl substituted *N*-Boc-2-aminophenol was used as a nucleophile to block the substitution at the 4-position, the substitution showed interesting results as depicted in Scheme 3. The AgOTf-promoted substitution of (*αR*)-**1a** with *N*-Boc-4-methyl-2-aminophenol provided a mixture of *C*-alkylation products **4b** and *O*-alkylation product **5** in a ratio of 2:1. A mixture of regioisomeric dialkyl substituted 2-aminophenols **4b** was produced in 38% yield, while α-aryloxy substituted phenylacetate **5** was isolated in 20% yield. After simple deprotection of *N*-Boc group of **5** with trifluoroacetic acid (TFA), Et_3N-promoted lactamization was completed within 1 h to ultimately afford 6-methyl-2-phenyl-1,4-benzoxazin-3-one **3f** in 59% yield with 93:7 er.

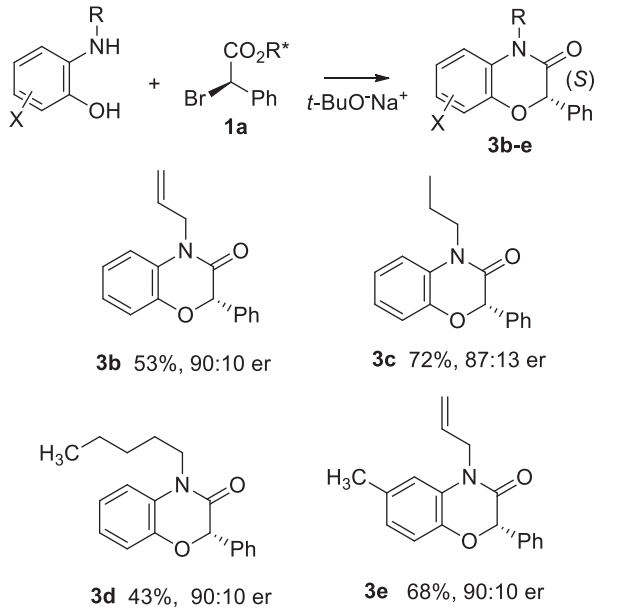
Table 2. Reactions of (α*R*)-**1a** with *N*-methyl-2-aminophenol and a base.



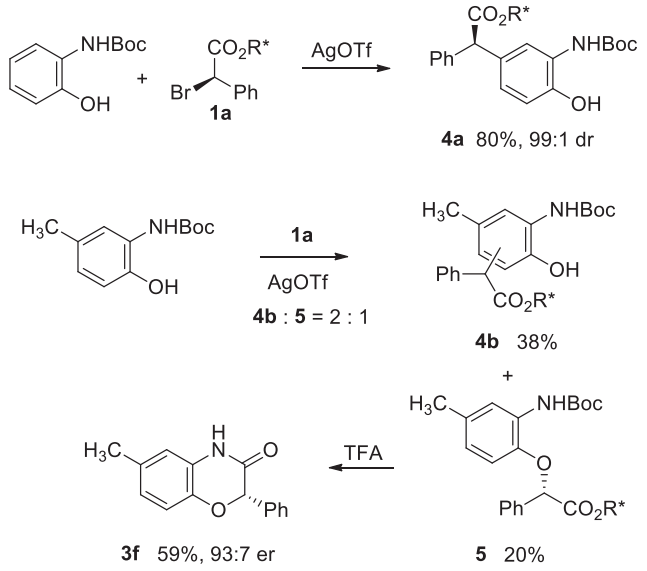
(R*OH: *N*-benzoyl *L*-threonine isopropyl ester)

Entry[a]	Base	**3a**:**2a**[b]	Yield[c]	Er[d]
1	K_2CO_3	67:33	85	84:16
2	*t*-BuO^-Na^+	86:14	68	93:7
3	*t*-BuO^-K^+	85:15	65	93:7
4	NaH	85:15	37	93:7

[a] All the reactions were carried out in DMF (0.2 M) with 1.3 equiv. of base and 1.5 equiv. of 2-aminophenol at ambient temp. For 0.5 h.
[b] The regioisomeric ratios(rr) were determined by ^{1}H-NMRspectroscopy of the reaction mixture.
[c] Combined isolated yield of **3a** and **2a**.
[d] The enantiomeric ratios were determined by chiral stationary phases (CSP) HPLC using a racemic mixture as a standard.



