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# Amidation of carboxylic acids via the mixed carbonic carboxylic anhydrides and its application to synthesis of antidepressant (1*S*,2*R*)-tranylcypromine

Tetsuya Ezawa, Yuya Kawashima, Takuya Noguchi, Seunghee Jung, Nobuyuki Imai\*

Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

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#### ABSTRACT

Primary amidations of carboxylic acids **1** or **3** with  $NH_4Cl$  in the presence of  $ClCO_2Et$  and  $Et_3N$  were developed to afford the corresponding primary amides in 22% to quantitative yields. Additionally, we have applied the amidation to the preparation of various amides containing hydroxamic acids and achieved the synthesis of (1*S*,2*R*)-tranylcypromine as an antidepressant medicine via Lossen rearrangement. © 2017 Elsevier Ltd. All rights reserved.

#### 1. Introduction

The amide group is one of the most important functional groups in organic chemistry. It is widely found in various compounds such as proteins, bioactive substances, drugs, and agrochemicals.<sup>1</sup> Therefore, development of convenient amidations has been a challenging subject in organic chemistry. Direct amidations of carboxylic acids with amines involving dehydration proceeds at high temperatures, but the conditions are not suitable for most functional molecules.<sup>2</sup> Generally, amides are prepared by reactions of activated carboxylic acids, such as acyl halides, acyl imidazole, mixed anhydrides, and esters with amines or by reductions of acyl azides and hydrazides.<sup>3</sup> The reagents, such as thionyl chloride,<sup>4</sup> (DCC),<sup>4d,4e</sup> chloride,<sup>4b,4c</sup> dicyclohexylcarbodiimide oxalyl diphenylphosphoryl azide (DPPA),4f carbonyldiimidazole (CDI),4g alkyl chloroformate,<sup>4h</sup> 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4methylmorpholinium chloride (DMT-MM),<sup>4i,4j</sup> and *N*-[1-(cyano-2ethoxy-2-oxoethylidenaminooxy)dimethylamino(morpholino)] uronium hexafluorophosphate (COMU)<sup>4k</sup> have often been used for activation of carboxylic acids. However, it has mainly been reported that secondary and tertiary amides are prepared using these reagents. The synthesis of primary amide is limited due to disadvantages of using ammonia such as low nucleophilicity, toxicity, and gas under ordinary conditions. On the other hand, ammonium chloride is very useful as an ammonia source

\* Corresponding author. Tel.: +81 479 30 4610. *E-mail address: nimai@cis.ac.jp* (N. Imai).

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because it is easy to handle, inexpensive, and safe. Nezhad et al. have reported the efficient primary amidation of carboxylic acids activated by tosyl chloride (TsCl) and 4.0 equiv of silicasupported ammonium chloride.<sup>5</sup> Bhanage et al. achieved the amidation of tert-butyl peroxybenzoate (TBPB) with ammonia to afford the corresponding primary amide with a stoichiometric amount of *tert*-butyl hydroperoxide as the by-product.<sup>6</sup> Furthermore, the hydration of nitriles in the presence of acids,<sup>7a-c</sup> bases,<sup>7d,7e</sup> the transition metal7f-h and the rearrangement of oximes using transition metal catalysts<sup>8</sup> have been developed as preparations for primary amides. Recently, interesting synthetic methods such as direct transformations of ethylarenes,<sup>9</sup> methyl ketones,<sup>10</sup> carbinols<sup>10</sup> via tandem Lieben-Haller-Bauer reactions, aminocarbonylations of aryl halides with NH<sub>4</sub>Cl and Co<sub>2</sub>(CO)<sub>8</sub> as a carbonyl source,<sup>11</sup> and amidations of ester using magnesium nitride (Mg<sub>3</sub>N<sub>2</sub>) as an ammonia source<sup>12</sup> have also been reported. Excess amounts of ammonia source, high temperatures, toxic reagents such as transition metals, and/or complicated procedures are required for the synthesis of primary amides.

Recently, we reported the synthesis of primary amides from general carboxylic acids, *N*-protected  $\alpha$ -amino acids, and *N*-protected dipeptides via the mixed carbonic carboxylic anhydrides.<sup>13</sup> Herein, we describe in detail the synthesis of various amides from carboxylic acids with ammonium chlorides and amines in the presence of water (Scheme 1). Our method is convenient and green because of inexpensive reagents, mild conditions, and safe by-products, such as triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols. Furthermore, its application to the synthesis of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **9** via Lossen rearrangement is also reported.





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Scheme 1. Amidation via the mixed carbonic carboxylic anhydrides.

#### 2. Results and discussion

In a preliminary investigation, we optimized the conditions of an ammonia source (NH<sub>3</sub>, NH<sub>4</sub>OH, NH<sub>4</sub>Cl, and MeCO<sub>2</sub>NH<sub>4</sub>), and the results are shown in Table 1. Primary amidation with NH<sub>3</sub>/ MeOH and NH<sub>4</sub>OH/H<sub>2</sub>O via the mixed carbonic carboxylic anhydride in tetrahydrofuran (THF) afforded 3-phenylpropanamide **2a** in good yields (entries 1 and 2). Excellent yields were obtained by the reactions of **1a** with NH<sub>4</sub>Cl and MeCO<sub>2</sub>NH<sub>4</sub> (entries 3 and 4). On the basis of these results, cost, and safety, we selected NH<sub>4</sub>-Cl as the optimal ammonia source.

The results of the primary amidation of several types of carboxylic acids 1a-10 with NH<sub>4</sub>Cl in the presence of ClCO<sub>2</sub>Et and Et<sub>3</sub>N are collected in Table 2. The reaction of cinnamic acid **1b** as a conjugated carboxylic acid afforded the corresponding primary amides 2b in 79% yield (entry 2). 4-Methoxycinnamic acid 1c containing an electron donating group reacted with NH<sub>4</sub>Cl to give the corresponding primary amide 2c in 33% yield (entry 3). The reaction of pivalic acid **1d** proceeded easily to afford the corresponding primary amide **2d** in excellent yield despite a bulky *tert*-butyl group on 1d (entry 4). Although benzamide 2e, 4-nitrobenzamide **2f**, and acetylsalicylamide **2g** were synthesized from benzoic acid 1e, 4-nitrobenzoic acid 1f, and acetylsalicylic acid 1g in 64%, 92%, and 56% yields, respectively (entries 5-7), the yield of 4-methoxybenzamide **2h** was low (entry 8). It is suggested that the carbonyl carbon on the mixed carbonic anhydride of 4-methoxybenzoic acid **1h** is deactivated by the strong electron donating effect of the methoxy group on the aromatic ring. The amidation of **1h** with NH<sub>4</sub>Cl via activation by ClCO<sub>2</sub>*i*-Bu was carried out to afford the corresponding amide 2h in 22% yield (entry 8). The reactions of heteroaromatic carboxylic acid 1i-10 with NH<sub>4</sub>Cl were also examined. Picolinic acid 1i, nicotinic acid 1j, and isonicotinic acid 1k were converted into the corresponding primary amides 2i-2k in 97%, 84%, and 95% yields, respectively. The low electron density of the pyridine ring contributes to these excellent yields (enrties 9–11). The primary amides **2l-2o** were prepared from the corresponding carboxylic acids **11-10** containing electron-rich heteroaromatic rings in moderate yields due to the increasing elec-

#### Table 1

Primary amidation of 3-phenylpropanoic acid 1a<sup>a</sup>

Ph OH 1a	1) CICO <sub>2</sub> Et, Et <sub>3</sub> N, THF, 0 <sup>o</sup> C, 30 min 2) ammonia source, 0 <sup>o</sup> C, 30 min	Ph NH <sub>2</sub>
Entry	Ammonia source	Yield <sup>e</sup> /%
1	NH <sub>3</sub> /MeOH <sup>b</sup>	85
2	NH <sub>4</sub> OH/H <sub>2</sub> O <sup>c</sup>	85
3	NH <sub>4</sub> Cl/H <sub>2</sub> O <sup>d</sup>	96
4	$MeCO_2NH_4/H_2O^d$	97

<sup>a</sup> All reactions were carried out with 0.50 mmol of 1a, 0.70 mmol of CICO<sub>2</sub>Et, 1.5 mmol of Et<sub>3</sub>N, and 0.75 mmol of ammonia source.

<sup>b</sup> 2.0 mol/L solution in MeOH was used.

<sup>c</sup> 28% aqueous solution was used.

<sup>d</sup> 1.0 M aqueous solution was used.

e Isolated yield.

tron density of the carbonyl carbons. (entries 12–15). Katritzky et al. reported the amidation of carboxylic acid activated by 1-(methanesulfonyl)benzotriazole and Et<sub>3</sub>N with ammonium hydroxide, in which the primary amides **2f** and **2i-2l** were obtained in quantitative yields.<sup>3b</sup> Moreover, the syntheses of the primary amides **2a**, **2b**, **2d**, **2e**, and **2h** via the activation of carboxylic acids with DMT-MM were achieved in excellent yields by Kunishima et al.<sup>4j</sup> The yields of the primary amides **2a**, **2b**, **2d**, **2f**, and **2l**. It is suggested that the electron density of the expected active carbonyl groups is similar to that of the ethoxycarbonyl group on the corresponding mixed carbonic carboxylic anhydrides in the cases of entries 3, 5, 7, 8, and 12–15.

