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Dynamic Resolution

Stereoselective Substitution of Configurationally Labile α-Bromo Arylacetates with Amines and Azlactones by L-Threonine-Mediated Crystallization-Induced Dynamic Resolution

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Abstract: We developed a highly stereoselective C–N and C–C bond-forming reaction by carrying out a crystallization-induced dynamic resolution (CIDR) of α-bromo arylacetates followed by a stereoselective substitution reaction with an amine or azlactone nucleophile. Applications of this synthetic method to the preparation of highly enantioenriched nitrogen-containing six-membered heterocycles and α,β-disubstituted aspartates are also presented.

Introduction

Several synthetic methods for the crystallization-induced dynamic resolution (CIDR) of configurationally labile compounds have been developed for practical asymmetric synthesis.[1] Recently, some successful chiral-auxiliary-mediated CIDRs of configurationally labile α-halo acid derivatives in nucleophilic substitution reactions have been reported.[2] We previously reported the *N*-benzoyl L-threonine isopropyl ester mediated CIDR of configurationally labile α-bromo phenylacetate **1**, in which the selective crystallization of (α*R*)-**1** was controlled by the thermodynamics of phase equilibrium. Highly diastereoenriched (α*R*)-**1** was obtained as a solid with a diastereomeric ratio (*dr*) of >98:2 and then efficiently used in the asymmetric synthesis of α-thio and α-oxy arylacetates.[2f] For the highly stereoselective substitution of (α*R*)-**1**, the reaction of a sulfur or oxygen nucleophile should be sufficiently fast relative to the rate of epimerization at the α-position, as (α*R*)-**1** is configurationally labile in the presence of a base or polar solvent.

In continuation of our work on CIDR and the stereoselective substitution of α-bromo arylacetates with nitrogen and carbon nucleophiles, we have developed a highly stereoselective C–N or C–C bond-formation method (Figure 1). Herein, we report the stereoselective substitution of configurationally labile α-bromo arylacetates with diverse amines and applications for the asymmetric synthesis of nitrogen-containing six-membered heterocyclic compounds such as dihydroquinoxalinones, piperazinones, and morpholinones. In addition, we wish to report the first example of a nucleophilic substitution of α-bromo arylacetates with azlactone as the carbon nucleophile to afford highly enantioenriched α,β-disubstituted aspartates.

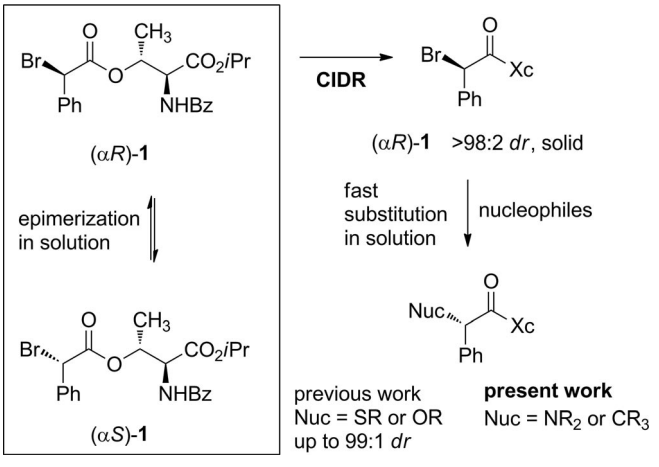

Figure 1. CIDR of α-bromo phenylacetate **1** followed by various nucleophilic substitution reactions (Nuc = nucleophile).

Results and Discussion

To apply the CIDR method to the preparation of highly diastereoenriched α-amino-substituted acetates, it is important to perform the nucleophilic substitution (S_N2) reaction under conditions that minimize the epimerization of (α*R*)-**1** upon exposure to base. Thus, we first investigated the substitution reaction of (α*R*)-**1** (>98:2 *dr*) with benzylamine at various concentrations to establish a relationship between the concentration and the diastereomeric excess (*de*) value of product **2**.[3] The reactions were monitored for % conversion and % *de* by NMR analysis of the crude reaction mixture with 2.5 equiv. of benzylamine in $CDCl_3$ at room temperature for 9 h. Figure 2 (a) clearly shows the relationship between the concentration and the *de* value of **2**. As the concentration of the reaction mixture increased, the

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final *de* value of **2** decreased. However, at high concentrations (above 1.0 M) the *de* value of **2** was not affected by the concentration of **1**, and the conversion reached >95 % after 9 h. This result indicates that (αR)-**1** underwent a fast epimerization process at high concentrations of benzylamine prior to the substitution reaction. Thus, the optimum concentration for the substitution reaction with amines was determined to be 0.1 M. As shown in Figure 2 (b), the reaction at 0.1 M was almost complete after 24 h (93 % conversion), and the *de* value of product **2** was constant during the reaction.

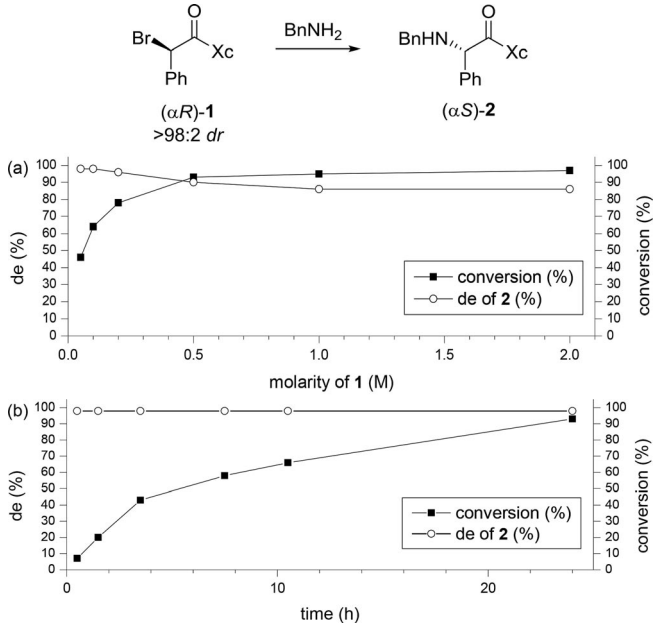
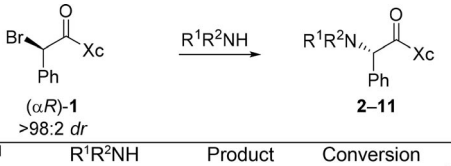
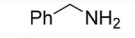
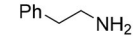
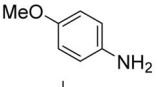
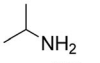
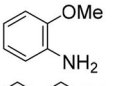
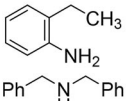
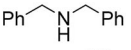
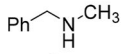
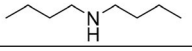


Figure 2. Substitution of (αR)-**1** (>98:2 *dr*) with benzylamine: (a) reactions of **1** at various concentrations with 2.5 equiv. of benzylamine in $CDCl_3$ at room temp. for 9 h; (b) reaction of **1** (0.1 M) with 2.5 equiv. of benzylamine in $CDCl_3$ at room temp. (*de* = diastereomeric excess).

