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Asymmetric nucleophilic substitution of α-bromo amides via dynamic kinetic resolution for the preparation of dipeptide analogues

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Abstract—Asymmetric nucleophilic substitution reactions of α-bromo α-aryl acetamides derived from L-amino acids are described. The simple and practical syntheses of dipeptide analogues have been developed with dibenzylamine, TBAI and a base to provide **2a**–**2n** and **4** in 50–98% yields with diastereomeric ratios from 74:26 to >99:1. Mechanistic investigations suggest that α-bromo acetamides are configurationally labile under the reaction condition and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. The semiempirical calculations of two epimeric transition states of **1b** found that (α*S*)-epimer is the faster reacting epimer with the formation of an intermolecular hydrogen bond that facilitates delivery of the amine nucleophile.

1. Introduction

Chiral auxiliary mediated dynamic resolution of α-halo carboxylic acid derivatives has been recently recognized as an effective synthetic method for asymmetric syntheses of α-amino acids, α-mercapto acids, and α-hydroxy acids.[1] Since α-haloacyl compounds are easily obtained in racemic form and configurational lability of them is readily induced, dynamic resolution in nucleophilic substitutions at α-halo carbon center can allow easy access to a wide range of enantioenriched α-heteroatom substituted carboxylic acid derivatives. Additionally, extension of this methodology to stereoselective modification of peptides is of obvious synthetic utility, in which chiral information of the adjacent amino acids is transferred to new bond formation at α-halo carbon center. The direct modification of peptide chain seems to be an attractive synthetic strategy for peptidomimetics since numerous peptide analogues can be efficiently prepared using easily accessible and relatively inexpensive amino acid precursor.[2] We have recently reported our preliminary results on dynamic resolution of α-bromo acetamides in nucleophilic substitution for asymmetric syntheses of di- and tripeptide analogues.[3] The chiral information of an amino acid precursor is efficiently transferred to the new C–N bond formation at α-halo carbon center, which can build an unnatural amino acid onto the amino acid precursor with remarkable stereoselectivity. Herein we describe our recent progress to extend the scope of the methodology and to provide the mechanistic and stereochemical rationale.

2. Results and discussion

We previously reported that L-proline and L-leucine are efficient precursors for asymmetric syntheses of dipeptide analogues via dynamic resolution of the corresponding α-bromo acetamides **1a** and **1b** as shown in Table 1, entries 1 and 2. When the two diastereomeric mixture (ca. 50:50) of *N*-(α-bromo-α-phenylacetyl)-(L)-proline methyl ester **1a** was treated with dibenzylamine (Bn_2NH), tetrabutylammonium iodide (TBAI) and triethylamine (Et_3N) in CH_2Cl_2 at room temperature, the dipeptide analogues **2a** was obtained in 93% yield with >99:1 diastereomeric ratio (dr, α*R*:α*S*). Also, the reactions of leucine methyl ester **1b** under the same condition gave the dipeptide analogue **2b** in 83% yield with 89:11 dr (α*R*:α*S*). In this paper, the scope of the observed dynamic resolution has been examined with 12 different L-amino acid precursors. The substitution reactions of α-bromo-α-phenyl acetamides **1c**–**1n** derived from the corresponding L-amino acid methyl esters and racemic α-bromo-α-phenyl acetic acid were investigated as

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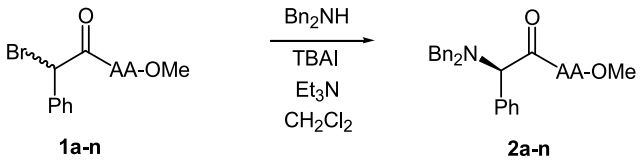
Table 1. Reactions of α-bromo acetamides **1a**–**1n**



1a-n **2a-n**

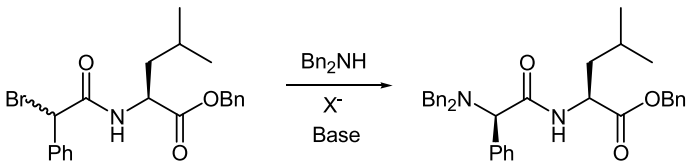
Entry[a]	S.M.[b]	L-AA[b]	Product	%Yield[c]	dr[d] (α*R*:α*S*)
1	**1a**	Pro	**2a**	93	>99:1
2	**1b**	Leu	**2b**	83	89:11
3	**1c**	Ala	**2c**	96	90:10
4	**1d**	Val	**2d**	81	95:5
5	**1e**	Ile	**2e**	95	93:7
6	**1f**	Phe	**2f**	91	90:10
7	**1g**	Trp	**2g**	98	90:10
8	**1h**	Phg	**2h**	52	84:16
9	**1i**	Tyr	**2i**	77	90:10
10	**1j**	Asp (*O*-Me)	**2j**	86	74:26
11	**1k**	Glu (*O*-Me)	**2k**	50	88:12
12	**1l**	Lys (*N*-Cbz)	**2l**	91	90:10
13	**1m**	Ser (*O*-Bn)	**2m**	50	91:9
14	**1n**	Cys (*S*-Bn)	**2n**	57	87:13

