

L-Lactate-mediated Dynamic Kinetic Resolution of α -Bromo Esters for Asymmetric Syntheses of α -Amino Acid Derivatives

Yelim Kim, Kon Ji Park, Yun Soo Choi, Myung-su Lee, and Yong Sun Park*

Department of Chemistry and KFnSC, Konkuk University, Seoul 143-701, Korea. *E-mail: parkyong@konkuk.ac.kr
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For asymmetric synthesis of α -substituted carboxylic acid derivatives, a variety of chiral auxiliaries have been used for the dynamic resolution of α -halo esters in nucleophilic substitution.¹ For example, L-lactamide-mediated dynamic kinetic resolution of α -bromo esters was successfully used for the asymmetric preparation of α -aryloxy carboxylic acids and oxazin-2-ones.² However, the application of L-lactate as a chiral auxiliary was not effective for the dynamic resolution of α -halo esters.³ In our continuous efforts to develop L-lactic acid as a chiral auxiliary for the dynamic resolution, we have recently found successful results with ethyl L-lactate. We herein report ethyl L-lactate-mediated dynamic kinetic resolution of α -bromo esters for the asymmetric preparation of α -amino acid derivatives.

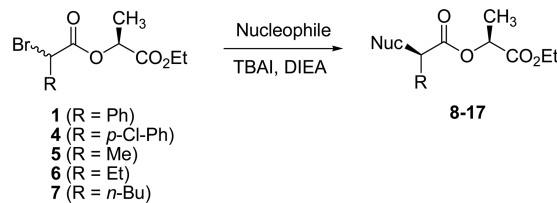
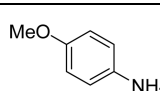
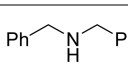

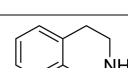
Treatment of racemic α -bromo- α -phenylacetic acid with ethyl L-lactate in the presence of DCC and DMAP provided α -bromo- α -phenyl ester (α RS)-**1** with 50:50 diastereomeric ratio (dr) in 78% yield. When the diastereomeric mixture (α RS)-**1** was treated with *p*-anisidine (*p*-MeOPhNH₂, 1.5 equiv), tetrabutylammonium iodide (TBAI, 1.0 equiv) and diisopropylethylamine (DIEA, 1.0 equiv) in CH₂Cl₂ at room temperature for 24 h, the amino acid derivative **2** was produced in 86% yield with 97:3 dr as shown in Scheme 1. Following removal of L-lactate chiral auxiliary with Et₃N in MeOH gave methyl phenylglycinate (*R*)-**3** with 97:3 enantiomeric ratio (er) in 65% yield.⁴ These results imply that α -bromo stereogenic center is configurationally labile with respect to the rate of substitution and (α RS)-**1** is dynamically resolved in the substitution with the amine nucleophile. In a solvent screen, the reactions in CHCl₃, ether, *n*-hexane and

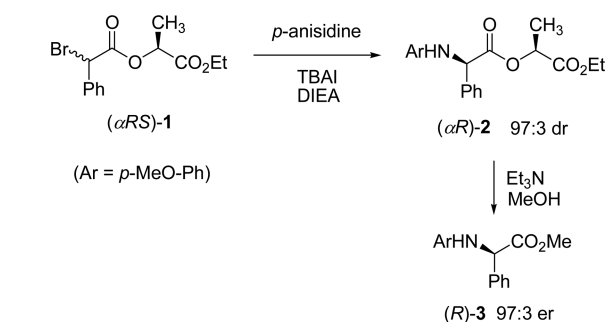
THF provided (α R)-**2** with the same dr as in CH₂Cl₂, while the lower selectivities of 92:8 dr and 93:7 dr were observed in the reactions in DMF and CH₃CN, respectively.

In order to understand the asymmetric reaction pathway, we carried out two reactions with α -bromo- α -phenyl ester **1** of 67:33 dr. When **1** of 67:33 dr was allowed to reach thermodynamic equilibrium in the presence of DIEA, the diastereomeric ratio of recovered **1** was determined to be 49:51 dr. The result indicates that the thermodynamic stabilities of two diastereomers are almost the same, ruling out dynamic thermodynamic resolution as a primary pathway. In the reaction of **1** (67:33 dr) with *p*-anisidine under the same condition, **2** was obtained with the same stereoselectivity (97:3 dr) as in the reaction of **1** with 50:50 dr. In other words, the dr of product **2** is not dependent on the initial dr of **1**. These preliminary results indicate that the epimerization is sufficiently fast with respect to the rate of substitution and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.¹

Next, the scope of the observed dynamic kinetic resolution

Table 1. Substitutions with various amine nucleophiles

				
Entry ^a	R	Nucleophile	Yield (%) ^b	Dr ^c
1	<i>p</i> -Cl-Ph		72 (8)	97:3
2	Me		56 (9)	93:7
3	Et		78 (10)	91:9
4	<i>n</i> -Bu		72 (11)	88:12
5	Ph		73 (12)	94:6
6	Me		51 (13)	90:10
7	Ph		58 (14)	89:11
8	Me		52 (15)	82:13
9	Ph		56 (16)	87:13
10	Me		65 (17)	77:23



Scheme 1. L-Lactate-mediated dynamic kinetic resolution of α -bromo ester.