Next, the scope of the efficient nucleophilic substitution reaction with various amine nucleophiles was investigated at the optimized reaction concentration (0.1 M) as shown in Table 1. When **1** (>98:2 *dr*) was treated with benzylamine (2.5 equiv.) in $CHCl_3$ at room temp. for 24 h, α-amino-substituted product **2** was afforded with 98:2 *dr* (Table 1, Entry 1).[4] Under the same conditions, the reactions with primary amines such as phenethylamine and *p*-anisidine afforded products **3** and **4** with 95:5 and 96:4 *dr*, respectively (Table 1, Entries 2 and 3). In contrast, the reaction with isopropylamine afforded a much lower *dr* value of 81:19 with a conversion of 86 % (Table 1, Entry 4). Moreover, the reactions of *ortho*-substituted arylamines such as *o*-anisidine and *o*-ethylaniline afforded lower *dr* values of the products with conversions of 87 and 85 %, respectively (Table 1, Entries 5 and 6). Limited results indicate that steric bulk at the α- or *ortho*-position relative to the amino group may affect the rate of substitution. A control experiment was carried out to compare the rates of substitution of *o*-anisidine versus *p*-anisidine. We found that the reaction rate of *o*-anisidine is more than twice as slow than that of *p*-anisidine. The substitution reaction with a sterically hindered nucleophile is also not sufficiently fast relative the rate of epimerization of (αR)-**1**. Therefore, the epimerization of (αR)-**1** is more likely under basic conditions, which results in lower *dr* values. Among the reactions with secondary amines, high stereoselectivities were observed by using dibenzylamine, benzylmethylamine, and piperidine to afford **8**, **9**, and **10**, respectively, whereas a moderate decrease in the stereoselectivity was observed with dibutylamine (Table 1, Entries 7–10). The absolute configurations of α-amino-substituted products were determined by the reductive cleavage of the chiral auxiliary. The treatment of **8** (96:4 *dr*) with $LiAlH_4$ in tetrahydrofuran (THF) furnished 2-(dibenzylamino)-2-phenylethanol with an enantiomeric ratio (*er*) of 96:4 in favor of the (*S*) enantiomer.[5]

Table 1. Nucleophilic substitution reactions with amines.

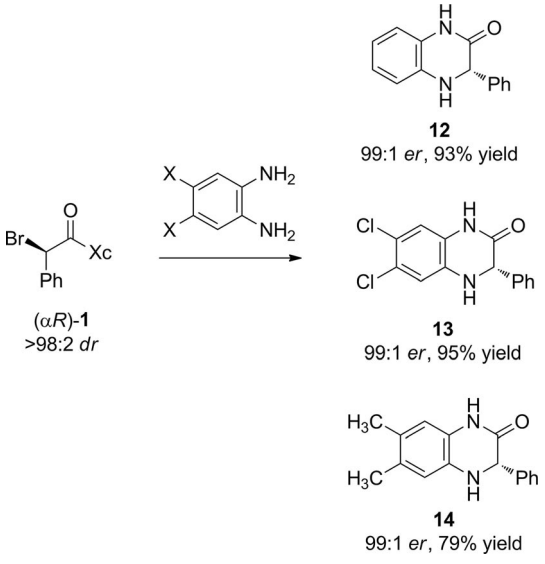


Entry[a]	R^1R^2NH	Product	Conversion (isolated yield) [%][b]	*dr*[c]
1		**2**	93 (78)	98:2
2		**3**	93 (82)	95:5
3		**4**	96 (95)	96:4
4		**5**	86 (71)	81:19
5		**6**	87 (82)	86:14
6		**7**	85 (84)	84:16
7		**8**	94 (89)	96:4
8		**9**	98 (90)	96:4
9		**10**	96 (74)	97:3
10		**11**	99 (90)	91:9

[a] All reactions were carried out with 2.5 equiv. of the amine in $CHCl_3$ (0.1 M) at room temp. for 24 h. [b] The conversions were determined after 24 h by ^1H NMR analysis of the reaction mixture. [c] The *dr* values were determined by ^1H NMR analysis of the reaction mixture.

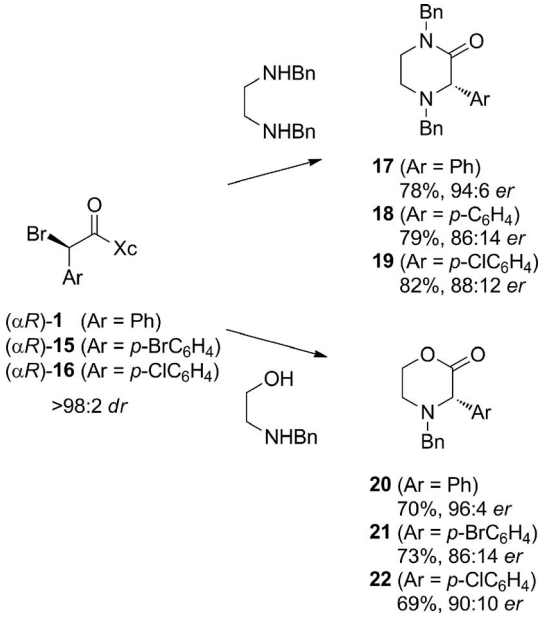
Encouraged by the high stereoselectivities of the reactions of (αR)-**1** with various amines (Table 1), we also investigated the substitution reaction with 1,2-diaminobenzenes for the asymmetric syntheses of 3-substituted dihydroquinoxalinones (Scheme 1). When (αR)-**1** was treated with three different 1,2-diaminobenzenes under the same reaction conditions, the substitution reaction, followed by a spontaneous cyclization step to remove the chiral auxiliary, afforded dihydroquinoxalinones **12**–**14** in yields of 79–95 % with *er* values of 99:1.[4g,4h]

In addition, the CIDR of **1** and the two α-bromo arylacetates **15** and **16** was applied to the asymmetric synthesis of 3-substituted piperazinones and morpholinones to further demonstrate the synthetic utility of this method (Scheme 2). Under the same optimized conditions, the reactions of (αR)-**1**, (αR)-**15**, and (αR)-**16** with *N*,*N*′-dibenzylethylenediamine afforded 3-aryl-substituted 1,4-dibenzylpiperazin-2-ones. The one-pot substitution-



Scheme 1. Asymmetric synthesis of dihydroquinoxalinones.

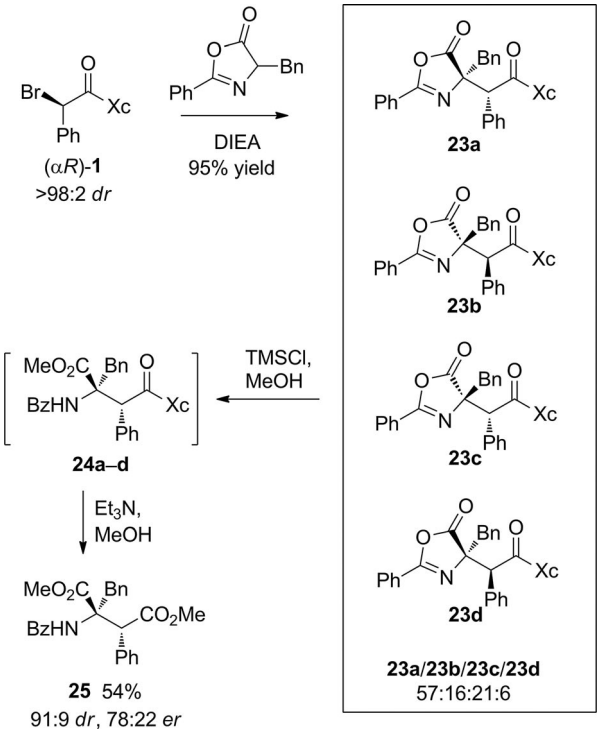
cyclization reaction proceeded for 48 h to afford **17**–**19** in yields of 78–82 % with *er* values of 94:6, 86:14, and 88:12, respectively. Moreover, we were pleased to observe that the substitution reaction with 2-(benzylamino)ethanol and subsequent spontaneous cyclization afforded 4-benzyl-substituted 3-arylmorpholinones **20**, **21**, and **22** in 69–73 % yield with 96:4, 86:14, and 90:10 *er*, respectively.