Next, we synthesized the primary amides 4a-4n from the corresponding *N*-protected  $\alpha$ -amino acids **3a-3n** without racemization under the optimized conditions and these results are shown in Table 3. First, we checked the effect of protecting groups such as carboxybenzyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), and tert-butoxycarbonyl (Boc). The mixed carbonic carboxylic anhydrides of Cbz-L-Phe-OH 3a, Fmoc-L-Phe-OH 3b, and Boc-L-Phe-OH **3c** reacted with NH<sub>4</sub>Cl to give the corresponding primary amides 4a, 4b, and 4c in excellent yields, and no racemization was observed (entries 1–3). The primary amide 4d was prepared from Cbz-L-Val-OH 3d in 93% (entry 4). The reactions of Fmoc-L-Val-OH 3e and Boc-L-Val-OH 3f afforded the corresponding primary amides 4e and 4f in 98% and 98% yields with >99% ee under the conditions, respectively (entries 5 and 6). Furthermore, 4g-4i were obtained in excellent yields by the reactions of Cbz-L-Met-OH 3g, Fmoc-L-Met-OH 3h, and Boc-L-Met-OH 3i containing a sulfide group (entries 7-9). Cbz-L-Ala-OH 3j was converted to the corresponding primary amide 4j in good yield with >99% (entry 10). The amidation of Cbz-L-Gln-OH 3k with NH4Cl under the conditions gave the corresponding primary amide 4k in 74% yield, but the enantiomeric excess of 4k was not determined by HPLC analysis because of the low solubility of **4k** in the eluent (entry 11). The low solubility of **3k** possessing the hydrophilic side chain in THF gave a lower yield of **4k** compared to the other primary amides. Cbz-L-Leu-NH<sub>2</sub> **4l** as a branched  $\alpha$ -amino acid was synthesized from Cbz-L-Leu-OH **3I** in good yield and with >99% ee (entry 12). The yield of the primary amide **4m** was slightly lower due to the bulky side chain (entry 13). Boc-O-Bn-L-Ser-OH 3n containing a hydrophilic side chain was condensed with NH<sub>4</sub>Cl via the mixed carbonic carboxylic anhydride to afford the corresponding primary amide 4n in 87% yield, and no racemization was observed in the reaction (entry 14). The results of the primary amidation of  $D-\alpha$ amino acids 3a'-3n' with NH<sub>4</sub>Cl were similar to those of the corresponding L-forms (see Experimental).

Hydroxamic acid is an important building block for many organic compounds. It is generally used as a starting material for preparation of amines, ureas, and carbamates via Lossen rearrangement. For the preparation of hydroxamic acids, there are a variety of reported reactions of carboxylic acids with toxic hydroxylamines using alkyl chloroformate,<sup>14</sup> with hydroxylamine hydrochlorides in the presence of expensive coupling reagents such as 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT)<sup>15</sup> and ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY),<sup>16</sup>

#### Table 2

Primary amidation of carboxylic acids **1a-10** with ammonium chloride<sup>a</sup>

$\begin{array}{c} 0 \\ \hline 1 \end{array} \begin{array}{c} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 $					
R 0 1a-1o	R 2:	NH <sub>2</sub> a-2o			
Entry	Primary amide <b>2</b>		Yield <sup>b</sup> /%		
1	NH <sub>2</sub>	2a	96		
2	NH <sub>2</sub>	2b	79		
3	MeO NH2	2c	33		
4	NH <sub>2</sub>	2d	87		
5	NH <sub>2</sub>	2e	64		
6	O <sub>2</sub> N NH <sub>2</sub>	2f	92		
7	O NH <sub>2</sub> OAc	2g	56		
8	MeO NH <sub>2</sub>	2h	25 (22) <sup>c</sup>		
9	NH <sub>2</sub>	2i	97		
10	NH <sub>2</sub>	2j	84		
11	NH <sub>2</sub>	2k	95		
12	NH <sub>2</sub>	21	59		
13	NH <sub>2</sub>	2m	45		
14	NH <sub>2</sub>	2n	42		

Table 2 (continued)



 $^a$  All reactions were carried out with 0.50 mmol of 1, 0.70 mmol of ClCo\_2Et, 1.5 mmol of Et\_3N, and 0.75 mmol of a 1.0 M aqueous solution of NH\_4Cl.

<sup>b</sup> Isolated yield.

<sup>c</sup> ClCO<sub>2</sub>*i*-Bu was used instead of ClCO<sub>2</sub>Et.

and so on.<sup>17</sup> Tranylcypromine containing a cyclopropylamine skeleton is well known as a monoamine oxidase (MAO) inhibitor and has been used as an antidepressant medicine. The first synthesis and biological activity were reported by Burger et al.<sup>18</sup> and the mechanism of MAO for inhibition has also been elucidated Silverman et al.<sup>19</sup> We have recently reported synthesis of tranylcypromine via catalytic enantioselective cyclopropanation in the presence of chiral ligand derived from L-phenylalanine in five steps.<sup>20,21</sup> This synthetic method has several disadvantages such the use of toxic, expensive, excessive reagents, and harsh conditions.

Therefore, we applied the amidation using mixed carbonic carboxylic anhydride to the synthesis of (1S,2R)-N-Cbz-tranylcypromine 9. We examined the amidation of Cbz-L-Phe-OH 3a with various amine hydrochlorides **5a-5h** for the preparation of *N*-hydroxy-2,3-methano-3-phenylpropanamide **8** and the results are indicated in Table 4. Ethylamine hydrochloride 5a and 2phenethylamine hydrochloride 5b reacted with 3a to afford the corresponding secondary amide **6aa** and **6ab** in good yields (entries 1 and 2). The secondary amide **6ac** was synthesized from 3a using cyclohexylamine hydrochloride 5c in 84% yield (entry 3). The amidation of **3a** with 1-adamantanamine hydrochloride **5d** effectively proceeded to afford the corresponding secondary amide **6ad** in 87% yield despite sterically hindered primary amine (entry 4). Dimethylamine hydrochloride **5e**, diethylamine hydrochloride 5f, and piperidine hydrochloride 5g as a secondary amine were also examined. The amine hydrochlorides 5e, 5f, and 5g worked as good nucleophiles under the conditions to give the corresponding tertiary amides **6ae**, **6af**, and **6ag** in 85%, 72%, and 84% yields, respectively (entries 5, 6, and 7). The hydroxamic acid 6ah was synthesized by the reaction of 3a with hydroxylamine hydrochloride **5h** in moderate yield (entry 8).

Finally, we optimized the reaction conditions for the amidation of (2S,3S)-(+)-2,3-methano-3-phenylpropanoic acid 7 prepared via two oxidations from (2S,3S)-(+)-2,3-methano-3-phenylpropanol<sup>20</sup> with hydroxylamine hydrochloride 5h and for the Lossen rearrangement of (2S,3S)-(+)-2,3-methano-3-phenylpropyryl hydroxamic acid 8. The reactions of carboxylic acids to amines, which are well known as Hofmann,<sup>22</sup> Curtius,<sup>23</sup> Schmidt,<sup>24</sup> and Lossen<sup>25</sup> rearrangements, have been widely used for syntheses of various organic compounds. The main disadvantages of the Hofmann rearrangement are the use of a strong base and toxic bromine at high temperature. It is necessary to use explosive azide for Curtius and Schmidt rearrangements. On the other hand, the reaction conditions of the Lossen rearrangement are milder than those of the other rearrangements. As a result, (25,35)-(+)-8 was obtained in 82% yield by the amidation of (2S,3S)-(+)-7 with 5h under the optimized conditions, followed by Lossen rearrangement of (2S,3S)-(+)-

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#### Table 3

Synthesis of the primary amides derived from *N*-protected  $\alpha$ -amino acids **3a-3n**<sup>a</sup>



Entry	Primary amide <b>4</b>		Yield <sup>b</sup> /%	% ee <sup>c</sup>
1	Cbz-L-Phe-NH <sub>2</sub>	4a	87	97
2	Fmoc-L-Phe-NH <sub>2</sub>	4b	96	>99
3	Boc-L-Phe-NH <sub>2</sub>	4c	Quant.	>99
4	Cbz-L-Val-NH <sub>2</sub>	4d	93	>99
5	Fmoc-L-Vla-NH <sub>2</sub>	4e	98	>99
6	Boc-L-Val-NH <sub>2</sub>	4f	98	>99
7	Cbz-L-Met-NH <sub>2</sub>	4g	92	>99
8	Fmoc-L-Met-NH <sub>2</sub>	4h	Quant.	>99
9	Boc-L-Met-NH <sub>2</sub>	4i	98	>99
10	Cbz-L-Ala-NH <sub>2</sub>	4j	79	>99
11	Cbz-L-Gln-NH <sub>2</sub>	4k	74	-
12	Cbz-L-Leu-NH <sub>2</sub>	41	86	>99
13	Cbz-L-Trp-NH <sub>2</sub>	4m	82	>99
14	Boc-O-Bn-L-Ser-NH <sub>2</sub>	4n	87	>99

<sup>a</sup> All reactions were carried out with 0.50 mmol of 3, 0.70 mmol of CICO<sub>2</sub>Et, 1.5 mmol of Et<sub>3</sub>N, and 0.75 mmol of a 1.0 M aqueous solution of NH<sub>4</sub>Cl.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis with a mixture of hexane-isopropanol as an eluent using Chiralcel (1.0 mL/min).