[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Initial drs of **1a**–**1n** are approximately 50:50.
[c] Isolated yields.
[d] The drs are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

shown in Table 1. Treatment of alanine methyl ester **1c** with Bn_2NH (1.2 equiv.), TBAI (1.0 equiv.) and Et_3N (1.0 equiv.) in CH_2Cl_2 for 24 h at room temperature gave **2c** in 96% yield with 90:10 dr (entry 3). Higher level of selectivities were observed with L-valine ester and L-isoleucine ester which have more sterically demanding secondary alkyl side chain (entries 4 and 5). The reactions of α-bromo acetamides **1f**, **1g** and **1i** derived from amino acids with aromatic side chain showed almost same drs as leucine methyl ester **1b**. Mild drops in stereoselectivity andyield were seen with α-bromo acetamide **1h** derived from L-phenylglycine (entry 8). α-Bromo acetamides **1j**–**1n** derived from L-aspartic acid, L-glutamic acid, L-lysine, L-serine, and L-cysteine were also examined with the protection of side chain functionality as shown in Table 1, entries 10–14. Considerable loss of stereoselectivity (74:26 dr) was observed with α-bromo acetamide **1j** derived from L-aspartic acid. Glutamic acid dimethyl ester **1k** and *N*-Cbz protected lysine methyl ester **1l** gave the dipeptide analogues **2k** and **2l** with 88:12 dr and 90:10 dr, respectively (entries 11 and 12). Similar stereoselectivities were observed in the reactions of *O*-benzyl protected serine derivative **1m** and *S*-benzyl protected cysteine derivative **1n** with moderate yields (entries 13 and 14). As can be seen in Table 1, the survey of various amino acid precursors indicates that highest stereoselectivity (>99:1) was observed with α-bromo acetamide **1a** derived from L-proline and other α-bromo acetamides **1b**–**1n** provided the dipeptide analogues **2b**–**2n** with good stereoselectivities, ranging from 74:26 dr to 95:5 dr.

In an effort to improve the stereoselectivity of the nucleophilic substitution of α-bromo acetamides **1b**–**1n** with dibenzylamine nucleophile, various reaction conditions have been examined as shown in Table 2 with leucine benzyl ester **3**. Of the solvents explored, CH_2Cl_2 consistently gave the best results (entry 1). The dipeptide analogue **4** was obtained from **3** with 87:13 dr in *n*-hexane, 85:15 dr in ether, 90:10 dr in CH_3CN, 89:11 dr in NMP, 92:8 dr in DMF, and 86:14 dr in *p*-dioxane (entries 2–7). We also examined the substitutions at 0 and 50 °C (entries 8 and 9).

Table 2. Effects of substitution conditions on the stereoselectivities



3 **4**

Entry[a]	Solvent	Base	X^-	Temperature	Yield[b]	dr[c] (α*R*:αS)
1	CH_2Cl_2	Et_3N	TBAI	rt	95	93:7
2	*n*-Hexane	Et_3N	TBAI	rt	55	87:13
3	Ether	Et_3N	TBAI	rt	73	85:15
4	CH_3CN	Et_3N	TBAI	rt	91	90:10
5	NMP	Et_3N	TBAI	rt	48	89:11
6	DMF	Et_3N	TBAI	rt	68	92:8
7	*p*-Dioxane	Et_3N	TBAI	rt	68	86:14
8	CH_2Cl_2	Et_3N	TBAI	0 °C	77	92:8
9	CH_2Cl_2	Et_3N	TBAI	50 °C	85	93:7
10	CH_2Cl_2	None	None	rt	43	66:34
11	CH_2Cl_2	Et_3N	None	rt	51	71:29
12	CH_2Cl_2	None	TBAI	rt	90	89:11
13	CH_2Cl_2	Et_3N	TBAI (0.1 equiv.)	rt	88	88:12
14	CH_2Cl_2	Et_3N	TBAB	rt	85	88:12
15	CH_3CN	Et_3N	KI	rt	73	92:8
16	CH_2Cl_2	DBN	TBAI	rt	10	90:10
17	CH_2Cl_2	DBU	TBAI	rt	46	86:14
18	CH_2Cl_2	DIEA	TBAI	rt	97	94:6

[a] All reactions were carried out for 24 h with **3** (1.0 equiv., ca. 50:50 dr), dibenzylamine (1.2 equiv.), X^- (1.0 equiv.) and a base (1.2 equiv.).
[b] Isolated yields.
[c] The drs of **4** are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

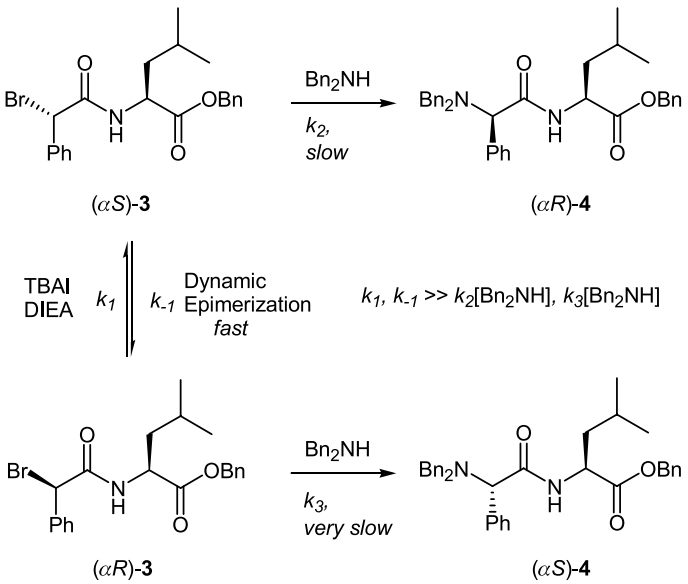
Temperature appeared to have little influence on the selectivity. The results in entries 10–12 pointed to the importance of the presence of TBAI for rate acceleration and high stereoselectivity. The reaction in the absence of both TBAI and Et_3N for 24 h gave the product with slower rate and much lower stereoselectivity (66:34 dr). The lack of stereoselectivity in the absence of TBAI may be explained by the slow epimerization of **3** with respect to the substitution with the amine nucleophile.[4] Use of catalytic amount of TBAI eroded the selectivity, probably due to less efficient epimerization process (entry 13). When KI was used as an epimerizing agent, the reaction gave almost same selectivity (92:8 dr) as the reaction with TBAI, which was better than the reaction with bromide epimerizing agent, TBAB (entries 14–15). Slightly diminished stereoselectivity with poor yield was observed by changing the base from Et_3N to DBU or DBN (entries 16 and 17). The addition of diisopropylethylamine (DIEA) afforded the dipeptide analogue **4** with highest stereoselctivity (94:6 dr) in 97% yield (entry 18). We were pleased to observe that DIEA promoted reactions of most α-bromo acetamides gave the improved stereoselectivities, compared to the stereoselectivities of the reactions with Et_3N shown in Table 1. The reactions of **1b**, **1e**, **1g**, **1h**, and **1i** with DIEA and TBAI provided the products with 93:7 dr, 97:3 dr, 93:7 dr, 87:13 dr and 93:7 dr, respectively.