^aAll reactions were carried out in CH₂Cl₂. ^bIsolated yields after 24 h. ^cThe drs are determined by ¹H NMR of reaction mixture.

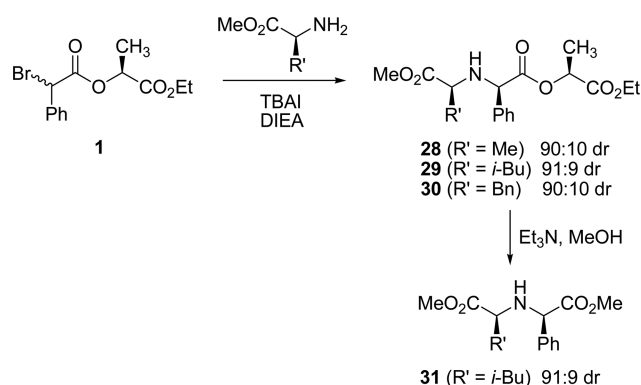
Table 2. Asymmetric synthesis of dihydroquinoxalinones and dihydrobenzoxazinones

1 and 5-7		(Y = NH or O)			18-27	
Entry ^a	R	Nucleophile	Yield (%) ^b	Er (R:S) ^c		
1	Ph		69 (18)	93:7		
2	Me		62 (19)	85:15		
3	Et		53 (20)	84:16		
4	<i>n</i> -Bu		50 (21)	88:12		
5	Ph		48 (22)	89:11		
6	Ph		67 (23)	90:10		
7	Me		49 (24)	81:19		
8	Et		57 (25)	90:10		
9	Ph		67 (26)	91:9		
10	Ph		64 (27)	88:12		

^aAll reactions were carried out in CH₂Cl₂. ^bIsolated yields after 24 h.^cThe ers are determined by CSP-HPLC.

has been examined with various α -substituents and amine nucleophiles as shown in Table 1. We were pleased to observe that the dynamic resolution is efficient for a variety of α -substituents (entries 1-4), affording amino acid derivatives **8-11** in 78-56% isolated yields with high stereoselectivities. The treatment of α -bromo- α -(*p*-chlorophenyl)-acetate **4** with *p*-anisidine in CH₂Cl₂ for 24 h at room temperature gave *N*-aryl amino ester **8** in 72% yield with 97:3 dr (entry 1). Under the same reaction condition, the reactions of α -methyl, α -ethyl and α -*n*-butyl substituted esters **5-7** gave *N*-aryl amino esters **9**, **10** and **11** with 93:7, 91:9 and 88:12 drs, respectively (entries 2-4). For asymmetric preparation of *N*-aryl amino esters, this methodology has potential advantages over *N*-arylation of optically active amino acid analogues in simplicity and cost. The reactions of **1** and **5** with alkyl substituted amine nucleophiles such as dibenzylamine, benzylamine and tetrahydroisoquinoline provided *N*-alkyl amino esters **12-17** in 73-51% yields with slightly lower stereoselectivities compared to the reactions with *p*-anisidine (entries 5-10). These results indicate that the size and nucleophilicity of amine nucleophile may have effect on the stereoselectivity and yield of the substitution.

Encouraged by the high diastereoselectivities in the reactions of α -bromo esters with the aryl amine, we also examined the substitutions with 1,2-diaminobenzene and 1,2-aminohydroxybenzene nucleophiles for asymmetric syntheses of 3-substituted dihydroquinoxalinone and dihydrobenzoxazinone as shown in Table 2. The heterocyclic compounds possess important biological and pharmaco-

