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Dynamic resolution of α-halo chiral esters for the synthesis of 3-substituted piperazin-2-ones

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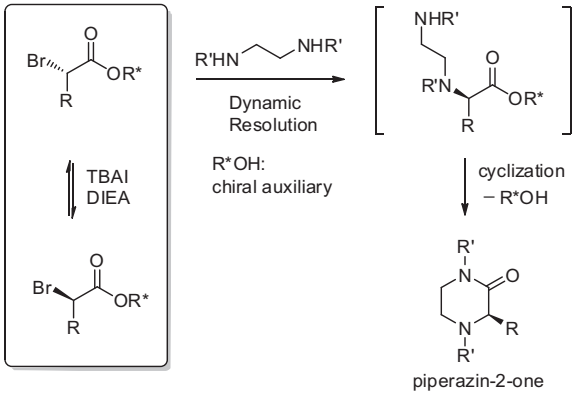
ABSTRACT

Dynamic resolution of α-halo esters derived from five chiral alcohols has been investigated in nucleophilic substitution with ethylenediamine nucleophiles. Stereoselective substitution of α-halo esters and following spontaneous cyclization provide a practical protocol for asymmetric syntheses of 3-substituted piperazin-2-ones up to 94:6 er.

1. Introduction

Piperazin-2-one rings are of great interest since they represent the structural core of several biologically active compounds and are useful synthetic intermediates of various piperazines.[1] While some progress has recently been made toward the development of asymmetric synthetic methods for these compounds, it still remains a great challenge in the field of organic synthesis.[2] In the course of our studies on dynamic resolution of α-halo esters in asymmetric synthesis, we envisaged a simple method for chiral piperazin-2-ones bearing variable substituents at C-3 position.[3] The strategy to obtain the enantioenriched piperazinone scaffold involves a chiral alcohol-controlled dynamic resolution of α-halo esters in nucleophilic substitution with ethylenediamine nucleophiles as shown in Scheme 1. The first step of this reaction would be the stereoselective nucleophilic attack of an amino group of 1,2-diamine at the α-halo carbon center. The subsequent nucleophilic attack of the second amino group at the ester function produces piperazin-2-ones by ring closure and loss of chiral auxiliary. Herein we report a novel asymmetric synthetic method for 3-substituted piperazin-2-ones via chiral alcohol-controlled dynamic resolution of α-halo esters in nucleophilic substitution with various ethylenediamine nucleophiles.



Scheme 1. Asymmetric synthesis of 3-substituted piperazin-2-one.

2. Results and discussion

Five different chiral alcohols, such as lactate, mandelate, diacetoneglucose, pantolactone, and *N*-methylpseudoephedrine have been tested for their stereocontrolling ability in dynamic resolution of α-halo esters. Initial studies on chiral alcohol-controlled asymmetric synthesis of piperazinones were carried out with ethyl (*S*)-lactate.[4] When the diastereomeric mixture (1:1) of α-bromo ester (α*RS*)-**1a** was treated with tetrabutylammonium iodide (TBAI, 1.0 equiv), diisopropylethylamine (DIEA, 1.0 equiv), and ethylenediamine ($H_2NCH_2CH_2NH_2$, 1.2 equiv) in CH_2Cl_2 at room

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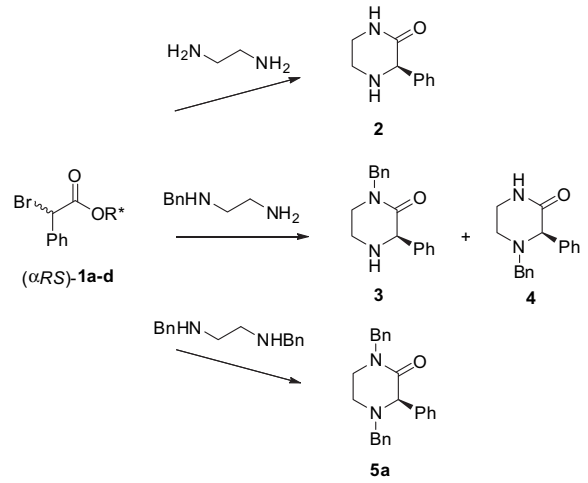
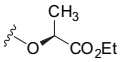
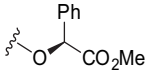
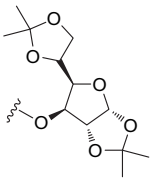
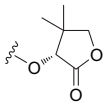
temperature for 12 h, the substitution and spontaneous cyclization produced piperazinone (*R*)-**2** in 48% yield with 80:20 enantiomeric ratio (er) as shown in Table 1, entry 1. When *N*-benzyl ethylenediamine ($BnHNCH_2CH_2NH_2$) was used as a nucleophile, the reaction produced two regioisomeric piperazinones. Treatment of **1a** with the nucleophile, TBAI, and DIEA for 12 h gave 1-benzyl-3-phenyl-2-piperazinone (**3**) as a major product with 80:20 er and 4-benzyl-3-phenyl-2-piperazinone (**4**) as a minor product with 87:13 er (entry 2). The regioselectivity of 67:33 suggests different reactivities of two amino groups. The sterically less hindered primary amino group of the nucleophile is more reactive than the secondary *N*-benzyl amino group. In addition, the reaction of **1a** with *N*,*N*-dibenzyl ethylenediamine ($BnHNCH_2CH_2NHBn$) nucleophile gave (*R*)-1,4-dibenzyl-3-phenyl-2-piperazinone (**5a**) with a comparable er of 83:17.