Scheme 2. Asymmetric synthesis of piperazinones and morpholinones.

Having successfully developed an asymmetric synthetic method for the preparation of α-amino arylacetates, we next focused our attention on a carbon nucleophile that would enable the stereoselective carbon–carbon bond formation in a reaction with (α*R*)-**1**. Thus, we explored the stereochemical consequences of such a substitution reaction with azlactones that were derived from *N*-benzoyl-α-amino carboxylic acids. Azlactones were selected as suitable carbon nucleophiles, because they are suitably acidic for enolate formation under weakly basic conditions and sufficiently nucleophilic for fast substitution, which is essential to achieve the highly stereoselective substitution of (α*R*)-**1**.[6]

When (α*R*)-**1** was treated with a phenylalanine-derived azlactone in the presence of DIEA in *N*,*N*-dimethylformamide (DMF; 0.5 M) at room temp. for 1 h, the substitution reaction successfully provided the four products **23a**–**23d**, which contain different substituted quaternary carbon centers, in 95 % yield with 57:16:21:6 *dr* (Scheme 3). To the best of our knowledge, there is no successful precedent of a direct nucleophilic substitution reaction between α-substituted α-halo acetates and alkylated azlactones for the construction of sterically congested C–C bonds.[7] This reaction provides access to an array of alkylated azlactones that contain adjacent tertiary and quaternary carbon centers. The subsequent ring opening of the azlactone by treatment with TMSCl in methanol, followed by the removal of chiral auxiliary with Et_3N in methanol, successfully afforded dimethyl aspartate derivative **25** with 91:9 *dr* and 78:22 *er*. The increase in the *dr* (91:9) of **25** relative to the ratio of (**23a** + **23b**)/(**23c** + **23d**) (73:27) is attributed to the rate difference in the removal of the chiral auxiliary of **24a**–**24d**. The reactions of **24c** and **24d** are much slower than those of **24a** and **24b** under the basic conditions.[8] The relative configuration of **25** was determined by analogy with the known ^1H NMR spectroscopic data of authentic **25**, and the absolute configuration was determined by assuming an inversion of stereochemistry at the site of the S_N2 substitution reaction of (α*R*)-**1**.[9] The nucleophilic substitution reactions of (α*RS*)-**1** (51:49 *dr*) with



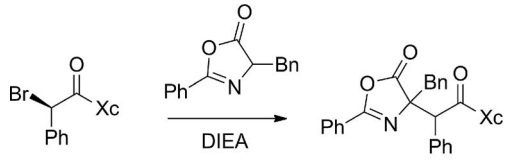
Scheme 3. Nucleophilic substitution with an azlactone (DIEA = *N*,*N*-diisopropylethylamine; TMS = trimethysilyl; Xc = *N*-benzoyl-L-threonine isopropyl ester).

phenylalanine-derived azlactone produced the corresponding products **23a**–**23d** with 36:35:14:15 *dr*, which indicates that the dynamic kinetic resolution of α-bromo phenylacetate (α*RS*)-**1** is not functioning in this reaction.[4]

As shown in Scheme 3, the substitution reaction in DMF produced **23a**–**23d** after 1 h in 95 % yield with 57:16:21:6 *dr* (Table 2, Entry 1). The comparatively low stereoselectivity may be attributed to the epimerization of (α*R*)-**1** that could have been promoted by the high concentration (0.5 M) of the reaction mixture in a polar solvent. Our initial attempt to improve the stereoselectivity by lowering the concentration did not improve the *dr* values of **23** (Table 2, Entry 2). These results indicate that the substitution reaction with the azlactone at both concentrations is not sufficiently fast relative to the rate of epimerization of **1** in DMF. The same reaction of (α*R*)-**1** was then carried out in the less polar $CHCl_3$ (0.1 M), which afforded **23a**–**23d** with a significantly improved *dr* value of 79:7:12:2 but in a much lower yield of 12 % (Table 2, Entry 3). To improve the low conversion, the substitution reaction was then carried out in $CHCl_3$ at higher concentrations. The stereoselectivities, however, decreased to 68:9:21:2 *dr* with a 59 % product yield at a concentration of 0.5 M and 62:14:20:4 *dr* with a 93 % product yield at a concentration of 2.0 M (Table 2, Entries 4 and 5). To our delight, lowering the reaction temperature to 0 °C increased the stereoselectivity to 78:3:18:1 *dr* in an excellent yield of 92 % (Table 2, Entry 6), whereas a slightly decreased stereoselectivity was observed when the reaction was performed at –10 °C. This implies that the substitution reaction with the azlactone in $CHCl_3$ (2.0 M) at 0 °C is sufficiently fast relative to the rate of epimerization of **1** in $CHCl_3$. Therefore, the reaction conditions of Table 2, Entry 6 were chosen as optimal for the following synthetic studies with the azlactones.

Having been successful in the three-step transformation of α-bromo phenylacetate (α*R*)-**1** into dimethyl aspartate derivative **25** (Scheme 3), we decided to probe the feasibility of a procedure that avoids the purification of **23**. Thus, the crude substitution reaction mixture was neutralized by the addition of a saturated NH_4Cl solution, and the resulting mixture was then subjected to subsequent steps. In addition, we developed a new one-pot reaction sequence for the ring opening and removal of the chiral auxiliary by employing sodium methoxide. When the crude reaction mixture, which resulted from (α*R*)-**1** and phenylalanine-derived azlactone at 0 °C in $CHCl_3$, was subjected to this optimized one-pot procedure with sodium methoxide (6.0 equiv.) in MeOH at –15 °C, both dimethyl aspar-

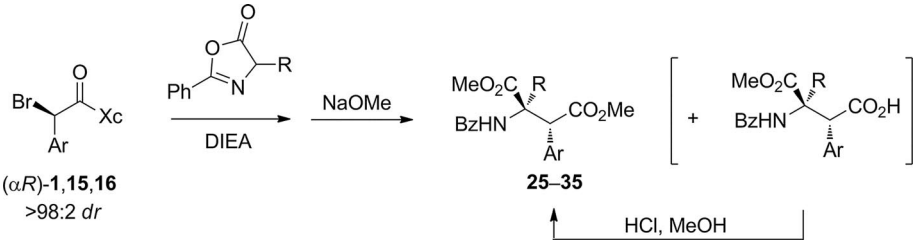
Table 2. Optimization of the substitution conditions.[a]



Entry	Reaction conditions	Yield [%]	*dr* of **23a**/**23b**/**23c**/**23d**[b]
1	DMF (0.5 M), r.t.	95	57:16:21:6
2	DMF (0.1 M), r.t.	93	56:15:21:8
3	$CHCl_3$ (0.1 M), r.t.	12	79:7:12:2
4	$CHCl_3$ (0.5 M), r.t.	59	68:9:21:2
5	$CHCl_3$ (2.0 M), r.t.	93	62:14:20:4
6	$CHCl_3$ (2.0 M), 0 °C	92	78:3:18:1

[a] All reactions were carried out with azlactone (1.4 equiv.) and DIEA (2.0 equiv.) for 1 h. [b] The *dr* values were determined by ^1H NMR analysis of the reaction mixture.

