1-(α-Boc-aminoacyl)benzotriazoles: stable chiral α-aminoacylation reagents

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Abstract

The chiral α-*N*-(tert-butoxycarbonyl)aminoacylbenzotriazoles [(*N*-Boc-aminoacyl)-benzotriazoles] **3a–e** are stable crystalline intermediates, easily prepared (61–88%) from *N*-Boc-α-amino acids **1a–e**. Compounds **3a–e** react with achiral or chiral amines at 0–20 °C to give α-(*N*-Boc-amino)amides with no detectable racemization.

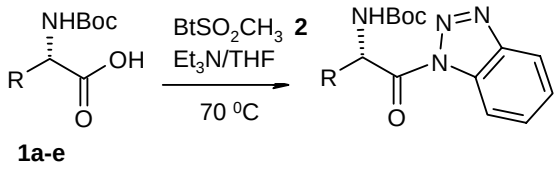
Keywords: α-(*N*-Boc-aminoacyl)benzotriazoles, α-aminoacylation

Introduction

Amide bond formation between amino-acid components is a main goal in the synthesis of many organic compounds of biological interest such as peptides, peptoids, oligocarbamates, oligoamides, β-lactams, polyenamides, benzodiazepines, diketopiperazines, and hydantoins. Contemporary protocols for the preparation of *N*-protected α-acylamino amides involve the formation of intermediate active esters. Many peptide coupling reagents[1] have essentially eliminated racemization of the amino acid component and the undesired side reactions[2] which can arise in direct synthesis of primary, secondary, and tertiary amides from acids or their classical activated derivatives (acyl halides, acid anhydrides, mixed anhydrides, or esters) with ammonia or amines. However, stable, crystalline chiral α-aminoacylation reagents have rarely been documented. Recent efforts to obtain easily isolated and stored active esters have linked modern activating groups (e.g., HOBt, HOAt, HOSu and PFP) to solid supports.[3] Recently, stable *N*-hydroxysuccinimide (HOSu) - derived active esters have been obtained crystalline.[4]

N-Protected amino acid chlorides have long been known,[5] their most successful application to peptide synthesis involved Fmoc-amino acids.[6] Most *N*-protected amino acid chlorides proved not to be generally storable because of their high reactivity and sensitivity to cause degradation,[7] decomposition and racemization[2] on storage. *N*-Protected amino acid fluorides are more stable than the corresponding chlorides toward neutral oxygen nucleophiles such as water and methanol, yet are of high reactivity toward anionic nucleophiles and amines. Acid fluorides display considerable advantages in peptide synthesis;[7,8] however, racemization was observed upon pretreatment of BOC-Phe-F with triethylamine in methylene chloride,[7] low temperature is required for storage, especially in the t-BOC series[7] and a large excess of acid fluorides was needed in the coupling step.[8b]

Acylbenzotriazoles have long been known as neutral acylating reagents.[9] More recent work has included simple methods for their preparation and their application to prepare primary, secondary and tertiary amides[10] and cinnamoyl hydrazides.[11] We now extend the acylbenzotriazole chemistry to prepare stable *N*-Boc-α-amino acylbenzotriazoles derived from *N*-Boc-α-amino acids and their utilization in the synthesis of chiral α-(*N*-protected amino)acid amides (Scheme 1).



	R	Yield (%)
3a	CH_3	61
3b	$(CH_3)_2CH$	83
3c	CH_3CH_2	78
3d	$(CH_3)_2CHCH_2$	66
3e	$PhCH_2$	81