In an effort to improve the stereoselectivity, we examined a series of substitution reactions of α-bromo α-phenyl acetates with three different chiral auxiliaries.[5–7] Nucleophilic substitutions of **1b**–**d** were conducted under the same reaction condition as that used for ethyl (*S*)-lactate-derived α-bromo ester **1a**. No substantial difference in stereoselectivity has been found in the reactions of **1b** derived from ethyl (*S*)-mandelate with three different ethylenediamine nucleophiles (entries 4–6). A higher regioselectivity was observed with *N*-benzyl ethylenediamine to produce **3** and **4** in a ratio of 77:23 (entry 5). Next, we examined the reactivity and the stereocontrolling ability of diacetone-D-glucose auxiliary in the

Table 1
Reactions of **1a**–**d** with ethylenediamine nucleophiles



Entry[a]	Substrate	OR*	Nucleophile	Time (h)	Yield (%)	er[d] (*R*/*S*)
1			$H_2NCH_2CH_2NH_2$	12	48	80:20
2	**1a**		$BnHNCH_2CH_2NH_2$	12	66[b] (67:33)[c]	80:20 87:13[e]
3			$BnHNCH_2CH_2NHBn$	12	70	83:17
4			$H_2NCH_2CH_2NH_2$	12	44	75:25
5	**1b**		$BnHNCH_2CH_2NH_2$	12	50[b] (77:23)[c]	82:18 81:19[e]
6			$BnHNCH_2CH_2NHBn$	12	87	87:13
7			$H_2NCH_2CH_2NH_2$	12	48	19:81
8	**1c**		$BnHNCH_2CH_2NH_2$	12	87[b] (89:11)[c]	15:85 20:80[e]
9			$BnHNCH_2CH_2NHBn$	12	54	15:85
10			$H_2NCH_2CH_2NH_2$	3	61	8:92
11	**1d**		$BnHNCH_2CH_2NH_2$	3	89[b] (58:42)[c]	10:90 13:87[e]
12			$BnHNCH_2CH_2NHBn$	3	73	6:94

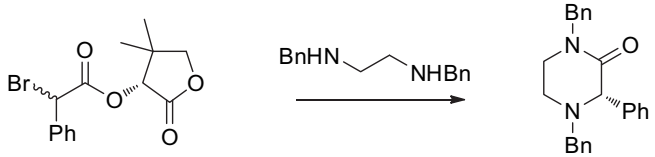
[a] All reactions are carried out with DIEA and TBAI in methylene chloride at rt.
[b] Combined isolated yields of **3** and **4**.
[c] The ratio (**3**/**4**) was determined by H NMR of the reaction mixture.
[d] Determined by CSP-HPLC.
[e] er of minor product **4**.

substitution reactions with the ethylenediamine nucleophiles. Treatment of α-bromo ester **1c** with ethylenediamine, TBAI, and DIEA gave the substitution product (*S*)-**2** in 48% yield with 81:19 er as shown in entry 7. Notably, the reaction of **1c** with *N*-benzyl ethylenediamine took place with a higher regioselectivity, affording **3** and **4** with a ratio of 89:11 (entry 8). In the substitution reactions of α-bromo ester **1d** derived from (*R*)-pantolactone, we are pleased to observe much higher stereoselectivities (entries 10–12). The reaction of **1d** with *N*,*N*-dibenzyl ethylenediamine gave (*S*)-**5a** with a highest stereoselectivity of 96:4 er compared to the reactions of **1a**–**c** (entry 12).

A series of reactions were examined with (*R*)-pantolactone-derived α-bromo ester **1d** to assess the effect of additive, solvent, and temperature on yield and stereoselectivity as shown in Table 2. In the presence of either DIEA or TBAI, almost same stereoselectivity was observed with slightly lower yields (entries 1 and 2). However, significant decrease in stereoselectivity was observed in the absence of both TBAI and DIEA (entry 3). We speculate that the lowering of er in the absence of an epimerizing agent probably results from the slower epimerization of α-bromo ester **1d**. None of other solvents explored gave better selectivities than CH_2Cl_2 and the reaction in acetone is very slow. As shown in entries 4–11, the substitution product **5a** was obtained with 94:6 er in $CHCl_3$, 94:6 er in ethyl acetate, 91:9 er in CH_3CN, 92:8 er in THF, 94:6 er in *p*-dioxane, 93:7 er in DMF, 93:7 er in acetone, and 91:9 er in diethyl ether. Both reactions at 50 °C and at 0 °C did not show better selectivity compared to the reactions at room temperature.