Table 3. Asymmetric syntheses of α,β-disubstituted aspartates.[a]



Entry	R	Ar	Product	Yield [%]	*dr*[b]	*er*[c,d]
1	Bn	Ph	**25**	65	74:26	95:5
2	*i*Bu	Ph	**26**	61	75:25	96:4
3	Me	Ph	**27**	75	76:24	99:1
4	Ph	Ph	**28**	74	61:39	92:8
5	$CH_3O_2CCH_2$	Ph	**29**	80	70:30	97:3
6	*p*-$MeOC_6H_4CH_2$	Ph	**30**	63	76:24	95:5
7	$CH_3SCH_2CH_2$	Ph	**31**	61	70:30	98:2
8	Bn	*p*-BrC_6H_4	**32**	63	63:37	91:9
9	Bn	*p*-ClC_6H_4	**33**	52	63:37	89:11
10	*i*Bu	*p*-BrC_6H_4	**34**	62	64:36	93:7
11	*i*Bu	*p*-ClC_6H_4	**35**	70	63:37	94:6

[a] All the substitution reactions were carried out in $CHCl_3$ (2.0 M) at 0 °C for 1 h. [b] The *dr* values were determined by ^1H NMR analysis of the final product. [c] The enantiomeric ratios of major diastereomer are reported. [d] The *er* values were determined by chiral stationary-phase high-performance liquid chromatography using a racemic material as the standard.

tate **25** and the corresponding aspartic acid derivative were produced in a ratio of 2:1. The conversion of the carboxylic acid into methyl ester **25** was carried out by treating the acid with HCl in MeOH. From the above reaction of (α*R*)-**1**, dimethyl aspartate **25** was successfully obtained in 65 % overall yield with 74:26 *dr* and 95:5 *er* (Table 3, Entry 1).[10]

With a practical procedure in hand, we examined the scope of this strategy with six different α-amino acid azlactones for the preparation of highly enantioenriched disubstituted aspartates (Table 3, Entries 2–7). Under the same reaction conditions as reported in Table 3, Entry 1, this simple procedure with azlactones that were derived from leucine, alanine, phenylglycine, aspartic acid, tyrosine, and methionine successfully provided highly enantioenriched α,β-disubstituted aspartates **26**–**31** with *er* values that ranged from 92:8 to 99:1 in overall yields of 61–80 %. In contrast, the variation in the aryl group of the α-bromo arylacetate affected the stereoselectivity of the reaction with the phenylalanine-derived azlactone. The reactions of highly diastereoenriched (α*R*)-**15** and (α*R*)-**16** with the phenylalanine-derived azlactone afforded both *p*-bromo-substituted (α*R*)-**32** with 63:37 *dr* and 91:9 *er* and *p*-chloro-substituted (α*R*)-**33** with 63:37 *dr* and 89:11 *er* (Table 3, Entries 8 and 9), respectively. In addition, when (α*R*)-**15** and (α*R*)-**16** were treated with the leucine-derived azlactone, the one-pot process that includes the substitution and ring-opening reactions along with the removal of the chiral auxiliary afforded α,β-disubstituted aspartates **34** with 64:36 *dr* and 93:7 *er* and **35** with 63:37 *dr* and 94:6 *er* (Table 3, Entries 10 and 11). This nucleophilic substitution can be further applied to the asymmetric synthesis of functionally diverse α,β-disubstituted aspartate derivatives and unnatural α-amino acids, which have been known as key building blocks in the syntheses of biologically active compounds.[11]

Conclusions

We have developed an efficient synthetic method for the highly stereoselective formation of carbon–nitrogen and carbon–carbon bonds by using the CIDR of α-bromo arylacetates and nucleophilic substitution reactions with amine and azlactone nucleophiles. Evidence for the efficiency of this method was demonstrated by the asymmetric preparation of 3-aryl-substituted dihydroquinoxalinones, piperazinones, and morpholinones with high stereoselectivities. Moreover, we reported the first example of the substitution of α-substituted α-bromo acetates with alkylated azlactone nucleophiles, which can be applied to the asymmetric synthesis of diverse α,β-disubstituted aspartates. This simple protocol, which employs mild reaction conditions and easily removes the chiral auxiliary, provides an impetus to further develop the CIDR approach.

Experimental Section

General Methods: All reactions were performed in oven-dried glassware under nitrogen. All chemicals were obtained from commercial sources and used as received. Analytical thin layer chromatography was performed on silica gel plates with QF-254 indicator, and the developed plates were visualized by using UV light. Flash column chromatography was performed with silica gel (230–400 mesh). The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker (400 MHz for ^{1}H NMR, 100.6 MHz for ^{13}C NMR) spectrometer, and $CDCl_3$ was used as the internal standard. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ ($CHCl_3$ at δ = 7.26 ppm for ^{1}H NMR, $CDCl_3$ at δ = 77.07 ppm for ^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), and br. (broad). Coupling constants (*J*) are reported in Hz. HR mass spectra were measured with a JEOL JMS-700 instrument by using ESI or FAB.

General Procedure for the Asymmetric Nucleophilic Substitution Reactions with Amines: To a solution of L-threonine-derived α-bromo ester **1**, **15**, or **16** (>98:2 *dr*) in $CHCl_3$ (0.1 M) at room temp. was added an amine nucleophile (2.5 equiv.). After the resulting reaction mixture had been stirred at room temp. for 24–72 h, the solvent was evaporated, and the crude material was purified by column chromatography to afford an α-amino ester or a heterocycle. The *dr* values of **2**–**11** were determined by ^{1}H NMR analysis using the proton integrations of the two diastereomers, and the *er* values of **12**–**14** and **17**–**22** were determined by chiral stationary-phase high-performance liquid chromatography (CSP-HPLC) analysis. The spectroscopic data of **2**, **4**, **6**, **8**, **9**, **12**–**14**, **17**, and **20** are identical to those of authentic materials, which had been previously reported.[4]

***N*-Benzoyl-*O*-[α-(phenethylamino)phenylacetyl]-L-threonine Isopropyl Ester (3):** Colorless oil (93 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, major epimer): δ = 7.66–7.09 (m, 15 H), 6.64 (d, *J* = 9.2 Hz, 1 H), 5.42–5.40 (m, 1 H), 4.89–4.84 (m, 2 H), 4.29 (s, 1 H), 2.76–2.67 (m, 4 H), 2.08 (br., 1 H), 1.22 (d, *J* = 6.0 Hz, 3 H), 1.18–1.09 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major epimer): δ = 171.6, 169.2, 167.6, 139.6, 137.9, 133.7, 132.0, 128.7, 128.6, 128.5, 128.2, 127.4, 127.2, 126.3, 71.9, 70.0, 65.6, 55.9, 49.0, 36.4, 21.7, 21.6, 16.8 ppm. HRMS: calcd. for $C_{30}H_{35}N_2O_5$ $[M + 1]^+$ 503.2546; found 503.2546.

