Dynamic Kinetic Resolution of α-Bromo Carboxylic Acid Derivatives in Asymmetric Nucleophilic Substitution with Chiral α-Amino Esters

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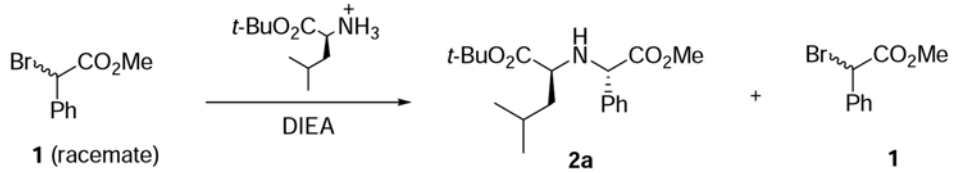
Dynamic kinetic resolution of α-bromo carboxylic acid derivatives in nucleophilic substitution with chiral α-amino ester nucleophiles in the presence of TBAI and DIEA has been investigated for stereoselective syntheses of 1,1'-iminodicarboxylic acid derivatives. Nucleophilic substitutions with various chiral α-amino esters gave iminodiacetates **2-8** with stereoselectivities up to 87 : 13 dr. Also, the reactions of *N*-(α-bromo-α-phenylacetyl)-*L*-alanine methyl ester with *L*-alanine, *D*-alanine and glycine methyl ester nucleophiles afforded *N*-carboxyalkyl dipeptide analogues **10-12** up to 90 : 10 dr.

Key Words : Dynamic kinetic resolution, Asymmetric syntheses, Nucleophilic substitution

1,1'-Iminodicarboxylic acid derivatives are pharmaceutically active as ACE-inhibitors and constitute interesting natural substances.[1] Substantial progress has been made toward the development of efficient methods for stereoselective preparation of these compounds.[2,3] One of the most attractive strategies is based on nucleophilic substitution reaction of optically pure or chiral auxiliary bound α-halo esters.[3] However, there is no successful example for stereoselective nucleophilic substitution of racemic α-halo carboxylic acid derivatives with chiral α-amino ester nucleophiles. Recently it has been shown from our group that the chiral information of adjacent amino acid residue is efficiently transferred to the new C-N bond formation in nucleophilic substitution reaction of *N*-(α-haloacetyl) *L*-amino acid derivatives with achiral amine nucleophiles.[4] Herein we describe our recent results on dynamic resolution of racemic α-bromo esters with chiral α-amino ester nucleophiles for asymmetric syntheses of 1,1'-iminodicarboxylic acid derivatives.

Initial studies on dynamic resolution of α-phenyl-α-bromo methyl acetate (**1**) were carried out with *L*-leucine *t*-butyl ester as a nucleophile. When the racemic α-bromo ester **1** was treated with *L*-leucine *t*-butyl ester hydrochloride (1.0 equiv) and diisopropylethylamine (DIEA, 2.2 equiv) in CH_2Cl_2 at 20 °C for 24 h, the iminodiacetate **2a** was produced in 46% conversion with 70 : 30 diastereomeric ratio (dr, α*S*:α*R*) as shown in Scheme 1. The absolute configuration of major (α*S*)-isomer was assigned by comparison to the ^{1}H-NMR of authentic epimer individually prepared from the substitution of methyl (*R*)-α-bromo α-isobutyl acetate with *L*-phenylglycine methyl ester on the basis of inversion mechanism (S_N2). The observed enantiomeric ratio (er) of **1** implies that α-bromo stereogenic center is configurationally labile under the reaction condition at 20 °C.[5] Also, the observed dr of **2a** indicates that (*R*)-**1** is more reactive elecrophile than (*S*)-**1** in the substitution reaction with the *L*-leucine ester nucleophile and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. The higher reaction temperature (50 °C) may have little effect on stereoselectivity as shown in Scheme 1. The reaction at –15 °C produced **2a** with higher diastereoselectivity (79 : 21 dr) and α-phenyl-α-bromo methyl acetate (**1**) was recovered with 61 : 39 er, which implies that racemization of **1** is slower at –15 °C. These results show that the chiral information of α-amino ester nucleophile can be transferred to the new C-N bond