**Scheme 2.** Asymmetric synthesis of 1,1'-iminodicarboxylic acid derivatives.

logical properties, and accordingly there is growing interest in developing the asymmetric synthetic methods for them.^{5,6} When α -bromo- α -phenylacetate **1** was treated with 1,2-diaminobenzene, TBAI and DIEA in CH₂Cl₂ for 24 h at room temperature, the substitution and following spontaneous cyclization occurred to give 3-phenyl dihydroquinoxalinone **18** in 56% yield with 93:7 er (entry 1). With α -alkyl substituted esters **5-7**, however, the reactions took place to afford dihydroquinoxalinones **19-21** with lower stereoselectivities (entries 2-4). Reactions with 4,5-dichloro-*o*-phenylenediamine and 4,5-dimethyl-*o*-phenylenediamine gave dihydroquinoxalinones **22-25** with enantioselectivities ranging from 90:10 er to 81:19 er (entries 5-8). In addition, we demonstrated that this methodology is efficient for the asymmetric preparation of 3-phenyl dihydrobenzoxazinones **26** and **27** with good stereoselectivities (entries 9-10). When 2-aminophenol was used as a nucleophile for the reaction with α -bromo- α -phenylacetate **1**, the substitution and cyclization produced **26** in 67% yield with 91:9 er. Also, the reaction of 4-butyl-2-aminophenol produced dihydrobenzoxazinone **27** in 88:12 er.

This synthetic methodology is also efficient for the substitution with various amino ester nucleophiles, affording 1,1'-iminodicarboxylic acid derivatives **28-30** with high stereoselectivities as shown in Scheme 2. As chiral 1,1'-iminodicarboxylic acid derivatives are pharmaceutically active and constitute interesting natural substance, substantial progress has recently been made toward the development of asymmetric synthetic methods for these compounds.⁷ Treatment of α -bromo- α -phenylacetate **1** with L-alanine methyl ester, TBAI and DIEA in CH₂Cl₂ at room temperature provided **28** in 67% yield with 90:10 dr (α R: α S). Under the same condition, 1,1'-iminodicarboxylic acid derivatives **29** and **30** were produced in 60-55% yields by the reactions of **1** with L-leucine methyl ester and L-phenylalanine methyl ester with 91:9 dr and 90:10 dr, respectively. The absolute configuration of (α R)-**29** was determined after removing L-lactate with Et₃N in MeOH, and by comparison of the ¹H-NMR spectrum with that of authentic diastereomer of (α R)-**31**.⁸

We conclude that ethyl L-lactate is an effective and convenient chiral auxiliary for dynamic kinetic resolution of α -bromo esters in nucleophilic substitution with various amine

nucleophiles. The methodology can provide a general procedure for asymmetric syntheses of dihydroquinoxalinones, dihydrobenzoxazinones and 1,1'-iminodicarboxylic acid derivatives. Simple and easy procedure in obtaining highly enantioenriched α -amino acid derivatives suggests that the dynamic kinetic resolution approach should be further developed.

Experimental

General Procedure for the Asymmetric Nucleophilic Substitution via Dynamic Kinetic Resolution: To a solution of α -bromo ester (**1**, **4**, **5**, **6** and **7**) in CH_2Cl_2 (ca. 0.1 M) at room temperature were added DIEA (1.0 equiv), TBAI (1.0 equiv) and an arylamine nucleophile (1.5 equiv). After the resulting reaction mixture was stirred at room temperature for 12–24 h, the solvent was evaporated and the crude material was purified by column chromatography to give a α -amino ester. The drs of **2**, **8–17** and **28–31** were determined by ^1H NMR integration of hydrogens of two diastereomers and the ers of **3** and **18–27** were determined by chiral stationary phase HPLC.

2-(*p*-Methoxyanilino)-(*R*)-phenylacetic Acid Ethyl L-Lactate Ester (2**).** A yellow oil was obtained in 86% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.52 (m, 2H), 7.33 (m, 3H), 6.72 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 5.12 (d, J = 6.0 Hz, 1H), 5.04 (q, J = 6.8 Hz, 1H), 4.59 (d, J = 6.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 171.5, 170.3, 152.6, 140.2, 137.5, 128.9, 128.4, 127.4, 114.8, 114.7, 69.7, 61.6, 55.7, 16.8, 14.1. For removal of chiral auxiliary, the mixture of **2** and Et_3N (10 equiv) in methanol (0.05 M) was stirred at room temperature for a day. The solvent was evaporated and the crude material was purified by column chromatography to give (*R*)-**3** in 65% yield. ^1H NMR (CDCl_3 , 400 MHz) δ 7.48–7.25 (m, 5H), 6.69 (d, J = 8.9 Hz, 2H), 6.52 (d, J = 8.9 Hz, 2H), 5.00 (s, 1H), 4.67 (br, 1H), 3.72 (s, 3H), 3.67 (s, 3H). The spectral data of **3** were identical to those of the authentic material reported. Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 66.2 min; t_R (*S*)-minor enantiomer, 74.3 min (Chiralcel OJ-H column; 20% 2-propanol in hexane; 0.5 mL/min).