***N*-Benzoyl-*O*-[α-(isopropylamino)phenylacetyl]-L-threonine Isopropyl Ester (5):** Pale yellow oil (86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, major epimer): δ = 7.69–7.19 (m, 10 H), 6.73 (d, *J* = 9.2 Hz, 1 H), 5.50–5.48 (m, 1 H), 5.01–4.94 (m, 2 H), 4.45 (s, 1 H), 2.72–2.69 (m, 1 H), 1.27 (d, *J* = 6.0 Hz, 3 H), 1.20–1.14 (m, 3 H), 1.06–1.03 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major epimer): δ = 172.3, 169.2, 167.6, 138.3, 133.7, 132.0, 128.8, 128.6, 128.1, 127.4, 127.3, 127.2, 72.0, 70.0, 63.2, 56.0, 46.7, 22.8, 21.7, 21.5, 16.7 ppm. HRMS: calcd. for $C_{25}H_{33}N_2O_5$ $[M + 1]^+$ 441.2389; found 441.2389.

***N*-Benzoyl-*O*-[α-(*o*-ethylanilino)phenylacetyl]-L-threonine Isopropyl Ester (7):** Pale yellow oil (85 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, major epimer): δ = 7.72–6.34 (m, 15 H), 5.51–5.49 (m, 1 H), 5.09 (s, 1 H), 5.04–4.95 (m, 2 H), 2.62 (q, *J* = 7.6 Hz, 2 H), 1.30–1.13 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major epimer): δ = 170.9, 169.1, 167.6, 143.3, 137.7, 133.6, 132.0, 129.0, 128.7, 128.4, 128.2, 128.1, 127.2, 127.1, 127.0, 118.2, 110.9, 72.9, 70.2, 60.9, 55.9, 24.1, 21.8, 21.6, 16.5, 13.0 ppm. HRMS: calcd. for $C_{30}H_{35}N_2O_5$ $[M + 1]^+$ 503.2546; found 503.2546.

***N*-Benzoyl-*O*-[α-(1-piperidinyl)phenylacetyl]-L-threonine Isopropyl Ester (10):** Pale yellow oil (96 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, major epimer): δ = 7.56–7.22 (m, 11 H), 5.54–5.49 (m, 1 H), 5.00–4.76 (m, 2 H), 3.93 (s, 1 H), 2.35 (br., 4 H), 1.56 (br., 4 H), 1.43 (br., 2 H), 1.26–1.19 (m, 6 H), 1.01 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major epimer): δ = 170.5, 169.1, 167.8, 135.9, 133.8, 131.9, 128.8, 128.7, 128.6, 128.3, 127.4, 75.4, 71.7, 69.8, 56.0, 52.4, 25.6, 24.2, 21.7, 21.4, 16.8 ppm. HRMS: calcd. for $C_{27}H_{35}N_2O_5$ $[M + 1]^+$ 467.2546; found 467.2546.

***N*-Benzoyl-*O*-[α-(dibutylamino)phenylacetyl]-L-threonine Isopropyl Ester (11):** Colorless oil (99 % yield). ^{1}H NMR (400 MHz,

$CDCl_3$, major epimer): δ = 7.80–7.27 (m, 10 H), 6.89 (d, J = 8.8 Hz, 1 H), 5.61–5.59 (m, 1 H), 4.99–4.93 (m, 2 H), 4.52 (s, 1 H), 2.51 (t, J = 7.6 Hz, 4 H), 1.41–1.11 (m, 17 H), 0.81 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major epimer): δ = 171.2, 169.2, 167.7, 137.0, 133.7, 131.9, 128.8, 128.7, 128.6, 128.3, 127.9, 127.2, 71.4, 69.9, 69.4, 56.0, 50.4, 50.3, 29.5, 21.8, 21.6, 20.3, 17.1, 14.0 ppm. HRMS: calcd. for $C_{30}H_{43}N_2O_5$ [M + 1]$^+$ 511.3172; found 511.3173.

1,4-Dibenzyl-3-(*p*-bromophenyl)piperazin-2-one (18): Pale yellow oil (79 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.20 (m, 14 H), 4.61 (d, J = 14.8 Hz, 1 H), 4.52 (d, J = 14.8 Hz, 1 H), 4.09 (s, 1 H), 3.72 (d, J = 13.4 Hz, 1 H), 3.48–3.41 (m, 1 H), 3.14 (d, J = 13.4 Hz, 1 H), 3.12 (m, 1 H), 2.98–2.93 (m, 1 H), 2.50–2.44 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 138.6, 137.4, 136.6, 131.6, 130.7, 128.8, 128.7, 128.4, 128.3, 127.6, 127.4, 121.9, 70.6, 58.9, 50.3, 46.7, 45.8 ppm. HRMS: calcd. for $C_{24}H_{24}BrN_2O$ [M + 1]$^+$ 435.1072; found 435.1072. HPLC (Chiralcel OD column, 10 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 27.5 min [(*S*)-**18**, major enantiomer] and t_R = 22.4 min [(*R*)-**18**, minor enantiomer]; 86:14 *er*.

1,4-Dibenzyl-3-(*p*-chlorophenyl)piperazin-2-one (19): Pale yellow oil (82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.14 (m, 14 H), 4.61 (d, J = 14.6 Hz, 1 H), 4.52 (d, J = 14.6 Hz, 1 H), 4.11 (s, 1 H), 3.71 (d, J = 13.4 Hz, 1 H), 3.48–3.42 (m, 1 H), 3.15–3.08 (m, 2 H), 2.98–2.93 (m, 1 H), 2.51–2.44 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 138.1, 137.4, 136.6, 133.7, 130.4, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 127.4, 70.5, 58.9, 50.3, 46.7, 45.8 ppm. HRMS: calcd. for $C_{24}H_{24}ClN_2O$ [M + 1]$^+$ 391.1577; found 391.1577. HPLC (Chiralcel OD column, 10 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 29.1 min [(*S*)-**19**, major enantiomer] and t_R = 24.5 min [(*R*)-**19**, minor enantiomer]; 88:12 *er*.

4-Benzyl-3-(*p*-bromophenyl)morpholin-2-one (21): Yellow oil (73 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.21 (m, 9 H), 4.53 (dt, J = 11.0, 3.1 Hz, 1 H), 4.38–4.34 (m, 1 H), 4.22 (s, 1 H), 3.74 (d, J = 13.4 Hz, 1 H), 3.17 (d, J = 13.3 Hz, 1 H), 3.02–2.97 (m, 1 H), 2.68–2.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 136.6, 136.5, 131.9, 130.6, 128.8, 128.6, 127.7, 122.5, 69.9, 68.7, 58.9, 46.9 ppm. HRMS: calcd. for $C_{17}H_{17}BrNO_2$ [M + 1]$^+$ 346.0442; found 346.0443. HPLC (Chiralcel AD-H column, 10 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 28.7 min [(*S*)-**21**, major enantiomer] and t_R = 25.1 min [(*R*)-**21**, minor enantiomer]; 84:16 *er*.