#### Table 4

Amidation of Cbz-L-Phe-OH 3a with primary or secondary amine hydrochlorides 5a-5h<sup>a</sup>



<sup>a</sup> All reactions were carried out with 0.50 mmol of **3a**, 0.70 mmol of ClCO<sub>2</sub>Et, 1.5 mmol of Et<sub>3</sub>N, and 0.75 mmol of a 1.0 M aqueous solution of amine hydrochlorides **5**. <sup>b</sup> Isolated yield.

**8** under Miller's conditions<sup>25g</sup> to afford (1S,2R)-(+)-N-Cbztranylcypromine 9 in 87% yield (Scheme 2). We also tried to prepare (1S,2R)-(+)-9 under the following conditions, but failed. Methanesulfonyl chloride (MsCl), p-toluenesulfonyl chloride (TsCl), and carbonyldiimidazole (CDI) were used instead of 4-NsCl, but no better results were observed. The addition of t-BuOH instead of BnOH to the isocyanate intermediate did not work well because of steric hindrance. The enantiomeric excess of (1S,2R)-(+)-9 could not be determined by HPLC analysis using general Chiralcels. Therefore, (1S,2R)-(+)-9 was deprotected under acidic conditions, followed by acetylation to afford (1S,2R)-(+)-*N*-acetyltranylcypromine **10** in quantitative yield and with 82% ee, which was determined by HPLC analysis using Chiralcel OD as indicated in Scheme 2.

#### 3. Conclusions

We have synthesized the primary amides 2a-2o in 22-97% yields from the corresponding carboxylic acids 1a-10 with NH<sub>4</sub>Cl under mild conditions. We have also succeeded in the preparation of primary amides **4a-4n** by the reactions of *N*-protected  $\alpha$ -amino acids **3a-3n** with NH<sub>4</sub>Cl in 74%-quantitative yields and with 97%->99% ee. Furthermore, the application to the synthesis of (1S,2R)-(+)-*N*-Cbz-tranylcypromine **9** via Lossen rearrangement have been also achieved in 71% overall yield and with 82% ee in three steps from (2S,3S)-(+)-7.

#### 4. Experimental

#### 4.1. General

All reagents were used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured with a Bruker UltrashieldTM 400 Plus (400 MHz) spectrometer. The chemical shifts of <sup>1</sup>H NMR spectra are expressed in parts per million downfield from tetramethylsilane ( $\delta = 0.00$ ) in MeOD- $d^4$  or dimethyl sulfoxide- $d^6$  ( $\delta =$ 2.50) as an internal standard. <sup>13</sup>C NMR spectra were calibrated with tetramethylsilane ( $\delta = 0.00$ ) in MeOD- $d^4$  or dimethyl sulfoxide- $d^6$  ( $\delta$  = 39.5). Chemical shifts ( $\delta$ ) are reported in ppm, and

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Scheme 2. Preparation of (1S,2R)-(+)-N-Cbz-tranylcypromine 9 via Lossen rearrangement.

spin-spin coupling constants (1) are given in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), g (guartet), m (multiplet), and br (broad). The high-resolution mass spectra (HRMS) of the compounds with a high molecular weight were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. Reactions were monitored using thinlayer chromatography with silica gel 60 F<sub>254</sub>. Purification of the products was carried out by column chromatography using silica gel (64-210 mesh). Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at room temperature. Infrared (IR) spectra were recorded on HORIBA FT-IR Fourier transform infrared spectrophotometer.

#### 4.2. Typical procedure for the primary amidation of 3phenylpropanoic acid 1a with NH<sub>4</sub>Cl

To a colorless solution of 75 mg (0.50 mmol) of 3-phenylpropanoic acid 1a in 10 mL of THF were added at 0 °C 67 µL (0.70 mmol, 1.4 equiv) of ClCO<sub>2</sub>Et and 209  $\mu$ L (1.5 mmol, 3.0 equiv) of Et<sub>3</sub>N. After stirring for 30 min at 0 °C, 0.75 ml of a 1.0 M aqueous solution of NH<sub>4</sub>Cl (0.75 mmol, 1.5 equiv) was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and 5 mL of H<sub>2</sub>O was added to the resulted mixture. The colorless clear solution was extracted with 30 mL of EtOAc and the aqueous layer was extracted with 20 mL of EtOAc. The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous MgSO<sub>4</sub>. The crude product was chromatographed on silica gel with EtOAc to afford 72 mg (96% yield) of 3-phenylpropanamide 2a.

#### 4.2.1. 3-Phenylpropanamide 2a

72 mg (96%); colorless solid; mp: 92-95 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.54 (t, J = 8.0 Hz, 2H, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 2.98 (t, J = 8.0 Hz, 2H, CH<sub>2</sub>CO), 5.29 (brs, 2H, NH<sub>2</sub>), 7.20-7.23, 7.26-7.32 (m, m, 3H, 2H,  $C_6H_5$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  31.4, 37.5, 126.3, 128.3, 128.6, 140.8, 174.6; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3394 (CONH), 3186 (CONH), 1646 (CON), 1628 (CON); HRMS (ESI-TOF): Calcd for C<sub>9</sub>H<sub>11</sub>NONa (M+Na)<sup>+</sup>: 172.0733, found: 172.0711.

#### 4.2.2. Cinnamamide 2b

58 mg (79%); colorless powder; mp: 140–142 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.52 (brs, 2H, NH<sub>2</sub>), 6.46 (d, J = 15.7 Hz, 1H, CHCO), 7.37–7.40, 7.51–7.54 (m, m, 3H, 2H, C<sub>6</sub>H<sub>5</sub>), 7.66 (d, J = 15.7 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 119.7, 128.1, 129.0, 130.1, 134.6, 142.6, 167.8; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3373 (CONH), 3168 (CONH), 1662 (CON); HRMS (ESI-TOF): Calcd for C9H9NONa (M+Na)<sup>+</sup>: 170.0576, found: 170.0556.

#### 4.2.3. 4-Methoxycinnamamide 2c

30 mg (33%); colorless powder; mp: 198–201 °C; <sup>1</sup>H NMR (400 MHz, MeOD- $d^4$ ):  $\delta$  3.82 (s, 3H, CH<sub>3</sub>), 6.49 (d, I = 15.9 Hz, 1H, CHCO), 7.50 (d, J = 15.9 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>), 6.94, 7.51 (d, d, J = 8.7, 8.7 Hz, 2H, 2H, C<sub>6</sub>H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, MeOD- $d^4$ ):  $\delta$  55.9, 115.4, 118.8, 128.8, 130.6, 142.6, 162.7, 171.5; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3361 (CONH), 3166 (CONH), 1684 (CON), 1662 (CON); HRMS (ESI-TOF): Calcd for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>Na (M+Na)<sup>+</sup>: 200.0682, found: 200.0673.

#### 4.2.4. Pivalamide 2d

44 mg (87%); colorless solid; mp: 105–108 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.23 (s, 9H, CH<sub>3</sub> ×3), 5.21 (br, 1H, NH<sub>A</sub>), 5.59 (br, 1H, NH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 27.7, 38.7, 181.6; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3398 (CONH), 3205 (CONH), 2960 (CH<sub>3</sub>), 1653 (CON), 1624 (CON); HRMS (ESI-TOF): Calcd for C<sub>5</sub>H<sub>11</sub>NONa (M+Na)<sup>+</sup>: 124.0733, found: 124.0723

#### 4.2.5. Benzamide 2e

39 mg (64%); colorless powder; mp: 109–110 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.67 (br, 1H, NH<sub>A</sub>), 6.08 (br, 1H, NH<sub>B</sub>), 7.44–7.49, 7.52–7.57, 7.81–7.84 (m, m, m, 2H, 1H, 2H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 127.4, 128.6, 132.0, 133.4, 169.4; IR (KBr,  $v_{\text{max}}/\text{cm}^{-1}$ ) = 3367 (CONH), 3170 (CONH), 1658 (CON), 1623 (CON); HRMS (ESI-TOF): Calcd for C<sub>7</sub>H<sub>7</sub>NONa (M+Na)<sup>+</sup>: 144.0420, found: 144.0411.

#### 4.2.6. 4-Nitrobenzamide 2f

76 mg (92%); colorless powder; mp: 202–204 °C; <sup>1</sup>H NMR (400 MHz, MeOD- $d^4$ ):  $\delta$  8.07, 8.32 (d, d, J = 9.0, 9.0 Hz, 2H, 2H, C<sub>6</sub>H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, MeOD-d<sup>4</sup>): δ 124.6, 130.0, 140.9, 151.2, 170.2; IR  $(\text{KBr}, v_{\text{max}}/\text{cm}^{-1}) = 3467$  (CONH), 1664 (CON), 1602 (CON), 1525 (NO<sub>2</sub>), 1342 (NO<sub>2</sub>); HRMS (ESI-TOF): Calcd for C<sub>7</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 189.0271, found: 189.0280.