Next, we examined the scope of the methodology in CH_2Cl_2 with various α-substituents as shown in Table 3. Initial studies were carried out with the substitution reactions of α-chloro-α-phenyl ester **1e** derived from (*R*)-pantolactone. When α-chloro ester **1e** was treated with *N*,*N*-dibenzyl ethylenediamine, TBAI, and DIEA for 5 h, the substitution provided (*S*)-**5a** in 72% yield with same enantioselectivity (94:6 er) as the reactions of α-bromo ester **1d** (entry 1). Under the same reaction condition, this methodology is also efficient for the asymmetric preparation of 3-(1-naphtyl) piperazinone **5b** with 94:6 er (entry 2). Reactions of α-(4-fluorophenyl) α-bromo ester **1g** and α-(4-methylphenyl) α-chloro ester **1h** gave the substitution products **5c** and **5d**, respectively, with a stereoselectivity of 93:7 er (entries 3 and 4). In addition, the reaction of α-(4-fluoro-2-methylphenyl) α-chloro ester **1i** took place with 94:6 er, affording **5e**, the key intermediate in the synthesis of GW597599 known as a potent NK1 receptor antagonist[2a,b] (entry 5).

Table 2
Synthesis of **5a** in various conditions

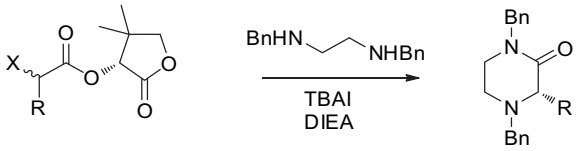


(α*RS*)-**1d** (*S*)-**5a**

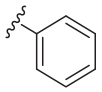
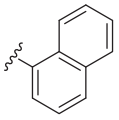
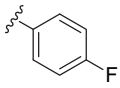
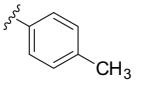
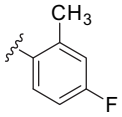
Entry[a]	Solvent	Additive	Temp	Yield[b] (%)	er[c] (*S*/*R*)
1	CH_2Cl_2	DIEA	rt	58	93:7
2	CH_2Cl_2	TBAI	rt	66	93:7
3	CH_2Cl_2	No additive	rt	48	65:35
4	$CHCl_3$	DIEA, TBAI	rt	66	94:6
5	Ethyl acetate	DIEA, TBAI	rt	72	94:6
6	CH_3CN	DIEA, TBAI	rt	58	91:9
7	THF	DIEA, TBAI	rt	62	92:8
8	Dioxane	DIEA, TBAI	rt	50	94:6
9	DMF	DIEA, TBAI	rt	72	93:7
10	Acetone	DIEA, TBAI	rt	18	93:7
11	Diethyl ether	DIEA, TBAI	rt	60	91:9
12	CH_2Cl_2	DIEA, TBAI	0 °C	43	93:7
13	CH_2Cl_2	DIEA, TBAI	50 °C	75	94:6

[a] All reactions are carried out for 3 h.
[b] Isolated yields.
[c] ers are determined by CSP-HPLC.

Table 3
Asymmetric synthesis of 3-substituted piperazinones **5a**–**h**



(α*RS*)-**1e-l** (*S*)-**5a-h**

Entry[a]	S.M.	X	R	Yield[b] (%)	er[c] (*S*/*R*)
1	**1e**	Cl		72 (**5a**)	94:6
2	**1f**	Cl		80 (**5b**)	94:6
3	**1g**	Br		90 (**5c**)	93:7
4	**1h**	Cl		72 (**5d**)	93:7
5	**1i**	Cl		55 (**5e**)	94:6
6	**1j**	Br	CH_3	56 (**5f**)	83:17
7	**1k**	Br	CH_2CH_3	77 (**5g**)	86:14
8	**1l**	Br	$CH_2CH_2CH_2CH_3$	62 (**5h**)	85:15

[a] All reactions are carried out for 3 h in methylene chloride at rt.
[b] Isolated yields.
[c] ers are determined by CSP-HPLC.

Encouraged by the observation of high stereoselectivities in the reactions with pantolactone-derived α-aryl esters **1d**–**i**, we carried out the nucleophilic substitutions of α-alkyl esters **1j**–**l** with *N*,*N*-dibenzyl ethylenediamine nucleophile. The reaction of α-bromo-α-methyl ester **1j** afforded 3-methyl piperazinone **5f** with 83:17 er in 56% yield (entry 6). As with α-bromo-α-ethyl ester **1k** and α-bromo-α-butyl ester **1l**, the reactions with *N*,*N*-dibenzyl ethylenediamine, DIEA, and TBAI took place to afford 3-ethyl piperazinone **5g** and 3-butyl piperazinone **5h** with 86:14 er and 85:15 er, respectively (entries 7 and 8). In all reactions of pantolactone-derived α-alkyl esters **1j**–**l**, much lower stereoselectivity was observed compared to α-aryl esters **1d**–**i**.