4-Benzyl-3-(*p*-chlorophenyl)morpholin-2-one (22): Yellow oil (69 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.22 (m, 9 H), 4.54 (dt, J = 11.0 Hz, 3.1 Hz, 1 H), 4.39–4.35 (m, 1 H), 4.23 (s, 1 H), 3.74 (d, J = 13.4 Hz, 1 H), 3.17 (d, J = 13.3 Hz, 1 H), 3.02–2.98 (m, 1 H), 2.69–2.62 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 136.6, 136.1, 134.4, 130.2, 129.0, 128.8, 128.6, 127.7, 69.8, 68.7, 58.9, 46.9 ppm. HRMS: calcd. for $C_{17}H_{17}ClNO_2$ [M + 1]$^+$ 302.0948; found 302.0948. HPLC (Chiralcel AD-H column, 10 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 25.2 min [(*S*)-**22**, major enantiomer] and t_R = 22.1 min [(*R*)-**22**, minor enantiomer]; 84:16 *er*.

Procedure for the Preparation of 23a–23d: To a solution of L-threonine-derived α-bromo ester **1** (>98:2 *dr*) in $CHCl_3$ (2.0 M) at 0 °C were added the phenylalanine-derived azlactone (1.4 equiv.) and DIEA (2.0 equiv.). After the resulting reaction mixture had been stirred at 0 °C for 1 h, the solvent was evaporated, and the crude material was purified by column chromatography to afford **23a**–**23d** in 95 % yield.

***N*-Benzoyl-*O*-{[(α*R*,4*R*)-4-benzyl-4,5-dihydro-5-oxo-α,2-diphenyloxazol-4-yl]acetyl}-L-threonine Isopropyl Ester (23a):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–6.97 (m, 20 H), 6.35 (d, J = 9.2 Hz, 1 H), 5.41–5.39 (m, 1 H), 5.01–4.98 (m, 1 H), 4.82 (dd, J = 9.2, 2.0 Hz, 1 H), 4.29 (s, 1 H), 2.94 (d, J = 13.2 Hz, 1 H), 2.84 (d, J = 13.2 Hz, 1 H), 1.23 (d, J = 6.0 Hz, 3 H), 1.19 (d, J = 6.0 Hz, 3 H), 1.10 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4, 169.2, 168.9, 167.4, 161.5, 133.9, 133.5, 133.0, 132.5, 131.9, 130.6, 130.4, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.3, 127.2, 125.8, 75.2, 72.7, 70.1, 57.8, 55.7, 42.5, 21.7, 21.5, 16.6 ppm. HRMS: calcd. for $C_{38}H_{37}N_2O_7$ [M + 1]$^+$ 633.2601; found 633.2600.

***N*-Benzoyl-*O*-{[(α*S*,4*S*)-4-benzyl-4,5-dihydro-5-oxo-α,2-diphenyloxazol-4-yl]acetyl}-L-threonine Isopropyl Ester (23b):** Compound **23b** was obtained as an inseparable mixture with **23a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–6.97 (m, 20 H), 6.38 (d, J = 9.2 Hz, 1 H), 5.56–5.49 (m, 1 H), 4.81 (d, J = 9.2 Hz, 1 H), 4.71–4.65 (m, 1 H), 4.32 (s, 1 H), 2.89 (d, J = 13.2 Hz, 1 H), 2.70 (d, J = 13.2 Hz, 1 H), 1.25 (d, J = 6.0 Hz, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H) ppm.

***N*-Benzoyl-*O*-{[(α*R*,4*S*)-4-benzyl-4,5-dihydro-5-oxo-α,2-diphenyloxazol-4-yl]acetyl}-L-threonine Isopropyl Ester (23c):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.01 (m, 20 H), 6.96 (d, J = 9.2 Hz, 1 H), 5.54–5.52 (m, 1 H), 4.96 (dd, J = 9.2, 1.6 Hz, 1 H), 4.85–4.82 (m, 1 H), 4.36 (s, 1 H), 3.19 (d, J = 13.2 Hz, 1 H), 2.95 (d, J = 13.2 Hz, 1 H), 1.15 (d, J = 6.0 Hz, 3 H), 1.11 (d, J = 6.0 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 169.1, 168.5, 167.7, 161.3, 133.5, 133.1, 132.7, 132.3, 132.0, 130.4, 130.2, 128.8, 128.7, 128.6, 128.0, 127.8, 127.4, 127.3, 127.2, 125.4, 74.4, 72.9, 70.0, 59.2, 55.7, 42.4, 21.7, 21.3, 16.7 ppm. HRMS: calcd. for $C_{38}H_{37}N_2O_7$ [M + 1]$^+$ 633.2601; found 633.2600.

***N*-Benzoyl-*O*-{[(α*S*,4*R*)-4-benzyl-4,5-dihydro-5-oxo-α,2-diphenyloxazol-4-yl]acetyl}-L-threonine Isopropyl Ester (23d):** Compound **23d** was obtained as an inseparable mixture with **23c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.03 (m, 20 H), 6.57 (d, J = 9.2 Hz, 1 H), 5.50–5.40 (m, 1 H), 4.82 (dd, J = 9.2, 1.6 Hz, 1 H), 4.75–4.65 (m, 1 H), 4.35 (s, 1 H), 3.20 (d, J = 13.2 Hz, 1 H), 2.95 (d, J = 13.2 Hz, 1 H), 1.15 (d, J = 6.0 Hz, 3 H), 1.11 (d, J = 6.0 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H) ppm.

General One-Pot Procedure for the Asymmetric Synthesis of Aspartates 25–35: To a solution of L-threonine-derived α-bromo ester **1**, **15**, or **16** (>98:2 *dr*) in $CHCl_3$ (2.0 M) at 0 °C were added an azlactone nucleophile (1.4 equiv.) and DIEA (2.0 equiv.). After the resulting mixture had been stirred at 0 °C for 1 h, the reaction mixture was washed with a saturated solution of NH_4Cl and then concentrated in vacuo. To a solution of the diastereomeric mixture in methanol (0.3 M) was added sodium methoxide (6.0 equiv.) at –15 °C. After the solution had been stirred at –15 °C for 4 h, the resulting mixture was dissolved in EtOAc, washed with a saturated NH_4Cl solution, concentrated in vacuo, and then treated with HCl in methanol. After the mixture had been stirred at room temp. for 48 h, the solvent was evaporated, and the crude material was purified by column chromatography to afford the dimethyl aspartate as an inseparable mixture of two diastereomers (75–52 % overall yield as shown in Table 3) The *dr* value was determined by ^{1}H NMR analysis using the proton integrations of the two diastereomers, and the *er* value was determined by CSP-HPLC analysis. The spectroscopic data of **25** is identical to that of the authentic material that had been reported previously.[9]

(2*R*,3*R*)-*N*-Benzoyl-2-isobutyl-3-phenyl-L-aspartic Acid Dimethyl Ester (26): Pale yellow oil (61 % overall yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.22 (m, 10 H), 7.11 (s, 1 H), 4.88 (s, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.05 (dd, J = 4.4, 14.0 Hz, 1 H), 2.08 (dd, J = 8.0, 14.4 Hz, 1 H), 1.64–1.57 (m, 1 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.6, 166.7, 135.4, 134.2, 131.4, 129.9, 128.5, 128.1, 128.0, 126.7, 66.7, 56.7, 52.9, 52.1, 42.0, 25.0, 23.9, 22.3 ppm. HRMS: calcd. for $C_{23}H_{28}NO_5$