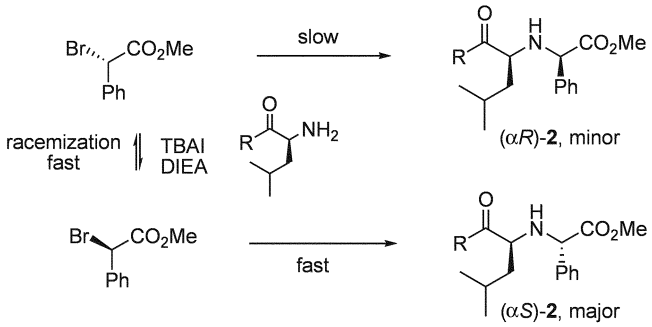
Temp.	% Conversion	Dr of **2a** (α*S*:α*R*)	Er of **1** (*S*:*R*)
20 °C	46	70:30	51:49
50 °C	32	70:30	50:50
-15 °C	33	79:21	61:39

Scheme 1

formation in nucleophilic substitution reaction of racemic α-bromo esters.

For an effort to improve the % conversion and stereoselectivity of the nucleophilic substitution, tetrabutylammonium iodide (TBAI, 1.0 equiv) was added as an iodide ion source in various reaction conditions shown in Table 1. It is well known that TBAI might produce the α-iodo ester intermediate and can enhance the rate of the substitution and stereoselectivity.[4,5] In the presence of TBAI the substitution with *L*-leucine *t*-butyl ester produced iminodiacetate **2a** with improved % conversion and stereoselectivity at 20 °C as shown in entry 1. Both *L*-leucine methyl ester and *L*-leucine benzyl ester gave slightly lower selectivities and *L*-leucine naphtyl amide gave the product **2d** with significantly decreased dr (55 : 45) as shown in entries 2-4. The reactions at lower temperature produced iminodiacetate **2a** with higher drs as shown in entries 5-7. It is also interesting to note here that the er of the recovered **1** from the reaction with TBAI at –15 °C is 50 : 50, which indicates that the racemization of **1** is faster compared to the reaction without TBAI. Turning then to the effect of solvents, we screened eleven different solvents. At –15 °C, iminodiacetate **2a** was

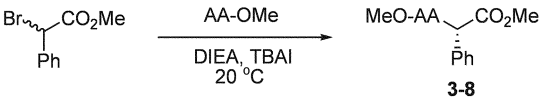
Table 1. Dynamic kinetic resolution in the presence of TBAI



Entry	R	Conditions	% Conv.[a]	Dr (αS:αR)[a]
1	*t*-BuO (**2a**)	CH_2Cl_2, 20 °C	80	77 : 23
2	MeO (**2b**)	CH_2Cl_2, 20 °C	72	74 : 26
3	BnO (**2c**)	CH_2Cl_2, 20 °C	90	73 : 27
4	NaphNH (**2d**)	CH_2Cl_2, 20 °C	84	55 : 45
5	*t*-BuO (**2a**)	CH_2Cl_2, 0 °C	79	80 : 20
6	*t*-BuO (**2a**)	CH_2Cl_2, –15 °C	83	83 : 17
7	*t*-BuO (**2a**)	CH_2Cl_2, –30 °C	65	82 : 18
8	*t*-BuO (**2a**)	$CHCl_3$, –15 °C	56	83 : 17
9	*t*-BuO (**2a**)	DMF, –15 °C	74	67 : 33
10	*t*-BuO (**2a**)	CH_3CN, –15 °C	66	75 : 25
11	*t*-BuO (**2a**)	ether, –15 °C	55	80 : 20
12	*t*-BuO (**2a**)	CCl_4, –15 °C	42	85 : 15
13	*t*-BuO (**2a**)	$Cl_2CHCHCl_2$, –15 °C	82	72 : 28
14	*t*-BuO (**2a**)	Ethanol, –15 °C	71	81 : 19
15	*t*-BuO (**2a**)	Toluene, –15 °C	40	87 : 13
16	*t*-BuO (**2a**)	Toluene/CH_2Cl_2, –15 °C	74	80 : 20
17	*t*-BuO (**2a**)	$BMIM^+BF_4^-$/ethanol,[b] –15 °C	84	71 : 29
18	*t*-BuO (**2a**)	$BMIM^+BF_4^-$/toluene,[b] –15 °C	46	80 : 20