The *R*-configuration at α-position of major product **4** was assigned by comparison to the ^1H NMR of authentic epimers individually prepared from the coupling of L-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative, and also confirmed by comparison of chiral-HPLC retention time with authentic epimers using racemic material as a standard. The configurational stability of the dipeptide analogue **4** was examined by the treatment with Bn_2NH (1.2 equiv.), TBAI (1.0 equiv.) and DIEA (1.0 equiv.) in CH_2Cl_2 for 24 h. No epimerization at two stereogenic centers of **4** was detected by ^1H NMR and Chiral-HPLC, ruling out the possibility of epimerization after the replacement of Br with dibenzylamine. Thus, the observed asymmetric induction is the results of dynamic resolution in nucleophilic substitution of two epimeric mixture of α-bromo acetamide **3**.

There are two limiting pathways which could account for the observed dynamic resolution in nucleophilic substitution of α-bromo acetamide **3**. In one limiting pathway, α-bromo stereogenic center undergoes rapid epimerization between (α*S*)-**3** and (α*R*)-**3** and one of two epimers reacts preferentially under the reaction condition. This is a case of dynamic kinetic resolution, in which the stereoselectivity is determined by the difference in the epimeric transition state energies for the reaction with dibenzylamine. In a different limiting pathway, the stereoselectivity of the reaction is determined by the ratio of (α*S*)-**3** and (α*R*)-**3** that is established before the substitution. This is termed dynamic thermodynamic resolution because the ratio of two epimers is thermodynamically controlled and the stereoselectivity of the reaction is not determined by the difference in the rates of substitutions with dibenzylamine.

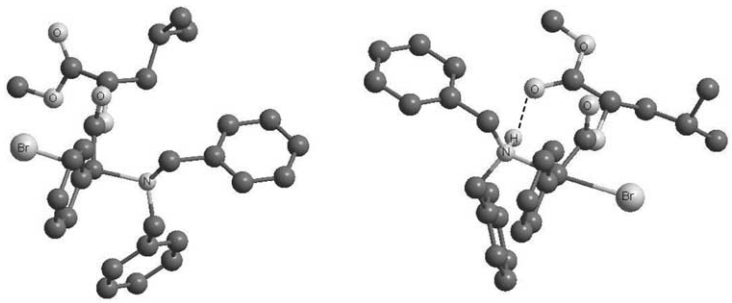
A series of reactions as shown in Table 3 has been carried

Table 3. Dynamic kinetic resolution of α-bromo acetamide **3**



Entry	S.M.	Condition	Product (α*R*:α*S*)	Yield (%)
1	**3** (57:43)	TBAI, DIEA, rt	**3** (52:48)	75
2	**3** (78:22)	TBAI, DIEA, rt	**3** (52:48)	78
3	**3** (72:28)	TBAI, DIEA, Bn_2NH, rt	**4** (94:6)	96
4	**3** (30:70)	TBAI, DIEA, Bn_2NH, rt	**4** (95:5)	98

All reactions were carried out for 24 h at rt. The drs of **3** and **4** were determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic α-bromo phenyl acetic acid and phenylglycine, respectively, as standards.



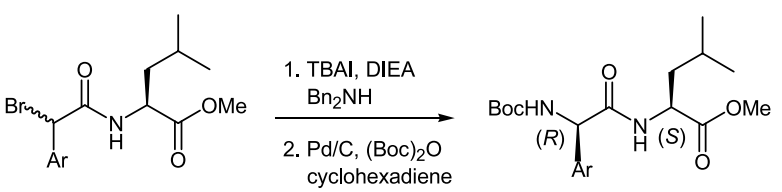
(αR)-**1b-TS;** ΔH = 109.04 kcal/mol (αS)-**1b-TS;** ΔH = 106.04 kcal/mol

Figure 1. Transition states for the reactions of slower reacting (α*R*)-**1b** and faster reacting (α*S*)-**1b** with dibenzylamine. Hydrogens have been removed for clarity.

out to differentiate the two possible pathways of asymmetric induction in nucleophilic substitution reactions of α-bromo amides. When the mixture of two epimers was allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the epimeric ratio of recovered **3** was analyzed by ^{1}H NMR, determined to be 52:48 in both cases with **3** of 57:43 dr and 78:22 dr, respectively (entries 1 and 2). These results indicate that α-bromo amide **3** 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 **3** with 72:28 dr was treated with dibenzylamine in the presence of both TBAI and DIEA, the reaction gave the product **4** with 94:6 dr as shown in entry 3. In addition, almost same dr of product **4** was observed in the reaction of **3** with reversed diastereomeric enrichment of 30:70 dr. Thus, the diastereomeric ratio of product **4** is independent of the starting ratio of two epimers of **3** and would depend solely on the difference in the epimeric transition state energies. These results could be taken to suggest that the epimerization of **3** promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution (k_1, $k_{-1} \gg k_2$[dibenzylamine], k_3[dibenzylamine]) and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.