Scheme 2. Asymmetric synthesis of 4-alkyl-2-phenyl-1,-4-benzoxazin-3-ones.



Scheme 3. Friedel–Crafts alkylation of *N*-Boc-2-aminophenols.

Conclusion

We have described the condition-based divergence in asymmetric synthesis of two regioisomeric 1,4-benzoxazinones from the substitution of highly diastereoenriched α-aryl-α-bromoacetates with *N*-alkyl-2-aminophenols. If no base is employed in $CHCl_3$, the nucleophilic substitution at α-bromo carbon with the amine nucleophile and spontaneous lactonization affords 3-aryl-1,4-benzoxazin-2-ones **2a-j** with up to 99:1 er. If *t*-BuO^-Na^+ is used as a base in DMF, regioisomeric 2-aryl-1,4-benzoxazin-3-ones **3a-e** are produced with ers up to 93:7 by the substitution with phenoxide and following spontaneous lactamization. In addition, AgOTf-promoted reactions with *N*-Boc-2-aminophenol afforded highly substituted aromatic compounds by Friedel–Crafts alkylation. While the er values of **3a-f** are not high compared to **2a-j**, the results are worth noting as it is the first example of asymmetric synthesis of *N*-alkyl substituted 2-aryl-1,-4-benzoxazin-3-ones. The condition-based skeletal divergence in substitutions of α-aryl-α-bromoacetate with 2-aminophenol should facilitate the asymmetric synthesis of highly functionalized 1,4-benzoxazinones that could be used for further transformations.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen and those not involving aqueous reagents were carried out in oven-dried glassware. Solvents were purified and dried using standard methods. Unless otherwise stated, all compounds were purchased from commercial sources and were used without further purification. ^1H and ^{13}C NMR spectroscopy were performed on Bruker spectrometer (400 MHz ^1H, 100.6 MHz ^{13}C) using $CDCl_3$ as the internal standard. The HRMS spectroscopic data were obtained using a JEOL JMS-700 by using the FAB or ESI technique. Analytical TLC was performed on silica gel 60F254 plates and visualized by UV irradiation (254 nm). Flash column chromatography was performed with 230–400 mesh silica gel and *n*-hexane-ethyl acetate mixtures as the eluent. Supporting Information (see footnote on the first page of this article): The NMR spectra of new compounds **2d, 2f, 2h, 3b, 3c, 3d, 3e, 4a** and **5** and the CSP-HPLC chromatograms.

General Procedure for the Asymmetric Preparation of 1,4-benzoxazin-2-ones (2a–j)**.** To a solution of (α*R*)-α-aryl-α-bromoacetate (**1a-c**, 1.0 mmol) in $CHCl_3$ (0.1 M) were added *N*-alkyl-2-aminophenol (10 equiv) at ambient temperature. After stirring for 1.5 h, the solution was concentrated and purified by column chromatography on silica gel to afford a 1,4-benzoxazin-2-one.

(*S*)-4-Methyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2a)**.** A pale yellow oil, 90% yield from **1a**; Known compound, ref. 2g; ^1H NMR (400 MHz, $CDCl_3$) 7.33–7.03 (m, 7H), 6.86–6.74 (m, 2H), 5.05 (s, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.6, 140.8, 134.6, 133.9, 129.1, 128.9, 127.3, 125.7, 119.2, 116.5, 112.3, 65.6, 35.3; CSP-HPLC (Chiralcel OD column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 99:1 er, t_R (*S*-enantiomer) = 14.9 min; t_R (*R*-enantiomer) = 18.4 min.