2-(*p*-Methoxyanilino)-(*R*)-*p*-chlorophenylacetic Acid Ethyl L-Lactate Ester (8**).** A pale yellow oil was obtained in 72% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.48 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.8 Hz, 2H), 5.10 (br, 1H), 5.04 (q, J = 7.2 Hz, 1H), 4.64 (br, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 171.0, 170.1, 152.7, 139.9, 136.1, 134.2, 128.9, 128.4, 114.9, 114.8, 69.9, 61.6, 60.9, 55.6, 16.8, 14.1.

2-(*p*-Methoxyanilino)-(*R*)-propanoic Acid Ethyl L-Lactate Ester (9**).** A pale yellow oil was obtained in 56% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 6.76 (d, J = 8.8 Hz, 2H), 6.61

(d, J = 8.8 Hz, 2H), 5.09 (q, J = 7.2 Hz, 1H), 4.16 (m, 3H), 3.89 (br, 1H), 3.73 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 174.2, 170.4, 152.7, 140.7, 115.0, 114.8, 69.0, 61.4, 55.7, 53.0, 18.9, 16.9, 14.0.

2-(*p*-Methoxyanilino)-(*R*)-butanoic Acid Ethyl L-Lactate Ester (10**).** A colorless oil was obtained in 78% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 6.75 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 5.08 (q, J = 6.8 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.99 (br, 1H), 3.90 (br, 1H), 3.71 (s, 3H), 1.93–1.80 (m, 2H), 1.44 (d, J = 6.8 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 173.5, 170.4, 152.7, 141.0, 115.0, 114.8, 68.9, 61.4, 58.9, 55.6, 26.2, 16.9, 14.0, 10.1.

2-(*p*-Methoxyanilino)-(*R*)-hexanoic Acid Ethyl L-Lactate Ester (11**).** A pale yellow oil was obtained in 72% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 6.68 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 5.01 (q, J = 6.8 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.96 (t, J = 6.4 Hz, 1H), 3.64 (s, 3H), 1.83–1.67 (m, 2H), 1.38 (d, J = 6.8 Hz, 3H), 1.42–1.20 (m, 4H), 1.12 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 173.8, 170.4, 152.7, 141.0, 115.0, 114.8, 68.9, 61.4, 57.7, 55.7, 32.8, 27.8, 22.4, 17.0, 14.0, 13.9.

2-Dibenzylamino-(*R*)-phenylacetic Acid Ethyl L-Lactate Ester (12**).** A yellow oil was obtained in 73% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.41–7.18 (m, 15H), 5.19 (q, J = 6.8 Hz, 1H), 4.73 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.82 (s, 4H), 1.47 (d, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 171.8, 170.8, 139.7, 136.7, 129.1, 128.9, 128.5, 128.4, 128.0, 127.1, 69.1, 65.5, 61.6, 54.1, 17.1, 14.4.

2-Dibenzylamino-(*R*)-propanoic Acid Ethyl L-Lactate Ester (13**).** A pale yellow oil was obtained in 51% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.42–7.23 (m, 10H), 5.11 (q, J = 6.8 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 14.0 Hz, 2H), 3.74 (d, J = 14.0 Hz, 2H), 3.57 (q, J = 6.8 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 173.2, 170.8, 140.0, 128.8, 128.2, 126.9, 68.7, 61.4, 55.8, 54.2, 17.2, 15.2, 14.2.

2-Benzylamino-(*R*)-phenylacetic Acid Ethyl L-Lactate Ester (14**).** A colorless oil was obtained in 58% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.32–7.17 (m, 10H), 4.99 (q, J = 6.8 Hz, 1H), 4.42 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.72 (ABq, 2H), 1.33 (d, J = 6.8 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 172.7, 170.5, 139.6, 137.8, 128.7, 128.4, 128.2, 127.6, 127.2, 69.3, 64.2, 61.5, 51.5, 16.8, 14.1.

2-Benzylamino-(*R*)-phenylacetic Acid Ethyl L-Lactate Ester (15**).** A yellow oil was obtained in 52% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.35–7.22 (m, 5H), 5.11 (q, J = 6.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.85 (d, J = 12.8 Hz, 1H), 3.69 (d, J = 12.8 Hz, 1H), 3.48 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz,

major diastereomer) δ 175.3, 170.6, 139.8, 128.4, 128.3, 127.1, 68.9, 61.4, 55.8, 51.8, 19.1, 17.0, 14.1.