#### 4.2.7. 2-Acetoxybenzamide 2g

50 mg (56%); colorless powder; mp: 130–132 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.36 (s, 3H, CH<sub>3</sub>), 5.75 (br, 1H, NH<sub>A</sub>), 6.27 (br, 1H, NH<sub>B</sub>), 7.13, 7.31–7.35, 7.49–7.53, 7.85 (d, m, m, d, J = 9.2, 7.7 Hz, 1H, 1H, 1H, 1H, C<sub>6</sub>H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 21.2, 123.3, 126.3, 127.2, 130.1, 132.4, 148.2, 167.5, 169.1; IR (KBr,  $v_{\text{max}}/\text{cm}^{-1}$ ) = 3392 (CONH), 3167 (CONH), 1741 (CO<sub>2</sub>), 1678 (CON), 1628 (CON); HRMS (ESI-TOF): Calcd for C9H9NO3Na (M+Na)<sup>+</sup>: 202.0475, found: 202.0496.

#### 4.2.8. 4-Metoxybenzamide 2h

19 mg (25%); coloress solid; mp: 139–142 °C; <sup>1</sup>H NMR (400 MHz, MeOD- $d^4$ ):  $\delta$  3.86 (s, 3H, CH<sub>3</sub>), 6.97, 7.84 (d, d, J = 9.0, 9.0

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Hz, 2H, 2H, C<sub>6</sub>H<sub>4</sub>); <sup>13</sup>C NMR (100 MHz, MeOD- $d^4$ ): δ 56.0, 114.7, 127.0, 130.7, 164.2, 172.1; IR (KBr,  $v_{max}/cm^{-1}$ ): 3392 (CONH), 3168 (CONH), 1646 (CON), 1618 (CON); HRMS (ESI-TOF): Calcd for C<sub>9</sub>H<sub>9</sub>NO<sub>3</sub>Na (M+Na)<sup>+</sup>: 202.0475, found: 202.0496.

#### 4.2.9. Picolinamide 2i

59 mg (97%); colorless solid; mp: 95–97 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.55 (br, 1H, NH<sub>A</sub>), 7.44–7.48, 7.85–7.89, 8.20–8.23, 8.57–8.59 (m, m, m, m, 1H, 2H, 1H, 1H, pyridyl, NH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  122.4, 126.5, 137.3, 148.3, 149.6, 167.0; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3417 (CONH), 3182 (CONH), 1662 (CON); HRMS (ESI-TOF): Calcd for C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>ONa (M+Na)<sup>+</sup>: 145.0372, found: 145.0370.

#### 4.2.10. Nicotinamide 2j

51 mg (84%); colorless solid; mp: 122–124 °C; <sup>1</sup>H NMR (400 MHz, DMSO- $d^6$ ):  $\delta$  7.50, 8.20, 8.70, 9.02 (dd, d, d, s, *J* = 4.8, 8.2, 8.2, 4.8 Hz, 1H, 1H, 1H, pyridyl, 7.61 (br, 1H, NH<sub>A</sub>), 8.16 (br, 1H, NH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, DMSO- $d^6$ ):  $\delta$  123.3, 129.6, 135.1, 148.6, 151.8, 166.4; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3367 (CONH), 3159 (CONH), 1699 (CON), 1682 (CON); HRMS (ESI-TOF): Calcd for C<sub>6</sub>H<sub>6</sub>-N<sub>2</sub>ONa (M+Na)<sup>+</sup>: 145.0372, found: 145.0370.

#### 4.2.11. Isonicotinamide 2k

58 mg (95%); colorless solid; mp: 151–153 °C; <sup>1</sup>H NMR (400 MHz, DMSO- $d^6$ ):  $\delta$  7.73 (br, 1H, NH<sub>A</sub>), 7.76, 8.72 (d, d, *J* = 6.0, 6.0 Hz, 2H, 2H, pyridyl), 8.25 (br, 1H, NH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, DMSO- $d^6$ ):  $\delta$  121.3, 141.2, 150.1, 166.2; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3334 (CONH), 1684 (CON), 1624 (CON); HRMS (ESI-TOF): Calcd for C<sub>6</sub>H<sub>7</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 123.0553, found: 123.0529.

#### 4.2.12. Furan-2-carboxamide 21

33 mg (59%); colorless powder; mp: 143–144 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.82 (br, 1H, NH<sub>A</sub>), 6.26 (br, 1H, NH<sub>B</sub>), 6.53, 7.17, 7.47 (dd, d, d, *J* = 1.8, 3.5, 3.5, 1.8 Hz, 1H, 1H, 1H, furanyl); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  112.3, 115.1, 144.4, 147.5, 160.4; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3352 (CONH), 3163 (CONH), 1664 (CON), 1624 (CON); HRMS (ESI-TOF): Calcd for C<sub>5</sub>H<sub>5</sub>NO<sub>2</sub>Na (M+Na)<sup>+</sup>: 134.0212, found: 134.0209.

#### 4.2.13. Furan-3-carboxamide 2m

25 mg (45%); colorless powder; mp: 162–164 °C; <sup>1</sup>H NMR (400 MHz, MeOD- $d^4$ ):  $\delta$  6.79, 7.56, 8.07 (dd, dd, dd, J = 0.9, 1.9, 1.7, 1.9, 0.9, 1.7 Hz, 1H, 1H, furanyl); <sup>13</sup>C NMR (100 MHz, MeOD- $d^4$ ):  $\delta$  110.0, 123.4, 145.3, 147.1, 167.6; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3309 (CONH), 1621 (CON); HRMS (ESI-TOF): Calcd for C<sub>5</sub>H<sub>5</sub>NO<sub>2</sub>Na (M +Na)<sup>+</sup>: 134.0212, found: 134.0209.

#### 4.2.14. Thiophene-2-carboxamide 2n

27 mg (42%); colorless solid; mp: 143–145 °C; <sup>1</sup>H NMR (400 MHz, MeOD-*d*<sup>4</sup>):  $\delta$  7.12, 7.66, 7.70 (dd, d, d, *J* = 3.9, 5.0, 5.0, 3.9 Hz, 1H, 1H 1H, thiophenyl); <sup>13</sup>C NMR (100 MHz, MeOD-*d*<sup>4</sup>):  $\delta$  128.9, 130.6, 132.2, 139.9, 166.7; IR (KBr,  $\nu_{max}/cm^{-1}$ ) = 3342 (CONH), 1612 (CON); HRMS (ESI-TOF): Calcd for C<sub>5</sub>H<sub>5</sub>NO<sub>2</sub>Na (M +Na)<sup>+</sup>: 134.0212, found: 134.0209.

#### 4.2.15. Thiophene-3-carboxamide 20

29 mg (45%); colorless powder; mp: 178–180 °C; <sup>1</sup>H NMR (400 MHz, MeOD- $d^4$ ):  $\delta$  7.46, 7.50, 8.08 (dd, dd, dd, J = 2.9, 5.1, 1.4, 5.1, 1.4, 2.9 Hz, 1H, 1H, thiophenyl); <sup>13</sup>C NMR (100 MHz, MeOD- $d^4$ ):  $\delta$  127.5, 127.9, 130.6, 138.1, 167.8; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3359 (CONH), 1622 (CON); HRMS (ESI-TOF): Calcd for C<sub>5</sub>H<sub>5</sub>NOSNa (M+Na)<sup>+</sup>: 149.9984, found: 150.0010.

# 4.3. Typical procedure for the primary amidation of Cbz-L-Phe-OH 3a with NH<sub>4</sub>Cl

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **3a** in 10 mL of THF were added 67  $\mu$ L (0.70 mmol, 1.4 equiv) of ClCO<sub>2</sub>Et and 209  $\mu$ L (1.5 mmol, 3.0 equiv) of Et<sub>3</sub>N at 0 °C. After stirring for 30 min at 0 °C, 0.75 ml of a 1.0 M aqueous solution of NH<sub>4</sub>-Cl (0.75 mmol, 1.5 equiv) were added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and 5 mL of H<sub>2</sub>O was added to the resulted mixture. The colorless clear solution was extracted with 30 mL of EtOAc and the aqueous layer was extracted with 5 mL of brine, and dried over anhydrous MgSO<sub>4</sub>. The crude product was chromatographed on silica gel with EtOAc to afford 129 mg (86% yield) of Cbz-L-Phe-NH<sub>2</sub> **4a**.

#### 4.3.1. Cbz-L-Phe-NH<sub>2</sub> 4a

129 mg (87%); 97% ee; colorless solid; mp: 163–164 °C;  $[\alpha]_D^{25} = -8.2$  (*c* 1.01, MeOH); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>):  $\delta$  2.73 (dd, *J* = 10.5, 13.6 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 2.99 (dd, *J* = 4.1, 13.6 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 4.17 (ddd, *J* = 4.1, 8.7, 10.5 Hz, 1H, CH), 4.94 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.08 (br, 1H, CONH<sub>A</sub>), 7.19–7.35 (m, 10H, C<sub>6</sub>H<sub>5</sub> × 2), 7.43 (d, *J* = 8.7 Hz, 1H, NHCH), 7.48 (br, 1H, CONH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>):  $\delta$  37.5, 56.1, 65.1, 126.2, 127.4, 127.7, 128.0, 128.3, 129.2, 137.1, 138.3, 155.9, 173.4; IR (KBr, v<sub>max</sub>/cm<sup>-1</sup>) = 3419 (CONH), 3318 (CONH), 3199 (CONH), 1691 (CON), 1657 (CON); HRMS (ESI-TOF): Calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 321.1210, found: 321.1290; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 23.0 min.

#### 4.3.2. Cbz-D-Phe-NH<sub>2</sub> 4a'

138 mg (93%); >99% ee; colorless solid;  $[\alpha]^{23}_{D}$  = +7.9 (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 18.2 min.