To understand the reaction pathway of asymmetric induction in nucleophilic substitution with *N*,*N*-dibenzyl ethylenediamine, we carried out a series of reactions of α-chloro ester **1e** as shown in Table 4. When a mixture of two epimers (69:31 dr) of **1e** was allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the epimeric ratio of recovered **1e** was determined to be 52:48 (entry 1). The result indicates that α-chloro ester **1e** is configurationally labile under the reaction condition and the thermodynamic stabilities of two epimers are almost same, ruling out dynamic thermodynamic resolution as a primary pathway. When

1e with 29:71 dr was treated with *N*,*N*-dibenzyl ethylenediamine in the presence of both TBAI and DIEA, the reaction gave 2-piperazinone **5a** with 94:6 er as shown in entry 2. In addition, almost same er of **5a** was observed in the reaction of **1e** with reversed diastereomeric enrichment of 67:33 dr (entry 3). Thus, the er of **5a** is independent of the starting ratio of two epimers of **1e** and would depend on the difference in the epimeric transition state energies. These results could be taken to suggest that the epimerization of **1e** promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.

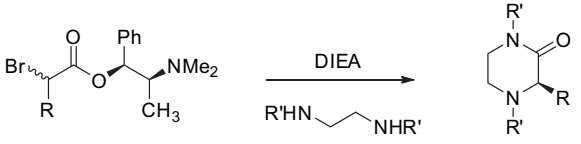
Table 4
Dynamic kinetic resolution of α-bromo ester **1e**

Entry[a]	Substrate (dr)[b]	Condition	Product	Yield (%)
1	**1e** (69:31)[b]	TBAI, DIEA	**1e** (52:48 dr)	95
2	**1e** (29:71)[b]	TBAI, DIEA, nucleophile	**5a** (94:6 er)[c]	77
3	**1e** (67:33)[b]	TBAI, DIEA, nucleophile	**5a** (94:6 er)[c]	74

[a] All reactions were carried out for 3 h at rt.
[b] The diastereomeric mixtures of **1e** are prepared by column chromatography with fractional collection and the drs were determined by ^{1}H NMR.
[c] *S*/*R*.

N-Methylpseudoephedrine-controlled asymmetric nucleophilic substitution of α-bromo esters has recently been developed in our laboratory for stereoselective preparation of α-heteroatom substituted carboxylic acids. The primary pathway of the asymmetric induction is a dynamic thermodynamic resolution (DTR) in which the product ratio is determined by the ratio of two epimeric species that is established before the addition of nucleophile.[8] The successful results on α-alkyl-α-bromo esters prompt us to extend the methodology to asymmetric syntheses of 3-alkyl substituted piperazinones. As shown in Table 5, the reactions of (*S*,*S*)-*N*-methylpseudoephedrine α-bromo-α-butyl ester (α*RS*)-**1m** of 56:44 diastereomeric ratio (dr) with ethylenediamine ($H_2NCH_2CH_2NH_2$) produced 3-butyl piperazinone (*R*)-**5i** with 60:40 er (entry 1). In contrast, when **1m** was allowed to equilibrate for 20 h before the addition of the nucleophile, the epimerization with DIEA gave the thermodynamically equilibrated mixture (89:11 dr) of **1m** and the following substitution provided (*R*)-**5i** with 91:9 er (entry 2). The dependency of product ratios on the dr of α-bromo ester of **1m** implied that the epimerization is not fast with respect to their rate of substitution enough to get to thermodynamic equilibrium before the substitution. When we used *N*,*N*-dibenzyl ethylenediamine ($BnHNCH_2CH_2NHBn$) as a nucleophile in the reaction of α-bromo-α-ethyl ester (α*RS*)-**1n** (52:48 dr), the substitution furnished 3-ethyl piperazinone **5g** in 68% yield with 85:15 er (*R*/*S*) (entry 3). Slower reaction of *N*,*N*-dibenzyl ethylenediamine compared to the reaction of ethylenediamine could provide α-bromo ester **1n** more time for epimerization before the substitution and the improved stereoselectivity. The stepwise epimerization–substitution protocol shown in entry 4 provided **5g** in 72% yield with an increased er of 94:6. The enhancement of product ratio compared to thermodynamic ratio (89:11 dr) of **1n** suggest an additional asymmetric induction by dynamic kinetic resolution.[8b,e] The epimerization–substitution protocol can provide for the formation of highly enantioenriched 3-alkyl piperazinones **5g** and **5i** from the reaction which may seem to have a low level of stereoselectivity at first sight.