In order to gain further understanding of the dynamic kinetic resolution, we proceed to calculate the transition states of both leucine methyl esters (α*R*)-**1b** and (α*S*)-**1b** using semi-empirical methods.[5] The main results of the calculations after full optimizations at HF/6-31G(d) level are shown in Figure 1. The only constraint was the distance between the two reaction centers during the transition state search. Starting from the sufficiently long distance, this distance constraint has been reduced systematically by monitoring the energy of the corresponding conformation. At this level of theory, only one transition state was found for each epimer, with the transition state (α*S*)-**1b**–**TS** having the lower enthalpy value. The energy difference of about 3.0 kcal/mol between the transition state structures (α*R*)-**1b**–**TS** and (α*S*)-**1b**–**TS** is fully consonant with the highly stereoselective character of the dynamic kinetic resolution process. Based on the results of the calculations, we conclude that the (α*S*)-**1b** is the faster reacting diastereomer and this is due to formation of an intermolecular hydrogen bond that facilitates delivery of the amine nucleophile. The model proposed here, by relying on hydrogen bonding, is consistent with the poor stereoselectivities of the reactions with thiol nucleophiles and metalated nucleophiles, relatively poor hydrogen bond donor nucleophiles.[6]

For further *N*-terminal functionalization of the dipeptide analogues, the *N*,*N*-dibenzyl protecting group is removed and converted to the Boc group with Pd/C, cyclohexadiene, and $(Boc)_2O$ as shown in Scheme 1.[7] *N*-Boc-D-phenylglycyl-L-leucine methyl ester **6** was obtained in 47% overall yield with 93:7 dr from α-phenylacetyl leucine methyl ester **1b**. The diastereomerically pure *N*-Boc dipeptide analogues **7** was obtained in 30% overall yield after silica gel column chromatography from α-(*p*-fluorophenyl)acetyl leucine methyl ester **5**. The isolated yields of **6** and **7** generally were not high, but the procedure was performed at a relatively small scale and no further attempts were made to optimize the yields for the deprotection. This methodology provides the unique possibility to synthesize a wide range of D-arylglycine dipeptide analogues with various L-amino acids. It is well known that D-phenylglycine dipeptides have interesting properties and can be applied, for example, as tumor and tissue-dissolving compounds of low toxicity and as resolving agents.[8]



Scheme 1.

3. Conclusion

We have shown that dynamic resolution of α-bromo amides can be successfully applied towards the preparation of enantioenriched dipeptide analogues. The methodology has been particularly successful for α-bromo α-aryl acetamides, affording a generalized and practical method for the asymmetric syntheses of D-arylglycine dipeptide analogues.[9] Mechanistic investigations along with semi-empirical calculations suggest that α-bromo α-aryl acetamides are configurationally labile under the reaction condition and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. The methodology of the present work should also be applicable to stereo-selective syntheses and mechanistic analysis of a number of related systems.

4. Experimental

4.1. General procedure for the preparation of 1a–1n, 3, and 5

L-Amino acid methyl (or benzyl) ester (1.0 equiv.), racemic α-bromo phenylacetic acid (1.0 equiv.), DCC (1.0 equiv.), Et_3N (1.1 equiv.) and DMAP (0.2 equiv.) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 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.

4.1.1. (*S*)-*N*-(α-Bromo-α-phenylacetyl) proline methyl ester (1a). A colorless oil was obtained in 36% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.32 (m, 5H), 5.64, 5.41 (s, 1H), 4.54, 4.45 (m, 1H), 3.72, 3.65 (s, 3H), 3.33 (m, 1H), 2.15–1.84 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 166.3, 136.0, 129.3, 128.9, 128.5, 60.0, 59.8, 52.6, 47.5, 29.2, 25.3. HRMS calcd for $C_{14}H_{16}BrNO_3$: 325.0314. Found: 325.0326.

4.1.2. (*S*)-*N*-(α-Bromo-α-phenylacetyl) leucine methyl ester (1b). A colorless oil was obtained in 34% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.07 (m, 6H), 5.46, 5.44 (s, 1H), 4.60 (m, 1H), 3.73, 3.72 (s, 3H), 1.63 (m, 3H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 167.5, 137.6, 129.4, 128.9, 128.3, 52.7, 51.0, 41.5, 25.2, 23.1, 22.3. Anal. calcd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.66; H, 5.92; N, 3.91.

4.1.3. (*S*)-*N*-(α-Bromo-α-phenylacetyl) alanine methyl ester (1c). A colorless oil was obtained in 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.28–7.49 (m, 6H), 5.45, 5.38 (s, 1H), 4.55 (m, 1H), 3.71, 3.70 (s, 3H), 1.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 167.4, 137.5, 129.5, 128.8, 128.3, 52.9, 50.8, 49.3, 18.2. Anal. calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.02; H, 4.82; N, 4.43.

4.1.4. (*S*)-*N*-(α-Bromo-α-phenylacetyl) valine methyl ester (1d). A colorless oil was obtained in 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.15 (m, 5H), 7.15, 7.08 (d, *J*=8.0, 8.2 Hz, 1H), 5.48, 5.45 (s, 1H), 4.55 (m, 1H), 3.74 (s 3H), 2.23 (m, 1H), 0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 167.5, 137.6, 129.5, 129.3, 128.8, 58.3, 52.7, 51.6, 31.8, 19.3, 18.1. Anal. calcd for $C_{14}H_{13}BrNO_3$: C, 51.23; H, 5.53; N, 4.27. Found: C, 51.42; H, 5.44; N, 3.95.

4.1.5. (*S*)-*N*-(α-Bromo-α-phenylacetyl) isoleucine methyl ester (1e). A colorless oil was obtained in 13% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.29 (m, 5H), 7.19, 7.12 (d, *J*=8.0, 8.0 Hz, 1H), 5.47, 5.44 (s, 1H), 4.59 (d, *J*=4.6 Hz, 1H), 3.74 (s, 3H), 1.97 (m, 1H), 1.44 (m, 1H), 1.19 (m, 1H), 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 167.3, 137.6, 129.5, 128.3, 128.7, 57.6, 52.6, 51.7, 38.3, 25.6, 15.9, 11.9. Anal. calcd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.66; H, 5.94; N, 4.15.