4-Allyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2b)**.** A yellow oil, 94% yield from **1a**; Known compound, ref. 2g; ^1H NMR (400 MHz, $CDCl_3$) 7.19–6.82 (m, 9H), 5.86–5.76 (m, 1H), 5.27–5.20 (m, 3H), 4.11–4.06 (m, 1H), 3.64–3.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.7, 141.0, 135.1, 133.1, 132.4, 129.0, 128.8, 127.3, 125.5, 119.5, 119.1, 116.8, 113.2, 62.8, 50.7; CSP-HPLC (Chiralcel OJ-H column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 97:3 er, t_R (*S*-enantiomer) = 34.5 min; t_R (*R*-enantiomer) = 24.6 min.

2-Oxo-3-phenyl-4-*n*-propyl-3,4-dihydro-2*H*-1,4-benzoxazine (2c)**.** A colorless oil, 88% yield from **1a**; Known compound, ref. 2g; ^1H NMR (400 MHz, $CDCl_3$) 7.28–6.78 (m, 9H), 5.19 (s, 1H), 3.46–3.43 (m, 1H), 3.03–2.99 (m, 1H), 1.69–1.61 (m, 2H), 0.96–0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.5, 140.8, 135.5, 133.1, 129.0, 128.7, 127.0, 125.6, 118.9, 116.8, 112.6, 63.6, 50.4, 20.2, 11.4; CSP-HPLC (Chiralcel OD column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 99:1 er, t_R (*S*-enantiomer) = 10.3 min; t_R (*R*-enantiomer) = 13.1 min.

2-Oxo-3-phenyl-4-*n*-pentyl-3,4-dihydro-2*H*-1,4-benzoxazine (2d)**.** A colorless oil, 78% yield from **1a**; ^1H NMR (400 MHz, $CDCl_3$) 7.27–6.78 (m, 9H), 5.19 (s, 1H), 3.50–3.43 (m, 1H), 3.05–2.97 (m, 1H), 1.66–1.59 (m, 2H), 1.32–1.28 (m, 4H), 0.90–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.5, 140.8, 135.5, 133.1, 129.0, 128.7, 127.0, 125.6, 118.9, 116.8, 112.5, 63.6, 48.6, 29.2, 26.6, 22.5, 14.1; CSP-HPLC (Chiralcel OD column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 97:3 er, t_R (*S*-enantiomer) = 10.8 min; t_R (*R*-enantiomer) = 13.2 min; HRMS: calcd. for $C_{19}H_{22}NO_2$ [M^++1] 296.1651; found 296.1649.

4-Benzyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2e)**.** A pale yellow, 63% yield from **1a**; Known compound, ref. 2g; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35–6.82 (m, 14H), 5.10 (s, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.10 (d, J = 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.7, 141.1, 135.7, 134.7, 133.3, 129.1, 129.0, 128.9, 128.0, 127.8, 127.3, 125.6, 119.7, 116.8, 113.4, 62.7, 51.7; CSP-HPLC (Chiralcel OD column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 96:4 er, t_R (*S*-enantiomer) = 14.3 min; t_R (*R*-enantiomer) = 17.5 min.

4-Allyl-6-methyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2f)**.** A yellow oil, 83% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.27–7.18 (m, 5H), 6.92–6.90 (m, 1H), 6.64–6.62 (m, 2H), 5.84–5.76 (m, 1H), 5.26–5.21 (m, 2H), 5.17 (s, 1H), 4.10–4.05 (m, 1H), 3.60–3.54 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.8, 139.1, 135.3, 135.1, 132.7, 132.5, 129.0, 128.8, 127.4, 120.0, 119.0, 116.4, 113.8, 62.7, 50.6, 21.5; CSP-HPLC (Chiralcel OJ-H column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 98:2 er, t_R (*S*-enantiomer) = 30.4 min; t_R (*R*-enantiomer) = 24.4 min; HRMS: calcd. for $C_{18}H_{18}NO_2$ [M^++1] 280.1338; found 280.1339.

