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Synthesis of *N*-alkyl-*N*-methyl amino acids. Scope and limitations of base-induced N-alkylation of Cbz-amino acids

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Abstract—The reaction of *N*-benzyloxycarbonyl derivatives of aliphatic amino acids with NaH/alkyl iodides gave the corresponding *N*-Cbz-*N*-alkyl derivatives in good to high yields. The scope and limitations of this simple N-alkylation reaction were investigated as a convenient and flexible attempt to prepare unsymmetrically N,N-diprotected α-amino acids. The procedure is based on the N-alkylation of *N*-carbamoyl amino acids, a one-pot deprotection/protection sequence without extensive purification of the products. Protection of the carboxyl function is not required while the starting materials are inexpensive and commercially available.

1. Introduction

Amino acids, which are essentially incorporated in proteins, peptides, enzymes, and large numbers of bio-active phenomena have recently gained much interest in synthetic organic chemistry as extremely desirable building blocks, chiral auxiliaries, catalysts, and ligands. While Nature's creativity and precision in the construction of various structures is impressive, the development of practical and efficient synthetic methodologies for the construction of amino acids is still in its infancy.

N-Methyl amino acids are a group of important modified amino acids, which have been widely used in medicinal chemistry and biochemistry to change the conformation, restrict the flexibility, and enhance the potency of the molecule.[1] Various protocols have been developed for the synthesis of optically active *N*-methyl amino acids,[2] but the methods for installing the *N*-methyl moiety in the full range of amino acids still remain difficult.[3]

Incorporation of *N*-alkyl amino acids into peptides often improves the biological profile by increasing the proteolytic stability, conformational rigidity, and lipophilicity. At the present time, however, flexible synthetic routes to higher *N*-alkyl amino acids are unknown[4,5] and the problem with the general N-alkylation of amino acids with non-methyl alkylating agents (Et, Pr, Bu, etc.) seems convoluted mostly due to the steric hindrance of longer carbon chains. In light of this, the synthesis of amino acids with two different alkyl groups attached to the N-terminus of the molecule seems to be even more challenging.

On the other hand, such complex yet simple molecules are desirable for the sensitive and iterative tuning of the ligand structure en route to various kind of asymmetric metal complexes.[6] Despite the hidden potential of these building blocks for asymmetric synthesis, knowledge about their synthetic and therapeutic properties remains narrow, and the number of structures tested is still restricted mostly due to the tedious and inefficient known synthetic procedures.[7]

Herein, we report our studies on the simple synthesis of *N*-alkyl-*N*-methyl amino acids without need for the protection of the carboxylic function. The efficient synthetic procedure is performed via consecutive alkylation of benzyloxycarbamoyl (Cbz) amino acids and smart one-pot Cbz-deprotection and methylation of amino function. An adequately selected simple reaction sequence resulted in clean and efficient formation of two different alkyl groups on the nitrogen-end of the molecule. The most important feature of this protocol is all-step chromatography-free process resulting from efficient reaction steps. In contrast to the previously described protocols, the separation of the reaction products after each step of the

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reaction is easy, and routine aqueous workup replaces the tedious and expensive chromatography. The important problem of the racemization of chiral amino acids under basic reaction conditions is investigated while scope and limitation of the elaborated base-induced N-alkylation of amino acids are recognized.

2. Results and discussion

2.1. Synthesis of *N*-alkyl-*N*-methyl amino acids

Commercially available *N*-methyl amino acids are still very expensive; therefore this method employs commercially available and relatively inexpensive Cbz-amino acids.[8] Our method started with the N-alkylation of the Cbz-protected amino acids. The most broadly applied method for the *N*-methyl amino acid synthesis is N-methylating an *N*-carbamoyl derivative with sodium hydride and methyl iodide in THF/DMF at 80 °C, as developed by Benoiton.[9] Subsequently, the same methylation in neat THF at room temperature was described.[10] The latter method is preferable since the former also esterifies the carboxyl group, while the removal of the ester group by saponification is accompanied by some level of racemization (Fig. 1). The carboxylic methyl ester, formed as an undesired co-product, was removed using harsh, basic conditions. This base-mediated method, of course, does not proceed without racemization at the α-carbon of the amino acids.