Table 5
Asymmetric synthesis of 3-substituted piperazinones **5g** and **5i**



(α*RS*)-**1m-n** **5g** and **5i**

Entry[a]	S.M.	R	Condition	R′	Yield[b] (%)	er[c] (*R*/*S*)
1	**1m**	*n*-Bu	No epimerization	H	67 (**5i**)	60:40
2	**1m**	*n*-Bu	20 h epimerization	H	60 (**5i**)	91:9
3	**1n**	Et	No epimerization	Bn	68 (**5g**)	85:15
4	**1n**	Et	20 h epimerization	Bn	72 (**5g**)	94:6

[a] All reactions are carried out in CH_3CN at rt and the substitution is performed for 12 h.
[b] Isolated yields.
[c] ers are determined by CSP-HPLC.

3. Conclusion

We have presented a novel and practical approach for the asymmetric syntheses of 3-substituted piperazin-2-ones via dynamic resolution of α-halo esters derived from various chiral alcohol auxiliaries. Pantolactone is an effective and convenient chiral auxiliary for the asymmetric syntheses of 3-aryl substituted piperazin-2-ones in the nucleophilic substitution with *N*,*N*-dibenzyl ethylenediamine nucleophile. Also, preparation of highly enantioenriched 3-alkyl substituted piperazin-2-ones was achieved using *N*-methyl pseudoephedrine-controlled epimerization–substitution process. The simple protocol with mild condition and the spontaneous removal of chiral auxiliary suggests further applications of these methodologies to asymmetric syntheses of various heterocyclic compounds.

4. Experimental

4.1. General procedure for the preparation of α-halo ester 1

A chiral alcohol (1.0 equiv) was treated with racemic α-bromo carboxylic acid (1.0 equiv), DCC, and DMAP (or α-chloro acid chloride and Et_3N) in CH_2Cl_2 and stirred at room temperature for 3–10 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide the crude product that was purified by column chromatography on silica gel. α-Halo esters **1b**–**d**, **1j**–**m**, and **1n** were prepared by previously reported procedure in Refs. 4–8.

*4.1.1. (2-Ethoxy-(S)-1-methyl-2-oxoethyl) 2-bromo-2-phenylacetate (**1a**).* A pale yellow oil was obtained in 72% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.59–7.55 (m, 2H), 7.37–7.30 (m, 3H), 5.44, 5.43 (s, 1H), 5.13 (m, 1H), 4.20, 4.12 (m, 2H), 1.50, 1.48 (d, *J*=7.2 Hz, 3H), 1.23, 1.15 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.2, 168.0, 135.9, 135.8, 129.7, 129.2, 70.1, 62.0, 46.5, 17.1, 14.4. Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.47; H, 4.91.

*4.1.2. 2-Chloro-2-phenylacetic acid (R)-pantolactone ester (**1e**).* A pale yellow oil was obtained in 83% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.54–7.48 (m, 2H), 7.38–7.33 (m, 3H), 5.54, 5.52 (s, 1H), 5.37, 5.34 (s, 1H), 3.97–3.88 (m, 2H), 1.13, 1.04, 0.98, 0.74 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 167.7, 134.7, 129.6, 128.9, 128.0, 76.6, 76.2, 58.8, 40.5, 23.0, 19.7. Anal. Calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35. Found: C, 59.49; H, 5.13.

*4.1.3. 2-Chloro-2-(1-nathtyl)acetic acid (R)-pantolactone ester (**1f**).* A colorless oil was obtained in 43% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.18–7.46 (m, 7H), 6.27, 6.23 (s, 1H), 5.43, 5.41 (s, 1H), 4.02–3.87 (m, 2H), 1.19, 1.02, 0.89, 0.47 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.4, 167.9, 134.1, 131.5, 130.6, 130.4, 129.2, 127.5, 127.1, 126.4, 125.4, 123.2,

76.5, 76.1, 57.6, 40.3, 22.6, 19.1; HRMS calcd for $C_{18}H_{18}ClO_4$ (M^++1): 333.0894. Found: 333.0889.

*4.1.4. 2-Bromo-2-(4-fluorophenyl)acetic acid (R)-pantolactone ester (**1g**).* A pale yellow oil was obtained in 51% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.61–7.56 (m, 2H), 7.09–7.04 (m, 2H), 5.53, 5.52 (s, 1H), 5.40 (s, 1H), 4.04, 4.01 (s, 2H), 1.23, 1.14, 1.12, 0.96 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.5, 167.7, 163.1 (d, J=248.0 Hz), 131.2, 130.7, 116.0 (d, J=28.0 Hz), 76.7, 76.1, 45.6, 40.6, 22.9, 19.7; HRMS calcd for $C_{14}H_{15}BrFO_4$ (M^++1): 345.0138. Found: 345.0137.