[a]The % conversion and drs are determined by ^{1}H NMR of reaction mixture after 24 h. [b]1 : 1 mixtute of two solvents

Table 2. Reactions with various chiral amino esters



3-8

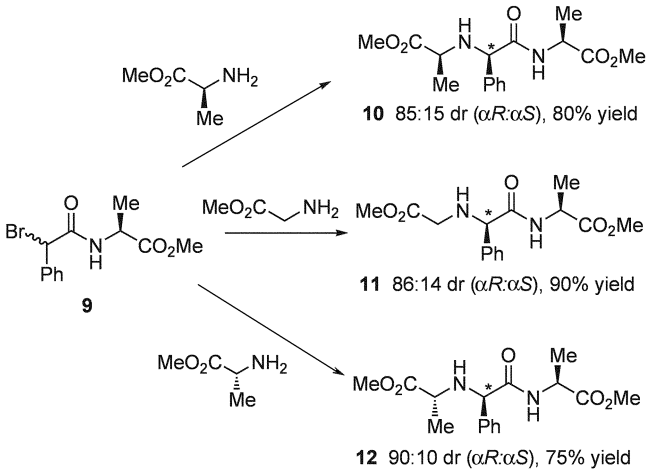
Entry	AA-OMe	Product	Yield[a] (%)	Dr[b] (αS:αR)
1	*L*-Ala-OMe	**3**	67	65 : 35
2	*L*-Pro-OMe	**4**	96	55 : 45
3	*L*-Lys (*N*-Cbz)-OMe	**5**	64	75 : 25
4	*L*-Ser (*O*-Bn)-OMe	**6**	85	60 : 40
5	*L*-Leu-*L*-Ala-OMe	**7**	53	64 : 36
6	*L*-Pro-*L*-Leu-OMe	**8**	96	56 : 44

[a]Isolated yields. [b]The drs are determined by ^{1}H NMR of reaction mixture.

obtained with 83 : 17 dr in $CHCl_3$, 67 : 33 dr in DMF, 75 : 25 dr in CH_3CN, 80 : 20 dr in ether, 85 : 15 dr in CCl_4, 72 : 28 dr in $Cl_2CHCHCl_2$, 81 : 19 dr in ethanol and 87 : 13 dr in toluene. Also, the addition of ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim]^+[BF_4]^-$) did not improve the stereoselectivity. (entries 17 and 18) In the presence of tetrabutyl ammonium bromide (TBAB), lower selectivity (79 : 21 dr) was observed at –15 °C. The lower selectivity may be explained by less efficient racemization process with TBAB. In addition, the configurational stability of **2** was examined by the treatment with TBAI and DIEA in CH_2Cl_2 for 48 h. No epimerization was detected by ^{1}H-NMR, which can rule out the possible epimerization of **2** after C-N bond formation.

With the identification of *L*-leucine ester as appropriate chiral nucleophile for dynamic kinetic resolution of racemic α-bromo-α-phenyl acetate, we set out to examine the scope of this methodology with six different α-amino ester nucleophiles as shown in Table 2. The substitutions afforded iminodicarboxylic acid derivatives **3-8** in 96-53% isolated yields with moderate stereoselectivities. *N*-Cbz-lysine ester nucleophile gave best stereoselectivity (75 : 25 dr) as shown in entry 3. The chirality of *L*-alanine, *L*-proline, and *L*-serine derived nucleophiles is not efficiently transferred to new C-N bond formation (entries 1, 2 and 4). The dipeptide methyl ester nucleophiles also produced the products **7** and **8** with low stereoselectivities (entries 5 and 6). The absolute configuration of major (αS)-**3** was assigned by comparison to the ^{1}H-NMR of authentic epimer individually prepared from the substitution of methyl (*R*)-α-bromo α-methyl acetate with *L*-phenylglycine methyl ester on the basis of inversion mechanism (S_N2). Those of **4-8** were assigned by analogy to the formation of **2** and **3**.