Thus, a direct route to *N*-methyl amino acids was necessary so as to avoid hydrolysis of the ester and therefore prevent racemization. It was also found that (ambient) reaction temperature was an important factor in avoiding O-alkylation leading to undesired methyl ester formation.[11] Many others have since utilized this method and variations thereof in producing optically active *N*-methyl amino acids in THF at rt.[12]

We checked, however, that this methodology failed for alkyl chains longer than methyl. All attempts to obtain *N*-alkyl amino derivative from Cbz-alanine with NaH and ethyl iodide at ambient temperature were unpromising. Application of other bases was also not efficient: LiHMDS was too weak and Cs_2CO_3 led to the clean formation of carboxylic esters as sole products.

Thus, we decided to test similar reaction conditions at elevated temperatures. When we applied this protocol (NaH, MeI, THF) to the synthesis of *N*-methyl Cbz-L-alanine **2**, the reaction was clean and efficient (Scheme 1). In general, N-alkylation was highly privileged (>90% isolated yield). At this stage, the temperature of the reaction was higher (60 °C) to check if some level of racemization affected the enantiomeric purity of the products. The measured specific rotation value of **2** ($[\alpha]_D = -24.9$) match perfectly the literature data for the same compound ($[\alpha]_D = +24.5$ for D-enantiomer).[12b] Having this evidence in hand, we started to test the alkylation of some other amino acids.

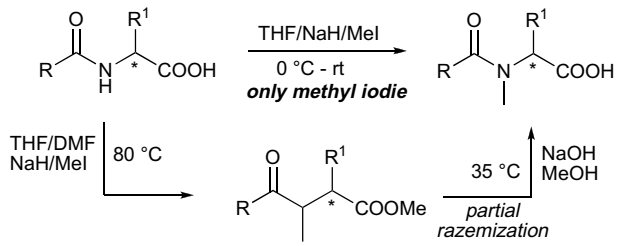
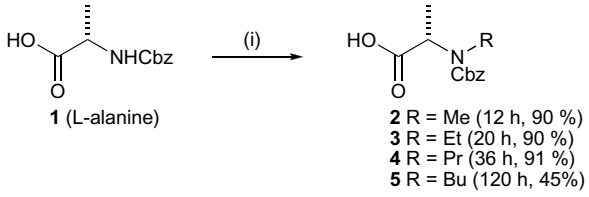


Figure 1. Reaction of derivatives of aliphatic amino acids with sodium hydride/methyl iodide to form the corresponding *N*-methyl amino acids.

To our delight, the same reaction of alanine with ethyl iodide in THF at 60 °C resulted in clean and efficient formation of desired product **3**. Our careful investigation of the reaction revealed that only 3 equiv of NaH allows for a good conversion after 20 h. We were pleased to find that not only ethyl iodide, but also other tested alkyl iodides delivered the desired *N*-alkyl-*N*-benzyloxycarbamoyl-α-alanines in good yields (Scheme 1).

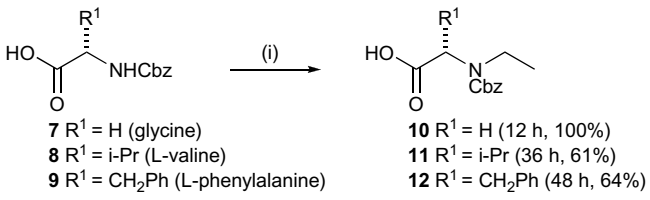


Scheme 1. Reagents and conditions: (i) NaH, alkyl iodide (RI), THF, 60 °C.