#### 4.3.3. Fmoc-L-Phe-NH<sub>2</sub> 4b

187 mg (96%); >99% ee; colorless powder; mp; 221–224 °C;  $[\alpha]_{D}^{26} = -8.4$  (*c* 1.01, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 2.78 (dd, *J* = 10.6, 13.6 Hz, 1H, *CH<sub>A</sub>C*<sub>6</sub>H<sub>5</sub>), 3.00 (dd, *J* = 4.2, 13.6 Hz, 1H, *CH<sub>B</sub>C*<sub>6</sub>H<sub>5</sub>), 4.11–4.20 (m, 4H, *CHC*H<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, *CH*<sub>2</sub>O, *CHC*H<sub>2</sub>O), 7.08 (br, 1H, CONH<sub>A</sub>), 7.45 (br, 1H, CONH<sub>B</sub>), 7.16–7.43, 7.54, 7.64, 7.88 (m, d, t, d, *J* = 8.8, 8.2, 7.6 Hz, 9H, 1H, 2H, 2H, NHCH, C<sub>6</sub>H<sub>5</sub>, Fmoc); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 37.5, 46.6, 56.1, 65.6, 120.1, 125.3, 125.4, 126.2, 127.0, 127.6, 128.0, 129.2, 138.3, 140.7, 143.8, 143.8, 155.8, 173.4; IR (KBr,  $\nu_{max}/cm^{-1}$ ) = 3375 (CONH), 3221 (CONH), 3207 (CONH), 1682 (CON), 1645 (CON), 1623 (CON); HRMS (ESI-TOF): Calcd for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 409.1523, found: 409.1519; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 22.2 min.

#### 4.3.4. Fmoc-D-Phe-NH<sub>2</sub> 4b'

190 mg (98%); >99% ee; colorless solid;  $[\alpha]_{D}^{26}$  = +10.6 (*c* 1.01, DMSO); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10):  $T_r$  24.4 min.

#### 4.3.5. Boc-L-Phe-NH<sub>2</sub> 4c

132 mg (quant.); >99% ee; colorless solid; mp: 142–144 °C;  $[\alpha]^{23}_{D}$  = +12.9 (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 1.30 (s, 9H, CH<sub>3</sub> ×3), 2.72 (dd, *J* = 10.2, 13.8 Hz, 1H, CH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 2.95 (dd, *J* = 4.4, 13.8 Hz, 1H, CH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 4.08 (ddd, *J* = 4.4, 8.8, 10.2 Hz, 1H, CH), 6.81 (d, *J* = 8.8 Hz, 1H, NHCH), 7.01 (br, 1H, CONH<sub>A</sub>), 7.16–7.21, 7.24–7.28 (m, m, 1H, 4H, C<sub>6</sub>H<sub>5</sub>), 7.37 (br, 1H, CONH<sub>B</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 28.1, 37.5, 55.6, 77.9, 126.1, 128.0, 129.2, 138.3, 155.2, 173.6; IR (KBr, *v*<sub>max</sub>/cm<sup>-1</sup>) = 3390 (CONH), 3346 (CONH), 3192 (CONH), 1684 (CON), 1660

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(CON); HRMS (ESI-TOF): Calcd for  $C_{14}H_{20}N_2O_3Na$  (M+Na)<sup>+</sup>: 287.1366, found: 287.1351; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 95/5):  $T_r$  20.7 min.

#### 4.3.6. Boc-D-Phe-NH<sub>2</sub> 4c'

132 mg (quant.); 96% ee; colorless solid;  $[\alpha]_D^{25} = -14.2$  (*c* 0.99, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 18.3 min.

#### 4.3.7. Cbz-L-Val-NH<sub>2</sub> 4d

117 mg (93%); >99% ee; coloress solid; mp: 172–175 °C;  $[\alpha]_D^{25} = +17.8$  (*c* 0.99, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 0.83 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>), 0.86 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>), 1.94 (ddd, *J* = 6.7, 6.8, 6.8 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.80 (dd, *J* = 6.7, 8.8 Hz, 1H, CH(CO), 5.03 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.03 (br, 1H, CONH<sub>A</sub>), 7.16 (d, *J* = 8.8 Hz, 1H, NHCH), 7.29–7.39 (m, 6H, CONH<sub>B</sub>, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 18.0, 19.3, 30.1, 60.0, 65.3, 127.6, 127.7, 128.3, 137.1, 156.1, 173.2; IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3381 (CONH), 3319 (CONH), 3203 (CONH), 1654 (CON); HRMS (ESI-TOF): Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 273.1210, found: 273.1193; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 11.5 min.

#### 4.3.8. Cbz-D-Val-NH<sub>2</sub> 4d'

121 mg (97%); >99% ee; coloress solid;  $[\alpha]_D^{26} = -17.9$  (*c* 1.00, DMSO); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10):  $T_r$  23.8 min.

#### 4.3.9. Fmoc-L-Val-NH<sub>2</sub> 4e

166 mg (98%); >99% ee; coloress solid; mp: 204–206 °C; [α]<sub>D</sub><sup>25</sup> = -3.0 (*c* 0.99, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 0.86 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>), 0.87 (d, *J* = 7.0 Hz, 3H, CH<sub>3</sub>), 1.96 (ddd, *J* = 6.8, 7.0, 8.2 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.80 (dd, *J* = 7.6, 8.2 Hz, 1H, CHCO), 4.22–4.29 (m, 3H, CHCH<sub>2</sub>O), 7.04 (br, 1H, CONH<sub>A</sub>), 7.29–7.44, 7.75, 7.90 (m, d, d, *J* = 5.9, 7.5 Hz, 6H, 2H, 2H, NHCH, CONH<sub>B</sub>, Fmoc); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 18.0, 19.2, 30.1, 46.6, 60.0, 65.6, 120.0, 125.3, 127.0, 127.5, 140.6, 143.7, 143.8, 156.0, 173.1; IR (KBr,  $v_{max}/cm^{-1}$ ): 3369 (CONH), 3311 (CONH), 3197 (CONH), 1689 (CON), 1660 (CON); HRMS (ESI-TOF): Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 361.1523, found: 361.1509; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 20.7 min.

#### 4.3.10. Fmoc-D-Val-NH<sub>2</sub> 4e'

169 mg (quant.); >99% ee; coloress solid;  $[\alpha]_D^{25}$  = +2.7 (*c* 1.00, DMSO); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 13.3 min.

#### 4.3.11. Boc-L-Val-NH<sub>2</sub> 4f

106 mg (98%); >99% ee; coloress solid; mp: 149–152 °C;  $\alpha$ ]<sup>30</sup><sub>D</sub> = -2.4 (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.94 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CH), 0.99 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CH), 1.45 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>C), 2.16 (ddd, *J* = 6.7, 6.8, 6.8 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.96 (dd, *J* = 6.7, 7.8 Hz, 1H, CHCO), 5.03, 5.42, 5.89 (br, br, br, 1H, 1H, 1H, NH, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  17.8, 19.3, 28.3, 30.8, 59.5, 79.9, 156.0, 174.4; IR (KBr,  $v_{max}/cm^{-1}$ ): 3386 (CONH), 3345 (CONH), 3205 (CONH), 1680 (CON), 1641 (CON); HRMS (ESI-TOF): Calcd for C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 239.1366, found: 239.1340; The enantiomeric ratio was determined by HPLC (Chiral-cel OD: hexane/2-propanol = 95/5): T<sub>r</sub> 9.4 min.

#### 4.3.12. Boc-D-Val-NH<sub>2</sub> 4f'

103 mg (95%); 98% ee; coloress solid;  $[\alpha]_D^{26} = +1.4$  (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 7.5 min.

#### 4.3.13. Cbz-L-Met-NH<sub>2</sub> 4g

130 mg (92%); >99% ee; colorless solid; mp: 108–112 °C;  $\alpha$ ]<sup>30</sup><sub>D</sub> = -14.9 (*c* 1.01, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.96–2.05 (m, 1H, CH<sub>A</sub>CH), 2.08–2.17 (m, 1H, CH<sub>B</sub>CH), 2.11 (s, 3H, CH<sub>3</sub>S), 2.52–2.66 (m, 2H, CH<sub>2</sub>S), 4.37–4.43 (m, 1H, CH), 5.12 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.39, 5.46, 6.08 (br, br, br, 1H, 1H, 1H, NH, NH<sub>2</sub>), 7.31–7.40 (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.3, 30.1, 31.6, 53.5, 67.2, 128.1, 128.3, 128.6, 136.1, 156.3, 173.8; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3386 (CONH), 3315 (CONH), 3201 (CONH), 1655 (CON); HRMS (ESI-TOF): Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>SNa (M+Na)<sup>+</sup>: 305.0930, found: 305.0908; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 21.2 min.

#### 4.3.14. Cbz-D-Met-NH<sub>2</sub> 4g'

133 mg (94%); >99% ee; colorless solid;  $[\alpha]^{29}_{D}$  = +13.3 (*c* 0.99, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10):  $T_r$  25.5 min.