*4.1.5. 2-Chloro-2-(4-methylphenyl)acetic acid (R)-pantolactone ester (**1h**).* A colorless oil was obtained in 60% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.43–7.38 (m, 2H), 7.26–7.19 (m, 2H), 5.50, 5.47 (s, 1H), 5.38, 5.35 (s, 1H), 4.13–3.95 (m, 2H), 2.36 (s, 3H), 1.21, 1.11, 1.06, 0.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.5, 167.7, 139.7, 132.6, 129.8, 128.1, 76.5, 76.2, 58.9, 40.6, 23.1, 21.3, 19.4. Anal. Calcd for $C_{15}H_{17}ClO_4$: C, 60.71; H, 5.77. Found: C, 60.85; H, 5.69.

*4.1.6. 2-Chloro-2-(4-fluoro-2-methylphenyl)acetic acid (R)-pantolactone ester (**1i**).* A colorless oil was obtained in 58% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.61–7.50 (m, 1H), 6.97–6.88 (m, 2H), 5.76, 5.72 (s, 1H), 5.42, 5.38 (s, 1H), 4.03, 4.00 (s, 2H), 2.40 (s, 3H), 1.20, 1.06, 0.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.4, 167.6, 162.9 (d, J=248.0 Hz), 139.1, 130.5, 129.3, 117.8, 114.0, 76.7, 76.1, 55.3, 40.3, 22.9, 19.7, 19.4; HRMS calcd for $C_{15}H_{17}ClFO_4$ (M^++1): 315.0799. Found: 315.0801.

4.2. General procedure for the asymmetric preparation of 2–4 and 5a–i

To a solution of α-halo ester in CH_2Cl_2 or CH_3CN (ca. 0.1 M) at room temperature were added DIEA (1.0 equiv), TBAI (1.0 equiv), and an ethylenediamine nucleophile (1.2 equiv). After the resulting reaction mixture was stirred at room temperature for 3–24 h, the solvent was evaporated and the crude material was purified by column chromatography to give a 3-substituted 2-piperazinone with 54–90% yields. The ers of **2**–**4** and **5a**–**i** were determined by chiral stationary phase HPLC.

*4.2.1. (S)-3-Phenyl-2-piperazinone (**2**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.44–7.29 (m, 5H), 6.57 (br, 1H), 4.59 (s, 1H), 3.53 (m, 1H), 3.39 (m, 1H), 3.16 (m, 1H), 3.08 (m, 1H), 1.95 (br, 1H). The spectral data of **2** were identical to those of the commercially available product. CSP-HPLC (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min) 92:8 er, 53.3 min (major enantiomer), 51.3 min (minor enantiomer).

*4.2.2. 1-Benzyl-(S)-3-phenyl-2-piperazinone (**3**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.28 (m, 10H), 4.63 (m, 3H), 3.40 (m, 1H), 3.21 (m, 1H), 3.08 (m, 1H), 3.02 (m, 1H), 2.05 (br, 1H). The spectral data of **3** were identical to those of the authentic material reported previously.[9a] CSP-HPLC (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min) 90:10 er, 26.4 min (major enantiomer), 47.1 min (minor enantiomer).

*4.2.3. 4-Benzyl-(S)-3-phenyl-2-piperazinone (**4**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.55–7.26 (m, 10H), 6.60 (br, 1H), 4.06 (s, 1H), 3.75 (d, J=13.4 Hz, 1H), 3.45 (m, 1H), 3.25 (m, 1H), 3.17 (d, J=13.4 Hz, 1H), 2.98 (m, 1H), 2.51 (m, 1H). The spectral data of **4** were identical to those of the authentic material reported previously.[9b] CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min) 87:13 er, 35.0 min (major enantiomer), 28.2 min (minor enantiomer).

*4.2.4. 1,4-Dibenzyl-(S)-3-phenyl-2-piperazinone (**5a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.57–7.21 (m, 15H), 4.62 (d, J=14.6 Hz, 1H), 4.53 (d, J=14.6 Hz, 1H), 4.13 (s, 1H), 3.74 (d, J=13.4 Hz, 1H), 3.42 (m, 1H), 3.13 (d, J=13.4 Hz, 1H), 3.10 (m, 1H), 2.94 (m, 1H), 2.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.8, 139.9, 138.2, 137.3, 129.5, 129.2, 129.1, 128.9, 128.7, 128.6, 128.3, 127.9, 127.6, 71.7, 59.3, 50.7, 47.1, 46.3; IR (KBr, cm^{-1}) 3029, 2923, 1650, 1453; EIMS (70eV) m/z (relative intensity) 356 (1, M^+), 327 (5), 265 (90), 251 (20), 118 (17), 91 (100). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.77; H, 6.84; N, 7.94; $[\alpha]_D^{20}$ +51.7 (c 0.17, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 94:6 er, 29.9 min (major enantiomer), 25.0 min (minor enantiomer).