Thus, the treatment of a THF solution of chiral L-alanine **1** with NaH in the presence of ethyl, propyl or butyl iodide at an elevated temperature afforded alkyl derivatives **2**–**5** in good to excellent yields ranging from 45% to 91%. In the case of propyl and butyl iodide, longer reaction time was necessary to complete the reaction. For the butyl iodide, the isolated yield of the product was, however, lower due to steric hindrance between alkyl group and the α-located methyl group of the amino acid.

In the case of methyl and ethyl derivatives, satisfactory levels of purity of the products were achieved after the usual wet-workup. The last two compounds needed filtration through a short pad of silica gel.

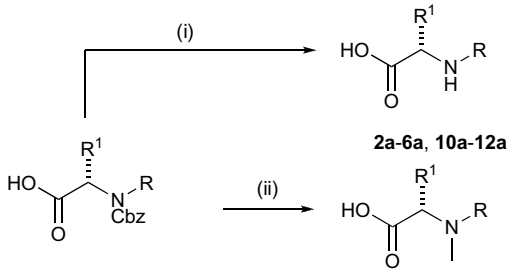
Encouraged by these promising results, we tested the reaction of ethyl iodide with another amino acids. Reaction of D-alanine with ethyl iodide led to desired product **6** with 78% isolated yield. The alkylation of glycine **7**, L-valine **8**, and L-phenylalanine **9** is depicted in Scheme 2.



Scheme 2. Reagents and conditions: (i) NaH, EtI, THF, 60 °C.

The ethylation of both 'higher' amino acids (valine and phenylalanine) has been easily achieved using elaborated conditions by using ethyl iodide in the presence of alkali. The reaction was virtually complete in 36–48 h for the sterically hindered amino acids. Unfortunately, as a result of the prolonged reaction time, the formation of some amount of the methyl esters of both valine and phenylalanine was observed (<10%).

Following the isolation of the *N*-alkyl derivatives, the Cbz group was removed via catalytic hydrogenolysis. For this purpose, we used two methods of deprotection leading to *N*-methyl- (Scheme 3, route (i)) and *N*-alkyl-*N*-methyl amino acids (Scheme 3, route (ii)), respectively. The simple deprotection of Cbz group revealed known *N*-alkyl amino acids **2a**–**6a** and **10a**–**12a** with high yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) H_2, Pd–C (10%), EtOH, H_2O, 20 h, rt; (ii) HCHO, H_2, Pd–C (10%), EtOH, H_2O, 20 h, rt.

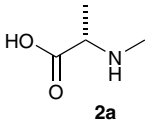
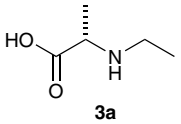
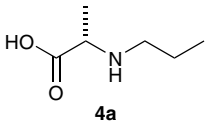
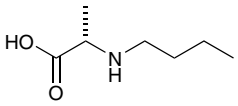
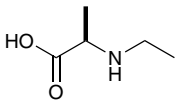
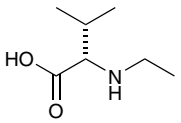
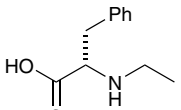
On the route to *N*-alkyl-*N*-methyl amino acids, we decided to modify slightly a routine protocol to combine two different reactions: deprotection and methyl protection using a one-pot, one-catalyst procedure. A promising and common method for installing the *N*-methyl function is reductive amination, which offers the possibility of placing alkyl groups other than methyl, by simply varying the carbonyl source. In our protocol, we devised a method for reducing the intermediate Schiff base involving palladium-catalyzed hydrogenation.

To complete the synthesis, previously prepared *N*-alkyl-*N*-benzyloxycarbamoyl-α-amino acids were submitted to hydrogenolysis in the presence of formaldehyde (2 equiv). Reactions were performed overnight in an aqueous ethanol. This protocol proved that if hydrogenolysis is carried out in the presence of a carbonyl source, the in situ released amine is directly and quantitatively converted to methyl derivatives **2b**–**6b** and **10b**–**12b** (Scheme 3). Despite its simplicity, this protection–deprotection protocol has never, to the best of our knowledge, been recorded in the literature. The crude reaction mixtures were filtered and evaporated to dryness desired *N*-alkyl-*N*-methyl amino acids in excellent yields and high level of purity.