4-Benzyl-7-methyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2g)**.** A colorless oil, 67% yield from **1a**; Known compound, ref. 2g; ^{1}H NMR (400 MHz, $CDCl_3$) 7.23–6.60 (m, 13H), 4.97 (s, 1H), 4.50 (d, J = 14.8 Hz, 1H), 3.97 (d, J = 14.8 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.0, 141.2, 136.0, 134.8, 130.9, 129.8, 129.0, 128.9, 128.8, 127.9, 127.8, 127.4, 126.0, 117.3, 113.5, 62.9, 52.1, 20.5; CSP-HPLC (Chiralcel OD column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 96:4 er, t_R (*S*-enantiomer) = 14.3 min; t_R (*R*-enantiomer) = 17.5 min.

7-Methyl-4-(*m*-methylbenzyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2h)**.** A colorless oil, 76% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28–6.64 (m, 12H), 5.05 (s, 1H), 4.64 (d, J = 14.4 Hz, 1H), 4.00 (d, J = 14.4 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.9, 139.1, 138.7, 135.7, 135.4, 134.8, 133.1, 129.0, 128.8, 128.7, 128.6, 127.3, 125.1, 120.1, 116.5, 113.7, 62.2, 51.4, 21.5; CSP-HPLC (Chiralcel OD column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 96:4 er, t_R (*S*-enantiomer) = 13.3 min; t_R (*R*-enantiomer) = 15.8 min; HRMS: calcd. for $C_{23}H_{22}NO_2$ [M^++1] 344.1651; found 344.1649.

3-(*p*-Chlorophenyl)-4-methyl-2-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (2i)**.** A pale yellow, 96% yield from **1b**; Known compound, ref. 2g; ^{1}H NMR (400 MHz, $CDCl_3$) 7.26–6.75 (m, 8H), 5.03 (s, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.1, 140.7, 135.0, 133.5, 133.0, 129.3, 128.7, 125.9, 119.5, 116.6, 112.4, 64.9, 35.4; CSP-HPLC (Chiralcel OJ-H column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 99:1 er, t_R (*S*-enantiomer) = 58.2 min; t_R (*R*-enantiomer) = 36.8 min.

3-(*p*-Bromophenyl)-4-methyl-2-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (2j)**.** A pale yellow, 89% yield from **1c**; Known compound, ref. 2g; ^{1}H NMR (400 MHz, $CDCl_3$) 7.47–6.75 (m, 8H), 5.01 (s, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.0, 140.7, 133.5, 132.3, 128.9, 125.9, 123.2, 119.5, 116.6, 112.4, 65.0, 35.4; CSP-HPLC (Chiralcel OJ-H column; 20% isopropanol in *n*-hexane; 0.5 mL/min): 99:1 er, t_R (*S*-enantiomer) = 39.3 min; t_R (*R*-enantiomer) = 27.7 min.

General Procedure for the Asymmetric Preparation of 1,4-benzoxazine-3-ones (3a–e)**.** Sodium *tert*-butoxide (t-BuO$^-$Na$^+$, 1.3 equiv) was added to a solution of *N*-alkyl-2-aminophenol phenol (1.5 equiv) in DMF (ca. 0.1 M) at ambient temperature and the resulting reaction mixture was stirred at 45°C for 10 min. To the above solution was added α-bromo-α-phenylacetate (**1a**, 1.0 mmol) at ambient temperature. After stiiring for 20 min. Under a nitrogen atmosphere, the mixture was treated with extractive work up and the solvent was evaporated. The crude mixture was purified by column chromatography on silica gel to afford a 1,4-benzoxazin-3-one.