*4.2.5. 1,4-Dibenzyl-(S)-3-(1-naphtyl)-2-piperazinone (**5b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 8.40 (d, J=7.6 Hz, 1H), 7.87–7.05 (m, 16H), 4.88 (d, J=14.4 Hz, 1H), 4.59 (s, 1H), 4.42 (d, J=14.4 Hz, 1H), 3.69 (d, J=13.6 Hz, 1H), 3.61 (m, 1H), 3.20 (s, 1H), 3.03 (m, 2H), 3.10 (m, 1H), 2.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.4, 137.9, 136.8, 134.9, 134.5, 131.8, 129.2, 129.0, 128.8, 128.7, 128.6, 128.2, 127.6, 127.1, 125.7, 125.6, 125.4, 125.1, 75.7, 59.2, 50.5, 47.6, 45.9; IR (KBr, cm^{-1}) 3061, 2926, 1650, 1453; EIMS (70eV) m/z (relative intensity) 406 (1, M^+), 377 (6), 315 (100), 251 (15), 167 (7), 141 (9), 91 (70); HRMS calcd for $C_{28}H_{27}N_2O$ (M^++1): 407.2123. Found: 407.2125; $[\alpha]_D^{20}$ +58.6 (c 0.13, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min) 94:6 er, 34.9 min (major enantiomer), 22.4 min (minor enantiomer).

*4.2.6. 1,4-Dibenzyl-(S)-3-(4-fluorophenyl)-2-piperazinone (**5c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.56–7.05 (m, 14H), 4.63 (d, J=14.4 Hz, 1H), 4.52 (d, J=14.4 Hz, 1H), 4.11 (s, 1H), 3.73 (d, J=13.2 Hz, 1H), 3.45 (m, 1H), 3.13 (d, J=13.2 Hz, 1H), 3.10 (m, 1H), 2.94 (m, 1H), 2.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.2, 162.5 (d, J=244.0 Hz), 137.6, 136.8, 135.4, 130.7, 128.8, 128.7, 128.4, 128.3, 127.6, 127.4, 115.3 (d, J=21.0 Hz), 70.5, 58.9, 50.3, 46.8, 45.7; IR (KBr, cm^{-1}) 3030, 2923, 1650, 1508, 1221; EIMS (70eV) m/z (relative intensity) 374 (1, M^+), 345 (3), 283 (100), 251 (20), 136 (12), 109 (8), 91 (75); HRMS calcd for $C_{24}H_{24}FN_2O$ (M^++1): 375.1873. Found: 375.1877; $[\alpha]_D^{20}$ +48.5 (c 0.27, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 93:7 er, 27.2 min (major enantiomer), 22.6 min (minor enantiomer).

*4.2.7. 1,4-Dibenzyl-(S)-3-(4-methylphenyl)-2-piperazinone (**5d**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.50–7.18 (m, 14H), 4.62 (d, J=14.6 Hz, 1H), 4.53 (d, J=14.6 Hz, 1H), 4.10 (s, 1H), 3.76 (d, J=13.2 Hz, 1H), 3.44 (m, 1H), 3.13 (d, J=13.2 Hz, 1H), 3.11 (m, 1H), 2.94 (m, 1H), 2.46 (m, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.6, 137.9, 137.5, 136.9, 136.4, 129.2, 128.9, 128.8, 128.7, 128.3, 127.5, 127.1, 71.0, 58.8, 50.2, 46.7, 45.9, 21.2; IR (KBr, cm^{-1}) 3030, 2922, 1650, 1453; EIMS (70eV) m/z (relative intensity) 370 (1, M^+), 341 (5), 279 (100), 251 (23), 132 (7), 105 (10), 91 (55); HRMS calcd for $C_{25}H_{27}N_2O$ (M^++1): 371.2123. Found: 371.2120; $[\alpha]_D^{20}$ +39.9 (c 0.09, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 93:7 er, 23.8 min (major enantiomer), 21.9 min (minor enantiomer).

*4.2.8. 1,4-Dibenzyl-(S)-3-(4-fluoro-2-methylphenyl)-2-piperazinone (**5e**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.52–6.93 (m, 15H), 4.63 (s, 2H), 4.28 (s, 1H), 3.73 (d, J=13.2 Hz, 1H), 3.50 (m, 1H), 3.12 (m, 1H), 3.06 (d, J=13.2 Hz, 1H), 2.99 (m, 1H), 2.05 (s, 3H), 2.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.2, 162.1 (d, J=244.0 Hz), 140.1, 140.0, 137.8, 136.7, 133.7, 133.6, 131.2, 128.7, 128.6, 128.5, 128.4, 127.6, 127.3, 117.6 (d, J=21.5 Hz), 112.6 (d, J=21.5 Hz), 69.0, 59.0, 50.3, 47.4, 45.9, 20.0; IR (KBr, cm^{-1}) 3039, 2970, 1676, 1366, 1217; EIMS (70eV) m/z (relative intensity) 388 (1, M^+), 359 (5), 297 (100), 251 (18), 150 (7), 123 (8), 91 (71); HRMS calcd for $C_{25}H_{26}FN_2O$ (M^++1): 389.2029. Found: 389.2028; $[\alpha]_D^{20}$ +41.7 (c 0.10, $CHCl_3$); CSP-HPLC (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/

min) 94:6 er, 49.4 min (major enantiomer), 25.5 min (minor enantiomer).