4.1.6. (*S*)-*N*-(α-Bromo-α-phenylacetyl) phenylalanine methyl ester (1f). A colorless oil was obtained in 30% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.26–7.00 (m, 11H), 5.37, 5.31 (s, 1H), 4.85 (m, 1H), 3.68, 3.66 (m, 3H), 3.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.8, 167.3, 137.5, 135.8, 129.7, 129.3, 129.0, 128.8, 128.3, 127.6, 54.3, 52.9, 51.1, 37.9. Anal. calcd for $C_{13}H_{13}BrNO_3$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.35; H, 4.76; N, 3.44.

4.1.7. (*S*)-*N*-(α-Bromo-α-phenylacetyl) tryptophan methyl ester (1g). A colorless oil was obtained in 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.3 (br, 1H), 7.54–7.06 (m, 10H), 6.82 (m, 1H), 5.32, 5.30 (s, 1H), 4.89 (m, 1H), 3.66, 3.64 (s, 3H), 3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 167.5, 137.5, 136.6, 129.5, 129.3, 128.9, 127.7, 123.6, 122.6, 120.1, 118.9, 111.8, 109.7, 54.1, 53.0, 51.2, 27.8. Anal. calcd for $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 6.75. Found: C, 57.80 H, 4.65; N, 6.48.

4.1.8. (*S*)-*N*-(α-Bromo-α-phenylacetyl) phenylglycine methyl ester (1h). A colorless oil was obtained in 33% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.72–7.21 (m, 11H), 5.53 (m, 1H), 5.44, 5.41 (s, 1H), 3.68, 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.2, 167.1, 137.5, 136.3, 129.5, 129.3, 129.2, 128.9, 128.4, 127.7, 57.6, 53.3, 51.0. Anal. calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.66; H, 4.30; N, 3.62.

4.1.9. (*S*)-*N*-(α-Bromo-α-phenylacetyl) tyrosine methyl ester (1i). A colorless oil was obtained in 39% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.42–6.54 (m, 11H), 5.39, 5,38 (s, 1H), 4.83 (m, 1H), 3.76, 3.74 (s, 3H), 3.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 167.6, 156.0, 137.3, 130.7, 129.6, 129.4, 128.7, 126.9, 116.1, 54.4, 53.0, 51.3, 37.3. Anal. calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 55.14; H, 4.45; N, 3.41.

4.1.10. (*S*)-*N*-(α-Bromo-α-phenylacetyl) aspartic acid dimethyl ester (1j). A colorless oil was obtained in 20% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.68–7.26 (m, 6H), 5.44, 5.40 (s, 1H), 4.60 (m, 1H), 3.77, 3.69 (s, 3H), 3.07, 2.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 170.9, 167.4, 137.5, 129.3, 128.7, 128.3, 53.4, 52.5, 51.1, 49.8, 36.0. Anal. calcd for $C_{14}H_{16}BrNO_5$:

C, 46.95; H, 4.50; N, 3.91. Found: C, 46.95; H, 4.65; N, 3.97.

4.1.11. (*S*)-*N*-(α-Bromo-α-phenylacetyl) glutamic acid dimethyl ester (1k). A colorless oil was obtained in 26% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.32 (m, 6H), 5.46, 5.45 (s, 1H), 4,61 (m, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.38 (m, 2H), 2.25 (m, 1H), 2,05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 172.0, 167.8, 137.2, 129.5, 128.8, 128.3, 61.3, 52.8, 52.3, 50.8, 30.3, 27.3. Anal. calcd for $C_{15}H_{18}BrNO_5$: C, 48.40; H, 4.87; N, 3.76. Found: C, 48.38; H, 4.72; N, 3.61.

4.1.12. (*S*)-*N*-(α-Bromo-α-phenylacetyl) lysine(*N*-benzyloxycarbonyl) methyl ester (1l). A colorless oil was obtained in 44% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.47–7.27 (m, 11H), 5.44, 5.43 (s, 1H), 5.07 (s, 2H), 5.02 (m, 1H), 4.56 (m, 1H), 3.71, 3.70 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.46 (m, 2H), 1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.6, 167.5, 157.0, 137.5, 137.0, 129.5, 129.2, 128.9, 128.5, 128.3, 128.1, 67.0, 53.1, 52.9, 51.0, 40.9, 32.0, 29.6, 22.7. Anal. calcd for $C_{23}H_{27}BrN_2O_3$: C, 56.22; H, 5.54; N, 5.70. Found: C, 56.19; H, 5.65; N, 5.58.

4.1.13. (*S*)-*N*-(α-Bromo-α-phenylacetyl) serine(*O*-benzyl) methyl ester (1m). A colorless oil was obtained in 22% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.24 (m, 11H), 5.44, 5.43 (s, 1H), 4.72 (m, 1H), 4.51 (m, 2H), 3.89 (m, 1H), 3.75 (m, 3H), 3.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.5, 167.3, 137.8, 129.5, 129.3, 128.9, 128.4, 128.3, 128.2, 128.0, 73.6, 69.4, 53.8, 53.1, 51.3. Anal. calcd for $C_{19}H_{20}BrNO_3$: C, 56.17 H, 4.96; N, 3.45. Found: C, 56.20; H, 4.97; N, 3.34.

4.1.14. (*S*)-*N*-(α-Bromo-α-phenylacetyl) cysteine(*S*-benzyl) methyl ester (1n). A colorless oil was obtained in 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.51–7.25 (m, 11H), 5.44, 5.43 (s, 1H), 4.78 (m, 1H), 3.74 (s, 3H), 3.68 (m,2H), 2.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.0, 167.3, 137.8, 129.4, 129.6, 129.4, 129.3, 129.0, 128.3, 127.7, 53.2, 52.8, 51.2, 37.0, 33.5. Anal. calcd for $C_{19}H_{20}BrNO_3S$: C, 54.03; H, 4.77; N, 3.32. Found: C, 54.25; H, 4.77; N, 3.15.