Scheme 1

Results and Discussion

Preparation of (*N*-Boc-α-aminoacyl)benzotriazoles 3a–e

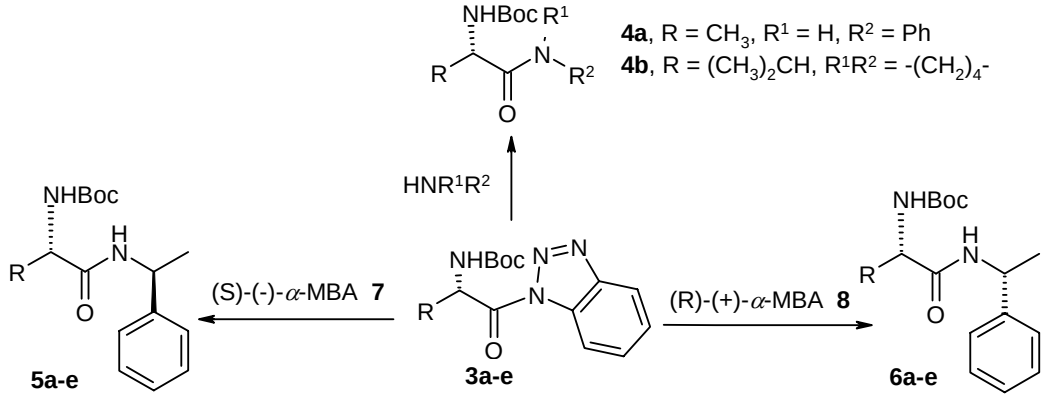
As shown in Scheme 1, the (*N*-Boc-α-aminoacyl)benzotriazoles **3a–e** were prepared in 61–88% yields from commercially available *N*-protected α-amino acids **1a–e** and $BtSO_2Me$ (**2**).[10] Compounds **3a–e** are colorless solids and crystallized from hexane–ethyl acetate; **3a–e** showed no detectable change on storage at 20 ^{o}C for 6 months. The ^{13}C NMR spectra of **3a–e** displayed the expected signals characteristic of acylbenzotriazoles at δ ca. 131 (d), 127 (d), 120 (d), and 114 (d), and of the carbonyl carbons of the amide and carbamate groups at δ ca. 173 (s) and 155 (s), respectively.

Preparation of *N*-(acylamino)amides 4a,b, 5a–e, 6a–e

Reactions of (*N*-Boc-α-aminoacyl)benzotriazoles **3a** and **3b** with amines in THF at room temperature afforded amides **4a** and **4b** in 82–87% yields (Table 1, Scheme 2). These yields and

the procedure are comparable with those previously reported for the preparation of simple amides from RCOBt and amines (e.g., *N*-(4-methoxyphenyl)-2-pyridinecarboxamide, 83%).[10]

The most reliable technique for the determination of enantiomer composition is by the NMR analysis of covalent diastereomer mixtures,[12] as exemplified by the preparation of derivatives of chiral alcohols or amines from optically active acids. α-Methylbenzylamides of *N*-protected amino acids have frequently served as model compounds for studies of optical purity and stability towards racemization.[13] With this in mind, (*S*)-(-)-α-methylbenzylamine **7** and its antipode (*R*)-(+)-α-methylbenzylamine **8** were converted into the corresponding diastereomeric modified amides **5a–e** and **6a–e**, respectively, in isolated yields of 85–99% (average 93%) by reactions with **3a–e** at 0–20 °C.



For designation of R in **5a–e** and **6a–e**, see Scheme 1 and Table 1

Scheme 2

The diastereomeric excess (*de*) values for compounds **5a–e** and **6a–e** were determined as 93–99% by ^{1}H NMR analysis of the amides after column chromatographic purification (Table 1). For compounds **5a–d** and **6a–d**, the resonances for the terminal methyl of the amino acid portion of the molecules were separated by 0.01–0.05 ppm (Figure 1). For compounds **5e** and **6e**, the α-methyl proton resonances were separated enough to allow determination of the diastereomeric ratio (Figure 2). The de values of **5a–e** and **6a–e** are summarized in Table 1. This indicated that the α-aminoacylations occurred with complete retention of the chirality of both the precursors in the products. Optical rotations were also examined for compound **4a**, which had a rotation of $[\alpha]_D^{20}$, -52°, that reported[14] is -61.2°. The measured $[\alpha]_D^{20}$ of **4b** is -5.5°, that reported[15] is +9.2°. Problems with the measurement of the optical rotation for the determination of enantiomeric purity of optically active compounds have been discussed.[12]

One-pot reaction has also been investigated for **4b**, **5e** and **6e**. After the formation of the (*N*-Boc-α-aminoacyl)benzotriazoles **3a–e** were completed, amines were added *in situ* to the reaction mixture at room temperature and stirred for an appropriate time to provide **4b**, **5e** and **6e** in very

good one-pot yields. In cases **5e** and **6e**, one-pot reaction gave the same de values as the above method. This success in the one-pot procedure should encourage the application of (*N*-Boc-α-aminoacyl)benzotriazoles in the formation of the amide bond.