We previously reported that *L*-alanine is an efficient precursor for asymmetric syntheses of dipeptide analogues via dynamic kinetic resolution of α-bromo acetamide.[4] When the two diastereomeric mixture (*ca.* 50 : 50) of *N*-(α-bromo-α-phenylacetyl)-*L*-alanine methyl ester (**9**) was treated with dibenzylamine (Bn_2NH), TBAI and Et_3N in CH_2Cl_2 at room temperature, the dipeptide analogue was obtained in 96% yield with 90 : 10 dr.[4b] As an extension of



Scheme 2

the dynamic resolution, the substitution reactions of *N*-(α-bromo-α-phenylacetyl)-*L*-alanine methyl ester (**9**) with α-amino ester nucleophiles such as glyine, *L*-alanine and *D*-alanine methyl esters were investigated for the preparation of *N*-carboxyalkyl peptide analogues as shown in scheme 2. Treatment with glycine methyl ester hydrochloride (1.0 equiv), TBAI (1.0 equiv) and DIEA (2.2 equiv) in CH_2Cl_2 at room temperature provided the tripeptide analogue **11** in 90% yield with 86 : 14 dr (α*R*:α*S*). When two enantiomers of alanine methyl esters were used as nucleophiles respectively, moderate double stereodifferentiation is observed as shown in Scheme 2. *N*-(α-Bromo-α-phenylacetyl)-*L*-alanine methyl ester experienced matching with *D*-alanine methyl esters to afford tripeptide analogue **12** in a ratio of 90 : 10 dr (α*R*:α*S*) and mismatching with *L*-alanine amino ester to provide **10** in a 85 : 15 (α*R*:α*S*) ratio. Even mismatched case gave still high stereoselectivity, which allows us to have easy access to diverse *N*-carboxyalkyl peptide analogues. The absolute configurations of **10**, **11** and **12** were assigned as α*R* by comparison to the ^{1}H-NMR of authentic epimers individually prepared from the *N*-alkylation of *D*-phenylglycine-*L*-alanine methyl ester with methyl α-bromo acetate or racemic methyl α-bromo-α-methyl acetate. Interestingly, both *L*- and *D*-alanine ester nucleophiles gave the same chirality at the α-center (*R* configuration), showing that the stereochemistry of the major product is dominated by the asymmetry of the adjacent amino acid and not that of the incoming amino ester nucleophile.

In summary, we have presented a novel and practical approach for the asymmetric syntheses of 1,1'-iminodicarboxylic acid derivatives *via* dynamic kinetic resolution of α-bromo α-phenyl esters in nucleophilic substitution with chiral α-amino esters. The methodology has also been successful for the preparation of *N*-carboxyalkyl peptides, affording tripeptidomimetics **10**-**12** with high stereoselectivities. The simple protocol with mild condition suggests further development of this methodology and reactions of various α-alkyl substituents and chiral α-amino ester nucleophiles are currently under investigation.