2.2. Determination of the enantiomeric purity of prepared amino acids

The elaborated base-mediated method, even at elevated temperature, proceeded mostly without racemization, as proven by the comparison of the specific rotation values with the published data (Table 1).

Table 1. Specific rotation values of *N*-alkyl amino acids

Entry	Product	Cond.	$[\alpha]_D$	Lit. $[\alpha]_D$
1	 **2a**	12 h, 60 °C	−5.6	+5.6[13]
2	 **3a**	20 h, 60 °C	+10.2	+10.0[5]
3	 **4a**	36 h, 60 °C	+6.8	+6.9[14]
4	 **5a**	120 h, 60 °C	+3.2	19.1[a,15] +6.6[b]
5	 **6a**	48 h, 60 °C	−10.5	+10.0 (ent)[5]
6	 **11a**	36 h, 60 °C	+27.5	+28.8[4]
7	 **12a**	48 h, 60 °C	+16.6	+33.3[4]

[a] Incorrect literature data which was corrected by additional experiment.
[b] Product was obtained using EtCHO, $NaBH_3CN$, MeOH, 0 °C (16 h).

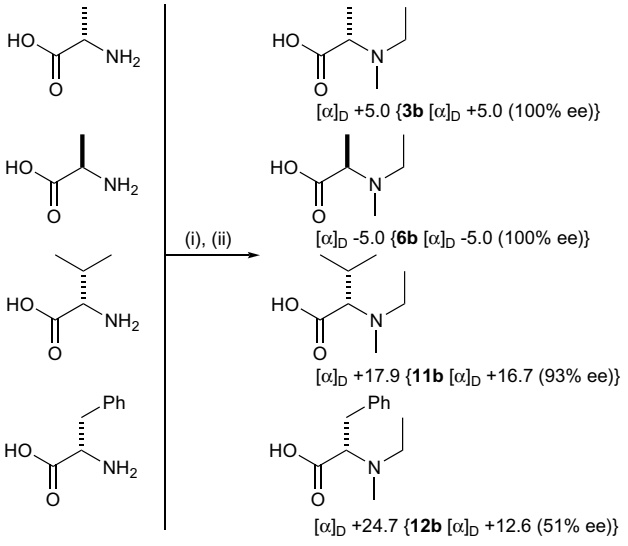
All collected data for both D- and L-alanine derivatives showed high enantiomeric purity of the products (entries 1–3 and 5). However, the observed situation in the case of butyl derivative was more puzzling. After a one-day reaction, only small amounts of desired product were detected (10%). Thus, a prolonged reaction time (120 h) was necessary for a satisfactory yield. Such harsh conditions resulted in a high level of racemization (48%

enantiomeric purity). This value was calculated from the specific rotation measured for the sample of *N*-butyl alanine prepared via an alternative route in our laboratory (+6.6) as the literature data for this compound was not correctly determined (+19.1).[15]

Thus, the α-carboxyl group when ionized provides some protection against racemization by preventing ionization at the α-carbon atom. This protection failed, however, when long exposure to basic conditions is necessary. It might be expected that amino acids with alkyl side-chains would be less prone to racemize during alkylation than amino acids with electron-withdrawing α-substituents. The specific rotations of the products obtained from valine (entry 6) showed only small levels of racemization, if any (>95% ee), while the calculated enantiomeric purity of phenylalanine (entry 7) was only 50%.

The enantiomeric integrity of products obtained under elaborated conditions of the both latter type amino acids still remains to be established by unambiguous synthetic methods. For the discussion above, we used the literature specific rotation values, in order to verify the results via an alternative path.