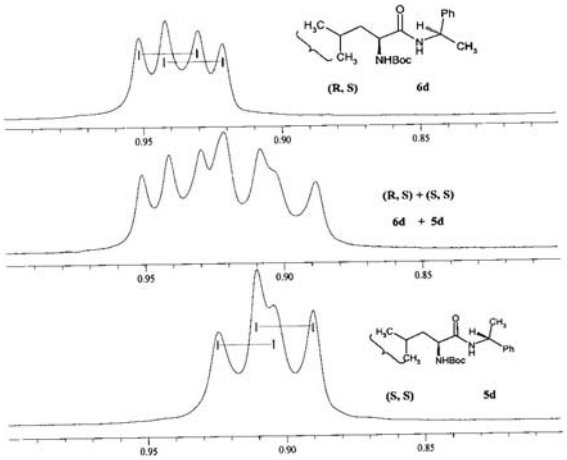


Figure 1. ^{1}H NMR spectra of compounds **5e** and **6e** in $CDCl_3$ (aliphatic region).

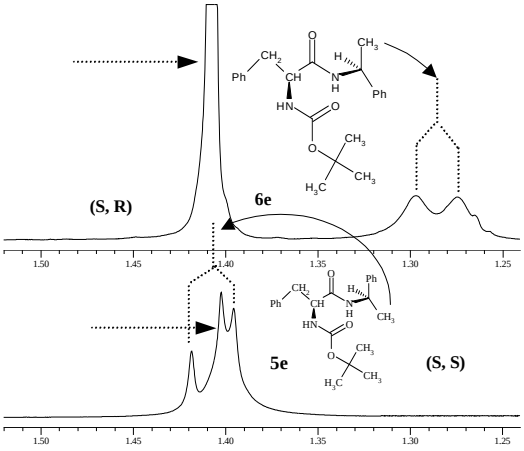


Figure 2. ^{1}H NMR spectra of compounds **5d** and **6d** in $CDCl_3$ (aliphatic region).

Table 1. *N*-(Acylamino)amides **4a,b**, **5a–e**, **6a–e**

Entry	R	$[\alpha]_{20}$	Mp (^{O}C)	De (%)	Yield (%)
4a	CH_3	-52	174	-	82
4b	$(CH_3)_2CH$	-5.5	oil	-	87 (82[a])
5a	CH_3	-	119.0–119.5	99	91
5b	$(CH_3)_2CH$	-	142–143	96	93
5c	CH_3CH_2	-	109–110	93	93
5d	$(CH_3)_2CHCH_2$	-	143–143.5	99	85
5e	$PhCH_2$	-	131–132	99	96 (80)
6a	CH_3	-	91.5–92.5	99	99
6b	$(CH_3)_2CH$	-	128–128	99	89
6c	CH_3CH_2	-	93–94	99	90
6d	$(CH_3)_2CHCH_2$	-	137–138	99	95
6e	$PhCH_2$	-	127–128	99	95 (77)

[a] Yields in parentheses are for the one-pot procedure.

In conclusion, we have described a methodology for the preparation and synthetic utilization of (*N*-Boc-α-aminoacyl)benzotriazoles **3a–e** *via* *N*-methanesulfonylbenzotriazole **2**. The excellent stability of the isolated (*N*-Boc-α-aminoacyl)benzotriazoles **3a–e** may provide broad applicability. The simplicity, operational ease and lack of racemization offer advantages over

conventional coupling techniques and could make this methodology a method of choice for the preparation of amides and peptides using solid phase combinatorial techniques where crystalline, stable reagents have obvious advantages.

Experimental Section

General Procedures. Melting points were determined on a capillary melting point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) and the solvent for ^{13}C (75 MHz) NMR. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere. Column chromatography was conducted using silica gel (230–400 mesh) and ethyl acetate–hexane.

General procedure for the preparation of 3a–e

To a solution of *N*-protected amino acid (10 mmol) in THF (50 mL), BtMs (11 mmol) and Et_3N (11 mmol) were added at room temperature. The reaction mixture was heated and refluxed 6–12 h. The solvent was removed *in vacuo* to dryness. The residue was dissolved in ethyl acetate and washed sequentially with sat. citric acid, sat. Na_2CO_3 and H_2O, and dried over $MgSO_4$. Concentration under reduced pressure gave desired product, which can be recrystallized from hexane–ethyl acetate.