Experimental Section

General procedure for asymmetric nucleophilic substitution. To a solution of (α*RS*)-α-bromo-α-phenyl ester (or amide) in dry CH_2Cl_2 (*ca.* 0.1 M) at room temperature was added α-amino ester hydrochloride (1.0 equiv), TBAI (1.0 equiv) and DIEA (2.2 equiv). After the resulting reaction mixture was stirred for 24 h, the solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel. The purity (> 95%) of products was estimated by NMR.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-leucine *t*-butyl ester (2a).** A colorless oil was obtained in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.40-7.27 (m, 5H), 4.40, 4.35 (s, 1H), 3.68, 3.65 (s, 3H), 3.22, 2.95 (t, 1H), 1.82-1.44 (m, 3H), 1.42 (s, 9H), 0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.8, 173.4, 138.8, 129.1, 128.6, 128.1, 81.4, 64.7, 59.2, 52.7, 43.2, 28.5, 25.1, 23.2, 22.6.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-leucine methyl ester (2b).** A colorless oil was obtained in 72% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.38-7.29 (m, 5H), 4.40, 4.34 (s, 1H), 3.70, 3.68 (s, 3H), 3.63, 3.59 (s, 3H), 3.38, 3.07 (t, 1H), 2.28 (br, 1H), 1.80 (m, 1H), 1.48 (m, 2H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.9, 173.3, 138.4, 129.0, 128.9, 128.7, 128.5, 128.1, 77.8, 64.6, 58.5, 57.1, 43.1, 25.2, 23.4, 22.6. HRMS calcd for $C_{16}H_{24}NO_4$ (M^++1): 294.1705. Found: 294.1685.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-leucine benzyl ester (2c).** A colorless oil was obtained in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.37-7.25 (m, 10H), 5.15, 5.03 (q, 2H), 4.38, 4.31 (s, 1H), 3.66, 3.63 (s, 1H), 3.39, 3.09 (t, 1H), 1.80 (m, 1H), 1.53 (m, 2H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.3, 173.3, 138.5, 136.1, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 66.8, 64.6, 58.7, 52.7, 43.1, 25.2, 23.4, 22.6.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-leucine naphthyl amide (2d).** A colorless oil was obtained in 84% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.35-7.33 (m, 13H), 4.37, 4.33 (d, 1H), 3.71, 3.70 (s, 3H), 3.35, 3.15 (m, 1H), 2.75,2.25 (br, 1H), 2.02-1.52 (m, 3H), 1.03 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.9, 173.2, 137.7, 135.5, 133.5, 129.2, 129.0, 128.9, 128.5, 128.0, 127.9, 127.5, 125.3, 120.1, 119.8, 116.3, 65.1, 62.5, 53.0, 43.9, 25.5, 23.8, 14.6.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-alanine methyl ester (3).** A colorless oil was obtained in 67% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.39-7.27 (m, 5H), 4.45, 4.43 (s, 1H), 3.71, 3.69 (s, 3H), 3.66, 3.64 (s, 3H), 3.40, 3.21 (q, 1H), 2.63 (br, 1H), 1.34 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.5, 173.3, 138.1, 129.4, 129.2, 128.9, 128.3, 127.0, 73.3, 64.1, 52.3, 52.2, 19.6. HRMS calcd for $C_{13}H_{18}NO_4$ (M^+ + 1): 252.1158. Found: 252.1231.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-proline methyl ester (4).** A colorless oil was obtained in 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.43-7.28 (m, 5H) 4.67, 4.57 (s, 1H), 3.71, 3.69 (s, 3H), 3.61, 3.50 (s,

3H), 3.12, 2.81 (m, 1H), 2.91 (m, 1H), 2.14 (m, 1H), 1.97-1.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.3, 172.7, 137.2, 129.3, 128.9, 128.8, 128.7, 128.6, 68.9, 63.3, 52.3, 51,9 .50.3, 30.29, 23.86. HRMS calcd for $C_{15}H_{20}NO_4$ ($M^+ + 1$): 278.1314. Found: 278.1391.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-lysine(N-carbonyloxybenzyl) methyl ester (5).** A colorless oil was obtained in 64% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.35-7.26 (m, 10H), 5.13 (s, 2H), 4.85, 4.70 (br, 1H), 4.39, 4.34 (s, 1H), 3.76, 3.70 (s, 3H), 3.67, 3.61 (s, 3H), 3.30, 3.04 (t, 1H), 3.18 (m, 2H), 1.71-1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.4, 173.3, 156.8, 138.2, 137.1, 129.1, 129.0, 128.9, 128.8, 128.5, 128.1, 67.0, 64.5, 59.6, 52.7, 52.2, 41.2, 33.1, 36.0, 23.1.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-serine(O-benzyl) methyl ester (6).** A colorless oil was obtained in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.43-7.26 (m, 10H), 4.53 (m, 3H), 3.71 (m, 8H), 3.56, 3.42 (t, 1H), 3.00, 2.80 (dr, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.5, 173.1, 138.3, 138.2, 129.0, 128.7, 128.5, 128.2, 128.1, 127.0, 73.6, 71.6, 64.3, 59.5, 53.4, 52.7.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-leucine-(*S*)-alanine methyl ester (7).** A colorless oil was obtained in 53% yield.^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.40-7.27 (m, 5H), 4.57 (m, 1H), 4.45, 4.44 (s, 1H), 3.80-3.70 (m, 6H), 3.23, 2.92 (m, 1H), 1.82-1.33 (m, 6H), 0.99 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.6, 174.2, 173.7, 138.0, 129.3, 128.9, 128.7, 128.0, 127.6, 64.2, 60.9, 57.7, 52.8, 47.8, 25.3, 24.7, 22.9, 18.5. HRMS calcd for $C_{19}H_{29}N_2O_5$ ($M^+ + 1$): 365.2076. Found: 365.2085.