The synthesis of the samples of amino acids required a reliable and racemization-free methodology. Thus, we decided to apply a safe step-by-step technique for the preparation of the final products. For this test, we chose representative ethyl derivatives of enantiomeric alanines—**3b**, **6b**, valine—**11b**, and phenylalanine—**12b** (Scheme 4). At first, we obtained *N*-methyl amino acids. The applied procedure was performed, without the protection of carboxylic function, via consecutive reductive amination reactions, first with benzaldehyde, then with paraformaldehyde. A similar protocol was adopted to the facile synthesis of *N*-methyl amino acid esters.[2b] Following the isolation, the benzyl group was removed via catalytic hydrogenation to afford *N*-methyl amino acids in poor yields. We proved that this procedure was not flexible enough to be adopted for free amino acids (yields less then 15%). Nevertheless, it delivered analytical samples of the desired amino acids. All the isolated compounds were subjected to a second reductive amination using acetic aldehyde and $NaBH_3CN$ in ethanol (Scheme 4).



Scheme 4. Reagents and conditions: (i) PhCHO (1 h), $NaBH_3CN$ (12 h), $(CH_2O)_n$ (5 h), $NaBH_3CN$ (12 h), MeOH, rt than H_2, Pd–C (10%), EtOH, 20 h, rt; (ii) CH_3CHO, $NaBH_3CN$, EtOH.

The properties of the derivatives prepared are recorded in Scheme 4. The results are in agreement with the previously presented data (Table 1). Only slight racemization was observed during base-induced alkylation of valine (95% enantiomeric purity), while alanine derivatives showed no racemization as verified by the specific rotation method. However, the prepared sample of *N*-ethyl-*N*-methyl-phenylalanine was found to be partially racemized. It is known that phenylalanine derivatives are more susceptible to the base-catalyzed racemization than most other amino acids.[9]

3. Conclusions

Herein, we have presented an insight into the simple preparation of some unsymmetrically protected di-*N*-alkyl amino acids with free carboxylic functions by way of the alkylation of benzyloxycarbamoyl derivatives and a one-pot, one-catalyst deprotection–protection sequence. The procedures are simple, practical, and scalable. The racemization of Cbz-amino acids during base-induced N-alkylation has also been investigated. The obtained methyl, ethyl, and butyl derivatives of alanine do not show any detectable racemization. The purification of the products requires only routine manipulations and chromatographical purification can be omitted in most cases.

4. Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under Ar before use. Solvents were dried according to the standard procedures. All organic solutions were dried over Na_2SO_4. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica (Merck). Plates were visualized using UV light (254 nm) and 10% ethanolic ninhydrine solution. Reaction products were purified by flash chromatography using Silica Gel 60 (240–400 mesh). (Merck). Optical rotations were measured with a JASCO Dip-360 Digital Polarimeter at room temperature. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in gram per 100 mL. ^{1}H NMR spectra were recorded on Varian-200 or Varian-400 spectrometers in CD_3OD or $CDCl_3$ with Me_4Si as the internal standard. High resolution mass spectra were taken on a Mariner PerSeptive Biosystems mass spectrometer with a time-of-flight (TOF) detector. IR spectra were taken with a Perkin Elmer FT-IR-1600 spectrophotometer as either a thin film on NaCl plates

(film), as a KBr disc (KBr), or chloroform solutions in 0.1 mm cells ($CHCl_3$), as stated.

4.1. General procedure for the synthesis of *N*-ethyl-*N*-methyl amino acids

N-Carbobenzoxy amino acid (223 mg, 1 mmol, Fluka) was dissolved in THF (5 mL). Ethyl iodide (0.65 mL, 8 mmol) was added and the mixture was cooled to 0 °C. Sodium hydride (144 mg, 50% suspension in mineral oil, 3 mmol) was slowly added. The cooling bath was removed, and the reaction mixture was heated to 60 °C. The temperature was maintained for 12–48 h (see Schemes 1 and 2). Excess of sodium hydride was destroyed with water and the resulting suspension was extracted with EtOAc (3 × 10 mL). The aqueous fraction was then acidified with citric acid solution to pH 4 and extracted with EtOAc (3 × 10 mL). The organic fraction was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give *N*-carbobenzoxy-*N*-ethyl amino acid which was subjected to further step without purification.