***L-tert*-Butyl-*N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (3a).** Colorless prisms (61%), mp 68–69 °C, $[\alpha]_D^{20}$ –17.7° ($CHCl_3$); ^1H NMR δ 8.27 (d, *J* = 8.1 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.67 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.52 (dd, *J* = 7.5, 7.6 Hz, 1H), 5.74 (m, 1H), 5.32 (d, *J* = 5.9 Hz, 1H), 1.65 (d, *J* = 7.3 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR δ 173.2, 155.5, 146.4, 131.6, 131.1, 126.9, 120.7, 114.8, 80.8, 50.6, 28.7, 19.4. Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.06; H, 6.44; N, 19.30.

***L-tert*-Butyl-*N*-[1-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)-2-methylpropyl]carbamate (3b).** Colorless needles (83%), mp 120–121 °C, $[\alpha]_D^{20}$: –47.5° (CH_3OH); ^1H NMR δ 8.28 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.68 (dd, *J* = 7.4, 7.3 Hz, 1H), 7.54 (dd, *J* = 7.4, 7.5 Hz, 1H), 5.70–5.66 (m, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 2.47–2.17 (m, 1H), 1.46 (s, 9H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.97(d, *J* = 6.7 Hz, 3H); ^{13} C NMR δ 171.9, 155.6, 145.9, 130.9, 130.5, 126.3, 120.2, 114.3, 80.1, 58.9, 31.4, 28.2, 19.6, 16.9. Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.96; N, 17.60. Found: C, 60.56; H, 7.13; N, 17.72.

***L-tert*-Butyl-*N*-[1-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)propyl]carbamate (3c).** Colorless needles (78%), mp 85–86 °C, $[\alpha]_D^{20}$: –45.0° ($CHCl_3$); ^1H NMR δ 8.29 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.68 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.54 (dd, *J* = 7.5, 7.8 Hz, 1H), 5.75–5.61 (m, 1H), 5.31 (brd, *J* = 7.2 Hz, 1H), 2.25–2.06 (m, 1H), 1.98–1.82 (m, 1H), 1.46 (s, 9H), 1.08 (t, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR δ 172.1, 155.4, 145.8, 131.0, 130.5, 126.3, 120.1, 114.2, 80.1, 55.2,

28.2, 26.2, 9.9. Anal. Calcd for $C_{15}H_{20}N_4O_3$: C, 59.20; H, 6.62; N, 18.41. Found: C, 59.52; H, 7.08; N, 18.60.

***L-tert*-Butyl-*N*-[1-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)-3-methylbutyl]carbamate (3d).** Colorless needles (66%), mp 134–136 °C, $[\alpha]_D^{20}$: –4.0° ($CHCl_3$); ^{1}H NMR δ 8.27 (d, *J* = 8.1 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.67 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.53 (dd, *J* = 7.7, 7.6 Hz, 1H), 5.80–5.74 (m 1H), 5.23 (brs, 1H), 1.88–1.80 (m, 2H), 1.74–1.64 (m, 1H), 1.45 (s, 9H), 1.10 (d, *J* = 5.6 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR δ 172.9, 155.5, 146.0, 131.2, 130.6, 126.4, 120.3, 114.4, 80.3, 53.1, 41.9, 28.3, 25.3, 23.2, 21.3. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.74; H, 7.10; N, 17.00.

***L-tert*-Butyl-*N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]carbamate (3e).** Colorless needles (81%), mp 144–145 °C; ^{1}H NMR δ 8.26 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.14 (dd, *J* = 5.9, 2.4 Hz, 1H), 7.68 (dd, *J* = 7.4, 7.7 Hz, 1H), 7.57–7.16 (m, 6H), 6.05–5.95 (m, 1H), 3.46 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.19 (dd, *J* = 7.4, 13.9 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR δ 171.3, 155.1, 146.0, 135.2, 131.0, 130.7, 129.2, 128.6, 127.2, 126.4, 120.3, 114.3, 80.3, 55.2, 38.8, 28.2. Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.68; H, 6.38; N, 14.90.

General procedure for the preparation of 4a,b, 5a–e, 6a–e

To a solution of the *N*- (*N*-Boc-α-aminoacyl)benzotriazole **3a–e** (5 mmol) in dry THF (30 mL), a solution of the corresponding amines (5 mmol) in THF (2 mL) was added at 0 °C over 5 min. The reaction mixture was stirred at 0–20 °C overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give the desired products, which can be recrystallized from hexane–ethyl acetate.