4.1.15. (*S*)-*N*-(α-Bromo-α-phenylacetyl) leucine benzyl ester (3). A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.45–7.29 (m, 10H), 7.01 (m, 1H), 5.45, 5.42 (s, 1H), 5.17 (m, 2H), 4.66 (m, 1H), 1.66 (m, 3H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 167.3, 137.6, 135.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.6, 67.6, 52.2, 51.5, 41.7, 25.3, 23.2, 22.3. Anal. calcd for $C_{21}H_{24}BrNO_3$: C, 60.29; H, 5.78; N, 3.35. Found: C, 60.54; H, 5.82; N, 3.12.

4.1.16. (*S*)-*N*-[α-Bromo-α-(*p*-fluorophenyl)acetyl] leucine methyl ester (5). A colorless oil was obtained in 47% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.43 (m, 2H), 7.06–7.01 (m, 3H), 5.45, 5.42 (s, 1H), 4.61 (m, 1H), 3.75, 3.74 (s, 3H), 1.64 (m, 3H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.2, 167.1, 164.5, 133.4, 130.8, 116.5, 52.8, 52.0, 50.0, 25.3, 23.2, 22.3. Anal. calcd for $C_{15}H_{19}BrFNO_3$: C, 50.01; H, 5.32; N, 3.89. Found: C, 50.09; H, 5.23; N, 3.74.

4.2. General procedure for asymmetric preparation of dipeptide analogues 2a–2n, and 4

To a solution of (α*RS*)-α-bromo acetamides in dry CH_2Cl_2 (ca. 0.1 M) at room temperature was added dibenzylamine (1.2 equiv.), TBAI (1.0 equiv.) and Et_3N (or DIEA, 1.2 equiv.). The resulting reaction mixture was stirred at room temperature for 24 h. The solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel.

4.2.1. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] proline methyl ester (2a). A colorless oil was obtained in 93% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.20 (m, 16H), 4.61 (m, 2H), 3.94–3.80 (m, 4H), 3.85 (s, 3H), 3.03 (m, 1H), 2.82 (m, 1H), 2.11 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 171.9, 141.1, 137.2, 129.6, 129.3, 129.0, 128.8, 128.2, 127.1, 64.1, 59.0, 54.6, 52.7, 46.8, 29.5, 25.2. Anal. calcd for $C_{23}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.98; H, 6.86; N, 6.20.

4.2.2. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] leucine methyl ester (2b). A colorless oil was obtained in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.78 (d, *J*=8.8 Hz, 1H), 7.47–7.18 (m, 15H), 4.72 (m, 1H), 4.45 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.28 (d, *J*=13.6 Hz, 2H), 1.63 (m, 3H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.8, 171.8, 139.0, 133.8, 131.0, 129.2, 129.0, 128.5, 128.3, 127.8, 67.5, 54.9, 52.6, 51.0, 42.1, 25.4, 23.3, 22.3. Anal. calcd for $C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.91; H, 7.46; N, 6.10.

4.2.3. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] alanine methyl ester (2c). A colorless oil was obtained in 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.81 (d, *J*=8.8 Hz, 1H), 7.40–7.23 (m, 15H), 4.65 (m, 1H), 4.43 (s, 1H), 3.89 (d, *J*=13.7 Hz, 2H), 3.76 (s, 3H), 3.28 (d, *J*=13.7 Hz, 2H), 1.42 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.8, 171.6, 139.0, 134.1, 130.9, 129.3, 129.0, 128.5, 128.3, 127.7, 67.8, 54.9, 52.9, 48.4, 18.8. Anal. calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 74.80; H, 6.91; N, 6.65.

4.2.4. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] valine methyl ester (2d). A colorless oil was obtained in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.95 (d, *J*=9.2 Hz, 1H), 7.45–7.23 (m 15H), 4.66 (m, 1H), 4.47 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.25 (d, *J*=13.6 Hz, 2H), 2.26 (m, 1H), 0.96 (d, *J*=7.2 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.8, 171.9, 138.9, 133.6, 131.1, 129.3, 129.0, 128.6, 128.3, 127.8, 67.5, 57.4, 54.8, 52.5, 31.8, 19.5, 18.1. Anal. calcd for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.73; H, 7.44; N, 6.21.

4.2.5. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] isoleucine methyl ester (2e). A colorless oil was obtained in 95% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.97 (d, *J*=9.2 Hz, 1H), 7.42–7.21 (m, 15H), 4.70 (m, 1H), 4.46 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.21 (d, *J*=13.6 Hz, 2H), 1.97 (m, 1H), 1.47 (m, 1H), 1.20 (m, 1H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.7, 171.7, 139.0, 133.6, 131.1, 129.3, 129.0, 128.5, 128.3, 127.8, 67.5, 56.8, 54.9, 52.4, 38.2, 25.7, 16.1, 12.1. Anal. calcd for

$C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.99; H, 7.60; N, 5.92.

4.2.6. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] phenylalanine methyl ester (2f). A colorless oil was obtained in 91% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.80 (d, *J*=8.4 Hz, 1H), 7.36–7.07 (m, 20H), 5.03 (m, 1H), 4.39 (s, 1H), 3.84 (m, 2H), 3.69 (s, 3H), 3.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.4, 171.8, 138.8, 136.3, 133.1, 131.2, 129.7, 129.2, 129.1, 129.0, 128.9, 128.4, 128.2, 127.6, 67.4, 54.7, 53.2, 52.6, 38.1. Anal. calcd for $C_{32}H_{32}N_2O_3$: C, 78.02; H, 6.55; N, 5.69. Found: C, 78.06; H, 6.65; N, 5.65.