The *N*-carbobenzoxy-*N*-ethyl amino acid was dissolved in ethanol–water (1:1, 2 mL). Formaline (2 equiv) and Pd (1 weight equiv, 10% on activated charcoal, Fluka) were added and the solution was vigorously stirred under H_2 atmosphere (balloon) for 20 h. Filtration through Celite and concentration in vacuo afforded the *N*-ethyl-*N*-methyl amino acid in an analytically pure form.

The known *N*-alkyl amino acids **2a** (97%),[13] **3a** (94%),[5] **4a** (91%),[14] **5a** (89%),[15] **6a** (95%),[13] **10a** (92%),[16] **11a** (83% after chromatography),[4] and **12a** (80% after chromatography)[4] were prepared according to the general procedure (deprotection of Cbz was performed without formaldehyde additive).

4.2. *N*-Ethyl-*N*-methyl-L-alanine 3b

By using the general procedure described above, **3b** was obtained from L-alanine in 95% yield and 100% ee. $[\alpha]_D^{19.8} = +5.0$ (*c* 0.5, EtOH). Mp 128–131 °C. IR (KBr): 3413, 3058, 2992, 2886, 2740, 1622, 1458, 1399, 1370 cm^{-1}. ^1H NMR (CD_3OD, 200 MHz): 1.44 (t, 3H, $J = 7.4$ Hz), 1.56 (d, 3H, $J = 7.0$ Hz), 2.89 (s, 3H), 3.26 (qd, 2H, $J = 8.0$, 2.4 Hz), 3.77 (q, 1H, $J = 7.0$ Hz). ^{13}C NMR (CD_3OD, 50 MHz): 11.8, 14.4, 39.3, 52.2, 67.4, 175.3. HRMS (EI): calcd for $C_6H_{13}NO_2$, M^+: 131.0946. Experimental: 131.0951.

4.3. *N*-Methyl-*N*-propyl-L-alanine 4b

By using the general procedure described above, **4b** was obtained from L-alanine in 90% yield and 99% ee. $[\alpha]_D^{20.3} = +3.2$ (*c* 1, EtOH). Mp 136–139 °C. IR (KBr): 3418, 3048, 2973, 2882, 2721, 1623, 1461, 1399, 1365 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 1.00 (t, 3H, $J = 7.5$ Hz), 1.47 (d, 3H, $J = 7.3$ Hz), 1.70–1.80 (m, 2H), 2.79 (s, 3H), 2.96–3.08 (m, 2H), 3.67 (q, 1H, $J = 7.3$ Hz). ^{13}C NMR (CD_3OD, 100 MHz): 11.2, 12.5, 19.2, 38.3, 66.4. 97.3, 173.4. HRMS (EI): calcd for $C_7H_{15}NO_2$, M^+: 145.1102. Experimental: 145.1098.

4.4. *N*-Butyl-*N*-methyl-L-alanine 5b

By using the general procedure described above, **5b** was obtained from L-alanine in 88% yield and 55% ee. $[\alpha]_D^{19.8} = +3.2$ (*c* 0.50, EtOH). Mp 115–117 °C. IR (KBr): 3427, 3043, 2963, 2940, 2875, 2723, 1624, 1466, 1398, 1366 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 0.98 (t, 3H, $J = 7.3$ Hz), 1.41 (q, 2H, $J = 7.7$ Hz), 1.47 (d, 3H, $J = 7.2$ Hz), 1.67–1.75 (m, 2H), 2.79 (s, 3H), 2.97–3.12 (m, 2H), 3.66 (q, 1H, $J = 7.2$ Hz). ^{13}C NMR (CD_3OD, 100 MHz): 12.6, 13.94, 20.9, 27.8, 38.3, 66.4, 97.2, 173.4. HRMS (EI): calcd for $C_8H_{17}NO_2$, M^+: 159.1259. Experimental: 159.1264.