$[M + 1]^+$ 398.1967; found 398.1967. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 47.7 min [(*R*,*R*)-**26**, major enantiomer] and t_R = 18.4 min [(*S*,*S*)-**26**, minor enantiomer]; 96:4 *er*. Diastereomer *epi*-**26** was obtained as an inseparable mixture with **26**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.22 (m, 11 H), 5.17 (s, 1 H), 3.79 (s, 3 H), 3.59 (s, 3 H), 2.82 (dd, *J* = 4.4, 13.6 Hz, 1 H), 1.53–1.44 (m, 2 H), 0.86 (d, *J* = 6.4 Hz, 3 H), 0.69 (d, *J* = 6.4 Hz, 3 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-methyl-3-phenyl-L-aspartic Acid Dimethyl Ester (27): Pale yellow oil (75 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.81–7.32 (m, 10 H), 4.26 (s, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 1.72 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 172.9, 167.2, 134.6, 133.2, 131.7, 130.0, 128.6, 128.5, 128.4, 127.0, 62.4, 56.7, 52.8, 52.6, 20.7 ppm. HRMS: calcd. for $C_{20}H_{22}NO_5$ $[M + 1]^+$ 356.1498; found 356.1499. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 21.2 min [(*R*,*R*)-**27**, major enantiomer] and t_R = 18.7 min [(*S*,*S*)-**27**, minor enantiomer]; 99:1 *er*. Diastereomer *epi*-**27** was obtained as an inseparable mixture with **27**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.30 (m, 10 H), 6.83 (s, 1 H), 4.75 (s, 1 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 1.76 (s, 3 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2,3-diphenyl-L-aspartic Acid Dimethyl Ester (28): Yellow oil (74 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.91–6.98 (m, 15 H), 4.63 (s, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 172.1, 167.0, 135.4, 134.6, 132.7, 131.8, 130.1, 128.8, 128.1, 128.0, 127.7, 127.6, 127.2, 127.0, 68.4, 57.9, 53.3, 52.7 ppm. HRMS: calcd. for $C_{25}H_{24}NO_5$ $[M + 1]^+$ 418.1654; found 418.1654. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 20.7 min [(*R*,*R*)-**28**, major enantiomer] and t_R = 23.8 min [(*S*,*S*)-**28**, minor enantiomer]; 92:8 *er*. Diastereomer *epi*-**28** was obtained as an inseparable mixture with **28**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.21 (m, 16 H), 5.15 (s, 1 H), 3.56 (s, 3 H), 3.47 (s, 3 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-(methoxycarbonylmethyl)-3-phenyl-L-aspartic Acid Dimethyl Ester (29): Colorless oil (80 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.24 (m, 11 H), 4.84 (s, 1 H), 4.07 (d, *J* = 16.8 Hz, 1 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.62 (s, 3 H), 3.31 (d, *J* = 16.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 171.4, 170.9, 167.1, 134.7, 133.1, 131.6, 130.1, 128.6, 128.4, 128.3, 126.9, 63.6, 55.1, 53.3, 52.5, 51.8, 38.1 ppm. HRMS: calcd. for $C_{22}H_{24}NO_7$ $[M + 1]^+$ 414.1553; found 414.1553. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 66.5 min [(*R*,*R*)-**29**, major enantiomer] and t_R = 34.0 min [(*S*,*S*)-**29**, minor enantiomer]; 97:3 *er*. Diastereomer *epi*-**29** was obtained as an inseparable mixture with **29**. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13–7.29 (m, 11 H), 5.04 (s, 1 H), 3.77 (s, 3 H), 3.75 (d, *J* = 16.0 Hz, 1 H), 3.67 (s, 3 H), 3.55 (s, 3 H), 3.06 (d, *J* = 16.0 Hz, 1 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-(*p*-methoxybenzyl)-3-phenyl-L-aspartic Acid Dimethyl Ester (30): Pale yellow oil (63 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.21 (m, 10 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.77 (s, 1 H), 6.71 (d, *J* = 8.8 Hz, 2 H), 5.14 (s, 1 H), 4.27 (d, *J* = 14.0 Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.57 (d, *J* = 14.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 171.4, 167.4, 158.6, 135.5, 134.4, 131.4, 131.0, 129.9, 128.5, 128.2, 128.0, 127.9, 126.6, 113.7, 68.5, 55.5, 55.1, 52.9, 52.3, 38.2 ppm. HRMS: calcd. for $C_{27}H_{28}NO_6$ $[M + 1]^+$ 462.1916; found 462.1916. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 83.8 min [(*R*,*R*)-**30**, major enantiomer] and t_R = 47.3 min [(*S*,*S*)-**30**, minor enantiomer]; 95:5 *er*. Diastereomer *epi*-**30** was obtained as an inseparable mixture with **30**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.36 (m, 11 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 5.35 (s, 1 H), 4.01 (d, *J* = 13.6 Hz, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.58 (s, 3 H), 2.85 (d, *J* = 13.6 Hz, 1 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-[2-(methylthio)ethyl]-3-phenyl-L-aspartic Acid Dimethyl Ester (31): Pale yellow oil (61 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.24 (m, 11 H), 4.69 (s, 1 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.30–3.22 (m, 1 H), 2.49–2.39 (m, 2 H), 2.31–2.23 (m, 1 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.0, 166.7, 135.0, 133.6, 131.6, 129.9, 128.6, 128.3, 128.2, 126.8, 66.4, 56.8, 53.2, 52.4, 33.6, 29.2, 15.5 ppm. HRMS: calcd. for $C_{22}H_{26}NO_5S$ $[M + 1]^+$ 416.1532; found 416.1532. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane. 0.5 mL min^{-1}): t_R = 60.5 min [(*R*,*R*)-**31**, major enantiomer] and t_R = 36.0 min [(*S*,*S*)-**31**, minor enantiomer]; 98:2 *er*. Diastereomer *epi*-**31** was obtained as an inseparable mixture with **31**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.32 (m, 11 H), 5.08 (s, 1 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.11–3.06 (m, 1 H), 2.46–2.39 (m, 1 H), 2.21–2.14 (m, 1 H), 2.02–1.96 (s, 4 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-benzyl-3-(*p*-bromophenyl)-L-aspartic Acid Dimethyl Ester (32): Colorless oil (63 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.06 (m, 14 H), 6.77 (s, 1 H), 5.21 (s, 1 H), 4.31 (d, *J* = 13.6 Hz, 1 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.62 (d, *J* = 13.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.9, 167.5, 135.7, 135.2, 133.5, 132.5, 131.6, 131.3, 129.9, 128.6, 128.3, 127.2, 126.6, 122.3, 68.3, 54.9, 53.1, 52.4, 39.1 ppm. HRMS: calcd. for $C_{26}H_{25}BrNO_5$ $[M + 1]^+$ 510.0916; found 510.0916. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 51.9 min [(*R*,*R*)-**32**, major enantiomer] and t_R = 36.3 min [(*S*,*S*)-**32**, minor enantiomer]; 91:9 *er*. Diastereomer *epi*-**32** was obtained as an inseparable mixture with **32**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–6.92 (m, 15 H), 5.38 (s, 1 H), 4.04 (d, *J* = 13.2 Hz, 1 H), 3.77 (s, 3 H), 3.59 (s, 3 H), 2.84 (d, *J* = 13.2 Hz, 1 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-2-benzyl-3-(*p*-chlorophenyl)-L-aspartic Acid Dimethyl Ester (33): Pale yellow oil (52 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.07 (m, 14 H), 6.77 (s, 1 H), 5.22 (s, 1 H), 4.31 (d, *J* = 13.6 Hz, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.63 (d, *J* = 13.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 171.0, 167.5, 135.7, 135.2, 134.0, 132.9, 132.1, 131.6, 131.2, 129.9, 128.6, 128.3, 127.2, 126.6, 68.4, 54.8, 53.0, 52.4, 39.1 ppm. HRMS: calcd. for $C_{26}H_{25}ClNO_5$ $[M + 1]^+$ 466.1421; found 466.1421. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 46.7 min [(*R*,*R*)-**33**, major enantiomer] and t_R = 32.8 min [(*S*,*S*)-**33**, minor enantiomer]; 89:11 *er*. Diastereomer *epi*-**33** was obtained as an inseparable mixture with **33**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–6.92 (m, 15 H), 5.39 (s, 1 H), 4.04 (d, *J* = 13.2 Hz, 1 H), 3.77 (s, 3 H), 3.60 (s, 3 H), 2.85 (d, *J* = 13.2 Hz, 1 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-3-(*p*-bromophenyl)-2-isobutyl-L-aspartic Acid Dimethyl Ester (34): Yellow oil (62 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 10 H), 4.89 (s, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.03 (dd, *J* = 4.8, 14.4 Hz, 1 H), 2.07 (dd, *J* = 8.0, 14.4 Hz, 1 H), 1.64–1.57 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 171.1, 166.7, 135.1, 133.3, 132.4, 131.6, 131.2, 128.7, 126.7, 122.3, 66.6, 56.0, 53.0, 52.2, 41.9, 25.1, 23.9, 22.3 ppm. HRMS: calcd. for $C_{23}H_{27}BrNO_5$ $[M + 1]^+$ 476.1072; found 476.1072. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 55.9 min [(*R*,*R*)-**34**, major enantiomer] and t_R = 28.2 min [(*S*,*S*)-**34**, minor enantiomer]; 93:7 *er*. Diastereomer *epi*-**34** was obtained as an inseparable mixture with **34**. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.10 (m, 10 H), 5.16 (s, 1 H), 3.80 (s, 3 H), 3.59 (s, 3 H), 2.78 (dd, *J* = 4.8, 14.0 Hz, 1 H), 1.55–1.48 (m, 1 H), 1.41 (dd, *J* = 7.6, 14.0 Hz, 1 H), 0.86 (d, *J* = 6.4 Hz, 3 H), 0.69 (d, *J* = 6.4 Hz, 3 H) ppm.