#### 4.3.15. Fmoc-L-Met-NH<sub>2</sub> 4h

185 mg (quant.); >99% ee; coloress solid; mp: 181–184 °C;  $[\alpha]_{D}^{27} = -2.0$  (*c* 1.00, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 1.78–1.83 (m, 1H, *CH*<sub>A</sub>CH), 1.88–1.94 (m, 1H, *CH*<sub>B</sub>CH), 2.04 (s, 3H, CH<sub>3</sub>S), 2.39–2.50 (m, 2H, CH<sub>2</sub>S), 3.99–4.02 (m, 1H, *CHC*H<sub>2</sub>CH<sub>2</sub>), 4.22–4.3 (m, 3H, CHCH<sub>2</sub>O), 7.04 (br, 1H, CONH<sub>A</sub>), 7.33–7.49, 7.72–7.75, 7.90 (m, m, d, *J* = 7.5 Hz, 6H, 2H, 2H, NHCH, CONH<sub>B</sub>, Fmoc); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 14.5, 29.7, 31.5, 46.6, 53.6, 65.5, 120.0, 125.2, 127.0, 127.5, 140.6, 143.7, 143.8, 155.9, 173.4; IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3367 (CONH), 3319 (CONH), 3201 (CONH), 1685 (CON), 1647 (CON), 1626 (CON); HRMS (ESI-TOF): Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>SNa (M+Na)<sup>+</sup>: 305.0930, found: 305.0908; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 80/20): *T<sub>r</sub>* 9.9 min.

#### 4.3.16. Fmoc-D-Met-NH<sub>2</sub> 4h'

185 mg (quant.); >99% ee; coloress solid;  $[\alpha]_D^{27}$  = +1.5 (*c* 1.00, DMSO); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 80/20): *T*<sub>r</sub> 13.6 min.

#### 4.3.17. Boc-L-Met-NH<sub>2</sub> 4i

122 mg (98%); >99% ee; coloress solid; mp: 118–120 °C;  $[\alpha]_{D}^{27} = -8.3$  (*c* 1.01, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.45 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>C), 1.89–1.98 (m, 1H, *CH*<sub>A</sub>CH), 2.08–2.16 (m, 1H, *CH*<sub>B</sub>CH), 2.12 (s, 3H, CH<sub>3</sub>S), 2.53–2.65 (m, 2H, CH<sub>2</sub>S), 3.99–4.02 (m, 1H, CH), 5.16, 5.46, 6.19 (br, br, br, 1H, 1H, 1H, NH, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.4, 28.4, 30.2, 31.7, 53.1, 80.3, 155.7, 174.3; IR (KBr,  $v_{max}/cm^{-1}$ ): 3390 (CONH), 3346 (CONH), 3188 (CONH), 1684 (CON), 1660 (CON); HRMS (ESI-TOF): Calcd for C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>SNa (M+Na)<sup>+</sup>: 271.1087, found: 271.1095; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 17.4 min.

#### 4.3.18. Boc-D-Met-NH<sub>2</sub> 4i'

118 mg (95%); >99% ee; coloress solid;  $[\alpha]_D^{26}$  = +5.0 (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 15.1 min.

#### 4.3.19. Cbz-L-Ala-NH<sub>2</sub> 4j

87 mg (79%); >99% ee; colorless powder; mp; 128–130 °C; [ $\alpha$ ]<sub>D</sub><sup>5</sup> = -4.9 (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.39 (d, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 4.23–4.31 (m, 1H, CHCH<sub>3</sub>), 5.08 (d, *J* = 12.2 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 5.12 (d, *J* = 12.2 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 5.48, 5.74, 6.19 (br, br, br, 1H, 1H, 1H, NH, NH<sub>2</sub>), 7.29–7.38 (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 18.5, 50.1, 67.1, 128.0, 128.2, 128.6, 136.1, 156.1, 175.1; IR (KBr,  $\nu_{max}/cm^{-1}$ ) = 3394 (CONH), 3311 (CONH), 3197 (CONH), 1682 (CON), 1643 (CON);

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HRMS (ESI-TOF): Calcd for  $C_{11}H_{14}N_2O_3Na$  (M+Na)<sup>+</sup>: 245.0897, found: 245.0916; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10):  $T_r$  13.6 min.

#### 4.3.20. Cbz-D-Ala-NH<sub>2</sub> 4j'

86 mg (77%); 99% ee; coloress solid;  $[\alpha]^{24}_{D}$  = +3.8 (*c* 1.01, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10):  $T_r$  15.7 min.

#### 4.3.21. Cbz-L-Gln-NH<sub>2</sub> 4k

103 mg (74%); colorless solid; 198–200 °C;  $[\alpha]_{D}^{25}$  = +11.7 (*c* 1.00, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>):  $\delta$  1.65–1.74 (m, 1H, *CH*<sub>A</sub>CH), 1.82–1.91 (m, 1H, *CH*<sub>B</sub>CH), 2.07–2.12 (m, 2H, CH<sub>2</sub>CO), 3.86–3.92 (m, 1H, CH), 5.02 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 6.76 (br, 1H, NH<sub>A</sub>), 7.02 (br 1H, NH<sub>B</sub>), 7.28–7.39 (m, 8H, NH, NH<sub>2</sub>, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>):  $\delta$  27.7, 31.5, 54.3, 65.4, 127.7, 127.8, 128.4, 137.1, 155.9, 173.6, 173.7; IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3446 (CONH), 3423 (CONH), 3328 (CONH), 3203 (CONH), 1658 (CON); HRMS (ESI-TOF): Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 302.1111, found: 302.1115.

#### 4.3.22. Cbz-D-Gln-NH<sub>2</sub> 4k'

108 mg (77%); colorless solid;  $[\alpha]_D^{25} = -10.5$  (*c* 0.99, DMSO).

#### 4.3.23. Cbz-L-Leu-NH<sub>2</sub> 41

114 mg (86%); >99% ee; colorless powder; mp; 123–125 °C;  $[\alpha]_{D}^{27} = -11.2$  (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.95 (d, *J* = 6.2 Hz, 6H, CH<sub>3</sub> × 2), 1.51–1.59 (m, 1H, CH<sub>A</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.66–1.74 (m, 2H, CH<sub>B</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH(CH<sub>3</sub>)<sub>2</sub>), 4.19–4.25 (m, 1H, CHCO), 5.12 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.12, 5.39, 6.00 (br, br, br, 1H, 1H, 1H, NH, NH<sub>2</sub>), 7.30–7.39 (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  21.9, 22.9, 24.7, 41.3, 53.1, 67.1, 128.0, 128.3, 128.6, 136.1, 156.4, 174.9; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3392 (CONH), 3321 (CONH), 3203 (CONH), 1666 (CON); HRMS (ESI-TOF): Calcd for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 287.1366, found: 287.1396; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 10.7 min.

#### 4.3.24. Cbz-D-Leu-NH<sub>2</sub> 4l'

114 mg (86%); >99% ee; colorless solid;  $[\alpha]_D^{2p}$  +11.1 (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): *T*<sub>r</sub> 14.4 min.

#### 4.3.25. Cbz-L-Trp-NH<sub>2</sub> 4m

138 mg (82%); >99% ee; colorless powder; mp; 186–188 °C;  $[α]^{28}_{D} = -30.0$  (*c* 1.00, DMSO); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 2.90 (dd, *J* = 9.5, 13.9 Hz, 1H, CH<sub>A</sub>-indolyl), 3.10 (dd, *J* = 4.3, 13.9 Hz, 1H, CH<sub>B</sub>-indolyl), 4.21 (ddd, *J* = 4.3, 8.2, 9.5 Hz, 1H, CH), 4.92 (d, *J* = 12.5 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 4.96 (d, *J* = 12.5 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 6.95–6.98, 7.04–7.08, 7.14, 7.25–7.35 (m, m, s, m, 1H, 2H, 1H, 7H, CONH<sub>A</sub>, C<sub>6</sub>H<sub>5</sub>, indolyl), 7.47 (br, 1H, CONH<sub>B</sub>), 7.64 (d, *J* = 8.2 Hz, 1H, NHCHCH<sub>2</sub>), 10.81 (br, 1H, indoleNH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 27.7, 55.3, 65.1, 110.2, 111.2, 118.1, 118.4, 120.7, 123.6, 127.2, 127.4, 127.6, 128.2, 136.0, 136.9, 155.7, 173.7; IR (KBr,  $ν_{max}/cm^{-1}$ ) = 3402 (NH), 3313 (OH), 1716 (CO<sub>2</sub>), 1662 (CON); HRMS (ESI-TOF): Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 360.1319, found: 360.1329; The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 85/15): *T*<sub>r</sub> 26.1 min.

#### 4.3.26. Cbz-D-Trp-NH<sub>2</sub> 4m'

133 mg (79%); >99% ee; colorless solid;  $[\alpha]_D^{27}$  = +29.2 (*c* 0.99, DMSO); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 85/15): *T*<sub>r</sub> 24.2 min.

#### 4.3.27. Boc-O-Bn-L-Ser-NH<sub>2</sub> 4n

128 mg (87%); >99% ee; colorless solid; mp: 86–89 °C;  $[\alpha]_D^{27}$  = +13.9 (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.45 (s, 9H, CH<sub>3</sub> × 3), 3.58 (dd, *J* = 6.9, 9.1 Hz, 1H, CH<sub>A</sub>CH), 3.93 (dd, *J* = 3.7, 9.1 Hz, 1H, CH<sub>B</sub>CH), 4.24–4.36 (m, 1H, CH), 4.53 (d, *J* = 11.6 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 4.61 (d, *J* = 11.6 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 5.42, 6.44 (br, br, 2H, 1H, NH, NH<sub>2</sub>), 7.29–7.38 (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  28.3, 53.6, 69.8, 73.5, 80.3, 127.8, 128.0, 128.5, 137.4, 155.5, 172.8; IR (KBr,  $\nu_{max}/cm^{-1}$ ) = 3390 (CONH), 3346 (CONH), 3192 (CONH), 1685 (CON), 1660 (CON); HRMS (ESI-TOF): Calcd for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 317.1472, found: 317.1490; The enantiomeric ratio was determined by HPLC (Chiral-cel AD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 23.8 min.