4.5. *N*-Ethyl-*N*-methyl-D-alanine 6b

By using the general procedure described above, **6b** was obtained from D-alanine in 95% yield and 100% ee. $[\alpha]_D^{17.5} = -5.0$ (*c* 0.28, EtOH). Mp 128–131 °C. IR (KBr): 3413, 3058, 2992, 2886, 2740, 1622, 1458, 1399, 1370 cm^{-1}. ^1H NMR (CD_3OD, 200 MHz): 1.44 (t, 3H, $J = 7.4$ Hz), 1.56 (d, 3H, $J = 7.0$ Hz), 2.89 (s, 3H), 3.26 (qd, 2H, $J = 8.0$, 2.4 Hz), 3.77 (q, 1H, $J = 7.0$ Hz). ^{13}C NMR (CD_3OD, 50 MHz): 11.8, 14.4, 39.3, 52.2, 67.4, 175.3. HRMS (EI): calcd for $C_6H_{13}NO_2$, M^+: 131.0946. Experimental: 131.0951.

4.6. *N*-Ethyl-*N*-methyl-glycine 10b

By using the general procedure described above, **10b** was obtained from glycine in 100% yield. Mp 115–117 °C. IR (KBr): 3414, 3056, 2986, 2879, 2842, 1629, 1472, 1402, 1325 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 1.28 (t, 3H, $J = 7.3$ Hz), 2.77 (s, 3H), 3.09 (q, 2H, $J = 7.3$ Hz), 3.49 (s, 2H). ^{13}C NMR (CD_3OD, 100 MHz): 10.2, 41.4, 52.8, 59.7, 171.4. HRMS (EI): calcd for $C_5H_{11}NO_2$, M^+: 117.0790. Experimental: 117.0792.

4.7. *N*-Ethyl-*N*-methyl-L-valine 11b

By using the general procedure described above, **11b** was obtained from L-valine in 80% yield and 95% ee. $[\alpha]_D^{19.5} = +16.7$ (*c* 0.10, EtOH). Mp 127–128 °C. IR ($CHCl_3$): 3401, 2970, 1617, 1467, 1384, 1332 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 1.00 (d, 3H, $J = 6.8$ Hz), 1.13 (d, 3H, $J = 6.8$ Hz), 1.30 (t, 3H, $J = 7.3$ Hz), 2.21–2.31 (m, 1H), 2.76 (s, 3H), 3.05–3.40 (m, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 9.7, 17.5, 20.9, 27.4, 76.1, 174.3. HRMS (EI): calcd for $C_8H_{17}NO_2$, M^+: 159.1259. Experimental: 159.1253.

4.8. *N*-Ethyl-*N*-methyl-L-phenylalanine 12b

By using the general procedure described above, **12b** was obtained from L-phenylalanine in 85% yield and 50% ee. $[\alpha]_D^{19.8} = +12.6$ (*c* 1.00, EtOH). Mp 165–168 °C. IR (KBr): 3448, 3062, 3029, 2982, 2960, 2299, 1628, 1354, 1271 cm^{-1}. ^1H NMR (CD_3OD, 200 MHz): 1.35 (t, 3H, $J = 7.3$ Hz), 2.86 (s, 3H), 3.15–3.40 (m, 4H), 3.96 (t, 1H, $J = 6.8$ Hz), 7.30–7.50 (m, 5H). ^{13}C NMR (CD_3OD): 11.0, 35.8, 39.4, 52.2, 72.3, 128.9, 130.1, 131.1, 139.0,

173.0. HRMS (EI): calcd for $C_{12}H_{17}NO_2$, M^+: 207.1259. Experimental: 207.1268.

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