(2*R*,3*R*)-*N*-Benzoyl-3-(*p*-chlorophenyl)-2-isobutyl-L-aspartic Acid Dimethyl Ester (35): Yellow oil (70 % overall yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.18 (m, 9 H), 7.10 (s, 1 H), 4.90 (s, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.04 (dd, *J* = 4.4, 14.0 Hz, 1 H), 2.07 (dd,

J = 8.0, 14.0 Hz, 1 H), 1.64–1.57 (m, 1 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 171.2, 166.7, 135.1, 134.0, 132.7, 131.6, 131.2, 128.7, 128.3, 126.6, 66.7, 55.9, 53.0, 52.2, 41.9, 25.1, 23.9, 22.3 ppm. HRMS: calcd. for $C_{23}H_{27}ClNO_5$ $[M + 1]^+$ 432.1578; found 432.1578. HPLC (Chiralpak AD-H column, 20 % 2-propanol in hexane, 0.5 mL min^{-1}): t_R = 49.0 min [(*R*,*R*)-**35**, major enantiomer] and t_R = 25.3 min [(*S*,*S*)-**35**, minor enantiomer]; 94:6 *er*. Diastereomer *epi*-**35** was obtained as an inseparable mixture with **35**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.18 (m, 10 H), 5.17 (s, 1 H), 3.80 (s, 3 H), 3.59 (s, 3 H), 2.79 (dd, J = 5.2 and 14.0 Hz, 1 H), 1.44–1.39 (m, 1 H), 1.42 (dd, J = 7.2 and 13.6 Hz, 1 H), 0.86 (d, J = 6.4 Hz, 3 H), 0.70 (d, J = 6.4 Hz, 3 H) ppm.

Supporting Information (see footnote on the first page of this article): NMR spectra of all new compounds.

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Keywords: Synthetic methods · Kinetic resolution · Nucleophilic substitution · Asymmetric synthesis · Chiral auxiliaries

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[3] We have improved the CIDR process of α-bromo phenylacetate **1** by using an *n*-hexane/diethyl ether (5:1) mixture at a 0.2 M concentration of **1** (50:50 *dr*). After the solvent had been allowed to evaporate at room temperature over 24 h, (α*R*)-**1** was quantitatively recovered with 90:10 *dr*. When **1** (90:10 *dr*) was dissolved in a minimum amount of *n*-hexane/diethyl ether (5:1), the recrystallization began within 4–5 h at room temperature. The mixture was allowed to stand at room temperature overnight and was then filtered to result in approximately 70 % crystallization yield with a *dr* of >98:2. Compared with the previous one-week crystallization process in *n*-hexane and ethyl acetate,[2f] the use of the *n*-hexane/diethyl ether mixture can shorten the crystallization time to obtain the same high optical purity of (α*R*)-**1**.

[4] A possible alternative to achieve the observed high stereoselectivity is through a dynamic kinetic resolution. In this pathway, α-bromo acetate **1** undergoes epimerization sufficiently fast relative to the rate of substitution, and under the reaction conditions, one of the two epimers of **1** preferentially undergoes a reaction with the nucleophile. In the reaction of α-bromo phenylacetate (α*RS*)-**1** (50:50 *dr*), moderate selectivities that ranged from 71:29 to 81:19 *dr* were observed in the substitution reactions with amine nucleophiles, which indicates that the dynamic kinetic resolution of α-bromo phenylacetate (α*RS*)-**1** is not the primary pathway for the high asymmetric induction. For reviews on dynamic kinetic resolution in the nucleophilic substitution of α-bromo carboxylic acid derivatives, see: a) Y. S. Park, *Tetrahedron: Asymmetry* **2009**, *20*, 2421–2427; b) R. N. Ben, T. Durst, *J. Org. Chem.* **1999**, *64*, 7700–7706; c) H. Kubota, A. Kubo, M. Takahashi, R. Shimizu, T. Da-te, K. Okamura, K. Nunami, *J. Org. Chem.* **1995**, *60*, 6776–6784; d) A. G. Santos, S. X. Candeias, C. A. M. Afonso, K. Jenkins, S. Caddick, N. R. Treweeke, D. Pardoe, *Tetrahedron* **2001**, *57*, 6607–6614; e) A. G. Santos, J. Pereira, C. A. M. Afonso, G. Frenking, *Chem. Eur. J.* **2005**, *11*, 330–343; f) Y. Kim, K. J. Park, M. Lee, H. Ryu, Y. S. Park, *Bull. Korean Chem. Soc.* **2014**, *35*, 265–268; g) Y. M. Lee, Y. S. Park, *Heterocycles* **2009**, *78*, 2233–2244; h) J. Baek, J. I. Jang, Y. S. Park, *Bull. Korean Chem. Soc.* **2011**, *32*, 4067–4070.

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