#### 4.3.28. Boc-O-Bn-D-Ser-NH<sub>2</sub> 4n'

133 mg (90%); >99% ee; colorless solid;  $[\alpha]_D^{27} = -12.2$  (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 95/5): *T*<sub>r</sub> 25.4 min.

# 4.4. Typical procedure for the amidation of Cbz-L-Phe-OH 3a with hydroxylamine hydrochloride 5h

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **3a** in 10 mL of THF were added 67  $\mu$ L (0.70 mmol, 1.4 equiv) of ClCO<sub>2</sub>Et and 209  $\mu$ L (1.5 mmol, 3.0 equiv) of Et<sub>3</sub>N at 0 °C. After stirring for 30 min at 0 °C, 0.75 mL of a 1.0 M aqueous solution of hydroxylamine hydrochloride (0.75 mmol, 1.5 equiv) were added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C, after which 5 mL of H<sub>2</sub>O were added to the resulted mixture. The colorless clear solution was extracted with 30 mL of EtOAc and the aqueous layer was extracted with 20 mL of EtOAc. The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 100 mg (64% yield) of Cbz-L-Phe-NHOH **6ah**.

#### 4.4.1. Cbz-L-Phe-NHEt 6aa

141 mg (87%); colorless solid; mp: 138–139 °C;  $[\alpha]_{D}^{26} = -6.6$  (c 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.97 (t, J = 7.3 Hz, 3H, CH<sub>3</sub>), 2.99 (dd, J = 8.1, 13.6 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 3.12–3.22 (m, 3H, *CH*<sub>2</sub>CH<sub>3</sub>, CHCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 4.30 (dd, J = 7.6, 8.4 Hz, 1H, *CHCH*<sub>2</sub>), 5.09 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.34, 5.43 (br, br, 1H, 1H, NH ×2), 7.19–7.38 (m, 10H, C<sub>6</sub>H<sub>5</sub> × 2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  14.5, 34.3, 39.0, 59.5, 67.0, 127.0, 128.0, 128.2, 128.6, 128.7, 129.3, 136.2, 136.6, 155.9, 170.4; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3315 (CONH), 1689 (CON), 1651 (CON); HRMS (ESI-TOF): Calcd for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>Na (M +Na)<sup>+</sup>: 349.1523, found: 349.1513.

#### 4.4.2. Cbz-L-Phe-NHCH<sub>2</sub>CH<sub>2</sub>Ph 6ab

169 mg (84%); colorless solid; mp: 118–120 °C;  $[\alpha]_D^{25} = -6.8$  (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.56–2.72 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 2.99 (dd, *J* = 7.8, 13.5 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 3.10 (dd, *J* = 6.0, 13.5 Hz, 1H, CHCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 3.23–3.50 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.29 (dd, *J* = 6.0, 7.8 Hz, 1H, CHCH<sub>2</sub>), 5.07 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.28, 5.60 (br, br, 1H, 1H, NH ×2), 7.02, 7.16–7.38 (d, m, *J* = 6.6 Hz, 2H, 13H, C<sub>6</sub>H<sub>5</sub> ×3); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 35.6, 38.9, 40.7, 56.6, 67.2, 126.7, 127.2, 128.1, 128.4, 128.7, 128.7, 128.8, 129.4, 136.2, 136.6, 138.6, 156.0, 170.8; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3305 (CONH), 1687 (CON), 1651 (CON); HRMS (ESI-TOF): Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 425.1836, found: 425.1827.

#### 4.4.3. Cbz-L-Phe-cyclohexylNH 6ac

160 mg (84%); colorless solid; mp: 151–153 °C;  $[\alpha]_D^{25}$  = +16.8 (*c* 1.00, DMSO); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.79–0.88, 0.92–1.03,

1.06–1.15, 1.19–1.35, 1.51–1.69, 1.74–1.81 (m, m, m, m, m, m, m, 1H, 1H, 2H, 4H, 1H, cyclohexylCH<sub>2</sub> ×5), 2.95 (dd, *J* = 8.2, 13.7 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 3.15 (dd, *J* = 5.7, 13.7 Hz, 1H, CHCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 3.61–3.69 (m, 1H, cyclohexylCH), 4.28 (dd, *J* = 5.7, 8.2 Hz, 1H, CHCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.10 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.25, 5.40 (br, br, 1H, 1H, NH ×2), 7.19–7.38 (m, 10H, C<sub>6</sub>H<sub>5</sub> ×2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  24.6, 25.4, 32.7, 32.8, 39.2, 48.2, 56.6, 67.0, 127.0, 128.1, 128.2, 128.6, 128.7, 129.4, 136.2, 136.6, 155.8, 169.4; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3317 (CONH), 3275 (CONH), 1689 (CON), 1647 (CON); HRMS (ESI-TOF): Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 403.1992, found: 403.1972.

#### 4.4.4. Cbz-L-Phe-adamantyINH 6ad

191 mg (87%); colorless solid; mp: 55–57 °C;  $[\alpha]_D^{25} = -1.1$  (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.59–1.64 (m, 6H, admantylCH<sub>2</sub> ×3), 1.75–1.82 (m, 6H, admantylCH<sub>2</sub> ×3), 1.97–2.04 (m, 3H, admantylCH ×3), 2.90 (dd, *J* = 8.7, 13.4 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 3.14 (dd, *J* = 5.0, 13.4 Hz, 1H, CHCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 4.25 (dd, *J* = 5.0, 8.7 Hz, 1H, CHCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.00 (br, 1H, NH), 5.10 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 5.43 (br, 1H, NH), 7.21–7.38 (m, 10H, C<sub>6</sub>H<sub>5</sub> ×2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  29.3, 36.2, 39.3, 41.3, 52.0, 56.9, 66.9, 127.0, 128.0, 128.2, 128.5, 128.7, 129.5, 136.3, 136.8, 155.8, 169.2; IR (KBr, *v*<sub>max</sub>/cm<sup>-1</sup>): 3307 (CONH), 1705 (CON), 1655 (CON); HRMS (ESI-TOF): Calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 455.2305, found: 455.2277.

#### 4.4.5. Cbz-L-Phe-NMe<sub>2</sub> 6ae

139 mg (85%); colorless oil;  $[\alpha]_D^{25}$  = +12.9 (*c* 1.21, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.62 (s, 3H, CH<sub>3</sub>), 2.86 (s, 3H, CH<sub>3</sub>), 2.93–3.03 (m, 2H, CHCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.85–4.91 (m, 1H, CHCH<sub>2</sub>), 5.06 (d, *J* = 12.4 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 5.10 (d, *J* = 12.4 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 5.69 (br, 1H, NH), 7.14–7.18, 7.21–7.38 (m, m, 2H, 8H, C<sub>6</sub>H<sub>5</sub> ×2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 35.5, 36.8, 40.2, 51.9, 66.8, 127.0, 128.0, 128.1, 128.4, 128.5, 129.4, 136.2, 136.4, 155.6, 171.2; IR (NaCl,  $v_{max}$ /cm<sup>-1</sup>) = 3280 (CONH), 1716 (CON), 1639 (CON); HRMS (ESI-TOF): Calcd for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 327.1703, found: 327.1726.

#### 4.4.6. Cbz-L-Phe-NEt<sub>2</sub> 6af

128 mg (72%); colorless oil;  $[\alpha]_D^{25} = -8.7$  (*c* 0.99, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.98 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 1.04 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 2.88–3.11 (m, 5H, CH<sub>2</sub>CH<sub>3</sub> ×2, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 3.49–3.58 (m, 1H, CHCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 4.76–4.82 (m, 1H, CHCH<sub>2</sub>), 5.05 (d, *J* = 12.3 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 5.12 (d, *J* = 12.3 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 5.61 (br, 1H, NH), 7.18–7.29, 7.30–7.37 (m, m, 5H, 5H, C<sub>6</sub>H<sub>5</sub> ×2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  12.8, 14.1, 40.4, 40.5, 41.6, 51.9, 66.8, 127.0, 128.0, 128.1, 128.4, 128.5, 129.6, 136.3, 136.4, 155.6, 170.5; IR (NaCl,  $\nu_{max}/cm^{-1}$ ) = 3273 (CONH), 1716 (CON), 1631 (CON); HRMS (ESI-TOF): Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 355.2016, found: 355.2022.