[1-(*N*-*tert*-Butyloxycarbonyl)amino-1-methyl]-*N*-phenylacetamide (4a). Colorless needles (82%), mp 174 °C (lit.[14] 175 °C), $[\alpha]_D^{20}$: –52° (lit.[14] –61.2°); ^{1}H NMR δ 8.44 (br s, 1H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.06 (br s, 1H), 4.32 (m, 1H), 1.47 (s, 9H), 1.43 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 171.1, 156.1, 137.8, 128.9, 124.2, 119.8, 80.5, 50.7, 28.3, 17.8.

[2-Methyl-1-(pyrrolidine-1-carbonyl)propyl]carbamic acid *tert*-butyl ester (4b). Colorless oil (87%), $[\alpha]_D^{20}$: –5.5 ° (lit.[15] +9.2 °C). ^{1}H NMR δ 5.31 (d, *J* = 9.0 Hz, 1H), 4.20–4.15 (m, 1H), 3.63–3.57 (m, 1H), 3.47–3.32 (m, 3H), 1.91–1.76 (m, 5H), 1.35 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 170.2, 155.4, 78.7, 56.6, 46.2, 45.3, 30.9, 27.9, 25.6, 23.8, 19.1, 17.1.

***tert*-Butyl *N*-((1*S*)-1-methyl-2-oxo-2-{[(1*S*)-1-phenylethyl]amino}ethyl)carbamate (5a).** Colorless needles (91%), mp 119–120 °C; ^{1}H NMR δ 7.35–7.22 (m, 5H), 6.62 (brs, 1H), 5.14–5.04 (m, 2H), 4.16 (brs, 1H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.33 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR δ 171.7, 155.6, 143.0, 128.6, 127.3, 126.0, 80.1, 50.1, 48.6, 28.2, 21.8, 18.0. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.66; H, 8.38; N, 9.60.

***tert*-Butyl *N*-[(1*S*)-2-methyl-1-({[(1*S*)-1-phenylethyl]amino}carbonyl)propyl]carbamate (5b).** Colorless macrocrystals (93%), mp 142–143 °C; ^{1}H NMR δ 7.41–7.28 (m, 5H), 6.34 (brd, *J* = 7.4 Hz, 1H), 5.25–5.10 (m, 2H), 3.93–3.88 (m, 1H), 2.20–2.05 (m, 1H), 1.53 (d, *J* = 6.9 Hz, 3H), 1.48 (s, 9H), 0.96–0.92 (m, 6H); ^{13}C NMR δ 170.9, 156.0, 143.1, 128.5, 127.1, 126.0, 79.6, 60.0, 48.6, 30.8, 28.2, 21.7, 19.2, 17.9. Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.71; H, 9.10; N, 8.73.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-phenylethyl]amino}carbonyl)propyl]carbamate (5c).** Colorless needles (93%), mp 109–110 °C (lit.[16] no melting point given); ^{1}H NMR δ 7.36–7.23 (m, 5H), 6.38 (brs, 1H), 5.16–5.00 (m, 2H), 4.02–3.92 (m, 1H), 1.91–1.76 (m, 1H), 1.66–1.56 (m, 1H) 1.48 (d, *J* = 6.9 Hz, 3H), 1.43 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 155.3, 144.7, 128.2, 126.6, 125.8, 77.9, 55.6, 47.7, 28.2, 25.4, 22.5, 10.3.

***tert*-Butyl *N*-[(1*S*)-3-methyl-1-([(1*S*)-1-phenylethyl]aminocarbonylbutyl]carbamate (5d).** Colorless needles (85%), mp 142–143 °C; ^{1}H NMR δ 7.37–7.22 (m, 5H), 6.45 (brd, *J* = 7.1 Hz, 1H), 5.12–5.05 (m, 1H), 4.89 (brs, 1H), 4.06 (brs, 1H), 1.67–1.53 (brs, 2H), 1.51–1.43 (m, 1H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.43 (s, 9H), 0.91 (d, *J* = 5.9 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR δ 171.7, 155.8, 143.2, 128.5, 127.2, 126.0, 79.9, 53.1, 48.6, 41.1, 28.3, 24.7, 22.9, 21.8. Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.38; H, 9.25; N, 8.41.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-oxo-2-{[(1*S*)-1-phenylethyl]amino}ethyl)carbamate (5e).** Colorless needles (96%), mp 131–132 °C (lit.[13] 138–139 °C); ^{1}H NMR δ 7.30–7.08 (m, 10H), 6.07 (d, *J* = 8.0 Hz, 1H), 5.12 (brs, 1H), 5.07–5.00 (m, 1H), 4.32–4.22 (m, 1H), 3.07 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.99 (dd, *J* = 7.7, 13.3 Hz, 1H), 1.41 (d, *J* = 6.7 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR δ 170.2, 155.4, 142.6, 136.6, 129.3, 128.6, 128.5, 127.2, 126.8, 126.0, 80.1, 55.9, 48.6, 38.5, 28.2, 21.5. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.48; H, 7.88; N, 7.57.