*4.2.9. 1,4-Dibenzyl-(S)-3-methyl-2-piperazinone (**5f**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.24 (m, 10H), 4.59 (m, 2H), 3.93 (d, J=13.5 Hz, 1H), 3.39 (d, J=13.5 Hz, 1H), 3.31 (q, J=6.5 Hz, 1H), 3.20 (m, 1H), 3.13 (m, 1H), 2.87 (m, 1H), 2.42 (m, 1H), 1.53 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.7, 137.9, 136.9, 128.9, 128.6, 128.4, 128.1, 127.5, 127.3, 60.6, 58.3, 50.0, 45.6, 45.5, 15.9; IR (KBr, cm^{-1}) 3031, 2924, 1645, 1453; EIMS (70eV) m/z (relative intensity) 294 (5, M^+), 279 (12), 265 (4), 251 (35), 203 (100), 91 (100). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.57; H, 7.45; N, 9.36; $[\alpha]_D^{20}$ +38.1 (c 0.07, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min) 83:17 er, 35.2 min (major enantiomer), 29.3 min (minor enantiomer).

*4.2.10. 1,4-Dibenzyl-(R)-3-ethyl-2-piperazinone (**5g**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34–7.23 (m, 10H), 4.69 (d, J=14.4 Hz, 1H), 4.53 (d, J=14.4 Hz, 1H), 3.96 (d, J=13.6 Hz, 1H), 3.29 (d, J=13.6 Hz, 1H), 3.20 (m, 2H), 3.07 (m, 1H), 2.89 (m, 1H), 2.39 (m, 1H), 2.14 (m, 1H), 1.94 (m, 1H), 1.00 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.1, 138.2, 137.0, 128.8, 128.6, 128.4, 128.2, 127.5, 127.2, 66.0, 58.4, 50.2, 46.0, 45.0, 23.4, 9.4; IR (KBr, cm^{-1}) 3029, 2969, 1644, 1453; EIMS (70eV) m/z (relative intensity) 308 (3, M^+), 279 (100), 251 (34), 217 (31), 91 (100). Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.76; H, 7.84; N, 9.24; $[\alpha]_D^{20}$ −31.0 (c 0.15, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 94:6 er, 18.7 min (major enantiomer), 26.1 min (minor enantiomer).

*4.2.11. 1,4-Dibenzyl-(S)-3-butyl-2-piperazinone (**5h**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33–7.22 (m, 10H), 4.66 (d, J=14.6 Hz, 1H), 4.54 (d, J=14.6 Hz, 1H), 3.93 (d, J=13.4 Hz, 1H), 3.33 (d, J=13.4 Hz, 1H), 3.19 (m, 2H), 3.10 (m, 1H), 2.90 (m, 1H), 2.39 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.52 (m, 1H), 1.32 (m, 2H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.8, 138.6, 137.4, 129.2, 129.0, 128.8, 128.6, 127.9, 127.6, 65.5, 58.8, 50.6, 46.1, 45.1, 30.7, 27.9, 23.2, 14.6; IR (KBr, cm^{-1}) 3029, 2955, 1645, 1454; EIMS (70eV) m/z (relative intensity) 336 (2, M^+), 279 (100), 251 (22), 91 (89). Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.53; H, 8.34; N, 8.39; $[\alpha]_D^{20}$ +39.7 (c 0.12, $CHCl_3$); CSP-HPLC (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min) 85:15 er, 18.3 min (major enantiomer), 15.6 min (minor enantiomer).

*4.2.12. (R)-3-Butyl-2-piperazinone (**5i**).* ^{1}H NMR ($CDCl_3$, 400 MHz) 7.12 (br, 1H), 3.41 (m, 2H), 3.30 (m, 1H), 3.14 (m, 1H), 2.94 (m, 1H), 1.97 (m, 2H), 1.65 (m, 1H), 1.36 (m, 4H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.0, 58.8, 43.1, 41.4, 31.6, 28.1, 22.6, 14.0. The spectral data of **5i** were identical to those of the commercially available material and **5i** was converted to *N*-benzoyl derivative for chromatographic analysis. $[\alpha]_D^{20}$ −19.1 (c 0.08, $CHCl_3$); CSP-HPLC (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min) 91:9 er, 56.8 min (major enantiomer), 78.1 min (minor enantiomer).

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