#### 4.4.7. Cbz-L-Phe-piperidyl 6ag

154 mg (84%); pale orange oil;  $[\alpha]_D^{25} = +2.5$  (*c* 1.01, MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.97–1.04 (m, 1H, piperidylCH<sub>A</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.34–1.58 (m, 5H, piperidyl CH<sub>B</sub>CH<sub>2</sub>CH<sub>2</sub>N, piperidylCH<sub>2</sub>CH<sub>2</sub>N × 2), 2.97 (br, 1H, piperidylCH<sub>A</sub>N), 2.99 (br, 1H, piperidylCH<sub>B</sub>N), 3.00 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>) 3.23 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>) 3.23 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>) 3.23 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 5.73 (d, *J* = 8.2 Hz, 1H, OCH<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 5.11 (d, *J* = 12.4 Hz, 1H, OCH<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 5.73 (d, *J* = 8.2 Hz, 1H, NH), 7.13–7.38 (m, 10H, C<sub>6</sub>H<sub>5</sub> × 2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 24.3, 25.3, 25.9, 40.2, 43.1, 46.6, 51.4, 66.7, 126.9, 128.0, 128.1, 128.5, 128.5, 129.6, 136.2, 136.5, 155.6, 169.3; IR (NaCl,  $\nu_{max}/cm^{-1}$ ) = 3280 (CONH), 1716 (CON), 1630 (CON); HRMS (ESI-TOF): Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 389.1836, found: 389.1808.

#### 4.4.8. Cbz-L-Phe-NHOH 6ah

129 mg (86%); colorless solid; mp: 139–141 °C;  $[\alpha]^{29}{}_{\rm D}$  = –11.8 (*c* 1.00, MeOH); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 2.78 (dd, *J* = 10.0, 13.7 Hz, 1H, CHC*H*<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 2.89 (dd, *J* = 4.9, 13.7 Hz, 1H, CHC*H*<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 4.10 (ddd, *J* = 4.9, 8.8, 10.0 Hz, 1H, CHCH<sub>2</sub>), 4.92 (d, *J* = 13.3 Hz, 1H, OC*H*<sub>A</sub>C<sub>6</sub>H<sub>5</sub>), 4.95 (d, *J* = 13.3 Hz, 1H, OC*H*<sub>B</sub>C<sub>6</sub>H<sub>5</sub>), 7.18–7.36 (m, 10H, C<sub>6</sub>H<sub>5</sub> × 2), 7.62 (d, *J* = 8.8 Hz, 1H, NHCH), 8.89 (s, 1H, NHOH), 10.73 (s, 1H, NHOH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sup>6</sup>): δ 37.6, 53.9, 65.1, 126.2, 127.4, 127.6, 128.0, 128.2, 129.1, 136.9, 137.8, 155.6, 168.0; IR (KBr, *v*<sub>max</sub>/cm<sup>-1</sup>) = 3315 (OH), 3255 (CONH), 3143 (CONH), 1701 (CON), 1668 (CON); HRMS (ESI-TOF): Calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 337.1159, found: 337.1129.

#### 4.5. Typical procedure for the amidation of (2*S*,3*S*)-(+)-2,3methano-3-phenylpropanoic acid 7 with hydroxylamine hydrochloride 5h

To a colorless solution of 162 mg (1.0 mmol) of (25,35)-(+)-2,3methano-3-phenylpropanoic acid 7 prepared from (2S,3S)-(+)-2,3methano-3-phenylpropanol<sup>20</sup> in 5 mL of THF were added 105  $\mu$ L (1.1 mmol, 1.1 equiv) of ClCO<sub>2</sub>Et and 419  $\mu$ L (3.0 mmol, 3.0 equiv) of Et<sub>3</sub>N at -15 °C. After stirring for 10 min at -15 °C, 1.0 mL of a 2.0 M aqueous solution of hydroxylamine hydrochloride (2.0 mmol, 2.0 equiv) was added at -15 °C to the colorless suspension. The mixture was stirred for 4 h at -15 °C after which 5 mL of 1.0 M aqueous HCl solution were added to the resulted mixture. The colorless clear solution was extracted with 10 mL of EtOAc and the aqueous layer was extracted with 10 mL of EtOAc ( $\times$ 2). The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was chromatographed on silica gel with a 15:1 mixture of CHCl<sub>3</sub> and MeOH to afford 146 mg (82% yield) of (2S,3S)-(+)-N-hydroxy-2,3-methano-3-phenylpropanamide 8. (2S,3S)-(+)-8: 146 mg (82%); colorless solid; mp: 125–127 °C;  $[\alpha]^{18}_{D}$  = +338.1 (*c* 1.13, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.33–1.37 (m, 1H, cyclopropylCH<sub>A</sub>), 1.65–1.70 (m, 2H, cyclopropylCH<sub>B</sub>, CHC<sub>6</sub>H<sub>5</sub>), 2.54–2.59 (m, 1H, CHCO), 7.06–7.11, 7.19-7.23, 7.26-7.30 (m, m, m, 2H, 1H, 2H, C<sub>6</sub>H<sub>5</sub>), 8.01 (brs, 1H, NH), 8.26 (brs, 1H, OH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, few drops of CD<sub>3</sub>OD for solubility): *δ* 15.5, 23.0, 24.7, 31.3, 126.2, 126.5, 128.5, 140.3, 171.3; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3361 (CONH), 3186 (OH), 1653 (CON); HRMS (ESI-TOF): Calcd for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>Na (M+Na)<sup>+</sup>: 200.0682, found: 200.0655.

#### 4.6. Typical procedure for the Lossen rearrangment of (25,35)-(+)-N-hydroxy-2,3-methano-3-phenylpropanamide 8

To a colorless solution of 100 mg (0.565 mmol) of (2S,3S)-(+)-Nhydroxy-2,3-methano-3-phenylpropanamide 8 and 142 mg (0.622 mmol, 1.1 equiv) of 4-nitrobenzenesulfonyl chloride in 5 mL of anhydrous THF was added 250 µL (1.41 mmol, 2.5 equiv) of *i*-Pr<sub>2</sub>-NEt at 0 °C. After stirring for 2 h at 0 °C, 9 µL (0.113 mmol, 0.2 equiv) of *N*-methylimidazole and 293 µL (2.82 mmol, 5.0 equiv) of benzylalcohol were added to the resulted mixture. The mixture was stirred for 15 h at 35 °C, diluted with 15 mL of EtOAc, and washed with 10 mL of half brine. The aqueous layer was extracted with 10 mL of EtOAc. The organic layers were combined and dried over anhydrous MgSO<sub>4</sub>. The crude product was chromatographed on silica gel with a 4:1 mixture of hexane and EtOAc to afford 131 mg (87% yield) of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **9**. (15,2R)-(+)-**9**: 131 mg (87%); colorless solid; mp: 67–69 °C;  $[\alpha]_{D}^{27}$ = +69.6 (c 1.01, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.12–1.27 (m, 1H, cyclopropylCH<sub>2</sub>), 2.05–2.12 (m, 1H, CHCHC<sub>6</sub>H<sub>5</sub>), 2.72–2.81 (m, 1H, CHCO), 5.09 (brs, 1H, NH), 5.12 (s, 2H, OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.10-7.41 (m, 10H, C<sub>6</sub>H<sub>5</sub> ×2); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  16.1, 25.1, 32.6, 66.8, 126.1, 126.6, 128.1, 128.3, 128.5, 136.4, 140.4, 156.8; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3342 (CONH), 1689 (CON); HRMS (ESI-TOF): Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>Na (M+Na)<sup>+</sup>: 290.1151, found: 290.1146.

# 4.7. Typical procedure for the preparation of (1*S*,2*R*)-(+)-*N*-acetyltranylcypromine 10

A colorless suspension of 30 mg (0.11 mmol) of (1S,2R)-(+)-N-Cbz-tranylcypromine 9 in 5 mL of a 6.0 M aqueous solution of HCl was stirred for 16 h at reflux and washed with 5 mL of EtOAc  $(\times 3)$ . The aqueous layer was concentrated in vacuo to afford a crude (15,2R)-tranylcypromine hydrochloride. To the crude residual solid were added 2 mL of pyridine, 23  $\mu L$  (0.22 mmol, 2.0 equiv) of Ac<sub>2</sub>O, and 31  $\mu$ L (0.22 mmol, 2.0 equiv) of Et<sub>3</sub>N at rt. After stirring for 12 h at rt, the colorless solution was quenched with 5 mL of H<sub>2</sub>O and extracted with 10 mL of EtOAc  $\times$ 2. The organic lavers were combined, washed with 5 mL of brine, and dried over MgSO<sub>4</sub>. The crude product was chromatographed on silica gel with EtOAc to afford 20 mg (quant.) of (1S,2R)-(+)-N-acetyltranylcypromine 10. (15,2R)-(+)-10: 131 mg (87%); 82% ee; colorless solid; mp: 90–93 °C;  $[\alpha]_{D}^{26}$  = +123.9 (c 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.14–1.18 (m, 1H, cyclopropylCH<sub>A</sub>), 1.20–1.28 (m, 1H, cyclopropylCH<sub>B</sub>), 1.98 (s, 3H, CH<sub>3</sub>), 2.02–2.06 (m, 1H, CHC<sub>6</sub>H<sub>5</sub>), 2.87-2.92 (m, 1H, CHNH), 5.77 (br, 1H, NH), 7.12-7.32 (m, 5H,  $C_{6}H_{5}$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  16.3, 23.1, 24.6, 126.1, 126.4, 128.4, 140.5, 171.3; IR (KBr,  $v_{max}/cm^{-1}$ ) = 3273 (CONH), 1647 (CON); HRMS (ESI-TOF): Calcd for C<sub>11</sub>H<sub>13</sub>NONa (M+Na)<sup>+</sup>: 198.0889, found: 198.0907. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5):  $T_{\rm r}$ (major) 54.2 min,  $T_{\rm r}$ (minor) 42.6 min (er 90.9:9.1).

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