***tert*-Butyl *N*-((1*S*)-1-methyl-2-oxo-2-[(1*R*)-1-phenylethyl]aminoethyl)carbamate (6a).** Colorless needles (99%), mp 91.5–93.0 °C; ^{1}H NMR δ 7.34–7.21 (m, 5H), 6.60 (brs, 1H), 5.12–5.03 (m, 1H), 4.94 (brs, 1H), 4.15–4.10 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.42 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 171.4, 155.6, 143.1, 128.6, 127.2, 125.9, 80.1, 49.9, 48.7, 28.2, 22.0, 17.6. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.70; H, 8.61; N, 9.62.

***tert*-Butyl *N*-[(1*S*)-2-methyl-1-({[(1*R*)-1-phenylethyl]amino}carbonyl)propyl]carbamate (6b).** Colorless macrocrystals (89%), mp 127–128 °C; ^{1}H NMR δ 7.34–7.22 (m, 5H), 6.28 (brd, *J* = 6.7 Hz, 1H), 5.13–5.06 (m, 2H), 3.88–3.82 (m, 1H), 2.19–2.08 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR δ 170.7, 155.9, 142.9, 128.5, 127.2, 126.0, 79.7, 60.2, 48.7, 30.5, 28.2 21.9, 19.3, 18.0. Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.67; H, 9.04; N, 8.61

***tert*-Butyl *N*-[(1*R*)-1-({[(1*R*)-1-phenylethyl]amino}carbonyl)propyl]carbamate (6c).** Colorless needles (90%), mp 93–94 °C (lit.[16] no melting point given); ^{1}H NMR δ 7.34–7.23 (m, 5H), 6.40 (m, 1H), 5.15–5.05 (m, 1H), 4.96 (brs, 1H), 4.05–3.85 (m, 1H), 1.95–1.80 (m, 1H), 1.81–1.54 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 155.3, 144.4, 128.1, 126.5, 126.0, 77.9, 55.6, 47.7, 28.2, 25.2, 22.5, 10.4.

***tert*-Butyl *N*-[(1*S*)-3-methyl-1-([(1*R*)-1-phenylethyl]aminocarbonyl)butyl]carbamate (6d).** Colorless needles (95%), mp 137–138 °C; ^{1}H NMR δ 7.35–7.23 (m, 5H), 6.56 (brs, 1H), 5.11–5.06 (m, 1H), 4.86 (d, *J* = 8.2 Hz, 1H), 4.88–4.08 (m, 1H), 1.72–1.64 (m, 2H), 1.49–1.43 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.43 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR δ 171.4, 155.8, 143.1, 135.5, 128.3, 127.1, 125.9, 80.1, 52.9, 48.6, 40.6, 28.2, 24.7, 22.8, 22.1, 22.0. Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.40; H, 9.42; N, 8.40.
***tert*-Butyl *N*-((1*S*)-1-benzyl-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)carbamate (6e).** Colorless needles (95%), mp 127–128 °C (lit.[17] no melting point given); ^{1}H NMR δ 7.32–7.15 (m, 10H), 5.91 (brs, 1H), 5.10 (brs, 1H), 5.02–4.90 (m, 1H), 4.31–4.25 (m, 1H), 3.12 (dd, *J* = 6.0, 13.6 Hz, 1H), 2.99 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.41 (s, 9H), 1.29 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 170.3, 152.6, 142.8, 129.6, 129.5, 128.9, 128.8, 127.5, 127.1, 126.2, 68.0, 56.2, 49.0, 38.9, 28.5, 21.9. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.36; H, 7.87; N, 7.96.

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