***N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl] (*S*)-proline-(*S*)-leucine methyl ester (8).** A colorless oil was obtained in 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.93 (m, 1H), 7.44-7.31 (m, 5H), 4.65, 4.57 (m, 2H), 3.77, 3.74 (s, 3H), 3.70, 3.67 (s, 3H), 3.56 (m, 1H), 3.15 (m, 1H), 2.88, 2.40 (m, 1H), 2.31-1.58 (m, 9H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.1, 173.8, 172.7, 136.9, 129.4, 129.3, 129.1, 128.9, 128.7, 68.2, 64.9, 52.6, 52.4, 50.8, 50.5, 42.2, 31.8, 25.4, 24.8, 23.2, 22.3. HRMS calcd for $C_{21}H_{30}N_2O_5$ (M^++1): 391.2233. Found: 391.2235.

***N*-[1-(*S*)-(Methoxycarbonyl)ethyl]-(*R*)-phenylglycine-(*S*)-alanine benzyl ester (10).** A colorless oil was obtained in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.98, 7.43 (d, J = 7.6 Hz, 1H), 7.36-7.29 (m, 10H), 5.18 (q, 2H), 4.64 (m, 1H), 4.30, 4.14 (s, 1H), 3.71, 3.69 (s, 3H), 3.28 (m, 1H), 2.21 (br, 1H), 1.42 (d, J = 7.1 Hz, 3H), 1.32 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.4, 172.9, 171.7, 138.8, 135.8, 129.3, 129.2, 129.0, 128.7, 128.5, 128.3, 67.5, 65.7, 54.7, 52.3, 48.3, 19.2, 18.7.

***N*-[1-(Methoxycarbonyl)methyl]-(*R*)-phenylglycine-(*S*)-alanine benzyl ester (11).** A colorless oil was obtained in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.63 (d, J = 7.8 Hz, 1H), 7.39-7.28 (m, 10H), 5.18 (q, 2H), 4.66 (m, 1H), 4.26 (s, 1H), 3.71 (s, 3H), 3.43 (q, 2H), 2.24 (br, 1H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 172.6, 171.6, 138.8, 135.8, 129.3, 129.0, 128.8, 128.5, 128.1, 127.8, 67.5, 67.4, 52.4, 49.5, 48.2, 18.8.

***N*-[1-(*R*)-(Methoxycarbonyl)ethyl]-(*R*)-phenylglycine-(*S*)-alanine benzyl ester (12).** A colorless oil was obtained in 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.90 (d, J = 7.9 Hz, 1H), 7.39-7.27 (m, 10H), 5.13 (m, 2H), 4.67 (m, 1H), 4.32, 4.15 (s, 1H), 3.70, 3.68 (s, 3H), 3.35 (m, 1H), 2.25 (br, 1H), 1.47 (d, J = 7.1 Hz, 3H), 1.34 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.8, 173.0, 171.9, 139.2, 135.8, 129.3, 129.1, 129.0, 128.8, 128.5, 127.4, 67.6, 66.7, 56.2, 52.5, 48.2, 19.9, 18.9.

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