2-(3,4-Dihydro-2(1H)-isoquinoliny)-(R)-phenylacetic Acid Ethyl L-Lactate Ester (16) A yellow oil was obtained in 56% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.55–6.92 (m, 9H), 5.07 (q, $J = 6.8$ Hz, 1H), 4.36 (s, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.75 (s, 2H), 2.89 (br, 4H), 1.43 (d, $J = 6.8$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 171.0, 170.6, 134.3, 130.3, 128.9, 128.8, 128.7, 128.6, 126.7, 126.2, 125.7, 72.7, 69.2, 61.5, 53.6, 48.2, 28.7, 16.8, 14.2.

2-(3,4-Dihydro-2(1H)-isoquinoliny)-(R)-propanoic Acid Ethyl L-lactate Ester (17) A colorless oil was obtained in 65% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.11–7.01 (m, 4H), 5.11 (q, $J = 7.2$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.89 (m, 2H), 3.61 (q, $J = 7.2$ Hz, 1H), 3.08 (m, 1H), 2.87 (m, 3H), 1.52 (d, $J = 7.2$ Hz, 3H), 1.44 (d, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 172.6, 170.6, 134.9, 134.4, 128.8, 126.6, 126.0, 125.5, 68.7, 61.8, 61.4, 52.0, 46.9, 29.8, 17.1, 15.3, 14.1.

Dihydroquinoxalinones 18–25 and Dihydrobenzoxazinones 26–27: The spectral data of **18–27** were identical to those of the authentic material reported previously.^{4c} The enantiomers were determined by chiral stationary phase HPLC using Chiralcel OJ-H column (for **18–25**) and Chiralcel OD column (for **26–27**).

***N*-[(*S*)-1-(Methoxycarbonyl)ethyl]-(*R*)-phenylglycine Ethyl L-Lactate Ester (28)** A yellow oil was obtained in 67% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.43–7.32 (m, 5H), 5.05 (q, $J = 7.2$ Hz, 1H), 4.54 (s, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.71 (s, 3H), 3.28 (q, $J = 7.2$ Hz, 1H), 2.65 (br, 1H), 1.37 (d, $J = 7.2$ Hz, 3H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 175.3, 171.8, 170.3, 137.4, 128.6, 128.2, 127.9, 69.4, 63.0, 61.4, 53.7, 51.9, 18.9, 16.7, 14.0.

***N*-[(*S*)-1-(Methoxycarbonyl)-3-methylbutyl]-(*R*)-phenylglycine Ethyl L-Lactate Ester (29)** A colorless oil was obtained in 60% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.43–7.29 (m, 5H), 5.02 (q, $J = 7.2$ Hz, 1H), 4.46 (s, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.71 (s, 3H), 3.11 (br, 1H), 2.57 (br, 1H), 1.82 (m, 1H), 1.48 (m, 2H), 1.35 (d, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.71 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 175.8, 171.6, 170.3, 137.6, 128.5, 128.2, 127.9, 69.4, 63.5, 61.4, 56.7, 51.7, 42.7, 24.5, 23.0, 21.7, 16.7, 14.0.

***N*-[(*S*)-1-(Methoxycarbonyl)phenethyl]-(*R*)-phenylglycine Ethyl L-Lactate Ester (30)** A colorless oil was obtained in 55% yield. ^1H NMR (CDCl_3 , 400 MHz, major diastereomer) δ 7.28–7.13 (m, 10H), 4.99 (q, $J = 7.2$ Hz, 1H), 4.45 (s, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.67 (s, 3H), 3.36 (br, 1H), 3.03–2.87 (m, 2H), 2.66 (br, 1H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 174.2, 171.5, 170.3, 137.2, 137.1, 129.4, 128.5, 128.4, 128.1, 128.0, 126.7, 69.4, 63.3, 61.4, 59.7, 51.8, 39.7, 16.7, 14.0.

***N*-[(*R*)-2-Methoxy-2-oxoethyl-1-phenyl]-(*S*)-leucine Methyl Ester (31)** The mixture of *N*-substituted α -amino ester **29** and Et_3N (10 equiv) in methanol (0.05 M) was stirred for a day. The solvent was evaporated and the crude material was purified by column chromatography to give a product in 68% yield. ^1H NMR (CDCl_3 , 400 MHz) δ 7.39–7.27 (m, 5H), 4.34 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.07 (m, 1H), 2.55 (br, 1H), 1.83 (m, 1H), 1.53–1.42 (m, 2H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.69 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, major diastereomer) δ 176.0, 172.7, 138.0, 128.6, 128.2, 128.1, 63.6, 56.7, 52.4, 51.8, 42.7, 24.6, 23.0, 21.6.

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