4.2.7. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] tryptophan methyl ester (2g). A colorless oil was obtained in 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.2 (br, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.56–7.07 (m, 20H), 6.81 (s, 1H), 5.04 (m,1H), 4.38 (s, 1H), 3.82 (d, *J*=13.6 Hz, 2H), 3.64 (s, 3H), 3.39 (m, 2H), 3.13 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.0, 172.0, 138.9, 136.7, 133.5, 131.2, 129.2, 128.8, 128.4, 128.2, 127.8, 127.6, 123.3, 122.7, 120.1, 119.0, 111.7, 110.2, 67.6, 54.8, 52.9, 52.7, 27.9. Anal. calcd for $C_{34}H_{33}N_3O_3$: C, 76.81; H, 6.26; N, 7.90. Found: C, 76.79; H, 6.19; N, 7.69.

4.2.8. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] phenylglycine methyl ester (2h). A colorless oil was obtained in 52% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.33 (m, 1H), 7.45–7.22 (m, 20H), 5.62 (m, 1H), 4.44 (s, 1H), 3.94 (d, *J*=13.6 Hz, 2H), 3.74 (m, 3H), 3.27 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 171.5, 139.0, 137.3, 133.7, 131.0, 129.3, 129.2, 129.1, 129.0, 128.9, 128.6, 128.3, 127.7, 67.6, 57.0, 55.0, 53.2. Anal. calcd for $C_{31}H_{30}N_2O_3$: C, 77.80; H, 6.32; N, 5.85. Found: C, 77.71; H, 6.39; N, 5.73.

4.2.9. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] tyrosine methyl ester (2i). A colorless oil was obtained in 77% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.84 (d, *J*=8.4 Hz, 1H), 7.38–7.20 (m, 15H), 6.95 (d, *J*=8.2 Hz, 2H), 6.73 (d, *J*=8.2 Hz, 2H), 5.72 (br, 1H), 4.95 (m, 1H), 3.84 (d, *J*=13.6 Hz, 2H), 3.69 (s, 3H), 3.09 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 172.1, 155.6, 138.7, 133.0, 131.2, 130.8, 129.2, 128.9, 128.4, 128.3, 127.8, 127.7, 116.1, 67.5, 54.7, 53.3, 52.7, 37.3. Anal. calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.53; H, 6.42; N, 5.40.

4.2.10. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] aspartic acid dimethyl ester (2j). A colorless oil was obtained in 86% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.51 (d, *J*=8.8 Hz, 1H), 7.44–7.24 (m, 15H), 4.99 (m, 1H), 4.42 (s, 1H), 3.92 (d, *J*=13.6 Hz, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.28 (d, *J*=13.6 Hz, 2H), 3.11 (m, 1H), 2.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 156.8, 139.0, 137.0, 133.8, 130.9, 129.3, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 67.6, 67.9, 54.9, 52.8, 52.2, 32.4. Anal. calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.81; H, 6.40; N, 5.71.

4.2.11. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] glutamic acid dimethyl ester (2k). A colorless oil was obtained in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.93 (d, *J*=8.4 Hz, 1H), 7.49–7.24 (m, 15H), 4.72 (m, 1H), 4.44 (s, 1H), 3.94 (d, *J*=13.6 Hz, 2H), 3.75 (s, 3H), 3,64 (s, 3H), 3.27 (d, *J*=13.6 Hz), 2.28 (m, 3H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 172.6, 172.0, 138.9, 133.7, 131.0, 129.3, 129.1, 128.9, 128.5, 127.8, 67.6, 54.9, 52.1, 51.8, 30.3, 27.7. Anal. calcd for $C_{29}H_{31}N_2O_5$: C, 70.72; H, 6.57; N, 5.89. Found: C, 70.89; H, 6.75; N, 5.67.

4.2.12. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] lysine(*N*-carbonyloxybenzyl) methyl ester (2l). A colorless oil was obtained in 91% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.88 (d, *J*=8.4 Hz, 1H), 7.40–7.22 (m, 20H), 5.04 (s, 2H), 4.68 (m, 1H), 4.44 (s, 1H), 3.88 (d, *J*=13.6 Hz, 2H), 3.74 (s, 3H), 3.27 (d, *J*=13.6 Hz, 2H), 3.08 (m, 2H), 1.91 (m, 1H), 1.70 (m, 1H), 1.46 (m, 2H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 156.8, 139.0, 137.0, 133.9, 130.9, 129.3, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 67.6, 66.9, 54.9, 52.8, 52.2, 41.1, 32.4, 29.7, 22.8. Anal. calcd for $C_{37}H_{41}N_2O_5$: C, 73.12; H, 6.80; N, 6.91. Found: C, 73.11; H, 6.67; N, 7.02.

4.2.13. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] serine(*O*-benzyl) methyl ester (2m). A colorless oil was obtained in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.35 (d, *J*=8.4 Hz, 1H), 7.39–7.19 (m, 20H), 4.84 (m, 1H), 4.58 (s, 2H), 4.45 (s, 1H), 4.03 (m, 1H), 3.95 (d, *J*=13.6 Hz, 2H), 3.72 (m, 4H), 3.22 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 171.2, 139.0, 137.9, 133.6, 131.2, 129.4, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 127.7, 73.9, 70.2, 67.6, 54.9, 52.9. Anal. calcd for $C_{33}H_{34}N_2O_3$: C, 75.84; H, 6.56; N, 5.36. Found: C, 75.91; H, 6.62; N, 5.34.

4.2.14. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] cysteine(*S*-benzyl) methyl ester (2n). A colorless oil was obtained in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.32 (d, *J*=7.2 Hz, 1H), 7.68–7.22 (m, 20H), 4.92 (m, 1H), 4.46 (s, 1H), 3.90 (d, *J*=13.6 Hz, 2H), 3.69 (m, 5H), 3.26 (d, *J*=13.6 Hz, 2H), 2.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.9, 171.7, 138.9, 137.9, 131.6, 131.1, 129.4, 129.2, 129.0, 128.9, 128.6, 128.3, 128.0, 127.7, 67.6, 55.0, 53.0, 51.6, 36.9, 33.8. Anal. calcd for $C_{33}H_{34}N_2O_3S$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.35; H, 6.34; N, 5.06.