(*S*)-4-Methyl-3-oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (3a)**.** A yellow oil, 55% yield from **1a**; Known compound, ref. 6; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41–7.29 (m, 5H), 7.06–6.93 (m, 4H), 5.72 (s, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.7, 144.0, 135.4, 129.3, 128.7, 128.6, 126.9, 124.1, 122.7, 117.5, 114.8, 78.6, 28.5; CSP-HPLC (Chiralcel OJ-H column; 40% isopropanol in *n*-hexane; 0.5 mL/min): 93:7 er, t_R (*S*-enantiomer) = 55.5 min; t_R (*R*-enantiomer) = 48.0 min.

4-Allyl-3-oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (3b)**.** A pale yellow oil, 53% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49–7.23 (m, 5H), 7.11–6.92 (m, 4H), 5.93–5.83 (m, 1H), 5.76 (s, 1H), 5.21–5.12 (m, 2H), 4.76–4.70 (m, 1H), 4.47–4.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.4, 144.1, 135.2, 131.6, 128.7, 128.6, 128.5, 126.8, 124.1, 122.7, 117.7, 117.2, 115.4, 78.5, 44.1; CSP-HPLC (Chiralcel OD column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 90:10 er, t_R (*S*-enantiomer) = 14.5 min; t_R (*R*-enantiomer) = 17.9 min; HRMS: calcd. for $C_{17}H_{16}NO_2$ [M^++1] 266.1181; found 266.1181.

3-Oxo-2-phenyl-4-*n*-propyl-3,4-dihydro-2*H*-1,4-benzoxazine (3c)**.** A colorless oil, 72% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41–7.27 (m, 5H), 7.05–6.94 (m, 4H), 5.71 (s, 1H), 4.00–3.89 (m, 2H), 1.75–1.68 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.4, 144.2, 135.4, 128.6, 128.5, 128.3, 126.9, 123.9, 122.7, 117.8, 114.8, 78.4, 43.2, 20.5, 11.2; CSP-HPLC (Chiralcel OJ-H column; 40% isopropanol in *n*-hexane; 0.5 mL/min): 87:13 er, t_R (*S*-enantiomer) = 39.0 min; t_R (*R*-enantiomer) = 55.0 min; HRMS: calcd. for $C_{17}H_{18}NO_2$ [M^++1] 268.1338; found 268.1337.

3-Oxo-4-*n*-pentyl-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (3d)**.** A colorless oil, 43% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41–7.28 (m, 5H), 7.06–6.94 (m, 4H), 5.70 (s, 1H), 4.01–3.92 (m, 2H), 1.71–1.67 (m, 2H), 1.38–1.35 (m, 4H), 0.92–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.3, 144.2, 135.4, 128.6, 128.5, 128.3, 126.9, 123.9, 122.7, 117.8, 114.7, 78.4, 41.7, 29.0, 26.9, 22.4, 14.0; CSP-HPLC (Chiralcel OJ-H column; 40% isopropanol in *n*-hexane; 0.5 mL/min): 90:10 er, t_R (*S*-enantiomer) = 17.7 min;

t_R (*R*-enantiomer) = 20.1 min; HRMS: calcd. for $C_{19}H_{22}NO_2$ [M^+ + 1] 296.1651; found 296.1651.

4-Allyl-6-methyl-3-Oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (3e)**.** A pale yellow oil, 68% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.34–7.28 (m, 5H), 6.96–6.72 (m, 3H), 5.94–5.84 (m, 1H), 5.73 (s, 1H), 5,21–5.12 (m, 2H), 4.76–4.70 (m, 1H), 4.45–4.40 (m, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.6, 141.8, 135.3, 132.3, 131.6, 128.6, 128.5, 128.2, 126.7, 124.5, 117.3, 117.1, 115.9, 78.4, 44.1, 21.1; CSP-HPLC (Chiralcel OD column; 10% isopropanol in *n*-hexane; 0.5 mL/min): 90:10 er, t_R (*S*-enantiomer) = 13.0 min; t_R (*R*-enantiomer) = 15.1 min; HRMS: calcd. for $C_{18}H_{18}NO_2$ [M^++1] 280.1338; found 280.1341.

6-Methyl-3-oxo-2-phenyl-3,4-dihydro-2H-1,4-benzoxazine (3f)**.** A colorless oil, 59% yield from **5**; Known compound, ref. 3b,7a; ^{1}H NMR (400 MHz, $CDCl_3$) 7.47–7.33 (m, 5H), 6.91–6.65 (m, 3H), 5.68 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.9, 140.5, 135.1, 132.5, 129.0, 128.8, 127.1, 125.5, 125.0, 117.0, 116.6, 78.4, 20.8; CSP-HPLC (Chiralcel OJ-H column; 40% isopropanol in *n*-hexane; 0.5 mL/min): 93:7 er, t_R (*S*-enantiomer) = 19.8 min; t_R (*R*-enantiomer) = 17.3 min.

General Procedure for the Preparation of 4a **and** 5**.** To a solution of α-bromo-α-phenylacetate **1a** of 99:1 dr (1.0 equiv) at ambient temperature were added *N*-Boc-2-aminophenol (10 equiv) and AgOTf (1.0 equiv). After the reaction mixture was stirred for 3 h, the resulting mixture was treated with extractive work up and the solvent was evaporated. The crude mixture was purified by column chromatography on silica gel to afford the product.

***N*-Benzoyl-*O*-[α-(*N*-Boc-3-amino-4-hydroxyphenyl) phenylacetyl]-L-threonine Isopropyl Ester** (4a)**.** A yellow oil, 99:1 dr, 80% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53–7.34 (m, 10H), 7.09–7.07 (m, 1H), 7.01–6.97 (m, 2H), 6.74–6.70 (m, 1H), 6.49–6.47 (m, 1H), 5.52–5.47 (m, 1H), 5.09–4.93 (m, 4H), 1.52 (s, 9H), 1.23 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.4, 169.0, 168.1, 151.6, 138.4, 138.0, 136.9, 133.7, 132.0, 129.1, 128.5, 127.4, 127.2, 121.9, 118.0, 112.7, 84.2, 73.1, 70.0, 60.8, 55.7, 27.6, 21.8, 21.5, 16.3; HRMS: calcd. for $C_{33}H_{39}N_2O_8$ [M^++1] 591.2706; found 591.2705.

***N*-Benzoyl-*O*-[α-(*N*-Boc-2-amino-4-methylphenoxy) phenylacetyl]-L-threonine Isopropyl Ester** (5)**.** A yellow oil, 20% yield from **1a**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (br, 1H), 7.72–7.70 (m, 2H), 7.55–7.20 (m, 8H), 6.86–6.82 (m, 1H), 6.67–6.57 (m, 2H), 5.57 (s, 1H), 5.54–5.48 (m, 1H), 5.00–4.86 (m, 2H), 2.24 (s, 3H), 1.50 (s, 9H), 1.22 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.0, 168.9, 167.8, 152.9, 143.6, 134.9, 133.5, 132.5, 132.1, 129.4, 129.0, 128.7, 128.6, 128.5, 127.2, 127.1, 127.0, 122.8, 119.7, 113.0, 80.5, 79.9, 72.8, 70.2, 55.8, 28.3, 21.8, 21.3, 21.1, 16.6; HRMS: calcd. For $C_{34}H_{41}N_2O_8$ [M^++1] 605.2863; found 605.2866.

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Conflict of interest. The authors declare no conflict of interest.

Supporting Information. Additional supporting information is available in the online version of this article. The NMR spectra of new compounds **2d**, **2f**, **2h**, **3b**, **3c**, **3d**, **3e**, **4a** and **5** and the CSP-HPLC chromatograms.

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