4.2.15. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] leucine benzyl ester (4). A colorless oil was obtained in 97% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.79 (d, *J*=8.4 Hz, 1H), 7.38–7.22 (m, 20H), 5.18 (m, 2H), 4.73 (m, 1H), 4.43 (s, 1H), 3.87 (d, *J*=13.6 Hz, 2H), 3.21 (d, *J*=13.6 Hz, 2H), 1.74 (m, 1H), 1.61 (m, 2H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 139.0, 135.8, 133.7, 131.0, 129.2, 129.0, 128.8, 128.6, 128.5, 128.2, 127.7, 67.5, 54.9, 51.2, 41.9, 25.4, 23.3, 22.2. Anal. calcd for $C_{35}H_{38}N_2O_3$: C, 78.62; H, 7.16; N, 5.24. Found: C, 78.83; H, 7.26; N, 4.90. The absolute configurations of two epimers of **4** were confirmed by comparison of Chiral-HPLC retention time with authentic material individually prepared from the coupling of L-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative using racemic material as a standard. [Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min; (α*R*)-epimer had a retention time of 14.8 min, (α*S*)-epimer had a retention time of 14.1 min].

4.3. General procedure for deprotection of *N*,*N*-dibenzyl group

To a solution of dibenzyl ester (1 equiv.) and $(Boc)_2O$ (2 equiv.) in absolute ethanol under an N_2 gas atmosphere was added 10% Pd–C followed by 1,4-cyclohexadiene (20 equiv.); 7 days later, the mixture was filtered through Celite and concentrated to provide the product after column chromatography on silica gel.

4.3.1. (*S*)-*N*-[(*R*)-α-Phenyl-*N*-(*tert*-butoxycarbonyl)-glycinyl] leucine methyl ester (6). A colorless oil was obtained in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38–7.27 (m, 5H), 6.42 (d, J=8.2 Hz, 1H), 5,80 (br, 1H), 5.20 (br, 1H), 4.58 (m, 1H), 3.72 (s, 3H), 1.20–1.65 (m, 3H), 1.40 (s, 9H), 0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 170.3, 155.3, 138.8, 129.3, 128.7, 127.6, 80.5, 52.7, 51.2, 41.5, 28.6, 25.1, 23.0, 21.9. The spectral data of **6** were identical to those of the authentic material reported previously.[10]

4.3.2. (*S*)-*N*-[(*R*)-α-(*p*-Fluorophenyl)-*N*-(*tert*-butoxycarbonyl)glycinyl] leucine methyl ester (7). A colorless oil was obtained in 32% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35 (m, 2H), 7.03 (m, 2H), 6.14 (d, J=8.4 Hz, 1H), 5.68 (br, 1H), 5.12 (br, 1H), 4.61 (m, 1H), 3.73 (s, 3H), 1.60–1.32 (m, 3H), 1.41 (s, 9H), 0.81 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 169.9, 155.3, 135.0, 129.5, 116.5, 116.2, 78.0, 52.8, 51.2, 41.6, 28.6, 25.0, 23.0, 22.0. $[\alpha]_D$=−76.4 (c=0.021, $CHCl_3$). HRMS calcd for $C_{20}H_{29}FN_2O_5$: 396.2061. Found: 396.2045. The absolute configuration of dipeptide analogue **7** is provisionally assigned to α*R* by analogy to the formation of (α*R*)-**6**.

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References and notes

1. (a) Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545. (b) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397. (c) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253. (d) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790. (e) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589. (f) Lee, S.-k.; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941. (g) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (h) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830. (i) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469.
2. For reviews on stereoselective modification of peptides, see: (a) Nandy, J. P.; Prabhakaran, E. N.; Kumar, S. K.; Kunwar, A. C.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 1679. (b) Miyashita, K.; Iwaki, H.; Tai, K.; Murafuji, H.; Sasaki, N.; Imanishi, T. *Tetrahedron* **2001**, *57*, 5773. (c) Ricci, M.; Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413. (d) Kazmaier, U.; Maier, S. *Chem. Commun.* **1998**, 2535. (e) Lenman, M. M.; Ingham, S. L.; Gani, D. *Chem. Commun.* **1996**, 85. (f) D'Angeli, F.; Marchetti, P.; Bertolasi, V. *J. Org. Chem.* **1995**, *60*, 4013. (g) Bossler, H. G.; Waldmeier, P.; Seebach, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 439.
3. Nam, J.; Chang, J.-Y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727.
4. The low selectivities in the absence of TBAI observed in entries 10 and 11, Table 2 suggest the possibility that the leaving group in the nucleophilic substitution in the presence of TBAI is iodide rather than bromide. Further mechanistic investigation for details of the process is underway.
5. Calculations are performed with a semiempirical approximation using AM1. The software used was Spartan 5.1, wavefunction, Inc.
6. When nucleophiles such as benzylthiol, tritylthiol, sodium malonate, sodium azide, potassium acetate, potassium thioacetate and potassium phthalate were used for the reaction with **1b**, the corresponding substitution products were obtained in 17–88% yields with diastereomeric ratios from 51:49 to 55:45.
7. (a) Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2955. (b) Tao, J.; Hoffman, R. V. *J. Org. Chem.* **1997**, *62*, 6240.
8. (a) Khimiuk, A. Y.; Korennykh, A. V.; Langen, L. M.; Rantwijk, F.; Sheldon, R. A.; Švedas, V. K. *Tetrahedron: Asymmetry* **2003**, *14*, 3123. (b) Langen, L. M.; Rantwijk, F.; Švedas, V. K.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1077. and references therein.
9. This study has also shown some limitation of the method, as it cannot be extended to α-bromo α-alkyl acetamides successfully. The substitution reactions of α-bromo α-methyl acetamides derived from various L-amino acids are generally very slow and showed lower stereoselectivities (ca. 80:20 dr) under the same reaction condition. All tested reactions of α-bromo α-ethyl acetamides gave very poor yields and selectivities.
10. Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669.